求核触媒を用いる位置選択的 C-C 結合形成反応の開発並びに C-O 結合形成による不斉誘導に関する研究

２０１９

権藤　匠洋

求核触媒を用いる位置選択的 C-C 結合形成反応の開発並びに C-O 結合形成による不斉誘導に関する研究

目次

実験の部

略語表

aq.	aqueous
Boc	*tert*-butoxycarbonyl
Cbz	carbobenzoxy
C-C	carbon-carbon
C-O	carbon-oxygen
CSA	10-camphorsulfonic acid
DMA	*N*,*N*-dimethylacetamide
DMAP	*N*,*N*-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
Dpp	diphenylphosphoryl
HPLC	high-performance liquid chromatography
HRMS	high-performance mass spectroscopy
IR	infrared
KIE	kinetic isotope effect
*m*CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
Nu	nucleophile
NMR	nuclear magnetic resonance
Ns	2-nitrobenzenesulfonyl
i-Pr	isopropyl
PPY	4-pyrrolidinopyridine
r.t.	room temperature
THF	tetrahydrofuran
Ts	*para*-toluenesulfonyl

理論の部

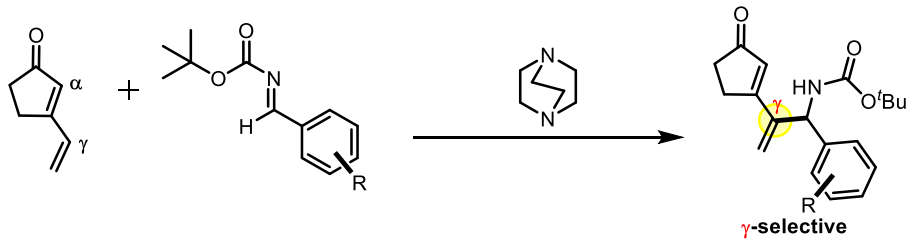
緒言

求核触媒作用はセリンプロテアーゼが加速するアミド結合の加水分解 [1] にみられるように最も基本的な触媒作用機構の 1 つである。これら求核触媒が媒介する反応はアシル化、環化付加、マイケル付加等多岐にわたり、有機合成化学においては 4-(dimethylamino)pyridine (DMAP) [2a] や、Tributylphosphine (PBu_3) [2b] 等の優れた求核触媒が見出されてきた。また、これら求核種に不斉要素を有する官能基を付与することで C-O 結合形成や C-C 結合形成過程で立体選択性を発現させる不斉求核触媒も数多く開発されている [3]。

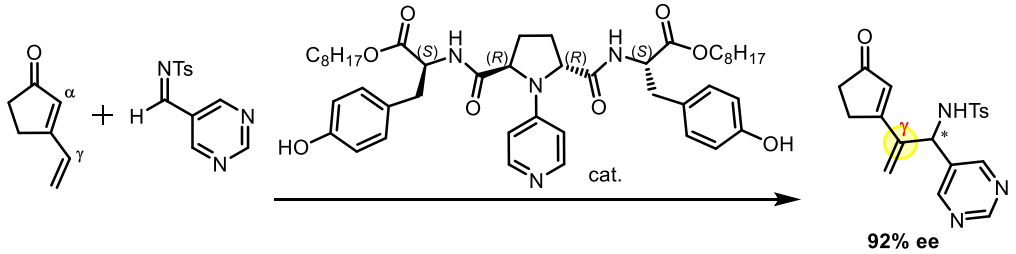
一方、位置選択性を触媒によって制御する方法論は現代有機合成における未解決課題であり [4]、所属研究室では独自の不斉求核触媒を設計・合成することで本課題の克服に向けて取り組んでいる [5]。特にこれまでに C-O 結合形成反応 (水酸基のアシル化) においては、触媒制御により位置選択性を発現する系を数多く見出している [5]。ここで触媒の不斉要素を活かし、位置選択性に加えてエナンチオ選択性を制御することができれば、より高度な分子変換が可能となり、求核触媒の化学の一層の発展に寄与するものと考えられる。

以上の背景のもと、著者は求核触媒を基盤として、第二章及び第三章では有機合成における最重要課題である C-C 結合形成反応開発に関して、位置及びエナンチオ選択的 aza-Morita-Baylis-Hillman (aza-MBH) 反応の開発に取り組んだ。また、第四章及び第五章では所属研究室で開発した触媒によるラセミ体ジオールの官能基の位置及びキラリティを精密に識別する触媒の特徴を生かし、C-O 結合形成による前例のない光学分割法を開発した。

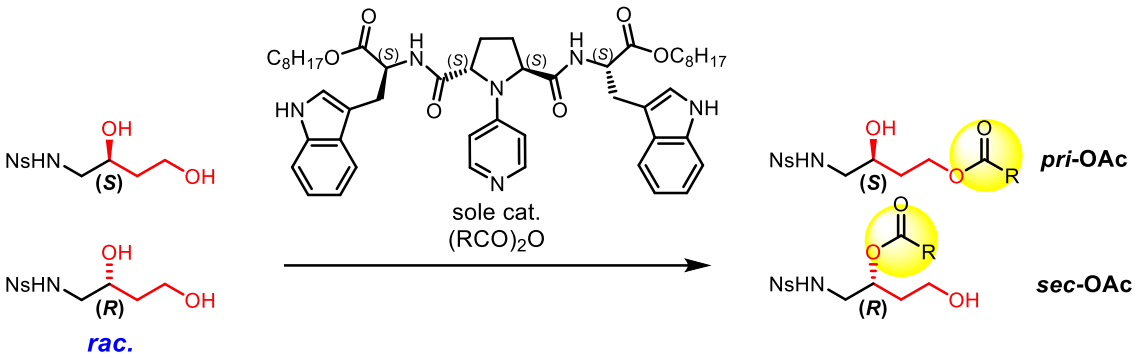
第二章 N-カルバモイルイミンを用いる位置選択的 vinylogous aza-Morita-Baylis-Hillman 反応 [6]



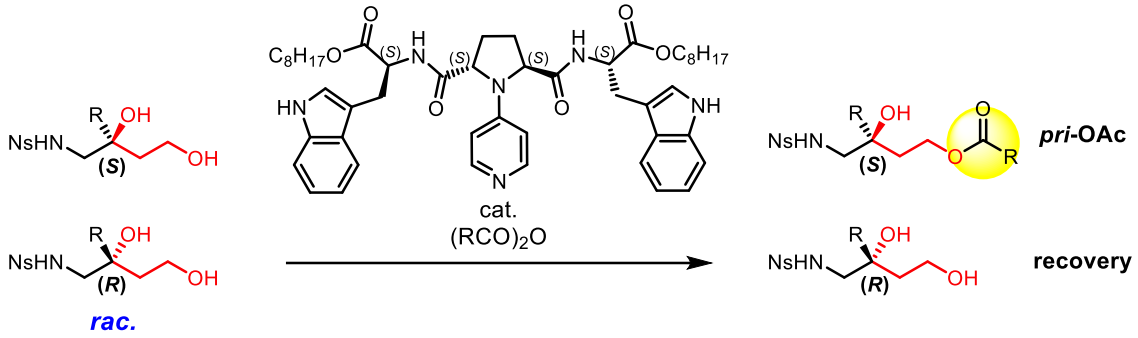
第三章 位置およびエナンチオ選択的 vinylogous aza-Morita-Baylis-Hillman 反応



第四章　アミノジオール類に対する Parallel Kinetic Resolution (PKR)



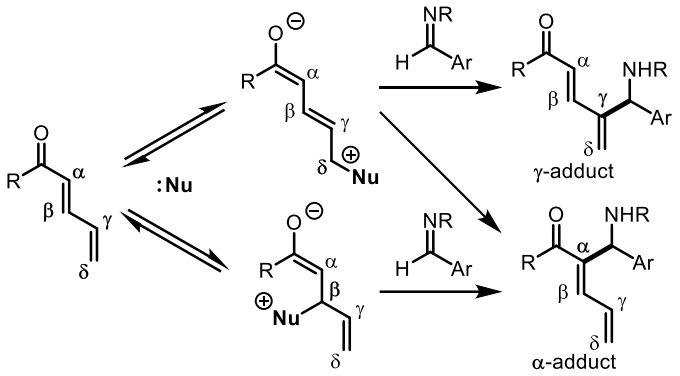
第五章 第三級アルコールの速度論的光学分割



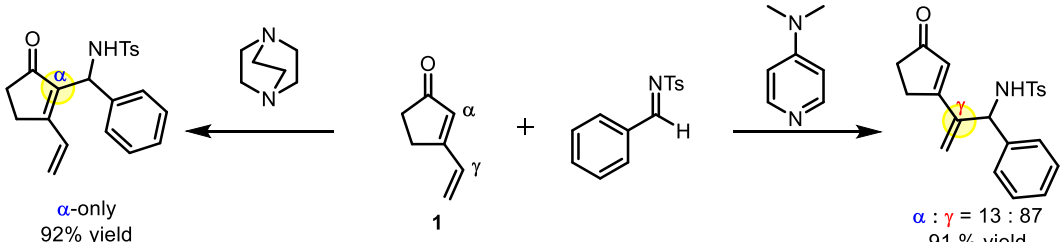
第二章　*N*-カルバモイルイミンを用いる位置選択的 vinylogous aza-Morita-Baylis-Hillman 反応

第一節　研究背景及び著者の研究方針

aza-Morita-Baylis-Hillman (aza-MBH) 反応は α,β-不飽和カルボニル化合物及びイミンに対し、第 3 級アミン或いは第 3 級ホスフィン、スルフィド等の求核触媒を作用させることで対応するアリルアミン誘導体を与える手法である[7]。本反応の利点としては保護アミノ基や二重結合、カルボニル基を有する多官能基性化合物の一挙構築が可能となる点及びアトムエコノミーに優れる点が挙げられる。基質としてビニル基が伸長した α,β,γ,δ-不飽和カルボニル化合物を用いる際には更に複雑な多官能基性化合物を合成できるが、この場合は位置選択性が問題となる。即ち、原理的には基質の α 位及び γ 位のいずれにおいても C-C 結合形成が進行しうる (Scheme 2-1.)。Vinylogous *aza*-MBH 反応は研究開始当初数例存在していたが、α 位付加体を選択的に生成する報告のみであった[8]。一方、著者の所属研究室では 3-vinylcyclopent-2-en-1-one (**1**) を基質とする vinylogous aza-MBH 反応において、触媒による C-C 結合の位置制御を報告した (Scheme 2-2)[9]。

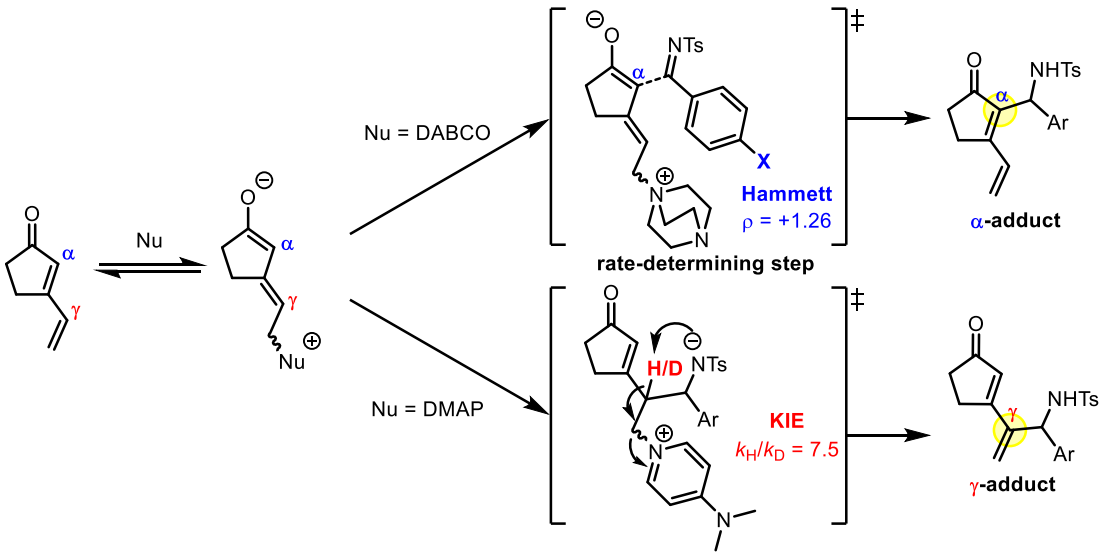


Scheme 2-1. Vinylogous *aza*-MBH reactions with α,β,γ,δ-unsaturated ketone



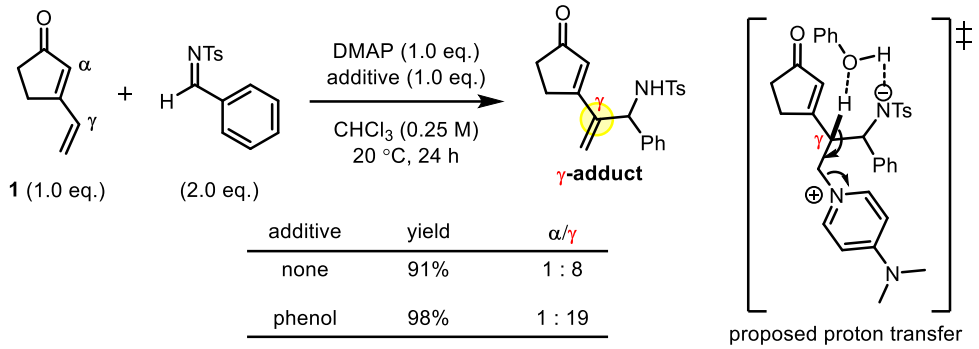
Scheme 2-2. Catalyst-controlled regiodivergent vinylogous aza-MBH reactions

上記手法は vinylogous aza-MBH 反応において α,β,γ,δ-不飽和カルボニル化合物の γ 位で C-C 結合を形成する初の報告である。本反応においては 1,4-diazabicyclo[2.2.2]octane (DABCO) 存在下では過去の報告[8]



Scheme 2-3. Catalyst dependancy in rate-determining step

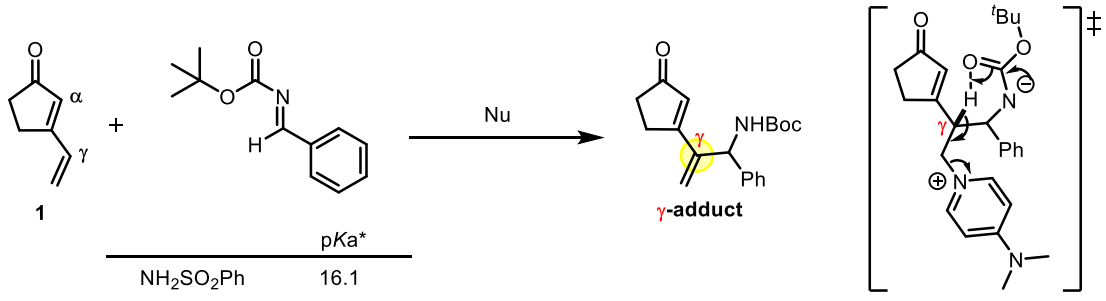
と同様、α 位付加体のみを与えたが、DMAP 存在下では位置選択性の逆転を伴い、γ 位付加体を選択的に与えた。興味深いことにそれぞれの生成物を与える律速段階が異なることが既に明らかにされている [9]。即ち、α 位付加体を与える条件にて、イミン芳香環上 *para* 位の置換基効果に関する Hammett plot では ρ=+1.26 となり、C-C 結合形成が律速段階である一方 [10]、γ 位付加体を与える条件における 1 次重水素同位体効果は反応速度定数比 k_H/k_D = 7.5 と算出され、律速段階はプロトン移動を伴う触媒脱離の段階であることが示されている [11]。本機構は MBH 反応においてプロトン移動を媒介し、触媒の脱離を加速することが知られているアルコール [12] としてフェノールを添加した際に γ 位選択性が向上した結果からも支持される [9](Scheme 2-4)。以上の結果から、γ 位付加体を与える反応ではフェノールの酸性プロトンを介した分子間六員環型プロトン移動が進行するものと考えた (Scheme 2-4 右図)。



additive	yield	α/γ
none	91%	1 : 8
phenol	98%	1 : 19

Scheme 2-4. Effects of protic additive in γ-selective *aza*-MBH reactions

上記のトシルアミドのアニオンとフェノールの酸性プロトンを介するプロトン移動は p*K*a の観点からすると不利ではあるが (類似したスルホンアミドであるベンゼンスルホンアミドの p*K*a[13a]: 16.1 vs フェノールの p*K*a[13b]: 18.0)、エネルギー的に不利な四員環型のプロトン移動を経由するのではなく、エネルギー的に有利な六員環型のプロトン移動を経由することが高選択性の要因と考えられる。以上の結果から著者はイミン保護基をスルホニル基からカルバモイル基へと変更することで、より高い選択性で γ 位付加体が得られるのではないかと考えた (Scheme 2-5.)。即ち、C-C 結合形成後生じるカルバメートアニオンはスルホンアミドアニオンと比較して塩基性が高く (類似したカーバメートであるエトキシカーバメートの p*K*a[13c]: 24.2)、分子内六員環型プロトン移動が円滑に進行すると想定した。

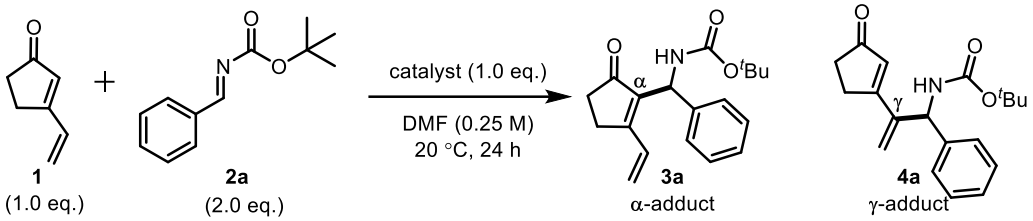


	p*K*a*
NH_2SO_2Ph	16.1
$NH_2(CO)OEt$	24.2
PhOH	18.0

*Acidity in DMSO

Scheme 2-5. Working hypothesis for high γ-selective *aza*-MBH reactions

第二節　反応条件の最適化



entry	catalyst	yield of γ-adduct	regioselectivity (α : γ)
1	DMAP	7%	1 : 5
2	**DABCO**	**39%**	**1 : 14**
3	DBU	complexed mixture	—
4	PBu_3	no reaction	—
5	Quinuclidine	32%	1 : 12
6	3-Quinuclidinol	19%	1 : 6

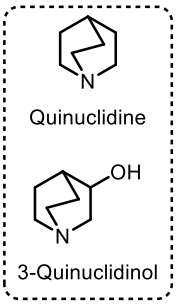
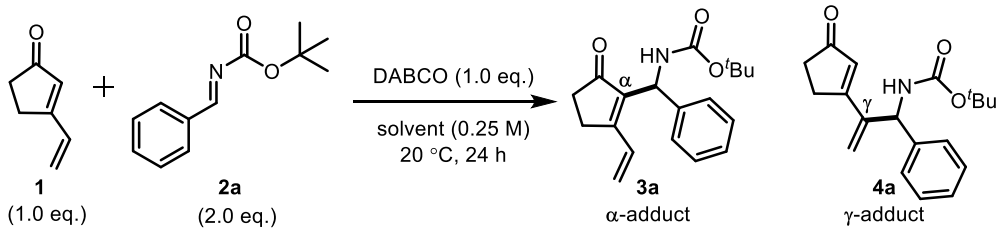


Table 2-2. Catalyst screening

ジエノン **1** を基質とし、DMF 溶媒中 *N*-Boc イミン **2a** を基質に対し二当量用いる条件で、求核触媒のスクリーニングを行った (Table 2-2)。DMAP を用いたところ期待通りγ位付加体 **4a** が優先的に得られたが、収率は 7%に留まり位置選択性も高くなかった (entry 1, α:γ=1:5)。DABCO を用いた場合、*N*-Ts イミンを用いる場合と対照的にγ位付加体 **4a** が良好な選択性で得られた (entry 2, 39% yield, α:γ=1:14)。本結果は、イミンの窒素上保護基によって位置異性体の作り分けが可能であることを示しており (基質制御の選択性)、興味深い結果と言える。DBU 及びトリブチルホスフィンを用いた場合は所望の生成物は全く得られなかった (entries 3, 4)。そこで、DABCO に類似した橋頭位第三級アミン構造を有するキヌクリジン及び 3-キヌクリジノールを用いたところ、収率及び位置選択性は低下した (entries 5, 6)。以上の結果から、DABCO を最適な求核触媒として更なる条件検討を行った (Table 2-3)。



entry	solvent	yield of γ-adduct	regioselectivity (α : γ)	dielectronic constant (ε)
1	MeOH	trace	—	32.35
2	DMSO	45%	1 : 17	46.71
3	DMF	39%	1 : 14	37.06
4	DMA	26%	1 : 10	38.30
5	CH_3CN	trace	—	36.00
6	Acetone	trace	—	21.36
7	DCM	trace	—	9.02
8	THF	trace	—	7.47
9[a]	**DMF**	**52%**	**1 : 14**	37.06
10[b]	DMF	12%	1 : 8	37.06

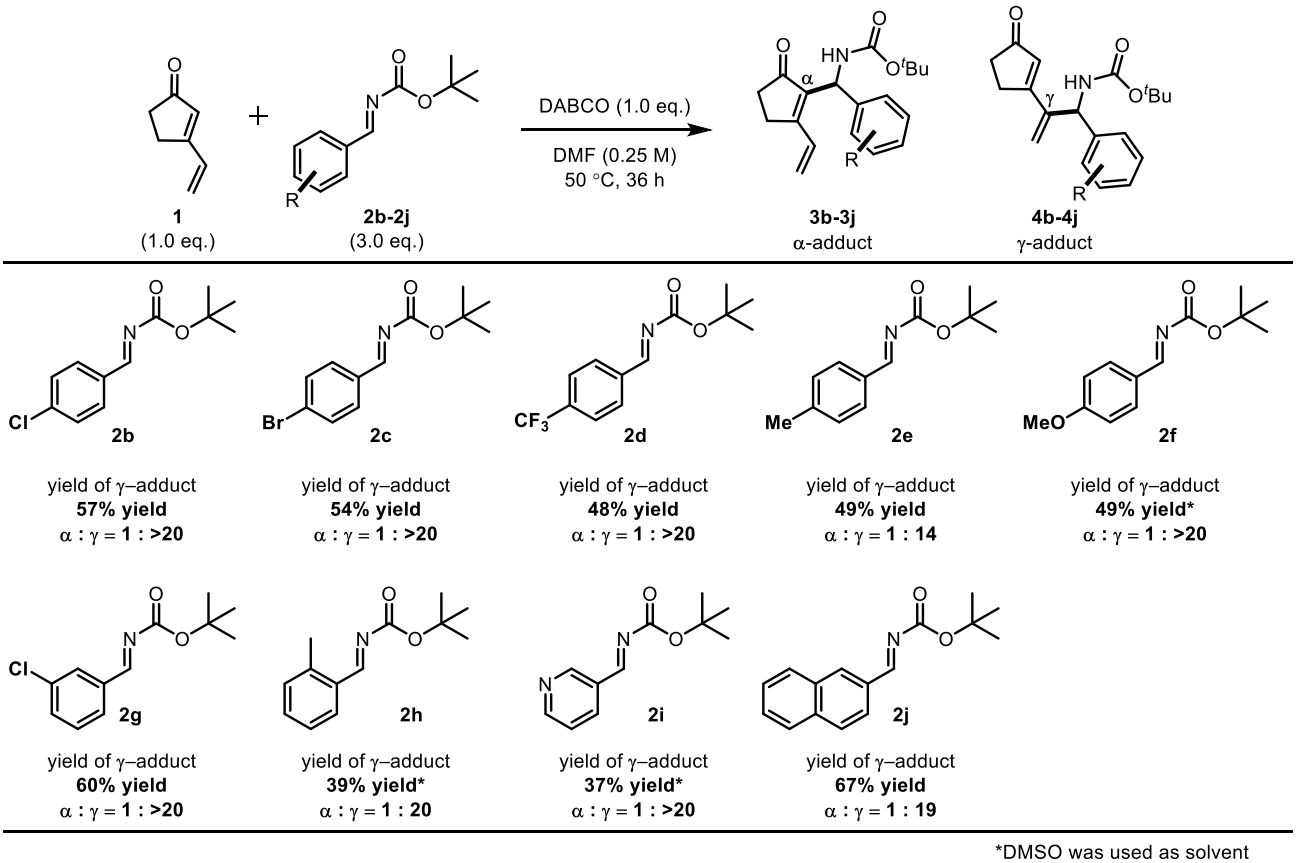
a) Run with 3.0 eq. of **2a** at 50 °C for 36 h. b) Run with 3.0 eq. of **2a** at 50 °C for 12 h in the presence of 0.2 eq. of DABCO.

Table 2-3. Optimization of conditions

プロトン性溶媒として MeOH を用いたところ、生成物は全く得られなかった一方で (entry 1)、非プロトン性極性溶媒として DMSO を用いたところ、DMF と同等の収率及び位置選択性で **4a** が得られた (entries 2 vs 3)。DMSO と比較してより誘電率の低い DMA では収率、選択性共に低下し、更に誘電率の低い溶媒では痕跡量しか得られなかった (entries 4-8)。本γ位選択的 aza-MBH 反応において、溶媒の誘電率と収率及び位置選択性に一定の相関が見られる点は反応機構に示唆を与える結果といえる。DMF を溶媒として収率の改善を目的とし、**2a** 三当量存在下 50 度で攪拌したところ、52%収率で **4ab** が得られた (entry 9)。触媒量の低減化を試みたところ収率の低下を招いたため (entry 10)、entry 9 に示す条件を最適条件とした。

第三節　基質適応範囲の検討

第二節で見出した最適条件下 (Table 2-3, entry 9)、γ 位選択的 vinylogous aza-MBH 反応においてイミン側の適応範囲を検討した (Scheme 2-6.)。ベンゼン環 *para* 位に電子求引基が置換したイミン **2b-2d** を用いた場合、いずれも良好な位置選択性および中程度の収率で所望の γ 位付加体が得られた。また、*para* 位に電子供与基が置換したイミン **2e** 及び **2f** を用いた場合も同等の収率および位置選択性で所望の γ 位付加体を与えた。ベンゼン環上の置換基効果が見られないことから律速段階は C-C 結合形成の段階でないことが示唆された。また、*meta* および *ortho* 位への置換基導入を行ったイミン **2g** 及び **2h** を用いた場合も問題なく γ 位付加体を選択的に得ることができた。芳香環としてピリジン環を有するイミン **2i** を用いたところ、イミンの不安定性に起因する収率の低下を招いたが、対応する γ 位付加体が選択的に得られた。2-Naphthyl 基を有するイミン **2j** を用いた場合、これまでで最高の 67%収率で γ 位付加体が得られた。このように本法はイミンの電子状態やその置換様式によらず高γ位選択的に進行したことから、幅広い基質適応範囲を有することが示された。尚、ジエン側の基質は **1** 以外の展開は行えていない。

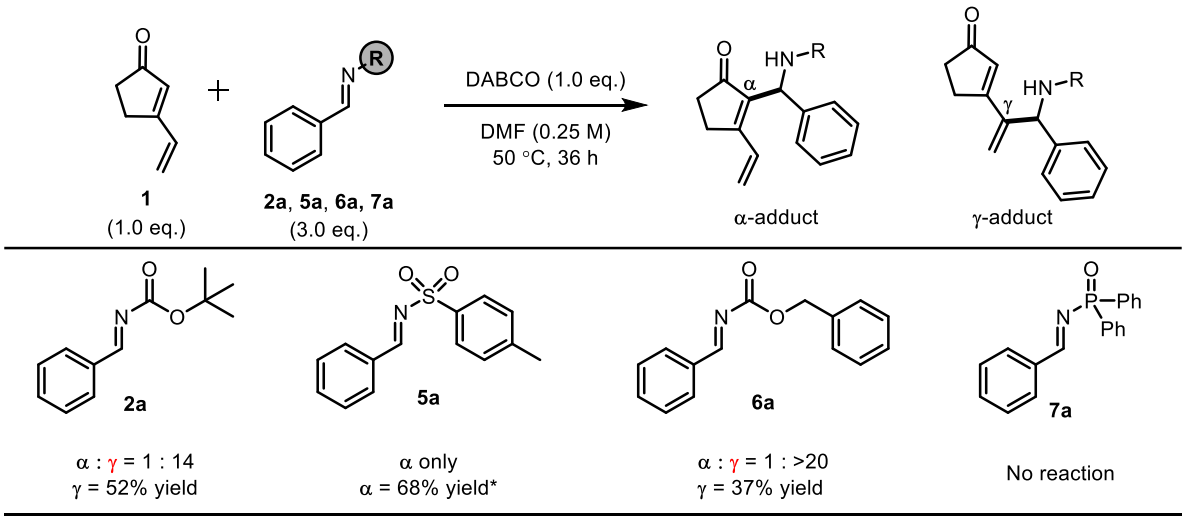


Scheme 2-6. Substrate scope of imines

第四節　反応機構についての考察

第一項　イミン保護基の効果

イミン保護基が位置選択性に与える影響を検証する目的で、ジエノン **1** に対し、異なるイミン保護基を有する **5a-7a** を検討した (Scheme 2-5)。*N*-Ts イミン **5a** を用いたところ、α位付加体のみが得られた[9]。**2a** と同様にカーバメート保護基を有する *N*-Cbz イミン **6a** を用いたところ、期待通り高いγ位選択性で生成物が得られた。イミンの求電子性は *N*-Ts イミン **5a** > *N*-Boc イミン **2a** > *N*-Dpp イミン **7a** の序列で求電子性が低下することが報告されている[14]。即ち、C-C 結合形成後生じるアミドアニオンの塩基性はカーバメート系のイミンの方がスルホンアミド系のイミンと比較してより強くなると予想される。そこで *N*-Boc イミンより更に求電子性の低い *N*-Dpp イミン **7a** を用いたが、低い求電子性が C-C 結合形成に不利に働いた為か生成物は全く得られなかった。以上の結果より、アルジミン保護基としてカーバメート系の保護基がγ位選択性の発現に有効であることが示された。

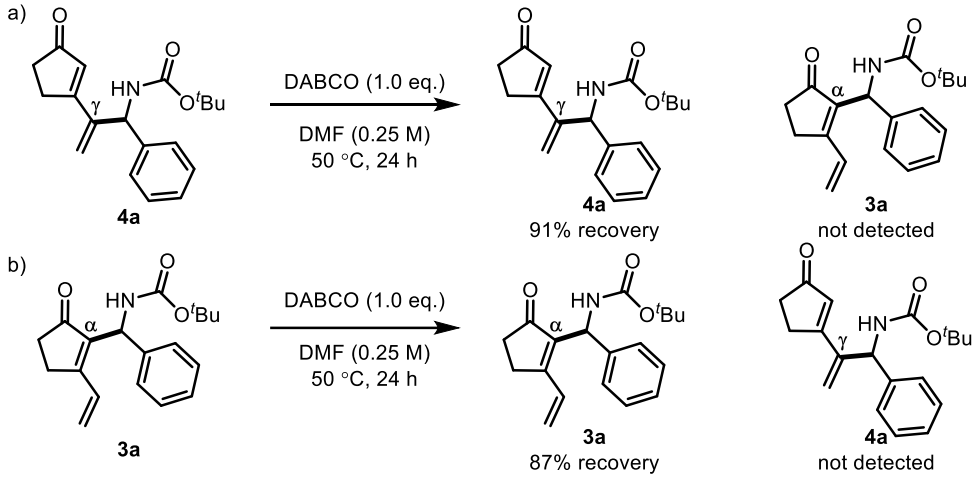


*Run with 2.0 eq. of imine at 20 °C for 9 h.

Scheme 2-7. Optimization of protecting group on imines

第二項　Retro aza-MBH 反応の有無

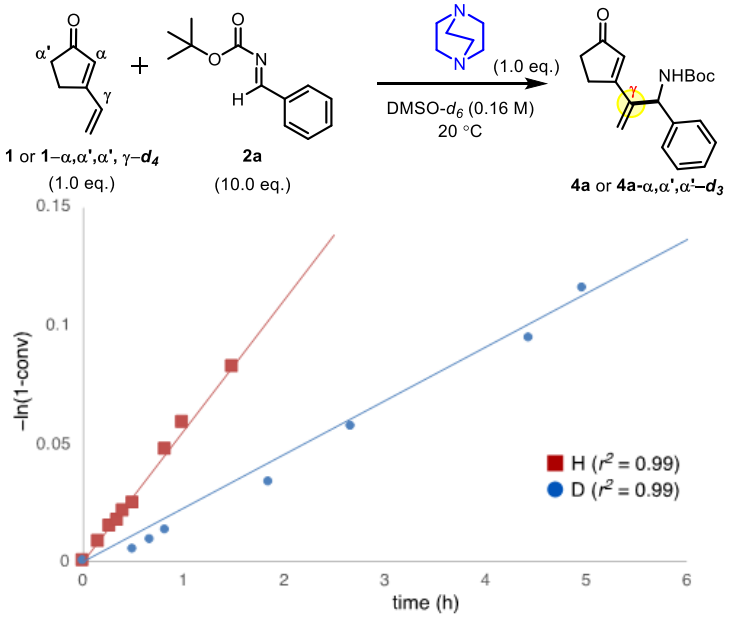
本反応において得られる生成物が熱力学的生成物か速度論的生成物かを検証するため、逆反応の有無を調査した (Scheme 2-8)。γ 位付加体 **4a** に対し、イミン非存在下反応条件に付したところ **3a** の生成は確認されなかった (Scheme 2-8a)。同様に **3a** から **4a** への変換も確認されなかったことから (Scheme 2-8b)、本反応条件下 retro aza-MBH 反応は進行しないことが分かった。以上の結果から、γ 位付加体 **4a** は速度論的生成物として得られていることが分かった。



Scheme 2-8. Retro vinylogous *aza*-MBH pathway is not involved

第三項　速度論的同位体効果

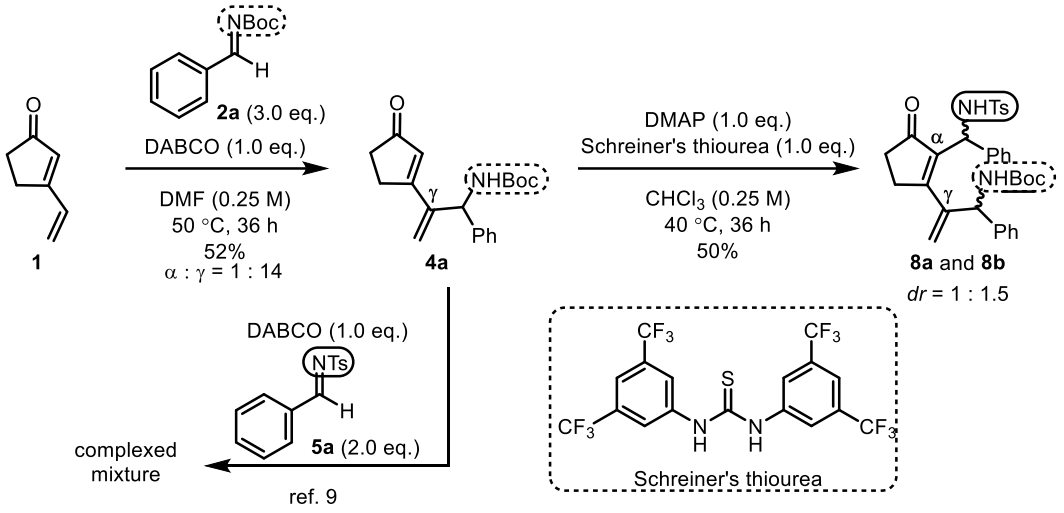
N-Boc イミン **2a** を 10 当量用いる擬一次反応条件下、**1** 及び対応する D 化体 **1-α, α', α', γ–*d*$_4$** を基質とする反応速度 k_H 及び k_D をそれぞれ求めると、$k_H = 5.5 \times 10^{-2}$ h^{-1}、$k_D = 2.3 \times 10^{-2}$ h^{-1} と算出された (Scheme 2-9)。速度論的同位体効果 (k_H/k_D) が観測されたことから、本反応の律速段階がプロトン移動の段階であることがわかった。本結果はイミンの芳香環上の置換基効果が見られなかった点からも支持される。



Scheme 2-9. Kinetic isotope effects on DABCO–catalyzed vinylogous aza-MBH reactions

第五節　Double aza-MBH 反応への展開

ジエノンに対する aza-MBH 反応は潜在的に α 位および γ 位双方で進行し得る。α 位および γ 位に異なるイミンを選択的に反応させることができれば高度に官能基化された化合物が得られるため、合成上価値が高い。今回開発した γ 位選択的反応によって得られる **4a** に対し、*N*-Ts イミン **5a** を作用させることで、α 位に Ts 保護されたアミノ基を、γ 位に Boc 保護されたアミノ基を持つジアミン化合物が得られると期待した。ジエノンに対して二度 aza-MBH 反応を進行させる double aza-MBH 反応は報告例がなく[15]、実現可能か検討を行った (Scheme 2-10)。DABCO 条件下ジエノン **1** と *N*-Boc イミン **2a** を用いることで γ 位付加体 **4a** を得た。**4a** に対して Scheme 2-7 に示す *N*-Ts イミン **5a** を用いる α 位付加体を与える最適条件を適用したところ、複雑な混合物を与えた。そこで、種々検討を行った結果 $CHCl_3$ 溶媒中、DMAP 及び Schreiner's thiourea 共存下で **5a** を作用させることで所望の double aza-MBH 成績体を 50%収率、ジアステレオ比 1 : 1.5 で得ることができた。現在のところその相対配置は決定できていない。



Scheme 2-10. doulbe aza-MBH reaction *via* sequential incorporation of imines

第三章　位置およびエナンチオ選択的 vinylogous aza-Morita-Baylis-Hillman 反応

第一節　研究背景及び著者の研究方針

触媒的不斉 MBH 及び aza-MBH 反応はそれぞれ光学活性アリルアルコール及びアリルアミン誘導体を与える手法として合成上有用であり、これまでに様々な不斉触媒が見出されてきた[7]。代表的な不斉触媒として(Fig. 3-1)、畑山らによって見出されたシンコナアルカロイド誘導体である β-ICD や、笹井ら、Shi らによって見出されたビナフトール誘導体である触媒 **9** 及び触媒 **10** 等が知られている[16]。これらの触媒に共通する点として、求核部位とブレンステッド酸部位を有する二官能性触媒であることが挙げられる。

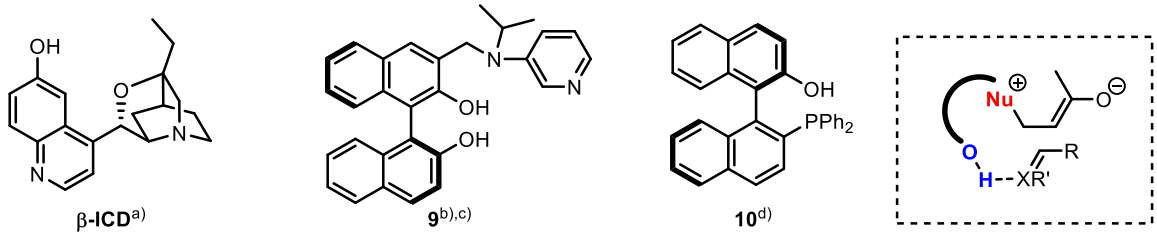


Fig. 3-1. Chiral bifunctional catalysts used for MBH reactions[16]

著者の所属研究室では 4-ジアルキルアミノピリジンを求核部位とする不斉求核触媒を独自に開発しており (Fig. 3-2)、ポリオールの位置選択的アシル化等への展開を報告している[6]。

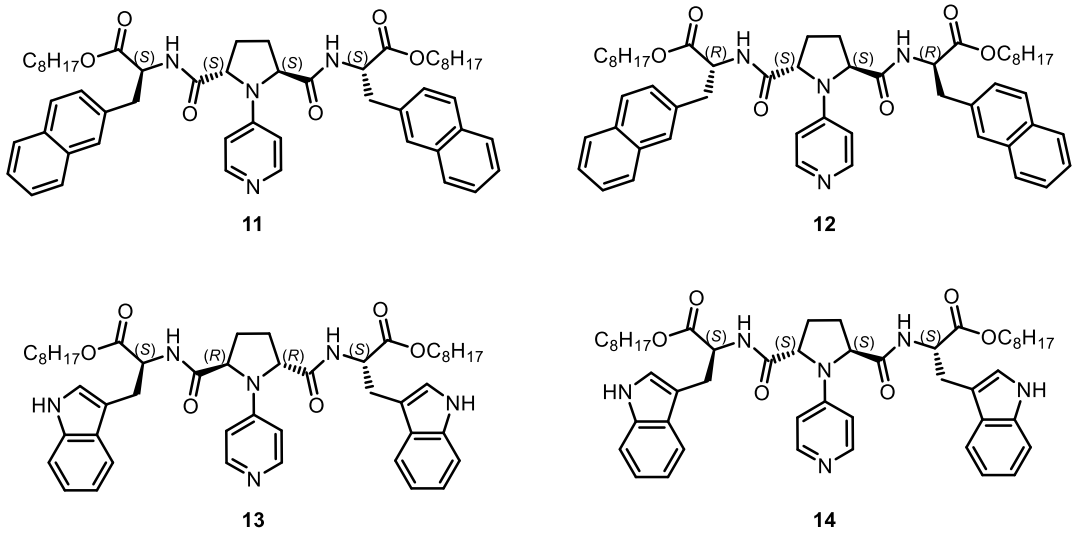
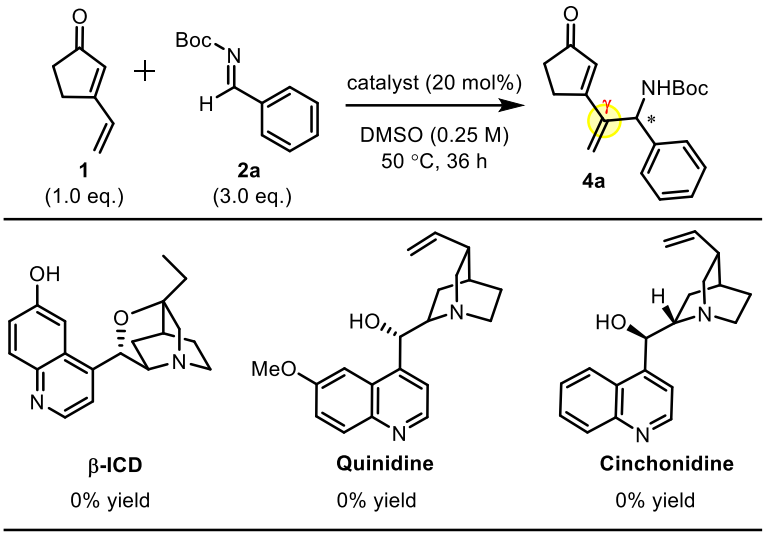


Fig. 3-2. 4-Pyrrolidinopyridine (PPY) derived asymmetric nucleophilic catalysts

本触媒の側鎖アミノ酸部位としてトリプトファン誘導体やチロシン誘導体を用いれば、不斉 aza-MBH 反応に有効な二官能性触媒として機能すると期待される。そこで、本章では所属研究室で見出した γ 位選択的 aza-MBH 反応を不斉反応へと展開すべく研究を行った。ジエノンの位置及びエナンチオ選択的 aza-MBH 反応は過去に報告例がなく、合成化学上大きなチャレンジであるといえる。

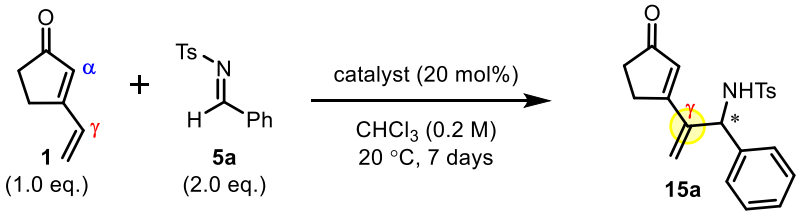
第二節　触媒検討

第二章において開発した *N*-Boc イミン **2a** を用いるジエノン **1** との aza-MBH 反応において橋頭位第三級アミン構造を有する様々な不斉触媒を検討したが、ほとんど反応は進行しなかった (Scheme 3-1)。

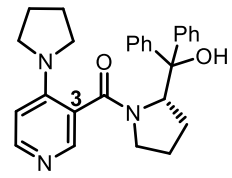


Scheme 3-1. *aza*-MBH reactions with *N*-Boc imine doesn't work

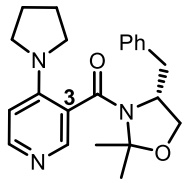
そこで、*N*-Ts イミン **5a** を用いる条件下、不斉 DMAP 誘導体について検討した (Scheme 3-2)。まず、Connon らによって開発されたピリジン環 3 位に置換基を有する触媒 **16a** 及び触媒 **16b**[17] を用いたところ、期待通り γ 位付加体が優先して得られたが、エナンチオ選択性はいずれも低かった (entries 1, 2)。次に、所属研究室で独自に開発した触媒 **11-14** について検討した。触媒側鎖に β-ナフチルアラニン誘導体が置換した触媒 **11** 及び触媒 **12** について検討したところエナンチオ選択性は最高で 15% ee に留まった。側鎖にトリプトファン誘導体が置換した触媒を用いたところ、特に触媒 **14** を用いた場合において 42% ee で γ 位付加体が得られた。この結果により、触媒側鎖にブレンステッド酸としての機能が期待できる酸性プロトンを有する触媒がジエノン γ 位での不斉発現に有効であることが示唆された。同様にブレンステッド酸としての機能が期待できる側鎖にチロシン誘導体が置換した触媒 **17** 及び触媒 **18** を用いたところ、エナンチオ選択性は 30% ee に留まった。



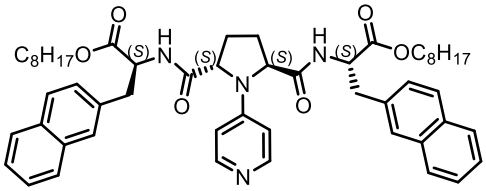
entry	catalyst	yield of **15a**	ee of **15a**
1	**16a**	22%	6%
2	**16b**	18%	18%
3	**11**	49%	15%
4	**12**	16%	-9%
5	**13**	14%	10%
6	**14**	43%	42%
7	**17**	14%	30%
8	**18**	14%	30%



16a



16b



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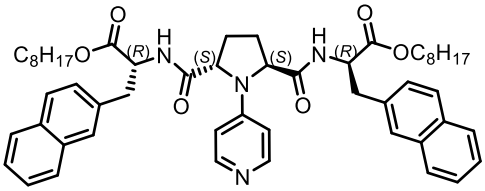

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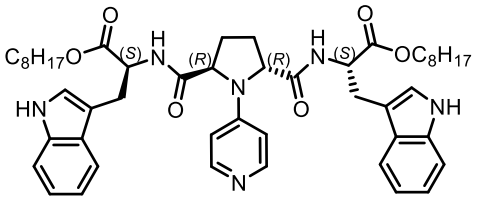

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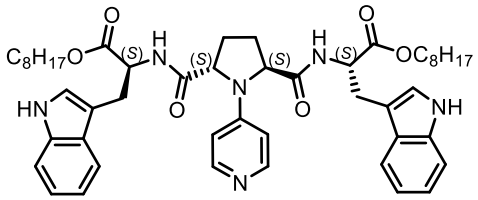

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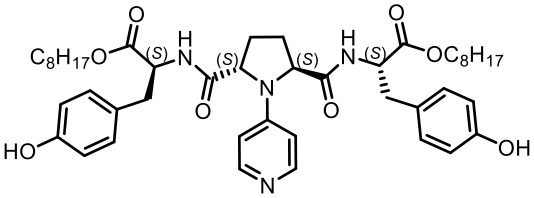

