博士論文

有機金属錯体を利用した有機小分子に対する新規プロパルギル化反応の開発と応用

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本学位論文は下記の原著論文を基に作成され，東北大学大学院薬学研究科に提出されたものである．

1. N. Kanoh*, T. Okamura, T. Suzuki, Y. Iwabuchi, A Mild Two-Step Propargylation of Aromatic Bioactive Small Moelcules, *Org. Biomol. Chem.*, **15**, 7190-7195 (2017).

2. T. Okamura, S. Fujiki, Y. Iwabuchi, N. Kanoh*, Gold(I)-catalyzed Nicholas Reaction with Aromatic Molecules Utilizaing a Bifunctional Propargyl Dicobalt Hexacarbonyl Complex, *Org. Biomol. Chem.*, **17**, 8422-8426 (2019).

3. T. Okamura, S. Egoshi, K. Dodo, M. Sodeoka, Y. Iwabuchi, N. Kanoh*, Highly Chemoselective *gem*-Difluoropropargylation of Aliphatic Alcohols, *Chem. Eur. J.*, **25**, 16002-16006 (2019).

略語表

本論文中において以下の用語及び反応剤は下記のように略記した.

Ac	acetyl
aq.	aqueous
AZADO	2-azaadamantane *N*-oxyl
Boc	*tert*-butoxycarbonyl
br	broad
Brsm	based on recovered starting material
Bu	butyl
Bz	benzyl
^{o}C	degree Celsius
calcd	calculated value
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
COSY	correlation spectroscopy
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMPU	*N,N'*-dimethylpropyleneurea
DMSO	dimethylsulfoxide
DTBMP	2,6-di-*tert*-butylmethylpyridine
DTBP	2,6-di-*tert*-butylpyridine
EI	electron ionization
ESI	electrospray ionization
esp	α,α,α',α'-tetramethyl-1,3-benzenedipropoinate
eq	equivalent
Et	ethyl
EWG	electron withdrawing group
FAB	fast atom bombardment
h	hour (s)
HFIP	hexafluoroisopropanol
HMBC	hetero-nuclear multiple-bond connectivity

HMQC	hetero-nuclear multiple quantum coherence
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
i	iso
IMes	1,3-bis(2,4,6-trimethoxyphenyl)imidazolium
IAd	1,3-bis(adamantyl)imidazolium
IR	infrared spectroscopy
J	coupling constant
M	molar
Me	methyl
MS4Å	molecular sieves 4 Å
min	minute (s)
mp	melting point
MS	mass spectrometry
NHC	*N*-heterocyclic carbene
NMO	*N*-methoxymorpholine *N*-oxide
NMR	nuclear magnetic resonance
p-	*para*-
pent	pentyl
Ph	phenyl
PMP	pentamethylpiperidine
*i*Pr	isopropyl
py	pyridine
rt	room temperature
t	tertiary
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetra-*n*-butylammonium fluoride
TBAT	tetra-*n*-butylammonium difluorotriphenylsilicate
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidine *N*-oxyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid

THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	tetramethylsilyl
TMG	tetramethylguanidine
TLC	thin layer chromatography
Ts	*p*-toluenesulfonyl
UV	ultraviolet

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総論

有機合成化学の発展は，化学のみならず，生物学，薬学にも大きな進展をもたらした．1899 年にドイツの Beyer 社より，初の人工合成医薬品である「アスピリン」が開発されたのを皮切りに，現在でも多くの小分子医薬品が有機合成化学の力を利用して開発されている [1]．一方で有機合成化学的な手法により得られた分子ツールを利用した生命現象の解明研究，すなわち「ケミカルバイオロジー」と呼ばれる領域が近年隆盛を極めている． Schreiber らによる FK506 固定化ビーズを利用した，標的タンパク質の同定研究とメカニズム解明研究を皮切りに [2]，多くの研究者が有機合成化学と生物学の垣根を超えた研究開発を行なっている．

アルキンは，有機合成化学において代表的な官能基の一つである．2 つの sp 混成軌道の炭素原子から成るアルキンは，ユニークな反応性や性質を示し，しばしば有用な反応前駆体となる．さらに，sp 混成軌道に基づくルイス塩基性により金属の良い配位子となるため，有機金属錯体を利用した反応においても重要である．アルキンの金属に対する配位は 3 種類の相互作用で説明可能である．すなわち，π 結合軌道のうち一方からの σ 供与，これと直交する π 結合軌道からの π 供与，そしてアルキンの π^* 軌道に対する逆供与である (**Figure 0-1**)[3]．これらの相互作用によってアルキンは金属に対して強く配位し，その構造や化学的性質が変化させるため，アルキンは化学反応の中でも金属を用いた反応が数多く報告されている [4]．

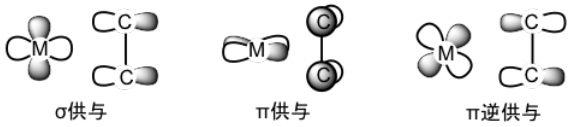
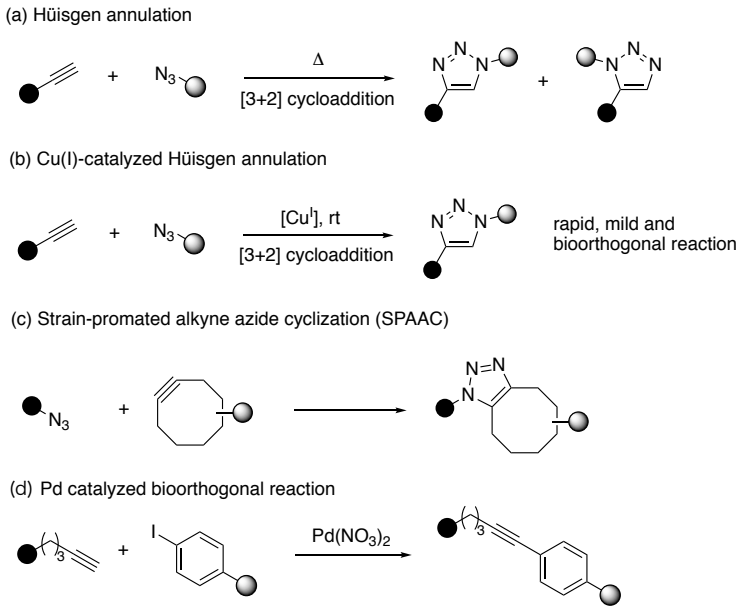


Figure 0-1. アルキンの金属原子に対する配位とその分子軌道

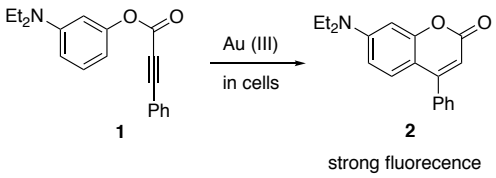
「バイオオルソゴナルケミストリー」の進展，すなわち夾雑系においても迅速かつ高い選択性で進行する反応の開発は，有機合成化学と薬学，生物学におけるアルキンの重要性をより強固にした [5]．特に，1961 年 Hüisgen らにより発見されたアルキンとアジドによる[3+2]環化付加反応は，バイオオルソゴナルケミストリーの代名詞的反応である (**Scheme 0-1a**) [6]．Hüisgen 環化は，2002 年に Mendal[7]，Sharpless[8] らにより，末端アルキンとアジドが銅触媒存在下，高化学選択的に反応することが報告されて以来，医薬品開発の誘導体合成や生物活性小分子を利用した標的タンパク質探索などに広く用いられている (**Scheme 0-1b**) [9]．その一方で，末端アルキンとアジド基の Hüisgen 環化を生細胞に利用したい場合，銅触媒による細胞毒性がしばしば問題となる．そこで Bertozzi らは，銅触媒非存在下でも室温で進行する歪みアルキンと

アジドの Hüisgen 環化の開発に成功している (**Scheme 0-1c**) [10]．さらに近年では，銅触媒よりも毒性の低いパラジウム触媒を利用した生体適合性の高い反応も報告されている．このパラジウムを利用した戦略は，とりわけタンパク質の修飾などに利用される (**Scheme 0-1d**)[11].



Scheme 0-1. アルキンを利用したバイオオルソゴナル反応概要

またアルキンのルイス塩基性を利用した，生体内の金属イオン検出法が開発されている [12]．例えば，Kim らはイノン単位を持つ分子 **1** を金イオン検出分子として報告している [13]．1 価の金イオンは，抗リウマチ薬であるオーラノフィンや金チオリンゴ酸ナトリウムに用いられる一方で，生体内で 3 価の金イオンへと変化することで重篤な肝臓，腎臓，末梢神経系に損傷を引き起こすため，金イオンの検出，定量を行うことのできる金イオンプローブの開発が求められていた．イノン **1** は，金イオン存在下でのみ環化反応が進行し蛍光分子 **2** へと変換される，*in vivo* 試験において 3 価の金イオンが存在する細胞を選択的に検出可能な分子である．



Scheme 0-2. 金イオン検出プローブ

さらにアルキンは，クリック反応など反応性に基づく応用のみならず生体内ラマンイメージングにも利用されている[14]．アルキンに由来するラマンピークは，2000-2200 cm^{-1} 付近に観測されるが，このピークは生体分子に由来するラマンピークと重複しない (**Figure 0-2**)．このため，アルキンのラマン散乱スペクトルは，生体成分によるラマン散乱スペクトルに邪魔されることなく選択的に観察可能であり，これを利用することで，上田，袖岡らは細胞のラマンイメージングに成功している[15]．

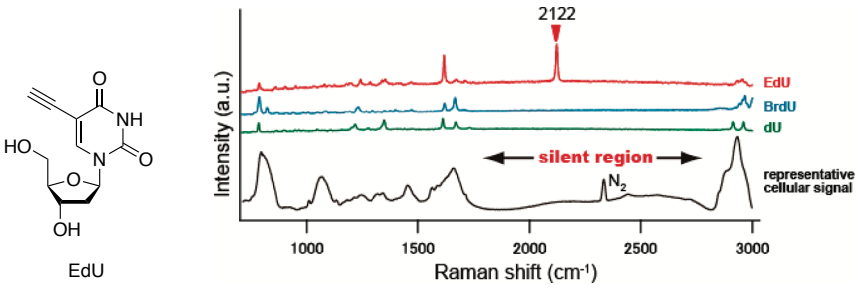
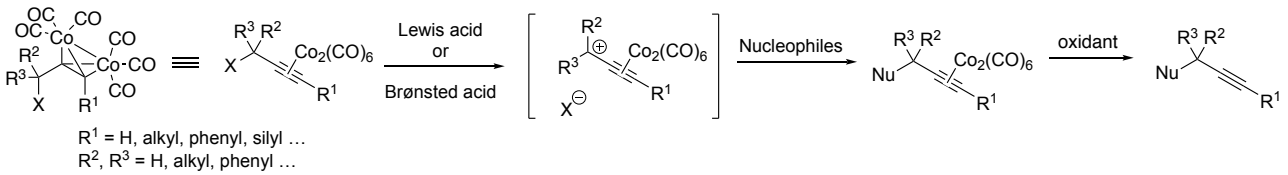


Figure 0-2．アルキンタグのラマンスペクトル

Yamakoshi, H.; Dodo, K.; Okada, M.; Ando, J.; Palonpon, A.; Fujita, K.; Kawata, S.; Sodeoka, M., *J. Am. Chem. Soc.* **2011**, *133*, 6102. © 2011 American Chemical Society.

Nicholas 反応は，アルキンと一つのメチレン炭素から成るプロパルギル基を導入する代表的な反応の一つであり，1972 年に Nicholas と Pettit らにより報告された[16]．ジコバルト錯体が配位したアルキン分子の隣接炭素は，安定なカルボカチオンが生じるため，この活性種を利用することで多数の求核剤との反応が報告されている[17]．反応後のアルキンコバルト錯体は，脱錯体化により対応するプロパルギル基へと変換可能できるほか，Pauson-Khand 反応などに応用することもできる (**Scheme 0-3**)[18]．



Scheme 0-3．ニコラス反応を利用したプロパルギル化の概要

今回，著者は，ケミカルプローブ創製を指向した，Nicholas 反応による芳香族生物活性分子に対する直接的なプロパルギル基導入法の開発をおこなった．さらに，従来とは異なる反応性を持つ Nicholas 反応の開発を目的とし，ジフルオロプロパルギルジコバルト錯体の合成と，これを利用した酸素原子に対す

るジフルオロプロパルギル化反応を開発した．本論文はその結果得られた学術的知見をまとめたものである．

第一章 プロパルギルジコバルト錯体を利用した芳香族生物活性分子の２工程プロパルギル化反応の開発

生物活性小分子や医薬品の標的分子を明らかにするため，これまで様々な標的同定技術が開発されてきた[19]．その一つに，小分子と標的分子の相互作用を利用して標的分子を捕獲する，”direct approach（化学的アプローチ）”が存在する[20]．小分子に何らかの目印を導入した「プローブ」を用いるこの手法を用いて，これまでに多くの標的分子同定成功例が報告されている．

プローブを作成する際に重要となるのが構造活性相関 (structure-activity relationships: SAR)である．構造活性相関とは，小分子の活性部位（ファルマコフォア）や構造可変部位の情報を与えるものであり，構造活性相関をもとに，小分子の活性部位から遠い位置の構造可変部位に目印となる官能基を導入することで，その生物活性小分子の活性をほとんど損なわずプローブ化し，標的同定に用いることができると期待される[21]．また，医薬品分子の構造最適化にも構造活性相関は用いられ，その重要性から今日でも多くの生物活性小分子や医薬品候補化合物の構造活性相関研究がアカデミアや製薬企業で展開されている．

構造活性相関研究の古典的な手法として，目的の生物活性小分子，医薬品候補化合物の誘導体を合成化学的手法により供給し，それらの活性を評価する方法が存在する．すなわち，設計した合成ルートに従って，原料から数工程の合成化学的変換により複数の誘導体を用意する．そして，これら誘導体の生物活性を観察することで，どの誘導体に活性があるのか，またその誘導体の構造から活性部位を推定することが可能となる (**Figure 0-3** 左)．しかしながら，この方法は，複数の誘導体を一つ一つ合成しなければならず，多くの時間と労力を消費しなければならないという欠点を有している．

近年，合成終盤もしくは生物活性小分子そのものに対して官能基化を行う Late-stage functionalization (LSF)と呼ばれる方法論が，医薬品創製やケミカルバイオロジー領域で注目されている (**Figure 0-3** 右)[22]．生物活性小分子の誘導体を数工程かけて合成するのではなく，生物活性小分子そのものに対して直接官能基化を行う本手法は，医薬品創製やケミカルプローブ創製に必須な構造活性相関研究において強力なツールになると考えられる．生物活性小分子はしばしば複雑な骨格や複数の官能基を持つことから，直接的かつ選択的な官能基化はチャレンジングである．しかしながら，目的の生物活性小分子が持つ構造や官能基によって，適切に試薬，反応条件を選択し，かつ小分子が持つ“innate (内因的)”な反応性を利用できれば，直接的かつ選択的な官能基化が達成できると考えられる．

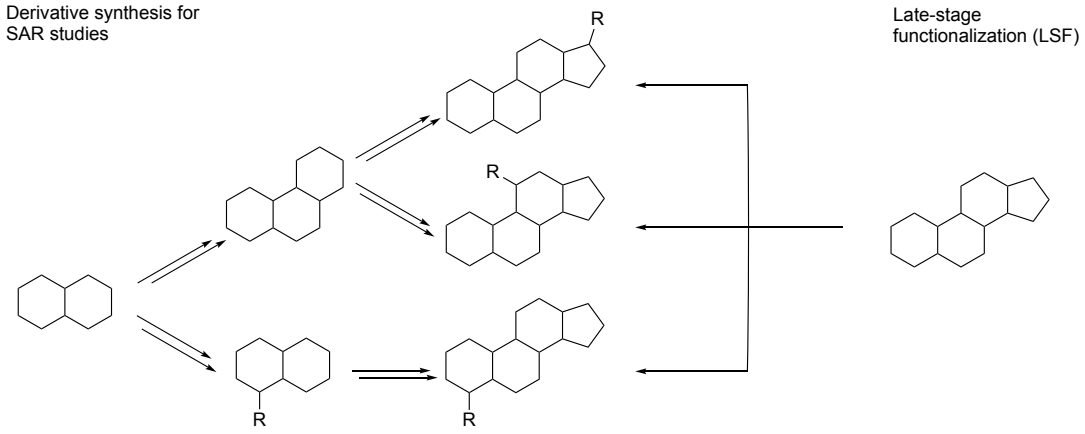
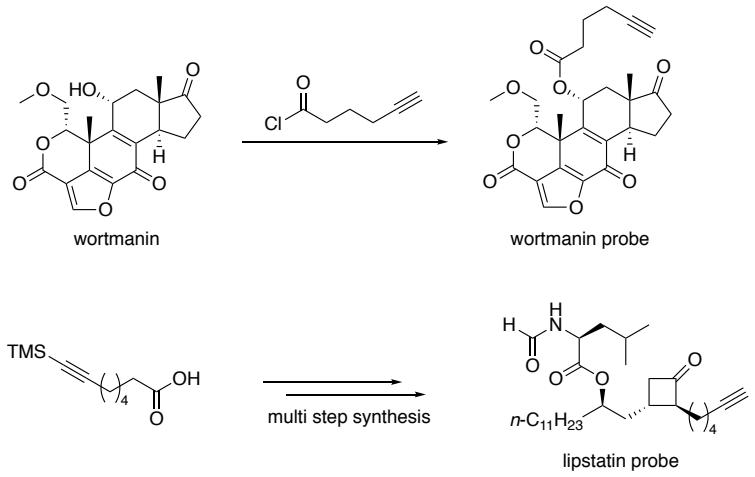


Figure 0-3. 構造活性相関研究における古典的誘導体合成法と late-stage functionalization の概念図

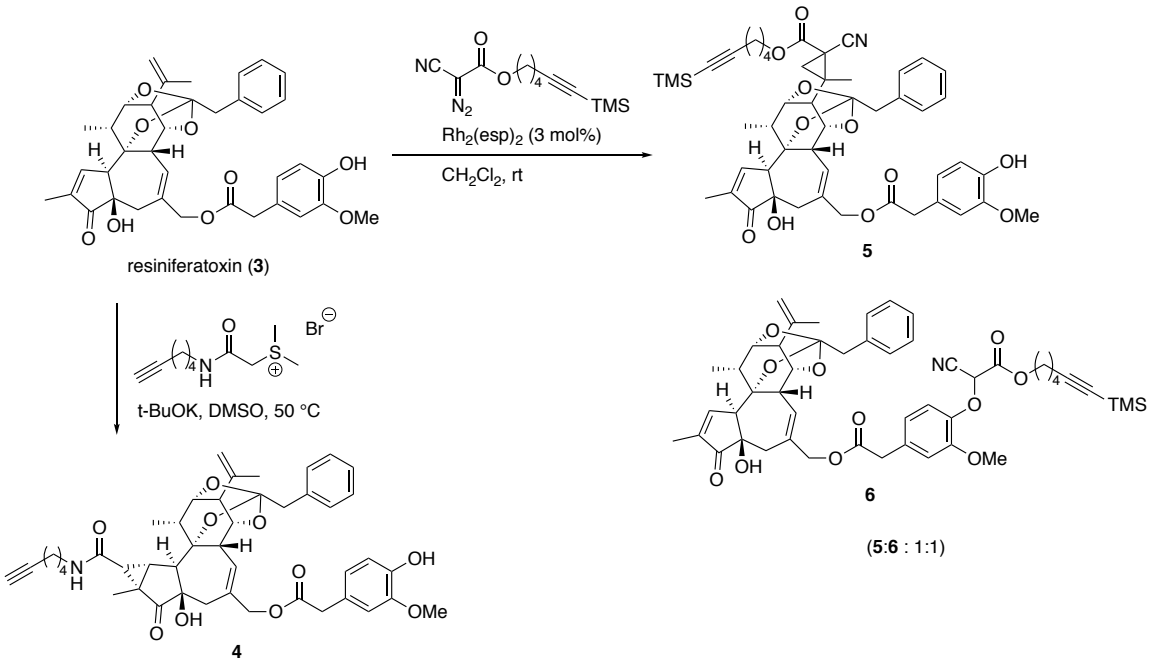
LSF は，末端アルキンをはじめとした，バイオオルソゴナル反応によりレポーター分子を連結可能な「タグ」を導入する際に効果を発揮すると考えられる．実際に，これまで分子に対して末端アルキンを導入する手法のほとんどは，多段階合成によりプローブを合成する手法や生物活性分子の極性官能基に限られていた (**Scheme 0-4**)[9]．よって，生物活性分子に存在するこれまで導入が困難であった官能基やユビキタスに存在する官能基，例えば C-H 結合に対してアルキンタグが導入できれば，より多くの誘導体合成が可能になると期待される．



Scheme 0-4. 従来のアルキンタグ導入法

2006 年に Romo らはアルキン部位と反応部位を試薬に持たせた「二重機能性分子」を設計し，これを利用したアルキンタグ導入法を報告した[23]．そして，生物活性小分子内に存在する水酸基[23b]などの極性官能基のみならず，アルケン[23c]やアリル位，ベンジル位[23d]の C-H 結合など多様な官能基に対して化学選

択的に導入することのできる試薬を複数用意し，迅速な構造活性相関研究とプローブ化を同時に達成している (**Scheme 0-5**).



Scheme 0-5. Romo らによる Simultaneous arming/SAR 法

さらに Romo らは，自身らの手法の有用性を実証すべく，抗がん活性を持つ一方で，その標的タンパク質が未知であった Eupalmerin acetate (EuPA:**7**)の誘導体化と，得られた誘導体に結合するタンパク質の定量的プロテオーム分析をおこなった (**Figure 0-4**) [23d]. すなわち Romo らは，独自に開発した試薬 **8** を EuPA に作用させることで，ほとんど同等の活性を持つ EuPAyne (**9**)を合成し，これを利用することでがん増殖に関連するタンパク質を含む EuPA の細胞内標的タンパク質の同定に成功している.

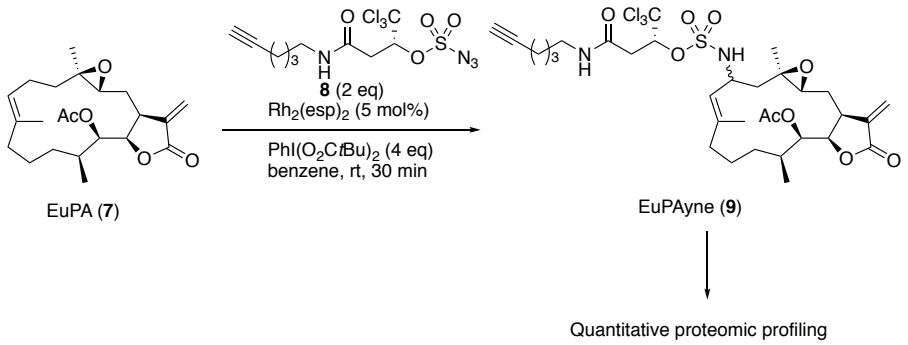
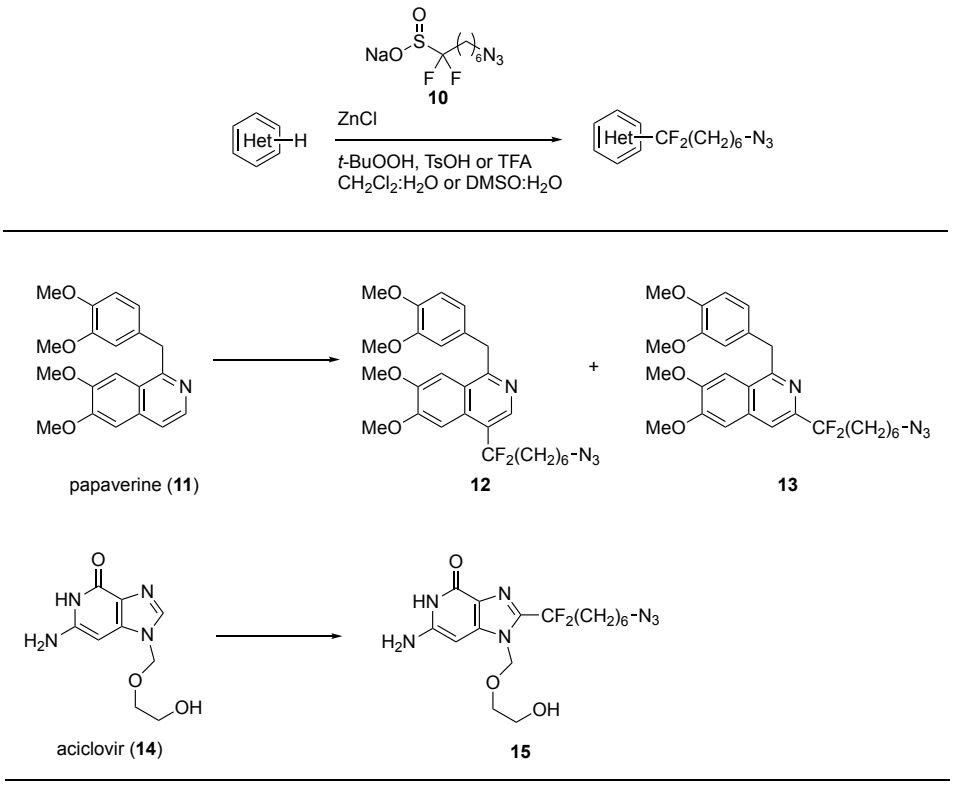


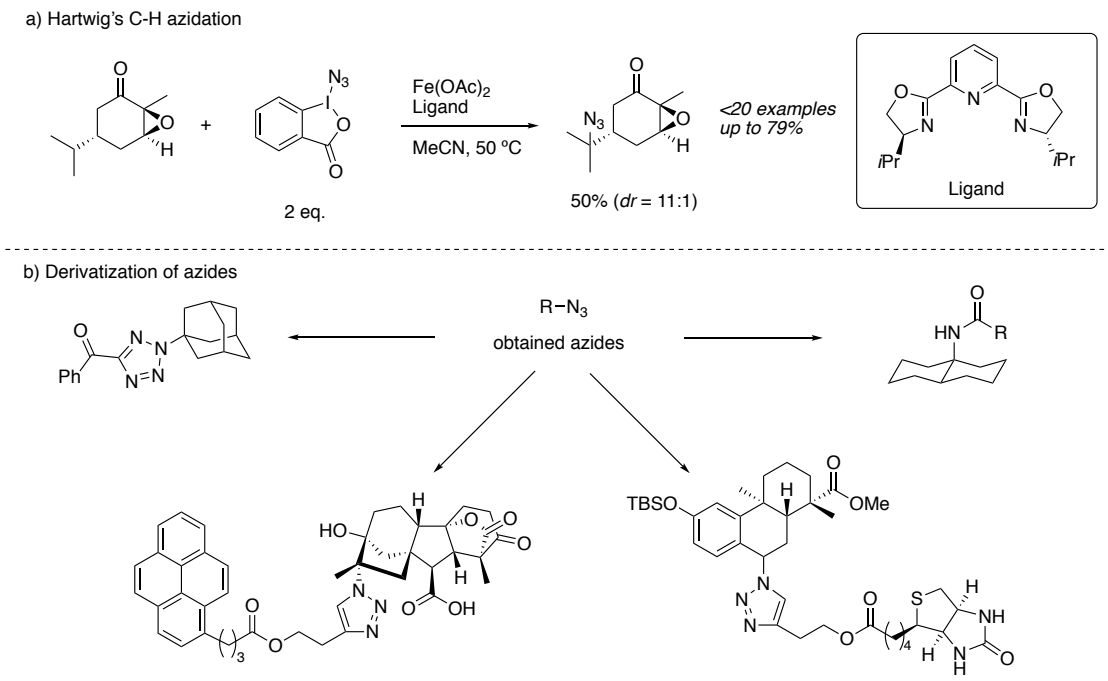
Figure 0-4. Romo らによる EuPAyne 合成とプロテオーム解析への応用

アジド基もまた生物活性分子に対して導入されるタグ分子の一つである. 例えば 2013 年に Baran らは, 独自に開発した sodium (difluoroalkylazide)sulfonate (DAAS-Na) (**10**)を利用したヘテロ芳香環の C-H 結合に対するアジドリンカー導入法を報告している (**Scheme0-6**)[24]. 彼らは papaverine (**11**)から誘導体 **12** と **13**, 更に aciclovir (**14**)から誘導体 **15** を得る事に成功している. さらに, 得られた誘導体を歪みアルキンを持たせた抗体と連結させることで, Antibody-Drug Conjugate (ADC)を調製することにも成功している.



Scheme 0-6. Baran らによるヘテロ芳香環上に対するタグ分子導入法

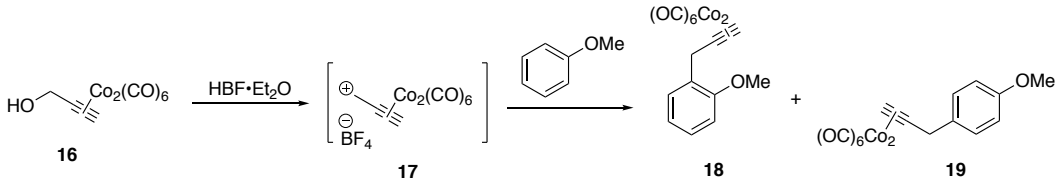
2016 年に Hartwig らは, 鉄触媒存在下, 超原子価ヨウ素-アジド試薬を利用した, 生物活性分子を含む有機小分子のメチン基, ベンジル基に対する C-H アジド化を報告している (**Scheme 0-7a**)[25]. また彼らは, 得られたアジ化物に対し, Hüisgen 環化など各種変換反応を利用することで, 多彩な誘導体の合成が可能であることを示した (**Scheme 0-7b**).



Scheme 0-7. Hartwig らによる sp^3 炭素，ベンジル位の C-H アジド化

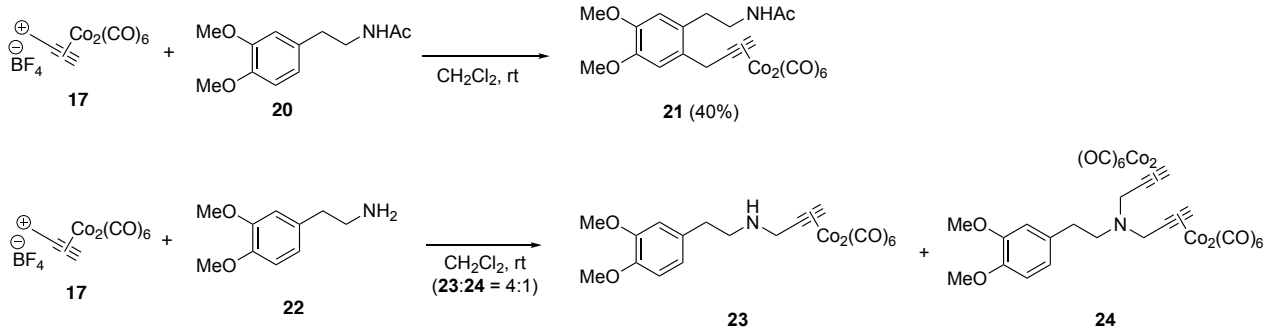
これらの背景から，著者は生物活性分子の C-H 結合に対して小さなアルキンタグを導入する手法の開発を計画した．小さなアルキンタグは，標的分子探索においてその活性を阻害しにくいと考えられるため，Romo らが開発した比較的大きなアルキンタグとは異なる役割を持てると考えられる．アルキンタグを導入する分子として，芳香族化合物に着目した．芳香環は天然物の約 40%，医薬品の約 80%に含まれる普遍的な構造単位であることから，その官能基化の開発は有用であると考えられる [26].

著者は，小さなアルキンタグを芳香環に導入する反応として Nicholas 反応に着目した．プロパルギルジコバルト錯体の隣接炭素原子に発生する安定なカチオンを利用した Nicholas 反応は，電子豊富な芳香環との反応例が，多くの研究者によって報告されている．例えば Nicholas らは，プロパルギルアルコールのジコバルト錯体 **16** に対し超強酸である HBF_4 を化学量論量用いることで，電子豊富な芳香族化合物である anisole の *o*-, *p*-置換反応を報告している (**Scheme 0-8**)[27].



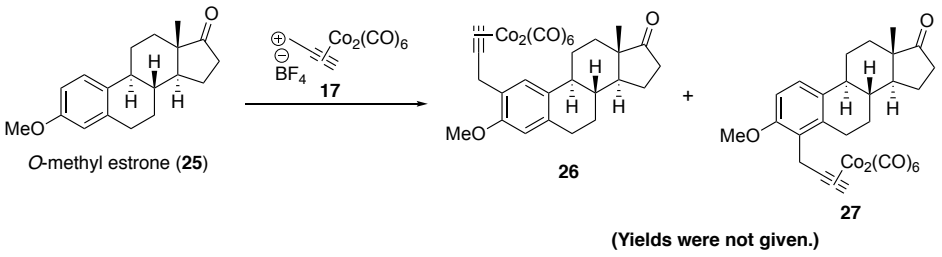
Scheme 0-8. Nicholas らによるアニソールに対する適用例

著者は，Nicholas らにより単離された活性種である錯体 **17** そのものを用いた反応に着目した．錯体 **17** は基質と混ぜるだけで反応が進行するため，簡便な操作で反応を行えることが利点である．実際に Nicholas らは，錯体 **17** を用いた *N*-acetylhomoveratrylamine **20** の官能基化が進行し，一方で，アミンが保護されていない基質 **22** においては，窒素原子上で反応が進行することを報告している (**Scheme 0-9**). [28] 錯体 **17** とアミンとの反応は，Roth らによって詳細に検討がなされており [29]，さらにシリルエノールエーテルなどとの反応も報告されている [30]．しかしながら，錯体 **17** は基質との反応後に超強酸である HBF_4 を発生させるため，強酸性による基質の分解が懸念された．



Scheme 0-9. Nicholas らによる錯体 **17** を利用した反応

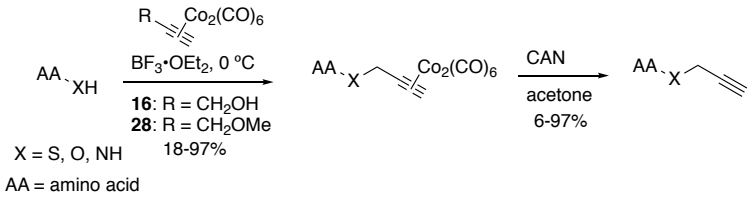
1987 年に Jaouen らは生物活性小分子である *O*-methyl estrone (**25**)の標識化を，プロパルギルジコバルト錯体 **17** を用いて行っている (**Scheme 0-10**)[31]．得られた標識体は，コバルト錯体上の一酸化炭素リガンドをマーカーとして，IR を用いて検出が可能であり，ケミカルプローブとして用いることができるだろうと述べている．しかしながら，彼らは収率を報告しておらず，<u>強酸条件下行われる Nicholas 反応が多様な官能基を持つ生物活性小分子に対してどの程度適用できるのかは未知のままであった．</u>



Scheme 0-10. Jaouen らによる生物活性分子に対する **17** を利用した官能基化

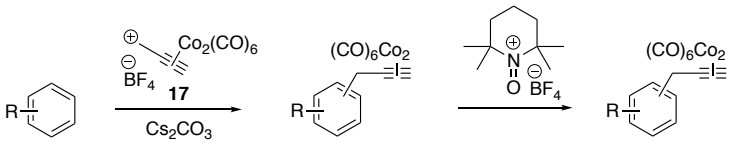
2016 年に Harki, Brummond らにより，アミノ酸および生物活性分子が持つヘテロ原子の Nicholas 反応を利用した 2 工程プロパルギル化が報告された (**Scheme 0-11**) [32]．彼らは，錯体 **17** もしくは前駆体 **16**, **28** と

ルイス酸を用いた，多様なアミノ酸のヘテロ原子に対する官能基化と，CAN を用いた脱錯体化により 2 工程プロパルギル化を達成している．しかしながら，彼らの反応は多くの基質で目的物を中程度の収率に与えるにとどまり，強酸性条件が収率の低下を招いていることが示唆されていた．



Scheme 0-11. Harki, Brummond らによる 2 工程プロパルギル化

以上の背景から，著者は，標的同定研究と構造活性相関研究の迅速化を指向した芳香族化合物のプロパルギル化，その中でも電子豊富な芳香環を持つ生物活性小分子のプロパルギル化に焦点を当てた研究を実施した．まず多様な官能基を持つ生物活性分子の官能基化を行うには，本来強酸条件下で行われる Nicholas 反応の条件改良が重要であると考え，添加物をはじめとした反応条件の最適化を行なった．実際に **17** のみで反応を行うと，基質との反応によって生じた HBF_4 によって基質，生成物が分解し，Harki, Brummond らの条件と同様，収率の低下が確認された．そこで，様々な塩基を添加することでその酸性条件の抑制を試みたところ，固体塩基である Cs_2CO_3 を添加することで，**17** の反応性を落とすことなく，収率を改善できることが判明した．さらに，水酸基を持つ芳香族生物活性小分子である mestranol においては，塩基を嵩高いピリジン塩基である DTBP に変更することで化学選択性が変化し，水酸基選択的に反応が行えることを見出した．得られたプロパルギルジコバルト錯体は，$TEMPO^+BF_4^-$を用いることで脱錯体化が可能であり，錯体 **17** が 2 工程でのプロパルギル化反応に適用できることを示した (**Scheme 0-12**). これらの研究の詳細は各論第一章で述べる．

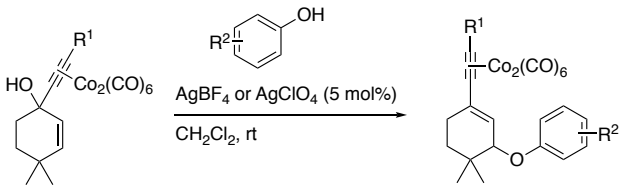


Scheme 0-12. **17** を利用した芳香族生物活性小分子の 2 工程プロパルギル化

<u>第二章　金触媒と *o*-アルキニルベンゾアートを有する Nicholas 試薬を利用した新規 Nicholas 反応の開発</u>

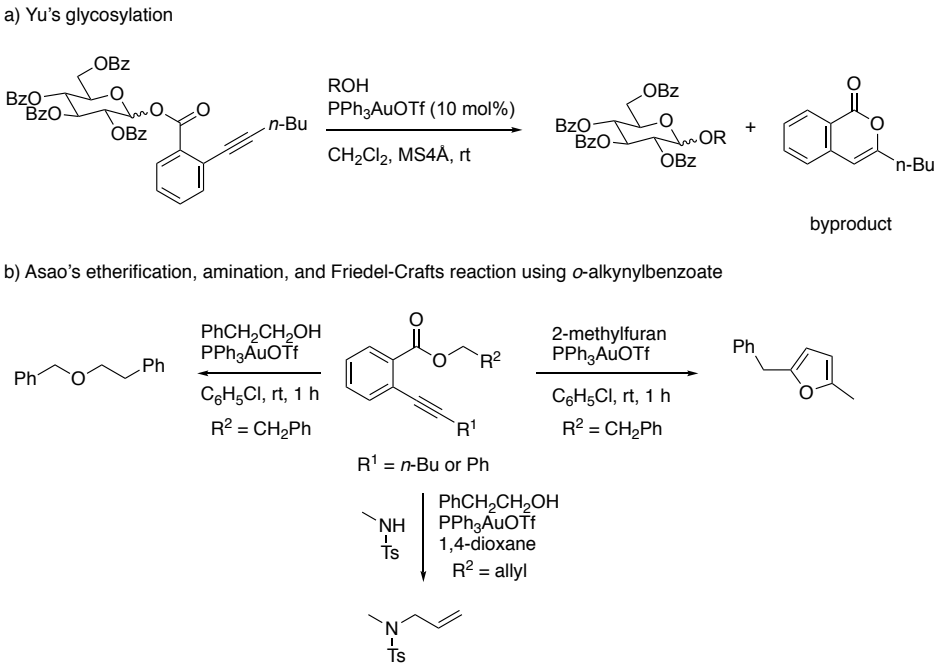
前述の反応条件は，様々な生物活性分子の芳香環のプロパルギル化反応を達成した一方で，過剰の塩基を用いるために，塩基に鋭敏な官能基を持つ基質に適用が困難であった．そこで著者は，そもそも超強酸

が生じない，もしくは触媒量の酸のみで Nicholas 反応が達成できれば，塩基を添加せずとも温和な条件での官能基化が可能になると考えた．酸触媒を利用した Nicholas 反応は，Sieera, Torre らにより報告されているが，彼らの反応では，カチオン性中間体を発生させるために，金属触媒が配位できるビニル基もしくはフェニル基がアルキンジコバルト錯体に必要であり，単純なプロパルギル基を導入する著者の目的に用いるには不適であった (**Scheme 0-13**) [33].



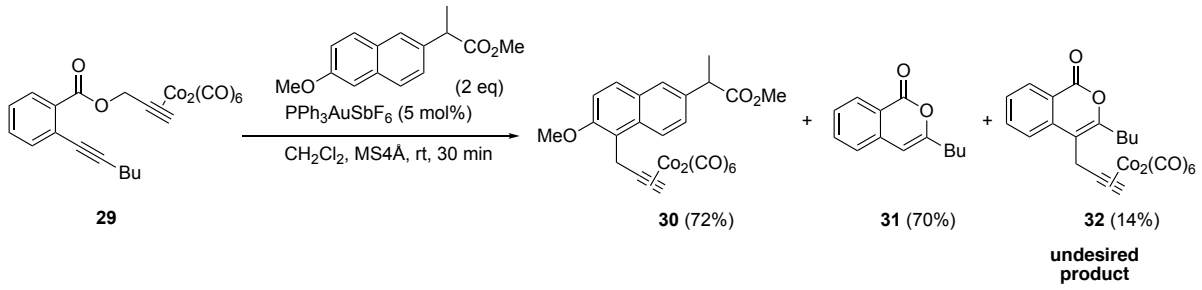
Scheme 0-13. Sierra, Torre らによる酸触媒を用いたニコラス反応

著者は，脱錯体化後に単純なプロパルギル基へと変換でき，かつ触媒量の Lewis 酸で活性化する試薬の創製を試みた．そこで，2008 年に報告された，Yu らによる *o*-アルキニルベンゾアート を脱離基として利用したグリコシル化に着目した（**Scheme 0-14a**）[34]．彼らは，金触媒によって活性化する *o*-アルキニルベンゾアート をグリコシル基に導入することで，温和な条件でのグリコシル化を達成している．本反応では，副生成物としてイソクマリンが生じるものの，多様なグリコシル基を導入できる有用な反応である．また，2009 年に浅尾らは，Yu らと同様に *o*-アルキニルベンゾアートを利用することで，金触媒を利用したベンジルカチオンのエーテル化とアミノ化，そして Friedel-Crafts 反応を報告している（**Scheme 0-14b**）[35].



Scheme 0-14. *o*-アルキニルベンゾアートと金触媒を利用した反応

著者は，Yu，浅尾らの報告例を参考に，試薬 **29** を新たに合成し芳香族化合物との反応をまず試みた．その結果，目的物 **30** を得ることに成功した一方で，カチオン性中間体とイソクマリン **31** の反応成績体である望まない副生成物 **32** が生じる結果を得た (**Scheme 0-15**)．副生成物 **31** の生成を防ぐ目的で，多様な金触媒を検討したもののいずれの場合も **32** の副生を避けることはできなかった．またイソクマリン **30** は，**29** とシリカゲルカラムクロマトグラフィーによって分離することができず，分離精製の面でも課題を残した．



Scheme 0-15. 試薬 **29** を用いた金触媒による Nicholas 反応の検討

そこで著者は，ブチル基の代わりにペルフルオロアルカン (フルオラスタグ)を導入した試薬を新たにデザインした (**Figure 0-5**)．副生成物 **32** は，イソクマリン C4 位の電子密度が高く，カチオン性プロパルギ

ルジコバルト錯体と反応したと考えられた．そこで，電子求引基であるフルオラスタグを導入し，生じたイソクマリンの C4 位の求電子性低下を期待した．さらにフルオラスタグを有する小分子は，Curran らにより報告されたフルオラスシリカゲルカラムクロマトグラフィーにより非フルオラスな小分子との分離が可能になることから，分離面の問題も解決できると期待した[36].

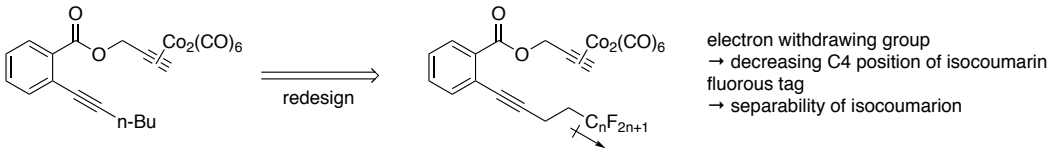
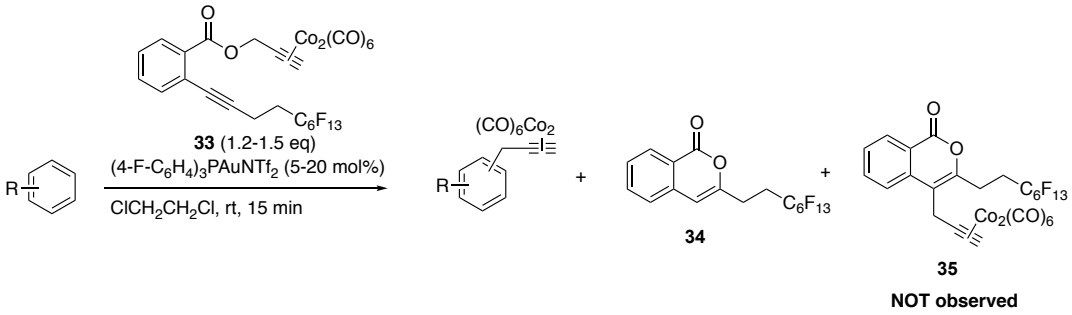


Figure 0-5. 新たにデザインした試薬

上記のコンセプトのもと合成した試薬 **33** は，**29** と同様に触媒量の金触媒により活性化され目的物を与えた一方で，副生成物 **35** を与えないことが判明した (**Scheme 0-16**). さらに炭素数 6 のペルフルオロアルキル基を用いる事で, 目的物とイソクマリン **34** のフルオラスシリカゲルカラムクロマトグラフィーによる分離が可能であった．実際に試薬 **33** を用いると，多様な芳香族小分子の官能基化が可能であり，錯体 **17** と炭酸セシウムを利用した反応条件では官能基化が難しい，酸や塩基に鋭敏な官能基を持つ基質においても高収率で反応が進行した．さらに金触媒のカウンターアニオンを変更する事で，反応の選択性を制御できることを明らかにした．これらの研究の詳細は各論第二章で述べる．

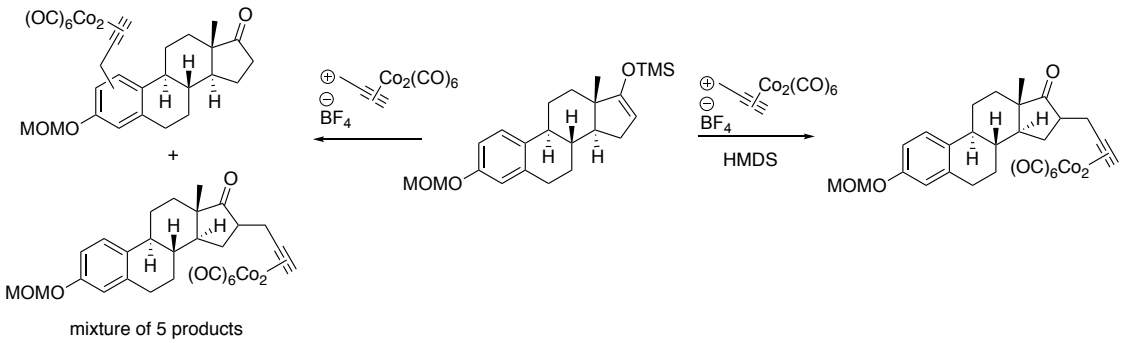


Scheme 0-16. 試薬 **33** を利用した芳香族化合物に対する酸触媒的ニコラス反応

<u>第三章　新規反応性獲得を指向した新規ジフルオロプロパルギルエーテル合成の開発と応用</u>

カチオン性プロパルギルジコバルト錯体は，電子豊富な芳香族化合物だけでなく，オレフィン，アミンやピリジン，シリルエノールエーテルなど様々な求核剤と反応し，対応するジコバルト錯体を与える．また，プロパルギルジコバルト錯体の隣接炭素のカルボカチオンの求電子性は，Mayr らによって置換基による反応性の傾向が報告されている[37].

その一方で化学選択的なニコラス反応はほとんど報告されておらず，以下に示す 1987 年に報告された Jaouen らによるエストロン誘導体に対する例のみである (**Scheme 0-17**) [38]．また，彼らはこの一例しか報告しておらず，様々な求核性官能基共存下，特定の官能基と反応するニコラス反応の条件は著者が知る限り報告されていない．

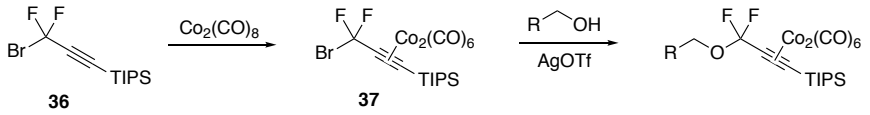


Scheme 0-17. Jaouen らによる化学選択的なニコラス反応

フッ素原子は，水素原子と比較して高い電気陰性度を持つ一方で，その原子半径はほとんど差がない (H = 1.20 Å， F = 1.47 Å)[39]．このことから，有機分子の水素原子の代わりにフッ素原子を導入することで，分子の大きさをほとんど変化させることなく，その化学的，物理化学的な性質を大きく変化させることができる．例えば，フッ素原子は，α炭素のカルボカチオンを安定化させることが知られており，これはフッ素の 2p 軌道の孤立電子対がカルボカチオンの空の p 軌道に対し電子を供与するためである [40]．またフッ素は，医薬品創製においても有用な原子であり，とりわけ水素をフッ素に置換した生物活性分子は，生体内で代謝を受けにくい，脂溶性が向上するといった利点がある [41]．ゆえにフッ素を導入した医薬品は精力的に開発されており，多くの含フッ素医薬品が新たに上市されている．このことから近年，有機小分子に対してフッ素原子を導入する反応や，フルオロアルキル基を導入する反応が精力的に開発されている [42]．

著者はニコラス反応の活性種であるアルキンコバルト錯体の隣接炭素のカルボカチオンに対し，上記の性質を持つフッ素がどのような影響を与えるか興味を持った．研究開始当初，プロパルギル位にフッ素を導入したアルキンコバルト錯体は報告されておらず，その合成検討も合わせて行った．検討の結果，difluoropropargyl bromide **36** に対し，$Co_2(CO)_8$ を作用させることで錯体 **37** を合成することに成功した．さらに錯体 **37** は，銀試薬によって活性化され，アルコールと反応することでエーテルを形成することを見出した (**Scheme 0-18**)．さらに得られたエーテルは，脱錯体化することでジフルオロプロパルギルエーテルへと変換可能であった．このためアルキンの多彩な反応性を利用したフルオロアルキルエーテル合成

への展開も合わせて計画した.



Scheme 0-18. ジフルオロプロパルギルブロミドジコバルト錯体 **37** の合成と応用

α-ジフルオロアルキルエーテルは，通常のエーテルと比較して生体内での酸化安定性や脂溶性の向上が期待される官能基であり，実際にいくつかの医薬品やその候補化合物に導入されている (**Figure 0-6**). しかし，この構造を持つ医薬品は，フッ素医薬品に占める割合で見ると非常に少なく，α-ジフルオロアルキルエーテル合成法がより進展すれば，これらの利点を生かした創薬研究を展開できると期待した.

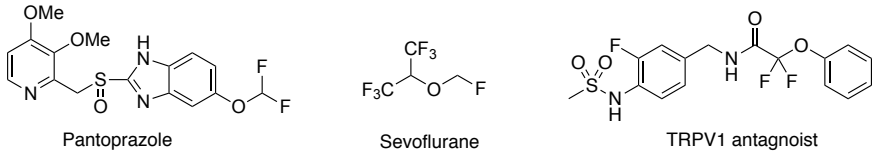
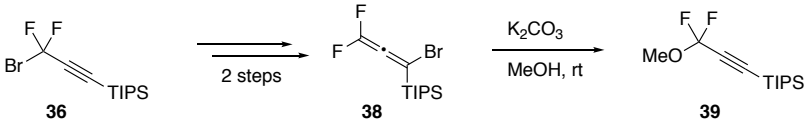


Figure 0-6. フルオロアルキルエーテルを含む医薬品及びその候補化合物

フルオロアルキルエーテル合成の手法は大きく分けて， (1)フッ素化試薬を用いる方法 [43]，(2)酸素原子に対してフルオロアルキル化を行う方法 [44]，(3) フルオロアルキルエーテルそのものを合成する方法 [45]，の 3 種類に大別される．しかし，方法 1 は多くの場合扱いの難しいフッ素化試薬を用いること，方法 2, 3 では導入できるフルオロアルキル基が単純なものに限られることが問題点であった．対してジフルオロプロパルギルエーテルは，アルキンの反応性を利用することで多様な誘導体へと変換可能であり，上記のボトルネックを解消できると期待される [46].

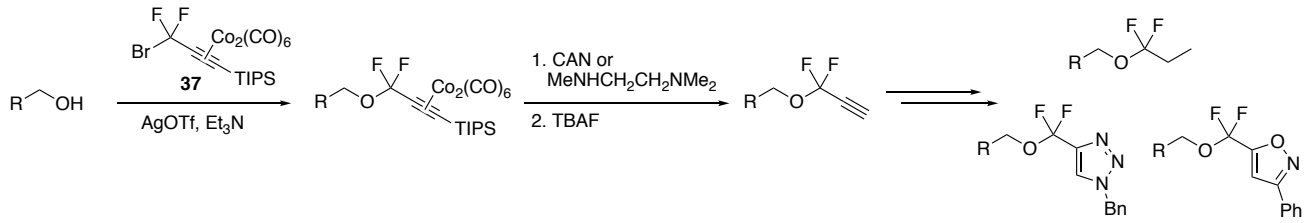
ジフルオロプロパルギル基を水酸基に導入する先行研究として，2005 年に報告された Hammond らによるジフルオロプロパルギル化が挙げられる (**Scheme 0-19**)[47]．彼らは，容易に調製可能なジフルオロプロパルギルブロミド **36**[48] より 2 工程で調製可能なジフルオロアレン **38** を利用することで，多様な求核剤へのジフルオロプロパルギル化を報告している．しかしながら，**38** は反応性に乏しく，エーテル **39** を得る際には溶媒量のアルコールを必要とすることが欠点であった.



Scheme 0-19. Hammond らによる求電子的ジフルオロプロパルギル化

そこで，新たに合成した錯体 **37** を，アルコールを基質としたジフルオロプロパルギルエーテル合成へと利用し，多様なα-ジフルオロアルキルエーテル合成が可能であるか検討を行った (**Scheme 0-20**). 検討の結果, **37** は塩基存在下, 試薬量のアルコールと反応し, 望むα-ジフルオロアルキルエーテルを与えた. 興味深いことに, 開発した反応は, 脂肪族アミンや電子豊富な芳香環, オレフィンなど通常の Nicholas 反応では反応しうる官能基存在下でも，アルコールと化学選択的に反応した．このことから，フッ素原子はカチオン性プロパルギルジコバルト錯体の反応性に大きな影響を与えることが示唆された.

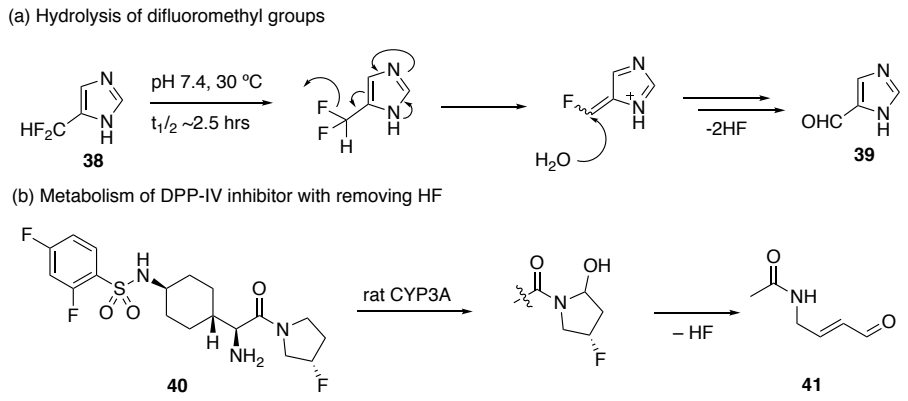
脱錯体化は，CAN もしくは *N,N,N'*-trimethylethylenediamine により達成し，続く TBAF を用いた脱シリル化によりジフルオロプロパルギルエーテルの合成に成功した．得られたエーテル群はどれも新規な構造単位であり，本反応が含フッ素化合物合成にも有用であること，さらにこれまで合成が難しかったα-ジフルオロアルキルエーテルを合成できることを証明した．これらの研究の詳細は第 3 章で述べる.



Scheme 0-20. アルコールに対する化学選択的なジフルオロプロパルギル化反応

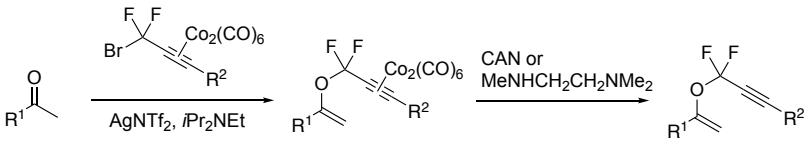
<u>第四章　新規ジフルオロプロパルギルビニルエーテル合成法の開発と含フッ素化合物合成への応用</u>

フッ素原子はしばしば分子の安定性にも影響を与え，フッ素が導入された生物活性分子の中には生体内で分解，有害なフッ化水素を生じるものが知られている (**Scheme 0-21**)[49]．例えば，4-(difluoromethyl)imidazole (**38**)は，窒素原子の孤立電子対の影響により半減期 2.5 時間でフッ素が脱離し水と反応することで，フッ化水素の脱離を伴いながら 4-formylimidazole (**39**)になることが知られている．また DPP-IV 阻害剤 **40** は，生体内で代謝されることでフッ化水素の脱離を伴いながら，マイケルアクセプター**41** を生じる生体内代謝に問題を抱える化合物である. このことから, 実際に含フッ素分子を合成し, その安定性や物性を評価することは医薬品開発において重要な課題である.



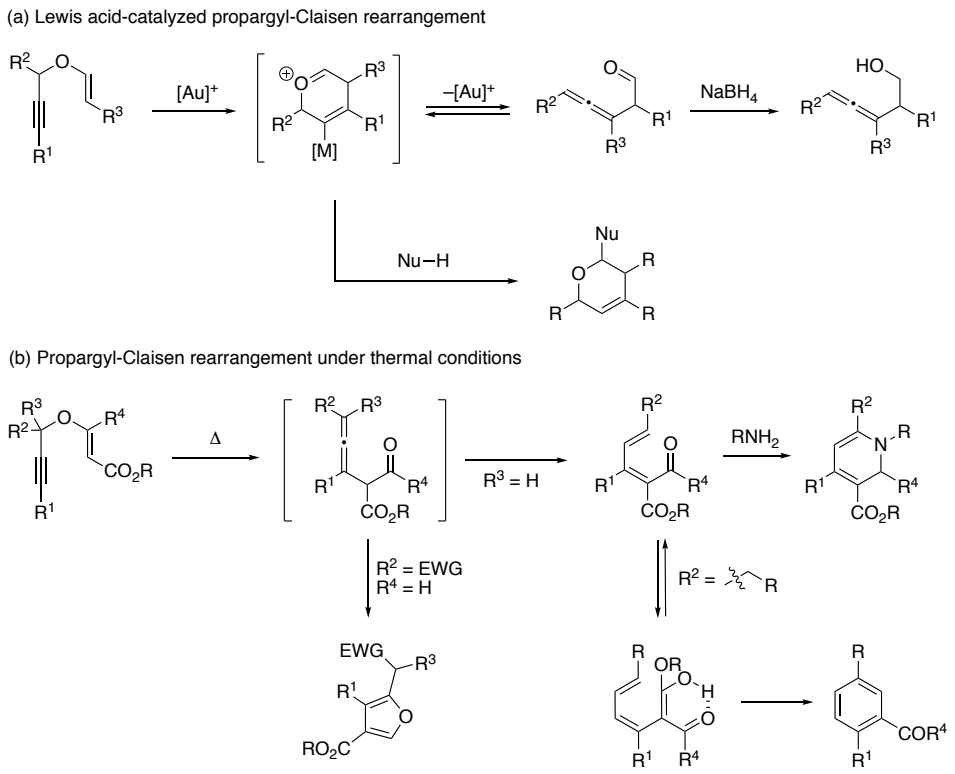
Scheme 0-21. フッ素原子が脱離する例

著者は，見出した錯体を利用したさらなる含フッ素化合物合成への応用を指向し，ジフルオロプロパルギルブロミドジコバルト錯体が他の求核剤と反応しないか検討を行う中で，ケトンと反応し対応するエノールエーテルを与えることを見出した (**Scheme 0-22**). 一般的に，カチオン性プロパルギルジコバルト錯体は，ケトンのα位と反応が優先することが知られており [50]，得られた前例のない反応性に興味が持たれた．よって著者は，様々なケトンに対して本反応が適用可能か検討を行った．また，得られたエノールエーテルは，前述のエーテルの錯体と同様に脱錯体化により，ジフルオロプロパルギルビニルエーテルへと導くことが可能であった．



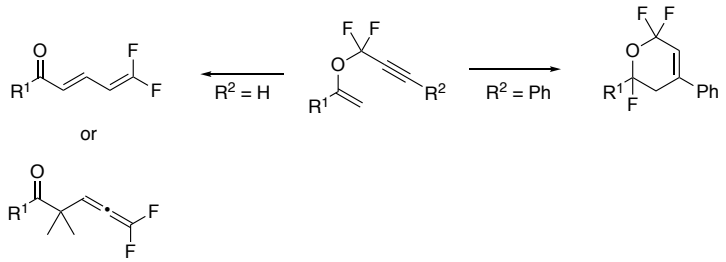
Scheme 0-22. ケトンに対する 2 工程ジフルオロプロパルギル化

プロパルギルビニルエーテルは，反応条件や基質の置換基によって多様な分子へと変換可能であることから，一つの分子から様々な誘導体を作る上で非常に有用な基質である [51]．Toste らは金触媒を用いたプロパルギル Claisen 転位を報告しており，触媒のみの反応条件ではアレニルアルデヒドが得られるのに対し [52]，水を添加した場合には，ヒドロピラン骨格が得られることを報告している (**Scheme 0-23a**)[53]．その一方で，ビニル基に電子求引基を持たせた基質では，熱的な条件でプロパルギル Claisen 転位が進行することが知られている．こちらも添加剤や置換基を変更することで，フラン，アレーン，ジヒドロピリジンなど様々な誘導体へと変換可能である (**Scheme 0-23b**)[54].



Scheme 0-23. プロパルギル Claisen 転位を利用した誘導体合成

これらの背景からジフルオロプロパルギルビニルエーテルを利用した含フッ素化合物の合成を試み，その安定性などを評価した．検討の結果，ジフルオロプロパルギルビニルエーテルは置換基や反応条件によって異なるフッ素化合物を与えることを明らかにした (**Scheme 0-24**)．すなわち，熱的条件ではプロパルギル Claisen 転位が進行し，ジフルオロアレン，もしくはジフルオロジエノンが得られることを明らかにした．その一方で，ルイス酸を利用した場合，トリフルオロピランを得ることに成功した．ジフルオロジエノンやトリフルオロピランは，これまでほとんど例のないフッ素化合物であり，本手法が新規かつ多様なフッ素化合物の合成に利用できることを明らかとした．詳細は第四章で述べる．



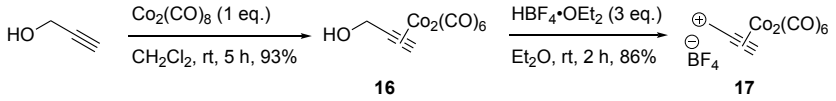
Scheme 0-24. ジフルオロプロパルギルビニルエーテルを利用した新規フッ素化合物合成

本論

第 1 章　カチオン性プロパルギルジコバルト錯体を用いた芳香族生物活性分子の 2 工程プロパルギル化反応の開発

第 1 節　カチオン性プロパルギルジコバルト錯体の合成と反応性評価

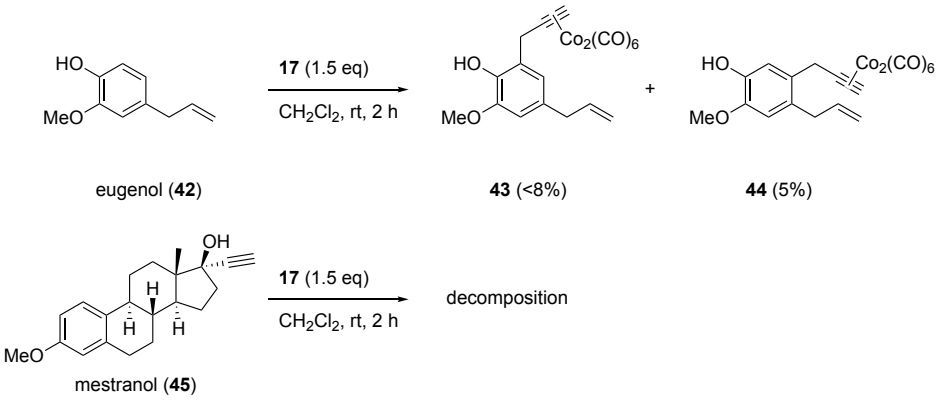
まず，Nicholas らの報告に従い 2 工程 [28]，総収率 80%で錯体 **17** を合成した（Scheme 1-1）.



Scheme 1-1. 錯体 **17** の合成

錯体 **17** は，反応後に超強酸である HBF_4 を生じる試薬である．そのため，そのまま用いた場合には，基質の分解が懸念された．実際に，錯体 **17** を用いた，天然物 eugenol (**42**)と医薬品 mestranol (**45**)の修飾を検討したところ，錯体 **17** を用いたのみでは，eugenol (**42**)の誘導体 **43**, **44** は低収率で得られるのみであり，また mestranol (**43**)においては基質の分解が見られ，生成物は全く得られなかった（**Scheme 1-2**）.

これらの結果から，まず単純な基質で塩基を添加する条件が有効か検討を行い，その後，実際に生物活性分子に対して適用可能か検討を行うこととした.



Scheme 1-2. 錯体 **17** を用いた官能基化初期検討

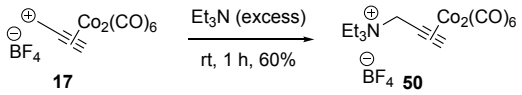
まず単純な基質である veratrol (**46**)を用いて検討を行った．また，同時に溶媒の検討も行い，錯体 **17** を用いた反応に汎用されているジクロロメタン [28] より良い溶媒があるか探索を行った（**Table 1-1**）.

塩基として炭酸カリウムを用いたところ，塩基を添加しない時と比較して目的物 **47**, **48** の収率がわずかに向上した（entry 1,2）．この結果から，炭酸カリウムを添加しても **17** の反応性に大きな影響がなく，

かつ酸性を抑制できていると判断し，次に炭酸カリウムを用いて，溶媒を変化させることで収率が向上するか検討した．

ハロゲン系溶媒としてジクロロメタン，ジクロロエタンを用いた場合反応は進行した一方で，四塩化炭素を用いた場合反応は全く進行しなかった (entry 2-4)．これは，**17** がジクロロメタン，ジクロロエタンは溶解するのに対し，四塩化炭素には全く溶解しなかったためである．同様に芳香族系溶媒においても，トリフルオロメチルベンゼンに試薬 **1-1** はわずかながら溶解し，反応が進行した一方で，ベンゼンには全く溶解せず，反応が全く進行しなかった (entry 5, 6)．HFIP を用いた場合は，**17** は完全に溶解したものの溶媒と反応した副生成物が得られた (entry 7)．　また，非プロトン性極性溶媒である DMF，DMSO についても反応が全く進行しなかった（entry 8, 9）．

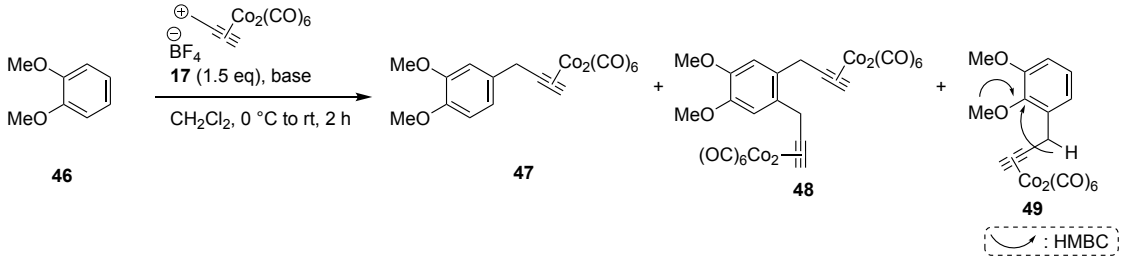
溶媒の検討結果，収率の向上が見られなかったため，さらに塩基を検討した．酸化マグネシウム，リン酸水素ナトリウムでは収率に大きな変化はなかった（entry 10, 11）．炭酸セシウムにおいては，原料がすべて消失し，この中で最も高い収率を与える結果となり，この時誘導体 **49** が得られた（entry 12）．なお誘導体 **49** の構造は HMBC により決定した．その一方で，窒素塩基であるトリエチルアミン，DBU, DMAP を用いると反応は全く進行しなかった（entry 13-15）．これはアルキンコバルト錯体の隣接炭素原子と窒素原子が結合を形成，もしくは強く相互作用したためだと考えられる [55]．実際に Et_3N と試薬を反応させると，塩基と試薬の複合体 **50** を単離することができた（Scheme 1-3）．



Scheme 1-3．トリエチルアミンと試薬 **17** の反応

以上の結果から，暫定の最適塩基を炭酸セシウム，最適溶媒をジクロロメタンとし，実際に生物活性小分子をモデル化合物として，反応条件のさらなる探索を行った．

Table 1-1. Veratrol をモデル基質とした塩基と溶媒の検討



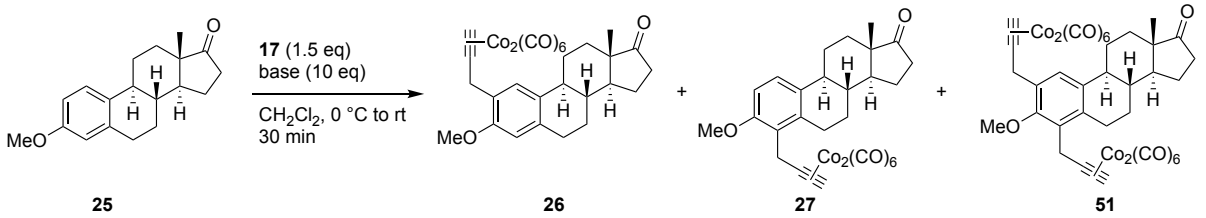
entry	base	equiv.	solvent	yield (%) 47	48	recovered SM
1	none		CH_2Cl_2	50	6	13
2	K_2CO_3	10	CH_2Cl_2	55	14	22
3	K_2CO_3	10	DCE	55	10	9
4	K_2CO_3	10	CCl_4	0	0	N.D.
5	K_2CO_3	10	benzene	0	0	N.D.
6	K_2CO_3	10	CF_3Ph	24	0	5
7	K_2CO_3	10	HFIP	0	0	N.D.
8	K_2CO_3	10	DMF	0	0	N.D.
9	K_2CO_3	10	DMSO	0	0	N.D.
10	MgO	10	CH_2Cl_2	44	3	18
11	Na_2HPO_4	10	CH_2Cl_2	48	8	13
12*	Cs_2CO_3	10	CH_2Cl_2	73	18	0
13	Et_3N	2	CH_2Cl_2	0	0	N.D.
14	DMAP	2	CH_2Cl_2	0	0	N.D.
15	DBU	2	CH_2Cl_2	0	0	N.D.

* **49** was also obtained in 5% yield. N.D.: Not determined.

