C-H 結合修飾を基盤とする
α-キラルアミン化合物合成法の開発

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目次

実験の部

略語表

Ac	acetyl
Boc	*tert*-butoxycarbonyl
t-Bu	*tert*-butyl
Bz	benzoyl
DBDMH	1,3-dibromo-5,5-dimethylhydantoin
DCM	dichloromethane
DFT	density functional theory
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
Et	ethyl
HOMO	highest occupied molecular orbital
HRMS	high-resolution mass spectrometry
IR	infrared
KIE	kinetic isotope effect
Me	methyl
m.p.	melting point
NBA	*N*-bromoacetoamide
NBP	*N*-bromophthalimide
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
Nos	4-nitrobenzenesulfonyl
Ns	2-nitrobenzenesulfonyl
Nu	nucleophile
PG	protecting group
Ph	phenyl
Phth	phthaloyl
pin	pinacol
PPY	4-pyrrolidinopyridine
i-Pr	isopropyl
n-Pr	*normal*-propyl
$Rh_2(tpa)_4$	tetrakis(triphenylacetato)dirhodium (II)
rt	room temperature
SES	2-(trimethylsilyl)ethylsulfonyl
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran

Toes	2,2,2-trichloroethoxysulfonyl
Troc	2,2,2-trichloroethoxycarbonyl
TS	transition state
Ts	*p*-toluenesulfonyl

理論の部

第一章　緒言

窒素原子 α 位に不斉点を有する α-キラルアミンは創薬化学における有力なファーマコフォアの一つであり、これまでに α-キラルアミン部位を有する多くの医薬品が上市されてきた (**Figure 1-1**)。光学活性 α-キラルアミン化合物の合成は、主としてエナミドやイミン等 sp^2 混成炭素を有する化合物群に対するエナンチオ面選択的な反応により達成されている (**Figure 1-2 (a)**)[1]。特に不斉水素化反応や、不斉求核付加反応については様々な触媒的不斉合成法が開発され、成熟を迎えつつあるといえる。一方で、これらの手法では合成が困難な骨格も多数存在することから、骨格の更なる多様化を志向し異なる方法論による合成法の開発が求められている。

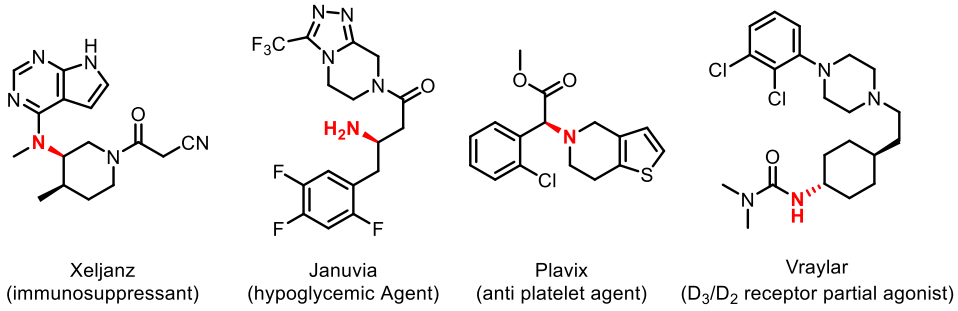


Figure 1-1. Examples of α-Chiral Amine Pharmaceutical Drugs [2]

不斉非対称化反応は光学活性化合物の強力な合成法である (**Figure 1-2 (b)**)[3]。プロキラル炭素に置換した二つのエナンチオトピックな置換基の片方を反応させることで新たな不斉点を構築することができ、適切な置換基を配置することで様々な反応を不斉反応へ展開することが可能である。著者は、α-キラルアミン化合物群の合成法開発を研究課題として、合成上有用な反応である二つの C-H 修飾反応(C-H アミノ化及び芳香族ハロゲン化)を不斉非対称化反応に展開し、従来法では困難であった分子変換に挑んだ。

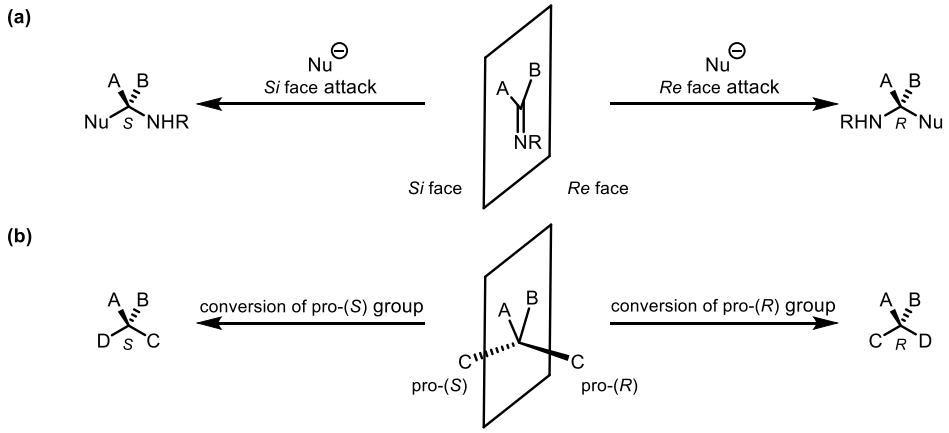


Figure 1-2. Types of Enantioselective Reaction (a) Enantiotopic-Face-Selective Reaction (b) Enantiotopic-Group-Selective Reaction (Desymmetrization) [4]

第二章、第三章ではロジウムナイトレン錯体による C-H 挿入反応に関する研究を行い、シリル基 β 位選択的 C-H アミノ化の機構解析[5]を行うと共にエナンチオ選択的シリル基 β 位 C-H アミノ化反応を開発した。第四章、第五章では古典的な C-H 修飾法である芳香族臭素化に着目し、所属研究室で開発した分子認識型触媒を用いて芳香族臭素化による σ-対称 1,*n*-ジアリールアルキルアミンの不斉非対称化法を開発した。

第二章　Rh 触媒を用いるシリル基 β 位 C(sp^3)-H アミノ化の反応機構解析

第一節　研究背景と著者の研究方針

創薬化学における生物学的等価体の利用は医薬品候補化合物探索の有効な手法の一つであり、炭素原子の生物学的等価体としてケイ素原子を医薬品候補化合物に導入する研究が行われている **(Figure 2-1)** [6]。ケイ素原子は炭素原子と同じ原子価を有する、四面体型構造を取るなどの類似した性質を持つが、原子半径の大きさ、疎水性の高さ及び電気陰性度などの違いにより、炭素原子に替えて導入することで薬理活性及び薬物動態の改善が期待される [7]。しかし、創薬上の利点があるにも関わらずケイ素原子を含む医薬品は未だ上市に至っておらず、これらの試みは未だ発展途上である。その一因は含ケイ素骨格合成の困難さにあると推察される。市販されているケイ素化合物が限られているとともに、含ケイ素骨格を変換する手法は乏しく、ケミカルスペース拡充のためにより自在な含ケイ素骨格合成法の開発が求められている。

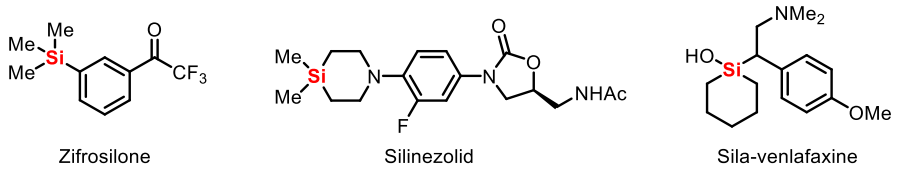
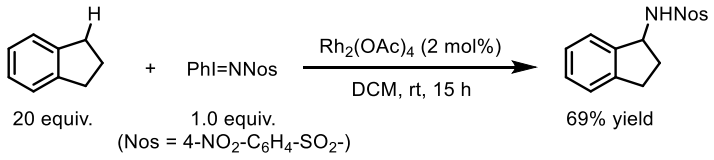


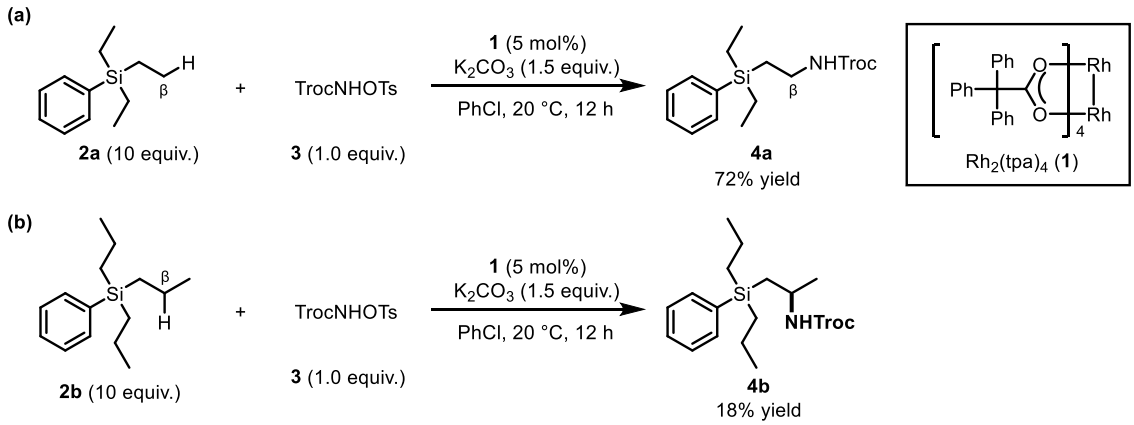
Figure 2-1. Silicon-Containing Drug Candidates

窒素官能基は医薬品の多くに含まれる重要な官能基であることから、ケイ素化合物の簡便なアミノ化法を開発することが出来れば含ケイ素医薬品探索の強力な方法論となり得る。近年では、有機化合物に最も直接的に窒素官能基を導入する手法として、遷移金属を用いた C-H アミノ化反応が精力的に研究されている [8]。特に、ロジウム二核錯体から生じるロジウムナイトレン錯体による C-H 挿入過程を経る C-H アミノ化は、配位性配向基を必要とせず脂肪族化合物から直接アミンを得る強力な手法である [9]。しかし、有機化合物は多数の C-H 結合を有するため、分子間反応における位置選択性の制御は困難であり、僅かな反応性の差を見分ける触媒系の開発が望まれる [10]。Müller らはロジウム二核錯体を用いて、イミノヨージナンをナイトレン源とする分子間 C-H アミノ化を初めて報告した **(Scheme 2-1)** [11a]。$Rh_2(OAc)_4$ 存在下過剰量のインダンにイミノヨージナンを作用させることで、ベンジル位 C-H 結合に対して位置選択的に C-H アミノ化が進行する。これ以降、金属ナイトレン錯体を活性種とする分子間 C-H アミノ化においては、ベンジル位、アリル位、酸素原子 α 位 C-H 結合又は第三級 C-H 結合といった立体電子効果によって電子豊富となる C-H 結合が高い反応性を有することが明らかとされ、位置選択的分子変換が達成されてきた [11]。



Scheme 2-1. Dirhodium-Catalyzed Intermolecular C(sp^3)-H Amination

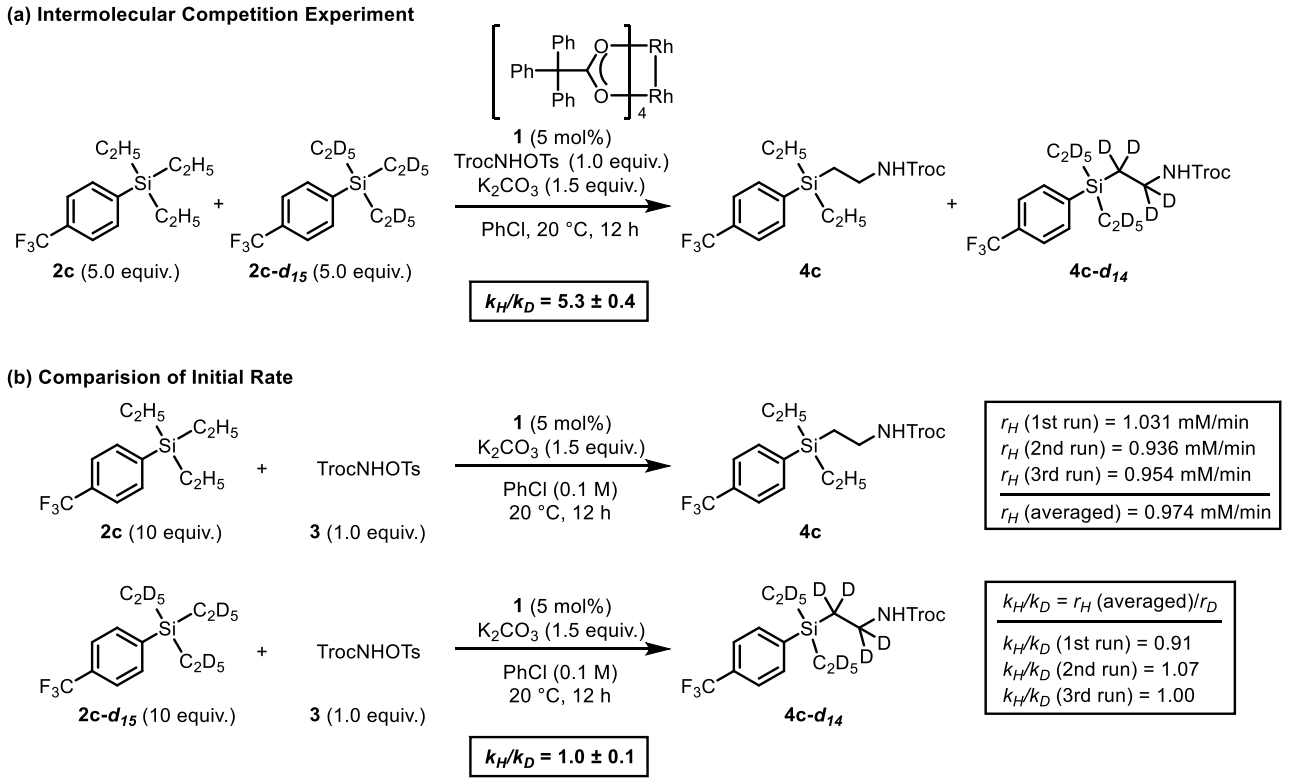
所属研究室ではロジウムナイトレン錯体を活性種としたアルキルシラン類の位置選択的 C-H アミノ化反応に取り組み、シリル基 β 位選択的分子間 C-H アミノ化を開発している **(Scheme 2-2)** [12]。$Rh_2(tpa)_4$ **(1)** 存在下、TrocNHOTs **(3)** に対して β 位に第一級 C-H 結合を持つエチルシラン類を作用させると、位置選択的に C-H アミノ化が進行する **(Scheme 2-2 (a))**。C-Si 結合の高い電子供与性に着目することで、これまでに報告例のないシリル基 β 位での分子間 C-H アミノ化を達成しており [13]、著者は本系の詳細な機構に関して知見を得るべく、以下の二つの課題を設定し反応機構解析に取り組んだ。第一に、速度論的同位体効果 (KIE) の測定による律速段階の決定を試みた。TrocNHOTs をアミノ化剤とする C(sp^3)-H アミノ化反応の律速段階は明らかになっておらず、種々の手法により KIE を測定することで律速段階を推定した。二つ目に、DFT 計算を用いた C-H 挿入段階の解析を行った。C-H 挿入段階の遷移状態を求めるとともに、遷移状態における NBO 解析を行い、シリル基の β 効果が反応に及ぼす影響を見積もった。また、本系は収率良く反応を進行させるために過剰のアルキルシランを必要とすること、第二級炭素の C-H 結合に対しては収率が低下することなどの課題を残していた **(Scheme 2-2 (b))**。著者は本系の不斉反応への展開を志向して本課題の解決にも取り組み、反応機構解析により存在が示唆された副反応の解析を行うとともに、より効率的な第二級炭素の C-H 結合アミノ化法の開発を行った。



Scheme 2-2. Dirhodium-Catalyzed Intermolecular C(sp^3)-H Amination at β Position of Si Atoms

第二節　速度論的同位体効果

始めに、シリル基 β 位選択的 C-H アミノ化の律速段階について考察するために、速度論的同位体効果の測定を行った (**Scheme 2-3**)。**2c** 及び **2c-*d*$_{15}$** の等量混合物を基質として C-H アミノ化の分子間競争実験を行ったところ、**4c** が 46−47%収率、**4c-*d*$_{14}$** が 9−10%収率で得られた。H 体の方が速く反応が進行し、k_H/k_D の値は 5.3 ± 0.4 となったことから (**Scheme 2-3 (a)**)、 C-H 結合切断段階は位置選択性の決定段階であることが分かった。一方で、**2c** 又は **2c-*d*$_{15}$** を単独の基質として用い、それぞれの基質の C-H アミノ化の反応速度論解析を行ったところ、k_H/k_D の値は 1.0 ± 0.1 となり、一次の速度論的同位体効果は観測されなかった (**Scheme 2-3 (b)**)。本結果より、C-H 結合切断段階は本系における律速段階ではないことが明らかになった。



Scheme 2-3. Kinetic Isotope Effects

第三節　推定反応機構

本反応の推定反応機構を以下に記述する **(Figure 2-2)** [11c, d, 14]。初めに、ロジウム二核錯体触媒と TrocNHOTs 及び塩基が反応することで、ロジウムナイトレン錯体が生成する。生じたロジウムナイトレン錯体が β 位 C-H 結合に挿入し、生成物である β-アミノシランを与える。反応速度解析により、C-H 挿入段階は位置選択性決定段階である一方で、律速段階ではないことが示された。律速段階は、ロジウムナイトレン錯体の生成段階あるいは、生成物の解離による触媒の再生段階の二つの可能性があるが、不安定化学種であるロジウムナイトレン錯体の生成段階と想定している。

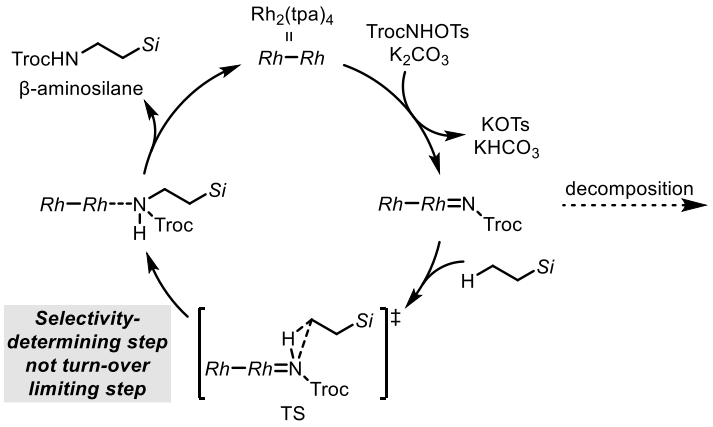


Figure 2-2. Proposed Catalytic Cycle

第四節　遷移状態解析

本系における位置選択性決定段階である C-H 挿入段階の基質、生成物と遷移状態の構造及びそれらの自由エネルギー差を DFT 計算により求めた (**Figure 2-3**)。配座自由度の低さ及び計算コストの面から、1,1-ジメチルシラシクロペンタンと $Rh_2(OAc)_4$ をモデルとして、一重項または三重項状態のロジウムナイトレン錯体についてそれぞれの構造最適化を行った。その結果、一重項状態のロジウムナイトレン錯体から導かれた遷移状態は ($\Delta G^{\ddagger}$ = 10.9 kcal/mol)、三重項状態のロジウムナイトレン錯体から導かれた遷移状態よりも低い活性化自由エネルギーを有しており ($\Delta G^{\ddagger}$ = 13.3 kcal/mol)、C-H 挿入段階は一重項状態のロジウムナイトレン錯体を経由して進行していることが示唆された。

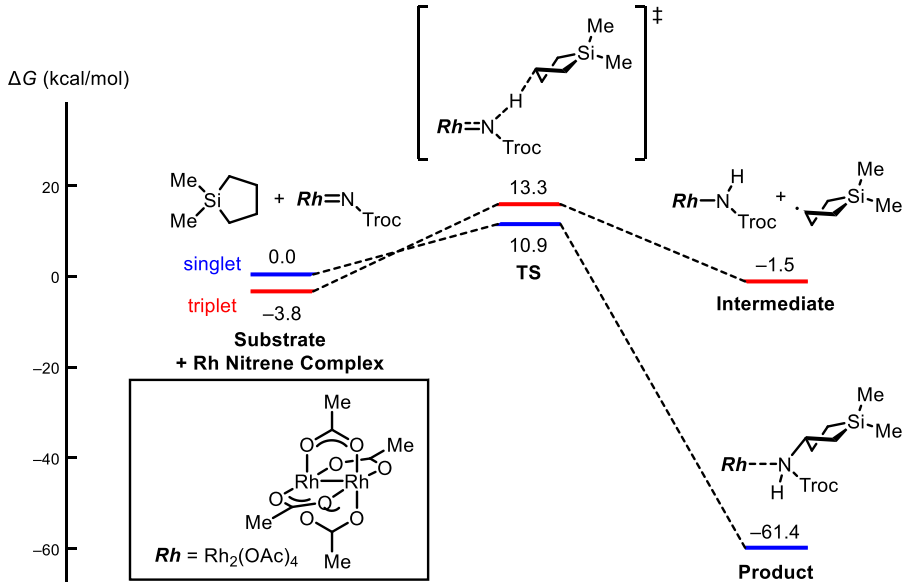


Figure 2-3. DFT Calculation on C-H Insertion Step

一重項ロジウムナイトレン錯体を経由する C-H 挿入段階の遷移状態構造を **Figure 2-4** に示す。**Figure 2-3** に図示した通り C-H 挿入反応は協奏的に進行するが、遷移状態における N-H-C 角は 152°であり、ヒドリドトランスファー及び C-N 結合形成が非同期的な協奏的機構により進行していることが示唆された。また、遷移状態における NBO 解析を行った所、C-Si 結合から $\sigma^*_{C\text{-}H}$ 軌道への電子供与による安定化相互作用は 4.07 kcal/mol だった (**Figure 2-4 (b)**)。これと比較して、炭素類縁体である 1,1-ジメチルシクロペンタンの C-H 挿入段階の遷移状態構造を別途計算し、同様に NBO 解析を行った (**Figure 2-4 (c)**)。炭素類縁体の遷移状態はより高い活性化自由エネルギーを有しており ($\Delta G^{\ddagger}$ = 12.9 kcal/mol)、C-C 結合から $\sigma^*_{C\text{-}H}$ 軌道への電子供与による安定化相互作用は 2.12 kcal/mol であった。これら二つの遷移状態間の活性化自由エネルギー差は ($\Delta\Delta G^{\ddagger}$ = 2.00 kcal/mol)、C-Si 結合及び C-C 結合から $\sigma^*_{C\text{-}H}$ 軌道への電子供与による安定化相互作用の差と近しく ($\Delta\Delta G_{stablization}^{\ddagger}$ = 1.95 kcal/mol)、軌道相互作用による安定化の差が遷移状態のエネルギー差として反映されていると考えられる。以上の結果より、シリル基の β 効果が位置選択性発現の鍵であることが支持された。

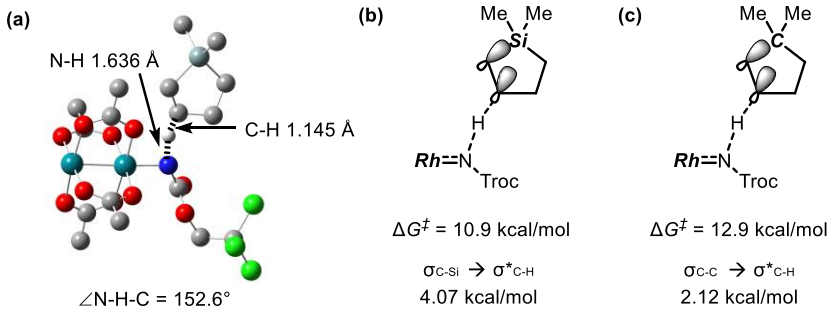
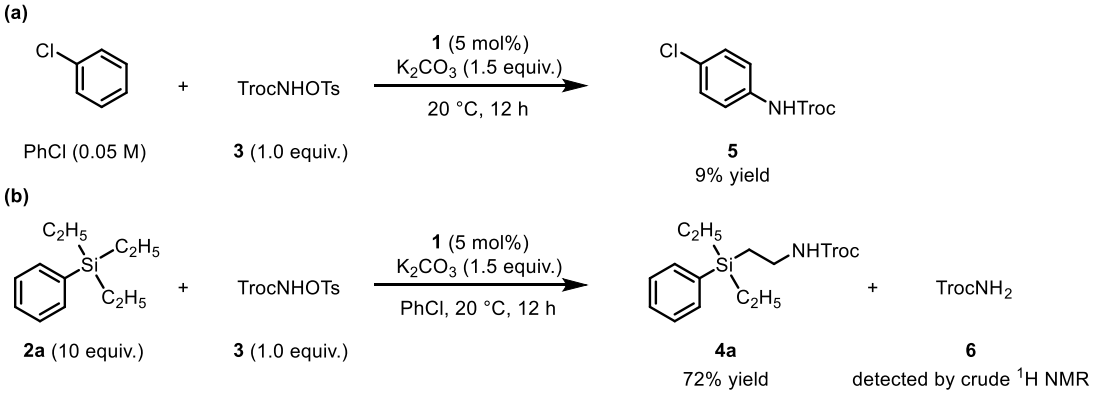


Figure 2-4. Calculated Transition State Structures on C-N Bond Formation Steps

第五節　副反応の解析

本系においては C-H 挿入段階が律速段階でないにもかかわらず、高収率で目的物を得るには高濃度のアルキルシランを用いる必要がある。これは、ロジウムナイトレン錯体形成後に、アルキルシランの C-H アミノ化反応の他に競合する副反応が存在することを示唆している。そこで、アルキルシランを用いずに、触媒 **1** 存在下、**3** 及び塩基をクロロベンゼン中攪拌した所、僅かながら溶媒であるクロロベンゼンに対して C(sp^2)-H アミノ化が進行し **5** の生成が確認された **(Scheme 2-4 (a))**。所属研究室ではアニソール類のパラ位選択的 C(sp^2)-H アミノ化を報告しており [15]、溶媒量のクロロベンゼンに対しても同様の C(sp^2)-H アミノ化が進行したと考えられる。また、トリエチルフェニルシラン **2a** に対する反応を詳細に解析した所、**3** が分解した生成物である $TrocNH_2$ **(6)** が副成していることがわかった **(Scheme 2-4 (b))** [16]。以上の結果より、ロジウムナイトレン錯体は短寿命中間体であり、高収率で C-H アミノ化体を得るには充分量のアルキルシランを用いて速やかに捕捉する必要があると判明した。



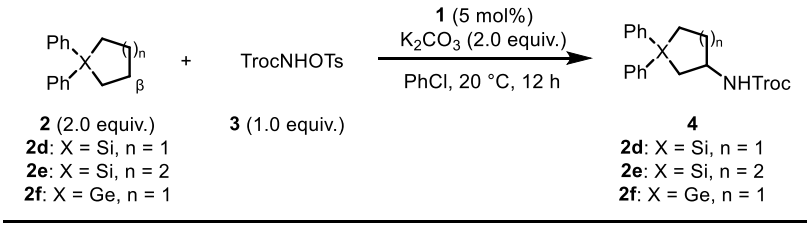
Scheme 2-4. Analysis of Side Reaction

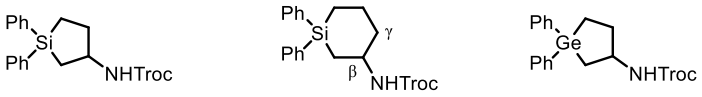
第六節　環状アルキルシランの C-H アミノ化

著者は反応性の高い基質を用いることで副反応を抑制し、基質量の低減が可能であると考えた。本系においてはシリル基 β 位第二級炭素の C-H 結合は反応性が低く、低収率でアミノ化体を与えることが報告されている一方で **(Scheme 2-2 (b))**、金属カルベン錯体や金属ナイトレン錯体による C-H 挿入反応では、環状基質が高い反応性を示すことが報告されている [11, 17]。そこで、環内にケイ素またはゲルマニウムを有する **2d–f** を合成し反応性の評価を行った **(Table 2-1)**。

触媒 **1** 存在下 **3** に対して 2 当量の 1,1-ジフェニルシラシクロペンタン **(2d)** を作用させると、アミノ化体 **4d** が 88%収率で得られた。また、1 当量の **2d** を用いた場合でも **4d** は 60%収率で得られ、**2d** がロジウムナイトレン錯体による C-H 挿入反応に対して高い反応性を持つことが明らかとなった。シラシクロヘキサン **(2e)** を用いた場合は、高い位置選択性を伴って C-H アミノ化が進行し 89%収率でアミノ化体 **4e** が得られた。また、1,1-ジフェニルゲルマシクロペンタン **(2f)** を用いた場合も高収率でアミノ化体 **4f** が得られた。以上の結果より、環内に高周期 14 族元素を有する基質を用いることで、第二級炭素の C-H 結合への高効率な C-H アミノ化が可能であることを見出し、基質量の低減を達成した。

Table 2-1. Dirhodium-Catalyzed C(sp^3)-H Amination of Cyclic Alkylsilanes and Alkylgermanes





4d
88% yield
60% yield with 1.0 equiv of **2b**

4e
89% yield (β:γ= 25:1)

4f
71% yield

鎖状アルキルシラン及び環状アルキルシランの反応性の違いについては以下のように考察している(**Figure 2-5**)。ケイ素原子のβ効果は、C-Si 結合と C-H 結合がアンチペリプラナーに位置する時最大になるとされる[18]。しかし、鎖状化合物である **2b** では、シリル基とメチル基が立体反発を避けるようアンチペリプラナーに位置する配座が安定となるため、β位 C-H 結合が $\sigma_{C\text{-}Si}$ 軌道からの電子供与を効率的に受けることが出来ず、低い反応性を示すと考えられる (**Figure 2-5 (a)**)。一方で、環状化合物である **2d** においては配座が固定されていることから、β位 C-H 結合が $\sigma_{C\text{-}Si}$ 軌道からの電子供与を受けて活性化され、高い反応性を示したと考えられる (**Figure 2-5 (b)**)。DFT 計算により **2d** の軌道エネルギーを解析したところ、HOMO が芳香環や C-Si 結合に加えてβ位の擬エクアトリアル位 C-H 結合に広がっており、基底状態においてもβ位 C-H 結合が活性化されていることが示唆された。

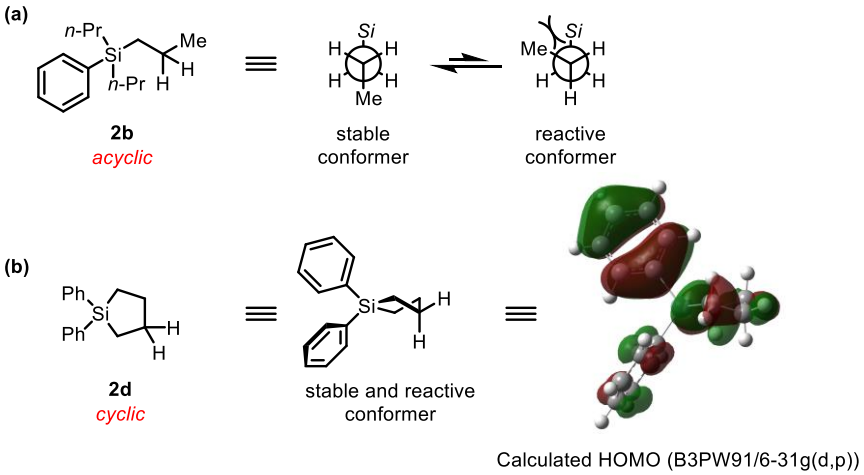


Figure 2-5. Evaluation of Reactivity of Silacyclopentane

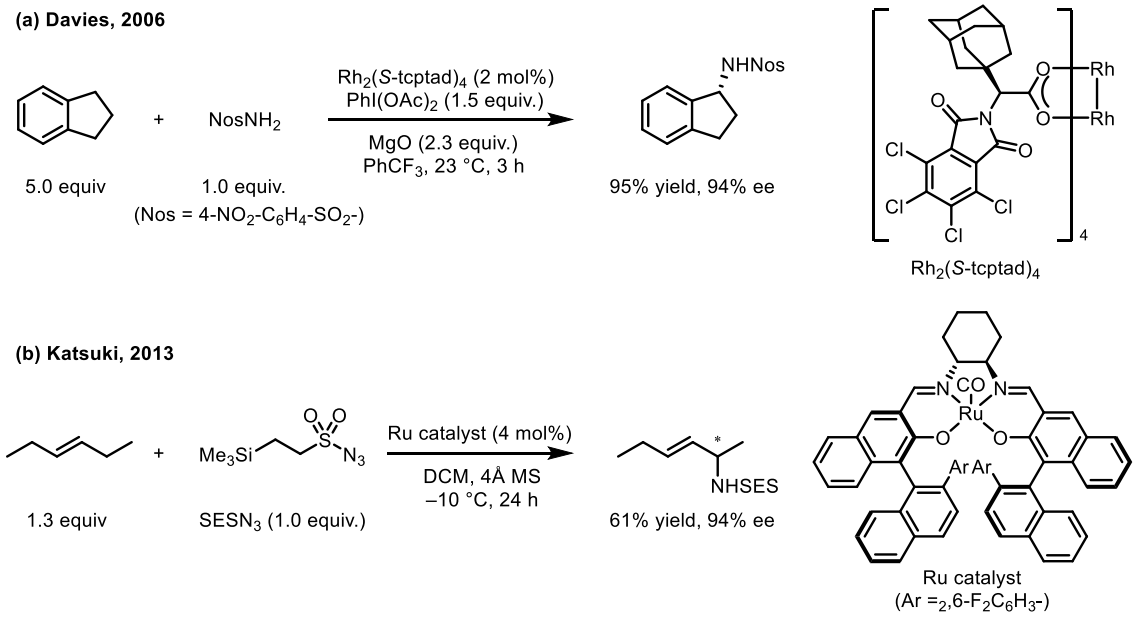
第七節　結論

ロジウムナイトレン錯体を活性種とするシリル基β位 C(sp^3)-H アミノ化の反応機構解析を行うとともに、環内にケイ素を有する基質が本系において高い反応性を持つことを見出し、基質量の低減を達成した。また、C-H 挿入段階について DFT 計算による解析を行った結果、本反応の進行に C-Si 結合の高い電子供与性が重要であることが示唆された

第三章　キラル Rh 触媒を用いるエナンチオ選択的シリル基 β 位 C(sp^3)-H アミノ化

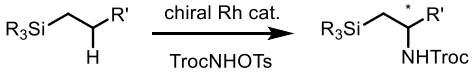
第一節　研究背景と著者の研究方針

エナンチオ選択的 C(sp^3)-H アミノ化は脂肪族化合物を直接光学活性アミンへと変換する強力な手法であり [19]、特に分子内反応において様々な金属及び不斉配位子を用いた手法が開発されてきた [20]。一方、分子間反応ではエナンチオ選択性に加えて位置選択性を制御する必要があり、その報告例は限られる [21]。Davies らはアダマンチル基を有する Rh_2(*S*-tcptad)$_4$ 存在下、系中でイミノヨージナンを発生させることでインダンのベンジル位 C-H 結合に対してエナンチオ選択的に C-H アミノ化が進行することを報告している(**Scheme 3-1 (a)**)[21a]。香月らはルテニウムサレン錯体存在下 $SESN_3$ に対して *trans*-3-ヘキセンを作用させることで、アリル位 C-H 結合に対してエナンチオ選択的に C-H アミノ化が進行することを報告している(**Scheme 3-1 (b)**)[21g]。アリル位に対する C-H アミノ化ではアルケンのアジリジン化が競合し得るが、本系では C-H アミノ化が優先的に進行する。しかし、これまでに報告されてきた分子間エナンチオ選択的 C-H アミノ化は、適用可能な基質がベンジル位又はアリル位 C-H 結合を反応点とするものに限られていた。



Scheme 3-1. Metal-Catalysed Intermoluculer Asymmetric C(sp^3)-H Amination

このような背景のもと、著者は Rh 触媒を用いるエナンチオ選択的シリル基 β 位 C(sp^3)-H アミノ化の検討を行うこととした。著者は第二章にて Rh 触媒を用いるシリル基 β 位選択的 C(sp^3)-H アミノ化に関する研究を行ったが、ケイ素の医薬品候補化合物への導入を志向し、本系をエナンチオ選択的反応へと展開することで、アルキルシランから直接光学活性アミンを合成するこれまでにない分子変換法を提示できると考えた (**Scheme 3-2**)。

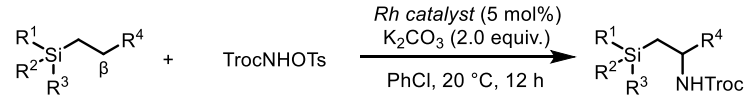


Scheme 3-2. Intermolecular Asymmetric C-H Amination at β Position of Silicon

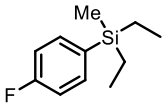
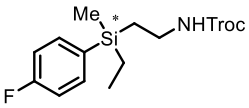
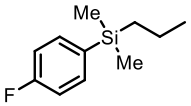
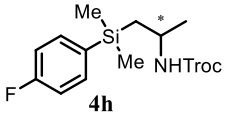
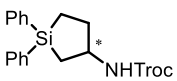
第二節　初期検討

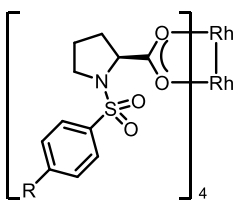
代表的な骨格の不斉 Rh 二核錯体として、プロリン由来の配位子を持つ Rh_2(*S*-dosp)$_4$ (**7**)[22a]、シクロプロパン型の配位子を持つ Rh_2(*S*-btpcp)$_4$ (**8**)[22b]、*tert*-ロイシン由来の配位子を持つ Rh_2(*S*-pttl)$_4$ (**9**)[22c] を用いて、TrocNHOTs (**3**) をナイトレン源とする不斉反応の検討を行った (**Table 3-1**)。シリル基 β 位に第一級 C-H 結合を持ち、プロキラルケイ素原子を有する **2g** を用いた場合、触媒 **7** では反応が進行せず (entry 2)、触媒 **8** または **9** を用いた場合アミノ化体 **4g** が得られたが、エナンチオ選択性の発現はほとんど見られなかった (entries 3 and 4)。そこで、シリル基 β 位第二級炭素に C-H 結合を有する基質の検討を試みた。フェニルトリプロピルシラン **2b** は立体効果により反応性が下がっていると考えられるため (**Table 2-1**)、シリル基上の立体障害が小さいアリールジメチルプロピルシラン **2h** について反応性を評価した。Rh_2(tpa)$_4$ (**1**) 存在下、**3** に対して 1.5 当量の **2h** を作用させると 39%収率でアミノ化体 **4h** が得られ、想定通り **2h** が十分な反応性を有していることが分かった (entry 5)。種々触媒を検討した結果、触媒 **9** を用いた場合にアミノ化体 **4h** が 48%収率、31% ee で得られ、シリル基 β 位第二級炭素に C-H 結合を持つ基質がエナンチオ選択的 C-H アミノ化に適している可能性が示唆された (entry 8)。そこで、高い反応性を有しており、配座自由度の低い環状アルキルシラン **2d** を用いて種々の触媒を検討した所、触媒 **9** を用いた場合にアミノ化体 **4d** が 90%収率、50% ee で得られた (entry 12, 絶対配置は未決定)。

Table 3-1. Initial Attempt of Asymmetric Primary or Secondary C-H Amination

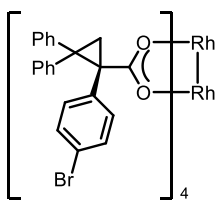


2 (1.5-10 equiv.)　　**3** (1.0 equiv.)　　**4**

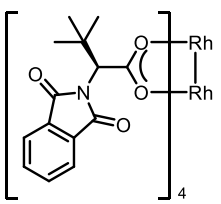
entry	substrate (**2**)	product (**4**)	Rh catalyst	yield	ee
1			**1**	51%	—
2			**7**	no reaction	
3			**8**	27%	0%
4	**2g** (10 equiv.)	**4g**	**9**	46%	2%
5			**1**	39%	—
6			**7**	no reaction	
7			**8**	20%	–3%
8	**2h** (1.5 equiv.)	**4h**	**9**	48%	31%
9			**1**	88%	—
10			**7**	no reaction	
11			**8**	76%	10%
12	**2d** (2.0 equiv.)	**4d**	**9**	90%	50%



Rh_2(*S*-dosp)$_4$ (**7**)
R = $C_{12}H_{25}$



Rh_2(*S*-btpcp)$_4$ (**8**)

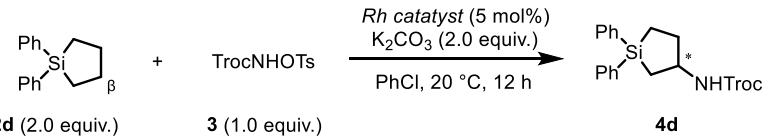


Rh_2(*S*-pttl)$_4$ (**9**)

第三節　反応条件の最適化

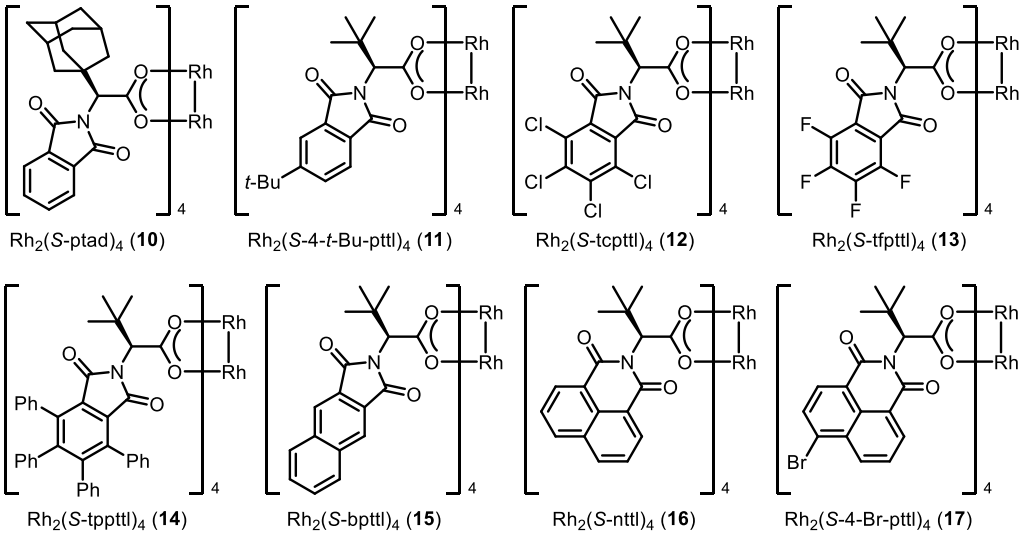
触媒 **9** の構造類縁体を用いて、**2d** のエナンチオ選択的アミノ化の検討を行った (**Table 3-2**)。*t*-Bu 基がアダマンチル基で置換された Rh_2(*S*-ptad)$_4$ (**10**) [22d] を用いた場合はエナンチオ選択性が僅かに低下した (entry 1)。フタロイル基上に *t*-Bu 基や複数のハロゲン、フェニル基などを導入した触媒 **11**−**14** [21a, 22e-g] についても検討を行ったが、いずれの場合も収率及びエナンチオ選択性の低下を招いた (entries 2−5)。一方、ナフタロイル基を持つ触媒 **15**−**17** [22h-j] を用いるとエナンチオ選択性が向上し (entries 6−8)、Müller らによって開発された Rh_2(*S*-nttl)$_4$ (**16**) を用いた場合にアミノ化体 **4d** が 93%収率、60% ee と最も良いエナンチオ選択性で得られた (entry 7)。

Table 3-2. Catalyst Screening for Asymmetic C-H Amination of **2d**



2d (2.0 equiv.)　　**3** (1.0 equiv.)　　**4d**

entry	Rh catalyst	yield	ee
1	**10**	83%	47%
2	**11**	63%	45%
3	**12**	53%	32%
4	**13**	76%	29%
5	**14**	27%	40%
6	**15**	88%	56%
7	**16**	93%	60%
8	**17**	95%	59%

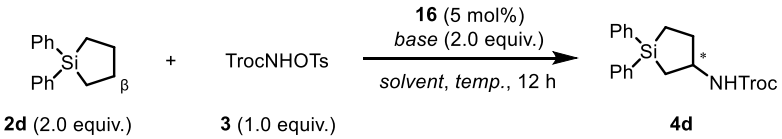


Rh_2(*S*-ptad)$_4$ (**10**)　Rh_2(*S*-4-*t*-Bu-pttl)$_4$ (**11**)　Rh_2(*S*-tcpttl)$_4$ (**12**)　Rh_2(*S*-tfpttl)$_4$ (**13**)

Rh_2(*S*-tpptl)$_4$ (**14**)　Rh_2(*S*-bpttl)$_4$ (**15**)　Rh_2(*S*-nttl)$_4$ (**16**)　Rh_2(*S*-4-Br-pttl)$_4$ (**17**)

エナンチオ選択性の向上を目的として、触媒 **16** を用いて反応条件の精査を行った (**Table 3-3**)。含ハロゲン溶媒であるジクロロメタンやテトラクロロエタンを用いると、エナンチオ選択性は僅かに向上したものの収率の低下を招いた (entries 2 and 3)。ベンゼンやトリフルオロトルエンを用いた場合はクロロベンゼンを用いた際と同等の収率及びエナンチオ選択性で反応が進行した (entries 4 and 5)。酢酸エチルを用いた場合は収率、エナンチオ選択性共に低下した (entry 6)。また、塩基として酢酸カリウムや炭酸セシウムを用いた場合も立体選択性の向上は見られなかった (entries 7 and 8)。以上の検討より、溶媒及び塩基は反応のエナンチオ選択性に大きな影響を与えないことが示唆された。また、クロロベンゼン中−20℃での反応も検討したが、収率の大幅な低下を招き、エナンチオ選択性が僅かに向上するに留まった (entry 9)。

Table 3-3. Effects of Solvents, Bases and Temperature on Enantioselectivity of Asymmetric C-H Amination

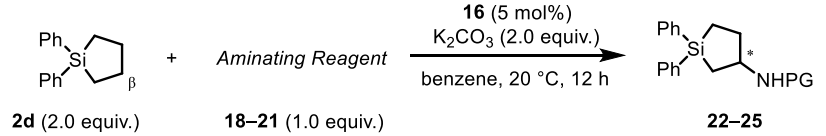


2d (2.0 equiv.) **3** (1.0 equiv.) **4d**

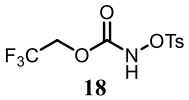
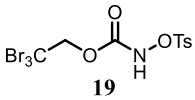
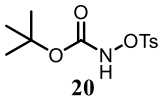
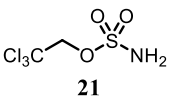
entry	solvent	base	temp.	yield	ee
1	PhCl	K_2CO_3	20 °C	93%	60%
2	CH_2Cl_2	K_2CO_3	20 °C	66%	64%
3	$(CHCl_2)_2$	K_2CO_3	20 °C	59%	67%
4	benzene	K_2CO_3	20 °C	90%	63%
5	$PhCF_3$	K_2CO_3	20 °C	94%	62%
6	AcOEt	K_2CO_3	20 °C	76%	52%
7	benzene	KOAc	20 °C	80%	61%
8	benzene	Cs_2CO_3	20 °C	99%	62%
9	PhCl	K_2CO_3	–20 °C	26%	67%

次に、用いるアミノ化剤について検討を行った (**Table 3-4**)。1,1,1-トリフルオロエチルカーバメート (**18**) や、1,1,1-トリブロモエチルカーバメート (**19**) を用いた場合は TrocNHOTs (**3**) を用いた場合と同等のエナンチオ選択性で C-H アミノ化が進行した。また、BocNHOTs (**20**) を用いた場合は反応が進行せず、Lebel らの報告にあるように分子内反応が優先して進行したものと考えられる [11d]。Du Bois らの報告を参考に、$ToesNH_2$ (**21**) と $PhI(OAc)_2$ を用いて系中でイミノヨージナンを生成させる系での反応も試みたが [11b]、エナンチオ選択性は顕著に低下し、カーバメート型構造がエナンチオ選択性の発現に重要であることが示唆された。

Table 3-4. Effects of Aminating Reagents on Enantioselectivity of Asymmetric C-H Amination



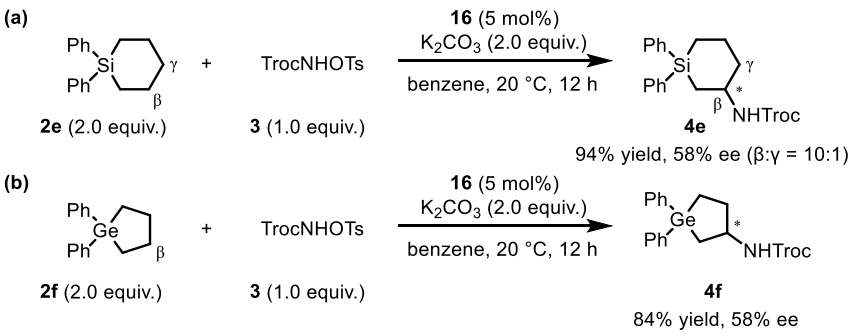
2d (2.0 equiv.) **18–21** (1.0 equiv.) **22–25**

amination reagent				
	18	**19**	**20**	**21**
results	76% yield, 58% ee	94% yield, 61% ee	not detected	78% yield, 3% ee[a]

[a] $PhI(OAc)_2$ (1.5 equiv.) was used instead of K_2CO_3.