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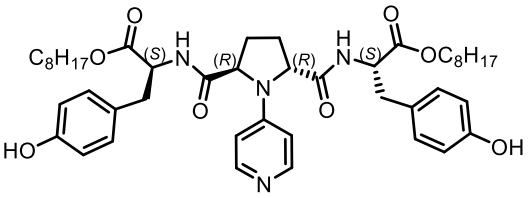
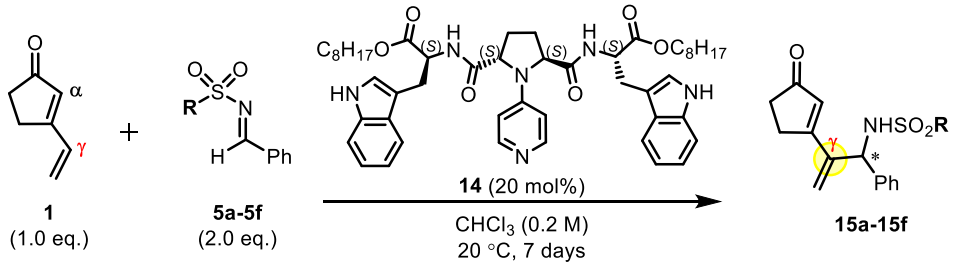


18

Table 3-1. Effects of catalysts on enantioselectivity of *aza*-MBH reaction with *N*-Ts imine

第三節　イミン保護基の検討

触媒 **14** を用い、種々のアルキルスルホニル保護イミンを用いて検討を行った (Table 3-2)。ベンゼンスルホンアミドのベンゼン環 *para* 位にメトキシ基およびトリフルオロメチル基を導入したイミン **5b** 及び **5c** を用いて反応を行った結果、何れの場合にもエナンチオ選択性の低下を招いた (entries 2, 3)。メシチル基を有するイミン **5d** を用いたところ、位置選択性が劇的に向上し、エナンチオ選択性についても 52% ee に向上した (entry 4)。また、脂肪族アルキル基として、メチル基及びシクロプロピル基を有するイミン **5e** 及び **5f** を用いると、何れの場合も高い位置選択性を示したが、エナンチオ選択性は改善されなかった (entries 5, 6)。上記の結果より、*N*-スルホニルイミンを用いる反応ではエナンチオ選択性の改善は困難と判断した。



1 (1.0 eq.)　**5a-5f** (2.0 eq.)　**15a-15f**

entry	R	yield of **15**	ee of **15**
1	**5a**	43% α : γ = 1 : 7	42%
2	**5b** (OMe)	37% α : γ = N.D.*	26%
3	**5c** (CF_3)	32% α : γ = N.D.*	10%
4	**5d**	45% α : γ = 1 : >20	52%
5	**5e** (Me)	47% α : γ = 1 : 14	30%
6	**5f**	42% α : γ = 1 : >20	32%

*N.D.; Not Determined

Table 3-2. The effect of alkyl substituents on sulfonyl group

第四節　アルジミンアリール部位の検討

二官能触媒のブレンステッド酸部位として多くの報告があるフェノール誘導体は、ピリジンとの水素結合が可能である[18]。作業仮説としてフェノール誘導体を側鎖に導入した触媒 **18** を用い、イミンアリール部位としてピリジン環を導入する事でエナンチオ選択性発現段階において水素結合のみを用いる場合と比べて有効な不斉場を構築できるものと考えた (Fig. 3-2.) 。水酸基-ピリジン間の水素結合による基質固定の有効性を検証する目的でピリジン環及びピリミジン環を有するイミンを合成し、vinylogous aza-MBH 反応へ適用した (Scheme 3-6)。

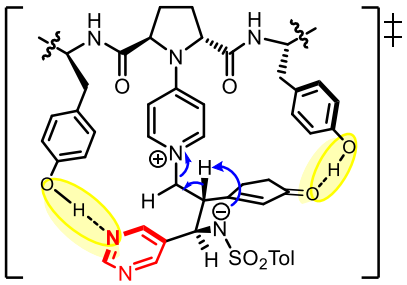
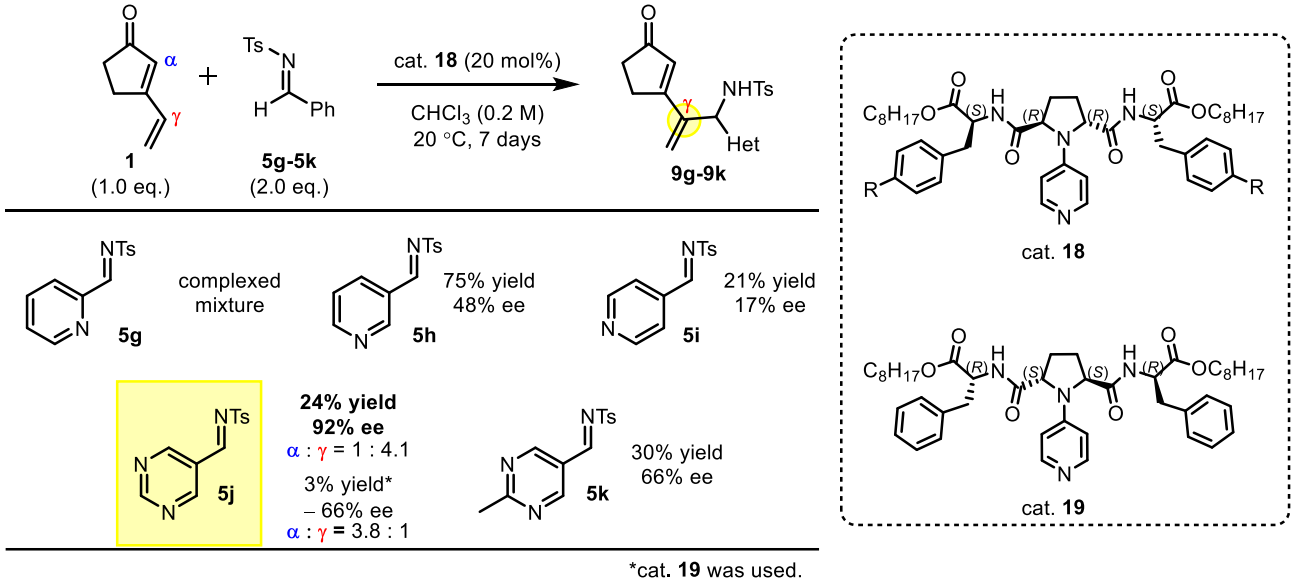


Fig. 3-2. Hypothetical conformational fixation by two attractive interactions

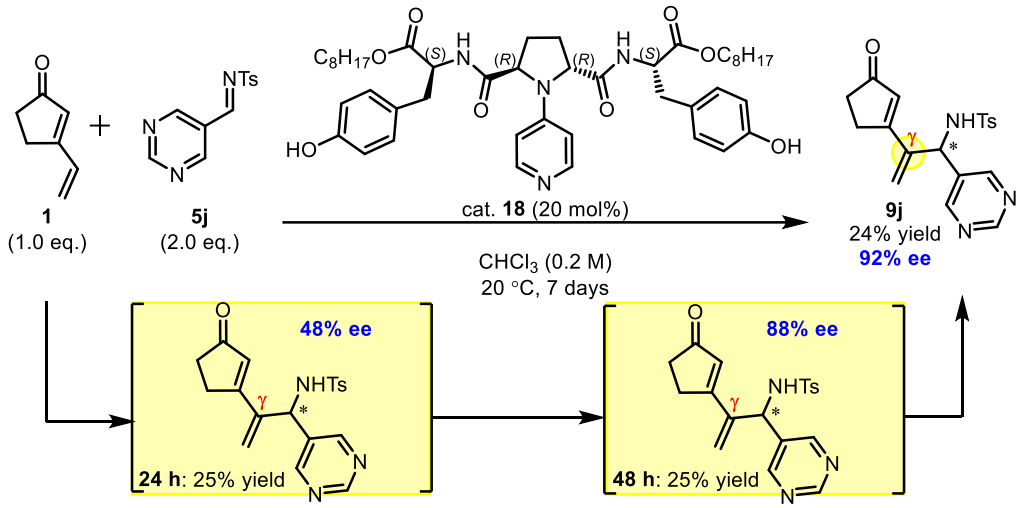
2-ピリジルイミン **5g** を用いた場合、複雑な混合物を与えた。一方で 3-ピリジルイミン **5h** を用いた場合、エナンチオ選択性及び収率の向上が見られた。4-ピリジルイミン **5i** を用いた場合、エナンチオ選択性が低下したことから、3-ピリジル構造が不斉発現に有効と考えた。そこで、さらに窒素原子を導入した、5-ピリミジルイミン **5j** を用いたところ 92% ee と非常に高いエナンチオ選択性で γ 位付加体が得られることを見出した。フェノール性水酸基欠損型の cat. **19** を用いた場合、エナンチオ選択性の低下に加えて収率の著しい低下が見られたことからフェノール性水酸基の重要性が示唆された。基質適応範囲を検証する目的でピリミジル基の 2 位にメチル基が置換したイミン **5k** を用いたが、この場合エナンチオ選択性の低下を招いた。



Scheme 3-6. Substrate optimization of pyridine or pyrimidine analogue

第五節　反応機構解析

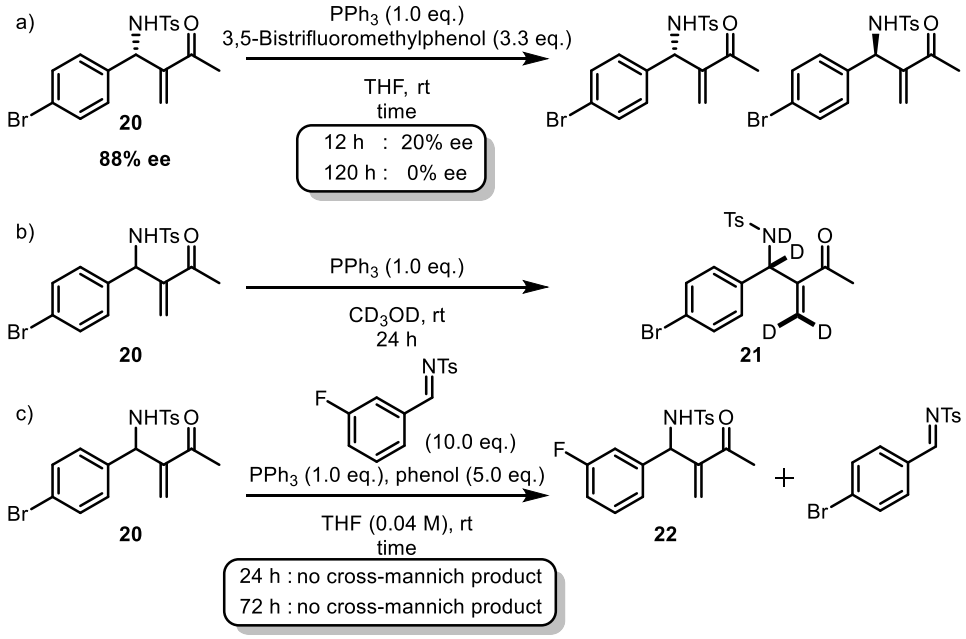
ここで、ピリミジンをアリール部位とした場合のみ高いエナンチオ選択性が発現したことに興味を持ち、7 日間の反応時間を 24 h および 48 h とした場合の収率及びエナンチオ選択性を測定した (Scheme 3-7)。



Scheme 3-7. Time-dependency of enantioselectivity of γ–adduct

その結果、反応時間を 7 日間とした場合は 92% ee であったエナンチオ選択性が、反応開始 24 時間の時点においては 48% ee に留まり、反応開始 48 時間の時点ではエナンチオ選択性が 88% ee に向上することが分かった。ここで、本反応によって得られる α 位付加体と γ 位付加体のそれぞれに触媒を作用させた場合、両生成物間の相互変換は確認されなかった事から生成物からの逆反応は関与しない点、及びイミン **5a** の場合では経時的なエナンチオ選択性の向上が見られなかったことからイミン **5j** 特異的にエナンチオ選択性が向上することが分かった。

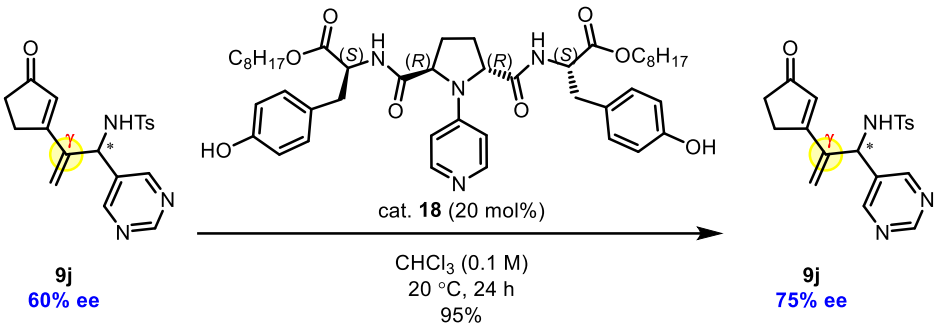
Leitner らは 2005 年に光学活性な aza-MBH 反応成績体 **20** に対してトリフェニルホスフィンを作用させることで室温中ラセミ化が進行することを報告している (Scheme 3-8 a)[19]。即ち、重メタノール中トリフ



Scheme 3-8. Deprotonation of allylic C-H bond by PPh_3

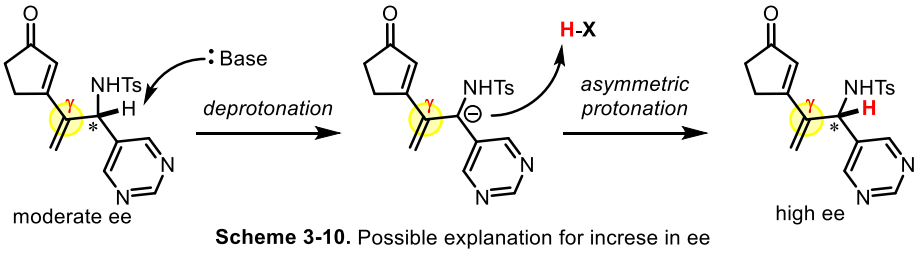
ェニルホスフィンを作用させた場合、NHTs 基の根元の C-H 及び末端ビニル位の C-H 結合の D 化が進行した **21** が得られる点 (Scheme 3-8 b)、**20** に対して他のイミンを反応させた場合、cross-Mannich 反応が進行した **22** が得られなかった点 (Scheme 3-8 c) から NHTs 基の根元の C-H 結合の脱プロトン化/プロトン化によるラセミ化機構を提唱している。

今回のピリミジンをアリール部位に有するイミン **5j** 特異的にエナンチオ選択性の向上が見られた理由として、Scheme 3-8 と同様に NHTs 基の根元の C-H 結合の脱プロトン化が関与しているものと考えた。γ 位付加体 **9j** に対する脱プロトン化/不斉プロトン化機構が関与したものと考え **9j** に対して触媒 **18** を加えることでエナンチオ選択性が向上するか検討した (Scheme 3-9.)。



Scheme 3-9. Increase in enantio-selectivity by cat. **18**

60% ee の **9j** に対して触媒 **18** 存在下 24 時間撹拌した。その結果、γ 位付加体が 95%収率で回収され、エナンチオ選択性が 75% ee に向上した。即ち、ラセミ化による光学純度の向上はキラル触媒介在型の脱プロトン化/不斉プロトン化機構によるものと推察される (Scheme 3-10)。

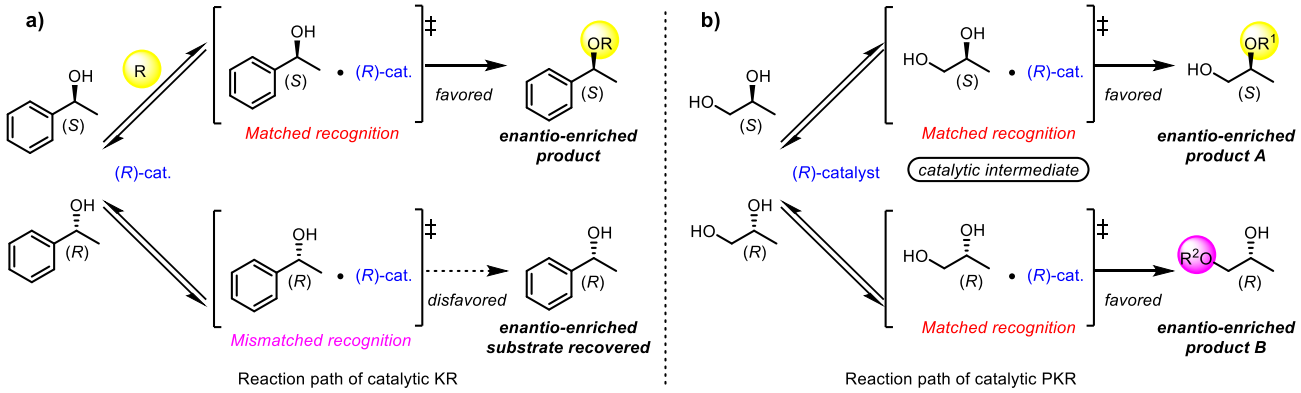


Scheme 3-10. Possible explanation for increse in ee

第四章　アミノジオール類に対する Parallel Kinetic Resolution (PKR) の開発

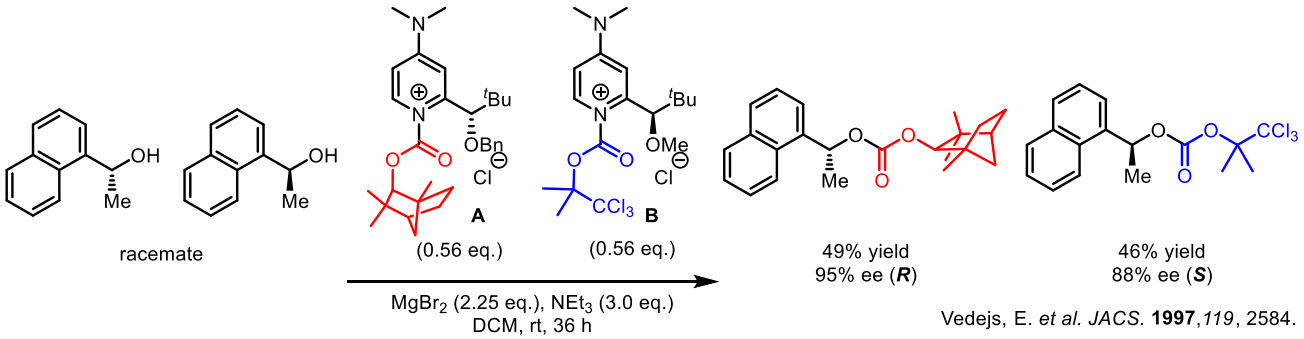
第一節　研究背景及び著者の研究方針

非酵素法を用いたラセミ体の触媒的光学分割法はこれまでに数多くの手法が開発されている [20]。特に有機分子触媒を用いたアシル化を基盤とする光学分割は光学活性キラルアルコール、アミン、チオールを得る手法として盛んに研究が行われてきた [21]。KR における基本概念は不斉触媒とラセミ体基質間での複合体形成の際に matched、mismatched のエネルギー差により *R* 体基質と *S* 体基質間での反応速度差を生み出す手法である (Scheme 4-1a)。これに対し Parallel Kinetic Resolution (PKR) はラセミ体基質に対し、異なる反応を進行させることで両生成物を高い光学純度で得る手法である (Scheme 4-1b)[22]。即ち、PKR が成立するためには単一のキラリティを有する触媒が *R* 体及び *S* 体の基質に対してそれぞれ matched の不斉識別を経て異なる反応を進行させる必要がある。故に、通常の KR と比べ格段に困難な方法論であり、特に単一触媒を用いる PKR は触媒化学における挑戦といえる。



Scheme 4-1. Schematic comparison between KR and PKR

このような PKR においてアシル化を基盤とする反応としては、2 種の量論量の擬エナンチオメリックなアシル化剤を用いる手法が知られている (Scheme 4-2.)[23]。効率的な PKR は 2 種類のエナンチオマーに

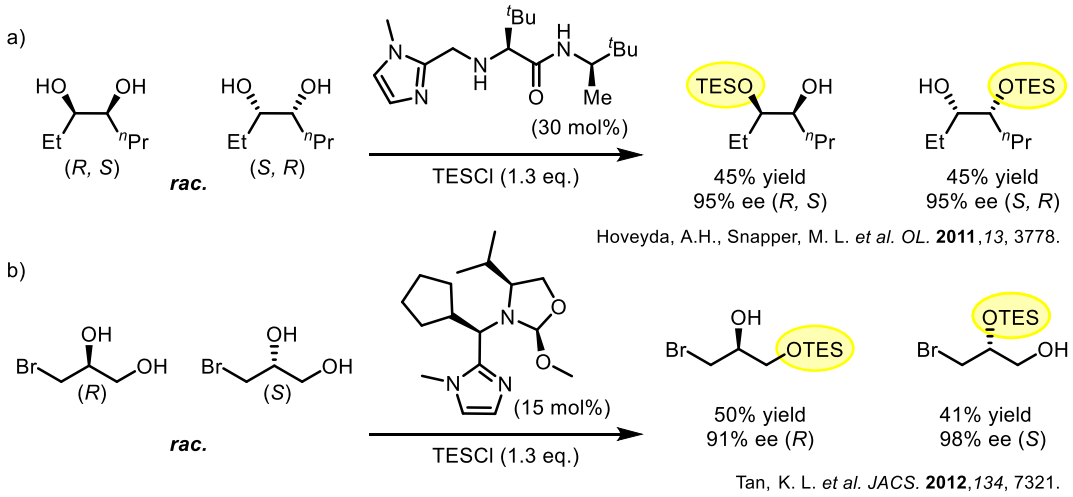


Scheme 4-2. Acylative parallel kinetic resolution[23]

対して相補的に反応が進行する必要があるが、Vedejs らは 1-(1-naphthyl)ethanol に対して *S* 体を *s* = 42 の選択性で転換させるアシルドナー**B**[24] (Scheme 4-2. 青色のアシル化剤)に加え、*R* 体を *s* = 41 の選択性で転換させるアシルドナー**A**　(Scheme 4-2. 赤色のアシル化剤) の 2 つの擬エナンチオメリックなアシル化剤を組み合わせることで PKR を達成した。しかし、本法は予め調製した化学量論量の擬エナンチオメリッ

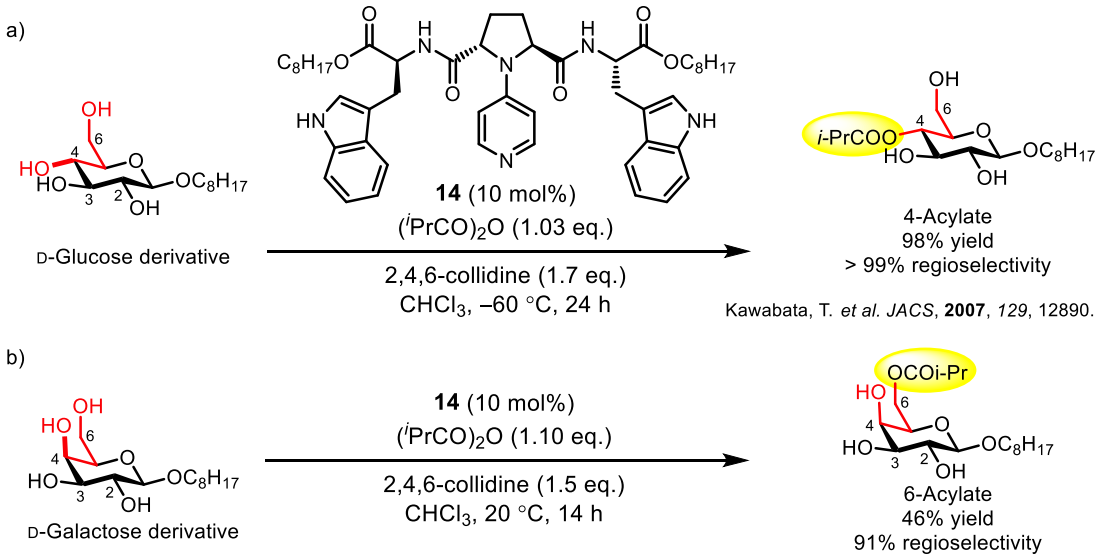
クなアシル化剤を必要とする点が課題として残る。このような背景のもと、単一触媒を用いるアシル化を基盤とする PKR の開発が求められる。

ジオール類を基質とした単一触媒を用いる PKR については 1,2-ジオール類を基質とする 2 例が報告されている (Scheme 4-3.)[25]。特に Tan らの報告基質 (Scheme 4-3b) は末端 1,2-ジオール部位を有しており、第一級水酸基及び第二級水酸基の化学選択性の識別に加え、不斉識別が必要となる。又、第二級水酸基のシリル化においては反応点と不斉炭素が直結しているため不斉識別は比較的容易であるが、第一級水酸基のシリル化においては反応点と不斉炭素がメチレンで隔てられており、不斉識別は特に困難である。



Scheme 4-3. Precedents for regiodivergent PKR of diols[25]

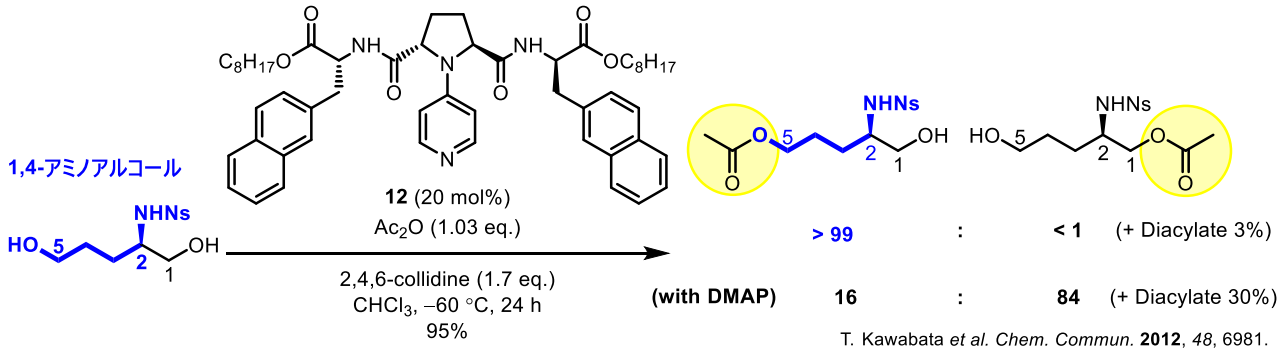
所属研究室ではポリオールもしくはジオール類の官能基間距離を識別する分子認識型触媒を用いることで化学選択性の逆転を伴ったアルコール類の位置選択的アシル化を報告している [26]。触媒による分子認識の知見を基に、キラリティに応じて異なる位置にアシル化を進行させる系を設計することでこれまで報告例のない単一触媒による水酸基のアシル化による PKR が可能と考えた。設計指針となる分子変換を Scheme 4-4 及び 4-5 に示した。1 つ目は D-グルコース誘導体の 4 位水酸基選択的アシル化法である [26(a)]。



Scheme 4-4. Regioselective acylation of carbohydrates *via* recognition of 1,3-diol substructure by catalyst **14**

本法は 6 位第一級水酸基と触媒アミドカルボニル基との水素結合及び 3 位第二級水酸基とインドール NH 基の水素結合により、4 位第二級水酸基が反応点に近接することが高選択性発現の要因と考えられている (Scheme 4-4a)。一方、4 位水酸基が逆の立体化学を有する D-ガラクトース誘導体に対するアシル化は、6 位水酸基で優先的に進行する (Scheme 4-4b)[27]。本結果は触媒 **14** が 1, 3-ジオール構造を有する基質に対し、基質のキラリティに応じた位置選択的アシル化を進行させることを示している。

2 つ目は NHNs 基を足掛かりとした官能基間距離選択的アシル化法である [26(b)] (Scheme 4-5)。DMAP を用いた場合、NHNs 基と 1,2-の関係にある水酸基が優先的にアシル化される一方、cat. **12** を用いた場合には位置選択性の逆転を伴い、NHNs 基から 1,4-の関係にある水酸基がほぼ完全な選択性でアシル化される。本結果は触媒 **12** が NHNs 基から 4 炭素隔てた位置の水酸基へ加速的なアシル化を進行させることを示している。



T. Kawabata *et al. Chem. Commun.* **2012**, *48*, 6981.

Scheme 4-5. Regiodivergent acylation of amino alcohol by catalyst **12**

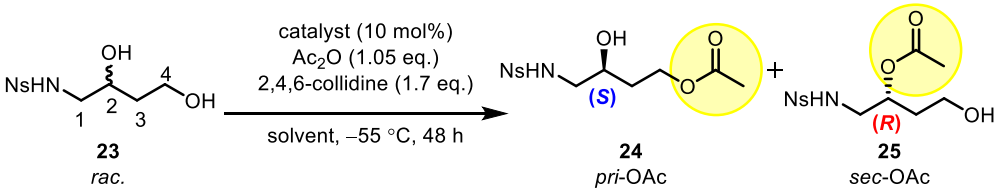
以上の知見を基に基質のキラリティに応じて 1,3-ジオールと 1,4-アミノアルコール認識とが別々に起こる基質に設計することで単一触媒を用いる水酸基のアシル化による PKR が可能と考えた (Fig. 4-2.)。

Fig. 4-2. Designed substrate for PKR

第二節　反応条件の最適化

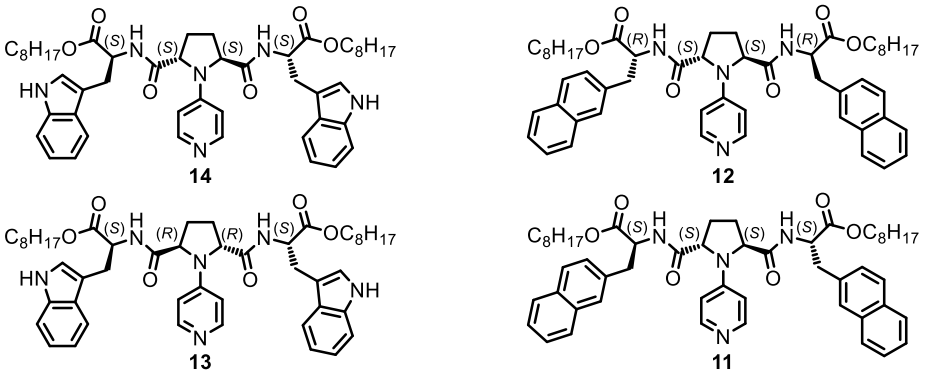
設計したラセミ体ジオール **23** に対し、単一触媒を用いるアシル化による PKR の検討を行った (Table 4-1)。1,3-ジオール構造の認識に有効であった触媒 **14** 存在下、クロロホルム溶媒中-55 ℃において無水酢酸を作用させると、*S* 体の第一級水酸基アシル化体 **24** を 46%収率、86% ee で、*R* 体の第二級水酸基アシル化体 **25** を 36%収率、95% ee で与えた　(entry 1)。即ち、期待通り触媒 **14** は基質のキラリティに応じて位置選択的アシル化を進行させることで設計した基質 **23** の PKR を進行させることが分かった。同様の条件下 1,4-アミノアルコールの認識に有効であった触媒 **12** を用いたが、第二級水酸基アシル化体 **25** の収率が著しく低下し、効率的な PKR は進行しなかった (entry 2)。触媒 **14** 及び触媒 **12** のジアステレオマーを用いた場合も効率的な PKR は進行しなかったことから (entries 3, 4)、entry 1 の触媒 **14** を最適触媒とした。

溶媒効果を検証する目的で、触媒 **14** 存在下、クロロホルムと比較してやや極性が高い塩化メチレンを用いた場合、両水酸基のアシル化体がクロロホルムの場合と同等の収率で得られたが、エナンチオ選択性はやや低下した (entry 5)。更に極性が高い THF を用いた場合、第一級水酸基アシル化体 **24** の収率が著しく低下し、エナンチオ選択性も発現しなかったことから (entry 6)、entry 1 のクロロホルムを最適溶媒とした。



23 *rac.*　　**24** *pri*-OAc　　**25** *sec*-OAc

entry	catalyst	solvent	*pri*-OAc	*sec*-OAc	Diacylate
1	**14**	$CHCl_3$	46% (86% ee, ***S***)	36% (95% ee, ***R***)	11%
2	**12**	$CHCl_3$	53% (80% ee, ***R***)	3% (88% ee, ***R***)	11%
3	**13**	$CHCl_3$	67% (30% ee, ***R***)	13% (81% ee, ***S***)	18%
4	**11**	$CHCl_3$	86% (10% ee, ***S***)	3% (27% ee, ***R***)	11%
5	**14**	CH_2Cl_2	34% (83% ee, ***S***)	42% (77% ee, ***R***)	16%
6	**14**	THF	65% (0% ee)	7% (56% ee, ***R***)	22%



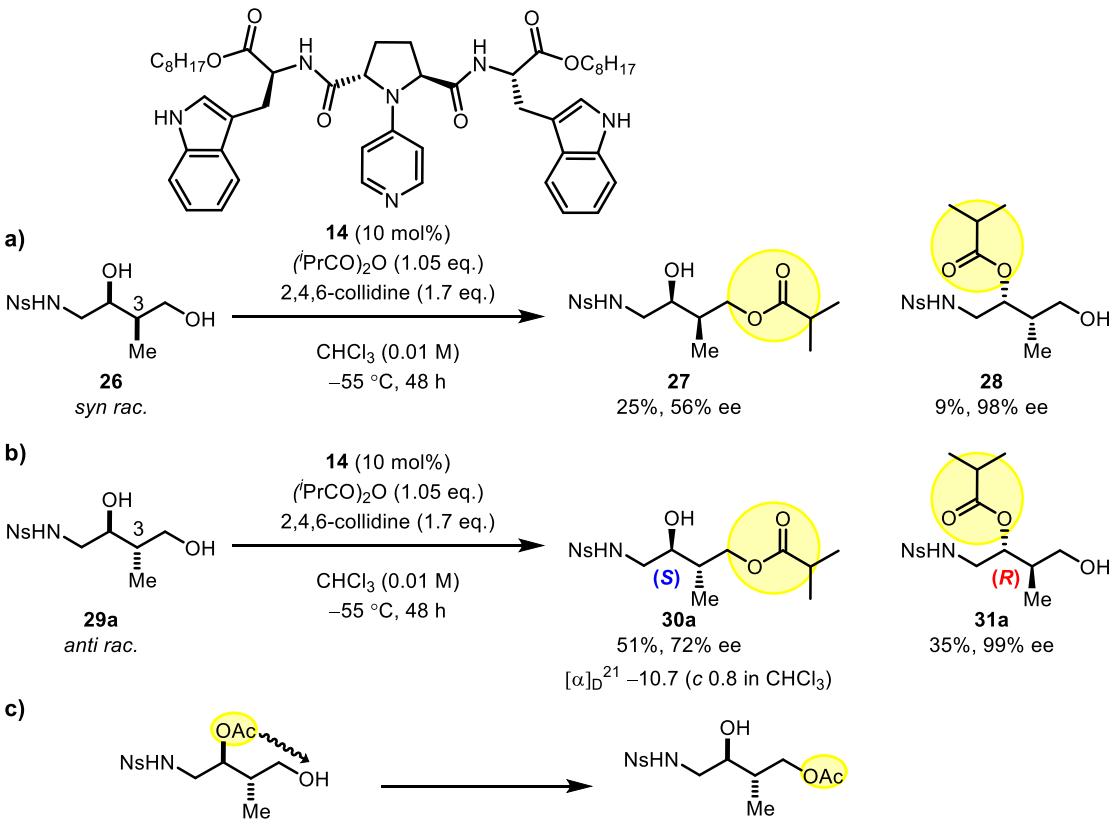
14　　**12**

13　　**11**

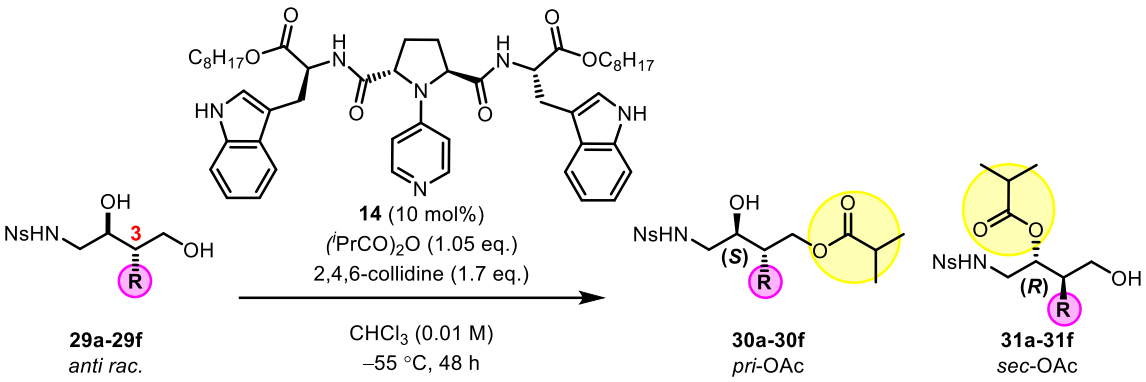
Table 4-1. Screening of catalysts for acylative PKR of **23**

第三節　基質一般性の拡張

次に、基質一般性の拡張を目的として基質の 3 位にメチル基を導入した基質に対して PKR を検討した。この際二種類のジアステレオマーが生じるため、双方の基質を合成し検討を行った (Scheme 4-6)。S*yn* 体(±)-**26** を用いた場合、第一級水酸基アシル化体 **27** は 25%収率、56% ee で得られた一方で第二級水酸基アシル化体 **28** は 9%収率に留まり、効率的な PKR は進行しなかった (Scheme 4-6a)。次に *anti* 体(±)-**29a** を用いると第一級水酸基アシル化体 **30a** が 51%収率、72% ee で、第二級水酸基アシル化体 **31a** が 35%収率、99% ee で得られ効率的な PKR が進行することが分かった (Scheme 4-6b)。なお、本系ではアシル化剤としてイソ酪酸無水物を用いて検討している。これはアシル化剤として無水酢酸を用いた場合、精製過程で第二級水酸基から第一級水酸基へのアシル転移が進行する為である (Scheme 4-6c)。以上の結果から、基質 3 位に *anti* の関係で置換基を導入した基質であれば PKR が進行することが示唆された為、3 位へ種々の置換基を導入した基質に対する PKR を検討した (Table 4-2)。



Scheme 4-6. Acylative PKR of diols **26** and **29a**



Entry	R		*pri*-OAc (**30a-30f**)	*sec*-OAc (**31a-31f**)	*A*-value of R group
1	-F	**(29b)**	35% yield, 99% ee	34% yield, 98% ee	0.15 kcal/mol
2	-≡	**(29c)**	39% yield, 97% ee	37% yield, 99% ee	0.41 kcal/mol
3	-=	**(29d)**	31% yield, 83% ee	37% yield, 99% ee	1.35 kcal/mol
4	-Me	**(29a)**	51% yield, 72% ee	35% yield, 99% ee	1.7 kcal/mol
5	-Ph	**(29e)**	41% yield, 77% ee	31% yield, 98% ee	1.8 kcal/mol
6	-C6H5	**(29f)**	56% yield, 71% ee	24% yield, 98% ee	3.0 kcal/mol

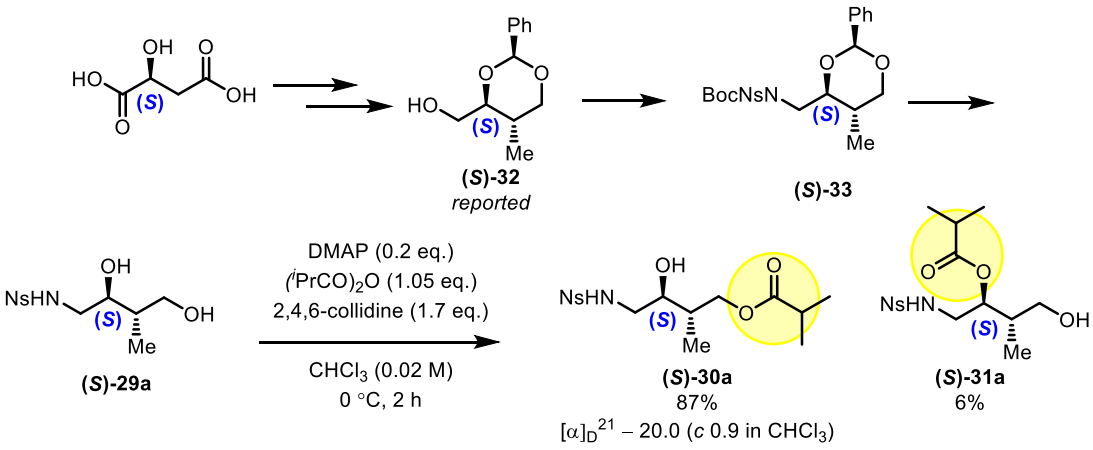
Table 4-2. Scope of substrates with various R groups at the 3-position

3 位にフッ素を導入した(±)-**29b** を基質とした場合、第一級水酸基アシル化体 **30b** が 35%収率、99% ee で、第二級水酸基アシル化体 **31b** が 34%収率、98% ee で得られ非常に高い選択性で PKR が進行することが分かった (entry 1)。エチニル基を導入した(±)-**29c** の場合も第一級水酸基アシル化体 **30c** が 39%収率、97% ee で、第二級水酸基アシル化体 **31c** が 37%収率、99% ee で得られ、**29b** と同様に高効率で PKR が進行した (entry 2)。以降より大きい置換基 (ビニル基、ベンジル基、フェニル基) を導入した基質 **29d-29f** では第一級水酸基アシル化体 **30d-30f** のエナンチオ選択性は僅かに低下したものの、第二級水酸基アシル化体は非常に高いエナンチオ選択性で得られ、PKR が高効率で進行した (entries 3, 5, 6)。

第四節　絶対配置の決定

anti 体(±)-**29a** を基質とする PKR の第一級水酸基アシル化体 **30a** の絶対配置を決定した (Scheme 4-6)。L-リンゴ酸より誘導可能な文献既知化合物(***S***)-**32** を合成した[28]。(***S***)-**32** に対して光延反応を行い NHNsBoc 基を導入することで(***S***)-**33** を合成し、塩酸による Boc 基及びベンジリデンアセタールの脱保護により(***S***)-**29a** を得た。得られた(***S***)-**29a** に対して DMAP 存在下、イソ酪酸無水物を作用させたところ第一級水酸基アシル化体 (***S***)-**30a** が主生成物として得られ、この比旋光度を測定したところ$[\alpha]_D^{21}$ – 20.0 であった。一方、Scheme 4-5 b) で得られた **30a** (72% ee) の比旋光度を測定すると$[\alpha]_D^{21}$ – 10.7 であり、符号が一致した。即ち、**29a** に対する触媒 **14** を用いる PKR により得られる第一級水酸基アシル化体の絶対配置は *S* と決定した。

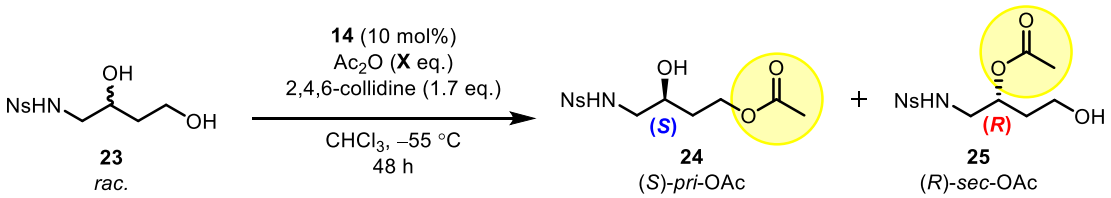
尚、Scheme 4-7 に示す DMAP を用いた(***S***)-**29** のアシル化は、第一級水酸基アシル化が第二級水酸基アシル化に優先した。触媒 **14** を用いた場合には両水酸基のアシル化体が同等の収率で得られたことから、触媒 **14** は基質固有の反応性とは独立した反応性の制御により、効率的な PKR を進行させることが示された。



Scheme 4-7. preparation of (*S*)-**30a**

第五節　反応機構解析

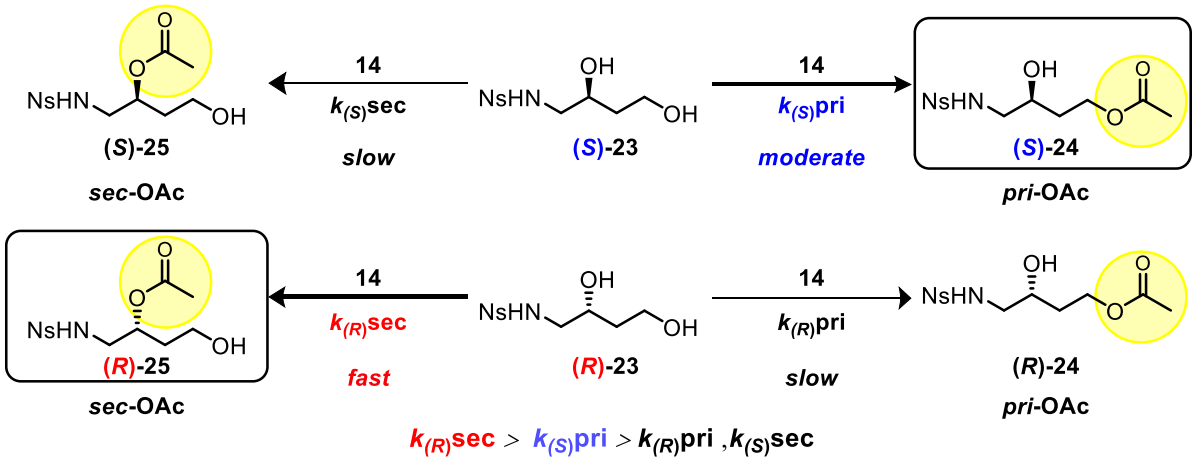
本 PKR においては基質 **23** の反応経路としては第一級水酸基のアシル化と第二級水酸基のアシル化の二つの経路がある。各エナンチオマーに対して双方の経路が存在するため、4 つの経路の相対速度によって PKR の成否が決まる。そこで相対反応速度に関して知見を得るべく、無水酢酸を 0.55 当量作用させたところ、第二級水酸基アシル化が第一級水酸基アシル化に優先して進行した (Table 4-3, entry 1)。また、この際第二級水酸基アシル化体 **25** のエナンチオ選択性は 97% ee であった一方、第一級水酸基アシル化体 **24** のエナンチオ選択性は 40% ee に留まった。即ち、反応の転換率が低い段階においては *R* 体の第二級水酸基アシル化が最も早く進行していることが分かった。一方で無水酢酸を 1.05 当量用いた場合、第一級水酸基アシル化体 **24** のエナンチオ選択性が 87% ee に向上した (Table 4-3, entry 2)。以上の結果か



entry	Ac_2O (eq.)	***pri*-acylate (*S*)**	***sec*-acylate (*R*)**	diacylate
1	0.55	18% (40% ee)	37% (**97**% ee)	–
2	1.05	46% (**86**% ee)	36% (**95**% ee)	11%