第 2 節　芳香族生物活性分子を利用した反応条件最適化

芳香族生物活性分子のモデル基質として，*O*-methyl estrone (**25**)を用い，望む一置換体 **26**, **27** が高い収率で得られる条件を検討した (Table 1-2). Jaouen らと同様にまず塩基を加えずに反応を行ったところ [31]，基質の分解が見られ，目的物の収率は中程度にとどまった（entry 1）．種々の塩基を添加すると収率は向上し，炭酸セシウムを添加した際に，試薬が過剰に反応した誘導体 **51** も得られたものの，最も収率よく **26**, **27** を得ることができた (entry 2-4). なお，嵩高いピリジン塩基である DTBP を用いると，先の Et_3N の例とは異なり複合体の形成が見られず，また，反応も収率よく進行した (entry 5). これは，DTBP が先に用いたアミン塩基と異なり，立体的に嵩高く，窒素原子とアルキンコバルト錯体隣接位の炭素原子が結合を形成できなかったためだったと推測される．

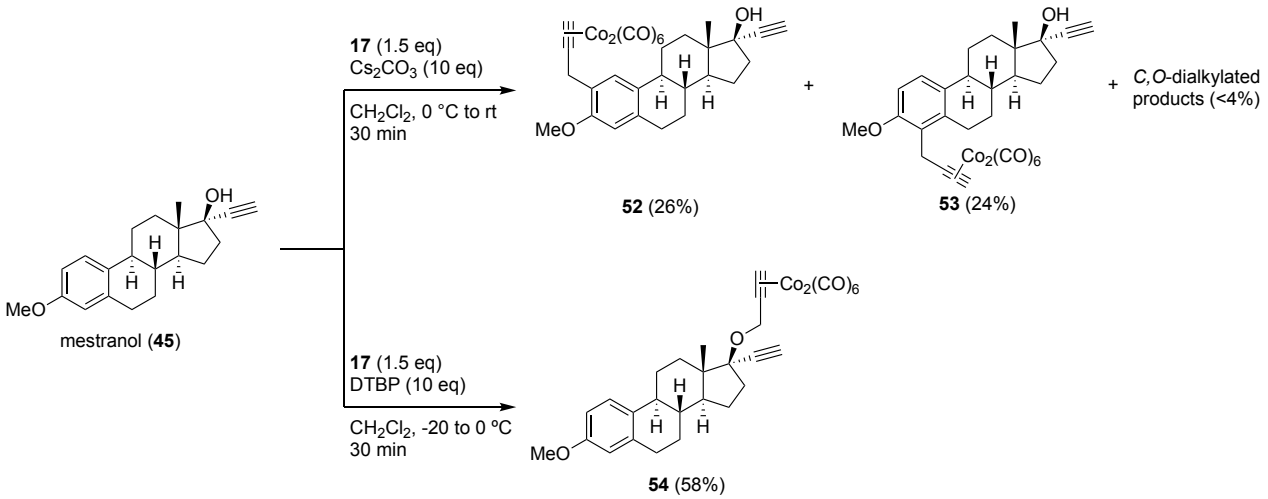
Table 1-2. *O*-methyl estrone (**25**)を用いた反応条件最適化



		yield (%)[a]			
entry	base	**26**	**27**	**51**	recovered SM
1	none	21	24	0	11
2	K_2CO_3	37	33	4	0
3	Cs_2CO_3	45	40	7	0
4	Et_3N	17	17	0	37
5	DTBP	44	36	0	15

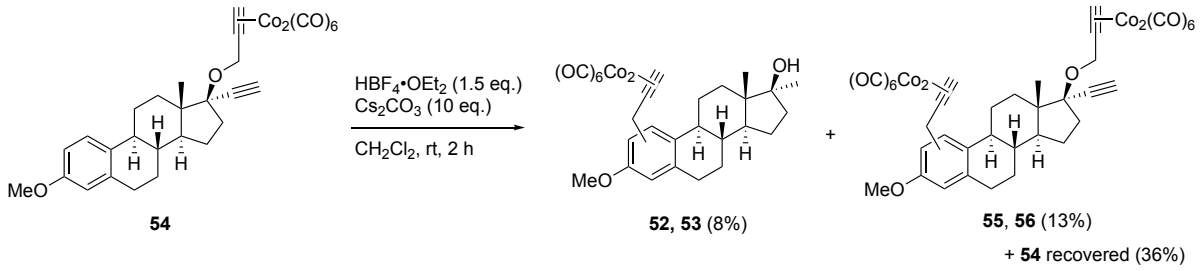
[a] Yields were calculated based on the total aomount of mixuture of **25**-**51** and its NMR peak ratio. See the experimental section for details.

次に酸性条件に鋭敏な官能基である 3 級アルコールを持つ mestranol (**45**)を用いて，さらなる塩基の検討を行った．(**Scheme 1-4**)．興味深いことに，本基質においては用いる塩基を変更することで，選択性が変化した．すなわち，炭酸セシウムを塩基として利用した場合，芳香環上での反応が進行し **52**, **53** が得られたのに対し，DTBP を用いると水酸基上で反応が進行した誘導体 **54** のみが選択的に得られた．詳しい理由は判明していないものの，pKa を考えるとピリジン塩基 (pKa＝4-5)が mestranol の第 3 級アルコール (pKa = 17-19)の脱プロトン化を起こし，水酸基の反応性が変化しているとは考えにくいため，**17** のカチオン性炭素原子と DTBP の窒素原子が相互作用し，反応性が変化したためと推測している．



Scheme 1-4. Mestranol を用いた官能基化の検討

また，エーテル **54** は中和しきれない HBF_4 により分解し，再度カチオン性プロパルギルジコバルト錯体を生じたのちに，誘導体 **52** や **53** を生じる可能性が考えられた．そこで，エーテル **54** に対して炭酸セシウム存在下, HBF_4 を作用させたところ, 僅かに芳香環上で置換した **52-56** が合計 21%で得られたものの, **54** も 34%で回収された (**Scheme 1-5**). 本結果から，エーテル **54** は，炭酸セシウム条件下一部が分解するものの，その全てが分解するわけではなく，反応の選択性は添加剤の変化によって引き起こされたことが明らかとなった．開発した条件は添加剤を加えることで化学選択性が変化した例であり，多様な官能基を持つ生物活性小分子の官能基化において有用なアプローチであるといえる．



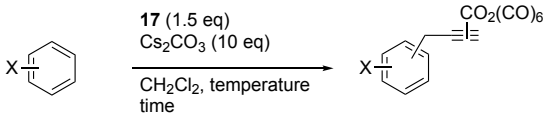
Scheme 1-5. エーテル **54** の分解実験

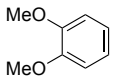
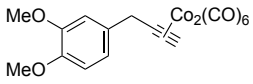
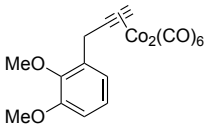
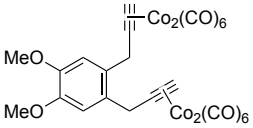
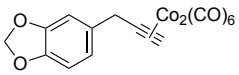
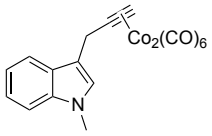
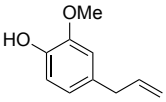
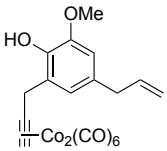
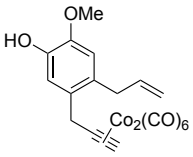
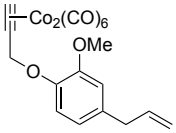
以上の結果から，錯体 **17** を用いた芳香族化合物の修飾には，塩基として炭酸セシウムが有効であることが分かった．

第 3 節 基質適用性の検討と芳香族生物活性分子への応用

まず，芳香族生物活性小分子や医薬品に多く見られる部分骨格を持つ単純な芳香族化合物が，著者の確立した反応条件で修飾できるか検討を行った（**Table 1-3**）．先の veratrol (**46**)では 2 置換体を含めて 3 種類の誘導体が得られた（entry 1）．一方で，2 つのフェノール性水酸基がメチレンで架橋された 1,3-benzodioxole (**57**)では低収率で 1 つの誘導体 **58** が得られるのみであった (entry 2). 1-methylindole (**59**)では，C3 位で反応した誘導体 **60** が中程度の収率で得られた (entry 3). フェノール性水酸基を持つ eugenol (**42**)では，芳香環上で置換した誘導体 **43**, **44** のほかに，フェノール性水酸基上で置換した誘導体 **61** が得られた (entry 4).

Table 1-3. 単純な芳香族化合物



entry	substrate	temperature	time (h)	products and yields
1	 veratrol (**46**)	0 °C to rt	1.5	 **47** (73%)  **49** (5%)  **48** (12%)
2	1,3-benzodioxole (**57**)	0 °C to rt	2	 **58** (22%)
3	1-methylindole (**59**)	0 °C to rt	2	 **60** (57%)
4[a]	 eugenol (**42**)	-20 °C to 0 °C	2	 **43** (15%)  **44** (18%)  **61** (7%)

[a] K_2CO_3 was used instead of Cs_2CO_3.

次に脂肪族アミンを持つ単純な芳香族化合物について検討を行った．アミノ基を持つ生物活性小分子は多数存在することから，アミノ基共存下でも芳香環上での反応を進行させる条件の検討は重要である．なお，電子豊富な芳香環を持つ 1 級アミン及び 2 級アミンでは，試薬 **17** は窒素と反応することが既に知られている [28]．このことから，アミノ基は保護する必要があると考え保護基の探索を行った．

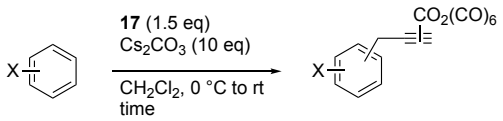
まず，Ac, Boc, Cbz 基でその窒素原子を保護したホモベラトリルアミンを用いて，芳香環上での反応が進行するか検討を行った (**Table 1-5**)．なお，窒素原子を Ac 基で保護した場合には，芳香環上での反応が優先することが，すでに Nicholas らによって報告されているが [28]，塩基を用いた条件では行われていないため，著者の開発した条件でも同様の結果が得られるか検討を行った．また，Cbz で保護された 2 級カーボネートに関しても反応する報告があるものの，電子豊富な芳香環存在下での検討は行われていないため，その反応性の確認を行った [29]．

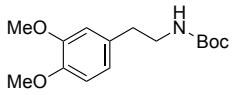
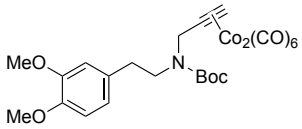
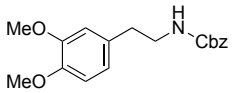
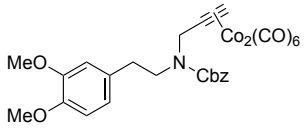
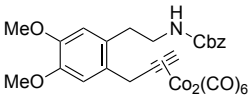
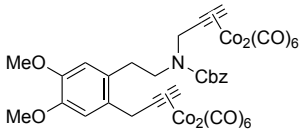
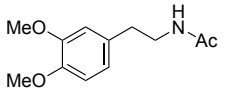
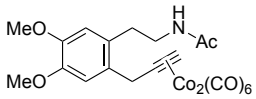
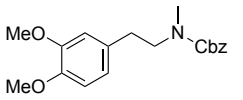
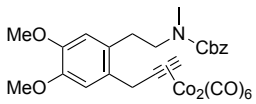
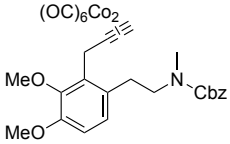
アミノ基窒素を Boc 基で保護した **62** では，窒素上で置換した誘導体 **63** のみが低収率で得られ，TLC 上では多くのスポットが得られた（entry 1）．これは，Boc 基が反応系内の酸によって分解したためだと考

えられる．一方，Cbz 基で保護した **64** では，窒素上で置換した **65**，芳香環上で置換した **66**，またその両方で置換した **67** の 3 種類が得られた（entry 2）．Ac で保護した **20** では，報告通り窒素上で置換された誘導体は全く得られず，芳香環上で置換した誘導体 **21** と原料のみが回収される結果となった (entry 3)．*N*-メチルホモベラトリルアミンの窒素原子を Cbz 基で保護した **68** では，芳香環上で置換した 2 種の誘導体 **69**, **70** が得られた (entry 4)．これらの結果から著者の条件では，1 級アミンに関してはアセチル化を行うことで，また，2 級アミンは Cbz 基で保護することで，2 級アミドは保護せずとも誘導体化を行えることが判明した．

これら誘導体は回転異性体が存在するため，脱錯体化に ^{1}H-NMR の温度可変モードで測定し，その芳香環のカップリング定数を測定することで構造を決定した．

Table 1-4. 脂肪族アミンを持つ分子及びその保護体の官能基化



entry	substrate	time (h)	products and yields
1	 *N*-Boc homoveratrylamine (**62**)	0.5	 **63** (29%)
2	 *N*-Cbz homoveratrylamine (**64**)	1.5	 **65** (16%)  **66** (11%)  **67** (27%)
3	 *N*-Ac homoveratrylamine (**20**)	1.0	 **21** (33%)
4	 *N*-Me, Cbz homoveratrylamine (**68**)	0.5	 **69** (70%)  **70** (5%)

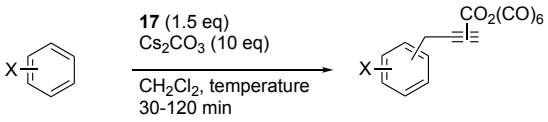
以上の知見をもとに，各種芳香族生物活性小分子の誘導体化の検討を行った（**Table 1-7**）． Naproxen methyl ether (**71**)では，ナフタレン環の C-1 位で反応した誘導体 **40** のみが得られた（entry 1）．**40** の構造は脱錯体化後に COSY, HMBC を測定し決定した．Indomethacin methyl ether (**72**)では，異なる位置で置換した 2 種の誘導体 **73**, **74** が得られた（entry 2）．インドール骨格を持ち，抗増殖活性を有する化合物 **75** では，インドールの 3 位で置換された誘導体 **76** が得られた（entry 3）[56].

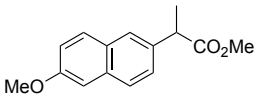
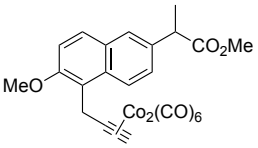
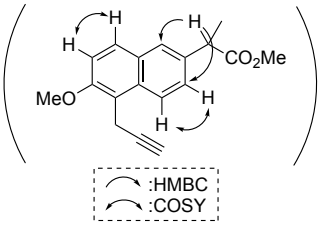
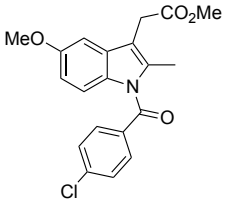
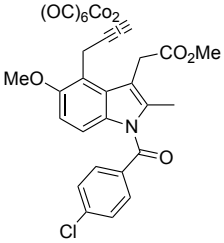
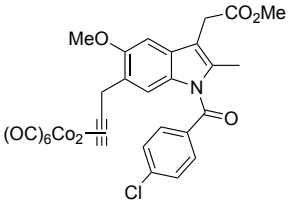
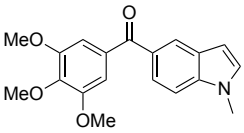
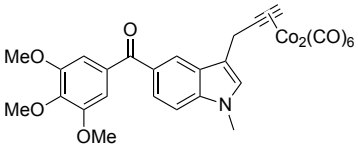
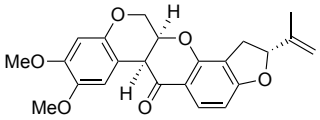
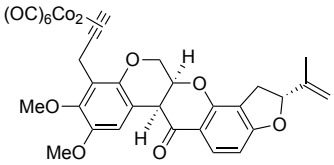
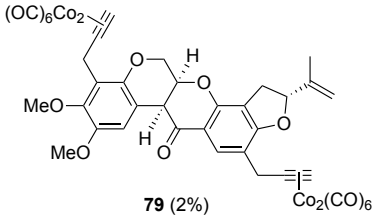
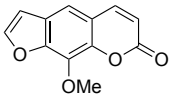
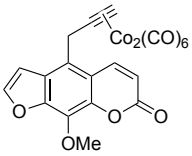
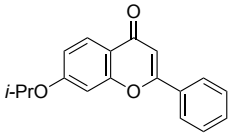
また，複雑な骨格を持つ rotenone (**77**)も誘導体化可能であった（entry 4）．ジメトキシベンゼン部位の立体的に空いている C-H 結合で置換した誘導体 **78** と，もう一つのベンゼン環でも置換した 2 置換体 **79** の 2 種が得られた．これらの誘導体の構造は，原料と ^{1}H-NMR スペクトルを比較することで決定した [57].

クマリン骨格を持つ xanthotoxin (**80**)では，マイクロウェーブ照射条件下，40ºC で反応を行うことでクマリンの C5 位が置換された誘導体 **81** が得られた（entry 5）．しかし，ipriflavone (**82**)においては，マイクロウェーブ照射下の条件でも反応は進行しなかった（entry 6）．イソプロポキシ基を持つことから反応が進行すると期待されたが，フラボン骨格が電子不足であること，また，イソプロポキシ基が嵩高い官能基であることが反応の進行しなかった理由として挙げられる．

これらの結果から，錯体 **17** は電子豊富な芳香環と Friedel-Crafts 型の反応が進行し，対応する生成物を与えることが判明した．また，基質によっては複数の誘導体が得られたが，複数の誘導体を一挙に得られることは，構造活性相関研究迅速化の観点から重要である．

Table 1-5. 生物活性小分子の官能基化



entry	substrate	temperature	products and yields
1	 naproxen methyl ester (**71**)	0 °C to rt	 **30** (93%) 
2	 indomethacin methyl ester (**72**)	0 °C to rt	 **73** (51%)  **74** (15%)
3	 **75**	0 °C to rt	 **76** (76%)
4	 rotenone (**77**)	0 °C to rt	 **78** (26%)  **79** (2%)
5	 xanthotoxin (**80**)	40 °C (microwave irradiation)	 **81** (28%)
6	 ipriflavone (**82**)	40 °C (microwave irradiation)	no reaction

続いて, 極性官能基を持つ基質についての検討を行った（**Table 1-8**）. 先の検討で用いた estrone, mestranol と同様に steroid 骨格を持つ estradiol (**83**)では，芳香環上で置換した誘導体 **84**, **85**, **86** のみが得られ，フェノール性水酸基及び，2 級水酸基上で置換した誘導体は全く得られなかった（entry 1）．フェノール性水酸基については, 反応性があまり高くないことが先の eugenol の誘導体化検討において判明している一方で, 2 級水酸基も隣接位にメチル基が存在し, 立体障害により反応性が低下していると考えられる. Jaouen らも，同様にニコラス反応を用いた estradiol の官能基化を行っているが，彼らは一つの誘導体のみしか得られていない点が本結果と異なる．複数の誘導体が得られることは，構造活性相関研究の迅速化という点で有用であり，著者の研究と Jaouen らの研究結果を差別化できる一因となる.

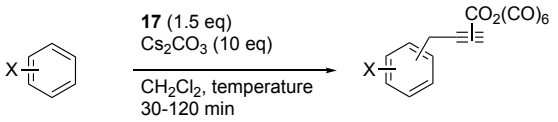
次に podophyllotoxin (**87**)の誘導体化を行った（entry 2）．本基質においては，先の estradiol の時とは異なり, 水酸基上で置換した誘導体 **88** のみが得られた. これは, 立体的に混んでいない水酸基であること，また，置換されることが期待される芳香環が嵩高い位置に存在しているためである．また収率が低い原因は，縮環部のカルボニル α 位が異性化したためだと考えられる．一方，TBS 基で水酸基を保護した基質 **89** の場合，芳香環上で置換された誘導体 **90** が得られた．このことから水酸基の場合も 1 級，２級アミンと同様に保護が有効だと考えられる.

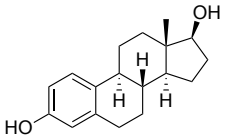
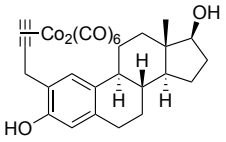
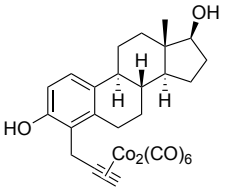
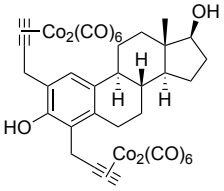
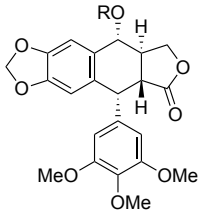
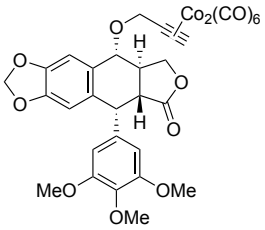
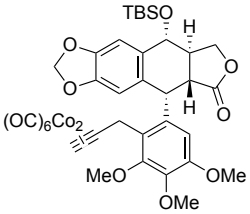
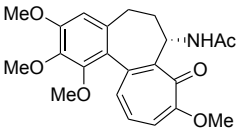
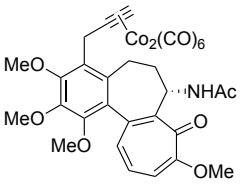
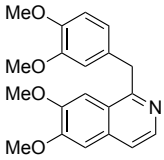
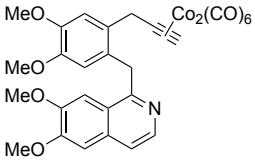
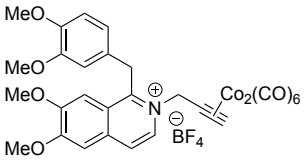
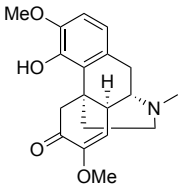
最後に窒素原子を含む芳香族生物活性小分子の誘導体化を行った（entry3-5）．また，2 級アミドを持つ colchicine (**91**)では，低収率ながら，電子豊富なトリメトキシベンゼン環上で置換した誘導体 **92** が得られた（entry 3）.

イソキノリン骨格を持つ papaverine (**11**)ではイソキノリンの窒素部分と反応することが予想されたが，炭素上で置換した誘導体 **93** も低収率ながら得ることができた（entry 4）．なお，塩基を添加すると基質が分解した一方で，塩基を加えない条件で目的物が得られた．最後に 3 級アミンを持つ chinomenine (**95**)について誘導体化を行った（entry 5）．Papaverine と同様に塩基を添加しないことで，誘導体が得られることが期待されたが，基質が分解するのみであった.

これらの結果から，アルコールは保護，嵩高いアルコールは保護せずとも官能基化が行えることが示唆された．また，ピリジンや 3 級アミンを持つ基質は，本条件では芳香環の官能基化は困難であった.

Table 1-6. 極性官能基を持つ生物活性小分子の官能基化



entry	substrate	temperature	products and yields		
1	 estradiol (**83**)	0 °C to rt	 **84** (15%)	 **85** (23%)	 **86** (17%)
2	 podophyllotoxin: R = H (**87**) podophyllotoxin: TBS ether R = TBS (**89**)	- 20 °C to 0 °C	 **88** (28%)		 **90** (19%)
3	 colchicine (**91**)	40 °C (microwave irradiation)	 **92** (8%)[a]		
4	 papaverine (**11**)	rt	 **93** (4%)[b]	 **94** (62%)[b]	
5	 chinomenine (**95**)	rt	decomposition		

[a] 3 equivalnt of **17** was added. [b] Cs_2CO_3 was not added.

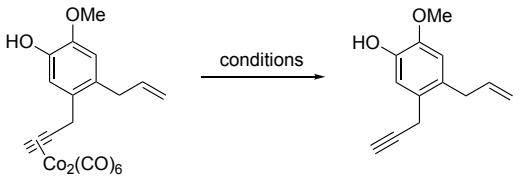
第 4 節　ジコバルト錯体の脱錯体化検討

次にジコバルト錯体の脱錯体化の検討を行った. ジコバルト錯体の脱錯体化は酸化剤である CAN や NMO を用いる報告例が多いものの [17c]，著者が誘導体化した生物活性小分子は，どれも電子豊富な芳香環を持ち，これらが酸化される懸念があった．そこで，モデル化合物として eugenol の誘導体 **42** を用いて種々の酸化剤の検討を行うこととした．誘導体 **42** はフェノール性水酸基を持つことから，非常に酸化されやすく，この基質において収率良くジコバルト錯体の脱錯体化が進行すれば，今回得られた他の生物活性小分子誘導体に関しても，容易に脱錯体化が行えると考えた．

その検討結果を示す（**Table 1-7**）．通常コバルト錯体の脱錯体化に用いられる CAN や NMO では，プロパルギル体 **96** は低収率か全く得られない結果となった（entry 1,2）．次に，山口，杉原らにより報告されたエチレンジアミンを用いたジコバルト錯体の脱錯体化についての検討を行った（entry 3）[58]．本反応では，酸化的なジコバルト錯体の脱錯体化とは異なるメカニズムで反応が進行することから，異なる結果が期待された．しかしながら，反応は複雑化するのみで目的物は全く得られなかった．

以上の結果から，他の酸化剤を検討した．検討の結果，アルコールの酸化反応に主に用いられる TEMPO のオキソアンモニウム塩 $TEMPO^{+}BF_4^{-}$が，中程度の収率で目的の脱コバルト体を与えることを見出した（entry 4）[59]．さらに，反応温度を低下させたところ，収率は徐々に向上し，–40 °C で反応を行うことで，目的物を 86%という高い収率で得ることに成功した（entry 5, 6）．

Table 1-7. 脱錯体化の条件検討



42　　**96**

entry	conditions	yield (%)
1	CAN (4.5 eq), NEt_3 (1.0 eq), Acetone (0.01 M), rt, 80 min	23%
2	NMO (ca. 3 eq), THF (0.01 M), rt	—[a]
3	ethylenediamine (0.2 M)	—[a]
4	$TEMPO^{+}BF_4^{-}$ (4.0 eq), MeCN (0.01 M), rt, 40 min	57%
5	$TEMPO^{+}BF_4^{-}$ (4.0 eq), MeCN (0.01 M), - 20 °C, 40 min	81%
6	$TEMPO^{+}BF_4^{-}$ (4.5 eq), MeCN (0.01 M), - 40 °C, 45 min	86%

[a] decomposition

最適化された条件をもとに様々なコバルト錯体の脱錯体化を行った（**Figure 1-1**）．ほとんどの基質において，中程度から高い収率でプロパルギル化体を得ることに成功した．一方で estradiol 誘導体 **106** では，目的物は低収率であった．この基質においてはフェノール性水酸基部分もまた酸化され，基質が分解し

たためだと考える．

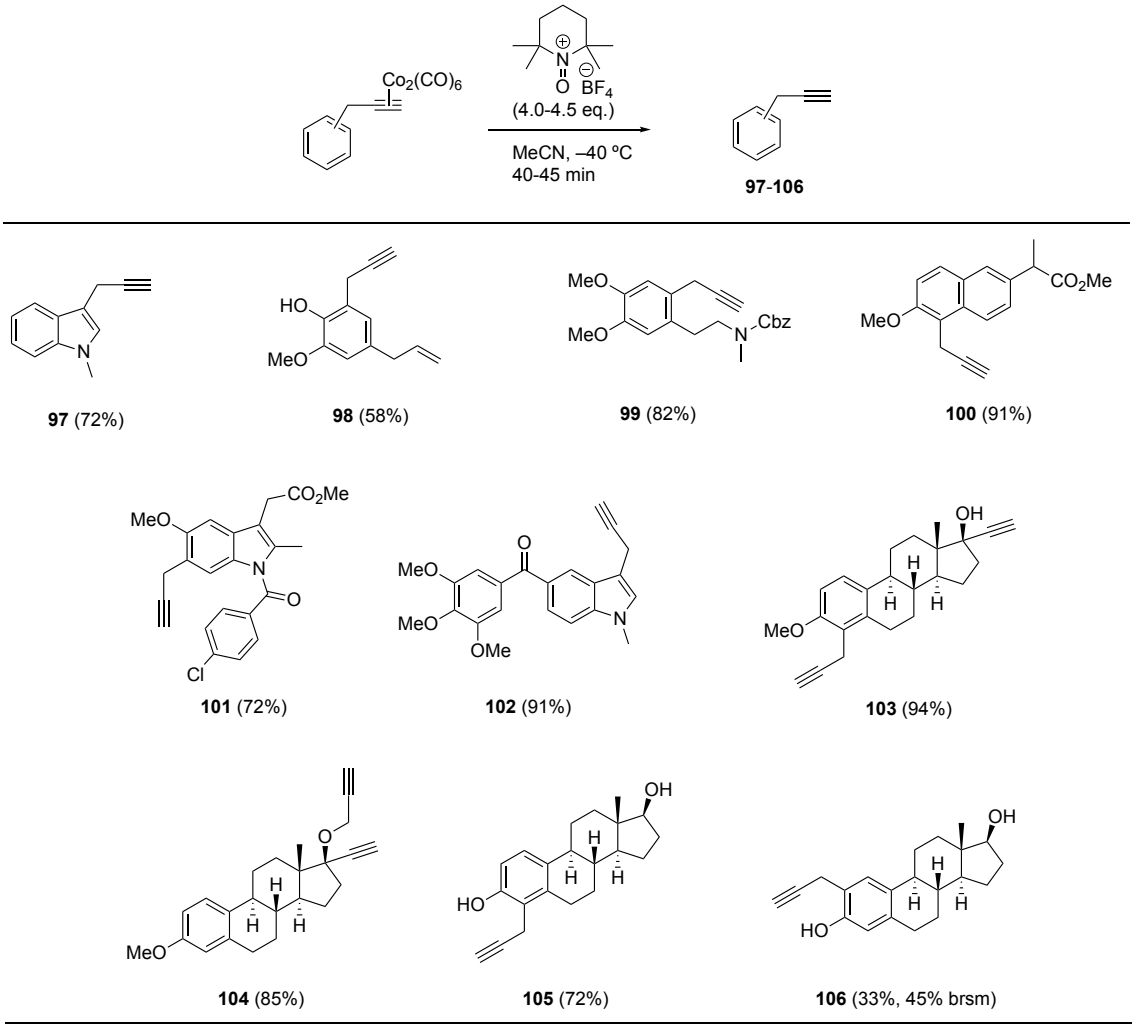


Figure 1-1. 最適化された脱錯体化条件の基質適用性

第 5 節　小括

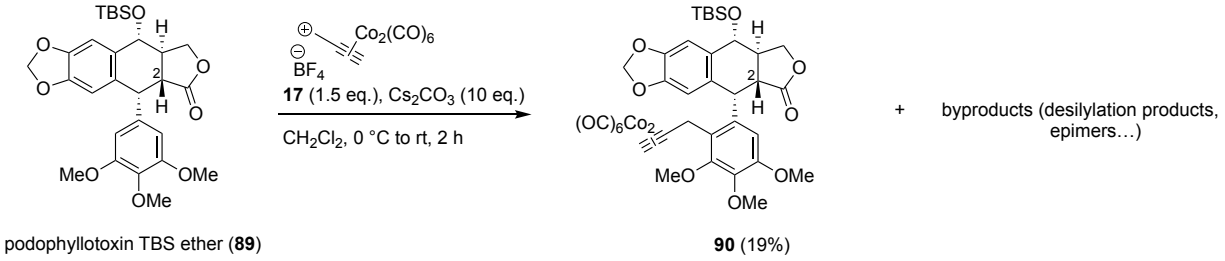
著者は，プロパルギルコバルト錯体 **17** を用いた生物活性小分子のプロパルギル化を行い，塩基として炭酸セシウムを添加することで，様々な芳香族生物活性小分子の修飾が可能であった．このとき，置換したプロトンの ^{1}H-NMR の化学シフト値を確認すると，その値は約 6-7 ppm の間であり，錯体 **17** を用いた修飾を行う際に一つの指標になると考えられる．

また，プロパルギルコバルト錯体の脱錯体化はオキソアンモニウム塩である $TEMPO^{+}BF_4^{-}$ で収率良く行うことができた．

第２章　金触媒と *o*-アルキニルベンゾアートを有する **Nicholas** 試薬を利用した新規 **Nicholas** 反応の開発

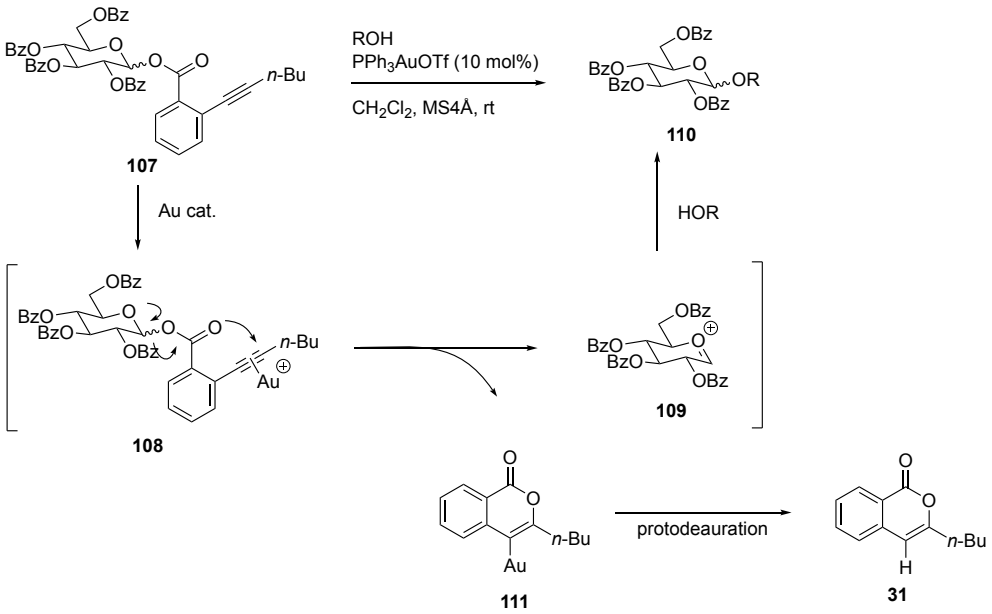
第１節　*o*-アルキニルベンゾアートを有する Nicholas 試薬の合成と評価

著者が開発した錯体 **17** と炭酸セシウムを用いた反応条件は，様々な置換基を持つ芳香族生物活性小分子の２工程プロパルギル化が可能な試薬であった．その一方で，**17** は基質と反応し試薬量の HBF_4 が発生するため，その酸性を中和するために塩基を添加しており，その塩基性が原因で基質によっては分解を招いていた．例えば，podophyllotoxin TBS ether (**89**)では，塩基性が原因と考えられる C2 位の異性化が観測された (**Scheme 2-1**)．このことから，試薬量の超強酸を発生しない新たな反応条件の開発に成功すれば，より温和な条件での官能基化が可能だと考えられる．



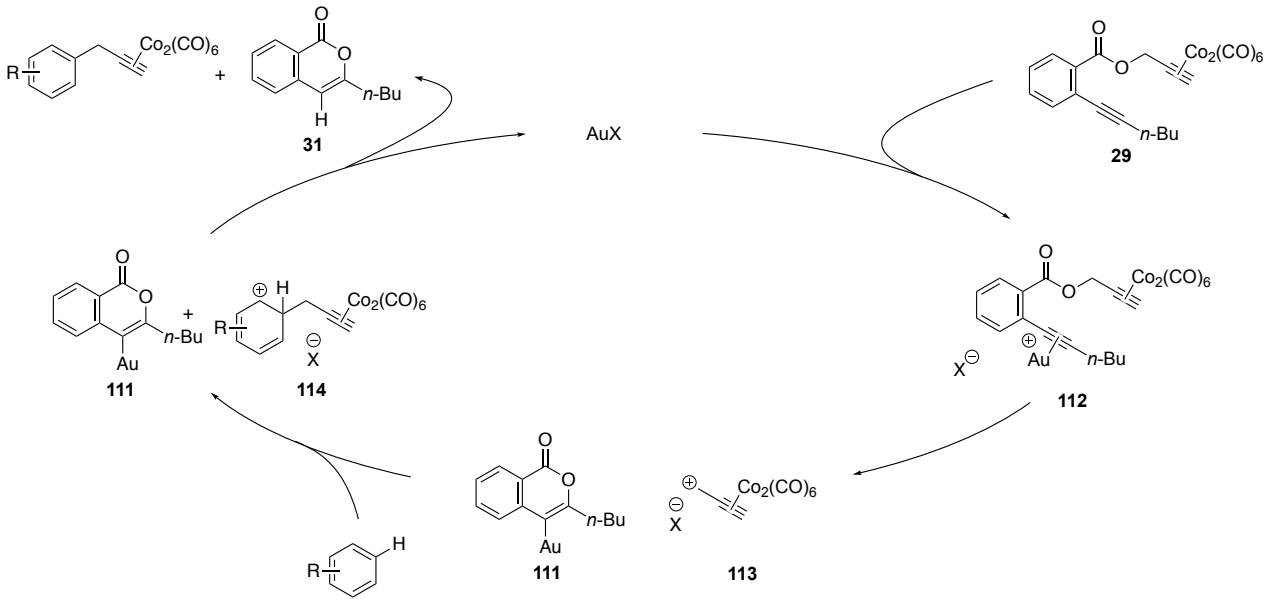
Scheme 2-1. 錯体 **17** を利用した Podophyllotoxin TBS ether (**89**)官能基化の際の問題点

そこで，Yu らにより報告された，金触媒を利用したグリコシル化反応に着目した．彼らは，金触媒で活性化する *o*-アルキニルベンゾアートを糖供与体に導入した **107** を用いた，温和な条件でのグリコシル化を達成している (**Scheme 2-2**)．この反応では，カチオン性金錯体が *o*-アルキニルベンゾアート **107** を活性化することで，中間体 **108** を経てオキソニウムイオン **109** を与えるため，試薬量の酸を必要としない．本コンセプトを，著者が用いてきたプロパルギルジコバルト錯体にも応用できるのではないかと考えた．



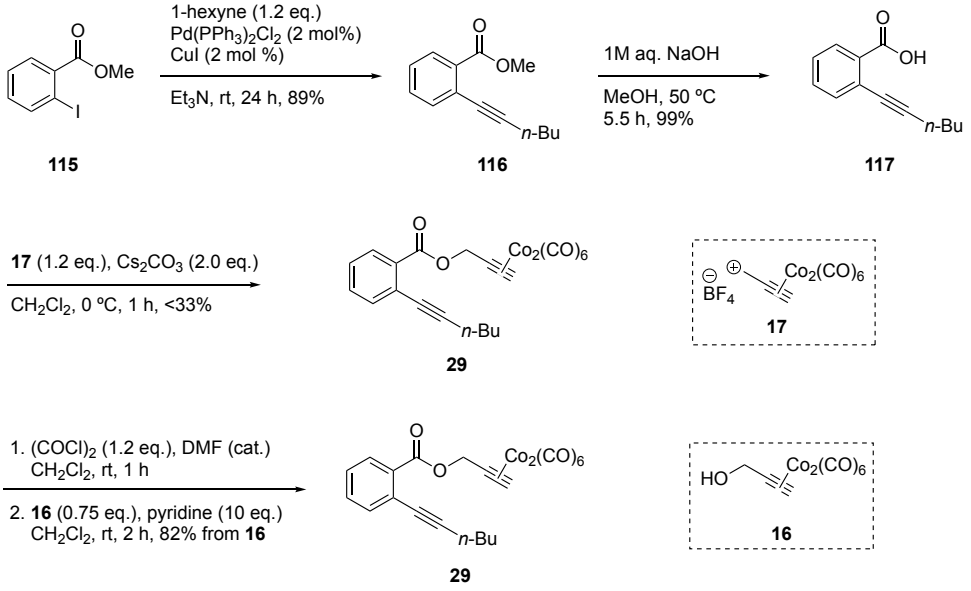
Scheme 2-2. Yu らによるグリコシル化とメカニズム

すなわち，著者が用いてきたカチオン性プロパルギルジコバルト錯体もまた，Yu らの用いた *o*-アルキニルベンゾアートによって発生させられると考えた (**Scheme 2-3**). すなわち，プロパルギルジコバルト錯体と *o*-アルキニルベンゾアートを連結した新規試薬 **29** を調製し，これに金触媒を作用させることで，糖供与体 **107** と同様に，金錯体が配位した中間体 **112** を経由したのちに，活性種である錯体 **113** とイソクマリン-金複合体 **111** が発生すると考えた．金錯体は，イソクマリン-金複合体 **111** と中間体 **114** 間での protodeaulation により再生すると考えられる. なお, 脱離したイソクマリン **31** は芳香族化合物であるが, 芳香環に電子求引基であるエステル基が隣接しているため，電子密度が低く，錯体 **113** と反応しないと考えた.



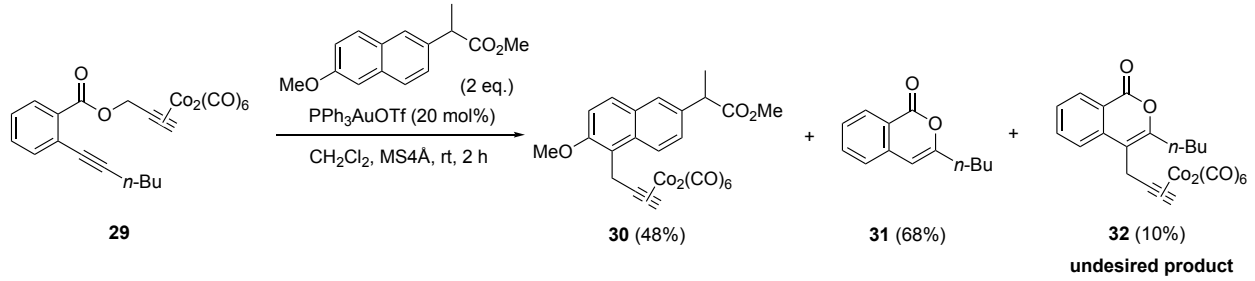
Scheme 2-3. 作業仮説

まず，設計した試薬 **29** の合成を行った（**Scheme 2-4**）．Methyl *o*-iodobenzoate (**115**)と 1-hexyne を薗頭カップリングによって連結しアルキン **116** を得たのちに，加水分解により文献既知の安息香酸 **117** を得た．その後，安息香酸 **117** に対して，第一章で述べた錯体 **17** を作用させたが，**29** は低収率で得られるのみであった．このため，カルボン酸 **117** を塩化アシルへと導いたのちに，プロパルギルジコバルト錯体 **16** を作用させることで, **29** を高い収率で得ることに成功した．



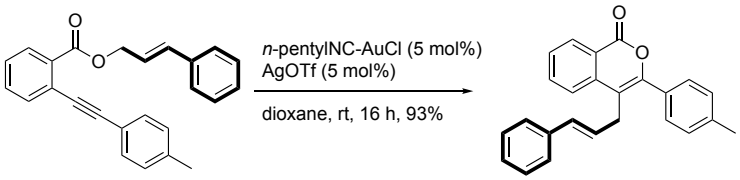
Scheme 2-4. 試薬 **29** の合成

試薬 **29** が得られたので，次に金触媒を作用させ，芳香族小分子の修飾が可能か検討を行った（**Scheme 2-5**）．第 1 章にて錯体 **17** を用いて良い収率で修飾が可能であった naproxen methyl ester (**71**)を基質とし，触媒として PPh_3AuCl と AgOTf より発生させた PPh_3AuOTf を用いて **29** を反応させたところ，反応は進行し中程度の収率で誘導体 **30** を得ることに成功した．また，試薬 **29** が金触媒により活性化された後に得られる副生成物であるイソクマリン **31** も単離されたため, 本反応が著者の作業仮説通りに進行していることが示された．一方，カチオン性中間体 **113** とイソクマリン **31** が反応した副生成物 **32** も 10%の収率で得られた.



Scheme 2-5. 試薬 **29** を利用した naproxen methyl ester (**71**)の官能基化

当初得られないと考えていた副生成物 **32** が得られたことについては以下のように考察した. すなわち，試薬由来の副生成物であるイソクマリン **31** の ^{1}H-NMR を確認するとイソクマリン環の C-4 位の化学シフトは 6.25 ppm と高磁場側に観測された．活性種 **113** は，^{1}H-NMR における化学シフトが 6-7 ppm 付近に存在する芳香環と反応することが第一章において判明しているため, イソクマリン **31** は反応性を持つと考えられる．また，類似した反応がすでに Hashmi らによって報告されており（**Scheme 2-6**），本副反応も同様のメカニズムで進行していると考えられる [60].



Scheme 2-6. Hashmi らによる金触媒を利用したイソクマリン誘導体合成

試薬 **29** を用いてさらなる収率の向上と副生成物 **32** の生成量低減が可能か確認するため，金触媒のスク

リーニングを行った．初期検討において用いた PPh_3AuOTf は PPh_3AuCl と AgOTf より調製される触媒であるが，金イオンのリガンドと銀塩のカウンターアニオン部を変更することで，様々な種類の組み合わせの触媒を調製することが可能である[61].

検討結果を示す（**Table 2-1**）．なお，金触媒は，別の反応容器で事前に調製し，基質と試薬 **29** の溶液中に添加している (実験項参照). 先の検討で用いた PPh_3AuOTf について，順次触媒量を低減していったところ，10 mol%以下では反応が完結しなかった（entry 1-3）．そこで，より触媒量を減ぜられる金触媒を探索すべく，以降の検討の触媒量を 10 mol%，またリガンドを PPh_3 に固定して，様々なカウンターアニオンの検討を行った（entry 4-7）．触媒のカウンターアニオンが ClO_4^-の場合，反応は完結しなかったものの，BF_4^-, NTf_2^-, SbF_6^-の際には反応は完結した．この 3 つの触媒について 5 mol%まで触媒量を低減して反応させたところ，SbF_6^-，NTf_2^-のとき反応を完結は完結し，10 mol%の時とほぼ同等の収率で目的物，副生成物が得られた.

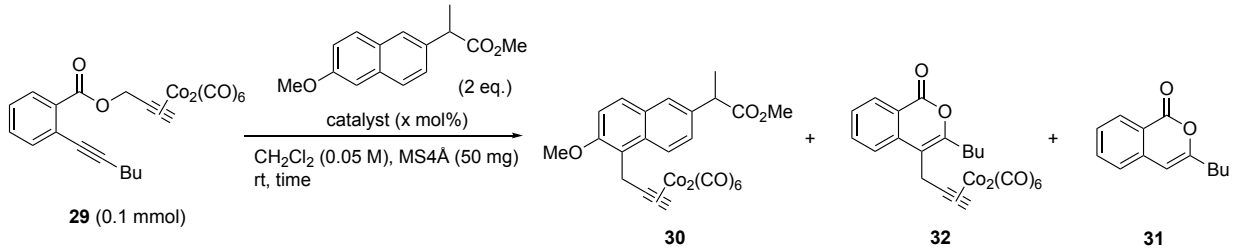
本反応で良い収率を与えたカウンターアニオンについて並び替えると，SbF_6^- ≒ NTf_2^- > BF_4^- > OTf^- の順となり，この傾向は Hydrogen Bond Basicity Index (HBI)によって説明できる．HBI は Hammond らによって定義され，OAc^-の HBI の値を 10, CTf_3^-の HBI の値を 0 として，各カウンターアニオンの水素結合エネルギーに従って相対的に設定された値である[62]．HBI の値はそれぞれ SbF_6 (2.8), NTf_2^- (1.0), BF_4^- (5.2), OTf^- (3.4)であり, HBI の値が小さい SbF_6^-, NTf_2 で良好な収率を与えた．Yu らは，中間体 **111** に対してもう一分子の金触媒が付加したビス金錯体の形成が o-アルキニルベンゾエートを用いた反応の触媒サイクルを妨げる要因の一つとしてあげている[63]．HBI の小さいカウンターアニオンは，中間体 **111** の protodeauration を促進しビス金錯体の形成を防ぐことで，反応を促進していると考えられる.

次に金触媒のリガンドについての検討も行った．NHC 錯体で高い電子供与能ある IMes をリガンドとして用い，先の検討においてもっともよい収率を与えた SbF_6^-をカウンターアニオンとして反応を行ったものの，反応はほとんど進行しなかった（entry 11）．このことから，リガンドはホスフィン配位子が適切であることが示唆された.

最後にプレ触媒として用いた PPh_3AuCl, $AgSbF_6$ をそれぞれ別々に用いたが，どちらの場合においても反応は進行しなかった（entry 12,13）．このことから，金触媒と銀触媒両方を用いて触媒を調製することが本反応には必須であることが示唆された.

検討の結果，収率の向上には成功した一方で副生成物 **32** の低減を防ぐことはできなかった．試薬 **29** でも生物活性小分子の修飾は行えるものの，脱離した後のイソクマリン **31** と錯体 **113** が反応しないことが望ましい．このため副生成物 **32** が発生しない試薬を新たに設計，合成することとした.

Table 2-1. 条件最適化

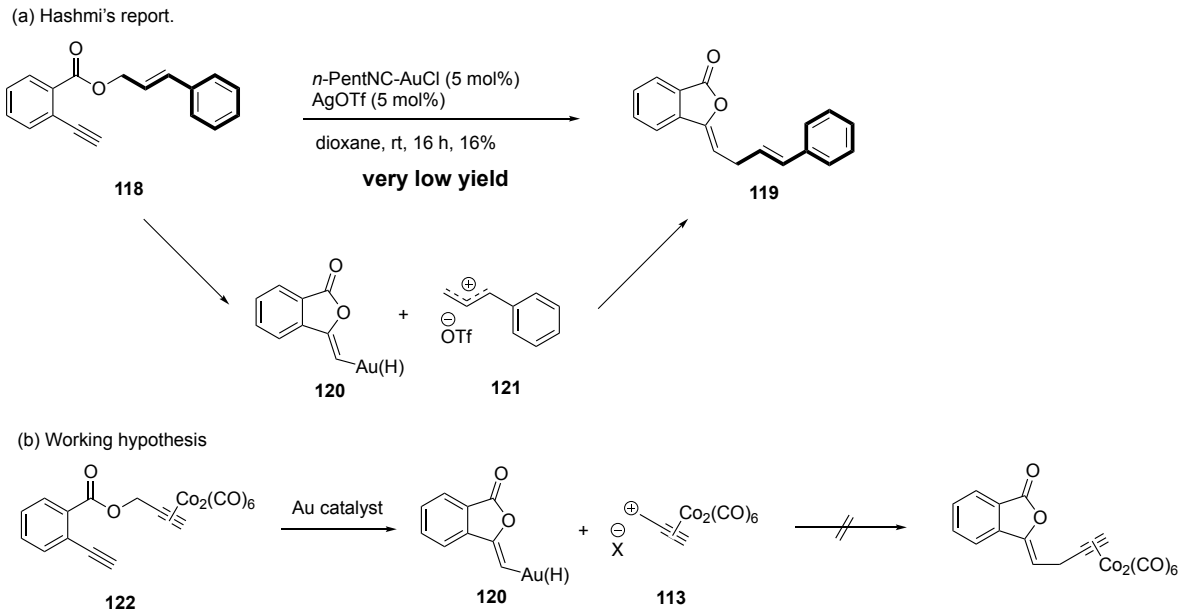


				yield (%)[a]			
entry	catalyst	x (mol %)	time	**30**	**32**	**31**	SM recovered
1	$PPh_3AuCl + AgOTf$	20	30 min	51	14	85	0
2	$PPh_3AuCl + AgOTf$	10	19 h	36	10	59	17
3	$PPh_3AuCl + AgOTf$	5	19 h	15	3	31	57
4	$PPh_3AuCl + AgBF_4$	10	30 min	52	12	72	0
5	$PPh_3AuCl + AgNTf_2$	10	30 min	67	15	70	0
6	$PPh_3AuCl + AgClO_4$	10	7 h	29	9	39	17
7	$PPh_3AuCl + AgSbF_6$	10	30 min	74	19	78	0
8	$PPh_3AuCl + AgSbF_6$	5	30 min	72	14	70	0
9	$PPh_3AuCl + AgBF_4$	5	3 h	26	4	25	64
10	$PPh_3AuCl + AgNTf_2$	5	30 min	71	14	68	0
11	$IMesAuCl + AgSbF_6$	10	3 h	12	9	12	73
12	PPh_3AuCl	10			no reaction		
13	$AgSbF_6$	10			no reaction		

[a] Yield determined by ^{1}H-NMR analysis with toulene as the internal standard.

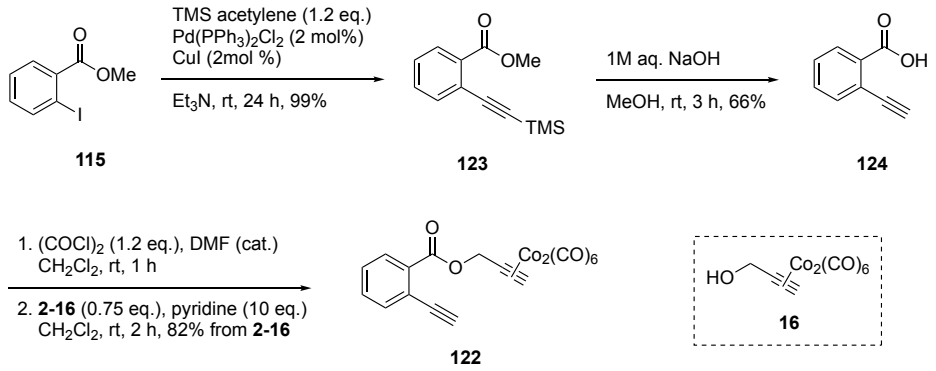
第 2 節　試薬構造の最適化

まず，先に述べた Hashmi らの反応 (**Scheme 2-6**)において，*o*-アルキニルベンゾエートのアルキン部分を末端アセチレンに変えると反応様式が変化する報告に着目した（**Scheme 2-7a**）[60]．すなわち，この反応では金触媒によって **118** から中間体 **120** と **121** が生じ，この 2 つが反応することで **119** が得られると考えられる．しかしながら，**119** は低収率で得られるのみであり，**120** とカチオン性中間体 **121** の反応性は高くないと考えられる．著者の反応にも適用されるのであれば，カチオン性プロパルギルジコバルト錯体 **113** は中間体 **120** と反応せず, ほとんどが生物活性小分子の官能基化に消費されると仮定した (**Scheme 2-7b**).



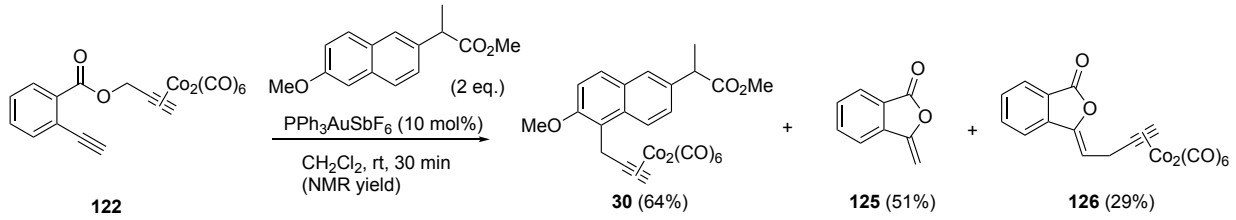
Scheme 2-7. Hashmi らによる報告と著者の作業仮説

試薬 **122** の合成を示す．**29** の合成と同様に薗頭カップリングによって，methyl *o*-iodobenzoate (**115**)にアルキンを導入したのちに，加水分解，酸塩化物に変換後，**16** を用いたアシル化を行うことで，アルキンコバルト錯体を導入した **122** を得た（**Scheme 2-8**）．



Scheme 2-8. 試薬 **122** の合成

続いて，**122** を用いて naproxen methyl ester (**71**)の誘導体化を検討した．**29** と同様に誘導体化を行うことはできたものの，**122** より生じたエキソメチレン化合物 **120** と反応した副生成物 **126** が 29%で得られた（**Scheme 2-9**）．先に用いていた試薬 **29** の時よりも高い割合で副生成物が得られる結果となり，Hashmi らの結果と同様の結果は得られなかった．



Scheme 2-9. 試薬 **2-21** を利用した官能基化

続いて著者は，イソクマリンの C4 位の電子密度の低下を目的として，ペルフルオロカーボン部位，すなわちフルオラスタグをアルキンの先に導入することとした (**Figure 2-1**)．さらにフルオラスタグは，フルオラスシリカゲルカラムクロマトグラフィーにより，目的物と副生成物であるイソクマリンの分離を容易にする目的も併せ持つ．また，どのような炭素長さのフルオラスタグが分離に適切か未知であったため，C_4F_9, C_6F_{13}, C_8F_{17} の 3 種類の試薬の合成を計画した．

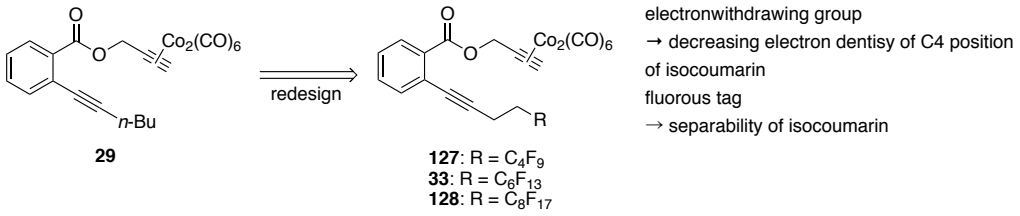
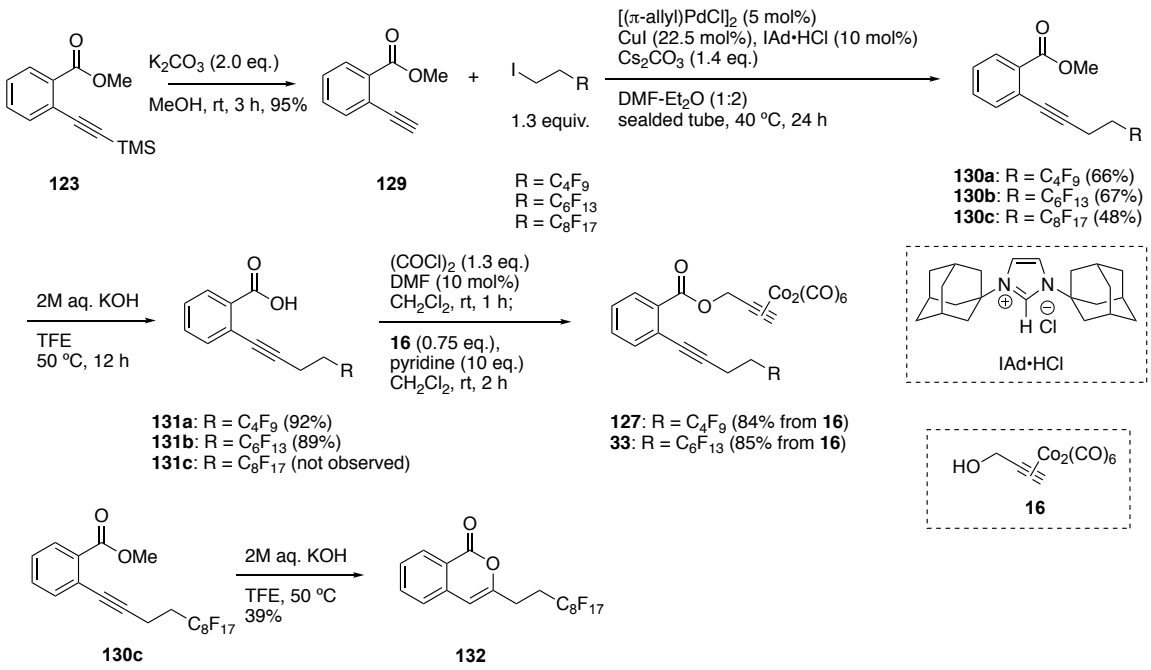


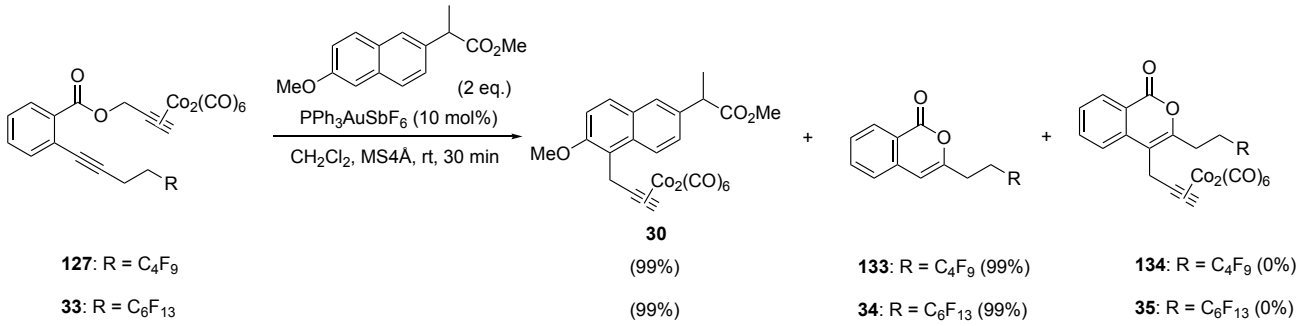
Figure 2-1. ペルフルオロアルキル基を導入した新規試薬設計

新たに設計した試薬合成を以下に示す (**Scheme 2-10**)．まず **123** の TMS 基を除去したのちに，Fu らによって報告された薗頭カップリング[64]により，フルオラスタグを導入した **130** を合成した．**130** をトリフルオロエタノール中，水酸化カリウム水溶液を利用しカルボン酸 **131** へと加水分解し，先と同様に塩化アシルへと変換後，アルコール **16** を作用させることで目的の試薬 **127**, **33** を得た．一方で C_8F_{19} のフルオラスタグを有するエステル **130c** は加水分解の際にカルボン酸 **131c** ではなく，イソクマリン **132** に変換されたため，続く試薬合成が困難であった．



Scheme 2-9. フルオラスタグを導入した試薬 **33**, **127** の合成

合成した新規試薬 **127** 及び **33** の反応性を評価した．naproxen methyl ester (**71**)を先と同様にモデル基質として反応を行ったところ，試薬 **127**, **33** 共に目的物である **30** とイソクマリン **133**, **34** のみを高い収率で得ることに成功し，イソクマリン **133**, **34** とアルキンジコバルト錯体が反応した副生成物 **134**, **35** は確認されなかった．



Scheme 2-10. 試薬 **127**, **33** を利用した官能基化検討

続いて，フルオラス基を有するイソクマリン **133**, **34** が，非フルオラスなイソクマリン **31** と分離可能か検討を行った．フルオラスシリカゲル (FluoroFlash®)を利用し，メタノール/水 (1:4)を溶出溶媒として分離を試みた (**Figure 2-1**)．ところ，C_4F_9 のフルオロカーボン鎖を持つイソクマリン **133** ではイソクマリン **31** と分離ができなかったのに対し，より長いフルオラス基を持つ **34** では **31** との分離を行うことができた．以上の結果から，試薬 **33** を最適な試薬とした．

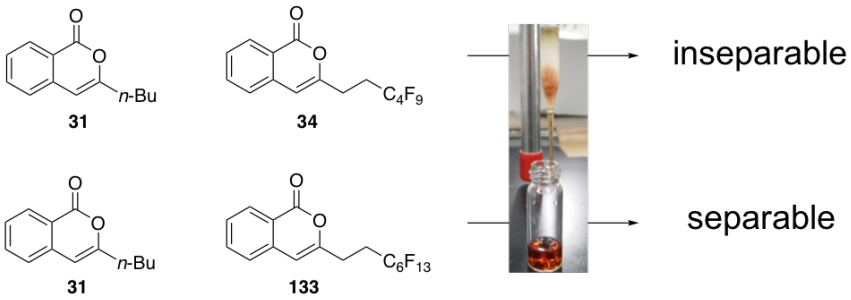
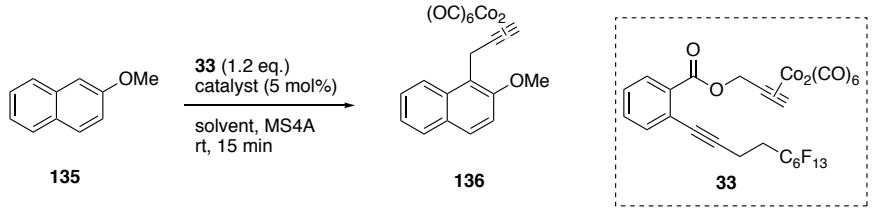


Figure 2-1. フルオラスシリカゲルを利用した分離試験

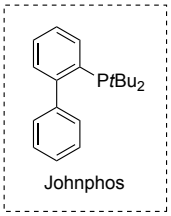
第 3 節　反応条件最適化と基質適用性の検討

2-methoxynaphthol (**135**)をモデル基質として，**33** を利用した官能基化の最適条件の検討を行った．第 2 章第 2 節において触媒のカウンターアニオンが反応に大きな影響を与えたことから, 良い収率を与えた BF_4^-, NTf_2^-, SbF_6^-の 3 つのカウンターアニオンを持つ触媒を検討したところ，PPh_3AuNTf_2 が最も良い収率で目的物 **136** を与えた (entry 1-3). 一方で，配位子として高い電子供与性を持つ Johnphos[65] と高い電子求引性を持つ triphenyl phosphite をそれぞれ用いたものの，目的物の収率は中程度であった (entry 4,5). 続いてトリフェニルホスフィンの置換基を変更することで収率の改善を試みたところ, 4 位にメトキシ基を導入した$(4\text{-MeO-}C_6H_4)_3P$，もしくはフルオロ基を導入した$(4\text{-F-}C_6H_4)_3P$ を配位子としたとき，良い収率を与えることを見出した (entry 6,7). さらに，溶媒としてジクロロメタンではなくジクロロエタンを用いることで，原料は消失し，目的物を高い収率で得ることに成功した (entry 8,9). 溶媒は，ハロゲン系が良く，ヘキサンやジエチルエーテルでは反応はほとんど進行しなかった (entry 10,11). これらの結果から，entry 9 を最適条件とした．なお，entry 6 以降の NTf_2^-をカウンターアニオンとした金触媒は，固体で安定な錯体であるため，用事調製ではなくあらかじめ合成して保存していたものを用いた [66].

Table 2-2. 試薬 **33** を利用した反応条件最適化



entry	catayst	solvent	yield of **136**[a] (%)
1	$PPh_3AuCl + AgBF_4$[b]	CH_2Cl_2	11
2	$PPh_3AuCl + AgSbF_6$	CH_2Cl_2	37
3	$PPh_3AuCl + AgNTf_2$	CH_2Cl_2	79
4	$JohnphosAuCl + AgNTf_2$	CH_2Cl_2	41
5	$(PhO)_3AuCl + AgNTf_2$	CH_2Cl_2	44
6	$(4\text{-}MeOC_6H_4)_3PAuNTf_2$	CH_2Cl_2	91
7	$(4\text{-}F\text{-}C_6H_4)_3AuNTf_2$	CH_2Cl_2	85
8	$(4\text{-}MeOC_6H_4)_3PAuNTf_2$	$ClCH_2CH_2Cl$	97
9	$(4\text{-}F\text{-}C_6H_4)_3PAuNTf_2$	$ClCH_2Cl_2Cl$	100
10	$(4\text{-}F\text{-}C_6H_4)_3PAuNTf_2$	hexane	5
11	$(4\text{-}F\text{-}C_6H_4)_3PAuNTf_2$	Et_2O	7



[a] Yield was determined by ^{1}H-NMR analysis using mesitylene as an internal standard.
[b] 10 mol% of catalyst was used.

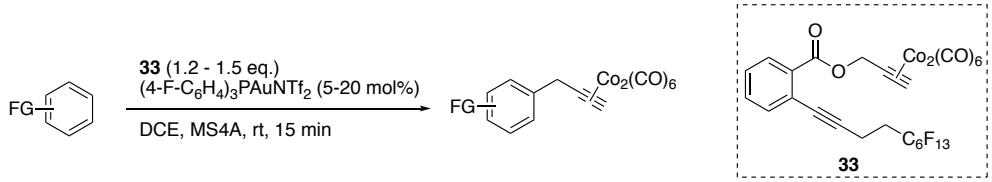
最適化した条件を利用して，基質適用性の検討を行った (**Table 2-3**). ナフタレンの C2 位の置換基を，プロピルエーテル(**137**)，フェニルエーテル(**139**)，ベンジルエーテル(**141**)とした基質では，反応は問題なく進行した (entry 1-3). 次に C2 位の置換基をメトキシ基に固定し，C6 位に様々な置換基を導入した誘導体群について検討を行った (entry 4-6). アリル基を持つ基質 **143** は本反応条件下，C1 位置換体を与えた．また，ブロモ基 (**145**)やアセチル基(**147**)といった官能基も本条件は許容した．なお，C6 位にブロモ基を持つものは低反応性であったものの，溶媒として HFIP を添加することで収率の改善に成功している[67]．HFIP は，触媒サイクルの protodeauration の過程を加速し，触媒効率を高めていると考えられる[68].

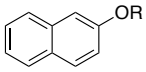
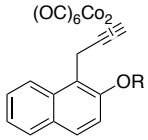
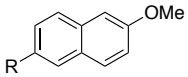
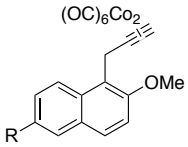
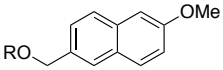
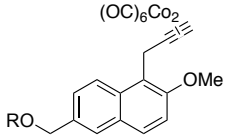
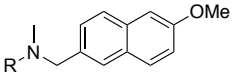
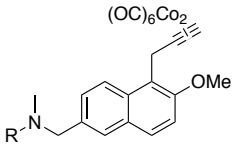
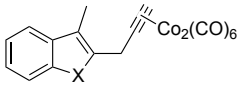
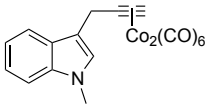
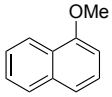
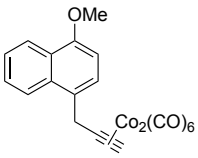
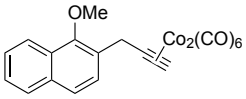
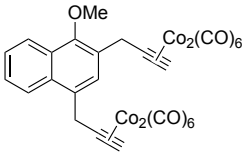
続いて，錯体 **17** を利用した条件では官能基化が困難であった，酸もしくは塩基に鋭敏な官能基を持つ基質について検討を行った (entry 7-11). 検討の結果，本条件は酸に鋭敏な MOM 基 (**149**)や Boc 基(**155**)を持つ基質においても目的物は良好な収率で得られた．また，TBS 基を持つ基質 **151** においても，良好な収率で反応が進行した. なお, 第一章にて開発した錯体 **17** と炭酸セシウムを利用した反応条件の場合，これらの目的物の収率は大きく低下した．酸に非常に弱い TMS エーテル **153** を用いた場合でも低収率ながら目的物を得ることに成功した．塩基に鋭敏な Fmoc 基を持つ基質 **157** では，以前の条件と比較して収率の大幅な改善に成功した.

本条件はヘテロ芳香族化合物に対しても適用可能であった．すなわち 3-methylbenzofuran (**159**)や 3-

methylbenzothiophene (**161**)に対しても適用可能であり，C2 位が官能基化された誘導体を得ることに成功した．また，*N*-methyl indole (**59**)に適用させた場合，3 位で置換した誘導体 **60** を以前開発した条件よりも良い収率で得ることができた．1-Methoxynaphthalene (**163**)を基質として利用した場合，３つの誘導体が得られた．すなわち，4 位と 2 位でそれぞれ置換された誘導体 **164**, **165** と，2, 4 位両方で置換された誘導体 **166** が得られた．

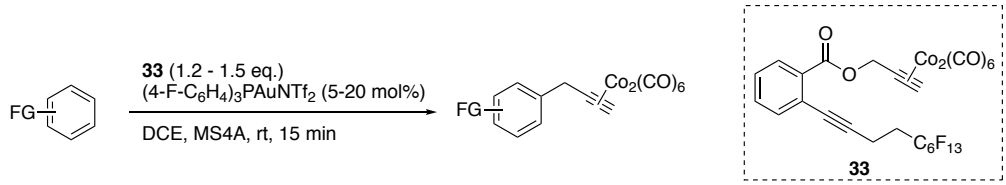
Table 2-3. 基質適用性

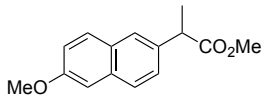
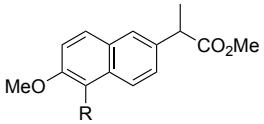
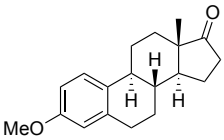
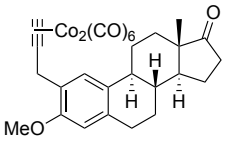
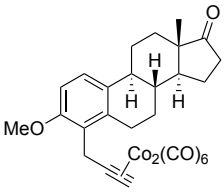
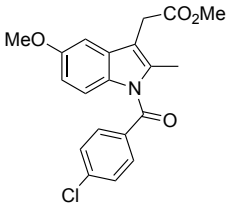
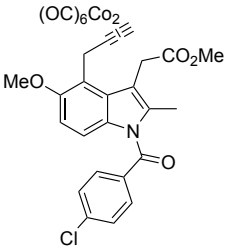
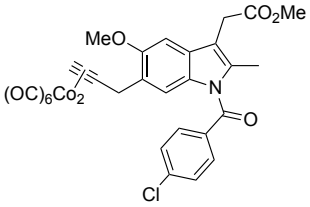
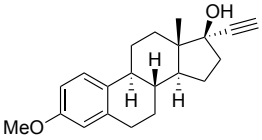
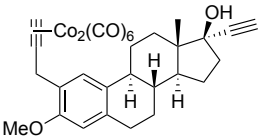
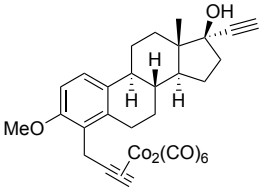
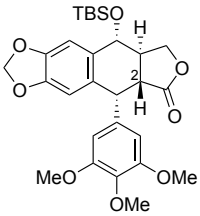
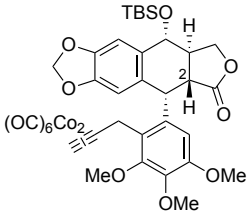
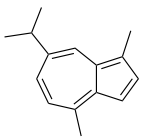
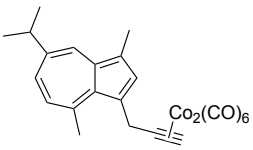


Entry	Aromatic substrates		Products (yield, previous yield[a])	
1		**137**: R = *i*Pr		**138**: R = *i*Pr (96%)
2		**139**: R = Ph		**140**: R = Ph (96%[b])
3		**141**: R = Bn		**142**: R = Bn (96%[b])
4		**143**: R = allyl		**144**: R = allyl (94%)
5		**145**: R = Br		**146**: R = Br (90%[b])
6		**147**: R = $COCH_3$		**148**: R = $COCH_3$ (74%)
7		**149**: R = MOM		**150**: R = MOM (58%, 14%)
8		**151**: R = TBS		**152**: R = TBS (100%, <33%)
9		**153**: R = TMS		**154**: R = TMS (31%[c], decomp.)
10		**155**: R = Boc		**156**: R = Boc (76%[b], 16%)
11		**157**: R = Fmoc		**158**: R = Fmoc (99%[b])
11		**159**: X = O		**160**: X = O (78%)
12		**161**: X = S		**162**: X = S (69%[b])
13	**59**		 **60** (69%)	
14	 **163**		 **164** (69%)	 **165** (21%)  **166** (8%)

[a] Condition: **17** (1.5 eq), Cs_2CO_3 (10 eq), CH_2Cl_2, 0 ºC to rt. [b] DCE-HFIP (10:1) was used as a solvent.
[c] Yield determined after desilylation.