第四節　基質一般性の検討

シラシクロヘキサン及びゲルマシクロペンタンのエナンチオ選択的 C-H アミノ化の検討を行った。触媒 **16** 存在下、ベンゼン中で **3** にシラシクロヘキサン **2e** を作用させると、C-H アミノ化は β 位選択的に進行し (β:γ= 10:1)、**4e** を 94%収率、58% ee で与えた (**Scheme 3-3 (a)**)。また、ゲルマシクロペンタン **2f** を用いた場合も C-H アミノ化は中程度のエナンチオ選択性で進行し、**4f** が 84%収率、58% ee で得られた (**Scheme 3-3 (b)**)。以上の結果より、14 族元素を環内に有する基質に対して、中程度のエナンチオ選択性を伴い高収率で C-H アミノ化が進行することが明らかとなった。



2e (2.0 equiv.) **3** (1.0 equiv.) **4e**

94% yield, 58% ee (β:γ = 10:1)

2f (2.0 equiv.) **3** (1.0 equiv.) **4f**

84% yield, 58% ee

Scheme 3-3. Asymmetric C-H Amination of Silacyclohexane **2e** and Germacyclopentane **2f**

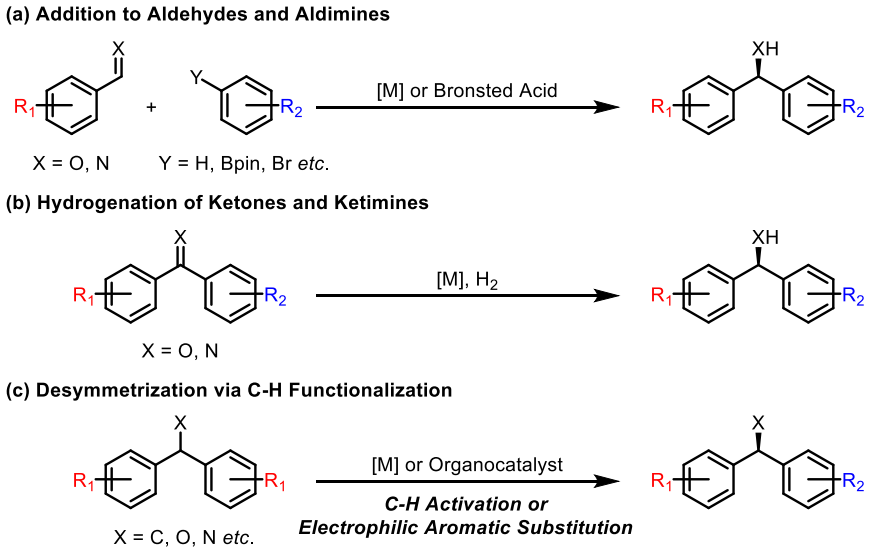
第五節　結論

開発したシリル基 β 位選択的 C(sp^3)-H アミノ化の不斉反応への展開を行い、アルキルシランの直接的な光学活性アミノシランへの変換を達成した。不斉ロジウム二核錯体触媒を用いることで、環内にケイ素を有する基質に対する C(sp^3)-H アミノ化が、高い位置選択性を伴いながら中程度の不斉収率で進行する。

第四章　芳香族臭素化による σ-対称 1,1-ジアリールメチルアミンの不斉非対称化

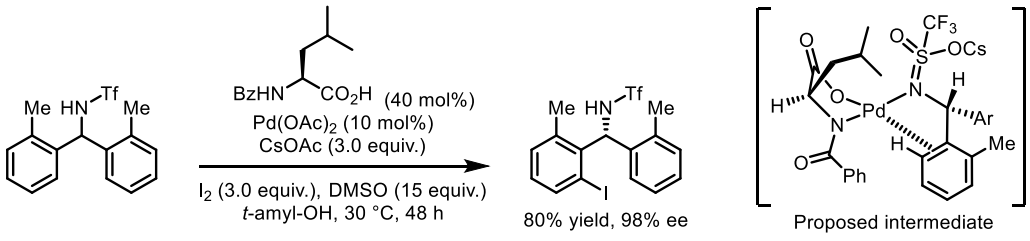
第一節　研究背景と著者の研究方針

光学活性ジアリールメチン類は医薬品に多く含まれる部分構造であり [23]、効率的不斉合成法の開発は創薬化学における重要な課題の一つである [24]。その構築法は 3 つに大別され、アルデヒド及びアルドイミンに対する求核付加や **(Scheme 4-1 (a))** [25]、ケトン及びケチミンの不斉水素化を用いることで光学活性ジアリールメチン類の合成が達成されてきた **(Scheme 4-1 (b))** [26]。一方、近年では新たな方法論として、芳香族官能基化を伴う σ-対称ジアリールメチン化合物の不斉非対称化が精力的に研究されている **(Scheme 4-1 (c))** [27-30]。



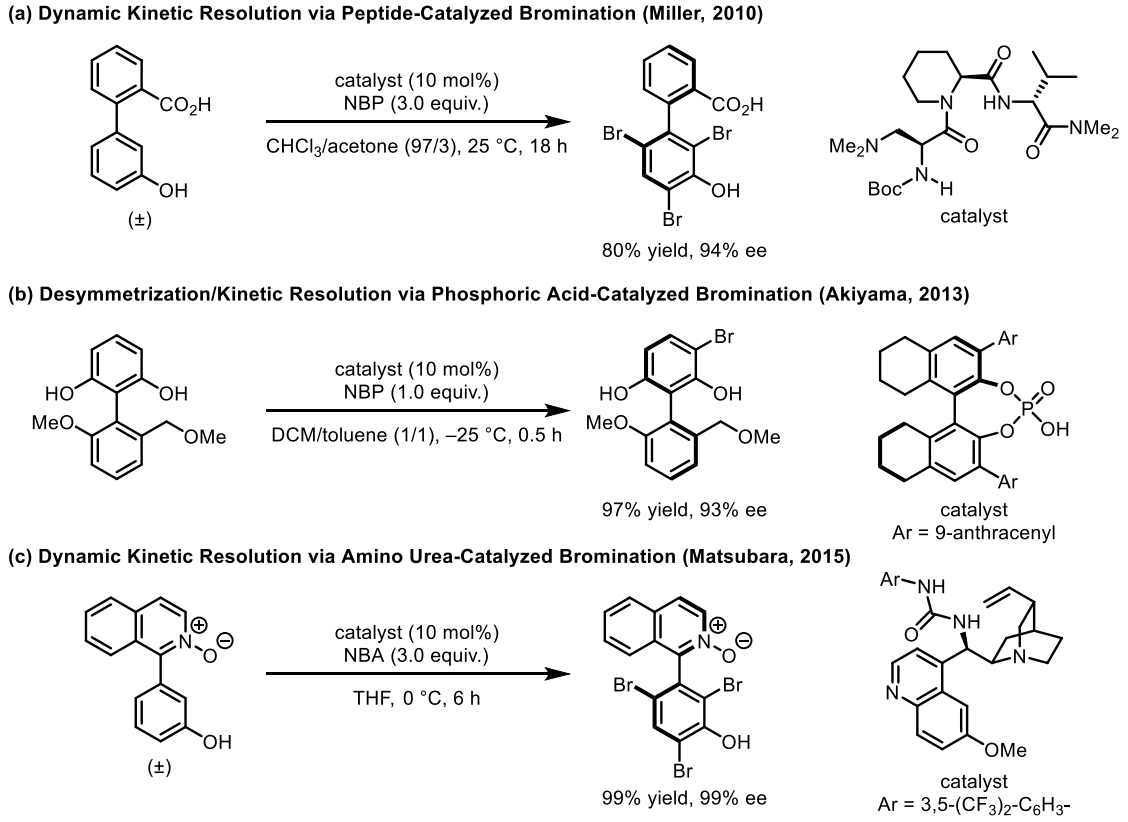
Scheme 4-1. Synthetic Approaches toward Optically Active Diarylmethines

2013 年、Yu らはパラジウムを用いた σ-対称ジアリールメチルアミンのエナンチオ選択的 C-H ヨウ素化を報告している **(Scheme 4-2)** [28a]。プロキラル炭素に直結したスルホンアミドが配位性配向基として働くことで、近傍のオルト位 C-H 結合がアミノ酸リガンドのキラリティを反映してエナンチオ選択的に活性化された後、炭素-ヨウ素結合が生成すると考えられる。この報告を皮切りに、遷移金属による C-H 活性化を経る σ-対称ジアリールメチルアミンの不斉非対称化が多数報告されたが [27, 28]、殆どの場合反応点はプロキラル炭素近傍であるオルト位に限られており、より多様な骨格構築の為に新規な方法論の開発が求められている。



Scheme 4-2. Metal-Catalyzed Desymmetrization via C-H Activation Pathway

電子豊富芳香環のハロゲン化は古典的な芳香環の修飾法であり [31]、有機分子触媒を用いたハロゲン化による軸不斉の制御法がこれまでに開発されてきた [32]。Miller らはペプチド触媒を用いた臭素化によるキラルビアリール化合物の合成を報告している (**Scheme 4-3 (a)**)[32a]。室温で容易にラセミ化するビアリール化合物に対してペプチド触媒存在下 *N*-ブロモフタルイミド (NBP) を作用させると、フェノール環の臭素化により動的速度論的光学分割が起こり、エナンチオ選択的にビアリール化合物が得られる。秋山らはリン酸触媒を用いた σ-対称ビアリール化合物のエナンチオ選択的臭素化を報告している (**Scheme 4-3 (b)**) [32c]。計算的手法によりリン酸触媒が二官能基性触媒として働き、ブレンステッド酸として NBP を活性化するとともに、ブレンステッド塩基としてフェノールを活性化する機構を実験及び計算の両面から提唱している。松原らは二官能基性アミノウレア触媒を用いた臭素化によるキラルビアリール化合物合成を報告している (**Scheme 4-3 (c)**) [32d]。軸不斉を有するイソキノリン *N*-オキシドに対して触媒存在下 *N*-ブロモアセトアミド (NBA) を作用させることで動的速度論的光学分割によりエナンチオ選択的にビアリール化合物が得られる。



Scheme 4-3. Precedents of Organocatalytic Enantioselective Halogenation of Biaryl Compounds

しかし、不斉ハロゲン化による軸不斉の制御法は多数報告例がある一方で、二つの芳香環の間にプロキラル炭素を有する σ-対称ジアリールメチン類のエナンチオ選択的ハロゲン化の報告は酵素法を含めて僅か 3 例に留まる [29, 30]。σ-対称ジアリールメチン類は、代表的な軸不斉を有する化合物であるビアリール化合物と比較して配座自由度が高く、プロキラル中心からより遠くに反応点を有する。そのため、多用される不斉誘導原理である、反応点近傍の立体障害に基づく不斉識別が困難であることが推察される (**Figure 4-1**) [33]。

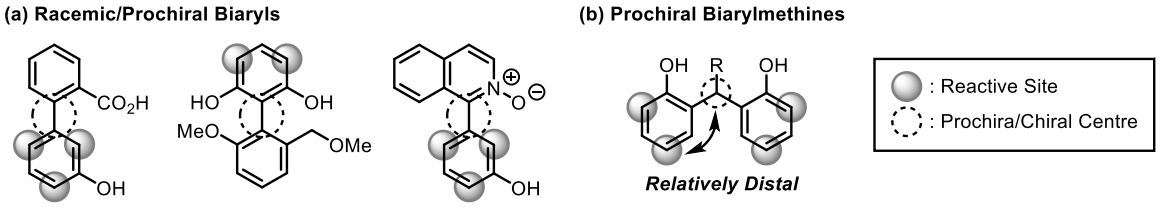
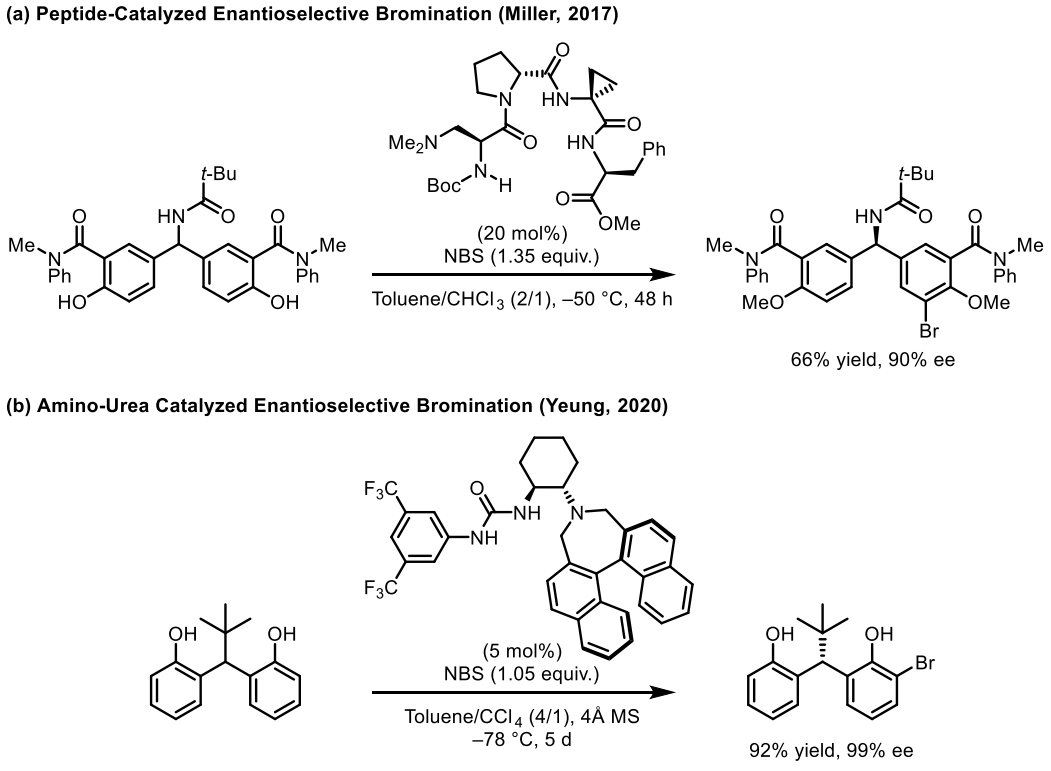


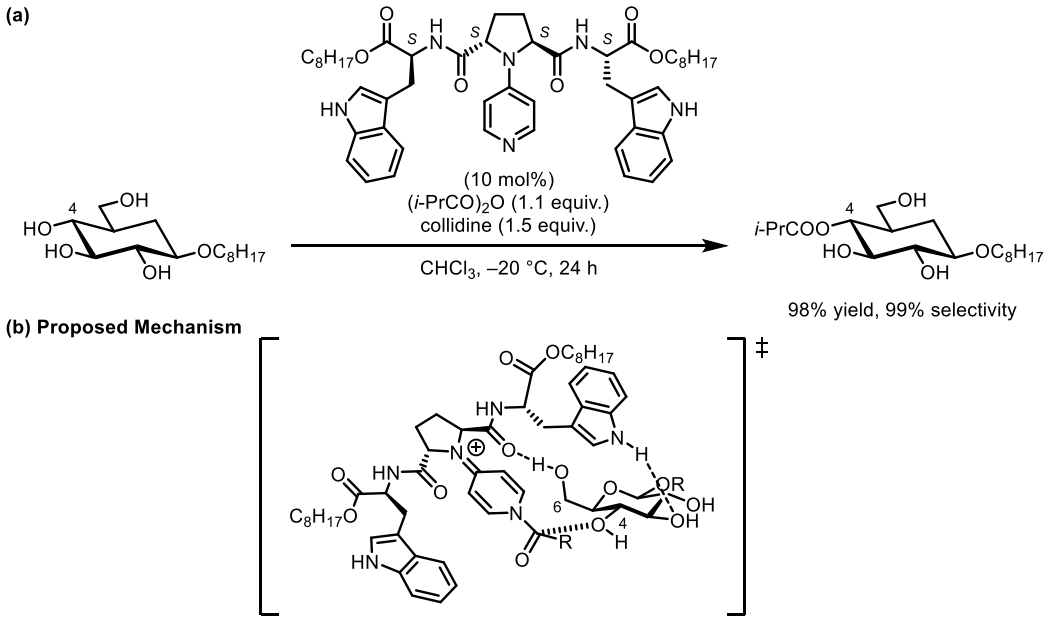
Figure 4-1. Racemic/Prochiral Substrates for Asymmetric Bromination

芳香族ハロゲン化による σ-対称ジアリールメチン化合物の不斉非対称化は電子供与性置換基によって反応位置の制御が容易であり、続くカップリング反応によって設計次第で多様な骨格構築が可能な点で魅力的な分子変換といえる。Miller らはペプチド触媒を用いた σ-対称ジアリールメチルアミンのエナンチオ選択的臭素化を報告している (**Scheme 4-4 (a)**)[29a]。基質のピバルアミド部と触媒官能基の水素結合により、pro-(*R*)側のフェノールが選択的に活性化され、効率的な不斉誘導が起こると提唱されている。2020 年 Yeung らはアミノウレア触媒を用い、*t*-ブチルジアリールメタンの不斉非対称化を報告した (**Scheme 4-4 (b)**)[29b]。本例では、*t*-ブチル基の立体障害及び、触媒－基質間の水素結合によって、エナンチオ選択性に加えて反応位置(オルト位)の制御にも成功している。いずれの報告においても触媒－基質間の水素結合がエナンチオ選択性発現の鍵であると提唱されており、触媒による基質の分子認識に基づく不斉誘導戦略が σ-対称ジアリールメチン類のエナンチオ選択的ハロゲン化に有効である可能性が示されている。



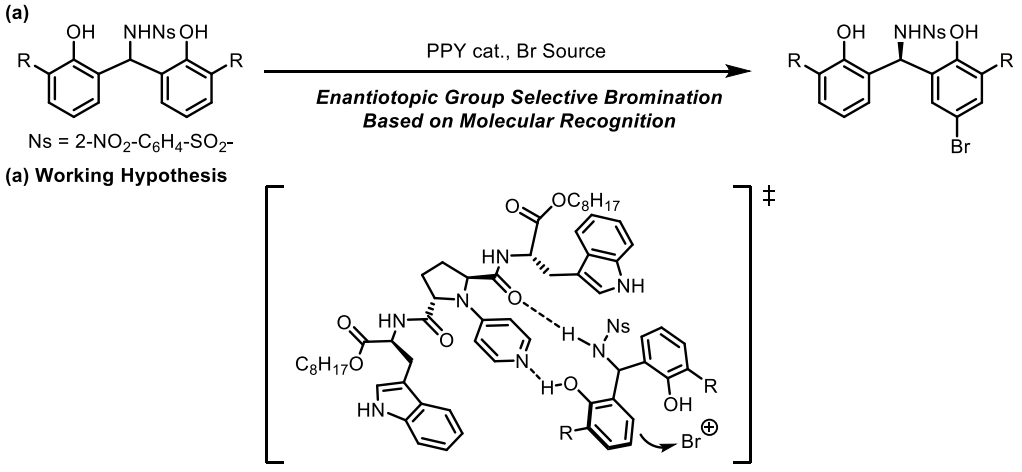
Scheme 4-4. Enantioselective Bromination of Diarylmethines via Electrophilic-Aromatic-Substitution

著者の所属研究室では 4-ピロリジノピリジン (PPY) を母骨格とする分子認識型求核触媒を用いた、グルコース誘導体の位置選択的アシル化を報告している (**Scheme 4-5 (a)**) [34]。本来反応性の高い 6 位第一級水酸基が側鎖アミノ酸のアミドカルボニル基と水素結合することで、より反応性の低い 4 位第二級水酸基が反応点に接近し、化学選択性の逆転を伴った位置選択的アシル化が進行すると想定している (**Scheme 4-5 (b)**)。本法を筆頭として、触媒による分子認識を基盤とした種々のポリオールの位置選択的アシル化が達成されてきた [35]。



Scheme 4-5. Organocatalytic Regioselective Acylation of Glucose Derivative

以上の背景を踏まえ、著者は所属研究室で開発された触媒をブレンステッド塩基触媒として用いることで、芳香族臭素化による σ-対称ジアリールメチルアミンの不斉非対称化が可能ではないかと考えた (**Scheme 4-6**)。フェノール及びスルホンアミドといった複数の酸性プロトンを持つ基質を用いることで触媒と基質が水素結合を介した酸塩基複合体を形成し、二つのエナンチオトピックな芳香環が非対称化されてエナンチオ選択的臭素化が進行すると期待した。

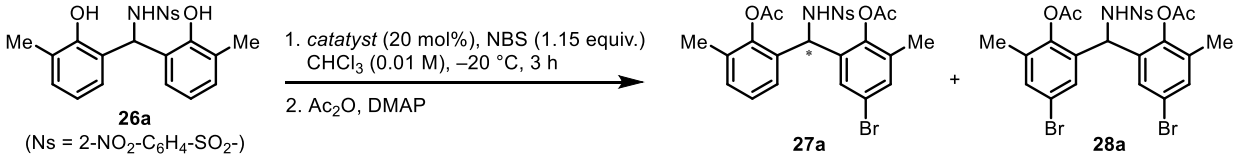


Scheme 4-6. Target Reaction and Working Hypothesis

第二節　反応条件の最適化

二つのフェノール環を有するσ-対称ジアリールメチルアミン **26a** を基質として、種々の側鎖構造を持つ触媒による不斉非対称化の検討を行った (**Table 4-1**)。β-ナフチルアラニン誘導体を側鎖に有する触媒 **29** 存在下、クロロホルム中−20 ℃において *N*-ブロモスクシンイミド (NBS) を作用させたところ、生成するモノ臭素化体、ジ臭素化体及び回収原料が分離困難であったため、フェノールのアセチル化後単離精製を行った。その結果、モノ臭素化体 **27a** が 38%収率、81% ee で得られ、PPY 型触媒が **26a** のエナンチオ選択的臭素化に有効であることが示唆された (entry 1)。続いて触媒 **29** のジアステレオマー触媒 **30** や、トリプトファン誘導体を側鎖に有する触媒 **31** および触媒 **32** についても検討を行った結果 (entries 2－4)、触媒 **31** を用いた場合に最も良いエナンチオ選択性でモノ臭素化体が得られることを見出した (entry 3、47%収率、94% ee)。一方で、*n*-ヘキシルアミド構造を有する触媒 **33** を用いた場合はエナンチオ選択性の低下を招き、アミノ酸側鎖がエナンチオ選択性の発現に重要であることがわかった (entry 5)。また、触媒 **31** のインドール環窒素をメチル化した触媒 **34** を用いた場合、エナンチオ選択性は僅かに低下するに留まり、インドール NH はエナンチオ選択性発現に大きく寄与していないことが明らかとなった (entry 6)。

Table 4-1. Catalyst Screening for Asymmetric Bromination of **26a**

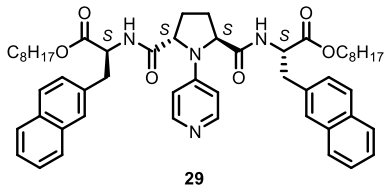


26a
(Ns = 2-NO_2-C_6H_4-SO_2-)

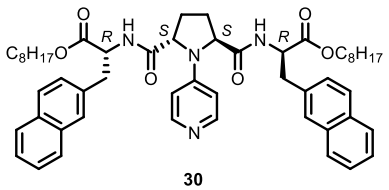
27a　　**28a**

entry	catalyst	**27a**[a]	ee of **27a**	**28a**[a]	**26a-diAc**[a]
1	**29**	38%	81%	43%	25%
2	**30**	41%	88%	26%	32%
3	**31**	47%	94%	34%	12%
4	**32**	32%	–50%	32%	35%
5	**33**	24%	47%	48%	26%
6	**34**	43%	90%	26%	23%

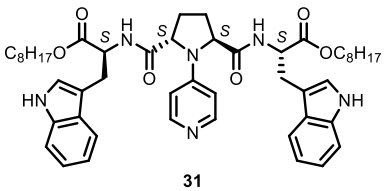
[a]Yield was determined by ^{1}H NMR using 1,3-dinitrobenzene as an internal standard.



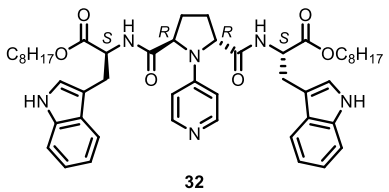
29



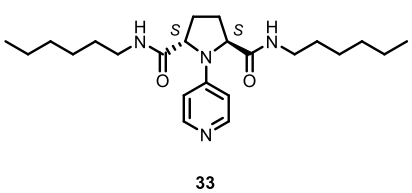
30



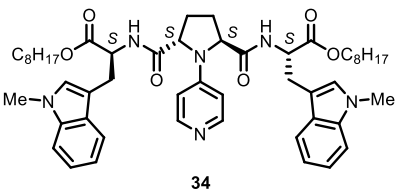
31



32



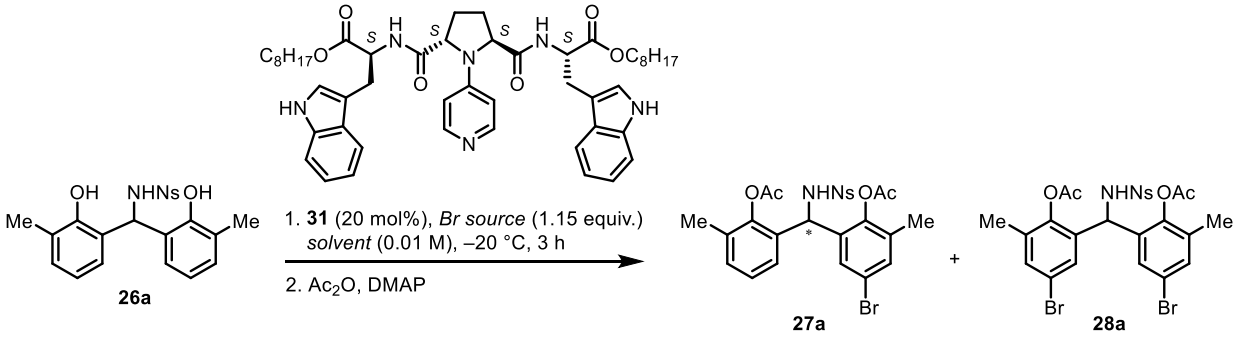
33



34

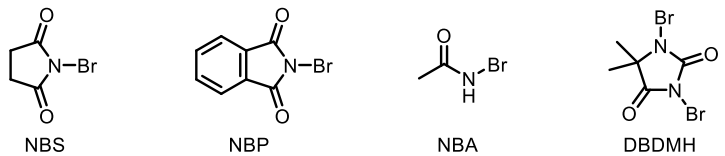
最も良いエナンチオ選択性を示した触媒 **31** を用いて反応条件を精査した (**Table 4-2**)。初めに臭素化剤の検討を行った。NBP を用いた場合はエナンチオ選択性が僅かに低下するに留まった一方で (entry 2)、NBA や 1,3-ジブロモ-5,5-ジメチルヒダントイン (DBDMH) を用いた場合はエナンチオ選択性の顕著な低下を招き (entries 3 and 4)、臭素化剤の構造が不斉誘導に影響を与えることが分かった。続いて、溶媒の検討を行った。低極性溶媒であるジクロロメタン中では、エナンチオ選択性は少し低下したものの、依然として高いエナンチオ選択性でモノ臭素化体が得られた (entry 5)。対して、高極性溶媒である THF や DMF 中で反応を行うとモノ臭素化体はほぼラセミ体として得られるのみであった (entries 6 and 7)。これらの溶媒効果は、本触媒が水素結合を介した相互作用により基質を精密に認識しエナンチオ選択性が誘起されるという仮説と合致する。また、基質の濃度を 0.005 M まで薄めた場合、収率及びエナンチオ選択性が僅かに向上した (entry 8)。

Table 4-2. Effects of Brominationg Reagents and Solvent on Enantioselectivity of Asymmetric Bromination



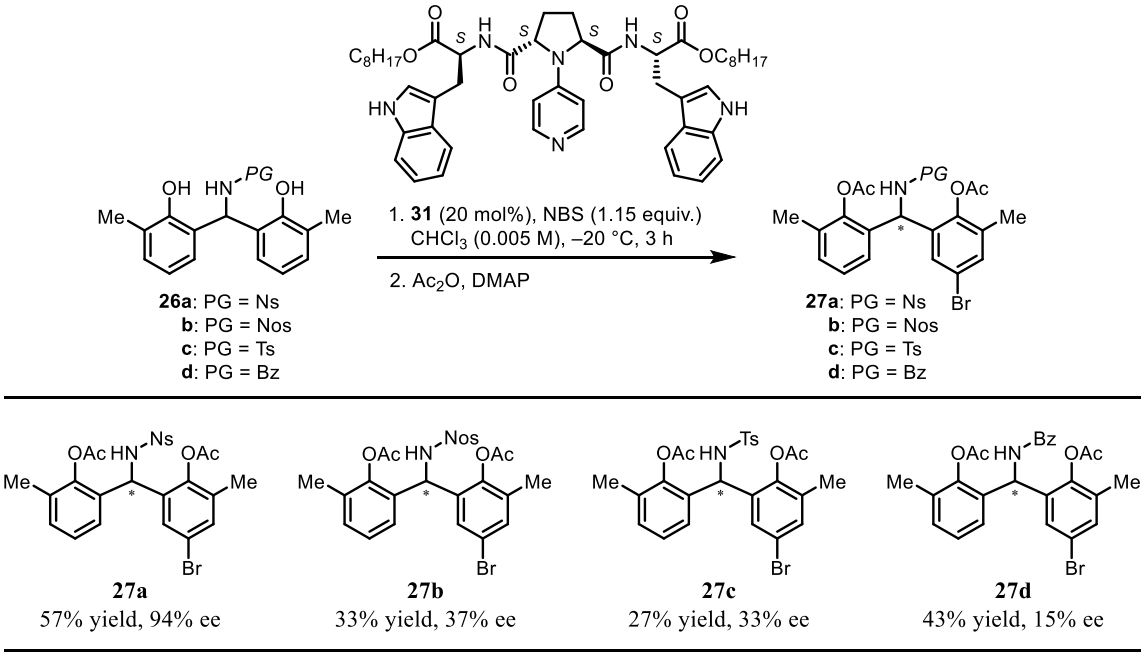
entry	Br source	solvent	**27a**[a]	ee of **27a**	**28a**[a]	**26a-diAc**[a]
1	NBS	$CHCl_3$	47%	94%	34%	12%
2	NBP	$CHCl_3$	47%	87%	15%	26%
3	NBA	$CHCl_3$	24%	2%	10%	23%
4	DBDMH[b]	$CHCl_3$	11%	38%	<5%	74%
5	NBS	DCM	50%	83%	22%	20%
6	NBS	THF	40%	2%	17%	35%
7	NBS	DMF	41%	1%	39%	19%
8	NBS	$CHCl_3$[c]	58%	96%	26%	14%

[a]Yield was determined by ^{1}H NMR using 1,3-dinitrobenzene as an internal standard. [b]0.6 equiv. [c]0.005 M.



続いて、窒素上の保護基の検討を行った (**Table 4-3**)。窒素保護基として Ns (2-nitrobenzenesulfonyl) 基の代わりに Nos (4-nitrobenzenesulfonyl) 基を持つ基質 **26b** を用いると、エナンチオ選択性は大きく低下した (**27b**)。また、Ts 基を持つ基質 **26c** や Bz 基を持つ **26d** を用いた場合もエナンチオ選択性は顕著に低下した (**27c, 27d**)。これらの結果から、2-ニトロベンゼンスルホンアミド構造が不斉誘導に決定的な役割を果たしていることがわかった。

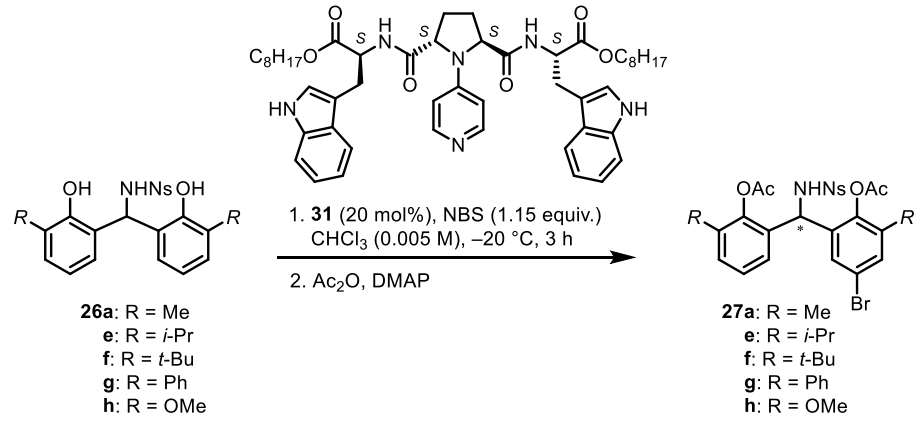
Table 4-3. Effects of Protecting Group of Nitrogen on Enantioselectivity of Asymmetric Bromination

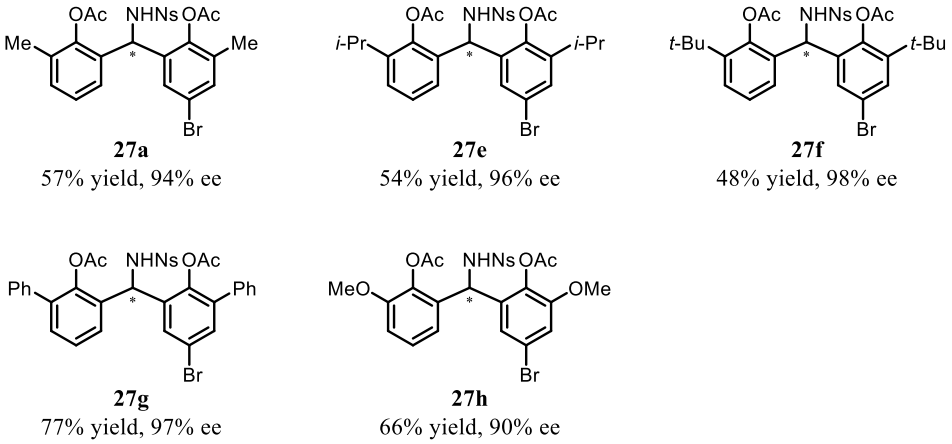


第三節　基質一般性の検討

前節で最適化した条件を用いて (**Table 4-2**, entry 8)、基質一般性の検討を行った (**Table 4-4**)。フェノールオルト位に嵩高いアルキル基を導入した基質に対しても臭素化は高エナンチオ選択的に進行し、*i*-Pr 基を持つ基質 **26e** を用いた場合モノ臭素化体 **27e** が 54%収率、96% ee で得られた。また、*t*-Bu 基を導入した基質 **26f** を用いた場合は特に良いエナンチオ選択性でモノ臭素化体 **27f** が得られた (48%収率、98% ee)。Ph 基を持つ基質 **26g** を用いた場合はモノ臭素化体 **27g** が高エナンチオ選択的かつ収率良く得られた (77%収率、97% ee)。電子供与基である MeO 基を持つ基質 **26h** を用いた場合も臭素化は円滑に進行し、66%収率、90% ee でモノ臭素化体 **27h** が得られた。フェノールオルト位の置換基の大小に関わらず、触媒による効果的な不斉誘導が実現できた。

Table 4-4. Scope of Substarte for Asymmetric Bromination

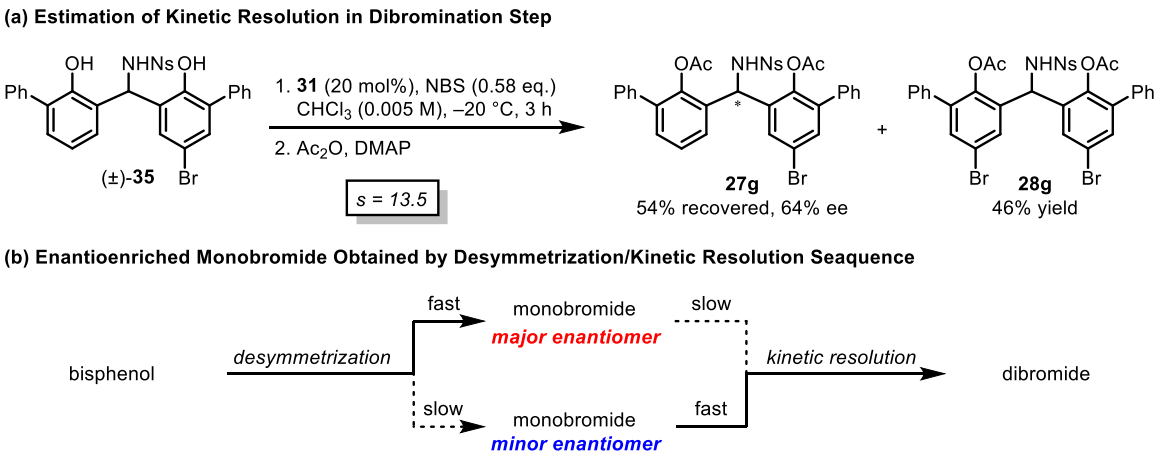




第四節　反応機構解析

第一項　選択性発現段階の検証

本系における不斉発現機構について知見を得るべく、種々の反応機構解析を行った。本不斉非対称化においては、基質の臭素化による不斉非対称化に加えて、モノ臭素化体の臭素化において速度論的光学分割が起こり得る。そこでモノ臭素化された **(±)-35** を基質として速度論的光学分割の *s* 値を評価した **(Scheme 4-7 (a))**。**(±)-35** に対して触媒 **31** 存在下、0.58 当量の NBS を作用させると、モノ臭素化体 **27g** が 54%収率、64% ee で回収され、中程度の選択性で速度論的光学分割が進行することが明らかとなった (*s* 値 13.5)。また、過剰に得られたエナンチオマーは、**26g** を基質として不斉非対称化を行った際と同じであった。本結果より、本反応では一段階目の臭素化で不斉非対称化が起こった後、二段階目の臭素化で速度論的光学分割が起こり、マイナーなエナンチオマーから優先的に臭素化が進行することで濃縮効果が働き、高いエナンチオ選択性でモノ臭素化体が得られたと考えられる **(Scheme 4-7 (b))**。



Scheme 4-7. Effect of Kinetic Resolution in Bromination of Monobromide and Possible Stereochemical Paths

第二項　触媒様式の決定

DMAP によるフェノールの臭素化の機構としては、DMAP がブレンステッド塩基としてフェノールを活性化する機構と **(Figure 4-2 (a))**、DMAP がルイス塩基として NBS と反応することで高活性なブロモニウム種が生成し、臭素化を促進する機構が考えられる **(Figure 4-2 (b))**[36]。そこで、本反応における **31** の触媒様式を決定するべく、モデル反応として種々の電子豊富芳香環を用いた DMAP 触媒による臭素化の解析を行った **(Scheme 4-8)**。酸性プロトンを持たない基質 **36** の臭素化においては、DMAP の添加が反応速度の低下を招いた **(Scheme 4-8 (a))**。DMAP と NBS が系中で不活性な付加体を形成することで、反応が阻害されたと考えており[36a]、本系では高活性ブロモニウム種は生成していないことが明らかとなった。一方で、酸性プロトンを持つ基質 **38** の臭素化においては、DMAP の添加により反応が顕著に加速された **(Scheme 4-8 (b))**。酸性プロトンを持つ基質の臭素化のみを DMAP が加速することから、DMAP はブレンステッド塩基として働くことで臭素化を触媒しており、触媒 **31** も同様にブレンステッド塩基触媒として働いていると結論付けた。

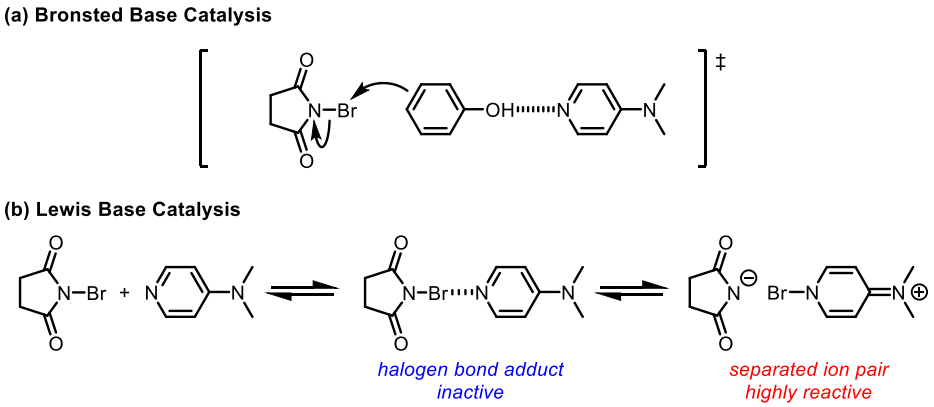
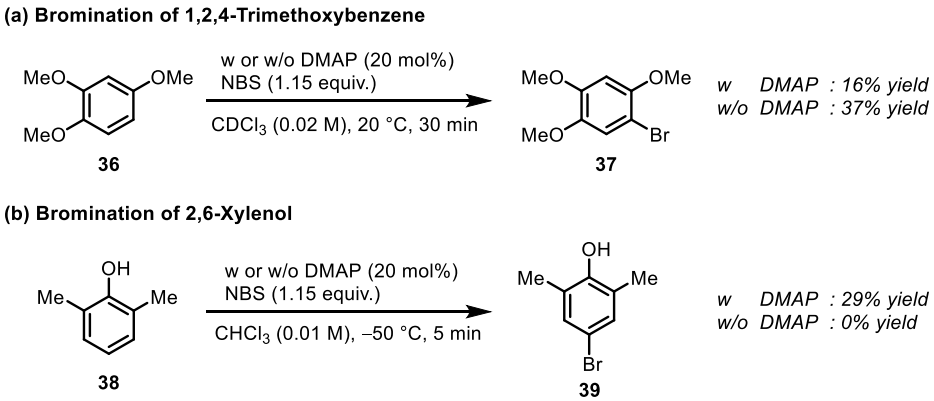


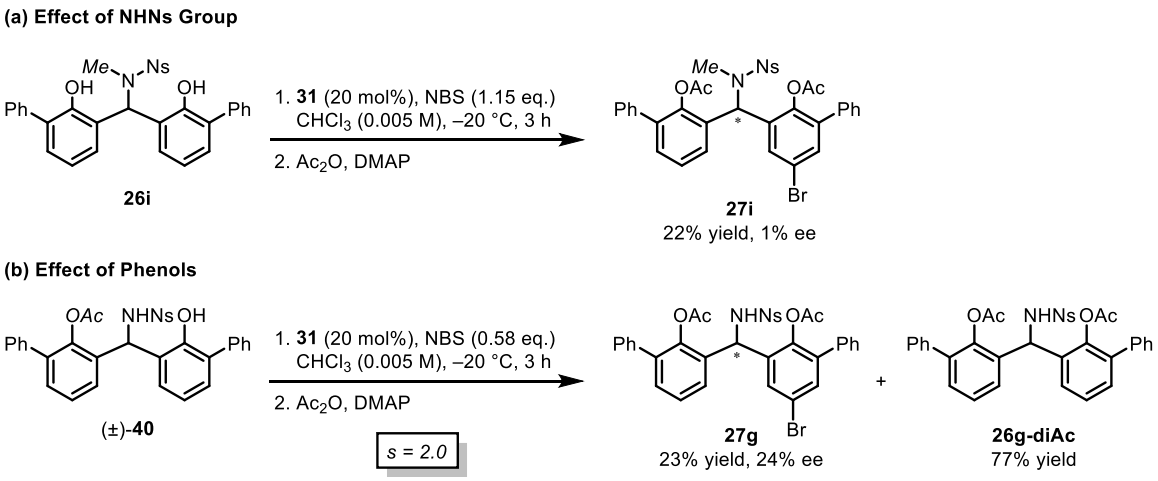
Figure 4-2. Possible Catalytic Modes of DMAP



Scheme 4-8. Mechanistic Insight of DMAP-Catalysed Bromination

第三項　基質酸性プロトンの効果

本系では触媒 **31** が基質を水素結合により認識し、エナンチオ選択的な臭素化を進行させていると想定されるため、基質酸性プロトンの影響を評価した **(Scheme 4-9)**。Ns アミドの窒素をメチル化した基質 **26i** を用いると、得られたモノ臭素化体 **27i** はほぼラセミ体であった **(Scheme 4-9 (a))**。また、片方のフェノール性水酸基をアセチル化した基質 **(±)-40** を用いて触媒 **31** 存在下、臭素化による速度論的光学分割を行った結果、その *s* 値は僅か 2.0 であった **(Scheme 4-9 (b))**。以上の結果より、NHNs 基及びフェノールの有する酸性プロトンのいずれもがエナンチオ選択性発現に必須であることが明らかとなった。



Scheme 4-9. Effects of Acidic Protons of Substrate on Asymmetric Bromination

第四項　触媒－基質複合体解析

触媒－基質間の相互作用について知見を得る為に、触媒 **31** 及び基質 **26a** の混合溶液の ^{1}H NMR 測定を行った (**Figure 4-3**)。基質 **26a** 由来のシグナルに着目すると、**26a** 単独では二つの Ha や芳香環上のメチル基は等価に観測されるが、**31** と **26a** の混合溶液はこれらが非等価な二種のピークとして観測され、**26a** の二つのフェノール環が非対称化されていることが分かった。また、触媒 **31** 由来のシグナルに着目すると、混合溶液中では PPY 部位周辺のプロトン (Hb, Hc, Hd)について顕著な高磁場シフトが観測された。以上の結果から、想定される触媒－基質複合体の構造を **Figure 4-4** に示した。触媒 **31** のピリジン環と基質の片方のフェノールとが酸塩基複合体を形成しカチオン性を帯びた結果、アミノ酸側鎖のインドール環が PPY 部位にスタッキングすることで、Hb－Hd がインドール環の遮蔽効果を受けたと考えた。このことは後述する σ-錯体の計算構造とも矛盾しない (**Figure 4-6 (b)**)。以上の結果より、触媒 **31** と基質が複合体を形成することで触媒の配座が変化するとともに基質の芳香環が非対称化され、不斉誘導が起こる可能性が示唆された。

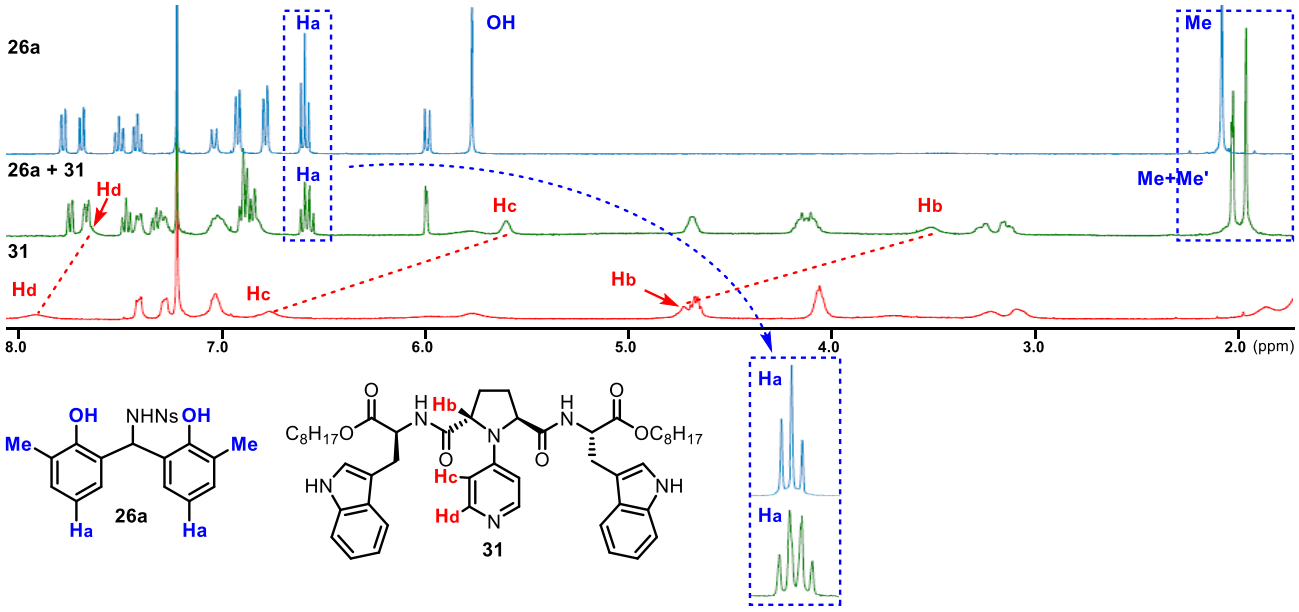


Figure 4-3. ^{1}H NMR Spectra of **26a**, **31** and a Mixture of **26a** + **31** ($CDCl_3$ (0.005 M), 400 MHz, 293K)

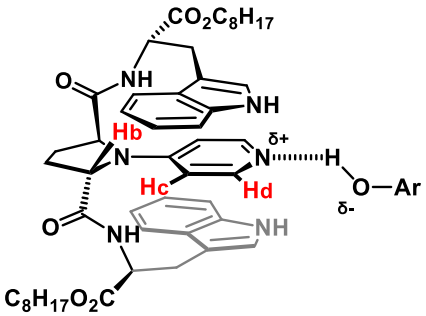
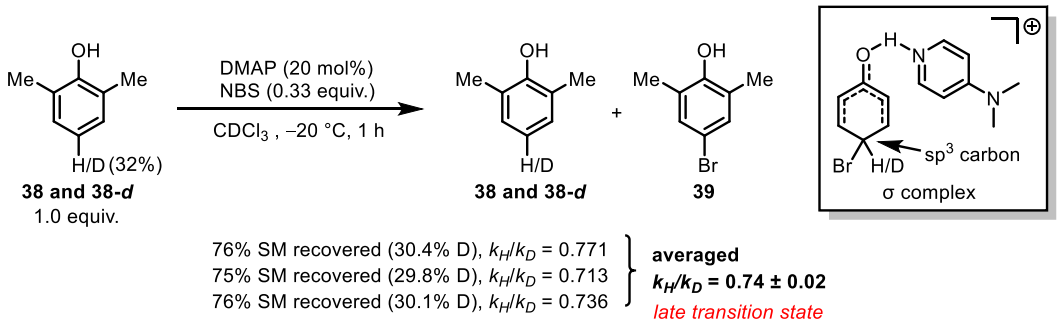


Figure 4-4. Proposed Structure of Complex between **26a** and **31**

第五項　律速段階の決定

続いて、遷移状態についての考察を行うために、DMAP によるフェノールの臭素化における速度論的同位体効果 (KIE) の測定を行った (**Scheme 4-10**)。**38** の 32% D 化体を用いて分子間での競争実験を行うと、回収原料の D 化率の減少が見られ、**38-*d*** の臭素化がより早く進行した。原料の変換率と D 化率から k_H/k_D の値は 0.74±0.02 となり、負の二次速度論的同位体効果が観測された [37]。本結果は律速段階においてフェノールパラ位炭素の混成が sp^2 から sp^3 に変化していることを意味し、本系は一般的な芳香族求電子置換反応と同様に σ 錯体の形成を経て進行していると考えられる [31]。また、負の二次速度論的同位体効果の最小値は理論上 0.7 であることから [37a]、本反応は late transition state を経て進行していることが示唆された。



Scheme 4-10. KIE Experiments

第五節　推定遷移状態

前節の結果より触媒－基質が水素結合を介した複合体を形成することがエナンチオ選択性発現の鍵であることが示唆された (**Scheme 4-9**, **Figure 4-3**)。しかしその相互作用様式については全くの未知数であったため、DFT 計算により DFT 計算により本系の遷移状態の導出を試みたが、触媒、基質及び臭素化剤の三者複合体計算は配座が膨大な数存在し計算コストの面からも困難であった。一方、前節の速度論的同位体効果から示唆されるとおり、σ 錯体の生成が late transition state であるとするならば、Hammond の仮説により遷移状態は σ 錯体に似た構造を持つと考えられる。そこで、σ 錯体の構造を計算することで、遷移状態での触媒－基質間の相互作用を見積もることとした (**Figure 4-5**)。

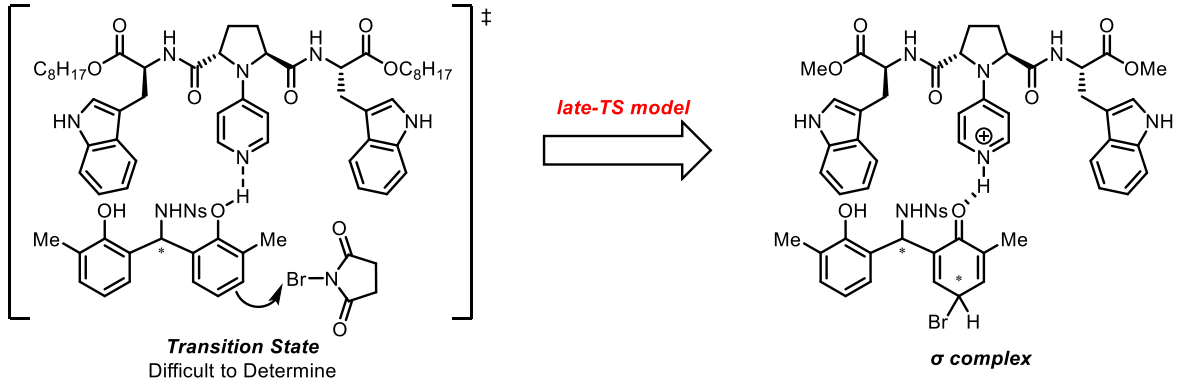


Figure 4-5. Calculation of σ Complex as Transition State Model

σ 錯体の各ジアステレオマーと、ピリジニウム塩との複合体に関して (**Figure 4-6 (a)**)、MacroModel による配座探索及び DFT 計算による構造最適化を行った所、(*S*, *S*)体の σ 錯体由来の複合体が再安定構造として得られた (**Figure 4-6 (b)**)。触媒部位に着目すると、アミノ酸側鎖インドールが PPY 部位にスタッキングした構造を取っており、^{1}H NMR で観測されたシグナル変化における考察と良い一致を示した (**Figure 4-3**)。ピリジニウム NH はフェノール由来のカルボニル酸素およびニトロ基酸素と水素結合しており、2-ニトロベンゼンスルホンアミド構造が不斉誘導に必須であるという実験事実と一致する (**Table 4-3**)。また、インドール環と PPY 部位のスタッキングにより触媒アミノ酸側鎖のエステルカルボニル基が基質側を向くことで、pro-(*R*)側のフェノール水酸基と水素結合しており、アミノ酸側鎖及び臭素化を受けないフェノール環の水酸基がエナンチオ選択性発現に重要であるという実験事実と一致する (**Table 4-1, Scheme 4-3**)。また、本反応においては臭素化剤によって大きく不斉収率が変化することから、遷移状態では臭素化剤官能基と触媒－基質複合体との間に相互作用が想定される。σ 錯体の構造中で NHNs 基の酸性プロトンは、触媒－基質間相互作用に関与していないことから、臭素化剤の活性化に関与していると考えた。NHNs 基の NH が臭素化剤と相互作用しているのではないかと考えた。すなわち、遷移状態においては σ 錯体と同様の相互作用が存在すると共に、NHNs 基 NH が NBS のカルボニル基と水素結合して活性化し、エナンチオ選択的臭素化が進行すると想定している (**Figure 4-6 (b)**)。

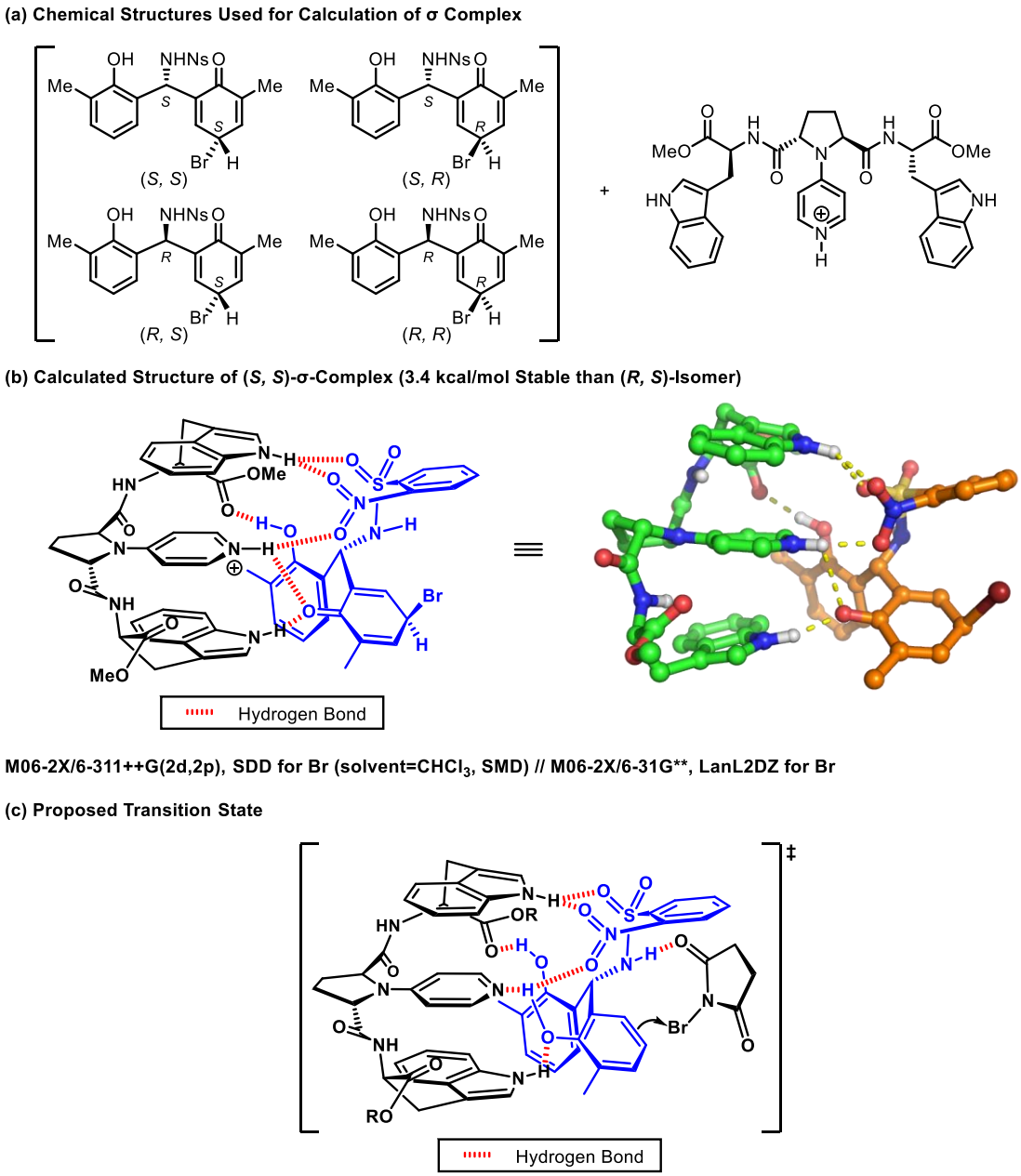


Figure 4-6. Calculated Structure of σ–Complex and Proposed Transition State

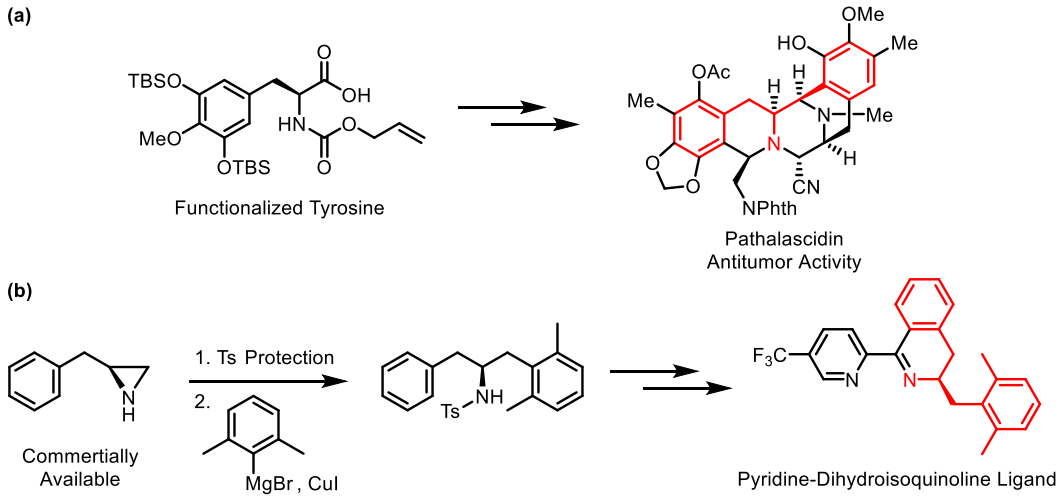
第六節　結論

有機触媒を用いた芳香族臭素化による σ-対称 1,1-ジアリールメチルアミンの不斉非対称化を達成した。また、芳香族臭素化において触媒 **31** がブレンステッド塩基触媒として働いていることを明らかにするとともに、実験及び計算化学的手法に基づき不斉発現機構を提唱した。

第五章　芳香族臭素化による σ-対称 1,3-ジアリールプロピルアミンの不斉非対称化

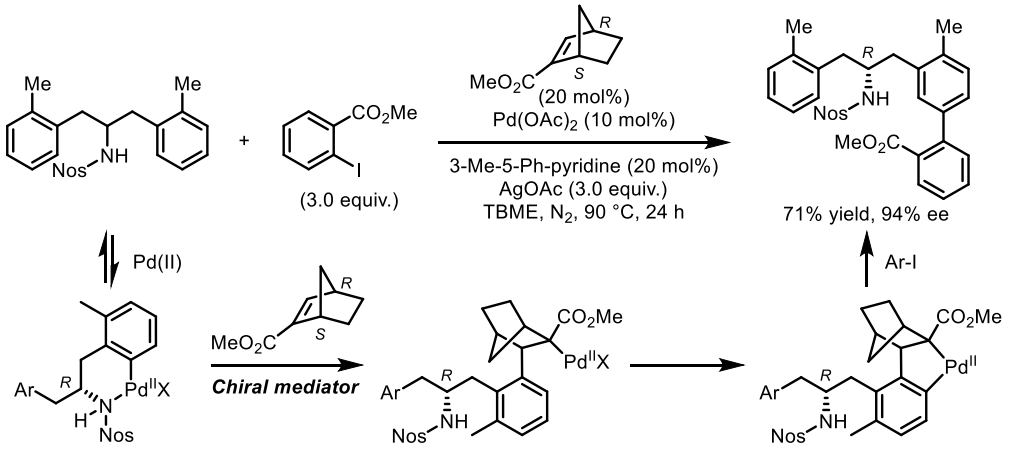
第一節　研究背景と著者の研究方針

第四章では芳香族臭素化による光学活性 1,1-ジアリールメチルアミンの効率的合成法を開発した。一方、芳香環間により長い脂肪鎖を有する、光学活性 1,3-ジアリールプロピルアミンの効率的合成法の開発は α-キラルアミン類の合成における未解決課題の一つである。光学活性 1,3-ジアリールプロピルアミンは生物活性物質の骨格に多く見られ **(Scheme 5-1 (a))**[38]、不斉リガンドとしての利用も為される等有用な構造である **(Scheme 5-1 (b))**[39]。しかし、その合成例の殆どは容易に入手、合成可能な天然及び非天然アミノ酸やキラルアジリジンからの誘導化によるものであり、光学活性 1,3-ジアリールプロピルアミン骨格を直接構築する報告例は非常に少ない。その原因の一つは、最も直截的な方法論であるイミンの不斉水素化及び求核付加においては **(Scheme 4-1 (a)** and **(b))**、芳香族イミンと比較して取り扱いが困難かつ、不斉面の識別が困難な脂肪族イミンを用いる必要があるためと推察される。



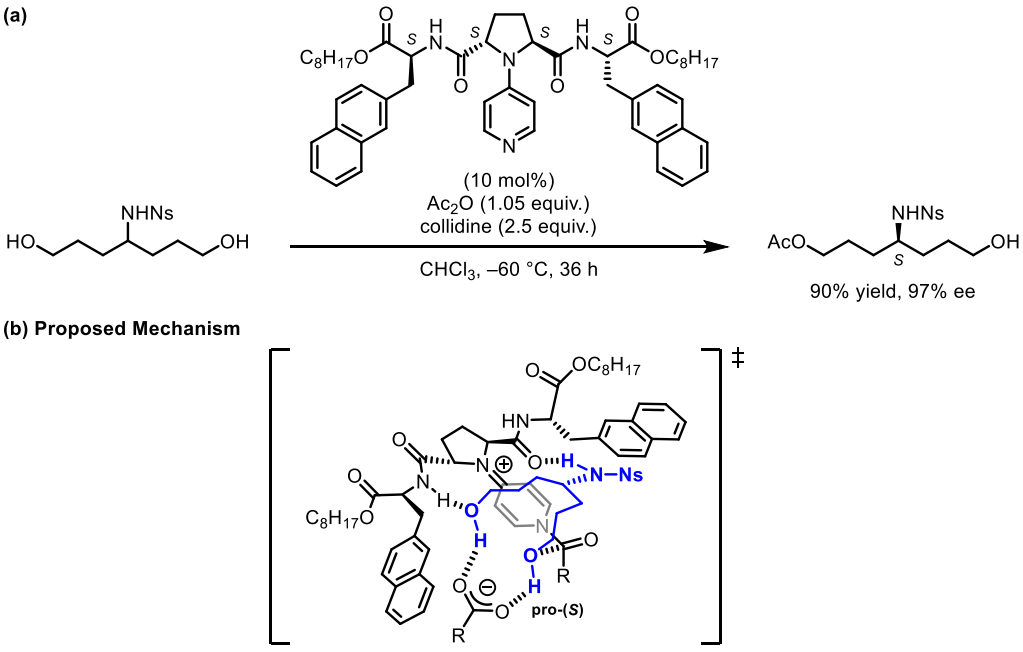
Scheme 5-1. Examples of Optically Active 1,3-Diarylpropylamines

上記課題を解決する手法として σ-対称 1,3-ジアリールプロピルアミンの不斉非対称化が試みられてきた。Yu らは、パラジウム/キラルノルボルネン共触媒系を用いる、σ-対称 1,3-ジアリールプロピルアミンのメタ位選択的かつエナンチオ選択的アリール化及びアルキル化を報告している **(Scheme 5-2)**[40a]。NHNos 基を配位性配向基とするオルト位 C-H 活性化は可逆的に進行し、続く Catellani 型反応の進行の際にノルボルネンのキラリティがプロキラル炭素へ転写される。しかし、σ-対称 1,3-ジアリールプロピルアミンの不斉非対称化の報告は類似の共触媒系を用いた 3 例に限られており[40]、プロキラル炭素から離れたエナンチオトピックな芳香環を識別する手法は確立されていないのが現状である。このような背景のもと、より多様な方法論の開発が求められている。



Scheme 5-2. Enantioselective Remote Meta-C-H Arylation.