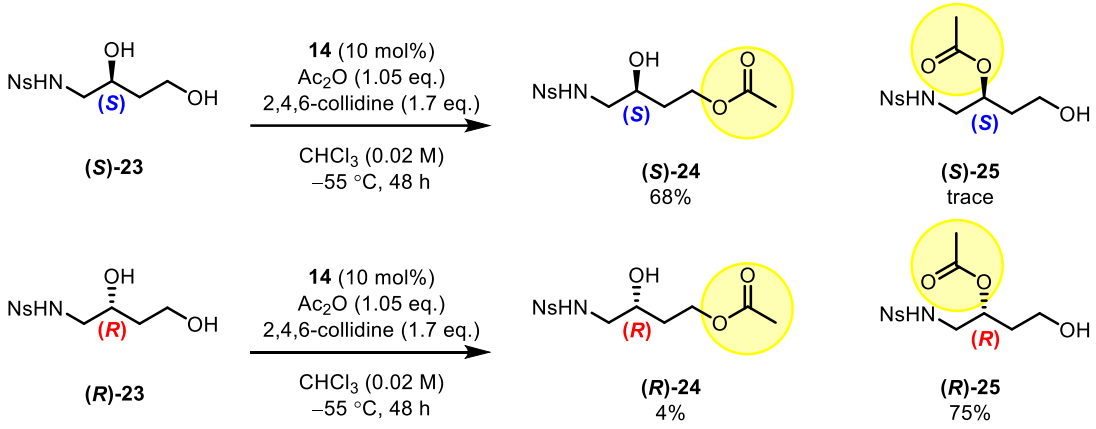
Table 4-3. Effects of amounts of acetic anhydride on the enantioselectivity of products

ら本 PKR における主な反応経路を Scheme 4-8 に示した。本反応においては(*R*)-**25** を与える反応 $k_{(R)}$sec が最も早い反応であり、反応の進行により原料の *S* 体の割合が濃縮されていくと考えられる (Scheme 4-8)。一方で反応初期においても第一級水酸基アシル化で中程度のエナンチオ選択性が発現していることから、触媒 **14** は(*S*)-**24** への反応も加速していると考えられる。反応後期では、*S* 体の比率が濃縮された原料に対して第一級水酸基選択的なアシル化が進行することで、結果としてキラリティに応じた位置選択的アシル化が進行したものと考えられる。



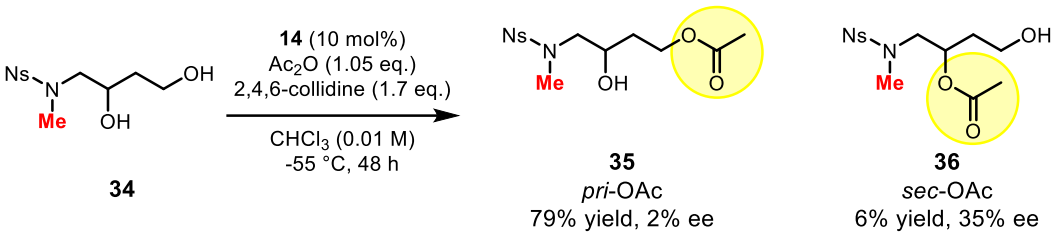
Scheme 4-8. Relative rates of acylation among four individual hydroxy groups

次に、上記のキラリティに応じた位置選択的アシル化がそれぞれ触媒による分子認識を経て進行しているか確認する目的で光学活性な基質 **23** に対し、触媒 **14** を用いたアシル化反応の検討を行ったところ、*S* 体の基質 **23** に対するアシル化は第一級水酸基選択的に進行した一方、*R* 体の基質 **23** に対するアシル化は第二級水酸基選択的に進行した (Scheme 4-9)。これら結果は、両水酸基へのアシル化が何れも分子認識を介して進行していることを示唆している。



Scheme 4-9. Effects of absolute configuration of **23** on the reaction path

触媒による分子認識への関与が示唆される NHNs 基をメチル基で保護した基質を用いる条件下 PKR が進行するか検討を行った (Scheme 4-10)。(±)-**34** の両水酸基へのアシル化は並行して進行せず、第一級水酸基アシル化体 **35** が主生成物として得られ、第二級水酸基アシル化体 **36** は 6%収率に留まった。この結果から、NHNs 基が有する酸性プロトンが PKR の進行に必須であることが分かった。ここで今回用いた



Scheme 4-10. Effects of protection of acidic NHNs proton on the reaction path

アミノジオールの基質と Scheme 4-4 a) に示した D-グルコース誘導体の基質構造を比較した場合、D-グルコースが 1,3-ジオール構造に加えて 3 位に水酸基を有しているのに対し、アミノジオールの基質は NHNs 基の N-H プロトンが D-グルコースにおける 3 位第二級水酸基と同様の位置に存在している (Fig. 4-3)。今回、NHNs 基をメチル基で保護した場合には PKR の効率が著しく低下したことから、NHNs 基の酸性

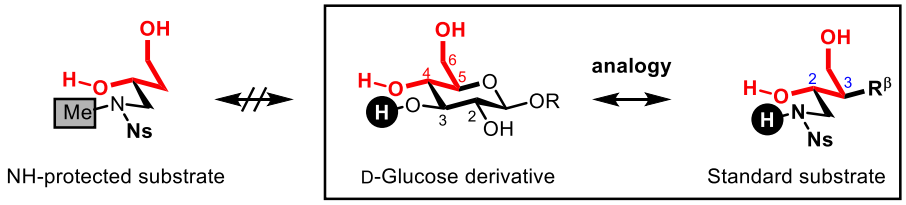


Fig. 4-3. Schematic comparison of substrate structure

プロトンは触媒による分子認識において D-グルコースの 3 位水酸基に対応する役割を果たしていることが示唆された。又、PKR における基質 3 位への置換基導入は 2 位水酸基との相対配置が *anti* の場合においてのみ効率的な PKR が進行したことから、D-グルコース 5 位の置換様式と同様に PKR の基質 3 位の置換基はβ配置の場合のみ効率的な PKR が進行すると考えられる。

今回のキラリティに応じた位置選択的アシル化は Table 4-3 の結果が示すようにキラル 1,3-ジオール構造の識別は *R* 体の第二級水酸基アシル化が最も早い反応であったが、*R* 体の消費後は、異なる基質認識機構を介することで *S* 体の第一級水酸基のアシル化が進行すると考えられる。ここで、PKR における第二級水酸基アシル化における選択性は D-グルコース誘導体の 4 位水酸基選択的アシル化と同様、最も酸性度の高い第一級水酸基が触媒のアミドカルボニル部位と水素結合することで、*R* 体の第二級水酸基がアシルピリジニウム部位に近接する為と考えられる。一方、第一級水酸基アシル化における選択性は分子認識の様式が変化し、第二級水酸基が触媒のアミドカルボニル部位と水素結合することで近接した *S* 体の第一級水酸基でのアシル化が進行したものと考えた (Fig. 4-4)。何れの遷移状態も 3 位置換基は触媒との立体障害を生まない方向に配向しており、触媒-基質間での分子間相互作用を阻害しない *anti* 型の基質が重要であることが分かる。

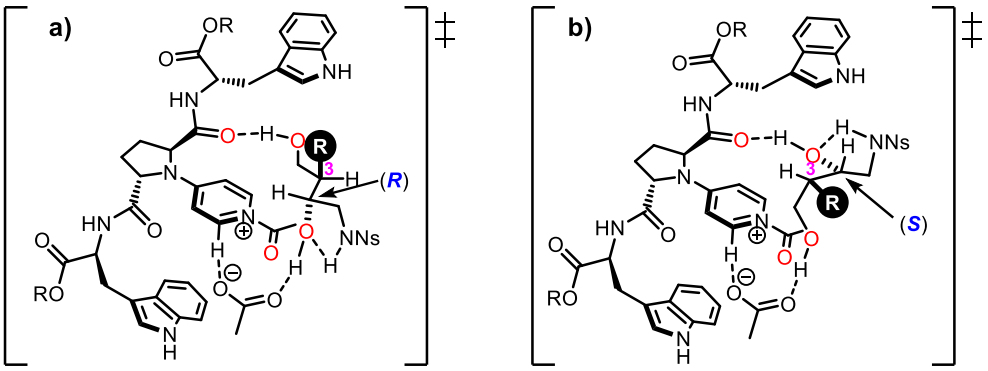


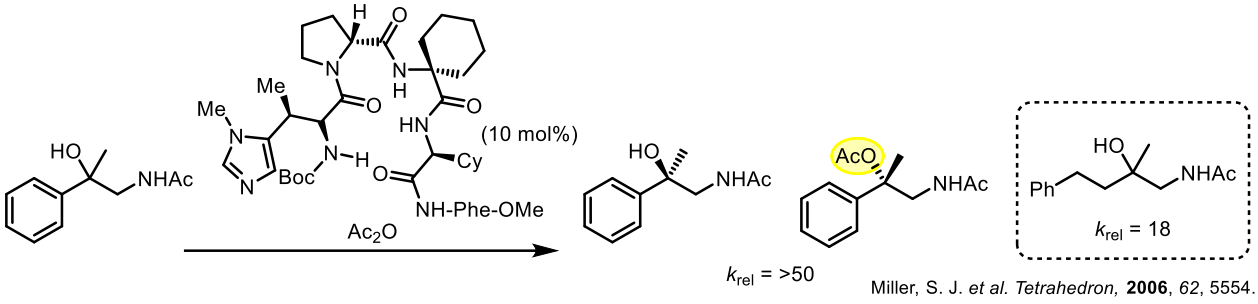
Fig. 4-4. Possible transition state structure for acylation.
a) acylation of secondary alcohol, b) acylation of primary alcohol

第五章　第三級アルコールの速度論的光学分割法の開発

第一節　研究背景及び著者の研究方針

第四章ではジオールの官能基間距離及びキラリティの識別を基盤とし、単一触媒を用いるアルコールのアシル化による初の PKR を達成した。ここで、アルコールのアシル化を鍵とする分子変換における未解決課題を考えた場合、第三級アルコールの KR が挙げられる。キラルな第三級アルコールを得る最も直線的な手法としてケトンへのグリニャール試薬等の有機金属試薬の付加が考えられる。しかし、エナンチオ選択性が担保できる基質としては α-ケトエステルやイサチン誘導体、α-トリフルオロメチルケトンに限定され、活性化されていないケトンに対する面選択的付加は現在においても挑戦的な課題である [29]。また、有機金属試薬を用いる事に起因する官能基共存性の低さも問題となり、温和な条件でのキラル第三級アルコール合成法が求められる。一方、アシル化反応は温和な条件にて実現可能である為、アシル化による KR はキラル第三級アルコールを与える有効な手法と考えられる。しかし、第三級アルコールの直接的な KR は 1) 第三級水酸基近傍の立体障害によりアシル化が進行し難い点及び 2) 第三級水酸基の隣接不斉炭素に置換した 3 つの異なる置換基を識別することが必要とされる点の 2 つの原因の為、現在においても人工触媒を用いる第三級アルコールのアシル化による KR は 3 例に限られる [30]。

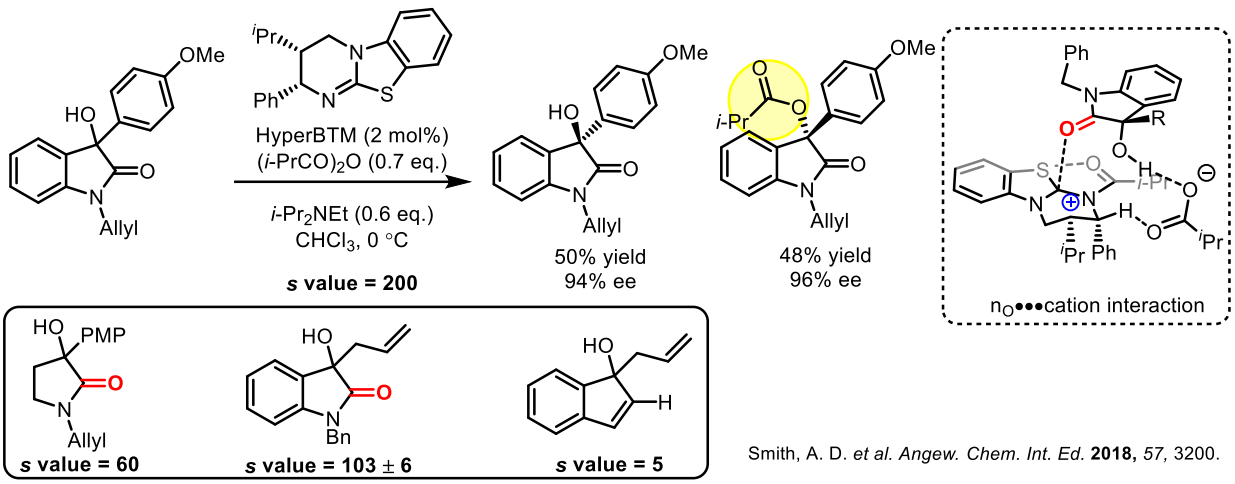
Miller らは *N*-メチルイミダゾールを触媒部位としたペプチド触媒を用いる三級水酸基のアシル化による KR を報告している (Scheme 5-1) [30b,c]。第三級水酸基の隣接不斉炭素の置換基としてメチル基 (A-value = 1.70 kcal/mol) 及びフェニル基 (A-value = 3.0 kcal/mol) 等の明確な立体障害の差がある基質においては効率的な KR が進行する一方、フェニル基に変えてメチレン鎖が置換した基質では KR の効率が大きく低下する。これは立体障害の識別を主とした手法では不斉点近傍の立体障害の大中小を区別することが困難な為であると考えられる。



Miller, S. J. *et al. Tetrahedron,* **2006**, *62*, 5554.

Scheme 5-1. Kinetic resolution of *tert*-alcohol by peptide catalyst

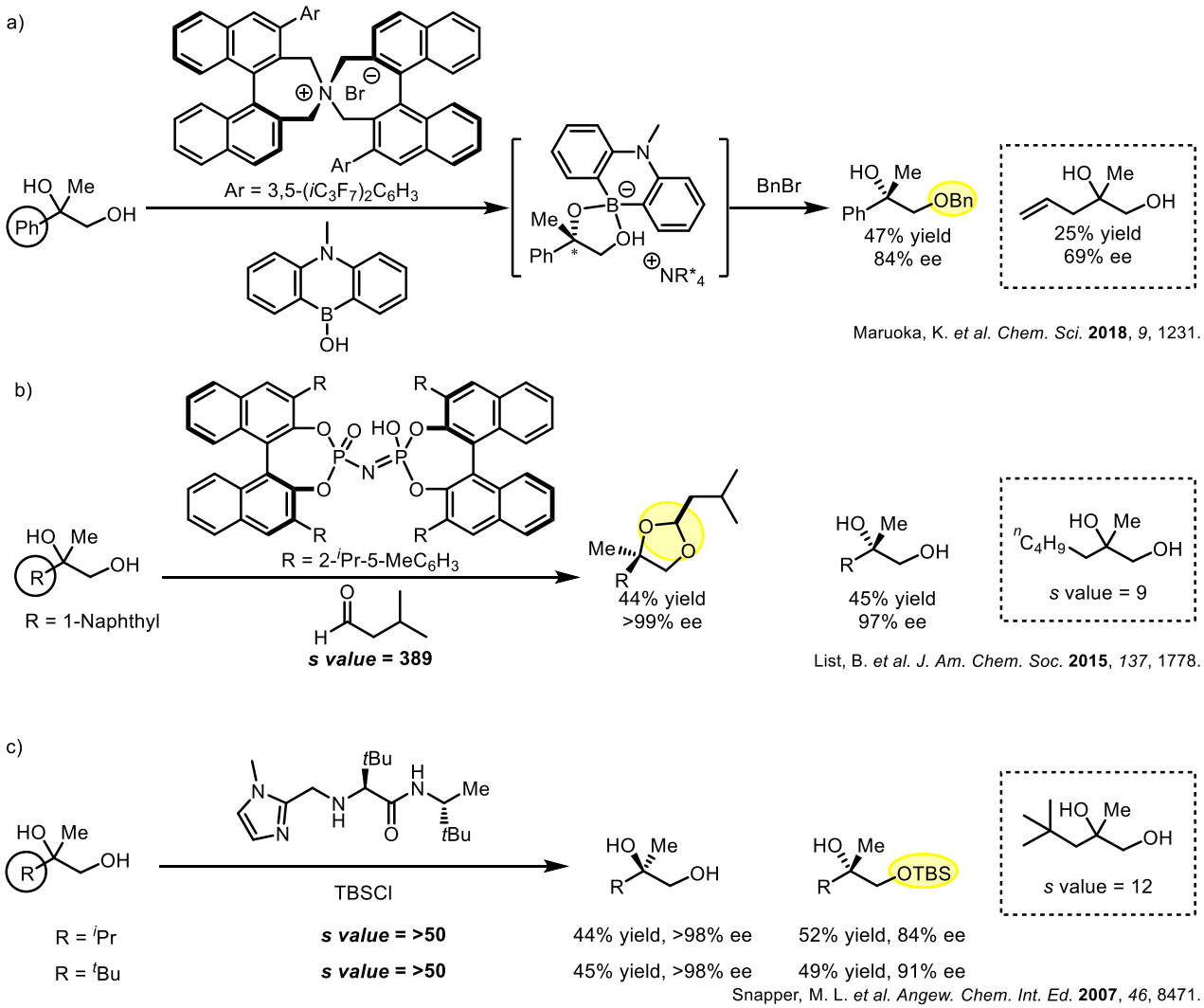
即ち上記課題の解決には、立体障害による識別に加え、触媒による基質の精密分子認識が必要となる。Smith らは触媒とアシル化剤が反応することで生じるキラルイソチオウレニウムカチオンとオキシインドールのカルボニル酸素との相互作用を基盤とする 3-ヒドロキシオキシインドールの高効率な KR を報告している (Scheme 5-2)[30a]。しかし、本法の鎖状化合物への適用例は報告されていない。



Smith, A. D. *et al. Angew. Chem. Int. Ed.* **2018,** *57,* 3200.

Scheme 5-2. Kinetic resolution of *tert*-alcohol by isothiourea catalyst

より多様な基質への展開として、反応性の低い第三級水酸基を反応点として利用するのではなく、近傍に反応性の高い第一級水酸基を反応点として配置した 1,n-ジオールの KR[31] が考案され、これまでに数例の報告が存在する。1,2-ジオールを基質とした場合、アシル化による例は存在しない一方で、アルキル化やシリル化、5 員環アセタール形成を基盤とする触媒的 KR が報告されている (Scheme 5-3)[32]。しかし、



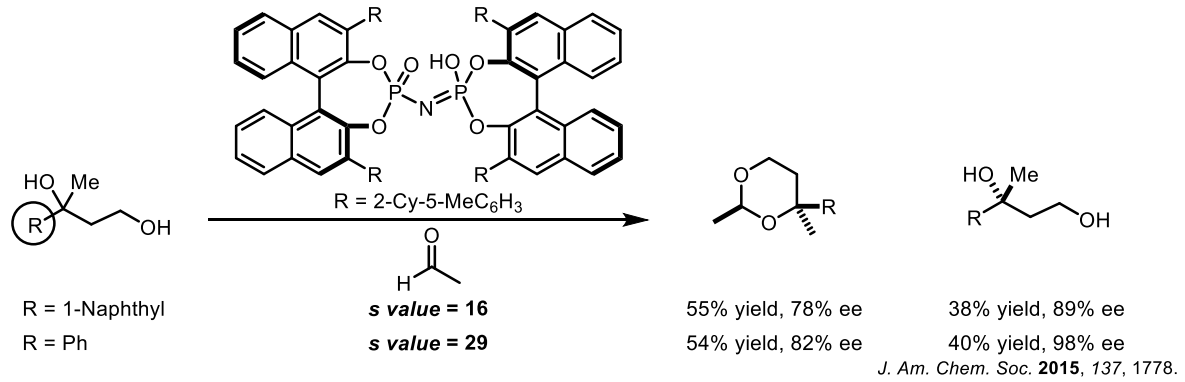
Maruoka, K. *et al. Chem. Sci.* **2018**, *9*, 1231.

List, B. *et al. J. Am. Chem. Soc.* **2015**, *137*, 1778.

Snapper, M. L. *et al. Angew. Chem. Int. Ed.* **2007**, *46*, 8471.

Scheme 5-3. Kinetic resolution of 1,2-diols with a tertiary hydroxy group

不斉炭素と反応点がより離れた 1,3-ジオールを基質とする KR では 6 員環アセタール形成による触媒的 KR が二種類の基質で報告されているのみであり、選択性に関しても改善の余地を残している (Scheme 5-4)。これは Fig. 5-1 に示すように、1,2-ジオールにおいては反応点と不斉炭素がメチレン基で隔てられている一方、1,3-ジオールにおいては反応点と不斉炭素がエチレン基で隔てられているため、不斉点近傍に明確な立体障害の違いが存在しても触媒による不斉識別が困難であるためと推察される。



J. Am. Chem. Soc. **2015**, *137*, 1778.

Scheme 5-4. Kinetic resolution of 1,3-diols with a tertiary hydroxy group

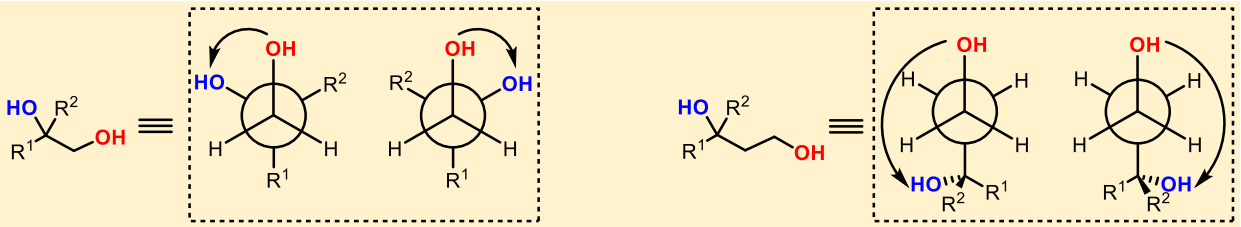
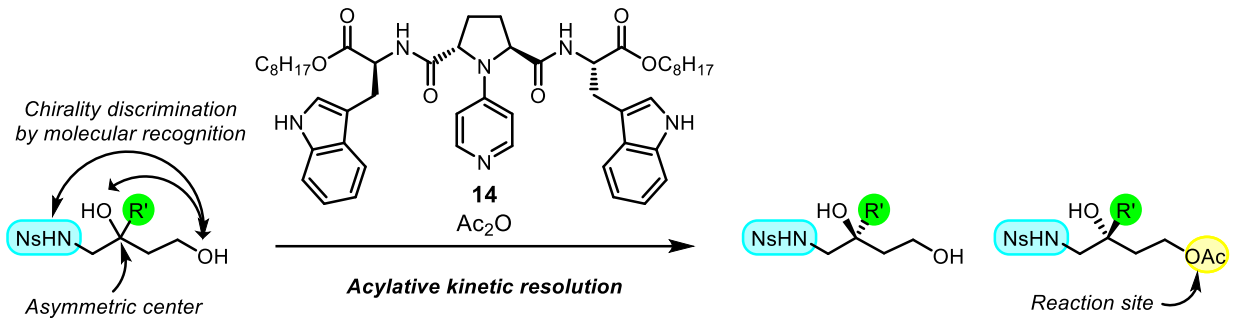


Fig. 5-1. Schematic presentation for discrimination of 1,2- and 1,3-diols

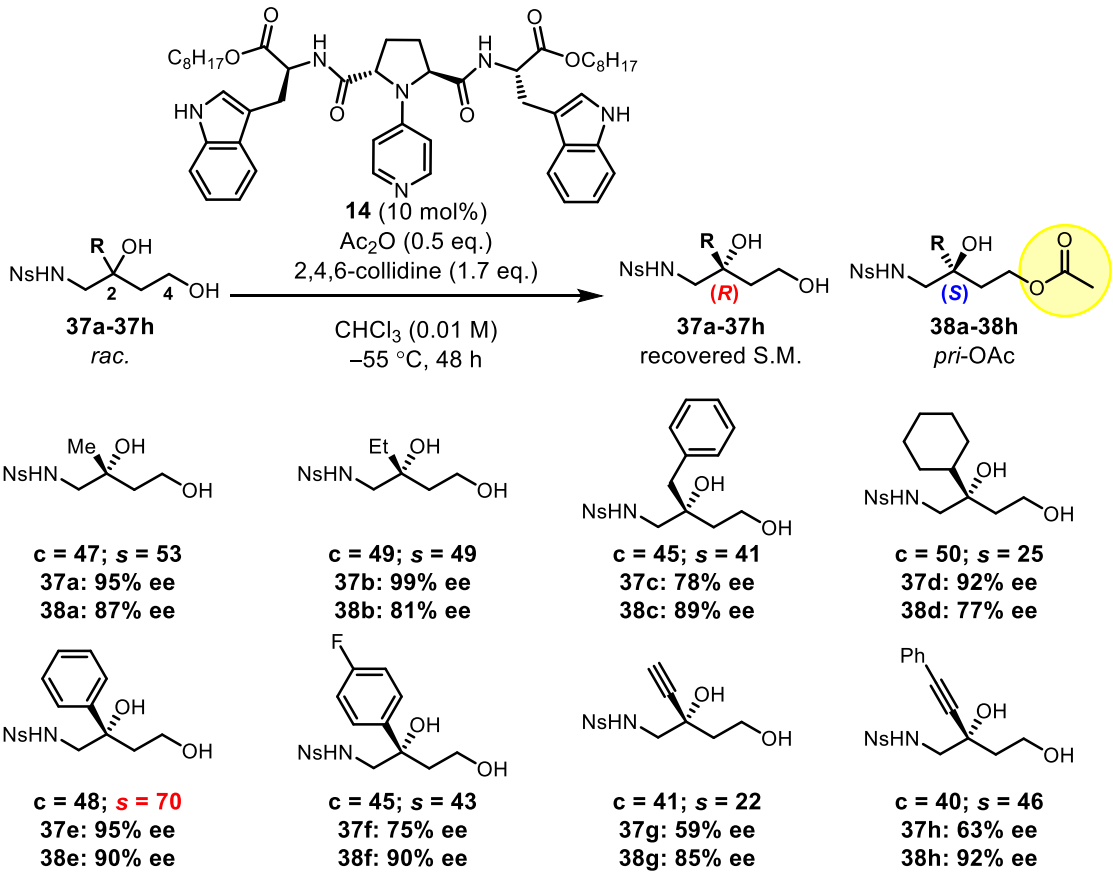
本章では、第四章で見出した PKR の知見に基づき、水酸基及び NHNs 基の分子認識を基盤とすれば、鎖状 1,3-ジオールのアシル化による触媒的 KR が可能と考えた (Scheme 5-5)。官能基間距離を利用することで、不斉炭素上置換基の大きさに寄らず同様の分子認識を経たアシル化が進行すれば、多様な基質に対して第三級アルコールの KR が可能と期待した。



Scheme 5-5. Kinetic resolution of *tert*-alcohols by acylation of a primary hydroxy group

第二節　基質一般性の検討

第 4 章において用いた基質 **23** の 2 位に炭素官能基を導入することで新たに第三級水酸基を構築し、第一級水酸基と第三級水酸基の 2 つの反応点を有する基質 **37a–37h** を合成した。得られた **37a–37h** に対し、触媒 **14** 存在下無水酢酸を 0.5 当量用いて KR の検討を行った (Scheme 5-6)。炭素官能基として第三級水酸基の隣接不斉炭素に sp^3 炭素を導入した **37a-37d** を検討した。メチル基を導入した **37a** では回収原料 **37a** が 95% ee、第一級水酸基アシル化体 **38a** が 87% ee で得られ、*s* 値は 53 であった。またエチル基を導入した **37b** では回収原料 **37b** が 99% ee で、第一級水酸基アシル化体 **38b** が 81% ee で得られ、*s* 値は 49 であった。特に **37b** を基質とした場合、隣接不斉炭素の置換基がすべてメチレン炭素を有するためその不斉識別は困難であることが予想されるが効率的な KR が進行した。ベンジル基を導入した **37c** を用いた場合、回収原料 **37c** が 78% ee で、第一級水酸基アシル化体 **38c** が 89% ee で得られ、*s* 値は 41 であり、**37b** と同様にすべての置換基がメチレンで置換されているにも関わらず高効率な KR が進行した。シクロヘキシル基を導入した **37d** では回収原料 **37d** が 92% ee、第一級水酸基アシル化体 **38d** が 77% ee で得られ、*s* 値は 25 であった。



Scheme 5-6. Kinetic resolution of tertiary hydroxy group

次に第三級水酸基の隣接不斉炭素に sp^2 炭素として芳香環を導入した **37e** 及び **37f** を検討した。フェニル基を導入した **37e** では回収原料 **37e** が 95% ee、第一級水酸基アシル化体 **38e** が 90% ee で得られ、これまでで最高の *s* 値 70 で KR が進行した。同様に *para*-フルオロフェニル基を導入した **37f** においても高効率な KR が進行し、回収原料 **37f** が 75% ee、第一級水酸基アシル化体 **38f** が 90% ee で得られ、*s* 値は 43

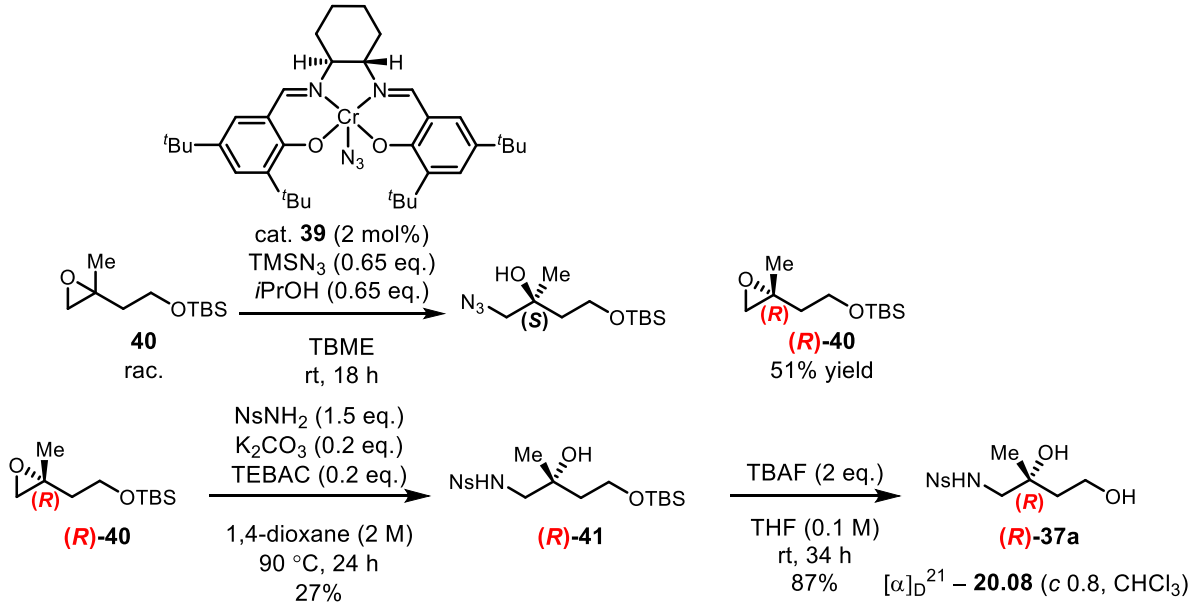
であった。

最後に第三級水酸基の隣接不斉炭素に sp 炭素を導入した **37g** 及び **37h** を検討した。エチニル基を導入した **37g** では回収原料 **37g** が 59% ee、第一級水酸基アシル化体 **38g** が 85% ee で得られ、*s* 値は 22 であった。フェニルエチニル基を導入した **37h** では回収原料 **37h** が 63% ee、第一級水酸基アシル化体 **38h** が 92% ee で得られ、*s* 値は 46 であった。

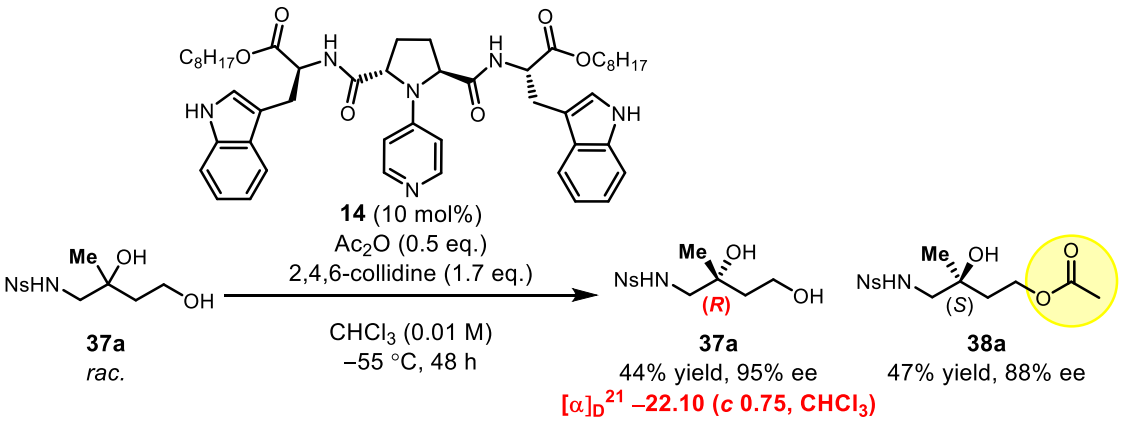
以上のように触媒 **14** は第三級水酸基に置換する官能基間に明確な立体障害の差がない場合や不斉点である第三級水酸基の近傍に嵩高い置換基を導入した場合においても高効率な光学分割を可能にした。このように本触媒は水酸基の官能基間距離や水酸基と NHNs 基が形成する不斉空間を精密に識別することにより立体環境の異なる種々の第三級アルコールの高効率な KR を可能にしたものと考えられる。

第三節　絶対配置の決定

第二節で検討した KR における回収原料の絶対配置を決定する目的で *s* 値 53 で KR が進行した、メチル基が置換した基質 **37a** の不斉合成を行った (Scheme 5-7)。Jacobsen らによって報告された Cr-salen 錯体 **39**[33a] を触媒とするエポキシドの開環による KR[33b] を用いて、エポキシド(*R*)-**40** を回収した。続いて、*ortho*-ノシルアミドによる求核的なエポキシドの開環と TBS 基の脱保護により(*R*)-**37a** を得た。この比旋光度を測定したところ$[\alpha]_D^{21}$ –20.08 であった。Scheme 5-8 に示す触媒 **14** を用いる KR の回収原料の比旋光度を測定すると$[\alpha]_D^{21}$ –22.10 であり、符号が一致したため回収原料は *R* 体、生成物は *S* 体と決定した。



Scheme 5-7. Preparation of (*R*)–**37a**

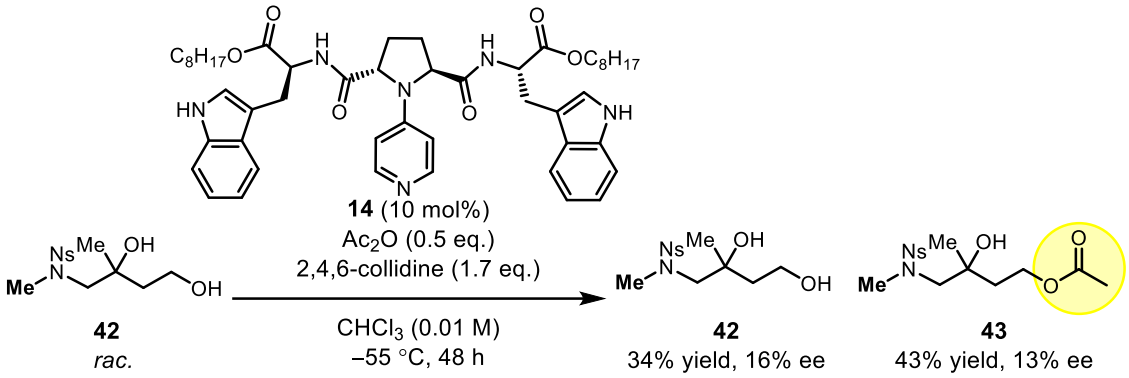


Scheme 5-8. Determination of absolute configuration of **37a**

尚、絶対配置を確認するために Scheme 5-7 で利用したエポキシドの開環を伴う KR はメチル基の代わりに、エチル基やイソプロピル基などを導入した場合は反応が進行しないことが報告されている[33b]、一方、本法では多様な置換基を持つ基質に適用可能なため、これらの点からも本手法の有用性を示している。尚、すべての場合で *S* 体の基質が *R* 体の基質に優先してアシル化されていることから *R* 体の基質では第一級水酸基の反応性が落ちていると考えられる。

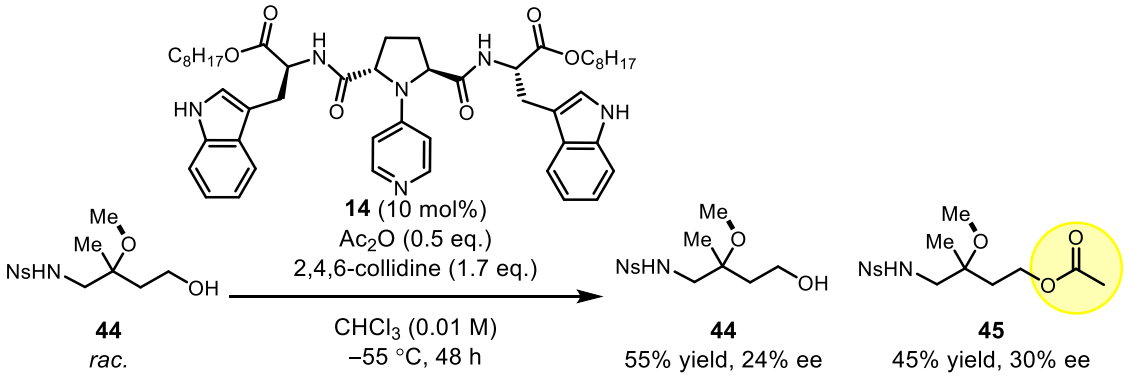
第四節　反応機構解析

第四章での PKR と同様、NHNs 基の酸性プロトンが選択性に関わっているかを確認すべく、NH プロトンをメチル保護した基質 **42** を用いてアシル化の検討を行った (Scheme 5-9)。その結果、回収原料 **42** は 34% 収率、16% ee で、第一級水酸基アシル化体 **43** は 43%収率、13% ee で得られた。このように NH 無保護体と比べ、エナンチオ選択性が劇的に低下したことから、触媒による分子認識には NHNs 基の酸性プロトンが必要不可欠であることが推測された。



Scheme 5-9. Effects of acidic proton of NHNs group on the reaction path of **42**

次に第三級水酸基がエナンチオ選択性発現に関わっているかを確認すべく、第三級水酸基をメチルエーテル化した基質を用いてアシル化の検討を行った。その結果、回収原料 **44** は 55% 収率、45% ee で、第一級水酸基アシル化体 **45** は 45%収率、30% ee で得られた。このように第三級水酸基無保護体と比べ、エナンチオ選択性が低下したことから第三級水酸基も触媒による分子認識に関与していることが分かった。即ち、触媒 **14** は NHNs 基及び第三級水酸基の双方の官能基を識別することで第三級アルコールの KR を進行させることが分かった。



Scheme 5-10. Effect of tertiary hydroxyl group on the reaction path of **44**

今回開発した PKR 及び KR において得られる第一級水酸基アシル化体の絶対配置はいずれも *S* であった。このことから、触媒 **14** は NHNs 基及び *S* のキラリティを有する不斉炭素上水酸基を水素結合によって認識し、第一級水酸基のアシル化を進行させることで、PKR や KR を可能にしていると考えられる。PKR の反応機構解析を行った Table 4-3 の結果が示すように、キラル 1,3-ジオール構造の識別は *R* 体の第

二級水酸基アシル化が最も早い反応であったが、立体保護により反応点が第一級水酸基のみとなる場合には、動的分子認識により第三級水酸基の内 *S* 体のキラリティを有する基質のアシル化が Fig. 4-4b と同様の分子認識を経ることで進行すると推測される。尚、*S* 体と *R* 体間での速度差は三級水酸基と NHNs 基が水素結合により配座固定を受けている基質のアシル化に対する遷移状態を考えた場合、*S* 体の第三級アルコールは置換基 R が立体障害とならない向きに配向する一方 (Fig5-2 a)、*R* 体の第三級アルコールは触媒の主骨格との立体反発を生じる (Fig5-2 b) ことに起因するものと推察される。

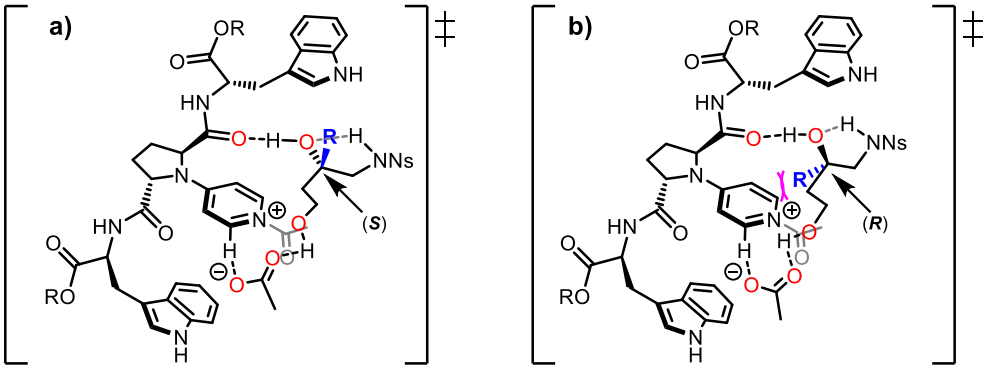


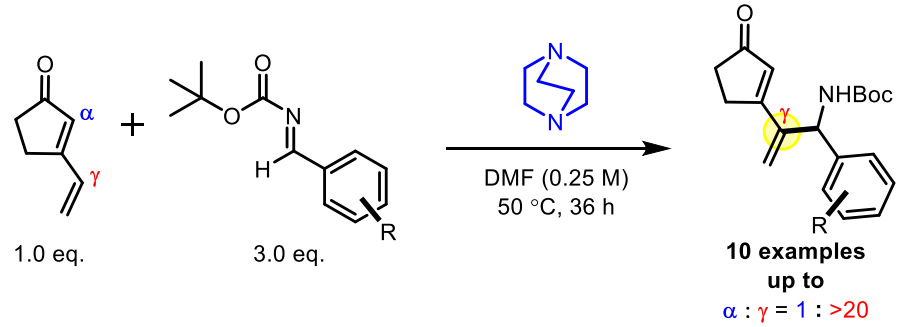
Fig. 5-2. Possible transition state structure for acylation of primary alcohol
a) acylation of (*S*)-^{tert}alcohol, b) acylation of (*R*)-^{tert}alcohol

第六章　結語及び要約

著者は求核触媒を基盤とする化学により、C-C 結合形成反応及び C-O 結合形成に関する有機合成化学における未解決課題に取り組んだ。C-C 結合形成反応においてはこれまでに開発されたジエノン γ 位選択的 vinylogous aza-MBH 反応においてプロトン移動に注目した基質設計により γ 位選択性の向上に挑んだ。また、vinylogous aza-MBH 反応の不斉触媒化では基質特異的に高エナンチオ選択的に γ 位付加体を与える手法を見出した。C-O 結合形成においてはジオールや NHNs 基を基軸とした触媒による分子認識機構を活用することで、稀有な光学分割法である PKR 及び第三級水酸基の KR に挑んだ。以下に本研究の成果を要約する。

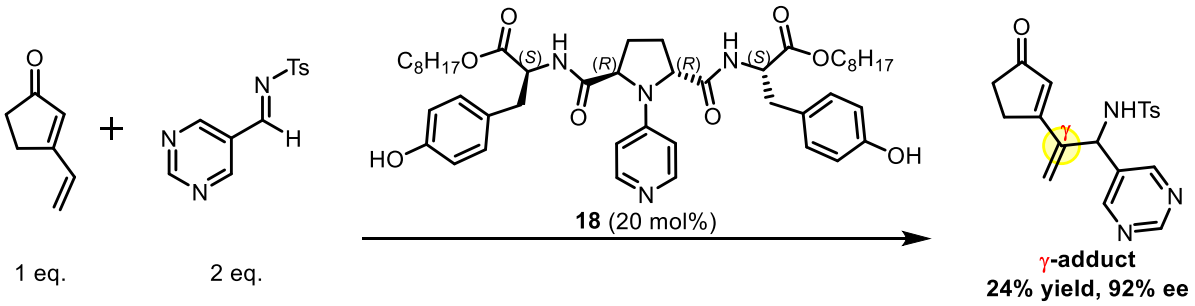
1. *N*-カルバモイルイミンを用いる位置選択的 vinylogous aza-Morita-Baylis-Hillman 反応

Aza-MBH 反応においてアルコールの添加によるプロトン移動の加速に関する報告に基づき、分子内にプロトン移動に関与可能なカーバメート構造を有する *N*-Boc イミンを用いることで、高 γ 位選択的 vinylogous *aza*-MBH 反応を開発した。



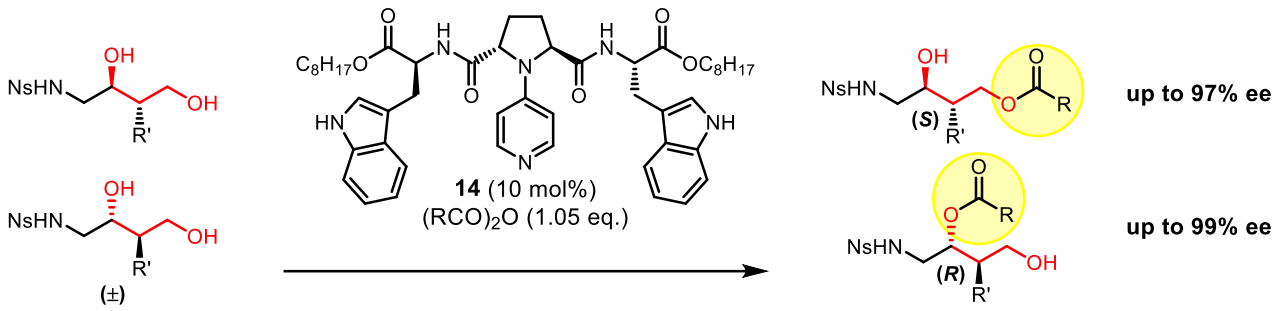
2. 位置およびエナンチオ選択的 vinylogous aza-Morita-Baylis-Hillman 反応

ジエノン γ 位での不斉発現に有効な触媒スクリーニング及び基質検討を行うことで、高エナンチオ選択的且つ γ 位選択的 vinylogous aza-MBH 反応を開発した。



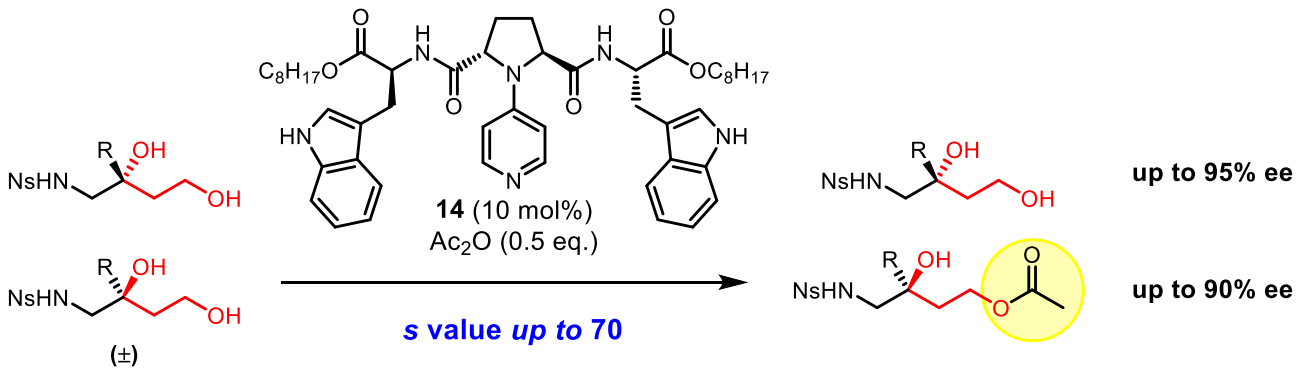
3. アミノジオール類に対する Parallel Kinetic Resolution (PKR) の開発

1,3-ジオール構造と 1,4-アミノアルコール構造を有するラセミ体ジオールの単一触媒を用いるアシル化による PKR を世界で初めて達成した。



4. 第三級アルコールの速度論的光学分割法の開発

立体的要因が異なる種々の置換基を持つ第三級アルコールの高選択的な KR を分子内に存在する第一級水酸基の触媒的アシル化により達成した。



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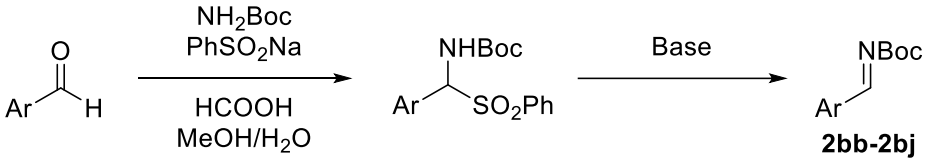
実験の部

実験及び測定に関する一般事項

All reactions were carried out under a argon atmosphere with magnetic stirring. Flash column chromatography was performed by silica gel 60N (spherical, neutral, KANTO) or Aluminum oxide (activated, basic, Brockmann I). Purification of reaction products was carried out by preparative thin layer chromatography on precoated plates (0.5 mm, silica gel Merck Kieselgel 60F245) and visualized with UV light. Analytical thin layer chromatography was performed on precoated plates (0.25 mm, silica gel Merck Kieselgel 60F245). Visualization was accomplished with UV light and p-anisaldehyde or $KMnO_4$ stain. IR spectra were recorded with a JASCO FT/IR-300 spectrometer. High resolution mass spectra were obtained by Bruker Impact HD mass spectrometers. 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). ^1H NMR spectra were recorded in $CDCl_3$ solution and referenced from TMS (0.00 ppm) using JEOL ECX-400 (400 MHz) spectrophotometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). ^{13}C NMR were measured in $CDCl_3$ solution and referenced to $CDCl_3$ (77.16 ppm) using JEOL ECX-400 (101 MHz) spectrophotometer. Data are reported as (ABq = AB quartet, s = singlet, d = doublet, t = triplet, td = triple doublet, tt = triple triplet, q = quartet, hep = heptet, dd = double doublet, dt = double triplet, ddd = double double doublet, m = multiplet, b = broad; integration; coupling constant(s) in Hz. Anhydrous methanol, dichloromethane, acetonitrile, tetahydrofuran were purchased from commercial suppliers and used without further treatment. Anhydrous $CHCl_3$, *N,N*-dimethylformamide, *N,N*-dimethylacetoamide and dimethylsulfoxide were purchased from commercial suppliers and kept with MS4A.