Table 2-3. 基質適用性 (continued)



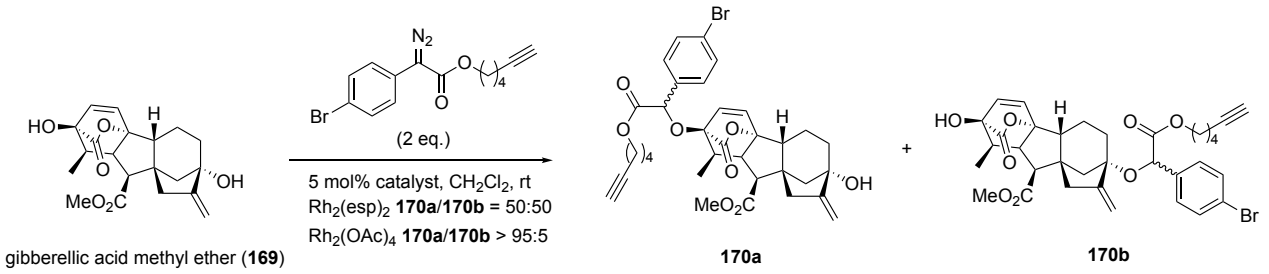
Entry	Aromatic substrates	Products (yield, previous yield[a])
15	 naproxen methyl ester (**71**)	 **30** (97%, 93%)
16	 *O*-Me estrone (**25**)	 **26** (53%[b], 45%)  **27** (46%[b], 40%)
17	 indomethacin methyl ester (**72**)	 **73** (42%[b], 51%)  **74** (45%[b], 15%)
18	 mestranol (**51**)	 **52** (37%[b, d], 26%)  **53** (33%[b, d], 24%)
19	 podophyllotoxin TBS ether (**89**)	 **90** (21% (99% brsm)[b], 19%)
20	 guaiazulene (**167**)	 **168** (37%[b])

[a] Condition: **17** (1.5 eq.), Cs_2CO_3 (10 eq.), CH_2Cl_2, 0 ºC to rt. [b] DCE-HFIP (10:1) was used as a solvent.
[d] *C,O*-disubstituted products **55** and **56** was also obtained in 16% (see the experimental section).

錯体 **17** と炭酸セシウムを用いた条件は，多様な生物活性分子の官能基化が可能であったが，試薬 **33** もまた多くの複雑な骨格を持つ分子の官能基化が可能であった．さらに, indomethacin methyl ether (**72**), mestranol (**51**)，では収率の改善が見られ，以前開発した手法より温和な条件で官能基化が進行していることが示唆された．また podophyllotoxin TBS ether (**89**)は，以前の条件では炭酸セシウムの塩基性による C2 位の異性化が観測されたが，本条件では観測されなかった．また，guaiazulene (**167**)の官能基化も達成した．

第 4 節　触媒依存的な位置選択性制御

生物活性分子の構造活性相関研究を行う際に，迅速な誘導体の供給は重要である．このため，複数の誘導体を一挙に得る反応条件は，構造活性相関研究において有用である．その一方で，構造活性相関研究後に，最適な誘導体を利用した標的分子探索を行う場合には，必要な単一の誘導体のみを選択的に得られる反応条件が望ましい．このことから，複数の誘導体を一挙に得る条件と，単一の誘導体のみを得られる両条件を開発することは重要である．実施に Romo らは，触媒を変更することで gibberellic acid methyl ether (**169**)の水酸基に対する選択性を変更させることに成功している [23b].

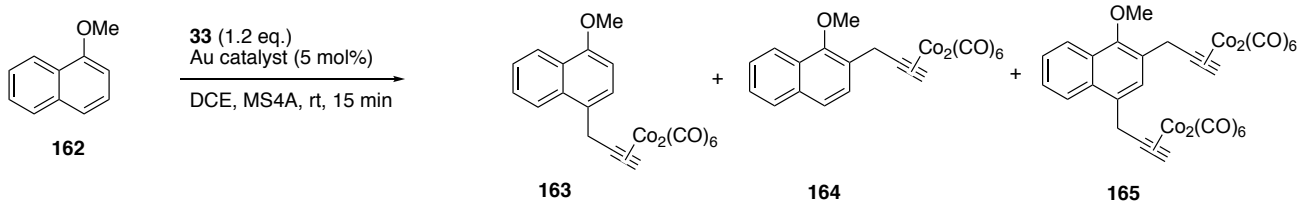


Scheme 2-11. Romo らによる触媒依存的な位置選択性の制御

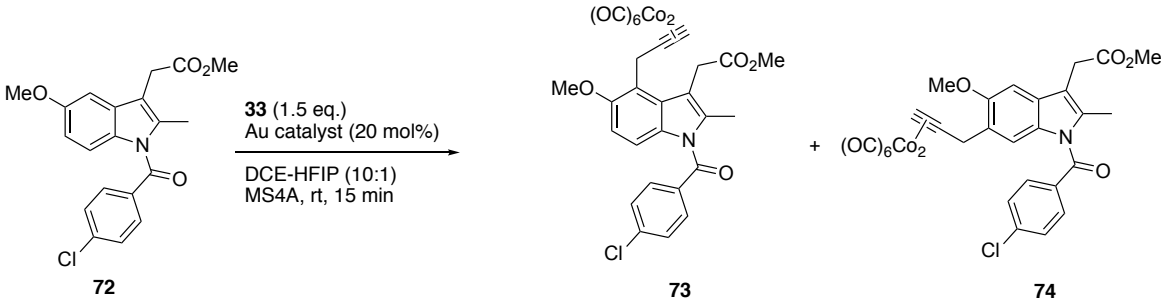
著者は Romo らの報告を参考に，複数の誘導体が得られた基質において，触媒を変更することで位置選択性の制御が可能か検討を行った (**Table 2-4**)，検討の結果，1-methoxynaphthalene (**162**), indomethacin methyl ether (**72**)の場合に選択性を制御できることを見出した．すなわち，触媒のカウンターアニオンを NTf_2^-から SbF_6^-へと変更することで，反応の位置選択性が変化した．1-methoxynaphthalene (**162**)では優先して得られていた誘導体 **163** がより高い収率で得られるようになった一方で，indomethacin methyl ether (**72**)では誘導体 **73** のみが選択的に得られるようになった．これは，触媒のカウンターアニオンを SbF_6^-へと変えることで NTf_2^-と比較して反応性が低下し (**Table 2-1** 参照)，より進行しやすい反応が優先したためだと考えられる．このように位置選択性を制御する手法は，Romo らが述べるように構造活性相関研究と標的分子探索研究の橋渡しに重要である．また，カウンターアニオンにより Nicholas 反応の選択性を

制御した例は他に例がなく，我々が初めて見出した現象である．

Table 2-4. 触媒変更による位置選択性の制御



Au catalyst	yield (%)		
	163	**164**	**165**
$(4\text{-F-}C_6H_4)_3PAuNTf_2$	69	21	8
$(4\text{-F-}C_6H_4)_3PAuSbF_6$	73	12	9



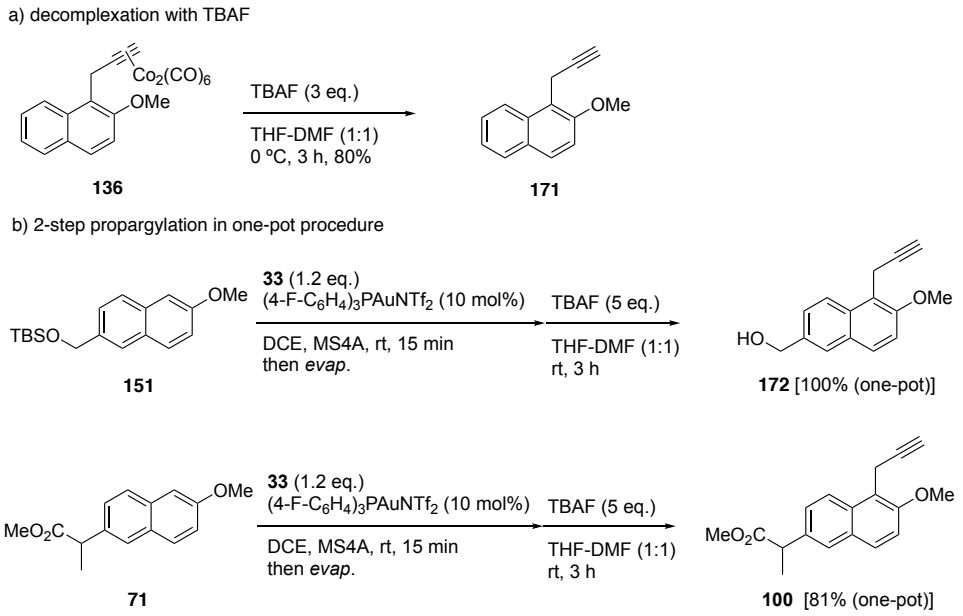
Au catalyst	yield (%)	
	73	**74**
$(4\text{-F-}C_6H_4)_3PAuNTf_2$	42	45
$(4\text{-F-}C_6H_4)_3PAuSbF_6$	78	trace

第 5 節　フッ素化試薬を利用した脱錯体化条件の開発

第 1 章第 4 節で開発した，$TEMPOBF_4$ を用いる条件は，電子豊富な芳香環存在下でもコバルト錯体の酸化的脱錯体化が優先して進行する有用な条件であった．その一方で，低温化で反応を行わなければならないため，より簡便な手法での脱錯体化が可能となれば，広く利用される条件になると考えらえる．

TBAF をはじめとした求核的フッ素化試薬は，ジコバルト錯体をアルキンへと変換する試薬の一つである [30,69]．求核的フッ素化試薬は強力な酸化剤ではないため，電子豊富な芳香環を持つ基質群においてより温和に脱錯体化が可能であると考えられる．実際に，条件を精査した結果 (**Scheme 2-13**)，DMF と THF の混合溶媒中，TBAF を反応させる条件において，**136** の脱錯体化が温和かつ速やかに進行し，プロパルギル **171** を得ることに成功した．また本手法は，官能基化を行った後に溶媒を除去し，同一フラスコ内

で脱錯体化を行うワンポットケミストリーへと適用することも可能であった[70]．すなわち，シリルエーテル **151** は，官能基化後に TBAF を用いた脱錯体化を行うことで，脱シリル化も同時に進行したプロパルギルアルコール **172** を与えた．さらに，naproxen methyl ether (**71**)もプロパルギル化体 **100** へとワンポットで導くことが可能であった．



Scheme 2-13. TBAF を用いた脱錯体化と one-pot での 2 工程プロパルギル化

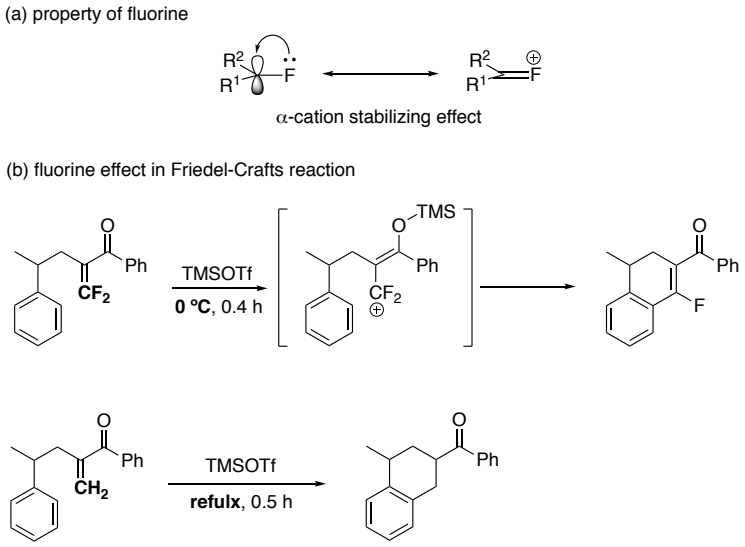
第 6 節 小括

著者は，触媒量の酸で進行する新規ニコラス試薬 **33** を新たに合成し，これを利用することで温和な条件での芳香族化合物の官能基化を達成した．得られた試薬は，金触媒によって活性化され，従来のニコラス反応条件では官能基化が困難であった．酸性に鋭敏な基質にも適用可能であった．さらに，本試薬は様々な芳香族生物活性分子にも適用可能であり，基質によっては第 2 章において著者が開発した条件よりも高い収率で目的物を与えた．さらに，触媒依存的に位置選択性を制御できることを見出し，ニコラス反応において反応性制御にカウンターカチオンが重要な役割を果たすことを明らかにした．一方，脱錯体化条件として，新たに TABF を利用した反応を開発し，one-pot でのプロパルギル化へと応用した．

第３章　アルコールに対する化学選択的なジフルオロプロパルギル化反応の開発と応用

第１節 発見の経緯

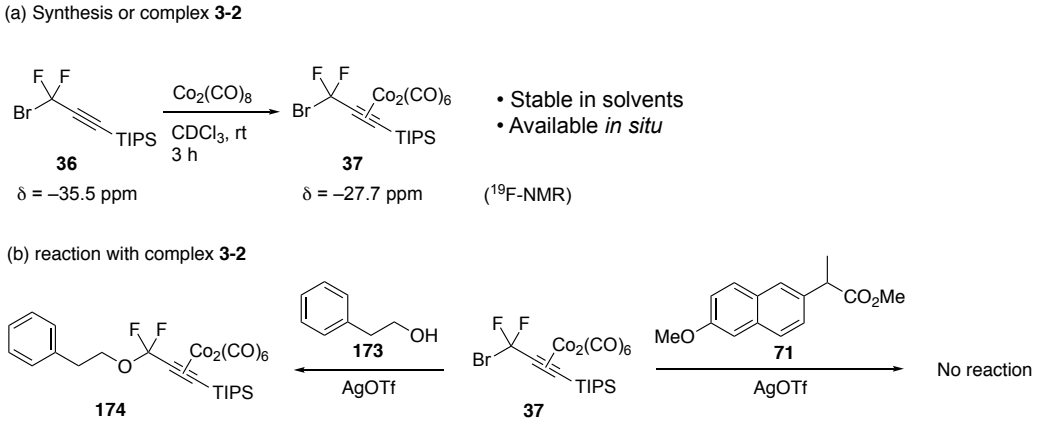
フッ素原子は，水素につぐ小さな原子半径と高い電気陰性度を有するハロゲン原子である．フッ素原子は 2p 軌道に非共有電子対を有し，隣接炭素に生じたカチオン (α-カルボカチオン)を非共有電子対の逆供与によって安定化させ，α -カルボカチオンの反応性を変化させるユニークな特性を持つ（α効果）．筑波大学の市川らはこの性質を利用することで，ジフルオロオレフィンを利用した分子内 Friedel-Crafts 反応を開発している (**Scheme 3-1**)[71]. 本反応は，ジフルオロオレフィンによってカチオンが安定化されるため，低温条件でも速やかに進行する．



Scheme 3-1. フッ素がα-カルボカチオンに与える効果

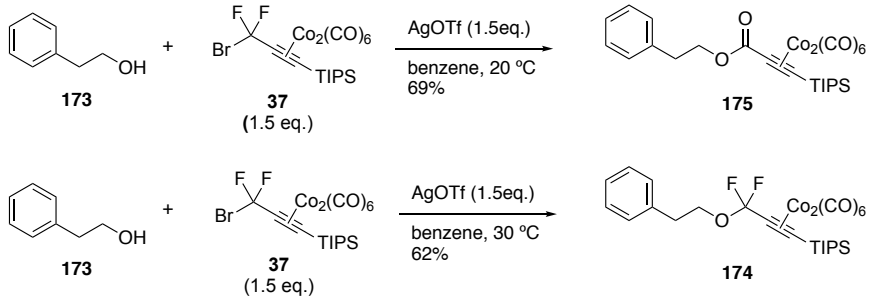
著者は，ジコバルト錯体の隣接炭素に生じるカルボカチオンの反応性が，フッ素原子の導入によって変化するか興味を持った．これまで，ジコバルト錯体の隣接炭素にフッ素原子を導入しその反応性を検討した報告は著者が知る限りないため，まずそのような錯体が合成可能か検討を行った．検討の結果，文献既知のジフルオロプロパルギルブロミド誘導体 **36**[48] に対しオクタカルボニルジコバルト錯体を作用させると，ジコバルト錯体 **37** が得られることを見出した (**Scheme 3-2**). 錯体 **37** は溶液中安定な錯体であり，検討の結果，精製せずとも次の反応に利用することが可能であった．さらに本錯体は銀試薬によって活性化可能であり，phenylethyl alcohol (**173**)と反応し，エーテル **174** を生成した．その一方で， naproxen methyl ether (**71**)など電子豊富な芳香環とは全く反応せず，従来のニコラス反応とは異なった反応性を持

つことが示唆された.



Scheme 3-2. 錯体 **37** の合成とアルコール，芳香環との反応

ところで，水酸基との反応は，反応温度によって望むエーテル **174** が優先して生成する場合と，エステル **175** が副生する場合があり当初再現性に難があった (**Scheme 3-3**). 検討の結果，温度の微妙な変化によって得られる生成物が変化することを見出した．すなわち溶媒をベンゼンとし，反応温度を 20 ºC で行った場合，エステル **175** が主生成物であったのに対し，反応温度を 30 ºC とした場合，エーテル **174** が主生成物になることを見出した．このことから，反応温度に依存せず，望むエーテルが優先的に得られる条件の探索を行った.



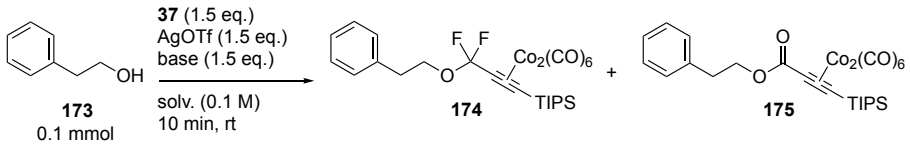
Scheme 3-3. 反応生成物の温度依存性

第 2 節 反応条件最適化

フェニルエチルアルコールをモデル基質として，室温下でエーテル **174** がもっとも良い収率で得られる反応条件を検討した (**Table 3-1**). なお，本検討において室温とは，15-25 度の温度幅である．先に述べた通り，錯体 **37** はトリフルオロメタンスルホン酸銀 (AgOTf)により活性化可能であり，ベンゼン，ジクロロメタン中で試薬量の基質と反応した (entry 1,2). しかし，望むエーテル **174** はほとんど得られず，先

に述べたようにエステル **175** が主生成物として得られた．

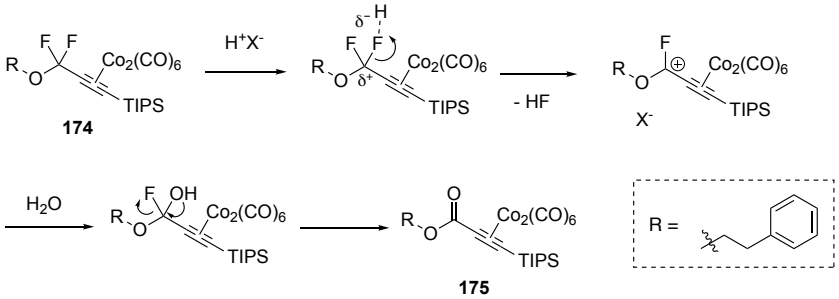
Table 3-1．条件最適化



entry	base	solv.	yield (%)[a] 174	175	SM
1	none	CH_2Cl_2	0	76	0
2	none	benzene	5	69	0
3[b]	none	toluene		—[c]	
4	Et_3N	benzene	85	0	9
5	Et_3N	CH_2Cl_2	88	0	0
6	Et_3N	toluene	99	0	0
7[d]	Et_3N	toluene	85	4	0
8[e]	Et_3N	toluene	<16	0	34

[a] The yields were determined by ^{1}H-NMR using mesitylene as a internal standard.
[b] MS4A was added. [c] **175** was only observed.[d] $AgNTf_2$ was used instead of AgOTf.
[e] $AgBF_4$ was used instead of AgOTf.

目的物が得られない理由について，アルコールと **37** が反応後に生じるトリフルオロメタンスルホン酸により反応系中が酸性となり，フッ素原子が脱離し水分子が付加することでエステルが生じると考察した (**Scheme 3-4**)．この仮説は，誘電率が高いジクロロメタン中ではフッ素原子の脱離が起こりやすく，エステルの生成が優先する一方で，誘電率が低い溶媒であるベンゼンでは，反応温度により目的物が得られた結果とも合致する [72]．この仮説から反応系中の水を除くことで目的物が得られると考え，モレキュラーシーブの添加を検討したが，エーテル **174** を得ることはできなかった (entry 3).



Scheme 3-4．エステル **175** 副生のメカニズム

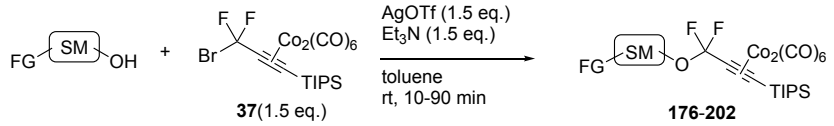
そこで反応系中の酸性化を防ぐ目的で，塩基である Et_3N を添加したところ，エステル **175** の副生はほとんど確認されず，目的のエーテル **174** を高い収率で得ることに成功した (entry 4). 溶媒をベンゼン，ジクロロメタン，トルエンの３種類について検討したところ，トルエンが最適であった (entry 4-6). 銀試薬を $AgNTf_2$ に変更した場合では収率がわずかに低下し (entry 7)，$AgBF_4$ を利用した場合反応が完結しなかった (entry 8). これらの結果から，entry 6 を最適条件とした.

第 3 節　基質適用性と化学選択性について

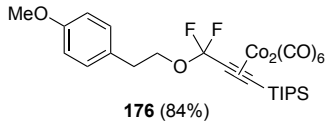
前節にて最適化した条件を用いて多様な官能基を持つアルコールのエーテル化を検討した (**Figure 3-1**). まず，非求核性官能基を持つ基質について検討を行った (**Figure 3-1a**). メトキシ基やブロモ基を持つフェネチルアルコール誘導体は，高い収率で目的のエーテル **176**, **177** を与えた．また，エーテル **176** は，1 mmol スケールでも，収率を損なうことなく合成可能であった．強い電子求引性を持つニトロ基では，より強いルイス酸である $AgNTf_2$ を利用することで，エーテル **178** を与えた．ベンジルアルコール誘導体もエーテル化可能であったが，目的物 **179**, **180** の収率は中程度であった．Boc 基や Fmoc 基 といった酸や塩基に弱い官能基を持つ基質も，高い収率で官能基化が可能であり，それぞれ **181**, **182** を与えた．試薬の当量を増やすことで３級アルコールのエーテル **183** の合成を達成した．この時，塩基として Et_3N ではなく DTBMP を用い，塩基性による AgOTf の活性低下を防ぐことで，収率の向上が見られた．また，TIPS 基の代わりにフェニル基で置換したジフルオロプロパルギルブロミドジコバルト錯体 **184** を用いた場合でも，エーテル **185** を得ることが可能であった.

続いて，求核性官能基を併せ持つアルコールに対しエーテル化を行い，本反応の化学選択性について確認を行った (**Figure 3-1b**). インドール，ピリジン，アニリン，のような弱い求核性官能基を持つ基質では，アルコールと優先的にエーテル化が進行した (**186-189**). さらに第三級アミン，第二級アミン，第一級アミンを持つ基質でさえアルコール選択的に本反応は進行し，それぞれ望むエーテル **190**, **191**, **192** を与えることを見出した．なおアニリン，ピリジン，第二級アミン，第一級アミンを持つ基質では，塩基として DTBMP を用いることで収率が向上し，第三級アミンを持つ基質では，塩基を添加せずとも望むエーテルが得られた．３級アミンを持つ基質は，分子内のアミンが塩基の代わりに作用したために，塩基の添加が不要であったと考えられる．フェノール性水酸基やオレフィン，電子豊富な芳香環を持つ基質でも，エーテル化が優先した (**193-195**). これらはどれも Nicholas 反応で反応剤として報告のある官能基である．そして通常の Nicholas 反応ではスルホニウムを形成することで知られる，スルフィド類を持つ基質においてもエーテル化が優先して進行した．この高い化学選択性の理由は現在明らかになっていないが，フッ素の影響によりこのような選択性が発現していることは明らかである.

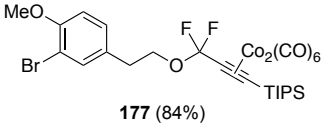
本反応は高いアルコール選択性を示すことから，アミノ酸誘導体や生物活性分子に対しても適用可能か検討した (**Figure 3-1c**)．スレオニン誘導体 からは，エーテル **198** が得られた一方で，ジペプチド **199** では基質が分解し，目的物は全く得られなかった．ジペプチド **199** が分解した理由について，錯体 **37** はアミドと反応し，不安定な生成物が得られた後に分解したためだと考察している．医薬品プロキシフィリンでは良好な収率で目的物 **200** を得ることに成功し，天然物ポドフィロトキシン，ヨヒンビンに対しても本条件は適用可能であり，対応するエーテル **201** と **202** を与えた．しかし，プロプラノロール (**203**) のエーテル化は進行しなかった．これは銀試薬とベータアミノアルコールが錯体を形成し，銀試薬が失活したためだと考えられる．



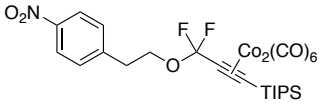
(a) substrates containig non-nucleophilic groups



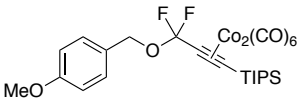
176 (84%)
1 mmol scale (91%)



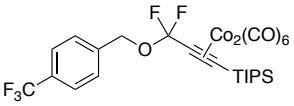
177 (84%)



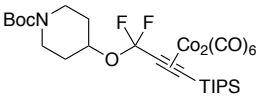
178 (60%)[a]



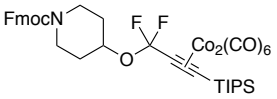
179 (64%)



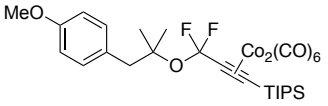
180 (63%)



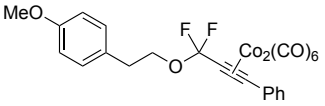
181 (89%)



182 (85%)

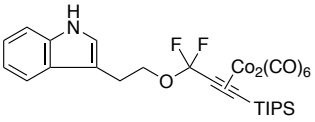


183 (64%)[b, c]

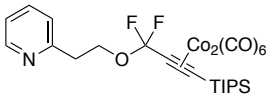


185 (94%)[d]

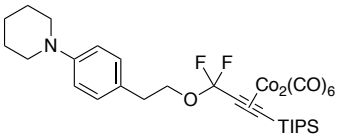
(b) substrates containig nucleophilic groups



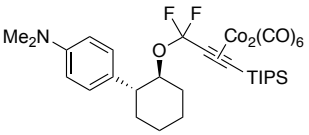
186 (47%)[e]



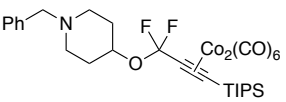
187 (58%)[b]



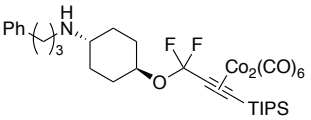
188 (83%)[b]



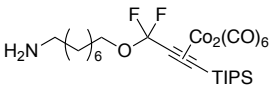
189 (60%)[b, f]



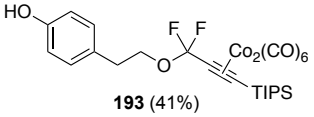
190 (76%)[g]



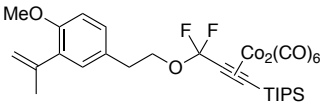
191 (64%)[h]



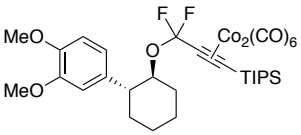
192 (62%)[b, h, i]



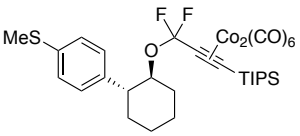
193 (41%)



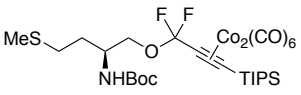
194 (84%)



195 (90%)



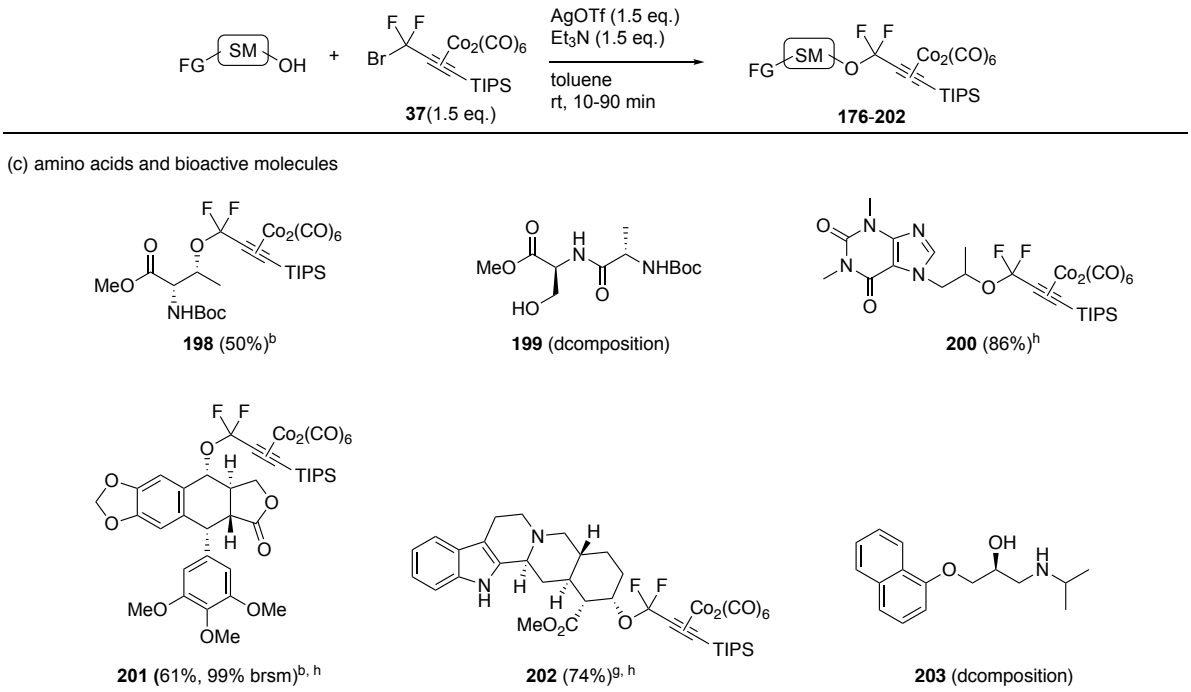
196 (84%)



197 (69%)

[a] $AgNTf_2$ was used instead of AgOTf. [b] DTBMP was used instead of Et_3N. [c] Reagents were used at 2 equiv.
[d] A phenyldifluorobromopropyne dicobalt complex **184** was used. [e] Reagents were used at 1.2 equiv. [f] Benzene was used instead of toluene.
[g] Et_3N was not added. [h] Toluene-CH_2Cl_2 was used. [i] The product was isolated after acetylation of the amino group.

Figure 3-1. 基質適用性



[a] $AgNTf_2$ was used instead of AgOTf. [b] DTBMP was used instead of Et_3N. [c] Reagents were used at 2 equiv.
[d] A phenyldifluorobromopropyne dicobalt complex **184** was used. [e] Reagents were used at 1.2 equiv. [f] Benzene was used instead of toluene.
[g] Et_3N was not added. [h] Toluene-CH_2Cl_2 was used. [i] The product was isolated after acetylation of the amino group.

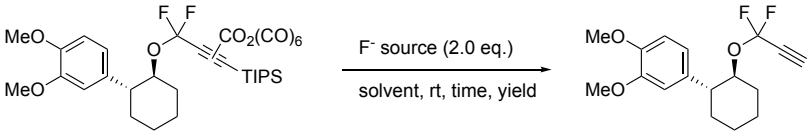
Figure 3-1. 基質適用性 (continued)

第 4 節　脱錯体化の検討

得られたジコバルト錯体は脱錯体化と脱シリル化により，誘導体合成において有用だと期待されるジフルオロプロパルギル基へと変換可能である．Schreiber らはアルキンがシリル基で置換したジコバルト錯体の脱錯体化と脱シリル化が TBAF によって同時に進行することを報告しており [30]，著者もこれに習い末端ジフルオロプロパルギルエーテルへの変換を検討した．

エーテル **195** をモデル基質として，目的のジフルオロプロパルギルエーテル **204** を高い収率で得られる条件を検討した (**Table 3-2**)．Schreiber らの条件と同様に，TBAF を THF 中作用させたところ，基質は分解するのみであった (entry 1)．これは利用した TBAF の THF 溶液中に存在する水分子によって発生するアルコキシドが，生成した末端ジフルオロプロパルギル基を分解したためだと考えられた．そこで無水のフッ化物イオン源として用いられる TBAT を用いて反応を行ったところ，目的物を低収率であるが得ることに成功した (entry 2)．さらに TBAT 同様に無水のフッ化物イオン源として利用される TASF を用いて検討を行ったところ，THF 中では基質が分解するのみであったものの (entry 3)，アセトニトリル中で反応を行うことで中程度の収率で目的のジフルオロプロパルギルエーテルを得ることに成功した (entry 4)．溶媒について DMF，ジクロロメタンについても検討を行ったものの，目的物は低収率か全く得られない結果になった (entry 5, 6)．

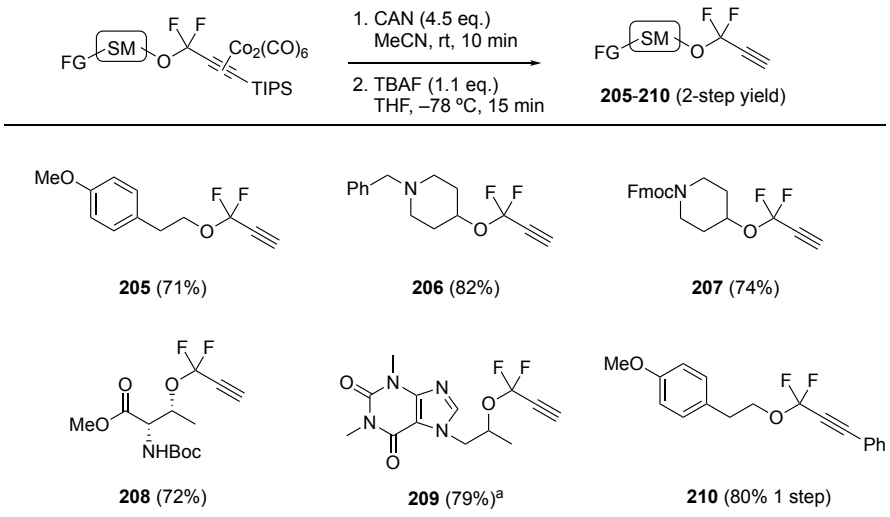
Table 3-2. フッ素化試薬を利用した脱錯体化と脱シリル化の検討



195 **204**

entry	F⁻ source	solvent	time (h)	results
1	TBAF	THF	—	decomposition
2	TBAT	THF	12	**204** (29%)
3	TASF	THF	—	decomposition
4	TASF	MeCN	2	**204** (48%)
5	TASF	DMF	3	**204** (7%)
6	TASF	CH_2Cl_2	—	decomposition

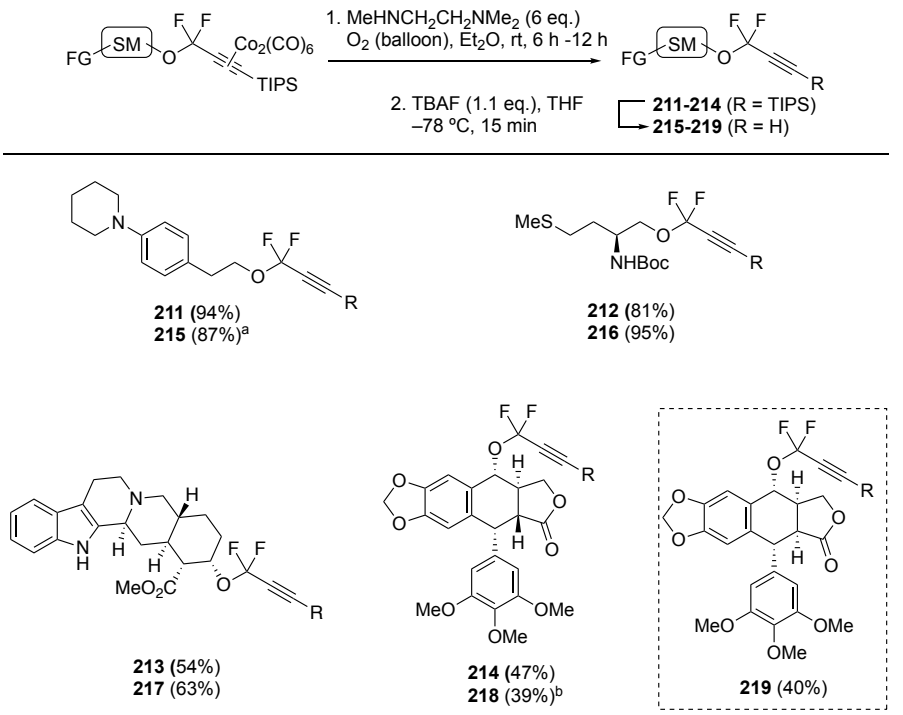
以上の検討から, 1 工程での脱錯体化と脱シリル化の条件を多様な基質に適用させることは難しいと判断した．そこで，脱錯体化と脱シリル化を段階的に行うこととした．検討の結果，CAN を用いて脱錯体化を行ったのちに，低温下で TBAF を作用させることで，様々な基質の脱錯体化と脱シリル化が可能であることを見出した (**Figure 3-2**)．本条件は，メトキシアレーン，３級アミン, 塩基に弱い Fmoc 基を許容し，それぞれ目的のジフルオロプロパルギルエーテル **205**, **206**, **207** を与えた．さらにアミノ酸誘導体 **208** や生物活性分子誘導体 **209** 得ることにも成功した．また，CAN を利用した条件は，フェニル基で置換されたジフルオロプロパルギル基の脱錯体化も可能であり，**210** が得られた．



[a] Acetone was used as a solvent in the first step.

Figure 3-2. CAN を利用した脱錯体化

CAN によって分解が進行する酸化を受けやすい官能基を持つ基質は，*N,N,N'*-trimethylethylenediamine を利用した条件が最適であった[58]．酸素雰囲気下，エーテル中で *N,N,N'*-trimethylethylenediamine を作用させることで，メトキシアレーンより電子豊富なアニリン，スルフィドを持つ基質であっても脱錯体化が高い収率で進行し，目的物 **211**, **212** を与え，これらの脱シリル化は，先と同様に低温条件で TBAF を利用することで **215**, **216** に変換可能であった．また，ヨヒンビン誘導体やポドフィロトキシン誘導体に対しても本条件は適用可能であった．なお，ポドフィロトキシン脱錯体化体 **214** に対して TBAF を用いると，目的物 **218** とは別にエピマー**219** が得られた．



[a] The yield was determined by ^{1}H-NMR using CH_2Br_2 as an internal standard.
[b] An epimer **219** was also obtained.

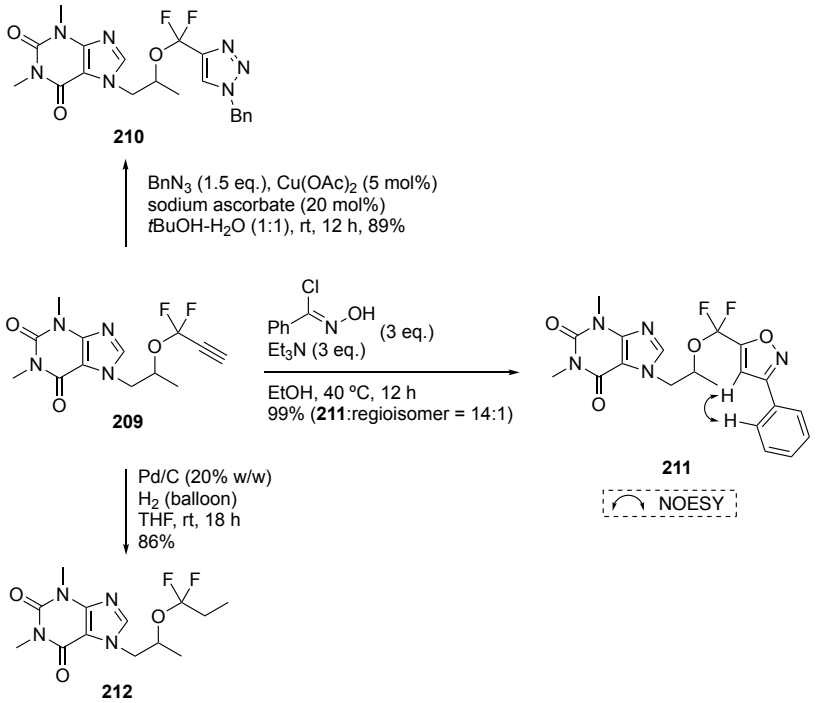
Figure 3-3. ジアミンを利用した脱錯体化の検討

第 5 節　ジフルオロプロパルギルエーテルを利用したジフルオロアルキルエーテル誘導体合成への応用

ジフルオロプロパルギル基は，アルキン部分の多彩な反応性を利用することで誘導体合成へと応用することが可能である．著者はプロキシフィリンより合成されたジフルオロプロパルギルエーテル **209** を利用して，多様なジフルオロエーテル誘導体が合成可能であるか検討を行った (**Scheme 3-2**).

ジフルオロプロパルギルエーテル **209** は，銅触媒存在下，ベンジルアジドと Hüisgen 反応によりトリアゾール **210** を与えた．この時，硫酸銅(II)を利用した場合エステル体の副生が確認されたため，より酸性

の低い酢酸銅(II)を利用した．続いてニトリル *N*-オキシドとの反応を試みた．反応は温和な条件下進行し，イソキサゾール **211** が高い収率で得られた．本反応では２つの位置異性体の生成が考えられるが，生成物の構造は NOESY を用いることで決定し，その位置異性体との選択性は 14:1 であった．またアルキン部分を還元することで，ジフルオロプロピルエーテル **212** へと変換可能であった．先に述べた通り，医薬品もしくはその候補物そのものを化学修飾し，多様な誘導体へと変換する手法は医薬品創製において有用である．



Scheme 3-2. ジフルオロプロパルギルエーテルを利用した誘導体合成

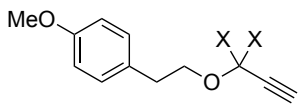
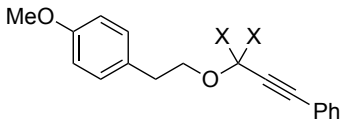
第 6 節　ジフルオロプロパルギルエーテルのラマンスペクトル測定

アルキンの特異なラマン散乱を利用したラマンイメージングへの応用を指向した，フェニルアセチレン，ジイン，アルキニルハライドなど多様なアルキンのラマンスペクトル測定がこれまで報告されている一方で，ジフルオロプロパルギル基のラマン測定は未だ行われてこなかった．著者は，ジフルオロプロパルギル基のさらなる応用適用性の拡張を目指し，ジフルオロプロパルギル基のラマンスペクトル測定を理化学研究所の袖岡有機合成化学研究室に依頼した．

スペクトルから得られたデータの結果を示す (**Table 3-3**)．ラマンスペクトルの強度は，EdU (5-ethynyl deoxyuridine)との相対強度で示した．ジフルオロプロパルギル基由来のラマンスペクトルは対応するプロパルギル基のものと比較して，強度がほとんど変化しない一方で，ラマン分光の波長が短波長側にシフトすることが明らかとなった．すなわち，ジフルオロプロパルギルエーテル **205** は，通常のプロパルギ

ルエーテル **213** と比較して無溶媒中では 28 cm^{-1}，DMSO 中では 20 cm^{-1} ほど長波数側にシフトした．フェニル基で置換されたジフルオロプロパルギルエーテル **210** においても，同様の長波数側へのシフトが観測されている．これらの結果から，ジフルオロプロパルギル基はその大きさをほとんど変えることなくラマンシフトを変化させることができるため，異なるラマンシフトを持つアルキンタグを複数利用したマルチイメージングへの応用が期待される．

Table 3-3. ジフルオロプロパルギル基と対応するプロパルギル基のラマンスペクトルデータ

alkynes	X =	Raman shift (cm^{-1}) Neat / DMSO	Raman intensity vs EdU
	F (**205**)	2147 / 2133	0.14
	H (**213**)	2119 / 2113	0.15
	F (**210**)	2251 / 2248	0.69
	H (**214**)	2241 / 2239	0.63

第 7 節　小括

著者は，独自に見出したジフルオロプロパルギルブロミドジコバルト錯体を利用した，脂肪族水酸基に対する 2-3 工程でのジフルオロプロパルギル化を達成した．錯体 **37** は Et_3N 存在下，AgOTf を作用させることで活性化可能であり, アルコールと反応することでエーテルを形成した. ジコバルト錯体は CAN, もしくは *N,N,N'*-trimethylethylenediamine により脱錯体化され，続く脱シリル化によって末端ジフルオロプロパルギルエーテルへと変換された．

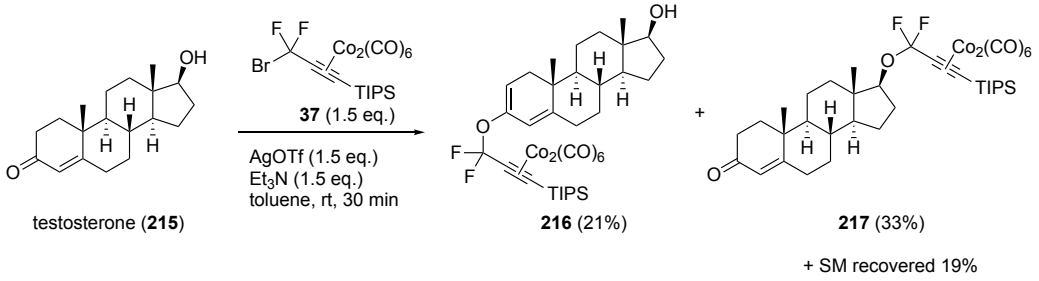
得られたジフルオロプロパルギルエーテルは，アルキンの反応性を利用することで多様な誘導体へと変換可能であった．さらに，ジフルオロプロパルギルエーテルのラマンスペクトルの測定を行い，通常のプロパルギル基とは異なるピークシフトを持つことを明らかとした．

今回開発反応は，前例のない高いアルコール選択性を持つニコラス反応である．これまでニコラス反応の化学選択性を制御した例は，Jaouen らの例のみであり，さらに彼らの反応は基質適用性についての言及がほとんどなかった．それに対して著者が開発した幅広い基質適用性を持つ，初の一般性の高い化学選択的なニコラス反応であると言える．

第 4 章　新規ジフルオロプロパルギルビニルエーテル合成法の開発と含フッ素化合物合成への応用

第 1 節　発見の経緯と反応条件最適化

ジフルオロプロパルギルブロミドジコバルト錯体 **37** は，多様な官能基存在下においてもアルコール選択的に反応し，対応するエーテルを与えた．一方で，アルコールとケトンを併せ持つ testosterone (**215**)に対し本条件を作用させたところ，エーテル **217** とは別にビニルエーテル **216** が得られることが明らかとなった (**Scheme 4-1**)．ケトンに対しフルオロアルキル基を導入する反応は，市川や柴田らによってすでに報告されているが [73]，ジフルオロプロパルギル基を導入する反応は未だ報告されていない．また，一般的にニコラス反応では，カルボニルのα位と反応することが知られているが [50]，今回の反応ではそのような生成物は全く得られなかった．著者はこのような特異な反応性に興味を持ち，さらなる反応の検討を行った．

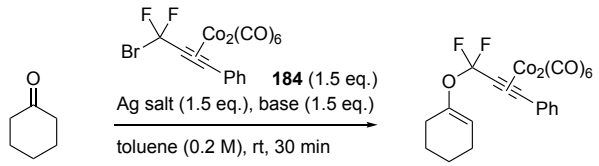


Scheme 4-1. ケトンに対する *O*-ジフルオロプロパルギル化

Cyclohexanone (**218**)をモデル基質，フェニル基で置換されたジフルオロプロパルギルブロミドジコバルト錯体 **184** を試薬として, もっとも良い収率でビニルエーテル **219** が得られる条件の検討を行った (**Table 4-1**)．エーテル化反応で最適とされた AgOTf を Et_3N 存在下用いる条件では，目的物 **219** の収率は中程度にとどまった (entry 1)．続いて塩基としてピリジンを用いたが，収率は低下した (entry 2)．塩基が銀塩の活性を低下させていると考え，より嵩高い塩基である iPr_2NEt を用いたところ，収率の向上が見られた (entry 3)．同じく嵩高い塩基である DTBMP は，iPr_2NEt と同程度の収率を与えた (entry 4)．続いてアミジン塩基である DBU, グアニジン塩基である TMG を用いたが，目的物は得られないか低収率で得られるにとどまった (entry 5, 6)．また，強塩基である *t*BuOK は目的物を全く与えなかった (entry 7)．これらの結果から，塩基を変更することでこれ以上収率を向上させることは困難だと考え，銀試薬を $AgNTf_2$ へと変更したところ, 目的物を高い収率で得ることに成功した (entry 8). $AgNTf_2$ が良い収率を与えた理由は，アルコールと比較してケトンの求核性は低いことから，錯体 **184** をより活性化するのにより強いルイス

酸が必要だったためだと考えられる．

Table 4-1. 反応条件最適化



218 **219**

entry	Ag salt	base	yield[a]
1	AgOTf	Et_3N	57%
2	AgOTf	pyridine	28%
3	AgOTf	iPr_2NEt	71%
4	AgOTf	DTBMP	65%
5	AgOTf	DBU	0%
6	AgOTf	TMG	33%
7	AgOTf	*t*BuOK	0%
8	$AgNTf_2$	iPr_2NEt	100% (95%)[b]

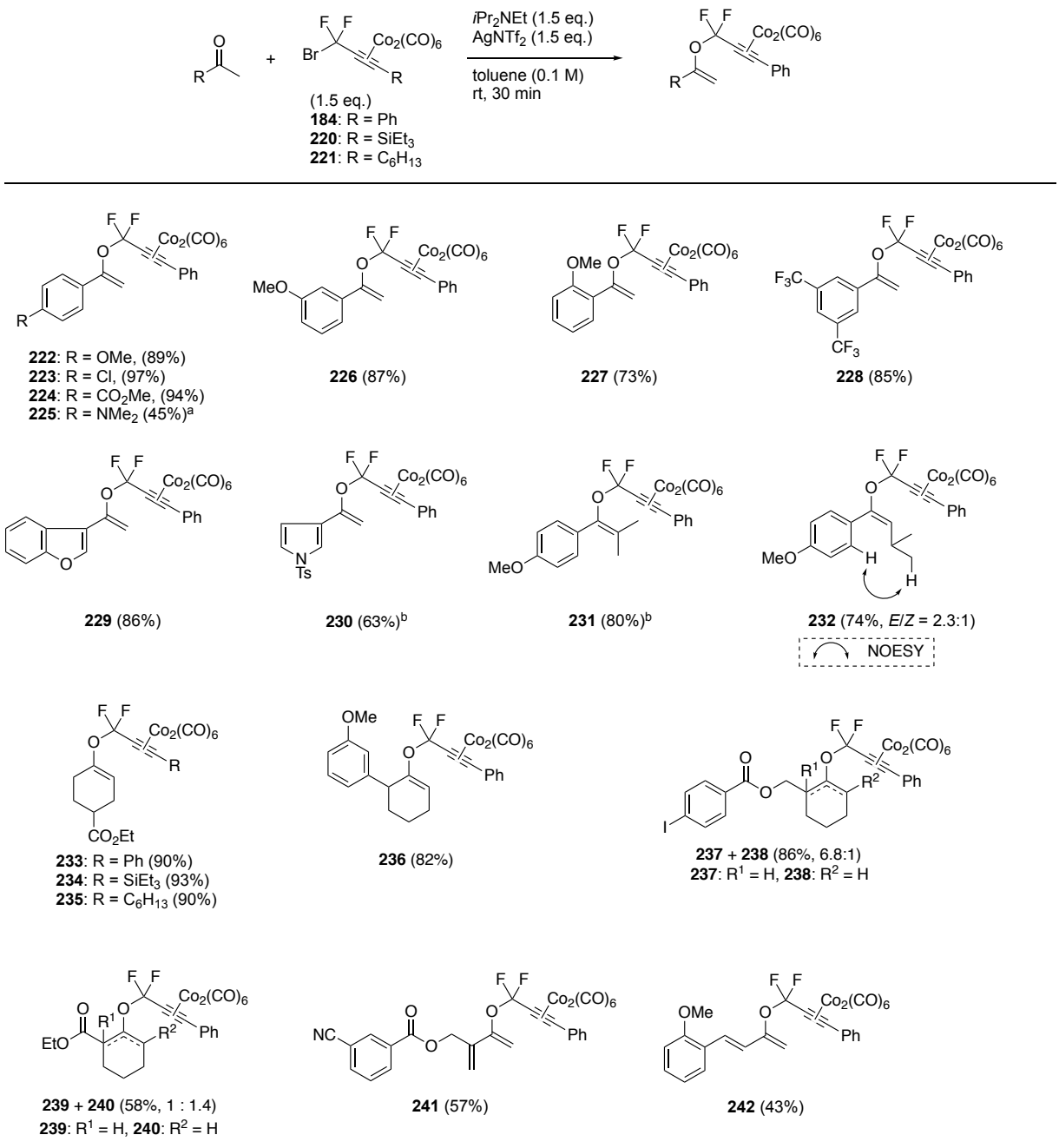
[a] Yield was determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard.
[b] isolated yield

第 2 節　ケトンとアルデヒドのエーテル化および生成したビニルエーテルの脱錯体化

得られた反応条件を用い，基質適用性について検討を行った．まずアセトフェノン誘導体を用い芳香環上の置換基を検討したところ，本反応は 4 位にメトキシ基，クロロ基，エステル基を持つ基質を許容し，それぞれ **222**, **223**, **224** を与えた．その一方でジアミノ基を持つ基質では，反応は進行したものの生成物 **225** は不安定であり，精製後すぐに分解する生成物であった．続いて芳香環上の 3 位及び 2 位にメトキシ基を持つアセトフェノンについて検討を行ったところ，若干の収率の低下が見られるものの，それぞれ目的物 **226**, **227** を得ることができた．強い電子求引基を持つトリフルオロメチル基を持つ基質についても収率の低下は見られず **228** が生成し，ヘテロ芳香族である 3-アセチルベンゾフェノン，*N*-Ts 3-アセチルピロールにおいてもビニルエーテル化合物 **229**, **230** が得られた．イソブチロフェノンを基質として用いた場合，4 置換オレフィン **231** が得られた．この時塩基として DTBMP を用いることで，反応が完結した．DTBMP は嵩高い塩基であるため，銀試薬の活性を損ないにくく，ケトンの酸素原子の求核性が低い基質に対して反応を行う場合は有効だと考えられる．イソバレリルフェノンのエーテル化では，*E/Z* 異性体の混合物 **232** が得られた．両異性体は分離不可の混合物であり，生成比は ^{1}H-NMR より決定した．また，NOESY を利用することで異性体の構造を決定した．

続いて ethyl 4-oxocyclohexanecarboxylate を用いて錯体 **184** の置換基について検討を行ったところ，本反

応はフェニル基だけでなく，トリエチルシリル基やヘキシル基のジフルオロプロパルギルブロミドジコバルト錯体 **220**, **221** を用いても反応が進行し，それぞれビニルエーテル **233**, **234**, **235** を与えた．続いて非対称ケトンについて検討を行った．2-(2-methoxyphenyl)cyclohexanone は，単一のエーテル **236** を選択的に与えた．それに対し，2-(hydroxymethyl) cyclohexanone 誘導体を基質として用いると，**237** と **238** が 6.8:1 の比率で得られた．さらに ethyl 2-oxocyclohexanecarboxylate を基質とした場合，4 置換オレフィンと 3 置換オレフィンの生成比が逆転した (**239**:**240** = 1:1.4)．このことから，非対称ケトンの脱プロトン化位置は立体障害及び引き抜かれる水素の pKa に依存することが示唆された．エノンを基質とした場合には対応するジエン **241**, **242** が得られた．



[a] **255** was unstable. [b] DTBMP was used instead of iPr$_2$NEt.

Figure 4-1. 基質適用性

脱錯体化は，第 3 章第 4 節同様 CAN もしくは，*N,N,N'*-trimethylethylenediamine を用いることで可能であった．電子豊富な芳香環を持つ基では，*N,N,N'*-trimethylethylenediamine が良い収率を与える傾向があった．得られたジフルオロプロパルギルビニルエーテルは-20 ^{o}C で保存することで分解しなかった．

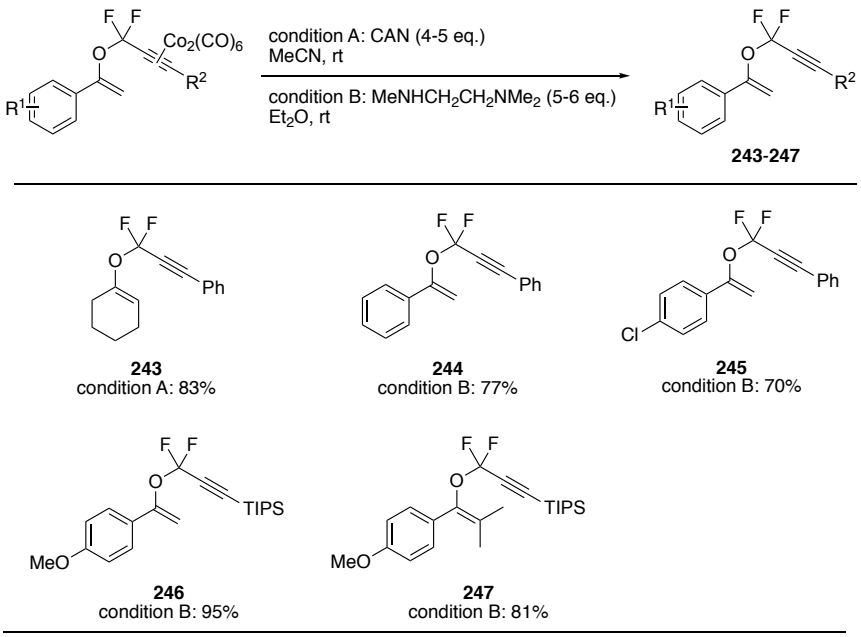


Figure 4-2. 脱錯体化の基質適用性

続いて基質としてアルデヒドが利用可能か検討を行った．塩基として DTBMP を用いることでアルデヒドもエーテル化に利用可能であり，対応するビニルエーテルを与えた (**Figure 4-3**)．驚くべきことに，ジコバルト錯体の立体的な嵩高さにも関わらず，本反応は Z 選択的に進行した．フェニルアセトアルデヒドの 4 位に置換基を導入した誘導体では，置換基によりその比率は変化するものの，高い Z 選択性で反応が進行した (**248-250**)．その一方で，(3-methoxyphenyl)acetoaldehyde では *Z* 体の比率が減少し(**251**, *Z*:*E* = 6:1)，(2-methoxyphenyl)acetoaldehyde はさらに低下した (**252**, *Z*:*E* = 2:1)．Hydrocinnamaldehyde は，対応するビニルエーテル **253** を高い Z 選択性で与えた．エステル誘導体やフタルイミドなど電子求引基を持つ基質においてもまた，その Z:E 比は減少した (**254**, **255**)．なお，一部の基質については反応後に脱錯体化を行い，得られたジコバルト錯体が実際にジフルオロプロパルギルビニルエーテルへと導けることを示した．

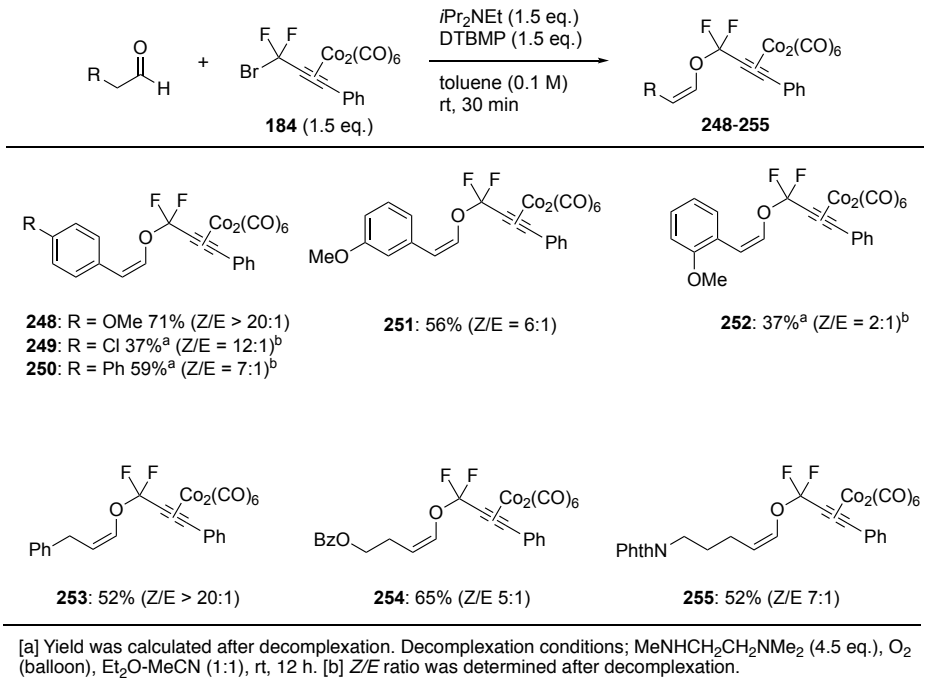


Figure 4-3. アルデヒドの基質適用性

高いＺ選択性は中間体の配座と脱プロトン化により説明できる．本反応では，カルボニル基に対し，錯体が配位した後に脱プロトン化が進行することで生成物が得られると考えられる．すなわち，本反応では中間体の配座が重要になるが，オキソニウムイオン中間体の配座は σ → π*相互作用により構造が安定化され，その後脱プロトン化が進行することでＥ体が優先して生成したと考えられる [74].

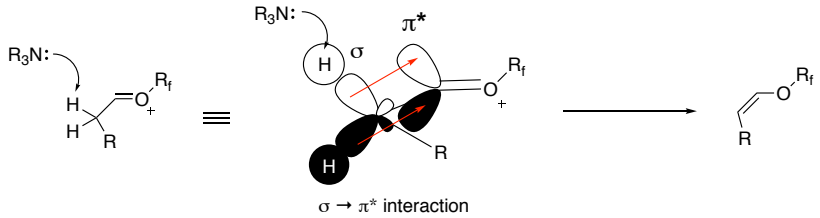
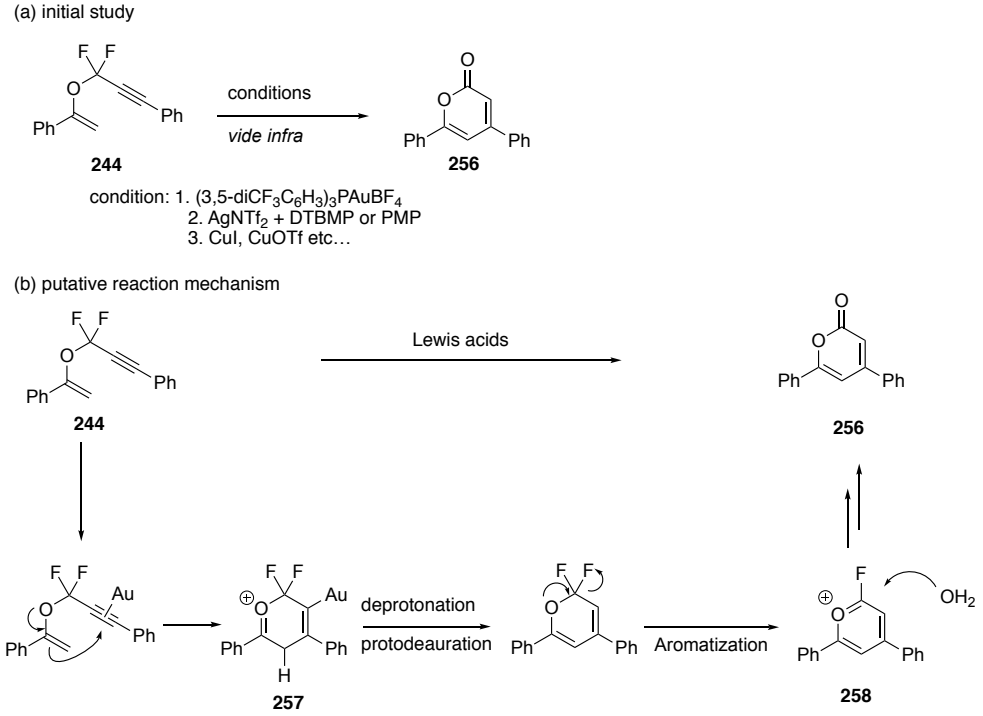


Figure 4-4. 選択性発現の推定メカニズム

第３節 ジフルオロプロパルギルビニルエーテルを利用した含フッ素化合物合成への応用

まず，ルイス酸を利用した酸性条件の検討を行なった．アセトフェノンより得られた **244** に対して様々なルイス酸を検討したが，フッ素化合物は全く得られず，ピロン **256** が得られるのみであった (**Scheme 4-2b**)．ピロンが得られるメカニズムについて次の経路を仮定した (**Scheme 4-2b**)．すなわち，オキソニウムイオン中間体 **257** 生成後，脱プロトン化が進行し，その後フッ素が脱離することでピリリウムイオン

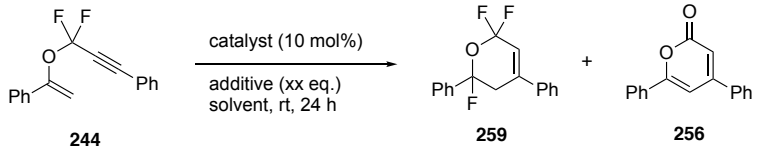
258 が生成，これに水が付加した事で **256** が得られたと考察した．



Scheme 4-2. ルイス酸を用いた環化反応初期検討とピロン生成メカニズム

そこで，$AgNTf_2$ を酸触媒とし，さらにオキソニウム中間体をトラップする目的で，フッ化水素トリエチルアミン錯体を添加したところ，これまで合成法がほとんど報告されていないトリフルオロピラン **259** を中程度の収率で得ることに成功した (**Table 4-2**, entry 1)．そこで，ピラン **259** が良い収率で得られる条件の検討を行った．銀触媒は $AgNTf_2$ を用いる条件が最適であった．そこで，他のフッ素化剤についても検討を行ったところ，HF･DMPU ではピロン **256** が得られるのみであり，塩基性フッ素化剤である TASF, TBAT については反応が全く進行しなかった．

Table 4-2. 銀触媒を用いた環状フルオロエーテル合成の条件最適化



entry	catalyst	additive	yield (%)[a] **259** : **256** : SM
1	$AgNTf_2$	$3HF{\bullet}Et_3N$ (0.4 eq.)	48 : 42 : 0 (isolated)
2[b]	$AgBF_4$	$3HF{\bullet}Et_3N$ (0.8 eq.)	25 : 36 : 18
3[b]	$AgSbF_6$	$3HF{\bullet}Et_3N$ (0.8 eq.)	17 : 12 : 23
4	$AgNTf_2$ + DTBMP	HF•DMPU (1.2 eq.)	only **256**
5	$AgNTf_2$	TASF (1.2 eq.)	no reaction
6	$AgNTf_2$	TBAT (1.2 eq.)	no reaction

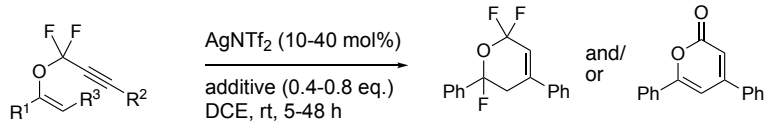
[a] Yiled Determined by ^{1}H-NMR using CH_2Br_2 as an internal standard.
[b] 20 mol% catalyst was used.

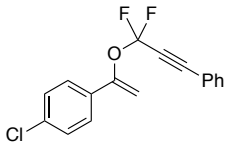
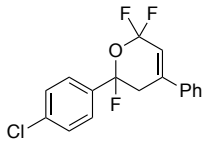
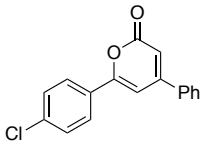
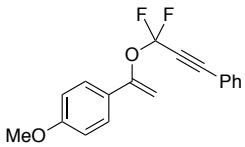
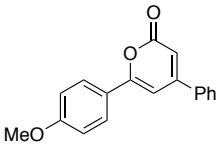
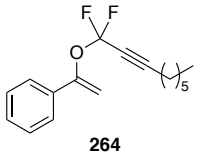
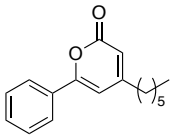
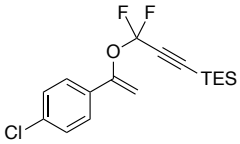
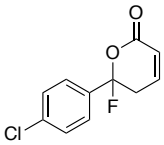
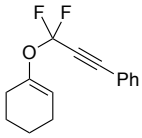
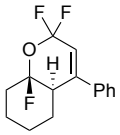
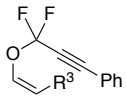
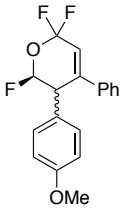
続いてプロパルギルビニルエーテルの置換基について検討を行った (**Table 4-3**). フェニル基の 4 位をクロロ基へと変更した **245** では，目的のトリフルオロピラン **260** が高い収率で得られ，ピロンの生成はほとんど確認なかった．その一方で，メトキシ基を持つ基質 **262** では，トリフルオロピランは全く得られず，ピロン **263** が得られるのみであった．またアルキンの置換基について検討を行った．ヘキシル基で置換した化合物ではピロン **265** のみが得られ，TES 基で置換した化合物 **266** では，反応混合物の ^{1}H-NMR 及び ^{19}F-NMR において目的物 **267** と考えられるピークの検出に成功したものの，単離することはできなかった．これは，**267** が高い揮発性を持つためだと考えられる．アセトフェノン誘導体ではなく，シクロヘキサノンから得られたジフルオロプロパルギルビニルエーテル **243** もまた，トリフルオロピランを含む 2 環性骨格化合物 **268** へと導くことが可能であった．

アルデヒドより得られたプロパルギルビニルエーテル **269** もまた，トリフルオロピランへと導くことが可能か検討を行った．4 位にメトキシ基を持つ基質では，反応が進行し目的物であるトリフルオロピラン **270** を 2 つの異性体混合物を得ることに成功した．

これら得られたトリフルオロピランは，-20 ºC 条件においても徐々に分解し，ピロンへと変換される化合物群であった．

Table 4-3. 銀触媒を利用したプロパルギルクライゼン転位の基質一般性

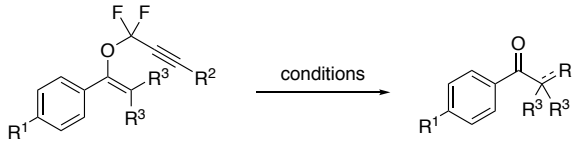


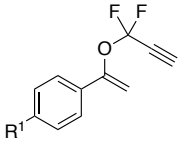
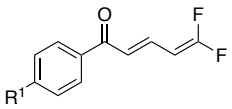
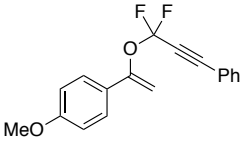
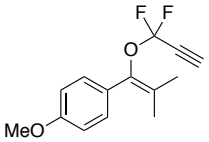
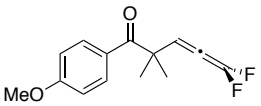
entry	substrates	products (yield)
1	 **245**	 **260** (73%)  **261** (4%)
2	 **262**	 **263** (only observed)
3	 **264**	 **265** (only observed)
4	 **266**	 **267** (not detected)*
5	 **243**	 **268** (79%, *dr* = 2.5:1)
6	 **269**: R^3 = 4MeO-C_6H_4	 **270** (73%, *cis*:*trans* = 2.2:1)

続いて熱的条件で反応が進行するか検討を行った．プロパルギルビニルエーテルのアルキンの置換基が水素の基質 **271** の際に，ジフルオロジエノン **272** が得られることを見出した．これは，[3,3]-シグマト

ロピー反応が進行した後に、異性化が起こる事で得られたと考えられる．本反応は，フェニル基の 4 位にメトキシ基を持つものでも進行し，**274** が得られた一方で，クロロ基を持つものでは，不安定なジフルオロジエノン **276** が低収率で得られるのみであった．**276** は不安定な化合物であり，単離後しばらくして分解が確認された．アルキンの置換基がフェニル基の基質 **277** では，熱的反応条件では目的物が全く得られなかった．このことから，アルキン部位に置換基が存在すると，立体障害により反応が進行しなくなると考えられる．また，イソブチロフェノンから得られたジフルオロプロパルギルビニルエーテル **278** では，Claisen 転位後の異性化が進行せず 1,1-ジフルオロアレン **279** が生成した．ジフルオロアレンは市川らにより合成法が報告されているが，著者の例は新たなジフルオロアレン合成法になるといえる[75].