所属研究室では分子認識型触媒を用いた σ-対称 1,7-ジオールのアシル化による不斉非対称化を達成している **(Scheme 5-3 (a))**[41]。長鎖ジオールは高い配座の自由度を持ち、反応点近傍に利用できる立体因子が存在しないことから不斉非対称化が困難であることが知られており、1,7-ジオール以上の不斉非対称化の報告例は存在しなかった。一方、所属研究室で開発した分子認識型触媒存在下 NHNs 基をプロキラル炭素上に有する σ-対称 1,7-ジオールに無水酢酸を作用させると、高エナンチオ選択的にアセチル化が進行する。実験及び計算的手法により、触媒が基質と多点水素結合することでエナンチオトピックな二つの水酸基を識別し、pro-(*S*)側水酸基が反応点に近づく遷移状態を提唱しており **(Scheme 5-3 (b))**、触媒による水素結合を介した分子認識による不斉誘導戦略が遠隔位不斉非対称化に有効であることが示唆された。



Scheme 5-3. Remote Asymmetric Induction on Enantioselective Acylation of 1,7-Diols

このような背景のもと、著者は σ-対称 1,7-ジオールと構造的に類似する σ-対称 1,3-ジアリールプロピルアミンを設計し、その不斉非対称化検討を行うこととした (**Figure 5-1**)。二つの水酸基とスルホンアミド部位を適切に配置することで、触媒－基質間に類似する官能基間相互作用が働き、芳香族臭素化による σ-対称 1,3-ジアリールプロピルアミンの遠隔位不斉非対称化が可能であると考えた。この際、前章の基質である 1,1-ジアリールメチルアミンと 1,3-ジアリールプロピルアミンとでは官能基間距離が異なるが、触媒の側鎖構造によって官能基配置を変化させることで、同一の母骨格を有する触媒によって効果的な不斉誘導が起きると期待した。

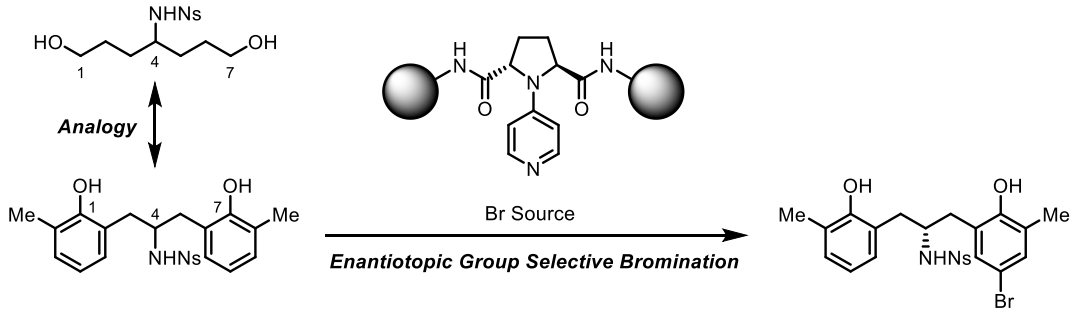
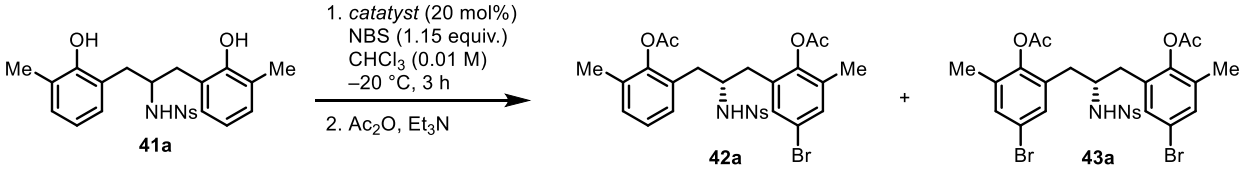


Figure 5-1. Working Hypothesis

第二節　反応条件の最適化

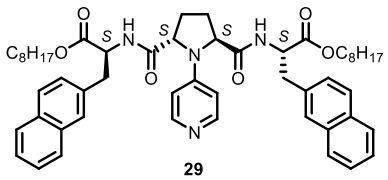
σ-対称ジアリールプロピルアミン **41a** を基質として、種々の側鎖構造を持つ触媒による不斉非対称化の検討を行った (**Table 5-1**)。前章同様、モノ臭素化体、ジ臭素化体及び回収原料の分離が困難であったため、フェノールのアセチル化後単離精製を行っている。β-ナフチルアラニン誘導体を側鎖に有する触媒 **29** 存在下、$CHCl_3$ 中−20 ℃において NBS を作用させるとモノ臭素化体 **42a** が 50%収率、78% ee で得られた (entry 1)。触媒 **29** のジアステレオマーである触媒 **30** を用いるとエナンチオ選択性の低下を招き (entry 2)、トリプトファン誘導体を側鎖に有する触媒 **31** 及び触媒 **32** を用いた場合はエナンチオ選択性が顕著に低下した (entries 3 and 4)。単純な脂肪鎖を側鎖に有する触媒 **33** を用いると、モノ臭素化体 **42a** が 61% 収率、82% ee と最も良いエナンチオ選択性で得られ、本系においては触媒のアミノ酸構造はエナンチオ選択性の向上に寄与しないことが示唆された (entry 5)。一方で、アミド窒素 α 位に三置換炭素を持つ触媒 **44**、四置換炭素を持つ触媒 **45** を用いた場合エナンチオ選択性が低下し、触媒アミド基周辺が嵩高くなるほど選択性が低下することが分かった (entries 6 and 7)。

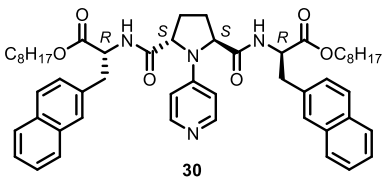
Table 5-1. Catalyst Screening for Asymmetric Bromination of **41**

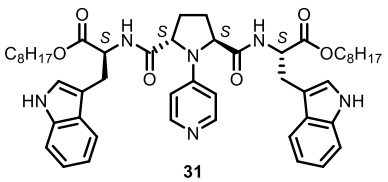


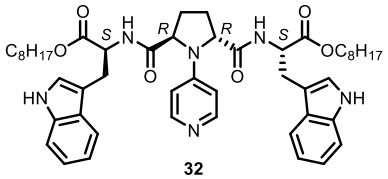
entry	catalyst	**42a**	ee of **42a**	**43a**	**42a-diAc**
1	**29**	50%	78%	26%	15%
2	**30**	42%	44%	21%	<20%[a]
3	**31**	45%	23%	15%	38%
4	**32**	48%	0%	23%	31%
5	**33**	61%	82%	24%	<20%[a]
6	**44**	48%	40%	22%	<31%[a]
7	**45**	40%	14%	20%	27%

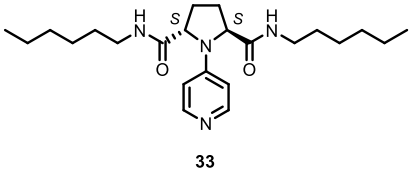
[a]With some impurity.

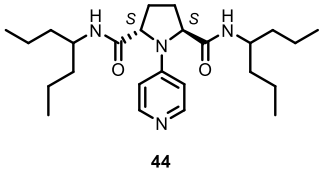


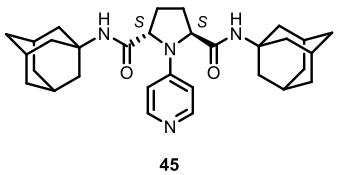






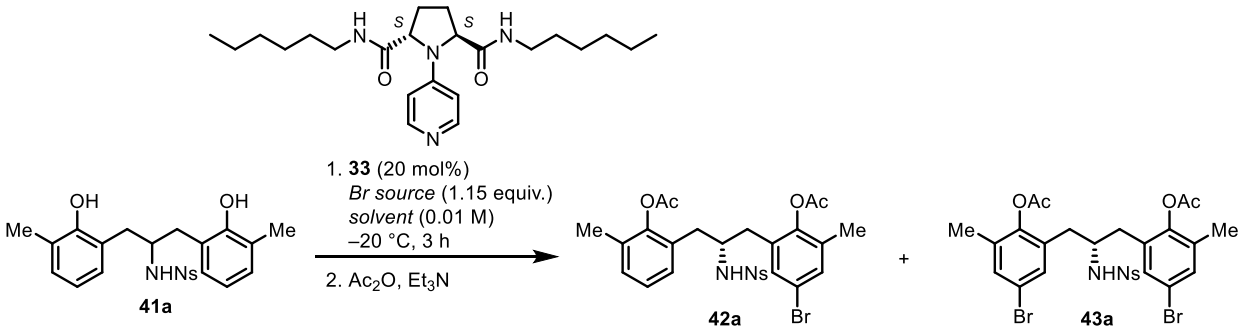






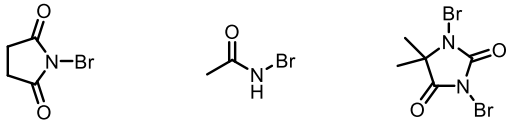
最も良いエナンチオ選択性を示した触媒 **33** を用いて (**Table 5-1**, entry 5)、収率及び選択性の向上を目的として反応条件を精査した (**Table 5-2**)。初めに臭素化剤の検討を行った。NBA や DBDMH を用いた場合はエナンチオ選択性が低下を招いたが、中程度のエナンチオ選択性で反応は進行した。 (entries 2 and 3)。続いて、溶媒の検討を行った。低極性溶媒である DCM 中では、エナンチオ選択性は低下したものの、中程度のエナンチオ選択性で反応が進行したのに対して (entry 4)、高極性溶媒である THF、DMF 中で反応を行うとモノ臭素化体はほぼラセミ体として得られた (entries 5 and 6)。これらの溶媒効果から、本系においても触媒 **33** が水素結合を介した相互作用により基質を精密に認識することでエナンチオ選択性が誘起されると考えられる。また、基質濃度を 0.005 M にすると収率及びエナンチオ選択性が僅かに向上した (entry 8)。

Table 5-2. Effects of Brominating Reagents and Solvent on Enantioselectivity of Asymmetric Bromination



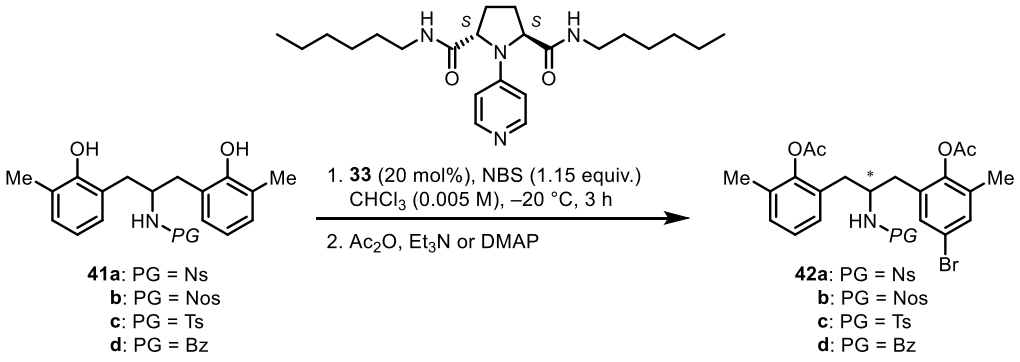
entry	Br source	solvent	**42a**	ee of **42a**	**43a**	**41a-diAc**
1	NBS	$CHCl_3$	61%	82%	21%	<20%[a]
2	NBA	$CHCl_3$	43%	51%	20%	27%
3	DBDMH[b]	$CHCl_3$	51%	66%	27%	21%
4	NBS	DCM	48%	55%	24%	27%
5	NBS	THF	48%	1%	28%	20%
6	NBS	DMF	50%	0%	21%	27%
7	NBS	$CHCl_3$[c]	59%	87%	26%	12%

[a]With some impurity. [b]0.6 equiv. [c]0.005 M.



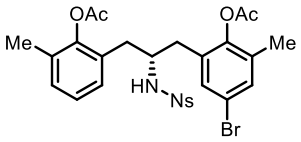
続いて、窒素上の保護基の検討を行った (**Table 5-3**)。窒素保護基として Ns 基の代わりに Nos 基を持つ基質 **41b** を用いると 50% ee でモノ臭素化体 **42b** が得られた。また、Ts 基を持つ **41c** や Bz 基を持つ **41d** を用いた場合はエナンチオ選択性が劇的に低下した (**42c, 2d**)。これらの結果から、本系においても 2-ニトロベンゼンスルホンアミド基が不斉誘導に影響を与えることが明らかとなった。

Table 5-3. Effects of Protecting Group of Nitrogen on Enantioselectivity of Asymmetric Bromination

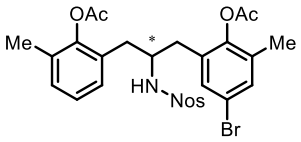


41a: PG = Ns
b: PG = Nos
c: PG = Ts
d: PG = Bz

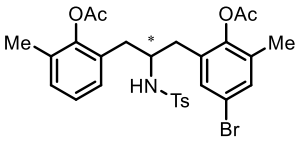
42a: PG = Ns
b: PG = Nos
c: PG = Ts
d: PG = Bz



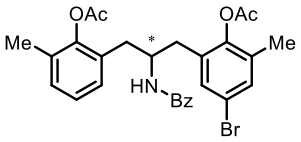
42a
55% yield, 85% ee



42b
38% yield, 50% ee



42c
37% yield, 6% ee

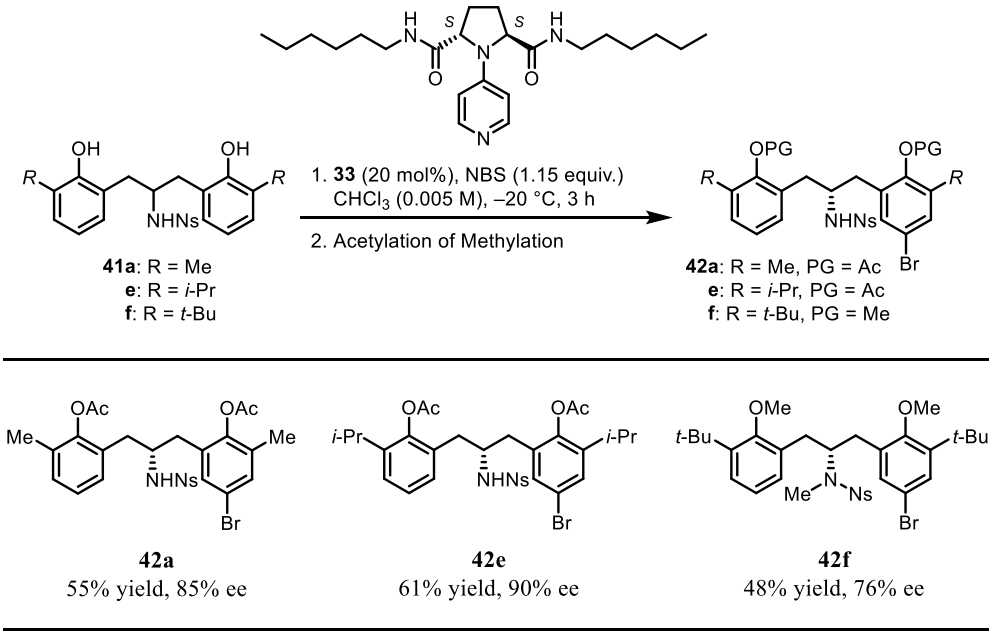


42d
37% yield, 2% ee

第三節　基質一般性の検討

前節で最適化した条件を用いて (**Table 5-2**, entry 7)、基質一般性の検討を行った (**Table 5-4**)。フェノールオルト位に *i*-Pr 基を持つ **41e** を用いた場合は、モノ臭素化体 **42e** が 61%収率、90% ee と最も良いエナンチオ選択性で得られた。フェノールオルト位に *t*-Bu 基を持つ **41f** を用いた場合は、モノ臭素化体 **42f** を 48%収率、76% ee で得た。なお、本基質及び臭素化体においてはアセチル化の進行が非常に遅く、副反応の進行も確認されたことから臭素化を行った後メチル化を行うことで生成物の単離精製を行った。本結果より、本反応がフェノールオルト位にアルキル基を持つ基質に適用可能であることが分かった。

Table 5-4. Scope of Substrate for Asymmetric Bromination



第四節　反応機構解析

第一項　絶対立体配置の決定

光学活性なモノ臭素化体 **42a** を分取用キラル HPLC によって精製することで光学純粋な **42a** を得て、単結晶を作成した。得られた単結晶の X 線結晶構造解析によって、生成物の絶対立体配置が *R* 体であることを決定した (**Figure 5-2**)。

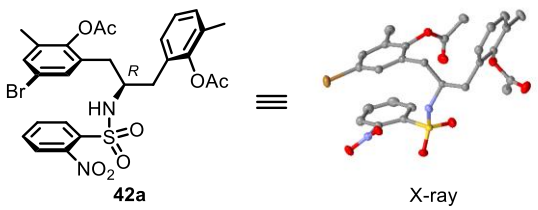
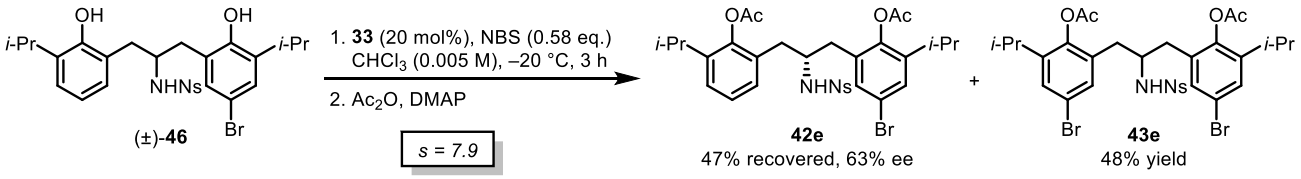


Figure 5-2. X-ray Anaylsis of **18a**

第二項　選択性発現段階の検証

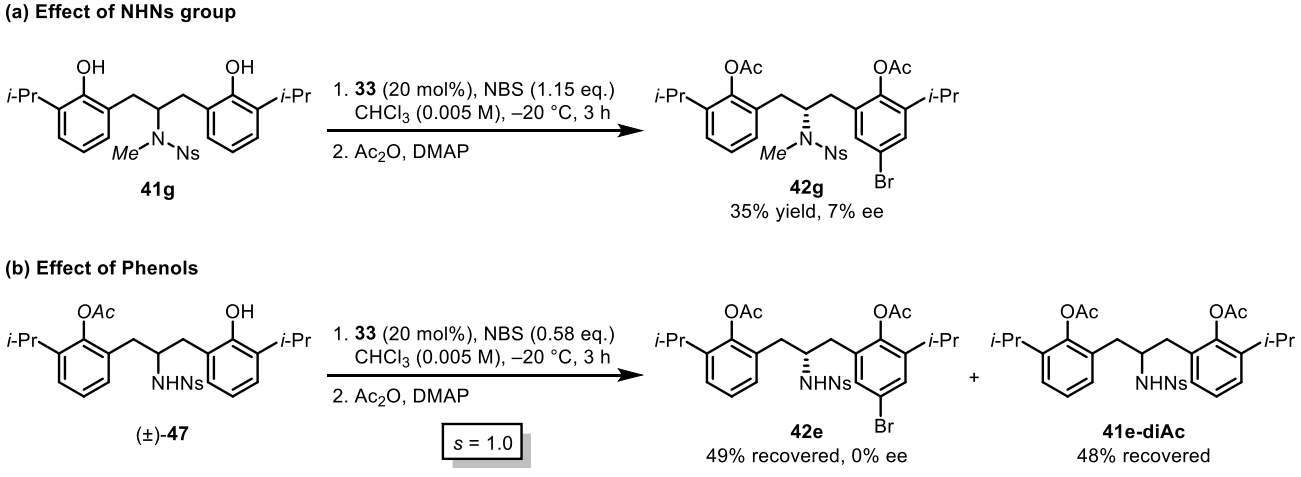
モノ臭素化された **(±)-46** を用いて、過剰な臭素化がエナンチオ選択性に与える影響を評価した **(Scheme 5-4)**。(±)-**46** に対して触媒 **33** 存在下、0.58 当量の NBS を作用させると、モノ臭素化体 **42e** が 47% 収率、63% ee で回収され、中程度の選択性で速度論的光学分割が進行することが明らかとなった (*s* 値 7.9)。回収原料は *R* 体が過剰であったことから、本系においても一段階目の臭素化で不斉非対称化が起こった後、二段階目の臭素化で速度論的光学分割が進行することでエナンチオ濃縮が起こっていると推察される **(Scheme 5-4 (b))**。



Scheme 5-4. Effect of Kinetic Resolution in Dibromination Step

第三項　基質酸性プロトンの効果

次に、基質の持つ酸性プロトンがエナンチオ選択性に与える影響を評価した **(Scheme 5-5)**。NHNs 基をメチル化した基質 **41g** に対して触媒 **33** 存在下 NBS を作用させると、モノ臭素化体 **42g** を 7% ee で与えた **(Scheme 5-5 (a))**。また、片方のフェノール水酸基をアセチル化した **(±)-47** を用いて触媒 **33** 存在下臭素化を行ったところ、モノ臭素化体 **42e** はラセミ体として得られ速度論的光学分割は進行しなかった **(Scheme 5-5 (b))**。以上の結果より、NHNs 基及びフェノールの有する酸性プロトンのいずれもがエナンチオ選択性の発現に重要であることが示唆された。



Scheme 5-5. Effects of Acidic Protons of Substrate on Asymmetic Bromination

第四項　触媒－基質複合体解析

次に、触媒－基質複合体の相互作用について知見を得る為に、触媒 **33** と基質 **41a** の混合溶液の ^{1}H NMR を測定した (**Figure 5-3**)。混合溶液中では触媒 **33** のアミド NH が低磁場側にシフトしており、基質 **41a** の NHNs 基及びフェノールの有する酸性プロトンが消失していることから、触媒のピリジン部位及びアミドカルボニル酸素がこれらの酸性プロトンと水素結合している可能性が示唆された。また、基質 **41a** 単独では同一のピークとして観測される二つの Ha、Ha'、Hb 及び Hc は触媒 **33** との混合溶液中ではそれぞれ二種のピークとして観測され、触媒 **33** と基質 **41a** が酸塩基複合体を形成することでプロキラル炭素上の二つのエナンチオトピックな置換基が非対称化されていることがわかった。以上の結果より、触媒－基質複合体の形成により二つの芳香環が非対称化され、エナンチオ選択的臭素化が進行している可能性が示唆された。

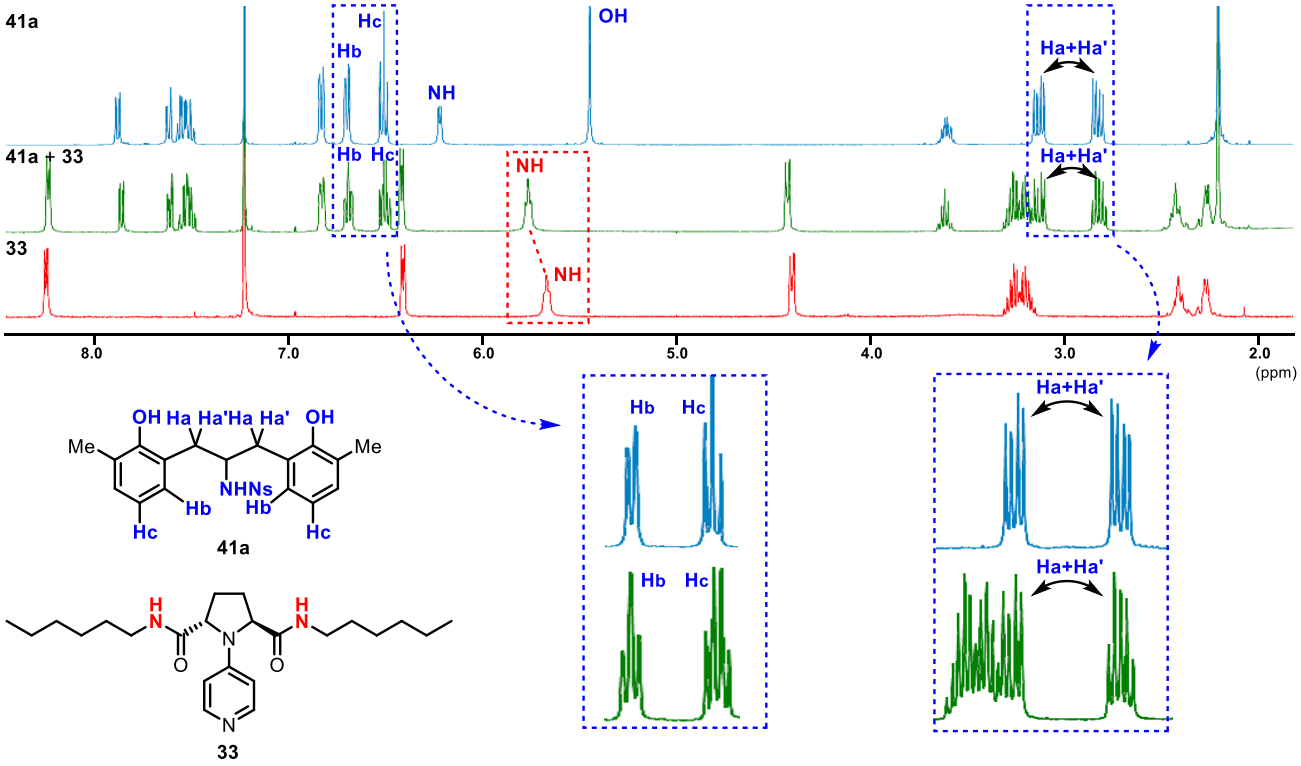


Figure 5-3. ^{1}H NMR Spectra of **41a**, **33** and a Mixture of **41a**+**33** ($CDCl_3$ (0.005 M), 400 MHz, 293K)

第五節　推定遷移状態

触媒 **33** によるフェノールの臭素化の遷移状態が late transition state であるという仮定のもと、前章同様に σ 錯体の構造を計算することで遷移状態における触媒－基質間の相互作用様式を見積もった (**Figure 5-4 (a)**)。本系における主生成物である *R* 体の σ 錯体について配座探索及び構造最適化を行った結果、得られた最安定構造を以下に示す (**Figure 5-4 (b)**)。触媒のピリジニウム NH はフェノール由来のカルボニル基と水素結合しており、想定反応機構である PPY 部位によるフェノールの活性化に相当している。また、NHNs 基の有する酸性プロトンが pro-(*S*)側フェノール水酸基の酸素と水素結合するとともに、酸性度が上がったフェノール水酸基が触媒アミドカルボニル基の酸素と水素結合しており、臭素化を受けないフェノール水酸基及び、NHNs 基の有する酸性プロトンがエナンチオ選択性発現に重要であるといった実験事実と一致する。2-ニトロ基は NHNs 基の有する酸性プロトン及び、触媒アミド α 位の C-H 結合と水素結合していることから、Ns 基の 2-ニトロ基がエナンチオ選択性発現に重要であるという実験事実とも良い一致を示した。一方、臭素化剤を活性化出来る酸性プロトンは存在しないため、本系においては臭素化剤のエナンチオ選択性に与える影響が比較的小さいと考えられる。本系においては、σ 錯体の最安定構造と類似する遷移状態を経て、エナンチオ選択的臭素化が進行すると想定している (**Figure 5-4 (c)**)。本結果及び第四章の結果より、鎖長の異なる 1,*n*-ジアリールアルキルアミンに対して適切な触媒を使い分けることで、異なる分子認識機構を経て基質のエナンチオトピックな二つの芳香環が非対称化され、エナンチオ選択的臭素化が進行することを見出した。

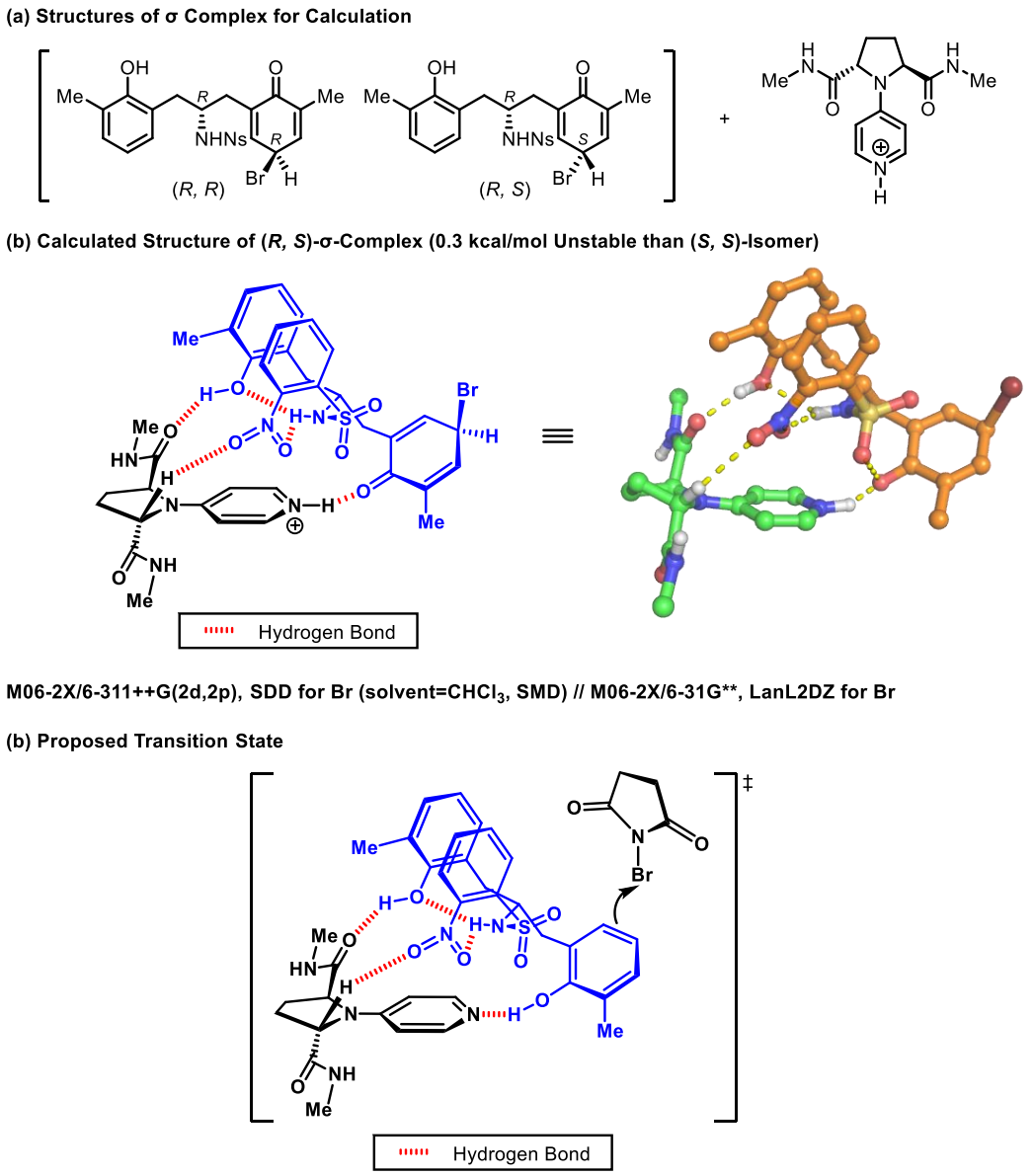


Figure 5-4. Calculated Structure of σ–Complex and Proposed Transition State

第六節　結論

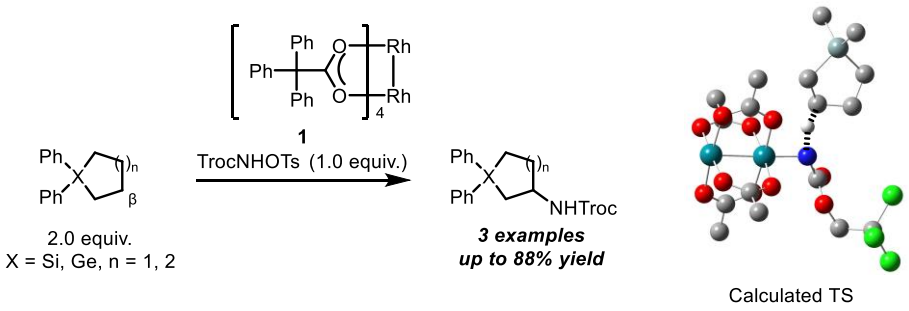
世界初の芳香族臭素化による σ-対称 1,3-ジアリールプロピルアミンの不斉非対称化を達成した。脂肪族アミドを側鎖とする触媒 **33** を用いることで、芳香環の間により長い鎖長を有する基質の不斉識別が可能となったと考えられる。

第六章　結論

α-キラルアミン化合物は多くの医薬品に含まれる重要な部分構造であり、その合成は主としてプロキラル sp^2 炭素を有する化合物群に対するエナンチオ面選択的な反応により達成されてきた。一方、従来の方法論では合成困難な化合物も多数存在しており、ケミカルスペース拡充のためにも新規な方法論による合成法の開発が求められていた。著者は、プロキラル sp^3 炭素を有する化合物群の C-H 修飾による不斉非対称化を軸として、従来法では困難であった α-キラルアミン化合物合成に取り組んだ。第二章、第三章では Rh 触媒による C-H アミノ化の反応機構解析を行うとともに、光学活性アミノシランの合成法を開発した。第四章、第五章では有機触媒による芳香族臭素化による、1,*n*-ジアリールアルキルアミンの不斉非対称化を達成した。以下に本研究の成果を要約する。

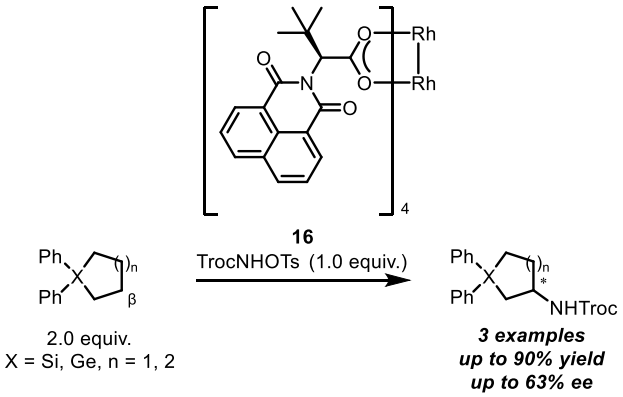
1. Rh 触媒を用いるシリル基 β 位 C(sp^3)-H アミノ化の反応機構解析

ロジウムナイトレノイドを活性種とするシリル基 β 位 C(sp^3)-H アミノ化の反応機構解析を行うとともに、不斉反応への展開を志向して第二級炭素の C-H 結合に対する C-H アミノ化法を開発した。DFT 計算により C-Si 結合の高い電子供与性が位置選択性の鍵であることが支持されており、シリル基の β 効果を利用した分子間 C-H アミノ化における新規位置選択性制御法を提示した。



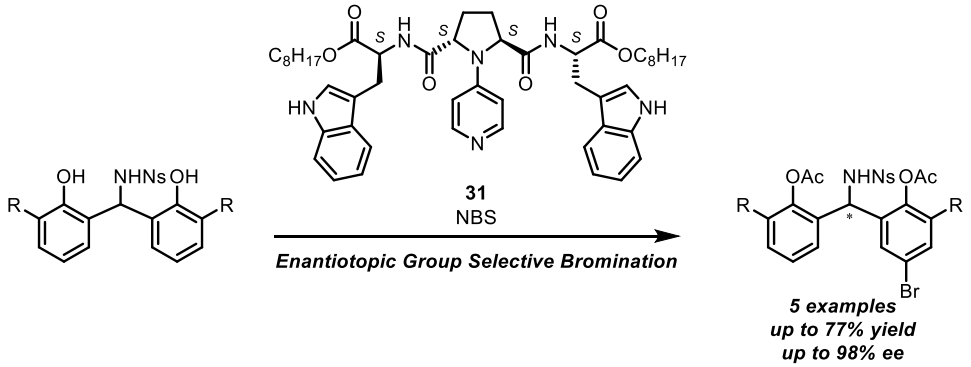
2. Rh 触媒を用いるエナンチオ選択的シリル基 β 位 C(sp^3)-H アミノ化

不斉 Rh 二核錯体触媒を用いることで、環内にケイ素を有する基質に対するエナンチオ選択的シリル基 β 位 C(sp^3)-H アミノ化を達成した。不斉収率は中程度に留まるものの、単純なアルキルシランを一段階で光学活性アミノシランへと変換することが可能であり、含ケイ素医薬品探索を志向したケイ素骨格構築法としての利用が期待される。



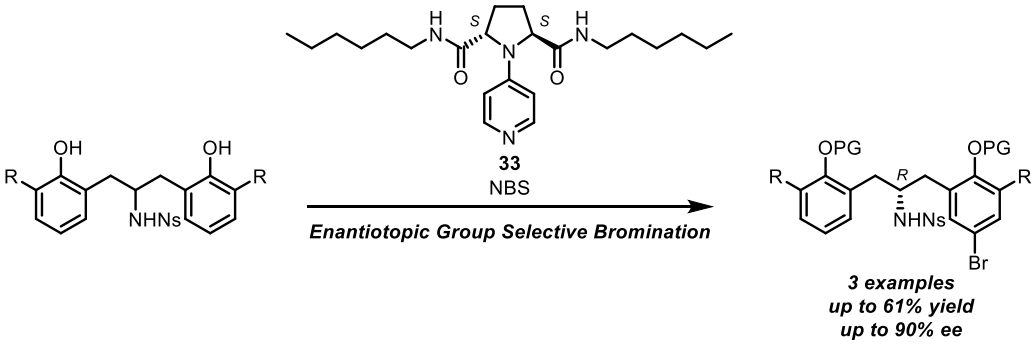
3. 芳香族臭素化による σ-対称 1,1-ジアリールメチルアミンの不斉非対称化

PPY を母骨格とする分子認識型触媒を用いて、芳香族臭素化による σ-対称 1,1-ジアリールメチルアミンの不斉非対称化を達成した。触媒 **31** は求核触媒として種々の位置選択的分子変換に用いられてきたが、フェノールの臭素化においては本触媒がブレンステッド塩基触媒として働いていることを明らかにした。NMR 実験及び DFT 計算により、触媒 **31** のトリプトファン側鎖が PPY 部位にスタッキングすることで高い不斉識別能が発現していると想定され、分子認識型触媒の設計における新たな知見を得た。



4. 芳香族臭素化による σ-対称 1,3-ジアリールプロピルアミンの不斉非対称化

α-キラルアミン化合物の合成における未解決課題である、光学活性 1,3-ジアリールプロピルアミンの効率的合成法の開発に取り組み、世界初の芳香族臭素化による σ-対称 1,3-ジアリールプロピルアミンの不斉非対称化を達成した。プロキラル炭素から遠隔位を反応点とする不斉非対称化は方法論が確立されていない未開拓な分野であるが、分子認識型触媒を用いた手法が遠隔位不斉非対称化の有力な方法論となり得る可能性を提示した。



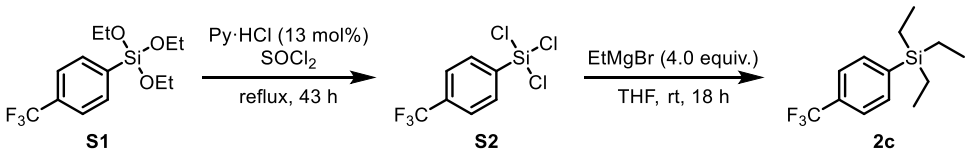
実験の部

実験及び測定に関する一般事項

All reactions were carried out under an argon atmosphere with magnetic stirring. ^{1}H NMR spectra were recorded on JEOL ECX-400 (400 MHz) and JEOL ECA-600 (600 MHz), and are reported in ppm using solvent resonance as the internal standard (acetone-d_6 at 2.05 ppm, $CDCl_3$ at 7.26 ppm, DMSO-d_6 at 2.50 ppm). Chemical shifts are reported in ppm. When peak multiplicities are reported, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; dd, double doublet; td, triple doublet; tt, triple triplet; ddd, double double doublet; m, multiplet; br, broadened. ^{13}C NMR spectra were recorded on JEOL ECX-400 (100 MHz), JEOL ECA-600 (150 MHz) and Bruker Avance 800 (200 MHz) are reported in ppm using solvent resonance as the internal standard (acetone-d_6 at 29.84 ppm, $CDCl_3$ at 77.16 ppm, DMSO-d_6 at 39.52 ppm). Infrared (IR) spectra were recorded with a JASCO FT/IR-300 spectrometer. High-resolution mass spectra (HRMS) were obtained on Bruker Impact HD mass spectrometers for ESI, and were obtained on JEOL JMS-700 mass spectrometer for EI. Melting points (m.p.) were recorded using Yanagimoto Micro Melting Point apparatus PM-500. Specific rotations were measured by JASCO P-2200 digital polarimeter using sodium D line and are reported as follows: $[\alpha]_D^t$ (*c* in solvent). Column chromatography was performed on silica gel 60N (spherical, neutral, KANTO). Preparative TLC was performed on precoated plates (0.50 mm, Merck). Anhydrous chlorobenzene and trifluoromethylbenzene were purchased from Sigma-Aldrich. Anhydrous AcOEt, $CHCl_3$, DCM, Et_2O and THF were purchased from Kanto Kagaku. Anhydrous DMF and MeCN were purchased from Nacalai tesque. Anhydrous benzene was purchased from Wako Chemical. Dry AcOEt, benzene, $CHCl_3$, DMF and MeCN were stored over activated molecular sieves.

第二章に関する実験及び物性値

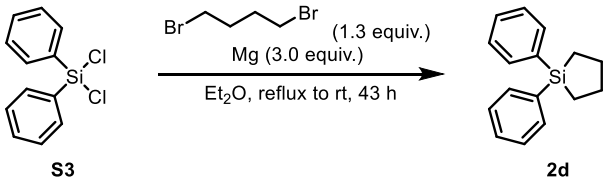
Synthesis of Substrates and Characterization Data



Triethyl(4-(trifluoromethyl)phenyl)silane (2c)

Following the literature procedure,[42] triethoxy(4-(trifluoromethyl)phenyl)silane (**S1**) (8.12 g, 26.3 mmol) was mixed with thionyl chloride (30 mL) and pyridinium hydrochloride (400 mg, 3.46 mmol), and the mixture was refluxed and stirred for 43 h. The excess thionyl chloride was removed under reduced the pressure to give the crude product.

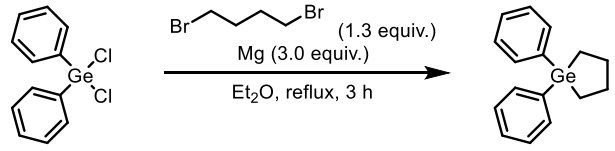
To a stirred solution of crude product in THF (130 mL) was added a solution of ethylmagnesium bromide in Et_2O (3.0 M, 31 mL, 93 mmol) dropwise at 0 ℃ and the mixture was allowed to warm up to room temperature. After stirred for 18 h, the reaction was quenched by 1*N* HCl aq. and extracted with Et_2O. The organic layer was washed with $NaHCO_3$ aq., brine, and dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane) to afford **2c** (3.79 g, 55% yield) as colorless oil. The spectral data of **2c** were identical to those reported.[43] **2c-*d*$_{15}$** (1.67 g, 49%) was also synthesized by the same procedure using the deuterated Grignard reagent (C_2D_5MgBr)



1,1-Diphenylsilolane (2d)

Following the literature procedure,[44] a portion of 1 mL of a solution of 1,4-dibromobutane (1.54 mL, 13 mmol) in Et_2O (5 mL) was added to a stirred suspension of magnesium turnings (729 mg, 30 mmol) in Et_2O (5 mL), and the reaction was started by gentle heating. Subsequently, the remaining 1,4-dibromobutane solution was added within 2 h, causing the mixture to boil under reflux. After the addition was complete, the mixture was heated under reflux for a further 90 min and then cooled to 20 ℃ within 1 h. The resulting two-phase Grignard reagent was added dropwise within 2 h to a solution of dichlorodiphenylsilane (**S3**) (2.08 mL, 10 mmol) in Et_2O (5 mL), causing the mixture to boil under reflux. The reaction mixture was stirred at 20 ℃ for 16 h and acidified with 1*N* HCl aq. The resulting mixture was extracted with Et_2O, the organic layer was washed with $NaHCO_3$ aq., brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by flash column chromatography (hexane) to afford **2d** (1.37 g, 57% yield) as colorless oil.

Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.59-7.55 (m, 4H), 7.42-7.35 (m, 6H), 1,85-1.80 (m, 4H), 1.17-1.11 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 137.1, 134.9, 129.3, 128.0, 27.9, 12.3; **IR** (neat, cm^{-1}): 3066, 2933, 1427, 1109, 694; **HRMS-EI$^+$** (*m/z*): Calcd. for $C_{18}H_{32}Si$ [M^+] 238.1178; found, 238.1175.



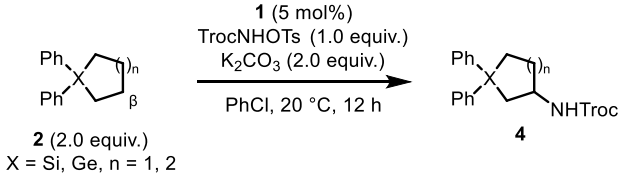
S4 **2f**

1,1-Diphenylgermolane (2f)

Following the literature procedure,[44] a portion of 0.2 mL of a solution of 1,4-dibromobutane (0.23 mL, 1.95 mmol) in Et_2O (1 mL) was added to a stirred suspension of magnesium turnings (109 mg, 4.5 mmol) in Et_2O (1 mL), and the reaction was started by gentle heating. Subsequently, the remaining 1,4-dibromobutane solution was added within 2 h, causing the mixture to boil under reflux. After the addition was complete, the mixture was heated under reflux for a further 90 min and then cooled to 20 °C within 1 h. The resulting two-phase Grignard reagent was added dropwise within 2 h to a solution of dichlorodiphenylgermane (**S4**) (0.31 mL, 1.5 mmol) in Et_2O (1 mL), causing the mixture to boil under reflux. The reaction mixture was stirred under reflux for 1 h and acidified with 1*N* HCl aq. The resulting mixture was extracted with Et_2O, the organic layer was washed with $NaHCO_3$ aq., brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by flash column chromatography (hexane) to afford **1r** (184 mg, 43% yield) as colorless oil.

Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.56-7.50 (m, 4H), 7.40-7.33 (m, 6H), 1,88-1.77 (m, 4H), 1.29-1.20 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 138.9, 134.4, 128.8, 128.3, 28.8, 13.5; **IR** (neat, cm^{-1}): 3064, 2924, 2850, 1429, 1092, 776, 697, 583, 461; **HRMS-EI$^+$** (*m/z*): Calcd. for $C_{18}H_{32}Ge$ [M^+] 284.0623; found, 284.0619.

General Procedure for Dirhodium-Catalyzed Intermolecular C-H Amination

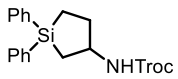


2 (2.0 equiv.)
X = Si, Ge, n = 1, 2

4

To a stirred suspension of silanes **2** (0.10 mmol, 2.0 equiv.), TrocNHOTs[11d] (18.1 mg, 0.05 mmol, 1.0 equiv.) and K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.) in PhCl (0.25 mL) were added **1**[9b] (3.4 mg, 0.0025 mmol, 0.05 equiv.) at 20 °C. After stirred for 12 h, the reaction was quenched by water and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by preparative TLC ($CHCl_3$/hexane = 2/1) to afford the aminated product **4**.