Preparation of Imines

1) *N*-Boc Imines



Following the previously reported method, *N*-Boc Imine was synthesized. Data for imines **2a** (Ar = Ph),[1] **2b** (Ar = 4-ClC_6H_4),[1] **2c** (Ar = 4-BrC_6H_4),[1] **2d** (Ar = 4-$CF_3C_6H_4$),[1] **2e** (Ar = 4-MeC_6H_4),[2] **2f** (Ar = 4-$OMeC_6H_4$),[3] **2g** (Ar = 3-ClC_6H_4),[2] **2h** (Ar = 2-MeC_6H_4),[1] **2i** (Ar = 3-Pyridyl)[4] and **2j** (Ar = 2-Naphthyl)[4] were in accordance with the literature.

2) *N*-Cbz Imine

Following the previously reported method, *N*-Cbz Imine (**6a**) was synthesized. Data was in accordance with the literature.[5]

3) *N*-Dpp Imine

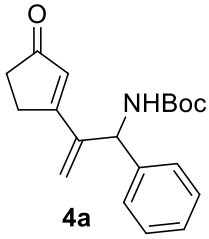
Following the previously reported method, *N*-Dpp (**7a**) Imine was synthesized. Data was in accordance with the literature.[6]

General Procedure for vinylogous *aza* Morita-Baylis-Hillman reactions:

DABCO (0.06 mmol, 1.0 eq) was added one portion to a solution of Diene (0.06 mmol, 1.0 eq) and Imine (0.18 mmol 3.0 eq) in anhydrous DMF (0.24 ml) at room temperature under Ar atmosphere and the resulting mixture was allowed to warm to 50 ℃. After stirred for 36 h, the reaction mixture was partitioned between ethyl acetate and 1N HCl. The layers were separated, and the water phase was extracted with ethyl acetate for three times. The combined organic layer was dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by preparative thin-layer chromatography to afford the γ adduct.

***tert*-Butyl (2-(3-oxocyclopent-1-en-1-yl)-1-phenylallyl)carbamate (4a)**

Prepared according to the general procedure. After preparative thin layer chromatography (silica gel, hexane/ethyl acetate = 2/1) to give **4a** as colorless oil: 8.02 mg, 46% yield.



4a

IR (neat) 3328, 2978, 2929, 1701, 1681, 1516, 1366, 1246, 1168, 866 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.24 (m, 5H), 5.98 (s, 1H), 5.90 (s, 1H), 5.66 (s, 1H), 5.61 (d, *J* = 7.6 Hz, 1H), 4.95–4.87 (brd, *J* = 5.9 Hz, 1H), 2.92–2.73 (m, 2H), 2.46–2.32 (m, 2H), 1.44 (s, 9H).

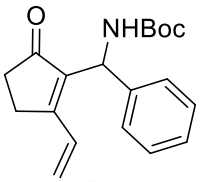
^{13}C NMR (101 MHz, $CDCl_3$) δ 209.75, 170.79, 154.74, 143.97, 139.49, 129.79, 129.20, 128.35,

127.53, 119.49, 80.32, 57.04, 34.54, 28.57, 28.47.

HRMS (ESI): Exact mass calcd for $C_{19}H_{23}NO_3Na$ [M+Na]+, 336.1570. Found 336.1540.

***tert*-Butyl ((5-oxo-2-vinylcyclopent-1-en-1-yl)(phenyl)methyl)carbamate (3a)**

Prepared according to the general procedure. After preparative thin layer chromatography (silica gel, hexane/Acetone = 2/1) to give **3a** as white amorphous powder.



3a

IR (neat) 3418, 2977, 2925, 1710, 1686, 1496, 1360, 1168, 703 cm^{-1}.

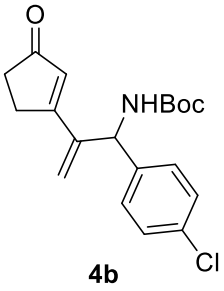
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.27 (m, 4H), 7.24–7.11 (m, 2H), 6.61 (d, *J* = 9.5 Hz, 1H), 5.93–5.82 (m, 2H), 5.66 (dd, *J* = 10.7, 1.0 Hz, 1H), 2.74 (t, *J* = 5.0 Hz, 2H), 2.54–2.35 (m, 2H), 1.43 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.92, 164.97, 155.56, 141.07, 138.76, 130.51, 128.72, 127.40, 126.42, 123.80, 79.71, 50.20, 34.31, 28.55, 25.42.

HRMS (ESI): Exact mass calcd for $C_{19}H_{23}NO_3Na$ [M+Na]+, 336.1570. Found 336.1550.

***tert*-Butyl (1-(3-chlorophenyl)-2-(3-oxocyclopent-1-en-1-yl)allyl)carbamate (4b)**

Prepared according to the general procedure. After preparative thin layer chromatography (silica gel, hexane/ethyl acetate = 2/1) to give **4b** as yellow amorphous powder: 11.91 mg, 57% yield.



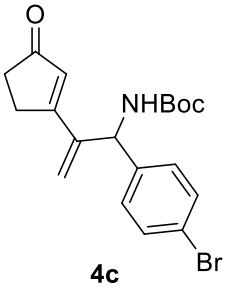
4b

IR (neat) 3323, 2978, 1702, 1575, 1492, 1366, 1248, 1167, 888, 732 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.5 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 5.97 (s, 1H), 5.89 (s, 1H), 5.60 (brs, 2H), 4.89 (brs, 1H), 2.92–2.72 (m, 2H), 2.41 (t, *J* = 5.1 Hz, 2H), 1.44 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.52, 170.44, 154.69, 143.81, 138.16, 134.19, 129.84, 129.35, 128.84, 120.13, 80.58, 56.35, 34.55, 28.56, 28.46. **HRMS** (ESI): Exact mass calcd for $C_{19}H_{22}NO_3ClNa$ [M+Na]+, 370.1180. Found 370.1182.

***tert*-Butyl (1-(4-bromophenyl)-2-(3-oxocyclopent-1-en-1-yl)allyl)carbamate (4c)**

Prepared according to the general procedure. After preparative thin layer chromatography (silica gel, hexane/ethyl acetate = 2/1) to give **4c** as yellow oil: 12.70 mg, 54% yield.



4c

IR (neat) 3327, 2977, 1701, 1575, 1489, 1366, 1247, 1166, 1012, 755 cm^{-1}.

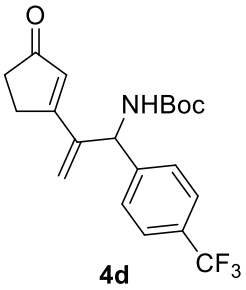
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.3 Hz, 2H), 7.15 (d, *J* = 8.3 Hz, 2H), 5.97 (s, 1H), 5.89 (s, 1H), 5.59 (brs, 2H), 4.89 (brs, 1H), 2.92–2.71 (m, 2H), 2.41 (t, *J* = 5.1 Hz, 2H), 1.44 (s. 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.51, 170.42, 154.68, 143.74, 138.70, 132.31, 129.85, 129.16, 122.30, 120.19, 80.59, 56.41, 34.55, 28.55, 28.46. **HRMS** (ESI): Exact mass calcd for

$C_{19}H_{22}NO_3BrNa$ [M+Na]+, 414.0765. Found 416.0655.

***tert*-Butyl (2-(3-oxocyclopent-1-en-1-yl)-1-(4-(trifluoromethyl)phenyl)allyl)carbamate (4d)**

Prepared according to the general procedure. After preparative thin layer chromatography (silica gel, hexane/ethyl acetate = 2/1) to give **4d** as yellow amorphous powder: 11.06 mg, 48% yield.



4d

IR (neat) 3319, 2979, 2933, 1704, 1575, 1515, 1326, 1166, 1125, 1067 cm^{-1}.

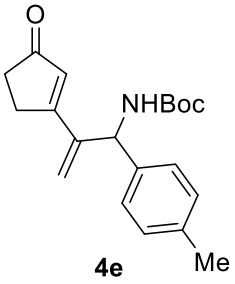
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.2 Hz , 2H), 5.99 (s, 1H), 5.92 (s, 1H), 5.71 (brd, J = 7.8 Hz, 1H), 5.56 (s, 1H), 4.94 (brd, *J* = 7.9 Hz, 1H), 2.93–2.73 (m, 2H), 2.43 (t, *J* = 5.1 Hz, 2H), 1.44 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.43, 170.24, 154.71, 143.71, 130.67, 130.35, 129.87, 127.76, 126.19, 126.15, 126.12, 125.36, 122.65, 120.83, 80.75, 56.53, 34.57, 28.52, 28.44.

HRMS (ESI): Exact mass calcd for $C_{20}H_{22}NO_3F_3Na$ [M+Na]+, 404.1444. Found 404.1439.

***tert*-Butyl (2-(3-oxocyclopent-1-en-1-yl)-1-(p-tolyl)allyl)carbamate (4e)**

Prepared according to the general procedure. After preparative thin layer chromatography (silica gel, hexane/ethyl acetate = 2/1) to give **4e** as white solid: 9.64 mg, 49% yield.



4e

IR (KBr) 3332, 2975, 2927, 1681, 1574, 1510, 1367, 1241, 1166, 890 cm^{-1}.

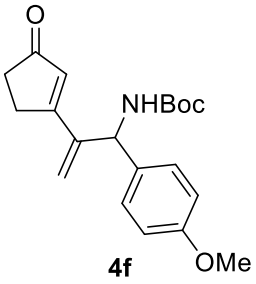
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.09 (m, 4H), 5.98 (s, 1H), 5.88 (s, 1H), 5.67 (s, 1H), 5.55 (brd, *J* = 7.4 Hz, 1H), 4.89 (brd, *J* = 7.4 Hz, 1H), 2.92–2.71 (m, 2H), 2.41–2.35 (m, 2H), 2.32 (s, 1H), 1.44 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.81, 170.90, 154.74, 144.08, 138.17, 136.51, 129.87, 129.78, 127.45, 119.14, 80.22, 56.79, 34.53, 28.58, 28.48, 21.21.

HRMS (ESI): Exact mass calcd for $C_{20}H_{25}NO_3Na$ [M+Na]+, 350.1727. Found 350.1743.

***tert*-Butyl (1-(4-methoxyphenyl)-2-(3-oxocyclopent-1-en-1-yl)allyl)carbamate (4f)**

Prepared according to the general procedure. After preparative thin layer chromatography (silica gel, hexane/ethyl acetate = 2/1) to give **4f** as yellow oil: 10.16 mg, 49% yield.



4f

IR (neat) 3332, 2975, 2930, 1704, 1679, 1511, 1248, 1169, 1032, 732 cm^{-1}.

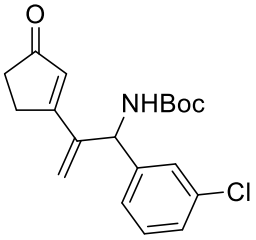
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 8.3 Hz, 2H), 5.97 (s, 1H), 5.88 (s, 1H), 5.67 (s, 1H), 5.54 (d, *J* = 7.3 Hz, 1H), 4.87 (brs, 1H), 3.79 (s, 3H), 2.92–2.71 (m, 3H), 2.38 (s, 2H), 1.44 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.82, 170.93, 159.56, 154.72, 144.16, 131.50, 129.80, 128.78, 118.99, 114.55, 80.25, 56.49, 55.46, 34.54, 28.60, 28.49.

HRMS (ESI): Exact mass calcd for $C_{20}H_{25}NO_4Na$ [M+Na]+, 366.1676. Found 366.1675.

***tert*-Butyl (1-(3-chlorophenyl)-2-(3-oxocyclopent-1-en-1-yl)allyl)carbamate (4g)**

Prepared according to the general procedure. After preparative thin layer chromatography (silica gel, hexane/ethyl acetate = 2/1) to give **4g** as yellow oil: 12.50 mg, 60% yield.



4g

IR (neat) 3329, 2978, 2929, 1704, 1681, 1574, 1516, 1367, 1247, 1167, 756 cm^{-1}.

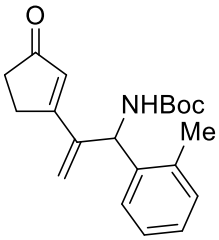
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.26 (m, 2H), 7.23–7.14 (m, 2H), 5.98 (s, 1H), 5.91 (s, 1H), 5.61 (brs, 2H), 4.91 (brd, *J* = 7.4 Hz, 1H), 2.93–2.73 (m, 2H), 2.42 (t, *J* = 5.0 Hz, 2H), 1.44 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.56, 170.37, 154.66, 143.56, 141.69, 135.08, 130.48, 129.81, 128.53, 127.43, 125.82, 120.38, 80.62, 56.52, 34.56, 28.54, 28.45.

HRMS (ESI): Exact mass calcd for $C_{19}H_{22}NO_3ClNa$ [M+Na]+, 370.1180. Found 370.1202.

***tert*-Butyl (2-(3-oxocyclopent-1-en-1-yl)-1-(o-tolyl)allyl)carbamate (4h)**

Prepared according to the general procedure. After preparative thin layer chromatography (silica gel, hexane/ethyl acetate = 2/1) to give **4h** as yellow amorphous powder: 7.74 mg, 39% yield.



4h

IR (neat) 3326, 2976, 1702, 1574, 1515, 1365, 1246, 1169, 756 cm^{-1}.

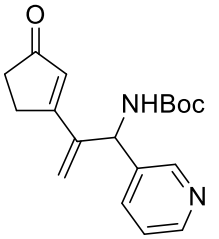
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.03 (m, 4H), 5.93 (s, 1H), 5.83 (s, 1H), 5.75 (d, *J* = 7.9 Hz, 1H), 5.62 (s, 1H), 4.76 (d, *J* = 7.9 Hz, 1H), 2.93–2.76 (m, 2H), 2.42–2.38 (m, 2H), 2.39 (s, 3H), 1.44 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.80, 171.06, 154.78, 144.01, 137.57, 136.66, 131.31, 129.53, 128.38, 126.55, 126.14, 119.66, 80.24, 53.39, 34.63, 28.50, 28.47, 19.20.

HRMS (ESI): Exact mass calcd for $C_{20}H_{25}NO_3Na$ [M+Na]+, 350.1727. Found 350.1701.

***tert*-Butyl (2-(3-oxocyclopent-1-en-1-yl)-1-(pyridin-3-yl)allyl)carbamate (4i)**

Prepared according to the general procedure. After preparative thin layer chromatography (silica gel, hexane/Acetone = 1/1) to give **4i** as colorless oil: 6.95 mg, 37% yield.



4i

IR (neat) 3312, 2978, 2929, 1703, 1575, 1522, 1366, 1250, 1167, 889, 717 cm^{-1}.

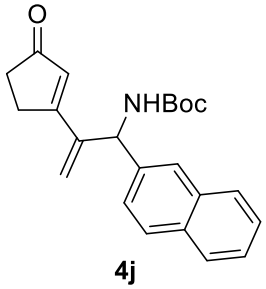
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 6.2 Hz, 2H), 7.60 (dt, *J* = 8.0, 2.2 Hz, 1H), 7.28 (dd, *J* = 7.8, 4.7 Hz, 1H), 5.98 (s, 1H), 5.93 (s, 1H), 5.70 (d, *J* = 7.8 Hz, 1H), 5.59 (s, 1H), 4.99 (brs, 1H), 2.93–2.74 (m, 2H), 2.50–2.39 (m, 2H), 1.44 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.36, 170.10, 154.69, 149.63, 149.07, 143.31, 135.27, 135.12, 129.90, 123.88, 120.80, 80.81, 54.85, 34.56, 28.52, 28.44.

HRMS (ESI): Exact mass calcd for $C_{18}H_{23}N_2O_3$ [M+H]+, 315.1703. Found 315.1700.

***tert*-Butyl (1-(naphthalen-2-yl)-2-(3-oxocyclopent-1-en-1-yl)allyl)carbamate (4j)**

Prepared according to the general procedure. After preparative thin layer chromatography (silica gel, hexane/ethyl acetate = 2/1) to give **4j** as yellow oil: 12.50 mg, 60% yield.



4j

IR (neat) 3328, 2976, 2928, 1703, 1681, 1574, 1511, 1366, 1248, 1166, 752 cm^{-1}.

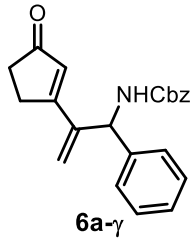
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.75 (m, 3H), 7.71 (d, *J* = 1.8 Hz, 1H), 7.54–7.43 (m, 2H), 7.38 (dd, *J* = 8.5, 1.9 Hz, 1H), 6.05 (s, 1H), 5.94 (s, 1H), 5.78 (d, *J* = 7.7 Hz, 1H), 5.70 (s, 1H), 5.01 (d, *J* = 6.8 Hz, 1H), 2.95–2.74 (m, 2H), 2.38 (dt, *J* = 6.5, 3.5 Hz, 2H), 1.45 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.67, 170.82, 154.78, 144.03, 136.92, 133.44, 133.13, 129.82, 129.15, 128.08, 127.82, 126.66, 126.55, 126.33, 125.40, 119.78, 80.39, 57.10, 34.55, 28.58, 28.48.

HRMS (ESI): Exact mass calcd for $C_{23}H_{25}NO_3Na$ [M+Na]+, 386.1727. Found 386.1730.

3-(3-amino-3-phenylprop-1-en-2-yl)cyclopent-2-en-1-one (6a-γ)

Prepared according to the general procedure. After preparative thin layer chromatography (silica gel, $CHCl_3$/MeOH = 40/1) to give **6a-γ** as colorless oil: 10.27 mg, 37% yield.



6a-γ

IR (neat) 3312, 1701, 1679, 1573, 1524, 1236, 1190, 1032, 734, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.27 (m, 9H), 7.25 (m, 1H), 5.98 (s, 1H), 5.90 (s, 1H), 5.72–5.66 (d, *J* = 7.5 Hz, 1H), 5.64 (s, 1H), 5.15 (d, *J* = 7.5 Hz, 1H), 5.12 (s, 2H), 2.91–2.72 (m, 2H), 2.46–2.31 (m, 2H).

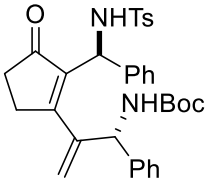
^{13}C NMR (101 MHz, $CDCl_3$) δ 209.66, 170.56, 155.29, 143.69, 139.12, 136.22, 129.91, 129.27, 128.72, 128.50, 128.44, 128.36, 127.44, 119.78, 67.33, 57.46, 34.53, 28.55.

HRMS (ESI): Exact mass calcd for $C_{22}H_{22}NO_3$ [M+H]+, 348.1594. Found 348.1593.

***tert*-Butyl (2-(2-(((4-methylphenyl)sulfonamido)(phenyl)methyl)-3-oxocyclopent-1-en-1-yl)-1-phenylallyl) carbamate (8a/8b)**

DMAP (0.059 mmol, 1.0 eq) was added one portion to a solution of **4a** (0.059 mmol, 1.0 eq), Schreiner's thiourea (0.059 mmol, 1.0 eq.) and Ts-Imine (**5a**) (0.12 mmol 2.0 eq) in anhydrous $CHCl_3$ (0.24 ml) at room temperature under Ar atmosphere and the resulting mixture was allowed to warm to 40 ℃. After stirred for 36 h, the reaction mixture was partitioned between ethyl acetate and 1N HCl. The layers were separated, and the water phase was

extracted with ethyl acetate for three times. The combined organic layer was dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by preparative thin-layer chromatography (silica gel, hexane/ethyl acetate = 3/1) to give **8a (major)** as colorless oil: 10.32 mg, 31% yield and **8b (minor)** as colorless oil: 6.70 mg, 19% yield. (Relative configuration has not been determined yet.)



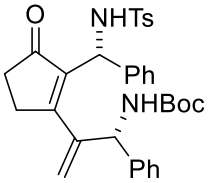
8a

IR (neat) 3362, 2978, 1692, 1496, 1335, 1161, 912, 732, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.28 (m, 3H), 7.24–7.13 (m, 7H), 7.11–7.04 (m, 2H), 6.48 (d, *J* = 10.3 Hz, 1H), 5.61 (t, *J* = 9.6 Hz, 2H), 5.50 (d, J = 8.6 Hz, 1H), 5.20 (s, 1H), 5.14 (s, 1H), 2.60 (dtd, *J* = 19.7, 17.2, 16.7, 6.6 Hz, 2H), 2.39 (s, 3H), 2.29 (ddd, *J* = 19.1, 6.5, 2.7 Hz, 1H), 2.13 (ddd, *J* = 19.1, 6.6, 2.8 Hz, 1H), 1.45 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.98, 172.06, 155.29, 145.48, 143.27, 139.14, 138.96, 138.86, 138.12, 129.49, 128.96, 128.70, 128.21, 127.77, 127.74, 127.28, 127.05, 118.52, 80.30, 57.01, 53.67, 34.35, 29.87, 28.43, 21.65.

HRMS (ESI): Exact mass calcd for $C_{33}H_{36}N_2O_5SNa$ [M+Na]+, 595.2237. Found 595.2245.



8b

IR (neat) 3355, 2978, 1691, 1495, 1336, 1162, 912, 733, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (m, 2H), 7.40 – 7.31 (m, 3H), 7.24 (m, 7H), 6.97 (d, *J* = 7.9 Hz, 2H), 6.56 (d, *J* = 10.2 Hz, 1H), 5.62 (d, *J* = 10.2 Hz, 1H), 5.45 (d, J = 7.9 Hz, 2H), 5.17 (s, 1H), 4.78 (d, *J* = 7.7 Hz, 1H), 2.61 (dd, *J* = 18.5, 7.1 Hz, 1H), 2.32 (m, 4H), 2.17 (ddd, *J* = 19.3, 7.3, 2.2 Hz, 1H), 1.81–1.70 (m, 1H), 1.41 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.08, 171.27, 154.70, 143.92, 142.84, 139.45, 138.37, 138.18, 137.94, 129.59, 129.13, 128.94, 128.87, 128.06 (2C), 127.56, 127.29, 119.26, 80.40, 57.02, 54.94, 34.15, 29.44, 28.43, 21.57.

HRMS (ESI): Exact mass calcd for $C_{33}H_{36}N_2O_5SNa$ [M+Na]+, 595.2237. Found 595.2251.

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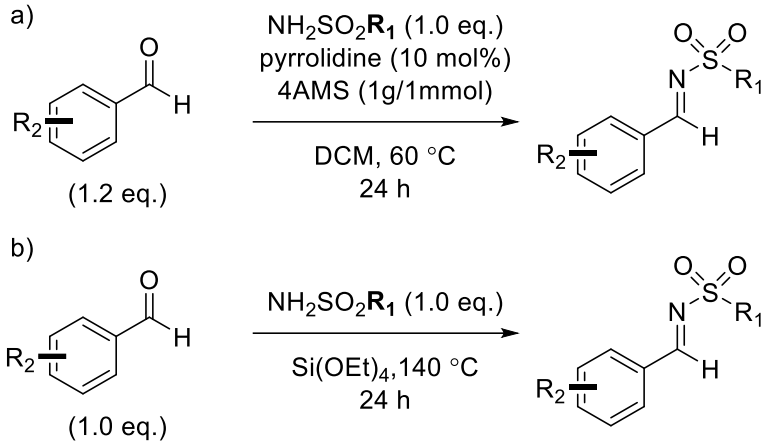
Preparation of Imines

N-Sulfonyl imines



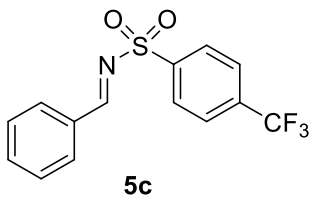
Procedure a)

Following the previously reported method [1].

$NH_2SO_2R_1$ (1 mmol) in a screw capped bial was added activated MS4A (1g), aldehyde (1.2 mmol, 1.2 eq.), pyrrolidine (6.22 μ L, 0.1 mmol, 10 mol%) and DCM (3.1 mL, 0.32 M). The bial was stirred at 60 ℃ for 24 h. The reaction mixture was cooled to rt and were filtered through a short pad of Celite®. The mixture was crystallized with hexane/ethyl acetate, and the resulting solid was collected by filtration and then dried in vacuum. Data for imines **5a** (R = Ph), [1] **5b** (R = 4-$OMeC_6H_4$), [1] **5f** (R = cyclopropyl),[3] **5g** (R = 2-pyridyl),[2] **5i** (R = 4-pyridyl)[4] were in accordance with the literature. Data for **5c** (R = 4-$CF_3C_6H_4$), **5j** (R^2=5-pyrimidyl), **5k** (R^2=2-methyl-5-pyrimidyl) was newly synthesized with procedure a) and characterized below.

***N*-benzylidene-4-(trifluoromethyl)benzenesulfonamide (5c)**

Prepared by the procedure a) (2 mmol scale) , **5c** was obtained 320 mg (51%) as white solid.



5c

IR (KBr) 1603, 1570, 1405, 1330, 1300, 1162, 1108, 809 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.16 (d, *J* = 8.12 Hz, 2H), 7.95 (d, *J* = 7.34 Hz, 2H), 7.83 (d, *J* = 8.12 Hz, 2H), 7.66 (t, *J* = 7.35Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 2H).

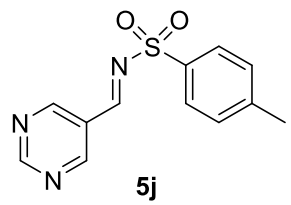
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.94, 142.04, 135.65, 135.21 (^2J (C, F) = 33.1 Hz), 132.13, 131.69, 129.39, 128.68, 126.39 (^3J (C, F) = 3.79 Hz), 123.25 (^1J (C, F) = 271 Hz).

HRMS (ESI): Exact mass calcd for $C_{14}H_{10}NSO_2F_3Na$ [M+Na]+, 336.0277. Found 336.0272.

m.p. 101–102 ℃

4-methyl-*N*-(pyrimidin-5-ylmethylene)benzenesulfonamide (5j)

Prepared by the procedure a) (1 mmol scale) , **5j** was obtained 170 mg (65%) as yellow solid.



5j

IR (KBr) 1614, 1578, 1553, 1408, 1323, 1163, 783, 683, 552 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (d, *J* = 2.2 Hz, 1H), 9.22 (d, *J* = 2.2 Hz, 2H), 9.09 (d, *J* = 2.1 Hz, 1H), 7.90 (dt, *J* = 8.7, 2.2 Hz, 2H), 7.39 (dd, *J* = 8.3, 2.1 Hz, 2H), 2.47 (s, 3H).

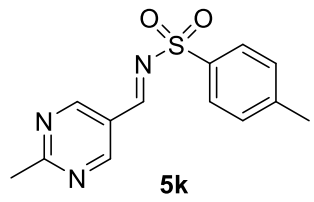
^{13}C NMR (101 MHz, $CDCl_3$) δ 164.99, 162.53, 158.77, 145.70, 133.93, 130.23, 128.60, 126.44, 21.89.

HRMS (ESI): Exact mass calcd for $C_{12}H_{11}N_3O_2SNa$ [M+Na]+, 284.0464. Found 284.0473.

m.p. 136–138 ℃

4-methyl-*N*-((2-methylpyrimidin-5-yl)methylene)benzenesulfonamide (**5k**)

Prepared by the procedure a) (2 mmol scale) , **5k** was obtained 230 mg (42%) as light orange solid.



5k

IR (KBr) 1594, 1547, 1447, 1322, 1159, 1089, 813, 769, 673 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 2H), 9.05 (s, 1H), 7.90 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 2.84 (s, 3H), 2.46 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.55, 165.29, 158.97, 145.47, 134.19, 130.15, 128.49, 123.48, 26.77, 21.87.

HRMS (ESI): Exact mass calcd for $C_{13}H_{14}N_3O_2S$ [M+H]+, 276.0801. Found 276.0801.

m.p. 127–128 ℃

Procedure b)

Following the previously reported method [2].

$NH_2SO_2R_1$ (10 mmol) in a two-neck flask was added aldehyde (10 mmol, 1.0 eq.), and tetraethoxysilane (2.35 mL, 10.5 mmol) was heated at 120 ℃ for 24 h. The reaction mixture was cooled to rt and crystallized with hexane/ethyl acetate. Data for imines **5d** (R = mesityl),[2] **5e** (R = Me),[2] **5h** (R^2 = 3-pyridyl)[2] were in accordance with the literature.

General Procedure for asymmetric vinylogous *aza* Morita-Baylis-Hillman reactions:

catalyst (0.01 mmol, 20 mol%) was added one portion to a solution of diene (0.05 mmol, 1.0 eq) and imine (1.0 mmol, 2.0 eq) in anhydrous $CHCl_3$ (0.25 ml) at 20 ℃ under Ar atmosphere and the resulting mixture was stirred for 7 days, the reaction mixture was directly charged on preparative thin-layer chromatography to afford the γ adduct.

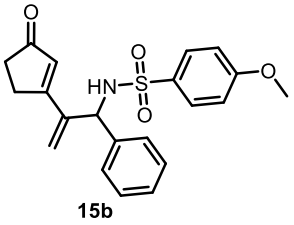
4-methyl-*N*-(2-(3-oxocyclopent-1-en-1-yl)-1-phenylallyl)benzenesulfonamide (**15a**)

The physical data of **15a** was previously reported.[5]

HPLC condition: (DAICEL CHIRALPAK AD-H, 2-propanol/hexane 2:8, flow 1.0 mL/min, 14.0 min (major),16.6 min (major).

4-methoxy-*N*-(2-(3-oxocyclopent-1-en-1-yl)-1-phenylallyl)benzenesulfonamide (15b)

Prepared according to the general procedure. After preparative thin layer chromatography (silica gel, hexane/ethyl acetate = 2/1) to give **15b** as yellowish oil: 7.10 mg, 37% yield.



15b

IR (neat) 3259, 1676, 1596, 1575, 1497, 1329, 1259, 1155, 558 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.9 Hz, 2H), 7.24–7.16 (m, 3H), 6.99–6.89 (m, 4H), 5.89 (s, 1H), 5.84 (d, *J* = 1.3 Hz, 1H), 5.81 (t, *J* = 1.6 Hz, 1H), 5.17 (d, *J* = 6.6 Hz, 1H), 4.92 (dd, *J* = 6.7, 1.6 Hz, 1H), 3.89 (s, 3H), 2.88–2.60 (m, 2H), 2.46–2.24 (m, 2H).

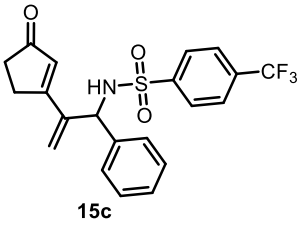
^{13}C NMR (101 MHz, $CDCl_3$) δ 209.54, 170.28, 163.21, 142.75, 138.43, 131.57, 129.61, 129.58, 129.29, 128.63, 127.17, 121.70, 114.36, 59.59, 55.84, 34.46, 28.55.

HRMS (ESI): Exact mass calcd for $C_{21}H_{21}NO_4SNa$ [M+Na]+, 406.1083. Found 406.1084.

HPLC condition: (DAICEL CHIRALPAK AD-H, 2-propanol/hexane 2:8, flow 1.0 mL/min, 20.6 min (major), 23.8 min (major).

***N*-(2-(3-oxocyclopent-1-en-1-yl)-1-phenylallyl)-4-(trifluoromethyl)benzenesulfonamide (15c)**

Prepared according to the general procedure. After preparative thin layer chromatography (silica gel, hexane/ethyl acetate = 2/1) to give **15c** as colorless oil: 6.80 mg, 32% yield.



15c

IR (neat) 3256, 1676, 1574, 1325, 1167, 1133, 1062, 734, 712 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.1 Hz, 2H), 7.68 (d, *J* = 8.1 Hz, 2H), 7.24–7.12 (m, 3H), 7.03–6.90 (m, 2H), 5.95 (t, *J* = 1.6 Hz, 1H), 5.86 (s, 1H), 5.67 (d, *J* = 1.3 Hz, 1H), 5.34 (d, *J* = 7.4 Hz, 1H), 5.18 (d, *J* = 7.4 Hz, 1H), 2.85–2.60 (m, 2H), 2.49–2.27 (m, 2H).

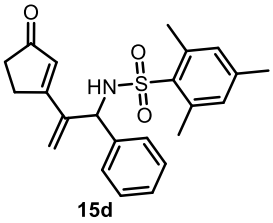
^{13}C NMR (101 MHz, $CDCl_3$) δ 209.43, 169.85, 143.92, 142.62, 137.62, 134.58 (^2J (C, F) = 33.1 Hz), 129.98, 129.29, 128.78, 127.80, 127.17, 126.27 (^3J (C, F) = 3.83 Hz), 123.02 (^1J (C, F) = 274 Hz), 121.66, 59.83, 34.46, 28.54.

HRMS (ESI): Exact mass calcd for $C_{21}H_{18}NO_3SF_3Na$ [M+Na]+, 444.0852. Found 444.0850.

HPLC condition: (DAICEL CHIRALPAK AD-H, 2-propanol/hexane 2:8, flow 1.0 mL/min, 19.3 min (major), 22.4 min (minor).

2,4,6-trimethyl-*N*-(2-(3-oxocyclopent-1-en-1-yl)-1-phenylallyl)benzenesulfonamide (15d)

Prepared according to the general procedure. After preparative thin layer chromatography (silica gel, hexane/ethyl acetate = 4/3) to give **15d** as yellowish oil: 8.90 mg, 45% yield.



15d

IR (neat) 3273, 1677, 1573, 1450, 1328, 1156, 755 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.16 (m, 3H), 6.98–6.91 (m, 4H), 5.87 (d, *J* = 6.4 Hz, 2H), 5.76 (s, 1H), 5.12 (d, *J* = 6.3 Hz, 1H), 4.86 (d, *J* = 6.4 Hz, 1H), 2.85–2.56 (m, 2H), 2.53–2.46 (m, 5H), 2.43–2.25 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.46, 170.23, 142.77, 142.69, 139.19, 138.44, 133.96, 132.18, 129.39, 129.27, 128.69, 127.04, 121.65, 59.54, 34.43, 28.52, 23.08, 21.12.

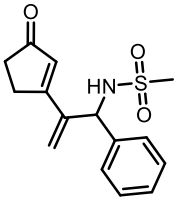
HRMS (ESI): Exact mass calcd for $C_{23}H_{25}NO_3SNa$ [M+Na]+, 418.1447. Found 418.1448.

HPLC condition: (DAICEL CHIRALPAK AD-H, 2-propanol/hexane 1:4, flow 1.0 mL/min, 8.9 min (major), 12.7 min (minor).

$[\alpha]_D^{21}$ +39.1 (*c* 0.8 in $CHCl_3$).

***N*-(2-(3-oxocyclopent-1-en-1-yl)-1-phenylallyl)methanesulfonamide (15e)**

Prepared according to the general procedure. After preparative thin layer chromatography (silica gel, $CHCl_3$/methanol = 35/1) to give **15e** as yellowish oil: 6.80 mg, 47% yield.



15e

IR (neat) 3263, 1676, 1574, 1452, 1321, 1192,1151, 980, 756 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.28 (m, 5H), 6.07 (d, *J* = 1.7 Hz, 1H), 5.97 (d, *J* = 1.4 Hz, 1H), 5.78 (d, *J* = 1.5 Hz, 1H), 5.48 (d, *J* = 7.4 Hz, 1H), 4.97 (t, *J* = 6.1 Hz, 1H), 2.93–2.70 (m, 5H), 2.40 (dtd, *J* = 6.0, 3.5, 2.8, 1.7 Hz, 2H).

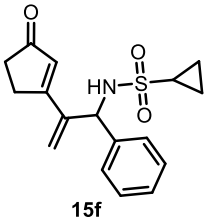
^{13}C NMR (101 MHz, $CDCl_3$) δ 209.44, 169.89, 143.51, 138.62, 130.16, 129.52, 128.90, 127.43, 121.04, 59.52, 42.16, 34.53, 28.62.

HRMS (ESI): Exact mass calcd for $C_{15}H_{17}NO_3SNa$ [M+Na]+, 314.0821. Found 314.0826.

HPLC condition: (DAICEL CHIRALPAK AD-H, 2-propanol/hexane 1:4, flow 1.0 mL/min, 10.7 min (major), 12.8 min (minor).

***N*-(2-(3-oxocyclopent-1-en-1-yl)-1-phenylallyl)cyclopropanesulfonamide (15f)**

Prepared according to the general procedure. After preparative thin layer chromatography (silica gel, $CHCl_3$/methanol = 35/1) to give **15f** as colorless oil: 6.70 mg, 42% yield.


15f

IR (neat) 3263, 1676, 1573, 1328, 1191, 1147, 756, 705 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.28 (m, 5H), 6.06 (t, *J* = 1.7 Hz, 1H), 5.97 (s, 1H), 5.83 (d, *J* = 1.3 Hz, 1H), 5.47 (d, *J* = 7.4 Hz, 1H), 4.83 (d, *J* = 7.4 Hz, 1H), 2.92–2.72 (m, 2H), 2.49–2.35 (m, 2H), 2.31–2.23 (m, 1H), 1.20–1.01 (m, 2H), 0.96–0.79 (m, 2H).

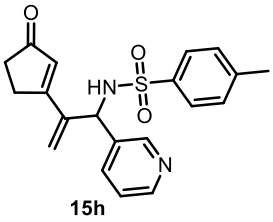
^{13}C NMR (101 MHz, $CDCl_3$) δ 209.47, 170.09, 143.74, 139.12, 130.02, 129.40, 128.75, 127.45, 121.29, 59.59, 34.55, 31.59, 28.64, 6.25, 5.89.

HRMS (ESI): Exact mass calcd for $C_{17}H_{19}NO_3SNa$ [M+Na]+, 340.0978. Found 340.0979.

HPLC condition: (DAICEL CHIRALPAK AD-H, 2-propanol/hexane 1:4, flow 1.0 mL/min, 12.2 min (major), 17.2 min (minor).

4-methyl-*N*-(2-(3-oxocyclopent-1-en-1-yl)-1-(pyridin-3-yl)allyl)benzenesulfonamide (15h)

Prepared according to the general procedure. After preparative thin layer chromatography (silica gel, $CHCl_3$/methanol = 40/1) to give **15h** as white solid: 5.53 mg, 75% yield. [reaction was conducted with using 0.02 mmol of diene]


15h

IR (neat) 3440, 3007, 1701, 1680, 1600, 1324, 1153 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.22 (d, *J* = 2.4 Hz, 1H), 7.65 (d, *J* = 8.20 Hz, 2H), 7.40 (dt, *J* = 8.1, 2.0 Hz, 1H), 7.28 (d, *J* = 8.20 Hz, 2H), 7.17 (dd, *J* = 7.9, 4.8 Hz, 1H), 5.91 (s, 1H), 5.79 (d, *J* = 1.7 Hz, 1H), 5.74–5.70 (m, 1H), 5.30 (d, *J* = 7.0 Hz, 1H), 5.12 (d, *J* = 7.0 Hz, 1H), 2.81–2.64 (m, 2H), 2.44 (s, 3H), 2.42–2.32 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.08, 169.45, 149.76, 148.83, 144.31, 142.07, 136.90, 134.91, 134.17, 130.00, 129.78, 127.34, 123.88, 122.56, 57.45, 34.46, 28.51, 21.74.

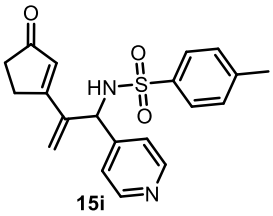
HRMS (ESI): Exact mass calcd for $C_{20}H_{21}N_2O_3S$ [M+H]+, 369.1267. Found 369.1297.

HPLC condition: (DAICEL CHIRALPAK AD-H, 2-propanol/hexane 3:7, flow 1.0 mL/min, 21.8 min (minor), 25.1 min (major).

m.p. 188–190 °C

4-methyl-*N*-(2-(3-oxocyclopent-1-en-1-yl)-1-(pyridin-4-yl)allyl)benzenesulfonamide (15i)

Prepared according to the general procedure. After preparative thin layer chromatography (silica gel, $CHCl_3$/methanol = 40/1) to give **15i** as colorless oil: 3.80 mg, 21% yield.



IR (neat) 3030, 1678, 1600, 1575, 1331, 1159, 754, 663 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50–8.38 (m, 2H), 7.68–7.58 (m, 2H), 7.25–7.21 (m, 2H), 7.03–6.94 (m, 2H), 5.84 (d, *J* = 2.2 Hz, 1H), 5.79 (dt, *J* = 2.9, 1.7 Hz, 1H), 5.56 (d, *J* = 2.1 Hz, 1H), 5.46 (s, 1H), 5.27 (s, 1H), 2.82–2.55 (m, 2H), 2.43 (s, 3H), 2.40–2.30 (m, 2H).

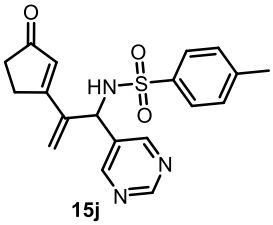
^{13}C NMR (101 MHz, $CDCl_3$) δ 208.95, 169.22, 150.48, 147.45, 144.37, 141.99, 136.94, 129.92, 129.81, 127.34, 123.04, 121.99, 58.69, 34.49, 28.46, 21.73.

HRMS (ESI): Exact mass calcd for $C_{20}H_{21}N_2O_3S$ [M+H]+, 369.1267. Found 369.1266.

HPLC condition: (DAICEL CHIRALPAK AD-H, 2-propanol/hexane 2:8, flow 1.0 mL/min, 23.6 min (minor), 26.4 min (major).

4-methyl-*N*-(2-(3-oxocyclopent-1-en-1-yl)-1-(pyrimidin-5-yl)allyl)benzenesulfonamide (15j)

Prepared according to the general procedure. After preparative thin layer chromatography (silica gel, ethyl acetate/methanol = 19/1) to give **15j** as white solid: 3.57 mg, 24% yield. [reaction was conducted with 0.04 mmol of diene]



IR (neat) 3117, 1677, 1569, 1412, 1334, 1159, 665 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.46 (s, 2H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 5.93 (s, 1H), 5.81 (d, *J* = 1.7 Hz, 1H), 5.60 (s, 1H), 5.35 (d, *J* = 6.8 Hz, 1H), 5.19 (d, *J* = 7.0 Hz, 1H), 2.85–2.63 (m, 2H), 2.50–2.35 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.60, 168.62, 158.54, 156.03, 144.77, 141.57, 136.55, 132.13, 130.17, 129.94, 127.31, 123.28, 55.56, 34.49, 28.47, 21.77.

HRMS (ESI): Exact mass calcd for $C_{19}H_{19}N_3O_3SNa$ [M+Na]+, 392.1039. Found 392.1041.

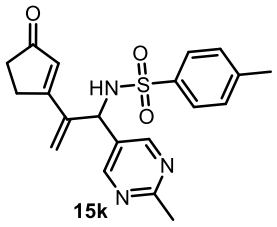
HPLC condition: (DAICEL CHIRALPAK AD-H, 2-propanol/hexane 3:7, flow 1.0 mL/min, 19.5 min (minor), 21.3 min (major).

$[\alpha]_D^{21}$ +51.8 (*c* 0.1 in THF).

m.p. 207 – 209 °C

4-methyl-*N*-(1-(2-methylpyrimidin-5-yl)-2-(3-oxocyclopent-1-en-1-yl)allyl)benzenesulfonamide (15k)

Prepared according to the general procedure. After preparative thin layer chromatography (silica gel, $CHCl_3$/methanol = 40/1) to give **15k** as white solid: 5.80 mg, 30% yield.



IR (neat) 3082, 1700, 11680, 1575, 1561, 1451, 1334, 1157 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 2H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 5.93 (s, 1H), 5.80 (d, *J* = 1.8 Hz, 1H), 5.66 (d, *J* = 1.2 Hz, 1H), 5.28 (d, *J* = 6.9 Hz, 1H), 5.04 (d, *J* = 7.0 Hz, 1H), 2.86–2.57 (m, 5H), 2.50–2.31 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.70, 168.80, 168.41, 156.11, 144.66, 141.59, 136.62, 130.14, 129.91, 128.66, 127.33, 122.95, 55.40, 34.48, 28.50, 25.84, 21.77.

HRMS (ESI): Exact mass calcd for $C_{20}H_{21}N_3O_3SNa$ [M+Na]+, 406.1196. Found 406.1197.

HPLC condition: (DAICEL CHIRALPAK AD-H, 2-propanol/hexane 3:7, flow 1.0 mL/min, 22.8 min (minor), 26.9 min (major).

m.p. 213–215 ℃

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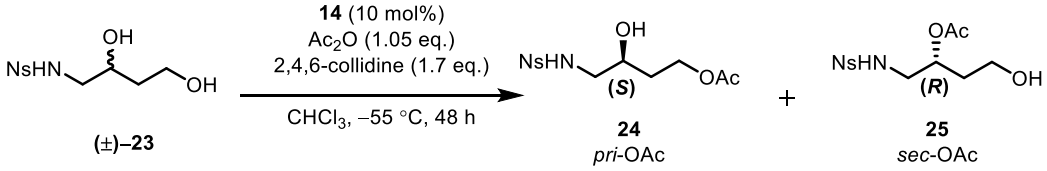
(A) Procedures for Acylative parallel kinetic resolution of amino-diols **23**



To a dry flask, equipped with a stir bar was added **23** (0.07 mmol), **14** (0.007 mmol, 0.1 eq.), dry $CHCl_3$ (7.0 mL, 0.01 M) under Argon. The reaction vessel was then sonicated for several minutes (to allow for mixing). Then 2.4.6-collidine (15.7 µL, 1.7 eq.) was added. The resulting solution was stirred for 15 min at -55 ℃ and then Ac_2O (7.0 µL, 1.05 eq.) was added in one portion. The mixture was stirred at -55 ℃ for 48 h. The reaction was subsequently quenched at -55 ℃ through the addition of methanol and warmed up to room temperature. Then, the solution was concentrated under vacuum and diluted with ethyl acetate, water and 1N HCl. The separated organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by preparative TLC purification (EA-hexane 4:1) to yield the product **24** (46%, 86% ee), **25** (36%, 95% ee).