Table 4-4. 熱的条件によるプロパルギルクライゼン転位の検討



entry	substrates	conditions	products
1 2 3	 **271**: R^1 = H **273**: R^1 = OMe **275**: R^1 = Cl	DTBMP (20 mol%) toluene, 80 ºC	 **272**: R^1 = H (63%) **274**: R^1 = OMe (72%) **276**: R^1 = Cl (<13%)
4	 **277**	toluene, 80-110 ºC	decomposition
5	 **278**	toluene, 100 ºC, 2 d 86%	 **279** (86%)

第 4 節　小括

著者は，ジフルオロプロパルギルブロミドジコバルト錯体とケトンの酸素原子が反応し，フルオロビニルエーテルが得られることを新たに見出した．得られたエーテルは脱錯体化により，様々な含フッ素化合物へと変換可能なジフルオロプロパルギルビニルエーテルへと変換可能であった．ケトンの酸素原

子に対するニコラス反応は前例がなく，プロパルギル位のフッ素がニコラス反応に大きな影響を与えることを支持する結果となった.

結論

著者はニコラス反応を利用したプロパルギル化に焦点を当て，強酸条件の緩和及び前例のない反応性を獲得したニコラス反応の研究を行なった．そして，温和な条件下での芳香族生物活性小分子の 2 工程プロパルギル化を開発し，さらに特異な反応性を持つジフルオロプロパルギルブロミドジコバルト錯体を利用したアルコール及びケトンのジフルオロプロパルギル化を達成した．

第 1 章

プロパルギルジコバルトヘキサカルボニル錯体テトラフルオロボレート塩を用いる際に最も問題であった超強酸である HBF_4 の発生を，固体塩基である炭酸セシウムを添加することで中和し，多様な官能基を持つ生物活性分子の芳香環に対する官能基化を達成した．ジコバルト錯体の脱錯体化は，低温下 $TEMPOBF_4$ を作用させることで達成し，目的のプロパルギル基へと変換可能であった．得られた誘導体は，構造活性相関研究のみならずアルキンを生かした標的分子探索への応用にも利用可能である．また，小さなプロパルギル基は活性を阻害しにくいことから，長いリンカーを持つアルキンタグとは異なる機能性を持つことが期待される．

第 2 章

第 1 章では，発生した HBF_4 を塩基で中和することで温和な反応条件を実現したが，そもそも触媒量の酸を用いて活性化する試薬が開発できれば，より温和な反応条件でのニコラス反応が実現可能だと考えられた．そこで，Yu や浅尾らにより報告された金触媒で活性化される *o*-alkynylbenzoate とニコラス試薬を組み合わせた試薬を新たに開発し，触媒的なニコラス反応を達成した．得られた試薬は，第 1 章の条件では官能基化が難しかった，非常に酸や塩基に弱い官能基を持つ芳香族化合物であっても，誘導体を得ることに成功した．さらに，脱錯体化試薬として TBAF を新たに用いることで，one-pot での 2 工程プロパルギル化を達成した．

第 3 章

新規含フッ素化合物合成法の開発と，フッ素原子がニコラス反応に与える影響に興味を持ち，ジフルオロプロパルギルブロミドジコバルト錯体を合成，これを利用することでアルコールに対するジフルオロプロパルギル化を達成した．見出した錯体は Et_3N 存在下，AgOTf を作用させることで活性化可能であり，アルコールと反応することで対応するエーテルを与えた．本反応は高い化学選択性で進行し，第一級か

ら第三級アミン，フェノール，スルフィド，オレフィン，電子豊富な芳香環存在下でもエーテル化が優先して進行した．このような高い化学選択性は，通常のニコラス反応では見られない，ジフルオロプロパルギルブロミドジコバルト錯体特有の反応である．また，脱錯体化は CAN もしくはトリメチルエチレンジアミンを利用することで達成され，アルキンが TIPS 基で保護されている場合には，TBAF を低温下作用させることで除去可能であった．

得られたジフルオロプロパルギルエーテルは，多様なジフルオロエーテル合成へと展開可能であった．例えば，Hüisgen 環化を利用したトリアゾール合成や，ニトリルオキシドを用いることでイソキサゾールへと変換可能であった．さらに，ジフルオロプロパルギルエーテルのラマンスペクトルを測定することで，ジフルオロプロパルギル基もまた，ラマンイメージングに有用なタグ分子になりうることを明らかにした．ジフルオロプロパルギルエーテルは，含フッ素医薬品合成やケミカルバイオロジー研究に有用であることを示すことに成功した．

第 4 章

著者はジフルオロプロパルギルブロミドジコバルト錯体が，アミン塩基である iPr$_2$NEt 存在下，銀試薬としてシルバートリフリックイミドを用いることでケトンと反応し，ビニルエーテルを与えることを見出した. 得られたビニルエーテルは CAN やトリメチルエチレンジアミンにより前例のないジフルオロプロパルギルビニルエーテルへと変換可能であった．ジフルオロプロパルギルビニルエーテルは置換基と反応条件により得られる生成物が変化し，熱的条件では，ジフルオロジエノンが，酸触媒条件ではトリフルオロピランが生成した．これらは，著者が初めて合成した構造単位であり，ジフルオロプロパルギルビニルエーテルが新規含フッ素骨格合成に有用な前駆体であることが示唆された．

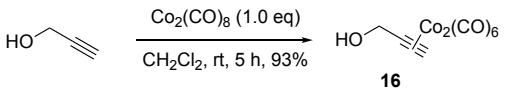
実験項

General Procedure

All reactions were carried out under an argon atmosphere with dehydrated solvents under anhydrous conditions, unless otherwise noted. Dehydrated THF and CH_2Cl_2 were purchased from Kanto Chemical Co., Inc. Other solvents were dehydrated and distilled according to standard protocols. Reagents were obtained from commercial suppliers, unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) carried out on Silica gel plates (Merck Kieselgel 60 F254) or Silica gel plates (Fuji Silysia Chemical Co., Ltd.). Column chromatography was performed on Silica gel 60N (Kanto Chemical Co., Inc., spherical, neutral, 63-210 μm) Silica gel 60 (Merck, 63-200 μm) or CHROMATOREX® -NH (FUJI SILYSIA CHEMICAL LTD., spherical, basic, 40-75 μm or 75-200 μm). Flash column chromatography was performed on Silica gel 60N (Kanto Chemical Co., Inc., spherical, neutral, 40-50 μm). High performance column chromatography was performed on Mightysil Si60 250-20 mm (Kanto Chemical Co., Inc., spherical, neutral, 5 μm). All melting points were determined with Yazawa Micro Melting Point BY-2 or AS ONE ATM-02 and are uncorrected. IR spectra were recorded on a JASCO FT/IR-410 Fourier Transform Infrared Spectrophotometer or JASCO *FT/IR*-4100 Fourier Transform Infrared Spectrophotometer. ^{1}H-NMR (400 and 600 MHz) and ^{13}C-NMR spectra (100 and 150 MHz) and ^{19}F-NMR spectra (560 MHz) were recorded on JEOL JNM-AL-400, JEOL JNM-ECA-600 spectrometers, respectively. For ^{1}H-NMR spectra, chemical shifts (δ) are given from TMS (0.00 ppm) or CHCl3 (7.26 ppm) in $CDCl_3$, CHD_2COCD_3 (2.05 ppm) in CD_3COCD_3 and CHD_2SOCD_3 (2.50 ppm) in CD_3SOCD_3 as internal standards. For ^{13}C-NMR spectra, chemical shifts (δ) are given from $CDCl_3$ (77.0 ppm), CD_3COCD_3 (29.84 ppm and 206.26 ppm) and CD_3SOCD_3 (39.52 ppm) as internal standards. ^{19}F-NMR spectra, chemical shifts (δ) are given from C_6F_6 (–164.9 ppm) as an internal standard. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sept = septet, dd = double doublet, dt = double triplet, ddt = double double triplet, tt = triple triplet, td = triple doublet, qd = quartet of doublet, m = multiplet, br = broad. EI mass spectra were recorded on JEOL JMS-DX303, JEOL JMS-700 and JEOL JMS-T 100 GC. FAB mass spectra were recorded on JEOL JMS-700. ESI mass spectra were recorded on Thermo Scientific Exactive Mass Spectrometer or JEOL JMS-T100LP. HPLC was performed by Mightysil Si60 250-20 mm (Kanto Chemical Co., Inc., spherical, neutral, 5 μm), Gilson Model 305, 306 as pomps and Gilson Model 118 as a detector at 254 nm. Microwave irradiation was performed by using a DiscoverTM system (CEM Japan Inc). GPC was performed on SHIMADZU LC-64D as a pump, SHIMADZU RID-10A as a refractive index detector, Prominence SPD-20A as a UV/VIS detector, and SHODEX GPC H-2001L as a column.

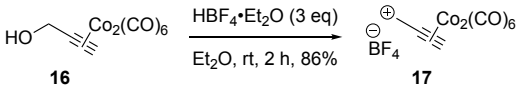
<Chapter 1>

Synthesis of (prop-2-yn-1-ol)dicobalt hexacarbonyl (16)



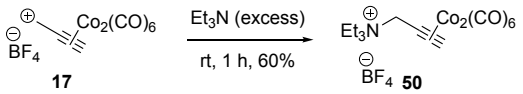
A mixture of prop-2-yn-1-ol (0.90 mL, 15.6 mmol) and $Co_2(CO)_8$ (5.22 g, 15.6 mmol) in CH_2Cl_2 (38 mL) was stirred at room temperature for 5 h. The solution was concentrated in vacuo. Column chromatography of the residue on silica gel (AcOEt : Hexane = 1 : 4) yielded cobalt complex **16** as a red solid (4.76 g, 13.9 mmol, 93%).

Synthesis of hexacarbonyl(2-propynylium)dicobalt tetrafluoroborate (17)



To a solution of HBF_4•Et_2O (1.10 mL, 6.99 mmol) in Et_2O (6.0 mL) was added a solution of cobalt complex **14** (798 mg, 2.33 mmol) in Et_2O (5.5 mL) dropwise over 15 min. The resulting mixture was stirred at room temperature for 2 h, causing precipitation of a red solid. The solid was filtered and rinsed three times with ether to remove fluoroboric acid. After vacuum drying, complex **17** was obtained as a fine red powder (828 mg, 2.01 mmol, 86%).

Synthesis of ammonium salt 50



To a suspension of complex **17** (100 mg, 0.243 mmol) in CH_2Cl_2 (4.0 mL) was added Et_3N (2.0 ml). The reaction mixture was stirred at room temperature for 1 h and then concentrated in vacuo. The residue was purified by silica gel column chromatography (MeOH : $CHCl_3$ = 1 : 4) to give complex **50** (74.5 mg, 0.145 mmol, 60%) as a red amorphous. **00**: red amorphous; IR (neat): 2055 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3COCD_3): δ 7.06 (s, 1H), 5.22 (s, 2H), 3.69 (q, J = 7.1 Hz, 6H), 1.47 (t, J = 7.1 Hz, 9H); ^{13}C-NMR (100 MHz, CD_3COCD_3): δ 199.7, 77.2, 75.7, 60.6, 53.6, 8.1; HRMS (ESI): calcd for $C_{15}H_{18}NO_6Co_2$ (M^+): 425.9793, found: 425.9778.

Functionalization of aromatic molecules

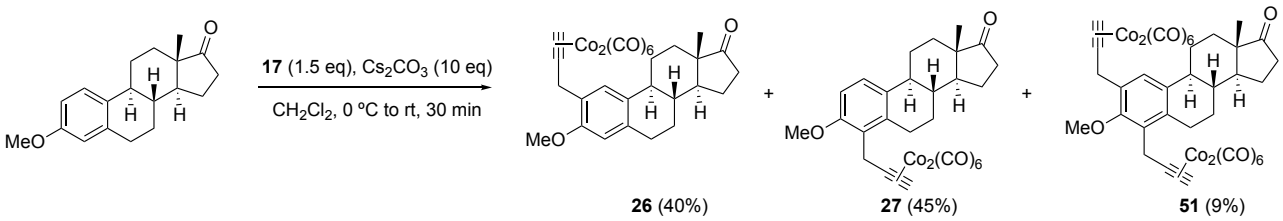
General procedure for the functionalization of aromatic molecules

Procedure A: To a suspension of complex **13** (0.150 mmol) and Cs_2CO_3 (1.0 mmol) in CH_2Cl_2 (1.0 mL) was added neat substrate (0.100 mmol) or a solution of substrate (0.100 mmol) in CH_2Cl_2 (1.0 mL) at -20 °C or 0 °C. The solution was allowed to warm to 0 °C or room temperature and stirred until completion of the reaction as monitored by TLC. The reaction mixture was diluted with water (2.0 mL) and extracted with CH_2Cl_2 (4.0 mL × 2). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography or HPLC.

Procedure B: The suspension of complex **17** (0.150 mmol), Cs_2CO_3 (0.100 mmol) and substrate (0.100 mmol) in CH_2Cl_2 (2.0 mL) was heated at 40 °C by microwave irradiation. After reaction was complete, the mixture was diluted with water (2.0 mL) and extracted with CH_2Cl_2 (4.0 mL × 2). The combined oragnic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography.

Procedure C: To a suspension of complex **17** (0.150 mmol) in CH_2Cl_2 (1.0 mL) was added a solution of substrate (0.100 mmol) in CH_2Cl_2 (1.0 mL) at room temperature. The reaction was stirred until completion of the reaction as monitored by TLC. The resulting mixture was diluted with water (2.0 mL) and extracted with CH_2Cl_2 (4.0 mL × 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography.

Functionalization of *O*-methyl estrone (25)



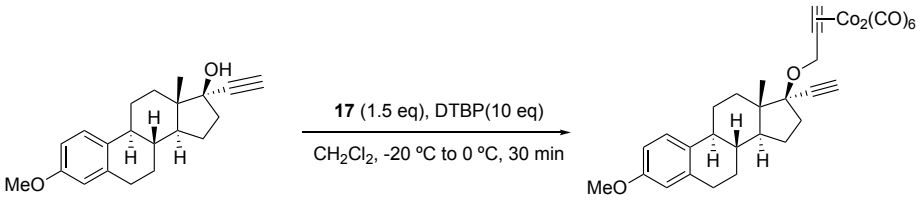
The procedure A was followed with a reaction time of 30 min at room temperature to provide a mixture (57.8 mg) of **51** (6.60 μmol, 7%) and **26** (0.0451 mmol, 45%) and **27** (0.0397 mmol, 40%). The product ratio was determined by ^{1}H-NMR. The analytical samples were obtained by HPLC separation (250-20 mm, AcOEt : Hexane = 15 : 85, 9 mL/min).

51 (retention time: 11.7 min): red oil; IR (neat): 2017 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.18 (s, 1H), 6.09 (s, 1H), 5.92 (s, 1H), 4.19 (s, 2H), 4.17 (s, 2H), 3.81 (s, 3H), 3.02 (dd, *J* = 17.1 Hz, 5.4 Hz, 1H), 2.90-2.81 (m, 1H), 2.51 (dd, *J* = 18.4 Hz, 8.6 Hz, 1H), 2.36 (br s, 1H), 2.21-2.04 (m, 4H), 1.97 (d, *J* = 9.6 Hz, 1H), 1.65-1.43 (m, 6H), 0.88 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 220.7, 199.7, 154.3, 136.4, 134.8, 131.9, 130.2, 126.5, 96.2, 95.2, 74.2, 61.4, 50.5, 47.9, 44.3, 37.4, 35.9, 34.7, 31.6, 31.2, 27.0, 26.4, 25.9, 21.6, 13.7; HRMS (ESI): calcd for $C_{37}H_{27}O_{14}Co_4$ ([M-H]$^-$): 930.8723, found: 930.8743.

26 (retention time: 13.5 min): red oil; IR (neat): 2018 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.07 (s, 1H), 6.57 (s, 1H), 6.00 (s, 1H), 4.07 (s, 2H), 3.79 (s, 3H), 2.89-2.86 (m, 2H), 2.50 (dd, *J* = 19.1 Hz, 8.5 Hz, 1H), 2.40-2.37 (m, 1H), 2.23-1.95 (m, 4H), 1.64-1.36 (m, 6H), 0.91 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 221.0, 199.9, 155.0, 136.4, 131.5, 127.6, 126.0, 110.6, 98.4, 73.7, 54.8, 50.4, 48.0, 43.8, 38.4, 35.9, 33.9, 31.6, 29.6, 26.6, 25.8, 21.6, 13.8; HRMS (ESI): calcd for $C_{28}H_{27}O_8Co_2$ ([M+H]$^+$): 609.0364, found: 609.0361.

27 (retention time: 14.3 min): red oil; IR (neat): 2014 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.19 (d, *J* = 8.8 Hz, 1H), 6.71 (d, *J* = 8.8 Hz, 1H), 5.94 (s, 1H), 4.26 (d, *J* = 15.1 Hz, 1H), 4.14 (d, *J* = 15.1 Hz, 1H), 3.81 (s, 3H), 3.06 (dd, *J* = 16.7 Hz, 5.8 Hz, 1H), 2.93-2.84 (m, 1H), 2.51 (dd, *J* = 18.5 Hz, 8.8 Hz, 1H), 2.39 (br s, 1H), 2.27 (br s, 1H), 2.20-2.05 (m, 4H), 1.66-1.40 (m, 6H), 0.90 (s, 3H);^{13}C-NMR (100 MHz, $CDCl_3$): δ 220.9, 199.8, 155.0, 135.5, 132.5, 126.7, 124.8, 107.8, 95.9, 73.6, 54.7, 50.5, 47.9, 44.2, 37.7, 35.9, 31.6, 29.8, 27.0, 26.5, 26.1, 21.6, 13.8; HRMS (ESI): calcd for $C_{28}H_{26}O_8Co_2Na$ ([M+Na]$^+$): 631.0184, found: 631.0184.

Functionalization of mestranol (45) using *2,6*-di-*tert*-butylpyridine as a base

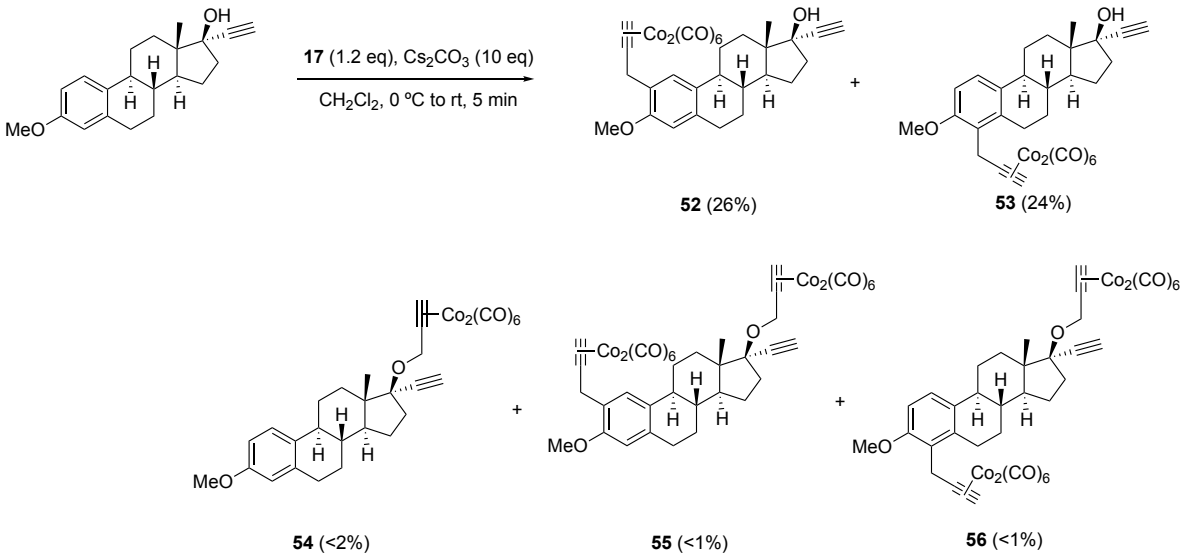


54 (58%)

The procedure A was followed, employing *2,6*-di-*tert*-butylpyridine instead of Cs_2CO_3 as a base, with a reaction time of 30 min. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 20) to provide **54** (36.7 mg, 0.0579 mmol, 58%) and recovered **45** (11.2 mg, 0.0361 mmol, 36%).

54: red oil; IR (neat): 2033 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.21 (d, *J* = 8.6 Hz, 1H), 6.71 (dd, *J* = 8.6 Hz, 2.6 Hz, 1H), 6.63 (d, *J* = 2.6 Hz, 1H), 5.99 (s, 1H), 4.86 (d, *J* = 13.0 Hz, 1H), 4.72 (d, *J* = 13.0 Hz, 1H), 3.78 (s, 3H), 2.85-2.84 (m, 2H), 2.63 (s, 1H), 2.32-2.24 (m, 3H), 2.12-2.02 (m, 2H), 1.99-1.77 (m, 4H), 1.51-1.35 (m, 4H), 0.93 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.7, 157.4, 137.9, 132.6, 126.4, 113.8, 111.5, 93.3, 85.7, 84.8, 76.1, 70.8, 65.8, 55.2, 49.4, 47.8, 43.5, 39.2, 36.7, 33.9, 29.8, 27.3, 26.5, 22.9, 12.8; HRMS (FAB): calcd for $C_{30}H_{29}O_8Co_2$ ([M+H]$^+$): 635.0526, found: 635.0537.

Functionalization of mestranol (45) using Cs_2CO_3 as a base



The procedure A was followed with a reaction time of 30 min to provide a mixture (36.2 mg) of **52** (0.0266 mmol, 26%), and **53** (0.0248 mmol, 24%) and a mixture (4.50 mg) of **54** (<1.58 μmmol, <2%), **55** (<0.689 μmmol, <1%), and **56** (<0.896 μmol, <1%) containing inseparable and unknown byproduct. The ratio was determined by ^{1}H-NMR. In this case, 1.2 equivalent of **17** was added.

The analytical samples were obtained by extensive silica gel column chromatography separation (AcOEt : hexane = 1 : 8 to 1 : 4).

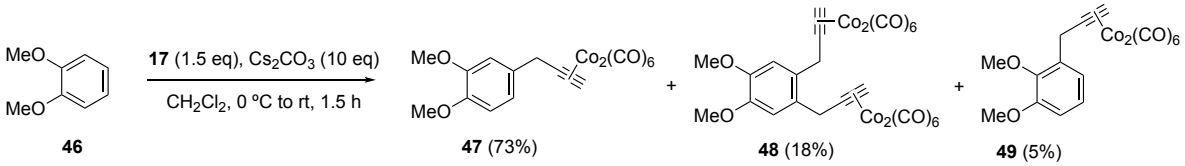
52: red oil; IR (neat): 2018 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.07 (s, 1H), 6.56 (s, 1H), 5.99 (s, 1H), 4.07 (s, 2H), 3.79 (s, 3H), 2.83 (br s, 2H), 2.60 (s, 1H), 2.37-2.30 (m, 2H), 2.20 (br s, 1H), 2.04-1.99 (m, 1H), 1.95-1.67 (m, 5H), 1.53-1.33 (m, 4H), 0.88 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.9, 154.9, 136.6, 132.0, 127.7, 125.9, 110.5, 98.5, 87.5, 79.9, 74.0, 73.7, 54.7, 49.4, 47.1, 43.4, 39.4, 39.0, 34.0, 32.8, 29.7, 27.3, 26.3, 22.8, 12.6; HRMS (ESI): calcd for $C_{30}H_{27}O_8Co_2$ ([M-H]$^-$): 633.0364, found: 633.0394.

53: red oil; IR (neat): 2018 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.20 (d, J = 8.7 Hz, 1H), 6.70 (d, J = 8.7 Hz, 1H), 5.93 (s, 1H), 4.24 (d, J = 15.0 Hz, 1H), 4.13 (d, J = 15.0 Hz, 1H), 3.80 (s, 3H), 3.01 (d, J = 16.8 Hz, 1H), 2.88-2.79 (m, 1H), 2.60 (br s, 1H), 2.35 (br s, 2H), 2.24 (br s, 1H), 2.06-1.67 (m, 6H), 1.53-1.29 (m, 4H), 0.87 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.8, 154.9, 135.7, 132.9, 126.6, 124.8, 107.7, 96.0, 87.5, 79.9, 74.0, 73.7, 54.7, 49.5, 47.0, 43.8, 39.0, 38.7, 32.7, 29.8, 27.2, 27.1, 26.6, 22.8, 12.6; HRMS (ESI): calcd for $C_{30}H_{27}O_8Co_2$ ([M-H]$^-$): 633.0364, found: 633.0388.

A 1 : 1 mixture of **55** and **56**: red oil; IR (neat): 2019 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.18 (d, J = 8.7 Hz, 0.5H), 7.07 (s, 0.5H), 6.70 (d, J = 8.7 Hz, 0.5H), 6.55 (s, 0.5H), 6.00 (s, 1.5H), 5.93 (s, 0.5H), 4.86 (d, J = 13.0 Hz, 1H), 4.72 (d, J = 13.0 Hz, 1H), 4.24 (d, J = 14.7 Hz, 0.5H), 4.13 (d, J = 14.7 Hz, 0.5H), 4.07 (s, 1H), 3.80 (s, 1.5H), 3.79

(s, 1.5H), 3.02-2.98 (m, 0.5H), 2.88-2.82 (m, 1.5H), 2.63 (s, 1H), 2.33-2.24 (m, 3H), 2.21-1.99 (m, 3H), 1.88-1.74 (m, 4H), 1.53-1.33 (m, 4H), 0.93 (s, 1.5H), 0.92 (s, 1.5H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.9, 154.87, 154.86, 136.6, 135.7, 133.0. 132.1, 127.7, 126.6, 125.8, 124.8, 110.5, 107.7, 98.5, 96.0, 93.3, 85.70, 85.67, 84.9, 84.8, 76.1, 73.7, 70.8, 65.8, 54.75, 54.71, 49.48, 49.42, 47.8, 47.7, 43.8, 43.4, 39.2, 38.5, 36.7, 34.0, 29.7, 27.3, 27.2, 26.7, 26.4, 22.9, 12.8; HRMS (FAB): calcd for $C_{36}H_{30}O_{11}Co_4$ ([M-3CO]$^+$): 873.9116, found: 873.9118.

Functionalization of veratrol (46)



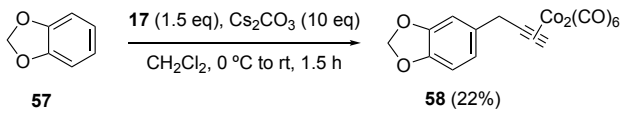
The procedure A was followed with a reaction time of 1.5 h. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 15) to provide **47** (33.8 mg, 0.0731 mmol, 73%), **48** (14.2 mg, 0.0184 mmol, 18%), and **49** (2.22 mg, 4.80 μmol, 5%).

47: red oil; IR (neat): 2018 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3COCD_3): δ 6.97, (s, 1H), 6.87 (m, 2H), 6.55 (s, 1H), 4.12 (s, 2H), 3.81 (s, 3H), 3.76 (s, 3H); ^{13}C-NMR (100 MHz, CD_3COCD_3): δ 200.9, 150.5, 149.6, 134.3, 121.9, 113.8, 112.9, 100.5, 75.0, 56.2, 56.0, 40.3; HRMS (EI): calcd for $C_{16}H_{12}O_7Co_2$ ([M-CO]$^+$): 433.9247, found: 433.9246.

48: red oil; IR (neat cm^{-1}): 2018 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.72 (s, 2H), 6.05 (s, 2H), 4.17 (s, 4H), 3.86 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.4, 148.3, 130.5, 113.4, 96.7, 73.2, 55.9, 37.1; HRMS (EI): calcd for $C_{26}H_{14}O_{14}Co_4$ (M$^+$): 785.7712, found: 785.7723.

49: red oil; IR (neat): 2018 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.01 (t, J = 7.9 Hz, 1H), 6.90-6.84 (m, 2H), 6.03 (s, 1H), 4.11 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.7, 152.9, 147.1, 133.9, 123.9, 122.5, 111.5, 97.2, 73.7, 60.6, 55.8, 34.2; HRMS (EI): calcd for $C_{14}H_{12}O_5Co_2$ ([M-3CO]$^+$): 377.9349, found: 377.9329.

Functionalization of 1,3-benzodioxole (57)

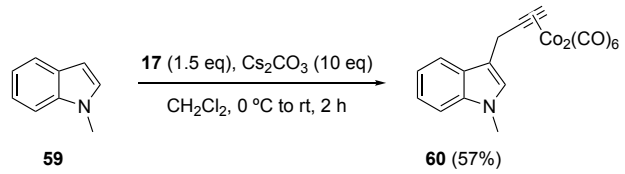


The procedure A was followed, employing K_2CO_3 instead of Cs_2CO_3 as a base, with a reaction time of 1.5 h. The crude was purified by silica gel column chromatography (hexane) to provide **58** (9.94 mg, 0.0223 mmol, 22%).

58: red oil; IR (neat): 2017 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.76 (d, J = 7.5 Hz, 1H), 6.75 (s, 1H), 6.71 (d, J =

7.5 Hz, 1H), 6.07 (s, 1H), 5.93 (s, 2H), 3.99 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.6, 147.7, 146.6, 134.3, 121.9, 109.2, 108.3, 101.0, 98.3, 73.3, 40.0; HRMS (EI): calcd for $C_{15}H_8O_7Co_2$ ([M-CO]$^+$): 417.8934, found: 417.8936.

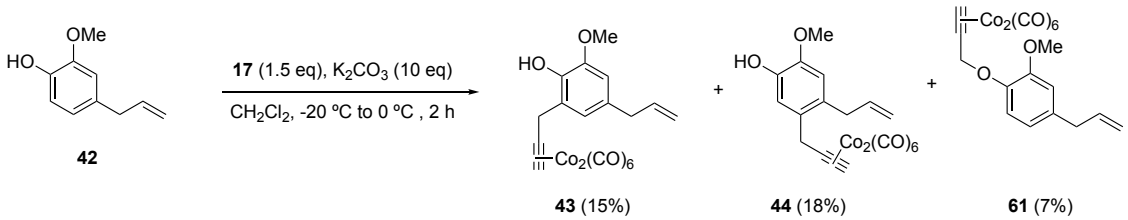
Functionalization of *N*-methylindole (59)



The procedure A was followed with a reaction time of 2 h. The crude was purified by silica gel column chromatography (hexane) to provide **60** (26.1 mg, 0.0573 mmol, 57%).

60: red oil; IR (neat): 2015 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.94 (s, 1H), 6.05 (s, 1H), 4.27 (s, 2H), 3.75 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.7, 137.0, 127.3, 126.9, 121.8, 119.0, 118.7, 114.1, 109.3, 98.9, 73.6, 32.6, 30.1; HRMS (EI): calcd for $C_{16}H_{11}NO_4Co_2$ ([M-2CO]$^+$): 398.9352, found: 398.9341.

Functionalization of eugenol (42)



On 0.200 mmol scale, the procedure A was followed, employing K_2CO_3 instead of Cs_2CO_3 as a base, with a reaction time of 2 h. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 20 to 1 : 8) to provide a mixture of **43** (18.4 mg, 0.0369 mmol, 15%) and **61** (7.23 mg, 14.5 μmol, 7%) and a single product of **44** (15.1 mg, 0.0303 mmol, 18%). The mixture of **43** and **61** was separated by HPLC (250-20 mm, AcOEt : hexane = 1 : 19, 9.4 mL/min).

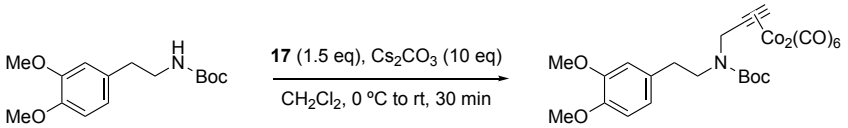
43 (retention time: 19.0 min): red oil; IR (neat): 2020 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.61 (s, 1H), 6.60 (s, 1H), 6.03 (s, 1H), 5.92 (ddt, *J* = 16.8 Hz, 10.0 Hz, 6.5Hz, 1H), 5.60 (s, 1H), 5.09-5.04 (m 2H), 4.10 (s, 2H), 3.86 (s, 3H), 3.30 (d, *J* = 6.5 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.7, 146.4, 141.9, 137.7, 131.3, 125.9, 122.7, 115.5, 109.9, 97.3, 73.7, 56.1, 39.9, 33.6; HRMS (EI): calcd for $C_{18}H_{14}O_7Co_2$ ([M-CO]$^+$): 459.9404, found: 459.9400.

44: red oil; IR (neat): 2020 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.81 (s, 1H), 6.65 (s, 1H), 6.04 (s, 1H), 5.97 (ddt, *J*

= 17.0 Hz, 10.3 Hz, 6.4 Hz, 1H), 5.46 (s, 1H), 5.11 (dt, J = 10.3 Hz, 1.4 Hz, 1H), 5.04 (dt, J = 17.0 Hz, 1.4 Hz, 1H), 4.04 (s, 2H), 3.85 (s, 3H), 3.43 (dd, J = 6.4 Hz, 1.4 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.6, 145.7, 144.1, 137.2, 131.6, 128.8, 116.1, 115.9, 112.2, 97.1, 73.5, 56.0, 36.82, 36.78; HRMS (ESI): calcd for $C_{19}H_{14}O_8Co_2Na$ ([M+Na]$^+$): 510.9245, found: 510.9238.

61 (retention time: 20.7 min): red oil; IR (neat): 2023 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.88 (d, J = 9.0 Hz, 1H), 6.73 (s, 1H), 6.72 (d, J = 9.0 Hz, 1H), 6.03 (s, 1H), 6.01-5.91 (m, 1H), 5.25 (s, 2H), 5.10-5.06 (m, 2H), 3.81 (s, 3H), 3.34 (d, J = 6.8 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$,): δ 199.2, 150.2, 145.9, 137.6, 134.1, 120.3, 115.7, 115.1, 112.9, 89.6, 72.4, 69.7, 55.7, 39.9; HRMS (EI): calcd for $C_{12}H_{14}O_2Co_2$ ([M-6CO]$^+$): 319.9658, found: 319.9637.

Functionalization of *N*-Boc homoveratrylamine (62)

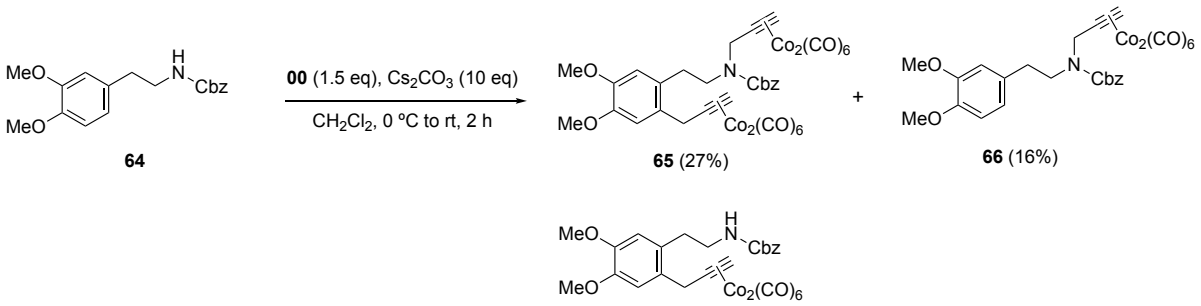


62 **63** (29%)

The procedure A was followed with a reaction time of 30 min. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 8) to provide **63** (18.7 mg, 0.0292 mmol, 29%).

63 (a mixture of two rotamers): red oil; IR (neat): 2022 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.82-6.68 (m, 3H), 6.03 (s, 1H), 4.36 (s, 1H), 3.86 (s, 3H), 3.86 (s, 3H), 3.50-3.46 (m, 2H), 2.86-2.79 (m, 2H), 1.46 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.4, 155.0, 154.5, 149.1, 147.7, 131.6, 120.8, 112.1, 112.0, 111.5, 91.5, 91.1, 80.4, 80.0, 73.3, 73.0, 55.9, 55.8, 49.5, 49.0, 48.7, 34.7, 33.7, 28.4, 28.3; HRMS (ESI): calcd for $C_{24}H_{25}NO_{10}Co_2Na$ ([M+Na]$^+$): 628.0035, found: 628.0021.

Functionalization of *N*-Cbz homoveratrylamine (64)



64 **65** (27%) **66** (16%)

67 (11%)

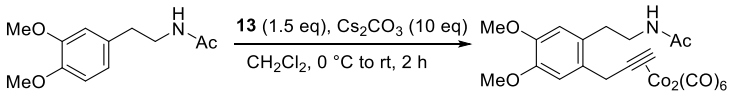
The procedure A was followed with a reaction time of 2 h. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 8 to 1 : 2) to provide **65** (11.2 mg, 0.0175 mmol, 18%), **66** (7.28 mg, 0.0114 mmol, 11%), **67** (26.4 mg, 0.0274 mmol, 27%), and recovered **64** (4.85 mg, 0.0154 mmol, 15%).

65 (a mixture of two rotamers): red oil; IR (neat): 2024 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.36 (br s, 5H), 6.80-6.73 (m, 2H), 6.64 (d, *J* = 8.3 Hz, 0.5H), 6.57 (s, 0.5H), 6.03 (s, 0.5H), 5.93 (s, 0.5H), 5.18 (s, 1H), 5.14 (s, 1H), 4.41 (s, 1H). 4.36 (s, 1H), 3.85 (s, 3H), 3.80 (s, 1.5H), 3.75 (s, 1.5H), 3.59-3.56 (m, 2H), 2.88 (t, *J* = 7.1 Hz, 1H), 2.80 (t, *J* = 7.1 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.3, 155.9, 155.3, 149.0, 147.7, 136.5, 131.4, 131.2, 128.5, 128.2, 128.04, 128.0, 120.7, 112.0, 111.8, 111.4, 90.6, 73.0, 72.8, 67.5, 67.3, 55.9, 55.7, 49.8, 49.6, 49.3, 34.8, 33.8; HRMS (EI): calcd for $C_{21}H_{23}NO_{10}Co_2$ ([M-6CO]$^+$): 471.0291, found: 471.0293.

66: red oil; IR (neat): 2025 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.38-7.32 (m, 5H), 6.73 (s, 1H), 6.64 (s, 1H), 6.04 (s, 1H), 5.11 (s, 2H), 4.81 (br s, 1H), 4.09 (s, 2H), 3.86 (s, 3H), 3.81 (s, 2H), 3.44 (q, *J* = 7.0 Hz, 2H), 2.87 (t, *J* = 7.0 Hz, 2H).^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.6, 156.3, 148.3, 147.7, 136.5, 131.1, 128.5, 128.4, 128.2, 128.1, 113.6, 112.7, 97.0, 73.3, 66.7, 56.0, 55.9, 42.2, 36.9, 32.7; HRMS (FAB): calcd for $C_{21}H_{23}NO_4Co_2$ ([M-6CO]$^+$): 471.0291, found: 471.0296.

67 (a mixture of two rotamers): red oil; IR (neat): 2021 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.36 (br s, 5H), 6.72 (s, 0.5H), 6.68 (s, 0.5H), 6.64 (s, 0.5H), 6.49 (s, 0.5H), 6.05 (s, 0.5H), 6.04 (s, 0.5H), 5.95 (s, 0.5H), 5.92 (s, 0.5H), 5.17 (s, 1H). 5.13 (s, 1H), 4.49 (s, 1H), 4.45 (s, 1H), 4.09 (s, 1H) 3.94 (s, 1H), 3.87 (s, 1.5H), 3.85 (s, 1.5H), 3.77 (s, 1.5H), 3.70 (s, 1.5H), 3.68-3.55 (m, 2H), 2.99-2.88 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.5, 155.8, 155.3, 148.42, 148.37, 147.8, 136.34, 136.27, 131.2, 130.8, 128.5, 128.4, 128.30, 128.23, 128.20, 128.1, 113.6, 113.5, 112.9, 112.7, 97.2, 96.9, 90.5, 90.4, 73.34, 73.26, 73.0, 72.8, 67.7, 67.4, 55.8, 49.6, 49.5, 48.9, 36.7, 36.5, 31.7, 30.8, 29.7; HRMS (FAB): calcd for $C_{26}H_{25}NO_6Co_4$ ([M-10CO]$^+$): 682.9010, found: 682.9001.

Functionalizaiton *of N*-(3,4-dimethoxyphenethyl)acetamide (20)

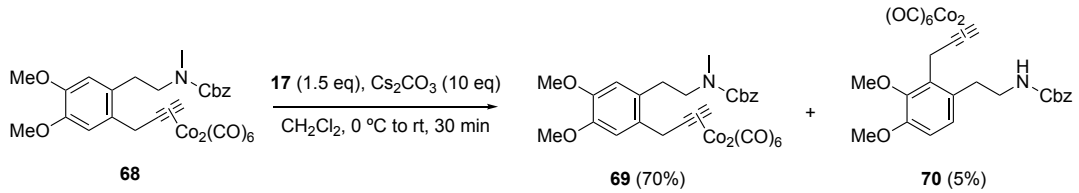


20 **21** (33%)

The procedure A was followed with a reaction time of 2 h. The crude was purified by PTLC (MeOH : $CHCl_3$ = 1 : 20) to provide **21** (17.9 mg, 0.0327 mmol, 33%) and recovered **20** (5.44 mg, 0.0243 mmol, 24%).

21: red oil; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.74 (s, 1H), 6.66 (s, 1H), 6.07 (s, 1H), 5.55 (br s, 1H), 4.10 (s, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.49 (q, *J* = 7.2 Hz, 2H), 2.87 (t, *J* = 7.2 Hz, 2H), 1.97 (s, 3H).^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.6, 170.0, 148.3, 147.7, 131.1, 128.5, 113.6, 112.7, 96.9, 73.4, 56.1, 55.9, 40.6, 36.9, 32.3, 23.3; HRMS (ESI): calcd for $C_{22}H_{25}NO_4Co_2$ ([M-6CO]$^+$): 485.0448, found: 485.0462.

Functionalization of benzyl (3,4-dimethoxyphenethyl)(methyl)carbamate (68)

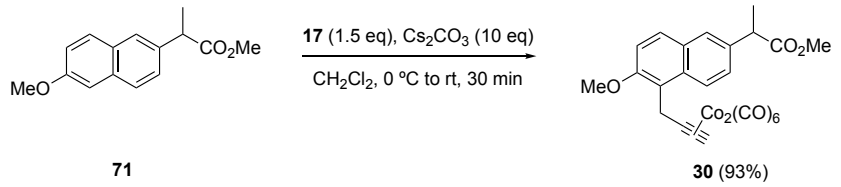


The procedure A was followed with a reaction time of 30 min. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 8 to 1 : 2) to provide **69** (45.5 mg, 0.0697 mmol, 70%) and **70** (3.09 mg, 4.73 μmol, 5%).

69 (a mixture of two rotamers): red oil; IR (neat): 2018 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.35-7.30 (m, 5H), 6.72 (s, 0.5H), 6.67 (s, 1H), 6.52 (s, 0.5H), 6.07 (s, 0.5H), 5.95 (s, 0.5H), 5.13 (s, 1H), 5.10 (s, 1H), 4.13 (s, 1H), 3.97 (s, 1H), 3.86 (s, 3H), 3.82 (s, 1.5H), 3.74 (s, 1.5H), 3.45 (br s, 2H), 2.93-2.84 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.8, 156.3, 148.5, 147.9, 137.1, 136.9, 131.2, 131.0, 128.8, 128.7, 128.2, 128.0, 113.7, 113.1, 97.4, 97.2, 73.6, 67.5, 67.2, 56.2, 56.0, 51.2, 50.8, 37.1, 36.8, 35.3, 34.8, 31.4, 30.9; HRMS (EI): calcd for $C_{22}H_{25}NO_4Co_2$ ([M-6CO]$^+$): 485.0448, found: 485.0462.

70 (a mixture of two rotamers): red oil; IR (neat): 2019 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.38-7.32 (m, 5H), 6.89 (d, J = 8.2 Hz, 0.5H), 6.79-6.73 (m, 1.5H), 5.98 (s, 0.5H), 5.88 (s, 0.5H), 5.12 (s, 1H), 5.11 (s, 1H), 4.23 (s, 1H), 4.06 (s, 1H), 3.85 (s, 2H), 3.82 (s, 4H), 3.44 (t, J = 7.6 Hz, 2H), 2.93 (s, 3H), 2.90-2.84 (m, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.7, 156.0, 151.4, 147.4, 137.0, 136.8, 132.8, 132.5, 129.7, 129.6, 128.5, 128.0, 127.9, 127.8, 125.0, 111.5, 111.4, 95.9, 95.6, 73.8, 67.2, 67.0, 60.3, 55.8, 51.2, 50.6, 35.0, 34.5, 31.4, 30.9, 30.6; HRMS (ESI) $C_{28}H_{25}Co_2O_{10}NNa$ ([M+Na]$^+$) calcd for 676.0035, found: 676.0017.

Functionalization of naproxen methyl ester (71)

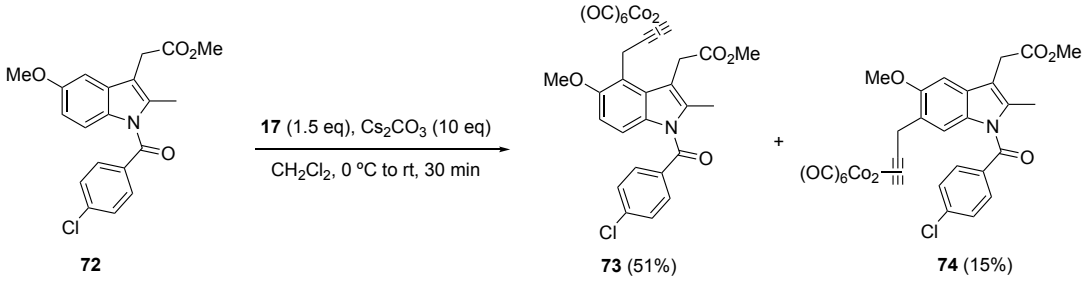


The procedure A was followed with a reaction time of 30 min. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 12) to provide **30** (52.6 mg, 0.0925 mmol, 93%).

30: red oil; IR (neat): 2019, 1738 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 8.9 Hz, 1H), 7.75 (d, J = 9.9 Hz, 1H), 7.68 (s, 1H), 7.48 (d, J = 8.9 Hz, 1H), 7.24 (d, J = 9.9 Hz, 1H), 5.91 (s, 1H), 4.61 (s, 2H), 3.96 (s, 3H), 3.87 (q, J = 7.1 Hz, 1H), 3.68 (s, 3H), 1.59 (d, J = 7.1 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.7, 175.1, 154.0, 135.3, 131.8, 129.1, 128.8, 126.8, 126.4, 123.7, 121.1, 112.7, 96.2, 73.5, 55.6, 52.0, 45.2, 29.0, 18.5; HRMS (EI): calcd for

$C_{19}H_{18}O_4Co_2$ ([M-5CO]$^+$): 427.9869, found: 427.9864.

Functionalization of indometacin methyl ester (72)

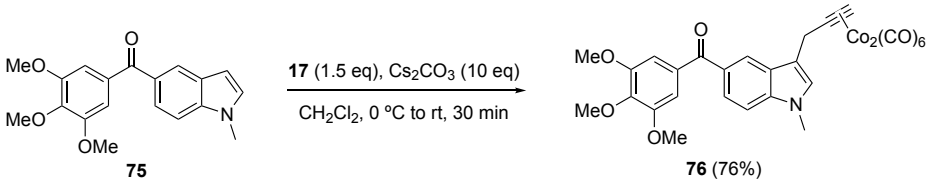


The procedure A was followed with a reaction time of 30 min. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 25) to provide **73** (35.6 mg, 0.0511 mmol, 51%) and **74** (10.2 mg, 0.0146 mmol, 15%).

73: red oil; IR (neat): 2020, 1740 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 7.8 Hz, 2H), 7.45 (d, *J* = 7.8 Hz, 2H), 6.90 (d, *J* = 9.0 H, 1H), 6.64 (d, *J* = 9.0 Hz, 1H), 5.91 (s, 1H), 4.55 (s, 2H), 3.90 (s, 2H), 3.83 (s, 3H), 3.70 (s, 3H), 2.37 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.9, 171.7, 168.3, 152.9, 139.5, 137.2, 133.9, 131.7, 131.3, 129.1, 128.2, 119.4, 113.3, 111.6, 106.9, 96.7, 73.2, 55.6, 52.2, 31.3, 29.5, 13.2; HRMS (ESI): calcd for $C_{29}H_{21}NO_{10}ClCo_2$ ([M+H]$^+$): 695.9513, found: 695.9503.

74: red oil; IR (neat): 2019, 1740 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.49 (d, *J* = 8.3 Hz, 2H), 6.91 (s, 1H), 6.90 (s, 1H), 5.89 (s, 1H), 4.03 (s, 2H), 3.88 (s, 3H), 3.68 (s, 3H), 3.67 (s, 2H), 2.33 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.7, 171.3, 168.4, 153.8, 139.3, 135.2, 131.1, 134.1, 130.3, 129.5, 129.1, 125.1, 116.0, 112.6, 99.1, 97.9, 73.7, 55.1, 52.1, 34.6, 30.3, 13.4; HRMS (ESI): calcd for $C_{29}H_{20}NO_{10}ClCo_2Na$ ([M+Na]$^+$): 717.9332, found: 717.9320.

Functionalization of compound 75

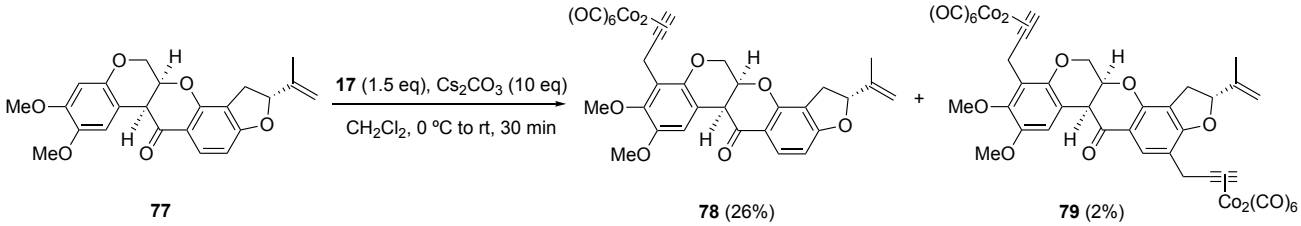


The procedure A was followed with a reaction time of 30 min. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 2) to provide **76** (49.2 mg, 0.0758 mmol, 76%).

76: red oil; IR (neat): 2018, 1647 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.35 (d, *J* = 8.7 Hz, 1H), 7.08 (s, 2H), 7.06 (s, 1H), 6.04 (s, 1H), 4.29 (s, 2H), 3.94 (s, 3H), 3.89 (s, 6H), 3.82 (s, 3H); ^{13}C-

NMR (100 MHz, $CDCl_3$): δ 199.6, 196.4, 152.8, 141.4, 139.2, 134.2, 129.1, 128.6, 126.9, 124.3, 122.7, 116.0, 108.9, 107.6, 97.8, 73.5, 60.9, 56.3, 32.9, 29.9; HRMS (ESI): calcd for $C_{28}H_{22}NO_{10}Co_2$ ($[M+H]^+$): 649.9902, found: 649.9902.

Functionalization of rotenone (77)

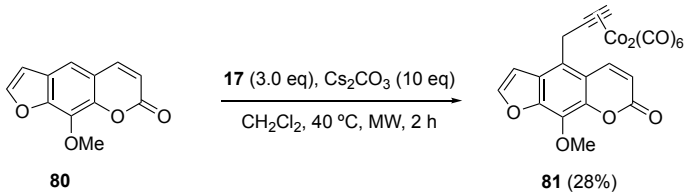


The procedure A was followed with a reaction time of 30 min. The crude was purified by HPLC (250-20 mm, AcOEt : hexane = 3 : 7, 9 mL/min) to provide **78**(18.9 mg, 0.0261 mmol, 26%) and **79** (2.11 mg, 2.02 μmol, 2%).

78 (retention time: 8.8 min): red oil; IR (neat): 2017, 1676 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.4 Hz, 1H), 6.78 (s, 1H), 6.51 (d, *J* = 8.4 Hz, 1H), 6.00 (s, 1H), 5.28 (dd, *J* = 9.9 Hz, 8.0 Hz, 1H), 5.09 (s, 1H), 4.95-4.93 (m, 2H), 4.66 (dd, *J* = 11.9 Hz, 2.9 Hz, 1H), 4.17 (d, *J* = 11.9 Hz, 1H), 4.14 (s, 2H), 3.85 (d, *J* = 3.9 Hz, 1H), 3.83 (s, 3H), 3.74 (s, 3H), 3.32 (dd, *J* = 15.7 Hz, 9.9 Hz, 1H), 3.01 (dd, *J* = 15.7 Hz, 8.0 Hz, 1H), 1.78 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.9, 188.8, 167.3, 158.0, 147.7, 147.2, 145.1, 143.0, 130.0, 122.3, 113.4, 112.8, 112.6, 110.8, 109.0, 104.8, 96.6, 87.8, 73.6, 72.1, 65.9, 60.5, 56.4, 45.0, 31.3, 27.6, 17.1; HRMS (ESI): calcd for $C_{32}H_{25}O_{12}Co_2$ ($[M+H]^+$): 719.0005, found: 718.9995.

79 (retention time: 10.8 min): red oil; IR (neat): 2018, 1677 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.73 (s, 1H), 6.73 (s, 1H), 6.03 (s, 1H), 5.99 (s, 1H), 5.29 (t, *J* = 9.2 Hz, 1H), 5.11 (s, 1H), 4.98 (s, 1H), 4.91-4.89 (m, 1H), 4.64 (dd, *J* = 11.8 Hz, 3.1 Hz, 1H), 4.17 (d, *J* = 12.1 Hz, 1H), 4.14 (s, 2H), 4.07 (d, *J* = 15.5 Hz, 1H), 3.98 (d, *J* = 15.5 Hz, 1H), 3.83 (s, 4H), 3.72 (s, 3H), 3.32 (dd, *J* = 15.9 Hz, 9.7 Hz, 1H), 3.04 (dd, *J* = 15.8 Hz, 8.4 Hz, 1H), 1.81 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.8, 188.8, 165.3, 157.1, 147.7, 147.1, 145.1, 142.8, 129.8, 122.3, 117.5, 113.3, 113.03, 112.98, 110.8, 109.0, 96.7, 96.2, 88.1, 73.67, 73.63, 72.2, 65.9, 60.6, 56.3, 45.1, 33.3, 31.6, 27.6, 17.3; HRMS (ESI): calcd for $C_{41}H_{27}O_{18}Co_4$ ($[M+H]^+$): 1042.8520, found: 1042.8508.

Functionalization of xanthotoxin (80)

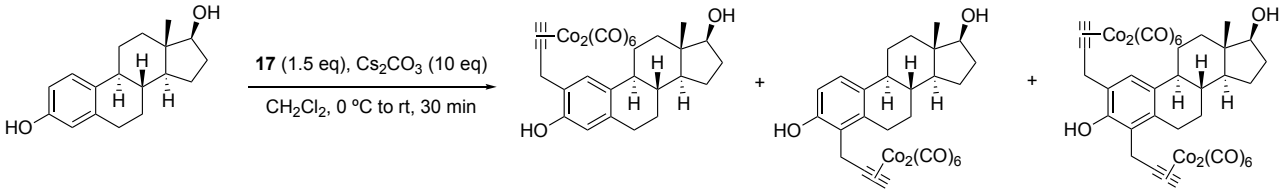


The procedure B was followed with a reaction time of 2 h. The crude was purified by silica gel column

chromatography (AcOEt : hexane = 1 : 4) to provide **81** (15.1 mg, 0.0280 mmol, 28%) along with recovered **80** (14.5 mg, 0.0669, 67%)

81: red oil; IR (neat): 2021 1736 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 9.8 Hz, 1H), 7.74 (d, *J* = 2.0 Hz, 1H), 6.91 (d, *J* = 2.0 Hz, 1H), 6.47 (d, *J* = 9.8 Hz, 1H), 5.95 (s, 1H), 4.50 (s, 2H), 4.24 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.1, 160.0, 147.3, 146.7, 143.9, 140.3, 132.3, 125.9, 123.5, 114.7, 114.1, 105.3, 94.2, 73.0, 61.5, 33.1; HRMS (ESI): calcd for $C_{21}H_{11}O_{10}Co_2$ ($[M+H]^+$): 540.9011, found: 540.8994.

Funtionalizaation of estradiol (83)



83 **84** (15%) **85** (23%) **86** (17%)

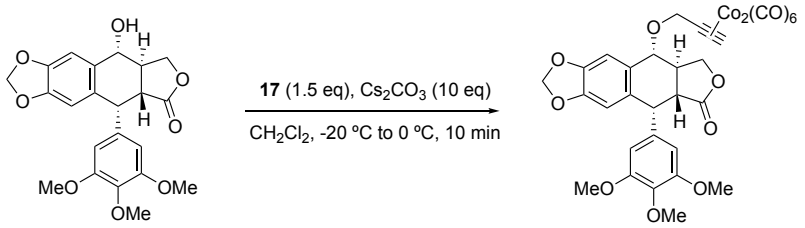
The procedure A was followed with a reaction time of 30 min. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 8) to provide **84** (8.88 mg, 0.0149 mmol, 15%), **85** (13.6 mg, 0.0227 mmol, 23%), **86** (15.3 mg, 0.0166 mmol, 17%) and recovered **83** (8.90 mg, 0.0327 mmol, 33%). In this case, starting material **83** was dissolved in 5 ml of CH_2Cl_2 (0.02 M) and added.

84: red oil; IR (neat): 2017 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3COCD_3): δ 8.15 (s, 1H), 7.11 (s, 1H), 6.57 (s, 1H), 6.40 (s, 1H), 4.17 (d, *J* = 15.0 Hz, 1H), 4.10 (d, *J* = 15.0 Hz, 1H), 3.65 (br s, 1H), 3.58 (br s, 1H), 2.30 (br s, 1H), 2.12-1.95 (m, 3H), 1.83 (br s, 1H), 1.64 (br s, 1H), 1.46-1.19 (m, 10H), 0.76 (s, 3H); HRMS (ESI): calcd for $C_{27}H_{25}O_8Co_2$ ($[M-H]^-$): 595.0208, found: 595.0211.

85: red oil; IR (neat): 2017 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3COCD_3): δ 8.25 (br s, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 6.37 (s, 1H), 4.28 (d, *J* = 14.7 Hz, 1H), 4.22 (d, *J* = 14.7 Hz, 1H), 3.66 (br s, 1H), 3.57 (br s, 1H), 3.03 (br s. 1H), 2.25 (brs, 1H), 2.13 (br s, 1H), 1.95 (br s, 4H), 1.48-1.19 (m, 8H), 0.75 (s, 3H); HRMS (ESI): calcd for $C_{27}H_{25}O_8Co_2$ ($[M-H]^-$): 595.0208, found: 595.0224.

86: red oil; IR (neat): 2017 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.02 (s, 1H), 6.04 (s, 1H), 5.98 (s, 1H), 4.80 (s, 1H), 4.18 (s, 2H), 4.13 (d, *J* = 16.1 Hz, 1H), 4.06 (d, *J* = 16.1 Hz, 1H), 3.73 (br d, *J* = 5.9 Hz, 1H), 2.94 (br d, *J* = 16.1 Hz, 1H), 2.81 (dd, *J* = 15.9 Hz, 10.5 Hz, 1H), 2.28 (br d, *J* = 11.2 Hz, 1H), 2.15 (br s, 2H), 1.95 (br d, *J* = 10.7 Hz , 2H), 1.70 (br s, 1H), 1.49-1.19 (m, 10H), 0.76 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.5, 149.2, 134.7, 133.6, 126.3, 125.2, 123.8, 95.6, 94.1, 81.9, 73.6, 72.9, 50.0, 44.1, 43.2, 38.1, 36.7, 35.3, 30.6, 27.2, 26.4, 23.1, 11.0; HRMS (ESI): calcd for $C_{36}H_{27}O_{14}Co_4$ ($[M-H]^-$): 918.8723, found: 918.8710.

Functionalization of podophyllotoxin (87)

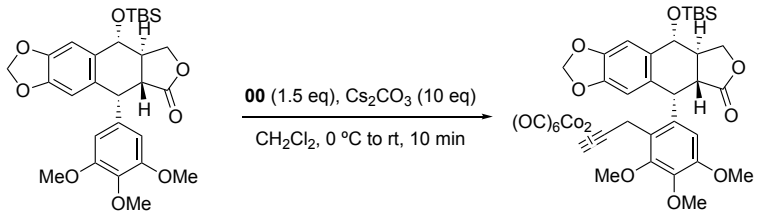


87 **88** (28%)

The procedure A was followed with a reaction time of 10 min. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 8) to provide **88** (20.4 mg, 0.0276 mmol, 28%).

88: red oil; IR (neat): 2029, 1780 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.07 (s, 1H), 6.52 (s, 1H), 6.37 (s, 2H), 6.08 (s, 1H), 5.98 (d, *J* = 1.0 Hz, 1H), 5.96 (d, *J* = 1.0 Hz, 1H), 4.82 (d, *J* = 10.7 Hz, 1H), 4.77 (d, *J* = 12.1 Hz, 1H), 4.69 (d, *J* = 12.1 Hz, 1H), 4.62-4.58 (m, 2H), 4.16 (t, *J* = 9.7 Hz, 1H), 3.81 (s, 3H), 3.72 (s, 6H), 3.04-2.95 (m, 1H), 2.87 (dd, *J* = 14.2 Hz, 4.6 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.3, 173.9, 152.6, 147.9, 147.7, 137.0, 135.3, 131.8, 130.3, 109.7, 107.9, 106.8, 101.5, 90.3, 78.0, 71.4, 71.2, 68.7, 60.7, 55.9, 45.5, 43.9, 37.8; HRMS (ESI): calcd for $C_{31}H_{25}O_{14}Co_2$ ($[M+H]^+$): 738.9903, found: 738.9888.

Functionalization of podophyllotoxin TBS ester (89)

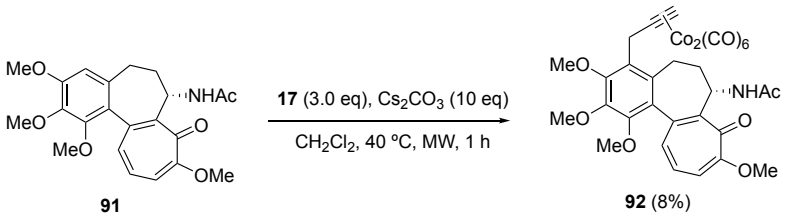


89 **90** (19%)

On 48.8 μmol scale, The procedure A was followed with a reaction time of 30 min. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 2) to provide **90** (8.05 mg, 8.86 μmol, 19%).

90: red oil; IR (neat): 2019, 1782 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 6.96 (s, 1H), 6.39 (s, 1H), 6.061 (s, 1H), 6.055 (s, 1H), 5.98 (s, 1H), 5.97 (s, 1H), 4.93 (d, *J* = 9.6 Hz, 1H), 4.91 (s, 1H), 4.81 (d, *J* = 9.6 Hz, 1H), 4.55 (t, *J* = 7.5 Hz, 1H), 4.43 (d, *J* = 15.7 Hz, 1H), 4.00 (dt, *J* = 11.1 Hz, *J* = 8.6 Hz, 1H), 3.90 (s, 3H), 3.79 (s, 3H), 3.58 (s, 3H), 3.11-3.01 (m, 1H), 2.98-2.89 (m, 1H), 0.97 (s, 9H), 0.30 (s, 1H), 0.14 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 173.7, 151.9, 151.8, 147.5, 147.3, 141.4, 133.64, 133.60, 132.1, 127.8, 110.8, 109.0, 106.6, 101.4, 96.8, 72.7, 72.3, 71.5, 60.5, 60.4, 55.8, 44.9, 40.9, 39.5, 31.5, 25.8, 18.0, -3.8, -4.1; HRMS (FAB): calcd for $C_{32}H_{38}O_9Co_2$ ($[M-5CO]^+$): 712.0949, found: 712.0972.

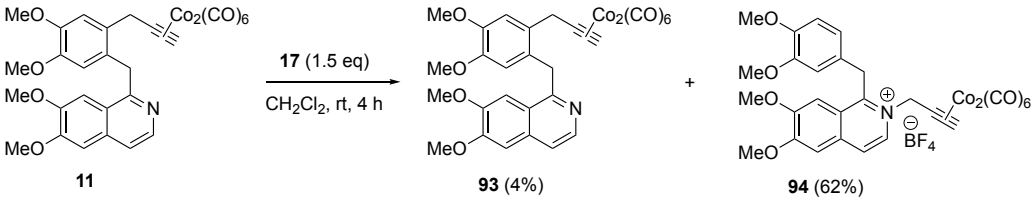
Functionalization of colchicine (91)



On 0.05 mmol scale, the procedure B was followed with a reaction time of 1 h. The crude was purified by silica gel column chromatography (MeOH : $CHCl_3$ = 1 : 40) to provide **92** (2.83 mg, 3.91 μmol, 8%) and recovered **91** (15.7 mg, 0.0392 mmol, 79%).

92: red oil; IR (neat): 2022, 1670 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.56 (br s, 1H), 7.54 (s, 1H), 7.21 (d, *J* = 10.7, 1H), 6.85 (d, *J* = 10.7 Hz, 1H), 5.93 (s, 1H), 4.66-4.60 (m, 1H), 4.32 (d, *J* = 13.4 Hz, 1H), 4.00 (s, 6H), 3.92 (d, *J* = 13.4 Hz, 1H), 3.91 (s, 3H), 3.61 (s, 3H), 2.90-2.88 (m, 1H), 2.27-2.25 (m, 2H), 2.00 (s, 3H), 1.90-1.87 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.7, 179.6, 170.1, 164.2, 152.1, 151.6, 150.5, 145.5, 136.7, 135.6, 132.1, 130.2, 129.4, 126.6, 112.7, 96.2, 96.1, 73.4, 61.4, 60.9, 60.7, 56.4, 52.5, 35.9, 30.3, 25.5, 22.9; HRMS (ESI): calcd for $C_{31}H_{27}NO_{12}Co_2Na$ ([M+Na]$^+$): 746.0089, found: 746.0067.

Functionalization of papaverine (11)



The procedure C was followed with a reaction time of 4 h. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 1 to MeOH : $CHCl_3$ = 1 : 4) to provide **93** (2.71 mg, 4.09 μmol, 4%), **94** (46.8 mg, 0.0623 mmol, 62%) and recovered **8** (2.33 mg, 6.87 μmol, 7%).

93: red oil; IR (neat): 2017 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3COCD_3): δ 8.24 (d, *J* = 5.6 Hz, 1H), 7.54 (s, 1H), 7.51 (d, *J* = 5.6 Hz, 1H), 7.30 (s, 1H), 6.94 (s, 1H), 6.81 (s, 1H), 6.48 (s, 1H), 4.72 (s, 2H), 4.40 (s, 2H), 3.97 (s, 3H), 3.91 (s, 3H), 3.80 (s, 3H), 3.61 (s, 3H); ^{13}C-NMR (100 MHz, CD_3COCD_3): δ 200.9, 158.6, 153.6, 151.1, 149.3, 148.9, 141.6, 134.2, 132.8, 131.0, 123.8, 119.3, 115.3, 106.4, 104.8, 99.1, 75.0, 56.2, 56.0, 39.9, 38.2; HRMS (FAB): calcd for $C_{29}H_{24}NO_{10}Co_2$ ([M+H]$^+$) calcd for 664.0059, found: 664.0067.

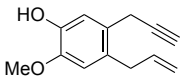
94: red oil; IR (neat): 2032 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.79 (d, *J* = 6.6 Hz, 1H), 8.41 (d, *J* = 6.6 Hz, 1H), 7.96 (s, 1H), 7.81 (s, 1H), 6.99 (s, 1H), 6.89 (s, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 6.74 (s, 1H), 6.61 (d, *J* = 8.3 Hz, 1H),

6.31 (s, 2H), 5.26 (s, 2H). 4.15 (s, 3H), 4.01 (s, 3H), 3.75 (s, 3H), 3.71 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.6, 159.2, 155.5, 154.6, 151.1, 150.0, 137.8, 136.2, 128.5, 125.5, 124.3, 120.9, 113.3, 113.1, 107.4, 106.9, 87.5, 75.9, 60.3, 57.5, 57.0, 56.2, 56.1, 35.2; HRMS (FAB): calcd for $C_{29}H_{24}NO_{10}Co_2$ (M^+): 664.0059, found: 664.0067.

Decomplexation of dicobalt hexacarbonyl complexes

Standard procedure: To a solution of cobalt complex in MeCN (0.01 M) was added $TEMPO^+BF_4^-$ (0.5 eq. × 8 or 9) every 5 min at - 40 °C. After completion of the reaction, the reaction was quenched with sat. $NaHCO_3$ (2 mL) and extracted with AcOEt (4 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography.

Decomplexation of eugenol analog 42

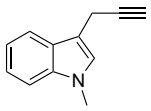


96

On 0.0234 mmol scale, the standard procedure was followed with $TEMPO^+BF_4^-$ (total 25.23 mg, 0.104 mmol) and a reaction time of 45 min. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 4) to provide **96** (4.05 mg, 0.0200 mmol, 86%).

96: colorless oil; IR (neat): 3294, 2054 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.06 (s, 1H), 6.66 (s, 1H), 5.93 (ddt, *J* = 16.9 Hz, 10.2 Hz, 6.3 Hz, 1H), 5.46 (s, 1H), 5.06 (dd, *J* = 10.2 Hz, 1.4 Hz, 1H), 4.99 (dd, *J* = 16.9 Hz, 1.4 Hz, 1H), 3.87 (s, 3H), 3.46 (d, *J* = 2.4 Hz, 2H), 3.35 (d, *J* = 6.3 Hz, 2H), 2.15 (t, *J* = 2.4 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 145.4, 144.1, 136.6, 128.8, 127.2, 115.8, 115.1, 112.3, 82.1, 70.4, 56.0, 36.8, 21.7; HRMS (EI): calcd for $C_{13}H_{14}O_2$ (M^+): 202.0994, found: 202.0986.

Decomplexation of 1-methylindole analog 60



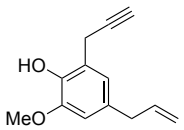
97

On 26.1 mg (0.0573 mmol) scale, the standard procedure was followed with $TEMPO^+BF_4^-$ (total 63.7 mg, 0.262 mmol) and a reaction time of 45 min. The crude was purified by silica gel column chromatography (hexane) to provide **97** (6.96 mg, 0.0441 mmol, 72%).

97: yellow oil; IR (neat): 3292 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.04 (s, 1H), 3.76 (s, 3H), 3.69 (d, *J* = 2.6 Hz, 2H), 2.13 (t, *J* = 2.6 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 137.2, 127.0, 126.8, 121.8, 119.0, 118.7, 109.4, 109.3, 82.6, 68.9,

32.7, 15.1; HRMS (ESI): calcd for $C_{12}H_{11}N$ ([M+H]$^+$): 169.0892, found: 169.0885.

Decomplexation of eugenol analog 44

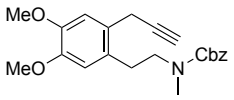


98

On 13.1 mg (0.0263 mmol) scale, the standard procedure was followed with TEMPO$^+$BF$_4^-$ (total 25.3 mg, 0.104 mmol) and a reaction time of 40 min. The crude was purified by silica gel column chromatography (CH_2Cl_2 : hexane = 1 : 4) to provide **98** (3.01 mg, 0.0149 mmol, 58%) and recovered **44** (1.27 mg, 2.55 μmol, 10%).

98: colorless oil; IR (neat): 3307, 2120 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.89 (d, *J* = 3.0 Hz, 1H), 6.61 (d, *J* = 3.0 Hz, 1H), 5.96 (ddt, *J* = 16.8 Hz, 10.0 Hz, 6.5 Hz, 1H), 5.62 (s, 1H), 5.11-5.05 (m, 2H), 3.87 (s, 3H), 3.58 (d, *J* = 2.8 Hz, 2H), 3.33 (d, *J* = 6.5 Hz, 2H), 2.15 (t, *J* = 2.8 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 146.1, 141.3, 137.8, 131.4, 121.7, 121.1, 115.6, 109.7, 81.9, 69.9, 56.1, 40.0, 18.8; HRMS (ESI): calcd for $C_{13}H_{15}O_2$ ([M+H]$^+$): 203.1067, found: 203.1068.

Decomplexation of *N*-Cbz, homoveratrylamine analog 69

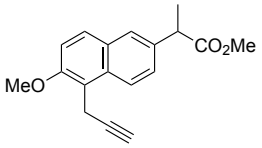


99

On 44.6 mg (0.0683 mmol) scale, the standard procedure was followed with TEMPO$^+$BF$_4^-$ (total 74.5 mg, 0.306 mmol) and a reaction time of 45 min. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 1) to provide **99** (20.4 mg, 0.0555 mmol, 81%).

99: colorless oil; IR (neat): 3286 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3SOCD_3): δ 7.36-7.30 (m, 5H), 6.97 (s, 1H), 6.72 (s, 1H), 5.06 (s, 2H), 3.74 (s, 1H), 3.70 (s, 3H), 3.49 (d, *J* = 2.5 Hz, 2H), 3.42 (t, *J* = 7.5 Hz, 2H), 2.86 (s, 3H), 2.78 (t, *J* = 7.5 Hz, 2H), 2.78 (t, *J* = 2.5 Hz, 1H); ^{13}C-NMR (100 MHz, CD_3SOCD_3): δ 154.9, 147.7, 147.3, 136.6, 128.8, 127.8, 127.1, 126.9, 126.6, 114.5, 113.8, 82.2, 71.7, 65.7, 55.7, 48.8, 40.1, 33.8, 29.6, 20.7; HRMS (EI): calcd for $C_{22}H_{25}NO_4$ (M$^+$): 367.1784, found: 367.1790.

Decomplexation of naproxen methyl ester analog 30

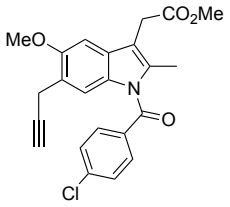


100

On 40.1 mg (0.0706 mmol) scale, the standard procedure was followed with $TEMPO^{+}BF_4^{-}$ (total 62.2 mg, 0.285 mmol) and a reaction time of 40 min. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 20) to provide **100** (18.2 mg, 0.0643 mmol, 91%).