Specific Procedure and Characterization data

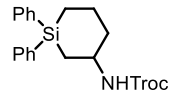


4d

2,2,2-Trichloroethyl (1,1-diphenylsilolan-3-yl)carbamate (4d)

Following the general procedure for intermolecular amination, **2d** (23.8 mg, 0.10 mmol, 2.0 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (13.8 mg, 0.10 mmol, 2.0 equiv.), and **1** (3.4 mg, 0.0025 mmol, 0.05 equiv.) were stirred at 20 °C in PhCl (0.25 mL) for 12 h. The crude material was purified by preparative TLC ($CHCl_3$/hexane = 2/1) to afford **4d** (18.8 mg, 88%) as colorless oil.

Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$, 313K) δ: 7.57-7.51 (m, 4H), 7.45-7.34 (m, 6H), 4.96 (br, 1H), 4.73 (s, 2H), 4.11-3.99 (m,1H), 2.41-2.32 (m, 1H), 1.83-1.74 (m, 1H), 1.69-1.57 (m, 1H), 1.41-1.33 (m, 1H), 1.20-1.10 (m, 1H) 1.09-1.02 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 153.9, 135.5, 135.3, 134.8, 129.9, 128.3, 128.2, 95.8, 74.5, 54.1, 33.8, 20.3, 9.7; **IR** (neat, cm^{-1}): 3327, 3052, 2949, 1718, 1519, 1125, 722; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{19}H_{20}Cl_3NO_2Si$ $[M+Na]^+$ 450.0221; found, 450.0221.

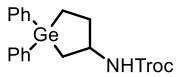


4e

2,2,2-Trichloroethyl (1,1-diphenylsilinan-3-yl)carbamate (4e)

Following the general procedure for intermolecular amination, **2e**[45] (25.2 mg, 0.10 mmol, 2.0 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (13.8 mg, 0.10 mmol, 2.0 equiv.), and **1** (3.4 mg, 0.0025 mmol, 0.05 equiv.) were stirred at 20 °C in PhCl (0.25 mL) for 12 h. The crude material was purified by preparative TLC ($CHCl_3$/hexane = 2/1) to afford a mixture of β-aminated and γ-aminated products (19.8 mg, 89%, β/γ = 25/1). The β-aminated product **4e** was isolated by preparative HPLC (AcOEt/Hexane = 15/85).

Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$, 313K) δ: 7.66-7.60 (m, 2H), 7.48-7.30 (m, 8H), 4.92 (br, 1H), 4.71 (s, 2H), 3.89-3.78 (m, 1H), 2.15-2.03 (m, 2H), 1.88 (m, 1H), 1.68-1.56 (m, 1H), 1.41-1.31 (m, 2H), 1.09-0.92 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 153.4, 136.3, 134.8, 134.4, 134.1, 129.8, 129.7, 128.4, 128.2, 95.9, 74.5, 50.5, 36.5, 21.7, 20.2, 10.4; **IR** (neat, cm^{-1}): 3335, 3064, 2921, 1718, 1503, 1117, 703; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{20}H_{22}Cl_3NO_2Si$ $[M+Na]^+$ 464.0378; found, 464.0385.



4f

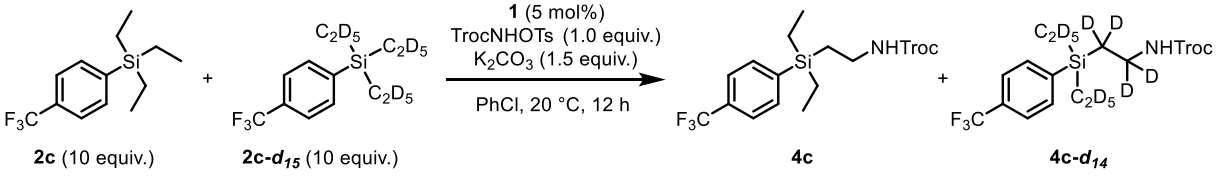
2,2,2-Trichloroethyl (1,1-diphenylgermolan-3-yl)carbamate (4f)

Following the general procedure for intermolecular amination, **2f** (28.8 mg, 0.10 mmol, 2.0 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (13.8 mg, 0.10 mmol, 2.0 equiv.), and **1** (3.4 mg, 0.0025 mmol, 0.05 equiv.) were stirred at 20 °C in PhCl (0.25 mL) for 12 h. The crude material was purified by preparative thin-layer chromatography purification ($CHCl_3$/hexane = 2/1) to afford **4f** (16.7 mg, 71%) as colorless oil.

Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$, 313K) δ: 7.53-7.48 (m, 4H), 7.42-7.35 (m, 6H), 4.93 (br, 1H), 4.73 (s, 2H), 4.09-4.02 (m,1H), 2.38-2.32 (m, 1H), 1.87-1.80 (m, 1H), 1.70-1.62 (m, 1H), 1.53-1.47 (m, 1H), 1.33-1.24 (m, 1H) 1.13 (dd, *J* = 8.8, 6.4 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 153.9, 137.4, 137.2, 134.2, 129.3, 129.0, 128.6, 128.5, 95.8, 74.5, 54.9, 34.5, 20.5, 11.0; **IR** (neat, cm^{-1}): 3407, 3319, 2917, 1726, 1503, 1225, 1120, 801, 739, 699; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{19}H_{20}Cl_3NO_2Ge$ $[M+Na]^+$ 491.9694; found, 491.9645.

KIE Measurement

Competitive KIE



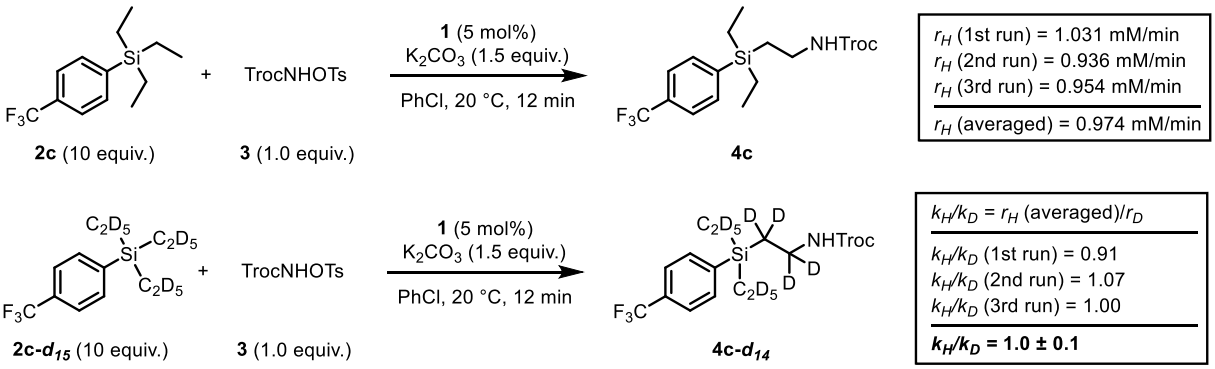
2c (10 equiv.) + **2c-*d*$_{15}$** (10 equiv.) → **4c** + **4c-*d*$_{14}$**

1st run, 55% yield, k_H/k_D = 5.67
2nd run, 57% yield, k_H/k_D = 4.90
3rd run, 55% yield, k_H/k_D = 5.46

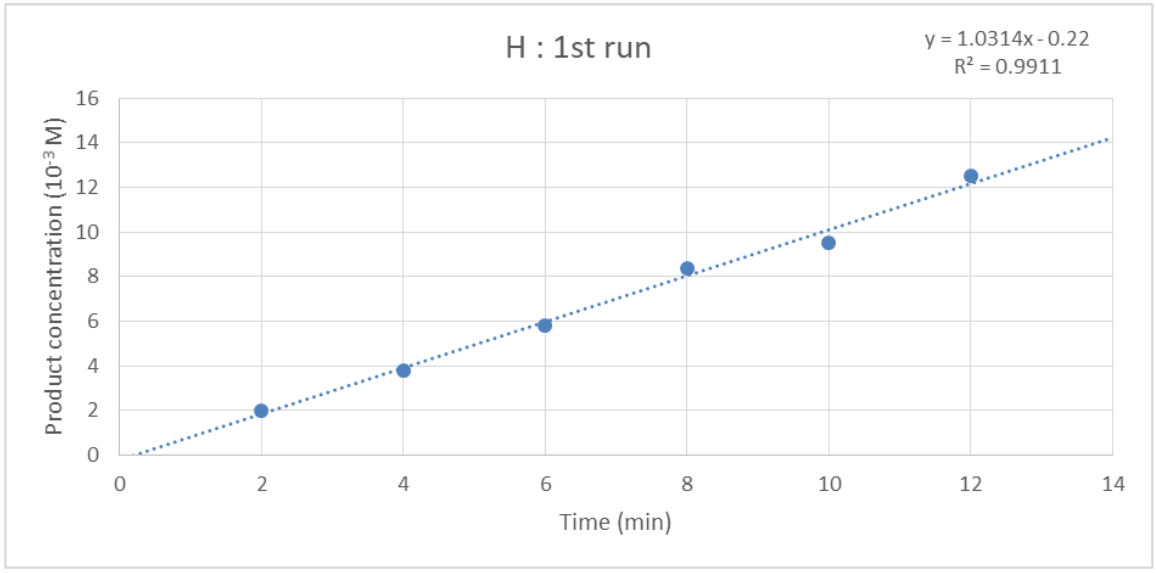
k_H/k_D = 5.3 ± 0.4

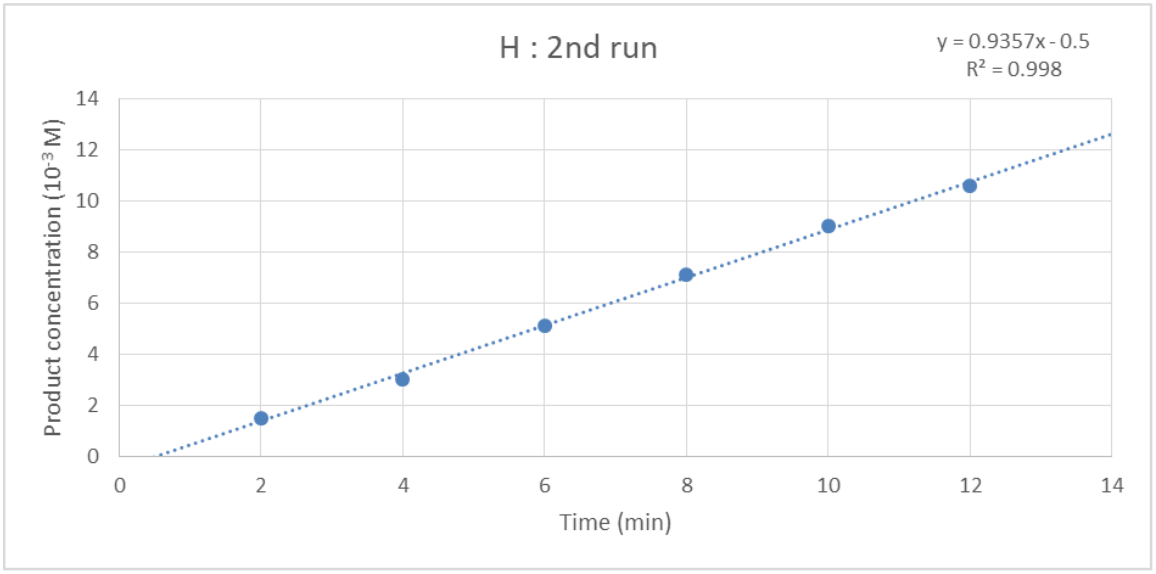
To a suspension of **2c** (65.1 mg, 0.25 mmol, 5.0 equiv.), **2c-*d*$_{15}$** (68.9 mg, 0.25 mmol, 5.0 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.) and K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.) in PhCl (0.5 mL) was added **1** (3.4 mg, 0.0025 mmol, 0.05 equiv.) at 20 °C. After being stirred for 12 h at 20 °C, the reaction was quenched by addition of water and extracted with $CHCl_3$. The organic layer was washed with brine, and dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC ($CHCl_3$/hexane =2/1) to afford a mixture of **4c** and **4c-*d*$_{14}$**. KIE was calculated from the comparison of the integrals between a nitrogen α signal (δ 3.42–3.25 ppm, 2H of **4c**) and a trichloroethyl signal (δ 4.69 ppm, 2H of **4c** and **4c-*d*$_{14}$**) in ^{1}H NMR of a solution of **4c** and **4c-*d*$_{14}$** ($CDCl_3$). The experiments were performed three times and the determined KIE was the average of three runs.

Parallel KIE



To a suspension of **2c** or **2c-*d*$_{15}$** (1.0 mmol, 10.0 equiv.), TrocNHOTs (36.3 mg, 0.10 mmol, 1.0 equiv.) and K_2CO_3 (20.7 mg, 0.15 mmol, 1.5 equiv.) in PhCl (1.0 mL) was added **1** (6.8 mg, 0.0050 mmol, 0.05 equiv.) at 20 °C. Aliquots (50 μL) were taken every 2 minites from the reaction flask for 12 minites, and filtered through a short silica pad with 1 mL of $CDCl_3$ for ^{19}F NMR analysis. The yield was determined from the comparison of the integrals of the product peaks relative to the 4-bromobenzofluoride internal standard. The experiments were performed three times for each substrate. The averaged r_H was calculated by the three runs. The k_H/k_D value (k_H/k_D = 1.0 ± 0.1) was determined by using the averaged r_H and r_D (**Figure S1** and **S2**; 1st-3rd runs).





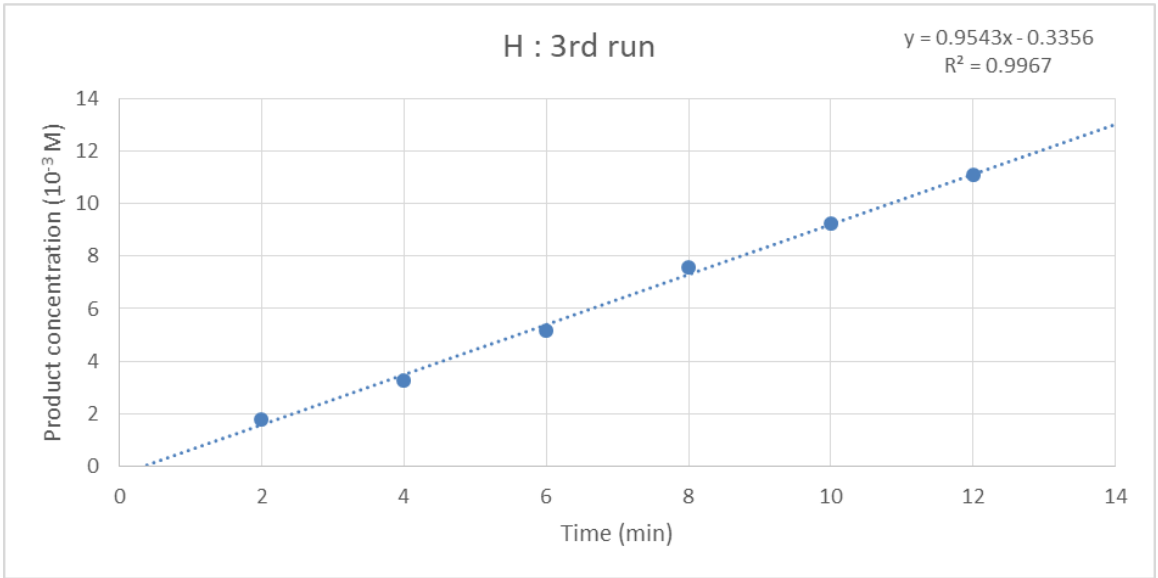
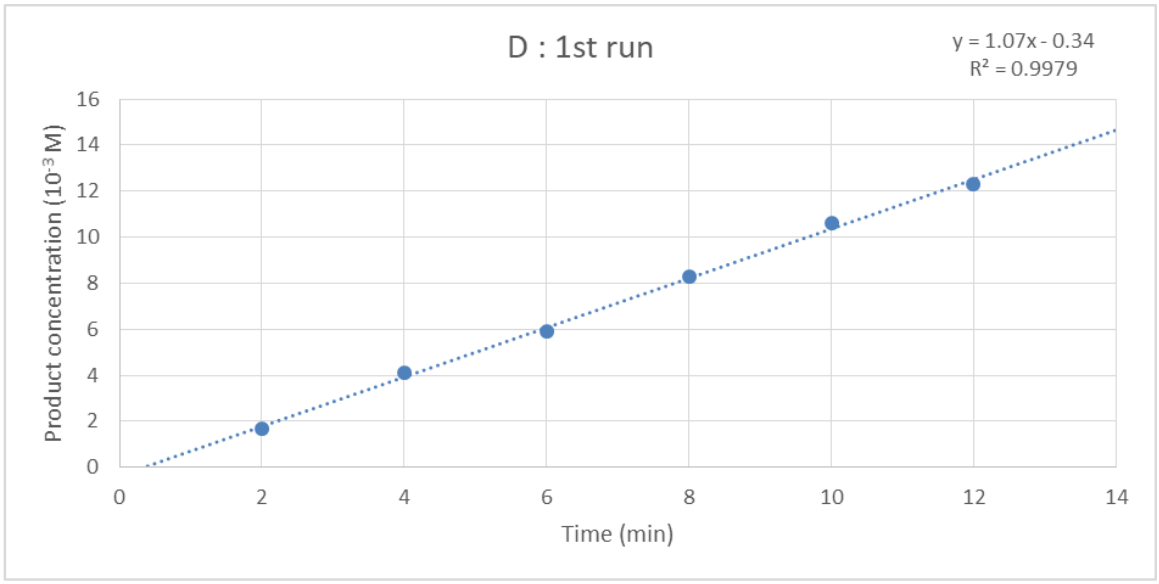
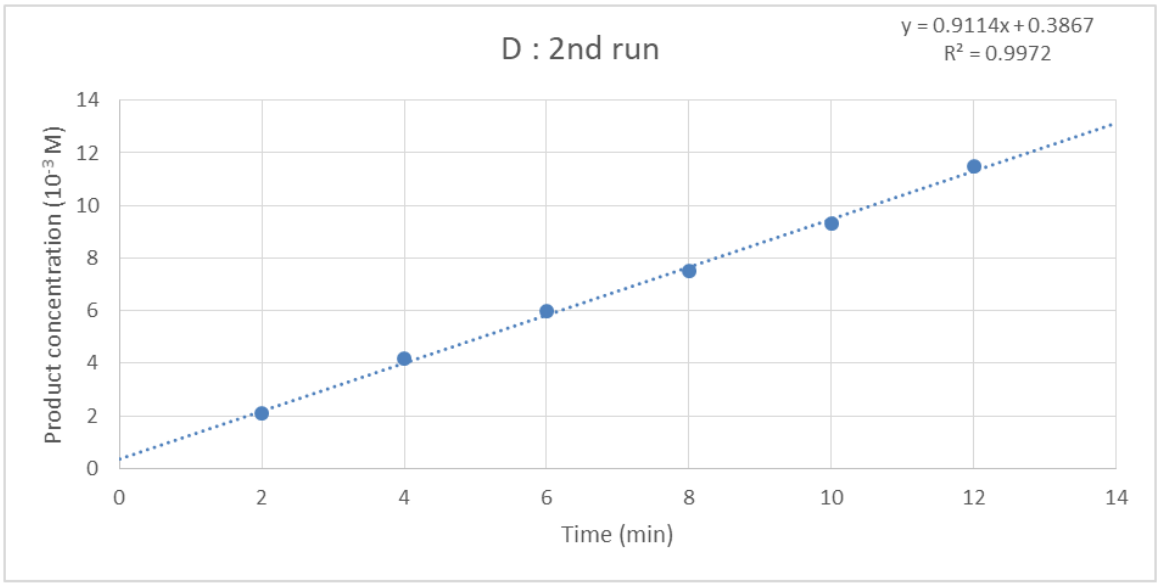


Figure S1. Initial Rate Analysis for C-H Amination of **2c**





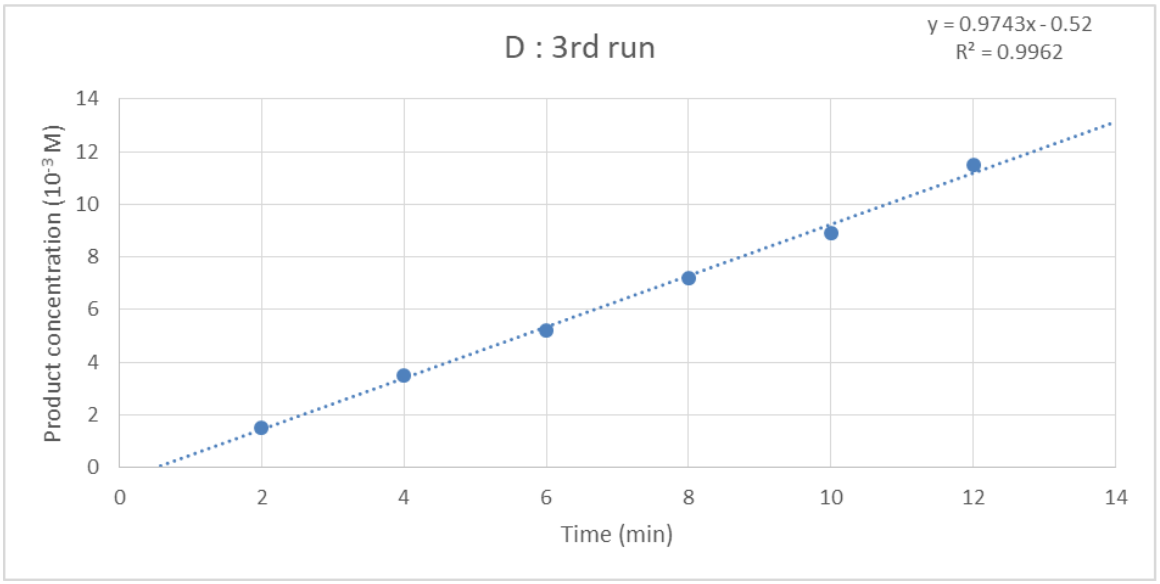


Figure S2. Initial Rate Analysis for C-H Amination of **2c-*d*$_{15}$**

Computational Details

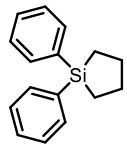
All calculation reported in the present study were carried out using density functional theory (DFT) with (U)M06[46] or B3PW91 functional, as implemented in the Gaussian 09 (Revision E.01)[47]. For geometry optimizations, the 6-31G(d,p) basis set was used for the H, C, N, O, Si, Cl elements, and the LANL2DZ[48] basis set and pseudopotential for Rh. Based on these optimized geometries, single-point energy calculations were performed using the 6-311++G(2d,2p) basis set for the H, C, N, O, Si, Cl elements, and the SDD[49] basis set and pseudopotential for Rh with solvents effects simulated by SMD[50] solvent model (chlorobenzene). The stationary points were confirmed as minima (no imaginary frequencies) or transition state (only one imaginary frequency) by analytical frequency calculations as the same theory level as the geometry optimizations. Computational time was generously provided by the Supercomputer Laboratory in the Institute for Chemical Research of Kyoto University.

Calculated Structures for Figure2-2

XYZ coordinates and thermochemical data (energies in Hartree)

Temperature = 298.15 K, Pressure = 1.00 atm

1,1-Diphenylsilolane (**2d**)



2d

B3PW91/6-31G(d,p)

Electronic Energy = –909.813987997 Electronic and Zero-Point Energy = –909.518600

Enthalpy = –909.502000 Free Energy = –909.563908

C	-0.19495200	2.02239100	1.40964000
C	0.06125200	3.36645900	0.69740200
C	-0.60263000	3.32219000	-0.68807900
C	-0.17022400	2.02516500	-1.40497500
H	0.49808600	1.85200100	2.23938900
H	-1.20698800	2.00354800	1.83415900
H	1.14259200	3.51017000	0.56805100
H	-0.29945000	4.21909900	1.28587100
H	-1.69410400	3.32451300	-0.56007400
H	-0.35893800	4.21564800	-1.27600100
H	-0.85062500	1.74932000	-2.21608800
H	0.82409000	2.16039200	-1.84935600

Si	-0.06768400	0.74286200	0.00365800
C	-1.50179800	-0.48854900	0.00331500
C	-1.29694500	-1.86863400	-0.15116600
C	-2.82675600	-0.03743200	0.13677500
C	-2.36813700	-2.76133100	-0.17313100
H	-0.28483400	-2.25246600	-0.25297400
C	-3.90087200	-0.92355300	0.11468800
H	-3.02867700	1.02489400	0.26141600
C	-3.67246600	-2.29051400	-0.04055500
H	-2.18310100	-3.82570500	-0.29265600
H	-4.91587300	-0.54925400	0.22011400
H	-4.50841500	-2.98477100	-0.05663300
C	1.56872400	-0.19929100	0.00597900
C	2.28794100	-0.42664500	-1.17874400
C	2.10282400	-0.71361700	1.19981800
C	3.48920500	-1.13420500	-1.17414000
H	1.90735500	-0.04460800	-2.12350200
C	3.30344700	-1.42080900	1.21233800
H	1.57411900	-0.55936300	2.13822600
C	3.99981800	-1.63179400	0.02315000
H	4.02745200	-1.29539400	-2.10450900
H	3.69687400	-1.80592500	2.14943000
H	4.93743400	-2.18113800	0.03003900

Calculated Structures for Figure2-4

XYZ coordinates and thermochemical data (energies in Hartree)

Temperature = 298.15 K, Pressure = 1.00 atm

Substrate (1,1-dimethylsilolane)

M06/6-31G(d,p)

Electronic Energy = –526.384354413

Electronic and Zero-Point Energy = –526.1994434

Enthalpy = –526.1887754

Free Energy = –526.2335804

M06/6-311++G(2d,2p)

Electronic Energy = –526.473103

C	-0.61013200	-0.53690400	-1.29524300
C	-1.91745800	-0.58755600	-0.49029600
C	-1.91743100	0.58755600	0.49040800
C	-0.61005600	0.53690800	1.29527800
H	-0.38487600	-1.48558400	-1.79536000
H	-0.68267900	0.23166900	-2.07876100
H	-1.95549200	-1.52577400	0.08722700
H	-2.80831100	-0.58125000	-1.13243000
H	-1.95550100	1.52577400	-0.08711200
H	-2.80824600	0.58124800	1.13259400
H	-0.38477200	1.48558900	1.79537900
H	-0.68255600	-0.23166300	2.07880300
Si	0.67295100	0.00000000	-0.00001900
C	1.73709800	-1.42865800	0.60467500
H	2.42827400	-1.77921100	-0.17004800
H	2.33211300	-1.14345300	1.47990200
H	1.10296000	-2.27537800	0.89571100
C	1.73706800	1.42865400	-0.60477600
H	2.42828300	1.77921400	0.16991000
H	2.33203800	1.14344400	-1.48003200
H	1.10291400	2.27537100	-0.89578600

Substrate (1,1-dimethylcyclopentane)

M06/6-31G(d,p)

Electronic Energy = –274.974048652

Electronic and Zero-Point Energy = –274.777917

Enthalpy = –274.769414

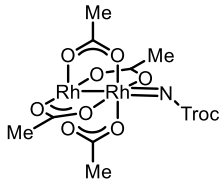
Free Energy = –274.808820

M06/6-311++G(2d,2p)

Electronic Energy = –275.045048687

C	-1.65259300	-0.77409200	-0.00868800
C	-0.22934400	-1.18397500	-0.40942000
C	0.66089800	0.00000100	-0.01004300
C	-0.22934600	1.18397400	-0.40942800
C	-1.65259600	0.77408800	-0.00869500
H	-2.40141400	-1.18992600	-0.69161000
H	-1.90105000	-1.15950100	0.98796900
H	-0.16677300	-1.31644900	-1.50022400
H	0.09733000	-2.12818700	0.04717000
H	0.09732700	2.12818700	0.04716100
H	-0.16677600	1.31645100	-1.50023200
H	-1.90104900	1.15950400	0.98796000
H	-2.40141800	1.18991600	-0.69161900
C	0.90856300	0.00000700	1.49734400
H	1.48168400	-0.88691800	1.79832500
H	1.48166000	0.88694600	1.79832300
H	-0.02706900	-0.00000500	2.06932900
C	1.99226700	-0.00000300	-0.74326000
H	2.58721000	0.88594800	-0.48400100
H	2.58720200	-0.88596300	-0.48400800
H	1.84604400	0.00000000	-1.83139800

Rh nitrenoid (singlet state)



M06/6-31G(d,p)[LANL2DZ]

Electronic Energy = –2833.52349

Electronic and Zero-Point Energy = –2833.255374

Enthalpy = –2833.227067

Free Energy = –2833.314106

M06/6-311++G(2d,2p)[SDD]

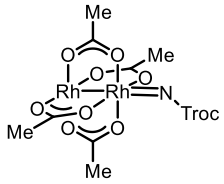
Electronic Energy = –2836.132154

Rh	0.000002686	0.000002787	0.000005616
Rh	-0.000001629	0.000000304	0.000001338

O	0.000001324	-0.000000116	-0.000000784
O	0.000005401	0.000002126	0.000003282
O	-0.000000428	0.000003479	0.000008449
O	-0.000004407	0.000001220	0.000004412
O	0.000001738	-0.000000297	-0.000001301
O	0.000005779	0.000001948	0.000002760
O	-0.000000341	.000003156	0.000007694
O	-0.000004469	0.000000874	0.000003605
C	0.000004147	0.000000892	0.000000698
C	0.000006266	0.000000462	-0.000000990
H	0.000004421	-0.000000186	-0.000001969
H	0.000007927	-0.000000157	-0.000003078
H	0.000008007	0.000001468	0.000000809
C	-0.000003264	0.000002601	0.000007289
C	-0.000005475	0.000003139	0.000009315
H	-0.000008350	0.000002680	0.000009209
H	-0.000005056	0.000002739	0.000008242
H	-0.000004686	0.000004334	0.000011921
C	-0.000003042	0.000002157	0.000006168
C	-0.000005316	0.000002474	0.000007742
H	-0.000007994	0.000002430	0.000008478
H	-0.000004000	0.000003583	0.000009908
H	-0.000005577	0.000001670	0.000005852
C	0.000004549	0.000000632	-0.000000115
C	0.000006690	0.000000010	-0.000002255
H	0.000005167	-0.000000316	-0.000002454
H	0.000007128	-0.000001001	-0.000004780
H	0.000009294	0.000000826	-0.000001186
N	-0.000004742	-0.000001694	-0.000002345
C	-0.000004070	-0.000002687	-0.000005006
O	-0.000006185	-0.000003063	-0.000005307
O	-0.000001199	-0.000003101	-0.000007007
C	-0.000000222	-0.000004070	-0.000009554
H	-0.000002192	-0.000004304	-0.000009535
H	0.000002459	-0.000003476	-0.000009132
C	-0.000000156	-0.000005420	-0.000012972
Cl	-0.000004464	-0.000006440	-0.000013848
Cl	0.000003061	-0.000005120	-0.000013180

Cl	0.000001220	-0.000006543	-0.000015988

Rh Nitrenoid (triplet state)



UM06/6-31G(d,p)[LANL2DZ]

Electronic Energy = –2833.530333

Electronic and Zero-Point Energy = –2833.262826

Enthalpy = –2833.235075

Free Energy = –2833.321382

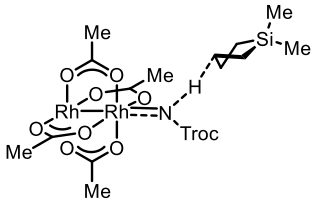
UM06/6-311++G(2d,2p)[SDD]

Electronic Energy = –2836.137797

Rh	-0.000000573	0.000000686	-0.000002045
Rh	0.000000673	0.000001570	0.000000674
O	-0.000002057	-0.000001884	-0.000001686
O	-0.000003253	-0.000002421	-0.000003412
O	-0.000000934	0.000003107	-0.000005858
O	-0.000000070	0.000003567	-0.000004708
O	0.000001339	-0.000000473	0.000003290
O	-0.000000164	-0.000001712	0.000001854
O	0.000002152	0.000003819	-0.000000625
O	0.000003217	0.000004891	0.000000201
C	-0.000003416	-0.000003032	-0.000002902
C	-0.000005340	-0.000005346	-0.000003813
H	-0.000005726	-0.000004685	-0.000005413
H	-0.000005329	-0.000006680	-0.000002077
H	-0.000006378	-0.000006336	-0.000004619
C	-0.000000697	0.000003951	-0.000006359
C	-0.000001079	0.000005552	-0.000009226
H	0.000000110	0.000007316	-0.000009109
H	-0.000002308	0.000004434	-0.000010256
H	-0.000001381	0.000006003	-0.000010417
C	0.000003434	0.000005267	0.000000136
C	0.000005385	0.000007620	0.000000991
H	0.000005832	0.000009360	-0.000000326

H	0.000005417	0.000007787	0.000000842
H	0.000006378	0.000007518	0.000003106
C	0.000000740	-0.000001709	0.000003653
C	0.000001184	-0.000003283	0.000006529
H	0.000002698	-0.000001942	0.000007854
H	0.000000897	-0.000004372	0.000007353
H	0.000000371	-0.000004574	0.000006581
N	0.000001276	0.000001674	0.000000442
C	0.000000195	-0.000000320	0.000000786
O	-0.000000650	-0.000000403	-0.000000813
O	0.000000193	-0.000002155	0.000003141
C	-0.000000958	-0.000004370	0.000003693
H	-0.000001818	-0.000004358	0.000001929
H	-0.000001833	-0.000006102	0.000004129
C	0.000000298	-0.000004414	0.000006236
Cl	0.000001741	-0.000001691	0.000005620
Cl	0.000001727	-0.000004497	0.000009159
Cl	-0.000001294	-0.000007363	0.000006816

TS for C-H insertion of 1,1-dimethylsilolane (singlet state)



M06/6-31G(d,p)[LANL2DZ]

Electronic Energy = –3359.90675919

Electronic and Zero-Point Energy = –3359.455442

Enthalpy = –3359.411894

Free Energy = –3359.536186

M06/6-311++G(2d,2p)[SDD]

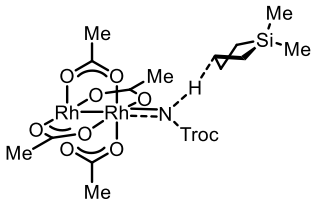
Electronic Energy = –3362.606526

Rh	-2.91839300	-1.74742900	0.06572100
Rh	-0.80023100	-0.56170600	-0.00771300
O	-0.20067200	-1.82790100	-1.51774400
O	-2.10876800	-3.03641200	-1.34754200

O	-3.59179900	-0.51432500	-1.45000000
O	-1.67241900	0.66692800	-1.40166100
O	-0.14430600	-1.93730300	1.38279900
O	-2.16802200	-2.92226900	1.57925200
O	-3.54532200	-0.34971300	1.45634000
O	-1.51218000	0.64543900	1.51498400
C	-0.97022500	-2.79588000	-1.83030800
C	-0.43251200	-3.74155600	-2.86366900
H	0.06793200	-3.18295000	-3.65842600
H	0.31431600	-4.39032200	-2.39409700
H	-1.23528400	-4.35888400	-3.26988800
C	-2.84376500	0.42012400	-1.83781900
C	-3.33802600	1.32764700	-2.92334000
H	-2.99411100	2.35018900	-2.74462200
H	-2.91581400	0.99759700	-3.87834900
H	-4.42679000	1.28777900	-2.98579300
C	-2.72663600	0.51530900	1.87196600
C	-3.20872400	1.50597000	2.89113300
H	-3.08152300	2.51917200	2.49534900
H	-4.25618100	1.32669700	3.13775000
H	-2.59190600	1.43060100	3.79150300
C	-0.95503400	-2.77446400	1.89108200
C	-0.40110000	-3.64303400	2.98059500
H	-0.40010300	-3.07406900	3.91619900
H	0.63300500	-3.91461800	2.75676700
H	-1.02063600	-4.53239400	3.10781900
N	0.87487200	0.44678800	0.00842700
C	1.90490700	0.01685000	-0.80056900
O	2.21554600	0.48537100	-1.87214600
O	2.56313300	-0.98583300	-0.15989500
C	3.77834100	-1.39343600	-0.73767800
H	3.88860300	-0.97798600	-1.74631200
H	3.79377300	-2.48802800	-0.77447100
C	4.95661000	-0.93063200	0.11147000
Cl	4.98468100	0.84794900	0.21241200
Cl	4.85914400	-1.62093100	1.75216100
Cl	6.44377100	-1.51718500	-0.69755500
C	1.49379600	5.08863100	-0.50937600

C	1.68810900	3.56091900	-0.54872500
C	0.34294000	2.94063000	-0.89283300
C	-0.71691800	3.44891000	0.06046300
H	2.29946500	5.59695500	0.03213100
H	1.48946000	5.49265300	-1.53221100
H	1.98340700	3.19780000	0.44950400
H	2.46878000	3.24506600	-1.25160100
H	0.07993300	3.09305600	-1.95147000
H	0.42393900	1.80334700	-0.78752600
H	-1.73752400	3.24423400	-0.28331500
H	-0.59547600	2.94967200	1.03490400
Si	-0.23704400	5.28758500	0.25157800
C	-0.20866100	5.80330700	2.05941000
H	0.13511600	6.83668800	2.18210200
H	-1.20469500	5.72574400	2.51118300
H	0.46691200	5.15346400	2.62899700
C	-1.34538200	6.41844800	-0.76296100
H	-2.37090000	6.43223200	-0.37649100
H	-0.97423900	7.44986600	-0.76325900
H	-1.38385300	6.07827300	-1.80525700

TS for C-H insertion of 1,1-dimethylsilolane (triplet state)



UM06/6-31G(d,p)[LANL2DZ]

Electronic Energy = –3359.903298

Electronic and Zero-Point Energy = –3359.45522

Enthalpy = –3359.412421

Free Energy = –3359.533915

UM06/6-311++G(2d,2p)[SDD]

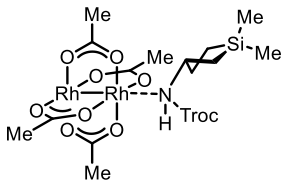
Electronic Energy = –3362.601964

Rh	3.81826300	0.19484600	-0.22856400

Rh	1.46413600	-0.26023200	0.11926800
O	1.50737900	-1.26328400	-1.68542900
O	3.70541700	-0.84319200	-2.00638400
O	4.21777900	-1.57571500	0.74873600
O	2.01996600	-1.98636500	1.08901600
O	1.07400400	1.52468700	-0.86157000
O	3.27064000	1.95089700	-1.18353100
O	3.79902100	1.20274600	1.57394100
O	1.59791400	0.79822400	1.88521500
C	2.59773200	-1.35118300	-2.33299800
C	2.53889800	-2.15034200	-3.60081900
H	1.70294200	-1.80618300	-4.21577700
H	3.47790300	-2.06745300	-4.15000000
H	2.34801600	-3.19862300	-3.35062600
C	3.25553600	-2.26367600	1.19165900
C	3.58911000	-3.51946700	1.94028300
H	3.63081500	-3.28894600	3.01012300
H	2.81082100	-4.26969600	1.78629400
H	4.56509300	-3.89638900	1.62848200
C	2.71984800	1.29678700	2.21922600
C	2.73684100	2.05950900	3.51075600
H	2.47486900	1.38522500	4.33164200
H	3.72162800	2.49493500	3.68615400
H	1.97544400	2.84412600	3.48031300
C	2.04522100	2.22690200	-1.28698600
C	1.66658400	3.49438200	-1.99690000
H	1.32475000	3.24504500	-3.00707500
H	2.52401500	4.16571500	-2.06758200
H	0.83526400	3.97980200	-1.47690800
N	-0.49185500	-0.52694100	0.25208900
C	-1.25473900	-1.58710900	-0.15022600
O	-0.90356500	-2.74428300	-0.17404200
O	-2.50347400	-1.16304300	-0.53880100
C	-3.41312100	-2.15904900	-0.92583300
H	-2.95041000	-3.15197800	-0.86956500
H	-3.74936300	-1.96289200	-1.95144000
C	-4.63581700	-2.13735700	-0.01980800
Cl	-4.16550400	-2.45811700	1.66567200

Cl	-5.46446300	-0.54937000	-0.12203600
Cl	-5.74455300	-3.41371900	-0.60027800
C	-2.43306200	2.12540100	-0.81173100
C	-1.78266200	1.74107000	0.49071500
C	-2.81200800	1.55398000	1.58953800
C	-3.73183600	2.79710900	1.60006900
H	-1.71010400	2.46026300	-1.56338800
H	-3.00103200	1.27574300	-1.22082800
H	-0.94802800	2.40222600	0.77134000
H	-1.17761100	0.65870600	0.34988900
H	-3.40866300	0.66132400	1.35114600
H	-2.33617000	1.37188800	2.56080800
H	-4.74004900	2.55387800	1.95672600
H	-3.33132600	3.56585900	2.27530600
Si	-3.66879800	3.44077400	-0.19185200
C	-5.32034700	3.42421100	-1.09020300
H	-6.01980900	4.13733700	-0.63846100
H	-5.20363600	3.69601200	-2.14541700
H	-5.78441100	2.43176600	-1.05078800
C	-2.88436000	5.15013400	-0.26512500
H	-2.75453900	5.49430100	-1.29765300
H	-3.48832900	5.89679600	0.26356600
H	-1.89460800	5.12864200	0.20936000

Product (singlet state)



M06/6-31G(d,p)[LANL2DZ]

Electronic Energy = –3360.043432

Electronic and Zero-Point Energy = –3359.581922

Enthalpy = –3359.540332

Free Energy = –3359.655018

M06/6-311++G(2d,2p)[SDD]

Electronic Energy = –3362.739627

Rh	0.86755300	-2.91013200	0.34853700
Rh	0.50829500	-0.58732400	-0.20455000
O	-0.40590000	-0.37997900	1.64061400
O	-0.07709700	-2.56214900	2.14798100
O	2.67650200	-2.38439300	1.20156900
O	2.31564000	-0.19708000	0.75803500
O	-1.28604200	-1.11466300	-1.06492000
O	-0.95902700	-3.29002300	-0.53488300
O	1.79306200	-3.10385100	-1.49594300
O	1.47979300	-0.92140800	-1.99761500
C	-0.49650500	-1.39410300	2.39548700
C	-1.18638900	-1.19959200	3.71584500
H	-1.32110900	-0.13828700	3.93261200
H	-2.16576300	-1.68901000	3.67888300
H	-0.61157500	-1.68528900	4.50871700
C	2.98760900	-1.16248900	1.23738100
C	4.26788800	-0.79338000	1.93168400
H	4.80630100	-0.04038700	1.34829600
H	4.02948600	-0.34741900	2.90344900
H	4.89065900	-1.67552000	2.08888600
C	1.89344100	-2.09799000	-2.24963600
C	2.55218200	-2.29304400	-3.58463800
H	3.32245000	-1.53088700	-3.73226900
H	2.98661100	-3.29118500	-3.65794800
H	1.80572200	-2.15988300	-4.37421400
C	-1.62512600	-2.34011300	-1.03434200
C	-2.95540400	-2.68537800	-1.63583800
H	-3.12765900	-2.08840600	-2.53475300
H	-3.74501600	-2.44033600	-0.91633300
H	-3.00176100	-3.75203100	-1.86239200
N	0.20314200	1.56278100	-1.03422700
C	-1.16458400	1.84757300	-1.18764800
O	-1.72057400	1.95988500	-2.24758700
O	-1.74832500	1.98593300	0.02052300
C	-3.06224800	2.49038500	0.04760900
H	-3.28329700	3.07202800	-0.85581700
H	-3.12681900	3.12977500	0.93432200

C	-4.13618600	1.41060100	0.18813300
Cl	-4.36244500	0.49201100	-1.31186500
Cl	-3.74043200	0.29981700	1.52140500
Cl	-5.65884500	2.29199900	0.56878700
C	1.65069300	4.80342900	0.44589400
C	0.62301700	3.97834700	-0.34411000
C	1.05790400	2.51092000	-0.25496700
C	2.49581000	2.43618500	-0.76210700
H	1.64365600	5.85820400	0.15112000
H	1.41522600	4.76958700	1.51871500
H	0.62901600	4.27487800	-1.40620900
H	-0.39924200	4.12432800	0.02817400
H	1.01037700	2.18537000	0.79680000
H	0.58059600	1.43368500	-1.97385500
H	2.95185400	1.46114500	-0.56621300
H	2.49999200	2.61678600	-1.84993800
Si	3.30244900	3.90777600	0.12073000
C	4.46972000	4.87615800	-0.98669900
H	4.84189300	5.77791700	-0.48759200
H	5.33821400	4.27368200	-1.27636400
H	3.95888300	5.18938700	-1.90526400
C	4.13087600	3.34580100	1.71084200
H	5.11907400	2.91245200	1.51727900
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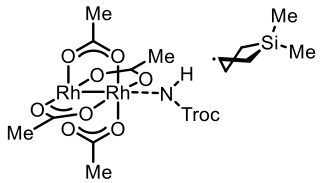
H	3.51340700	2.56977000	2.18221400

Intermediate (triplet state)



UM06/6-31G(d,p)[LANL2DZ]

Electronic Energy = –3359.926392

Electronic and Zero-Point Energy = –3359.472912

Enthalpy = –3359.429006

Free Energy = –3359.552601

UM06/6-311++G(2d,2p)[SDD]

Electronic Energy = –3362.629534

Rh	3.83302400	0.27093200	0.28627800
Rh	1.49874100	-0.13639100	-0.17211500
O	2.10381000	-1.41947000	-1.65845500
O	4.28911000	-1.07992500	-1.19772100
O	3.76810300	-1.28032000	1.63984600
O	1.58597900	-1.66194700	1.19834000
O	1.56175400	1.46045300	-1.48379200
O	3.76323100	1.79395300	-1.10387200
O	3.23341100	1.60679600	1.74480700
O	1.04913500	1.20513000	1.33046300
C	3.34479500	-1.62328700	-1.83782400
C	3.69686300	-2.60111400	-2.91729100
H	3.28675100	-2.25074700	-3.86903600
H	4.77903500	-2.71582600	-2.99380600
H	3.22725200	-3.56415000	-2.69727700
C	2.68068000	-1.90566400	1.79423300
C	2.65253800	-3.02605100	2.78905000
H	2.25550200	-2.64625600	3.73638300
H	1.98692600	-3.81823900	2.43976800
H	3.66101600	-3.40733000	2.95905500
C	2.00010900	1.78336500	1.94622500
C	1.59072100	2.74272700	3.02328000
H	1.26416900	2.17131100	3.89849700
H	2.42817400	3.38252100	3.30614400
H	0.73972200	3.34077500	2.68566500
C	2.66566500	2.06528000	-1.66459100
C	2.64103800	3.19466100	-2.65043600
H	2.49833700	2.78625100	-3.65590700
H	3.57557500	3.75632800	-2.61351600
H	1.79036400	3.84833800	-2.44004700
N	-0.43256300	-0.37345900	-0.56745600
C	-1.12691600	-1.51223600	-0.80631400
O	-0.71524600	-2.64837200	-0.80370300
O	-2.44864500	-1.18848100	-1.07948500
C	-3.33180200	-2.26350600	-1.22767900

H	-2.78370300	-3.21171800	-1.28628000
H	-3.92691700	-2.11543500	-2.13670000
C	-4.29418100	-2.33495400	-0.04816600
Cl	-3.40161000	-2.57795000	1.47155600
Cl	-5.25635500	-0.82692500	0.06143700
Cl	-5.39429600	-3.71470800	-0.34076800
C	-2.82058300	2.45702300	-1.07681500
C	-1.94238100	2.24823400	0.10638100
C	-2.62788300	1.62104600	1.28264800
C	-4.01099800	2.29987400	1.47913400
H	-2.38785200	3.10658400	-1.84383400
H	-3.09590000	1.49677800	-1.55261400
H	-0.96722400	2.72573600	0.20233200
H	-0.98590900	0.49092500	-0.59516300
H	-2.79956000	0.54737600	1.07600000
H	-2.00682400	1.66000800	2.18552400
H	-4.77771200	1.58324100	1.79779400
H	-3.95142400	3.07001400	2.25991900
Si	-4.36686600	3.14086800	-0.19088100
C	-6.00699000	2.69271700	-0.99650400
H	-6.85297700	2.95602500	-0.35114300
H	-6.13441200	3.22826800	-1.94447300
H	-6.06808400	1.61963100	-1.21134600
C	-4.21573500	5.00879900	-0.01237800
H	-4.32986900	5.52368400	-0.97326500
H	-4.96893600	5.41003100	0.67595200
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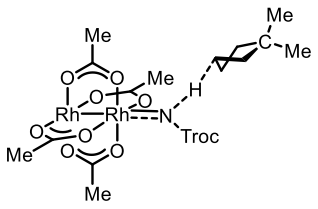
TS for C-H insertion of 1,1-dimethylcyclopentane (singlet state)



M06/6-31G(d,p)[LANL2DZ]

Electronic Energy = –3108.49541320

Electronic and Zero-Point Energy = –3108.032977

Enthalpy = –3107.992282

Free Energy = –3108.107547

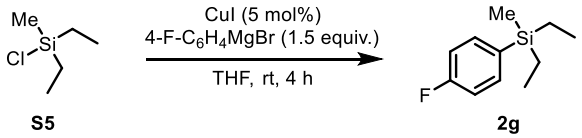
M06/6-311++G(2d,2p)[SDD]

Electronic Energy = –3111.17669927

Rh	-3.45990600	-0.05040800	0.76138500
Rh	-1.31846700	-0.13049900	-0.36909500
O	-0.92408100	-1.89315100	0.63739100
O	-2.92190800	-1.81600100	1.69911000
O	-4.27258400	-1.11930300	-0.79610000
O	-2.27700500	-1.18814200	-1.85549300
O	-0.53905000	0.91979800	1.22240600
O	-2.53489500	1.02628700	2.27166500
O	-3.82930100	1.70827500	-0.26531800
O	-1.81330500	1.64801200	-1.29521500
C	-1.79930100	-2.33348500	1.45085300
C	-1.42964000	-3.57908600	2.20235500
H	-0.85033400	-3.29696000	3.08828700
H	-2.32876500	-4.10360200	2.53091600
H	-0.80646800	-4.22627900	1.58114700
C	-3.51246200	-1.46248400	-1.74380300
C	-4.09918900	-2.29088100	-2.84737400
H	-3.77838900	-1.89962700	-3.81607300
H	-3.71281300	-3.31183500	-2.76405300
H	-5.18779900	-2.30736100	-2.77618400
C	-2.95660300	2.15586200	-1.05875700
C	-3.29253200	3.39956800	-1.82865500
H	-3.58249400	3.11502500	-2.84557300
H	-4.12379000	3.92674700	-1.35745700
H	-2.41492800	4.04591900	-1.90446100
C	-1.30795900	1.28524100	2.17119900
C	-0.66452100	2.11015300	3.24646600
H	0.24382400	1.61387000	3.60033900
H	-1.35825700	2.27269700	4.07251000
H	-0.36598000	3.07567300	2.82333000
N	0.42612700	-0.12042400	-1.35604100
C	1.21906700	-1.20625700	-1.10709100
O	1.05797200	-2.20494300	-1.77785200

O	2.12791400	-1.06652500	-0.11087300
C	2.93209100	-2.20191200	0.12132300
H	2.72956700	-2.97324500	-0.63090400
H	2.71760400	-2.59711300	1.12133800
C	4.40614100	-1.83444600	0.05704700
Cl	4.79373400	-1.10677000	-1.52368300
Cl	4.83298100	-0.69490600	1.36564200
Cl	5.33025200	-3.34928200	0.27270600
C	2.47138300	2.26895700	0.55161000
C	1.58445200	2.07196100	-0.65338100
C	2.49615600	2.26588800	-1.84114400
C	3.26502400	3.51971900	-1.41697500
H	1.91250600	2.51182300	1.46319000
H	3.02745100	1.34135300	0.74751300
H	0.68738600	2.70785200	-0.67754700
H	1.09119000	1.01521500	-0.67786700
H	3.18040300	1.40544300	-1.91825100
H	1.96840000	2.36016400	-2.79498700
H	4.22197900	3.63421300	-1.94164900
H	2.66290900	4.40975900	-1.65062500
C	4.89141000	3.01947800	0.46102500
H	5.58497000	3.83110800	0.20297000
H	5.00379700	2.80685200	1.53293200
H	5.20160300	2.12144000	-0.09071200
C	3.08807400	4.71105900	0.80917600
H	3.24910300	4.65176900	1.89378600
H	3.69652800	5.54032100	0.42369600
H	2.03219700	4.96284400	0.63684100
C	3.45574100	3.40091700	0.12274000

Synthesis of Substrates and Characterization Data



S5 **2g**

Diethyl(4-fluorophenyl)(methyl)silane (2g)

Following the literature procedure,[51] to a suspension of chlorodiethylmethylsilane (**S5**) (3.04 mL, 20 mmol) and CuI (190 mg, 1.0 mmol) in THF (100 mL) was added a solution of 4-fluorophenylmagnesium bromide in THF (1.0 M, 30 mL, 30 mmol) dropwise at 0°C and the resulting mixture was allowed to warm to room temperature. After stirred for 4 h, the reaction was quenched by saturated aq. NH_4Cl and extracted with AcOEt. The organic layer was washed by aq. NH_4Cl and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane) to afford **2g** (1.19 g, 33%) as colorless oil.

Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.46 (td, *J* = 8.8, 1.4 Hz, 2H), 7.04 (t, *J* = 8.8 Hz, 2H), 0.93 (t, *J* = 7.8 Hz, 6H), 0.73 (td, *J* = 7.8 Hz, 4H), 0.22 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 163.7 (d, *J* = 247.1 Hz), 135.9 (d, *J* = 7.2 Hz), 133.9 (d, *J* = 4.4 Hz), 115.0 (d, *J* = 20.1 Hz), 7.5, 5.6, -5.9; **^{19}F NMR** (376 MHz, $CDCl_3$) δ: -112.4 (tt, *J* = 9.5, 6.5 Hz); **IR** (neat, cm^{-1}): 2955, 2877, 1589, 1233, 1163, 1104, 823, 790, 747; **HRMS-EI$^+$** (*m/z*): Calcd. for $C_{11}H_{17}FSi$ $[M]^+$ 196.1084; found, 196.1088.

S6 **2h**

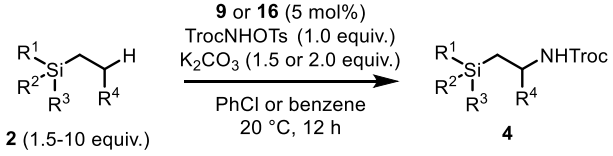
(4-Fluorophenyl)dimethyl(propyl)silane (2h)

Following the literature procedure,[51] to a suspension of chlorodimethylpropylsilane (**S6**) (1.25 mL, 8.0 mmol) and CuI (76 mg, 0.40 mmol) in THF (40 mL) was added a solution of 4-fluorophenylmagnesium bromide in THF (1.0 M, 12 mL, 12 mmol) dropwise at 0°C and the resulting mixture was allowed to warm to room temperature. After stirred for 7 h, the reaction was quenched by saturated aq. NH_4Cl and extracted with AcOEt. The organic layer was washed by aq. NH_4Cl and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane) to afford **2h** (1.35 g, 80%) as colorless oil.

Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$, 313K) δ: 7.47 (dd, *J* = 8.0, 6.0 Hz, 2H), 7.04 (t, *J* = 9.0 Hz, 2H), 1.40-1.28 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.76-0.68 (m, 2H), 0.24 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 163.7 (d, *J* = 245.6 Hz), 135.6 (d, *J* = 7.2 Hz), 135.3 (d, *J* = 2.9 Hz), 115.0 (d, *J* = 18.6 Hz), 18.6, 18.4, 17.5, -2.7; **^{19}F NMR** (376

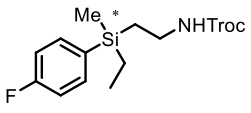
MHz, $CDCl_3$) δ: -112.6 (m); **IR** (neat, cm^{-1}): 2956, 1588, 1499, 1254, 1232, 1163, 1104, 837, 822, 766; **HRMS-EI**$^+$ (*m/z*): Calcd. for $C_{11}H_{17}FSi$ $[M]^+$ 196.1084; found, 196.1089.

General Procedure for Dirhodium-Catalyzed Asymmetric Intermolecular C-H Amination



To a stirred suspension of silanes **2**, TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.) and K_2CO_3 in PhCl or benzene were added **9** or **16** (0.0025 mmol, 0.05 equiv.) at 20 °C. After stirred for 12 h, the reaction was quenched by water and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by preparative TLC to afford the aminated product **4**.

Specific Procedure and Characterization data

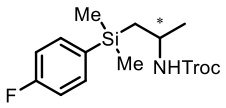


4g

2,2,2-Trichloroethyl (2-(ethyl(4-fluorophenyl)(methyl)silyl)ethyl)carbamate (4g)

Following the general procedure for asymmetric intermolecular amination, **2g** (98.2 mg, 0.50 mmol, 10 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.), and **9** (3.6 mg, 0.0025 mmol, 0.05 equiv.) were stirred at 20 °C in PhCl (0.50 mL) for 12 h. The crude material was purified by preparative TLC ($CHCl_3$/hexane = 2/1) to afford **4g** (9.0 mg, 46%, 2% ee) as colorless oil.

Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$, 323K) δ: 7.47 (dd, *J* = 7.6, 6.0 Hz, 2H), 7.06 (t, *J* = 9.0 Hz, 2H), 4.82 (br s, 1H), 4.69 (s, 2H), 3.33-3.21 (m, 2H), 1.11 (t, *J* = 8.4 Hz, 2H), 0.98 (t, *J* = 7.8 Hz, 3H), 0.80 (q, *J* = 7.6 Hz, 2H), 0.31 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$, 323K) δ: 164.1 (d, *J* = 247.1 Hz), 154.4, 135.8 (d, *J* = 7.2 Hz), 132.6, 115.4 (d, *J* = 20.3 Hz), 95.9, 74.7, 37.9, 15.9, 7.3, 6.0, -5.4; **^{19}F NMR** (376 MHz, $CDCl_3$) δ: -111.5 (tt, *J* = 9.0, 6.0 Hz); **IR** (neat, cm^{-1}): 3339, 2952, 1723, 1587, 1501, 1234, 1137, 822, 790, 723; **HRMS-ESI**$^+$ (*m/z*): Calcd. for $C_{14}H_{19}Cl_3FNO_2Si$ $[M+H]^+$ 386.0307; found, 386.0285; ee was determined after deprotection of Troc group[ref] and subsequent benzoylation.; HPLC conditions: column: Daicel Chiralpak AD-H, flow rate: 1.0 mL/min, eluent: hexane/IPA = 98/2, retention time (min): 69.9 (minor), 74.2 (major).

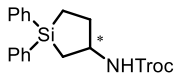


4h

2,2,2-Trichloroethyl (1-((4-fluorophenyl)dimethylsilyl)propan-2-yl)carbamate (4h)

Following the general procedure for asymmetric intermolecular amination, **2h** (15.8 mg, 0.075 mmol, 1.5 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.), and **9** (3.6 mg, 0.0025 mmol, 0.05 equiv.) were stirred at 20 °C in PhCl (0.50 mL) for 12 h. The crude material was purified by preparative TLC ($CHCl_3$/hexane = 2/1) to afford **4h** (9.4 mg, 48%) as colorless oil.

Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$, 323K) δ: 7.48 (dd, *J* = 8.4, 6.4 Hz, 2H), 7.06 (t, *J* = 9.0 Hz, 2H), 4.80-4.60(m, 3H), 3.95-3.82 (m, 1H), 1.21-1.12 (m, 4H), 1.03 (dd, *J* = 14.8, 7.4 Hz, 1H), 0.34 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$, 323K) δ: 164.5 (d, *J* = 247.1 Hz), 153.5, 135.6 (d, *J* = 7.2 Hz), 134.2, 115.3 (d, *J* = 18.6 Hz), 95.9, 74.6, 45.6, 25.8, 24.7, -2.1, -2.3; **^{19}F NMR** (376 MHz, $CDCl_3$) δ: -111.7 (tt, *J* = 9.4, 6.4 Hz); **IR** (neat, cm^{-1}):3335, 2960, 1718, 1589, 1502, 1233, 1163, 1108, 822, 728; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{14}H_{19}Cl_3FNO_2Si$ $[M+Na]^+$ 408.0127; found, 408.0107.; ee was determined after deprotection of Troc group and subseaquent benzoylation.; HPLC conditions: column: Daicel Chiralcel OD-H, flow rate: 1.0 mL/min, eluent: hexane/IPA = 99/1, retention time (min): 35.4 (minor), 40.0 (major).

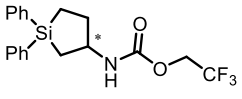


4d

2,2,2-Trichloroethyl (1,1-diphenylsilolan-3-yl)carbamate (4d)

Following the general procedure for asymmetric intermolecular amination, **2d** (23.8 mg, 0.10 mmol, 2.0 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (13.8 mg, 0.10 mmol, 2.0 equiv.), and **16** (3.6 mg, 0.0025 mmol, 0.05 equiv.) were stirred at 20 °C in benzene (0.25 mL) for 12 h. The crude material was purified by preparative TLC (AcOEt/hexane = 75/25) to afford **4d** (18.8 mg, 90%, 63% ee) as colorless oil.

Analytical data: $[\alpha]_D^{20}$ = -125 (c 0.62, $CHCl_3$, 63% ee); HPLC conditions: column: Daicel Chiralpak AD-H, flow rate: 1.0 mL/min, eluent: hexane/IPA = 98/2, retention time (min): 14.2 (major), 15.7 (minor).

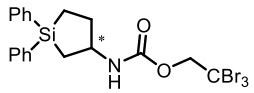


22

2,2,2-Trifluoroethyl (1,1-diphenylsilolan-3-yl)carbamate (22)

Following the general procedure for asymmetric intermolecular amination, **2d** (23.8 mg, 0.10 mmol, 2.0 equiv.), **18**[14] (15.6 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (13.8 mg, 0.10 mmol, 2.0 equiv.), and **16** (3.6 mg, 0.0025 mmol, 0.05 equiv.) were stirred at 20 °C in benzene (0.25 mL) for 12 h. The crude material was purified by preparative TLC ($CHCl_3$/hexane = 60/40) to afford **22** (14.6 mg, 76%, 58% ee) as white amorphous.

Analytical data: $[\alpha]_D^{20}$ = -29.2 (c 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$, 323K) δ: 7.54 (t, *J* = 7.6 Hz, 4H), 7.45-7.33 (m, 6H), 4.87 (br s, 1H), 4.45 (q, *J* = 8.0 Hz, 2H), 4.10-3.96 (m, 1H), 2.34 (br s, 1H), 1.76 (dd, *J* = 14.4, 6.0 Hz, 1H), 1.68-1.54 (m, 1H), 1.36 (ddd, *J* = 15.2, 7.2, 3.2 Hz, 1H), 1.20-1.09 (m, 1H), 1.03 (dd, *J* = 14.8, 10.4 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$, 323K) δ:153.8, 135.6, 135.4, 134.8, 129.9, 128.3, 128.3, 123.4 (q, *J* = 275.7 Hz), 61.3 (q, *J* = 37.4 Hz), 54.3, 33.8, 20.4, 9.7; **^{19}F NMR** (564 MHz, $CDCl_3$, 323K) δ: -74.2; **IR** (KBr, cm^{-1}): 3290, 1711, 1537, 1303, 1282, 1242, 1171, 1121, 737, 701; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{19}H_{20}F_3NO_2Si$ $[M+Na]^+$ 402.1108; found, 402.1101.; HPLC conditions: column: Daicel Chiralpak AD-H, flow rate: 1.0 mL/min, eluent: hexane/IPA =98/2, retention time (min): 10.7 (major), 11.8 (minor).

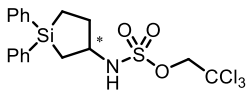


23

2,2,2-Tribromoethyl (1,1-diphenylsilolan-3-yl)carbamate (23)

Following the general procedure for asymmetric intermolecular amination, **2d** (23.8 mg, 0.10 mmol, 2.0 equiv.), **19**[52] (24.8 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (13.8 mg, 0.10 mmol, 2.0 equiv.), and **16** (3.6 mg, 0.0025 mmol, 0.05 equiv.) were stirred at 20 °C in benzene (0.25 mL) for 12 h. The crude material was purified by preparative TLC ($CHCl_3$/hexane = 80/20) to afford **23** (26.4 mg, 94%, 61% ee) as colorless oil.

Analytical data: $[\alpha]_D^{20}$ = -29.2 (c 1.0, $CHCl_3$, 61% ee); **^{1}H NMR** (600 MHz, $CDCl_3$, 323K) δ: 7.59-7.49 (m, 4H), 7.45-7.32 (m, 6H), 4.98 (br s, 1H), 4.91 (s, 2H), 2.38 (br s, 1H), 1.80 (br s, 1H), 1.70-1.60 (m, 1H), 1.38 (ddd, *J* = 15.0, 7.2, 3.0 Hz, 1H), 1.21-1.11 (m, 1H), 1.07 (dd, *J* = 15.0, 10.2 Hz, 1H),; **^{13}C NMR** (150 MHz, $CDCl_3$, 323K) δ: 153.9, 135.6, 135.5, 134.8, 129.9, 128.3, 128.3, 77.6, 54.2, 37.7, 33.8, 20.4, 9.7; **IR** (neat, cm^{-1}): 3323, 2937, 1722, 1509, 1228, 1115, 798, 731, 699, 508; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{19}H_{20}Br_3NO_2Si$ $[M+H]^+$ 559.8886; found, 559.8866; HPLC conditions: column: Daicel Chiralpak AD-H, flow rate: 1.0 mL/min, eluent: hexane/IPA = 95/5, retention time (min): 14.6 (major), 17.1 (minor).

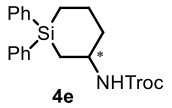


25

2,2,2-Trichloroethyl (1,1-diphenylsilolan-3-yl)sulfamate (25)

To a stirred suspension of silanes **2d** (23.8 mg, 0.10 mmol, 2.0 equiv.), **16** (3.6 mg, 0.0025 mmol, 0.05 equiv.) and $ToesNH_2$ (**21**) (11.4 mg, 0.05 mmol, 1.0 equiv.) in benzene (0.25 mL) were added $PhI(OAc)_2$ (24.2 mg, 0.075 mmol, 1.5 equiv.) at 20 °C. After stirred for 12 h, the resulting mixture was filtered by celite pad and the filterate was concentrated in *vacuo*. The residue was purified by preparative TLC ($CHCl_3$/hexane = 75/25) to afford **25** (17.0 mg, 78%, 3% ee) as yellow oil.

Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.57-7.48 (m, 4H), 7.46-7.35 (m, 6H), 4.70-4.58 (m, 3H), 4.00-3.88 (m, 1H), 2.51-2.41 (m, 1H), 1.86 (ddd, *J* = 14.8, 6.4, 2.0 Hz, 1H), 1.78-1.65 (m, 1H), 1.41 (ddd, *J* = 14.8, 7.2, 2.4 Hz, 1H), 1.20-1.08 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 134.8, 134.7, 134.7, 134.1, 134.1, 128.4, 128.3, 93.6, 78.3, 57.6, 34.3, 21.0, 9.4; **IR** (neat, cm^{-1}): 3303, 3068, 2948, 1428, 1364, 1182, 1018, 854, 758, 726; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{18}H_{20}Cl_3NO_3SSi$ $[M+Na]^+$ 485.9891; found, 485.9859; HPLC conditions: column: Daicel Chiralcel OD-H, flow rate: 1.0 mL/min, eluent: hexane/IPA = 95/5, retention time (min): 15.0 (minor), 22.7 (major).

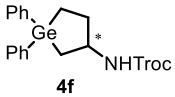


4e

2,2,2-Trichloroethyl (1,1-diphenylsilinan-3-yl)carbamate (4e)

Following the general procedure for asymmetric intermolecular amination, **2e** (25.2 mg, 0.10 mmol, 2.0 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (13.8 mg, 0.10 mmol, 2.0 equiv.), and **16** (3.6 mg, 0.0025 mmol, 0.05 equiv.) were stirred at 20 °C in benzene (0.25 mL) for 12 h. The crude material was purified by preparative TLC ($CHCl_3$/hexane = 80/20) to afford a mixture of β-aminated and γ-aminated products (20.8 mg, 94%, 58% ee, β/γ = 10/1).

Analytical data: $[\alpha]_D^{20}$ = -54 (c 0.52, $CHCl_3$, 58% ee); ee was determined after deprotection of Troc group[ref] and subseaquent benzoylation; HPLC conditions: column: Daicel Chiralpak AD-H, flow rate: 1.0 mL/min, eluent: hexane/IPA = 90/10, retention time (min): 12.1 (minor), 28.1 (major).



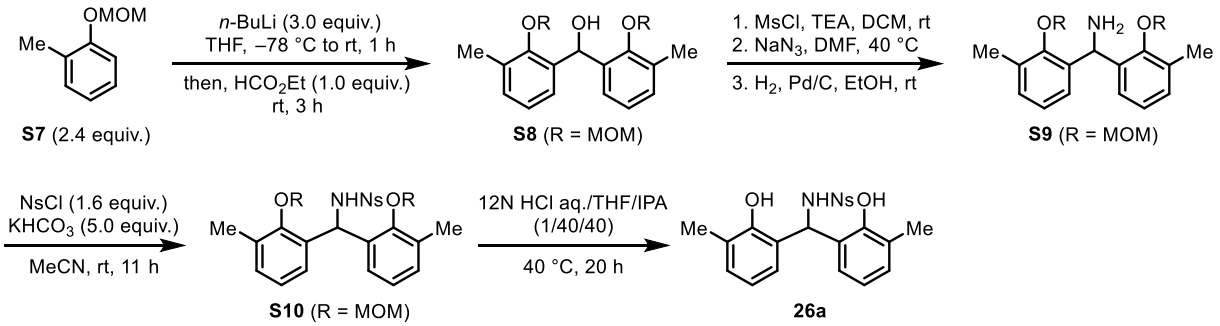
4f

2,2,2-Trichloroethyl (1,1-diphenylgermolan-3-yl)carbamate (4f)

Following the general procedure for asymmetric intermolecular amination, **2f** (28.2 mg, 0.10 mmol, 2.0 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (13.8 mg, 0.10 mmol, 2.0 equiv.), and **16** (3.6 mg, 0.0025 mmol, 0.05 equiv.) were stirred at 20 °C in benzene (0.25 mL) for 12 h. The crude material was purified by preparative TLC (AcOEt/hexane = 75/25) to afford **4f** (20.0 mg, 84%, 58% ee) as colorless oil.

Analytical data: $[\alpha]_D^{20}$ = -29.2 (c 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$, 313K) δ: 7.53-7.48 (m, 4H), 7.42-7.35 (m, 6H), 4.93 (br, 1H), 4.73 (s, 2H), 4.09-4.02 (m,1H), 2.38-2.32 (m, 1H), 1.87-1.80 (m, 1H), 1.70-1.62 (m, 1H), 1.53-1.47 (m, 1H), 1.33-1.24 (m, 1H) 1.13 (dd, *J* = 8.8, 6.4 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 153.9, 137.4, 137.2, 134.2, 129.3, 129.0, 128.6, 128.5, 95.8, 74.5, 54.9, 34.5, 20.5, 11.0; **IR** (neat, cm^{-1}): 3407, 3319, 2917, 1726, 1503, 1225, 1120, 801, 739, 699; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{19}H_{20}Cl_3NO_2Ge$ $[M+Na]^+$ 491.9694; found, 491.9645..; HPLC conditions: column: Daicel Chiralpak AD-H, flow rate: 1.0 mL/min, eluent: hexane/IPA = 98/2, retention time (min): 13.4 (major), 14.9 (minor).

Synthesis of Substrates and Characterization Data



Bis(2-(methoxymethoxy)-3-methylphenyl)methanol (S8)

To a stirred solution of 1-(methoxymethoxy)-2-methylbenzene (**S7**)[53] (3.76 g, 24.7 mmol) in THF (100 mL) was added a solution of *n*-BuLi in hexane (1.6 M, 19.3 mL, 30.9 mmol) dropwise at -78 ℃ and the resulting mixture was allowed to warm to 0 ℃. The solution was stirred for 1 h before adding ethyl formate (0.832 mL, 10.3 mmol) and the resulting mixture was stirred at room temperature. After stirred for 3 h, the reaction was quenched by saturated aq. NH_4Cl and extracted with AcOEt. The organic layer was washed by aq. NH_4Cl and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/hexane = 15/85 to 25/75) to give a mixture of **S8** and byproducts. It was further purified by recrystallization from hexane to afford **S8** (1.81 g, 53%) as white solid.

Analytical data of **S8**: **m.p.** 68°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.19 (dd, *J* = 7.6, 1.6 Hz, 2H), 7.14 (d, *J* = 7.6 Hz, 2H), 7.04 (t, *J* = 7.6, 1.6 Hz, 2H), 6.53 (d, *J* = 3.2 Hz, 1H), 4.91 (d, *J* = 6.0 Hz, 2H), 4.80 (dd, *J* = 6.0 Hz, 2H), 4.06 (d, *J* = 3.2 Hz, 1H), 3.58 (s, 6H), 2.29 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 154.2, 136.9, 130.9, 130.8, 126.1, 124.7, 64.9, 57.6, 17.1; **IR** (KBr, cm^{-1}): 3422, 1470, 1251, 1811, 1148, 1067, 1054, 980, 909, 771; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{19}H_{24}O_5$ $[M+Na]^+$ 355.1516; found, 355.1501.

Bis(2-(methoxymethoxy)-3-methylphenyl)methanamine (S9)

To a stirred solution of **S8** (1.81 g, 5.44 mmol) and TEA (1.36 mL, 9.79 mmol) in DCM (25 mL) was added MsCl (0.69 mL, 8.98 mmol) at 0 ℃ and the mixture was gradually warmed to room temperature. After stirred for 2 h, the reaction was quenched by water and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product.

A suspension of crude product and NaN_3 (1.06 g, 16.3 mmol) in DMF (25 mL) was stirred at 40 ℃ for 18 h. The reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product.

A suspension of crude product and Pd/C (200 mg) in EtOH (20 mL) was stirred at room temperature under H_2 atomsphere for 18 h. The mixture was filtered through celite pad. The filtrate was concentrated *in vacuo* and the

residue was purified by flash column chromatography (AcOEt/hexane = 25/75 to 100/0) to afford **S9** (1.81 g, 53%) as yellow oil.

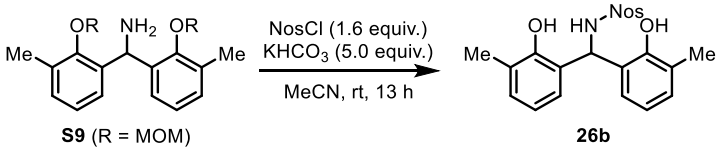
Analytical data of **S9**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.14 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.09 (dd, *J* = 7.2, 1.6 Hz, 2H), 7.01 (t, *J* = 7.6 Hz, 2H), 5.87 (s, 1H), 4.90 (d, *J* = 5.6 Hz, 2H), 4.83 (d, *J* = 6.0 Hz, 2H), 3.59 (s, 6H), 2.30 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 154.2, 138.8, 131.3, 130.2, 125.6, 124.5, 99.6, 57.5, 48.1; **IR** (neat, cm^{-1}): 3367, 3307, 2951, 1591, 1467, 1253, 1157, 1069, 972, 767; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{19}H_{25}NO_4$ $[M+H]^+$ 332.1856; found, 332.1888.

***N*-(Bis(2-hydroxy-3-methylphenyl)methyl)-2-nitrobenzenesulfonamide (26a)**

To a stirred suspension of **S9** (860 mg, 2.59 mmol) and $KHCO_3$ (1.30 g, 13.0 mmol) in MeCN (12.5 mL) was added NsCl (917 mg, 4.14 mmol) at 0 ℃ and the mixture was gradually warmed to room temperature. After stirred for 11 h, the reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/hexane = 20/80) to give the crude product as a mixture of **S10** and NsCl.

A solution of crude product in 12 *N* HCl aq./THF/IPA (1/40/40, 8.0 mL) was stirred at 40 ℃ for 20 h. The reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/hexane = 25/75 to 40/60) to give a mixture of **26a** and NsCl. It was further purified by recrystallization from EtOH/hexane to afford **26a** (579 mg, 52%) as white solid.

Analytical data of **26a**: **m.p.** 160 ℃ (decomp.); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.82 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.72 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.54 (td, *J* = 7.6, 1.2 Hz, 1H), 7.45 (td, *J* = 7.2, 1.2 Hz, 1H), 7.08 (d, *J* = 9.6 Hz, 1H), 6.96 (d, *J* = 6.8 Hz, 2H), 6.83 (d, *J* = 7.6 Hz, 2H), 6.63 (t, *J* = 7.6 Hz, 2H), 6.03 (t, *J* = 9.6 Hz, 2H), 2.15 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 151.8, 147.1, 133,7, 133.3, 132.7, 131.2, 130.9, 126.8, 125.1, 124.7, 123.8, 120.5, 56.8, 15.8; **IR** (KBr, cm^{-1}): 3550, 3435, 3331, 2909, 1539, 1471, 1363, 1316, 1197, 1157; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{21}H_{20}N_2O_6S$ $[M+Na]^+$ 451.0934; found, 451.0945.



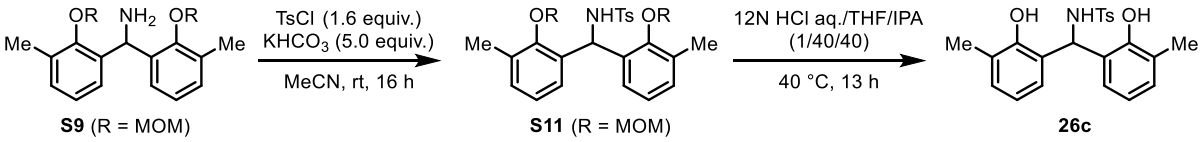
S9 (R = MOM) **26b**

***N*-(Bis(2-hydroxy-3-methylphenyl)methyl)-4-nitrobenzenesulfonamide (26b)**

To a stirred suspension of **S9** (166 mg, 0.50 mmol) and $KHCO_3$ (250 mg, 2.50 mmol) in MeCN (5.0 mL) was added NosCl (177 mg, 0.80 mmol) at 0 ℃ and the mixture was gradually warmed to room temperature. After stirred for 13 h, the reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude solid was washed by EtOH/hexane to afford **26b** (138 mg,

64%) as yellow solid.

Analytical data of **26b**: **m.p.** 184 ℃ (decomp.); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.02 (d, *J* = 8.3 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H), 6.99 (d, *J* = 7.4 Hz, 2H), 6.73 (d, *J* = 7.3 Hz, 2H), 6.67 (t, *J* = 7.6 Hz, 2H), 6.11 (br d, *J* = 9.2 Hz, 1H), 5.91 (d, *J* = 8.2 Hz, 2H), 5.63 (s, 2H), 2.15 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 151.6, 149.9, 144.9, 131.1, 128.5, 126.9, 124.7, 123.5, 123.4, 120.8, 56.6, 15.7; **IR** (KBr, cm^{-1}): 3591, 3497, 3293, 3096, 1529, 1469, 1349, 1167, 743, 632; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{21}H_{20}N_2O_6S$ $[M+K]^+$ 467.0674; found, 467.0694.



S9 (R = MOM) **S11** (R = MOM) **26c**

***N*-(Bis(2-(methoxymethoxy)-3-methylphenyl)methyl)-4-methylbenzenesulfonamide (S11)**

To a stirred suspension of **S9** (166 mg, 0.50 mmol) and $KHCO_3$ (250 mg, 2.50 mmol) in MeCN (5.0 mL) was added TsCl (153 mg, 0.80 mmol) at 0 ℃ and the mixture was gradually warmed to room temperature. After stirred for 16 h, the reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/hexane = 15/85 to 25/75) to afford **S11** (240 mg, 99%) as white solid.

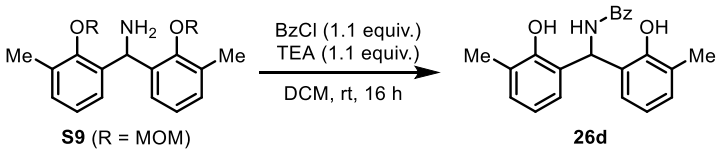
Analytical data of **S11**: **m.p.** 96 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.54 (d, *J* = 8.3 Hz, 2H), 7.07 (d, *J* = 8.2 Hz, 2H), 7.02 (d, *J* = 7.2 Hz, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.81 (t, *J* = 7.4 Hz, 2H), 6.25 (d, *J* = 7.4 Hz, 1H), 5.73 (d, *J* = 7.3 Hz, 1H), 4.90 (d, *J* = 5.5 Hz, 2H), 4.79 (d, *J* = 5.5 Hz, 2H), 3.59 (s, 6H) , 2.34 (s, 3H) , 2.25 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 154.0, 142.8, 138.0, 133.4, 131.5, 131.0, 129.1, 127.3, 127.1, 124.0, 99.7, 57.7, 52.8, 21.6, 17.3; **IR** (KBr, cm^{-1}): 3272, 2929, 1471, 1332, 1181, 1157, 1094, 1069, 962, 665; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{26}H_{31}NO_6S$ $[M+Na]^+$ 508.1764; found, 508.1776.

***N*-(Bis(2-hydroxy-3-methylphenyl)methyl)-4-methylbenzenesulfonamide (26c)**

A solution of **S11** in 12 *N* HCl aq./THF/IPA (1/40/40, 4.0 mL) was stirred at 40 ℃ for 13 h. The reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude solid was purified by recrystallization from EtOH/hexane to afford **26c** (107 mg, 54%) as white solid.

Analytical data of **26c**: **m.p.** 164 ℃ (decomp.); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.48 (d, *J* = 8.2 Hz, 2H), 7.03-6.95 (m, 4H), 6.65 (d, *J* = 4.8 Hz, 4H), 5.92-5,87 (m, 3H), 5.78 (d, *J* = 4.7 Hz, 1H), 2.30 (s, 3H), 2.17 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 152.0, 143.6, 135.6, 130.8, 129.0, 127.3, 126.9, 124.8, 123.5, 120.5, 56.9, 21.5, 15.8; **IR** (KBr, cm^{-1}): 3516, 3268, 1598, 1469, 1315, 1194, 1155, 746, 673; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{22}H_{23}NO_4S$ $[M+Na]^+$

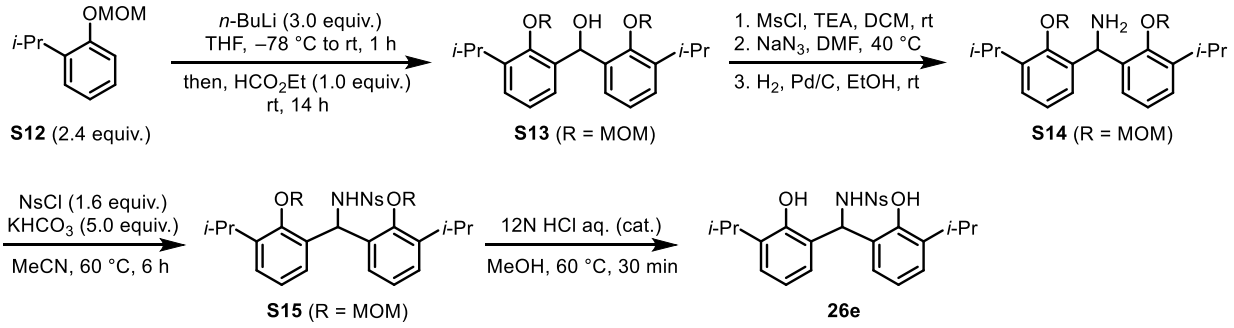
420.1240; found, 420.1257.



***N*-(Bis(2-hydroxy-3-methylphenyl)methyl)benzamide (26d)**

To a stirred suspension of **S9** (166 mg, 0.50 mmol) and TEA (77 μL, 0.55 mmol) in DCM (5.0 mL) was added BzCl (64 μL, 0.55 mmol) at 0 ℃ and the mixture was gradually warmed to room temperature. After stirred for 16 h, the reaction was quenched by water and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude solid was purified by recrystallization from EtOH/hexane to afford **26d** (113 mg, 65%) as white solid.

Analytical data of **26d**: **m.p.** 212 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.64 (br d, *J* = 8.7 Hz, 1H), 7.82 (d, *J* = 6.7 Hz, 2H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.35 (s, 1H), 7.10 (d, *J* = 7.3 Hz, 2H), 6.99 (d, *J* = 6.8 Hz, 2H), 6.78 (t, *J* = 7.6 Hz, 2H), 6.66 (d, *J* = 9.2 Hz, 1H), 2.34 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ:168.5, 152.4, 133.1, 132.2, 130.7, 128.7, 127.4, 127.2, 126.1, 125.5, 120.7, 52.2, 16.4; **IR** (KBr, cm^{-1}): 3392, 3235, 1618, 1533, 1469, 1356, 1252, 1190, 689, 637; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{22}H_{21}NO_3$ $[M+H]^+$ 348.1594; found, 348.1608.



Bis(3-isopropyl-2-(methoxymethoxy)phenyl)methanamine (S14)

To a stirred solution of 1-isopropyl-2-(methoxymethoxy)benzene (**S12**)[54] (855 mg, 4.74 mmol) in THF (10 mL) was added a solution of *n*-BuLi in hexane (1.6 M, 3.70 mL, 5.93 mmol) dropwise at -78 ℃ and the resulting mixture was allowed to warm to 0 ℃. The solution was stirred for 1 h before adding ethyl formate (0.160 mL, 1.98 mmol) and the resulting mixture was stirred at room temperature. After stirred for 14 h, the reaction was quenched by saturated aq. NH_4Cl and extracted with AcOEt. The organic layer was washed by aq. NH_4Cl and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/hexane = 10/90 to 25/75) to give the crude product as a mixture of **S13** and byproducts.

To a stirred solution of crude product and TEA (0.496 mL, 3.56 mmol) in DCM (10 mL) was added MsCl (0.253 mL, 3.27 mmol) at 0 ℃ and the mixture was gradually warmed to room temperature. After stirred for 3 h, the reaction was quenched by water and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product.

A suspension of crude product and NaN_3 (1.06 g, 16.3 mmol) in DMF (25 mL) was stirred at 40 ℃ for 23 h. The reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product.

A suspension of crude product and Pd/C (60 mg) in EtOH (6.0 mL) was stirred at room temperature under H_2 atomsphere for 22 h. The mixture was filtered through celite pad. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (AcOEt/hexane = 10/90 to 75/25) to afford **S14** (335 mg, 44%) as yellow oil.

Analytical data of **S14**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.21-7.06 (m, 6H), 5.88 (s, 1H), 4.90 (d, *J* = 6.0 Hz, 2H), 4.79 (d, *J* = 5.6 Hz, 2H), 4.83 (d, *J* = 6.0 Hz, 2H), 3.58 (s, 6H), 3.40-3.29 (m, 2H), 1.22 (dd, *J* = 6.8, 9.2 Hz, 12H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 152.9, 142.2, 138.8, 125.6, 125.5, 124.9, 100.3, 57.4, 48.4, 26.8, 24.1, 24.0; **IR** (neat, cm^{-1}): 3371, 3307, 2963, 1591, 1453, 1158, 1069, 971, 798, 766; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{23}H_{33}NO_4$ $[M+H]^+$ 388.2482; found, 388.2518.

***N*-(Bis(3-isopropyl-2-(methoxymethoxy)phenyl)methyl)-4-nitrobenzenesulfonamide (S15)**

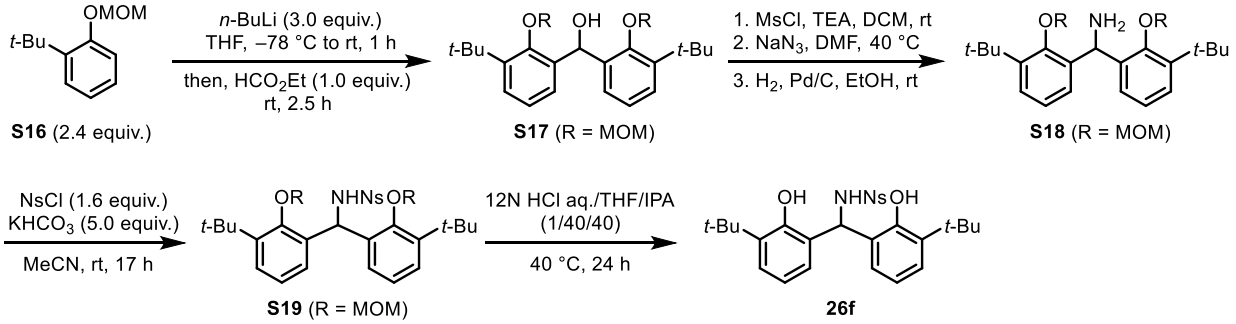
To a stirred suspension of **S14** (335 mg, 0.864 mmol) and $KHCO_3$ (432 mg, 4.32 mmol) in MeCN (5.0 mL) was added NsCl (306 mg, 1.38 mmol) at 0 ℃ and the mixture was allowed to warm to 60 ℃. After stirred for 6 h, the reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by recrystallization from EtOH/hexane to afford **S15** (302 mg, 61%) as yellow solid.

Analytical data of **S15**: **m.p.** 141 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.74 (d, *J* = 8.0 Hz, 1H), 7.61 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.52 (td, *J* = 7.6, 1.2 Hz, 1H), 7.30 (td, *J* = 7.8, 1.2 Hz, 1H), 7.11 (dd, *J* = 9.6, 5.6 Hz, 2H), 7.00 (dd, *J* = 7.8, 1.4 Hz, 2H), 6.82 (t, *J* = 7.8 Hz, 2H), 6.65 (d, *J* = 8.8 Hz, 1H), 6.12 (d, *J* = 9.2 Hz, 1H), 4.88 (dd, *J* = 8.2, 1.4 Hz, 2H), 3.59 (s, 6H), 3.44-3.33 (m, 2H), 1.21 (d, *J* = 6.9 Hz, 6H), 1,15 (d, *J* = 6.8 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 153.0, 147.5, 143.0, 134.9, 132.8, 132.5, 132.4, 130.7, 126.8, 126.4, 124.8, 124.5, 100.7, 57.7, 52.2, 26.6, 24.1, 23.8; **IR** (KBr, cm^{-1}): 3447, 3244, 2961, 1541, 1362, 1164, 970, 950, 767, 546; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{29}H_{36}N_2O_8S$ $[M+Na]^+$ 595.2085; found, 595.2092.

***N*-(Bis(2-hydroxy-3-isopropylphenyl)methyl)-4-nitrobenzenesulfonamide (26e)**

A solution of **S15** (292 mg, 0.510 mmol) and 12 *N* HCl aq. (0.15 mL) in MeOH (5.0 mL) was stirred at 60 ℃ for 30 min. The reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/hexane = 25/75) to afford **26e** (218 mg, 88%) as white solid.

Analytical data of **26e**: **m.p.** 131 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.81 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.52 (td, *J* = 7.6, 1.4 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.15 (br d, *J* = 9.2 Hz, 1H), 7.04 (dd, *J* = 7.6, 1.6 Hz, 2H), 6.77 (dd, *J* = 7.6, 1.4 Hz, 2H), 6.69 (t, *J* = 7.4 Hz, 2H), 6.06 (d, *J* = 7.6 Hz, 1H), 5.96 (br s, 2H), 3.13-3.01 (m, 2H), 1.23 (d, *J* = 7.2 Hz, 6H), 1.15 (d, *J* = 6.8 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 151.0, 147.2, 135.3, 133.6, 133.4, 132.7, 131.4, 126.5, 126.3, 125.1, 123.7, 120.7; **IR** (KBr, cm^{-1}): 3445, 3299, 3267, 2962, 1543, 1450, 1351, 1171, 735, 475; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{25}H_{28}N_2O_6S$ $[M+Na]^+$ 507.1560; found, 507.1570.



Bis(3-(*tert*-butyl)-2-(methoxymethoxy)phenyl)methanol (S17)

To a stirred solution of 1-(*tert*-butyl)-2-(methoxymethoxy)benzene (**S16**)[55] (1.94 g, 10.0 mmol) in THF (20 mL) was added a solution of *n*-BuLi in hexane (1.6 M, 7.81 mL, 12.5 mmol) dropwise at -78 °C and the resulting mixture was allowed to warm to 0 °C. The solution was stirred for 1 h before adding ethyl formate (0.337 mL, 4.17 mmol) and the resulting mixture was stirred at room temperature. After stirred for 2.5 h, the reaction was quenched by saturated aq. NH_4Cl and extracted with AcOEt. The organic layer was washed by aq. NH_4Cl and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/toluene = 0/100 to 5/95) to afford **S17** (1.17 g, 68%) as white solid.

Analytical data of **S17**: **m.p.** 95 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.31 (dd, *J* = 7.6, 1.6 Hz, 4H), 7.06 (t, *J* = 7.8 Hz, 2H), 6.46 (d, *J* = 4.2 Hz, 1H), 4.97 (d, *J* = 5.5 Hz, 2H), 4.83 (d, *J* = 5.5 Hz, 2H), 4.37 (d, *J* = 4.6 Hz, 1H), 3.63 (s, 6H), 1.40 (s, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 155.0, 143.2, 137.8, 127.4, 127.0, 124.2, 100.2, 65.4, 57.4, 35.2, 31.3; **IR** (KBr, cm^{-1}): 3436, 1956, 1479, 1432, 1397, 1199, 1161, 1083, 1040, 934; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{25}H_{36}O_5$ $[M+Na]^+$ 439.2455; found, 439.2467.

***N*-(bis(3-(*tert*-butyl)-2-(methoxymethoxy)phenyl)methyl)-4-nitrobenzenesulfonamide (S19)**

To a stirred solution of **S17** (1.15 g, 2.76 mmol) and TEA (0.693 mL, 4.97 mmol) in DCM (15 mL) was added MsCl (0.353 mL, 4.56 mmol) at 0 °C and the mixture was gradually warmed to room temperature. After stirred for 2 h, the reaction was quenched by water and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product.

A suspension of crude product and NaN_3 (538 mg, 8.28 mmol) in DMF (15 mL) was stirred at 40 °C for 12 h. The

reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product.

A suspension of crude product and Pd/C (110 mg) in EtOH (10 mL) was stirred at room temperature under H_2 atomsphere for 3 h. The mixture was filtered through celite pad. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (AcOEt/hexane = 10/90 to 20/80) to give the crude product as a mixture of **S18** and byproducts.

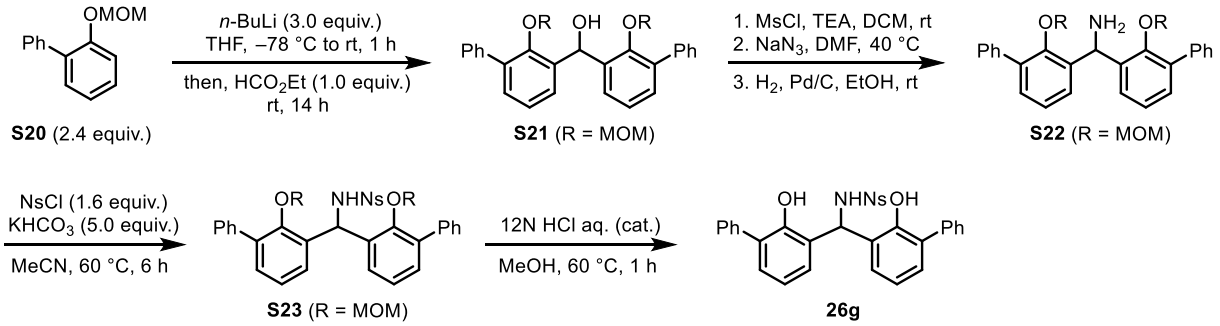
To a stirred suspension of crude product and $KHCO_3$ (478 mg, 4.78 mmol) in MeCN (5.0 mL) was added NsCl (232 mg, 1.05 mmol) at 0 ℃ and the mixture was allowed to warm to room temperature. After stirred for 18 h, the reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/hexane = 10/90 to 20/80) to give a mixture of **S19** and byproducts. It was further purified by recrystallization from AcOEt/hexane to afford **S19** (154 mg, 9 %) as white solid.

Analytical data of **S19**: **m.p.** 179 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.71 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.49 (td, *J* = 7.6, 1.3 Hz, 1H), 7.32 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.22-7.14 (m, 3H), 7.07 (dd, *J* = 7.6, 1.4 Hz, 2H), 6.70-6.65 (m, 3H), 6.06 (d, *J* = 9.2 Hz, 1H), 5.04 (dd, *J* = 7.2, 4.0 Hz, 4H), 3.71 (s, 6H), 1.44 (s, 18H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 154.9, 147.4, 144.2, 134.9, 133.0, 132.6, 132.4, 130.3, 127.7, 127.6, 124.6, 123.6, 100.2, 57.7, 52.2, 35.4, 31.0; **IR** (KBr, cm^{-1}): 3333, 2960, 2912, 1538, 1437, 1357, 1165, 954, 739, 584; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{31}H_{40}N_2O_8S$ $[M+Na]^+$ 623.2398; found, 623.2401.

***N*-(Bis(3-(*tert*-butyl)-2-hydroxyphenyl)methyl)-4-nitrobenzenesulfonamide (26f)**

A solution of **S19** (100 mg, 0.166 mmol) in 12 *N* HCl aq./THF/IPA (1/40/40, 2.0 mL) was stirred at 40 ℃ for 24 h. The reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/hexane = 15/85) to afford **26f** (79 mg, 93%) as white solid.

Analytical data of **26f**: **m.p.** 70 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.78 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.17-7.07 (m, 3H), 6.75 (dd, *J* = 7.6, 1.4 Hz, 2H), 6.67 (d, *J* = 7.4 Hz, 2H), 6.15 (s, 2H), 6.07 (d, *J* = 9.2 Hz, 1H), 1.36 (s, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 153.1, 147.4, 137.3, 133.5, 133.4, 132.7, 131.5, 127.4, 127.1, 125.1, 124.2, 120.5, 58.1, 34.5, 30.1; **IR** (KBr, cm^{-1}): 3599, 3479, 3322, 2961, 1542, 1439, 1359, 1170, 752, 743; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{27}H_{32}N_2O_6S$ $[M+Na]^+$ 535.1873; found, 535.1882.



Bis(2-(methoxymethoxy)-[1,1'-biphenyl]-3-yl)methanamine (S22)

To a stirred solution of 2-(methoxymethoxy)-1,1'-biphenyl (**S20**)[56] (1.90 mg, 8.88 mmol) in THF (18 mL) was added a solution of *n*-BuLi in hexane (1.6 M, 6.94 mL, 11.1 mmol) dropwise at -78 ℃ and the resulting mixture was allowed to warm to 0 ℃. The solution was stirred for 1 h before adding ethyl formate (0.299 mL, 3.70 mmol) and the resulting mixture was stirred at room temperature. After stirred for 14 h, the reaction was quenched by saturated aq. NH_4Cl and extracted with AcOEt. The organic layer was washed by aq. NH_4Cl and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/hexane = 10/90 to 25/75) to give the crude product as a mixture of **S21** and byproducts.

To a stirred solution of crude product and TEA (0.928 mL, 6.66 mmol) in DCM (20 mL) was added MsCl (0.473 mL, 6.11 mmol) at 0 ℃ and the mixture was gradually warmed to room temperature. After stirred for 3 h, the reaction was quenched by water and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product.

A suspension of crude product and NaN_3 (722 mg, 11.1 mmol) in DMF (18 mL) was stirred at 40 ℃ for 23 h. The reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product.

A suspension of crude product and Pd/C (140 mg) in EtOH (10 mL) was stirred at room temperature under H_2 atomsphere for 22 h. The mixture was filtered through celite pad. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (AcOEt/hexane = 10/90 to 75/25) to afford **S22** (945 mg, 56%) as yellow oil.

Analytical data of **S22**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.56-7.50 (m, 4H), 7.44-7.29 (m, 8H), 7.28-7.24 (m, 2H), 7.19 (t, *J* = 7.6 Hz, 2H), 6.10 (s, 1H), 4.51 (q, *J* = 5.5 Hz, 4H), 3.22 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 152.6, 139.3, 139.1, 135.4, 130.2, 129.5, 128.5, 127.4, 127.2, 124.6, 99.5, 57.4, 48.2; **IR** (neat, cm^{-1}): 3363, 3299, 2945, 2825, 1599, 1429, 1156, 1068, 962, 763; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{29}H_{29}NO_4$ $[M+H]^+$ 456.2169; found, 456.2215.

***N*-(Bis(2-(methoxymethoxy)-[1,1'-biphenyl]-3-yl)methyl)-4-nitrobenzenesulfonamide (S23)**

To a stirred suspension of **S22** (945 mg, 2.07 mmol) and $KHCO_3$ (1.04 g, 10.4 mmol) in MeCN (10 mL) was added NsCl (734 mg, 3.31 mmol) at 0 ℃ and the mixture was allowed to warm to 60 ℃. After stirred for 6 h, the reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over

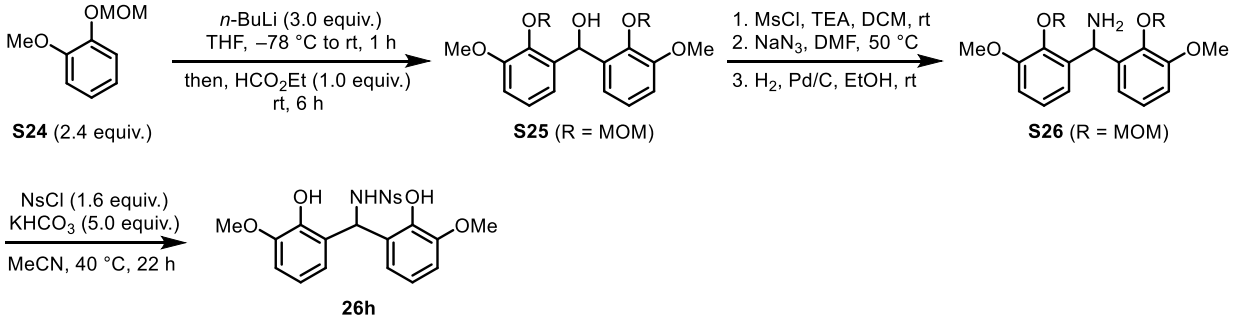
Na_2SO_4 and concentrated *in vacuo*. The crude solid was washed by EtOH to afford **S23** (1.10 g, 83%) as yellow solid.

Analytical data of **S23**: **m.p.** 128 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.94 (d, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.49-7.29 (m, 13H), 7.18 (dd, *J* = 8.0, 0.8 Hz, 2H), 7.00 (t, *J* = 7.6 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 1H), 6.60 (d, *J* = 8.8 Hz, 1H), 4.48 (q, *J* = 5.5 Hz, 4H), 3.15 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 152.2, 147.6, 138.8, 135.7, 134.9, 133.6, 133.0, 132.4, 131.2, 131.2, 129.3, 128.6, 128.5, 127.4, 124.9, 124.2, 99.4, 57.7, 53.8; **IR** (KBr, cm^{-1}): 3339, 1538, 1344, 1166, 1070, 962, 767, 701, 508, 465; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{35}H_{32}N_2O_8S$ $[M+Na]^+$ 663.1772; found, 663.1764.

***N*-(Bis(2-hydroxy-[1,1'-biphenyl]-3-yl)methyl)-4-nitrobenzenesulfonamide (26g)**

A solution of **S23** (513 mg, 0.800 mmol) and 12 *N* HCl aq. (0.24 mL) in MeOH (8.0 mL) was stirred at 60 ℃ for 1 h. The reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/hexane = 15/85 to 50/50) to afford **26g** (431 mg, 97%) as white solid.

Analytical data of **26g**: **m.p.** 209 ℃ (decomp.); **^{1}H NMR** (400 MHz, acetone-*d6*) δ: 7.87 (d, *J* = 8.0 Hz, 1H), 7.82-7.67 (m, 4H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.42-7.27 (m, 13H), 6.98 (dd, *J* = 7.6, 1.2 Hz, 2H), 6.75 (t, *J* = 7.6 Hz, 1H), 6.46 (s, 1H); **^{13}C NMR** (100 MHz, acetone-*d6*) δ: 151.4, 148.5, 138.7, 134.6, 133.3, 131.4, 130.6, 130.2, 129.5, 129.0, 128.4, 128.2, 125.7, 121.0, 55.5; **IR** (KBr, cm^{-1}): 3510, 3483, 3362, 1537, 1435, 1401, 1221, 1173, 767, 591; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{31}H_{24}N_2O_6S$ $[M+Na]^+$ 575.1247; found, 575.1253.



Bis(3-methoxy-2-(methoxymethoxy)phenyl)methanamine (S26)

To a stirred solution of 1-methoxy-2-(methoxymethoxy)benzene (**S24**)[57] (1.64 g, 9.74 mmol) in THF (20 mL) was added a solution of *n*-BuLi in hexane (1.6 M, 7.63 mL, 12.2 mmol) dropwise at -78 ℃ and the resulting mixture was allowed to warm to 0 ℃. The solution was stirred for 1 h before adding ethyl formate (0.328 mL, 4.06 mmol) and the resulting mixture was stirred at room temperature. After stirred for 14 h, the reaction was quenched by saturated aq. NH_4Cl and extracted with AcOEt. The organic layer was washed by aq. NH_4Cl and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/hexane = 10/90 to 50/50) to give the crude product as a mixture of **S25** and byproducts.

To a stirred solution of crude product and TEA (1.02 mL, 7.31 mmol) in DCM (20 mL) was added MsCl (0.520 mL, 6.70 mmol) at 0 ℃ and the mixture was gradually warmed to room temperature. After stirred for 4 h, the reaction was quenched by water and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product.

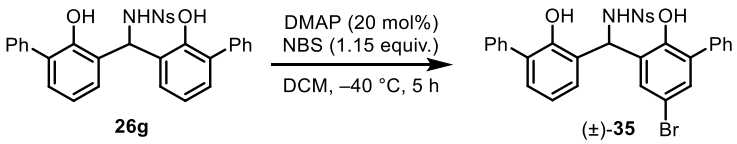
A suspension of crude product and NaN_3 (780 mg, 12.0 mmol) in DMF (20 mL) was stirred at 50 ℃ for 20 h. The reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product.

A suspension of crude product and Pd/C (140 mg) in EtOH (15 mL) was stirred at room temperature under H_2 atomsphere for 21 h. The mixture was filtered through celite pad. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (AcOEt) to afford **S26** (740 mg, 50%) as yellow oil.

***N*-(Bis(2-hydroxy-3-methoxyphenyl)methyl)-4-nitrobenzenesulfonamide (26h)**

To a stirred suspension of **S26** (720 mg, 1.98 mmol) and $KHCO_3$ (991 mg, 9.90 mmol) in MeCN (10 mL) was added NsCl (703 mg, 3.17 mmol) at 0 ℃ and the mixture was allowed to warm to 40 ℃. After stirred for 22 h, the reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by recrystallization from EtOH to afford **26h** (635 mg, 70%) as yellow solid.

Analytical data of **26h**: **m.p.** 192 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.86 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 9.6 Hz, 1H), 7.00-6.94 (m, 2H), 7.56 (d, *J* = 7.4 Hz, 1H), 6.67-6.59 (m, 4H), 6.23 (d, *J* = 9.6 Hz, 1H), 5.83 (br s, 2H), 3.78 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 147.4, 146.5, 142.7, 134.9, 132.7, 132.3, 131.0, 125.3, 124.9, 120.8, 119.5, 109.9, 56.2, 54.4; **IR** (KBr, cm^{-1}): 3515, 3470, 3347, 1538, 1481, 1355, 1276, 1168, 1080, 741; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{21}H_{20}N_2O_8S$ $[M+Na]^+$ 483.0833; found, 483.0850.

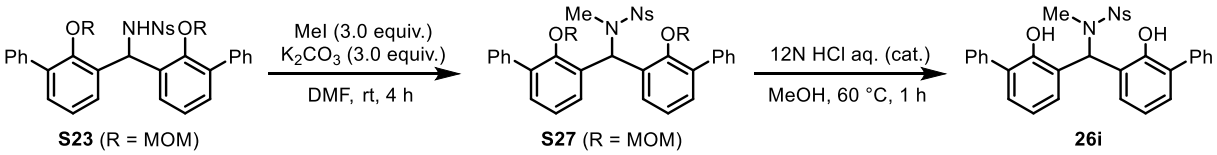


26g (±)-**35**

***N*-((5-Bromo-2-hydroxy-[1,1'-biphenyl]-3-yl)(2-hydroxy-[1,1'-biphenyl]-3-yl)methyl)-4-nitrobenzenesulfonamide ((±)-35)**

To a stirred solution of **26g** (45.6 mg, 0.080 mmol) and DMAP (2.0 mg, 0.016 mmol) in DCM (16 mL) was added NBS (16.4 mg, 0.092 mmol) at -40 ℃. After stirred for 5 h, the reaction was quenched by saturated aq. $Na_2S_2O_3$ and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by preparative TLC (AcOEt/Toluene = 3/97) to give a mixture of (±)-**35**, **26g** and dibromide. It was further purified by recrystallization from $CHCl_3$/hexane to afford (±)-**35** (5.0 mg, 10 %) as white solid.