(*S*)-3-hydroxy-4-((4-nitrophenyl)sulfonamido)butyl acetate (**24**)

Yellow oil: 10.5 mg

IR (neat): 3546, 3332, 3098, 2936, 2889, 1731, 1541, 1365, 1342, 1242, 1166 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.19–8.06 (m, 1H), 7.94–7.82 (m, 1H), 7.81–7.69 (m, 2H), 5.82 (t, *J* = 5.8 Hz, 1H), 4.42–4.32 (m, 1H), 4.11–4.05 (m, 1H), 3.86–3.77 (m, 1H), 3.25 (ddd, *J* = 12.8, 7.0, 3.3 Hz, 1H), 2.99 (ddd, *J* = 12.7, 7.8, 4.8 Hz, 1H), 2.85 (d, *J* = 4.3 Hz, 1H), 2.06 (s, 3H), 1.86–1.65 (m, 2H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 171.3, 148.0, 133.9, 133.8, 133.0, 130.9, 125.5, 69.8, 58.0, 46.6, 34.3, 20.9.

HRMS (ESI) *m/z*: [M+H$^+$] Calcd for $C_{12}H_{18}N_2O_7S$ 333.0751; Found 333.0754.

HPLC condition: (DAICEL CHIRALPAK ID, 2-propanol/hexane 3:7, flow 1 mL/min, 18.2 min (minor), 20.3 min (major).

$[\alpha]_D^{22}$ –41.8 (*c* 1.2 in $CHCl_3$).

(*R*)-4-hydroxy-1-((4-nitrophenyl)sulfonamido)butan-2-yl acetate (**25**)

Yellow oil: 8.22 mg

IR (neat): 3505, 3334, 3098, 2931, 1730, 1542, 1365, 1342, 1248, 1167 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.19–8.08 (m, 1H), 7.91–7.83 (m, 1H), 7.80–7.72 (m, 2H), 5.78 (t, *J* = 6.4 Hz, 1H), 5.01–4.92 (m, 1H), 3.69 (dt, *J* = 11.5, 4.9 Hz, 1H), 3.54 (ddd, *J* = 11.4, 9.1, 3.8 Hz, 1H), 3.44 (ddd, *J* = 14.0, 6.9, 3.8 Hz, 1H), 3.30 (ddd, *J* = 14.0, 6.8, 5.7 Hz, 1H), 2.05 (s, 1H), 2.04 (s, 3H), 1.92–1.65 (m, 2H).

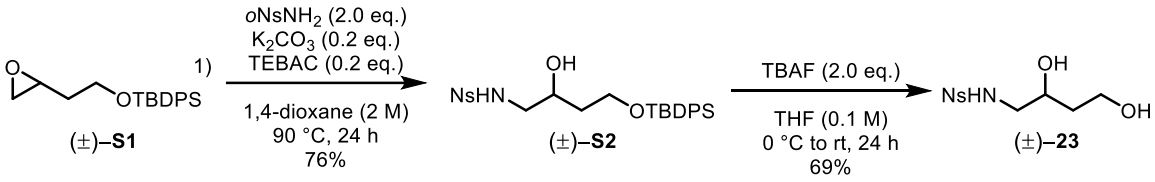
^{13}C NMR: (100 MHz, $CDCl_3$) δ 171.8, 148.1, 133.7, 133.4, 132.8, 131.0, 125.5, 67.1, 60.9, 49.0, 33.6, 21.0.

HRMS (ESI) *m/z*: [M+H$^+$] Calcd for $C_{12}H_{17}N_2O_7S$ 333.0751; Found 333.0748.

HPLC condition: (DAICEL CHIRALPAK ID, 2-propanol/hexane 3:7, flow 1 mL/min, 52.8 min (minor), 57.7 min (major).

[α]$_D^{22}$ –41.8 (*c* 1.2 in $CHCl_3$).

Substrate synthesis of (±)–23



(±)–**S2**

To a screw capped vial equipped with a stir bar was added tert-butyl(2-(oxiran-2-yl)ethoxy)diphenylsilane (**S1**) (1.96 g, 6 mmol, *prepared according to a literature method*[1]) was added *o*$NsNH_2$ (2.43 g, 12 mmol, 2.0 eq.), K_2CO_3 (166 mg, 1.2 mmol, 0.2 eq.), Benzyltriethylammonium Chloride (273 mg, 1.2 mmol, 0.2 eq.) and dry 1,4-dioxane (3 mL). The reaction mixture was stirred at 90 °C for 24 h. The reaction mixture was diluted with EtOAc, washed by H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica chromatography (EA-hexane 1:3) to yield (±)–**S2** (2.42 g, 4.58 mmol, 76%).

Yellow oil: **IR** (neat): 3503, 3350, 2932, 2859, 1541, 1425, 1361, 1169, 1110 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.15–8.09 (m, 1H), 7.89–7.83 (m, 1H), 7.76–7.67 (m, 2H), 7.75–7.69 (m, 4H), 7.49–7.37 (m, 6H), 5.83 (d, J = 6.1 Hz, 1H), 4.10–4.00 (m, 1H), 3.91–3.78 (m, 2H), 3.50 (d, J = 2.6 Hz, 1H), 3.30–3.22 (m, 1H), 3.10–3.00 (m, 1H), 1.84–1.58 (m, 2H), 1.03 (s, 9H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 148.22, 135.61, 133.67, 133.67, 132.85, 132.75, 132.66, 131.18, 130.15, 130.12, 128.02, 125.54, 70.17, 62.93, 49.30, 35.57, 26.90, 19.10.

HRMS (ESI) *m/z*: [M+Na$^+$] Calcd for $C_{26}H_{32}N_2SO_6SiNa$ 551.1643; Found 551.1661.

(±)–**23**

To a solution of (±)–**S2** (0.528g, 1 mmol) in THF (0.1 M, 10 mL) was cooled to 0 °C was added a solution of TBAF [1 mol/L in THF] (2 mL, 2 mmol, 2.0 eq.). The mixture was warmed up to room temperature for 24 h and quenched with sat. $NH_4Cl_{(aq)}$. The aqueous phase was extracted with EtOAc twice, and the combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (EA-Hexane 3:1 to 5:1) to give (±)–**23** (199 mg, 0.686 mmol, 69 %).

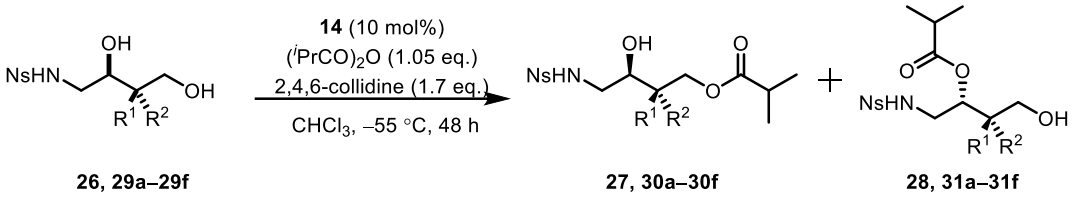
Yellow oil: **IR** (neat): 3526, 3335, 3099, 2938, 2890, 1540, 1440, 1411, 1362, 1337, 1165 cm^{-1}.

^{1}H NMR: (400 MHz, CD_3OD) δ 8.16–7.97 (m, 1H), 7.87 (dt, *J* = 7.0, 3.5 Hz, 1H), 7.84–7.78 (m, 2H), 3.86–3.76 (m, 1H), 3.70–3.61 (m, 2H), 3.22–2.91 (m, 2H), 1.80–1.49 (m, 2H).

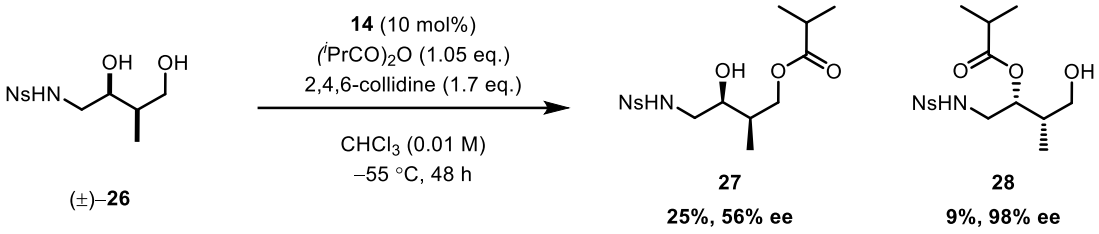
^{13}C NMR: (100 MHz, $CDCl_3$) δ 148.0, 133.6, 133.4, 132.8, 131.0, 125.4, 69.9, 60.9, 49.2, 35.4.

HRMS (ESI) *m/z*: [M+H$^+$] Calcd for $C_{10}H_{15}N_2O_6S$ 291.0645; Found 290.0649.

(B) General Procedures for Acylative parallel kinetic resolution of substituted amino-diols (**26**, **29a-29f**)



To a dry flask, equipped with a stir bar was added (±)–**26**, **29a-29f** (0.07 mmol), **14** (0.007 mmol, 0.1 eq.), dry $CHCl_3$ (7.0 mL, 0.01 M) under Argon. The reaction vessel was then sonicated for several minutes (to allow for mixing). Then 2.4.6-collidine (15.7 µL, 1.7 eq.) was added. The resulting solution was stirred for 15 min at -55 ℃ and then (^{i}PrCO)$_2$O (12.2 µL, 1.05 eq.) was added in one portion. The mixture was stirred at -55 ℃ for 48 h. The reaction was subsequently quenched at -55 ℃ through the addition of methanol and warmed up to room temperature. Then, the solution was concentrated under vacuum and the crude material was added 1N HCl (1.4 ml) and the phase was separated and aqueous phase was extracted twice with EtOAc. The combined organics were dried (Na_2SO_4), filtered, and concentrated and the crude product was purified by preparative TLC purification (EA-hexane 1:1) to yield the primary acylate **27**, **30a－30f**, secondary acylate **28**, **31a－31f**.



Following the general procedure for PKR, (±)–**26** (25.0 mg, 0.082 mmol), isobutyric anhydride (14.3 µl, 0.086 mmol, 1.05 eq.), 2,4,6-collidine (18.5 µl, 0.14 mmol, 1.7 eq), **14** (6.84 mg, 0.0082 mmol, 0.1 eq.), dry $CHCl_3$ (8.2 mL, 0.01 M) under Argon were stirred at –55 ℃ for 48 h. The crude material was purified by preparative thin-layer chromatography purification (hexane/ethyl acetate = 1 : 1) to give **27** and **28**.

***Syn*-3-hydroxy-2-methyl-4-((4-nitrophenyl)sulfonamido)butyl isobutyrate** (**27**)

Yellow oil: 7.83 mg

IR (neat): 3522, 3335, 2975, 1719, 1542, 1344, 1166, 1082 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.19–8.06 (m, 1H), 7.91–7.84 (m, 1H), 7.79–7.70 (m, 2H), 5.76 (dd, *J* = 8.0, 4.1 Hz, 1H), 4.17 (dd, *J* = 11.3, 8.2 Hz, 1H), 3.88 (dd, *J* = 11.3, 5.2 Hz, 1H), 3.76–3.69 (m, 1H), 3.23 (ddd, *J* = 12.9, 7.9, 3.3 Hz, 1H), 3.04 (ddd, *J* = 13.0, 9.1, 4.1 Hz, 1H), 2.64–2.47 (m, 2H), 2.00–1.86 (m, 1H), 1.16 (d, *J* = 7.0 Hz, 6H), 0.90 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 177.90, 148.27, 133.82, 133.61, 132.95, 131.20, 125.67, 70.25, 65.88, 47.29, 36.41, 34.15, 19.15, 19.09, 10.61.

HRMS (ESI) *m/z*: [M+Na$^+$] Calcd for $C_{15}H_{22}N_2O_7SNa$ 397.1040; Found 397.1064.

HPLC condition: (DAICEL CHIRALPAK IC, 2-propanol/hexane 5:5, flow 1.4 mL/min, 9.5 min (minor), 12.7 min (major).

[α]$_D^{22}$ –51.1 (*c* 0.5 in $CHCl_3$).

***Syn*-4-hydroxy-3-methyl-1-((4-nitrophenyl)sulfonamido)butan-2-yl isobutyrate (28)**

Yellow oil: 2.65 mg

IR (neat): 3343, 2974, 2937, 1723, 1541, 1345, 1166 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.20–8.09 (m, 1H), 7.93–7.82 (m, 1H), 7.82–7.69 (m, 2H), 5.72 (t, *J* = 6.4 Hz, 1H), 4.98–4.86 (m, 1H), 3.54–3.45 (m, 1H), 3.44–3.38 (m, 2H), 3.25–3.15 (m, 1H), 2.56 (hept, *J* = 7.0 Hz, 1H), 2.27 (dd, *J* = 7.7, 4.9 Hz, 1H), 2.00–1.90 (m, 1H), 1.16 (d, *J* = 7.0 Hz, 3H), 1.13 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H).

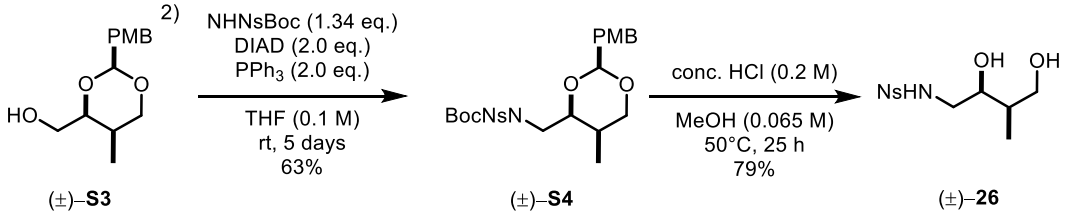
^{13}C NMR: (100 MHz, $CDCl_3$) δ 177.90, 148.17, 134.27, 133.87, 133.21, 130.98, 125.70, 71.85, 64.09, 45.54, 37.57, 34.25, 19.38, 18.86, 10.88.

HRMS (ESI) *m/z*: [M+Na$^+$] Calcd for $C_{15}H_{22}N_2O_7SNa$ 397.1040; Found 397.1065.

HPLC condition: (DAICEL CHIRALPAK IC, 2-propanol/hexane 4:6, flow 1 mL/min, 11.2 min (major), 27.0 min (minor).

[α]$_D^{22}$ –81.3 (*c* 0.3 in $CHCl_3$).

<u>Substrate synthesis of (±)–26</u>



(±)–**S3** (±)–**S4** (±)–**26**

(±)–**S4**

To a 50 mL flask, (±)–**S3** (479 mg, 1.97 mmol, *prepared according to a literature method*[2]) was added NHNsBoc (800 mg, 2.64 mmol, 1.34 eq,), PPh_3 (1.03 g, 3.94 mmol, 2.0 eq.) and dry THF (19.7 mL). The reaction mixture was cooled to 0 ℃ then DIAD (0.78 mL, 3.94 mmol, 2.0 eq.) was slowly added. The reaction was warmed up to room

temperature and stirred for 5 days. The crude product was directly concentrated, and the residue was purified by silica chromatography (Acetone: Hexane 4:1) to afford white amorphous (±)–**S4** (646 mg, 1.24 mmol, 63%).

White amorphous:

IR (neat): 2977, 1733, 1615, 1588, 1544, 1367, 1250, 1151, 1034 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.1 Hz, 1H), 7.79–7.66 (m, 2H), 7.63–7.57 (m, 1H), 7.46 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 5.50 (s, 1H), 4.27 (dt, *J* = 9.2, 2.6 Hz, 1H), 4.20–4.06 (m, 2H), 4.00 (dd, *J* = 11.2, 1.4 Hz, 1H), 3.81–3.72 (m, 4H), 1.81–1.69 (m, 1H), 1.26 (m, 12H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 159.86, 150.40, 147.67, 134.21, 133.64, 133.05, 131.81, 131.15, 127.49, 124.44, 113.46, 101.54, 85.15, 78.08, 73.63, 55.32, 49.56, 30.44, 27.70, 11.18.

HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{24}H_{30}N_2O_9SNa$ 545.1564; Found 545.1576.

(±)–**26**

To a 10 mL flask, (±)–**S4** (509 mg, 0.97 mmol) was added MeOH (15 mL) and conc. HCl (4.9 mL). The reaction mixture was stirred at 50 °C for 25 h. The reaction was cooled to room temperature and quenched with $NaHCO_{3(aq.)}$. The aqueous product was extracted twice with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica chromatography ($CHCl_3$-MeOH 100:1) to afford white solid (±)–**26** (236 mg, 0.77 mmol, 79%).

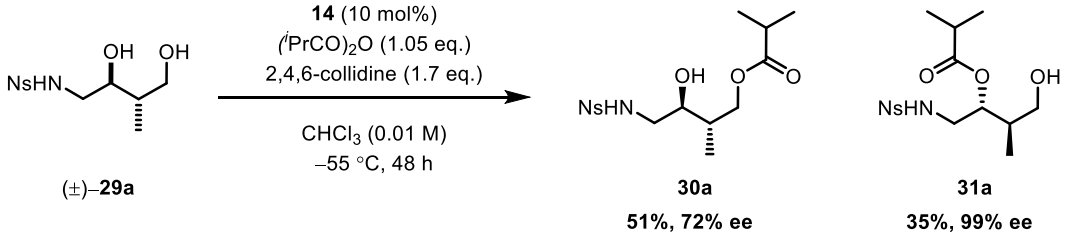
Yellow oil: **IR** (neat): 3348, 2965, 1541, 1409, 1362, 1333, 1161, 1035 cm^{-1}.

^{1}H NMR: (400 MHz, Acetone-d^6) δ 8.19–8.09 (m, 1H), 8.01–7.94 (m, 1H), 7.94–7.84 (m, 2H), 6.47 (s, 1H), 4.07 (d, *J* = 5.1 Hz, 1H), 3.82 (dt, *J* = 8.7, 4.3 Hz, 2H), 3.57–3.48 (m, 2H), 3.31–3.04 (m, 2H), 1.81–1.67 (m, 1H), 0.87 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 148.05, 133.84, 133.42, 133.06, 131.12, 125.53, 72.03, 65.71, 47.28, 37.99, 10.86.

HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{11}H_{16}N_2O_6SNa$ 327.0621; Found 327.0631.

m.p.; 118–120 °C



Following the general procedure for PKR, (±)–**29a** (18.6 mg, 0.061 mmol), isobutyric anhydride (10.6 µl, 0.064 mmol, 1.05 eq.), 2,4,6-collidine (13.8 µl, 0.10 mmol, 1.7 eq), **14** (5.09 mg, 0.006 mmol, 0.1 eq.), dry $CHCl_3$ (6.1 mL, 0.01 M) under Argon were stirred at −55 °C for 48 h. The crude material was purified by preparative thin-layer chromatography purification (hexane/ethyl acetate = 1 : 2) to give **30a** and **31a**.

***Anti*-3-hydroxy-2-methyl-4-((4-nitrophenyl)sulfonamido)butyl isobutyrate (30a)**

Yellow oil: 11.7 mg

IR (neat): 3502, 3335, 2974, 1723, 1542, 1345, 1166 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.18–8.05 (m, 1H), 7.90–7.85 (m, 1H), 7.77–7.71 (m, 2H), 5.85 (dd, *J* = 7.1, 4.8 Hz, 1H), 4.45 (dd, *J* = 11.4, 3.8 Hz, 1H), 3.91 (dd, *J* = 11.4, 4.5 Hz, 1H), 3.50–3.41 (m, 1H), 3.34 (ddd, *J* = 12.5, 7.2, 2.9 Hz, 1H), 3.26 (d, *J* = 4.2 Hz, 1H), 3.00 (ddd, *J* = 12.6, 8.0, 4.7 Hz, 1H), 2.56 (hept, *J* = 7.0 Hz, 1H), 1.89–1.78 (m, 1H), 1.16 (d, *J* = 2.0 Hz, 3H), 1.15 (d, *J* = 1.9 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$) 178.26, 148.32, 133.77, 133.58, 132.86, 131.17, 125.65, 77.48, 77.16, 76.84, 71.52, 66.02, 47.22, 37.32, 34.22, 19.23, 19.05, 13.70.

HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{15}H_{22}N_2O_7SNa$ 397.1040; Found 397.1040.

HPLC condition: (DAICEL CHIRALPAK IC, 2-propanol/hexane 5:5, flow 1.4 mL/min, 15.7 min (minor), 20.5 min (major).

$[\alpha]_D^{22}$ –10.7 (*c* 0.8 in $CHCl_3$).

***Anti*-4-hydroxy-3-methyl-1-((4-nitrophenyl)sulfonamido)butan-2-yl isobutyrate (31a)**

Yellow oil: 8.07 mg

IR (neat): 3343, 2972, 2881, 1726, 1542, 1346, 1165 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.19–8.08 (m, 1H), 7.93–7.84 (m, 1H), 7.80–7.72 (m, 2H), 5.75 (t, *J* = 6.3 Hz, 1H), 4.79 (td, *J* = 7.2, 3.7 Hz, 1H), 3.56–3.41 (m, 3H), 3.38–3.29 (m, 1H), 2.56 (hept, *J* = 7.0 Hz, 1H), 1.96–1.86 (m, 2H), 1.16 (d, *J* = 7.1 Hz, 3H), 1.13 (d, *J* = 7.1 Hz, 3H), 0.98 (d, *J* = 7.0 Hz, 3H).

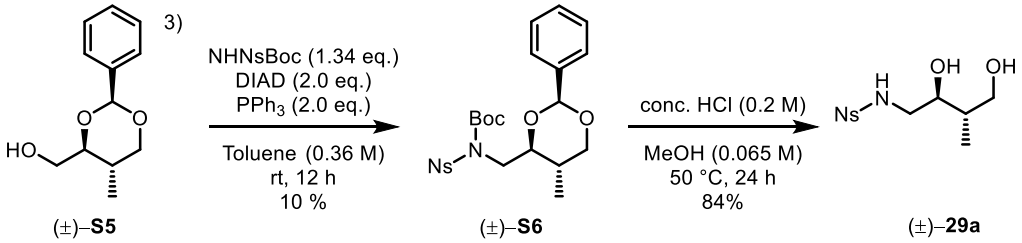
^{13}C NMR: (100 MHz, $CDCl_3$) δ 177.41, 148.14, 133.91, 133.86, 133.11, 131.02, 125.62, 73.01, 63.58, 44.97, 37.09, 34.18, 19.18, 18.85, 13.39.

HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{15}H_{22}N_2O_7SNa$ 397.1040; Found 397.1033.

HPLC condition: (DAICEL CHIRALPAK IC, 2-propanol/hexane 4:6, flow 1 mL/min, 12.2 min (major), 16.7 min (minor).

$[\alpha]_D^{22}$ –83.9 (*c* 0.6 in $CHCl_3$).

<u>Substrate synthesis of (±)–29a</u>



(±)–**S6**

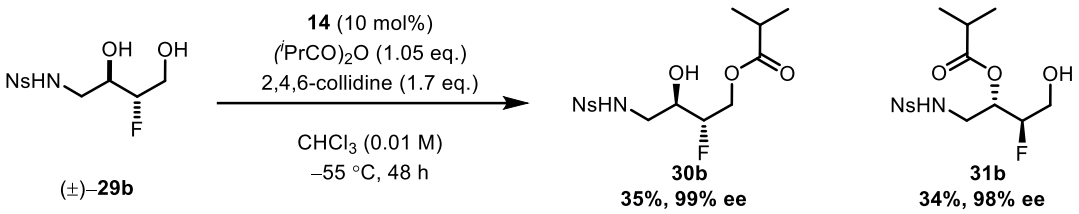
To a 30 mL flask, (±)–**S5** (800.6 mg, 6.67 mmol, *prepared according to a literature method*[3]) was added NHNsBoc (2.82 g, 9.34 mmol, 2.0 eq,), PPh_3 (2.45 g, 9.34 mmol, 2.0 eq.) and dry Toluene (18.7 mL). The reaction mixture was cooled to 0 ℃ then DIAD (1.81 mL, 9.34 mmol, 2.0 eq.) was slowly added. The reaction was warmed up to room temperature and stirred for 12 h. The crude product was directly concentrated, and the residue was purified by silica chromatography (EA-hexane 1:6) then recrystallized with EA/hexane systems to afford white crystals. The crystals were collected by filtration and were washed with hexane to afford (±)–**S6** (235 mg, 0.47 mmol, 10%).

White solid: **IR** (KBr): 2972, 2833, 1746, 1541, 1454, 1368, 1283, 1148 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.78–7.66 (m, 2H), 7.62–7.54 (m, 3H), 7.40–7.28 (m, 3H), 5.54 (s, 1H), 4.21–4.00 (m, 3H), 3.85 (td, *J* = 9.5, 2.9 Hz, 1H), 3.55 (t, *J* = 11.2 Hz, 1H), 2.02–1.86 (m, 1H), 1.27 (d, *J* = 0.8 Hz, 9H), 0.93 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR: (100 MHz, $CDCl_3$) δ 150.48, 147.77, 138.37, 134.07, 133.98, 133.22, 131.80, 128.69, 128.15, 126.30, 124.46, 100.91, 85.15, 81.07, 72.67, 49.30, 32.28, 27.83, 12.32.
HRMS (ESI) *m*/*z*: [M+Na^+] Calcd for $C_{23}H_{28}N_2O_8SNa$ 515.1459; Found 515.1463.
m.p.; 136–138 ℃

(±)–**29a**

To a 10 mL flask, rac **15** (410.0 mg, 0.830 mmol) was added MeOH (15 mL) and conc. HCl (5.0 mL). The reaction mixture was stirred at 50 ℃ for 24 h. The reaction was cooled to room temperature and quenched with $NaHCO_{3(aq.)}$. The aqueous product was extracted twice with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica chromatography ($CHCl_3$-MeOH 15:1) to afford (±)–**29a** (213 mg, 0.70 mmol, 84%).

Yellow oil: **IR** (neat): 3518, 3347, 2885, 1541, 1408, 1363, 1338, 1167 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.17–8.04 (m, 1H), 7.91–7.81 (m, 1H), 7.79–7.69 (m, 2H), 6.01 (s, 1H), 4.22–4.06 (m, 1H), 3.75 (dd, *J* = 10.8, 3.7 Hz, 1H), 3.71–3.64 (m, 1H), 3.59 (dd, *J* = 10.8, 8.0 Hz, 1H), 3.25 (d, *J* = 12.7 Hz, 1H), 3.14–3.03 (m, 1H), 2.97 (s, 1H), 1.88–1.75 (m, 1H), 0.84 (d, *J* = 7.0 Hz, 3H).
^{13}C NMR: (100 MHz, $CDCl_3$) δ 148.08, 133.86, 133.28, 132.99, 131.08, 125.52, 74.89, 67.06, 47.55, 37.61, 13.27.
HRMS (ESI) *m*/*z*: [M+Na^+] Calcd for $C_{11}H_{16}N_2O_6SNa$ 327.0621; Found 327.0628.



Following the general procedure for PKR, (±)–**29b** (24.3 mg, 0.079 mmol), isobutyric anhydride (13.7 µl, 0.083 mmol, 1.05 eq.), 2,4,6-collidine (17.7 µl, 0.13 mmol, 1.7 eq), **14** (6.56 mg, 0.0079 mmol, 0.1 eq.), dry $CHCl_3$ (7.9 mL, 0.01 M) under Argon were stirred at –55 °C for 48 h. The crude material was purified by preparative thin-layer chromatography purification (hexane/ethyl acetate = 1 : 1) to give **30b** and **31b**.

***Anti*-2-fluoro-3-hydroxy-4-((4-nitrophenyl)sulfonamido)butyl isobutyrate (30b)**

Yellow oil: 10.1 mg

IR (neat): 3508, 3342, 2977, 1730, 1542, 1346, 1166, 1067 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.20–8.08 (m, 1H), 7.95–7.85 (m, 1H), 7.83–7.72 (m, 2H), 5.82 (s, 1H), 4.62–4.23 (m, 3H), 3.79 (s, 1H), 3.46 (d, *J* = 13.6 Hz, 1H), 3.29 (s, 1H), 3.24–3.14 (m, 1H), 2.62 (hept, *J* = 7.0 Hz, 1H), 1.18 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 178.24, 148.23, 133.98, 133.33, 133.04, 131.33, 125.69, 90.76 (^1J (C, F) = 175 Hz), 67.78 (^2J (C, F) = 26 Hz), 62.57 (^2J (C, F) = 20 Hz), 45.63, 34.06, 19.06 (^3J (C, F) = 7.6 Hz).

^{19}F NMR: (400 MHz, $CDCl_3$) δ -196.51.

HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{14}H_{19}N_2O_7FSNa$ 401.0789; Found 401.0811.

HPLC condition: (DAICEL CHIRALPAK ID, 2-propanol/hexane 5:5, flow 1 mL/min, 6.1 min (minor), 13.8 min (major).

$[\alpha]_D^{22}$ –20.7 (*c* 1.1 in $CHCl_3$).

***Anti*-3-fluoro-4-hydroxy-1-((4-nitrophenyl)sulfonamido)butan-2-yl isobutyrate (31b)**

Yellow oil: 10.4 mg

IR (neat): 3534, 3340, 2976, 1736, 1542, 1423, 1346, 1167 cm^{-1}

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.20–8.08 (m, 1H), 7.91–7.84 (m, 1H), 7.82–7.72 (m, 2H), 5.70 (t, *J* = 6.4 Hz, 1H), 5.08–5.00 (m, 1H), 4.66–4.50 (m, 1H), 3.97–3.37 (m, 4H), 2.58 (hept, *J* = 7.0 Hz, 1H), 2.13 (d, *J* = 7.3 Hz, 1H), 1.16 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 176.63, 148.15, 134.00, 133.72, 133.21, 131.17, 125.66, 91.27 (^1J (C, F) = 175 Hz), 69.02 (^2J (C, F) = 27 Hz), 61.33 (^2J (C, F) = 21 Hz), 43.30 (^3J (C, F) = 4.9 Hz), 34.05, 18.90 (^2J (C, F) = 22 Hz).

^{19}F NMR: (400 MHz, $CDCl_3$) δ -200.89.

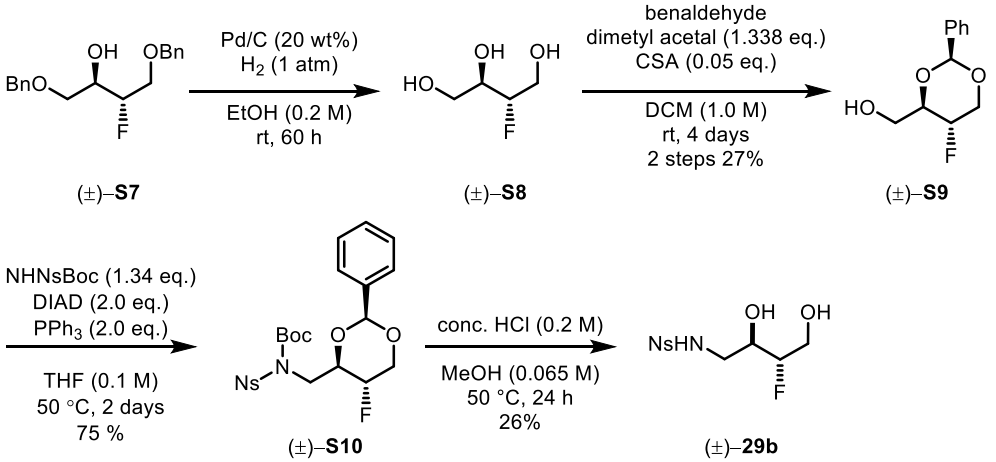
HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{14}H_{19}N_2O_7FSNa$ 401.0789; Found 401.0815.

HPLC condition: (DAICEL CHIRALPAK ID, 2-propanol/hexane 4:6, flow 1 mL/min, 8.3 min (minor), 11.7 min

(major).

[α]$_D^{22}$ –27.5 (*c* 1.1 in $CHCl_3$).

Substrate synthesis of (±)–29b



(±)–**S9**

To a 50 mL flask, (±)–**S7** (905 mg, 2.97 mmol, *prepared according to a literature method*[3]) was added Pd/C (180mg, 20 wt%) and EtOH (15 mL). The reaction vessel was charged with H_2 atmosphere and stirred rt for 24 h. The crude mixture was filtrated and washed with EtOH and concentrated in vacuo to give (±)–**8**. The crude product was used without purification and used for next reaction.

To a 20 mL flask with (±)–**8** was added Benzaldehyde dimethylacetal (0.593 ml, 3.98 mmol, 1.34 eq,), CSA (35 mg, 0.15 mmol, 0.05 eq.) and dry DCM (3.0 mL). The reaction mixture was stirred at room temperature for 4 days. The reaction mixture was quenched with NEt_3 (0.3 mL) and stirred for 15 min. The reaction mixture was diluted with water and the phase was separated and the aqueous phase was extracted twice with EtOAc. The combined organics were dried (Na_2SO_4), filtered, and concentrated and the crude product was purified by silica chromatography (MeOH: $CHCl_3$ 1:20) to afford (±)–**S9** (170 mg, 0.80 mmol, 2 steps 26%).

White solid: **IR** (KBr): 3344, 2950, 2870, 1454, 1387, 1219, 1152, 1101, 1027 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.55–7.46 (m, 2H), 7.46–7.34 (m, 3H), 5.54 (s, 1H), 4.79–4.57 (m, 1H), 4.45 (dd, *J* = 10.7, 5.6 Hz, 1H), 4.04–3.74 (m, 4H), 2.16 (dd, *J* = 7.1, 6.0 Hz, 1H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 136.86, 129.47, 128.49, 126.28, 101.33, 80.06 (^1J (C, F) = 178 Hz), 79.58 (^2J (C, F) = 25 Hz),68.06 (^2J (C, F) = 28 Hz), 61.58.

^{19}F NMR: (400 MHz, $CDCl_3$) δ -202.47.

HRMS (ESI) *m/z*: [M+H$^+$] Calcd for $C_{11}H_{14}FO_3$ 213.0921; Found 213.0921.

m.p.; 58–60 ℃

(±)–**S10**

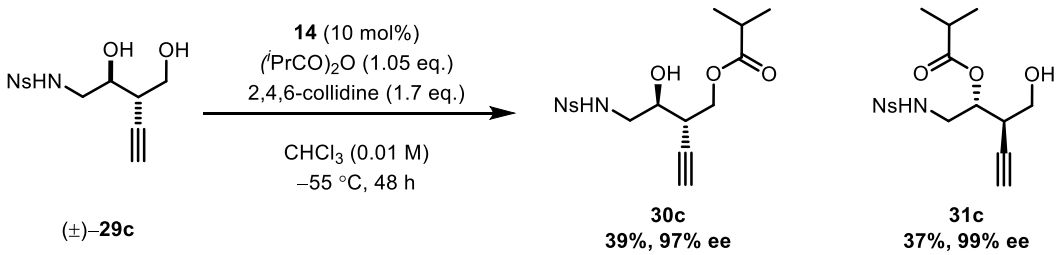
To a 50 mL flask, (±)–**S9** (150 mg, 0.71 mmol) was added NHNsBoc (286 mg, 0.95 mmol, 1.34 eq,), PPh_3 (371 mg, 1.42 mmol, 2.0 eq.) and dry THF (7.1 mL). The reaction mixture was cooled to 0 ℃ then DIAD (0.28 mL, 1.42 mmol, 2.0 eq.) was slowly added. The reaction was warmed to 50 ℃ and stirred for 2 days. The crude product was directly concentrated, and the residue was purified by silica chromatography (Acetone-hexane 1:8 to 1:5), then Al_2O_3 chromatography (EtOAc-Hexane 2:1) to afford (±)–**S10** (263 mg, 0.53 mmol, 75%).

Colorless oil: **IR** (neat): 2981, 2872, 1734, 1544, 1456, 1368, 1178, 1121, 1038 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.75–7.60 (m, 3H), 7.58–7.51 (m, 2H), 7.40–7.28 (m, 3H), 5.57 (s, 1H), 4.69–4.39 (m, 2H), 4.32–4.10 (m, 3H), 3.87–3.76 (m, 1H), 1.32 (s, 9H).
^{13}C NMR: (100 MHz, Acetone-d_6) δ 150.87, 148.57, 138.32, 135.81, 133.74, 133.32, 132.92, 129.54, 128.72, 127.09, 125.44, 101.26, 83.62 (^1J (C, F) = 178 Hz), 79.12, 77.78 (^2J (C, F) = 24 Hz), 68.11 (^2J (C, F) = 28 Hz), 48.64, 27.79.
^{19}F NMR: (400 MHz, $CDCl_3$) δ -201.64.
HRMS (ESI) *m*/*z*: [M+Na^+] Calcd for $C_{22}H_{25}FN_2O_8SNa$ 519.1208; Found 519.1185.

(±)–**29b**

To a 20 mL flask, (±)–**S10** (263 mg, 0.53 mmol) was added MeOH (8.2 mL) and conc. HCl (2.7 mL). The reaction mixture was stirred at 50 ℃ for 24 h. The reaction was cooled to room temperature and quenched with $NaHCO_{3(aq.)}$. The aqueous product was extracted twice with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica chromatography (EtOAc-Hexane 2:1) to afford rac (±)–**29b** (43 mg, 0.14 mmol, 26%).

Colorless oil: **IR** (neat): 3332, 2920, 2371, 2317, 1540, 1338, 1167 cm^{-1}.
^{1}H NMR: (400 MHz, Acetone-d_6+D_2O) δ 8.19–8.10 (m, 1H), 8.00–7.84 (m, 3H), 4.49–4.30 (m, 1H), 4.00–3.90 (m, 1H), 3.90–3.68 (m, 2H), 3.40 (ddd, *J* = 13.1, 3.8, 1.9 Hz, 1H), 3.17 (ddd, *J* = 13.1, 7.4, 1.1 Hz, 1H).
^{13}C NMR: (100 MHz, Acetone-d_6) δ 149.16, 134.95, 133.99, 133.65, 131.54, 125.93, 95.07 (^1J (C, F) = 173 Hz), 68.98 (^2J (C, F) = 26 Hz), 61.71 (^2J (C, F) = 21 Hz), 46.76 (^3J (C, F) = 5.0 Hz).
^{19}F NMR: (400 MHz, Acetone-d_6) δ -197.80.
HRMS (ESI) *m*/*z*: [M+H^+] Calcd for $C_{10}H_{14}N_2O_6FS$ 309.0551; Found 309.0538.



(±)–**29c**

30c
39%, 97% ee

31c
37%, 99% ee

Following the general procedure for PKR, (±)–**29c** (21.1 mg, 0.067 mmol), isobutyric anhydride (11.7 μl, 0.070 mmol, 1.05 eq.), 2,4,6-collidine (15.1 μl, 0.11 mmol, 1.7 eq), **14** (5.59 mg, 0.0067 mmol, 0.1 eq.), dry $CHCl_3$ (6.7 mL, 0.01 M) under Argon were stirred at –55 ℃ for 48 h. The crude material was purified by preparative thin-layer chromatography purification (hexane/ethyl acetate = 1 : 2) to give **30c** and **31c**.

***Anti*-2-Ethynyl-3-hydroxy-4-((4-nitrophenyl)sulfonamido)butyl isobutyrate (30c)**

Yellow oil: 10.0 mg

IR (neat): 3494, 3290, 2976, 1726, 1541, 1346, 1165, 1085 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.21–8.08 (m, 1H), 7.94–7.82 (m, 1H), 7.79–7.70 (m, 2H), 5.84 (dd, *J* = 7.2, 4.9 Hz, 1H), 4.53 (dd, *J* = 11.3, 4.0 Hz, 1H), 4.12 (dd, *J* = 11.3, 4.2 Hz, 1H), 3.73–3.50 (m, 2H), 3.43 (dd, *J* = 4.9, 0.8 Hz, 1H), 3.21–3.13 (m, 1H), 2.71–2.65 (m, 1H), 2.59 (h, *J* = 7.0 Hz, 1H), 2.21 (d, *J* = 2.5 Hz, 1H), 1.18 (d, *J* = 2.5 Hz, 3H), 1.17 (d, *J* = 2.5 Hz, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 178.34, 148.27, 133.83, 133.54, 132.93, 131.31, 125.65, 79.89, 73.48, 69.39, 62.49, 47.36, 36.84, 34.15, 19.22, 19.02.

HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{16}H_{20}N_2O_7SNa$ 407.0883; Found 407.0880.

HPLC condition: (DAICEL CHIRALPAK IC, 2-propanol/hexane 5:5, flow 1.4 mL/min, 10.2 min (minor), 12.4 min (major).

$[\alpha]_D^{23}$ +2.15 (*c* 0.9 in $CHCl_3$).

***Anti*-3-Ethynyl-4-hydroxy-1-((4-nitrophenyl)sulfonamido)butan-2-yl isobutyrate (31c)**

Yellow oil: 9.63 mg

IR (neat): 3526, 3288, 2975, 1727, 1541, 1348, 1166, 1073 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.19–8.10 (m, 1H), 7.93–7.83 (m, 1H), 7.82–7.71 (m, 2H), 5.71 (t, *J* = 6.5 Hz, 1H), 4.95–4.88 (m, 1H), 3.76–3.46 (m, 4H), 2.89–2.80 (m, 1H), 2.57 (hept, *J* = 7.0 Hz, 1H), 2.25 (d, *J* = 2.5 Hz, 1H), 2.13 (t, *J* = 6.9 Hz, 1H), 1.17 (dd, *J* = 7.0, 5.3 Hz, 6H).

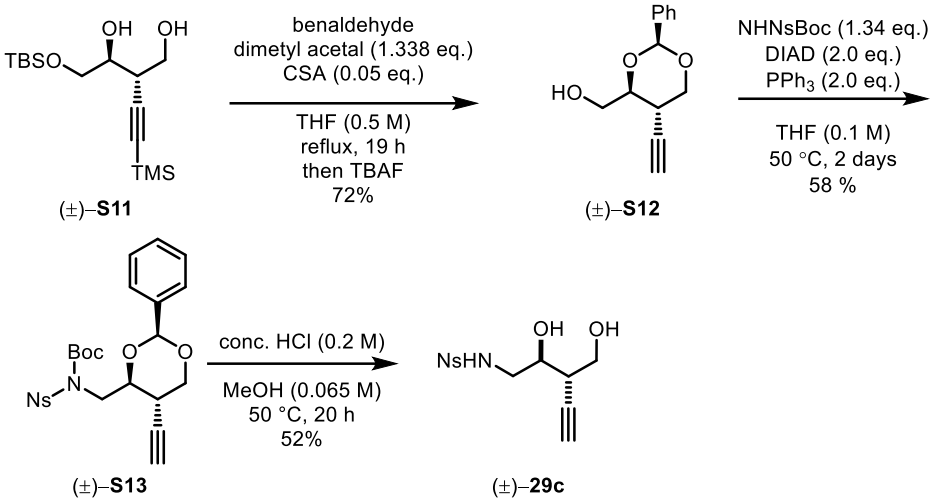
^{13}C NMR: (100 MHz, $CDCl_3$) δ 177.04, 148.15, 133.95, 133.90, 133.20, 131.15, 125.67, 79.85, 74.01, 70.20, 61.44, 45.15, 37.11, 34.13, 19.15, 18.81.

HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{16}H_{20}N_2O_7SNa$ 407.0883; Found 407.0881.

HPLC condition: (DAICEL CHIRALPAK IC, 2-propanol/hexane 4:6, flow 1 mL/min, 11.7 min (minor), 27.2 min (major).

$[\alpha]_D^{23}$ –46.4 (*c* 0.7 in $CHCl_3$).

<u>Substrate synthesis of (±)–29c</u>



(±)–**S12**

To a 20 mL flask, (±)–**S11** (362 mg, 1.14 mmol, *prepared according to a literature method*[4]) was added Benzaldehyde dimethylacetal (0.341 ml, 2.28 mmol, 2.0 eq,), CSA (26.6 mg, 0.11 mmol, 0.1 eq.) and dry THF (2.3 mL). The reaction mixture was stirred reflux for 19 h. The reaction mixture was quenched with NEt_3 (0.08 mL) and stirred for 15 min. Then Tetrabutylammonium fluoride (10 mmol) was added and stirred for additional 24 h. The reaction mixture was diluted with water and the phase was separated and the aqueous phase was extracted twice with EtOAc. The combined organics were dried (Na_2SO_4), filtered, and concentrated and the crude product was purified by silica chromatography (EtOAc: Hexane 1:3) to afford (±)–**S12** (179 mg, 0.82 mmol, 72%).

White solid: **IR** (neat): 3444, 3289, 2861, 1456, 1399, 1371, 1135, 1086, 1022 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.49 (m, 2H), 7.46–7.33 (m, 3H), 5.53 (s, 1H), 4.38 (dd, J = 11.2, 4.9 Hz, 1H), 4.00–3.91 (m, 1H), 3.90–3.74 (m, 3H), 2.93–2.83 (m, 1H), 2.37 (s, 1H), 2.20 (d, J = 2.4 Hz, 1H).
^{13}C NMR: (100 MHz, $CDCl_3$) δ 137.61, 129.27, 128.38, 126.20, 101.43, 80.78, 79.13, 73.00, 69.81, 63.42, 28.28.
HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{13}H_{14}O_3Na$ 241.0835; Found 241.0820.
m.p.: 71 °C

(±)–**S13**

To a 50 mL flask, (±)–**S12** (178 mg, 0.82 mmol) was added NHNsBoc (330 mg, 1.09 mmol, 1.34 eq,), PPh_3 (427 mg, 1.64 mmol, 2.0 eq.) and dry THF (8.1 mL). The reaction mixture was cooled to 0 °C then DIAD (0.32 mL, 1.64 mmol, 2.0 eq.) was slowly added. The reaction was warmed to 50 °C and stirred for 2 days. The crude product was directly concentrated and the residue was purified by silica chromatography (Acetone-hexane 1:8 to 1:4), then Al_2O_3 chromatography (EtOAc-Hexane 1:4) to afford (±)–**S13** (236 mg, 0.47 mmol, 58%).

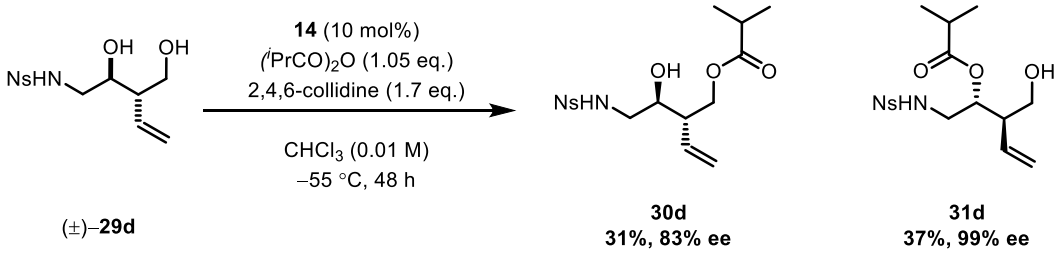
White solid: **IR** (neat): 3289, 2980, 1734, 1544, 1369, 1254, 1149, 1120, 1000 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.31 (dd, J = 7.9, 1.4 Hz, 1H), 7.74–7.64 (m, 2H), 7.63–7.52 (m, 3H), 7.39–7.27 (m, 3H), 5.57 (s, 1H), 4.39 (dd, J = 11.3, 4.9 Hz, 1H), 4.35–4.26 (m, 1H), 4.20–4.10 (m, 2H), 3.88 (t, J = 11.1 Hz, 1H), 2.81–2.66 (m, 1H), 2.26 (d, J = 2.4 Hz, 1H), 1.32 (s, 9H).