100: colorless oil; IR (neat): 3290 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.9 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.69 (s, 1H), 7.50 (d, *J* = 8.9 Hz, 1H), 7.26 (d, *J* = 7.9 Hz, 1H), 3.97 (d, *J* = 2.3 Hz, 1H), 3.97 (s, 3H), 3.87 (q, *J* = 7.0 Hz, 1H), 3.67 (s, 3H), 1.97 (t, *J* = 2.3 Hz, 1H), 1.58 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 175.0, 154.0, 135.6, 131.8, 129.3, 128.8, 126.7, 123.8, 117.5, 113.9, 82.8, 67.9, 56.8, 52.0, 45.2, 18.5, 14.4; HRMS (ESI): calcd for $C_{18}H_{19}O_3$ ($[M+H]^+$): 283.1329, found: 283.1324.

Decomplexation of indomethacin methyl ester analog 74

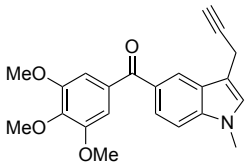


101

On 10.4 mg (0.0149 mmol) scale, the standard procedure was followed with $TEMPO^{+}BF_4^{-}$ (total 15.9 mg, 0.0656 mmol) and a reaction time of 40 min to provide **101** (4.42 mg, 0.0108 mmol, 72%).

101: colorless oil; IR (neat): 3301, 1738 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.7 Hz, 2H), 7.48 (d, *J* = 8.7 Hz, 2H), 7.01 (s, 1H), 6.89 (s, 1H), 3.87 (s, 3H), 3.70 (s, 3H), 3.68 (s, 2H), 3.49 (d, *J* = 2.6 Hz, 2H), 2.46 (s, 3H), 1.97 (t, *J* = 2.6 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.4, 168.4, 153.4, 139.0, 135.5, 134.0, 131.1, 130.2, 129.14, 129.08, 120.7. 114.7, 112.5, 98.7, 81.5, 70.6, 55.7, 52.1, 30.2, 19.7, 13.3; HRMS (ESI): calcd for $C_{23}H_{21}NO_4Cl$ ($[M+H]^+$): 410.1154, found: 410.1148.

Decomplexation of 76

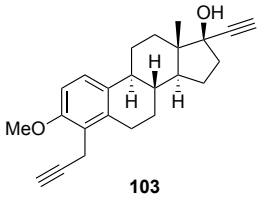


102

On 49.2 mg (0.0758 mmol) scale, the standard procedure was followed with $TEMPO^{+}BF_4^{-}$ (total 84.1 mg, 0.346 mmol) and a reaction time of 45 min to provide **102** (25.6 mg, 0.0704 mmol, 93%).

102: white amorphous; IR (neat): 3285, 1644 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 1.4 Hz, 1H), 7.80 (dd, *J* = 8.7 Hz, 1.4 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.13 (s, 1H), 7.10 (s, 2H), 3.95 (s, 3H), 3.88 (s, 6H), 3.82 (s, 3H), 3.70 (d, *J* = 2.6 Hz, 2H), 2.13 (t, 2.6 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 196.2, 152.8, 141.4, 139.4, 134.1, 129.0, 128.4, 126.3, 124.2, 122.9, 111.5, 109.1, 107.7, 82.0, 69.3, 61.0, 56.3, 32.9, 15.1; HRMS (EI): calcd for $C_{22}H_{21}NO_4$ (M^{+}): 363.1471, found 363.1485.

Decomplexation of mestranol analog 53

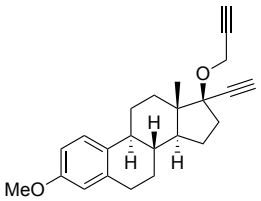


103

On 0.208 mmol scale, the standard procedure was followed with $TEMPO^{+}BF_4^{-}$ (total 22. 7 mg, 0.093 mmol) and a reaction time of 45 min. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 8 to 1 : 4) to provide **103** (6.83 mg, 0.0196 mmol, 94%).

103: colorless oil; IR (neat): 3301 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.5 Hz, 1H), 6.76 (d, *J* = 8.5 Hz, 1H), 3.84 (s, 3H), 3.55 (s, 2H), 3.02 (dd, *J* = 17.4 Hz, 4.8 Hz, 1H), 2.89-2.80 (m, 1H), 2.61 (s, 1H), 2.39-2.23 (m, 3H), 2.04-1.66 (m, 8H), 1.56-1.33 (m, 5H), 0.88 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 154.8, 136.5, 133.2, 124.9, 122.9, 108.5, 87.6, 82.5, 79.9, 74.0, 67.0, 55.9, 49.5, 47.0, 43.8, 39.0, 38.6, 32.8, 27.3, 26.7, 26.6, 22.8, 14.9, 12.6; HRMS (ESI): calcd for $C_{24}H_{29}O_2$ ($[M+H]^{+}$): 349.2162, found: 349.2160.

Decomplexation of mestranol analog 54

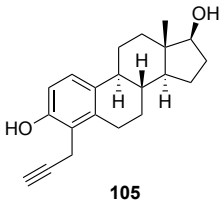


104

On 32.5 mg (0.0511 mmol) scale, the standard procedure was followed with $TEMPO^{+}BF_4^{-}$ (total 59.0 mg, 0.243 mmol) and a reaction time of 45 min. The crude was purified by silica gel column chromatography (CH_2Cl_2 : hexane = 1 : 4) to provide **104** (15.1 mg, 0.0434 mmol, 85%).

104: colorless oil; IR (neat): 3288 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.4 Hz, 1H), 6.71 (dd, *J* = 8.4 Hz, 2.2 Hz, 1H), 6.63 (s, 1H), 4.34 (s, 2H), 3.77 (s, 3H), 2.87-2.84 (m, 2H), 2.67 (s, 1H), 2.43 (s, 1H), 2.35-2.25 (m, 3H), 2.22-2.09 (m, 1H), 2.02-1.94 (m, 1H), 1.88-1.71 (m, 4H), 1.54-1.30 (m, 4H), 0.92 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 157.4, 137.9, 132.5, 126.3, 113.8, 111.5, 86.1, 83.9, 80.8, 76.8, 73.5, 55.2, 53.9, 49.4, 47.7, 43.4, 39.2, 37.1, 33.9, 29.8, 27.2, 26.5, 22.8, 12.8; HRMS (ESI): calcd for $C_{24}H_{29}O_2$ ($[M+H]^+$): 349.2162, found: 349.2159.

Decomplexation of estradiol analog 85

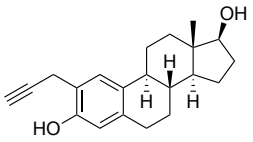


105

On 19.0 mg (0.0318 mmol) scale, the standard procedure was followed with $TEMPO^{+}BF_4^{-}$ (total 31.9 mg, 0.131 mmol) and a reaction time of 45 min. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 4 to 1 : 2) to provide **105** (7.13 mg, 0.0230 mmol, 72%).

105: colorless oil; IR (neat): 3305, 2115 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.12 (d, *J* = 8.3 Hz, 1H), 6.67 (d, *J* = 8.3 Hz, 1H), 5.23 (br s, 1H), 3.74 (t, *J* = 8.3 Hz, 1H), 3.55 (d, *J* = 2.4 Hz, 1H), 2.99-2.93 (m, 1H), 2.85-2.81 (m, 1H), 2.33-2.27 (m, 1H), 2.23-2.10 (m, 2H), 2.02 (t, *J* = 2.4 Hz, 1H), 2.00-1.92 (m, 2H), 1.75-1.68 (m, 1H), 1.54-1.14 (m, 7H), 0.77 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 151.3, 136.2, 133.5, 125.1, 120.8, 113.3, 81.9, 81.8, 68.4, 50.0, 44.2, 43.2, 38.0, 36.7, 30.6, 27.3, 26.9, 26.6, 23.1, 15.2, 11.0; HRMS (ESI): calcd for $C_{21}H_{25}O_2$ ($[M-H]^-$): 309.1849, found: 309.1863.

Decomplexation of estradiol analog 84

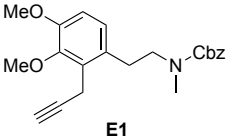


106

On 15.43 mg (0.0260 mmol) scale, the standard procedure was followed with $TEMPO^{+}BF_4^{-}$ (total 30.5 mg, 0.125 mmol) and a reaction time of 45 min. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 8 to 1 : 4) to provide **106** (2.68 mg, 8.63 μmol, 33%) and recovered **84** (4.03 mg, 6.76 μmol, 26%).

106: colorless oil; IR (neat): 3306 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.22 (s, 1H), 6.54 (s, 1H), 5.12 (br s, 1H), 3.73 (t, *J* = 8.5 Hz, 1H), 3.54 (d, *J* = 2.8 Hz, 2H), 2.82-2.78 (m, 2H), 2.35-2.31 (m, 1H), 2.22 (t, *J* = 2.8 Hz, 1H), 2.17-2.07 (m, 2H), 1.98-1.93 (m, 1H), 1.88-1.84 (m, 1H), 1.73-1.66 (m, 1H), 1.52-1.15 (m, 8H), 0.78 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 151.3, 137.0, 133.0, 126.5, 119.5, 115.9, 81.9, 81.6, 70.9, 50.0, 44.0, 43.3, 38.8, 36.7, 30.6, 29.7, 29.2, 27.2, 26.4, 23.1, 19.8, 11.0; HRMS (ESI): calcd for $C_{21}H_{25}O_2$ ($[M-H]^-$): 309.1849, found: 309.1860.

Decomplexation of *N*-Cbz, methyl homoveratrilamine 70



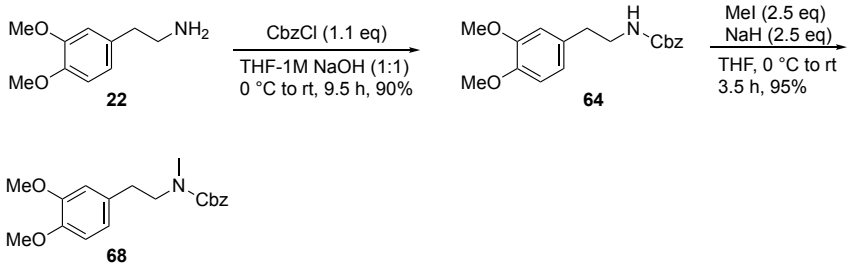
E1

On 8.73 mg (0.0133 mmol) scale, the standard procedure was followed with TEMPO (13.0 mg, 0.0535 mmol) and a reaction time of 40 min. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 4 to 1 : 1) to provide **E1** (3.86 mg, 0.0105 mmol, 79%).

E1: colorless oil; IR (neat): 3289 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3SOCD_3): δ 7.36-7.30 (m, 5H), 7.36 (d, *J* = 8.6 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 1H), 5.07 (s, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.51 (d, *J* = 2.7 Hz, 2H), 3.44 (t, *J* = 7.8 Hz, 2H), 2.86 (s, 3H), 2.84 (t, *J* = 7.8 Hz, 2H), 2.60 (t, *J* = 2.7 Hz, 1H); ^{13}C-NMR (100 MHz, CD_3SOCD_3): δ 154.9. 150.6, 146.6, 136.7, 129.6, 128.7, 127.8, 127.1, 126.9, 124.4, 111.8, 82.6, 69.7, 65.7, 59.7, 55.5, 49.1, 33.8, 29.8, 14.6; HRMS (ESI) $C_{22}H_{26}O_4N$ ($[M+H]^+$) calcd for 368.1856, found 368.1852.

Preparation of substrates

Synthesis of benzyl (3,4-dimethoxyphenethyl)(methyl)carbamate (68)



Benzyl (3,4-dimethoxyphenethyl)carbamate (**64**)

To a solution of homoveratrylamine (**22**) (0.9 ml, 5.44 mmol) in THF (14 ml) and 1M NaOH aq. (14 ml) was added CbzCl (0.85 ml, 6.03 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 9.5 h. The reaction mixture was dilutied with water (10 ml) and extracted with Et_2O (20 ml × 2), washed with brine and dried over $MgSO_4$ The organic layer was concentrated under vacuum and purified with column chromatography on silica gel (AcOEt : Hexane = 1 : 1) to give carbamate **64** (1.54 g, 4.88 mmol, 90%).

64: white solid; IR (solid): 3331 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.38-7.30 (m, 5H), 6.80 (d, J = 8.2 Hz, 1H), 6.73-6.70 (m, 2H), 5.10 (s, 2H), 4.75 (br s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.44 (q, J = 6.5 Hz, 2H), 2.76 (t, J = 6.5 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 156.3, 149.0, 147.7, 136.5, 131.1, 128.5, 128.1, 126.9, 120.6, 111.9, 111.3, 66.6, 55.9, 55.8, 42.3, 35.6; HRMS (ESI): calcd for $C_{18}H_{21}O_4NNa$ ([M+Na]$^+$): 338.1363, found 338.1357.

Benzyl (3,4-dimethoxyphenethyl)(methyl)carbamate (**68**)

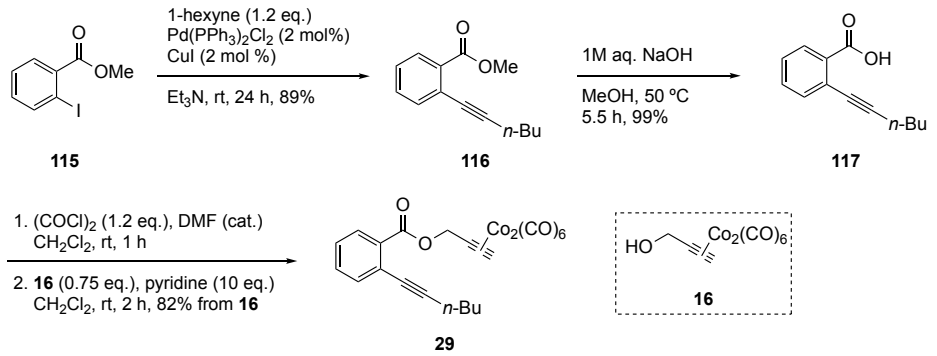
To a solution of carbamate **64** (1.00g, 3.17 mmol) in THF (16 ml) was added 60% NaH (387 mg, 9.68 mmol) at 0 °C and stirred for 30 min at room temperature. The reaction mixture was cooled at 0 °C and added MeI (0.5 ml, 0.80 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 3.5 h. The solution was quenched with sat. NH_4Cl (5 ml) and extracted with Et_2O (20 ml × 2), washed with brine and dried over Mg_2SO_4. The organic layer was concentrated under vacuum and purified with column chromatography on silica gel (AcOEt : hexane = 1 : 1) to give **68** (998 mg, 3.03 mm, 95%) as a yellow oil.

68: yellow oil; IR (neat): 1700 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3SOCD_3): δ 7.35-7.30 (m, 5H), 6.84 (d, J = 8.2 Hz, 1H), 6.77 (s, 1H), 6.79 (d, J = 8.2 Hz, 1H), 5.04 (s, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 3.46 (t, J = 7.2 Hz, 2H), 2.83 (s, 3H), 2.73 (t, J = 7.2 Hz, 2H); ^{13}C-NMR (100 MHz, CD_3SOCD_3): δ 154.9, 148.8, 147.4, 136.7, 131.4, 127.7, 127.1, 126.8, 120.4, 113.3, 112.7, 65.6, 56.0, 55.5, 49.5, 33.7, 32.6; HRMS (ESI): calcd for $C_{19}H_{23}O_4N$ ([M+H]$^+$): 352.1519, found 352.1505.

<Chapter 2>

Reagent synthesis

2-1. Synthesis of reagent 29



Methyl 2-(hex-1-yn-1-yl)benzoate (116)

To a solution of methyl 2-iodobenzoate (524 mg, 2.00 mmol) and 1-hexyne (0.28 mL, 2.44 mmol) in Et_3N (6.0 mL) was added $Pd(PPh_3)_2Cl_2$ (28.0 mg, 39.9 μmol) and CuI (8.97 mg, 47.0 μmol) at room temperature. The reaction mixture was stirred at the same temperature for 24 h, then concentrated under vacuo. CH_2Cl_2 (30 mL) was added to the residue, and the organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by column chromatography on silica gel (AcOEt : Hexane = 1 : 20) to give alkyne **116** (385 mg, 1.78 mmol, 89%).

2-(Hex-1-yn-1-yl)benzoic acid (117)

To a solution of benzoate **116** (1.27 g, 5.89 mmol) in MeOH (25 mL) was added 1 M NaOH (25 mL) at room temperature. The reaction mixture was stirred at the same temperature for 5.5 h. The mixture was poured into 1 M HCl (30 mL), and extracted with Et_2O (40 mL × 2). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by column chromatography on silica gel (AcOEt : Hexane = 1 : 1) to give benzoic acid **117** (1.18 g, mmol, 99%).

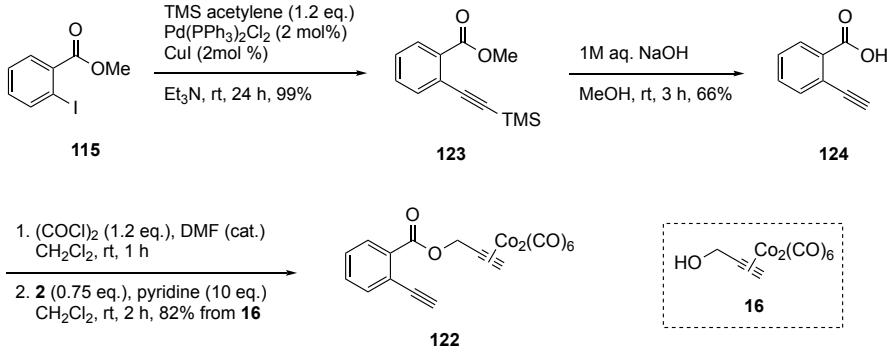
Reagent 29

To a solution of benzoic acid **117** (296 mg, 1.46 mmol) in CH_2Cl_2 (4.8 mL) was added $(COCl)_2$ (150 μL, 1.75 mmol) and DMF (10 μL, 0.13 μmol) at room temperature. The reaction mixture was stirred at the same temperature for 1 h. The reaction mixture was concentrated under vacuo. To the residue was added CH_2Cl_2 (7.3 mL), pyridine (1.2 mL), and alkyne cobalt complex **16** (370 mg, 1.10 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 2 h. The reaction mixture was quenched with water (4 mL) and extracted with CH_2Cl_2 (10 mL × 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified with silica gel column chromatography (AcOEt : Hexane = 1 : 20) to give complex **29** (471 mg, 0.90 mmol,

82% from **16**).

29: red oil; IR (neat): 2022 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 7.6 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.43 (td, *J* = 7.6, 1.0 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 6.12 (s, 1H), 5.52 (s, 2H), 2.50 (t, *J* = 7.1 Hz, 2H), 1.69-1.58 (m, 2H), 1.58-1.45 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.1, 165.6, 134.5, 131.8, 131.0, 130.1, 127.1, 125.2, 96.5, 88.7, 79.3, 72.2, 65.4, 30.8, 22.1, 19.6, 13.7; HRMS (ESI): calcd for $C_{22}H_{16}O_8Co_2Na$ ($[M+Na]^+$): 548.9401, found 548.9393.

2-2. Synthesis of reagent 122



Methyl 2-((trimethylsilyl)ethynyl)benzoate (123)

To a solution of methyl 2-iodobenzoate (5.24 g, 20.0 mmol) and TMS acetylene (3.39 mL, 24.0 mmol) in Et_3N (60 mL) was added $Pd(PPh_3)_2Cl_2$ (14.0 mg, 0.02 mmol) and CuI (3.8 mg, 0.02 mmol) at room temperature. The reaction mixture was stirred at the same temperature overnight and concentrated under vacuo. To the residue was added CH_2Cl_2 (30 mL) and the organic layer was washed with saturated aqueous .NH_4Cl (30 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated under vacuo and purified by column chromatography on silica gel (AcOEt : hexane = 1 : 30) to give alkyne **123** (5.14 g, quant.). Characterization data were in agreement with previously reported values.[3]

2-Ethynylbenzoic acid (124)

To a solution of benzoate **123** (996 mg, 4.29 mmol) in MeOH (18 mL) was added 1 M NaOH (18 mL) at room temperature. The reaction mixture was stirred at the same temperature for 3 h. The mixture was poured into conc. HCl (4 mL), and extracted with Et_2O (30 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated under vacuo and purified by column chromatography on silica gel (AcOEt : hexane = 4 : 1 to 1 : 1) to give benzoic acid **124** (412 mg, 2.82 mmol, 66%). Characterization data were in agreement with previously reported values.[4]

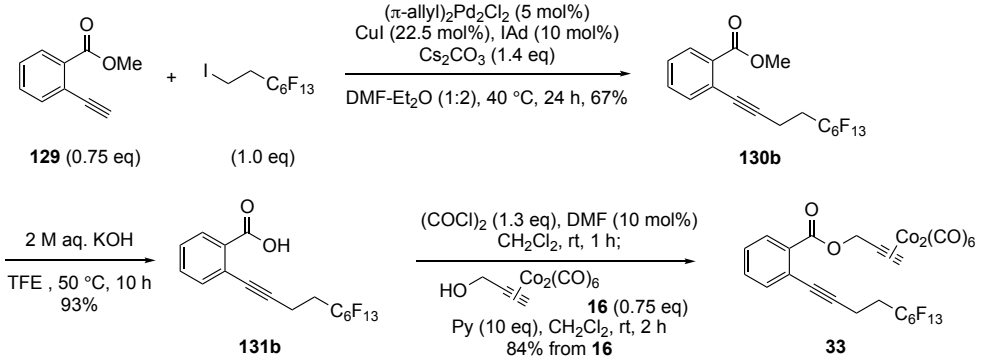
Reagent 122

To a solution of benzoic acid **124** (295 mg, 2.02 mmol) in CH_2Cl_2 (6.8 mL) was added $(COCl)_2$ (0.21 mL, 2.42 mmol)

and DMF (10 μL, 0.13 μmol) at room temperature. The reaction mixture was stirred at the same temperature for 1 h. The reaction mixture was concentrated in vacuo. To the residue was added CH_2Cl_2 (10 mL), pyridine (1.6 mL) and alkyne cobalt complex **16** (345 mg, 1.01 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 2 h. The reaction mixture was quenched with water (10 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt : Hexane = 1 : 20) to give complex **122** (395 mg, 0.830 mmol, 82% from **16**).

122: red oil; IR (neat): 2036 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 7.4 Hz, 1H), 7.65 (d, J = 7.4 Hz, 1H), 7.50 (t, J = 7.4 Hz, 1H), 7.41 (t, J = 7.4 Hz, 1H), 6.13 (s, 1H), 5.54 (s, 2H), 3.44 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.1, 165.3, 135.2, 132.0, 131.7, 130.2, 128.5, 123.1, 88.3, 82.6, 82.0, 72.3, 65.6; HRMS (ESI): calcd for $C_{18}H_8O_8Co_2Na$ ([M+Na]$^+$): 492.8775, found 492.8754.

2-3. Synthesis of reagent 33



Methyl 2-(5,5,6,6,7,7,8,8,9,9,10,10,10-tridecafluorodec-1-yn-1-yl)benzoate (130b)

To a solution of (π-allyl)$_2$Pd$_2$Cl$_2$ (46 mg, 0.13 mmol), IAd (99 mg, 0.25 mmol), CuI (108 mg, 0.56 mmol), and Cs_2CO_3 (1.14 g, 3.5 mmol) in DMF-Et_2O (1:2) (5 mL) was added alkyne **129** (0.46 mL, 1.88 mmol), and 1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoro-8-iodooctane (0.60 mL, 2.5 mmol) at room temperature. The reaction mixture was stirred at 40 °C for 24 h and concentrated under vacuo and purified by column chromatography on silica gel (CH_2Cl_2 : Hexane = 1 : 30 to 1 : 8) to give alkyne **130b** (629 mg, 1.24 mmol, 67% from **129**).

130b: yellow oil; IR (neat): 1733 cm^{-1}; 1H-NMR (600 MHz, $CDCl_3$): δ 7.91 (d, J = 7.6 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 3.92 (s, 3H), 2.82 (t, J = 7.6 Hz, 2H), 2.56-2.42 (m, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 166.6, 134.2, 132.0, 131.6, 130.3, 127.7, 123.6, 91.5, 80.4, 52.0, 30.6 (t, $^1J_{CF}$ = 21.7 Hz), 11.9 (t, $^2J_{CF}$ = 5.8 Hz); ^{19}F-NMR (562 MHz, $CDCl_3$): δ 83.9 (s, 3F), 118.3 (s, 2F), 125.1 (s, 2F), 126.0 (s, 2F), 126.7 (s, 2F), 129.3 (s, 2F); HRMS (EI): calcd for $C_{18}H_{11}O_2F_{13}$ (M^+): 506.0551, found 506.0543.

2-(5,5,6,6,7,7,8,8,9,9,10,10,10-Tridecafluorodec-1-yn-1-yl)benzoic acid (131b)

To a solution of benzoate **131b** (1.37 g, 2.71 mmol) in TFE (7.3 mL) was added 2 M KOH (7.3 mL) at room temperature. The reaction mixture was stirred at 50 °C for 10 h. The mixture was added 1 M HCl (15 mL), and the mixture was extracted with Et_2O (20 mL × 3), and concentrated under vacuo. The crude mixture was dissolved in CH_2Cl_2 (10 mL) and extracted with 1 M NaOH (15 mL × 2), and neutralized with 1 M HCl (30 mL), and the mixture was extracted with Et_2O (30 mL × 3). The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuo to give carboxylic acid **131b** (1.24 g, 2.5 mmol, 93%).

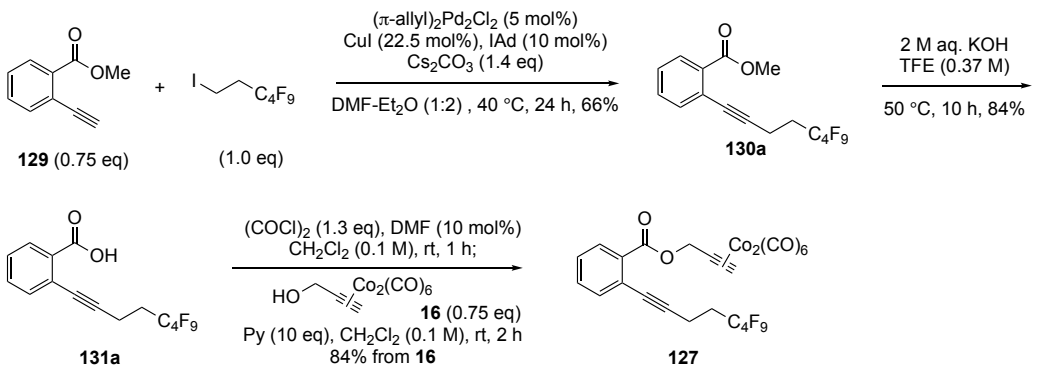
131b: white solid; mp. 78-80 °C; IR (neat): 1698 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.06 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 2.83 (t, J = 7.6 Hz, 2H), 2.56-2.44 (m, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 170.5, 134.3, 132.5, 131.2, 130.7, 127.9, 124.1, 92.7, 80.2, 30.4 (t, $^1J_{CF}$ = 21.7 Hz), 11.9 (t, $^2J_{CF}$ = 5.8 Hz); ^{19}F-NMR (562 MHz, $CDCl_3$): δ 83.9 (s, 3F), 118.3 (s, 2F), 125.1 (s, 2F), 126.0 (s, 2F), 126.7 (s, 2F), 129.3 (s, 2F); HRMS (EI): calcd for $C_{17}H_9O_2F_{13}$ (M^+): 492.0395, found 492.0373.

Reagent 33

To a solution of benzoic acid **131b** (248 mg, 0.50 mmol) in CH_2Cl_2 (5.0 mL) was added $(COCl)_2$ (56 μL, 0.65 mmol) and DMF (10 μL, 0.13 μmol) at room temperature. The reaction mixture was stirred at the same temperature for 1 h. The reaction mixture was concentrated under vacuo. To the residue was added CH_2Cl_2 (5.0 mL), pyridine (0.38 mL, 5.0 mmol) and then alkyne cobalt complex **16** (128 mg, 0.38 mmol). The reaction mixture was stirred at the same temperature for 2 h. The reaction mixture was quenched with water (10 mL), extracted with CH_2Cl_2 (15 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by silica gel column chromatography (AcOEt : Hexane = 1 : 100) to give reagent **33** (257 mg, 0.31 mmol, 84% from **16**).

33: red solid; IR (neat): 2029, 1733 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.01 (d, J = 7.6 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 6.13 (s, 1H), 5.52 (s, 2H), 2.83 (t, J = 7.6 Hz, 2H), 2.61-2.45 (m, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.1, 165.2, 134.4, 132.0, 131.1, 130.2, 127.7, 124.3, 92.0, 88.6, 80.4, 72.1, 65.4, 30.5 (t, $^1J_{CF}$ = 23.1 Hz), 11.9 (t, $^2J_{CF}$ = 5.8 Hz); ^{19}F-NMR (562 MHz, $CDCl_3$): δ 83.9 (s, 3F), 118.3 (s, 2F), 125.0 (s, 2F), 125.9 (s, 2F), 126.6 (s, 2F), 129.2 (s, 2F); HRMS (ESI): calcd for $C_{26}H_{11}O_8Co_2F_{13}Na$ ($[M+Na]^+$): 838.8803, found 838.8793.

2-4. Synthesis of reagent 127



Methyl 2-(5,5,6,6,7,7,8,8,8-nonafluorooct-1-yn-1-yl)benzoate (130a)

To a solution of (π-allyl)$_2$Pd$_2$Cl$_2$ (92 mg, 0.25 mmol), 1,3-di(1-adamantyl)imidazolium hydrochloride (IAd) (198 mg, 0.5 mmol), CuI (216 mg, 1.12 mmol), and Cs_2CO_3 (2.28 g, 7.0 mmol) in DMF-Et_2O (1:2) (10 mL) was added alkyne **129** (0.92 mL, 3.75 mmol) and 2-(nonafluorobutyl)ethyl iodide (0.86 mL, 5.0 mmol) at room temperature. The reaction mixture was stirred at 40 °C for 24 h, the reaction mixture was concentrated under vacuo and purified by column chromatography on silica gel (CH_2Cl_2 : Hexane = 1 : 30 to 1 : 8) to give alkyne **130a** (1.08 g, 2.70 mmol, 53% from **129**).

130a: yellow oil; IR (neat): 2955, 1734 cm^{-1}; 1H-NMR (600 MHz, $CDCl_3$): δ 8.02 (d, J = 8.2 Hz, 1H), 7.70 (t, J = 7.6 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 3.88 (s, 3H), 3.37 (t, J = 7.6 Hz, 2H), 2.56-2.41 (m, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 195.8, 193.3, 167.3, 138.2, 133.4, 131.5, 129.5, 129.2, 129.1, 52.9, 27.9, 24.8 (t, $^1J_{CF}$ = 23.1 Hz); ^{19}F-NMR (562 MHz, $CDCl_3$): δ 84.1 (s, 3F), 117.5 (s, 2F), 127.5 (s, 2F), 129.2 (s, 2F); HRMS (ESI): calcd for $C_{11}H_{11}O_2F_9Na$ ([M+Na]$^+$): 429.0508, found 429.0505.

2-(5,5,6,6,7,7,8,8,8-Nonafluorooct-1-yn-1-yl)benzoic acid (131a)

To a solution of benzoate **130a** (274 mg, 0.67 mmol) in 2,2,2-trifluoroethanol (TFE) (1.8 mL) was added 2 M KOH (1.8 mL) at room temperature. The reaction mixture was and stirred at 50 °C for 16 h. To the mixture was added 1 M HCl (5 mL), and the resulting mixture was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by column chromatography on silica gel (AcOEt : Hexane = 1 : 20) to give benzoic acid **131a** (244 mg, 0.62 mmol, 92%).

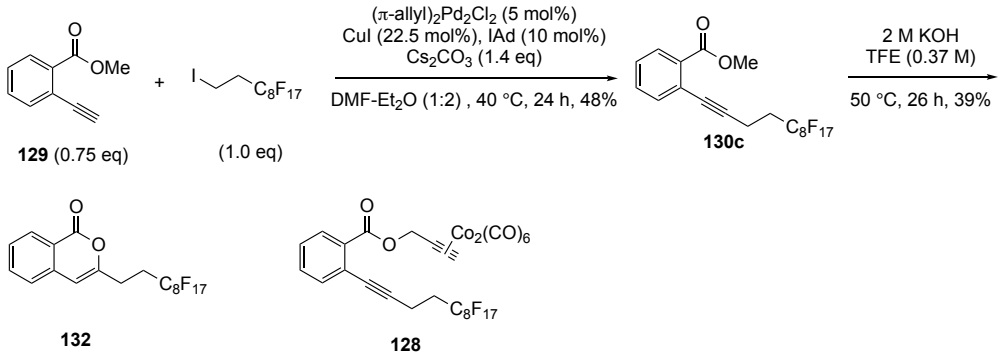
131a: white solid; mp. 82-84 °C; IR (neat): 1705 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 7.7 Hz, 1H), 7.56 (d, J = 7.7 Hz, 1H), 7.51 (t, J = 7.7, 1H), 7.40 (t, J = 7.7 Hz, 1H), 2.82 (t, J = 7.7 Hz, 2H), 2.64-2.38 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.8, 134.3, 132.6, 131.2, 130.8, 127.9, 124.2, 92.7, 80.2, 30.3 (t, $^1J_{CF}$ = 21.3 Hz), 11.9 (t, $^2J_{CF}$ = 4.9 Hz) ; ^{19}F-NMR (562 MHz, $CDCl_3$): δ 84.1 (s, 3F), 118.5 (s, 2F) 127.6 (s, 2F), 129.1 (s, 2F); HRMS (EI): calcd for $C_{15}H_9O_2F_9$ (M$^+$): 392.0459, found 392.0440.

Reagent 127

To a solution of benzoic acid **131a** (196 mg, 0.50 mmol) in CH_2Cl_2 (1.7 mL) was added $(COCl)_2$ (58 μL, 0.65 mmol) and DMF (4.0 μL, 0.05 μmol) at room temperature. The reaction mixture was stirred at the same temperature for 1 h. The reaction mixture was concentrated under vacuo. To the residue was added CH_2Cl_2 (2.5 mL), pyridine (0.38 mL, 5.0 mmol) and then alkyne cobalt complex **16** (128 mg, 0.38 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 2 h. The reaction mixture was quenched with water (5 mL), extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified with silica gel column chromatography (AcOEt : Hexane = 1 : 100) to give reagent **127** (231 mg, 0.32 mmol, 84% from **16**).

129: red oil; IR (neat): 2030, 1732 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.01 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 6.13 (s, 1H), 5.53 (s, 2H), 2.82 (t, J = 6.8 Hz, 2H), 2.56-2.43 (m, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.0, 165.2, 134.4, 132.0, 131.1, 130.2, 127.7, 124.3, 92.0, 88.6, 80.4, 72.1, 65.4, 30.4 (t, $^1J_{CF}$ = 21.5 Hz), 11.9 (t, $^2J_{CF}$ = 5.7 Hz) ; ^{19}F-NMR (562 MHz, $CDCl_3$): δ 84.1 (s, 3F), 118.6 (s, 2F), 127.7 (s, 2F), 129.9 (s, 2F); HRMS (EI): calcd for $C_{21}H_{11}F_9O_5Co_2$ ([M-3CO]$^+$): 631.9127, found: 631.9111.

2-5. Attempted synthesis of reagent 128



2-(5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-Heptadecafluorododec-1-yn-1-yl)benzoate (130c)

To a solution of (π-allyl)$_2$Pd$_2$Cl$_2$ (28 mg, 75 μmol), IAd (56 mg, 0.15 mmol), CuI (65 mg, 0.34 mmol), Cs_2CO_3 (684 mg, 2.1 mmol) in DMF-Et_2O (1:2) (3 mL) was added alkyne **129** (0.16 mL, 1.1 mmol), 1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-heptadecafluoro-10-iododecane (861 mg, 1.5 mmol) at room temperature. The reaction mixture was stirred at 40 °C for 24 h and concentrated under vacuo and purified by column chromatography on silica gel (CH_2Cl_2 : Hexane = 1 : 30 to 1 : 8) to give alkyne **130c** (327 mg, 0.54 mmol, 48% from **129**).

130c: yellow oil; IR (neat): 2926, 1735 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.92 (d, J = 7.6 Hz, 1H), 7.52 (d, J = 8.3 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 3.92 (s, 3H), 2.82 (t, J = 7.6 Hz, 2H), 2.57-2.44 (m, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 166.6, 134.2, 132.0, 131.6, 130.3, 127.7, 123.6, 91.5, 80.4, 52.1, 30.6 (t, $^1J_{CF}$

= 21.7 Hz), 11.9 (t, $^2J_{CF}$ = 5.8 Hz); ^{19}F-NMR (562 MHz, $CDCl_3$): δ 83.9 (s, 3F), 117.8 (s, 2F), 1118.3 (s, 2F), 124.8 (s, 2F), 125.0 (s, 2F), 125.8 (s, 2F), 126.6 (s, 2F), 129.2 (s, 2F); HRMS (EI): calcd for $C_{20}H_{11}O_2F_{17}$ (M^+): 606.0488, found 606.0482.

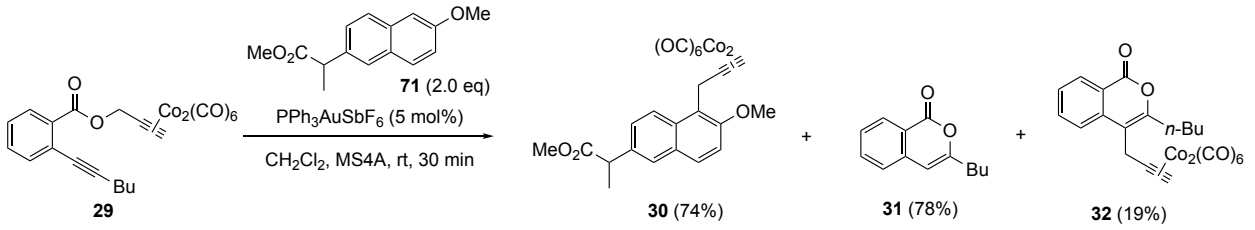
3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)-1*H*-isochromen-1-one (132)

To a solution of benzoate **130c** (327 mg, 0.54 mmol) in TFE (1.5 mL) was added 2 M KOH (1.5 mL) at room temperature. The reaction mixture was stirred at the same temperature for 26 h. The mixture was added 1 M HCl (5 mL), and the mixture was extracted with Et_2O (15 mL × 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by column chromatography on silica gel (AcOEt : Hexane = 1 : 20) to give isocoumarin **132** (124 mg, 0.21 mmol, 39%). Carboxylic acid was not obtained.

132: white solid; mp. 74-76 °C; IR (neat): 1718 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.27 (d, *J* = 7.5 Hz, 1H), 7.71 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 2.86 (t, *J* = 7.5 Hz, 2H), 2.62-2.49 (m, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 162.4, 154.2, 136.9, 135.0, 129.7, 128.3, 125.3, 120.3, 104.2, 28.7 (t, $^1J_{CF}$ = 22.9 Hz), 25.0 (t, $^2J_{CF}$ = 4.3 Hz); ^{19}F-NMR (562 MHz, $CDCl_3$): δ 83.9 (s, 3F), 117.5 (s, 2F), 117.9 (s, 2F), 124.8 (s, 2F), 125.0 (s, 2F), 125.8 (s, 2F), 126.5 (s, 2F), 129.2 (s, 2F); HRMS (EI): calcd for $C_{19}H_9O_2F_{17}$ (M^+): 592.0331, found 592.0310.

3. Reagent screening

3-1. Reaction of reagent 29 with substrate 71



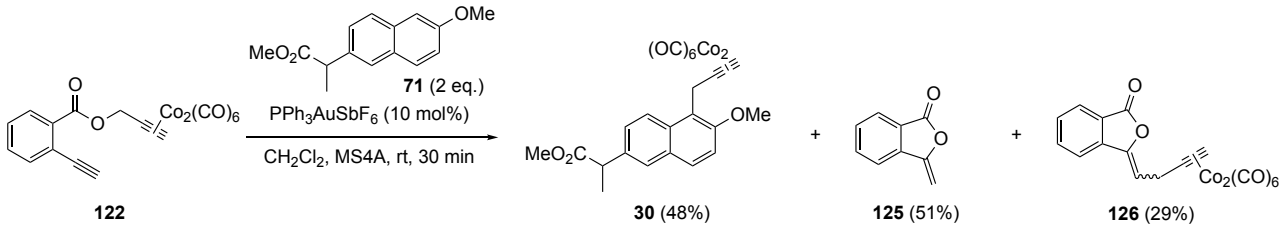
To a solution of **29** (0.1 mmol), naproxen methyl ester **71** (0.2 mmol) and MS4A (50 mg) in CH_2Cl_2 (1.6 mL) was added a solution of 2.5 mM PPh_3AuSbF_6 in CH_2Cl_2 (0.4 mL) at room temperature. The reaction mixture was stirred at the same temperature for 30 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (2 mL), extracted with CH_2Cl_2 (4 mL × 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo to give a crude mixture of **71**, **30**, **31,** and **32**. The ratio was determined by ^{1}H-NMR used toluene as the internal standard. The analytical samples were obtained by extensive PTLC (AcOEt : hexane = 1 : 8).

31: colorless oil; IR (neat): 1729 cm^{-1}; ^{1}H-NMR (400 Hz, $CDCl_3$): δ 8.25 (d, J = 7.7 Hz, 1H), 7.67 (td, *J* = 7.7 Hz, 1.4 Hz, 1H), 7.45 (td, *J* = 7.7 Hz, 1.4 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 6.25 (s, 1H), 2.53 (t, *J* = 7.5 Hz, 2H), 1.70 (quint, *J* = 7.5 Hz, 2H), 1.41 (sext, J = 7.5 Hz, 2H), 0.95 (t, *J* = 7.5 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.1, 165.6, 134.5, 131.8, 131.0, 130.1, 127.1, 125.2, 96.5, 88.7, 79.3, 72.2, 65.4, 30.8, 22.1, 19.6, 13.7; HRMS (EI): calcd

for $C_{13}H_{15}O_2$ ([M+H]$^+$): 203.1067, found 203.1063.

32: red oil; IR (neat): 2017 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.33 (d, J = 7.6 Hz, 1H), 7.80 (t, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 7.6, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 5.93 (s, 1H), 4.19 (s, 2H), 2.69 (t, *J* = 7.5 Hz, 2H), 1.77 (quint, *J* = 7.5 Hz, 2H), 1.45 (sext, *J* = 7.5 Hz, 2H), 0.98 (t, *J* = 7.5 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.3, 162.2, 155.6, 137.0, 134.5, 130.2, 127.7, 122.8, 120.8, 111.5, 93.1, 73.8, 30.9, 29.8, 22.5, 13.8; HRMS (EI): calcd for $C_{19}H_{16}O_5Co_2$ ([M-3CO]$^+$): 441.9662, found 441.9668.

3-2. Reaction of reagent 122 with substrate 71

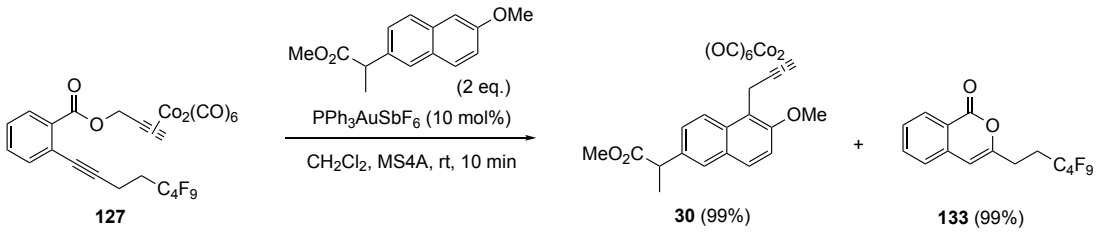


To a solution of **122** (0.1 mmol), naproxen methyl ester **71** (0.2 mmol) and MS4A (50 mg) in CH_2Cl_2 (1.6 mL) was added a solution of 2.5 mM PPh_3AuSbF_6 in CH_2Cl_2 (0.4 mL) at room temperature. The reaction mixture was stirred at the same temperature for 30 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (2 mL), extracted with CH_2Cl_2 (4 mL × 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo to give crude mixture of **71**, **30**, **125**, and **126**. The ratio was determined by ^{1}H-NMR used toluene as the internal standard. The analytical samples were obtained by PTLC (AcOEt : Hexane 1 : 8).

125: gray solid; IR (solid): 1765 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.92 (d, J = 7.6 Hz, 1H), 7.73 (d, J = 4.1 Hz, 2H), 7.60-7.58 (m, 2H), 5.25 (d, J = 3.4 Hz, 1H), 4.23 (d, J = 3.4 Hz, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 166.8, 131.8, 139.0, 134.4, 130.5, 125.3, 125.2, 120.6, 91.2; HRMS (ESI): calcd for $C_9H_6O_2Na$ ([M+Na]+): 169.0260, found 160.0255.

126: red oil; IR (neat): 2019 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 7.8 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.61 (t, *J* = 7.4 Hz, 1H), 6.09 (s, 1H), 6.01 (t, *J* = 8.3 Hz, 1H), 4.11 (d, *J* = 8.3 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.3, 166.5, 146.8, 137.6, 134.5, 130.3, 126.4, 125.9, 122.9, 110.8, 93.2, 72.8, 30.5; HRMS (ESI): calcd for $C_{18}H_8O_8Co_2Na$ ([M+Na]$^+$): 492.8775, found 492.8765.

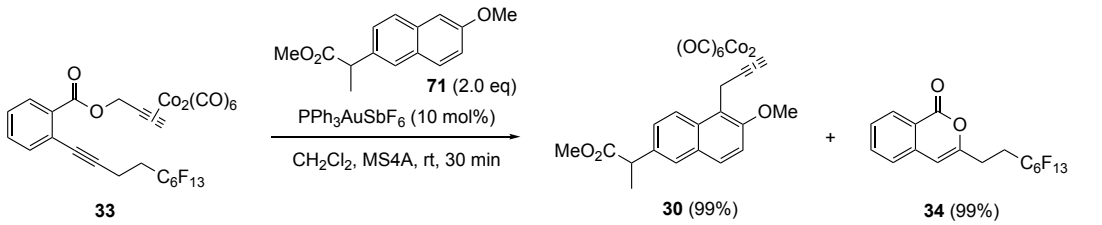
3-3. Reaction of reagent 127 with naproxen methyl ether



To a solution of **127** (71.6 mg, 0.1 mmol), naproxen methyl ester **71** (60.6 mg, 0.2 mmol) and MS4A (50 mg) in CH_2Cl_2 (1.6 mL) was added a solution of 2.5 mM PPh_3AuSbF_6 in CH_2Cl_2 (0.4 mL) at room temperature. The reaction mixture was stirred at the same temperature for 30 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (2 mL), extracted with CH_2Cl_2 (7 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo to give crude mixture of **30** and **71** and **133**. The ratio was determined by ^{1}H-NMR used toluene as the internal standard. The analytical samples were obtained by PTLC (AcOEt : Hexane 1 : 8).

133: white solid; mp. 50-52 °C; IR (neat): 1734 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.27 (d, J = 8.2 Hz, 1H), 7.71 (t, J = 7.6 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 6.37 (s, 1H), 2.86 (t, J = 7.6 Hz, 2H), 2.65-2.47 (m, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 162.3, 154.2, 136.9, 135.0, 129.7, 128.3, 125.3, 120.3, 104.3, 28.6 (t, $^1J_{CF}$ = 21.7 Hz), 25.0 (t, $^2J_{CF}$ = 4.3 Hz); HRMS (EI): calcd for $C_{15}H_9F_9O_2$ (M^+): 392.0459, found 392.0477.

3-4. Reaction of reagent 33 with naproxen methyl ether

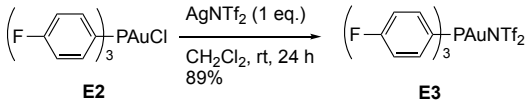


To a solution of **33** (81.6 mg, 0.1 mmol), naproxen methyl ester **71** (60.6 mg, 0.2 mmol) and MS4A (50 mg) in CH_2Cl_2 (1.6 mL) was added a solution of 2.5 mM PPh_3AuSbF_6 in CH_2Cl_2 (0.4 mL) at room temperature. The reaction mixture was stirred at the same temperature for 30 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (2 mL), extracted with CH_2Cl_2 (7 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo to give crude mixture of **30** and **34** and **71**. The ratio was determined by ^{1}H-NMR used toluene as the internal standard. The analytical samples were obtained by PTLC (AcOEt : Hexane 1 : 8).

34: white solid; mp. 54-56 °C; IR (neat): 1736 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.28 (d, J = 8.2 Hz, 1H), 7.71 (t, J = 7.5 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.39 (d, J = 7.5 Hz, 1H), 6.38 (s, 1H), 2.87 (t, J = 8.2 Hz, 2H), 2.61-2.48 (m, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 162.3, 154.2, 136.9, 135.0, 129.7, 128.3, 125.3, 120.3, 104.2, 28.7 (t, $^1J_{CF}$ = 22.9 Hz), 25.0 (t, $^2J_{CF}$ = 4.3 Hz); ^{19}F-NMR (562 MHz, $CDCl_3$): δ 83.9 (s, 3F), 117.9 (s, 2F), 125.0 (s, 2F), 126.0 (s,

2F), 126.5 (s, 2F), 129.2 (s, 2F) ; HRMS (EI): calcd for $C_{17}H_9F_{13}O_2$ (M^+): 492.0395, found: 492.0366.

4. Synthesis of gold catalyst E2



To CH_2Cl_2 (5.2 mL) was added gold catalyst **E2** (164 mg, 0.3 mmol), $AgNTf_2$ (116 mg, 0.3 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 24 h. AgCl was removed by filtration through Celite and concentrated under vacuo to give gold catalyst **E3** (211 mg, 0.27 mmol, 89%).

E3: white crystal; IR (neat): 1590, 1496 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.55-7.44 (m, 2H), 7.30-7.19 (m, 2H) ; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 165.5 (dd, $^1J_{CF}$ = 257.2 Hz, $^1J_{CP}$ = 3.3 Hz), 136.3 (dd, $^2J_{CP}$ = 15.6 Hz, $^2J_{CF}$ = 9.0 Hz), 122.7 (dd, $^3J_{CP}$ = 69.6 Hz, $^3J_{CF}$ = 3.3 Hz), 119.4 (q, $^5J_{CF}$ = 322.8 Hz), 117.5 (dd, $^4J_{CF}$ = 22.1 Hz, $^4J_{CP}$ = 13.9 Hz); HRMS (EI): calcd for $C_{20}H_{12}F_9NO_4PS_2Au$ (M^+): 792.9467, found: 792.9479.

Functionalization

Procedure A; Two-necked flask containing MS4A (50 mg) was dried using heat gun under vacuo and then cooled to room temperature. After done heating and cooling three times, in the flask was added substrate (50 μmol), reagent **33** (50 mg, 60 μmol), and DCE (1.0 mL) at room temperature. To the reaction mixture was added (4-F-C_6H_4)$_3$PAuNTf$_2$ (5-20 mol%) and stirred at the same temperature for 15 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (2 mL), and extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by silica gel column chromatography to give a desired product.

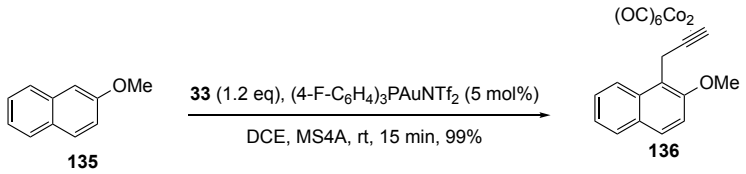
Procedure B; Two-necked flask containing MS4A (50 mg) was dried using heat gun under vacuo and then cooled to room temperature. After done heating and cooling three times, in the flask was added substrate (50 μmol), reagent **33** (50 mg, 60 μmol), DCE (1.0 mL), and HFIP (0.1 mL) at room temperature. To the reaction mixture was added (4-F-C_6H_4)$_3$PAuNTf$_2$ (5-20 mol%) and stirred at the same temperature for 15 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (2 mL), and extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by silica gel column chromatography to give a desired product.

Procedure C; Two-necked flask containing MS4A (50 mg) was dried using heat gun under vacuo and then cooled to room temperature. After done heating and cooling three times, in the flask was added substrate (50 μmol), reagent **33** (61 mg, 75 μmol), DCE (1.0 mL), and HFIP (0.1 mL) at room temperature. To the reaction mixture was added (4-F-C_6H_4)$_3$PAuNTf$_2$ (5-20 mol%) and stirred at the same temperature for 15 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (2 mL), and extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by silica gel column

chromatography to give a desired product.

Procedure D; Two-necked flask containing MS4A (50 mg) was dried using heat gun under vacuo and then cooled to room temperature. After done heating and cooling three times, in the flask was added substrate (50 μmol), reagent **33** (50 mg, 60 μmol), and DCE (1.0 mL) at room temperature. To the reaction mixture was added (4-F-$C_6H_4)_3PAuNTf_2$ (5-20 mol%) and stirred at the same temperature for 15 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (2 mL), and extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by silica gel column chromatography. After concentrated under vacuo, the residue was purified fluorous silica gel chromatography (H_2O : MeOH = 1 : 4). Fraction was extracted with CH_2Cl_2 (3 mL × 3) and then dried over $MgSO_4$, filtered, and concentrated under vacuo to give a desired product.

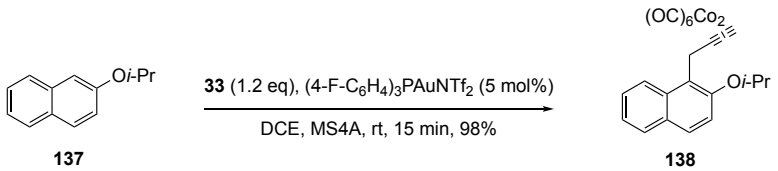
Functionalization of 2-methoxynaphthalene (135)



Procedure A was followed and used (4-F-$C_6H_4)_3PAuNTf_2$ (1.98 mg, 2.5 μmol). The crude mixture was purified by silica gel column chromatography (Hexane) to give **136** (23.8 mg, 49.3 μmol, 99%).

136: red oil; IR (neat): 2017 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 8.7 Hz, 1H), 7.82-7.74 (m, 2H), 7.52 (brt, J = 7.2 Hz, 1H), 7.35 (t, J = 7.2 Hz, 1H), 7.26 (d, J = 8.7 Hz, 1H), 5.93 (s, 1H), 4.63 (s, 2H), 3.97 (s, 3H) ; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.8, 154.1, 132.7, 129.2, 128.9, 128.7, 126.5, 123.3, 123.2, 121.3, 112.4, 96.4, 73.6, 55.6, 29.0 ; HRMS (EI): calcd for $C_{19}H_{12}O_6Co_2$ ([M-CO]$^+$): 453.9298, found: 453.9312.

Functionalization of 2-isopropoxynaphthalene (137)

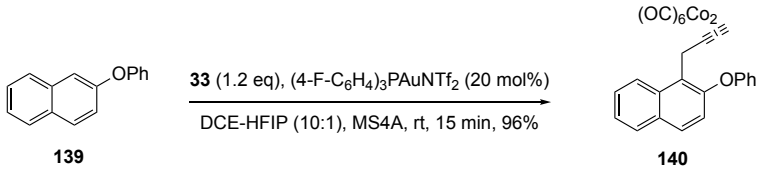


Procedure A was followed and used (4-F-$C_6H_4)_3PAuNTf_2$ (1.98 mg, 2.5 μmol). The crude mixture was purified by silica gel column chromatography (Hexane) to give **138** (30.0 mg, 48.9 μmol, 98%).

138: red oil; IR (neat): 2017 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 9.2 Hz, 1H), 7.52 (t, J = 8.2 Hz, 1H), 7.35 (t, J = 7.7 Hz, 1H), 7.23 (d, J = 9.2 Hz, 1H), 5.91 (s, 1H), 4.72 (quint, J = 6.3 Hz, 1H), 4.63 (s, 2H), 1.42 (d, J = 6.3 Hz, 6H) ; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.9, 152.7, 132.8, 129.2, 128.7, 128.6, 126.4, 123.41, 123.36, 122.6, 115.4, 96.4, 73.9, 71.3, 29.6, 22.4; HRMS (EI): calcd for

$C_{19}H_{18}O_4Co_2$ ([M-5CO]$^+$): 369.9814, found: 369.9786.

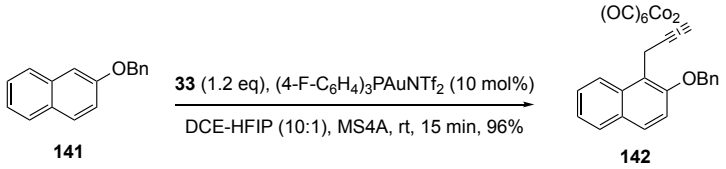
Functionalization of 2-phenoxynaphthalene (139)



Procedure B was followed and used (4-F-C_6H_4)$_3$PAuNTf$_2$ (7.92 mg, 10 μmol). The crude mixture was purified by silica gel column chromatography (Hexane) to give **140** (26.2 mg, 48.2 μmol, 96%).

140: red oil; IR (neat): 2019 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.7 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.74 (d, *J* = 8.7 Hz, 1H), 7.60 (dt, *J* = 7.7 Hz, *J* = 1.0 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.14 (d, *J* = 7.7 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 7.7 Hz, 2H), 5.91 (s, 1H), 4.63 (s, 2H) ; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.6, 157.8, 151.0, 132.7, 131.1, 129.8, 129.2, 128.8, 126.7, 125.9, 124.9, 123.9, 122.8, 119.9, 117.6, 95.5, 73.7, 29.8; HRMS (EI): calcd for $C_{22}H_{14}O_4Co_2$ ([M-3CO]$^+$): 459.9556, found: 459.9544.

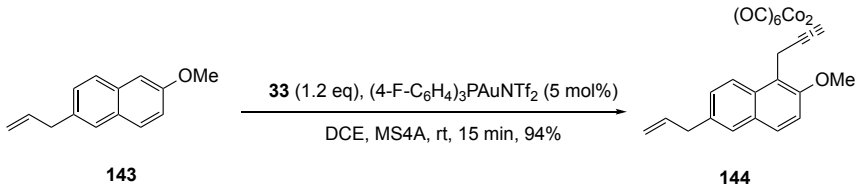
Functionalization of 2-(benzyloxy)naphthalene (S20)



Procedure B was followed and used (4-F-C_6H_4)$_3$PAuNTf$_2$ (3.96 mg, 5.0 μmol). The crude mixture was purified by silica gel column chromatography (Hexane to CH_2Cl_2 : Hexane = 1 : 50) to give **142** (26.7 mg, 47.8 μmol, 96%).

142: red oil; IR (neat): 2018 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.75 (d, *J* = 9.2 Hz, 1H), 7.53 (dt, *J* = 8.2 Hz, *J* = 1.2 Hz, 1H), 7.51-7.45 (m, 2H), 7.43-7.32 (m, 4H), 7.30 (d, *J* = 9.2 Hz, 1H), 5.90 (s, 1H), 5.26 (s, 2H), 4.68 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.7, 153.4, 137.1, 132.7, 129.4, 128.9, 128.64, 128.59, 127.9, 127.3, 126.6, 123.6, 123.4, 122.1, 114.2, 96.1, 73.9, 70.9, 29.5; HRMS (EI): calcd for $C_{23}H_{16}O_4Co_2$ ([M-3CO]$^+$): 473.9713, found: 473.9738.

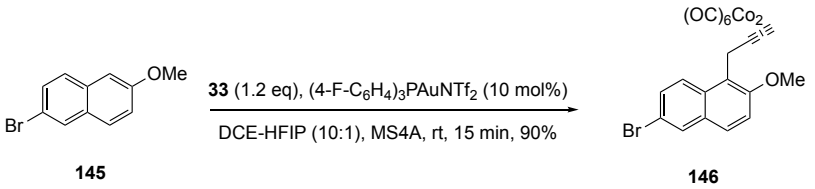
Functionalization of 2-allyl-6-methoxynaphthalene (143)



Procedure A was followed and used $(4\text{-F-}C_6H_4)_3PAuNTf_2$ (1.98 mg, 2.5 μmol). The crude mixture was purified by silica gel column chromatography (Hexane) to give **144** (24.5 mg, 46.8 μmol, 94%).

144: red oil; IR (neat): 2017 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.7 Hz, 1H), 7.72 (d, *J* = 8.7 Hz, 1H), 7.57 (s, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 7.22 (d, *J* = 9.2 Hz, 1H), 6.13-5.98 (m, 1H), 5.92 (s, 1H), 5.14 (d, *J* = 5.8 Hz, 1H), 5.10 (s, 1H), 4.61 (s, 2H), 3.96 (s, 3H), 3.52 (d, *J* = 6.3 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.8, 153.7, 137.4, 134.8, 131.3, 129.3, 128.4, 128.1, 127.4, 123.3, 121.1, 116.0, 112.5, 96.4, 73.6, 55.6, 40.0, 29.0; HRMS (EI): calcd for $C_{18}H_{16}O_2Co_2$ ([M-5CO]$^+$): 381.9814, found: 381.9833.

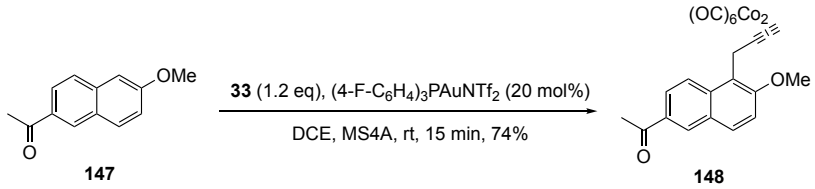
Functionalization of 2-bromo-6-methoxynaphthalene (145)



Procedure B was followed and used $(4\text{-F-}C_6H_4)_3PAuNTf_2$ (3.96 mg, 5.0 μmol). The crude mixture was purified by silica gel column chromatography (Hexane) to give **146** (25.2 mg, 44.9 μmol, 90%).

146: red oil; IR (neat): 2017 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 1.4 Hz, 1H), 7.82 (d, *J* = 9.2 Hz, 1H), 7.70 (d, *J* = 9.2 Hz, 1H), 7.58 (dd, *J* = 9.2 Hz, *J* = 1.4 Hz, 1H), 7.28 (s, 1H), 5.92 (s, 1H), 4.59 (s, 2H), 3.97 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.7, 154.3, 131.1, 130.5, 130.2, 129.8, 128.0, 125.0, 121.5, 117.0, 113.4, 95.7, 73.4, 55.6, 28.8; HRMS (EI): calcd for $C_{16}H_{11}{}^{79}BrO_3Co_2$ ([M-4CO]$^+$): 447.8556, found: 447.8568.

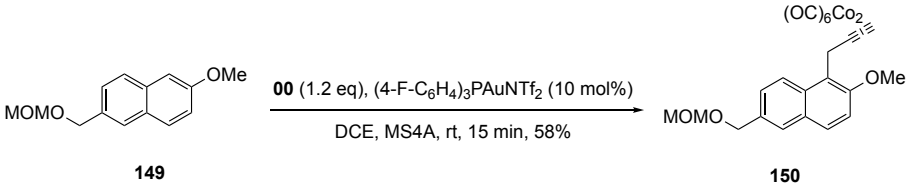
Functionalization of 2-acetyl-6-methoxynaphthalene (147)



Procedure A was followed and used $(4\text{-F-}C_6H_4)_3PAuNTf_2$ (7.92 mg, 10 μmol). The crude mixture was purified by silica gel column chromatography (AcOEt : Hexane = 1 : 50 to 1 : 20) to give **148** (19.5 mg, 37.2 μmol, 74%).

148: red oil; IR (neat): 2017, 1677 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 1H), 8.08 (dd, *J* = 9.2 Hz, 1.9 Hz, 1H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.92 (d, *J* = 9.2 Hz, 1H), 7.33 (d, *J* = 9.2 Hz, 1H), 5.93 (s, 1H), 4.63 (s, 2H), 4.00 (s, 3H), 2.71 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.7, 197.7, 156.3, 135.0, 132.3, 131.2, 130.9, 127.9, 124.6, 123.6, 121.6, 113.1, 95.6, 73.5, 55.6, 28.8, 26.5; HRMS (EI): calcd for $C_{17}H_{14}O_3Co_2$ ([M-5CO]$^+$): 383.9607, found: 383.9607.

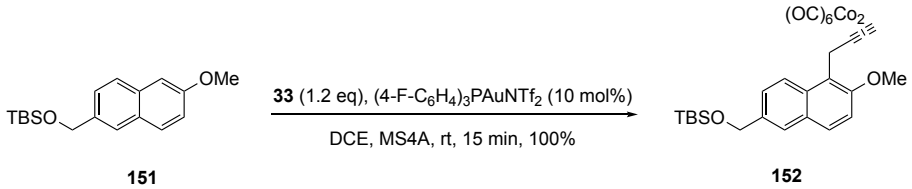
Functionalization of 2-methoxy-6-((methoxymethoxy)methyl)naphthalene (149)



Procedure D was followed and used (4-F-C_6H_4)$_3$PAuNTf$_2$ (3.96 mg, 5.0 μmol). The crude mixture was purified by silica gel column chromatography (AcOEt : Hexane = 1 : 50) and then fluorous silica gel column chromatography to give **150** (16.1 mg, 29 μmol, 58%).

150: red oil; IR (neat): 2017 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.7 Hz, 1H), 7.77 (d, *J* = 9.2 Hz, 1H), 7.76 (s, 1H), 7.52 (dd, *J* = 9.2 Hz, *J* = 1.9 Hz, 1H), 7.25 (d, *J* = 9.2 Hz, 1H), 5.92 (s, 1H), 4.75 (s, 2H), 4.74 (s, 2H), 4.62 (s, 2H), 3.97 (s, 3H), 3.45 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.8, 154.2, 132.6, 132.2, 128.92, 128.88, 127.6, 126.7, 123.6, 121.2, 112.6, 96.2, 73.5, 69.2, 55.6, 55.4, 29.0; HRMS (EI): calcd for $C_{20}H_{18}O_6Co_2$ ([M-3CO]$^+$): 471.9767, found: 471.9776.

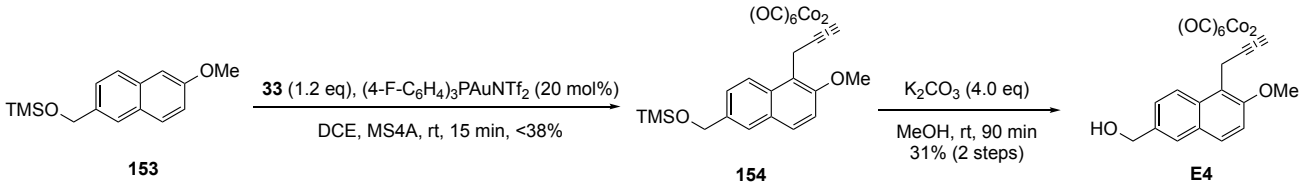
Functionalization of *tert*-butyl((6-methoxynaphthalen-2-yl)methoxy) dimethylsilane (151)



Procedure A was followed and used (4-F-C_6H_4)$_3$PAuNTf$_2$ (3.96 mg, 5.0 μmol). The crude mixture was purified by silica gel column chromatography ($CHCl_3$: Hexane = 1 : 20 to $CHCl_3$: Hexane = 1 : 15) to give **152** (29.0 mg, quant.).

152: red oil; IR (neat): 2019 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.7 Hz, 1H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.71 (s, 1H), 7.48 (dd, *J* = 8.7 Hz, *J* = 1.0 Hz, 1H), 7.23 (d, *J* = 8.7 Hz, 1H), 5.92 (s, 1H), 4.88 (s, 2H), 4.62 (s, 2H), 3.96 (s, 3H), 0.97 (s, 9H), 0.13 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.8, 153.9, 136.3, 131.9, 129.0, 128.8, 125.5, 125.3, 123.2, 121.2, 112.4, 96.4, 73.5, 65.1, 55.6, 29.1, 26.0, 18.5, -5.2; HRMS (EI): calcd for $C_{25}H_{28}O_6SiCo_2$ ([M-2CO]$^+$): 570.0319, found: 570.0313.

Functionalization of ((6-methoxynaphthalen-2-yl)methoxy)trimethylsilane (153)

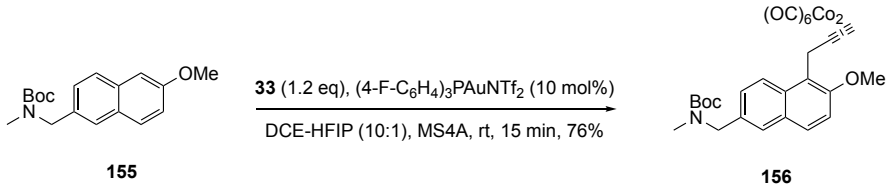


Procedure A was followed and used $(4\text{-F-}C_6H_4)_3PAuNTf_2$ (7.92 mg, 10 μmol). The crude mixture was purified by silica gel column chromatography ($CHCl_3$: Hexane = 1 : 20 to $CHCl_3$: Hexane = 1 : 15) to give **154** (<10.46 mg, <17.9 μmol, <36%).

To a solution of **154** (<10.46 mg, <17.9 μmol, <36%) in MeOH (2.0 mL) was added K_2CO_3 (10 mg, 7.23 μmol) at room temperature. The reaction mixture was stirred for 90 min at the same temperature. The solution was quenched with saturated aqueous NH_4Cl (1 mL) and extracted with CH_2Cl_2 (3 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by column chromatography on silica gel (AcOEt : Hexane = 1 : 30 to AcOEt : Hexane = 1 : 4) to give **E4** (7.86 mg, 15.3 μmol, 31% over 2 steps)

E4: red oil; IR (neat): 3321, 2017 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.7 Hz, 1H), 7.77 (d, *J* = 9.2 Hz, 1H), 7.76 (s, 1H), 7.53 (d, *J* = 8.7 Hz, 1H), 7.25 (d, *J* = 8.7 Hz, 1H), 5.92 (s, 1H), 4.84 (s, 2H), 4.62 (s, 2H), 3.97 (s, 3H), 1.70 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.8, 154.2, 135.7, 132.2, 129.0, 128.9, 126.4, 126.0, 123.7, 121.3, 112.7, 96.3, 73.5, 65.4, 55.6, 29.0; HRMS (EI): calcd for $C_{16}H_{14}O_3Co_2$ ($[M\text{-}5CO]^+$): 371.9607, found: 371.9633.

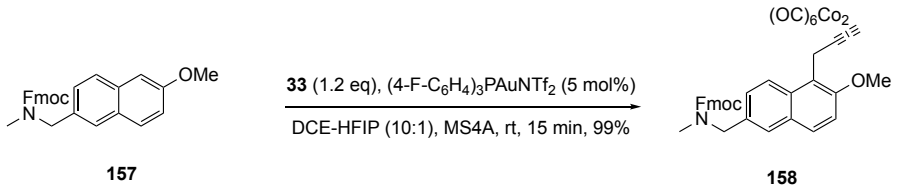
Functionalization of *tert*-butyl ((6-methoxynaphthalen-2-yl)methyl)(methyl) carbamate (155)



Procedure B was followed and used $(4\text{-F-}C_6H_4)_3PAuNTf_2$ (3.96 mg, 5.0 μmol). The crude mixture was purified by silica gel column chromatography (AcOEt : Hexane = 1 : 50 to 1 : 20) to give **156** (23.8 mg, 38.0 μmol, 76%).

156 (a mixture of two rotamers): red oil; IR (neat): 2019, 1694 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.9 Hz, 1H), 7.74 (d, *J* = 8.9 Hz, 1H), 7.58 (brs, 1H), 7.41 (brs, 1H), 7.27-7.23 (m, 1H), 5.93 (s, 1H), 4.62 (s, 2H), 4.55 (brs, 2H), 3.97 (s, 3H), 2.88 (brs, 1.5H), 2.80 (brs, 1.5H), 1.49 (s, 9H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.8, 156.3, 155.9, 154.1, 133.0, 131.9, 129.0, 128.6, 127.5, 127.4, 127.3, 126.7, 126.2, 123.7, 121.3, 112.7, 96.3, 79.8, 73.5, 55.6, 52.6, 51.8, 33.9, 33.8, 29.0, 28.5; HRMS (FAB): calcd for $C_{22}H_{25}NO_4Co_2$ ($[M\text{-}5CO]^+$): 485.0448, found: 485.0455.

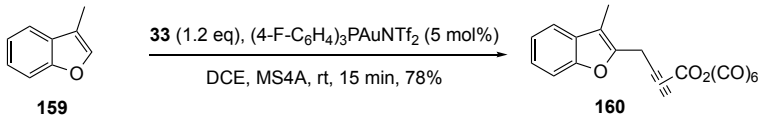
Functionalization of (9*H*-fluoren-9-yl)methyl ((6-methoxynaphthalen-2-yl)methyl)(methyl)carbamate (157)



Procedure B was followed and used $(4\text{-F-C}_6\text{H}_4)_3\text{PAuNTf}_2$ (3.96 mg, 5.0 μmol). The crude mixture was purified by silica gel column chromatography (AcOEt : Hexane = 1 : 30 to 1 : 10) to give **158** (35.4 mg, 49.9 μmol, 99%).