Analytical data of (±)-**35**: **m.p.** 216 ℃ (decomp.); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.92 (dd, *J* = 7.8, 2.6 Hz, 1H), 7.76 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.59 (td, *J* = 7.8, 1.4 Hz, 1H), 7.55-7.27 (m, 14H), 7.14 (d, *J* = 2.4 Hz, 1H), 7.08 (dd, *J* = 7.4, 1.4 Hz, 1H), 6.81 (t, *J* = 7.6 Hz, 1H), 6.19 (d, *J* = 9.6 Hz, 1H), 5.75 (s, 1H), 5.73 (s, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 149.6, 148.9, 147.4, 136.1, 135.2, 134.4, 132.5, 132.0, 131.3, 131.0, 130.6, 130.1, 129.7, 129.2, 129.1, 128.9, 128.8, 128.5, 127.7, 125.1, 124.8, 120.6, 112.5, 55.7; **IR** (KBr, cm^{-1}): 3521, 1539, 1461, 1437, 1356, 1226, 1170, 1092, 734, 704; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{31}H_{23}BrN_2O_6S$ $[M+Na]^+$ 653.0352; found, 653.0362.



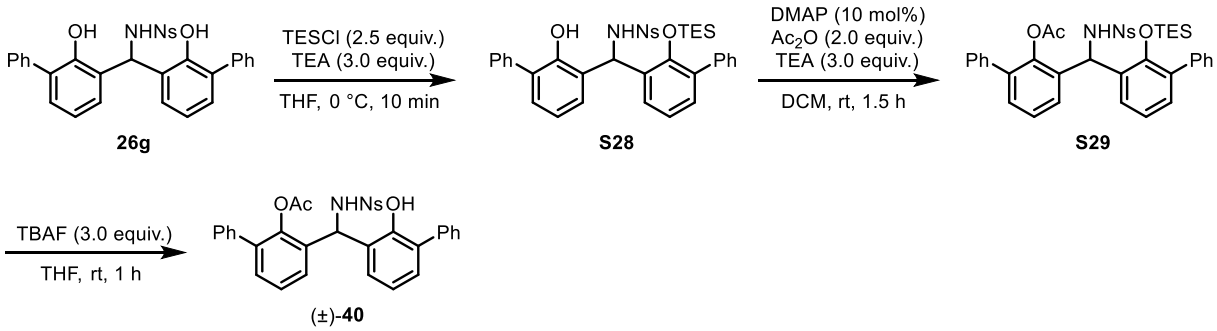
S23 (R = MOM) **S27** (R = MOM) **26i**

***N*-(Bis(2-hydroxy-[1,1'-biphenyl]-3-yl)methyl)-*N*-methyl-4-nitrobenzenesulfonamide (26i)**

To a stirred suspension of **S23** (128 mg, 0.20 mmol) and K_2CO_3 (83.0 g, 0.60 mmol) in DMF (2.0 mL) was added MeI (37 μL, 0.60 mmol) at 0 ℃ and the mixture was gradually warmed to room temperature. After stirred for 4 h, the reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product.

A solution of crude product and 12 *N* HCl aq. (90 μL) in MeOH (3.0 mL) was stirred at 60 ℃ for 1 h. The reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/hexane = 15/85 to 50/50) to afford **26i** (40 mg, 35%) as white solid.

Analytical data of **26i**: **m.p.** 156 ℃ (decomp.); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.88 (d, *J* = 8.4 Hz, 1H), 7.55-7.35 (m, 13H), 7.17 (dd, *J* = 7.6, 1.6 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.89-6.83 (m, 3H), 5.67 (s, 2H), 3.07 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 150.4, 136.8, 133.5, 133.2, 131.4, 131.1, 130.2, 129.4, 129.3, 128.7, 128.5, 128.1, 124.6, 123.8, 120.5, 55.9, 33.9; **IR** (KBr, cm^{-1}): 3541, 3489, 3048, 1541, 1335, 1218, 1146, 948, 759, 700; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{32}H_{26}N_2O_6S$ $[M+Na]^+$ 589.1404; found, 589.1414.



***N*-((2-Hydroxy-[1,1'-biphenyl]-3-yl)(2-((triethylsilyl)oxy)-[1,1'-biphenyl]-3-yl)methyl)-4-nitrobenzenesulfonamide (S28)**

To a stirred solution of **26g** (55.3 mg, 0.10 mmol) and TEA (42 μL, 0.30 mmol) in THF (1.0 mL) was added TESCl (42 μL, 0.20 mmol) at 0 ℃ and the mixture was gradually warmed to room temperature. After stirred for 10 min, the reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/hexane = 25/75) to afford **S28** (66 mg, 99%) as colorless oil.

Analytical data of **S28**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.87 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.75 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.56-7.30 (m, 13H), 7.16 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.04 (dd, *J* = 7.4, 1.8 Hz, 1H), 6.95 (dd, *J* = 7.8, 1.4 Hz, 1H), 6.80 (td, *J* = 7.8, 1.1 Hz, 2H), 6.48 (td, *J* = 9.2, 6.0 Hz, 2H), 6.00 (s, 1H), 0.70 (t, *J* = 8.0 Hz, 9H), 0.21 (q, *J* = 8.0 Hz, 6H),; **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 151.1, 150.7, 147.5, 139.5, 136.9, 134.7, 134.2, 133.1, 132.5, 131.0, 130.9, 130.6, 129.9, 129.9, 129.4, 129.3, 129.3, 128.8, 128.4, 128.1, 127.7, 127.4, 125.4, 125.0, 121.5, 120.3, 53.7, 6.9, 4.9; **IR** (neat, cm^{-1}): 3534, 3347, 2956, 2877, 1539, 1431, 1353, 1169, 743, 702; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{37}H_{38}N_2O_6SSi$ $[M+Na]^+$ 689.2112; found, 689.2108.

3-(((4-Nitrophenyl)sulfonamido)(2-((triethylsilyl)oxy)-[1,1'-biphenyl]-3-yl)methyl)-[1,1'-biphenyl]-2-yl acetate (S29)

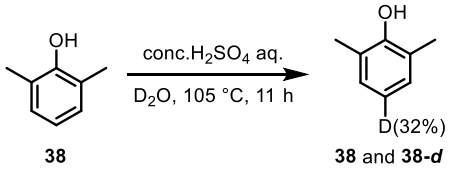
To a stirred solution of **S28** (65 mg, 0.093 mmol), DMAP (1.0 mg, 0.0090 mmol) and TEA (39 μL, 0.279 mmol) in DCM (1.0 mL) was added Ac_2O (18 μL, 0.186 mmol) at room temperature. After stirred for 1.5 h, the reaction was quenched by water and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/hexane = 25/75) to afford **S29** (54 mg, 82%) as colorless oil.

Analytical data of **S29**: **^{1}H NMR** (400 MHz, $CDCl_3$, 313K) δ: 7.73 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.48-7.29 (m, 13H), 7.15-7.09 (m, 2H), 6.99-6.93 (m, 2H), 6.70-6.59 (m, 2H), 5.99 (br d, 7.4 Hz, 1H), 2.14 (s, 3H), 0.72 (t, *J* = 7.6 Hz, 9H), 0.18 (q, *J* = 7.6 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$, 323K) δ: 168.8, 151.3, 147.7, 147.6, 139.7, 138.0, 137.2, 135.2, 134.5, 132.9, 132.2, 131.8, 131.3, 131.1, 130.6, 129.9, 129.0, 128.8, 128.5, 128.5, 128.1, 127.7, 127.5, 126.0, 124.7, 121.4, 52.4, 21.0, 6.8, 5.1; **IR** (neat, cm^{-1}): 3371, 2956, 1768, 1540, 1455, 1430, 1352, 1182, 741, 701; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{39}H_{40}N_2O_7SSi$ $[M+Na]^+$ 731.2218; found, 731.2209.

3-((2-Hydroxy-[1,1'-biphenyl]-3-yl)((4-nitrophenyl)sulfonamido)methyl)-[1,1'-biphenyl]-2-yl acetate ((±)-35)

To a stirred solution of **S29** (54 mg, 0.076 mmol) in THF (1.0 mL) was added a solution of TBAF in THF (1.0 M, 0.20 mL, 0.20 mmol) at room temperature. After stirred for 1 h, the reaction was quenched by saturated aq. NH_4Cl and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/hexane = 50/50) to afford (±)-**35** (42 mg, 93%) as white amorphous.

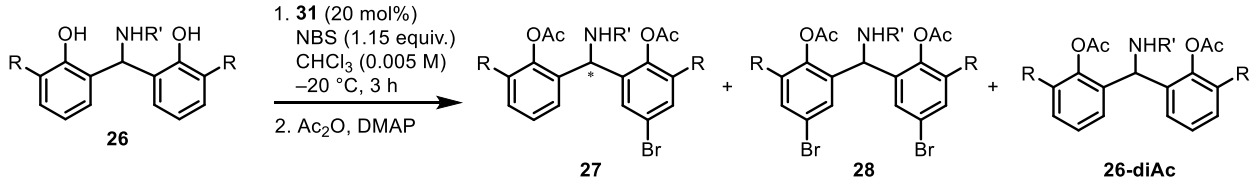
Analytical data of (±)-**35**: **^{1}H NMR** (400 MHz, $CDCl_3$, 323K) δ: 7.89 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.72 (dd, *J* = 8.0, 1.2Hz, 1H), 7.54 (td, *J* = 7.8, 1.5 Hz, 1H), 7.49-7.22 (m, 13H), 7.06-7.04 (m, 3H), 6.80 (t, *J* = 7.6 Hz, 1H), 6.74 (br d, *J* = 9.2 Hz, 1H), 6.24 (d, *J* = 8.7 Hz, 1H), 5.51 (s, 1H), 1.98 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$, 323K) δ: 168.5, 149.9, 147.7, 146.2, 137.9, 136.4, 136.2, 134.9, 133.0, 132.4, 132.2, 131.2, 130.6, 130.2, 129.7, 129.1, 129.0, 128.9, 128.5, 128.4, 128.0, 127.7, 126.0, 125.1, 124.8; **IR** (KBr, cm^{-1}): 3528, 1766, 1540, 1459, 1434, 1358, 1212, 1170, 759, 703; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{33}H_{26}N_2O_7S$ $[M+Na]^+$ 617.1353; found, 617.1356.



2,6-Xylenol-4-*d* (38-*d*)

A solution of 2,6-xylenol (**38**) (244 mg, 2.0 mmol) and conc. H_2SO_4 (0.20 mL) in D_2O (2.0 mL) was stirred at 105 ℃ for 11 h. The reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford **38** and **38-*d*** (32% D, 237 mg, 97%) as brown solid.

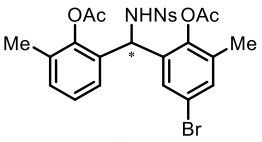
<u>General Procedure for Asymmetric Bromination of σ-Symmetric 1,1-Diarylmethylamines</u>



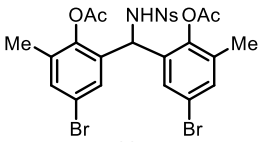
To a stirred solution of **26** (0.030 mmol, 1.0 equiv.) and **31**[34a] (5.00 mg, 0.0060 mmol, 0.20 equiv.) in $CHCl_3$ (6.0 mL) was added NBS (6.14 mg, 0.00345 mmol, 1.15 equiv.) at -20 ℃. The solution was stirred for 3 h before adding Ac_2O (22.7 μL, 0.24 mmol, 8.0 equiv.) and DMAP (22.0 mg, 0.18 mmol, 6.0 equiv.) and the resulting mixture was

stirred at room temperature. After stirred overnight, the reaction was quenched by water and extracted with AcOEt. The organic layer was washed by 1*N* HCl aq., saturated $NaHCO_3$ aq. and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by preparative TLC (AcOEt/toluene or AcOEt/hexane) to afford the monobromide **27**, dibromide **28** and **26-diAc**.

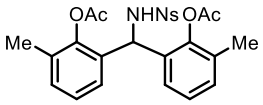
Specific Procedure and Characterization Data



27a



28a



26a-diAc

Following the general procedure for asymmetric bromination, **26a** (12.9 mg, 0.030 mmol), **31** (5.00 mg, 0.0060 mmol) and NBS (6.14 mg, 0.0345 mmol) were stirred at -20 ℃ in $CHCl_3$ (6.0 mL). After stirred 3 h, Ac_2O (22.7 μL, 0.24 mmol) and DMAP (22.0 mg, 0.18 mmol) were added to the mixture. The crude residue was purified by preparative TLC (AcOEt/toluene = 5/95) to afford **27a** (10.1 mg, 57%, 94% ee), **28a** (5.3 mg, 26%) and **26a-diAc** (2.7 mg, 18%).

2-((2-Acetoxy-3-methylphenyl)((2-nitrophenyl)sulfonamido)methyl)-4-bromo-6-methylphenyl acetate (27a)

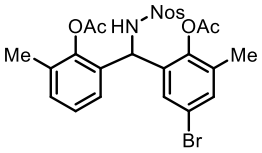
White amorphous: $[\alpha]_D^{20}$ = -141 (c 1.0, $CHCl_3$, 92% ee); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.78 (d, *J* = 7.2 Hz, 1H), 7.73 (d, *J* = 7.2 Hz, 1H), 7.57 (td, *J* = 7.8, 1.3 Hz, 1H), 7.40 (td, *J* = 7.8, 0.8 Hz, 1H), 7.19 (d, *J* = 2.0 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.02 (br s, 1H), 6.92 (t, *J* = 7.8 Hz, 1H), 6.77 (br d, *J* = 6.4 Hz, 1H), 6.05 (br d, *J* = 9.2 Hz, 1H), 5.97 (br d, *J* = 9.2 Hz, 1H), 2.37 (s, 3H), 2.27 (s, 3H), 2.13 (s, 3H), 2.06 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 168.4, 167.9, 147.2, 146.9, 146.2, 133.7, 133.6, 133.2, 133.0, 132.0, 131.4, 131.2, 130.3, 129.3, 128.5, 125.8, 125.5, 124.4, 118.4, 52.3, 20.2, 20.0, 16.0, 15.9; **IR** (KBr, cm^{-1}): 3447, 1762, 1541, 1468, 1442, 1366, 1209, 1173, 905, 742; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{25}H_{23}BrN_2O_8S$ $[M+Na]^+$ 613.0251; found, 613.0262.; HPLC conditions: column: Daicel Chiralpak IA, flow rate: 1.0 mL/min, eluent: hexane/IPA = 80/20, retention time (min): 9.8 (minor), 14.2 (major).

(((2-Nitrophenyl)sulfonamido)methylene)bis(4-bromo-6-methyl-2,1-phenylene) diacetate (28a)

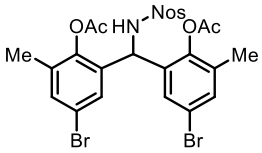
White amorphous: **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.81 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 6.9 Hz, 1H), 7.44 (d, *J* = 7.4 Hz, 1H), 7.24 (s, 2H), 6.95 (br s, 2H), 6.01 (d, *J* = 9.2 Hz, 1H), 5.96 (d, *J* = 9.6 Hz, 1H), 2.31 (s, 6H), 2.08 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 168.5, 147.3, 146.7, 134.3, 134.2, 133.9, 133.8, 132.6, 131.9, 130.7, 129.0, 125.2, 119.0, 53.0, 20.6, 16.4; **IR** (KBr, cm^{-1}): 3442, 1762, 1543, 1443, 1360, 1208, 1173, 858, 592, 507; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{25}H_{22}Br_2N_2O_8S$ $[M+Na]^+$ 690.9356; found, 690.9379.

(((2-Nitrophenyl)sulfonamido)methylene)bis(6-methyl-2,1-phenylene) diacetate (26a-diAc)

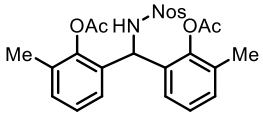
White amorphous: **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.72 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.89-6.78 (m, 4H), 6.13 (d, *J* = 9.6 Hz, 1H), 5.99 (d, *J* = 9.6 Hz, 1H), 2.33 (s, 6H), 2.11 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 168.9, 147.7, 147.5, 134.5, 133.0, 132.5, 131.7, 131.2, 131.1, 130.4, 126.2, 125.7, 124.6, 52.8, 20.7, 16.5; **IR** (KBr, cm^{-1}): 3375, 1761, 1541, 1468, 1441, 1367, 1211, 1171, 758, 597; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{25}H_{24}N_2O_8S$ $[M+Na]^+$ 535.1146; found, 535.1163.



27b



28b



26b-diAc

Following the general procedure for asymmetric bromination, **26b** (12.9 mg, 0.030 mmol), **31** (5.00 mg, 0.0060 mmol) and NBS (6.14 mg, 0.0345 mmol) were stirred at -20 ℃ in $CHCl_3$ (6.0 mL). After stirred 3 h, Ac_2O (22.7 μL, 0.24 mmol) and DMAP (22.0 mg, 0.18 mmol) were added to the mixture. The crude residue was purified by preparative TLC (AcOEt/toluene = 5/95) to afford **27b** (5.9 mg, 33%, 37% ee), **28b** (6.6 mg, 33%) and **26b-diAc** (4.9 mg, 32%).

2-((2-Acetoxy-3-methylphenyl)((4-nitrophenyl)sulfonamido)methyl)-4-bromo-6-methylphenyl acetate (27b)

White solid: **m.p.** 185 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.13 (d, *J* = 8.8 Hz, 2H), 7.81 (d, *J* = 8.8 Hz, 2H), 7.21 (d, *J* = 1.8 Hz, 1H), 7.16 (d, *J* = 7.8 Hz, 1H), 6.92 (t, *J* = 7.6 Hz, 1H), 6.72 (d, *J* = 1.8 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 5.98 (br, d, *J* = 10.4 Hz, 1H), 5.16 (d, *J* = 6.4 Hz, 1H), 2.41 (s, 3H), 2.26 (br s, 3H), 2.16 (s, 3H), 2.08 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$, 323K) δ: 169.2, 168.4, 150.3, 147.8, 146.8, 146.2, 134.3, 133.8, 132.6, 132.1, 131.9, 130.2, 129.2, 128.6, 126.5, 126.2, 124.1, 119.0, 52.0, 20.7, 20.4, 16.5, 16.3; **IR** (KBr, cm^{-1}): 3250, 1761, 1531, 1469, 1371, 1347, 1208, 1173, 1087, 739; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{25}H_{23}BrN_2O_8S$ $[M+Na]^+$ 613.0251; found, 613.0268.; HPLC conditions: column: Daicel Chiralpak IA, flow rate: 1.0 mL/min, eluent: hexane/IPA = 80/20, retention time (min): 24.6 (minor), 34.3 (major).

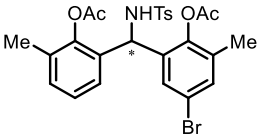
(((4-Nitrophenyl)sulfonamido)methylene)bis(4-bromo-6-methyl-2,1-phenylene) diacetate (28b)

White solid: **m.p.** 237 ℃ (decomp.); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.15 (d, *J* = 9.2 Hz, 2H), 7.80 (td, *J* = 8.4, 2.0 Hz, 2H), 7.26 (s, 2H), 6.69 (s, 2H), 5.88 (d, *J* = 9.2 Hz, 1H), 5.30 (br d, *J* = 6.9 Hz, 1H),; **^{13}C NMR** (100 MHz, $CDCl_3$, 323K) δ: 168.7, 150.5, 146.8, 145.9, 134.4, 134.3, 132.1, 129.1, 128.6, 124.2, 119.3, 52.0, 20.5, 16.4; **IR** (KBr, cm^{-1}): 3445, 3259, 1761, 1532, 1348, 1207, 1174, 1086, 1012, 462; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{25}H_{22}Br_2N_2O_8S$ $[M+Na]^+$ 690.9356; found, 690.9392.

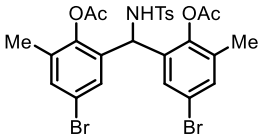
(((4-Nitrophenyl)sulfonamido)methylene)bis(6-methyl-2,1-phenylene) diacetate (26b-diAc)

White solid: **m.p.** 184 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.00 (d, *J* = 8.0 Hz, 2H), 7.71 (dd, *J* = 9.0, 1.8 Hz, 2H), 7.07 (d, *J* = 7.3 Hz, 2H), 6.82 (t, *J* = 7.8 Hz, 2H), 6.65 (d, *J* = 7.3 Hz, 2H), 6.08 (d, *J* = 8.2 Hz, 1H), 5.71 (br s, 1H), 2.36 (br s, 6H), 2.13 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$, 323K) δ: 168.9, 150.0, 147.47, 146.4, 131.8, 131.2, 130.7,

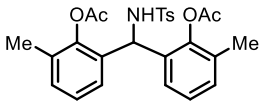
128.7, 126.3, 125.9, 123.8, 51.9, 20.6, 16.4; **IR** (KBr, cm^{-1}): 3293, 1758, 1533, 1371, 1345, 1211, 1165, 1082, 743, 618; **HRMS-ESI**$^+$ (*m/z*): Calcd. for $C_{25}H_{24}N_2O_8S$ $[M+Na]^+$ 535.1146; found, 535.1163.



27c



28c



26c-diAc

Following the general procedure for asymmetric bromination, **26c** (11.9 mg, 0.030 mmol), **31** (5.00 mg, 0.0060 mmol) and NBS (6.14 mg, 0.0345 mmol) were stirred at -20 ℃ in $CHCl_3$ (6.0 mL). After stirred 3 h, Ac_2O (22.7 μL, 0.24 mmol) and DMAP (22.0 mg, 0.18 mmol) were added to the mixture. The crude residue was purified by preparative TLC (AcOEt/hexane = 10/90) to afford **27c** (4.5 mg, 27%, 33% ee), **28c** (5.8 mg, 30%) and **26c-diAc** (6.1 mg, 42%).

2-((2-Acetoxy-3-methylphenyl)((4-methylphenyl)sulfonamido)methyl)-4-bromo-6-methylphenyl acetate (27c)

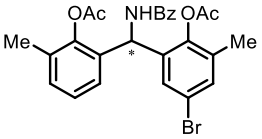
White solid: **m.p.** 177 ℃; $[\alpha]_D^{21}$ = -8.7 (c 1.0, $CHCl_3$, 33% ee); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.53 (d, *J* = 8.6 Hz, 2H), 7.20-7.09 (m, 4H), 6.94 (d, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 1.6 Hz, 1H), 6.67 (d, *J* = 7.6 Hz, 1H), 5.90 (br d, *J* = 3.2 Hz, 1H), 4.83 (br d, *J* = 6.0 Hz, 1H), 2.37 (s, 3H), 2.36 (s, 3H), 2.17 (br s, 3H), 2.14 (s, 3H), 2.04 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$, 313K) δ: 169.1, 168.2, 147.6, 146.5, 143.6, 137.5, 133.7, 133.3, 131.7, 131.5, 131.0, 129.5, 129.3, 127.3, 126.8, 126.1, 119.0, 52.0, 21.6, 20.7, 20.4, 16.5, 16.3, ; **IR** (KBr, cm^{-1}): 3445, 3248, 1761, 1467, 1442, 1369, 1335, 1210, 1172, 1088; **HRMS-ESI**$^+$ (*m/z*): Calcd. for $C_{26}H_{26}BrNO_6S$ $[M+Na]^+$ 582.0556; found, 582.0569.; HPLC conditions: column: Daicel Chiralpak IA, flow rate: 1.0 mL/min, eluent: hexane/IPA = 90/10, retention time (min): 27.6 (minor), 31.9 (major).

(((4-Methylphenyl)sulfonamido)methylene)bis(4-bromo-6-methyl-2,1-phenylene) diacetate (28c)

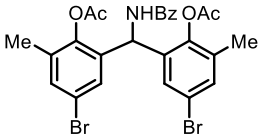
White solid: **m.p.** 248 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.53 (d, *J* = 7.8 Hz, 2H), 7.25 (d, *J* = 5.0 Hz, 2H), 7.14 (d, *J* = 7.8 Hz, 2H), 6.77 (s, 2H), 5.78 (d, *J* = 6.4 Hz, 1H), 4.87 (br s, 1H), 2.39 (s, 3H), 2.26 (br s, 6H), 2.07 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$, 313K) δ: 168.5, 146.6, 144.0, 137.3, 134.0, 133.9, 132.9, 129.7, 129.4, 127.3, 119.2, 52.2, 21.7, 20.5, 16.4; **IR** (KBr, cm^{-1}): 3435, 3236, 1763, 1467, 1444, 1335, 1205, 1173, 1088, 664; **HRMS-ESI**$^+$ (*m/z*): Calcd. for $C_{26}H_{25}Br_2NO_6S$ $[M+Na]^+$ 659.9662; found, 659.9683.

(((4-Methylphenyl)sulfonamido)methylene)bis(6-methyl-2,1-phenylene) diacetate (26c-diAc)

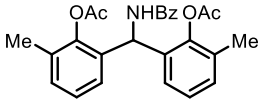
White solid: **m.p.** 147 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.52 (d, *J* = 7.8 Hz, 2H), 7.09 (d, *J* = 8.2 Hz, 2H), 7.07 (d, *J* = 8.2 Hz, 2H), 6.88 (t, *J* = 7.6 Hz, 2H), 6.76 (d, *J* = 8.0 Hz, 2H), 5.99 (d, *J* = 6.9 Hz, 1H), 4.90 (d, *J* = 6.6 Hz, 1H), 2.33 (s, 3H), 2.25 (br s, 6H), 2.10 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$, 313K) δ: 168.8, 147.5, 143.1, 137.9, 131.4, 130.8, 129.3, 127.4, 126.6, 125.8, 52.0, 21.5, 20.6, 16.4; **IR** (KBr, cm^{-1}): 3256, 1762, 1467, 1444, 1369, 1330, 1208, 1171, 1088, 905; **HRMS-ESI**$^+$ (*m/z*): Calcd. for $C_{26}H_{27}NO_6S$ $[M+Na]^+$ 504.1451; found, 504.1466.



27d



28d



26d-diAc

Following the general procedure for asymmetric bromination, **26d** (10.4 mg, 0.030 mmol), **31** (5.00 mg, 0.0060 mmol) and NBS (6.14 mg, 0.0345 mmol) were stirred at -20 ℃ in $CHCl_3$ (6.0 mL). After stirred 3 h, Ac_2O (22.7 μL, 0.24 mmol) and DMAP (22.0 mg, 0.18 mmol) were added to the mixture. The crude residue was purified by preparative TLC (AcOEt/hexane = 20/80) to afford **27d** (6.6 mg, 43%, 15% ee), **28d** (3.3 mg, 19%) and **26d-diAc** (5.5 mg, 42%).

2-((2-Acetoxy-3-methylphenyl)(benzamido)methyl)-4-bromo-6-methylphenyl acetate (27d)

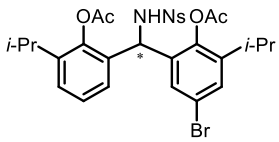
White amorphous: **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.79 (d, *J* = 7.2 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.35 (d, *J* = 2.0 Hz, 1H), 7.22 (d, *J* = 9.2 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.02 (br s, 1H), 6.64 (d, *J* = 6.8 Hz, 1H), 6.57 (br s, 1H), 2.19 (br s, 3H), 2.15 (s, 3H), 2.10 (s, 3H), 2.07 (br s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$, 323K) δ: 169.1, 168.2, 166.4, 147.8, 146.8, 135.1, 134.2, 134.0, 133.6, 132.1, 131.9, 131.8, 131.4, 128.8, 128.7, 127.3, 126.5, 119.5, 48.7, 20.5, 20.3, 16.5, 16.4; **IR** (KBr, cm^{-1}): 3410, 1762, 1660, 1523, 1482, 1369, 1208, 1168, 1011, 414; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{26}H_{24}BrNO_5$ $[M+H]^+$ 510.0911; found, 510.0927.; HPLC conditions: column: Daicel Chiralpak IA, flow rate: 1.0 mL/min, eluent: hexane/IPA = 95/5, retention time (min): 24.0 (minor), 27.0 (major).

(Benzamidomethylene)bis(4-bromo-6-methyl-2,1-phenylene) diacetate (28d)

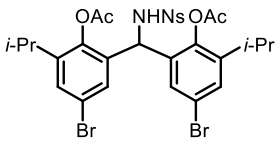
White amorphous: **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.79 (d, *J* = 7.6 Hz, 2H), 7.53 (tt, *J* = 7.4, 2.2 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.37 (d, *J* = 1.8 Hz, 2H), 7.21 (br s, 2H), 6.58 (d, *J* = 6.8 Hz, 1H), 6.57 (br s, 1H), 2.14 (br s, 6H), 2.11 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$, 323K) δ: 168.5, 166.4, 146.8, 134.4, 134.2, 134.0, 133.9, 132.1, 129.0, 128.9, 127.3, 119.6, 48.7, 20.4, 16.4; **IR** (KBr, cm^{-1}): 3409, 1765, 1661, 1520, 1483, 1442, 1369, 1259, 1206, 1170; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{26}H_{23}Br_2NO_5$ $[M+H]^+$ 588.0016; found, 588.0029.

(Benzamidomethylene)bis(6-methyl-2,1-phenylene) diacetate (26d-diAc)

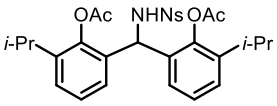
White amorphous: **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.78 (d, *J* = 7.4 Hz, 2H), 7.50 (tt, *J* = 7.6, 1.7 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.13 (t, *J* = 7.6 Hz, 2H), 7.08 (br s, 2H), 6.71 (d, *J* = 7.6 Hz, 1H), 6.53 (br s, 1H), 2.14 (br s, 12H); **^{13}C NMR** (100 MHz, $CDCl_3$, 323K) δ: 168.8, 166.4, 147.8, 134.5, 132.7, 131.7, 131.6, 131.0, 128.8, 127.2, 126.3, 126.1, 48.7, 20.4, 16.5; **IR** (KBr, cm^{-1}): 3455, 3263, 1760, 1640, 1534, 1367, 1212, 1165, 909, 702; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{26}H_{25}NO_5$ $[M+H]^+$ 432.1805; found, 432.1823.



27e



28e



26e-diAc

Following the general procedure for asymmetric bromination, **26e** (14.5 mg, 0.030 mmol), **31** (5.00 mg, 0.0060 mmol) and NBS (6.14 mg, 0.0345 mmol) were stirred at -20 ℃ in $CHCl_3$ (6.0 mL). After stirred 3 h, Ac_2O (22.7 μL, 0.24 mmol) and DMAP (22.0 mg, 0.18 mmol) were added to the mixture. The crude residue was purified by preparative TLC (AcOEt/toluene = 5/95) to afford **27e** (10.5 mg, 54%, 96% ee), **28e** (5.9 mg, 27%) and **26e-diAc** (3.3 mg, 19%).

2-((2-Acetoxy-3-isopropylphenyl)((2-nitrophenyl)sulfonamido)methyl)-4-bromo-6-isopropylphenyl acetate (27e)

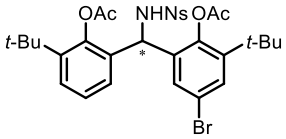
White amorphous: $[\alpha]_D^{21}$ = -60.2 (c 1.0, $CHCl_3$, 96% ee); **^{1}H NMR** (400 MHz, $CDCl_3$, 323K) δ: 7.75 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.25-7.10 (m, 2H), 7.03 (br s, 1H), 6.99 (d, *J* = 7.8 Hz, 1H), 6.76 (br d, *J* = 5.2 Hz, 1H), 6.05 (d, *J* = 9.2 Hz, 1H), 5.86 (d, *J* = 9.4 Hz, 1H), 2.98-2.87 (m, 1H), 2.85-2.75 (m, 1H), 2.39 (s, 3H), 2.28 (s, 3H), 1.22 (d, *J* = 6.8 Hz, 3H), 1.17 (d, *J* = 6.8 Hz, 6H), 1.12 (d, *J* = 7.2 Hz, 3H),; **^{13}C NMR** (150 MHz, $CDCl_3$, 323K) δ: 169.5, 169.0, 147.6, 146.7, 145.6, 144.4, 142.1, 134.5, 133.3, 132.9, 132.3, 131.0, 130.0, 129.9, 129.2, 127.3, 126.4, 126.3, 124.8, 119.6, 53.0, 27.8, 27.7, 23.4, 23.1, 20.8, 20.6; **IR** (KBr, cm^{-1}): 3446, 2969, 1763, 1541, 1443, 1366, 1207, 1174, 1065, 739; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{29}H_{31}BrN_2O_8S$ $[M+Na]^+$ 669.0877; found, 669.0885.; HPLC conditions: column: Daicel Chiralpak IA, flow rate: 1.0 mL/min, eluent: hexane/IPA = 95/5, retention time (min): 11.0 (minor), 13.3 (major).

(((2-Nitrophenyl)sulfonamido)methylene)bis(4-bromo-6-isopropyl-2,1-phenylene) diacetate (28e)

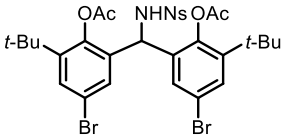
White amorphous: **^{1}H NMR** (400 MHz, $CDCl_3$, 323K) δ: 7.79 (d, *J* = 7.6 Hz, 1H), 7,76 (br s, 1H), 7.58 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.28 (br d, *J* = 1.6 Hz, 2H), 6.95 (br, s 2H), 5.96 (d, *J* = 9.2 Hz, 1H), 5.89 (d, *J* = 9.6 Hz, 1H), 2.89-2.77 (m, 2H), 2.32 (s, 6H), 1.19 (d, *J* = 6.8 Hz, 6H), 1.14 (d, *J* = 6.8 Hz, 6H),; **^{13}C NMR** (100 MHz, $CDCl_3$, 323K) δ: 169.0, 147.5, 145.7, 144.6, 134.2, 133.6, 132.4, 130.9, 130.4, 129.2, 125.1, 119.8, 53.1, 27.8, 23.2, 23.0,20.7; **IR** (KBr, cm^{-1}): 3446, 2969, 1763, 1541, 1445, 1366, 1207, 1174, 1065, 742; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{29}H_{30}Br_2N_2O_8S$ $[M+Na]^+$ 746.9982; found, 747.0006.

(((2-Nitrophenyl)sulfonamido)methylene)bis(4-bromo-6-isopropyl-2,1-phenylene) diacetate (26e-diAc)

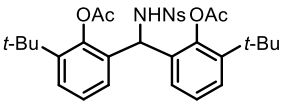
White amorphous: **^{1}H NMR** (400 MHz, $CDCl_3$, 323K) δ: 7.74 (br d, *J* = 8.8 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.91 (t, *J* = 7.6 Hz, 2H), 6.82 (br d, *J* = 6.0 Hz, 2H), 6.14 (d, *J* = 9.2 Hz, 1H), 5.89 (d, *J* = 9.6 Hz, 1H), 2.96-2.83 (m, 2H), 2.35 (s, 6H), 1.20 (d, *J* = 6.8 Hz, 6H), 1.15 (d, *J* = 6.8 Hz, 6H),; **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 168.9, 147.7, 147.5, 134.5, 133.0, 132.5, 131.7, 131.2, 131.1, 130.4, 126.2, 125.7, 124.6, 52.8, 20.7, 16.5; **IR** (KBr, cm^{-1}): 3383, 2968, 1766, 1543, 1450, 1366, 1205, 1173, 1101, 907; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{29}H_{32}N_2O_8S$ $[M+Na]^+$ 591.1772; found, 591.1784.



27f



28f



26f-diAc

Following the general procedure for asymmetric bromination, **26f** (15.4 mg, 0.030 mmol), **31** (5.00 mg, 0.0060 mmol) and NBS (6.14 mg, 0.0345 mmol) were stirred at -20 ℃ in $CHCl_3$ (6.0 mL). After stirred 3 h, Ac_2O (22.7 μL, 0.24 mmol) and DMAP (22.0 mg, 0.18 mmol) were added to the mixture. The crude residue was purified by preparative TLC (AcOEt/Toluene = 5/95) to afford **27f** (9.7 mg, 48%, 98% ee), **28f** (7.7 mg, 34%) and **26f-diAc** (2.1 mg, 12%).

2-((2-Acetoxy-3-(tert-butyl)phenyl)((2-nitrophenyl)sulfonamido)methyl)-4-bromo-6-(*tert*-butyl)phenyl acetate (27f)

Colorless oil: $[\alpha]_D^{21}$ = -62.2 (c 1.0, $CHCl_3$, 98% ee); **^{1}H NMR** (600 MHz, DMSO-d_6, 393K) δ: 8.49 (br s, 1H). 7.74 (d, *J* = 8.4 Hz, 1H), 7.69 (br s, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 2.4 Hz, 1H), 7.31 (t, *J* = 4.5 Hz, 1H), 7.23 (br s, 1H), 6.98 (d, *J* = 4.8 Hz, 2H), 5.89 (d, *J* = 9.0 Hz, 1H), 2.31 (s, 3H), 2.29 (s, 3H), 1.31 (s, 9H), 1.28 (s, 9H); **^{13}C NMR** (200 MHz, $CDCl_3$) δ: 170.4, 169.7, 169.6, 169.4, 169.3, 169.0, 148.6, 148.0, 147.7, 147.4, 147.3, 147.0, 146.6, 146.0, 145.0, 144.6, 142.8, 142.6, 142.4, 135.4, 134.6, 134.5, 134.4, 134.3, 133.7, 133.3, 133.2, 132.8, 132.3, 132.2, 131.9, 131.5, 131.2, 131.1, 130.8, 130.7, 130.7, 130.6, 130.4, 130.0, 129.4, 129.2, 128.9, 128.3, 128.1, 127.9, 127.4, 126.3, 126.2, 125.9, 125.8, 125.3, 124.9, 124.7, 119.2, 119.1, 118.8, 54.2, 53.3, 52.8, 51.8, 35.2, 35.1, 34.9, 30.8, 30.6, 30.5, 30.4, 29.7, 21.7, 21.6, 21.5, 21.3; **IR** (neat, cm^{-1}): 3379, 2965, 1762, 1541, 1364, 1197, 1171, 1142, 910, 733; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{31}H_{35}BrN_2O_8S$ $[M+Na]^+$ 697.1190; found, 697.1192; HPLC conditions: column: Daicel Chiralpak IA, flow rate: 1.0 mL/min, eluent: hexane/IPA = 95/5, retention time (min): 9.1 (minor), 11.1 (major).

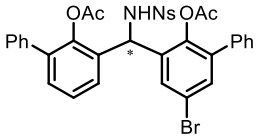
(((2-Nitrophenyl)sulfonamido)methylene)bis(4-bromo-6-(*tert*-butyl)-2,1-phenylene) diacetate (28f)

Colorless oil: **^{1}H NMR** (600 MHz, DMSO-d_6, 373K) δ: 8.78 (br s, 1H), 7.79 (d, *J* = 7.2 Hz, 1H), 7.74-7.60 (m, 2H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.37 (s, 2H), 7.17 (br s, 2H), 5.83 (d, *J* = 9.0 Hz, 1H), 2.34 (s, 6H), 1.29 (s, 18H); **^{13}C NMR** (200 MHz, $CDCl_3$) δ: 170.2, 169.3, 169.2, 168.9, 147.7, 147.3, 147.1, 146.9, 146.5, 146.1, 145.2, 145.1, 144.8, 134.4, 134.1, 134.0, 133.8, 133.5, 133.1, 133.0, 132.4, 132.2, 131.4, 131.2, 130.9, 130.9, 130.3, 129.1, 129.0, 125.2, 124.9, 119.5, 119.4, 119.3, 118.9, 53.8, 52.7, 51.9, 35.2, 35.1, 30.5, 30.4, 30.3, 30.3, 21.5. 21.5; **IR** (neat, cm^{-1}): 3379, 2966, 1763, 1541, 1432, 1364, 1197, 1144, 909, 734; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{31}H_{34}Br_2N_2O_8S$ $[M+Na]^+$ 775.0295; found, 775.0318.

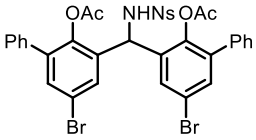
(((2-Nitrophenyl)sulfonamido)methylene)bis(6-(*tert*-butyl)-2,1-phenylene) diacetate (26f-diAc)

Colorless oil: **^{1}H NMR** (600 MHz, DMSO-d_6, 373K) δ: 8.43 (br s, 1H), 7.79-7.57 (m ,3H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 2H), 7.02 (br s, 2H), 6.94 (t, *J* = 7.5 Hz, 2H), 5.92 (d, *J* = 9.0 Hz, 1H), 2.29 (s, 6H), 1.29 (s, 18H); **^{13}C NMR** (200 MHz, DMSO-d_6) δ: 169.6, 169.4, 169.3, 147.8, 147.3, 147.1, 146.9, 146.8, 146.5, 141.5, 141.4, 141.2, 133.8, 133.7, 133.5, 133.3, 133.2, 133.1, 131.8, 131.7, 131.6, 131.6, 131.3, 131.0, 130.3, 129.3, 129.0, 127.9, 127.1,

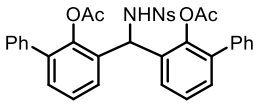
127.0, 125.4, 125.3, 125.1, 123.8, 123.7, 51.6, 51.0, 50.7, 39.7, 34.7, 30.8, 30.7, 21.7, 21.7, 21.6, 21.6; **IR** (neat, cm^{-1}): 3375, 2961, 1761, 1541, 1364, 1201, 1171, 1135, 910, 735; **HRMS-ESI**$^+$ (*m/z*): Calcd. for $C_{31}H_{36}N_2O_8S$ $[M+Na]^+$ 619.2085; found, 619.2095.



27g



28g



26g-diAc

Following the general procedure for asymmetric bromination, **26g** (16.6 mg, 0.030 mmol), **31** (5.00 mg, 0.0060 mmol) and NBS (6.14 mg, 0.0345 mmol) were stirred at -20 ℃ in $CHCl_3$ (6.0 mL). After stirred 3 h, Ac_2O (22.7 μL, 0.24 mmol) and DMAP (22.0 mg, 0.18 mmol) were added to the mixture. The crude residue was purified by preparative TLC (AcOEt/toluene = 5/95) to afford **27g** (16.6 mg, 77%, 97% ee), **28g** (2.7 mg, 11%) and **26g-diAc** (1.6 mg, 8%).

3-((2-Acetoxy-5-bromo-[1,1'-biphenyl]-3-yl)((2-nitrophenyl)sulfonamido)methyl)-[1,1'-biphenyl]-2-yl acetate (27g)

White amorphous: $[\alpha]_D^{21}$ = -10.6 (c 1.0, $CHCl_3$, 97% ee); **^{1}H NMR** (400 MHz, $CDCl_3$, 323K) δ: 7.78 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.68 (d, *J* = 8.0, 1.2 Hz, 1H), 7.48 (td, *J* = 7.8, 1.4 Hz, 1H), 7.34 (td, *J* = 7.8, 1.0 Hz, 1H), 7.32-7.17 (m, 13H), 7.02 (t, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 6.8 Hz, 1H), 6.07 (d, *J* = 8.8 Hz, 1H), 5.96 (d, *J* = 9.2 Hz, 1H), 2.03 (s, 3H), 1.94 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$, 323K) δ: 168.8, 168.2, 147.7, 146.6, 145.5, 138.7, 137.5, 136.9, 136.3, 134.4, 133.5, 133.5, 132.5, 131.4, 131.1, 130.8, 130.6, 129.0, 128.8, 128.6, 128.5, 128.4, 127.9, 126.3, 125.0, 119.2, 53.2, 20.7, 20.5; **IR** (KBr, cm^{-1}): 3367, 1766, 1540, 1458, 1434, 1364, 1210, 1178, 760, 701; **HRMS-ESI**$^+$ (*m/z*): Calcd. for $C_{35}H_{27}BrN_2O_8S$ $[M+Na]^+$ 737.0564; found, 737.0564.; HPLC conditions: column: Daicel Chiralpak IA, flow rate: 1.0 mL/min, eluent: hexane/IPA = 95/5, retention time (min): 22.2 (minor), 24.5 (major).

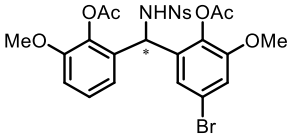
(((2-Nitrophenyl)sulfonamido)methylene)bis(5-bromo-[1,1'-biphenyl]-3,2-diyl) diacetate (28g)

White amorphous: **^{1}H NMR** (400 MHz, $CDCl_3$, 323K) δ: 7.88 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.83 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.63 (td, *J* = 7.8, 1.4 Hz, 1H), 7.50 (td, *J* = 7.8, 1.0 Hz, 1H), 7.42-7.29 (m, 12H), 7.23 (d, *J* = 2.4 Hz, 2H), 6.11 (d, *J* = 9.6 Hz, 1H), 6.06 (d, *J* = 9.6 Hz, 1H), 1.96 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$, 323K) δ: 168.3, 147.6, 145.6, 138.9, 136.2, 134.2, 134.0, 133.8, 132.9, 132.6, 131.0, 130.5, 128.9, 128.7, 128.4, 125.2, 119.4, 53.5, 20.6; **IR** (KBr, cm^{-1}): 3339, 1766, 1540, 1435, 1364, 1176, 1111, 757, 702, 591, 445; **HRMS-ESI**$^+$ (*m/z*): Calcd. for $C_{35}H_{26}Br_2N_2O_8S$ $[M+Na]^+$ 814.9669; found, 814.9694.

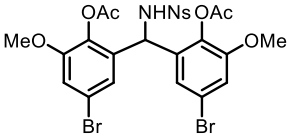
(((2-Nitrophenyl)sulfonamido)methylene)bis([1,1'-biphenyl]-3,2-diyl) diacetate (26g-diAc)

White amorphous: **^{1}H NMR** (400 MHz, $CDCl_3$, 323K) δ: 7.85 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.73 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.53 (td, *J* = 7.8, 1.0 Hz, 1H), 7.43-7.30 (m, 11H), 7.27-7.23 (m, 2H), 7.12 (d, *J* = 6.4 Hz, 2H), 7.06 (t, *J* = 7.4 Hz, 2H), 6.26 (d, *J* = 9.2 Hz, 1H), 6.08 (d, *J* = 9.2 Hz, 1H), 1.99 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$, 323K) δ:

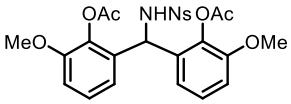
168.7, 147.8, 146.5, 137.7, 136.7, 134.8, 133.1, 132.4, 131.4, 131.3, 131.0, 129.0, 128.5, 127.9, 126.1, 124.7, 53.2, 20.6; **IR** (KBr, cm^{-1}): 3379, 1766, 1540, 1458, 1432, 1365, 1212, 1178, 760, 702; **HRMS-ESI**$^+$ (*m/z*): Calcd. for $C_{35}H_{28}N_2O_8S$ $[M+Na]^+$ 659.1459; found, 659.1461.



27h



28h



26h-diAc

Following the general procedure for asymmetric bromination, **26h** (13.8 mg, 0.030 mmol), **31** (5.00 mg, 0.0060 mmol) and NBS (6.14 mg, 0.0345 mmol) were stirred at -20 ℃ in $CHCl_3$ (6.0 mL). After stirred 3 h, Ac_2O (22.7 μL, 0.24 mmol) and DMAP (22.0 mg, 0.18 mmol) were added to the mixture. The crude residue was purified by preparative TLC (AcOEt/toluene = 10/90) to afford **27h** (12.4 mg, 66%, 90% ee), **28h** (4.4 mg, 21%) and **26h-diAc** (2.9 mg, 18%).

2-((2-Acetoxy-3-methoxyphenyl)((2-nitrophenyl)sulfonamido)methyl)-4-bromo-6-methoxyphenyl acetate (27h)

White amorphous: $[\alpha]_D^{20}$ = -29.2 (c 1.0, $CHCl_3$, 90% ee); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.78 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 6.98 (t, *J* = 8.0 Hz, 1H), 6.90-6.83 (m, 3H), 6.59 (d, *J* = 7.2 Hz, 1H), 6.08 (d, *J* = 9.2 Hz, 1H), 6.05 (d, *J* = 9.6 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 2.33 (s, 3H), 2.24 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 168.4, 168.0, 152.4, 151.8, 147.4, 138.1, 137.2, 134.2, 133.4, 133.3, 132.6, 131.0, 130.9, 126.5, 125.0, 122.6, 119.8, 119.1, 115.6, 112.7, 56.5, 56.2, 52.4, 20.6, 20.4; **IR** (KBr, cm^{-1}): 3367, 2921, 1769, 1541, 1480, 1415, 1366, 1280, 1172, 1043; **HRMS-ESI**$^+$ (*m/z*): Calcd. for $C_{25}H_{23}BrN_2O_{10}S$ $[M+Na]^+$ 645.0149; found, 645.0158.; HPLC conditions: column: Daicel Chiralpak IA, flow rate: 1.0 mL/min, eluent: hexane/IPA = 70/30, retention time (min): 9.5 (minor), 12.2 (major).

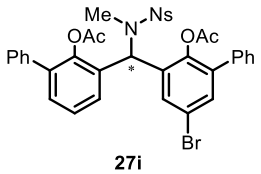
(((2-Nitrophenyl)sulfonamido)methylene)bis(4-bromo-6-methoxy-2,1-phenylene) diacetate (28h)

White amorphous: **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.82 (d, *J* = 8.2 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.47 (d, *J* = 7.7 Hz, 1H), 6.93 (d, *J* = 1.8 Hz, 2H), 6.78 (d, *J* = 2.3 Hz, 2H), 6.08 (d, *J* = 9.6 Hz, 1H), 5.97 (d, *J* = 9.6 Hz, 1H), 3.77 (s, 6H), 2.28 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 167.9, 152.5, 147.4, 137.3, 134.0, 133.7, 132.6, 132.6, 130.8, 125.2, 122.5, 119.2, 116.0, 56.5, 52.6, 20.5; **IR** (KBr, cm^{-1}): 3375, 1770, 1541, 1479, 1412, 1365, 1291, 1173, 1044, 853; **HRMS-ESI**$^+$ (*m/z*): Calcd. for $C_{25}H_{22}Br_2N_2O_{10}S$ $[M+Na]^+$ 722.9254; found, 722.9272.

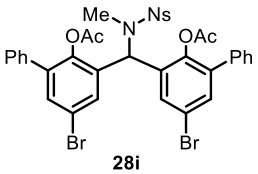
(((2-Nitrophenyl)sulfonamido)methylene)bis(6-methoxy-2,1-phenylene) diacetate (26h-diAc)

White amorphous: **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.77 (d, *J* = 7.4 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 6.93 (t, *J* = 8.0 Hz, 2H), 6.81 (d, *J* = 8.0 Hz, 2H), 6.65 (d, *J* = 8.0 Hz, 2H), 6.17 (d, *J* = 9.2 Hz, 1H), 6.06 (d, *J* = 9.6 Hz, 1H), 3.77 (s, 6H), 2.28 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 168.4, 151.7,

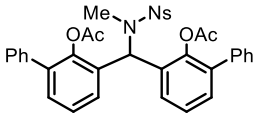
147.5, 138.1, 134.6, 133.0, 132.5, 131.7, 131.1, 126.2, 124.8, 119.8, 112.2, 56.2, 52.4, 20.6; **IR** (KBr, cm^{-1}): 3438, 3160, 2960, 1770, 1549, 1481, 1264, 1192, 1049, 807, ; **HRMS-ESI**$^+$ (*m/z*): Calcd. for $C_{25}H_{24}N_2O_{10}S$ $[M+Na]^+$ 567.1044; found, 567.1061.



27i



28i



26i-diAc

Following the general procedure for asymmetric bromination, **26i** (11.3 mg, 0.020 mmol), **31** (3.33 mg, 0.0040 mmol) and NBS (4.09 mg, 0.023 mmol) were stirred at -20 ℃ in $CHCl_3$ (4.0 mL). After stirred 3 h, Ac_2O (15.1 μL, 0.16 mmol) and DMAP (14.7 mg, 0.12 mmol) were added to the mixture. The crude residue was purified by preparative TLC (AcOEt/toluene = 5/95) to afford **27i** (3.1 mg, 22%, 1% ee), **28i** (2.1 mg, 13%) and **26i-diAc** (7.6 mg, 60%).

3-((2-Acetoxy-5-bromo-[1,1'-biphenyl]-3-yl)((*N*-methyl-4-nitrophenyl)sulfonamido)methyl)-[1,1'-biphenyl]-2-yl acetate (27i)

White amorphous: **^{1}H NMR** (400 MHz, $CDCl_3$, 323K) δ: 7.79 (d, *J* = 8.4 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 8.4 Hz, 1H), 7.44-7.27 (m, 13H), 7.18 (s, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 7.2 Hz, 1H), 6.68 (s, 1H) 3.03 (s, 3H), 2.04 (s, 3H), 1.89 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$, 323K) δ: 169.1, 168.4, 147.5, 147.2, 145.7, 138.6, 137.6, 136.7, 136.4, 133.7, 133.4, 133.3, 131.7, 131.4, 131.1, 130.7, 130.1, 129.0, 128.8, 128.7, 128.5, 128.3, 127.9, 126.3, 123.7, 119.4, 55.8, 34.2, 20.8, 20.4; **IR** (KBr, cm^{-1}): 3445, 1766, 1545, 1433, 1370, 1211, 1180, 964, 762, 701; **HRMS-ESI**$^+$ (*m/z*): Calcd. for $C_{36}H_{29}BrN_2O_8S$ $[M+Na]^+$ 751.0720; found, 751.0724.; HPLC conditions: column: Daicel Chiralpak ID, flow rate: 1.0 mL/min, eluent: hexane/IPA = 90/10, retention time (min): 20.1 (major), 26.1 (minor).

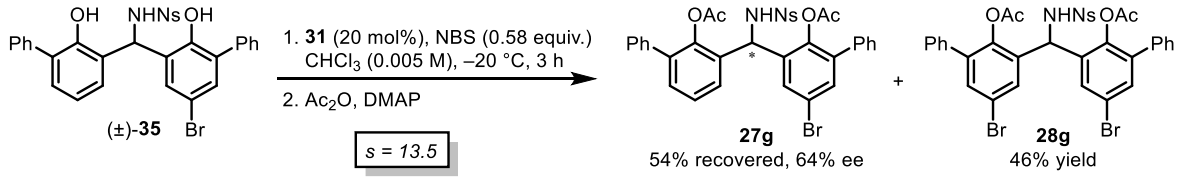
(((*N*-Methyl-2-nitrophenyl)sulfonamido)methylene)bis(5-bromo-[1,1'-biphenyl]-3,2-diyl) diacetate (28i)

White amorphous: **^{1}H NMR** (400 MHz, $CDCl_3$, 323K) δ: 7.79 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.44-7.30 (13H), 7.10 (br s, 2H),6.59 (s, 1H), 3.04 (s, 3H), 1.96 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$, 323K) δ: 168.6, 147.4, 146.0, 138.7, 136.2, 133.9, 133.6, 133.5, 132.5, 131.6, 131.2, 131.1, 128.9, 128.7, 128.4, 123.9, 119.5, 55.7, 34.2, 20.6; **IR** (KBr, cm^{-1}): 3446, 1766, 1545, 1434, 1369, 1209, 1179, 1083, 763, 701; **HRMS-ESI**$^+$ (*m/z*): Calcd. for $C_{36}H_{28}Br_2N_2O_8S$ $[M+Na]^+$ 828.9825; found, 828.9850.