^{13}C NMR: (100 MHz, $CDCl_3$) 150.27, 147.62, 137.55, 134.22, 133.64, 133.30, 131.79, 128.81, 128.13, 126.14, 124.44, 100.96, 85.33, 78.51, 78.03, 73.64, 69.84, 49.67, 30.69, 27.83.
HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{24}H_{26}SN_2O_8Na$ 525.1302; Found 525.1276.
m.p.: 65 ℃

(±)–**29c**

To a 10 mL flask, (±)–**S13** (236 mg, 0.47 mmol) was added MeOH (7.2 mL) and conc. HCl (2.4 mL). The reaction mixture was stirred at 50 ℃ for 20 h. The reaction was cooled to room temperature and quenched with $NaHCO_{3(aq.)}$. The aqueous product was extracted twice with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica chromatography (EtOAc-Hexane 3:1) then recrystallized with $CHCl_3$/hexane systems to afford white crystals. The crystals were collected by filtration and were washed with hexane to afford (±)–**29c** (76.3 mg, 0.24 mmol, 52%).

White solid: **IR** (neat): 3363, 3300, 1539, 1417, 1359, 1338, 1163, 1097, 1026 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.21–8.10 (m, 1H), 7.92–7.85 (m, 1H), 7.83–7.70 (m, 2H), 5.87 (d, *J* = 6.5 Hz, 1H), 4.03–3.77 (m, 3H), 3.52 (ddd, *J* = 13.2, 6.5, 3.1 Hz, 1H), 3.33–3.20 (m, 2H), 2.74–2.64 (m, 1H), 2.31–2.16 (m, 2H).
^{13}C NMR: (100 MHz, $CDCl_3$) δ 148.04, 133.96, 133.26, 133.10, 131.26, 125.60, 80.58, 73.71, 71.20, 63.28, 47.76, 38.04.
HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{12}H_{14}N_2O_6SNa$ 337.0465; Found 337.0450.
m.p.: 105 ℃



(±)–**29d** → **30d** 31%, 83% ee; **31d** 37%, 99% ee

Following the general procedure for PKR, (±)–**29d** (27.2 mg, 0.086 mmol), isobutyric anhydride (15.0 µl, 0.090 mmol, 1.05 eq.), 2,4,6-collidine (19.3 µl, 0.15 mmol, 1.7 eq), **14** (7.16 mg, 0.00086 mmol, 0.1 eq.), dry $CHCl_3$ (8.6 mL, 0.01 M) under Argon were stirred at −55 ℃ for 48 h. The crude material was purified by preparative thin-layer chromatography purification (hexane/ethyl acetate = 1 : 3) to give **30d** and **31d**.

***Anti*-2-ethenyl-3-hydroxy-4-((4-nitrophenyl)sulfonamido)butyl isobutyrate (30d)**

Yellow oil: 10.2 mg
IR (neat): 3506, 3335, 2977, 2937, 1722, 1539, 1360, 1169, 1077 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.13–8.07 (m, 1H), 7.90–7.85 (m, 1H), 7.77–7.71 (m, 2H), 5.82 (dd, *J* = 7.3, 4.5 Hz,

1H), 5.70–5.59 (m, 1H), 5.28–5.12 (m, 2H), 4.55 (dd, *J* = 11.3, 4.3 Hz, 1H), 4.01 (dd, *J* = 11.3, 4.1 Hz, 1H), 3.64–3.55 (m, 1H), 3.34 (ddd, *J* = 12.8, 7.5, 3.0 Hz, 1H), 3.26 (d, *J* = 4.5 Hz, 1H), 3.00 – 2.91 (m, 1H), 2.56 (hept, *J* = 7.0 Hz, 1H), 2.43–2.33 (m, 1H), 1.16 (d, *J* = 1.8 Hz, 3H), 1.15 (d, *J* = 1.8 Hz, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 178.25, 148.29, 134.40, 133.76, 133.59, 132.88, 131.21, 125.63, 119.70, 69.41, 64.54, 48.36, 47.45, 34.21, 19.21, 19.05.

HRMS (ESI) *m/z*: [M+Na$^+$] Calcd for $C_{16}H_{22}N_2O_7SNa$ 409.1040; Found 409.1017.

HPLC condition: (DAICEL CHIRALPAK IC, 2-propanol/hexane 5:5, flow 1.4 mL/min, 12.3 min (minor), 17.7 min (major).

[α]$_D^{21}$ –14.5 (*c* 0.8 in $CHCl_3$).

***Anti*-3-Ethenyl-4-hydroxy-1-((4-nitrophenyl)sulfonamido)butan-2-yl isobutyrate (31d)**

Yellow oil: 12.2 mg

IR (neat): 3342, 2977, 1728, 1541, 1418, 1237, 1167 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.18–8.05 (m, 1H), 7.93–7.68 (m, 3H), 7.26 (s, 1H), 5.78–5.67 (m, 1H), 5.64 (t, *J* = 6.4 Hz, 1H), 5.33–5.17 (m, 2H), 4.92–4.84 (m, 1H), 3.65–3.39 (m, 3H), 3.32–3.23 (m, 1H), 2.57 (h, *J* = 7.0 Hz, 1H), 2.51–2.42 (m, 1H), 1.16 (t, *J* = 7.3 Hz, 6H).

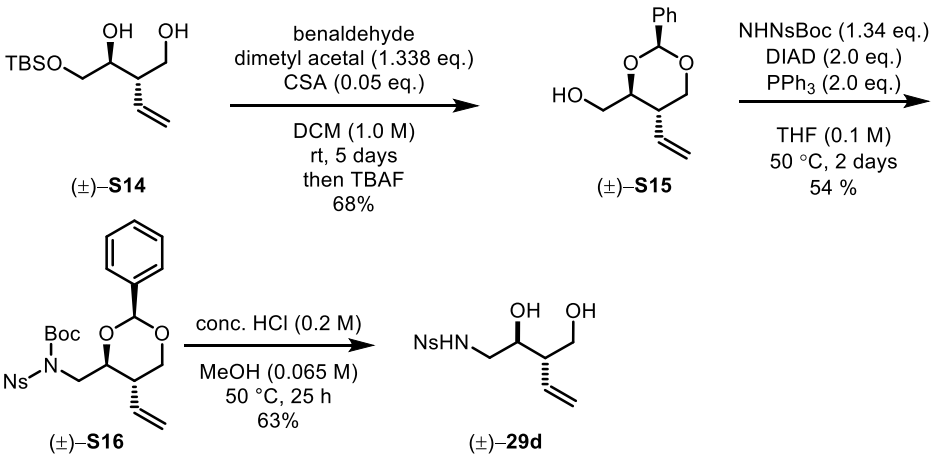
^{13}C NMR: (100 MHz, $CDCl_3$) δ 177.50, 148.15, 134.40, 133.93, 133.90, 133.17, 131.02, 125.68, 120.24, 70.88, 62.23, 48.37, 45.38, 34.21, 19.22, 18.87.

HRMS (ESI) *m/z*: [M+Na$^+$] Calcd for $C_{16}H_{22}N_2O_7SNa$ 409.1040; Found 409.1028.

HPLC condition: (DAICEL CHIRALPAK IC, 2-propanol/hexane 4:6, flow 1 mL/min, 11.0 min (major), 14.3 min (minor).

[α]$_D^{21}$ –65.5 (*c* 1.2 in $CHCl_3$).

<u>Substrate synthesis of (±)–29d</u>



(±)–**S15**

To a 50 mL flask, (±)–**S14** (1.00 g, 4.07 mmol, *prepared according to a literature method*[5]) was added Benzaldehyde dimethylacetal (0.813 ml, 5.45 mmol, 1.34 eq,), CSA (47.3 mg, 0.20 mmol, 0.05 eq.) and dry DCM (19.7 mL). The reaction mixture was stirred at room temperature for 5 days. The reaction mixture was quenched with NEt_3 (0.4 mL) and stirred for 15 min. Then Tetrabutylammonium fluoride (16 mmol) was added and stirred for additional 24 h. The reaction mixture was diluted with water and the phase was separated and the aqueous phase was extracted twice with EtOAc. The combined organics were dried (Na_2SO_4), filtered, and concentrated and the crude product was purified by silica chromatography (EtOAc: Hexane 1:5) to afford (±)–**S15** (610 mg, 2.77 mmol, 68%).

Colorless oil: **IR** (neat): 3444, 2848, 1456, 1399, 1368, 1311, 1216, 1137, 1080, 1024 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.56–7.48 (m, 2H), 7.44–7.32 (m, 3H), 5.55–5.42 (m, 2H), 5.28–5.14 (m, 2H), 4.13 (dd, *J* = 11.3, 5.1 Hz, 1H), 3.79–3.56 (m, 4H), 2.67–2.52 (m, 2H).
^{13}C NMR: (100 MHz, $CDCl_3$) δ 138.09, 133.17, 128.99, 128.24, 126.19, 119.59, 101.06, 80.87, 70.42, 63.29, 40.54.
HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{13}H_{16}O_3Na$ 243.0992; Found 243.0991.

(±)–**S16**

To a 100 mL flask, (±)–**S15** (603 mg, 2.74 mmol) was added NHNsBoc (1.11 g, 3.67 mmol, 1.34 eq,), PPh_3 (1.44 g, 5.48 mmol, 2.0 eq.) and dry THF (27.4 mL). The reaction mixture was cooled to 0 ℃ then DIAD (1.08 mL, 5.48 mmol, 2.0 eq.) was slowly added. The reaction was warmed to 50 ℃ and stirred for 2 days. The crude product was directly concentrated and the residue was purified by silica chromatography (Acetone-hexane 1:8) then recrystallized with EA/hexane systems to afford white crystals. The crystals were collected by filtration and were washed with hexane to afford (±)–**S16** (747 mg, 1.48 mmol, 54%).

White solid: **IR** (neat): 2976, 2848, 1728, 1542, 1366, 1308, 1178, 1153, 1018 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.74–7.63 (m, 2H), 7.61–7.51 (m, 3H), 7.38–7.28 (m, 3H), 5.68–5.58 (m, 1H), 5.57 (s, 1H), 5.36–5.24 (m, 2H), 4.19–3.98 (m, 4H), 3.74 (t, *J* = 11.2 Hz, 1H), 2.60–2.47 (m, 1H), 1.27 (s, 9H).
^{13}C NMR: (100 MHz, $CDCl_3$) δ 150.40, 147.71, 138.15, 134.08, 133.92, 133.06, 132.85, 131.79, 128.74, 128.16, 126.26, 124.45, 120.21, 100.81, 85.17, 78.29, 70.67, 49.51, 43.19, 27.81.
HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{24}H_{28}SN_2O_8Na$ 527.1459; Found 527.1453.
m.p.: 133 ℃

(±)–**29d**

To a 20 mL flask, (±)–**S16** (659 mg, 1.31 mmol) was added MeOH (6.5 mL) and conc. HCl (20 mL). The reaction mixture was stirred at 50 ℃ for 28 h. The reaction was cooled to room temperature and quenched with $NaHCO_{3(aq.)}$. The aqueous product was extracted twice with EtOAc. The organic layer was dried over Na_2SO_4, filtered and

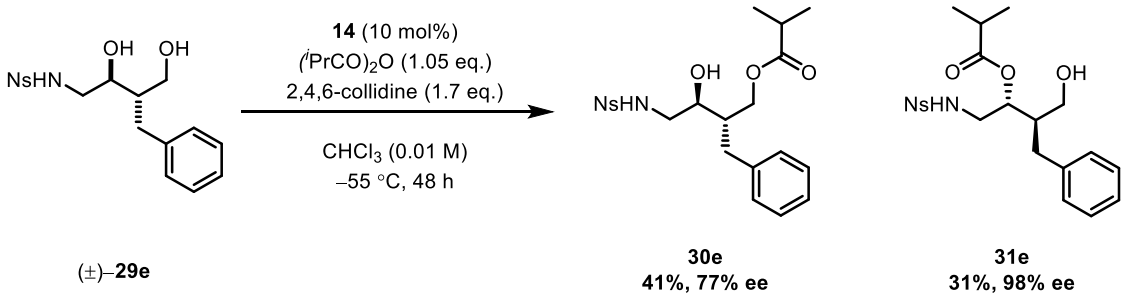
concentrated under vacuum. The residue was purified by silica chromatography (EtOAc-Hexane 3:1) to afford (±)–**29d** (261 mg, 0.83 mmol, 63%).

Yellow oil: **IR** (neat): 3349, 2889, 1542, 1410, 1361, 1168, 1125, 1088 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.16–8.03 (m, 1H), 7.91–7.82 (m, 1H), 7.81–7.69 (m, 2H), 5.93 (t, *J* = 6.0 Hz, 1H), 5.66–5.46 (m, 1H), 5.19 (t, *J* = 1.6 Hz, 1H), 5.18–5.13 (m, 1H), 3.90–3.82 (m, 2H), 3.78 (d, *J* = 6.0 Hz, 2H), 3.27 (ddd, *J* = 12.9, 6.6, 2.9 Hz, 1H), 3.02 (ddd, *J* = 12.8, 7.3, 5.4 Hz, 1H), 2.67 (s, 1H), 2.45 – 2.34 (m, 1H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 148.16, 134.33, 133.84, 133.43, 132.99, 131.21, 125.61, 119.55, 72.74, 65.36, 49.01, 47.89.

HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{12}H_{16}N_2O_6SNa$ 339.0621; Found 339.0630.



(±)–**29e** **30e** 41%, 77% ee **31e** 31%, 98% ee

Following the general procedure for PKR, (±)–**29e** (27.0 mg, 0.071 mmol), isobutyric anhydride (12.4 µl, 0.075 mmol, 1.05 eq.), 2,4,6-collidine (16.0 µl, 0.12 mmol, 1.7 eq), **14** (5.91 mg, 0.0071 mmol, 0.1 eq.), dry $CHCl_3$ (7.1 mL, 0.01 M) under Argon were stirred at −55 °C for 48 h. The crude material was purified by preparative thin-layer chromatography purification (hexane/ethyl acetate = 1 : 1) to give **30e** and **31e**.

***Anti*-2-benzyl-3-hydroxy-4-((4-nitrophenyl)sulfonamido)butyl isobutyrate (30e)**

Yellow oil: 15.3 mg

IR (neat): 3527, 3343, 2974, 2934, 1723, 1541, 1344, 1166 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.14–8.06 (m, 1H), 7.92–7.83 (m, 1H), 7.79–7.68 (m, 2H), 7.33–7.28 (m, 2H), 7.25–7.20 (m, 1H), 7.16 (dd, *J* = 6.9, 1.6 Hz, 2H), 5.82 (t, *J* = 6.1 Hz, 1H), 4.40 (dd, *J* = 11.7, 3.4 Hz, 1H), 3.85 (dd, *J* = 11.7, 4.4 Hz, 1H), 3.67–3.52 (m, 1H), 3.38 (ddd, *J* = 12.6, 7.1, 3.0 Hz, 1H), 3.22 (d, *J* = 4.5 Hz, 1H), 3.14 (ddd, *J* = 12.9, 8.0, 5.0 Hz, 1H), 2.74 (dd, *J* = 13.6, 6.0 Hz, 1H), 2.65–2.50 (m, 2H), 2.05–1.94 (m, 1H), 1.18 (dd, *J* = 7.0, 3.8 Hz, 6H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 178.21, 148.28, 138.83, 133.79, 133.63, 132.90, 131.15, 129.21, 128.84, 126.71, 125.64, 70.05, 62.31, 47.47, 44.21, 34.26, 34.10, 19.26, 19.11.

HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{21}H_{26}N_2O_7SNa$ 473.1353; Found 473.1364.

HPLC condition: (DAICEL CHIRALPAK IC, 2-propanol/hexane 5:5, flow 1.4 mL/min, 11.2 min (minor), 25.5 min (major).

[α]$_D^{23}$ +5.39 (*c* 0.2 in $CHCl_3$).

***Anti*-3-Benzyl-4-hydroxy-1-((4-nitrophenyl)sulfonamido)butan-2-yl isobutyrate (31e)**

Yellow oil: 7.81 mg

IR (neat): 3565, 3343, 2935, 1728, 1541, 1346, 1166 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.17–8.06 (m, 1H), 7.88–7.83 (m, 1H), 7.77–7.71 (m, 2H), 7.31–7.26 (m, 2H), 7.24–7.17 (m, 1H), 7.16–7.11 (m, 2H), 5.89 (t, *J* = 6.4 Hz, 1H), 4.94 (td, *J* = 6.3, 4.4 Hz, 1H), 3.62–3.35 (m, 4H), 2.69–2.50 (m, 3H), 2.16–2.01 (m, 1H), 1.83 (dd, *J* = 6.7, 4.4 Hz, 1H), 1.17 (dd, *J* = 10.0, 7.0 Hz, 6H).

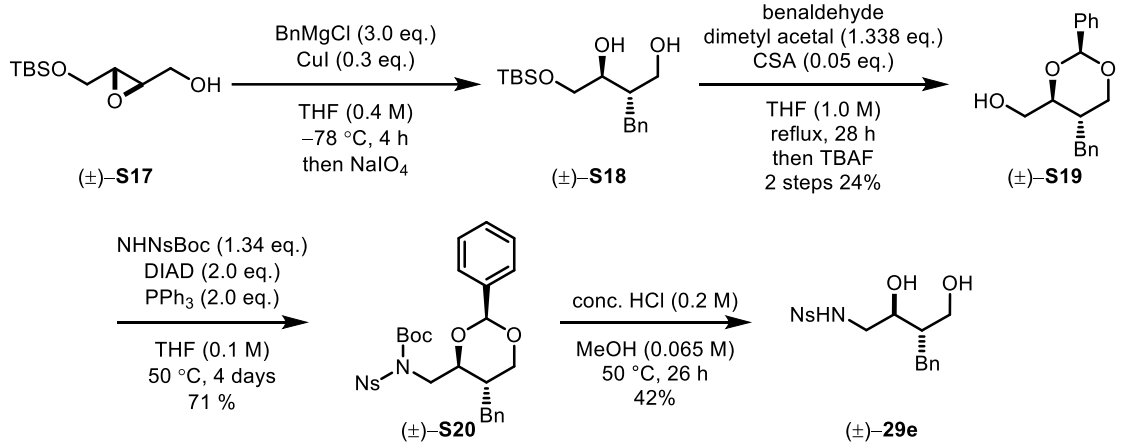
^{13}C NMR: (100 MHz, $CDCl_3$) δ 177.12, 148.15, 139.14, 134.03, 133.82, 133.14, 131.06, 129.22, 128.76, 126.59, 125.60, 72.24, 60.18, 45.07, 44.27, 34.26, 33.51, 19.27, 18.94.

HRMS (ESI) *m/z*: [M+Na$^+$] Calcd for $C_{21}H_{26}N_2O_7SNa$ 473.1353; Found 473.1363..

HPLC condition: (DAICEL CHIRALPAK IC, 2-propanol/hexane 4:6, flow 1 mL/min, 11.4 min (major), 16.5 min (minor).

[α]$_D^{22}$ –48.2 (*c* 0.4 in $CHCl_3$)

Substrate synthesis of (±)–29e



(±)–**S19**

To a 10 mL flask, CuI (523 mg, 2.75 mmol, 0.3 eq.) in THF (13 mL, 0.7 mmol) was cooled to −78 °C. Then, BnMgBr (3.0 eq.) was slowly added to the flask and stirred for 1 h. Then, (±)–**S17** (2.0 g, 9.12 mmol, *prepared according to a literature method*[7]) in THF (10 mL) was slowly added over 30 min and stirred for another 4 h at −78 °C. The reaction was warmed to r.t. and quenched with NH_4Cl(aq) and diluted with NH_3OH (aq.) the phase was separated and the aqueous phase was extracted three times with EtOAc. The combined organics were dried (Na_2SO_4), filtered, and concentrated in vacuo. To the crude product, $NaIO_4$ (12.0 mmol, 1.32 eq.) and THF:H_2O 1:1 (80 mL) was added and stirred for 16 h to give crude (±)–**S18** (Small amount of crude mixture was purified by thin-layer preparative TLC: hexane/ethyl acetate = 4 : 1).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.32–7.25 (m, 2H), 7.24–7.16 (m, 3H), 3.83–3.71 (m, 2H), 3.70–3.56 (m, 3H), 3.00 (t, *J* = 5.8 Hz, 1H), 2.86 (d, *J* = 3.8 Hz, 1H), 2.82–2.67 (m, 2H), 1.93–1.83 (m, 1H), 0.90 (s, 9H), 0.07 (s, 6H).
^{13}C NMR: (100 MHz, $CDCl_3$) δ 140.15, 129.27, 128.58, 126.27, 74.60, 65.92, 63.08, 44.01, 35.14, 25.98, 18.38, -5.25, -5.30.

To a 50 mL flask, (±)–**S18** was added Benzaldehyde dimethylacetal (1.69 ml, 11.3 mmol, 2.0 eq,), CSA (131 mg, 0.57 mmol, 0.1 eq.) and dry THF (11 mL). The reaction mixture was stirred reflux for 28 h. The reaction mixture was quenched with NEt_3 (0.4 mL) and stirred for 15 min. Then Tetrabutylammonium fluoride (16.8 mmol) was added and stirred for additional 24 h. The reaction mixture was diluted with water and the phase was separated and the aqueous phase was extracted twice with EtOAc. The combined organics were dried (Na_2SO_4), filtered, and concentrated and the crude product was purified by silica chromatography (EtOAc: Hexane 1:4) to afford (±)–**S19** (658 mg, 2.32 mmol, 41%).

Colorless oil: **IR** (neat): 3445, 2847, 1495, 1454, 1395, 1137, 1088, 1024 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.66–7.55 (m, 2H), 7.49–7.35 (m, 5H), 7.34–7.28 (m, 1H), 7.25–7.18 (m, 2H), 5.54 (s, 1H), 4.07 (dd, *J* = 11.4, 4.7 Hz, 1H), 3.93–3.84 (m, 1H), 3.80–3.68 (m, 2H), 3.57 (t, *J* = 11.3 Hz, 1H), 2.92 (s, 1H), 2.82 (dd, *J* = 13.7, 4.4 Hz, 1H), 2.45–2.30 (m, 1H), 2.25 (dd, *J* = 13.7, 9.9 Hz, 1H).
^{13}C NMR: (100 MHz, $CDCl_3$) δ 138.17, 138.03, 128.77, 128.62, 128.38, 128.07, 126.27, 126.12, 100.86, 81.98, 70.68, 62.84, 35.72, 33.92.
HRMS (ESI) *m*/*z*: [M+Na^+] Calcd for $C_{18}H_{20}O_3Na$ 307.1305; Found 307.1289.

(±)–**S20**

To a 20 mL flask, (±)–**S19** (620 mg, 2.18 mmol) was added NHNsBoc (883 mg, 2.92 mmol, 1.34 eq,), PPh_3 (1.14 g, 4.36 mmol, 2.0 eq.) and dry THF (22 mL). The reaction mixture was cooled to 0 ℃ then DIAD (0.86 mL, 4.36 mmol, 2.0 eq.) was slowly added. The reaction was warmed to 50 ℃ and stirred for 4 days. The crude product was directly concentrated and the residue was purified by silica chromatography (EtOAc-hexane 1:6), then Al_2O_3 chromatography (EtOAc-Hexane 1:10 to 3:1) to afford (±)–**S20** (890 mg, 1.56 mmol, 71%).

White amorphous: **IR** (neat): 2980, 1732, 1534, 1455, 1368, 1279, 1148, 1026 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.71–7.60 (m, 2H), 7.57–7.48 (m, 3H), 7.35–7.25 (m, 5H), 7.25–7.13 (m, 3H), 5.52 (s, 1H), 4.16 (d, *J* = 5.9 Hz, 2H), 4.07–3.98 (m, 2H), 3.58 (t, *J* = 11.2 Hz, 1H), 2.95 (dd, *J* = 14.0, 4.6 Hz, 1H), 2.34 (dd, *J* = 14.0, 9.7 Hz, 1H), 2.26–2.12 (m, 1H), 1.25 (s, 9H).
^{13}C NMR: (100 MHz, $CDCl_3$) δ 150.37, 147.63, 138.22, 138.02, 134.14, 133.69, 132.90, 131.73, 128.81, 128.66, 128.61, 128.03, 126.56, 126.22, 124.39, 100.69, 85.14, 79.84, 70.96, 49.16, 38.45, 34.19, 27.69.
HRMS (ESI) *m*/*z*: [M+Na^+] Calcd for $C_{29}H_{32}SN_2O_8Na$ 591.1772: Found 591.1784.

(±)–**29e**

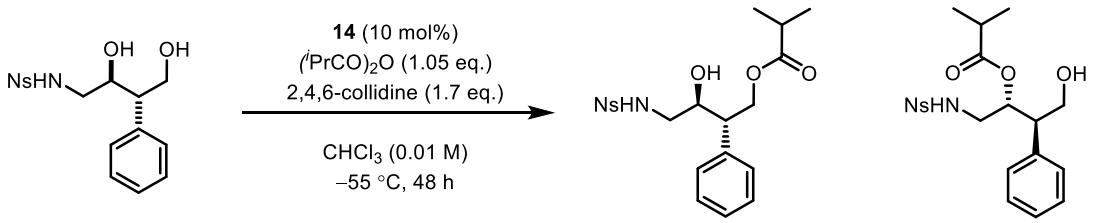
To a 20 mL flask, (±)–**S20** (403 mg, 0.71 mmol) was added MeOH (10.9 mL) and conc. HCl (3.54 mL). The reaction mixture was stirred at 50 ℃ for 26 h. The reaction was cooled to room temperature and quenched with $NaHCO_{3(aq.)}$. The aqueous product was extracted twice with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica chromatography (EtOAc-Hexane 2:1) to afford rac (±)–**29e** (115 mg, 0.30 mmol, 42%).

Yellowish oil: **IR** (neat): 3344, 3026, 2928, 1540, 1410, 1340, 1166, 1080 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 5.9, 3.4 Hz, 1H), 7.96–7.78 (m, 1H), 7.75–7.66 (m, 2H), 7.25–7.11 (m, 5H), 6.02 (t, *J* = 6.1 Hz, 1H), 3.84–3.70 (m, 3H), 3.60 (dd, *J* = 11.1, 6.0 Hz, 1H), 3.35–3.12 (m, 2H), 2.84–2.49 (m, 3H), 1.97–1.87 (m, 1H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 148.08, 139.46, 133.82, 133.45, 133.00, 131.10, 129.17, 128.67, 126.44, 125.55, 72.93, 62.96, 48.03, 44.13, 34.75.

HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{17}H_{20}N_2O_6SNa$ 403.0934; Found 403.0902.



(±)–**29f**

30f
56%, 71% ee

31f
24%, 98% ee

Following the general procedure for PKR, (±)–**29f** (23.6 mg, 0.064 mmol), isobutyric anhydride (11.2 µl, 0.067 mmol, 1.05 eq.), 2,4,6-collidine (14.5 µl, 0.11 mmol, 1.7 eq), **14** (5.37 mg, 0.0064 mmol, 0.1 eq.), dry $CHCl_3$ (6.4 mL, 0.01 M) under Argon were stirred at −55 ℃ for 48 h. The crude material was purified by preparative thin-layer chromatography purification (hexane/ethyl acetate = 1 : 1) to give **30f** and **31f**.

***Anti*-2-phenyl-3-hydroxy-4-((4-nitrophenyl)sulfonamido)butyl isobutyrate (30f)**

Yellow oil: 15.7 mg

IR (neat): 3490, 3343, 2976, 1724, 1541, 1346, 1198, 1166, 1082 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.90 (ddd, *J* = 37.4, 7.5, 1.7 Hz, 2H), 7.75–7.64 (m, 2H), 7.39–7.27 (m, 3H), 7.16–7.07 (m, 2H), 5.79 (t, *J* = 5.9 Hz, 1H), 4.67 (dd, *J* = 11.4, 5.4 Hz, 1H), 4.25 (dd, *J* = 11.4, 4.6 Hz, 1H), 4.05–3.89 (m, 1H), 3.32 (d, *J* = 4.4 Hz, 1H), 3.06 (ddd, *J* = 13.0, 7.1, 2.9 Hz, 1H), 2.92 (dt, *J* = 9.8, 5.0 Hz, 1H), 2.83 (ddd, *J* = 12.8, 7.8, 4.9 Hz, 1H), 2.52 (hept, *J* = 7.0 Hz, 1H), 1.10 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 177.94, 148.22, 138.33, 133.73, 133.42, 132.82, 131.27, 129.10, 128.41, 127.84, 125.59, 71.03, 65.47, 49.52, 47.63, 34.18, 19.08, 19.01.

HRMS (ESI): calcd for $C_{20}H_{24}N_2O_7SNa$ [M+Na$^+$]: *m*/*z*=459.1196, found: *m*/*z*=459.1192.

HPLC condition: (DAICEL CHIRALPAK IC, 2-propanol/hexane 5:5, flow 1.4 mL/min, 15.4 min (minor), 22.8 min (major).

[α]$_D^{23}$ +12.8 (*c* 1.2 in $CHCl_3$).

***Anti*-3-Phenyl-4-hydroxy-1-((4-nitrophenyl)sulfonamido)butan-2-yl isobutyrate (31f)**

Yellow oil: 6.80 mg

IR (neat): 3534, 3346, 2975, 1727, 1541, 1349, 1167, 1077 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.98–7.91 (m, 1H), 7.89–7.84 (m, 1H), 7.72 (pd, *J* = 7.5, 1.7 Hz, 2H), 7.39–7.27 (m, 3H), 7.25–7.20 (m, 2H), 5.56 (t, *J* = 6.3 Hz, 1H), 5.17 (ddd, *J* = 9.9, 6.5, 3.2 Hz, 1H), 3.83 – 3.69 (m, 2H), 3.23 (ddd, *J* = 14.0, 6.7, 3.2 Hz, 1H), 3.13–3.05 (m, 1H), 3.05–2.96 (m, 1H), 2.63 (hept, *J* = 7.0 Hz, 1H), 1.87 (dd, *J* = 7.6, 5.8 Hz, 1H), 1.20 (dd, *J* = 8.8, 7.0 Hz, 6H).

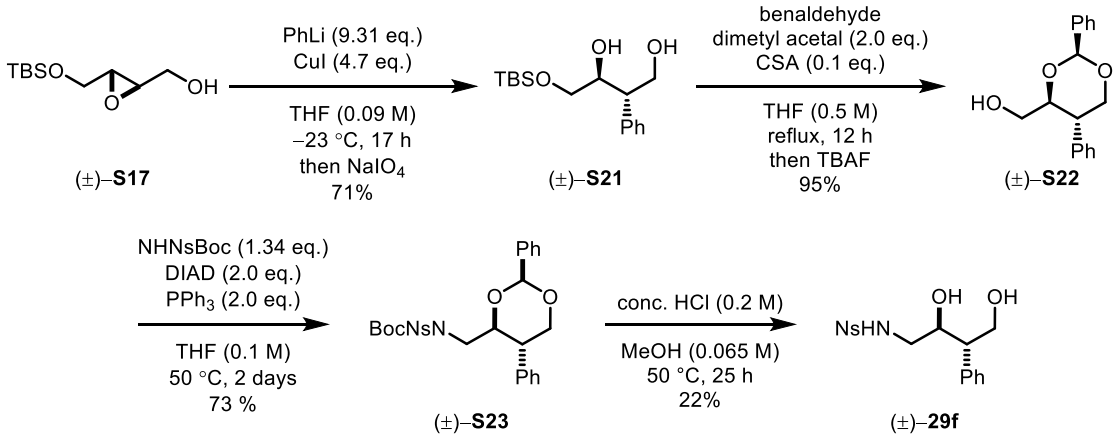
^{13}C NMR: (100 MHz, $CDCl_3$) δ 177.52, 148.10, 138.03, 133.88, 133.76, 133.07, 131.06, 129.31, 128.71, 128.07, 125.68, 72.10, 63.30, 49.73, 45.42, 34.31, 19.23, 18.91.

HRMS (ESI) *m*/*z*: [M+Na$^+$] Calcd for $C_{20}H_{24}N_2O_7SNa$ 459.1196; Found 459.1179.

HPLC condition: (DAICEL CHIRALPAK IC, 2-propanol/hexane 4:6, flow 1 mL/min, 10.8 min (minor), 12.6 min (major).

[α]$_D^{23}$ –32.4 (*c* 0.5 in $CHCl_3$).

<u>Substrate synthesis of (±)–29f</u>



(±)–**S21**

To a dry flask, equipped with a stir bar was added CuI (8.95 g, 47.0 mmol, 4.7 eq.), dry THF (111 mL, 0.09 M) under Argon. The reaction vessel was cooled to -23 °C and PhLi (93.1 mmol, 9.31 eq.) was slowly added. The reaction

mixture was stirred for another 1 h at the same temperature. Then (±)–**S17** (2.18 g, 10 mmol, *prepared according to a literature method*[7]) in dry THF (25 mL) was added dropwise and warmed up to room temperature and stirred for over night. The reaction mixture was quenched with NH_4Cl and diluted with NH_3OH aq. the phase was separated and the aqueous phase was extracted twice with EtOAc. The combined organics were dried (Na_2SO_4), filtered, and concentrated in vacuo. To the crude product, $NaIO_4$ (13.2 mmol, 1.32 eq.) and THF:H_2O 1:1 (104 mL) was added and stirred for 10 h. The crude product was concentrated and was purified by silica chromatography (EtOAc: Hexane 1:4 to 1:3) to afford (±)–**S21** (2.09 g, 7.06 mmol, 71%).

Colorless oil: **IR** (neat): 3382, 2953, 2930, 2857, 1467, 1122, 1079, 1005 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.38–7.27 (m, 3H), 7.21–7.11 (m, 2H), 4.12 (ddd, *J* = 11.0, 7.9, 4.0 Hz, 1H), 4.07–4.00 (m, 1H), 3.87–3.78 (m, 1H), 3.48–3.24 (m, 2H), 3.09 (dd, *J* = 8.4, 4.0 Hz, 1H), 2.98 (d, *J* = 4.5 Hz, 1H), 2.91 (ddd, *J* = 9.6, 7.8, 4.6 Hz, 1H), 0.87 (d, *J* = 0.9 Hz, 9H), -0.02 (s, 6H).
^{13}C NMR: (100 MHz, $CDCl_3$) δ 139.50, 128.87, 128.19, 127.24, 75.93, 66.97, 65.38, 50.27, 25.92, 18.29, -5.39, -5.43.
HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{16}H_{28}O_3SiNa$ 319.1700; Found 319.1689.

(±)–**S22**
To a 10 mL flask, (±)–**S21** (95.8 mg, 0.323 mmol) was added Benzaldehyde dimethylacetal (0.096 ml, 0.646 mmol, 2.0 eq,), CSA (7.5 mg, 0.03 mmol, 0.1 eq.) and dry THF (0.65 mL). The reaction mixture was stirred reflux for 12 h. The reaction mixture was quenched with NEt_3 (0.02 mL) and stirred for 15 min. Then Tetrabutylammonium fluoride (2.5 mmol) was added and stirred for additional 24 h. The reaction mixture was diluted with water and the phase was separated and the aqueous phase was extracted twice with EtOAc. The combined organics were dried (Na_2SO_4), filtered, and concentrated and the crude product was purified by silica chromatography (EtOAc: Hexane 1:5 to 1:4) to afford (±)–**S22** (83.1 mg, 0.31 mmol, 95%).

Colorless oil: **IR** (neat): 3453, 3033, 2923, 2860, 1455, 1378, 1135, 1088, 1023 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.65–7.58 (m, 2H), 7.47–7.28 (m, 6H), 7.27–7.14 (m, 2H), 5.72 (s, 1H), 4.28 (dd, *J* = 11.3, 4.9 Hz, 1H), 4.18–4.10 (m, 1H), 4.01 (t, *J* = 11.4 Hz, 1H), 3.60–3.43 (m, 2H), 3.16 (td, *J* = 11.0, 4.9 Hz, 1H), 2.53–2.45 (m, 1H).
^{13}C NMR: (100 MHz, $CDCl_3$) δ 138.09, 137.06, 129.07, 128.89, 128.31, 128.19, 127.53, 126.26, 101.37, 81.88, 71.86, 63.06, 42.44.
HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{17}H_{18}O_3Na$ 293.1148; Found 293.1120.

(±)–**S23**

To a 20 mL flask, (±)–**S22** (83 mg, 0.31 mmol) was added NHNsBoc (125 mg, 0.42 mmol, 1.34 eq,), PPh_3 (161 mg, 0.62 mmol, 2.0 eq.) and dry THF (3.1 mL). The reaction mixture was cooled to 0 °C then DIAD (0.12 mL, 0.62

mmol, 2.0 eq.) was slowly added. The reaction was warmed to 50 ℃ and stirred for 2 days. The crude product was directly concentrated and the residue was purified by silica chromatography (Acetone-hexane 1:4), then recrystallized with EA/hexane systems to afford white crystals. The crystals were collected by filtration and were washed with hexane to afford (±)–**S23** (124 mg, 0.22 mmol, 73%).

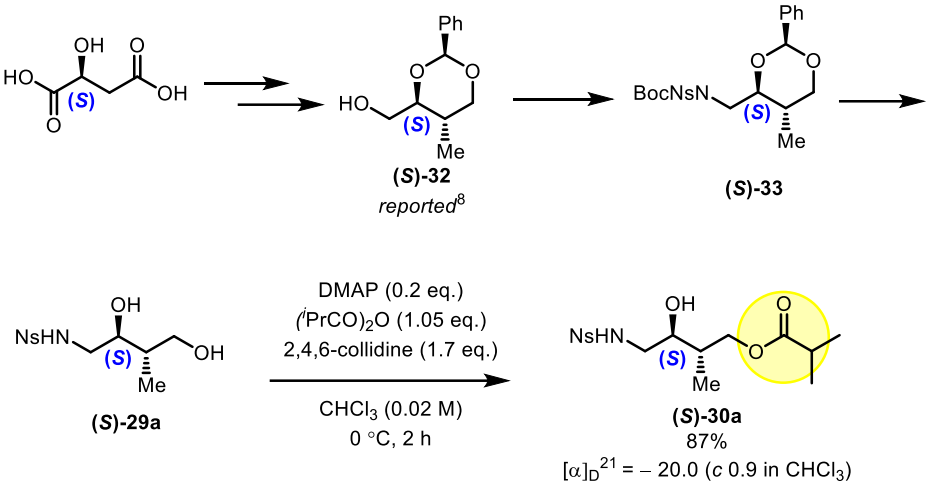
White solid: **IR** (neat): 2985, 1740, 1543, 1454, 1366, 1281, 1178, 1151, 1120 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.76–7.60 (m, 4H), 7.51 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.42–7.27 (m, 8H), 5.74 (s, 1H), 4.52 (td, *J* = 10.3, 2.5 Hz, 1H), 4.26 (dd, *J* = 11.4, 4.8 Hz, 1H), 4.11 (dd, *J* = 15.1, 10.3 Hz, 1H), 3.98 (t, *J* = 11.3 Hz, 1H), 3.73 (dd, *J* = 15.1, 2.5 Hz, 1H), 3.04 (td, *J* = 10.8, 4.8 Hz, 1H), 1.23 (s, 9H).
^{13}C NMR: (100 MHz, $CDCl_3$) δ 150.38, 147.71, 138.12, 136.58, 134.10, 133.93, 132.96, 131.80, 129.17, 128.85, 128.30, 128.24, 127.87, 126.37, 124.43, 101.17, 85.11, 78.44, 72.56, 49.36, 45.45, 27.83.
HRMS (ESI) *m*/*z*: [M+Na^+] Calcd for $C_{28}H_{30}SN_2O_8Na$ 577.1615; Found 577.1627.
m.p.: 160 ℃

(±)–**29f**

To a 10 mL flask, (±)–**S23** (230 mg, 0.41 mmol) was added MeOH (6.4 mL) and conc. HCl (2.1 mL). The reaction mixture was stirred at 50 ℃ for 25 h. The reaction was cooled to room temperature and quenched with $NaHCO_{3(aq.)}$. The aqueous product was extracted twice with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica chromatography (EtOAc-Hexane 2:1) to afford (±)–**23f** (33 mg, 0.09 mmol, 22%).

Colorless oil: **IR** (neat): 3343, 2928, 1595, 1540, 1409, 1362, 1167, 1080 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.84 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.75–7.60 (m, 2H), 7.37–7.27 (m, 3H), 7.17–7.06 (m, 2H), 5.86 (t, *J* = 6.0 Hz, 1H), 4.24–4.15 (m, 1H), 4.11–4.00 (m, 2H), 3.96–3.86 (m, 1H), 3.00 (ddd, *J* = 13.0, 6.1, 3.0 Hz, 1H), 2.96–2.80 (m, 2H), 2.69 (d, *J* = 5.6 Hz, 1H).
^{13}C NMR: (100 MHz, $CDCl_3$) δ 148.10, 138.36, 133.75, 133.20, 132.85, 131.22, 129.18, 128.19, 127.70, 125.55, 74.36, 66.85, 50.62, 47.88.
HRMS (ESI) *m*/*z*: [M+Na^+] Calcd for $C_{16}H_{18}N_2O_6S$ 389.0778; Found 389.0769.

Determination of absolute configuration of (*S*)-30a



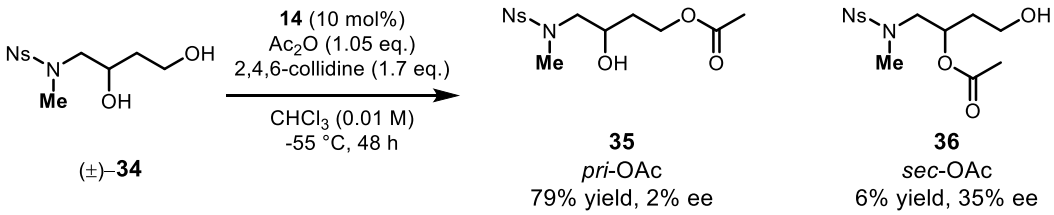
(*S*)-**32** was prepared by previously reported mrthod[8]. The experimental procedure for Mitsunobu reaction and deprotection of *N*-Boc, and benzylidene acetal is already reported above (p.65-66).

(*S*)-**33: [α]$_D^{23}$** +56.1 (*c* 1.0 in $CHCl_3$).
(*S*)-**29a: [α]$_D^{23}$** +32.2 (*c* 0.9 in $CHCl_3$).

Synthesis of (*S*)-30a

To a dry flask, equipped with a stir bar was added (*S*)-**29a** (0.048 mmol), DMAP (0.0096 mmol, 0.2 eq.), dry $CHCl_3$ (2.4 mL, 0.02 M) under Argon. The reaction vessel was then sonicated for several minutes (to allow for mixing). Then 2.4.6-collidine (10.8 µL, 1.7 eq.) was added. The resulting solution was stirred for 15 min at -55 °C and then (^{i}PrCO)$_2$O (8.37 µL, 1.05 eq.) was added in one portion. The mixture was stirred at 0 °C for 2 h. The reaction was subsequently quenched at rt through the addition of methanol. Then, the solution was concentrated under vacuum and diluted with ethyl acetate, water and 1N HCl. The separated organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by preparative TLC purification (EA-hexane 4:3) to yield the **(*S*)-30a: 87%, (*S*)-31a: 5%, diacylate: 6%**

Acylation of N-H protected substrate (±)–34



To a dry flask, equipped with a stir bar was added (±)–**34** (0.07 mmol), **14** (0.007 mmol, 0.1 eq.), dry $CHCl_3$ (7.0 mL, 0.01 M) under Argon. The reaction vessel was then sonicated for several minutes (to allow for mixing). Then 2.4.6-collidine (15.7 µL, 1.7 eq.) was added. The resulting solution was stirred for 15 min at -55 °C and then Ac_2O (7.0 µL, 1.05 eq.) was added in one portion. The mixture was stirred at -55 °C for 48 h. The reaction was subsequently

quenched at -55 °C through the addition of methanol and warmed up to room temperature. Then, the solution was concentrated under vacuum and the crude product was added 1N HCl (1.4 ml) and the phase was separated and aqueous phase was extracted twice with EtOAc. The combined organics were dried (Na_2SO_4), filtered, and concentrated and the crude product was purified by preparative TLC purification (EA-hexane 1:2) for 3 times to yield the product **35** (79%, 2% ee), **36** (7%, 35% ee)**.**

3-hydroxy-4-((N-methyl-4-nitrobenzene)sulfonamido)-1-butyl acetate (35)

Yellow oil: 19.1 mg

IR (neat): 3515, 2965, 2921, 1732, 1545, 1371, 1247, 1166, 1049 cm^{-1}.

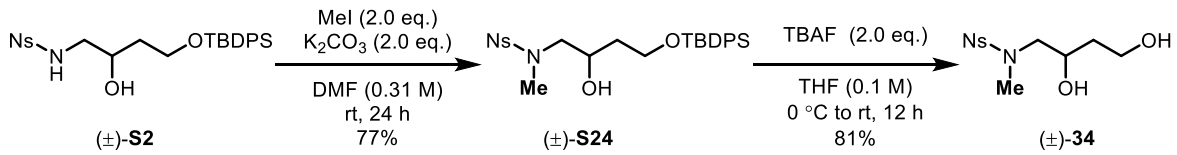
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.04–7.94 (m, 1H), 7.76–7.66 (m, 2H), 7.66–7.57 (m, 1H), 4.33 (ddd, *J* = 11.3, 8.9, 4.8 Hz, 1H), 4.16 (dt, *J* = 11.1, 5.4 Hz, 1H), 3.99–3.87 (m, 1H), 3.33–3.20 (m, 2H), 3.00 (s, 3H), 2.76 (dd, *J* = 4.3, 2.6 Hz, 1H), 2.05 (s, 3H), 1.91–1.62 (m, 2H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 171.69, 148.29, 133.86, 131.99, 131.78, 131.17, 124.27, 67.00, 61.13, 55.99, 36.32, 33.76, 21.09.

HRMS (ESI) *m/z*: [M+H^+] Calcd for $C_{13}H_{19}N_2O_7S$ 347.0907; Found 347.0907.

HPLC condition: (DAICEL CHIRALPAK ID, 2-propanol/hexane 3:7, flow 1 mL/min, 24.5 min (minor), 37.5 min (major).

Synthesis of (±)–34



(±)-**S24**

To a 10 mL flask, (±)-**S2** (200 mg, 0.38 mmol) was added K_2CO_3 (105 mg, 0.76 mmol), MeI (47.1 μL, 0.76 mmol) and DMF (1.2 mL). The reaction vessel was stirred rt for 24 h. The reaction was quenched with H_2O and the phase was separated and the aqueous phase was extracted twice with EtOAc/Hexane 1/1. The combined organics were dried (Na_2SO_4), filtered, and concentrated and the crude product was purified by silica chromatography (EtOAc: Hexane 1:1) to afford (±)-**S24** (158 mg, 0.29 mmol, 77%).

Yellow oil: **IR** (neat): 3498, 2932, 2859, 1546, 1369, 1167, 1110, 909 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.04 – 7.95 (m, 1H), 7.74 – 7.64 (m, 6H), 7.64 – 7.57 (m, 1H), 7.50 – 7.35 (m, 6H), 4.17 (qd, *J* = 4.8, 2.2 Hz, 1H), 3.97 – 3.83 (m, 2H), 3.47 (d, *J* = 2.8 Hz, 1H), 3.40 – 3.25 (m, 2H), 3.03 (s, 3H), 1.82 – 1.71 (m, 2H), 1.06 (s, 9H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ148.31, 135.59, 135.56, 133.65, 132.92, 132.81, 132.16, 131.67, 130.95, 130.01,

129.99, 127.93, 124.15, 70.02, 62.79, 55.89, 36.30, 35.80, 26.87, 19.09.
HRMS (ESI) : calcd for $C_{27}H_{34}N_2O_6SSiNa$ [M+Na^+]: *m*/*z*=565.1799, found: *m*/*z*=565.1798.