158 (a mixture of two rotamers): red oil; IR (neat): 2019, 1702 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.9 Hz, 0.5H), 7.87 (d, *J* = 8.2 Hz, 0.5H), 7.82-7.68 (m, 3H), 7.63 (brs, 1.5H), 7.51 (brd, *J* = 8.2 Hz, 1.5H), 7.41 (t, *J* = 6.8 Hz, 1.5H), 7.38-7.29 (m, 2H), 7.26 (d, *J* = 6.8 Hz, 1H), 7.18 (brd, *J* = 6.8 Hz, 1.5H), 5.92 (s, 1H), 4.69-4.59 (m, 3H), 4.57-4.46 (m, 3H), 4.31 (brs, 0.5H), 4.25 (brs, 0.5H), 3.97 (s, 3H), 2.92 (brs, 1.5H), 2.88 (brs, 1.5H) ; ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.8, 156.8, 156.4, 154.2, 144.0, 141.4, 132.2, 132.0, 128.9, 128.7, 127.7, 127.6, 127.4, 127.0, 126.7, 126.1, 125.0, 124.9, 123.9, 121.3, 120.0, 112.7, 96.2, 73.5, 67.5, 55.6, 52.5, 52.2, 47.4, 34.4, 33.4, 29.7, 29.0; HRMS (FAB): calcd for $C_{34}H_{27}NO_6Co_2$ ([M-3CO]$^+$): 663.0502, found: 663.0504.

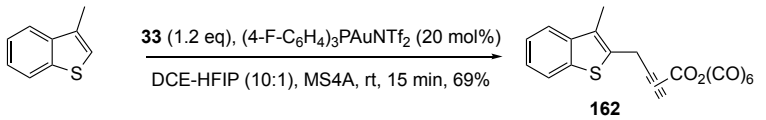
Functionalization of 3-methylbenzofuran (159)



Procedure A was followed and used $(4\text{-F-C}_6\text{H}_4)_3\text{PAuNTf}_2$ (1.98 mg, 2.5 μmol). The crude mixture was purified by silica gel column chromatography (Hexane) to give **160** (17.8 mg, 39.0 μmol, 78%).

160: red oil; IR (neat): 2019 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.45 (dd, *J* = 6.8 Hz, 1.4 Hz, 1H), 7.38 (dd, *J* = 6.8 Hz, 1.4 Hz, 1H), 7.24 (d, *J* = 7.2 Hz, 1.9 Hz, 1H), 7.20 (dt, *J* = 7.2 Hz, 1.4 Hz, 1H), 6.09 (s, 1H), 4.23 (s, 2H), 2.23 (s, 3H) ; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.4, 153.9, 150.9, 129.8, 123.9, 122.2, 119.1, 111.1, 110.9, 93.3, 73.1, 30.4, 7.9; HRMS (EI): calcd for $C_{17}H_{10}O_7Co_2$ ([M-5CO]$^+$): 427.9141, found: 427.9161.

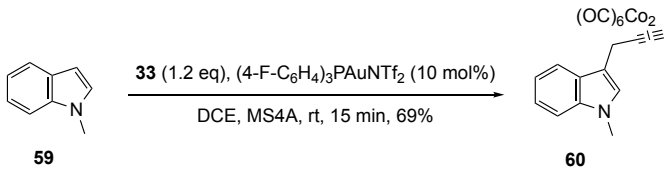
Functionalization of 3-metylbenzothiophene (161)



Procedure B was followed and used $(4\text{-F-C}_6\text{H}_4)_3\text{PAuNTf}_2$ (7.92 mg, 10 μmol). The crude mixture was purified by silica gel column chromatography (Hexane) to give **162** (16.2 mg, 34.2 μmol, 68%).

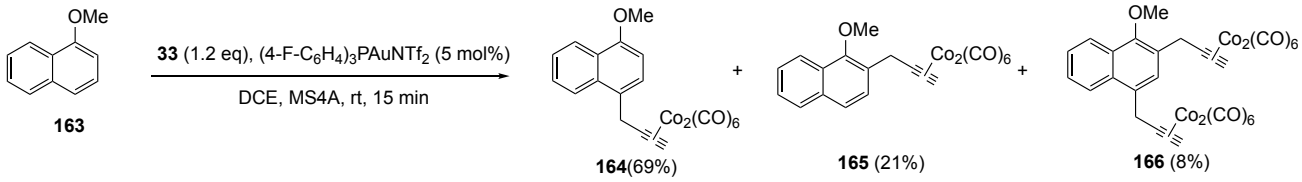
31: red oil; IR (neat): 2018 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.2 Hz, 1H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 6.10 (s, 1H), 4.37 (s, 2H), 2.40 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.4, 140.3, 138.3, 136.5, 128.1, 124.2, 124.0, 122.2, 121.7, 95.1, 73.6, 32.7, 11.7; HRMS (EI): calcd for $C_{17}H_{10}O_5SCo_2$ ([M-CO]$^+$): 443.8913, found: 443.8926.

Functionalization of 1-methylindole (59)



Procedure A was followed and used (4-F-C_6H_4)$_3$PAuNTf_2 (3.96 mg, 5.0 μmol). The crude mixture was purified by silica gel column chromatography (Hexane) to give **60** (15.7 mg, 34.4 μmol, 69%).

Functionalization of 1-methoxynaphthalene (163)



Procedure A was followed and used (4-F-C_6H_4)$_3$PAuNTf_2 (1.98 mg, 2.5 μmol). The crude mixture was purified by silica gel column chromatography (Hexane) to give **164** (16.6 mg, 34.7 μmol, 69%), **165** (5.17 mg, 10.7 μmol, 21%), **166** (3.22 mg, 4.2 μmol, 8%).

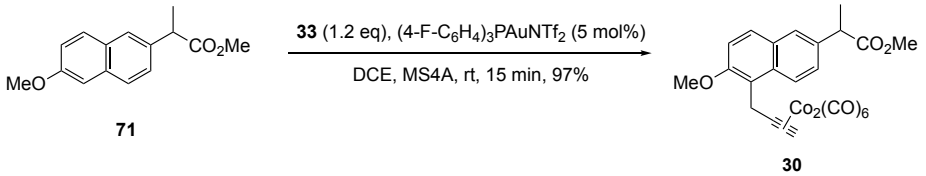
164: red oil; IR (neat): 2016 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.30 (d, *J* = 8.2 Hz, 1H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.30 (d, *J* = 7.2 Hz, 1H), 6.74 (d, *J* = 7.2 Hz, 1H), 5.94 (s, 1H), 4.49 (s, 2H), 3.98 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.6, 155.2, 132.2, 128.8, 126.9, 126.5, 126.1, 125.1, 123.7, 122.8, 103.3, 97.4, 73.7, 55.5, 37.5; HRMS (EI): calcd for $C_{15}H_{12}O_2Co_2$ ([M-5CO]$^+$): 341.9501, found: 341.9494.

165: red oil; IR (neat): 2020 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.54-7.43 (m, 2H), 7.46 (dt, *J* = 8.2 Hz, *J* = 1.5 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 6.07 (s, 1H), 4.30 (s, 2H), 3.99 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.7, 153.7, 134.4, 128.4, 128.2, 128.1, 126.0, 125.7, 125.6, 124.3, 122.3, 96.6, 73.6, 62.2, 34.3; HRMS (EI): calcd for $C_{15}H_{12}O_2Co_2$ ([M-5CO]$^+$): 341.9501, found: 341.9510.

166: red oil; IR (neat): 2018 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.15-8.10 (m, 1H), 8.06-8.01 (m, 1H), 7.58-7.50 (m, 2H), 7.30 (s, 1H), 6.05 (s, 1H), 5.97 (s, 1H), 4.51 (s, 2H), 4.28 (s, 2H), 3.90 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$):

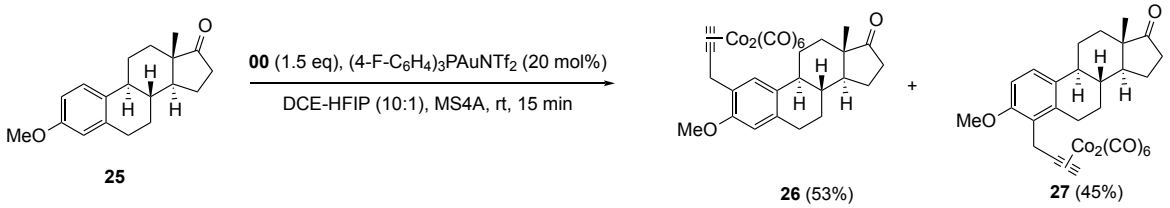
δ 199.7, 153.5, 133.1, 132.0, 129.2, 128.7, 127.9, 126.02, 125.99, 124.3, 123.1, 96.8, 96.2, 73.8, 73.5, 62.2, 37.3, 34.3; HRMS (EI): calcd for $C_{28}H_{14}O_{12}Co_4$ ([M-CO]$^+$): 777.7813, found: 777.7826.

Functionalization of naproxen methyl ester (71)



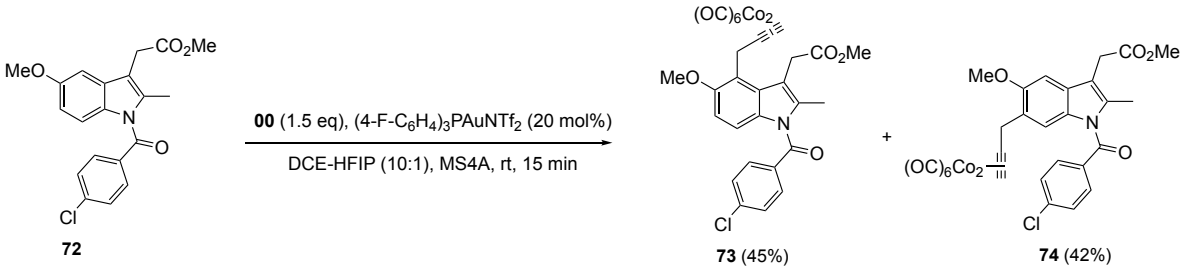
Procedure D was followed and used (4-F-C_6H_4)$_3$PAuNTf$_2$ (1.98 mg, 2.5 μmol). The crude mixture was purified by silica gel column chromatography (AcOEt : Hexane = 1 : 30), and then fluorous silica gel column chromatography to give **30** (27.5 mg, 48.4 μmol, 97%).

Functionalization of *O*-methyl estrone (25)



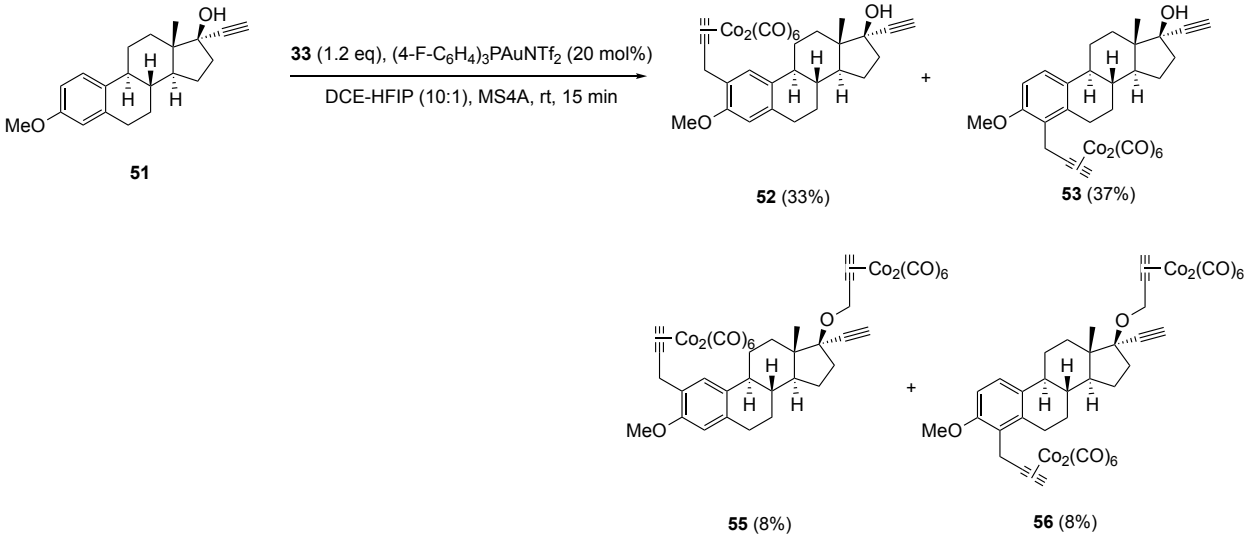
Procedure C was followed and used (4-F-C_6H_4)$_3$PAuNTf$_2$ (7.92 mg, 10 μmol). The crude mixture was purified by silica gel column chromatography (AcOEt : Hexane = 1 : 20) to give a mixture of **26** and **27** (62.02 mg).

Functionalization of indometacin methyl ester (72)



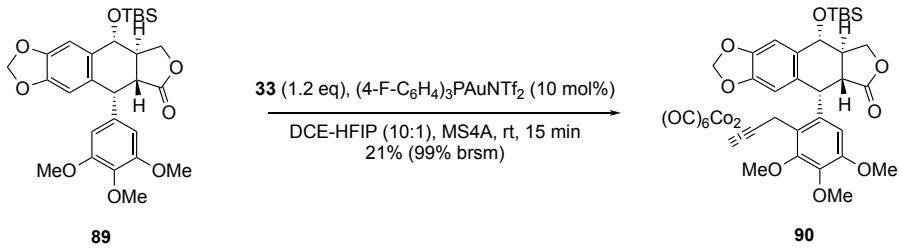
Procedure C was followed and used (4-F-C_6H_4)$_3$PAuNTf$_2$ (7.92 mg, 10 μmol). The crude mixture was purified by silica gel column chromatography (AcOEt : Hexane = 1 : 50 to AcOEt : Hexane = 1 : 20) to give **73** (15.6 mg, 22.5 μmol, 45%) and **74** (14.52 mg, 20.9 μmol, 42%).

Functionalization of mestranol (36)



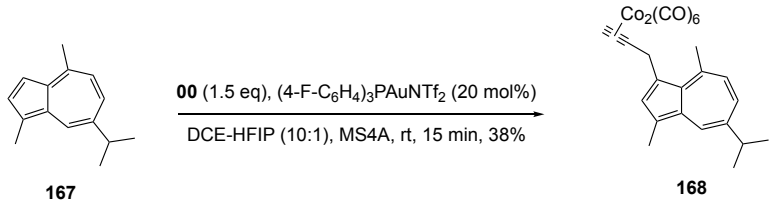
Procedure B was followed and used (4-F-C_6H_4)$_3$PAuNTf$_2$ (7.92 mg, 10 μmol). The crude mixture was purified by silica gel column chromatography (Pentane) to give a mixture of **52** and **53** (12.56 mg) and a mixture of **55** and **56** (21.98 mg).

Functionalization of podophylltoxin TBS ether (37).



Procedure C was followed and used (4-F-C_6H_4)$_3$PAuNTf$_2$ (7.92 mg, 10 μmol). The crude mixture was purified by silica gel column chromatography (AcOEt : Hexane = 1 : 50 to 1 : 4) to give **90** (9.58 mg, 11.2 μmol, brsm 99%).

Functionalization of guaiazulene (38)



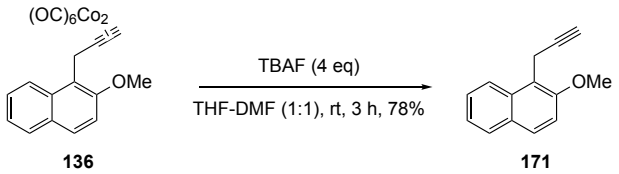
Procedure C was followed and used (4-F-C_6H_4)$_3$PAuNTf$_2$ (7.92 mg, 10 μmol). The crude mixture was purified by silica gel column chromatography (Pentane) to give **168** (9.05 mg, 19.2 μmol, 38%).

168: black oil; IR (neat): 2021 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 2.0 Hz, 1H), 7.48 (s, 1H), 7.30 (d, J = 11.0 Hz, 1H), 6.90 (d, J = 11.0 Hz, 1H), 5.99 (s, 1H), 4.71 (s, 2H), 3.09-2.96 (m, 4H), 2.58 (s, 3H), 1.33 (d, J =

6.8 Hz, 6H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.8, 144.6, 140.5, 139.6, 138.2, 134.6, 133.7, 131.8, 126.7, 126.0, 124.5, 99.6, 73.9, 37.7, 36.2, 26.5, 24.5, 12.7; HRMS (EI): calcd for $C_{24}H_{20}O_6Co_2$ ([M]$^+$): 521.9924, found: 521.9934.

7. Decomplexation of dicobalt hexacarbonyl complexes

Decomplexation of 136

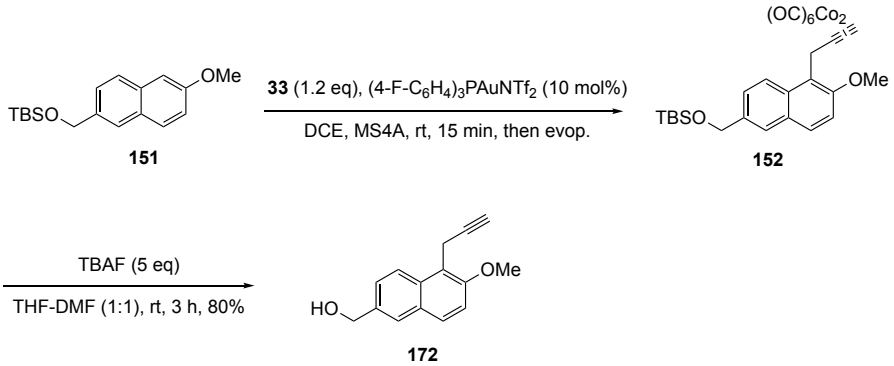


To solution of functionalized compound **136** (5.32 mg, 35 μmol) in THF (0.35 mL) and DMF (0.35 mL) was dropwised 1 M TBAF in THF (0.14 mL, 0.14 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 2 h. The solution was quenched with saturated aqueous NH_4Cl (1 mL) at room temperature and extracted with Et_2O (5 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by column chromatography on silica gel (Hexane) to **171** (5.32 mg, 27.1 μmol, 78%).

171: white solid; IR (neat): 3291 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 8.3 Hz, 1H), 7.88-7.72 (m, 2H), 7.54 (t, J = 7.3 Hz, 1H), 7.37 (t, J = 7.3 Hz, 1H), 7.28 (d, J = 8.8 Hz, 1H), 4.00 (d, J = 2.9 Hz, 2H), 3.98 (s, 3H), 1.97 (t, J = 2.9 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 154.0, 132.6, 129.3, 129.0, 128.5, 126.8, 123.6, 123.3, 117.7, 113.6, 82.9, 67.9, 56.9, 14.4; HRMS (EI): calcd for $C_{14}H_{12}O$ ([M]$^+$): 196.0888, found: 196.0895.

1-Pot propargylation

1-Pot propargylation of 151

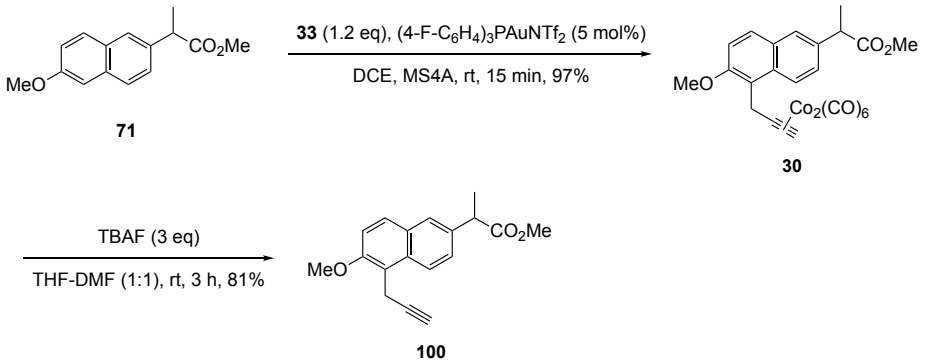


A solution of reagent **33** (50 mg, 60 μmol), **151** (50 μmol) and MS4A (50 mg) in DCE (1.0 mL) was added (4-F-$C_6H_4)_3PAuNTf_2$ (3.96 mg, 5.0 μmol) at room temperature. The reaction mixture was stirred at the same temperature for 15 min. The reaction mixture was concentrated in vacuo. The residue was dissolved in THF (0.5 mL) and DMF (0.5 mL) and dropwised 1 M TBAF in THF (0.25 mL, 0.25 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 3 h. The solution was quenched with saturated aqueous NH_4Cl (2 mL) at room

temperature and extracted with Et_2O (5 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by column chromatography on silica gel (AcOEt : Hexane = 1 : 20 to 1 : 4) to **172** (9.10 mg, 40.2 μmol, 80%).

172: white solid; IR (neat): 3407 (br), 3288 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.7 Hz, 1H), 7.83-7.75 (m, 2H), 7.55 (dd, *J* = 9.2 Hz, *J* = 1.4 Hz, 1H), 7.34 (d, *J* = 9.2 Hz, 1H), 4.84 (s, 2H), 4.03-3.95 (m, 5H), 1.98 (t, *J* = 2.7 Hz, 1H), 1.70 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 154.1, 136.0, 132.2, 129.2, 128.9, 126.2, 123.9, 120.3, 117.7, 113.9, 82.8, 67.9, 65.4, 56.8, 14.4; HRMS (EI): calcd for $C_{15}H_{14}O_2$ ([M]$^+$): 226.0994, found: 226.0991.

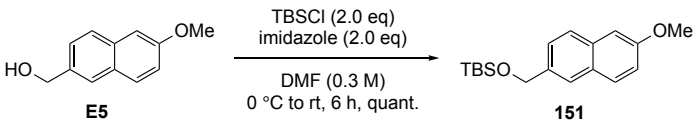
1-Pot propargylation of 71



A solution of reagent **33** (50 mg, 60 μmol), **71** (50 μmol) and MS4A (50 mg) in DCE (1.0 mL) was added (4-F-C_6H_4)$_3$PAuNTf$_2$ (3.96 mg, 5.0 μmol) at room temperature. The reaction mixture was stirred at the same temperature for 15 min. The reaction mixture was concentrated in vacuo. The residue was dissolved in THF (0.5 mL) and DMF (0.5 mL) and dropwised 1 M TBAF in THF (0.15 mL, 0.15 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 3 h. The solution was quenched with saturated aqueous NH_4Cl (2 mL) at room temperature and extracted with Et_2O (5 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by column chromatography on silica gel (AcOEt : Hexane = 1 : 50 to 1 : 30) and then fluorous silica gel column chromatography to give **100** (11.4 mg, 40.5 μmol, 81%).

Synthesis of substrates

***Tert*-butyl((6-methoxynaphthalen-2-yl)methoxy)dimethylsilane (151)**

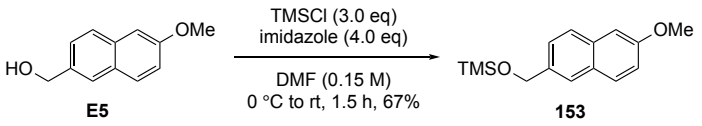


To a solution of alcohol **E5** (94 mg, 0.5 mmol) and imidazole (64 mg, 1.0 mmol) in DMF (1.7 mL) was added TBSCl (150 mg, 1.0 mmol) at 0 °C. The reaction mixture was stirred for 6 h at room temperature. The solution was quenched with saturated aqueous NH_4Cl (2 mL) at 0 °C and extracted with Et_2O (5 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was concentrated under vacuo and purified

by column chromatography on silica gel (AcOEt : Hexane = 1 : 30) to give TBS ether **151** (153 mg, quant.).

151: white solid; IR (neat): 1606 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.76-7.67 (m, 3H), 7.45 (d, *J* = 8.7 Hz, 1H), 7.13 (dd, *J* = 7.2 Hz, *J* = 2.4 Hz, 1H), 7.12 (s, 1H), 4.86 (s, 2H), 3.92 (s, 3H), 0.96 (s, 9H), 0.12 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 157.4, 136.8, 133.8, 129.3, 128.8, 126.7, 125.3, 124.4, 118.7, 105.8, 65.2, 55.3, 26.0, 18.5, -5.2; HRMS (EI): calcd for $C_{18}H_{26}O_2Si$ (M^+): 302.1702, found: 302.1703.

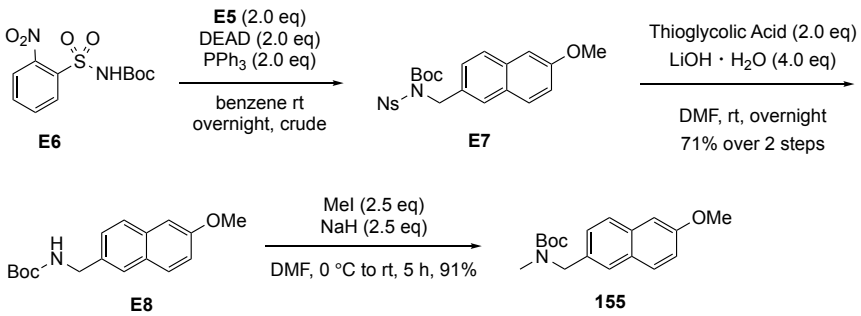
((6-Methoxynaphthalen-2-yl)methoxy)trimethylsilane (153)



To a solution of alcohol **E5** (94 mg, 0.5 mmol) and imidazole (136 mg, 2.0 mmol) in DMF (3.3 mL) was dropwised TMSCl (0.19 mL, 1.5 mmol) at 0 °C. The reaction mixture was stirred for 1.5 h at room temperature. The solution was quenched with H_2O (2 mL) at 0 °C and extracted with Hexane (5 mL × 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by column chromatography on silica gel (AcOEt : Hexane = 1 : 100) to give TMS ether **153** (87.7 mg, 0.34 mmol, 67%).

153: white solid; IR (neat): 1609 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.84-7.64 (m, 3H), 7.40 (dd, *J* = 8.5 Hz, *J* = 1.4 Hz, 1H), 7.18-7.08 (m, 2H), 4.82 (s, 2H), 3.92 (s, 3H), 0.17 (s, 9H) ; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 157.5, 136.2, 133.9, 129.3, 128.8, 126.9, 125.7, 125.0, 118.7, 105.7, 64.8, 55.3, -0.3; HRMS (EI): calcd for $C_{15}H_{20}O_2Si$ (M^+): 260.1233, found: 260.1233.

***Tert*-butyl ((6-methoxynaphthalen-2-yl)methyl)carbamate (155)**



To a solution of alcohol **E6** (263 mg, 1.38 mmol), carbamate **E5** (235 mg, 0.77 mmol), and PPh_3 (367 mg, 1.54 mmol) in benzene (4.5 mL) was dropwised ca. 2.2 M DEAD in toluene (0.71 mL, 1.56 mmol) at 0 °C. The reaction mixture was stirred overnight at room temperature. The solution was quenched with H_2O (5 mL) at 0 °C and extracted with CH_2Cl_2 (7 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$) to give carbamate **E7** (crude).

To a solution of carbamate **E7** (crude) in DMF (4.0 mL) was added LiOH•H_2O (130 mg, 3.08 mmol), and thioglycol

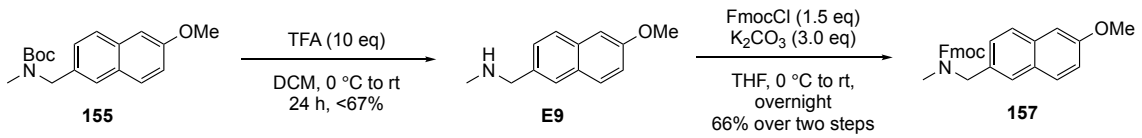
acid (0.11 mL, 1.54 mmol) at room temperature. The reaction mixture was stirred overnight. The solution was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with Et_2O (8 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by column chromatography on silica gel (AcOEt : Hexane = 1 : 5) to give carbamate **E8** (156 mg, 0.54 mmol, 71% over 2 steps).

E8: white solid; IR (neat): 3350 (br), 1697 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.7, 1H), 7.70 (d, J = 8.7, 1H), 7.64 (s, 1H), 7.37 (d, J = 8.2 Hz, 1H), 7.20-7.08 (m, 2H), 4.87 (brs, 1H), 4.44 (d, J = 5.3 Hz, 2H), 3.92 (s, 3H), 1.48 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 157.5, 155.9, 134.0, 133.7, 129.0, 128.7, 127.0, 126.2, 125.7, 118.8, 105.6, 79.2, 55.1, 44.6, 28.3; HRMS (EI): calcd for $C_{17}H_{21}NO_3$ (M^+): 287.1521, found: 287.1504.

To a solution of carbamate **E8** (156 mg, 0.54 mmol) in DMF (1.8 mL) was added 60% NaH (82 mg, 1.4 mmol) at 0 °C. The reaction mixture was stirred for 30 min at room temperature. The reaction mixture cooled to 0 °C and added MeI (86 μL, 1.0 mmol). The reaction mixture was allowed to room temperature and stirred for 5 h. The solution was quenched with saturated aqueous NH_4Cl (2 mL) at 0 °C and extracted with Et_2O (5 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by column chromatography on silica gel (AcOEt : Hexane = 1 : 10) to give carbamate **155** (149 mg, 0.49 mmol, 91%).

155 (a mixture of two rotamers): yellowish oil; IR (neat): 1692 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.69 (d, J = 8.3, 1H), 7.68 (d, J = 8.9, 1H), 7.56 (s, 1H), 7.32 (brs, 1H), 7.19-7.05 (m, 2H), 4.52 (s, 2H), 3.88 (s, 3H), 2.86 (brs, 1.5H), 2.79 (brs, 1.5H), 1.50 (s, 9H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 157.6, 156.2, 155.9, 133.8, 133.2, 129.1, 128.8, 127.2, 126.6, 126.3, 126.0, 125.8, 118.9, 105.7, 79.7, 55.2, 52.7, 52.0, 33.8, 28.5; HRMS (EI): calcd for $C_{18}H_{23}NO_3$ (M^+): 301.1678, found: 301.1702.

(9*H*-Fluoren-9-yl)methyl ((6-methoxynaphthalen-2-yl)methyl)(methyl)carbamate (S30)



To a solution of carbamate **155** (160 mg, 0.53 mmol) in CH_2Cl_2 (5.3 mL) was dropwised TFA (0.41 mL, 5.3 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 24 h. The solution was quenched with 1 M NaOH (10 mL) at 0 °C and extracted with CH_2Cl_2 (15 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo to give amine **E9** (73.8 mg, <0.36 mmol, <67%).

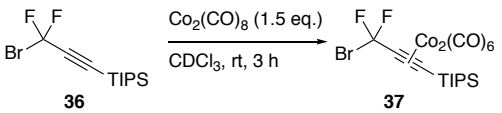
To solution of crude in THF (3.6 mL) was added K_2CO_3 (150 mg, 1.09 mmol) and FmocCl (140 mg, 0.54 mmol) at 0 °C. The reaction mixture was stirred at the same temperature overnight. The solution was quenched with saturated aqueous NH_4Cl (5 mL) at 0 °C and extracted with Et_2O (8 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by column chromatography on silica gel

(toluene : Hexane = 1 : 8) to give carbamate **157** (149 mg, 0.35 mmol, 66% over 2 steps).

157 (a mixture of two rotamers): amorphous; IR (neat): 1699 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.85-7.56 (m, 5H), 7.55-7.22 (m, 5H), 7.21-7.07 (m, 4H), 4.63 (s, 1H), 4.51 (s, 3H), 4.30 (brs, 0.5H), 4.25 (brs, 0.5H), 3.93 (s, 3H), 2.92 (brs, 1.5H), 2.87 (brs, 1.5H) ; ^{13}C-NMR (150 MHz, $CDCl_3$): δ 157.6, 156.7, 156.3, 144.03, 143.96, 141.3, 133.9, 132.5, 132.3, 129.2, 128.7, 127.6, 127.3, 127.0, 126.5, 125.8, 125.7, 125.0, 124.8, 119.9, 118.9, 105.7, 67.4, 55.2, 52.6, 52.2, 47.4, 47.3, 34.4, 33.4; HRMS (EI): calcd for $C_{28}H_{25}NO_3$ (M^+): 423.1834, found: 423.1815.

<Chapter 3>

Identification of difluoropropargyl bromide dicobalt complex 37



To a solution of triisopropylsilyldifluorobromopropyne (**36**) (31.0 mg, 1.00 mmol) in $CDCl_3$ (0.7 mL) was added $Co_2(CO)_8$ (53.2 mg, 1.56 mmol) and stirred at room temperature. After 3 h, the reaction mixture was monitored by ^{19}F-NMR and observed a new fluorine peak derived from **37**. The analytical sample was obtained by silica gel column chromatography (hexane).

37: red oil; IR (neat): 2033 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 1.23 (s, 21H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 198.5, 118.4 (t, $^{1}J_{CF}$ = 299.1 Hz), 104.2 (t, $^{2}J_{CF}$ = 35.4 Hz), 74.6, 19.0, 14.0; ^{19}F-NMR (560 MHz, $CDCl_3$): δ –27.7 (s, 2F); HRMS (EI): calcd for $C_{17}H_{21}{}^{79}BrCo_2F_2O_5Si$ ($[M-CO]^+$): 567.8974, found: 567.8952.

Etherification of alcohol substrates

Standard procedure for the etherification of alcohol substrates

Procedure A: A solution of **36** (0.15 mmol) and $Co_2(CO)_8$ (0.15 mmol) in toluene (1 mL) was stirred at room temperature. After 3 h, alcohol (0.1 mmol), triethylamine (0.15 mmol) and AgOTf (0.15 mmol) were added and stirred until completion of the reaction as monitored by TLC. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (1 mL) and extracted with AcOEt (5mL × 2). The combined organic layers were washed with brine and dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (Because desired products were converted to corresponded esters during silica gel column chromatography, the eluent containing 1% Et_3N was used.).

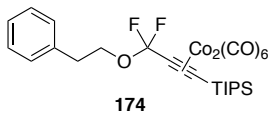
Procedure B: A solution of **36** (0.15 mmol) and $Co_2(CO)_8$ (0.15 mmol) in toluene (1 mL) was stirred at room temperature. After 3 h, alcohol (0.1 mmol), DTBMP (0.15 mmol) and AgOTf (0.15 mmol) were added and stirred until completion of the reaction as monitored by TLC. The reaction mixture was diluted with saturated aqueous

$NaHCO_3$ (1 mL) and extracted with AcOEt (5mL × 2). The combined organic layers were washed with brine and dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (Because desired products were converted to corresponded esters during silica gel column chromatography, the eluent containing 1% Et_3N was used.).

Etherification of phenylethylalcohol

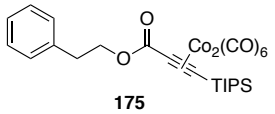
The procedure A was followed with a reaction time of 10 min. The yield determined by ^{1}H-NMR (99%). The analytical sample was purified by flash silica gel column chromatography (hexane containing 1% Et_3N).

When the procedure A was followed with a reaction time of 10 min without Et_3N in CH_2Cl_2, Ester **175** was obtained (85%, ^{1}H-NMR yield). The analytical sample was purified by flash silica gel column chromatography (AcOEt : hexane = 1 : 20).



174

174: red oil; IR (neat): 2029 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.29 (t, J = 7.6 Hz, 2H), 7.25-7.19 (m, 3H), 4.26 (t, J = 7.2 Hz, 2H), 2.98 (t, J = 7.2 Hz, 2H), 1.32-1.08 (m, 21H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.2, 137.4, 128.7, 128.5, 126.6, 125.0 (t, $^1J_{CF}$ = 255.8 Hz), 101.3 (t, $^2J_{CF}$ = 49.9 Hz), 72.2, 64.9 (t, $^3J_{CF}$ = 5.1 Hz), 35.5, 18.8, 13.7; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -60.2 (s, 2F); HRMS (EI): calcd for $C_{25}H_{30}Co_2F_2O_6Si$ ([M-CO]$^+$): 610.0444, found: 610.0418.

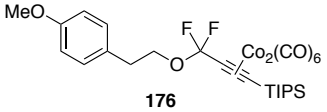


175

175: red oil; IR (neat): 2029, 1708 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.29 (t, J = 7.2 Hz, 2H), 7.25-7.19 (m, 3H), 4.49 (t, J = 7.0 Hz, 2H), 3.01 (t, J = 7.0 Hz, 2H), 1.25 (quint, J = 7.2 Hz, 3H), 1.15 (d, J = 7.2 Hz, 18H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.1, 170.0, 137.4, 128.7, 128.5, 126.6, 95.6, 75.0, 66.5, 34.9, 18.8, 13.4; HRMS (EI): calcd for $C_{21}H_{30}Co_2O_3Si$ ([M-5CO]$^+$): 476.0628, found: 476.0628.

Etherification of 4-methoxyphenethyl alcohol

The procedure A was followed with a reaction time of 30 min. The crude was purified by flash silica gel column chromatography (AcOEt : hexane = 1 : 50 containing 1% Et_3N) to provide **176** (59.6 mg, 82.5 μmol, 84%).

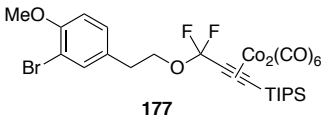


176

176: red oil; IR (neat): 2029 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.14 (d, J = 8.2 Hz, 2H), 6.83 (d, J = 8.2 Hz, 2H), 4.21 (t, J = 7.3 Hz, 2H), 3.79 (s, 3H), 2.91 (t, J = 7.3 Hz, 2H), 1.36-1.04 (m, 21H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.2, 158.4, 129.7, 129.4, 124.9 (t, $^{1}J_{CF}$ = 256.1Hz), 113.9, 101.4 (t, $^{2}J_{CF}$ = 50.5 Hz), 72.2, 65.2 (t, $^{3}J_{CF}$ = 5.4 Hz), 55.2, 34.7, 18.8, 13.7; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -60.2 (s, 2F); HRMS (EI): calcd for $C_{21}H_{32}Co_2F_2O_2Si$ ([M-6CO]$^+$): 500.0804, found: 500.0815.

Etherification of 3-bromo-4-methoxy-phenethyl alcohol

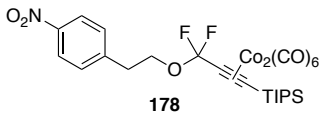
The procedure A was followed with a reaction time of 60 min. The crude was purified by flash silica gel column chromatography (hexane containing 1% Et_3N) to provide **177** (59.4 mg, 79.4 μmol, 79%).



177: red oil; IR (neat): 2029 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.41 (d, J = 1.9 Hz, 1H), 7.13 (dd, J = 8.3 Hz, 1.9 Hz, 1H), 6.82 (d, J = 8.3 Hz, 1H), 4.22 (t, J = 7.1 Hz, 2H), 3.87 (s, 3H), 2.90 (t, J = 7.1 Hz, 2H), 1.31-0.94 (m, 21H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.2, 154.6, 133.5, 131.1, 128.6, 124.9 (t, $^{1}J_{CF}$ = 255.6 Hz), 112.0, 111.6, 101.1 (t, $^{2}J_{CF}$ = 48.3 Hz), 72.2, 64.7 (t, $^{3}J_{CF}$ = 5.3 Hz), 56.3, 34.3, 18.8, 13.7; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -60.2 (s, 2F); HRMS (EI): calcd for $C_{21}H_{31}{}^{79}BrCo_2F_2O_2Si$ ([M-6CO]$^+$): 577.9909, found: 577.9889.

Etherification of 4-nitrophenethyl alcohol

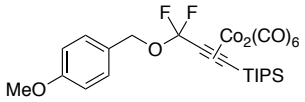
The procedure A was followed, employing 1.5 equiv. of $AgNTf_2$ instead of AgOTf, with a reaction time of 30 min. The crude was purified by flash silica gel column chromatography (hexane containing 1% Et_3N) to provide **178** (41.8 mg, 61.1 μmol, 61%).



178: red oil; IR (neat): 2031 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.16 (d, J = 8.7 Hz, 2H), 7.40 (d, J = 8.7 Hz, 2H), 4.34 (t, J = 6.8 Hz, 2H), 3.10 (t, J = 6.8 Hz, 2H), 1.31-0.94 (m, 21H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.1, 146.9, 145.4, 129.5, 125.0 (t, $^{1}J_{CF}$ = 256.7 Hz), 123.7, 100.6 (t, $^{2}J_{CF}$ = 50.9 Hz), 72.3, 63.8, 35.2, 18.8, 13.6; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -60.2 (s, 2F); HRMS (FAB): calcd for $C_{22}H_{29}Co_2F_2NO_5Si$ ([M-4CO]$^+$): 571.0447, found: 571.0436.

Etherification of 4-methoxybenzyl alcohol

The procedure A was followed with a reaction time of 10 min. The crude was purified by flash silica gel column chromatography (hexane containing 1% Et_3N) to provide **179** (42.6 mg, 65.0 μmol, 65%).

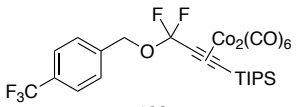


179

179: red oil; IR (neat): 2060 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.27 (d, J = 9.5 Hz, 2H), 6.86 (d, J = 9.5 Hz, 2H), 4.98 (s, 2H), 3.81 (s, 3H), 1.36-1.02 (m, 21H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.2, 159.6, 130.1, 127.6, 125.0 (t, $^{1}J_{CF}$ = 255.7 Hz), 113.7, 101.4 (t, $^{2}J_{CF}$ = 48.8 Hz), 72.4, 66.5 (t, $^{3}J_{CF}$ = 5.8 Hz), 55.2, 18.8, 13.6; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -59.5 (s, 2F); HRMS (EI): calcd for $C_{23}H_{30}Co_2F_2O_5Si$ ([M-3CO]$^+$): 570.0495, found: 570.0502.

Etherification of (4-trifluoromethyl)benzyl alcohol

The procedure A was followed with a reaction time of 10 min. The crude was purified by flash silica gel column chromatography (hexane containing 1% Et_3N) to provide **180** (43.5 mg, 62.8 μmol, 63%).

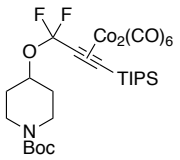


180

180: red oil; IR (neat): 2032 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 7.8 Hz, 2H), 7.48 (d, J = 7.8 Hz, 2H), 5.11 (s, 2H), 1.32-1.00 (m, 21H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.1, 139.4, 130.5 (q, $^{1}J_{CF}$ = 33.4 Hz), 128.3, 125.4, 125.1 (t, $^{1}J_{CF}$ = 257.0 Hz), 100.5 (t, $^{2}J_{CF}$ = 48.0 Hz), 72.6, 65.8 (t, $^{3}J_{CF}$ = 5.4 Hz), 18.8, 13.7; ^{19}F-NMR (560 MHz, $CDCl_3$): -59.7 (s, 2F), -65.8 (s, 3F); HRMS (EI): calcd for $C_{23}H_{27}Co_2F_5O_4Si$ ([M-3CO]$^+$): 608.0263, found: 608.0242 .

Etherification of 1-boc-4-hydeoxypiperidine

The procedure A was followed with a reaction time of 40 min. The crude was purified by flash silica gel column chromatography (AcOEt : hexane = 1 : 20 containing 1% Et_3N) to provide **181** (63.6 mg, 88.6 μmol, 89%).



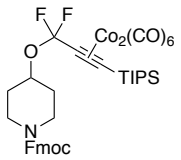
181

181: red oil; IR (neat): 2029, 1701 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 4.69-4.60 (m, 1H), 3.72 (brs, 2H), 3.27-3.19 (m, 2H), 1.92 (brs, 2H), 1.71 (brs, 2H), 1.46 (s, 9H), 1.25 (sept, J = 7.4 Hz, 3H), 1.18 (d, J = 7.4 Hz, 18H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.2, 154.7, 125.2 (t, $^{1}J_{CF}$ = 256.5 Hz), 101.6 (t, $^{2}J_{CF}$ = 49.9 Hz), 79.7, 72.0, 40.9, 32.0, 28.4, 18.9, 13.6; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -57.2 (s, 2F); HRMS (EI): calcd for $C_{25}H_{39}Co_2F_2NO_6Si$ ([M-3CO]$^+$): 633.1179, found: 633.1183.

Etherification of 1-Fmoc-4-hydeoxypiperidine

The procedure A was followed with a reaction time of 60 min. The crude was purified by flash silica gel column

chromatography (AcOEt : hexane = 1 : 20 containing 1% Et_3N) to provide **182** (72.4 mg, 86.2 μmol, 86%).

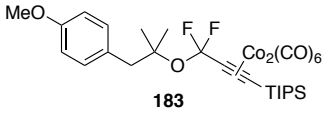


182

182: red oil; IR (neat): 2032, 1705 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.76 (d, J = 7.4 Hz, 2H), 7.57 (d, J = 7.4 Hz, 2H), 7.40 (t, J = 7.4 Hz, 2H), 7.31 (t, J = 7.4 Hz, 2H), 4.66 (brs, 1H), 4.45 (d, J = 6.6 Hz, 2H), 4.25 (t, J = 6.6 Hz, 1H), 3.70 (brs, 2H), 3.32 (brs, 2H), 1.90 (brs, 2H), 1.69 (brs, 2H), 1.35-0.96 (m, 21H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.2, 155.1, 144.0, 141.4, 127.7, 127.0, 125.2 (t, $^1J_{CF}$ = 256.3 Hz), 124.9, 119.9, 101.5 (t, $^2J_{CF}$ = 48.8 Hz), 72.0, 71.6, 67.2, 47.4, 40.9, 31.9, 18.9, 13.6; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -57.3 (s, 1F), -57.2 (s, 1F); HRMS (FAB): calcd for $C_{32}H_{41}Co_2F_2NO_3Si$ ([M-6CO]$^+$): 671.1488, found: 671.1484.

Etherification of 2-(4-methoxyphenyl)-1-methyl-2-propanol

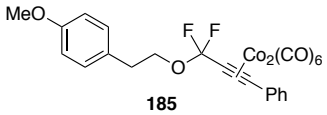
The procedure A was followed, employing 2.0 equiv. of **37**, AgOTf, and Et_3N, with a reaction time of 10 min. The crude was purified by flash silica gel column chromatography (hexane containing 1% Et_3N) to provide **183** (44.4 mg, 63.7 μmol, 64%) and starting material (2.07 mg, 11.5 μmol, 11%).



183

183: red oil; IR (neat): 2027 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.13 (d, J = 8.2 Hz, 2H), 6.82 (d, J = 8.2 Hz, 2H), 3.79 (s, 3H), 3.00 (s, 2H), 1.43 (s, 6 H), 1.33-1.02 (m, 21H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.4, 158.4, 131.6, 129.3, 125.7 (t, $^1J_{CF}$ = 256.7 Hz), 113.4, 104.6 (t, $^2J_{CF}$ = 48.8 Hz), 85.9, 71.8, 55.2, 48.1, 26.8, 19.0, 13.7; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -49.5 (s, 2F); HRMS (FAB): calcd for $C_{26}H_{36}Co_2F_2O_5Si$ ([M-3CO]$^+$): 612.0964, found: 612.0966.

Etherification of 4-methoxyphenylethyl alcohol using reagent 184



185

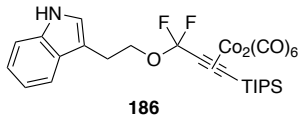
The procedure A was followed, employing **184** instead of **37**, with a reaction time of 50 min. The crude was purified by flash silica gel column chromatography (hexane containing 1% Et_3N) to provide **185** (55.5 mg, 94.3 μmol, 94%). **184** was prepared from phenyldifluorobromopropyne (39.4 mg, 0.171 mmol) and $Co_2(CO)_8$ (54.5 mg, 0.159 mmol).

185: red oil; IR (neat): 2064, 1614 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 6.3 Hz, 2H), 7.39-7.22 (m, 3H), 7.15 (d, J = 8.3 Hz, 2H), 6.82 (d, J = 8.3 Hz, 2H), 4.30 (t, J = 6.7 Hz, 2H), 3.79 (s, 3H), 2.96 (t, J = 6.7 Hz, 2H); ^{13}C-

NMR (100 MHz, $CDCl_3$): δ 198.1, 158.3, 136.5, 130.0, 129.9, 129.8, 128.8, 128.3, 125.5 (t, $^1J_{CF}$ = 255.7 Hz), 113.9, 88.1, 83.3 (t, $^2J_{CF}$ = 50.1 Hz), 65.2 (t, $^3J_{CF}$ = 4.5 Hz), 55.2, 34.8; ^{19}F-NMR (560 MHz, $CDCl_3$): -62.6 (s, 2F); HRMS (EI): calcd for $C_{21}H_{16}Co_2F_2O_5$ ([M-3CO]$^+$): 503.9630, found: 503.9678.

Etherification of 2-indoleethanol

The procedure B was followed, employing 1.2 equiv. of DTBMP, AgOTf and **37**, with a reaction time of 30 min. The crude was purified by flash silica gel column chromatography (AcOEt : hexane = 1 : 8 containing 1% Et_3N) to provide **186** (32.3 mg, 47.7 μmol, 48%).

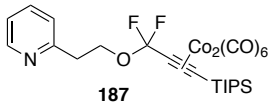


186

186: red oil; IR (neat): 3421, 2031 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.98 (brs, 1H), 7.60 (d, J = 7.3 Hz, 1H), 7.37 (d, J = 7.3 Hz, 1H), 7.20 (t, J = 7.3 Hz, 1H), 7.14 (t, J = 7.3 Hz, 1H), 7.06 (s, 1H), 4.32 (t, J = 7.5 Hz, 1H), 3.14 (t, J = 7.5 Hz, 1H), 1.49-0.94 (m, 21H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.2, 136.2, 127.4, 125.0 (t, $^1J_{CF}$ = 255.0 Hz), 119.5, 118.5, 111.6, 111.1, 101.6 (t, $^2J_{CF}$ = 51.3 Hz), 72.2, 64.4, 25.3, 18.9, 13.7; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -60.1 (s, 2F); HRMS (EI): calcd for $C_{25}H_{31}Co_2F_2NO_4Si$ ([M-3CO]$^+$): 593.0654, found: 593.0654.

Etherification of 2-pyridineethanol

The procedure B was followed with a reaction time of 90 min. The crude was purified by flash silica gel column chromatography (AcOEt : hexane = 1 : 8 containing 1% Et_3N) to provide **187** (36.8 mg, 57.5 μmol, 58%).

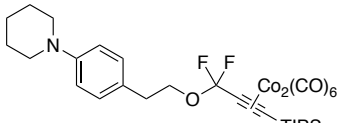


187

187: red oil; IR (neat): 2029 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.54 (d, J = 4.4 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 7.18 (d, J = 7.8 Hz, 1H), 7.13 (dd, J = 10.3, 5.4 Hz, 1H), 4.47 (t, J = 6.8 Hz, 2H), 3.14 (t, J = 6.8 Hz, 2H), 1.25-1.09 (m, 21H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.1, 157.7, 149.5, 136.3, 124.9 (t, $^1J_{CF}$ = 255.7 Hz), 123.4, 121.6, 101.3 (t, $^2J_{CF}$ = 50.0 Hz), 72.2, 63.6 (t, $^3J_{CF}$ = 5.8 Hz), 37.8, 18.8, 13.6; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -60.3 (s, 2F); HRMS (EI): calcd for $C_{22}H_{29}Co_2F_2NO_4Si$ ([M-3CO]$^+$): 555.0498, found: 555.0488.

Etherification of 2-(4-(piperidin-1-yl)phenyl)ethan-1-ol

The procedure B was followed with a reaction time of 30 min. The crude was purified by flash silica gel column chromatography (AcOEt : hexane = 1 : 20 containing 1% Et_3N) to provide **188** (59.6 mg, 82.5 μmol, 83%).



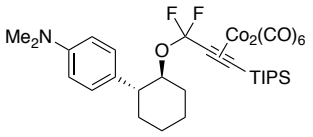
188

188: red oil; IR (neat): 2029 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.09 (d, J = 7.9 Hz, 2H), 6.87 (d, J = 7.9 Hz, 2H),

4.19 (t, J = 7.3 Hz, 2H), 3.11 (t, J = 5.1 Hz, 4H), 2.88 (t, J = 7.3 Hz, 2H), 1.75-1.66 (m, 4H), 1.60-1.53 (m, 2H), 1.33-1.02 (m, 21H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.2, 151.1, 129.3, 127.9, 124.9 (t, $^1J_{CF}$ = 255.8 Hz), 116.8, 101.5 (t, $^2J_{CF}$ = 49.1 Hz), 72.1, 65.3 (t, $^3J_{CF}$ = 5.1 Hz), 50.9, 34.7, 25.9, 24.3, 18.9, 13.7; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -60.1 (s, 2F); HRMS (EI): calcd for $C_{25}H_{39}Co_2F_2NOSi$ ([M-6CO]$^+$): 553.1433, found: 553.1438.

Etherification of trans-2-(4-dimethylaminophenyl)-cyclohexanol

The procedure B was followed, employing benzene instead of toluene, with a reaction time of 15 min. The crude was purified by flash silica gel column chromatography (hexane containing 1% Et_3N) to provide **189** (43.8 mg, 59.5 µmol, 60%).

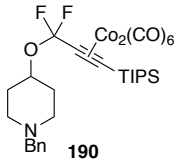


189

189: red oil; IR (neat): 2026 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.07 (d, J = 8.6 Hz, 2H), 6.68 (d, J = 8.2 Hz, 2H), 4.51 (td, J = 10.3, 4.1 Hz, 1H), 2.87 (s, 6H), 2.55-2.46 (m, 1H), 2.35 (d, J = 9.6 Hz, 1H), 1.90 (brd, J = 13.7 Hz, 1H), 1.84 (brd, J = 11.0 Hz, 1H), 1.72 (brd, J = 13.1 Hz, 1H), 1.60-1.40 (m, 4H), 1.38-1.19 (m, 1H), 1.17-1.04 (m, 21H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.2, 149.6, 131.7, 128.2, 124.8 (t, $^1J_{CF}$ = 255.8 Hz), 113.0, 102.1 (t, $^2J_{CF}$ = 47.6 Hz), 79.1, 71.8, 49.6, 41.0, 35.1, 34.4, 25.8, 25.0, 18.9, 13.7; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -54.8 (d, J = 139.5 Hz, 1F), -57.3 (d, J = 139.5 Hz, 1F); HRMS (EI): calcd for $C_{26}H_{41}Co_2F_2NOSi$ ([M-6CO]$^+$): 567.1589, found: 567.1578.

Etherification of 1-benzyl-4-hydroxypiperidine

The procedure A without Et_3N was followed with a reaction time of 60 min. The crude was purified by flash silica gel column chromatography (AcOEt : hexane = 1 : 4 containing 1% Et_3N) to provide **190** (54.2 mg, 76.6 µmol, 77%).



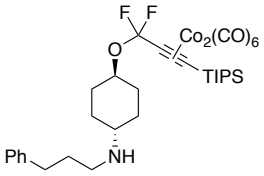
190

190: red oil; IR (neat): 2030 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.43-7.20 (m, 5H), 4.49 (brs, 1H), 3.48 (s, 2H), 2.72 (brs, 2H), 2.23 (brs, 2H), 2.02-1.96 (m, 2H), 1.90-1.75 (m, 2H), 1.39-1.00 (m, 21H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.3, 138.2, 129.1, 128.2, 127.1, 125.2 (t, $^1J_{CF}$ = 255.8 Hz), 102.1 (t, $^2J_{CF}$ = 49.9 Hz), 72.6, 71.9, 63.0, 50.7, 32.3, 18.9, 13.6; ^{19}F-NMR (560 MHz, $CDCl_3$): δ 57.1; HRMS (EI): calcd for $C_{25}H_{37}Co_2F_2NO_7Si$ ([M-5CO]$^+$): 567.1226, found: 567.1208.

Etherification of aminoalcohol

The procedure A was followed with a reaction time of 60 min. The crude was purified by flash silica gel column

chromatography (AcOEt : hexane = 1 : 2 containing 1% Et_3N) to provide **191** (47.6 mg, 63.5 μmol, 64%).

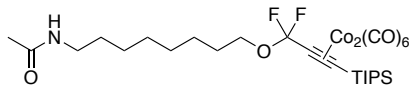


191

191: red oil; IR (neat): 3289, 2030 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.33-7.27 (m, 2H), 7.23-7.11 (m, 3H), 4.45-4.32 (m, 1H), 2.64 (q, J = 7.9 Hz, 4H), 2.43 (t, J = 10.3 Hz, 1H), 2.09 (d, J = 11.0 Hz, 2H), 1.93 (d, J = 12.4 Hz, 2H), 1.80 (quint, J = 7.2 Hz, 2H), 1.46 (q, J = 11.5 Hz, 2H), 1.33-1.03 (m, 23H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.3, 142.1, 128.4, 125.8 (t, $^1J_{CF}$ = 255.0 Hz), 102.3 (t, $^2J_{CF}$ = 50.6 Hz), 75.1, 71.8, 55.5, 46.9, 33.8, 32.0, 31.5, 31.2, 18.9, 13.7; ^{19}F-NMR (560 MHz, $CDCl_3$): -57.6 (s, 2F); HRMS (EI): calcd for $C_{32}H_{43}Co_2F_2NO_6Si$ (M^+): 721.1492, found: 721.1495.

Etherification of 8-amino-1-octanol

The procedure B was followed with a reaction time of 90 min. To the reaction mixture Ac_2O (35 μL, 0.368 mmol) and pyridine (81 μL, 1.00 mmol) was added at room temperature and stirred for 1 h. The crude was purified by flash silica gel column chromatography (AcOEt : hexane = 1 : 8 to 1: 2 to 1 : 1 containing 1% Et_3N) to provide **192** (43.7 mg, 62.4 μmol, 62%).

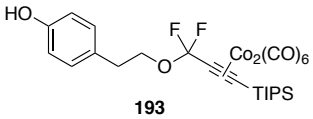


192

192: red oil; IR (neat): 3291, 2029, 1652 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 5.39 (brs, 1H), 4.01 (t, J = 6.5 Hz, 2H), 3.22 (q, J = 6.6 Hz, 2H), 1.97 (s, 3H), 1.67-1.60 (m, 2H), 1.53-1.46 (m, 2H), 1.38-1.34 (m, 2H), 1.22-1.31 (m, 9H), 1.18 (d, J = 6.9 Hz, 18H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.2, 167.0, 124.9 (t, $^1J_{CF}$ = 255.0 Hz), 101.7 (t, $^2J_{CF}$ = 49.9 Hz), 64.5, 39.6, 29.5, 29.1, 29.0, 26.8, 25.7, 23.3, 18.8, 13.6; ^{19}F-NMR (560 MHz, $CDCl_3$): -60.2 (s, 2F); HRMS (ESI): calcd for $C_{28}H_{41}Co_2F_2NO_8SiNa$ ([M+Na]$^+$): 726.1131, found: 726.1152.

Etherification of 4-hydroxyphenethyl alcohol

The procedure A was followed, employing 2 mL of toluene instead of 1 mL with a reaction time of 30 min. The crude was purified by flash silica gel column chromatography (AcOEt : Hexane = 1 : 4 containing 1% Et_3N) to provide **193** (26.3 mg, 40.2 μmol, 40%).



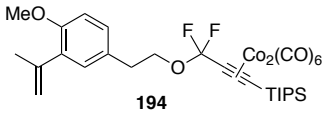
193

193: red oil; IR (neat): 2029 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.09 (d, J = 7.5 Hz, 2H), 6.76 (brs, 2H), 4.21 (t, J = 7.2 Hz, 2H), 2.90 (t, J = 7.2 Hz, 2H), 1.41-0.94 (m, 21H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.2, 154.2, 129.9,

129.6, 124.9 (t, $^1J_{CF}$ = 254.6 Hz), 115.3, 101.3 (t, $^2J_{CF}$ = 49.5 Hz), 72.1, 65.1, 34.6, 18.8, 13.7; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -60.2 (s, 2F); HRMS (EI): calcd for $C_{23}H_{30}Co_2F_2O_5Si$ ([M-3CO]$^+$): 570.0496, found: 570.0500.

Etherification of 3-propenyl-4-methoxy-phenethyl alcohol

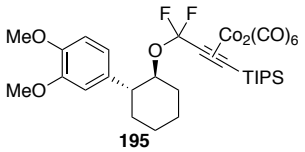
The procedure A was followed with a reaction time of 30 min. The crude was purified by flash silica gel column chromatography (hexane containing 1% Et_3N) to provide **194** (47.14 mg, 66.5 μmol, 67%).



194: red oil; IR (neat): 2032 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.09 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.03 (d, *J* = 2.0 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 5.13 (s, 1H), 5.03 (s, 1H), 4.22 (t, *J* = 7.4 Hz, 2H), 3.81 (s, 3H), 2.91 (d, *J* = 7.4 Hz, 2H), 2.10 (s, 3H), 1.31-1.05 (m, 21H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.2, 155.4, 144.3, 132.9, 129.7, 129.2, 128.4, 124.9 (t, $^1J_{CF}$ = 255.7 Hz), 115.0, 111.0, 101.4 (t, $^2J_{CF}$ = 50.9 Hz), 72.2, 65.1 (t, $^3J_{CF}$ = 5.0 Hz), 55.6, 34.7, 23.1, 18.9, 13.7; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -60.2 (s, 2F); HRMS (EI): calcd for $C_{24}H_{36}Co_2F_2O_2Si$ ([M-6CO]$^+$): 540.1117, found: 540.1117.

Etherification of *trans*-2-(3,4-dimethoxy-phenyl)-cyclohexanol

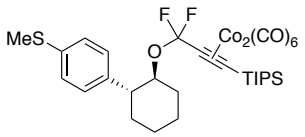
The procedure A was followed, employing 0.5 mL toluene instead of 1.0 mL, with a reaction time of 60 min. The crude was purified by flash silica gel column chromatography (AcOEt : hexane = 1 : 20 containing 1% Et_3N) to provide **195** (67.7 mg, 89.9 μmol, 90%).



195: red oil; IR (neat): 2028 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.88-6.63 (m, 3H), 4.59 (dt, *J* = 9.5, 3.9 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 2.57 (t, *J* = 9.8 Hz, 1H), 2.40 (d, *J* = 11.2 Hz, 1H), 1.89 (t, *J* = 15.8 Hz, 2H), 1.74 (d, *J* = 12.7 Hz, 1H), 1.63-1.22 (m, 4H), 1.22-0.94 (m, 21H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.1, 148.7, 147.6, 136.1, 124.9 (t, $^1J_{CF}$ = 256.6 Hz), 120.0, 111.1, 111.0, 101.8, (t, $^2J_{CF}$ = 48.9 Hz), 78.5, 71.9, 55.8, 55.7, 50.3, 35.7, 34.4, 25.7, 24.9, 18.8, 13.6; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -55.1 (d, *J* = 156.9 Hz, 1F), -57.1 (d, *J* = 156.9 Hz, 1F); HRMS (EI): calcd for $C_{27}H_{40}Co_2F_2O_4Si$ ([M-5CO]$^+$): 612.1328, found: 612.1326.

Etherification of *trans*-2-(4-methylthio-phenyl)-cyclohexanol

The procedure A was followed with a reaction time of 60 min. The crude was purified by flash silica gel column chromatography (hexane containing 1% Et_3N) to provide **196** (62.6 mg, 84.7 μmol, 85%).

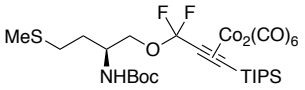


196

196: red oil; IR (neat): 2028 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.19 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 8.2 Hz, 2H), 4.55 (td, *J* = 10.6, 4.1 Hz, 1H), 2.58 (td, *J* = 11.5, 3.0 Hz, 1H), 2.43 (s, 3H), 2.41-2.35 (m, 1H), 1.95-1.82 (m, 2H), 1.74 (d, *J* = 13.0 Hz, 1H), 1.63-1.42 (m, 3H), 1.40-1.30 (m, 1H), 1.19-1.03 (m, 21H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.2, 140.6, 135.8, 128.3, 127.1, 124.8 (t, $^{1}J_{CF}$ = 261.0 Hz), 101.7, (t, $^{2}J_{CF}$ = 48.8 Hz), 78.7, 71.9, 50.2, 35.1, 34.4, 25.7, 24.9, 18.9, 16.3, 13.7; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -55.1 (d, *J* = 148.2 Hz, 1F), -57.2 (d, *J* = 148.2 Hz, 1F); HRMS (EI): calcd for $C_{25}H_{38}Co_2F_2O_7SSi$ ([M-5CO]$^+$): 570.1045, found: 570.1052.

Etherification of alcohol S11

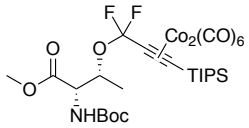
The procedure A was followed with a reaction time of 30 min. The crude was purified by flash silica gel column chromatography (AcOEt : hexane = 1 : 20 containing 1% TEA) to provide **197** (51.8 mg, 68.8 μmol, 69%).



197

197: red oil; IR (neat): 2059, 1720 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 4.57 (d, *J* = 8.2 Hz, 1H), 4.18-4.10 (m, 1H), 4.06 (dd, *J* = 9.6, 2.7 Hz, 1H), 3.94 (brs, 1H), 2.60-2.49 (m, 2H), 2.09 (s, 3H), 1.92-1.74 (m, 2H), 1.43 (s, 9H), 1.26 (sept, *J* = 6.8 Hz, 3H), 1.19 (d, *J* = 6.8 Hz, 18H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.1, 155.2, 125.0 (t, $^{1}J_{CF}$ = 256.7 Hz), 100.6 (t, $^{2}J_{CF}$ = 48.8 Hz), 79.6, 72.3, 65.9, 49.0, 31.2, 30.5, 28.3, 18.8, 15.4, 13.7; ^{19}F-NMR (560 MHz, $CDCl_3$): -59.7 (s, 2F); HRMS (EI): calcd for $C_{23}H_{41}Co_2F_2NO_4SSi$ ([M-5CO]$^+$): 611.1158, found: 611.1150.

Etherification of *N*-boc threonine methyl ether

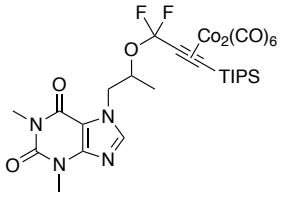


198

The procedure B was followed with a reaction time of 60 min. The crude was purified by flash silica gel column chromatography (AcOEt : hexane = 1 : 20 containing 1% Et_3N) to provide **198** (37.0 mg, 49.4 μmol, 50%).

198: red oil; IR (neat): 3457, 2031, 1756, 1724 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.20–5.03 (m, 2H), 4.40 (d, *J* = 9.8 Hz, 1H), 3.75 (s, 3H), 1.50-1.36 (m, 12H), 1.30-1.12 (m, 21H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.1, 170.2, 155.9, 124.9 (t, $^{1}J_{CF}$ = 258.1 Hz), 100.4 (t, $^{2}J_{CF}$ = 48.0 Hz), 79.9, 73.4, 72.4, 57.7, 52.5, 28.2, 18.9, 13.7; ^{19}F-NMR (560 MHz, $CDCl_3$): -58.4 (d, *J* = 156.9 Hz, 1F), -57.5 (d, *J* = 156.9 Hz, 1F); HRMS (FAB): calcd for $C_{25}H_{39}Co_2F_2NO_8Si$ ([M-3CO]$^+$): 665.1077, found: 665.1073.

Etherification of proxyphylline



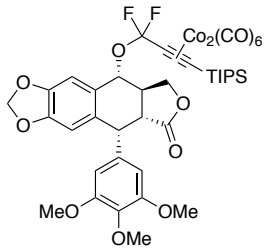
200

The procedure A was followed, employing toluene:CH_2Cl_2 (1 : 1, 1mL) instead of toluene, with a reaction time of 30 min. The crude was purified by flash silica gel column chromatography (AcOEt : hexane = 1 : 4 to 1 : 1 containing 1% TEA) to provide **200** (64.9 mg, 86.0 μmol, 86%).

200: red powder; IR (neat): 2030, 1708, 1665 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.51 (s, 1H), 5.08 (brs, 1H), 4.50 (d, J = 14.0 Hz, 1H), 4.19 (dd, J = 14.0, 7.5 Hz, 1H), 3.57 (s, 3H), 3.43 (s, 3H), 1.43 (d, J = 7.5 Hz, 3H), 1.33-1.03 (m, 21H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.0, 155.4, 151.6, 149.1, 141.8, 125.0 (t, $^1J_{CF}$ = 257.4 Hz), 106.8, 100.1 (dd, $^2J_{CF}$ = 44.7, 38.8 Hz), 72.8, 71.6, 53.4, 51.9, 29.7, 28.0, 18.8, 13.7; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -57.0 (d, J = 148.7 Hz, 1F), -57.5 (d, J = 148.7 Hz, 1F); HRMS (ESI): calcd for $C_{28}H_{35}Co_2F_2N_4O_9Si$ ([M+H]$^+$): 755.0800, found: 755.0784.

Etherification of podophyllotoxin

The procedure B was followed, employing toluene:CH_2Cl_2 (1 : 1, 1 mL) instead of toluene, with a reaction time of 30 min. The crude was purified by flash silica gel column chromatography (AcOEt : hexane = 1 : 4 to 1 : 1 containing 1% TEA) to provide **201** (57.5 mg, 61.8 μmol, 61%) and starting material (15.8 mg, 38.1 μmol, 38%).

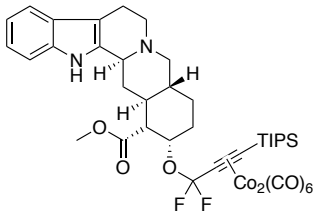


201

201: red amorphous; IR (neat): 2033, 1782 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.02 (s, 1H), 6.51 (s, 1H), 6.35 (s, 2H), 6.01 (s, 1H), 5.97 (s, 1H), 5.57 (d, J = 8.2 Hz, 1H), 4.62 (d, J = 4.1 Hz, 1H), 4.51 (t, J = 7.5 Hz, 1H), 4.18 (t, J = 7.2 Hz, 1H), 3.80 (s, 3H), 3.68 (s, 6H), 3.04-2.89 (m, 2H), 1.33-1.11 (m, 21H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.0, 173.7, 152.7, 148.2, 147.6, 137.2, 134.9, 132.1, 128.5, 125.5 (t, $^1J_{CF}$ = 257.4 Hz), 109.7, 108.1, 107.4, 101.6, 99.5 (t, $^2J_{CF}$ = 46.6 Hz), 76.0, 73.0, 71.1, 71.0, 60.7, 56.0, 45.4, 43.7, 38.2, 18.9, 13.7; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -54.4 (d, J = 148.2 Hz, 1F), -56.3 (d, J = 148.2 Hz, 1F); HRMS (FAB): calcd for $C_{34}H_{42}Co_2F_2O_8Si$ ([M-6CO]$^+$): 762.1281, found: 762.1262.

Etherification of yohimbine

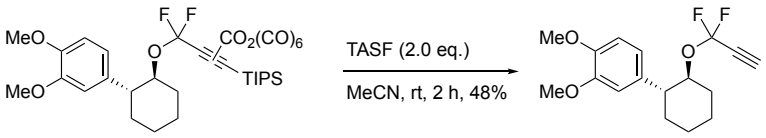
The procedure A was followed, employing toluene:CH_2Cl_2 (1 : 3, 2mL) instead of toluene, with a reaction time of 30 min. The crude was purified by flash silica gel column chromatography (AcOEt : hexane = 1 : 4 to 1 : 1 containing 1% TEA) to provide **202** (64.7 mg, 74.3 μmol, 74%).



202

202: red oil; IR (neat): 2030, 1745 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.27 (d, *J* = 8.9 Hz, 1H), 7.12 (t, *J* = 7.2 Hz, 1H), 7.07 (t, *J* = 7.2 Hz, 1H), 5.08 (s, 1H), 3.72 (s, 3H), 3.27 (d, *J* = 10.9 Hz, 1H), 3.07-3.03 (m, 1H), 2.99-2.90 (m, 2H), 2.71 (d, *J* = 12.3 Hz, 1H), 2.61 (td, *J* = 11.1, 3.9 Hz, 1H), 2.43-2.34 (m, 2H), 2.21-2.11 (m, 2H), 2.09-2,01 (m, 1H), 1.76-1.62 (m, 1H), 1.57-1.46 (m, 4H), 1.28 (sept, *J* = 7.4 Hz, 3H), 1.21 (d, *J* = 7.4 Hz, 18H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.2, 171.3, 135.9, 134.6, 127.3, 125.2 (t, $^1J_{CF}$ = 257.2 Hz), 121.3, 119.3, 118.0, 110.7, 108.0, 100.6 (dd, $^2J_{CF}$ = 48.4 Hz, 44.1 Hz), 72.9, 72.5, 61.3, 60.4, 60.0, 52.9, 51.6, 51.5, 40.1, 36.1, 34.0, 31.4, 23.4, 21.7, 19.0, 13.8; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -56.7 (d, *J* = 148.2 Hz, 1F), -57.2 (d, *J* = 148.2 Hz, 1F); HRMS (FAB): calcd for $C_{37}H_{47}Co_2F_2N_2O_7Si$ ([M+H-3CO]$^+$): 815.1785, found: 815.1789.

Simultaneous Decomplexation and Desilylation with TASF



195 **204**

To a solution of **195** (19.4 mg, 25.8 μmol) in MeCN (2.5 mL) was added TASF (14.2 mg, 45.8 μmol). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (1 mL) and extracted with Et_2O (4 mL × 3). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified with flash silica gel column chromatography (silica gel 60 (Merck), AcOEt : hexane = 1 : 20) to give **204** (3.88 mg, 12.5 μmol, 48%).

204: white solid; IR (neat): 2126 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.88-6.68 (m, 3H), 4.21 (td, *J* = 10.5 Hz, 4.5 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 2.66-2.46 (m, 2H), 2.36-2.20 (m, 1H), 1.94 (d, *J* = 13.5 Hz, 1H), 1.87 (d, *J* = 10.0 Hz, 1H), 1.77 (d, J = 8.8 Hz, 1H), 1.65-1.14 (m, 4H);^{13}C-NMR (100 MHz, $CDCl_3$): δ 148.4, 147.5, 135.4, 119.5, 113.4 (dd, $^1J_{CF}$ = 242.5 Hz, 215.1 Hz), 111.5, 110.8, 80.1, 74.0 (dd, $^2J_{CF}$ = 54.9 Hz, 53.3 Hz), 72.2 (t, $^2J_{CF}$ = 6.6 Hz), 55.80, 55.78, 49.5, 34.0, 33.4, 25.5, 24.8; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -54.5 (d, *J* = 169.3 Hz, 1F), -55.0 (d, *J* = 169.3 Hz, 1F); HRMS (EI): calcd for $C_{17}H_{20}F_2O_3$ (M^+): 310.1381, found: 310.1402.