(((*N*-Methyl-2-nitrophenyl)sulfonamido)methylene)bis([1,1'-biphenyl]-3,2-diyl) diacetate (26i-diAc)

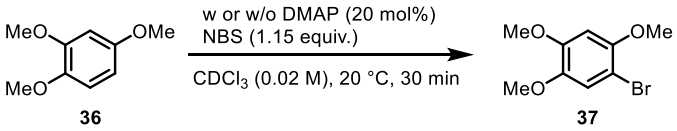
White amorphous: **^{1}H NMR** (600 MHz, $CDCl_3$, 323K) δ: 7.76 (d, *J* = 7.2 Hz, 1H), 7.48-7.32 (m, 12H), 7.29-7.23 (m, 3H), 7.04 (t, *J* = 7.8 Hz, 2H), 6.99 (br d, *J* = 7.8 Hz, 2H), 6.77 (s, 1H), 3.04 (s, 3H), 1.97 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$, 323K) δ: 168.9, 147.7, 146.9, 137.8, 136.6, 134.0, 132.9, 132.0, 131.0, 130.8, 129.0, 128.5, 127.8, 126.1, 123.2, 56.0, 34.1, 20.7; **IR** (KBr, cm^{-1}): 3423, 1766, 1545, 1431, 1370, 1211, 1182, 961, 761, 701; **HRMS-ESI**$^+$ (*m/z*): Calcd. for $C_{36}H_{28}N_2O_8S$ $[M+Na]^+$ 673.1615; found, 673.1621.

Kinetic Resolution of (±)-35



Following the general procedure for asymmetric bromination, (±)-**35** (9.47 mg, 0.015 mmol), **31** (2.50 mg, 0.0030 mmol) and NBS (1.55 mg, 0.0087 mmol) were stirred at -20 ℃ in $CHCl_3$ (3.0 mL). After stirred 3 h, Ac_2O (11.4 μL, 0.12 mmol) and DMAP (11.0 mg, 0.090 mmol) were added to the mixture. The crude residue was purified by preparative TLC (AcOEt/toluene = 5/95) to afford **27g** (5.8 mg, 54%, 64% ee) and **28g** (5.5 mg, 46%).

Model Experiment of DMAP-Catalyzed Bromination



To a stirred solution of **36** (33.6 mg, 0.20 mmol, 1.0 equiv.) and DMAP (4.89 mg, 0.040 mmol, 0.20 equiv.) in $CDCl_3$ (10 mL) was added NBS (40.9 mg, 0.23 mmol, 1.15 equiv.) at 20 ℃. The reaction was monitored by ^1H NMR measurement for every 10 minites and the yield of **37** was determined from the comparison of the integrals of the product peaks relative to the 1,3-dinitrobenzene internal standard (**Figure S3**). The experiments were performed with/without DMAP.

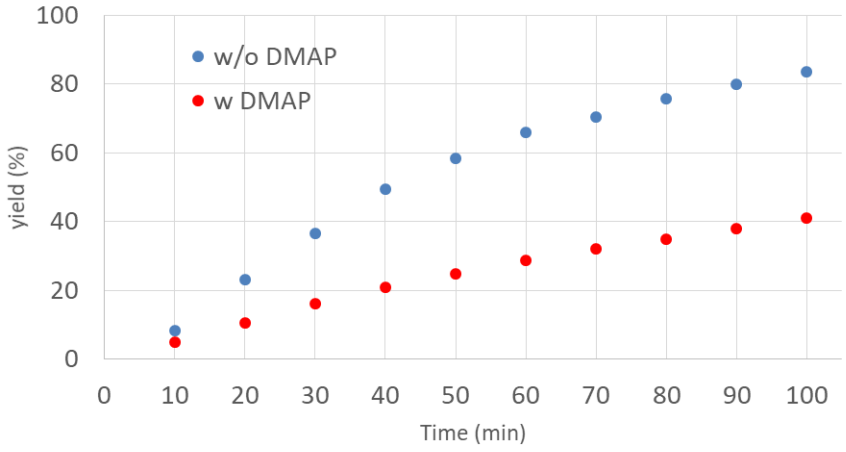
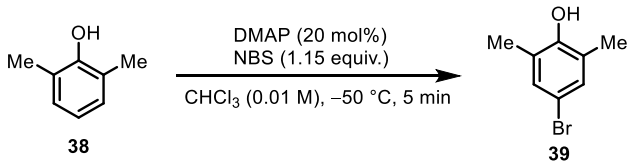
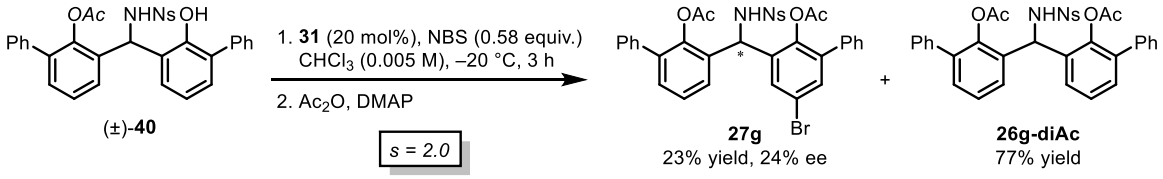


Figure S3. Rate Analysis for Bromination of **36**



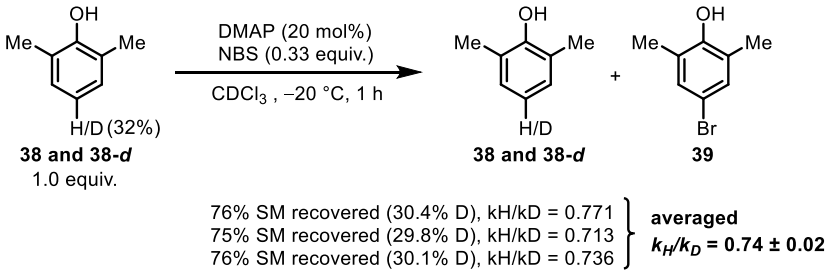
To a stirred solution of **38** (6.1 mg, 0.050 mmol, 1.0 equiv.) and DMAP (1.22 mg, 0.010 mmol, 0.20 equiv.) in $CHCl_3$ (5.0 mL) was added NBS (10.2 mg, 0.0575 mmol, 1.15 equiv.) at -50 °C. After stirred for 5 minites, the reaction was quenched by saturated $Na_2S_2O_3$ aq. and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product. The yield of **39** was determined from the comparison of the integrals of the product peaks relative to the 1,3-dinitrobenzene internal standard (29%).

<u>Kinetic Resolution of (±)-40</u>



Following the general procedure for asymmetric bromination, (±)-**40** (11.9 mg, 0.020 mmol), **31** (3.33 mg, 0.0040 mmol) and NBS (2.06 mg, 0.0116 mmol) were stirred at -20 °C in $CHCl_3$ (4.0 mL). After stirred 3 h, Ac_2O (15.1 μL, 0.16 mmol) and DMAP (14.7 mg, 0.12 mmol) were added to the mixture. The crude residue was purified by preparative TLC (AcOEt/toluene = 5/95) to afford **27g** (3.3 mg, 23%, 24% ee) and **26g-diAc** (9.8 mg, 77%).

KIE Mesurement of DMAP-Catalyzed Bromination



To a stirred solution of **38** and **38-*d*** (12.3 mg, 0.10 mmol, 1.0 equiv.) and DMAP (2.44 mg, 0.020 mmol, 0.20 equiv.) in $CHCl_3$ (20 mL) was added NBS (5.87 mg, 0.033 mmol, 0.33 equiv.) at -20 °C. After reaction completion, KIE was calculated from the comparison the integrals between a para C-H signal (δ 6.79–6.73 ppm, 1H of **38**) and a meta C-H signal (δ 7.01–6.94 ppm, 2H of **38** and **38-*d***) in ^{1}H NMR. The experiments were performed three times and the determined KIE was the average of three runs.

Computational Details

The conformational search was conducted by molecular mechanics simulation using Monte-Carlo Multiple Minimum (MCMM) method (MacroModel in Material Science Suite 2019-4, Force Field: 0PLS_2005) with the constraint of (2.2 ± 0.6) Å for the distance between red-colored H of the protonated catalyst and red-colored O of σ complexes (Figure S1). 36 conformers of the complex with the (*R*,*R*)-isomer, 148 conformers of the complex with the (*R*,*S*)-isomer, 145 conformers of the complex with the (*S*,*R*)-isomer, and 145 conformers of the complex with the (*S*,*S*)-isomer were obtained with energies within 5.0 kcal/mol of the most stable structures. Geometry optimization and frequency calculation of all conformers were performed at the M06-2X/LanL2DZ(Br)/6-31G(d,p) level of theory. The single-point energy calculations of all conformers were performed at the M06-2X/SDD(Br)/6-311++G(2d,2p) level of theory with solvation effects using the SMD solvation model ($CHCl_3$). XYZ coordinates and thermochemical data at 298.15 K (energies in Hartree) of the most stable structures were described below.

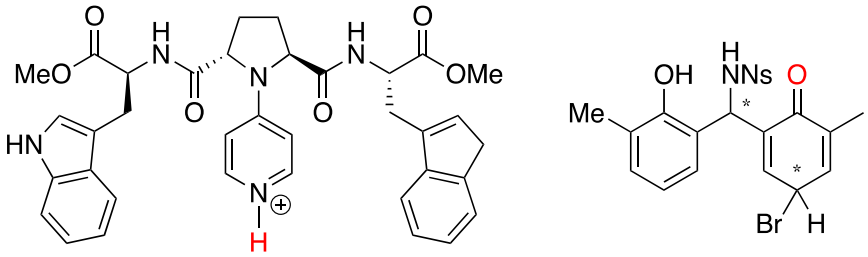
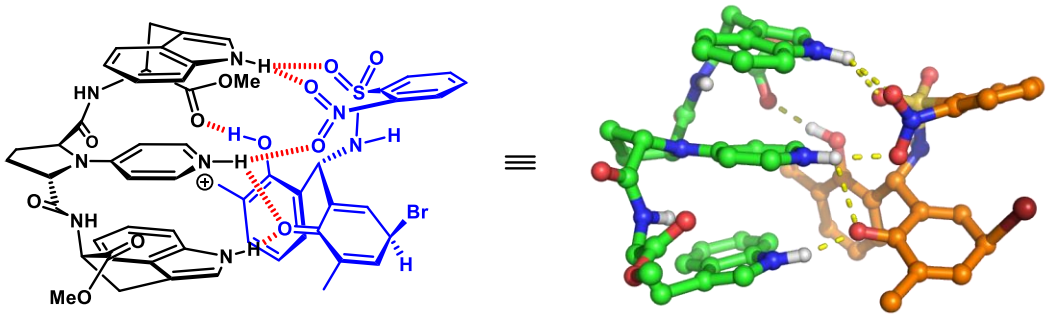


Figure S4. Chemical Models for Calculations.

σ-Complex ((*S*,*S*)-isomer)



M06-2X/LanL2DZ(Br)/6-31G(d,p)

Electronic Energy = –3918.087584

Free Energy = –3917.115828

M06-2X/SDD(Br)/6-311++G(2d,2p), SMD (chloroform)

Electronic Energy = –3919.519519

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C	4.98775100	-1.35412100	-1.40517800
C	3.66700000	-1.14739700	-1.41893900
C	2.72825500	-2.27656700	-1.21174600
C	3.27226800	-3.65178100	-1.12886700
C	4.60234100	-3.82613700	-1.11150800
C	3.01245000	0.20135400	-1.54670600
C	2.35907200	0.44659400	-2.89138300
C	2.61177200	-0.32939500	-4.01996400
C	1.93746300	-0.07567000	-5.20945800
C	1.01356500	0.96358800	-5.26700700
C	0.73971400	1.76654100	-4.15885200
C	1.42575600	1.49135500	-2.96908600
N	3.94767800	1.29307000	-1.22132900
O	1.52624300	-2.06013800	-1.09058600
O	1.24596300	2.21467200	-1.83189100
C	2.27309200	-4.76348700	-1.02874300
C	-0.26986900	2.88216400	-4.21312400
Br	6.56281700	-2.60926700	0.60130900
S	3.82901800	2.02125600	0.26293700
O	4.38099500	3.35024000	0.08626600
O	2.51265800	1.83569600	0.87165900
C	4.95761700	1.10352700	1.31119600
C	4.52708800	0.18962300	2.27160300
C	5.38446500	-0.33206800	3.22622100
C	6.72785900	0.03179400	3.18550400
C	7.18440200	0.92109200	2.21737700
C	6.29748100	1.47522800	1.29718000
N	3.14093600	-0.29726100	2.30485200
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O	2.49076200	-0.10127100	3.30982400
H	6.38793000	-2.91380600	-1.88129700
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H	5.02680700	-4.82259300	-1.02262400
H	2.21262800	0.21485200	-0.80394700
H	3.33412200	-1.13801600	-3.96364500
H	2.13020400	-0.68211700	-6.08678700
H	0.48624900	1.16431000	-6.19563500
H	3.98728500	2.03207700	-1.92112100

H	0.45432000	2.78485500	-1.85890400
H	1.58408000	-4.74020500	-1.87816100
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H	1.67072100	-4.64860200	-0.12216600
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C	-6.24059300	1.24172600	0.37346400
C	-5.83301100	1.29936300	-1.10226900
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C	-5.65583300	-1.14122900	1.01042800
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C	-4.83227300	-3.94617500	1.29707300
O	-5.42344500	-5.10530400	1.58311900
O	-3.90298900	-3.49081000	1.92286900
O	-3.95892800	3.58988500	-1.90095600
N	-3.34042900	3.26317400	0.25823200
C	-2.62616700	4.50982800	0.36203400
C	-1.37693800	4.49425300	-0.51739700
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C	-2.20121400	4.73322000	1.82614500
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C	-1.37325700	3.59346500	2.34741700
C	-3.42007000	-3.39962300	-1.50097600
C	-0.03068800	3.38271500	2.15696900
N	0.36130600	2.23374400	2.79625000
C	-0.72081000	1.66857800	3.42208700
C	-1.84441500	2.48327900	3.13573700
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C	-2.06109500	0.19673600	4.72693700
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H	0.74270700	-0.96376500	1.39008400
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H	-7.24803500	0.86000100	0.54365900
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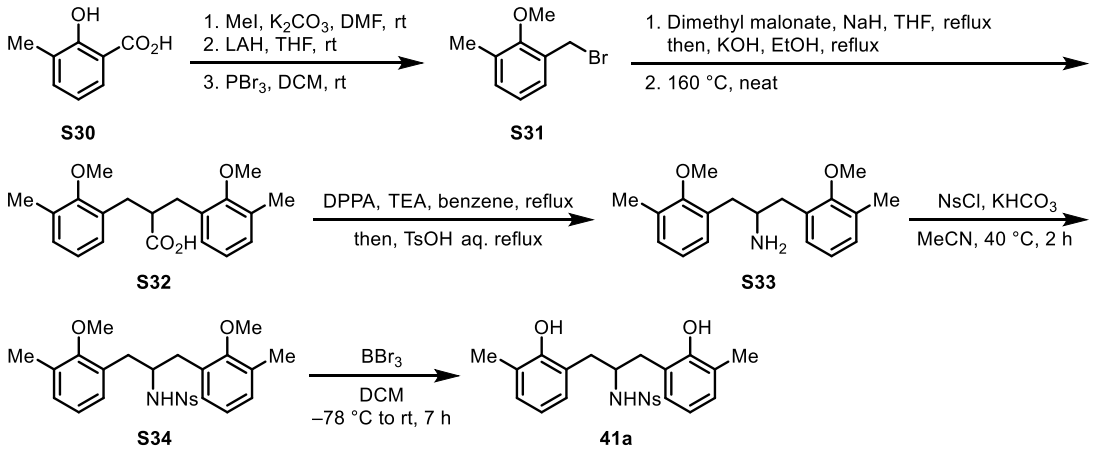
H	-1.68391200	0.49811100	-4.61490500
H	-0.18424900	-0.75150400	-3.07757900

Synthesis of Substrates and Characterization Data



2-(2-Methoxy-3-methylbenzyl)-3-(2-methoxy-3-methylphenyl)propanoic acid (S32)

To a stirred suspension of 3-Me-salitylic acid (**S30**) (4.56 g, 30.0 mmol) and K_2CO_3 (12.4 g, 90 mmol) in DMF (100 mL) was added MeI (5.60 mL, 90.0 mmol) at 0 ℃ and the mixture was gradually warmed to room temperature. After stirred for 17 h, the reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product.

To a stirred suspension of LAH (1.62 g, 42.6 mmol) in THF (60 mL) was added crude product in THF (20 mL) at 0 ℃ and the mixture was gradually warmed to room temperature. After stirred for 30 min, the resulting mixture was quenched by Na_2SO_4·10 H_2O. After stirred for 1 h, AcOEt was added to the mixture and the resulting mixture was filtered through celite pad. The filtrate was concentrated *in vacuo* to give the crude product.

To a stirred solution of crude product in DCM (50 mL) was added PBr_3 (3.78 mL, 39.8 mmol) at 0 ℃ and the mixture was gradually warmed to room temperature. After stirred for 2.5 h, the reaction was quenched by water and extracted with DCM. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product.

To a stirred suspension of NaH (60%, dispersion in paraffin liquid, 1.20 g, 30.0 mmol) in THF (20 mL) was added dimethyl malonate (1.14 mL, 10.0 mmol) at 0 ℃. The solution was stirred for 15 min before adding crude product in THF (5.0 mL) and the resulting mixture was heated under reflux for 11 h. After reaction completion, EtOH (25 mL) and KOH (2.81 g, 50.0 mmol) was added to the reaction mixture and the resuting mixture was heated under reflux. After heated for 7 h, the reaction was quenched by 1*N* HCl aq. and extracted with AcOEt. The organic layer was washed by brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/hexane = 25/75 to 100/0) to give the dicarboxylic acid. The dicarboxylic acid was heated at 160 ℃ for 1 h to afford **S32** (2.64 g, 81%) as brown solid.

Analytical data of **S32**: **m.p.** 107 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.03 (d, *J* = 7.4 Hz, 4H), 6.93 (t, *J* = 7.0 Hz, 2H), 3.62 (s, 6H), 3.26-3.16 (m, 1H), 2.96 (dd, *J* = 13.6, 8.4 Hz, 2H), 2.85 (dd, *J* = 13.6, 8.4 Hz, 2H), 2.28 (s, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ: 181.5, 157.2, 132.1, 131.1, 130.0, 128.5, 124.0, 60.2, 46.9, 32.7, 16.4; **IR** (KBr, cm^{-1}): 2996, 2830, 1700, 1469, 1427, 1258, 1213, 1090, 1010, 768; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{20}H_{24}O_4$ $[M+Na]^+$ 351.1567; found, 351.1579.

***N*-(1,3-Bis(2-methoxy-3-methylphenyl)propan-2-yl)-2-nitrobenzenesulfonamide (S34)**

To a stirred solution of **S32** (2.62 g, 7.98 mmol) and TEA (4.45 mL, 31.9 mmol) in benzene (25 mL) was added DPPA (2.57 mL, 12.0 mmol) at 0 ℃. The resulting mixture was heated under reflux for 1.5 h. After reaction completion, TsOH aq. (4.8 M, 10 mL, 48.0 mmol) was added to the reaction mixture and the resuting mixture was heated under reflux. After heated for 5 h, the reaction was quenched by saturated $NaHCO_3$ aq. and extracted with AcOEt. The organic layer was washed by saturated $NaHCO_3$ aq. and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography (MeOH/AcOEt = 0/100 to 10/90) to give the crude product as a mixture of **S33** and byproducts (3.45 g).

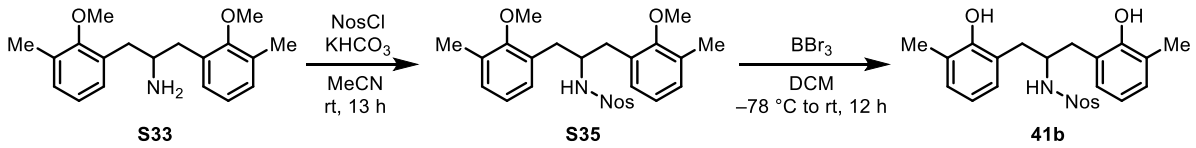
To a stirred suspension of crude product (1.93 g) and $KHCO_3$ (2.23 g, 22.3 mmol) in MeCN (13 mL) was added NsCl (1.98 g, 8.92 mmol) at 0 ℃ and the mixture was allowed to warm to 40 ℃. After stirred for 2 h, the reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude solid was washed by EtOH/hexane to afford **S34** (1.30 g, 60%) as white solid.

Analytical data of **S34**: **m.p.** 159 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.81-7.78 (m, 1H), 7.64-7.60 (m, 1H), 7.53-7.45 (m, 2H), 6.87 (t, *J* = 7.8 Hz, 4H), 6.74 (t, *J* = 7.4 Hz, 2H), 5.79 (d, *J* = 6.0 Hz, 1H), 4.12-4.03 (m, 1H), 3.60 (s, 6H), 2.90 (dd, *J* = 13.6, 7.6 Hz, 1H), 2.77 (d, *J* = 13.4, 6.6 Hz, 1H), 2.17 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 157.1, 146.7, 134.2, 132.7, 132.5, 131.0, 130.7, 130.4, 130.1, 129.0, 125.4, 123.9, 60.2, 57.7, 36.9, 16.3; **IR** (KBr, cm^{-1}): 3339, 2945, 1536, 1469, 1406, 1348, 1211, 1171, 1008, 781; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{25}H_{28}N_2O_6S$ $[M+Na]^+$ 507.1560; found, 507.1574.

***N*-(1,3-Bis(2-hydroxy-3-methylphenyl)propan-2-yl)-2-nitrobenzenesulfonamide (41a)**

To a stirred solution of **S34** (1.21 g, 2.50 mmol) in DCM (50 mL) was added BBr_3 in DCM (1.0 M, 10 mL, 10.0 mmol) at -78 ℃ and the mixture was gradually warmed to room temperature. After stirred for 7 h, the reaction was quenched by water and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude solid was purified by recrystallization from EtOH/hexane to afford **41a** (700 mg, 61%) as yellow solid.

Analytical data of **41a**: **m.p.** 160 ℃; **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.92 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.65 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.62-7.51 (m, 2H), 6.86 (d, *J* = 7.2 Hz, 2H), 6.72 (d, *J* = 6.8 Hz, 2H), 6.53 (t, *J* = 7.6 Hz, 2H), 6.22 (d, *J* = 4.4 Hz, 1H), 5.45 (s, 2H), 3.65-3.53 (m, 1H), 3.11 (dd, *J* = 14.4, 7.2 Hz, 2H), 2.81 (dd, *J* = 14.2, 7.0 Hz, 2H), 2.16 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 151.4, 146.5, 134.2, 133.2, 133.0, 130.7, 128.5, 125.9, 124.8, 123.0, 120.5, 58.0, 36.7, 27.1, 23.1, 22.4; **IR** (KBr, cm^{-1}): 3486, 3337, 2875, 1595, 1535, 1471, 1349, 1318, 1197, 1158, 854, 779, 742; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{23}H_{24}N_2O_8S$ $[M+Na]^+$ 479.1247; found, 479.1250.



S33 **S35** **41b**

***N*-(1,3-Bis(2-methoxy-3-methylphenyl)propan-2-yl)-4-nitrobenzenesulfonamide (S35)**

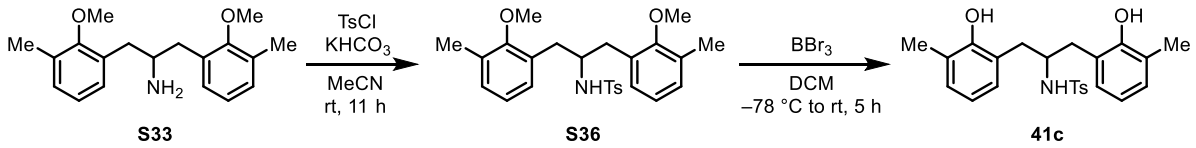
To a stirred suspension of crude product (207 mg) and $KHCO_3$ (240 mg, 2.40 mmol) in MeCN (5.0 mL) was added NosCl (171 mg, 0.77 mmol) at 0 ℃ and the mixture was allowed to warm to room temperature. After stirred for 13 h, the reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/hexane = 25/75) to afford **S35** (172 mg, 74 %) as colorless oil.

Analytical data of **S35**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.93 (td, *J* = 8.8, 2.0 Hz, 2H), 7.55 (td, *J* = 9.2, 2.0 Hz, 2H), 6.94 (dd, *J* = 7.0, 1.4 Hz, 2H), 6.82-6.72 (m, 4H), 5.94 (d, *J* = 5.6 Hz, 1H), 3.68 (s, 6H), 3.59-3.49 (m, 1H), 2.95 (dd, *J* = 13.4, 7.8 Hz, 2H), 2.62 (dd, *J* = 13.6, 6.4 Hz, 2H), 2.24 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 156.7, 149.3, 145.1, 131.2, 130.7, 130.3, 129.0, 127.5, 124.5, 123.7, 60.3, 58.0, 36.7, 16.3; **IR** (neat, cm^{-1}): 3291, 2941, 1528, 1471, 1348, 1165, 1092, 1009, 739, 412; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{25}H_{28}N_2O_6S$ $[M+H]^+$ 485.1741; found, 485.1759.

***N*-(1,3-Bis(2-hydroxy-3-methylphenyl)propan-2-yl)-4-nitrobenzenesulfonamide (41b)**

To a stirred solution of **S35** (159 mg, 0.33 mmol) in DCM (6.0 mL) was added BBr_3 in DCM (1.0 M, 1.32 mL, 1.32 mmol) at -78 ℃ and the mixture was gradually warmed to room temperature. After stirred for 12 h, the reaction was quenched by water and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude solid was purified by recrystallization from EtOH/hexane to afford **41b** (54 mg, 36%) as white solid.

Analytical data of **41b**: **m.p.** 183 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.96 (td, *J* = 9.0, 2.2 Hz, 2H), 7.56 (td, *J* = 9.0, 2.2 Hz, 2H), 6.94 (d, *J* = 7.6 Hz, 2H), 6.73 (d, *J* = 8.0 Hz, 2H), 6.64 (d, *J* = 7.4 Hz, 2H), 5.68 (d, *J* = 6.0 Hz, 1H), 5.25 (s, 2H), 3.46-3.36 (m, 1H), 3.00 (dd, *J* = 14.2, 7.0 Hz, 2H), 2.79 (dd, *J* = 13.8, 6.2 Hz, 2H), 2.20 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 152.1, 150.0, 144.6, 129.9, 129.3, 127.6, 123.9, 123.7, 123.1, 120.8, 57.1, 36.7, 16.1; **IR** (KBr, cm^{-1}): 3504, 3297, 1529, 1472, 1349, 1309, 1200, 1158, 1091, 741; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{23}H_{24}N_2O_6S$ $[M+H]^+$ 457.1428; found, 457.1443.



S33 **S36** **41c**

***N*-(1,3-Bis(2-methoxy-3-methylphenyl)propan-2-yl)-4-methylbenzenesulfonamide (S36)**

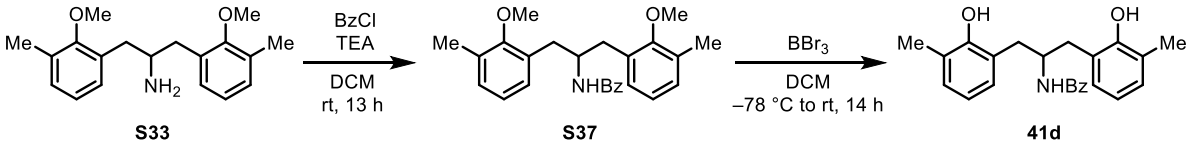
To a stirred suspension of crude product (277 mg) and $KHCO_3$ (321 mg, 3.21 mmol) in MeCN (6.0 mL) was added TsCl (196 mg, 1.03 mmol) at 0 ℃ and the mixture was allowed to warm to room temperature. After stirred for 11 h, the reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography ($CHCl_3$/hexane = 50/50 to 100/0) to afford **S36** (290 mg, 99%) as colorless oil.

Analytical data of **S36**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.29 (d, *J* = 8.4 Hz, 2H), 6.96 (dd, *J* = 7.0, 1.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.84-6.77 (m, 4H), 5.72 (d, *J* = 4.4 Hz, 1H), 3.66 (s, 6H), 3.55-3.45 (m, 1H), 2.94 (dd, *J* = 13.4, 7.4 Hz,2H), 2.62 (dd, *J* = 13.6, 6.4 Hz, 2H), 2.29 (s, 3H), 2.25 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 156.8, 142.1, 136.5, 131.1, 131.0, 130.0, 129.1, 129.0, 126.5, 124.3, 60.3, 57.3, 36.3, 21.5, 16.3; **IR** (neat, cm^{-1}): 3283, 2942, 1470, 1421, 1326, 1159, 1092, 1010, 759, 664; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{26}H_{31}NO_4S$ $[M+Na]^+$ 476.1866; found, 476.1880.

***N*-(1,3-Bis(2-hydroxy-3-methylphenyl)propan-2-yl)-4-methylbenzenesulfonamide (41c)**

To a stirred solution of **S36** (290 mg, 0.639 mmol) in DCM (12 mL) was added BBr_3 in DCM (1.0 M, 1.92 mL, 1.92 mmol) at -78 ℃ and the mixture was gradually warmed to room temperature. After stirred for 5 h, the reaction was quenched by water and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude solid was purified by recrystallization from EtOH/hexane to afford **41c** (104 mg, 38%) as white solid.

Analytical data of **41c**: **m.p.** 137 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.30 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.0 Hz, 4H), 6.74 (d, *J* = 7.2 Hz, 2H), 6.65 (t, *J* = 7.2 Hz, 2H), 5,54 (s, 2H), 5.50 (d, *J* = 4.8 Hz, 1H), 3.38-3.28 (m, 1H), 2.96 (dd, *J* = 14.0, 6.4 Hz, 2H), 2.80 (dd, *J* = 14.4, 6.4 Hz, 2H), 2.31 (s, 3H), 2.21 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 152.3, 143.0, 135.4, 129.7, 129.4, 129.3, 126.6, 124.0, 123.1, 120.4, 56.5, 36.7, 21.6, 16.2; **IR** (KBr, cm^{-1}): 3503, 3257, 2933, 1471, 1305, 1200, 1154, 1090, 678, 553; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{24}H_{27}NO_4S$ $[M+H]^+$ 426.1734; found, 426.1745.



S33 **S37** **41d**

***N*-(1,3-Bis(2-methoxy-3-methylphenyl)propan-2-yl)benzamide (S37)**

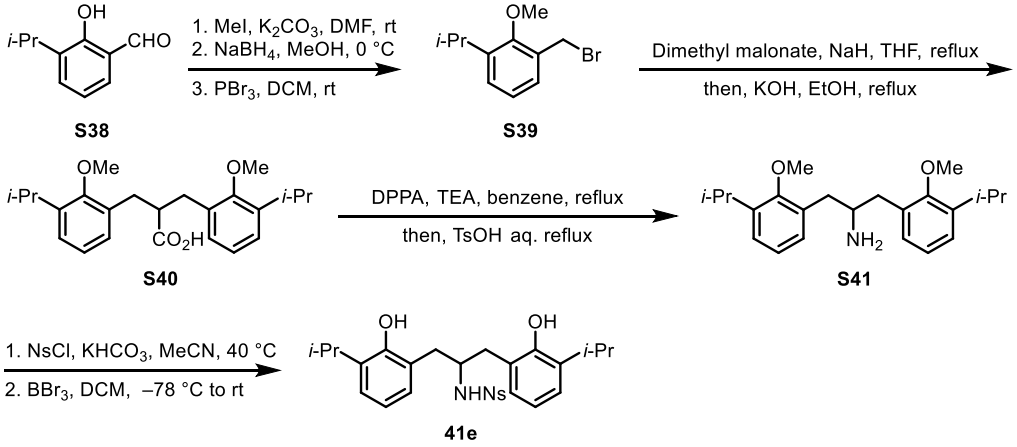
To a stirred solution of crude product (333 mg) and TEA (0.21 mL, 1.54 mmol) in DCM (3.5 mL) was added BzCl (0.13 mL, 1.12 mmol) at 0 ℃ and the mixture was allowed to warm to room temperature. After stirred for 13 h, the reaction was quenched by water and extracted with AcOEt. The organic layer was washed by 1N HCl aq., saturated $NaHCO_3$ aq. and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude solid was purified by recrystallization from EtOH/hexane to afford **S37** (171 mg, 55 %) as white solid.

Analytical data of **S37**: **m.p.** 123 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.72 (d, *J* = 6.6 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.27 (d, *J* = 7.2 Hz, 1H), 7.07 (d, *J* = 7.2 Hz, 2H), 7.04 (d, *J* = 7.8 Hz, 2H), 6.96 (t, *J* = 7.5 Hz, 2H), 4.44-4.36 (m, 1H), 3.76 (s, 6H), 3.07 (dd, *J* = 13.5, 7.5 Hz, 2H), 2.81 (dd, *J* = 13.8, 6.0 Hz, 2H), 2.31 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 167.2, 160.0, 135.1, 131.6, 131.1, 131.0, 129.9, 129.1, 128.4, 127.0, 124.4, 60.5, 54.0, 34.4, 16.4; **IR** (KBr, cm^{-1}): 3299, 2941, 1640, 1537, 1469, 1207, 1092, 1015, 770, 702; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{26}H_{29}NO_3$ $[M+H]^+$ 404.2220; found, 404.2235.

***N*-(1,3-Bis(2-hydroxy-3-methylphenyl)propan-2-yl)benzamide (41d)**

To a stirred solution of **S37** (121 mg, 0.30 mmol) in DCM (6.0 mL) was added BBr_3 in DCM (1.0 M, 1.20 mL, 1.20 mmol) at -78 °C and the mixture was gradually warmed to room temperature. After stirred for 14 h, the reaction was quenched by water and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude solid was washed by Et_2O/hexane to afford **41d** (97 mg, 86%) as white solid.

Analytical data of **41d**: **m.p.** 181 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.93 (br d, *J* = 4.8 Hz, 1H), 7.78 (td, *J* = 6.8, 1.4 Hz, 2H), 7.52 (td, *J* = 7.2, 1.4 Hz, 1H), 7.43 (td, *J* = 6.8, 1.4 Hz, 2H), 7.23 (s, 2H), 7.05 (d, *J* = 7.2 Hz, 2H), 6.98 (dd, *J* = 7.8, 1.4 Hz, 2H), 6.79 (t, *J* = 7.6 Hz, 2H),4.01-3.92 (m, 1H), 3.22 (dd, *J* = 13.8, 5.4 Hz, 2H), 2.79 (dd, *J* = 14.0, 6.8 Hz, 2H), 2.31 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 168.9, 153.1, 133.5, 132.0, 129.9, 129.3, 128.7, 127.1, 124.5, 123.9, 120.3, 54.9, 35.1, 16.4; **IR** (KBr, cm^{-1}): 3431, 3276, 1638, 1543, 1469, 1446, 1336, 1201, 1101, 705; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{24}H_{25}NO_3$ $[M+H]^+$ 376.1907; found, 376.1922.



***N*-(1,3-Bis(2-hydroxy-3-isopropylphenyl)propan-2-yl)-2-nitrobenzenesulfonamide (41e)**

To a stirred suspension of 2-hydroxy-3-isopropylbenzaldehyde (**S38**)[58] (1.94 g, 11.8 mmol) and K_2CO_3 (4.89 g, 35.4 mmol) in DMF (20 mL) was added MeI (2.20 mL, 35.4 mmol) at 0 °C and the mixture was gradually warmed to room temperature. After stirred for 2 h, the reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product.

To a stirred solution of crude product in MeOH (20 mL) was added $NaBH_4$ (893 mg, 23.6 mmol) at 0 ℃. After stirred for 2.5 h, the resulting mixture was quenched by saturated $NaHCO_3$ aq. and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product.

To a stirred solution of crude product in DCM (20 mL) was added PBr_3 (1.66 mL, 17.4 mmol) at 0 ℃ and the mixture was gradually warmed to room temperature. After stirred for 14 h, the reaction was quenched by water and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product.

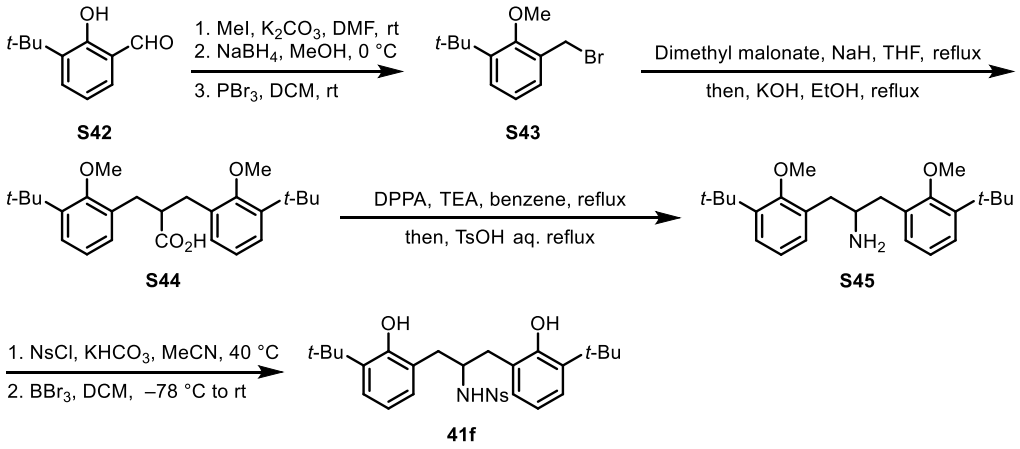
To a stirred suspension of NaH (60%, dispersion in paraffin liquid, 472 mg, 11.8 mmol) in THF (16 mL) was added dimethyl malonate (0.45 mL, 3.93 mmol) at 0 ℃. The solution was stirred for 15 min before adding crude product in THF (4.0 mL) and the resulting mixture was heated under reflux for 8 h. After reaction completion, EtOH (20 mL) and KOH (1.01 g, 19.6 mmol) was added to the reaction mixture and the resuting mixture was heated under reflux. After heated for 14 h, the reaction was quenched by 1*N* HCl aq. and extracted with AcOEt. The organic layer was washed by brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/hexane = 10/90 to 25/75) to give the crude product as a mixture **S40** of and byproducts.

To a stirred solution of crude product and TEA (1.73 mL, 12.4 mmol) in benzene (10 mL) was added DPPA (1.00 mL, 4.64 mmol) at 0 ℃. The resulting mixture was heated under reflux for 1 h. After reaction completion, TsOH aq. (4.6 M, 4.0 mL, 18.4 mmol) was added to the reaction mixture and the resuting mixture was heated under reflux. After heated for 11 h, the reaction was quenched by saturated $NaHCO_3$ aq. and extracted with AcOEt. The organic layer was washed by saturated $NaHCO_3$ aq. and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product.

To a stirred suspension of crude product and $KHCO_3$ (1.55 g, 15.5 mmol) in MeCN (15 mL) was added NsCl (1.10 g, 4.94 mmol) at 0 ℃ and the mixture was allowed to warm to 40 ℃. After stirred for 3 h, the reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography ($CHCl_3$) to give the crude product (802 mg).

To a stirred solution of crude product (640 mg) in DCM (10 mL) was added BBr_3 in DCM (1.0 M, 4.72 mL, 4.72 mmol) at -78 ℃ and the mixture was gradually warmed to room temperature. After stirred for 3 h, the reaction was quenched by water and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude solid was purified by recrystallization from EtOH/hexane to afford **41e** (275 mg, 17% from dimethyl malonate) as yellow solid.

Analytical data of **41e**: **m.p.** 135 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.93 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.64-7.51 (m, 3H), 6.96 (dd, *J* = 7.4, 1.8 Hz, 2H), 6.71 (dd, *J* = 7.4, 1.4 Hz, 2H), 6.60 (t, *J* = 7.6 Hz, 2H), 6.25 (d, *J* = 4.0 Hz, 1H), 5.60 (br s, 2H), 3.63-3.54 (m, 1H), 3.17-3.04 (m, 4H), 2.81 (dd, *J* =14.0, 6.8 Hz, 2H), 1.24 (d, *J* = 6.8 Hz, 6H), 1.20 (d, *J* = 6.8 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 151.4, 146.5, 134.2, 133.2, 133.0, 130.7, 128.5, 125.9, 124.8, 123.0, 120.5, 58.0, 36.7, 27.1, 23.1, 22.4; **IR** (KBr, cm^{-1}): 3519, 3314, 2965, 1537, 1459, 1360, 1163, 785, 752, 656, 596; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{27}H_{32}N_2O_6S$ $[M+Na]^+$ 535.1873; found, 535.1849.



***N*-(1-(3-(*tert*-Butyl)-2-hydroxyphenyl)-3-(2-hydroxy-3-isopropylphenyl)propan-2-yl)-2-nitrobenzenesulfonamide (41f)**

To a stirred suspension of 3-(*tert*-butyl)-2-hydroxybenzaldehyde (**S42**) (939 mg, 5.27 mmol) and K_2CO_3 (2.19 g, 15.8 mmol) in DMF (10 mL) was added MeI (0.98 mL, 15.8 mmol) at 0 ℃ and the mixture was gradually warmed to room temperature. After stirred for 2 h, the reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product.

To a stirred solution of crude product in MeOH (10 mL) was added $NaBH_4$ (399 mg, 10.5 mmol) at 0 ℃. After stirred for 2.5 h, the resulting mixture was quenched by saturated $NaHCO_3$ aq. and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product.

To a stirred solution of crude product in DCM (10 mL) was added PBr_3 (0.75 mL, 7.91 mmol) at 0 ℃ and the mixture was gradually warmed to room temperature. After stirred for 14 h, the reaction was quenched by water and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product.

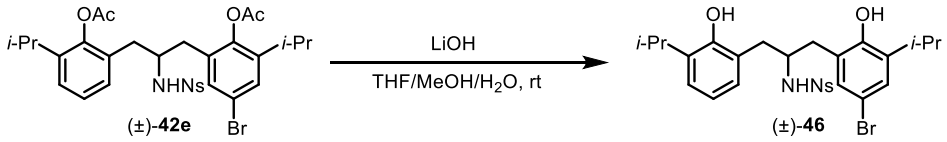
To a stirred suspension of NaH (60%, dispersion in paraffin liquid, 211 mg, 5.27 mmol) in THF (8.0 mL) was added dimethyl malonate (0.20 mL, 1.76 mmol) at 0 ℃. The solution was stirred for 15 min before adding crude product in THF (2.0 mL) and the resulting mixture was heated under reflux for 8 h. After reaction completion, EtOH (10 mL) and KOH (493 mg, 8.78 mmol) was added to the reaction mixture and the resuting mixture was heated under reflux. After heated for 14 h, the reaction was quenched by 1*N* HCl aq. and extracted with AcOEt. The organic layer was washed by brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/hexane = 10/90 to 25/75) to give the crude product as a mixture **S44** of and byproducts.

To a stirred solution of crude product and TEA (0.83 mL, 5.92 mmol) in benzene (5.0 mL) was added DPPA (0.48 mL, 2.22 mmol) at 0 ℃. The resulting mixture was heated under reflux for 1 h. After reaction completion, TsOH aq. (4.4 M, 2.0 mL, 8.80 mmol) was added to the reaction mixture and the resuting mixture was heated under reflux. After heated for 11 h, the reaction was quenched by saturated $NaHCO_3$ aq. and extracted with AcOEt. The organic layer was washed by saturated $NaHCO_3$ aq. and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product.

To a stirred suspension of crude product and $KHCO_3$ (741 mg, 7.41 mmol) in MeCN (7.5 mL) was added NsCl (525 mg, 2.37 mmol) at 0 ℃ and the mixture was allowed to warm to 40 ℃. After stirred for 3 h, the reaction was quenched

by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography ($CHCl_3$) to give the crude product. To a stirred solution of crude product in DCM (6.0 mL) was added BBr_3 in DCM (1.0 M, 2.26 mL, 2.26 mmol) at -78 ℃ and the mixture was gradually warmed to room temperature. After stirred for 3 h, the reaction was quenched by water and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude solid was purified by recrystallization from EtOH/hexane to afford **41f** (141 mg, 15% from dimethyl malonate) as brown solid.

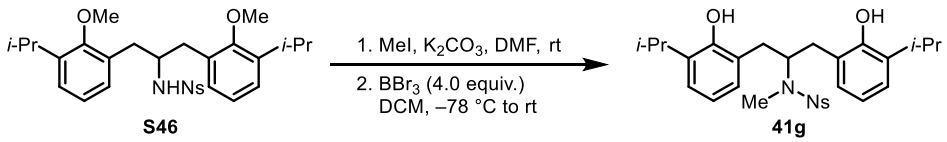
Analytical data of **41f**: **m.p.** 168 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.99-7.94 (m, 1H), 7.71-7.65 (m, 1H), 7.62-7.54 (m, 2H), 7.05 (dd, *J* = 7.8, 1.4 Hz, 2H), 6.75 (dd, *J* = 7.6, 1.6 Hz, 2H), 6.58 (t, *J* = 7.8 Hz, 2H), 6.10 (d, *J* = 4.4 Hz, 1H), 5.56 (br s, 1H), 3.62-3.53 (m, 1H), 3.07 (dd, *J* = 14.4, 6.4 Hz, 2H), 2.82 (dd, *J* = 14.4, 6.8 Hz, 2H), 1.39 (s, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 152.9, 146.9, 136.1, 133.3, 133.1,133.1, 130.7, 129.0, 126.0, 126.0, 123.6, 120.1, 57.0, 36.7, 34.5, 30.1; **IR** (KBr, cm^{-1}): 3518, 3364, 2959, 1537, 1438, 1357, 1317, 1199, 1159, 752; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{29}H_{36}N_2O_6S$ $[M+H]^+$ 541.2367; found, 541.2382.



***N*-(1-(5-Bromo-2-hydroxy-3-isopropylphenyl)-3-(2-hydroxy-3-isopropylphenyl)propan-2-yl)-2-nitrobenzenesulfonamide ((±)-46)**

A suspension of (±)-**42e** (23 mg, 0.0340 mmol) and $LiOH·H_2O$ (40 mg, 0.95 mmol) in THF/MeOH/H_2O (1/1/1, 1.0 mL) was stirred at room temperature for 7 h. The reaction was quenched by saturated NH_4Cl aq. and extracted with AcOEt. The organic layer was washed by brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative TLC (AcOEt/hexane = 25/75) to afford (±)-**46** (14 mg, 70%) as white solid.

Analytical data of **(±)-46**: **m.p.** 140 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.94-7.87 (m, 1H), 7.67-7.57 (m, 3H), 7.00 (d, *J* = 2.0 Hz, 1H), 6.98 (dd, *J* = 7.8, 1.4 Hz, 1H), 6.78 (d, *J* = 2.8 Hz, 1H), 6.72 (dd, *J* = 7.4, 1.4 Hz, 1H), 6.63 (t, *J* = 7.6 Hz, 1H), 6.24 (br s, 1H), 5.72 (br s, 1H), 5.57 (br s, 1H), 3.62-3.50 (m, 1H), 3.20-3.01 (m, 4H), 2.81 (dd, *J* = 14.4, 7.2 Hz, 1H), 2.74 (dd, *J* = 14.4, 6.8 Hz, 1H), 1.25 (d, *J* = 6.8 Hz, 3H), 1.22 (d, *J* = 6.8 Hz, 3H), 1.21 (d, *J* = 6.8 Hz, 3H), 1.18 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 151.3, 150.7, 146.4, 136.6, 134.2, 133.5, 133.1, 132.8, 130.7, 130.6, 128.5, 127.8, 125.8, 125.5, 124.9, 122.7, 120.6, 112.7, 57.9, 37.0, 36.2, 27.2, 27.1, 23.1, 23.0, 22.4, 22.2; **IR** (KBr, cm^{-1}): 3501, 2960, 1746, 1539, 1464, 1447, 1360, 1204, 1165, 1061; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{27}H_{31}BrN_2O_6S$ $[M+H]^+$ 591.1159; found, 591.1171.

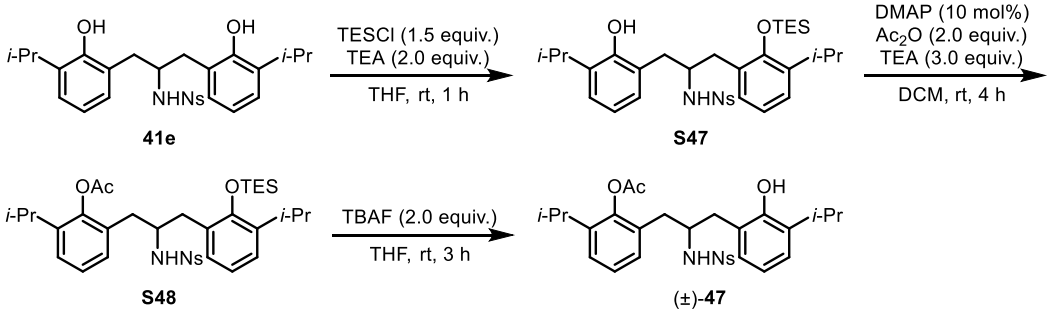


***N*-(1,3-Bis(2-hydroxy-3-isopropylphenyl)propan-2-yl)-*N*-methyl-2-nitrobenzenesulfonamide (41g)**

To a stirred suspension of crude product (162 mg) and K_2CO_3 (124 mg, 0.90 mmol) in DMF (3.0 mL) was added MeI (56 μL, 0.90 mmol) at 0 ℃ and the mixture was gradually warmed to room temperature. After stirred for 7 h, the reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product.

To a stirred solution of crude product in DCM (6.0 mL) was added BBr_3 in DCM (1.0 M, 1.20 mL, 1.20 mmol) at -78 ℃ and the mixture was gradually warmed to room temperature. After stirred for 17 h, the reaction was quenched by water and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude solid was purified by recrystallization from EtOH/hexane to afford **41g** (90 mg, 18% from dimethyl malonate) as white solid.

Analytical data of **41g**: **m.p.** 135 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.67 (d, *J* = 8.0 Hz, 1H), 7.48-7.44 (m, 2H), 7.41-7.34 (m, 1H), 6.94 (d, *J* = 7.2 Hz, 2H), 6.74 (d, *J* = 7.6 Hz, 2H), 6.60 (t, *J* = 7.6 Hz, 2H), 5.29 (s, 2H), 4.20-4.10 (m, 1H), 3.20 (s, 3H), 3.13-2.97 (m, 4H), 2.85 (dd, *J* = 14.2, 7.4 Hz, 2H), 1.20 (d, *J* = 6.8 Hz, 6H), 1.20 (d, *J* = 6.8 Hz, 6H),; **^{13}C NMR** (100 MHz, $CDCl_3$, 323K) δ: 151.6, 147.4, 134.7, 133.4, 133.0, 131.7, 131.0, 128.5, 124.9, 124.7, 123.5, 120.6, 58.9, 33.8, 28.7, 27.3, 22.8, 22.7; **IR** (KBr, cm^{-1}): 3549, 3493, 2963, 1541, 1462, 1355, 1321, 1209, 1148, 752; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{28}H_{34}N_2O_6S$ $[M+H]^+$ 527.2210; found, 527.2230.



***N*-(1-(2-Hydroxy-3-isopropylphenyl)-3-(3-isopropyl-2-((triethylsilyl)oxy)phenyl)propan-2-yl)-2-nitrobenzenesulfonamide (S47)**

To a stirred solution of **41e** (51 mg, 0.10 mmol) and TEA (28 μL, 0.15 mmol) in THF (1.0 mL) was added TESCl (25 μL, 0.15 mmol) at 0 ℃ and the mixture was gradually warmed to room temperature. After stirred for 1 h, the reaction was quenched by water and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/hexane

= 15/85) to afford **S47** (34 mg, 54%) as colorless oil.

Analytical data of **S47**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.85-7.80 (m, 1H), 7.64-7.51 (m, 3H), 7.07 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.86 (td, *J* = 7.4, 1.6 Hz, 2H), 6.75 (t, *J* = 7.6 Hz, 1H), 6.51 (dd, *J* = 7.6, 2.0 Hz, 1H), 6.46 (t, *J* = 7.6 Hz, 1H), 5.93 (s, 2H), 5.88 (d, *J* = 4.2 Hz, 1H), 3.69-3.60 (m, 1H), 3.31-3.06 (m, 3H), 2.92-2.83 (m, 2H), 2.77 (dd, *J* = 13.8, 5.0 Hz, 1H), 1.27 (d, *J* = 7.6 Hz, 3H), 1.25 (d, *J* = 7.2 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.93 (t, *J* = 7.8 Hz, 9H), 0.68 (q, *J* = 8.0 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 151.9, 151.5, 147.1, 139.5, 135.0, 133.2, 133.1, 132.8, 130.4, 129.0, 127.2, 127.0, 125.6, 125.2, 124.8, 122.6, 121.8, 120.3, 57.8, 38.7, 34.9, 27.1, 26.7, 23.6, 23.4, 22.9, 22.6, 6.9, 5.6; **IR** (neat, cm^{-1}): 3515, 2960, 2876, 1542, 1457, 1357, 1264, 1201, 1167, 745; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{33}H_{46}N_2O_6SSi$ $[M+H]^+$ 627.2919; found, 627.2928.

2-Isopropyl-6-(3-(3-isopropyl-2-((triethylsilyl)oxy)phenyl)-2-((2-nitrophenyl)sulfonamido)propyl)phenyl acetate (S48)

To a stirred solution of **S47** (34 mg, 0.054 mmol), DMAP (1.0 mg, 0.0090 mmol) and TEA (23 μL, 0.162 mmol) in DCM (1.0 mL) was added Ac_2O (10 μL, 0.108 mmol) at room temperature. After stirred for 4 h, the reaction was quenched by water and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/hexane = 20/80) to afford **S48** (32 mg, 89%) as colorless oil.