(±)–**34**

To a 20 mL flask, (±)-**S24** (158 mg, 0.29 mmol) was added THF (5.8 mL) and the reaction vessel was stirred at 0 ℃ for 10 min. Then TBAF (0.58 mmol) was added and stirred for 12 h. The reaction was diluted with water and the phase was separated and the aqueous phase was extracted twice with EtOAc. The combined organics were dried (Na_2SO_4), filtered, and concentrated and the crude product was purified by silica chromatography ($CHCl_3$: MeOH 40:1) to afford (±)–**34** (72 mg, 0.23 mmol, 81%).

Yellow oil: **IR** (KBr): 3384, 2936, 1544, 1441, 1343, 1165, 1058 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.01–7.93 (m, 1H), 7.74–7.64 (m, 2H), 7.64–7.57 (m, 1H), 4.09 (td, *J* = 7.8, 3.8 Hz, 1H), 3.83 (dtd, *J* = 15.4, 11.2, 5.1 Hz, 2H), 3.35–3.20 (m, 3H), 2.99 (s, 3H), 2.62–2.57 (m, 1H), 1.80–1.60 (m, 2H).
^{13}C NMR: (100 MHz, $CDCl_3$) δ148.30, 133.87, 131.92, 131.82, 130.91, 124.26, 69.12, 60.63, 56.17, 36.25, 35.83.
HRMS (ESI) *m*/*z*: [M+Na^+] Calcd for $C_{11}H_{16}N_2O_6SNa$ 327.0621; Found 327.0600.

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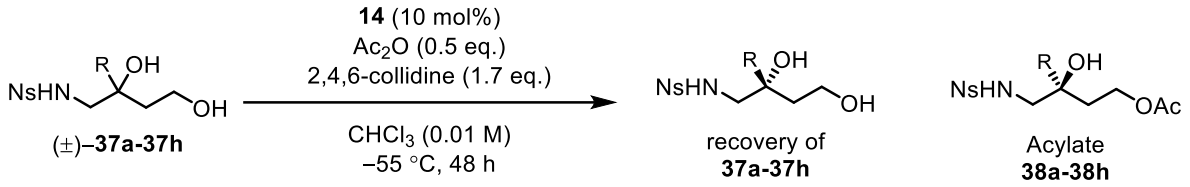
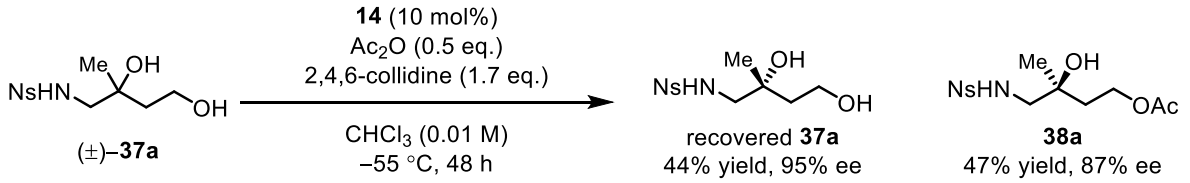
General Procedures for kinetic resolution of tertiary alcohols ((±)–37a-37h)



To a dry flask, equipped with a stir bar was added (±)–**37a-37h** (0.08 mmol), **14** (0.008 mmol, 0.1 eq.), dry $CHCl_3$ (9.0 mL, 0.01 M) under Argon. The reaction vessel was then sonicated for several minutes (to allow for mixing). Then 2.4.6-collidine (18.0 μL, 1.7 eq.) was added. The resulting solution was stirred for 15 min at -55 ℃ and then Ac_2O (3.8 μL, 0.50 eq.) was added in one portion. The mixture was stirred at -55 ℃ for 48 h. The reaction was subsequently quenched at -55 ℃ through the addition of methanol and warmed up to room temperature. Then, the solution was concentrated under vacuum and diluted with ethyl acetate, water and 1N HCl. The separated organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by preparative TLC purification (EA-hexane 2:1) to yield the acylate **38a-38h** and recovery of **37a-38h**.



Following the general procedure for KR, (±)–**37a** (21.0 mg, 0.069 mmol), acetic anhydride (3.25 μl, 0.034 mmol, 0.50 eq.), 2,4,6-collidine (15.5 μl, 0.12 mmol, 1.7 eq), **14** (5.74 mg, 0.0069 mmol, 0.1 eq.), dry $CHCl_3$ (6.9 mL, 0.01 M) under Argon were stirred at –55 ℃ for 48 h. The crude material was purified by preparative thin-layer chromatography purification (hexane/ethyl acetate = 1 : 2) to give **37a** and **38a**.

(*R*)-*N*-(2,4-dihydroxy-2-methylbutyl)-4-nitrobenzenesulfonamide (37a)

Yellow oil: 9.22 mg.

IR (neat): 3343, 1541, 1409, 1362, 1344, 1166, 1345, 1166 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.17–8.07 (m, 1H), 7.93–7.82 (m, 1H), 7.80–7.69 (m, 2H), 5.92 (s, 1H), 4.04–3.89 (m, 2H), 3.26 (s, 1H), 3.08 (q, *J* = 12.5 Hz, 2H), 2.00–1.93 (m, 2H), 1.67 (ddd, *J* = 14.9, 5.9, 3.4 Hz, 1H), 1.28 (s, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 148.20, 133.75, 133.59, 132.93, 131.20, 125.55, 72.40, 59.48, 53.26, 39.54, 25.19.

HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{11}H_{16}N_2O_6SNa$ 327.0621; Found 327.0621.

HPLC condition: (DAICEL CHIRALPAK AD-H, 2-propanol/hexane 3:7, flow 1.0 mL/min, 9.2 min (major), 11.7

min (minor).

[α]$_D^{21}$ –22.1 (*c* 0.8 in $CHCl_3$).

(*S*)-3-hydroxy-3-methyl-4-((4-nitrophenyl)sulfonamido)butyl acetate (38a)

Yellow oil: 11.3 mg.

IR (neat): 3518, 3349, 1733, 1541, 1365, 1248, 1167 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.18–8.05 (m, 1H), 7.94–7.84 (m, 1H), 7.78–7.71 (m, 2H), 5.76 (t, *J* = 6.4 Hz, 1H), 4.23 (t, *J* = 6.5 Hz, 2H), 3.12–2.96 (m, 2H), 2.24 (s, 1H), 2.05 (s, 3H), 1.99–1.76 (m, 2H), 1.26 (s, 3H).

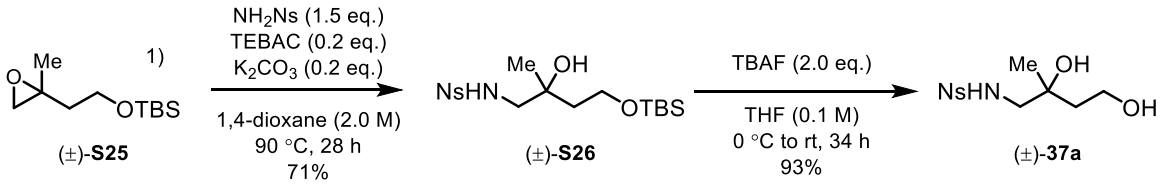
^{13}C NMR: (100 MHz, $CDCl_3$) δ 171.19, 148.21, 133.85, 133.53, 132.97, 131.22, 125.59, 71.34, 60.77, 53.01, 37.74, 25.04, 21.16.

HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{13}H_{18}N_2O_7SNa$ 369.0727; Found 369.0722.

HPLC condition: (DAICEL CHIRALPAK IC, 2-propanol/hexane 4:6, flow 1 mL/min, 29.5 min (minor), 67.9 min (major).

[α]$_D^{21}$ +2.22 (*c* 0.9 in $CHCl_3$).

Synthesis of (±)–37a



***N*-(4-((tert-butyldimethylsilyl)oxy)-2-hydroxy-2-methylbutyl)-4-nitrobenzenesulfonamide ((±)–S26)**

To a screw capped vial equipped with a stir bar was added tert-butyldimethyl(2-(2-methyloxiran-2-yl)ethoxy)silane (±)–**S25** (866 mg, 4 mmol, prepared according to a literature method[1]) was added o$NsNH_2$ (1.21 g, 6 mmol, 1.5 eq.), K_2CO_3 (111 mg, 0.8 mmol, 0.2 eq.), Benzyltriethylammonium Chloride (182 mg, 10.8 mmol, 0.2 eq.) and dry 1,4-dioxane (2 mL). The reaction mixture was stirred at 90 ℃ for 28 h. The reaction mixture was diluted with EtOAc, washed by H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica chromatography (EA-hexane 1:2) to yield (±)–**S26** (1.20 g, 2.86 mmol, 71%).

Yellow oil: **IR** (neat): 3456, 2954, 2931, 2858, 1542, 1406, 1361, 1170, 1083 cm^{-1}.

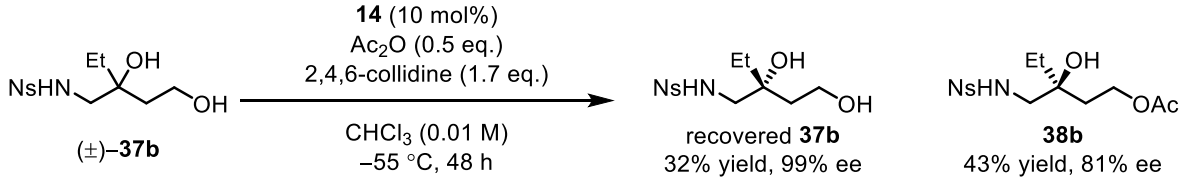
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.11–7.96 (m, 1H), 8.05–8.01 (m, 1H), 7.71–7.67 (m, 2H), 5.76 (t, *J* = 6.1 Hz, 1H), 4.11 (s, 1H), 3.98–3.73 (m, 2H), 3.09–2.90 (m, 2H), 1.94–1.84 (m, 1H), 1.57-1.51 (m, 1H), 1.18 (s, 3H), 0.80 (s, 9H), 0.01 (s, 3H), -0.01 (s, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 147.93, 133.64, 133.11, 132.70, 130.89, 125.18, 71.88, 60.10, 53.03, 38.84, 25.65, 24.63, 17.83, -5.81, -5.84.

HRMS (ESI) *m/z*: [M+Na$^+$] Calcd for $C_{17}H_{30}N_2O_6SSiNa$ 441.1486; Found 441.1472.

***N*-(2,4-dihydroxy-2-methylbutyl)-4-nitrobenzenesulfonamide ((±)–37a)**

To a solution of (±)–**S26** (556 mg, 1.33 mmol) in THF (0.1 M, 10 mL) was cooled to 0 ℃ was added a solution of TBAF [1 mol/L in THF] (2.66 mL, 2.66 mmol, 2.0 eq.). The mixture was warmed up to room temperature for 24 h and quenched with sat. NH_4Cl(aq). The aqueous phase was extracted with EtOAc twice, and the combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (EA only) to give (±)–**37a** (376 mg, 1.24 mmol, 93 %).



Following the general procedure for KR, (±)–**37b** (22.3 mg, 0.070 mmol), acetic anhydride (3.31 µl, 0.035 mmol, 0.50 eq.), 2,4,6-collidine (15.8 µl, 0.12 mmol, 1.7 eq), **14** (5.83 mg, 0.0070 mmol, 0.1 eq.), dry $CHCl_3$ (7.0 mL, 0.01 M) under Argon were stirred at −55 ℃ for 48 h. The crude material was purified by preparative thin-layer chromatography purification (hexane/ethyl acetate = 1 : 2) to give **37b** and **38b**.

(*R*)-*N*-(2-ethyl-2,4-dihydroxybutyl)-4-nitrobenzenesulfonamide (**37b**)

Colorless oil: 7.10 mg.

IR (neat): 3360, 2971, 2942, 2887, 1542, 1409, 1362, 910 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.18–8.07 (m, 1H), 7.92–7.82 (m, 1H), 7.81–7.67 (m, 2H), 4.00–3.80 (m, 2H), 3.08 (ABq, 2H, $\Delta\delta_{AB}$ = 0.02, J_{AB} = 12.4 Hz), 1.92–1.70 (m, 2H), 1.63 (q, J = 7.5 Hz, 2H), 0.88 (t, J = 7.5 Hz, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 148.24, 133.74, 133.55, 132.91, 131.22, 125.57, 74.37, 59.31, 50.60, 36.76, 30.55, 8.09.

HRMS (ESI) *m/z*: [M+Na$^+$] Calcd for $C_{12}H_{18}N_2O_6SNa$ 341.0778; Found 341.0762.

HPLC condition: (DAICEL CHIRALPAK ID, 2-propanol/hexane 4:6, flow 1.0 mL/min, 11.7 min (minor), 18.9 min (major).

$[\alpha]^D_{21}$ −17.2 (*c* 0.8 in $CHCl_3$).

(*S*)-3-hydroxy-3-(((4-nitrophenyl)sulfonamido)methyl)pentyl acetate (38b)

Colorless oil: 10.9 mg.

IR (neat): 3514, 3352, 2972, 1732, 1542, 1365, 1251, 1170, 913 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.18–8.05 (m, 1H), 7.92–7.84 (m, 1H), 7.79–7.71 (m, 2H), 5.71 (t, *J* = 6.4 Hz, 1H), 4.19 (t, *J* = 6.6 Hz, 2H), 3.05 (s, *J* = 6.5 Hz, 2H), 2.20 (s, 1H), 2.05 (s, 3H), 1.88 (t, *J* = 7.1 Hz, 2H), 1.66–1.48 (m, 2H), 0.89 (t, *J* = 7.5 Hz, 3H).

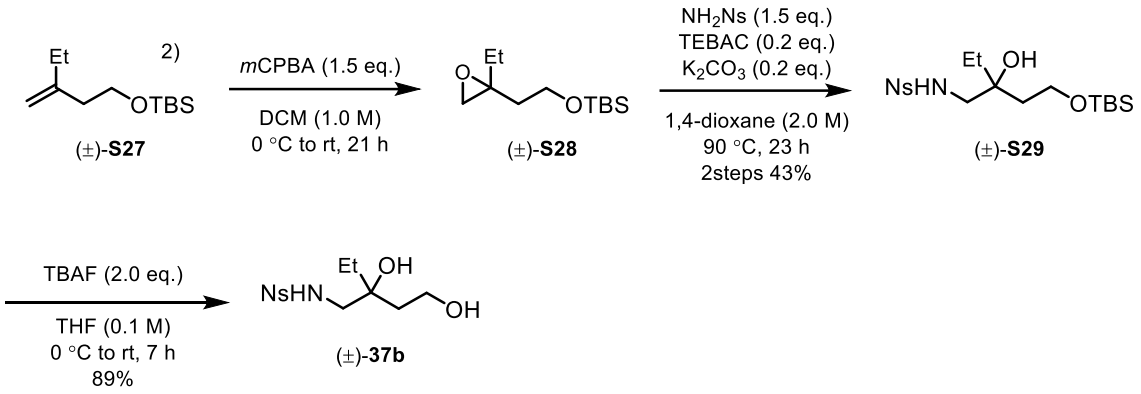
^{13}C NMR: (100 MHz, $CDCl_3$) δ 171.18, 148.23, 133.84, 133.48, 132.96, 131.23, 125.60, 73.44, 60.58, 50.58, 34.59, 30.14, 21.14, 7.95.

HRMS (ESI) *m/z*: [M+H$^+$] Calcd for $C_{14}H_{21}N_2O_7S$ 361.1064; Found 361.1046.

HPLC condition: (DAICEL CHIRALPAK ID 2-propanol/hexane 4:6, flow 1 mL/min, 36.2 min (major), 42.9 min (minor).

[α]$^D_{21}$ –7.63 (*c* 1.1 in $CHCl_3$).

Synthesis of (±)–37b



***N*-(4-((tert-butyldimethylsilyl)oxy)-2-ethyl-2-hydroxybutyl)-4-nitrobenzenesulfonamide** ((±)–**S29**)

To a solution of (±)–**S27** (411 mg, 1.92 mmol, prepared according to a literature method[2]) in DCM (1.0 M, 1.92 mL) was cooled to 0 ℃ was added *m*CPBA (496 mg, 2.88 mmol, 1.5 eq.). The mixture was warmed up to room temperature for 21 h and quenched with sat. $NaHCO_3$ (aq) and $Na_2S_2O_3$ (aq). The aqueous phase was extracted with DCM twice, and the combined organics were dried over Na_2SO_4, filtered, and concentrated to give (±)–**S28**. The crude material was used without purification.

To a screw capped vial equipped with a stir bar was added tert-butyl(2-(2-ethyloxiran-2-yl)ethoxy)dimethylsilane ((±)–**S28**) was added *o*$NsNH_2$ (528 mg, 2.61 mmol, 1.5 eq.), K_2CO_3 (48 mg, 0.35 mmol, 0.2 eq.), Benzyltriethylammonium Chloride (79 mg, 0.35 mmol, 0.2 eq.) and dry 1,4-dioxane (0.87 mL). The reaction mixture was stirred at 90 ℃ for 23 h. The reaction mixture was diluted with EtOAc, washed by H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica chromatography (EA-hexane 1:3) to yield (±)–**S29** (352 mg, 0.81 mmol, 2 steps 47%).

Yellow oil: **IR** (neat): 3456, 2954, 2932, 2885, 2859, 1542, 1406, 1361, 1171, 1084 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.09–7.98 (m, 1H), 7.83–7.75 (m, 1H), 7.74–7.65 (m, 2H), 5.72 (t, *J* = 6.1 Hz, 1H), 4.09 (s, 1H), 3.88–3.78 (m, 2H), 3.06–2.94 (m, 2H), 1.87–1.44 (m, 4H), 0.86–0.74 (m, 12H), 0.02 (s, 3H), -0.01 (s,

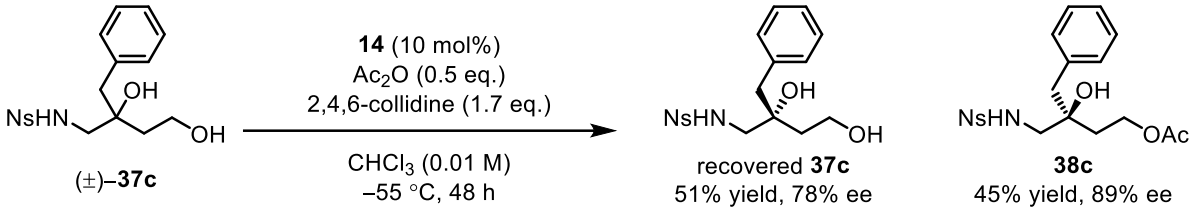
3H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 148.09, 133.67, 133.18, 132.73, 131.02, 125.30, 74.02, 60.09, 50.32, 35.92, 30.18, 25.72, 17.92, 8.09, -5.75.

HRMS (ESI) *m/z*: [M+Na$^+$] Calcd for $C_{18}H_{32}N_2O_6SSiNa$ 455.1643; Found 455.1620.

***N*-(2,4-dihydroxy-2-methylbutyl)-4-nitrobenzenesulfonamide** ((±)–**37b**)

To a solution of **S29** (352 mg, 0.814 mmol) in THF (0.1 M, 8.1 mL) was cooled to 0 ℃ was added a solution of TBAF [1 mol/L in THF] (1.63 mL, 1.63 mmol, 2.0 eq.). The mixture was warmed up to room temperature for 7 h and quenched with sat. NH_4Cl (aq). The aqueous phase was extracted with EtOAc twice, and the combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (EA only) to give (±)–**37b** (284 mg, 0.73 mmol, 89%).



Following the general procedure for KR, (±)–**37c** (26.6 mg, 0.070 mmol), acetic anhydride (3.31 µl, 0.035 mmol, 0.50 eq.), 2,4,6-collidine (15.8 µl, 0.12 mmol, 1.7 eq), **14** (5.83 mg, 0.0070 mmol, 0.1 eq.), dry $CHCl_3$ (7.0 mL, 0.01 M) under Argon were stirred at –55 ℃ for 48 h. The crude material was purified by preparative thin-layer chromatography purification (hexane/ethyl acetate = 1 : 2) to give **37c** and **38c**.

(*R*)-*N*-(2-benzyl-2,4-dihydroxybutyl)-4-nitrobenzenesulfonamide (**37c**)

Colorless oil: 13.5 mg.

IR (neat): 3358, 2929, 1540, 1412, 1362, 1168, 1064, 910, 734 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.08–8.03 (m, 1H), 7.88–7.82 (m, 1H), 7.75–7.68 (m, 2H), 7.32–7.26 (m, 2H), 7.24–7.19 (m, 3H), 6.03 (s, 1H), 3.99–3.81 (m, 2H), 3.24 (s, 1H), 3.06 (s, 3H), 2.89 (ABq, 2H, $\Delta\delta_{AB}$ = 0.03, J_{AB} = 13.7 Hz), 2.21 (brs, 1H), 1.90–1.69 (m, 2H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 148.21, 136.11, 133.75, 133.46, 132.90, 131.23, 130.64, 128.64, 127.04, 125.55, 74.07, 59.21, 50.63, 44.38, 37.68.

HRMS (ESI) *m/z*: [M+Na$^+$] Calcd for $C_{17}H_{20}N_2O_6SNa$ 403.0934; Found 403.0949.

HPLC condition: (DAICEL CHIRALPAK IC, 2-propanol/hexane 3:7, flow 1.0 mL/min, 16.2 min (major), 29.8 min (minor).

$[\alpha]_D^{21}$ –8.84 (*c* 0.4 in $CHCl_3$).

(*S*)-3-benzyl-3-hydroxy-4-((4-nitrophenyl)sulfonamido)butyl acetate (**38c**)

Colorless oil: 10.9 mg.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.14–8.02 (m, 1H), 7.93–7.81 (m, 1H), 7.79–7.69 (m, 2H), 7.35–7.26 (m, 3H), 7.24–7.17 (m, 2H), 5.77 (t, *J* = 6.3 Hz, 1H), 4.32–4.14 (m, 2H), 3.08 (d, *J* = 6.2 Hz, 2H), 2.88 (s, 2H), 2.17 (d, *J* = 0.8 Hz, 1H), 2.04 (d, *J* = 0.8 Hz, 3H), 1.86 (t, *J* = 6.5 Hz, 2H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 171.15, 148.25, 135.47, 133.86, 133.40, 132.94, 131.25, 130.60, 128.86, 127.32, 125.62, 72.99, 60.51, 50.50, 43.85, 35.51, 21.16.

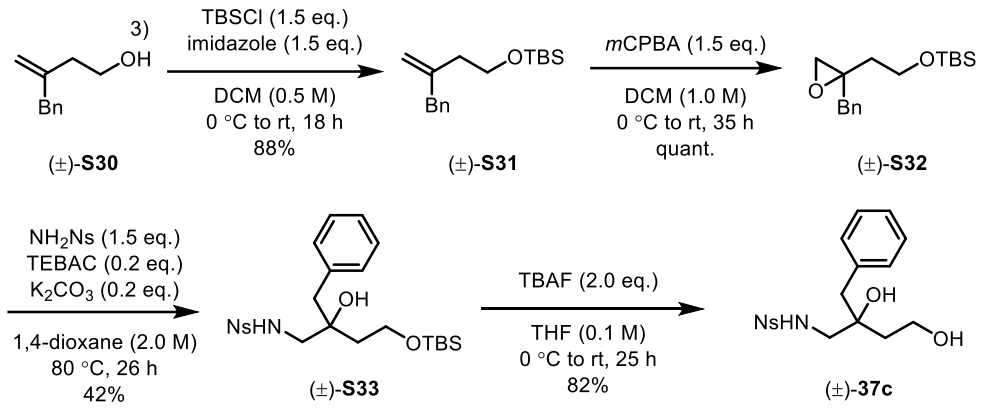
HRMS (ESI) *m/z*: [M+Na$^+$] Calcd for $C_{19}H_{22}N_2O_7SNa$ 445.1040; Found 445.1053.

IR (neat): 3523, 3342, 1732, 1541, 1411, 1364, 1249, 1169, 734 cm^{-1}.

HPLC condition: (DAICEL CHIRALPAK ID, 2-propanol/hexane 4:6, flow 1 mL/min, 12.4 min (major), 25.7 min (minor).

$[\alpha]_D^{21}$ +2.37 (*c* 1.2 in $CHCl_3$).

Synthesis of (±)–37c



((3-benzylbut-3-en-1-yl)oxy)(tert-butyl)dimethylsilane ((±)–**S31**)

To a solution of (±)–**S30** (203 mg, 1.25 mmol, prepared according to a literature method[3]) in DCM (0.5 M, 2.5 mL) was cooled to 0 ℃ was added imidazole (128 mg, 1.88 mmol, 1.5 eq.) and TBSCl (283 mg, 1.88 mmol, 1.5 eq.). The mixture was warmed up to room temperature for 18 h and quenched with 1N HCl (aq). The aqueous phase was extracted with DCM three times, and the combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica chromatography (Acetone-hexane 1:80) to yield (±)–**S31** (303 mg, 1.10 mmol, 88%).

Colorless oil: **IR** (neat): 2953, 2930, 2857, 1469, 1254, 1099, 835 cm-^{1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.35–7.29 (m, 2H), 7.26–7.19 (m, 3H), 4.91–4.88 (m, 1H), 4.84–4.82 (m, 1H), 3.72 (t, *J* = 7.0 Hz, 2H), 3.40 (s, 2H), 2.25 (t, *J* = 7.0 Hz, 2H), 0.93 (s, 9H), 0.07 (s, 6H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 146.29, 139.74, 129.18, 128.42, 126.22, 112.93, 62.44, 43.60, 38.83, 26.09, 18.45, -5.17.

HRMS (ESI) *m*/*z*: [M+H$^+$] Calcd for $C_{17}H_{29}OSi$ 277.1982; Found 277.1957.

(2-(2-benzyloxiran-2-yl)ethoxy)(tert-butyl)dimethylsilane ((±)–**S32)**

To a solution of (±)–**S31** (303 mg, 1.10 mmol) in DCM (1.0 M, 1.1 mL) was cooled to 0 ℃ was added *m*CPBA (283 mg, 1.75 mmol, 1.5 eq.). The mixture was warmed up to room temperature for 35 h and quenched with sat. $NaHCO_3$ (aq) and $Na_2S_2O_3$ (aq). The aqueous phase was extracted with DCM twice, and the combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica chromatography (EA-hexane 1:15) to yield (±)–**S32** (303 mg, 1.10 mmol, quant.).

Colorless oil: **IR** (neat): 2953, 2929, 2857, 1469, 1254, 1099, 836 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.32–7.17 (m, 5H), 3.76–3.62 (m, 2H), 2.92 (s, 2H), 2.62 (ABq, 2H, $\Delta\delta_{AB}$ = 0.14, J_{AB} = 5.03 Hz), 1.90–1.81 (m, 1H), 1.71–1.62 (m, 1H),0.89 (s, 9H), 0.04 (s, 6H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 137.06, 129.83, 128.34, 126.60, 59.51, 58.20, 52.14, 41.24, 36.97, 25.97, 18.25, -5.34.

HRMS (ESI) *m*/*z*: [M+H$^+$] Calcd for $C_{17}H_{29}O_2Si$ 293.1931; Found 293.1934.

***N*-(2-benzyl-4-((tert-butyldimethylsilyl)oxy)-2-hydroxybutyl)-4-nitrobenzenesulfonamide** ((±)–**S33**)

To a screw capped vial equipped with a stir bar was added (±)–**S32** (322 mg, 1.10 mmol) was added o$NsNH_2$ (334 mg, 1.65 mmol, 1.5 eq.), K_2CO_3 (30 mg, 0.22 mmol, 0.2 eq.), Benzyltriethylammonium Chloride (50 mg, 0.22 mmol, 0.2 eq.) and dry 1,4-dioxane (0.55 mL). The reaction mixture was stirred at 80 ℃ for 26 h. The reaction mixture was diluted with EtOAc, washed by H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica chromatography (EA-hexane 1:5) to yield (±)–**S33** (228 mg, 0.46 mmol, 42%).

Yellow oil: **IR** (neat): 3439, 2930, 2857, 1541, 1404, 1170, 1088 cm-^{1}.

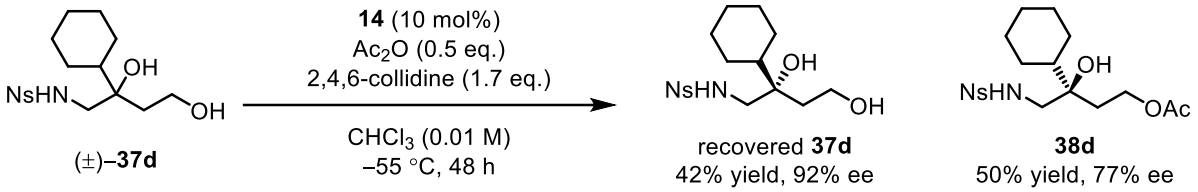
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.08–8.01 (m, 1H), 7.87–7.80 (m, 1H), 7.76–7.67 (m, 2H), 7.33–7.26 (m, 2H), 7.25–7.17 (m, 3H), 5.84 (t, *J* = 6.1 Hz, 1H), 4.29 (s, 1H), 4.00–3.84 (m, 2H), 3.13–2.80 (m, 4H), 1.85–1.64 (m, 2H), 0.86 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 148.14, 136.55, 133.67, 133.13, 132.70, 131.09, 130.50, 128.31, 126.67, 125.34, 74.10, 60.21, 50.37, 44.12, 36.65, 25.76, 17.97, -5.69, -5.74.

HRMS (ESI) *m*/*z*: [M+Na$^+$] Calcd for $C_{23}H_{34}N_2O_6SSiNa$ 495.1980; Found 495.1976.

***N*-(2-benzyl-2,4-dihydroxybutyl)-4-nitrobenzenesulfonamide (**(±)–**37c)**

To a solution of (±)–**S33** (194 mg, 0.40 mmol) in THF (0.1 M, 4.0 mL) was cooled to 0 °C was added a solution of TBAF [1 mol/L in THF] (0.80 mL, 0.80 mmol, 2.0 eq.). The mixture was warmed up to room temperature for 24 h and quenched with sat. NH_4Cl(aq). The aqueous phase was extracted with EtOAc twice, and the combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (EA-hexane 1:1) to give (±)–**37c** (125 mg, 0.33 mmol, 82 %).



Following the general procedure for KR, (±)–**37d** (25.7 mg, 0.069 mmol), acetic anhydride (3.26 µl, 0.034 mmol, 0.50 eq.), 2,4,6-collidine (15.5 µl, 0.12 mmol, 1.7 eq), **14** (5.74 mg, 0.0069 mmol, 0.1 eq.), dry $CHCl_3$ (6.9 mL, 0.01 M) under Argon were stirred at –55 °C for 48 h. The crude material was purified by preparative thin-layer chromatography purification (hexane/ethyl acetate = 1 : 2) to give **37d** and **38d**.

(*R*)-*N*-(2-(cyclohexylmethyl)-2,4-dihydroxybutyl)-4-nitrobenzenesulfonamide (37d)

Colorless oil: 10.8 mg.

IR (neat): 3518, 3353, 2930, 1541, 1445, 1361, 1167, 1067 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.15–8.06 (m, 1H), 7.89–7.82 (m, 1H), 7.78–7.70 (m, 2H), 5.98 (t, *J* = 6.2 Hz, 1H), 3.89 (t, *J* = 5.6 Hz, 2H), 3.37 (s, 1H), 3.17–3.06 (m, 2H), 2.47 (s, 1H), 1.83–1.51 (m, 8H), 1.26–0.84 (m, 5H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 148.21, 133.71, 133.52, 132.92, 131.17, 125.54, 75.55, 59.33, 49.13, 45.06, 35.09, 27.05, 26.92, 26.74, 26.71, 26.50.

HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{16}H_{24}N_2O_6SNa$ 395.1247; Found 395.1244.

HPLC condition: (COSMOSIL CHiRAL 5A, 2-propanol/hexane 3:7, flow 1.0 mL/min, 7.1 min (major), 8.3 min (minor).

$[\alpha]_D^{21}$ –25.6 (*c* 1.0 in $CHCl_3$).

(*S*)-4-cyclohexyl-3-hydroxy-3-(((4-nitrophenyl)sulfonamido)methyl)butyl acetate (38d)

Colorless oil: 14.2 mg.

IR (neat): 3524, 3345, 2930, 2855, 1733, 1542, 1364, 1245, 1169 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.15–8.07 (m, 1H), 7.92–7.85 (m, 1H), 7.79–7.72 (m, 2H), 5.68 (t, *J* = 6.4 Hz, 1H), 4.19 (td, *J* = 6.7, 1.5 Hz, 2H), 3.13 (dd, *J* = 12.7, 6.0 Hz, 1H), 3.06 (dd, *J* = 12.7, 6.8 Hz, 1H), 2.21 (s, 1H), 2.04 (s, 3H), 1.90 (td, *J* = 6.7, 1.5 Hz, 2H), 1.83–7.67 (m, 4H), 1.52 (tt, *J* = 11.9, 2.9 Hz, 1H), 1.31–0.83 (m, 6H).

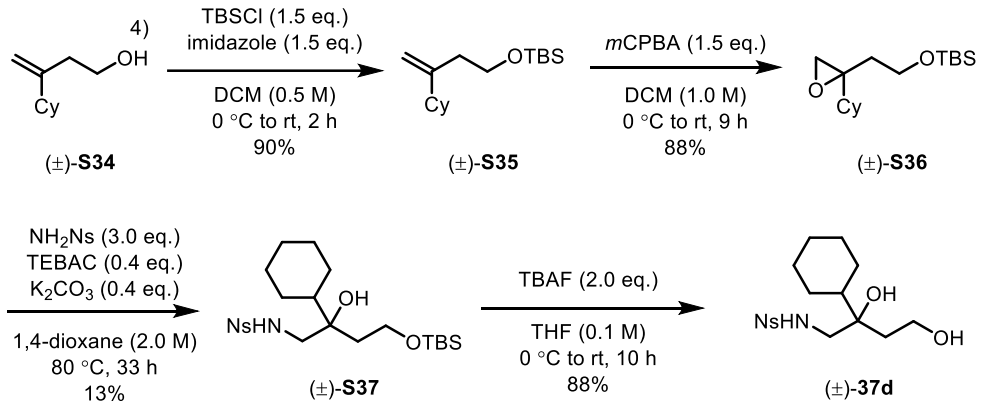
^{13}C NMR: (100 MHz, $CDCl_3$) δ 171.16, 148.26, 133.81, 133.49, 132.96, 131.23, 125.61, 74.73, 60.75, 48.95, 44.55, 33.20, 26.99, 26.88, 26.63, 26.37, 21.18.

HRMS (ESI) *m/z*: [M+Na$^+$] Calcd for $C_{18}H_{26}N_2O_7SNa$ 437.1353; Found 437.1345.

HPLC condition: (DAICEL CHIRALPAK IC, 2-propanol/hexane 3:7, flow 1 mL/min, 31.4 min (minor), 46.1 min (major).

[α]$_D^{21}$ +14.7 (*c* 1.2 in $CHCl_3$).

Synthesis of (±)–37d



***tert*-butyl((3-cyclohexylbut-3-en-1-yl)oxy)dimethylsilane ((±)–S35)**

To a solution of (±)–**S34** (220 mg, 1.43 mmol, prepared according to a literature method[4]) in DMF (0.5 M, 2.9 mL) was cooled to 0 ℃ was added imidazole (146 mg, 2.15 mmol, 1.5 eq.) and TBSCl (324 mg, 2.15 mmol, 1.5 eq.). The mixture was warmed up to room temperature for 2 h and quenched with 1N HCl (aq). The aqueous phase was extracted with Et_2O three times, and the combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica chromatography (EA-hexane 1:40) to yield (±)–**S35** (346 mg, 1.29 mmol, 90%).

Colorless oil: **IR** (neat): 2928, 2855, 1640, 1468, 1447, 1254, 1098, 835 cm^{-1}

^{1}H NMR: (400 MHz, $CDCl_3$) δ 4.76–4.74 (m, 1H), 4.69–4.67 (m, 1H), 3.68 (dd, *J* = 7.4 Hz, 2H), 2.25 (td, *J* = 7.4, 1.2 Hz, 2H), 1.92–1.63 (m, 7H), 1.36–1.00 (m, 6H), 0.89 (s, 9H), 0.05 (s, 6H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 152.31, 108.56, 63.20, 44.71, 38.29, 32.47, 26.92, 26.55, 26.10, 18.46, -5.13.

HRMS (ESI) *m/z*: [M+H$^+$] Calcd for $C_{16}H_{33}OSi$ 269.2295; Found 269.2295.

***tert*-butyl(2-(2-cyclohexyloxiran-2-yl)ethoxy)dimethylsilane ((±)–S36)**

To a solution of (±)–**S35** (346 mg, 1.29 mmol) in DCM (1.0 M, 1.3 mL) was cooled to 0 ℃ was added mCPBA (335 mg, 1.94 mmol, 1.5 eq.). The mixture was warmed up to room temperature for 9 h and quenched with sat. $NaHCO_3$ (aq) and $Na_2S_2O_3$ (aq). The aqueous phase was extracted with DCM twice, and the combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica chromatography (EA-hexane 1:40) to yield (±)–**S36** (321 mg, 1.13 mmol, 88%).

Colorless oil: **IR** (neat): 2929, 2856, 1469, 1431, 1254, 1099, 835, 776 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 3.67–3.52 (m, 2H), 2.66–2.56 (m, 2H), 1.96–1.85 (m, 1H), 1.83–1.57 (m, 6H), 1.37 (tt, *J* = 11.8, 3.0 Hz, 1H), 1.25–0.97 (m, 5H), 0.86 (s, 9H), 0.01 (s, 6H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 60.62, 59.20, 51.15, 42.74, 34.75, 28.56, 28.21, 26.44, 26.41, 26.31, 25.97, 18.26, -5.28, -5.31.

HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{16}H_{32}O_2SiNa$ 307.2064; Found 307.2053.

***N*-(4-((tert-butyldimethylsilyl)oxy)-2-(cyclohexylmethyl)-2-hydroxybutyl)-4-nitrobenzenesulfonamide** ((±)–**S37**)

To a screw capped vial equipped with a stir bar was added (±)–**S36** (288 mg, 1.01 mmol) was added $oNsNH_2$ (610 mg, 3.02 mmol, 3.0 eq.), K_2CO_3 (56 mg, 0.40 mmol, 0.4 eq.), Benzyltriethylammonium Chloride (92 mg, 0.40 mmol, 0.4 eq.) and dry 1,4-dioxane (0.51 mL). The reaction mixture was stirred at 80 °C for 33 h. The reaction mixture was diluted with EtOAc, washed by H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica chromatography (EA-hexane 1:10 to 1:5) to yield (±)–**S37** (64 mg, 0.13 mmol, 13%).

Yellow oil: **IR** (neat): 3461, 2930, 2856, 1542, 1403, 1362, 1171, 1080, 837, 782, 735 cm^{-1}.

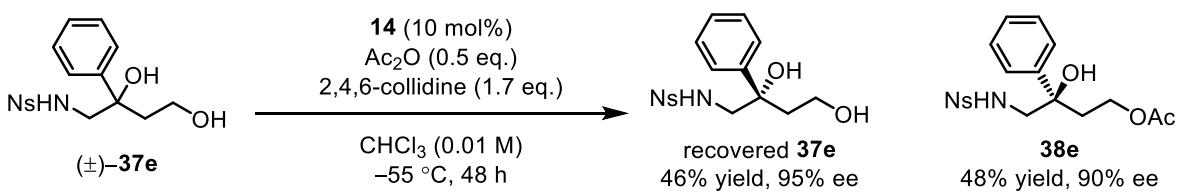
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.12–8.05 (m, 1H), 7.87–7.80 (m, 1H), 7.76–7.68 (m, 2H), 5.73 (t, *J* = 5.9 Hz, 1H), 4.10 (s, 1H), 3.87 (t, *J* = 5.6 Hz, 2H), 3.06 (d, *J* = 5.5 Hz, 2H), 1.84–1.68 (m, 6H), 1.54 (tt, *J* = 12.1, 2.8 Hz, 1H), 1.27–0.89 (m, 6H), 0.84 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 148.31, 133.58, 133.49, 132.72, 131.16, 125.44, 75.38, 60.33, 48.82, 44.76, 34.30, 27.33, 26.87, 26.83, 26.57, 25.82, 18.04, -5.61, -5.65.

HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{22}H_{38}N_2O_6SSiNa$ 509.2112; Found 509.2091.

***N*-(2-(cyclohexylmethyl)-2,4-dihydroxybutyl)-4-nitrobenzenesulfonamide** ((±)–**37d**)

To a solution of (±)–**S37** (64 mg, 0.13 mmol) in THF (0.1 M, 1.3 mL) was cooled to 0 °C was added a solution of TBAF [1 mol/L in THF] (0.26 mL, 0.26 mmol, 2.0 eq.). The mixture was warmed up to room temperature for 10 h and quenched with sat. NH_4Cl(aq). The aqueous phase was extracted with EtOAc twice, and the combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (EA-hexane 1:2 to 2:1) to give (±)–**37d** (45 mg, 0.12 mmol, 88 %).



Following the general procedure for KR, (±)–**37e** (25.7 mg, 0.070 mmol), acetic anhydride (3.31 µl, 0.035 mmol, 0.50 eq.), 2,4,6-collidine (15.8 µl, 0.12 mmol, 1.7 eq), **14** (5.83 mg, 0.0070 mmol, 0.1 eq.), dry $CHCl_3$ (7.0 mL, 0.01 M) under Argon were stirred at −55 °C for 48 h. The crude material was purified by preparative thin-layer chromatography purification (hexane/ethyl acetate = 1 : 2) to give **37e** and **38e**.

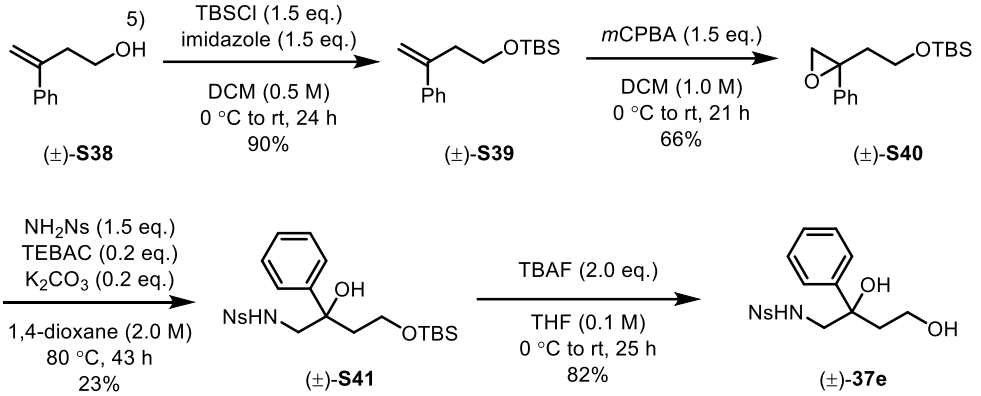
(*S*)-*N*-(2,4-dihydroxy-2-phenylbutyl)-4-nitrobenzenesulfonamide (**37e**)

Colorless oil: 11.9 mg.
IR (neat): 3367, 2932, 2892, 1540, 1409, 1359, 1167, 1068 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.00–7.93 (m, 1H), 7.83–7.76 (m, 1H), 7.72–7.60 (m, 2H), 7.36–7.27 (m, 3H), 7.25–7.15 (m, 2H), 5.91 (s, 1H), 4.71 (s, 1H), 3.72 (dt, *J* = 10.6, 3.9 Hz, 1H), 3.51–3.41 (m, 2H), 3.21 (d, *J* = 12.4 Hz, 1H), 2.62 (brs, 1H), 2.34 (ddd, *J* = 14.9, 10.7, 4.2 Hz, 1H), 1.94 (ddd, *J* = 14.9, 3.9, 2.6 Hz, 2H).
^{13}C NMR: (100 MHz, $CDCl_3$) δ 147.76, 142.89, 133.57, 133.49, 132.98, 130.94, 128.53, 127.46, 125.49, 125.34, 77.12, 59.69, 54.20, 39.02.
HRMS (ESI) *m/z*: [M+H^+] Calcd for $C_{16}H_{19}N_2O_6S$ 367.0958; Found 367.0939.
HPLC condition: (DAICEL CHIRALPAK IC, 2-propanol/hexane 3:7, flow 1.0 mL/min, 17.7 min (minor), 27.7 min (major).
$[\alpha]_D^{21}$ –98.2 (*c* 1.1 in $CHCl_3$).

(*R*)-3-hydroxy-4-((4-nitrophenyl)sulfonamido)-3-phenylbutyl acetate (**38e**)

White solid: 13.8 mg.
IR (KBr): 3498, 3367, 1735, 1544, 1407, 1363, 1327, 1248, 1166 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.05–7.98 (m, 1H), 7.89–7.80 (m, 1H), 7.75–7.65 (m, 2H), 7.35–7.28 (m, 4H), 7.25–7.19 (m, 1H), 5.69 (t, *J* = 5.9 Hz, 1H), 4.23–4.14 (m, 1H), 4.00–3.90 (m, 1H), 3.45 (dd, *J* = 12.8, 7.5 Hz, 1H), 3.31 (s, 1H), 3.25 (dd, *J* = 12.8, 4.1 Hz, 1H), 2.31 (td, *J* = 6.3, 1.1 Hz, 2H), 1.85 (s, 3H).
^{13}C NMR: (100 MHz, $CDCl_3$) δ 171.25, 147.97, 142.20, 133.68, 133.64, 132.99, 131.10, 128.79, 127.83, 125.59, 125.23, 75.42, 60.77, 54.44, 37.44, 20.87.
HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{18}H_{20}N_2O_7SNa$ 431.0883; Found 431.0880.
HPLC condition: (DAICEL CHIRALPAK ID 2-propanol/hexane 4:6, flow 1.0 mL/min, 15.5 min (major), 23.3 min (minor).
$[\alpha]_D^{21}$ +28.2 (*c* 1.0 in Acetone).
m.p. 151–153°C.

Synthesis of (±)–37e



***tert*-butyl((3-cyclohexylbut-3-en-1-yl)oxy)dimethylsilane ((±)–S39)**

To a solution of (±)–**S38** (437 mg, 2.95 mmol, prepared according to a literature method[5]) in DCM (0.5 M, 5.9 mL) was cooled to 0 ℃ was added imidazole (301 mg, 4.43 mmol, 1.5 eq.) and TBSCl (533 mg, 3.54 mmol, 1.2 eq.). The mixture was warmed up to room temperature for 24 h and quenched with 1N HCl (aq). The aqueous phase was extracted with DCM three times, and the combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica chromatography (Hexane only to EA-Hexane 1:30) to yield (±)–**S39** (694 mg, 2.64 mmol, 90%).

Colorless oil: **IR** (neat): 2954, 2930, 2857, 1254, 1097, 836, 776, 704 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.44–7.40 (m, 2H), 7.35–7.27 (m, 3H), 5.34 (d, J = 1.4 Hz, 1H), 5.11–5.09 (m, 1H), 3.72 (td, J = 7.2, 0.8 Hz, 2H), 2.75 (td, J = 7.2, 1.1 Hz, 2H), 0.87 (d, J = 0.7 Hz, 9H), 0.00 (s, 6H).
^{13}C NMR: (100 MHz, $CDCl_3$) δ 145.41, 141.16, 128.41, 127.52, 126.21, 114.03, 62.56, 38.94, 26.06, 18.45, -5.19.
HRMS (ESI) *m/z*: [M+H$^+$] Calcd for $C_{16}H_{28}OSi$ 263.1826; Found 263.1825.