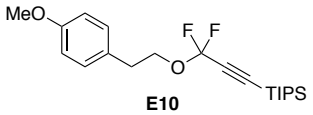
Decomplexation using Cerium Ammonium Nitrate (CAN)

Standard procedure: To a solution of cobalt complex in MeCN (0.02 M) was added CAN (4.5 equiv.) at room temperature. After 10 min, the reaction was quenched with sat. aqueous $Na_2S_2O_3$ (1 mL) and extracted with AcOEt (4 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was used in the next reaction without further purification.

To a solution of the residue in THF (0.02 M) was added TBAF (1M in THF, 1.1 equiv.) at -78 ºC. After 15 min, the reaction was quenched with sat. aqueous NH_4Cl (1 mL) and extracted with Et_2O (4 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (Silica gel 60 (Merck) was used.).

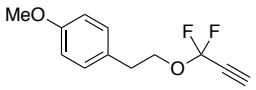
Decomplexation and desilylation of ether 176

On 610 mg (0.913 mmol) scale, the standard procedure was followed with CAN (2.25 g, 4.10 mmol) and TBAF (1M in THF, 10 mL, 1.00 mmol). The crude was purified by silica gel column chromatography (Et_2O: hexane =1 : 100) to provide **205** (147 mg, 65.0 μmol, 71%).



E10

E10: colorless oil; IR (neat): 1613 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.13 (d, J = 8.2 Hz, 2H), 6.84 (d, J = 8.2 Hz, 2H), 4.05 (t, J = 7.5 Hz, 2H), 3.79 (s, 3H), 2.92 (t, J = 7.5 Hz, 2H), 1.18-1.03 (m, 21H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 158.4, 130.0, 129.8, 129.3, 113.6 (t, $^1J_{CF}$ = 239.6 Hz), 95.5 (t, $^2J_{CF}$ = 52.3 Hz), 88.3 (t, $^3J_{CF}$ = 5.0 Hz), 66.6, 55.0 (t, $^2J_{CF}$ = 5.7 Hz), 34.7, 18.4, 10.9; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -57.7 (s, 2F); HRMS (EI): calcd for $C_{21}H_{32}F_2O_2Si$ (M^+): 382.2140, found: 382.2136.



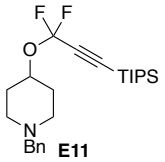
205

205: colorless oil; IR (neat): 3230, 2144 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.14 (d, J = 8.2 Hz, 2H), 6.85 (d, J = 8.2 Hz, 2H), 4.06 (t, J = 7.2 Hz, 2H), 3.79 (s, 3H), 2.92 (t, J = 7.2 Hz, 2H), 2.71 (t, J = 2.7 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 158.4, 129.9, 129.1, 114.0, 113.6 (t, $^1J_{CF}$ = 242.8 Hz), 73.6 (t, $^2J_{CF}$ = 54.2 Hz), 73.0 (t, $^3J_{CF}$ = 6.5 Hz), 66.3, 55.2, 34.6; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -59.2 (s, 2F); HRMS (EI): calcd for $C_{12}H_{12}F_2O_2$ (M^+): 226.0805, found: 226.0820.

Decomplexation and desilylation of ether 190

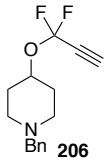
On 54.1 mg (74.1 μmol) scale, the standard procedure was followed with CAN (183 mg, 0.334 mmol) and TBAF (1M in THF, 80 μL, 80 μmol). The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 :

8) to provide **206** (12.1 mg, 45.6 µmol, 61%).



E11

E11: colorless oil; IR (neat): 1464, 1252 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.36-7.28 (m, 4H), 7.26-7.22 (m, 1H), 4.29 (brs, 1H), 3.49 (s, 2H), 2.73 (brs, 2H), 2.20 (brs, 2H), 1.97-1.89 (m, 2H), 1.86-1.75 (m, 2H), 1.17-1.00 (m, 21H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 138.5, 129.0, 128.2, 127.0, 113.8 (t, $^{1}J_{CF}$ = 240.6 Hz), 95.8 (t, $^{2}J_{CF}$ = 53.5 Hz), 88.1 (t, $^{3}J_{CF}$ = 5.1 Hz), 73.9, 62.8, 50.7, 32.1, 18.4, 10.9; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -53.4 (s, 2F); HRMS (EI): calcd for $C_{24}H_{37}F_2NOSi$ (M^+): 421.2612, found: 421.2584.

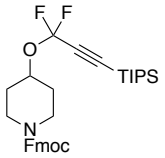


206

206: colorless oil; IR (neat): 3301, 2145 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.36-7.22 (m, 5H), 4.31 (brs, 1H), 3.49 (s, 2H), 2.79-2.64 (m, 3H), 2.64 (brs, 2H), 2.22 (brs, 2H), 1.91-1.75 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 138.4, 129.0, 128.2, 127.0, 113.7 (t, $^{1}J_{CF}$ = 243.2 Hz), 74.1 (t, $^{2}J_{CF}$ = 54.5 Hz), 73.6, 72.6 (t, $^{3}J_{CF}$ = 5.7 Hz), 62.9, 50.6, 32.1; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -55.6 (s, 2F); HRMS (EI): calcd for $C_{15}H_{17}F_2NO$ (M^+): 265.1278, found: 265.1279.

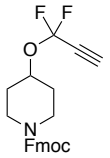
Decomplexation and desilylation of ether 182

On 81.4 mg (96.9 µmol) scale, the standard procedure was followed with CAN (260 mg, 0.474 mmol) and TBAF (1M in THF, 0.11 mL, 0.11 mmol). The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 8) to provide **207** (28.4 mg, 71.4 µmol, 74%).



E12

E12: colorless oil; IR (neat): 1706 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.76 (d, J = 7.3 Hz, 2H), 7.57 (d, J = 7.3 Hz, 2H), 7.40 (t, J = 7.3 Hz, 2H), 7.32 (t, J = 7.3 Hz, 2H), 4.53-4.37 (m, 3H), 4.24 (t, J = 6.2 Hz, 1H), 3.70 (brs, 2H), 3.33 (brs, 2H), 1.94-1.71 (m, 4H), 1.26-1.00 (m, 21H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 155.1, 144.0, 141.4, 127.7, 127.0, 124.9, 120.0, 113.7 (t, $^{1}J_{CF}$ = 241.3 Hz), 95.5 (t, $^{2}J_{CF}$ = 52.7 Hz), 88.6 (t, $^{3}J_{CF}$ = 5.1 Hz), 72.4, 67.2, 47.4, 40.8, 31.5, 18.4, 10.9; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -54.1 (s, 2F); HRMS (FAB): calcd for $C_{32}H_{42}F_2NO_3Si$ ($[M+H]^+$): 554.2902, found: 554.2863.

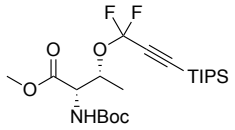


207

207: colorless oil; IR (neat): 2138, 1698 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 7.5 Hz, 2H), 7.57 (d, J = 7.5 Hz, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.30 (t, J = 7.5 Hz, 2H), 4.53-4.34 (m, 3H), 4.24 (t, J = 6.5 Hz, 1H), 3.69 (brs, 2H), 3.34 (brs, 2H), 2.75 (t, J = 3.4 Hz, 1H), 1.82 (brs, 2H), 1.70 (brs, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 155.1, 144.0, 141.3, 127.7, 127.0, 124.9, 120.0, 113.6 (t, $^{1}J_{CF}$ = 243.7 Hz), 73.8 (t, $^{2}J_{CF}$ = 54.1 Hz), 73.0 (t, $^{3}J_{CF}$ = 6.1 Hz), 72.2, 67.2, 47.4, 40.7, 31.5; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -56.2 (s, 2F); HRMS (EI): calcd for $C_{23}H_{21}F_2NO_3$ (M^+): 397.1489, found: 397.1495.

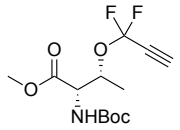
Decomplexation and desilylation of ether 198

On 86.4 mg (0.115 mmol) scale, the standard procedure was followed with CAN (288 mg, 0.525 mmol) and TBAF (1M in THF, 0.13 mL, 0.130 mmol). The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 8) to provide **35** (25.3 mg, 82.4 μmol, 72%).



E13

E13: colorless oil; IR (neat): 3451, 1758, 1722 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.24 (d, J = 9.7 Hz, 1H), 5.01-4.80 (m, 1H), 4.41 (d, J = 9.7 Hz, 1H), 3.75 (s, 3H), 1.47 (s, 9H), 1.39 (d, J = 6.7 Hz, 3H), 1.19-1.01 (m, 21H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.1, 155.9, 113.2 (t, $^{1}J_{CF}$ = 243.3 Hz), 94.8 (t, $^{2}J_{CF}$ = 51.2 Hz), 89.2, 80.3, 74.0, 57.7, 52.6, 28.2, 18.4, 10.8; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -53.9 (d, J = 165.7 Hz, 1F), -54.3 (d, J = 165.7 Hz, 1F); HRMS (EI): calcd for $C_{15}H_{24}F_2NO_5Si$ (M^+-*t*Bu-*i*Pr): 364.1392, found: 364.1393.



208

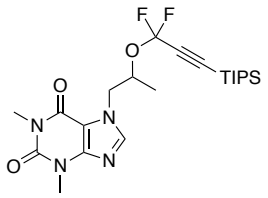
208: colorless oil; IR (neat): 3249, 2141, 1755, 1716 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.25 (d, J = 9.7 Hz, 1H), 5.02-4.87 (m, 1H), 4.41 (d, J = 9.7 Hz, 1H), 3.76 (s, 3H), 2.76 (t, J = 3.1 Hz, 1H), 1.47 (s, 9H), 1.40 (d, J = 6.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.1, 155.9, 113.1 (t, $^{1}J_{CF}$ = 245.8 Hz), 80.3, 73.9, 73.3 (t, $^{3}J_{CF}$ = 6.6 Hz), 73.2 (t, $^{2}J_{CF}$ = 52.8 Hz), 57.6, 53.0, 28.2, 18.4; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -56.3 (d, J = 166.0 Hz, 1F), -57.1 (d, J = 166.0 Hz, 1F); HRMS (EI): calcd for $C_{13}H_{19}F_2NO_5$ (M^+): 307.1231, found: 307.1224.

Decomplexation and desilylation of ether 200

To a solution of cobalt complex **28** (101 mg, 0.134 mmol) in acetone (5.4 mL) was added CAN (300 mg, 0.547 mmol) at room temperature. After 60 min, the reaction was quenched with sat. aqueous $Na_2S_2O_3$ (2 mL) and extracted

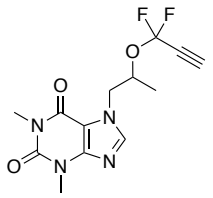
with Et_2O (10 mL × 2). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt : hexane = 1 : 1) to give **E14** (52.0 mg, 0.111 mmol, 83%).

To a solution of **E14** (71.8 mg, 0.153 mmol) in THF (7.7 mL) was added TBAF (1M in THF; 0.17 mL, 0.170 mmol) at -78 ºC. After 15 min, the reaction was quenched with sat. aqueous NH_4Cl (2 mL) and extracted with Et_2O (4 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography to give **209** (45.6 mg, 0.146 mmol, 95%).



E14

E14: colorless oil; IR (neat): 1708, 1664 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.60 (s, 1H), 4.83-4.69 (m, 1H), 4.57 (dd, J = 14.4 Hz, 2.4 Hz, 1H), 4.26 (dd, J = 14.4 Hz, 7.4 Hz, 1H), 3.60 (s, 3H), 3.41 (s, 3H), 1.40 (d, J = 7.4 Hz, 3H), 1.17-0.97 (m, 21H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 155.4, 151.6, 148.8, 142.1, 113.2 (t, $^1J_{CF}$ = 248.7 Hz), 106.6, 94.7 (t, $^2J_{CF}$ = 51.2 Hz), 89.3 (t, $^3J_{CF}$ = 4.9 Hz), 72.5, 51.2, 29.8, 27.9. 18.3, 10.8; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -54.5 (d, J = 165.7 Hz), -55.0 (d, J = 165.7 Hz),; HRMS (EI): calcd for $C_{22}H_{34}F_2N_4O_3Si$ (M^+): 468.2368, found: 468.2345.



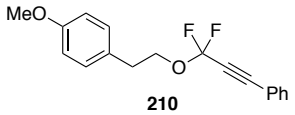
209

209: white solid; mp = 130-131 ºC; IR (neat): 2144, 1704, 1659 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.60 (s, 1H), 4.83-4.73 (m, 1H), 4.57 (d, J = 13.7 Hz, 1H), 4.22 (dd, J = 8.4, 8.2 Hz, 1H), 3.60 (s, 3H), 3.41 (s, 3H), 2.68 (t, J = 3.1 Hz, 1H), 1.41 (d, J = 6.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 155.4, 151.6, 148.9, 142.1, 113.2 (t, $^1J_{CF}$ = 245.6 Hz), 106.7, 73.3 (t, $^3J_{CF}$ = 6.5 Hz), 73.1 (t, $^2J_{CF}$ = 52.7 Hz), 72.4, 51.3, 29.8, 27.9, 18.5; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -57.0 (d, J = 156.9 Hz), -57.5 (d, J = 156.9 Hz); HRMS (EI): calcd for $C_{13}H_{14}F_2N_4O_3$ (M^+): 312.1034, found: 312.1038.

Decomplexation and desilylation of ether 185

To a solution of cobalt complex (55.5 mg, 94.3 μmol) in MeCN (4.7 mL) was added CAN (250 mg, 0.456 mmol) at room temperature. After 10 min, the reaction was quenched with sat. aqueous $Na_2S_2O_3$ (2 mL) and extracted with Et_2O (10 mL × 2). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chroamrography (AcOEt : hexane = 1 : 50) to give **210** (22.8

mg, 75.4 μmol, 80%).



210

210: colorless oil; IR (neat): 2248, 1613 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 6.8 Hz, 2H), 7.47-7.31 (m, 3H), 7.17 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 4.12 (t, J = 7.2 Hz, 2H), 3.79 (s, 3H), 2.96 (t, J = 7.2 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 158.4, 132.3, 130.1, 129.9, 129.2, 128.5, 119.6, 114.9 (t, $^{1}J_{CF}$ = 242.5 Hz), 113.9, 84.4 (t, $^{2}J_{CF}$ = 6.1 Hz), 78.8 (t, $^{2}J_{CF}$ = 54.1 Hz), 66.3 (t, $^{3}J_{CF}$ = 3.3 Hz), 55.2, 34.7; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -57.5 (s, 2F); HRMS (EI): calcd for $C_{18}H_{16}F_2O_2$ (M^+): 302.1118, found: 302.1157.

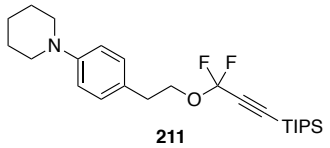
3. Decomplexation using *N,N,N'*-trimethyl ethylenediamine

Standard procedure: To a solution of cobalt complex in Et_2O (0.02 M) was added *N,N,N'*-trimethyl ethylenediamine (6 equiv.) at room temperature. After completed the reaction, the reaction mixture was added H_2O (2 mL) and Et_2O (2 mL) and extracted with Et_2O (5 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified with flash silica gel column chromatography.

To a solution of the residue in THF (0.02 M) was added TBAF (1M in THF, 1.1 equiv.) at -78 ºC. After 15 min, the reaction was quenched with sat. aqueous NH_4Cl (1 mL) and extracted with Et_2O (4 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (Silica gel 60 (Merck) was used.).

Decomplexation of ether 188

On 76.3 mg (106 μmol) scale, the standard procedure was followed with *N,N,N'*-trimethyl ethylenediamine (87 μL, 0.635 mmol) in Et_2O (5.2 mL) for 12 h. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 20) to provide **211** (42.4 mg, 97.3 μmol, 92%).

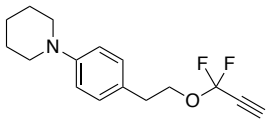


211

211: colorless oil; IR (neat): 1614, 1385 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.09 (d, J = 8.2 Hz, 2H), 6.87 (d, J = 8.2 Hz, 2H), 4.04 (t, J = 7.6 Hz, 2H), 3.12 (t, J = 5.3 Hz, 2H), 2.90 (t, J = 7.6 Hz, 2H), 1.75-1.65 (m, 4H), 1.61-1.51 (m, 2H), 1.26-1.03 (m, 21H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 151.0, 129.5, 127.7, 116.7, 113.6 (t, $^{1}J_{CF}$ = 242.6 Hz), 95.5 (t, $^{2}J_{CF}$ = 52.4 Hz), 88.2 (t, $^{2}J_{CF}$ = 5.3 Hz), 66.7, 50.8, 34.7, 25.9, 24.3, 18.4, 10.9; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -57.6 (s, 2F); HRMS (EI): calcd for $C_{25}H_{39}F_2NO_2Si$ (M^+): 435.2769, found: 435.2742.

On 35.8 mg (82.2 mmol) scale, the standard procedure was followed with TBAF (1M in THF, 90 μL, 90 μmol) in THF (4.1 mL). The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 20) to provide

28.6 mg of the crude mixture containing **215** (71.7 μmol, 87%). Yield determined ^{1}H-NMR using CH_2Br_2 as an internal standard. The analytical sample was purified by GPC.

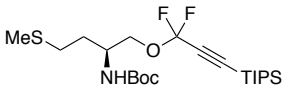


215

215: colorless oil; IR (neat): 2138, 1614 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.09 (d, J = 8.6 Hz, 2H), 6.91 (d, J = 8.2 Hz, 2H), 4.06 (t, J = 7.6 Hz, 2H), 3.13 (t, J = 5.5 Hz, 4H), 2.90 (t, J = 7.6 Hz, 2H), 2.71 (t, J = 3.3 Hz, 1H), 1.79-1.65 (m, 4H), 1.64-1.53 (m, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 150.9, 129.5, 127.7, 116.8, 114.5 (t, $^{1}J_{CF}$ = 244.5 Hz), 73.7 (t, $^{2}J_{CF}$ = 54.2 Hz), 72.9 (t, $^{2}J_{CF}$ = 6.5 Hz), 66.4, 50.9, 34.6, 25.8, 24.2; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -59.1 (s, 2F); HRMS (ESI): calcd for $C_{16}H_{20}F_2NO$ ([M+H]$^{+}$): 280.1513, found: 280.1523.

Decomplexation of ether 197

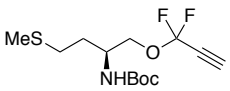
On 68.1 mg (90.6 μmol) scale, the standard procedure was followed with *N,N,N'*-trimethyl ethylenediamine (74.5 μL, 0.543 mmol) in Et_2O (4.5 mL) for 12 h. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 15) to provide **212** (34.0 mg, 73.0 μmol, 81%).



212

212: colorless oil; IR (neat): 3342, 2188, 1716 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.70 (brs, 1H), 3.93 (s, 3H), 2.55 (t, J = 7.5 Hz, 2H), 2.11 (s, 3H), 1.95-1.74 (m, 2H), 1.45 (s, 9H), 1.21-1.01 (m, 21H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 155.3, 113.5 (t, $^{1}J_{CF}$ = 241.7 Hz), 94.9 (t, $^{2}J_{CF}$ = 51.6 Hz), 89.2, 79.7, 67.3, 48.7, 31.2, 30.5, 28.3, 18.4, 15.4, 10.8; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -58.0 (s, 2F); HRMS (FAB): calcd for $C_{22}H_{40}F_2NO_3SSi$ ([M-H]$^{+}$): 464.2466, found: 464.2463.

On 34.0 mg (73.0 mmol) scale, the standard procedure was followed with TBAF (1M in THF, 80 μL, 80 μmol) in THF (3.7 mL). The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 20 to 1 : 8) to provide **216** (21.4 mg, 69.2 μmol, 95%).



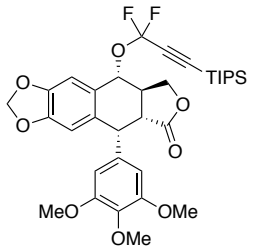
216

216: White amorphous; IR (neat): 3305, 2140, 1697 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 4.70 (d, J = 7.6 Hz, 1H), 4.02-3.86 (m, 3H), 2.75 (t, J = 3.4 Hz, 1H), 2.56 (s, 2H), 2.12 (s, 3H), 1.93-1.76 (m, 2H), 1.44 (s, 9H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 155.3, 113.5 (t, $^{1}J_{CF}$ = 244.2 Hz), 79.7, 73.5 (t, $^{3}J_{CF}$ = 6.5 Hz), 73.2 (t, $^{2}J_{CF}$ = 53.2 Hz), 67.0,

48.7, 31.0, 30.5, 28.3, 15.5; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -56.2 (s, 2F); HRMS (ESI): calcd for $C_{13}H_{22}F_2NO_3S$ ($[M+H]^+$): 310.1288, found: 310.1278.

Decomplexation of ether 201

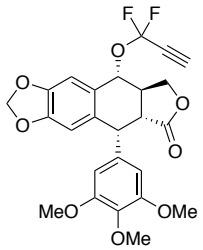
On 100 mg (107 µmol) scale, the standard procedure was followed with *N,N,N'*-trimethyl ethylenediamine (88 µL, 0.642 mmol) in Et_2O (5.4 mL) for 10 h. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 6) to provide **214** (32.3 mg, 50.1 µmol, 47%).



214

214: white amorphous; IR (neat): 1783 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.03 (s, 1H), 6.53 (s, 1H), 6.38 (s, 2H), 6.00 (s, 1H), 5.99 (s, 1H), 5.38 (d, J = 9.2 Hz, 1H), 4.63-4.55 (m, 2H), 4.06 (t, J = 9.9 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 6H), 3.11-2.95 (m, 1H), 2.86 (dd, J = 14.5, 4.3 Hz, 1H), 1.23-1.01 (m, 21H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 173.6, 152.6, 148.3, 147.7, 137.0, 134.6, 132.4, 128.1, 113.5 (dd, $^1J_{CF}$ = 247.4, 243.3 Hz), 109.4, 108.0, 107.9, 101.6, 94.8 (dd, $^2J_{CF}$ = 52.1, 48.7 Hz), 89.9, 75.9, 71.1, 60.7, 56.0, 45.6, 43.7, 38.3, 18.4, 10.8; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -53.4 (d, J = 165.7 Hz, 1F), -54.6 (d, J = 165.7 Hz, 1F); HRMS (EI): calcd for $C_{34}H_{42}F_2O_8Si$ (M^+): 644.2617, found: 644.2589.

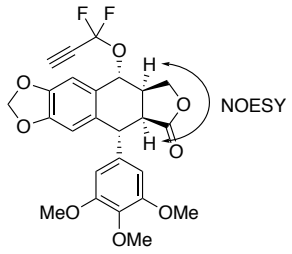
On 43.5 mg (67.5 mmol) scale, the standard procedure was followed with TBAF (1M in THF, 74 µL, 74 µmol) in THF (3.4 mL). The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 6) to provide **218** (12.9 mg, 26.4 µmol, 39%) and epimer **219** (13.1 mg, 26.8 µmol, 40%).



218

218: white amorphous; IR (neat): 2142, 1781 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 6.98 (s, 1H), 6.53 (s, 1H), 6.37 (s, 2H), 6.00 (d, J = 1.4 Hz, 1H), 5.99 (d, J = 1.4 Hz, 1H), 5.40 (d, J = 9.3 Hz, 1H), 4.60 (d, J = 4.5 Hz, 1H), 4.55 (t, J = 8.1 Hz, 1H), 4.07 (t, J = 9.8 Hz, 1H), 3.81 (s, 3H), 3.76 (s, 6H), 3.06-2.95 (m, 1H), 2.87 (dd, J = 14.6, 4.6 Hz, 1H), 2.85 (t, J = 3.2 Hz, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 173.5, 152.7, 148.4, 147.8, 137.2, 134.5, 132.5, 127.8, 113.5 (t, $^1J_{CF}$ = 245.6 Hz), 109.6, 108.0, 107.7, 101.7, 76.0, 74.1 (t, $^3J_{CF}$ = 5.8 Hz), 73.1 (t, $^2J_{CF}$ = 51.3 Hz), 71.0 (t,

$^{3}J_{CF}$ = 6.5 Hz), 65.1, 60.8, 56.1, 45.5, 43.7, 38.2; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -55.4 (s, 2F); HRMS (ESI): calcd for $C_{25}H_{23}F_2O_8$ ([M+H]$^+$): 489.1361, found: 489.1390.

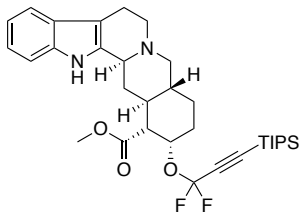


219

219: white amorphous; IR (neat): 2141, 1774 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 6.88 (s, 1H), 6.49 (s, 1H), 6.44 (s, 2H), 5.97 (d, *J* = 1.0 Hz, 1H), 5.96 (d, *J* = 1.4 Hz, 1H), 5.24 (d, *J* = 5.5 Hz, 1H), 4.42 (dd, *J* = 9.8, 6.4 Hz, 1H), 4.37 (dd, *J* = 9.8, 2.6 Hz, 1H), 4.30 (d, *J* = 4.1 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 6H), 3.22 (dd, *J* = 8.9, 4.1 Hz, 1H), 3.13-3.07 (m, 1H), 2.81 (t, *J* = 3.3 Hz, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 177.0, 153.4, 148.6, 147.3, 138.4, 136.8, 131.3, 126.0, 113.6 (t, $^{1}J_{CF}$ = 264.4 Hz), 109.3, 108.1, 105.3, 101.5, 75.1, 74.1 (t, $^{3}J_{CF}$ = 5.8 Hz), 73.2 (t, $^{2}J_{CF}$ = 52.7 Hz), 70.6, 60.8, 56.1, 45.8, 44.3, 40.8; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -55.0 (d, *J* = 174.4 Hz, 1F), -55.6 (d, *J* = 174.4 Hz, 1F); HRMS (ESI): calcd for $C_{25}H_{23}F_2O_8$ ([M+H]$^+$): 489.1361, found: 489.1389.

Decomplexation of analog 202

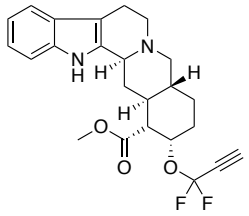
On 58.9 mg (67.6 µmol) scale, the standard procedure was followed with *N,N,N'*-trimethyl ethylenediamine (65 µL, 0.406 mmol) in Et_2O (2.1 mL) at 12 h. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 2) to provide **213** (21.2 mg, 36.3 µmol, 54%).



213

213: colorless oil; IR (neat): 3384, 1732 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.82 (brs, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 4.89 (s, 1H), 3.74 (s, 3H), 3.40 (d, *J* = 10.9 Hz, 1H), 3.08 (dd, *J* = 11.3, 5.8 Hz, 1H), 3.03-2.92 (m, 2H), 2.72 (d, *J* = 15.0 Hz, 1H), 2.64 (td, *J* = 11.3, 3.8 Hz, 1H), 2.43 (d, *J* = 12.3 Hz, 1H), 2.36 (d, *J* = 11.6 Hz, 1H), 2.31-2.20 (m, 2H), 2.08-1.98 (m, 1H), 1.64-1.42 (m, 4H), 1.31-1.03 (m, 21H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 171.4, 136.0, 134.7, 127.4, 121.3, 119.3, 118.1, 113.5 (t, $^{1}J_{CF}$ = 241.3 Hz), 110.8, 108.1, 95.3 (t, $^{2}J_{CF}$ = 52.7 Hz), 89.2 (t, $^{3}J_{CF}$ = 5.1 Hz), 74.3, 61.1, 59.8, 52.9, 51.8, 51.6, 40.4, 36.3, 34.3, 30.7, 23.3, 21.8, 18.4, 10.9; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -53.4 (d, *J* = 165.7 Hz, 1F), -53.8 (d, *J* = 165.7 Hz, 1F); HRMS (ESI): calcd for $C_{33}H_{47}F_2N_2O_3Si$ ([M+H]$^+$): 582.3426, found: 582.3320.

On 35.5 mg (60.7 mmol) scale, the standard procedure was followed with TBAF (1M in THF, 74 μL, 74 μmol) in THF (3.4 mL). The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 1) to provide **217** (16.6 mg, 38.7 μmol, 64%).

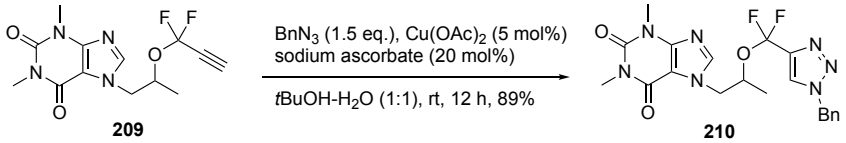


217

217: white amorphous; IR (neat): 2137, 1727 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.12 (t, *J* = 6.9 Hz, 1H), 7.08 (t, *J* = 6.9 Hz, 1H), 4.89 (d, *J* = 2.1 Hz, 1H), 3.75 (s, 3H), 3.41 (d, *J* = 11.7 Hz, 1H), 3.07 (dd, *J* = 11.0, 5.5 Hz, 1H), 3.04-2.95 (m, 1H), 2.95 (dd, *J* = 11.3, 3.4 Hz, 1H), 2.74 (t, *J* = 3.4 Hz, 1H), 2.72 (dd, *J* = 16.9, 4.8 Hz, 1H), 2.64 (td, *J* = 11.5, 4.4 Hz, 1H), 2.45-2.33 (m, 2H), 2.28 (t, *J* = 10.7 Hz, 1H), 2.13-2.22 (m, 1H), 2.04 (qd, *J* = 11.2, 3.6 Hz, 1H), 1.78-1.45 (m, 5H) ^{13}C-NMR (150 MHz, $CDCl_3$): δ 171.4, 136.0, 134.6, 127.3, 121.3, 119.3, 118.1, 113.4 (t, $^{1}J_{CF}$ = 244.9 Hz), 110.8, 108.1, 73.7, 73.5 (t, $^{2}J_{CF}$ = 52.7 Hz), 73.0 (t, $^{3}J_{CF}$ = 5.8 Hz), 61.0, 59.8, 52.9, 51.8, 51.6, 40.2, 36.2, 34.1, 31.0, 23.3, 21.7; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -56.5 (d, *J* = 174.4 Hz, 1F), -56.8 (d, *J* = 174.4 Hz, 1F); HRMS (ESI): calcd for $C_{24}H_{27}F_2N_2O_3$ ([M+H]$^+$): 429.1990, found: 429.1993.

Syntheses of α-difluoroehters

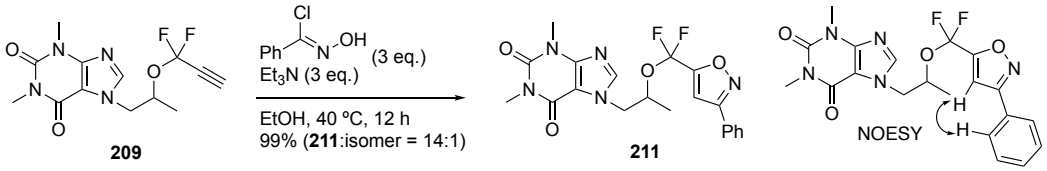
Synthesis of triazole 210



To a solution of difluoropropargyl ether **209** (31.3 mg, 0.100 mmol) and benzyl azide (20.3 mg, 0.152 mmol) in *t*-BuOH-H_2O (1:1, 1 mL) was added $Cu(OAc)_2$ (0.9 mg, 5.0 μmol) and sodium ascorbate (3.6 mg, 18.2 μmol). The reaction was stirred at room temperature for 12 h. the reaction mixture was diluted with Et_2O (5 mL) and H_2O (5 mL) and extracted with $CHCl_3$ (10 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified with flash silica gel column chromatography (AcOEt : hexane = 1 : 1 to MeOH : $CHCl_3$ = 1 : 20) to give **210** (39.5 mg, 88.6 μmol, 89%).

210: white solid; mp = 120-121 ºC; IR (neat): 1703, 1660 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.56 (s, 1H), 7.36-7.44 (m, 3H), 7.28-7.32 (m, 2H), 5.53 (s, 2H), 4.88-4.96 (m, 1H), 4.61 (dd, *J* = 14.1, 2.4 Hz, 1H), 4.30 (dd, *J* = 14.1, 8.2 Hz, 1H), 3.57 (s, 3H), 3.40 (s, 3H), 1.44 (d, *J* = 6.5 Hz, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 155.4, 151.5, 148.8, 142.3, 133.6, 129.3, 129.2, 129.1, 128.2, 122.3, 119.1 (t, $^{1}J_{CF}$ = 255.0 Hz), 106.8, 71.2, 54.4, 51.4, 29.8, 27.8, 18.7; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -67.5 (d, *J* = 157.0 Hz, 1F), 68.0 (d, *J* = 157.0 Hz, 1F); HRMS (ESI): calcd for $C_{20}H_{22}F_2N_7O_3$ ([M+H]$^+$): 446.1752, found: 446.1753.

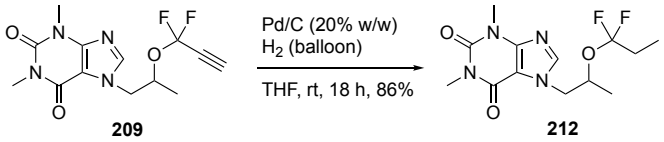
Synthesis of isoxazole 211



To a solution of difluoroproaprgyl ether **209** (30.9 mg, 98.9 µmol) and (*Z*)-*N*-hydroxybenzimidoyl chloride (46.8 mg, 0.301 mmol) in EtOH (1 mL) was added Et_3N (42 µL, 0.301 mmol). The reaction mixture was stirred at 40 ºC for 12 h. The reaction mixture was diluted with H_2O (4 mL) and extracted with Et_2O (10 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified with flash silica gel column chromatography (AcOEt : hexane = 1 : 1 to MeOH : $CHCl_3$ = 1 : 20) to give **211** (42.1 mg, 97.6 µmol, 99%).

211: white amorphous; IR (neat): 1704, 1660 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.79-7.73 (m, 2H), 7.62 (s, 1H), 7.50-7.42 (m, 3H), 6.76 (s, 1H), 4.99-4.91 (m, 1H), 4.60 (d, *J* = 14.4 Hz, 1H), 4.26 (dd, *J* = 14.3, 8.4 Hz, 1H), 3.56 (d, *J* = 1.4 Hz, 3H), 3.37 (d, *J* = 1.4 Hz, 3H), 1.49 (d, *J* = 6.2 Hz, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 162.2, 162.1 (t, $^2J_{CF}$ = 55.1 Hz), 155.4, 151.5, 148.9, 142. 0, 130.6, 129.1, 127.6, 126.8, 117.0 (t, $^1J_{CF}$ = 257.2 Hz), 106.6, 102.1, 72.2, 51.4, 29.8, 27.9, 18.8; ^{19}F-NMR (560 MHz, $CDCl_3$): δ 70.5 (d, *J* = 157.0 Hz, 1F), 71.0 (d, *J* = 157.0 Hz, 1F); HRMS (ESI): calcd for $C_{20}H_{20}F_2N_5O_4$ ($[M+H]^+$): 432.1483, found: 432.1505.

Synthesis of fluoropropyl ether 212



To a solution of difluoropropargyl ether **209** (28.4 mg, 90.9 µmol) in THF (1.8 mL) was added 10% Pd/C (8.5 mg) and hydrogenated (H_2, 1 atm). After 16 h, the catalyst was filtered through a pad of Celite followed by washed with Et_2O (20 mmol). The Filtrate was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified with flash silica gel column chromatography (AcOEt : hexane = 1 : 1) to give **212** (24.8 mg, 78.4 µmol, 86%).

212: colorless oil; IR (neat): 1705, 1661 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.52 (s, 1H), 4.69-4.77 (m, 1H), 4.51 (dd, *J* = 14.1, 2.4 Hz, 1H), 4.14 (dd, *J* = 14.3, 8.4 Hz, 1H), 3.58 (s, 3H), 3.39 (s, 3H), 1.92-1.79 (m, 2H), 1.32 (d, *J* = 6.5 Hz, 3H), 0.94 (t, *J* = 7.6 Hz, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 155.3, 151.6, 148.7, 141.9, 125.9 (t, $^1J_{CF}$ = 262.3 Hz), 106.8, 69.3 (t, $^2J_{CF}$ = 5.0 Hz), 51.7, 29.8, 29.1 (t, $^2J_{CF}$ = 30.3 Hz), 27.9, 18.8, 6.9; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -78.1 (s, 2F); HRMS (ESI): calcd for $C_{13}H_{19}F_2N_4O_3$ ($[M+H]^+$): 317.1425, found: 317.1428.

Raman spectrum

Raman Spectra of CH_2Alkynes/CF_2Alkynes

Raman spectra were obtained with a RAMAN-11 slit-scanning Raman microscope (Nanophoton, Japan) with 532 nm excitation. Samples were placed on a quartz substrate during the measurements. The laser output was focused into the sample by a 60X/1.27 numerical aperture (NA) water immersion objective lens (CFI Plan Apo IR 60X WI, NIKON, Japan). The slit width of the spectrograph was 70 μm. The light intensity at the sample plane was calculated as 6.0 mW/μm^2 from the ratio of the measured laser power between the sample position and the area of the illumination line. The exposure time for each line was 10 sec.

Relative Raman intensity vs EdU (RIE)[3]

The 1 μL each of DMSO solutions of the test compound (10 or 100 mM) and internal standard (10 or 100 mM stock solution of EdU or PhCN) were mixed on quartz, and Raman spectrum of the mixture was measured by using RAMAN-11 slit-scanning Raman microscope (Nanophoton, Japan) with 532 nm excitation. The measurement was repeated 4 times for each test compound. The light intensity at the sample plane was calculated as 6.0 mW/μm^2 from the ratio of the measured laser power between the sample position and the area of the illumination line. The exposure time for each line was 120 sec. The background of DMSO was subtracted from the measured spectra, and obtained spectra were fitted with a Gaussian function. The peak areas were calculated by "Raman viewer" software equipped on the Raman microscope. Finally, RIE (relative Raman intensity vs EdU) was calculated from the area ratio of 4 spectra and concentrations of the sample and standard (in the case of PhCN as a standard, RIE was calculated from the peak areas of sample vs PhCN and PhCN vs EdU).

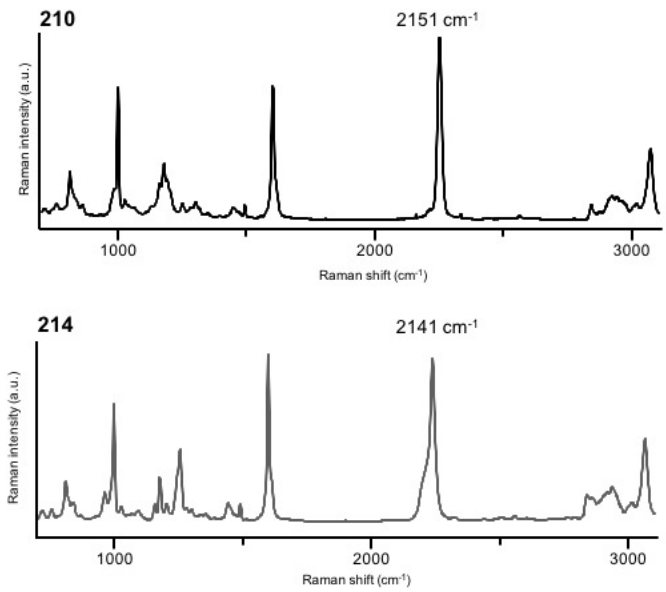


Figure S1. Raman spectra of **205** and **213**.

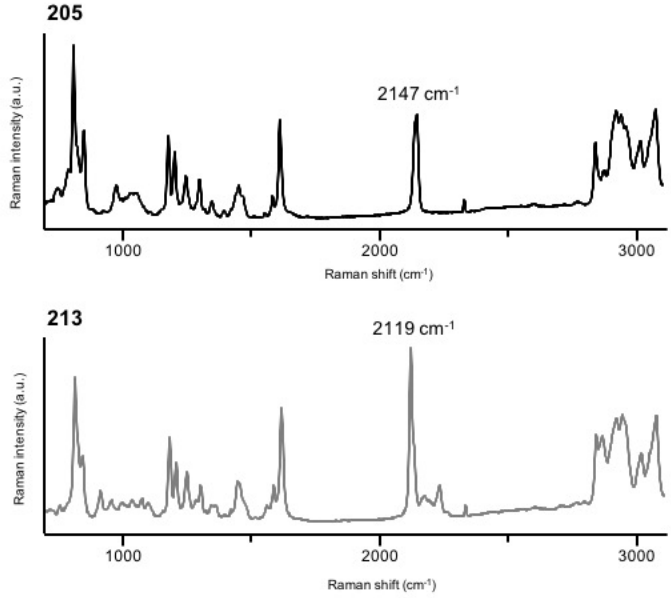
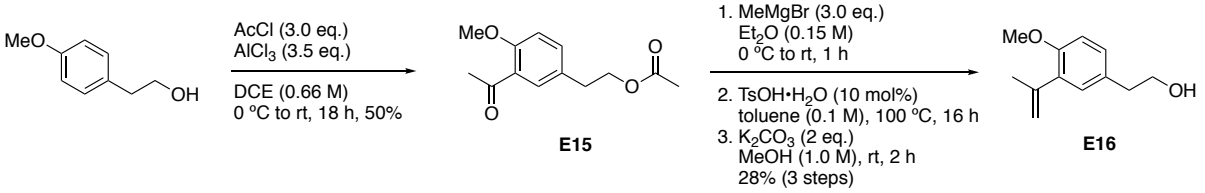


Figure S2. Raman spectra of **210** and **214**.

Synthesis of substrates

2-(4-Methoxy-3-(prop-1-en-2-yl)phenyl)ethan-1-ol (E16)



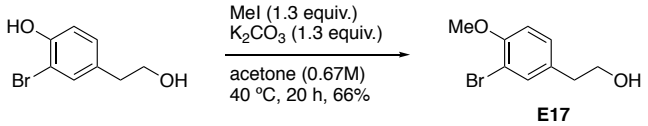
To a solution of 4-methoxyphenylethyl alcohol (3.36 g, 22.0 mmol) and AcCl (4.7 mL, 66.0 mmol) in $Cl_2CHCHCl_2$ (33 mL) was added $AlCl_3$ (10.3 g, 77.2 mmol) portionwise over 1 h at 0 ºC. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. Then the reaction mixture was cooled at 0 ºC and quenched with ice water (20 mL) and extracted with CH_2Cl_2 (40 mL × 2). The combined organic layer was washed with water and then brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt : hexane = 1 : 4) to give **E15** (2.68 g, 10.9 mmol, 50%) as a colorless oil.

To a solution of **E15** (924 mg, 3.91 mmol) in Et_2O (26 mL) was added MeMgBr (3M in Et_2O: 3.8mL) dropwise over 30 min at 0 ºC and then stirred for 2 h. The reaction mixture was quenched with sat. NH_4Cl aq. (10 mL) and extracted with Et_2O (20 mL × 2). The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. To the residue were added toluene (34 mL) and TsOH•H_2O (64.5 mg, 0.338 mmol) at room temperature. The reaction mixture was warm to 100 ºC and stirred for 16 h. The reaction mixture was concentrated in vacuo and AcOEt (50 mL) was added. The organic layers were washed with sat. $NaHCO_3$ aq. and brine. The organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. To the residue was added K_2CO_3 (937 mg, 6.78 mmol) and MeOH (34 mL) at room temperature. After stirring 2 h, the reaction mixture was quenched with water (20 mL) and extracted with Et_2O (25 mL × 2). The combined organic layer was

dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt : hexane = 1 : 2) to give alcohol **E16** (209 mg, 1.09 mmol, 28% for 3 steps).

E16: Pale yellow oil; IR (neat): 3341 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.09 (dd, *J* = 8.5, 1.9 Hz, 2H), 7.04 (d, *J* = 1.9 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 5.14 (s, 1H), 4.99 (s, 1H), 3.82 (t, *J* = 6.5 Hz, 2H), 3.81 (s, 3H), 2.79 (t, *J* = 6.5 Hz, 2H), 2.11 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 155.3, 144.1, 132.9, 130.2, 129.9, 128.6, 115.0, 111.0, 63.7, 55.5, 38.2, 23.1; HRMS (EI): calcd for $C_{12}H_{16}O_2$ (M^+): 192.1150, found: 192.1153.

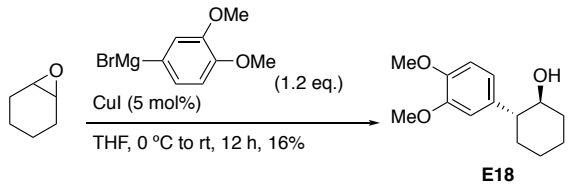
2-(3-Bromo-4-methoxyphenyl)ethanol (E17)



To the solution of 3-bromo-4-hydroxyphenylethyl alcohol (1.09 g, 5.02 mmol) in acetone (7.5 mL) was added MeI (0.41 mL, 6.59 mmol) and K_2CO_3 (0.90 g, 6.52 mmol) and stirred at 40 ºC for 20 h. The reaction mixture was quenched with water and extracted with Et_2O. The combined organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt : hexane = 1 : 2) to give **E17** (761 mg, 3.29 mmol, 66%).

E17: yellow oil; IR (neat): 3342 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 2.3 Hz, 1H), 7.13 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 1H), 3.87 (s, 3H), 3.81 (t, *J* = 6.4 Hz, 2H), 2.78 (t, *J* = 6.4 Hz, 2H), 1.61 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 154.5, 133.6, 132.2, 129.0, 112.0, 111.6, 63.4, 56.2, 37.8; HRMS (EI): calcd for $C_9H_{11}{}^{79}BrO_2$ (M^+): 229.9942, found: 229.9936.

***trans*-2-(3,4-Dimethoxyphenyl)cyclohexan-1-ol (E18)**

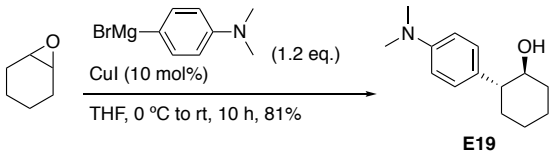


One crystal of iodine was added to a mixture of magnesium (375 mg, 15.4 mmol) and THF (10 mL) in a dry 2-neck flask with fitted with a Liebig condenser. To this, 2 ml of a solution of 4-bromo-*N,N*-dimethylaniline in THF was added and stirred vigorously. As soon as the color of iodine disappeared, a solution of 4-Bromo-1,2-dimethoxybenzene (1.90 mL, 13.2 mmol) in THF (20 mL) was added slowly over a period of 30 minutes while refluxing. The reaction was stirred at Almost magnesium was consumed, CuI (109 mg, 0.57 mmol) was added to the reaction mixture. To this a solution of cyclohexene oxide (1.1 mL, 10.9 mmol) in THF (10 mL) was added slowly dropwise at 0 °C. Then it was allowed to stir at room temperature for 12 h, then quenched with saturated aq. NH_4Cl

(5 mL). The reaction mixture was filtered through Celite® and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt : hexane = 1 : 8 to 1 : 1) to give **E18** (423 mg, 1.79 mmol, 16%).

E18: white solid; IR (solid): 3384, 1589 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.90-6.74 (m, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 3.72-3.52 (m, 1H), 2.49-2.30 (m, 1H), 2.12 (brd, *J* = 11.7 Hz, 1H), 1.86 (brd, *J* = 12.1 Hz, 1H), 1.77 (brd, *J* = 12.1 Hz, 1H), 1.58-1.21 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 149.2, 147.9, 135.7, 119.6, 111.6, 111.1, 74.5, 55.9, 55.8, 52.8, 34.3, 33.3, 26.1, 25.0; HRMS (EI): calcd for $C_{14}H_{20}O_3$ (M^+): 236.1412, found: 236.1414.

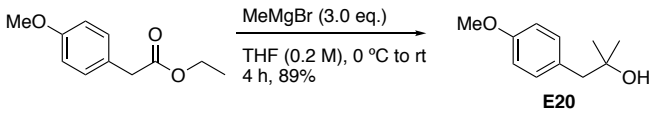
***trans*-2-(4-(Dimethylamino)phenyl)cyclohexan-1-ol (E19)**



One crystal of iodine was added to a mixture of magnesium (169 mg, 7.0 mmol) and THF (5 mL). To this, 2 ml of a solution of 4-bromo-*N,N*-dimethylaniline in THF was added and stirred vigorously. As soon as the color of iodine disappeared, a solution of 4-bromo-*N,N*-dimethylaniline (1.2 g, 6.0 mmol) in THF (10 mL) was added slowly over a period of 30 minutes while refluxing. The reaction was stirred at almost magnesium was consumed, CuI (95 mg, 0.50 mmol) was added to the reaction mixture. To this a solution of cyclohexene oxide (505 µl, 5.0 mmol) in THF (3 mL) was added slowly dropwise at 0 °C. Then it was allowed to stir at room temperature for 10 h, then quenched with saturated aquous $NaHCO_3$ (5 mL). The reaction mixture was filtered through Celite® and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt : hexane = 1 : 4) to give **E19** (890 mg, 4.05 mmol, 81%).

E19: light brown solid: IR (neat): 3436, 1613 cm^{-1}: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.13 (d, *J* = 8.8 Hz, 2H), 6.73 (d, *J* = 8.8 Hz, 2H), 2.32 (dt, *J* = 10.0, 4.0 Hz, 1H), 2.93 (s, 6H), 2.32 (ddd, *J* = 13.0, 9.6, 4.0 Hz, 1H), 2.15-2.09 (m, 1H), 1.90-1.80 (m, 2H), 1.80-1.70 (m, 1H), 1.60-1.25 (m, 5H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 149.7, 130.8, 128.5, 113.1, 74.6, 52.2, 40.7, 34.3, 33.4, 26.2, 25.1: HRMS (EI): calcd for $C_{14}H_{21}NO$ (M^+): 219.1623, found: 219.1623.

1-(4-Methoxyphenyl)-2-methylpropan-2-ol (E20)

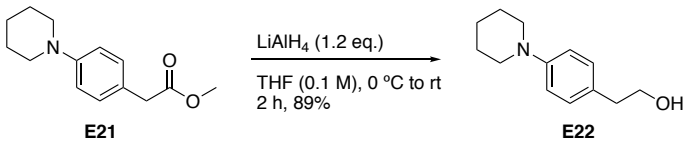


To a solution of Ethyl 4-methoxyphenylacetate (971 mg, 5.00 mmol) in Et_2O (25 mL) was added MeMgBr (3M in Et_2O: 5.0 mL) dropwise over 10 min at 0 ºC. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was cooled to 0 ºC and quenched with saturated aqueous NH_4Cl (15 mL) and extracted with Et_2O (20 mL × 2). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered

and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt : hexane = 1 : 4) to give **E20** (885 mg, 4.91 mmol, 98%).

E20: colorless oil; IR (neat): 3328 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.13 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 3.80 (s, 3H), 2.71 (s, 2H), 1.21 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 158.3, 131.4, 129.8, 113.6, 70.7, 55.2, 48.8, 29.1; HRMS (EI): calcd for $C_{11}H_{16}O_2$ (M^+): 180.1150, found: 180.1150.

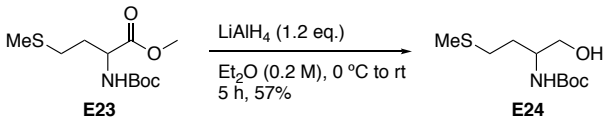
2-(4-(Piperidin-1-yl)phenyl)ethan-1-ol (E22)



To a solution of ester **E21** (347 mg, 1.49 mmol) in THF (0.1 M) was added $LiAlH_4$ (68.5 mg, 1.81 mmol) at 0 ºC. After stirring for 2 h at room temperature, the reaction mixture was quenched with saturated aqueous Rochelle salt and stirred at room temperature for 30 min. The solution was extracted with Et_2O (20 mL × 2). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt : hexane 1 : 2) to give **E22** (273 mg, 1.33 mmol, 89%)

E22: colorless oil; IR (neat): 3255 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.10 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 3.80 (t, J = 6.5 Hz, 2H), 3.12 (t, J = 5.3 Hz, 4H), 2.77 (t, J = 6.5 Hz, 2H), 1.80-1.65 (m, 4H), 1.62-1.52 (m, 2H), 1.49 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 151.0, 129.6, 128.8, 116.9, 63.8, 50.9, 38.2, 25.8, 24.2; HRMS (EI): calcd for $C_{18}H_{19}NO$ ($[M]^+$): 205.1467, found: 205.1497.

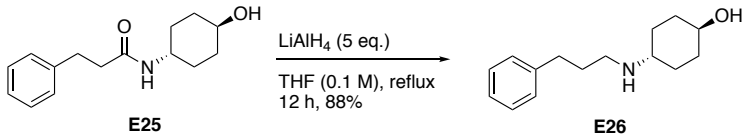
***tert*-Butyl (1-hydroxy-4-(methylthio)butan-2-yl)carbamate (E24)**



To a solution of ester **E23** (1.93 g, 7.74 mmol) in THF (38 mL) was added $LiAlH_4$ (377 mg, 9.93 mmol) at 0 ºC. After stirring for 5 h at room temperature, the reaction mixture was quenched with saturated aqueous Rochelle salt (20 mL) and stirred at room temperature for 30 min. The solution was extracted with Et_2O (40 mL × 2). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt : hexane 1 : 2) to give alcohol **E24** (273 mg, 1.33 mmol, 89%).

E24: white solid; IR (neat): 3358, 1681 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.78 (brs, 1H), 3.85-3.53 (m, 3H), 2.66-2.48 (m, 2H), 2.43 (brs, 1H), 2.12 (s, 3H), 1.91-1.64 (m, 2H), 1.45 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 156.2, 79.7, 65.4, 52.0, 31.0, 30.7, 28.4, 15.6; HRMS (EI): calcd for $C_{10}H_{21}NO_3S$ (M^+): 235.1242, found: 235.1234.

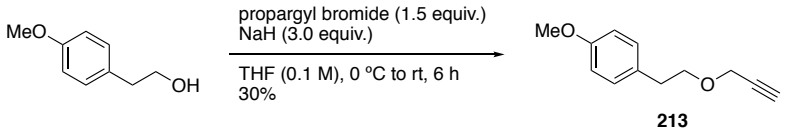
4-((3-Phenylpropyl)amino)cyclohexan-1-ol (E26)



To a solution of ester **E25** (500 mg, 2.02 mmol) in THF (30 mL) was added $LiAlH_4$ (335 mg, 8.83 mmol) portionwise at 0 ºC. After stirring for 12 h at reflux, the reaction mixture was cooling at 0 ºC and quenched with sat. Rochelle salt (20 mL) and stirred at room temperature for 30 min. The solution was extracted with Et_2O (40 mL × 2). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (CHROMATOREX® -NH, $CHCl_3$) to give aminoalcohol **E26** (415 mg, 1.78 mmol, 88%).

E26: white solid; IR (solid): 3260 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.34-7.24 (m, 2H), 7.22-7.11 (m, 3H), 3.60 (tt, *J* = 10.7, 4.1 Hz, 1H), 2.71-2.57 (m, 4H), 2.41 (tt, *J* = 11.0, 3.7 Hz, 1H), 1.97-1.86 (m, 4H), 1.80 (quint. *J* = 7.9 Hz, 2H), 1.37-1.20 (m, 2H), 1.17-1.05 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 142.1 139.0, 128.3, 125.8, 70.5, 56.0, 46.9, 34.1, 33.7, 32.0, 31.3; HRMS (EI): calcd for $C_{15}H_{23}NO$ (M^+): 233.1780, found: 233.1773.

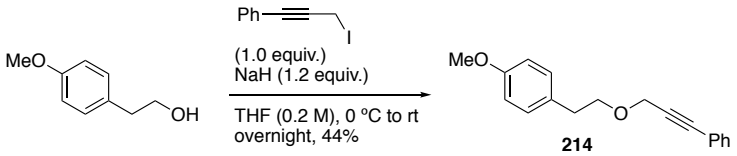
1-Methoxy-4-(2-(prop-2-yn-1-yloxy)ethyl)benzene (213)



To a solution of 4-methoxyphenethyl alcohol (112 mg, 0.736 mmol) in THF (7.4 mL) was added 60% NaH (82.6 mg, 2.07 mmol) at 0 ºC. The mixture was stirred at room temperature for 30 min. Propargyl bromide (84 µL, 1.11 mmol) was added to the mixture at 0 ºC. The reaction mixture was allowed to warm to room temperature and stirred for 6 h. The reaction mixture was quenched with sat. aqueous NH_4Cl (4 mL) and extracted with hexane (4 mL × 3). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt : hexane = 1 : 20) to give **213** (42.4 mg, 0.223 mmol, 30%).

213: yellow oil; IR (neat): 3286 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.15 (d, *J* = 8.2 Hz, 2H), 6.84 (d, *J* = 8.2 Hz, 2H), 4.15 (t, *J* = 1.9 Hz, 2H), 3.78 (s, 3H), 3.71 (t, *J* = 7.2 Hz, 2H), 2.86 (t, *J* = 7.2 Hz, 2H), 2.42 (t, *J* = 1.9 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 158.1, 130.6, 129.8, 113.8, 80.0, 74.3, 71.1, 58.1, 55.2, 35.1; HRMS (EI): calcd for $C_{12}H_{14}O_2$(M^+): 190.0994, found: 190.1001.

1-methoxy-4-(2-((3-phenylprop-2-yn-1-yl)oxy)ethyl)benzene (214)



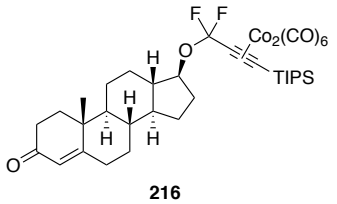
To a solution of 4-methoxyphenethyl alcohol (103 mg, 0.677 mmol) in THF (3.6 mL) was added 60% NaH (36 mg, 0.90 mmol) at 0 ºC. The mixture was stirred at room temperature for 50 min. (3-Iodoprop-1-yn-1-yl)benzene (164 mg, 0.677 mmol) was added to the mixture at 0 ºC. The reaction mixture was allowed to warm to room temperature and stirred for overnight. The reaction mixture was quenched with sat. aqueous NH_4Cl (2 mL) and extracted with Et_2O (10 mL × 2). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt : hexane = 1 : 200) to give **214** (78.8 mg, 0.296 mmol, 44%).

214: yellow oil; IR (neat): 2236 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.49-7.41 (m, 2H), 7.34-7.29 (m, 3H), 7.17 (d, J = 7.5 Hz, 2H), 6.84 (d, J = 7.5 Hz, 2H), 4.38 (s, 2H), 3.79 (s, 3H), 3.78 (t, J = 7.2 Hz, 2H), 2.90 (t, J = 7.2 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 158.1, 131.7, 130.7, 129.9, 129.8, 128.4, 128.2, 113.8, 86.1, 85.2, 71.2, 58.9, 55.2, 35.2; HRMS (EI): calcd for $C_{18}H_{18}O_2$ (M^+): 266.1307, found: 266.1306.

<Chapter 4>

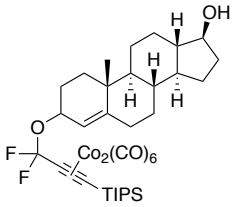
Etherification of testosterone

A solution of **37** (48.8 mg, 0.16 mmol) and $Co_2(CO)_8$ (55.6 mg, 0.16 mmol) in toluene (1 mL) was stirred at room temperature. After 3 h, testosterone (25.3 mg, 87.7 μmol), triethylamine (21 μL, 0.15 mmol) and AgOTf (42.7 mg, 0.17 mmol) were added. After 30 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ (1 mL) and extracted with AcOEt (5mL × 2). The combined organic layers were washed with brine and dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (AcOEt : Hexane = 1 : 8) to provide **216** (15.1 mg, 18.8 μmol, 21%) and **217** (23.3 mg, 29.0 μmol, 33%).



216: red oil; IR (neat): 2038, 1676 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 5.73 (s, 1H), 4.30 (t, J = 7.7 Hz, 1H), 2.27-2.42 (m, 4H), 2.13 (s, 1H), 2.02 (d, J = 12.0 Hz, 1H), 1.84-1.91 (m, 2H), 1.59-1.75 (m, 5H), 1.02-1.42 (m, 35H), 0.94 (t, J = 9.6 Hz, 1H), 0.82-0.88 (m, 4H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.5, 199.3, 171.0, 124.8 (t, $^1J_{CF}$ = 255.8 Hz), 123.9, 101.9 (t, $^2J_{CF}$ = 50.6 Hz), 84.4, 71.9, 53.7, 49.9, 42.3, 38.6, 36.2, 35.7, 35.4, 33.9, 32.7, 31.4, 28.4, 23.3, 20.5, 18.9, 17.4, 13.6, 11.6; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -55.1 (d, J = 157.0 Hz, 1F), -55.5 (d, J = 157.0 Hz, 1F);

HRMS (EI): calcd for $C_{35}H_{48}Co_2F_2O_6Si$ ([M-2CO]$^+$): 748.1852, found: 748.1873.



217

217: red oil; IR (neat): 3412, 2059 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 5.86 (s, 1H), 5.42 (s, 1H), 3.67 (s, 1H), 2.41-2.46 (m, 1H), 2.05-2.27 (m, 4H), 1.84-1.89 (m, 2H), 1.56-1.73 (m, 6H), 1.25-1.47 (m, 10H), 1.08-1.20 (m, 23H), 0.96-1.04 (m, 4H), 0.77-0.84 (m, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.1, 146.6, 139.6, 124.4 (t, $^1J_{CF}$ = 260.1 Hz), 123.4, 115.3, 101.3 (t, $^2J_{CF}$ = 49.1 Hz), 81.8, 72.3, 51.4, 48.2, 46.1, 42.9, 36.5, 34.8, 33.8, 31.8, 31.5, 30.5, 25.6, 23.4, 20.8, 18.9, 13.6, 11.1; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -55.4 (d, J = 157.0 Hz, 1F), -56.7 (d, J = 157.0 Hz, 1F); HRMS (EI, FAB, ESI) was not detected.

Formation of propargyl vinyl ether

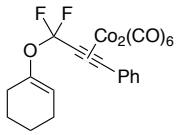
Standard procedure for the etherification of ketones and aldehydes

Procedure A: A solution of phenyldifluorobromopropyne (0.15 mmol) and $Co_2(CO)_8$ (0.15 mmol) in toluene (1 mL) was stirred at room temperature. After 3 h, ketone (0.1 mmol), iPr$_2$NEt (0.15 mmol) and $AgNTf_2$ (0.15 mmol) was added and stirred at room temperature for 30 min. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (1 mL) and extracted with AcOEt (5mL x 2). The combined organic layers were washed with brine and dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (Kanto).

Procedure B: A solution of phenyldifluorobromopropyne (0.15 mmol) and $Co_2(CO)_8$ (0.15 mmol) in toluene (1 mL) was stirred at room temperature. After 3 h, ketone (0.1 mmol), DTBMP (0.15 mmol) and $AgNTf_2$ (0.15 mmol) was added and stirred at room temperature for 30 min. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (1 mL) and extracted with AcOEt (5mL x 2). The combined organic layers were washed with brine and dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (Kanto).

Etherification of cyclohexanone

The procedure A was followed. The crude was purified by silica gel column chromatography (hexane) to provide **219** (50.6 mg, 94.6 μmol, 95%).

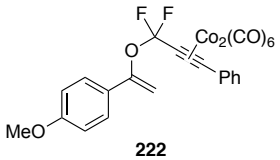


219

219: red oil; IR (neat): 2034 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.70-7.60 (m, 2H), 7.40-7.31 (m, 3H), 5.61 (s, 1H), 2.26 (brs, 2H), 2.19-2.09 (m, 2H), 1.80-1.70 (m, 2H), 1.66-1.57 (m, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 198.1, 148.0, 136.6, 130.0, 128.9, 128.4, 124.9 (t, $^{1}J_{CF}$ = 259.4 Hz), 112.7, 88.0, 83.8 (t, $^{2}J_{CF}$ = 49.9 Hz), 28.0, 23.8, 22.8, 21.7; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -58.3 (s, 2F); HRMS (EI): calcd for $C_{21}H_{14}Co_2F_2O_7$ (M^+): 533.9372, found: 533.9361.

Etherification of 4'-methoxyacetophenone

The procedure A was followed. The crude was purified by silica gel column chromatography (hexane containing 1% TEA) to provide **222** (59.6 mg, 82.5 μmol, 84%).

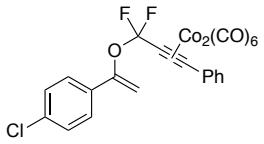


222

222: red oil; IR (neat): 2035 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.67 (t, J = 1.7 Hz, 2H), 7.48 (d, J = 7.5 Hz, 2H), 7.36 (s, 3H), 6.83 (d, J = 7.5 Hz, 2H), 5.28 (s, 1H), 5.23 (s, 1H), 3.81 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 198.0, 160.1, 152.4, 136.4, 130.0, 128.9, 128.5, 127.8, 126.9, 125.2 (t, $^{1}J_{CF}$ = 260.1 Hz), 113.6, 97.7, 88.5, 83.0 (t, $^{2}J_{CF}$ = 48.4 Hz), 55.2; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -59.2 (s, 2F); HRMS (EI): calcd for $C_{21}H_{14}Co_2F_2O_5$ ($[M-3CO]^+$): 501.9473, found: 501.9470.

Etherification of 4'-chloroacetophenone

The procedure A was followed. The crude was purified by silica gel column chromatography (hexane containing 1% TEA) to provide **223** (57.4 mg, 97.1 μmol, 97%).

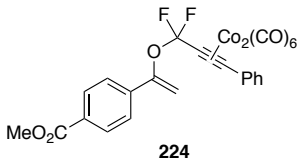


223

223: red oil; IR (neat): 2036 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.68-7.62 (m, 2H), 7.46 (d, J = 8.6 Hz, 2H), 7.40-7.34 (m, 3H), 7.28 (d, J = 8.6 Hz, 2H), 5.38 (d, J = 2.4 Hz, 1H), 5.34 (s, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 197.9, 151.6, 136.3, 134.8, 133.7, 130.0, 129.0, 128.6, 128.5, 126.8, 125.3 (t, $^{1}J_{CF}$ = 262.3 Hz), 99.94, 88.68, 82.5 (t, $^{2}J_{CF}$ = 49.1 Hz); ^{19}F-NMR (560 MHz, $CDCl_3$): δ -59.4 (s, 2F); HRMS (EI): calcd for $C_{23}H_{11}{}^{35}ClCo_2F_2O_7$ (M^+): 589.8825, found: 589.8820.

Etherification of methyl 4'-carboxyacetophenone

The procedure A was followed. The crude was purified by silica gel column chromatography (AcOEt : hexane 1:20 containing 1% TEA) to provide **224** (57.1 mg, 93.0 μmol, 93%).

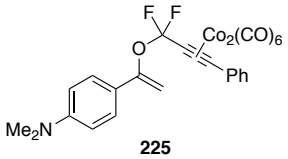


224

224: red oil; IR (neat): 2036 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.98 (d, J = 7.5 Hz, 2H), 7.69-7.63 (m, 2H), 7.61 (t, J = 8.9 Hz, 2H), 7.37 (s, 3H), 5.51 (s, 1H), 5.45 (s, 1H), 3.92 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 197.9, 166.6, 151.6, 139.4, 136.3, 130.8, 130.0, 129.6, 129.0, 128.7, 125.4, 125.4 (t, $^{1}J_{CF}$ = 261.6 Hz), 101.5, 88.7, 82.3 (t, $^{2}J_{CF}$ = 47.7 Hz), 52.1; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -59.4 (s, 2F); HRMS (EI): calcd for $C_{22}H_{14}Co_2F_2O_6$ ([M-3CO]$^+$): 529.9422, found: 529.9432.

Etherification of 4'-dimethylaminoacetophenone

The procedure A was followed. The crude was purified by silica gel column chromatography (hexane containing 1% TEA) to provide **225** (27.1 mg, 45.1 μmol, 45%).

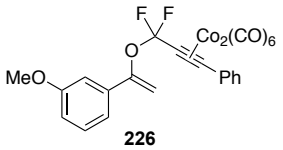


225

225: red oil; IR (neat): 2036 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.66-7.73 (m, 2H), 7.43 (d, J = 8.8 Hz, 2H), 7.32-7.40 (m, 3H), 6.63 (d, J = 8.2 Hz, 2H), 5.21 (d, J = 2.1 Hz, 1H), 5.12 (s, 1H), 2.97 (s, 6H); ^{19}F-NMR (560 MHz, $CDCl_3$): δ -58.9 (s, 2F); HRMS (EI): calcd for $C_{22}H_{17}Co_2F_2NO_4$ ([M-3CO]$^+$): 514.9790, found: 514.9782.

Etherification of 3'-methoxyacetophenone

The procedure A was followed. The crude was purified by silica gel column chromatography (hexane containing 1% TEA) to provide **226** (50.5 mg, 86.2 μmol, 86%).

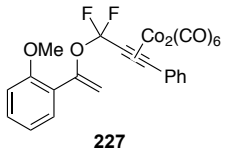


226

226: red oil; IR (neat): 2036 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.67 (s, 2H), 7.35 (s, 3H), 7.23 (t, J = 8.3 Hz, 1H), 7.15 (d, J = 7.2 Hz, 1H), 7.05 (s, 1H), 6.87 (d, J = 7.2 Hz, 1H), 5.39 (s, 1H), 5.33 (s, 1H), 3.68 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 197.9, 159.5, 152.4, 136.6, 136.4 , 130.0, 129.2, 129.0, 128.6, 125.3 (t, $^{1}J_{CF}$ = 261.5 Hz), 118.1, 114.9, 110.7, 99.7, 88.5, 82.7 (t, $^{2}J_{CF}$ = 49.1 Hz), 55.1; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -59.4 (s, 2F); HRMS (EI): calcd for $C_{21}H_{14}Co_2F_2O_5$ ([M-3CO]$^+$): 501.9473, found: 501.9472.

Etherification of 2'-methoxyacetophenone

The procedure A was followed. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 50 containing 1% TEA) to provide **227** (43.0 mg, 73.3 μmol, 73%).

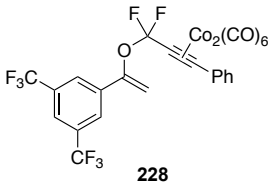


227

227: red oil; IR (neat): 2035 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.66 (s, 2H), 7.46 (d, J = 7.2 Hz, 1H), 7.40-7.26 (m, 4H), 6.92 (d, J = 6.5 Hz, 2H), 5.48 (s, 1H), 5.44 (s, 1H), 3.84 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 198.0, 157.1, 150.2, 136.5, 130.04, 129.98, 129.6, 128.8, 128.4, 125.1 (t, $^{1}J_{CF}$ = 260.8 Hz), 124.7, 120.1, 110.9, 104.8, 88.3, 83.3 (t, $^{2}J_{CF}$ = 49.1 Hz), -55.4 (s, 2F); ^{19}F-NMR (560 MHz, $CDCl_3$): δ 59.3; HRMS (EI): calcd for $C_{21}H_{14}Co_2F_2O_5$ ([M-3CO]$^{+}$): 501.9473, found: 501.9468.

Etherification of 3',5'-bistrifluoromethylacetophenone

The procedure A was followed. The crude was purified by silica gel column chromatography (hexane containing 1% TEA) to provide **228** (58.5 mg, 64.6 μmol, 85%).

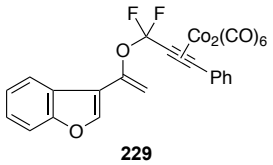


228

228: red oil; IR (neat): 2039 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.98 (s, 2H), 7.84 (s, 1H), 7.65 (s, 2H), 7.37 (s, 3H), 5.59 (s, 1H), 5.56 (s, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 197.8, 149.8, 137.4, 136.1, 132.0 (q, $^{2}J_{CF}$ = 33.6 Hz), 129.8, 129.1, 128.8, 125.6 (t, $^{1}J_{CF}$ = 263.0 Hz), 125.5, 123.1 (q, $^{1}J_{CF}$ = 271.3 Hz), 122.5, 102.5, 88.9, 81.3 (t, $^{2}J_{CF}$ = 44.8 Hz); ^{19}F-NMR (560 MHz, $CDCl_3$): δ -59.7 (s, 2F), -66.3 (s, 3F); HRMS (EI): calcd for $C_{25}H_{10}Co_2F_8O_7$ (M^{+}): 691.8963, found: 691.8971.

Etherification of 3-acetylbenzophenone

The procedure A was followed. The crude was purified by silica gel column chromatography (hexane containing 1% TEA) to provide **229** (53.4 mg, 89.5 μmol, 86%).



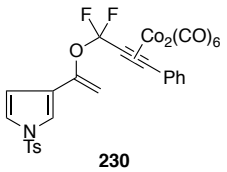
229

229: red oil; IR (neat): 2036 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.77 (d, J = 7.5 Hz, 1H), 7.71-7.64 (m, 3H), 7.50 (d, J = 7.5 Hz, 1H), 7.42-7.36 (m, 3H), 7.35 (t, J = 8.2 Hz, 1H) 7.31 (t, J = 7.5 Hz, 1H), 5.45 (s, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 197.9, 155.6, 146.0, 143.7, 136.3, 130.0, 129.0, 128.7, 125.3 (t, $^{2}J_{CF}$ = 261.5 Hz), 124.9, 124.5, 123.3, 120.6, 117.8, 111.9, 100.3, 88.7, 82.6 (t, $^{2}J_{CF}$ = 47.7 Hz); ^{19}F-NMR (560 MHz, $CDCl_3$): δ -59.1 (s, 2F); HRMS

(EI): calcd for $C_{21}H_{12}Co_2F_2O_4$ (M^+): 483.9368, found: 438.9363.