Analytical data of **S48**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.76 (dd, *J* = 7.8, 1.8Hz, 1H), 7.61 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.55-7.46 (m, 2H), 7.07 (dd, *J* = 6.4, 2.8 Hz, 1H), 6.96-6.89 (m, 3H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.61 (t, *J* = 7.4 Hz, 1H), 5.62 (d, *J* = 5.6 Hz, 1H), 3.87-3.76 (m, 1H), 3.21-3.10 (m, 1H), 2.93-2.67 (m, 5H), 2.21 (s, 3H), 1.14 (d, *J* = 6.8 Hz, 6H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.72 (q, *J* = 8.0 Hz, 6H),; **^{13}C NMR** (100 MHz, $CDCl_3$, 313K) δ: 169.8, 151.6, 147.4, 147.2, 141.0, 139.4, 134.6, 132.7, 130.1, 130.0, 128.9, 127.8, 127.6, 126.2, 125.4, 125.2, 124.7, 122.0, 57.9, 37.3, 36.0, 27.6, 26.8, 23.6, 23.3, 23.2, 20.7, 6.9, 5.8; **IR** (neat, cm^{-1}): 3335, 2961, 2876, 1761, 1541, 1454, 1361, 1209, 1169, 745; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{35}H_{48}N_2O_7SSi$ $[M+Na]^+$ 691.2844; found, 691.2851.

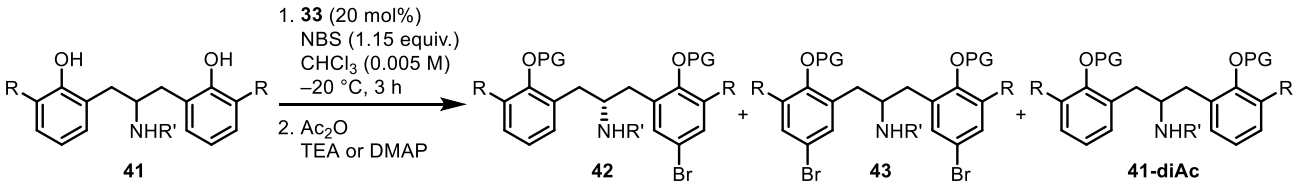
2-(3-(2-Hydroxy-3-isopropylphenyl)-2-((2-nitrophenyl)sulfonamido)propyl)-6-isopropylphenyl acetate ((±)-47)

To a stirred solution of **S48** (32 mg, 0.0478mmol) in THF (1.0 mL) was added a solution of TBAF in THF (1.0 M, 96 μL, 0.096 mmol) at room temperature. After stirred for 3 h, the reaction was quenched by saturated aq. NH_4Cl and extracted with AcOEt. The organic layer was washed by water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/hexane = 25/75) to afford (±)-**47** (25 mg, 94%) as white amorphous.

Analytical data of (±)-**47**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.91-7.85 (m, 1H), 7.67-7.61 (m, 1H), 7.57-7.50 (m, 2H), 7.01 (dd, *J* = 7.6, 1.4 Hz, 1H), 6.98 (dd, *J* = 7.2, 2,4 Hz, 1H), 6.85 (br s, 2H), 6.81 (dd, *J* = 7.4, 1.4 Hz, 1H), 6.69 (t,

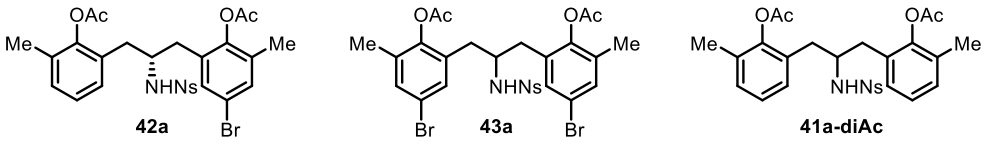
J = 7.6 Hz, 1H), 5.84 (br s, 1H), 5.79 (br s, 1H), 3.72-3.62 (m, 1H), 3.26-3.12 (m, 2H), 2.88-2.62 (m, 4H), 1.25 (d, *J* = 6.4 Hz, 3H), 1.23 (d, *J* = 6.8 Hz, 3H), 1.08 (d, *J* = 7.6 Hz, 3H), 1.06 (d, *J* = 7.2 Hz, 3H),; **^{13}C NMR** (100 MHz, $CDCl_3$, 313K) δ: 169.9, 151.7, 147.0, 147.0, 141.0, 134.9, 133.9, 133.0, 132.9, 130.5, 129.5, 128.9, 128.7, 126.2, 125.5, 125.5, 125.2, 123.0, 120.6, 56.8, 38.4, 36.6, 27.5, 27.2, 23.3, 23.2, 23.0, 22.6, 20.2; **IR** (KBr, cm^{-1}): 3510, 2965, 1757, 1541, 1461, 1412, 1364, 1212, 1166, 746; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{29}H_{34}N_2O_7S$ $[M+Na]^+$ 577.1979; found, 577.1996.

General Procedure for Asymmetric Bromination of σ-Symmetric 1,3-Diarylpropylamines



To a stirred solution of **41** (0.030 mmol, 1.0 equiv.) and **33**[35c] (2.42 mg, 0.0060 mmol, 0.20 equiv.) in $CHCl_3$ (6.0 mL) was added NBS (6.14 mg, 0.00345 mmol, 1.15 equiv.) at -20 ℃. The solution was stirred for 3 h before adding Ac_2O and TEA or DMAP and the resulting mixture was stirred at room temperature. After stirred overnight, the reaction was quenched by water and extracted with AcOEt. The organic layer was washed by 1*N* HCl aq., saturated $NaHCO_3$ aq. and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by preparative TLC (AcOEt/toluene) to afford the monobromide **42**, dibromide **43** and **41-diAc**.

Specific Procedure and Characterization Data



Following the general procedure for asymmetric bromination, **41a** (13.7 mg, 0.030 mmol), **33** (2.42 mg, 0.0060 mmol) and NBS (6.14 mg, 0.0345 mmol) were stirred at -20 ℃ in $CHCl_3$ (6.0 mL). After stirred 3 h, Ac_2O (45.4 μL, 0.48 mmol) and TEA (66.9 μL, 0.48 mmol) were added to the mixture. The crude residue was purified by preparative TLC (AcOEt/toluene = 8/92) to afford **42a** (10.2 mg, 55%, 85% ee), **43a** (6.1 mg, 29%) and **41a-diAc** (2.0 mg, 12%).

(*R*)-2-(3-(2-Acetoxy-3-methylphenyl)-2-((2-nitrophenyl)sulfonamido)propyl)-4-bromo-6-methylphenyl acetate (42a)

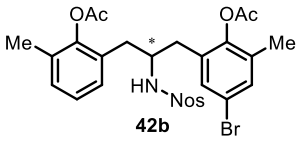
White solid: **m.p.** 184 ℃; $[\alpha]_D^{21}$ = +27.4 (c 1.0, $CHCl_3$, 85% ee); **^{1}H NMR** (600 MHz, $CDCl_3$, 323K) δ: 7.78-7.74 (m, 1H), 7.73-7.68 (m, 1H), 7.53-7.48 (m, 2H), 7.04 (d, *J* = 1.8 Hz, 1H), 7.02-6.96 (m, 2H), 6.96-6.90 (m, 2H), 5.51 (d, *J* = 7.2 Hz, 1H), 3.95-3.86 (m, 1H), 2.93 (dd, *J* = 13.8, 6.0 Hz, 1H), 2.74-2.67 (m, 2H), 2.58 (dd, *J* = 14.4, 9.0 Hz, 2H), 2.32 (s, 3H), 2.12 (s, 3H), 2.08 (s, 3H), 1.97 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$, 323K) δ: 169.3, 168.8, 148.6, 147.5, 147.0, 134.6, 133.0, 132.8, 132.7, 132.6, 132.2, 131.9, 131.1, 130.2, 130.0, 129.7, 129.5, 126.1, 125.3, 118.8, 56.7, 38.6, 36.7, 20.6, 20.1, 16.6, 16.3; **IR** (KBr, cm^{-1}): 3366, 2930, 1759, 1540, 1470, 1367, 1213, 1170, 784, 600; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{27}H_{27}BrN_2O_8S$ $[M+Na]^+$ 641.0564; found, 641.0557; HPLC conditions: column: Daicel Chiralpak IA, flow rate: 1.0 mL/min, eluent: hexane/IPA = 75/25, retention time (min): 9.5 (minor), 13.8 (major).

(2-((2-Nitrophenyl)sulfonamido)propane-1,3-diyl)bis(4-bromo-6-methyl-2,1-phenylene) diacetate (43a)

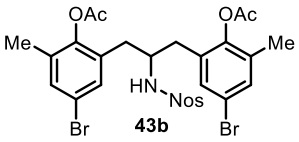
White solid: **m.p.** 244-248 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.81-7.69 (m, 2H), 7.58-7.48 (m, 2H), 7.07 (s, 2H), 7.03 (s, 2H), 5.51 (d, *J* = 8.0 Hz, 1H), 3.89-3.79 (m, 1H), 2.78-2.62 (m, 4H), 2.25 (s, 6H), 2.02 (s, 6H); **^{13}C NMR** (150 MHz, DMSO-d_6, 323K) δ: 168.1, 146.9, 146.1, 133.3, 133.1, 132.6, 132.4, 132.1, 131.8, 131.6, 128.5, 124.1, 117.5, 54.9, 39.9, 19.6, 19.4; **IR** (KBr, cm^{-1}): 3363, 1764, 1525, 1421, 1364, 1339, 1207, 1172, 1066, 868, 781, 594; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{27}H_{26}Br_2N_2O_8S$ $[M+Na]^+$ 720.9650; found, 720.9637.

(2-((2-Nitrophenyl)sulfonamido)propane-1,3-diyl)bis(6-methyl-2,1-phenylene) diacetate (41a-diAc)

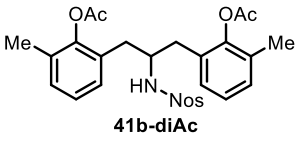
White amorphous: **^{1}H NMR** (400 MHz, $CDCl_3$, 323K) δ: 7.81-7.75 (m, 1H), 7.64-7.58 (m, 1H), 7.52-7.44 (m, 2H), 6.94 (d, *J* = 7.6 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 7.6 Hz, 2H), 5.53 (d, *J* = 6.8 Hz, 1H), 3.97-3.86 (m, 1H), 2.80 (dd, *J* = 13.2, 7.6 Hz, 2H), 2.73 (d, *J* = 13.2, 7.0 Hz, 2H), 2.20 (s, 6H), 2.02 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$, 323K) δ: 169.2, 148.4, 147.0, 130.8, 130.3, 130.0, 129.8, 129.4, 125.9, 56.6, 37.7, 20.4, 16.5; **IR** (KBr, cm^{-1}): 3330, 2927, 1759, 1540, 1422, 1367, 1214, 1168, 1091, 783, 600; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{27}H_{28}N_2O_8S$ $[M+Na]^+$ 563.1459; found, 563.1464.



42b



43b



41b-diAc

Following the general procedure for asymmetric bromination, **41b** (13.7 mg, 0.030 mmol), **33** (2.42 mg, 0.0060 mmol) and NBS (6.14 mg, 0.0345 mmol) were stirred at -20 ℃ in $CHCl_3$ (6.0 mL). After stirred 3 h, Ac_2O (22.7 μL, 0.24 mmol) and DMAP (22.0 mg, 0.18 mmol) were added to the mixture. The crude residue was purified by preparative TLC (AcOEt/toluene = 8/92) to afford **42b** (7.0 mg, 38%, 50% ee), **43b** (4.6 mg, 22%) and **41b-diAc** (2.8 mg, 17%).

2-(3-(2-Acetoxy-3-methylphenyl)-2-((4-nitrophenyl)sulfonamido)propyl)-4-bromo-6-methylphenyl acetate (42b)

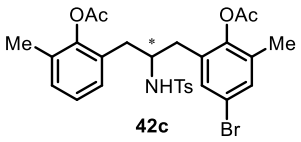
Colorless oil: $[\alpha]_D^{21}$ = -17.3 (c 1.0, $CHCl_3$, 50% ee); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.04 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.10-7.02 (m, 2H), 6.94-6.81 (m, 3H), 5.07 (br s, 1H), 3.61-3.48 (m, 1H), 2.89 (br s, 1H), 2.70-2.60 (m, 2H), 2.60 (br s, 1H), 2.37 (s, 3H), 2.20 (s, 3H), 2.11 (s, 3H), 2.02 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$, 313K) δ: 170.0, 169.6, 149.8, 148.5, 147.5, 145.7, 133.3, 132.6, 132.0, 131.6, 131.2, 130.2, 129.4, 129.1, 127.7, 126.2, 123.9, 119.2, 55.5, 37.6, 36.3, 20.7, 20.4, 16.6, 16.4; **IR** (neat, cm^{-1}): 3299, 1758, 1528, 1369, 1348, 1213, 1167, 853, 756, 616; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{27}H_{27}BrN_2O_8S$ $[M+Na]^+$ 641.0564; found, 641.0580.; HPLC conditions: column: Daicel Chiralpak IA, flow rate: 1.0 mL/min, eluent: hexane/IPA = 90/10, retention time (min): 17.6 (minor), 19.9 (major).

(2-((4-Nitrophenyl)sulfonamido)propane-1,3-diyl)bis(4-bromo-6-methyl-2,1-phenylene) diacetate (43b)

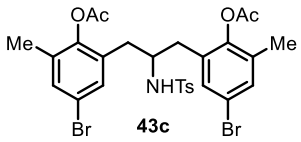
White solid: **m.p.** 185 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.08 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.14 (s, 2H), 6.91 (s, 2H), 5.12 (br s, 1H), 3.59-3.46 (m, 1H), 2.71 (br s, 2H), 2.62 (d, *J* = 9.8, 6.4 Hz, 2H), 2.33 (s, 6H), 2.08 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$, 313K) δ: 169.8, 149.9, 147.6, 145.6, 133.5, 132.8, 131.7, 131.6, 127.6, 124.0, 119.3, 55.4, 36.7, 20.6, 16.5; **IR** (KBr, cm^{-1}): 3455, 3299, 1757, 1529, 1350, 1213, 1163, 739, 614, 576; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{27}H_{26}Br_2N_2O_8S$ $[M+Na]^+$ 718.9669; found, 718.9701.

(2-((4-Nitrophenyl)sulfonamido)propane-1,3-diyl)bis(6-methyl-2,1-phenylene) diacetate (41b-diAc)

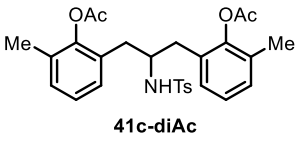
White solid: **m.p.** 159 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.97 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.01 (d, *J* = 6.8 Hz, 2H), 6.90-6.77 (m, 4H), 5.01 (d, *J* = 6.4 Hz, 1H), 3.63-3.49 (m, 1H), 2.77 (br s, 2H), 2.68 (dd, *J* = 13.6, 6.8 Hz, 2H), 2.25 (s, 6H), 2.05 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$, 313K) δ: 169.9, 149.6, 148.4, 145.7, 131.1, 130.0, 129.7, 129.1, 127.8, 126.2, 123.8, 55.5, 37.1, 20.5, 16.5; **IR** (KBr, cm^{-1}): 3459, 1762, 1727, 1533, 1475, 1351, 1221, 1168, 1092, 610; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{27}H_{28}N_2O_8S$ $[M+Na]^+$ 563.1459; found, 563.1471.



42c



43c



41c-diAc

Following the general procedure for asymmetric bromination, **41c** (12.8 mg, 0.030 mmol), **33** (2.42 mg, 0.0060 mmol) and NBS (6.14 mg, 0.0345 mmol) were stirred at -20 °C in $CHCl_3$ (6.0 mL). After stirred 3 h, Ac_2O (22.7 μL, 0.24 mmol) and DMAP (22.0 mg, 0.18 mmol) were added to the mixture. The crude residue was purified by preparative TLC (AcOEt/toluene = 8/92) to afford **42c** (6.5 mg, 37%, 6% ee), **43c** (4.8 mg, 24%) and **41c-diAc** (3.4 mg, 22%).

2-(3-(2-Acetoxy-3-methylphenyl)-2-((4-methylphenyl)sulfonamido)propyl)-4-bromo-6-methylphenyl acetate (42c)

Colorless oil: **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.32 (d, *J* = 8.4 Hz, 2H), 7.10-6.86 (m, 5H), 4.74 (d, *J* = 6.8 Hz, 1H), 3.57-3.45 (m, 1H), 2.91 (br s, 1H), 2.61 (dd, *J* = 14.0, 7.6 Hz, 2H), 2.57 (br s, 1H), 2.36 (s, 3H), 2.34 (s, 3H), 2.15

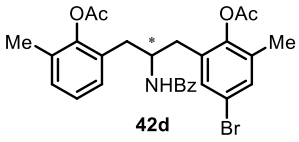
(br s, 3H), 2.10 (s, 3H), 2.00 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$, 313K) δ: 169.6, 169.1, 148.5, 147.4, 142.7, 137.0, 133.0, 132.4, 132.2, 131.7, 131.1, 129.9, 129.7, 129.4, 129.2, 126.6, 126.2, 119.2, 54.9, 37.6, 36.3, 21.6, 20.7, 20.3, 16.6, 16.4; **IR** (neat, cm^{-1}): 3283, 2921, 1759, 1370, 1213, 1166 1092, 757, 663, 551; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{28}H_{30}BrNO_6S$ $[M+Na]^+$ 610.0869; found, 610.0880.; HPLC conditions: column: Daicel Chiralpak IA, flow rate: 1.0 mL/min, eluent: hexane/IPA = 80/20, retention time (min): 11.3 (minor), 18.4 (major).

(2-((4-Methylphenyl)sulfonamido)propane-1,3-diyl)bis(4-bromo-6-methyl-2,1-phenylene) diacetate (43c)

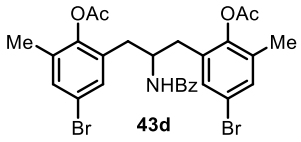
White amorphous: **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.34 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 2.0 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 1.2 Hz, 2H), 4.80 (d, *J* = 6.4 Hz, 1H), 3.54-3.43 (m, 1H), 2.71 (br s, 2H), 2.56 (dd, *J* = 13,6, 6.8 Hz, 2H), 2.37 (s, 3H), 2.29 (s, 6H), 2.05 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$, 313K) δ: 169.3, 147.5, 143.0, 136.9, 133.2, 132.6, 132.0, 131.7, 129.5, 126.5, 119.2, 54.9, 36.8, 21.8, 20.5, 16.5; **IR** (KBr, cm^{-1}): 3438, 1764, 1469, 1369, 1210, 1169, 869, 665, 579, 552; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{28}H_{29}Br_2NO_6S$ $[M+Na]^+$ 687.9975; found, 687.9998.

(2-((4-Methylphenyl)sulfonamido)propane-1,3-diyl)bis(6-methyl-2,1-phenylene) diacetate (41c-diAc)

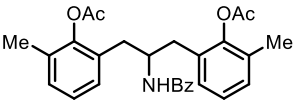
White solid: **m.p.** 127 ℃; **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.29 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 7.8 Hz, 2H), 6.97 (d, *J* = 7.8 Hz, 2H), 6.91 (t, *J* = 7.8 Hz, 2H), 6.85 (d, *J* = 7.8 Hz, 2H), 4.70 (d, *J* = 6.0 Hz, 1H), 3.58-3.48 (m, 1H), 2.77 (br s, 2H), 2.63 (dd, *J* = 13.5, 6.9 Hz, 2H), 2.33 (s, 3H), 2.21 (br s, 6H), 2.06 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$, 313K) δ: 169.5, 148.4, 142.4, 137.2, 130.9, 129.9, 129.8, 129.3, 129.2, 126.7, 126.1, 54.8, 37.0, 21.6, 20.5, 16.5; **IR** (KBr, cm^{-1}): 3371, 1759, 1738, 1470, 1371, 1215, 1164, 1092, 663, 573; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{28}H_{31}NO_6S$ $[M+Na]^+$ 532.1764; found, 532.1781.



42d



43d



41d-diAc

Following the general procedure for asymmetric bromination, **41d** (11.3 mg, 0.030 mmol), **33** (2.42 mg, 0.0060 mmol) and NBS (6.14 mg, 0.0345 mmol) were stirred at -20 ℃ in $CHCl_3$ (6.0 mL). After stirred 3 h, Ac_2O (22.7 μL, 0.24 mmol) and DMAP (22.0 mg, 0.18 mmol) were added to the mixture. The crude residue was purified by preparative TLC (AcOEt/toluene = 8/92) to afford **42d** (6.0 mg, 37%, 2% ee), **43d** (4.4 mg, 24%) and **41d-diAc** (3.4 mg, 25%).

2-(3-(2-Acetoxy-3-methylphenyl)-2-benzamidopropyl)-4-bromo-6-methylphenyl acetate (42d)

White solid: **m.p.** 173 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.63 (d, *J* = 8.0 Hz, 2H), 7.44 (t, *J* = 6.8 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 2H), 7.14-7.03 (m, 3H), 6.43 (br s, 1H), 4.60-4.48 (m, 1H), 2.99-2.58 (m, 4H), 2.33 (s, 3H), 2.30 (s, 3H), 2.15 (s, 3H), 2.12 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$, 313K) δ: 169.7, 169.4, 167.5, 148.5, 147.7, 134.9, 133.2, 132.8, 132.5, 131.7, 131.4, 130.8, 130.2, 129.8, 128.5, 127.1, 126.4, 119.2, 50.6, 35.1, 34.3, 20.6, 20.5, 16.6, 16.5; **IR** (KBr, cm^{-1}): 3399, 1759, 1638, 1531, 1470, 1442, 1369, 1220, 1171, 1013; **HRMS-ESI$^+$** (*m/z*): Calcd. for

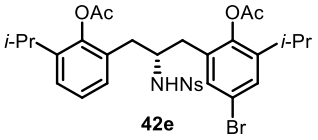
$C_{28}H_{28}BrNO_5$ $[M+H]^+$ 538.1224; found, 538.1247.; HPLC conditions: column: Daicel Chiralpak IA, flow rate: 1.0 mL/min, eluent: hexane/IPA = 80/20, retention time (min): 7.7 (major), 13.9 (minor).

(2-Benzamidopropane-1,3-diyl)bis(4-bromo-6-methyl-2,1-phenylene) diacetate (43d)

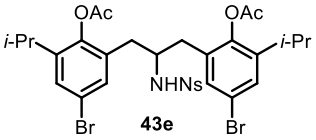
White solid: **m.p.** 224 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$, 323K) δ: 7.66 (d, *J* = 8.0 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.25 (s, 4H), 6.40 (br d, *J* = 6.4 Hz, 1H), 4.55-4.43 (m, 1H), 2.95-2.61 (m, 4H), 2.33 (s, 6H), 2.12 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$, 313K) δ: 169.4, 167.5, 147.6, 134.8, 133.2, 132.6, 132.6, 131.5, 131.5, 128.6, 127.1, 119.3, 50.5, 34.7, 20.6, 16.5; **IR** (KBr, cm^{-1}): 3287, 2928, 1756, 1637, 1532, 1470, 1370, 1221, 1171, 706; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{28}H_{27}Br_2NO_5$ $[M+H]^+$ 616.0329; found, 616.0341.

(2-Benzamidopropane-1,3-diyl)bis(6-methyl-2,1-phenylene) diacetate (41d-diAc)

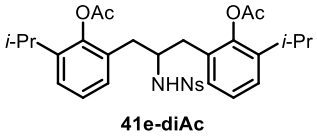
White solid: **m.p.** 195 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.62 (d, *J* = 8.4 Hz, 2H), 7.43 (t, *J* = 6.8 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 2H), 7.15-7.03 (m, 6H), 6.43 (br s, 1H), 4.64-4.52 (m, 1H), 2.85 (br s, 2H), 2.75 (dd, *J* = 13.8, 6.6 Hz, 2H), 2.29 (br s, 6H), 2,14 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$, 313K) δ: 169.7, 167.4, 148.5, 135.0, 131.3, 130.8, 130.5, 129.7, 128.8, 128.5, 127.1, 126.3, 50.6, 34.9, 20.6, 16.6; **IR** (KBr, cm^{-1}): 3323, 1757, 1636, 1534, 1470, 1369, 1221, 1171, 1091, 786; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{28}H_{29}NO_5$ $[M+H]^+$ 460.2118; found, 460.2144.



42e



43e



41e-diAc

Following the general procedure for asymmetric bromination, **41e** (15.4 mg, 0.030 mmol), **33** (2.42 mg, 0.0060 mmol) and NBS (6.14 mg, 0.0345 mmol) were stirred at -20 ℃ in $CHCl_3$ (6.0 mL). After stirred 3 h, Ac_2O (22.7 μL, 0.24 mmol) and DMAP (22.0 mg, 0.18 mmol) were added to the mixture. The crude residue was purified by preparative TLC (AcOEt/toluene = 5/95) to afford **42e** (11.4 mg, 61%, 90% ee), **43e** (5.2 mg, 25%) and **41e-diAc** (1.9 mg, 12%).

(*R*)-2-(3-(2-Acetoxy-3-isopropylphenyl)-2-((2-nitrophenyl)sulfonamido)propyl)-4-bromo-6-isopropylphenyl acetate (42e)

White solid: **m.p.** 159 ℃; $[\alpha]_D^{20}$ = +20.7 (c 0.43, $CHCl_3$, 90% ee); **^{1}H NMR** (400 MHz, $CDCl_3$, 323K) δ: 7.75 (d, *J* = 7.4 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.59-7.40 (m, 2H), 7.12 (dd, *J* = 6.4, 2.2 Hz, 1H), 7.09-6.88 (m, 4H), 5.52 (d, *J* = 6.8 Hz, 1H), 3.99-3.80 (m, 1H), 3.00-2.68 (m, 5H), 2.56 (dd, *J* = 13.7, 8.7 Hz, 1H), 2.31 (s, 3H), 2.09 (s, 3H), 1.17 (d, *J* = 6.9 Hz, 6H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H),; **^{13}C NMR** (150 MHz, $CDCl_3$, 323K) δ: 169.9, 169.4, 147.3, 147.2, 146.3, 143.3, 141.2, 134.7, 132.9, 132.8, 132.4, 131.7, 129.9, 129.7, 129.1, 128.5, 126.4, 125.8, 125.3, 119.4, 56.5, 38.5, 36.7, 27.8, 27.7, 23.5, 23.2, 23.0, 20.7, 20.3; **IR** (KBr, cm^{-1}): 3346, 2968, 1761, 1541, 1444, 1366, 1210, 1169, 784, 737, 596; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{31}H_{35}BrN_2O_8S$ $[M+Na]^+$ 699.1190; found, 699.1180.; HPLC conditions: column: Daicel Chiralpak IA, flow rate: 1.0 mL/min, eluent: hexane/IPA = 90/10,

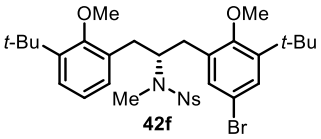
retention time (min): 15.8 (minor), 18.7 (major).

(2-((2-Nitrophenyl)sulfonamido)propane-1,3-diyl)bis(4-bromo-6-isopropyl-2,1-phenylene) diacetate (43e)

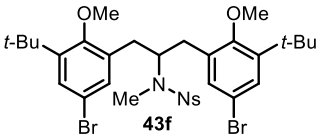
White solid: **m.p.** 218-222 ℃; **^{1}H NMR** (600 MHz, $CDCl_3$, 323K) δ: 7.82-7.71 (m, 2H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.48 (t, *J* = 5.0 Hz, 1H), 7.13 (s, 2H), 7.07 (s, 2H), 5.51 (d, *J* = 7.2 Hz, 1H), 3.92-3.82 (m, 1H), 2.87-2.75 (m, 2H), 2.70 (d, *J* = 7.3 Hz, 4H), 2.23 (s, 6H), 1.15 (d, *J* = 7.2 Hz, 6H), 1.13 (d, *J* = 7.2 Hz, 6H),; **^{13}C NMR** (150 MHz, $CDCl_3$, 323K) δ: 169.5, 147.2, 146.4, 143.6, 134.5, 133.0, 132.9, 132.1, 131.7, 129.8, 129.0, 125.5, 119.6, 56.3, 37.5, 27.9, 23.2, 23.0, 20.5; **IR** (KBr, cm^{-1}): 3352, 2972, 1761, 1527, 1426, 1366, 1207, 1169, 784, 597; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{31}H_{34}Br_2N_2O_8S$ $[M+Na]^+$ 777.0277; found, 777.0275.

(2-((2-Nitrophenyl)sulfonamido)propane-1,3-diyl)bis(6-isopropyl-2,1-phenylene) diacetate (41e-diAc)

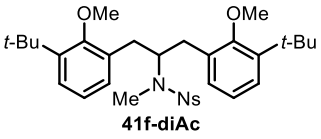
White amorphous: **^{1}H NMR** (600 MHz, $CDCl_3$, 323K) δ: 7.78 (d, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.54-7.40 (m, 2H), 7.04 (d, *J* = 7.6 Hz, 2H), 6.96-6.82 (m, 4H), 5.52 (d, *J* = 6.5 Hz, 1H), 3.97-3.85 (m, 1H), 2.89-2.66 (m, 6H), 2.20 (s, 6H), 1.15 (d, *J* = 5.8 Hz, 6H), 1.14 (d, *J* = 5.4 Hz, 6H),; **^{13}C NMR** (150 MHz, acetone-d_6, 323K) δ: 168.3, 146.4, 139.9, 133.8, 132.2, 131.8, 129.7, 128.3, 125.1, 124.3, 123.8, 55.8, 36.2, 26.4, 21.9, 21.6, 18.8; **IR** (KBr, cm^{-1}): 3351, 2966, 1760, 1541, 1456, 1367, 1213, 1168, 792, 737, 597; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{31}H_{36}N_2O_8S$ $[M+Na]^+$ 619.2085; found, 619.2081.



42f



43f



41f-diAc

To a stirred solution of **41f** (16.2 mg, 0.030 mmol) and **33** (2.42 mg, 0.0060 mmol) in $CHCl_3$ (6.0 mL) was added NBS (6.14 mg, 0.00345 mmol) at -20 ℃. After stirred for 3 h, the reaction was quenched by saturated $Na_2S_2O_3$ aq. and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product.

To a stirred suspension of crude product and K_2CO_3 (83 mg, 0.60 mmol) in acetone (1.0 mL) was added MeI (0.188 mL, 3.00 mmol) at room temperature. The reaction vial was sealed by a Teflon cap and the mixture was allowed to warm to 65 ℃. After stirred for 15 h, the reaction was quenched by water and extracted with AcOEt. The organic layer was washed by brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative TLC (AcOEt/toluene = 1/199) to afford **42f** (9.6 mg, 48%, 76% ee), **43f** (6.8 mg, 31%) and **41f-diAc** (2.2 mg, 13%).

(*R*)-*N*-(1-(5-Bromo-3-(*tert*-butyl)-2-methoxyphenyl)-3-(3-(*tert*-butyl)-2-methoxyphenyl)propan-2-yl)-*N*-methyl-2-nitrobenzenesulfonamide (42f)

Colorless oil: $[\alpha]_D^{21}$ = +32.0 (c 1.0, $CHCl_3$, 76% ee); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.55-7.46 (m, 2H), 7.39-7.32 (m, 1H), 7.28-7.23 (m, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 1.6 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 2H), 6.87 (t, *J* = 7.6Hz, 1H), 4.63-4.53 (m, 1H), 3.67 (s, 3H), 3.46 (s, 3H), 3.02 (s, 3H), 3.00 (dd, *J* = 14.4, 6.8 Hz, 1H), 2.88-2.78 (m,

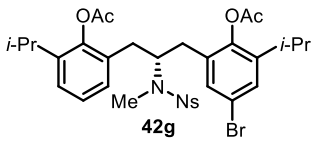
2H), 2.70 (dd, *J* = 14.2, 5.8 Hz, 1H), 1.37 (s, 9H), 1.30 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 158.9, 158.0, 147.9, 145.4, 143.4, 134.4, 133.7, 132.8, 131.9, 131.8, 131.7, 130.2, 129.6, 129.1, 126.1, 124.2, 123.9, 116.6, 62.1, 62.1, 59.9, 35.3, 35.2, 33.8, 32.4, 31.2, 31.0, 28.8; **IR** (neat, cm^{-1}): 2958, 1546, 1443, 1418, 1345, 1224, 1161, 1005, 961, 757; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{32}H_{41}BrN_2O_6S$ $[M+Na]^+$ 683.1761; found, 683.1775.; HPLC conditions: column: Daicel Chiralcel OD-H, flow rate: 1.0 mL/min, eluent: hexane/IPA = 95/5, retention time (min): 14.0 (major), 15.5 (minor).

***N*-(1,3-Bis(5-bromo-3-(*tert*-butyl)-2-methoxyphenyl)propan-2-yl)-*N*-methyl-2-nitrobenzenesulfonamide (43f)**

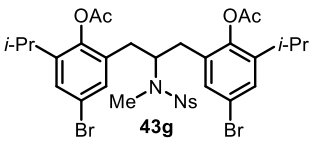
Colorless oil: **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.59-7.50 (m, 2H), 7.45-7.36 (m, 2H), 7.16 (d, *J* = 1.6 Hz, 2H), 7.10 (d, *J* = 1.2 Hz, 2H), 4.55-4.45 (m, 1H), 3.57 (s, 6H), 3.06 (s, 3H), 2.89 (dd, *J* = 14.0, 7.6 Hz, 2H), 2.72 (dd, *J* = 13.8, 7.0 Hz, 2H), 1.32 (s, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 158.0, 147.6, 145.6, 134.1, 133.6, 133.0, 132.0, 131.8, 130.2, 129.3, 124.4, 116.7, 62.1, 59.7, 35.4, 33.0, 31.0, 28.8; **IR** (neat, cm^{-1}): 2960, 1546, 1465, 1417, 1348, 1224, 1158, 1003, 755, 580; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{32}H_{40}Br_2N_2O_6S$ $[M+H]^+$ 739.1047; found, 739.1061.

***N*-(1,3-Bis(3-(*tert*-butyl)-2-methoxyphenyl)propan-2-yl)-*N*-methyl-2-nitrobenzenesulfonamide (41f-diAc)**

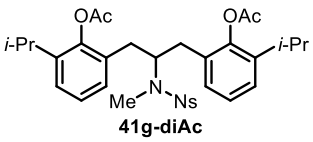
Colorless oil: **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.52-7.45 (m, 2H), 7.31-7.24 (m, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 2H), 6.82 (t, *J* = 7.2 Hz, 2H), 4.73-4.64 (m, 1H), 3.58 (s, 6H), 2.97 (s, 3H), 2.94 (dd, *J* = 14.0, 7.6 Hz, 2H), 2.81 (dd, *J* = 14.2, 7.4 Hz, 2H), 1.34 (s, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 158.9, 158.0, 147.9, 145.4, 143.4, 134.4, 133.7, 132.8, 131.9, 131.8, 131.7, 130.2, 129.6, 129.1, 126.1, 124.2, 123.9, 116.6, 62.1, 62.0, 59.9, 35.3, 35.2, 33.7, 32.3, 31.2, 31.0, 28.8; **IR** (neat, cm^{-1}): 2956, 1546, 1419, 1341, 1223, 1162, 1007, 957, 770, 583; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{32}H_{42}N_2O_6S$ $[M+Na]^+$ 605.2656; found, 605.2671.



42g



43g



41g-diAc

Following the general procedure for asymmetric bromination, **41g** (15.8 mg, 0.030 mmol), **33** (2.42 mg, 0.0060 mmol) and NBS (6.14 mg, 0.0345 mmol) were stirred at -20 °C in $CHCl_3$ (6.0 mL). After stirred 3 h, Ac_2O (22.7 μL, 0.24 mmol) and DMAP (22.0 mg, 0.18 mmol) were added to the mixture. The crude residue was purified by preparative TLC (AcOEt/toluene = 5/95) to afford **42g** (7.2 mg, 35%, 7% ee), **43g** (5.2 mg, 23%) and **41g-diAc** (5.9 mg, 32%).

(*R*)-2-(3-(2-Acetoxy-3-isopropylphenyl)-2-((*N*-methyl-2-nitrophenyl)sulfonamido)propyl)-4-bromo-6-isopropylphenyl acetate (42g)

Colorless oil: **^{1}H NMR** (400 MHz, $CDCl_3$, 313K) δ: 7.54 (br s, 1H), 7.50 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.41 (td, *J* = 7.6, 1.0 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 4.6 Hz, 1H), 7.10-6.97 (m, 4H), 4.25 (br s, 1H), 3.14 (s, 3H), 2.97-2.83 (m, 2H), 2.79-2.66 (m, 3H), 2.60 (dd, *J* = 13.8, 9.0 Hz, 1H), 2.27 (s, 3H), 1.90 (br s, 3H), 1.19 (d, *J* = 7.2 Hz,

6H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H),; **^{13}C NMR** (150 MHz, $CDCl_3$, 313K) δ: 170.2, 169.5, 147.4, 146.1, 143.0, 141.3, 133.9, 132.6, 131.9, 131.7, 130.7, 130.1, 129.4, 128.7, 126.5, 125.7, 124.1, 119.4, 59.4, 34.6, 32.0, 28.7, 27.7, 23.5, 23.2, 20.8, 20.1; **IR** (neat, cm^{-1}): 2965, 1760, 1544, 1446, 1369, 1210, 1161, 916, 772, 585; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{32}H_{37}BrN_2O_8S$ $[M+Na]^+$ 711.1346; found, 711.1354.; HPLC conditions: column: Daicel Chiralpak IA, flow rate: 1.0 mL/min, eluent: hexane/IPA = 90/10, retention time (min): 9.7 (major), 16.3 (minor).

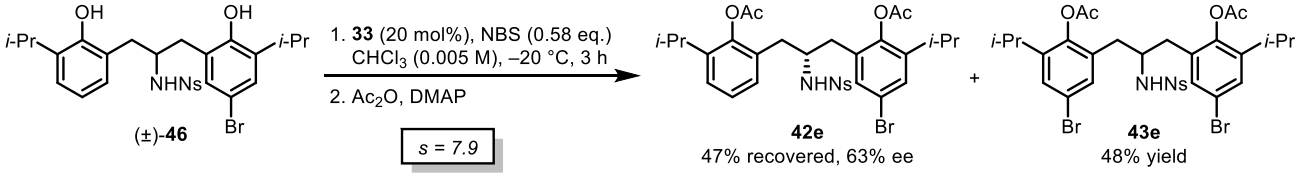
(2-((*N*-Methyl-2-nitrophenyl)sulfonamido)propane-1,3-diyl)bis(4-bromo-6-isopropyl-2,1-phenylene) diacetate (43g)

Colorless oil: **^{1}H NMR** (400 MHz, $CDCl_3$, 313K) δ: 7.59 (br d, *J* = 8.0 Hz, 1H), 7.56 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.43 (td, *J* = 7.6, 1.0 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.13 (s, 4H), 4.25-4.15 (m, 1H), 3.14 (s, 3H), 2.85-2.64 (m, 6H), 2.12 (s, 6H), 1.15 (d, *J* = 6.8 Hz, 6H), 1.12 (d, *J* = 6.8 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$, 313K) δ: 169.6, 147.2, 146.3, 143.3, 133.7, 132.8, 132.5, 132.0, 131.8, 130.7, 128.9, 124.3, 119.6, 59.2, 33.1, 28.7, 27.8, 23.2, 20.4; **IR** (neat, cm^{-1}): 2969, 1759, 1544, 1440, 1368, 1346, 1208, 1159, 772, 759; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{32}H_{36}Br_2N_2O_8S$ $[M+K]^+$ 805.0191; found, 805.0195.

(2-((*N*-methyl-2-nitrophenyl)sulfonamido)propane-1,3-diyl)bis(6-isopropyl-2,1-phenylene) diacetate (41g-diAc)

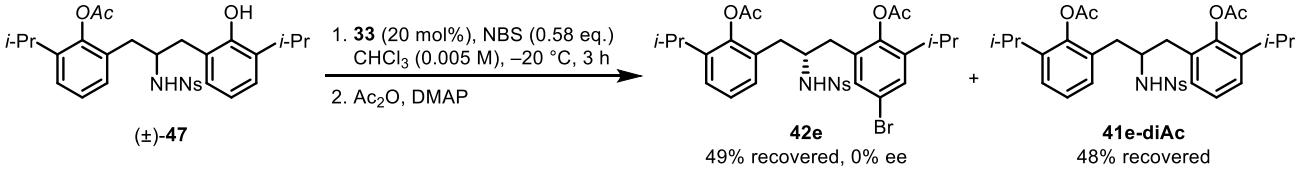
Colorless oil: **^{1}H NMR** (400 MHz, $CDCl_3$, 313K) δ: 7.46-7.37 (m, 3H), 7.26-7.18 (m, 1H), 7.06 (d, *J* = 7.6 Hz, 2H), 7.00 (d, *J* = 6.8 Hz, 2H), 6.93 (t, *J* = 7.6 Hz, 2H), 4.39-4.28 (m, 1H), 3.11 (s, 3H), 2.89-2.72 (m, 6H), 2.10 (s, 6H), 1.17 (d, *J* = 6.8 Hz, 6H), 1.14 (d, *J* = 6.8 Hz, 6H),; **^{13}C NMR** (100 MHz, $CDCl_3$, 313K) δ: 170.0, 147.7, 147.2, 141.0, 133.9, 132.5, 131.7, 130.9, 130.2, 129.2, 126.3, 125.5, 123.7, 59.5, 33.6, 28.7, 27.6, 23.4, 23.3, 20.5; **IR** (neat, cm^{-1}): 2966, 1759, 1544, 1370, 1343, 1212, 1166, 917, 754, 585; **HRMS-ESI$^+$** (*m/z*): Calcd. for $C_{32}H_{38}N_2O_8S$ $[M+Na]^+$ 633.2241; found, 633.2252.

Kinetic Resolution of (±)-46



Following the general procedure for asymmetric bromination, (±)-**46** (8.87 mg, 0.015 mmol), **33** (1.21 mg, 0.0030 mmol) and NBS (1.55 mg, 0.0087 mmol) were stirred at -20 ℃ in $CHCl_3$ (3.0 mL). After stirred 3 h, Ac_2O (11.4 μL, 0.12 mmol) and DMAP (11.0 mg, 0.090 mmol) were added to the mixture. The crude residue was purified by preparative TLC (AcOEt/toluene = 5/95) to afford **42e** (4.8 mg, 47%, 63% ee) and **43e** (5.4 mg, 48%).

Kinetic Resolution of (±)-47



Following the general procedure for asymmetric bromination, (±)-**47** (8.32 mg, 0.015 mmol), **33** (1.21 mg, 0.0030 mmol) and NBS (1.55 mg, 0.0087 mmol) were stirred at -20 ℃ in $CHCl_3$ (3.0 mL). After stirred 3 h, Ac_2O (11.4 μL, 0.12 mmol) and DMAP (11.0 mg, 0.090 mmol) were added to the mixture. The crude residue was purified by preparative TLC (AcOEt/toluene = 5/95) to afford **42e** (5.0 mg, 49%, 0% ee) and **41e-diAc** (4.3 mg, 48%).

X-ray Crystallographic Analysis

42a (78% ee) was separated by HPLC (HPLC conditions: column: Chiralpak ID, flow rate = 2.0 ml/min, eluent: hexane/IPA = 70/30) to afford major enantiomer of **42a** (>99% ee).Single crystal of [**42a**] was obtained from recrystallization in THF/hexane at room temperature. Intensity data were collected on a RIGAKU Saturn70 CCD (system) with VariMax Mo Optic Using MoK α radiation (λ = 0.71070 Å). Crystal data are summarized in **Table S1**. The structure was solved by a direct method (SHELXT-2014) and refined by a full-matrix least square method on F^2 for all reflections (SHELXL-2014). All hydrogen atoms were placed using AFIX instructions, while all other atoms were refined anisotropically.

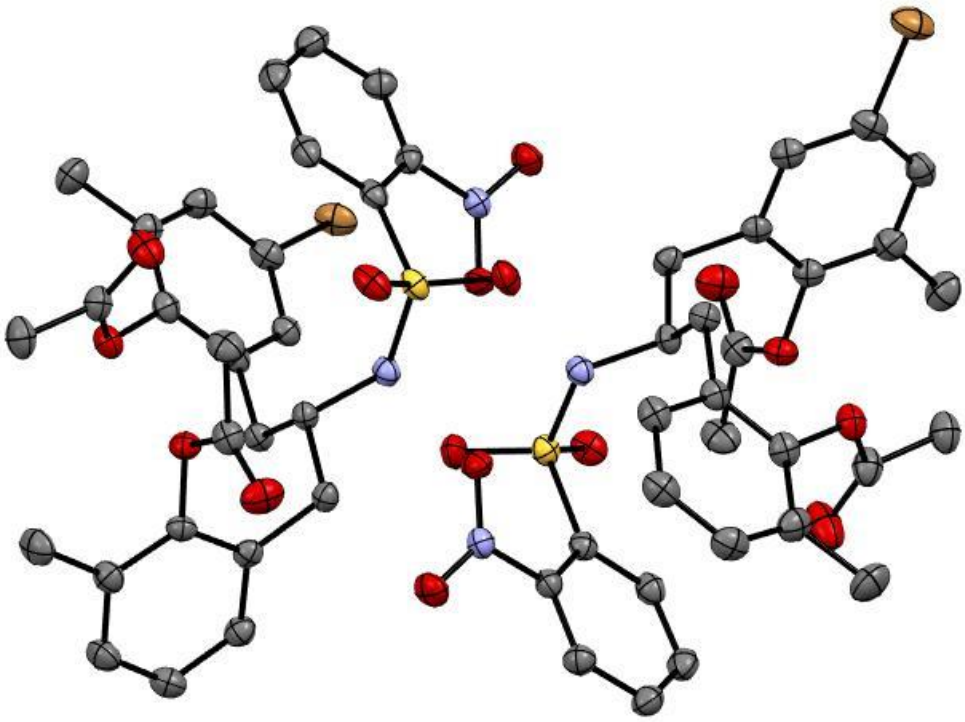


Figure S5. Molecular structure of **42a** (ORTEP drawing; thermal ellipsoids set at 50% probability).
Hydrogen atoms were omitted for clarity.

Table S1. Crystal data and structure refinement for **42a**

Empirical formula	$C_{27}H_{27}BrN_2O_8S$
Formula weight	619.47
Temperature	103(2) K
Wavelength	0.71075 Å
Crystal system	Monoclinic
Space group	$P2_1$ **(#4)**
Unit cell dimensions	a = 9.47850(10) Å α= 90°.
	b = 13.28570(10) Å β= 90.2525(5)°.
	c = 21.4835(2) Å γ= 90°.
Volume	2705.36(4) $Å^3$
Z	4
Density (calculated)	1.521 Mg/m^3
Absorption coefficient	1.650 mm^{-1}
F(000)	1272
Crystal size	0.200 x 0.100 x 0.080 mm^3
Theta range for data collection	2.845 to 26.986°
Index ranges	-12<=h<=12, -16<=k<=16, -27<=l<=26
Reflections collected	46809
Independent reflections	10920 [R(int) = 0.0338]
Completeness to theta = 25.242°	99.7 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	10920 / 1 / 865
Goodness-of-fit on F2	1.052
Final R indices [I>2sigma(I)]	R1 = 0.0251, wR2 = 0.0611
R indices (all data)	R1 = 0.0256, wR2 = 0.0614
Absolute structure parameter	0.117(3)
Extinction coefficient	n/a
Largest diff. peak and hole	0.511 and -0.574 $e.Å^{-3}$

Computational Details

The conformational search was conducted by molecular mechanics simulation using Monte-Carlo Multiple Minimum (MCMM) method (MacroModel in Material Science Suite 2019-4, Force Field: 0PLS_2005) with the constraint of (2.2 ± 0.6) Å for the distance between red-colored H of the protonated catalyst and red-colored O of σ complexes (Figure S2). 26 conformers of the complex with the (*R*,*R*)-isomer and 66 conformers of the complex with the (*R*,*S*)-isomer were obtained with energies within 5.0 kcal/mol of the most stable structures. Geometry optimization and frequency calculation of all conformers were performed at the M06-2X/LanL2DZ(Br)/6-31G(d,p) level of theory. The single-point energy calculations of all conformers were performed at the M06-2X/SDD(Br)/6-311++G(2d,2p) level of theory with solvation effects using the SMD solvation model ($CHCl_3$). XYZ coordinates and thermochemical data at 298.15 K (energies in Hartree) of the most stable structures were described below.

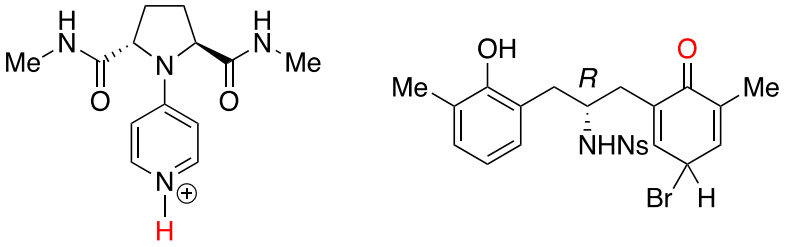
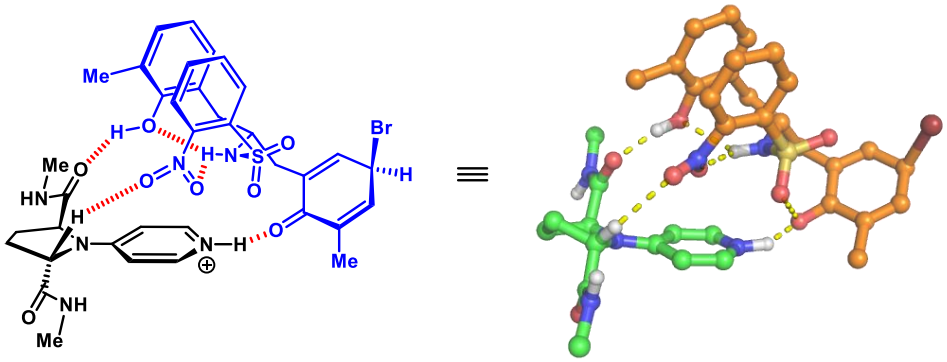


Figure S6. Chemical Models for Calculations.

σ-Complex ((*R*,*S*)-isomer)



M06-2X/LanL2DZ(Br)/6-31G(d,p)

Electronic Energy = –2737.50067

Free Energy = –2736.819237

M06-2X/SDD(Br)/6-311++G(2d,2p), SMD (chloroform)

Electronic Energy = –2738.568532

C	2.59327300	2.33873000	0.52647800
C	1.30296400	2.78311800	0.48560100

N	0.55580600	2.63447700	-0.62551600
C	1.04990400	2.05498500	-1.73378400
C	2.33291700	1.58133800	-1.76816900
C	3.13458900	1.65573800	-0.59731700
N	4.34758800	1.09136600	-0.54050800
C	5.08786100	0.92260600	0.70745400
C	6.11091100	-0.17051300	0.35475500
C	6.37436000	0.07538000	-1.13310700
C	4.97438900	0.42382700	-1.66891000
C	4.18696600	-0.84415900	-2.01940100
C	5.80526500	2.23039200	1.06582500
N	4.26582600	-1.25563300	-3.29557500
O	3.54025800	-1.43600100	-1.15847100
C	3.64031200	-2.50031200	-3.72440900
N	5.90103200	2.47865200	2.39478300
O	6.26289400	2.94691300	0.19329000
C	6.66155600	3.60361100	2.91281000
H	-0.44457300	2.85962000	-0.62730200
H	3.17247600	2.47906100	1.42928000
H	0.81450500	3.24923600	1.33127000
H	0.35589700	1.97648500	-2.56197500
H	2.68948900	1.10537700	-2.67198300
H	4.39969300	0.59453200	1.49428200
H	7.01442100	-0.10084600	0.96355900
H	5.65083700	-1.14971200	0.50760700
H	6.81014800	-0.78630100	-1.64295700
H	7.02420500	0.94281300	-1.26425600
H	5.02738800	1.09798300	-2.53195100
H	4.86138600	-0.75480800	-3.93849400
H	4.15520300	-3.36409200	-3.29497100
H	2.59721500	-2.51527000	-3.40229900
H	3.68385100	-2.55933100	-4.81078800
H	5.53007700	1.80088100	3.04392300
H	6.89292700	4.25494600	2.07088600
H	6.07219400	4.15517700	3.64752700
H	7.59509600	3.27262600	3.37535600
C	-1.51273500	-4.78235200	0.32337900
C	-2.02671100	-3.96605900	-0.67763000

C	-1.21323400	-3.05009500	-1.34202700
C	0.13973900	-2.96477200	-0.98947100
C	0.68278400	-3.78076500	0.01383300
C	-0.16712600	-4.67903800	0.66064900
C	-1.79222400	-2.09107600	-2.34933200
C	-2.42934300	-0.88761100	-1.63948700
C	-3.01462100	0.13937900	-2.62980000
C	-3.83314200	1.16989700	-1.90315700
C	-5.15061700	1.03225300	-1.69917300
C	-5.93221100	1.94838800	-0.83462700
C	-5.15445600	3.00384000	-0.14275100
C	-3.84103400	3.18527900	-0.33784600
C	-3.12563000	2.32836700	-1.30927600
N	-1.43603800	-0.24689100	-0.75948200
S	-1.77141700	0.09954800	0.80288900
O	-3.21955100	0.08205400	0.92463900
C	-1.16011300	-1.22826000	1.86151400
O	-1.03653700	1.29276400	1.20872700
C	0.16792200	-1.36911300	2.28127400
C	0.53657000	-2.28547900	3.25276500
C	-0.43869700	-3.10923400	3.80918500
C	-1.75856300	-2.99912100	3.39168800
C	-2.12172600	-2.05043200	2.43403500
N	1.25348500	-0.61041000	1.65573900
O	1.12516700	-0.31395400	0.48073700
O	2.24423800	-0.36974100	2.32044300
O	0.88879600	-2.04439100	-1.66784500
O	-1.96105200	2.57626200	-1.61882100
C	2.14434500	-3.69861400	0.36920700
C	-3.02101000	4.22192400	0.36672500
Br	-6.80936000	0.78902700	0.60459200
H	-2.15115900	-5.49626800	0.83243400
H	-3.07610800	-4.03449800	-0.95421000
H	0.24638900	-5.31497900	1.43897800
H	-1.02179000	-1.74579000	-3.04523300
H	-2.57102900	-2.58503700	-2.93858300
H	-3.24595300	-1.24997700	-1.00588500
H	-2.19705500	0.61615600	-3.17873200

H	-3.64599900	-0.39487400	-3.34711100
H	-5.69597600	0.20568000	-2.14818500
H	-6.80875800	2.35386000	-1.34444000
H	-5.70412500	3.64266400	0.54312400
H	-0.45205300	-0.43463100	-0.95151300
H	1.57767100	-2.35123900	3.54553600
H	-0.15989600	-3.83529000	4.56448800
H	-2.52145900	-3.63807800	3.82263900
H	-3.15820900	-1.91412400	2.14576500
H	1.78635600	-1.94651300	-1.29551400
H	2.38493900	-4.42098700	1.15152800
H	2.44333300	-2.70391400	0.72012500
H	2.78022800	-3.91105300	-0.49670700
H	-2.50082200	4.86017200	-0.35259200
H	-3.64288600	4.84371100	1.01176200
H	-2.26603500	3.72347000	0.98598900

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