***tert*-butyldimethyl(2-(2-phenyloxiran-2-yl)ethoxy)silane ((±)–S40)**

To a solution of (±)–**S39** (694 mg, 2.64 mmol) in DCM (1.0 M, 1.3 mL) was cooled to 0 ℃ was added mCPBA (684 mg, 3.96 mmol, 1.5 eq.). The mixture was warmed up to room temperature for 21 h and quenched with sat. $NaHCO_3$ (aq) and $Na_2S_2O_3$ (aq). The aqueous phase was extracted with DCM twice, and the combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica chromatography (Et_2O-hexane 1:50) to yield (±)–**S40** (487 mg, 1.75 mmol, 66%).

Colorless oil: **IR** (neat): 2954, 2930, 2887, 2857, 1254, 1102, 837, 776 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.37–7.14 (m, 6H), 3.88–3.40 (m, 3H), 2.97 (d, J = 5.5 Hz, 1H), 2.68 (d, J = 5.4 Hz, 1H), 2.32–1.74 (m, 3H), 0.81 (d, J = 0.7 Hz, 9H), -0.05 (s, 3H), -0.06 (s, 3H).
^{13}C NMR: (100 MHz, $CDCl_3$) δ 140.07, 128.37, 127.57, 126.10, 59.36, 58.59, 55.53, 38.68, 25.96, 18.25, -5.35.
HRMS (ESI) *m/z*: [M+Na$^+$] Calcd for $C_{16}H_{26}O_2SiNa$ 301.1594; Found 301.1603.

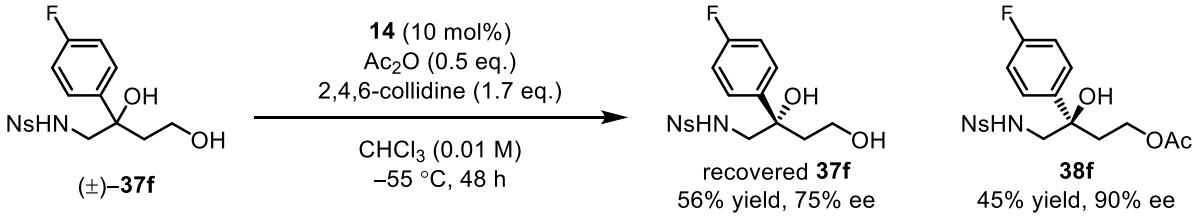
***N*-(2-benzyl-4-((tert-butyldimethylsilyl)oxy)-2-hydroxybutyl)-4-nitrobenzenesulfonamide ((±)–S41)**

To a screw capped vial equipped with a stir bar was added (±)–**S40** (487 mg, 1.75 mmol) was added oNsNH$_2$ (531 mg, 2.63 mmol, 1.5 eq.), K_2CO_3 (48 mg, 0.35 mmol, 0.2 eq.), Benzyltriethylammonium Chloride (80 mg, 0.35 mmol, 0.2 eq.) and dry 1,4-dioxane (0.88 mL). The reaction mixture was stirred at 80 ℃ for 43 h. The reaction mixture was diluted with EtOAc, washed by H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica chromatography (EA-hexane 1:4) to yield (±)–**S41**(194 mg, 0.39 mmol, 23%).

Yellow oil: **IR** (neat): 3434, 2953, 2930, 2884, 2858, 1541, 1406, 1359, 1170, 1076 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.99–7.91 (m, 1H), 7.82–7.73 (m, 1H), 7.68–7.59 (m, 2H), 7.36–7.29 (m, 2H), 7.27–7.22 (m, 2H), 7.20–7.14 (m, 1H), 5.87 (dd, *J* = 7.2, 4.2 Hz, 1H), 5.08 (s, 1H), 3.73 (ddd, *J* = 10.2, 4.3, 3.2 Hz, 1H), 3.55–3.32 (m, 2H), 3.17 (dd, *J* = 12.3, 4.2 Hz, 1H), 2.39 (ddd, *J* = 14.6, 11.5, 4.3 Hz, 1H), 1.93 (dt, *J* = 14.7, 2.8 Hz, 1H), 0.83 (s, 9H), -0.04 (s, 3H), -0.12 (s, 3H).
^{13}C NMR: (100 MHz, $CDCl_3$) δ 147.82, 143.07, 133.76, 133.32, 132.80, 130.93, 128.34, 127.33, 125.44, 125.41, 77.05, 60.67, 54.41, 38.37, 25.75, 17.95, -5.81, -5.90.
HRMS (ESI) *m/z*: [M+H$^+$] Calcd for $C_{22}H_{33}N_2O_6SSi$ 481.1823; Found 481.1801.

***N*-(2,4-dihydroxy-2-phenylbutyl)-4-nitrobenzenesulfonamide** ((±)–**37e**)

To a solution of (±)–**S41** (194 mg, 0.40 mmol) in THF (0.1 M, 4.0 mL) was cooled to 0 ℃ was added a solution of TBAF [1 mol/L in THF] (0.80 mL, 0.80 mmol, 2.0 eq.). The mixture was warmed up to room temperature for 25 h and quenched with sat. NH_4Cl(aq). The aqueous phase was extracted with EtOAc twice, and the combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (EA-hexane 1:1) to give (±)–**37e** (125 mg, 0.33 mmol, 82 %).



Following the general procedure for KR, (±)–**37f** (26.9 mg, 0.070 mmol), acetic anhydride (3.31 µl, 0.035 mmol, 0.50 eq.), 2,4,6-collidine (15.8 µl, 0.12 mmol, 1.7 eq), **14** (5.83 mg, 0.0070 mmol, 0.1 eq.), dry $CHCl_3$ (7.0 mL, 0.01 M) under Argon were stirred at –55 ℃ for 48 h. The crude material was purified by preparative thin-layer chromatography purification (hexane/ethyl acetate = 1 : 2) to give **37f** and **38f**.

(*S*)-*N*-(2-(4-fluorophenyl)-2,4-dihydroxybutyl)-4-nitrobenzenesulfonamide (**37f**)

Colorless oil: 15.2 mg.

IR (neat): 3377, 2933, 1540, 1510, 1410, 1360, 1227,1166, 735 cm-1.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.99–7.95 (m, 1H), 7.84–7.81 (m, 1H), 7.71–7.64 (m, 2H), 7.34–7.28 (m, 2H), 6.95–6.88 (m, 2H), 5.92 (t, *J* = 5.8 Hz, 1H), 4.71 (s, 1H), 3.82 (ddt, *J* = 10.5, 4.0, 2.2 Hz, 1H), 3.60–3.38 (m, 2H), 3.21 (dd, *J* = 12.6, 4.7 Hz, 1H), 2.43–2.29 (m, 2H), 1.94 (ddd, *J* = 14.9, 3.9, 2.6 Hz, 1H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 162.05 (^1J (C, F) = 246 Hz), 147.87, 138.81 (^4J (C, F) = 3.0 Hz), 133.85, 133.49, 132.96, 130.93, 127.29 (^3J (C, F) = 8.1 Hz), 125.55, 115.39 (^2J (C, F) = 20.7 Hz), 76.94, 59.97, 54.45, 38.85.

HRMS (ESI) *m*/*z*: [M+Na$^+$] Calcd for $C_{16}H_{17}N_2O_6SFNa$ 407.0684; Found 407.0701.

HPLC condition: (DAICEL CHIRALPAK IC, 2-propanol/hexane 3:7, flow 1.0 mL/min, 14.6 min (minor), 23.2 min (major).

[α]$_D^{21}$ –76.3 (*c* 1.4 in $CHCl_3$).

(*R*)-3-(4-fluorophenyl)-3-hydroxy-4-((4-nitrophenyl)sulfonamido)butyl acetate (38f)

White solid: 13.4 mg.

IR (KBr): 3495, 3353, 1736, 1550, 1412, 1365, 1327, 1244, 1165 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.02–7.95 (m, 1H), 7.86–7.82 (m, 1H), 7.74–7.65 (m, 2H), 7.33–7.27 (m, 2H), 6.98–6.90 (m, 2H), 5.71 (s, 1H), 4.24–4.12 (m, 1H), 3.97–3.91 (m, 1H), 3.48–3.20 (m, 3H), 2.28 (t, *J* = 6.5 Hz, 2H), 1.87 (s, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 171.25, 161.66 (^1J (C, F) = 244 Hz), 147.91, 137.99, 133.78, 133.64, 133.03, 130.96, 127.20 (^3J (C, F) = 8.1 Hz), 125.59, 115.57 (^2J (C, F) = 21.5 Hz), 75.20, 60.66, 54.57, 37.53, 20.89.

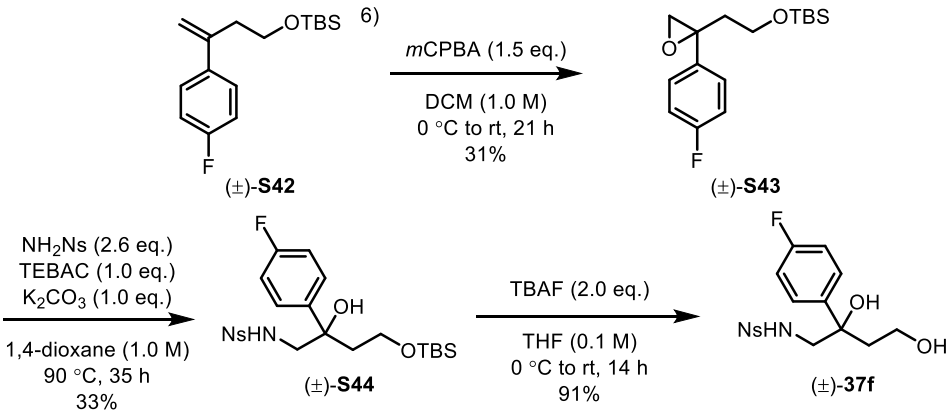
HRMS (ESI) *m*/*z*: [M+Na$^+$] Calcd for $C_{18}H_{19}N_2O_7SFNa$ 449.0789; Found 449.0785.

HPLC condition: (DAICEL CHIRALPAK ID, 2-propanol/hexane 4:6, flow 1.0 mL/min, 12.7 min (major), 15.7 min (minor).

[α]$_D^{21}$ +28.0 (*c* 1.0 in Acetone).

m.p. 133–135℃.

<u>Synthesis of (±)–37f</u>



***tert*-butyl(2-(2-(4-fluorophenyl)oxiran-2-yl)ethoxy)dimethylsilane** ((±)–**S43**)

To a solution of (±)–**S42** (473 mg, 1.69 mmol, prepared according to a literature method[6]) in DCM (1.0 M, 1.7 mL) was cooled to 0 ℃ was added mCPBA (437 mg, 2.54 mmol, 1.5 eq.). The mixture was warmed up to room temperature for 21 h and quenched with sat. $NaHCO_3$ (aq) and $Na_2S_2O_3$ (aq). The aqueous phase was extracted with DCM twice, and the combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica chromatography (Acetone-hexane 1:60) to yield (±)–**S43** (157 mg, 0.53 mmol, 31%).

Colorless oil: **IR** (neat): 2954, 2930, 2858, 1513, 1255, 1227, 1102, 836, 777 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.39–7.32 (m, 2H), 7.06–6.96 (m, 2H), 3.74–3.55 (m, 2H), 3.02 (d, *J* = 5.4 Hz, 1H), 2.72 (d, *J* = 5.4 Hz, 1H), 2.32–2.21 (m, 1H), 2.12–2.02 (m, 1H), 0.86 (s, 9H), 0.00 (s, 3H), -0.01 (s, 3H).
^{13}C NMR: (100 MHz, $CDCl_3$) δ 162.26 (^1J (C, F) = 246 Hz), 135.95 (^4J (C, F) = 3.0 Hz), 127.94 (^3J (C, F) = 8.1 Hz), 115.25 (^2J (C, F) = 21.5 Hz), 59.29, 58.31, 55.55, 38.78, 25.95, 18.26, -5.36.
HRMS (ESI) *m/z*: [M+H^+] Calcd for $C_{16}H_{26}O_2SiF$ 267.1681; Found 267.1671.

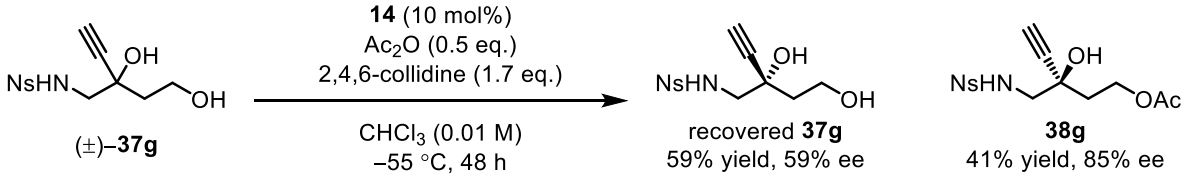
***N*-(4-((tert-butyldimethylsilyl)oxy)-2-hydroxy-2-phenylbutyl)-4-nitrobenzenesulfonamide** ((±)–**S44**)

To a screw capped vial equipped with a stir bar was added (±)–**S43** (157 mg, 0.53 mmol) was added *o*$NsNH_2$ (279 mg, 1.38 mmol, 2.6 eq.), K_2CO_3 (73 mg, 0.53 mmol, 1.0 eq.), Benzyltriethylammonium Chloride (121 mg, 0.35 mmol, 1.0 eq.) and dry 1,4-dioxane (0.27 mL). The reaction mixture was stirred at 90 ℃ for 35 h. The reaction mixture was diluted with EtOAc, washed by H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica chromatography (EA-hexane 1:6 to 1:4) to yield (±)–**S44** (87.2 mg, 0.18 mmol, 33%).

Yellow oil: **IR** (neat): 3398, 2954, 2931, 2886, 2859, 1542, 1509, 1408, 1359, 1168, 1078 cm-1.
^{1}H NMR: (400 MHz, $CDCl_3$) δ7.96–7.90 (m, 1H), 7.83–7.77 (m, 1H), 7.69–7.60 (m, 2H), 7.33–7.26 (m, 2H), 6.94–6.84 (m, 2H), 5.86 (t, *J* = 5.6 Hz, 1H), 5.12 (s, 1H), 3.74 (ddd, *J* = 10.2, 4.2, 3.2 Hz 1H), 3.48–3.35 (m, 2H), 3.18 (dd, *J* = 12.4, 4.8 Hz, 1H), 2.37 (ddd, *J* = 15.3, 11.5, 4.3 Hz, 1H), 1.90 (dt, *J* = 14.7, 2.8 Hz, 1H), 0.83 (s, 9H), -0.03 (s, 3H), -0.11 (s, 3H).
^{13}C NMR: (100 MHz, $CDCl_3$) δ 161.98 (^1J (C, F) = 246 Hz), 147.84, 138.92 (^4J (C, F) = 3.0 Hz), 134.03, 133.29, 132.84, 130.86, 127.35 (^3J (C, F) = 8.3 Hz), 125.45, 115.17 (^2J (C, F) = 21.2 Hz), 76.87, 60.65, 54.61, 38.39, 25.78, 17.99, -5.75, -5.85.
HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{22}H_{31}N_2O_6SSiFNa$ 521.1548; Found 521.1552.

***N*-(2-(4-fluorophenyl)-2,4-dihydroxybutyl)-4-nitrobenzenesulfonamide** ((±)–**37f**)

To a solution of (±)–**S44** (87.2 mg, 0.18 mmol) in THF (0.1 M, 1.8 mL) was cooled to 0 ℃ was added a solution of TBAF [1 mol/L in THF] (0.35 mL, 0.35mol, 2.0 eq.). The mixture was warmed up to room temperature for 14 h and quenched with sat. NH_4Cl(aq). The aqueous phase was extracted with EtOAc twice, and the combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (EA-hexane 1:1) to give (±)–**37f** (61 mg, 0.17 mmol, 91%.)



Following the general procedure for KR, (±)–**37g** (16.5 mg, 0.052 mmol), acetic anhydride (2.48 µl, 0.026 mmol, 0.50 eq.), 2,4,6-collidine (11.8 µl, 0.089 mmol, 1.7 eq), **14** (4.37 mg, 0.0052 mmol, 0.1 eq.), dry $CHCl_3$ (5.2 mL, 0.01 M) under Argon were stirred at –55 ℃ for 48 h. The crude material was purified by preparative thin-layer chromatography purification (hexane/ethyl acetate = 1 : 2) to give **37g** and **38g**.

(*S*)-*N*-(2-hydroxy-2-(2-hydroxyethyl)but-3-yn-1-yl)-4-nitrobenzenesulfonamide (37g)

Yellow oil: 9.7 mg.

IR (neat): 3290, 1540, 1415, 1360, 1168, 1074, 736 cm-1.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.16–8.09 (m, 1H), 7.93–7.84 (m, 1H), 7.78–7.72 (m, 2H), 5.96 (t, J = 6.5 Hz, 1H), 4.35 (s, 1H), 4.21 (t, J = 10.7 Hz, 1H), 4.02–3.93 (m, 1H), 3.31 (d, J = 6.2 Hz, 2H), 2.52 (d, J = 0.8 Hz, 1H), 2.25 (brs, 1H), 2.17–2.08 (m, 1H), 1.87–1.77 (m, 1H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 148.10, 133.84, 133.81, 133.03, 131.20, 125.61, 83.47, 74.78, 70.84, 60.35, 53.07, 39.02.

HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{12}H_{14}N_2O_6SNa$ 337.0465; Found 337.0457.

HPLC condition: (DAICEL CHIRALPAK IC, 2-propanol/hexane 3:7, flow 1.0 mL/min, 25.1 min (major), 30.2 min (minor).

$[\alpha]_D^{21}$ –14.4 (*c* 1.0 in $CHCl_3$).

(*R*)-3-hydroxy-3-(((4-nitrophenyl)sulfonamido)methyl)pent-4-yn-1-yl acetate (38g)

Yellow oil: 7.9 mg.

IR (KBr): 3286, 1734, 1541, 1415, 1364, 1250, 1169, 586 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.16–8.09 (m, 1H), 7.93–7.86 (m, 1H), 7.79–7.72 (m, 2H), 5.90 (s, 1H), 4.51–4.24 (m, 2H), 3.32 (s, 2H), 3.20 (s, 1H), 2.51 (s, 1H), 2.11–2.00 (m, 5H).

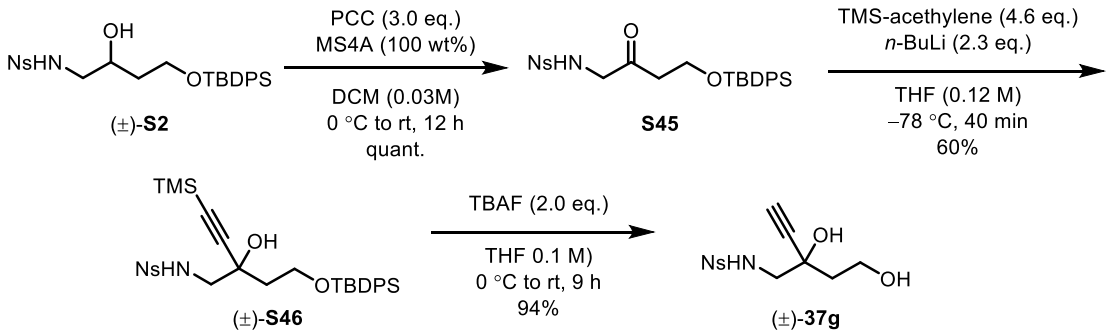
^{13}C NMR: (100 MHz, $CDCl_3$) δ 171.34, 148.12, 133.87, 133.06, 131.19, 125.65, 82.93, 75.06, 68.87, 60.89, 53.01, 37.44, 21.17.

HRMS (ESI) *m/z*: [M+Na$^+$] Calcd for $C_{14}H_{16}N_2O_7SNa$ 379.0570; Found 379.0567.

HPLC condition: (DAICEL CHIRALPAK IC, 2-propanol/hexane 3:7, flow 1.0 mL/min, 33.8 min (minor), 49.6 min (major).

[α]$_D^{21}$ +28.1 (*c* 0.9 in $CHCl_3$).

Synthesis of (±)–37g



***N*-(4-((tert-butyldiphenylsilyl)oxy)-2-oxobutyl)-4-nitrobenzenesulfonamide (S45)**

To a solution of (±)–**S2** (937 mg, 1.77 mmol) in DCM (1.0 M, 66 mL, 0.03 M) at 0°C was added PCC (1.15 g, 5.31 mmol, 3.0 eq.) and MS4A (100wt%). The mixture was warmed up to room temperature for 12 h and the reaction mixture was diluted with Et_2O (177 mL). The resulting solution was directly charged and the black gum was separated by florisil (Et_2O as eluent) to yield **S45** (932 mg, 1.77 mmol, quant.).

Yellow oil: **IR** (neat): 2957, 2932, 2858, 1728, 1542, 1358, 1172, 1009, 910, 734 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 7.71 – 7.57 (m, 6H), 7.48 – 7.34 (m, 6H), 6.26 (t, *J* = 4.8 Hz, 1H), 4.18 (d, *J* = 4.6 Hz, 2H), 3.88 (t, *J* = 5.8 Hz, 2H), 2.59 (t, *J* = 5.8 Hz, 2H), 0.98 (s, 9H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 202.84, 147.82, 135.48, 133.76, 133.56, 132.94, 132.91, 130.63, 129.97, 127.88, 125.66, 59.46, 53.46, 42.87, 26.77, 19.09.

HRMS-ESI : calcd for $C_{26}H_{30}N_2O_6SiSNa$ [M+Na]+: *m/z*=549.1486, found: *m/z*=549.1480.

***N*-(2-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-2-hydroxy-4-(trimethylsilyl)but-3-yn-1-yl)-4-nitrobenzenesulfonamide ((±)–S46)**

To a flame dried flask was added TMS-acetylene (0.19 mL, 1.33 mmol, 4.6 eq.), THF (2.4 mL). The flask was cooled to -78 °C and *n*BuLi (0.67 mmol, 2.3 eq.) was added over 5 min. Then, **S45** (152 mg, 0.29 mmol) in THF (5.8 mL) was slowly added to the flask and stirred for 40 min, the flask was warmed up to r.t. ant stirred for another 22 h. The reaction mixture was quenched with NH_4Cl_{aq} and extracted with EtOAc twice, washed by H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica chromatography (EA-hexane 1:5) to yield (±)–**S46** (109 mg, 0.17 mmol, 60%).

Yellow oil: **IR** (neat):3352, 2930, 2851, 1541, 1361, 1167, 1067, 743 cm^{-1}.

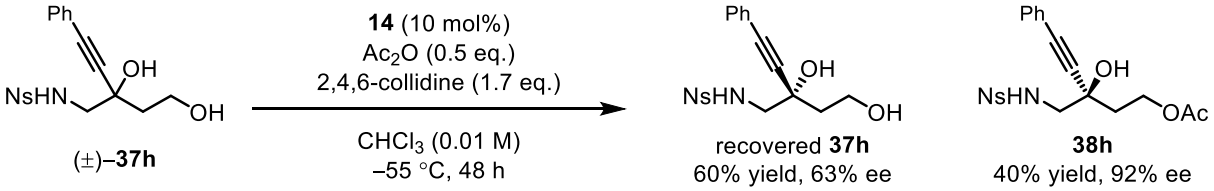
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.21–8.07 (m, 1H), 7.93–7.84 (m, 1H), 7.75–7.63 (m, 6H), 7.50–7.38 (m, 6H), 5.91 (t, *J* = 6.3 Hz, 1H), 5.02 (s, 1H), 4.29 (td, *J* = 10.8, 2.6 Hz, 1H), 3.88 (dt, *J* = 10.4, 3.8 Hz, 1H), 3.40–3.22 (m, 2H), 2.21 (ddd, *J* = 14.9, 11.1, 4.2 Hz, 1H), 1.77 (dt, *J* = 14.4, 2.9 Hz, 1H), 1.04 (s, 9H), 0.18 (s, 9H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 148.10, 135.60, 135.52, 133.85, 133.63, 132.87, 132.30, 132.24, 131.21, 130.20, 130.16, 128.06, 128.01, 125.48, 104.79, 91.40, 71.30, 62.50, 53.00, 38.71, 26.80, 19.09, -0.07.

HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{31}H_{40}N_2O_6SSi_2Na$ 647.2038; Found 647.2019.

***N*-(2-hydroxy-2-(2-hydroxyethyl)but-3-yn-1-yl)-4-nitrobenzenesulfonamide** ((±)–**37g**)

To a solution of (±)–**S46** (330 mg, 0.53 mmol) in THF (0.1 M, 5.3 mL) was cooled to 0 °C was added a solution of TBAF [1 mol/L in THF] (1.59 mL, 1.59 mmol, 3.0 eq.). The mixture was warmed up to room temperature for 9 h and quenched with sat. NH_4Cl(aq). The aqueous phase was extracted with EtOAc twice, and the combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (EA-hexane 2:1) to give (±)–**37g** (155 mg, 0.49 mmol, 94%.)



Following the general procedure for KR, (±)–**37h** (27.3 mg, 0.070 mmol), acetic anhydride (3.31 µl, 0.035 mmol, 0.50 eq.), 2,4,6-collidine (15.8 µl, 0.12 mmol, 1.7 eq), **14** (5.83 mg, 0.0070 mmol, 0.1 eq.), dry $CHCl_3$ (7.0 mL, 0.01 M) under Argon were stirred at −55 °C for 48 h. The crude material was purified by preparative thin-layer chromatography purification (hexane/ethyl acetate = 1 : 2) to give **37h** and **38h**.

(*S*)-*N*-(2-hydroxy-2-(2-hydroxyethyl)-4-phenylbut-3-yn-1-yl)-4-nitrobenzenesulfonamide (**37h**)

Yellow oil: 16.3 mg.

IR (neat): 3360, 1540, 1414, 1359, 1168, 1072, 735 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.20–8.07 (m, 1H), 7.86–7.81 (m, 1H), 7.74–7.63 (m, 2H), 7.43–7.36 (m, 2H), 7.36–7.27 (m, 3H), 6.03 (s, 1H), 4.35–4.22 (m, 2H), 4.01 (dt, *J* = 10.9, 4.2 Hz, 1H), 3.39 (s, 2H), 2.32 (brs, 1H), 2.19 (ddd, *J* = 14.3, 10.1, 3.9 Hz, 1H), 1.92 (ddd, *J* = 14.6, 4.5, 2.9 Hz, 1H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 148.07, 133.85, 133.69, 133.00, 131.94, 131.13, 129.01, 128.48, 125.56, 121.76, 88.28, 86.67, 71.44, 60.54, 53.30, 39.50.

HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{18}H_{18}N_2O_6SNa$ 413.0778; Found 413.0789.

HPLC condition: (DAICEL CHIRALPAK IC, 2-propanol/hexane 3:7, flow 1.0 mL/min, 22.7 min (major), 28.9 min (major).

[α]$_D^{21}$ +5.04 (*c* 1.4 in $CHCl_3$).

(*R*)-3-hydroxy-3-(((4-nitrophenyl)sulfonamido)methyl)-5-phenylpent-4-yn-1-yl acetate (38h)

Yellow oil: 12.5mg.

IR (neat): 3474, 3365, 1735, 1541, 1363, 1248, 1169, 735 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.16–8.10 (m, 1H), 7.87–7.81 (m, 1H), 7.76–7.65 (m, 2H), 7.42–7.27 (m, 5H), 5.96 (t, *J* = 5.8 Hz, 1H), 4.56–4.30 (m, 2H), 3.40 (d, *J* = 5.8 Hz, 2H), 3.18 (s, 1H), 2.15 (t, *J* = 6.3 Hz, 2H), 2.04 (s, 3H).

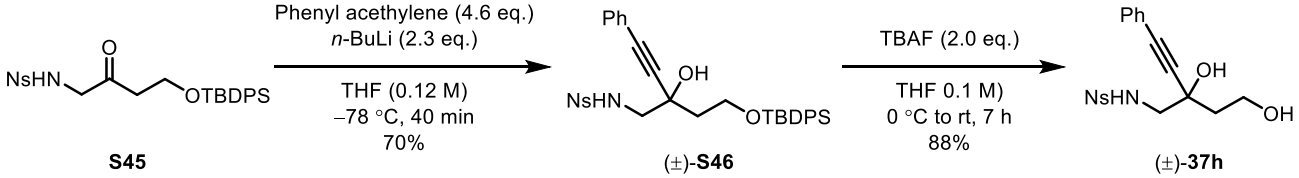
^{13}C NMR: (100 MHz, $CDCl_3$) δ 171.39, 148.08, 133.91, 133.72, 133.01, 131.93, 131.11, 129.18, 128.52, 125.59, 121.47, 87.69, 86.92, 69.46, 61.07, 53.24, 37.76, 21.18.

HRMS (ESI) *m/z*: [M+Na$^+$] Calcd for $C_{20}H_{20}N_2O_7SNa$ 455.0883; Found 455.0887.

HPLC condition: (DAICEL CHIRALPAK ID, 2-propanol/hexane 4:6, flow 1.0 mL/min, 14.5 min (major), 21.5 min (minor).

[α]$_D^{21}$ +1.69 (*c* 1.3 in $CHCl_3$).

Synthesis of (±)–37h



***N*-(2-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-2-hydroxy-4-phenylbut-3-yn-1-yl)-4-nitrobenzenesulfonamide ((±)–S46)**

To a flame dried flask was added Phenylacetylene (0.49 mL, 4.46 mmol, 4.6 eq.), THF (8 mL). The flask was cooled to -78 ℃ and *n*BuLi (1.13 mL, 2.3 eq.) was added over 5 min. Then, **S45** (511 mg, 0.97 mmol) in THF (16 mL) was slowly added to the flask and stirred for 40 min, the flask was warmed up to r.t. ant stirred for another 4 h. The reaction mixture was quenched with NH_4Cl_{aq} and extracted with EtOAc twice, washed by H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica chromatography (EA-hexane 1:5) to yield (±)–**S46** (427 mg, 0.68 mmol, 70%).

Brown amorphous: **IR** (neat): 3443, 2931, 1540, 1423, 1358, 1170, 1111, 1082, 739, 703cm-1.

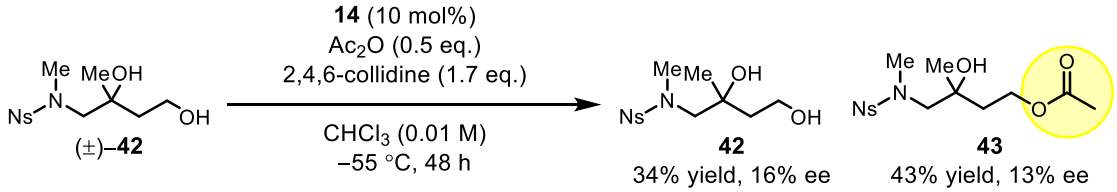
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 7.3, 2.0 Hz, 1H), 7.77 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.73–7.57 (m, 6H), 7.44–7.23 (m, 11H), 6.04 (t, *J* = 6.1 Hz, 1H), 5.11 (s, 1H), 4.35 (td, *J* = 10.8, 2.7 Hz, 1H), 3.93 (dt, *J* = 10.4, 3.8 Hz, 1H), 3.53–3.40 (m, 2H), 2.30 (ddd, *J* = 14.9, 11.0, 4.3 Hz, 1H), 1.84 (dt, *J* = 14.5, 3.0 Hz, 1H), 1.03 (s, 9H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 147.88, 135.50, 133.79, 133.51, 132.81, 132.07, 131.98, 131.85, 130.98, 130.13, 130.01, 128.79, 128.32, 127.99, 127.90, 125.34, 121.90, 88.54, 86.47, 71.44, 62.35, 53.22, 38.97, 26.69, 18.90.
HRMS (ESI) *m/z*: [M+Na$^+$] Calcd for $C_{34}H_{36}N_2O_6SSiNa$ 651.1956; Found 651.1954.

***N*-(2-hydroxy-2-(2-hydroxyethyl)-4-phenylbut-3-yn-1-yl)-4-nitrobenzenesulfonamide** ((±)–**37h**)

To a solution of (±)–**S46** (427 mg, 0.68 mmol) in THF (0.1 M, 6.8 mL) was cooled to 0 °C was added a solution of TBAF [1 mol/L in THF] (1.36 mL, 1.36 mmol, 2.0 eq.). The mixture was warmed up to room temperature for 7 h and quenched with sat. NH_4Cl(aq). The aqueous phase was extracted with EtOAc twice, and the combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (EA-hexane 1:1) to give (±)–**37h** (233 mg, 0.60 mmol, 94%.)

Effects of acidic NHNs group on reaction path of (±)–**42**



Following the general procedure for KR, (±)–**42** (22.3 mg, 0.070 mmol), acetic anhydride (3.31 µl, 0.035 mmol, 0.50 eq.), 2,4,6-collidine (15.8 µl, 0.12 mmol, 1.7 eq), **14** (5.83 mg, 0.0070 mmol, 0.1 eq.), dry $CHCl_3$ (7.0 mL, 0.01 M) under Argon were stirred at –55 °C for 48 h. The crude material was purified by preparative thin-layer chromatography purification (Ethyl acetate only) to give **42** and **43**.

***N*-(2,4-dihydroxy-2-methylbutyl)-N-methyl-4-nitrobenzenesulfonamide** (**42**)

Yellow oil: 7.64 mg.
IR (neat): 3391, 2976, 2931, 1545, 1372, 1345, 1165, 912, 734 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.00–7.96 (m, 1H), 7.75–7.67 (m, 2H), 7.65–7.60 (m, 1H), 4.06–3.91 (m, 2H), 3.47 (s, 1H), 3.30 (ABq, 2H, $\Delta\delta_{AB}$ = 0.12, J_{AB} = 14.8 Hz), 3.06 (s, 3H), 2.35 (s, 1H), 2.06–1.97 (m, 1H), 1.74–1.58 (m, 1H), 1.33 (s, 3H).
^{13}C NMR: (100 MHz, $CDCl_3$) δ 148.40, 133.82, 131.77, 131.55, 130.98, 124.26, 74.70, 60.27, 59.46, 39.51, 37.69, 25.06.
HRMS (ESI) *m/z*: [M+Na$^+$] Calcd for $C_{12}H_{18}N_2O_6SNa$ 341.0778; Found 341.0785.
HPLC condition: (COSMOSIL CHiRAL 5A, 2-propanol/hexane 1:9, flow 1.0 mL/min, 37.9 min (major), 41.5 min (minor).

3-hydroxy-3-methyl-4-((N-methyl-4-nitrophenyl)sulfonamido)butyl acetate (**43**)

Yellow oil: 10.9 mg.

IR (neat): 3526, 1735, 1544, 1370, 1344, 1242, 1164, 767 cm^{-1}.

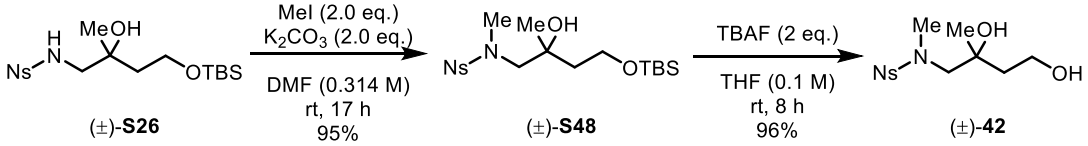
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.02–7.96 (m, 1H), 7.76–7.67 (m, 2H), 7.66–7.60 (m, 1H), 4.35–4.23 (m, 2H), 3.28 (s, 2H), 3.04 (s, 3H), 2.28 (s, 1H), 2.07 (s, 3H), 2.02–1.79 (m, 2H), 1.30 (s, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 171.20, 148.46, 133.84, 131.66, 131.49, 124.30, 73.38, 60.87, 60.19, 38.27, 37.81, 25.30, 21.21.

HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{14}H_{20}N_2O_7SNa$ 383.0883; Found: *m/z*=383.0874.

HPLC condition: (DAICEL CHIRALPAK IC, 2-propanol/hexane 3:7, flow 1.0 mL/min, 15.4 min (major), 17.0 min (minor).

Synthesis of (±)–42



***N*-(4-((tert-butyldimethylsilyl)oxy)-2-hydroxy-2-methylbutyl)-N-methyl-4-nitrobenzenesulfonamide ((±)–S48)**

To a round bottom flask was added (±)–**S26** (200 mg, 0.48 mmol), DMF (1.5 mL) and K_2CO_3 (132 mg, 0.96 mmol, 2.0 eq.). MeI (60 μL, 0.96 mmol, 2.0 eq.) was added at r.t. and stirred for another 17 h. The reaction mixture was quenched with NH_4Cl_{aq} and extracted with EtOAc twice, washed by H_2O, dried over Na_2SO_4, and concentrated under reduced pressure to yield (±)–**S48** (196 mg, 0.45 mmol, 95%).

Yellow oil: **IR** (neat): 3473, 2954, 2931, 2858, 1546, 1371, 1349, 1166, 910, 735 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.95–7.85 (m, 1H), 7.72–7.63 (m, 2H), 7.62–7.55 (m, 1H), 4.22 (s, 1H), 4.06–3.83 (m, 2H), 3.24 (ABq, 2H, $\Delta\delta_{AB}$ = 0.09, J_{AB} = 14.5 Hz), 3.03 (d, J = 0.9 Hz, 3H), 2.04 – 1.94 (m, 1H), 1.56 (ddd, J = 14.6, 4.5, 3.3 Hz, 1H), 1.24 (s, 3H), 0.86 (s, 9H), 0.07 (t, J = 1.1 Hz, 6H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 148.36, 133.59, 131.87, 131.59, 130.94, 124.12, 74.43, 60.47, 60.10, 38.86, 37.14, 25.83, 24.86, 18.01, -5.59, -5.65.

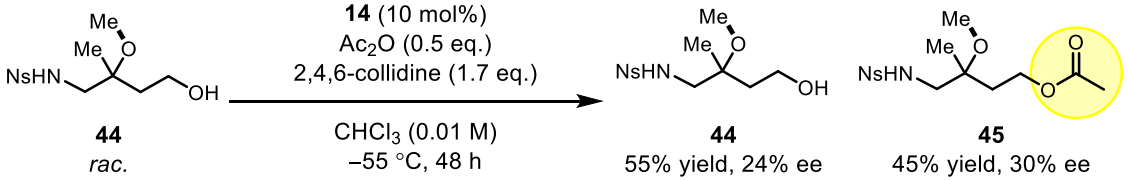
HRMS (ESI) *m/z*: [M+H^+] Calcd for $C_{18}H_{33}N_2O_6SSi$ 433.1823; Found 433.1808.

***N*-(2,4-dihydroxy-2-methylbutyl)-N-methyl-4-nitrobenzenesulfonamide ((±)–42)**

To a solution of (±)–**S48** (196 mg, 0.45 mmol) in THF (0.1 M, 4.5 mL) was cooled to 0 ℃ was added a solution of TBAF [1 mol/L in THF] (0.91 mL, 0.91 mmol, 2.0 eq.). The mixture was warmed up to room temperature for 9 h and quenched with sat. NH_4Cl(aq). The aqueous phase was extracted with EtOAc twice, and the combined

organics were dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (EA only) to give (±)–**42** (139 mg, 0.44 mmol, 96%.)

Effects of tertiary hydroxyl group on reaction path of (±)–**44**



Following the general procedure for KR, (±)–**44** (20.8 mg, 0.065 mmol), acetic anhydride (3.09 µl, 0.033 mmol, 0.50 eq.), 2,4,6-collidine (14.7 µl, 0.11 mmol, 1.7 eq), **14** (5.44 mg, 0.0065 mmol, 0.1 eq.), dry $CHCl_3$ (6.5 mL, 0.01 M) under Argon were stirred at –55 ℃ for 48 h. The crude material was purified by preparative thin-layer chromatography purification (hexane/ethyl acetate = 1 : 3) to give **44** and **45**.

***N*-(4-hydroxy-2-methoxy-2-methylbutyl)-4-nitrobenzenesulfonamide** (**44**)

Colorless oil: 11.8 mg.

IR (neat): 3546, 3353, 2944, 1541, 1405, 1362, 1167, 1066, 735 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.17–8.04 (m, 1H), 7.88–7.81 (m, 1H), 7.77–7.67 (m, 2H), 5.92 (s, 1H), 3.85–3.59 (m, 2H), 3.14–3.08 (m, 5H), 2.30 (brs, 1H), 1.93–1.66 (m, 2H), 1.21 (s, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 148.11, 133.71, 133.65, 132.87, 131.19, 125.44, 76.20, 58.56, 49.66, 49.33, 37.73, 20.70.

HRMS (ESI) *m/z*: [M+H$^+$] Calcd for $C_{12}H_{19}N_2O_6S$ 319.0958; Found 319.0987.

HPLC condition: (DAICEL CHIRALPAK AD-H, 2-propanol/hexane 3:7, flow 1.0 mL/min, 10.0 min (major), 11.7 min (minor).

3-methoxy-3-methyl-4-((4-nitrophenyl)sulfonamido)butyl acetate (**45**)

Colorless oil: 10.5 mg.

IR (neat): 1735, 1542, 1407, 1364, 1243, 1170, 1069, 757 cm^{-1}.

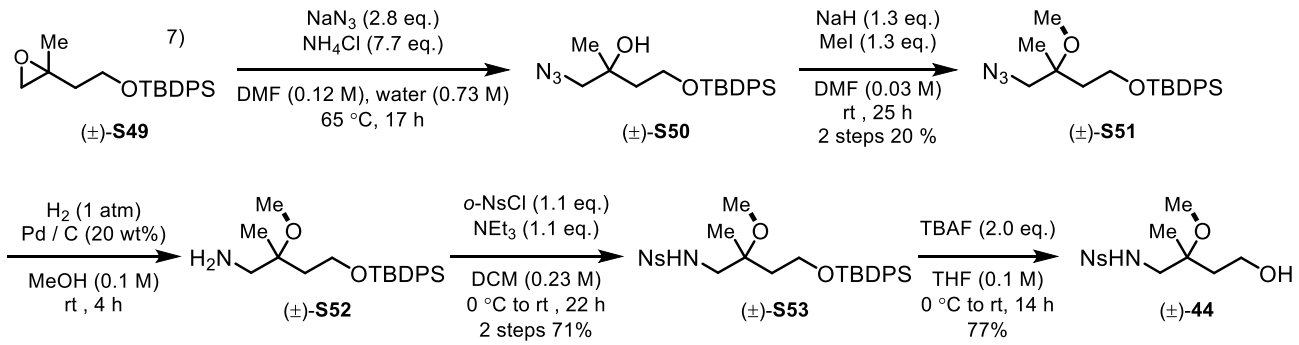
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.18–8.05 (m, 1H), 7.91–7.83 (m, 1H), 7.78–7.71 (m, 2H), 5.64 (t, *J* = 6.0 Hz, 1H), 4.15–4.04 (m, 2H), 3.21–2.98 (m, 5H), 2.03 (s, 3H), 1.88 (t, *J* = 7.0 Hz, 2H), 1.20 (s, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 171.13, 148.23, 133.71, 133.65, 132.86, 131.24, 125.55, 75.00, 60.28, 49.94, 49.40, 34.14, 21.12, 20.72.

HRMS (ESI) *m/z*: [M+Na$^+$] Calcd for $C_{14}H_{20}N_2O_7SNa$ 383.0883; Found 383.0882.

HPLC condition: (DAICEL CHIRALPAK IC, 2-propanol/hexane 3:7, flow 1.0 mL/min, 38.5 min (minor), 57.2 min (major).

Synthesis of (±)–44



***tert*-butyl(2-(2-(4-fluorophenyl)oxiran-2-yl)ethoxy)dimethylsilane ((±)–S51)**

To a solution of (±)–**S49** (341 mg, 1.00 mmol, prepared according to a literature method[7]) in DMF (0.12 M, 8.3 mL), H_2O (0.73 M, 1.37 mL) was added NaN_3 (184 mg, 2.83 mmol, 2.83 eq.) and NH_4Cl (410 mg, 7.66mmol, 7.66 eq.). The mixture was warmed up to 65 ℃ for 17 h. Then H_2O (21 mL) was added and the aqueous phase was extracted with EA twice, and the combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was directly used for the next step.

To a round bottom flask was added (±)–**S50**, DMF (11 mL, 0.03 M) and the reaction vessel was cooled down to 0 ℃. NaH (17.6 mg, 1.3 eq.) was slowly added and stirred for 10 min. Then MeI (27.5 μL, 1.3 eq.) was added and warmed up to rt and stirred for another 25 h. The reaction mixture was quenched with NH_4Cl_{aq} and extracted with EtOAc twice, washed by H_2O, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by preparative TLC purification (EA-hexane 1:10) to yield (±)–**S51** (54.1 mg, 0.14 mmol, 2 steps 20%).

Colorless oil: **IR** (neat): 2934, 2890, 2858, 2101, 1468, 1428, 1295, 1110, 1081, 705 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.67–7.72 (m, 4H), 7.48–7.38 (m, 6H), 3.81–3.69 (m, 2H), 3.27 (ABq, 2H, $\Delta\delta_{AB}$ = 0.09, J_{AB} = 12.8 Hz), 3.14 (s, 3H), 1.90–1.77 (m, 2H), 1.19 (s, 3H), 1.07 (s, 9H).
^{13}C NMR: (100 MHz, $CDCl_3$) δ 135.69, 133.67, 129.81, 127.82, 76.43, 59.78, 57.48, 49.38, 38.06, 26.94, 21.05, 19.20.
HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{22}H_{31}N_3O_2SiNa$ 420.2078; Found 420.2057.

***N*-(4-((*tert*-butyldiphenylsilyl)oxy)-2-methoxy-2-methylbutyl)-4-nitrobenzenesulfonamide ((±)–S53)**

To a flask was added (±)–**S51** (54.1 mg, 0.14 mmol), MeOH (1.36 mL, 0.1 M) and Pd / C (10.8 mg, 20 wt%). The flask was charged with H_2 and stirred for 4 h. The reaction mixture was filtrated with celite and washed with MeOH and concentrated under reduced pressure to give **S52**. The crude residue was directly used for next reaction.

To a flask was added (±)–**S52**, DCM (0.59 mL, 0.23 M) and NEt_3 (20.9 μL, 0.15 mmol, 1.1 eq.). The flask was cooled to 0 ℃ and *o*NsCl (33.9 mg, 1.5 mmol, 1.1 eq.) was added and was warmed up to r.t. ant stirred for another

22 h. The reaction mixture was concentrated, and the crude residue was purified by preparative TLC purification (EA-hexane 1:2) to yield **S53** (54.0 mg, 0.097 mmol, 2 steps 71%).

Colorless oil: **IR** (neat): 2934, 2858, 1542, 1403, 1360, 1170, 1109, 1086, 736 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.08–8.02 (m, 1H), 7.86–7.81 (s, 1H), 7.74–7.56 (m, 6H), 7.49–7.31 (m, 6H), 5.69 (t, *J* = 5.9 Hz, 1H), 3.78–3.57 (m, 2H), 3.25–3.08 (m, 2H), 2.98 (s, 3H), 1.83–1.69 (m, 2H), 1.16 (s, 3H), 1.02 (s, 9H).
^{13}C NMR: (100 MHz, $CDCl_3$) δ 148.16, 135.67, 133.89, 133.43, 132.73, 131.26, 129.89, 129.86, 127.87, 125.43, 75.41, 59.72, 50.67, 49.15, 38.03, 26.94, 20.75, 19.18.
HRMS (ESI) *m/z*: [M+Na^+] Calcd for $C_{28}H_{36}N_2O_6SiSNa$ 579.1956; Found 579.1944.

***N*-(4-hydroxy-2-methoxy-2-methylbutyl)-4-nitrobenzenesulfonamide** ((±)–**44**)

To a solution of **S53** (54.0 mg, 0.097 mmol) in THF (0.1 M, 97 μL) was cooled to 0 ℃ was added a solution of TBAF [1 mol/L in THF] (0.194 mL, 0.194 mmol, 2.0 eq.). The mixture was warmed up to room temperature for 14 h and quenched with sat. NH_4Cl(aq). The aqueous phase was extracted with EtOAc twice, and the combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (EA only) to give (±)–**44** (23.9 mg, 0.075 mmol, 77%.)

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