Etherification of 1-Ts-3-acetyl pyrrole

The procedure A was followed. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1:20 containing 1% TEA) to provide **230** (43.6 mg, 62.3 μmol, 62%).

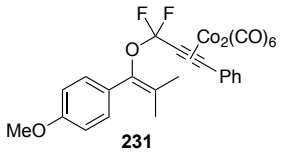


230

230: red oil; IR (neat): 2036 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.77 (d, J = 7.5 Hz, 1H), 7.71-7.64 (m, 3H), 7.50 (d, J = 7.5 Hz, 1H), 7.42-7.36 (m, 3H), 7.35 (t, J = 8.2 Hz, 1H) 7.31 (t, J = 7.5 Hz, 1H), 5.45 (s, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 197.9, 147.2, 145.2, 136.3, 135.7, 130.0, 129.9, 129.1, 128.7, 126.9, 125.2 (t, $^1J_{CF}$ = 263.0 Hz), 125.0, 121.4, 117.9, 110.9, 96.9, 88.6, 82.5 (t, $^2J_{CF}$ = 48.4 Hz), 21.6; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -59.7 (s, 2F); HRMS (FAB): calcd for $C_{25}H_{17}Co_2F_2NO_6S$ ($[M-3CO]^+$): 614.9409, found: 614.9415.

Etherification of 4'-methoxyisobutyrophenone

The procedure B was followed. The crude was purified by silica gel column chromatography (hexane containing 1% TEA) to provide **231** (49.8 mg, 81.1 μmol, 80%).

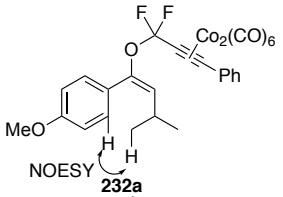


231

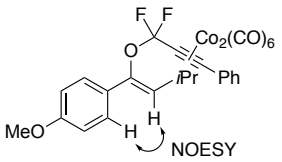
231: red oil; IR (neat): 2035 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.62-7.58 (m, 2H), 7.36-7.32 (m, 3H), 7.33 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.9 Hz, 2H), 3.83 (s, 3H), 1.90 (s, 3H), 1.76 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 198.1, 158.9, 140.8, 136.5, 130.3, 130.1, 129.7, 128.8, 128.4, 125.5 (t, $^1J_{CF}$ = 263.0 Hz), 123.8, 113.2, 88.38, 83.8 (t, $^2J_{CF}$ = 48.4 Hz), 55.2, 20.2, 18.9; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -56.3 (s, 2F); HRMS (EI): calcd for $C_{26}H_{18}Co_2F_2O_8$ (M^+): 613.9634, found: 613.9645.

Etherification of 4'-methoxyisovalerophenone

The procedure A was followed. The crude was purified by silica gel column chromatography (hexane containing 1% TEA) to provide the mixture of a inseparable *E*/*Z* isomer of **232** (49.1 mg, 78.2 μmol, 74%). The *E*/*Z* ratio was determined by ^{1}H-NMR (*E*/*Z* = 2.3:1).



232a
major



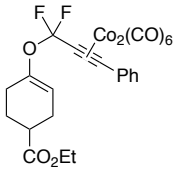
232b
minor

232a (major): red oil; IR (neat): 2036 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.63-7.56 (m, 2H), 7.35 (d, *J* = 8.9 Hz, 2H), 7.41-7.29 (m, 3H), 6.89 (d, *J* = 8.2 Hz, 2H), 5.55 (d, *J* = 10.3 Hz, 1H), 3.83 (s, 3H), 2.60-2.45 (m, 1H), 1.07 (d, *J* = 6.8 Hz, 6H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ198.1, 159.5, 144.6, 136.6, 130.1, 129.9, 128.9, 128.4, 127.4, 127.0, 125.2 (t, $^{1}J_{CF}$ = 258.7 Hz), 113.4, 88.3, 83.9 (t, $^{2}J_{CF}$ = 49.1 Hz), 55.3, 27.3, 23.4; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -57.7 (s, 2F); HRMS (EI): calcd for $C_{27}H_{20}Co_2F_2O_8$ (M^+): 627.9790, found: 627.9798.

232b (minor): ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.71-7.64 (m, 2H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.41-7.29 (m, 3H), 6.86 (d, *J* = 8.2 Hz, 2H), 5.43 (d, *J* = 9.6 Hz, 1H), 3.82 (s, 3H), 3.00-2.88 (m, 1H), 1.06 (d, *J* = 8.9 Hz, 6H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 198.1, 159.5, 143.9, 136.6, 129.9, 129.0, 128.6, 128.1, 127.8, 125.1 (t, $^{1}J_{CF}$ = 258.7 Hz), 113.6, 88.7, 83.6 (t, $^{2}J_{CF}$ = 23.1 Hz), 55.3, 26.5, 22.6; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -56.7 (s, 2F); HRMS (EI): calcd for $C_{27}H_{20}Co_2F_2O_8$ (M^+): 627.9790, found: 627.9798.

Etherification of ethyl 4-oxocyclohexanecarboxylate

The procedure A was followed. The crude was purified by silica gel column chromatography (AcOEt : hexane containing 1% TEA) to provide **233** (53.2 mg, 89.7 μmol, 90%).

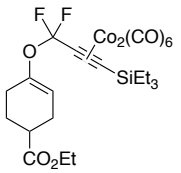


233

233: red oil; IR (neat): 2035, 1734 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.74-7.58 (m, 2H), 7.46-7.32 (m, 3H), 5.60 (brs, 1H), 4.16 (q, *J* = 7.0 Hz, 2H), 2.67-2.52 (m, 1H), 2.41 (brs, 2H), 2.35 (brs, 2H), 2.19-2.04 (m, 1H), 1.97-1.78 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ198.0, 175.0, 147.3, 136.5, 129.9, 128.9, 128.5, 124.9 (t, $^{1}J_{CF}$ = 258.7 Hz), 110.9, 88.1, 83.32 (t, $^{2}J_{CF}$ = 49.9 Hz), 60.5, 38.6, 27.1, 26.2, 25.3, 14.2; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -58.9 (d, *J* = 167.0 Hz, 1F), -58.1 (d, *J* = 167.0 Hz, 1F); HRMS (EI): calcd for $C_{21}H_{18}Co_2F_2O_6$ ($[M-3CO]^+$): 521.9735, found: 521.9379.

Etherification of ethyl 4-oxocyclohexanecarboxylate with 220

The procedure A was followed with complex **220** instead of **184**. The crude was purified by silica gel column chromatography (hexane) to provide **234** (60.1 mg, 93.3 μmol, 93%).

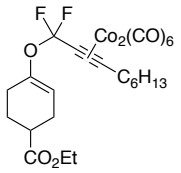


234

234: red oil; IR (neat): 2031, 1736 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 5.54 (s, 1H), 4.15 (1, *J* = 7.1 Hz, 2H), 2.63-2.50 (m, 1H), 2.48 (brs, 2H), 2.29 (brs, 2H), 1.92-1.75 (m, 1H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.06 (t, *J* = 7.8 Hz, 9H), 0.81 (q, *J* = 7.8 Hz, 6H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 198.9, 175.0, 147.3, 124.4 (t, $^{1}J_{CF}$ = 259.4 Hz), 110.6, 99.2 (t, $^{2}J_{CF}$ = 49.1 Hz), 75.3, 60.4, 38.6, 27.1, 26.2, 25.3, 14.2, 7.3, 5.6; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -57.8 (d, *J* = 139.5 Hz, 1F), -57.0 (d, *J* = 139.5 Hz, 1F); HRMS (EI): calcd for $C_{21}H_{28}Co_2F_2O_6Si$ ([M-3CO]$^{+}$): 560.0287, found: 560.0278.

Etherification of ethyl 4-oxocyclohexanecarboxylate with 221

The procedure A was followed with complex **220** instead of **184**. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1:20 containing 1% TEA) to provide **235** (55.2 mg, 89.9 μmol, 90%).

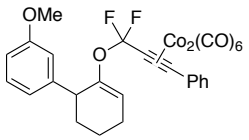


235

235: red oil; IR (neat): 2032, 1736 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.53 (s, 1H), 4.15 (q, J = 7.0 Hz, 2H), 2.81 (t, J = 7.5 Hz, 2H), 2.62-2.49 (m, 2H), 2.38 (brs, 2H), 2.29 (brs, 2H), 2.10 (brd, 1H), 1.93-1.76 (m, 1H), 1.65, (t, J = 7.5 Hz, 2H), 1.46 (brs, 1H), 126 (t, J = 7.0 Hz, 3H), 0.91 (brs, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 198.5, 175.0, 147.2, 124.6 (t, $^{1}J_{CF}$ = 260.1 Hz), 110.5, 97.8, 84.0 (t, $^{2}J_{CF}$ = 49.9 Hz), 60.5, 38.6, 33.3, 31.6, 29.2, 27.0, 26.2, 25.2, 22.5, 14.2, 14.0; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -58.9 (d, *J* = 148.3 Hz, 1F), -58.2 (d, *J* = 148.3 Hz, 1F); HRMS (EI): calcd for $C_{21}H_{26}Co_2F_2NO_6$ ([M-3CO]$^{+}$): 530.0361, found: 530.0357.

Etherification of 2-(3-methoxyphenyl)cyclohexanone

The procedure A was followed. The crude was purified by silica gel column chromatography (hexane containing 1% TEA) to provide **236** (53.4 mg, 83.3 μmol, 83%).



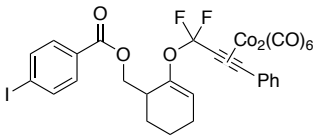
236

236: red oil; IR (neat): 2036 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.5 Hz, 2H), 7.23-7.16 (m, 3H), 6.86 (d, *J* = 7.5 Hz, 1H), 6.82 (s, 1H), 6.75 (dd, *J* = 8.2, 2.1 Hz, 1H), 5.97 (s, 1H), 3.75 (s, 3H), 3.66 (s, 1H), 2.33-2.20 (m, 2H), 2.16-2.07 (m, 1H), 1.81-1.73 (m, 1H), 1.73-1.52 (m, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 197.9, 159.6, 147.7,

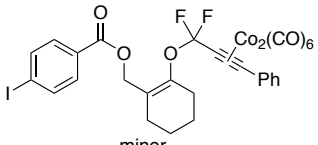
144.8 , 136.4, 129.9, 129.1, 128.7, 128.2, 125.0 (t, $^{1}J_{CF}$ = 258.7 Hz), 120.8, 115.0, 113.8, 111.8, 87.9, 83.4 (t, $^{2}J_{CF}$ = 49.9 Hz), 55.1, 44.4, 33.0, 24.2, 18.4; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -60.2 (d, *J* = 148.3 Hz), -58.3 (d, *J* = 148.3 Hz); HRMS (EI): calcd for $C_{28}H_{20}Co_2F_2O_8$ (M^+): 639.9790, found: 639.9777.

Etherification of (2-oxocyclohexyl)methyl 4-iodobenzoate

The procedure A was followed. The crude was purified by silica gel column chromatography (hexane) to provide the mixture of **237** and **238** (69.4 mg, 87.4 μmol, 86%). The ratio was determined by ^{1}H-NMR (**237** : **238** = 6.8 : 1). The mixture of **237** and **238** was inseparable.



major
237

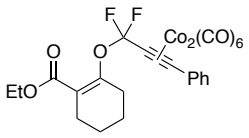


minor
238

237 (major): red oil; IR (neat): 2035, 1725 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ7.78 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.66-7.59 (m, 2H), 7.36-7.29 (m, 3H), 5.88 (s, 1H), 4.49 (dd, *J* = 10.8, 2.9 Hz, 1H), 4.33 (dd, *J* = 11.0, 7.9 Hz, 1H), 2.84 (brs, 1H), 2.23-2.16 (m, 2H), 1.96-1.87 (m, 1H), 1.86-1.77 (m, 1H), 1.76-1.69 (m, 1H), 1.68-1.60 (m, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 197.9, 165.9, 146.2, 137.7, 136.4, 131.0, 129.9, 128.9, 128.5, 125.2 (t, $^{1}J_{CF}$ = 259.4 Hz),116.5, 100.6, 88.3, 83.0 (t, $^{2}J_{CF}$ = 49.1 Hz), 64.99, 37.65, 26.12, 24.04, 19.03; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -58.1 (d, *J* = 157.0 Hz, 1F), -59.0 (d, *J* = 139.5 Hz, 1F); HRMS (EI): calcd for $C_{26}H_{19}Co_2F_2O_6I$ ([M-3CO]$^+$): 709.8858, found: 709.8849.

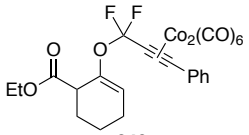
Etherification of ethyl 2-oxocyclohexanecarboxylate

The procedure A was followed. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1 : 20 containing 1% TEA) to provide the mixture of **239** and **240** (35.3 mg, 58.2 μmol, 58%, **239** : **240** = 1.4 : 1). The ratio was determined by ^{1}H-NMR. The analytical sample was prepared by flash silica gel column chromatography (AcOEt : hexane = 1 : 20).



239

239: red oil; IR (neat): 2035, 1731 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.5 Hz, 2H), 7.40-7.30 (m, 3H), 4.08 (q, *J* = 7.1 Hz, 2H), 2.50 (brs, 2H), 2.40 (brs, 2H), 1.81-1.74 (m, 2H), 1.71-1.65 (m, 2H), 1.18 (t, *J* = 6.8 Hz, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 198.0, 166.6, 150.6, 136.6, 130.0, 128.8, 128.4, 125.2 (t, $^{1}J_{CF}$ = 260.1 Hz), 121.1, 88.3, 82.4 (t, $^{2}J_{CF}$ = 49.1 Hz), 60.3, 29.5, 26.2, 22.4, 21.5, 14.1; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -55.5 (s, 2F); HRMS (EI): calcd for $C_{22}H_{18}Co_2F_2O_7$ ([M-2CO]$^+$): 549.9685, found: 549.9691.

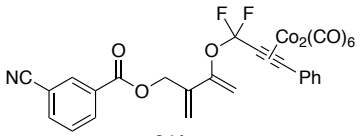


240

240: red oil; IR (neat): 2035, 1737 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.66-7.59 (m, 2H), 7.40-7.30 (m, 3H), 5.90 (s, 1H), 4.10-4.03 (m, 2H), 3.33 (t, J = 5.1 Hz, 1H), 2.30-2.24 (m, 1H), 2.20-2.14 (m, 1H), 1.99-2.02 (m, 2H), 1.67-1.80 (m, 1H), 1.59-1.66 (m, 1H), 1.17 (q, J = 6.8 Hz, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 197.9, 172.7, 144.2, 136.4, 130.0, 128.9, 128.4, 125.1 (t, $^{1}J_{CF}$ = 260.1 Hz), 115.7, 88.2, 83.1 (t, $^{2}J_{CF}$ = 49.1 Hz), 60.8, 44.5, 27.3, 23.8, 19.1, 14.0; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -59.2 (d, *J* = 148.3 Hz), -58.7 (d, *J* = 148.3 Hz); HRMS (EI): calcd for $C_{21}H_{18}Co_2F_2O_6$ ([M-3CO]$^{+}$): 521.9735, found: 521.9726.

Etherification of 2-methylene-3-oxobutyl 3-cyanobenzoate

The procedure A was followed. The crude was purified by silica gel column chromatography (hexane) to provide **241** (38.0 mg, 57.2 μmol, 57%).

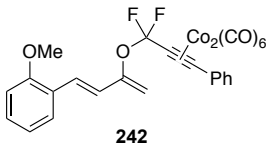


241

241: red oil; IR (neat): 2036, 1731 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.34 (s, 1H), 8.29 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.68-7.63 (m, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.33-7.40 (m, 3H), 5.68 (s, 1H), 5.46 (s, 1H), 5.36 (s, 1H), 5.15 (d, *J* = 2.7 Hz, 1H), 5.06 (s, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 197.9, 164.1, 150.1, 136.7, 136.3, 136.2, 133.7, 133.3, 131.2, 129.9, 129.5, 129.0, 128.6, 125.2 (t, $^{1}J_{CF}$ = 261.5 Hz), 118.4, 117.8, 113.1, 101.8, 88.7, 82.3 (t, $^{2}J_{CF}$ = 47.7 Hz), 65.1; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -59.3 (s, 2F); HRMS (FAB): calcd for $C_{25}H_{15}Co_2F_2NO_6$ ([M-3CO]$^{+}$): 580.9531, found: 580.9549.

Etherification of (*E*)-4-(2-methoxyphenyl)but-3-en-2-one

The procedure A was followed. The crude was purified by silica gel column chromatography (hexane containing 1% TEA) to provide **242** (26.4 mg, 43.1 μmol, 43%).



242

242: red oil; IR (neat): 2036 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.75-7.67 (m, 2H), 7.42-7.35 (m, 4H), 7.22 (t, *J* = 7.9 Hz, 1H), 7.17 (d, *J* = 15.7 Hz, 1H), 6.91 (t, *J* = 7.2 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.71 (d, *J* = 15.7 Hz, 1H), 5.24 (s, 1H), 4.99 (s, 1H), 3.75 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 198.0, 157.3, 152.0, 136.4, 130.0, 129.6, 129.2, 129.2, 128.9, 128.5, 127.2, 125.6, 125.2, 125.1 (t, $^{1}J_{CF}$ = 260.8 Hz), 124.1, 120.5, 110.8, 102.5, 84.5, 82.8 (t, $^{2}J_{CF}$ = 49.1 Hz), 55.15; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -59.2 (s, 2F); HRMS (EI): calcd for $C_{23}H_{16}Co_2F_2O_5$ ([M-

3CO]$^+$): 527.9630, found: 527.9630.

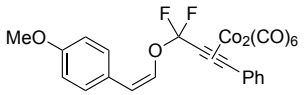
Etherification of aldehydes

General Procedure. A solution of **184** (0.15 mmol) and $Co_2(CO)_8$ (0.15 mmol) in toluene (1 mL) was stirred at room temperature. After 3 h, ketone (0.1 mmol), *i*Pr_2NEt (0.15 mmol) and $AgNTf_2$ (0.15 mmol) was added and stirred at room temperature for 30 min. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (1 mL) and extracted with AcOEt (5mL x 2). The combined organic layers were washed with brine and dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (Kanto). When it is difficult to identify the obtained products by ^{1}H-NMR, these products decoplexed following procedure.

To a solution of dicobalt complex in Et_2O-MeCN (1:1, 0.02 M) was added *N,N,N'*-trimethylethylenediamine (4.5 eq.). The reaction mixture was stirred at room temperature under O_2 atmosphere. After 16 h, the reaction mixture was diluted with H_2O (5 mL) and Et_2O (5 mL) and extracted with Et_2O (5 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (hexane).

Etherification of 2-(4-methoxyphenyl)acetaldehyde

The general procedure was followed. The crude was purified by silica gel column chromatography (hexane) to provide **248** (42.3 mg, 72.2 μmol, 72%, Z/E > 20/1).



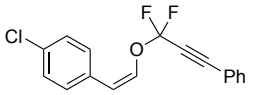
248

248: red oil; IR (neat): 2036 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.65 (d, *J* = 6.2 Hz, 2H), 7.44-7.39 (m, 2H), 7.37-7.30 (m, 3H), 6.80 (d, *J* = 7.5 Hz, 1H), 6.68 (d, *J* = 8.9 Hz, 2H), 5.68 (d, *J* = 6.8 Hz, 1H), 3.76 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): 197.8, 158.6, 136.2, 133.1, 130.2, 130.0, 129.0, 128.6, 126.3 (t, $^1J_{CF}$ = 260.1 Hz), 125.0, 113.5, 111.9, 89.0, 80.7 (t, $^2J_{CF}$ = 44.1 Hz), 55.2; ^{19}F-NMR (560 MHz, $CDCl_3$): δ 59.8; HRMS (EI): calcd for $C_{24}H_{14}Co_2F_2O_8$ (M$^+$): 585.9321, found: 585.9331.

Etherification of 2-(4-chlorophenyl)acetaldehyde

The general procedure was followed. The crude was purified by silica gel column chromatography (hexane) to provide **249** (32.9 mg).

The decomplexation procedure was followed. The crude was purified silica gel column chromatography (hexane) to give **249'** (12.5 mg, 37.0 μmol, 37%)



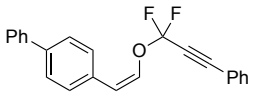
249'

249': colorless oil; IR (neat): 2249, 1666 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.65 (d, *J* = 6.2 Hz, 2H), 7.44-7.39 (m, 2H), 7.37-7.30 (m, 3H), 6.80 (d, *J* = 7.5 Hz, 1H), 6.68 (d, *J* = 8.9 Hz, 2H), 5.68 (d, *J* = 6.8 Hz, 1H), 3.76 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): 197.8, 158.6, 136.2, 133.1, 130.2, 130.0, 129.0, 128.6, 126.3 (t, $^{1}J_{CF}$ = 260.1 Hz), 125.0, 113.5, 111.9, 89.0, 80.7 (t, $^{2}J_{CF}$ = 44.1 Hz), 55.2; ^{19}F-NMR (560 MHz, $CDCl_3$): δ 59.8; HRMS (EI): calcd for $C_{17}H_{11}{}^{35}ClF_2O$ (M^+): 304.0466, found: 304.0461.

Etherification of 2- 2-([1,1'-biphenyl]-4-yl)acetaldehyde

The general procedure was followed. The crude was purified by silica gel column chromatography (hexane) to provide **250** (48.0 mg).

The decomplexation procedure was followed. The crude was purified silica gel column chromatography (hexane) to give **250'** (20.2 mg, 58.3 μmol, 58% 2 steps).

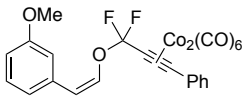


250'

250': colorless oil; IR (neat): 2248, 1666 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.61-7.53 (m, 6H), 7.48-7.42 (m, 3H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 1H), 6.69 (d, *J* = 6.9 Hz, 1H), 5.75 (d, *J* = 6.9 Hz, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$): 140.7, 140.1, 134.5, 132.6, 132.4, 130.5, 129.5, 128.8, 128.6, 127.3, 127.1, 127.0, 119.1, 114.3 (t, $^{1}J_{CF}$ = 254.6 Hz), 112.4, 86.5 (t, $^{3}J_{CF}$ = 5.8 Hz), 77.7 (t, $^{2}J_{CF}$ = 52.0 Hz); ^{19}F-NMR (560 MHz, $CDCl_3$): δ -57.6; HRMS (EI): calcd for $C_{23}H_{16}F_2O$ (M^+): 346.1169, found: 346.1168.

Etherification of 2-(3-methoxyphenyl)acetaldehyde

The general procedure was followed. The crude was purified by silica gel column chromatography (hexane) to provide **251** (32.6 mg, 55.7 μmol, 56%, Z/E = 6/1).



251

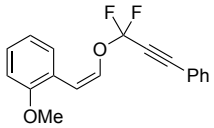
251: red oil; IR (neat): 2037 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.69-7.59 (m, 2H), 7.38-7.29 (m, 2H), 7.16 (d, *J* = 7.4 Hz, 2H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.91 (s, 1H), 6.88 (d, *J* = 7.1 Hz, 1H), 6.72 (d, *J* = 6.72 Hz, 1H), 5.71 (d, *J* = 7.1 Hz, 1H), 3.761 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): 197.8, 159.4, 136.2, 134.7, 123.0, 129.1, 129.0, 128.6, 125.1 (t, $^{1}J_{CF}$ = 260.1 Hz), 121.5, 114.4, 112.9, 112.3, 88.8, 80.5 (t, $^{2}J_{CF}$ = 48.4 Hz), 55.0; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -59.6; HRMS (EI): calcd for $C_{24}H_{14}Co_2F_2O_8$ ($[M-CO]^+$): 557.9372, found: 557.9383.

Etherification of 2-(2-methoxyphenyl)acetaldehyde

The general procedure was followed. The crude was purified by silica gel column chromatography (hexane) to

provide **252** (33.3 mg).

The decomplexation procedure was followed. The crude was purified silica gel column chromatography (hexane) to give **252'** (11.0 mg, 36.6 μmol, 37% 2 steps).

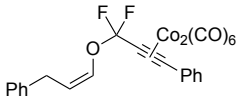


252'

252': red oil; IR (neat): 2036 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.65 (d, J = 6.2 Hz, 2H), 7.39-7.44 (m, 2H), 7.30-7.37 (m, 3H), 6.80 (d, J = 7.5 Hz, 1H), 6.68 (d, J = 8.9 Hz, 2H), 5.68 (d, J = 6.8 Hz, 1H), 3.76 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): 197.8, 158.6, 136.2, 133.1, 130.2, 130.0, 129.0, 128.6, 126.3 (t, $^{1}J_{CF}$ = 260.1 Hz), 125.0, 113.5, 111.9, 89.0, 80.7 (t, $^{2}J_{CF}$ = 44.1 Hz), 55.2; ^{19}F-NMR (560 MHz, $CDCl_3$): δ 59.8; HRMS (EI): calcd for $C_{24}H_{14}Co_2F_2O_8$ (M^+): 585.9321, found: 585.9331.

Etherification of dihydrocinnamaldehyde

The general procedure was followed. The crude was purified by silica gel column chromatography (hexane) to provide **253** (29.8 mg, 52.3 μmol, 52%, *Z/E* = 20:1).

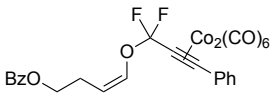


253

253: red oil; IR (neat): 2036 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.64 (d, J = 6.8 Hz, 2H), 7.35-7.30 (m, 3H), 7.28 (d, J = 7.5 Hz, 2H), 7.22-7.17 (m, 3H), 6.81 (d, J = 6.2 Hz, 1H), 5.12 (q, J = 7.1 Hz, 1H), 3.47 (d, J = 7.5 Hz, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 197.9, 140.0, 136.3, 134.7, 134.6, 134.8, 130.0, 129.0, 128.6, 128.5, 128.3, 126.1, 124.9 (t, $^{1}J_{CF}$ = 260.1 Hz), 113.0, 88.5, 81.3 (t, $^{2}J_{CF}$ = 46.2 Hz), 30.1; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -60.4 (s, 2F); HRMS (EI): calcd for $C_{24}H_{14}Co_2F_2O_8$ (M^+): 569.9372, found: 569.9380.

Etherification of 4-oxobutyl benzoate

The general procedure was followed. The crude was purified by silica gel column chromatography (hexane) to provide **254** (40.8 mg, 65.0 μmol, 65%, *Z/E* = 5:1).



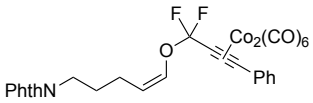
254

254 (Z isomer): red oil; IR (neat): 2036, 1720 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.02 (d, J = 7.2 Hz, 2H), 7.62-7.67 (m, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.9 Hz, 2H), 7.38-7.31 (m, 4H), 6.81 (d, J = 6.5 Hz, 1H), 5.03 (q, J = 7.0 Hz, 1H), 4.32 (t, J = 6.7 Hz, 2H), 2.59 (qd, J = 6.9, 1.1 Hz, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 197.8, 166.5, 136.3, 136.1 (t, $^{2}J_{CF}$ = 5.8 Hz), 132.9, 129.9, 129.5, 129.0, 128.6, 128.3, 124.8 (t, $^{1}J_{CF}$ = 259.4 Hz), 109.4, 88.49, 81.1 (t, $^{2}J_{CF}$ = 49.9 Hz), 63.7, 23.7; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -60.5 (s, 2F); HRMS (EI): calcd for $C_{23}H_{16}Co_2F_2O_6$

([M-3CO]$^+$): 543.9579, found: 543.9581.

Etherification of 5-(1,3-dioxoisoindolin-2-yl)pentanal

The general procedure was followed. The crude was purified by silica gel column chromatography (hexane) to provide **255** (34.9 mg, 52.3 μmol, 52%, *Z/E* = 7:1).

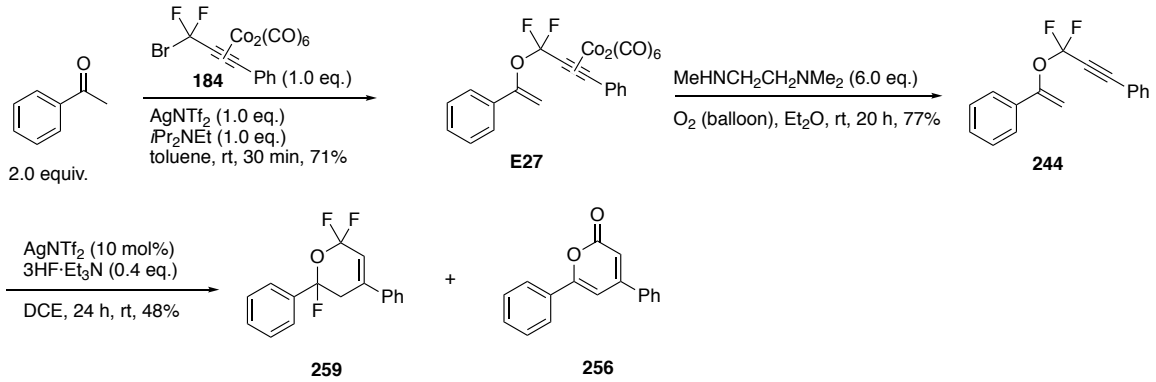


255

255 (*Z* isomer): red oil; IR (neat): 2036, 1716 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.82 (dd, *J* = 5.4, 2.9 Hz, 2H), 7.70 (dd, *J* = 5.7, 2.9 Hz, 2H), 7.62 (d, *J* = 7.6 Hz, 2H), 7.31-7.39 (m, 3H), 6.70 (d, *J* = 6.5 Hz, 1H), 4.96 (q, *J* = 7.1 Hz, 1H), 3.64 (t, *J* = 7.4 Hz, 2H), 2.18 (q, *J* = 7.6 Hz, 2H), 1.75 (quint, *J* = 7.5 Hz, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 197.9, 168.3, 136.3, 134.9 (t, $^2J_{CF}$ = 5.8 Hz), 133.8, 132.2, 129.9, 129.0, 128.6, 124.8 (t, $^1J_{CF}$ = 260.1 Hz), 123.1, 112.7, 88.4, 81.3 (t, $^2J_{CF}$ = 47.3 Hz), 37.4, 28.0, 21.3; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -60.5 (s, 2F); HRMS (FAB): calcd for $C_{25}H_{17}Co_2F_2NO_6$ ([M-3CO]$^+$): 582.9688 found: 582.9669.

255 (*E* isomer): ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.85 (dd, *J* = 2.9 Hz, 2H), 7.72-7.68 (m, 2H), 7.61 (d, *J* = 10.0 Hz, 2H), 7.39-7.31 (m, 3H), 5.41 (dt, *J* = 12.4, 7.4 Hz, 1H), 3.72 (t, *J* = 7.0 Hz, 2H), 2.09 (q, *J* = 7.4 Hz, 2H), 1.81 (quint, *J* = 7.3 Hz, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ -60.8 (s, 2F).

The synthesis of trifluoropyrane 259



The 1 mmol scale synthesis of E27

A solution of phenyldifluorobromopropyne (**184**) (160 mg, 693 μmol) and $Co_2(CO)_8$ (246 mg, 719 μmol) in toluene (7 mL) was stirred at room temperature. After 3 h, acetophenone (160 μL, 1.63 mmol), *i*Pr_2NEt (125 μL, 717 μmol) and $AgNTf_2$ (272 mg, 701 μmol) was added and stirred at room temperature for 30 min. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (5 mL) and extracted with hexane (20 mL x 2). The combined organic layers

were washed with brine and dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane) to provide **E27** (275 mg, 494 μmol, 71%).

E27: red oil; IR (neat): 2035 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.67 (q, *J* = 3.0 Hz, 2H), 7.58-7.52 (m, 2H), 7.41-7.36 (m, 3H), 7.34-7.29 (m, 3H), 5.40 (d, *J* = 2.7 Hz, 1H), 5.33 (s, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 198.0, 152.6, 136.4, 135.2, 130.0, 128.9, 128.6, 128.2, 125.5, 125.3 (t, $^1J_{CF}$ = 267.5 Hz), 99.5, 88.6, 82.8 (t, $^2J_{CF}$ = 49.5 Hz); ^{19}F-NMR (560 MHz, $CDCl_3$): δ -59.3 (s, 2F); HRMS (EI): calcd for $C_{20}H_{12}Co_2F_2O_4$ ([M-3CO]$^+$): 471.9368, found: 471.9359.

The synthesis of 244

To a solution of **E27** (275 mg, 494 μmol) in Et_2O (20 mL) was added *N,N,N'*-trimethylethylenediamine (410 μL, 2.99 mmol). The reaction mixture was stirred at room temperature under O_2 atmosphere. After 20 h, the reaction mixture was diluted with H_2O (10 mL) and Et_2O (10 mL) and extracted with Et_2O (20 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (hexane) to provide **244** (103 mg, 381 μmol, 71%).

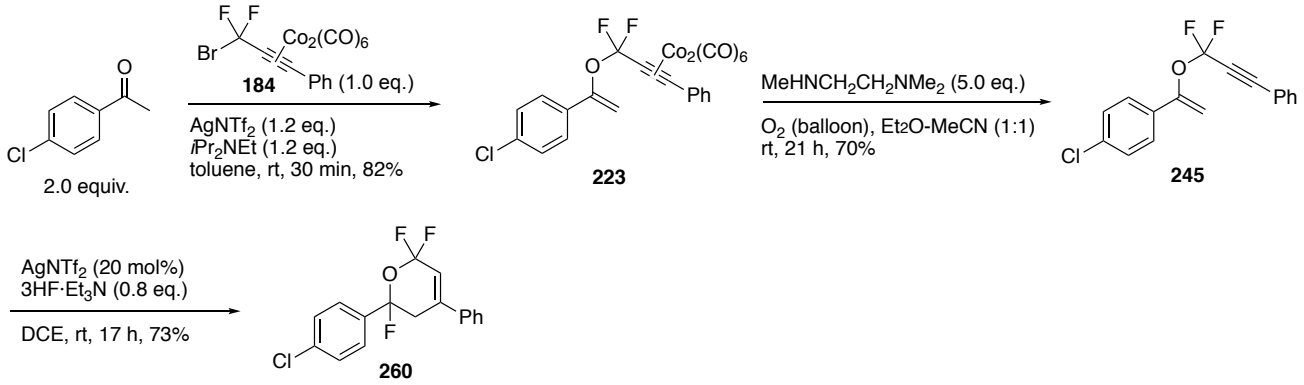
244: colorless oil; IR (neat): 2245 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.63 (d, *J* = 7.5 Hz, 2H), 7.45-7.36 (m, 6H), 7.33 (t, *J* = 7.5 Hz, 2H), 5.38 (s, 1H), 5.19 (s, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 153.0, 134.5, 132.3, 130.2, 129.1 , 128.44, 128.38, 125.5, 119.4, 114.4 (t, $^1J_{CF}$ = 243.1 Hz), 99.1, 86.1 (t, $^3J_{CF}$ = 5.7 Hz), 78.2 (t, $^2J_{CF}$ = 52.3 Hz); ^{19}F-NMR (560 MHz, $CDCl_3$): δ -53.3 (s, 2F); HRMS (EI): calcd for $C_{17}H_{12}F_2O$ (M^+): 270.0856, found: 270.0877.

The synthesis of trifluoropyrane 259

To a solution of **244** (27.0 mg, 99.8 μmol) and 3HF·Et_3N (6.6 μL, 40.4 μmol) in DCE (1 mL) was $AgNTf_2$ (1.8 mg, 4.6 μmol, 10 mol%) and stirred at room temperature. After 20 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (1 mL) and extracted with CH_2Cl_2 (2 mL × 2). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by PTLC (AcOEt : hexane = 1 : 8) to provide **259** (13.9 mg, 47.9 μmol, 48%).

259: colorless oil; IR (neat): 1666 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.69-7.61 (m, 2H), 7.52-7.46 (m, 5H), 7.43-7.39 (m, 3H), 6.34 (s, 1H), 3.22-3.05 (m, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ140.2 (t, $^3J_{CF}$ = 8.6 Hz), 138.2 (t, $^2J_{CF}$ = 24.4 Hz), 129.8, 128.9, 128.6, 125.7 , 124.8 (t, $^3J_{CF}$ = 7.2 Hz), 120.1 (dd, $^1J_{CF}$ = 251.0, 233.8 Hz), 113.9 (dd, $^2J_{CF}$ = 37.3, 33.0 Hz), 112.1 (dd, $^1J_{CF}$ = 227.0 Hz, $^3J_{CF}$ = 7.2 Hz), 37.0 (d, $^2J_{CF}$ =33.0 Hz); ^{19}F-NMR (560 MHz, $CDCl_3$): δ -54.5 (d, *J* = 174.4 Hz), -66.5 (d, *J* = 191.8 Hz), -107.5 (d, *J* = 34.9 Hz); HRMS (EI): calcd for $C_{17}H_{13}Co_2F_3O$ (M^+): 290.0919, found: 290.0909.

The synthesis of trifluoropyrane 260



The 1 mmol scale synthesis of 223

A solution of phenyldifluorobromopropyne (**184**) (231 mg, 1.00 mmol) and $Co_2(CO)_8$ (350 mg, 1.02 mmol) in toluene (10 mL) was stirred at room temperature. After 3 h, 4'-chloroacetophenone (258 µL, 2.00 mmol), iPr_2NEt (210 µL, 1.21 mmol) and $AgNTf_2$ (450 mg, 1.16 mmol) was added and stirred at room temperature for 30 min. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (5 mL) and extracted with hexane (20 mL x 2). The combined organic layers were washed with brine and dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane) to provide **223** (482 mg, 817 µmol, 82%).

The synthesis of **245**

To a solution of **223** (482 mg, 817 µmol) in Et_2O (20 mL) and MeCN (20 mL) was added *N,N,N'*-trimethylethylenediamine (560 µL, 4.08 mmol). The reaction mixture was stirred at room temperature under O_2 atmosphere. After 20 h, the reaction mixture was diluted with H_2O (20 mL) and Et_2O (20 mL) and extracted with Et_2O (20 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (hexane) to provide **245** (173 mg, 568 µmol, 70%).

245: colorless oil; IR (neat): 2246, 1637 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.56-7.53 (m, 2H), 7.42 (t, J = 7.7 Hz, 1H), 7.41 (d, J = 7.6 Hz, 2H), 7.35-7.33 (m, 4H), 5.42-5.38 (m, 1H), 5.23-5.18 (m, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 152.0, 135.1, 133.0, 132.2, 130.4, 128.6, 128.5, 126.8, 119.2, 114.3 (t, $^1J_{CF}$ = 243.5 Hz),99.5, 86.32 (t, $^3J_{CF}$ = 6.5 Hz), 78.0 (t, $^2J_{CF}$ = 52.0 Hz); ^{19}F-NMR (560 MHz, $CDCl_3$): δ -53.5 (s, 2F); HRMS (EI): calcd for $C_{17}H_{11}{}^{35}ClF_2O$ (M^+): 304.0466, found: 304.1468.

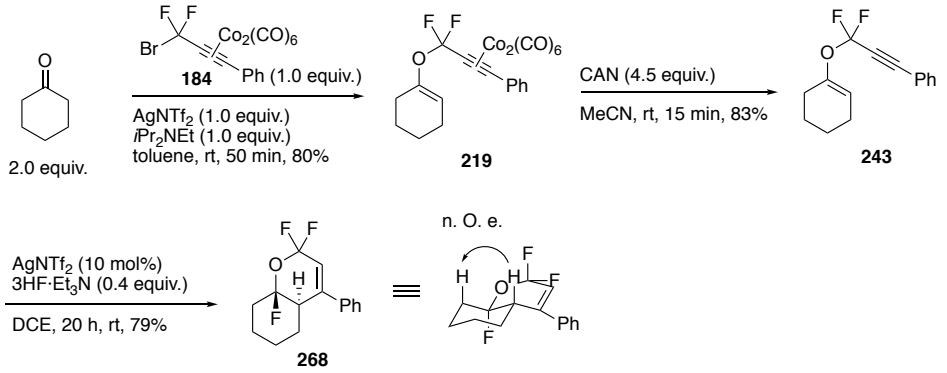
The synthesis of trifluoropyrane **260**

To a solution of **245** (29.6 mg, 97.1 µmol) and 3HF·Et_3N (13.5 µL, 82.8 µmol) in DCE (2 mL) was $AgNTf_2$ (8.0 mg, 20 µmol, 20 mol%) and stirred at room temperature. After 17 h, the reaction mixture was quenched with sat. $NaHCO_3$

aq. (1 mL) and extracted with CH_2Cl_2 (4 mL × 2). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by PTLC (AcOEt : hexane = 1 : 8) to provide diastereomeric mixture of **260** (23.0 mg, 70.8 μmol, 73%). The diastereomeric ratio was determined by ^{1}H-NMR.

260: colorless oil; IR (neat): 1666, 1603 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.57 (dt, J = 8.9, 2.1 Hz, 2H), 7.39-7.50 (m, 7H), 6.33 (t, J = 2.1 Hz, 1H), 3.17 (dt, J = 17.5, 6.9 Hz, 1H), 3.05 (ddtd, J = 34.0, 17.6, 5.5, 2.7 Hz, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 140.1 (t, $^3J_{CF}$ = 9.4 Hz), 136.7 (t, $^2J_{CF}$ = 24.6 Hz), 136.0 (t, $^2J_{CF}$ = 33.2 Hz), 129.9, 128.94, 128.86, 126.4 (t, $^3J_{CF}$ = 5.8 Hz), 125.6, 120.0 (dd, $^1J_{CF}$ = 235.5, 251.4 Hz), 113.9 (dd, $^2J_{CF}$ = 37.6, 33.2 Hz), 11.7 (dd, $^1J_{CF}$ = 229.8 Hz, $^3J_{CF}$ = 5.8 Hz), 36.9 (d, $^2J_{CF}$ = 33.2 Hz); ^{19}F-NMR (560 MHz, $CDCl_3$): δ -54.7 (d, J = 191.8 Hz, 1F), -66.6 (d, J = 174.4 Hz, 1F), -107.0 (d, J = 34.9 Hz, 1F); HRMS (EI): calcd for $C_{17}H_{12}{}^{35}ClF_3O$ (M^+): 324.0529, found: 324.0545.

The synthesis of trifluoropyrane 268



The 1 mmol scale synthesis of 219

A solution of phenyldifluorobromopropyne (**184**) (205 mg, 887 μmol) and $Co_2(CO)_8$ (316 mg, 924 μmol) in toluene (9 mL) was stirred at room temperature. After 3 h, cyclohexane (190 μL, 1.83 mmol), iPr$_2$NEt (160 μL, 919 μmol) and $AgNTf_2$ (344 mg, 887 μmol) was added and stirred at room temperature for 30 min. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (5 mL) and extracted with hexane (20 mL x 2). The combined organic layers were washed with brine and dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane) to provide **219** (380 mg, 711 μmol, 80%).

The synthesis of 243

To a solution of **219** (380 mg, 355 μmol) in MeCN (28 mL) was added cerium ammonium nitrate (1.80 g, 3.28 mmol). After 15 min, the reaction mixture was diluted with satirated aqueous $Na_2S_2O_3$ (10 mL) and extracted with AcOEt (20 mL × 2). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (hexane) to provide **243**(159 mg, 585 μmol, 83%).

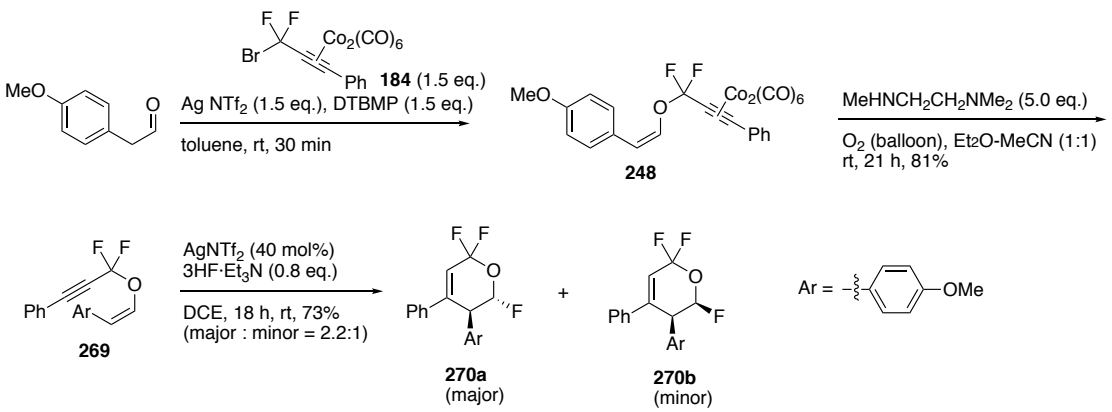
243: colorless oil; IR (neat): 2048 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.52 (d, *J* = 6.8 Hz, 2H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 2H), 5.58 (s, 1H), 2.24 (brs, 2H), 2.12 (brd, *J* = 3.4 Hz, 2H), 1.66-1.81 (m, 2H), 1.48-1.65 (m, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ148.1, 132.2, 130.1, 128.5, 119.7, 114.3 (t, $^{1}J_{CF}$ = 241.7 Hz), 113.7, 85.1 (t, $^{3}J_{CF}$ = 5.7 Hz), 78.9 (t, $^{2}J_{CF}$ = 53.8 Hz), 27.9, 23.8, 22.8, 21.7; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -52.3 (s, 2F); HRMS (EI): calcd for $C_{15}H_{14}F_2O$ (M^+): 248.1013, found: 248.0986.

The synthesis of trifluoropyrane 268

To a solution of **243** (12.7 mg, 51.2 μmol) and 3HF·Et_3N (3.3 μL, 20.2 μmol) in DCE (1 mL) was $AgNTf_2$ (1.8 mg, 4.6 μmol, 10 mol%) and stirred at room temperature. After 20 h, the reaction mixture was quenched with sat. $NaHCO_3$ aq. (1 mL) and extracted with CH_2Cl_2 (2 mL × 2). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by PTLC (AcOEt : hexane = 1 : 8) to provide diastereomeric mixture of **268** (10.8 mg, 40.3 μmol, 79%, major : minor = 2.5:1). The diastereomeric ratio was determined by ^{1}H-NMR.
The analytical sample was prepared followed procedure. To a solution of **243** (12.4 mg, 45.8 μmol) and in DCE (1 mL) was $AgNTf_2$ (0.90 mg, 2.3 μmol, 5 mol%) and stirred at room temperature. After 14 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (1 mL) and extracted with CH_2Cl_2 (2 mL × 2). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by PTLC (AcOEt : hexane = 1 : 8) to provide single diastereomer **268** (5.93 mg, 22.1 μmol, 48%).

268 (major isomer): colorless oil; IR (neat): 1660 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.40-7.52 (m, 2H), 7.36-7.40 (m, 3H), 6.09 (s, 1H), 2.79-2.86 (m, 1H), 2.32 (d, *J* = 13.7 Hz, 1H), 1.91-1.97 (m, 1H), 1.74-1.91 (m, 3H), 1.60-1.70 (m, 1H), 1.20-1.39 (m, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ146.1 (t, $^{3}J_{CF}$ = 9.3 Hz), 135.9, 129.6, 128.9, 126.1, 120.0 (dd, $^{1}J_{CF}$ = 248.1, 233.8 Hz), 114.4 (t, $^{3}J_{CF}$ = 4.3 Hz), 112.9 (dd, $^{2}J_{CF}$ = 38.7, 31.6 Hz), 41.6 (d, $^{2}J_{CF}$ = 24.4 Hz), 35.3 (d, $^{2}J_{CF}$ = 21.5 Hz), 31.2 (d, $^{3}J_{CF}$ = 7.2 Hz), 24.3, 22.7 (d, $^{3}J_{CF}$ = 10.0 Hz); ^{19}F-NMR (560 MHz, $CDCl_3$): δ -103.0 (s, 1F), -65.5 (d, *J* = 191.8 Hz, 1F), -52.7 (d, *J* = 174.4 Hz, 1F); HRMS (EI): calcd for $C_{25}H_{17}Co_2F_2NO_6S$ (M^+): 268.1075, found: 268.1075.

The synthesis of trifluoropyrane 270



The 1 mmol scale synthesis of 248

A solution of phenyldifluorobromopropyne (**184**) (277 mg, 1.20 mmol) and $Co_2(CO)_8$ (560 mg, 1.64 mmol) in toluene (8 mL) was stirred at room temperature. After 3 h, 4-methoxyphenylacetoaldehyde (130 mg, 866 μmol), DTBMP (210 μL, 1.21 mmol) and $AgNTf_2$ (450 mg, 1.16 mmol) was added and stirred at room temperature for 30 min. The reaction mixture was diluted with sat. $NaHCO_3$ aq. (5 mL) and extracted with hexane (20 mL x 2). The combined organic layers were washed with brine and dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt : hexane = 1:50) to provide **248** (331 mg, 565 μmol, 65%).

The synthesis of phenyl difluoropropargyl vinyl ether 269

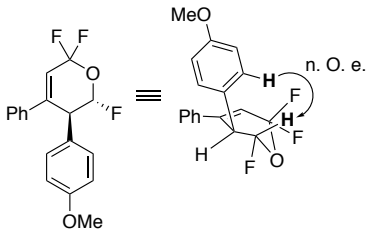
To a solution of **248** (331 mg, 565 μmol) in Et_2O (14 mL) and MeCN (14 mL) was added *N,N,N'*-trimethylethylenediamine (390 μL, 2.84 mmol). The reaction mixture was stirred at room temperature under O_2 atmosphere. After 21 h, the reaction mixture was diluted with H_2O (20 mL) and Et_2O (20 mL) and extracted with Et_2O (20 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (AcOEt : hexane = 1:20) to provide **269** (138 mg, 460 μmol, 81%).

269: colorless oil; IR (neat): 2248, 1607 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.59-7.52 (m, 4H), 7.46 (t, J = 7.6 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 6.88 (d, J = 8.6 Hz, 2H), 6.58 (d, J = 6.9 Hz, 1H), 5.66 (d, J = 6.9 Hz, 1H), 3.82 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): 158.9, 132.9 (t, $^3J_{CF}$ = 3.6 Hz), 132.5, 130.6, 130.5, 128.7, 126.4, 119.3, 114.4 (t, $^1J_{CF}$ = 244.9 Hz), 113.9, 112.6, 86.4 (t, $^3J_{CF}$ = 5.8 Hz), 78.29, 77.9 (t, $^2J_{CF}$ = 52.7 Hz), 55.33; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -57.5 (s, 2F); HRMS (EI): calcd for $C_{18}H_{14}F_2O_2$ (M^+): 300.0962, found: 300.0932.

The synthesis of trifluoropyrane 270

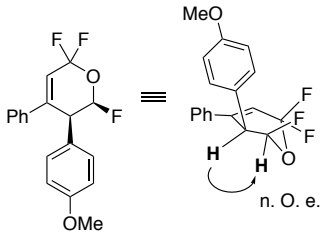
To a solution of **269** (15.3 mg, 50.9 μmol) and 3HF·Et_3N (6.6 μL, 40.2 μmol) in DCE (1 mL) was $AgNTf_2$ (7.3 mg, 19 μmol, 40 mol%) and stirred at room temperature. After 18 h, the reaction mixture was quenched with sat. $NaHCO_3$ aq. (1 mL) and extracted with CH_2Cl_2 (4 mL × 2). The combined organic layers were dried over $MgSO_4$ and

concentrated in vacuo. The residue was purified by PTLC (AcOEt : hexane = 1 : 4) to provide diastereomeric mixture of **270** (11.8 mg, 70.8 μmol, 73% **270a** : **270b** = 2.2:1). The diastereomeric ratio was determined by ^{1}H-NMR.The analytical sample was obtained by PTLC (AcOEt : hexane = 1 : 4).



270a

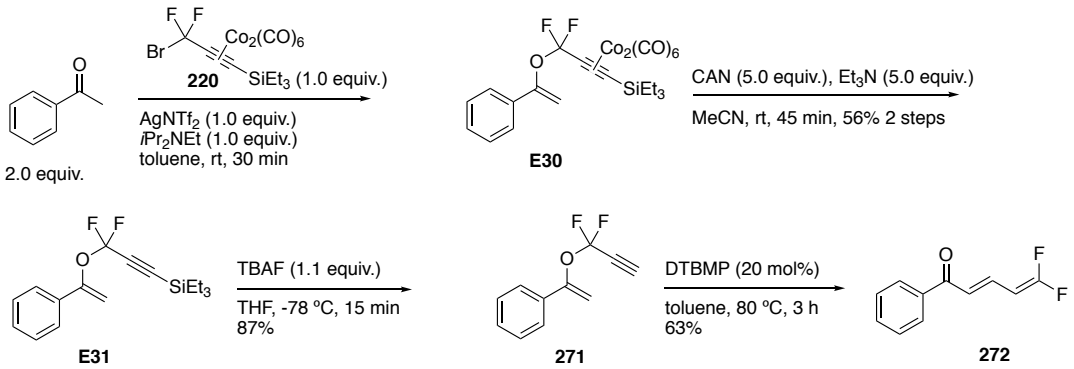
270a: colorless oil; IR (neat): 1614 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.46-7.41 (m, 3H), 7.40-7.37 (m, 2H), 7.28 (d, J = 8.9 Hz, 2H), 6.87 (d, J = 8.9 Hz, 2H), 6.16 (d, J = 1.4 Hz, 1H), 5.68-5.58 (m, 1H), 5.54 (d, J = 44.0 Hz, 1H), 3.81 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 160.01, 148.2 (t, J_{CF} = 5.1 Hz), 130.14, 130.10, 129.1, 128.09, 128.05, 127.3 (d, ^{2}J = 21.7 Hz), 127.1, 117.6 (d, ^{2}J = 33.3 Hz), 113.7, 90.5 (d, $^{1}J_{CF}$ = 183.5 Hz), 86.8 (d, $^{2}J_{CF}$ = 24.6 Hz), 55.27; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -58.8 (d, J = 165.7Hz, 1F), -61.6 (d, J = 165.7Hz, 1F), -191.9 (s, 1F); HRMS (EI): calcd for $C_{18}H_{15}F_3O_2$ (M^+): 320.1024, found: 320.1011.



270b

270b: colorless oil; IR (neat): 1648, 1613 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.47-7.39 (m, 3H), 7.37-7.31 (m, 2H), 7.01 (d, J = 8.6 Hz, 2H), 6.78 (d, J = 8.6 Hz, 2H), 5.97 (s, 1H), 5.93-5.84 (m, 1H), 5.59 (dd, J = 43.6, 2.7 Hz, 1H), 3.78 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 160.0, 148.2, 132.2 (dd, $^{1}J_{CF}$ = 249.3, 245.4 Hz), 130.2, 129.1, 128.3, 128.2, 127.1, 125.5 (d, $^{2}J_{CF}$ = 21.7 Hz), 117.6 (t, $^{2}J_{CF}$ = 33.2 Hz), 113.2, 92.9 (dd, $^{1}J_{CF}$ = 176.3 Hz, $^{2}J_{CF}$ = 7.2 Hz), 86.5 ($^{2}J_{CF}$ = 27.5 Hz), 55.2; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -58.4 (d, J = 165.7Hz, 1F), -60.1 (d, J = 165.7Hz, 1F), -191.9 (s, 1F); HRMS (EI): calcd for $C_{18}H_{15}F_3O_2$ (M^+): 320.1024, found: 320.1046.

Synthesis of phenyl difluorodienone 272



The synthesis of E30

A solution of triethylsilyldifluorobromopropyne (**220**) (96.7 mg, 359 μmol) and $Co_2(CO)_8$ (142 mg, 415 μmol) in toluene (4 mL) was stirred at room temperature. After 3 h, acetophenone (90 μL, 772 μmol), iPr$_2$NEt (70 μL, 402 μmol) and $AgNTf_2$ (156 mg, 402 μmol) was added and stirred at room temperature for 30 min. The reaction mixture was diluted with sat. $NaHCO_3$ aq. (2 mL) and extracted with hexane (10 mL x 2). The combined organic layers were washed with brine and dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (Kanto) to provide **E30** containing acetophenone (211 mg).

E30: red oil; IR (neat): 2062 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ δ 7.60-7.53 (m, 2H), 7.38-7.34 (m, 3H), 5.35 (d, J = 2.1 Hz, 1H), 5.25 (s, 1H), 1.08 (t, J = 7.9 Hz, 9H), 0.85 (q, J = 7.9 Hz, 6H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 153.0, 134.4, 129.0, 128.3, 125.4, 112.9 (t, $^1J_{CF}$ = 243.1 Hz), 98.9, 93.7 (t, $^2J_{CF}$ = 50.2 Hz), 91.2 (t, $^3J_{CF}$ = 5.0 Hz), 7.12, 3.64; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -57.6 (s, 2F); HRMS (EI): calcd for $C_{20}H_{22}Co_2F_2O_6Si$ ([M-3CO]$^+$): 509.9919, found: 509.9903.

The synthesis of E31

To a solution of **E30** containing acetophenone (211 mg) and triethylamine (220 μL, 1.58 mmol) in MeCN (14 mL) was added cerium ammonium nitrate (1.01 g, 1.84 mmol). After 30 min, the reaction mixture was diluted with sat. $Na_2S_2O_3$ (10 mL) and extracted with AcOEt (20 mL × 2). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (hexane) to provide **E31** (60.8 mg, 197 μmol, 56%, 2 steps).

E31: colorless oil; IR (neat): 1638 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.58 (d, J = 6.2 Hz, 2H), 7.36-7.30 (m, 3H), 5.34 (s, 1H), 5.12 (s, 1H), 0.93 (t, J = 7.9 Hz, 9H), 0.58 (q, J = 8.0 Hz, 6H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 153.0, 134.4, 129.0, 128.3, 125.4, 112.9 (t, $^1J_{CF}$ = 243.1 Hz), 99.0, 93.6 (t, $^2J_{CF}$ = 50.9 Hz), 91.2 (t, $^3J_{CF}$ = 5.0 Hz), 7.1, 3.6; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -53.8 (s, 2F); HRMS (EI): calcd for $C_{17}H_{22}F_2O_6Si$ (M$^+$): 308.1408, found: 308.1418.

The synthesis of *gem*-difluoropropargyl vinyl ether 271

To a solution of **E31** (60.8 mg, 197 μmol) in THF (10 mL) was added TBAF (1M in THF, 240 μL, 240 μmol) at –78 ºC. The reaction mixture was stirred at –78 ºC for 15 min and then quenched with sat. NH_4Cl aq. (5 mL). The mixture was extracted with Et_2O (10 mL × 3) and the combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane, Merck) to provide **271** (33.4 mg, 172 μmol, 87%).

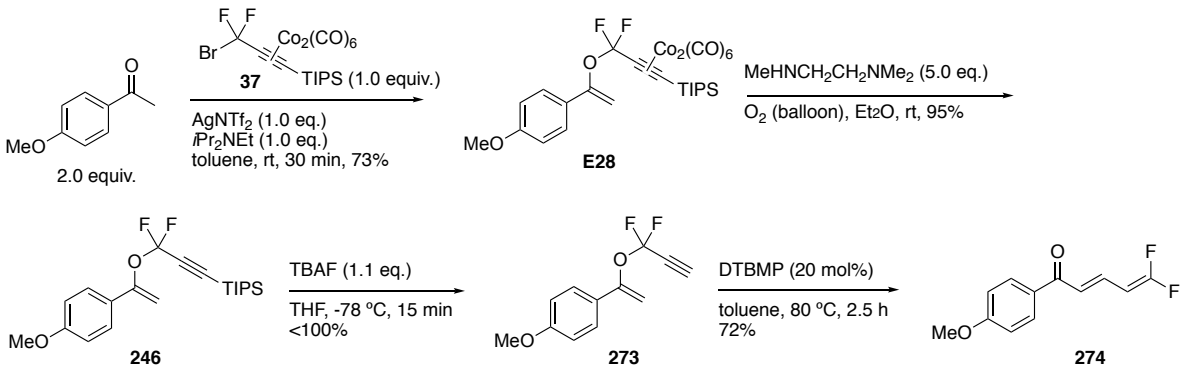
271: colorless oil; IR (neat): 2142, 1639 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.58 (d, J = 6.2 Hz, 2H), 7.43-7.35 (m, 3H), 5.36 (d, J = 1.0 Hz, 1H), 5.13 (d, J = 1.0 Hz, 1H), 2.75 (t, J = 3.4 Hz, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 152.7, 134.1, 129.2, 128.4, 125.4, 113.0 (t, $^1J_{CF}$ = 244.5 Hz), 98.7, 74.5 (t, $^3J_{CF}$ = 6.5 Hz), 72.9 (t, $^2J_{CF}$ = 52.3 Hz); ^{19}F-NMR (560 MHz, $CDCl_3$): δ -54.8 (s, 2F); HRMS (EI): calcd for $C_{11}H_8F_2O$ (M^+): 194.0543, found: 194.0542.

The synthesis of difluorodienone 272

The solution of **271** (16.1 mg, 82.9 μmol) DTBMP (3.40 mg, 16.6 μmol) in toluene (4.1 mL) was heated at 80 ºC for 3 h. The reaction mixture was cooled at room temperature and concentrated in vacuo. The residue was purified by PTLC (AcOEt : hexane = 1 : 4) to provide **272** (10.1 mg, 52.0 μmol, 63%).

272: white solid; IR (neat): 1708 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.94 (d, J = 6.9 Hz, 2H), 7.57 (t, J = 6.9 Hz, 1H), 7.53-7.44 (m, 3H), 6.99 (d, J = 15.1 Hz, 1H), 5.29 (dd, J = 23.0, 11.3 Hz, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 189.5, 159.3 (dd, $^1J_{CF}$ = 304.9 Hz, 299.1 Hz), 137.7, 134.3 (d, $^4J_{CF}$ = 5.8 Hz), 132.9, 128.6, 128.4, 124.9 (d, $^3J_{CF}$ = 10.1 Hz), 82.4 (dd, $^2J_{CF}$ = 28.1, 15.2 Hz); ^{19}F-NMR (560 MHz, $CDCl_3$): δ -79.9, -80.7; HRMS (EI): calcd for $C_{11}H_8F_2O$ (M^+): 194.0543, found: 194.0531.

Synthesis of 4'methoxyphenyl-difluorodienone 274



The large synthesis of E28

A solution of triisopropylsilyldifluorobromopropyne (**37**) (305 mg, 983 μmol) and $Co_2(CO)_8$ (351 mg, 1.03 mmol) in toluene (10 mL) was stirred at room temperature. After 3 h, 4'-methoxyacetophenone (295 mg, 1.96 mmol),

iPr_2NEt (170 μL, 976 μmol) and $AgNTf_2$ (381 mg, 982 μmol) was added and stirred at room temperature for 30 min. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (5 mL) and extracted with hexane (20 mL x 2). The combined organic layers were washed with brine and dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (hexane, Kanto) to provide **E28** (478 mg, 717 μmol, 73%).

E28: red oil; IR (neat): 2029 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.2 Hz, 2H), 6.86 (d, *J* = 8.2 Hz, 2H), 5.23 (s, 1H), 5.13 (s, 1H), 3.82 (s, 3H), 1.28 (sept, *J* = 7.0 Hz, 3H), 1.20 (d, *J* = 6.8 Hz, 18H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.1, 160.1, 152.7, 128.0, 127.1, 124.5 (t, $^1J_{CF}$ = 261.5 Hz), 113.5, 101.1 (t, $^2J_{CF}$ = 48.4 Hz), 99.1, 73.1, 55.3, 18.9, 13.8; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -56.5 (s, 2F); HRMS (EI): calcd for $C_{24}H_{30}Co_2F_2O_5Si$ ([M-3CO]$^+$): 582.0495, found: 582.0489.

The synthesis of 246

To a solution of **E28** (478 mg, 717 μmol) in Et_2O (29 mL) was added *N,N,N'*-trimethylethylenediamine (500 μL, 3.60 mmol). The reaction mixture was stirred at room temperature under O_2 atmosphere. After 16 h, the reaction mixture was diluted with H_2O (10 mL) and Et_2O (10 mL) and extracted with Et_2O (20 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (hexane) to provide **246** (258 mg, 678 μmol, 95%).

246: colorless oil; IR (neat): 1610 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.2 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 5.21 (s, 1H), 5.02 (s, 1H), 3.82 (s, 3H), 1,07-0.99 (m, 21H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 160.3, 153.0, 127.1, 126.8, 113.7, 113.0 (t, $^1J_{CF}$ = 261.5 Hz), 96.9, 94.5 (t, $^2J_{CF}$ = 51.3 Hz), 90.2 (t, $^3J_{CF}$ = 5.1 Hz), 55.3, 18.3, 10.8; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -52.9 (s, 2F); HRMS (EI): calcd for $C_{25}H_{17}F_2O_2Si$ (M$^+$): 380.1983, found: 380.1982.

The synthesis of difluoropropargyl vinyl ether **273**

To a solution of **246** (258 mg, 678 μmol) in THF (23 mL) was added TBAF (1M in THF, 750 μL, 750 μmol) at –78 ºC. The reaction mixture was stirred at –78 ºC for 15 min and then quenched with saturated aqueous NH_4Cl (4 mL). The mixture was extracted with Et_2O (10 mL × 3) and the combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt : hexane = 1:20, Merck) to provide **273** containing *i*Pr_3SiF (162 mg <729 μmol, <100%).

273: colorless oil; IR (neat): 3299, 2140 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.2 Hz, 2H), 6.86 (d, *J* = 8.2 Hz, 2H), 5.23 (s, 1H), 5.13 (s, 1H), 3.82 (s, 3H), 1.28 (sept, *J* = 7.0 Hz, 3H), 1.20 (d, *J* = 6.8 Hz, 18H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 160.4, 152.6, 130.5, 126.8, 113.8, 113.0 (t, $^1J_{CF}$ = 243.8 Hz), 97.0, 74.4 (t, $^3J_{CF}$ = 6.5 Hz), 73.0 (t, $^2J_{CF}$ = 53.1 Hz), 55.32; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -54.5 (s, 2F); HRMS (EI): calcd for $C_{12}H_{10}F_2O_2$ (M$^+$):

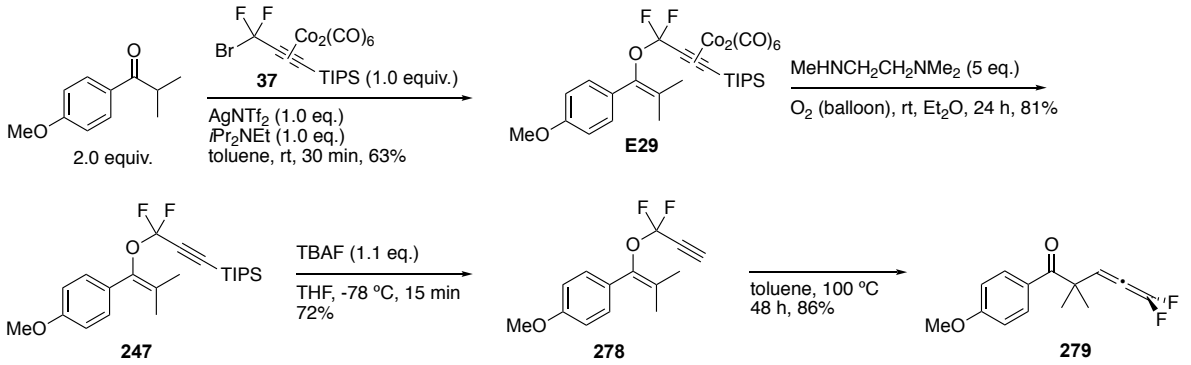
224.0649, found: 224.0641.

The synthesis of **274**

The solution of **273** (28.0 mg, 125 μmol) and DTBMP (5.80 mg, 28.2 μmol) in toluene (6.5 mL) was heated at 80 ºC for 2.5 h. The reaction mixture was cooled at room temperature and concentrated in vacuo. The residue was purified by PTLC (AcOEt : hexane = 1 : 4) to provide **274** (20.1 mg, 89.6 μmol, 72%).

274: white solid; IR (neat): 1708 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.95 (d, J = 8.9 Hz, 2H), 7.44 (dd, J = 14.4, 12.3 Hz, 1H), 6.99 (d, J = 15.0 Hz, 1H), 6.96 (d, J = 8.9 Hz, 2H), 5.27 (dd, J = 23.2 Hz, 11.6 Hz, 1H), 3.88 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 187.8, 163.5, 159.2 (dd, $^{1}J_{CF}$ = 304.0 Hz, 298.3 Hz), 133.5, 130.7, 130.6, 124.7 (dd, $^{3}J_{CF}$ = 38.7 Hz, 12.9 Hz), 113.9 (dd, $^{2}J_{CF}$ = 52.3 Hz, 16.0 Hz), 82.4 (dd, $^{4}J_{CF}$ = 28.0 Hz, 12.2 Hz), 55.5; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -81.4, -80.5; HRMS (EI): calcd for $C_{12}H_{10}F_2O_2$ (M^+): 224.0649, found: 224.0653.

Synthesis of difluoroallene 279



The large-scale synthesis of E29

A solution of triisopropylsilyldifluorobromopropyne (**37**) (121 mg, 390 μmol) and $Co_2(CO)_8$ (141 mg, 412 μmol) in toluene (4 mL) was stirred at room temperature. After 3 h, isobutylacetophenone (145 mg, 814 μmol), iPr$_2$NEt (70 μL, 402 μmol) and $AgNTf_2$ (162 mg, 412 μmol) was added and stirred at room temperature for 30 min. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (5 mL) and extracted with hexane (20 mL x 2). The combined organic layers were washed with brine and dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane) to provide **E29** (170 mg, 245 μmol, 63%).

E29: red oil; IR (neat): 2028 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.27 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 3.82 (s, 3H), 1.89 (s, 3H), 1.73 (s, 3H), 1.30-1.21 (m, 3H), 1.17 (d, J = 7.2 Hz, 18H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ199.2, 158.8, 140.9, 130.3, 129.6, 124.9 (t, $^{1}J_{CF}$ = 256.7 Hz), 124.0, 113.1, 101.6 (t, $^{2}J_{CF}$ = 47.3 Hz), 72.7, 55.2, 20.3, 18.9, 13.8; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -53.7 (s, 2F); HRMS (EI): calcd for $C_{29}H_{34}Co_2F_2O_6Si$ ([M-

3CO]$^+$): 610.0808, found: 610.0813.

Synthesis of TIPS-difluoropropargyl vinyl ether 247

To a solution of **E29** (130 mg, 187 μmol) in Et_2O (9.4 mL) was added *N,N,N'*-trimethylethylenediamine (140 μL, 1.02 mmol). The reaction mixture was stirred at room temperature under O_2 atmosphere. After 24 h, the reaction mixture was diluted with H_2O (10 mL) and Et_2O (10 mL) and extracted with Et_2O (20 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (AcOEt : hexane = 1:20,) to provide **247** (62.1 mg, 152μmol, 81%).

247: colorless oil; IR (neat): 2028 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.28 (d, J = 8.2 Hz, 2H), 6.85 (d, J = 8.2 Hz, 2H), 3.81 (s, 3H), 1.88 (s, 3H), 1.72 (s, 3H), 1.08 (s, 21H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 159.1, 141.4, 130.7, 128.0, 123.7, 114.1 (t, $^1J_{CF}$ = 244.2 Hz), 113.1, 95.3 (t, $^2J_{CF}$ = 50.6 Hz), 89.4, 55.2, 20.1, 18.7, 18.4, 10.9; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -50.1 (s, 2F); HRMS (EI): calcd for $C_{23}H_{34}F_2O_2Si$ (M$^+$): 408.2296, found: 408.2284.

Synthesis of difluoropropargyl vinyl ether 278

To a solution of **247** (66.7 mg, 163 μmol) in THF (6.5 mL) was added TBAF (1M in THF, 180 μL, 180 μmol) at –78 ºC. The reaction mixture was stirred at –78 ºC for 15 min and then quenched with saturated aqueous NH_4Cl (5 mL). The mixture was extracted with Et_2O (6 mL × 3) and the combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (AcOEt : hexane = 1:50, Merck) to provide **278** (29.6 mg, 117 μmol, 72%).

278: colorless oil; IR (neat): 3299, 2140 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.27 (t, J = 6.8 Hz, 3H), 6.87 (d, J = 6.8 Hz, 2H), 3.82 (s, 3H), 2.66 (s, 1H), 1.88 (s, 3H), 1.74 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 159.2, 140.7, 130.7, 128.0, 124.2, 113.8 (t, $^1J_{CF}$ = 243.8 Hz), 113.2, 73.9 (t, $^3J_{CF}$ = 6.5 Hz), 73.6 (t, $^2J_{CF}$ = 53.1 Hz), 55.2, 20.0, 18.7; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -52.6 (s, 2F); HRMS (EI): calcd for $C_{14}H_{14}F_2O_2$ (M$^+$): 252.0962, found: 252.0957.

Synthesis of difluoroallene 279

The solution of **278** (29.6 mg, 117 μmol) in toluene (6 mL) was heated at 100 ºC for 48 h. The reaction mixture was cooled at room temperature and concentrated in vacuo. The residue was purified by PTLC (AcOEt : hexane = 1 : 4) to provide **279** (25.4 mg, 101 μmol, 86%).

279: colorless oil; IR (neat): 2011 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.90 (d, J = 8.9 Hz, 2H), 6.88 (d, J = 8.9 Hz, 2H), 6.73 (s, 1H), 3.85 (s, 3H), 1.47 (s, 6H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.9, 169.1 (t, $^2J_{CF}$ = 36.6 Hz), 162.9, 153.9 (t, $^1J_{CF}$ = 263.9 Hz), 131.8, 130.7, 128.5, 127.9 (t, $^3J_{CF}$ = 5.0 Hz), 113.4, 55.4, 50.6, 25.9; ^{19}F-NMR (560 MHz, $CDCl_3$): δ -114.2 (s, 2F); HRMS (EI): calcd for $C_{14}H_{14}F_2O_2$ (M$^+$): 252.0962, found: 252.0947.

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