

Development of a New Heterocycle-Forming Reaction
and
Kinetic Resolution with N-Heterocyclic Carbenes

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Abbreviations

Å	Ångström
Ac	acetyl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
calcd.	calculated
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
DMAP	4-(dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
dr	diastereomeric ratio
ee	enantiomeric excess
equiv.	equivalent
Et	ethyl
EWG	electron withdrawing group
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoric triamide
HOBt	1-hydroxybenzotriazole
HPLC	high resolution liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IR	infrared
<i>m</i> -CPBA	<i>m</i> -chloroperbenzoic acid
LG	leaving group
Me	methyl
mp	melting point
Ms	methanesulfonyl
MS	molecular sieves
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy

Ph	phenyl
ppm	perts per million
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBS	<i>tert</i> -butyldimetylsilyl
<i>t</i> -Bu	<i>tert</i> -butyl
Tf	trifluoromethaneulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
tol	toluene
Tr	triphenylmethyl
Ts	<i>p</i> -toluenesulfonyl

Preface

While appreciating the many benefits of modern industry, we should be aware of the associating risks, including higher pollution levels, overuse of natural resources, and increased amounts of waste. During the past few decades, these problems have intensified owing due to demographic growth, the planet's limited resources, and social inequality. In particular, individual consumption has been increasing considerably as less-developed countries attempt to catch up with the others. Greenhouse gas emissions, resulting from human activity, are a major contributor to the acceleration of global warming and have many negative impacts, including glacier retreat, variation in the timing of seasonal events, and changes in agricultural productivity. In recent years, another severe problem associated with industrial expansion and urbanization has been the increasingly frequent occurrence of haze or smog episodes characterized by high levels of fine particulate matter, which originates mainly from sources such as traffic-related emissions and road dust, as well as biomass burning. This problem has been reported on a national scale in my home country, China.

Responding to these problems, sustainable development, which is defined as “development that meets the needs of the present without compromising the ability of future generations to meet their own needs” was raised in the famous Brundtland Report in 1987.¹ In 2015, the United Nations formally adopted the “2030 Agenda for Sustainable Development,” which consists of 17 sustainable development goals (SDGs) and calls for sustainable consumption and production. Promoting industrialization, ensuring access to sustainable energy, and facilitating well-being for all people at all ages were among the goals advocated.

On the road to sustainable development, there is an urgent need to improve productivity and reduce consumption in the manufacture of commodities and materials. These needs may be achieved by designing and producing appropriate catalysts. These work by facilitating routes between starting materials and products with lower activation barriers than that of the uncatalyzed process, while the catalyst itself is not consumed and can continue to act repeatedly.² Catalyst development is one of the key points in the design of efficient catalytic processes to maximize the value of starting materials while minimizing waste generation and energy requirements.

Modern catalysis is built on three branches—biocatalysis, metal catalysis, and organocatalysis. Organocatalysis is defined as using a substoichiometric amount of an organic compound, which does not contain a metal atom to catalyze organic transformations. In contrast to many metal catalysts, which are limited in nature, mostly toxic for human health and the

environment, and may cause metal impurities in the final products,³ as well as biocatalysts, which lack robustness and commercial availability, organocatalysts meet the requirements of green and sustainable chemistry. This is because they are not exhaustible resources like metals, and are expected to enable new functions that have not been achieved by metal catalysts.

The field of organocatalysis has experienced huge growth in the past two decades, as researchers have sought to reduce energy consumption and optimize the use of the available resources, with the aim of developing a sustainable strategy for chemical transformations. However, the relatively low reactivity of most known organocatalysts means they require high catalyst loading, while lack of diversity limits the range of applications.

In order to contribute to the progress of green and sustainable chemistry, my research focused on creating a highly reactive organocatalyst and developing new catalytic reactions, thereby producing useful organic structures. In this thesis, an N-heterocyclic carbene promoted cyclization of propargyl sulfones with 1,2-migration of sulfonyl groups (Chapter 2) and kinetic resolution of α -hydroxy carboxylic acid derivatives based on chiral recognition of the substrate–cocatalyst complex (Chapter 3).

1. Introduction

1.1. N-heterocyclic carbene

Carbenes are highly reactive carbon-containing compounds, consisting of a divalent carbon atom with a six-electron valence shell. Over the past few decades, stable carbenes have received a great deal of attention from various researchers.⁴ In singlet carbene compounds, a carbon center bears a lone pair of electrons in an sp^2 hybridized orbital, while a p orbital remains vacant (Figure 1.1a). Triplet carbenes are also known, where each of the two electrons occupy a degenerate p orbital (Figure 1.1b). Molecular orbital calculations predicted that the triplet carbene is about 8 kcal/mol lower in energy than the singlet for simple hydrocarbons.⁵ The nature of substituents R^1 and R^2 have profound effects on the electronics of the carbenes and their reactions.

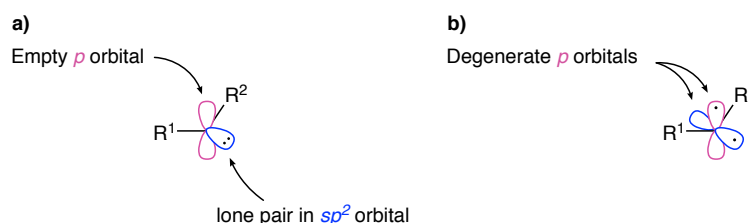


Figure 1.1 a) Singlet Carbenes; b) Triplet Carbenes

Free carbenes are inherently unstable, and they have traditionally been considered only as highly reactive transient intermediates in organic transformations such as cyclopropanation. In 1968, Wanzlick and Öfele independently reported a stable and isolable carbene N-heterocyclic carbene (NHC) as a metal–carbene complex, which was stabilized by favorable interactions with adjacent heteroatoms.⁶ Inspired by these insightful studies, Arduengo and coworkers reported the first stable and isolable carbene 1,3-di(adamantyl)imidazol-2-ylidene (IAd, Figure 1.2), which is electronically stabilized by the adjacent nitrogen and sterically stabilized by the bulky N-substituents, preventing undesired carbene dimerization.⁷ Since then, contributions from many different groups on NHCs have led to a wide variety of applications across many different fields.

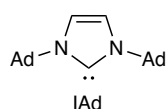


Figure 1.2 The first reported stable and isolatable NHC.

NHCs are heterocyclic species containing a carbene carbon and at least one nitrogen atom within the ring structure. The ground-state electronic structure of NHC-imidazolyldene is shown in Figure 1.3. NHCs exhibit a singlet ground-state electronic configuration with a formally sp^2 -hybridized lone pair and an unoccupied p -orbital at the carbene carbon. The adjacent σ -electron-withdrawing and π -electron-donating nitrogen atoms stabilize this structure. NHCs generally feature bulky substituents (R) adjacent to the carbene carbon, which help to kinetically stabilize the species by sterically disfavoring dimerization to the corresponding olefin. The cyclic nature of NHCs also helps to favor the singlet state by forcing the carbene carbon into a more sp^2 -like arrangement.

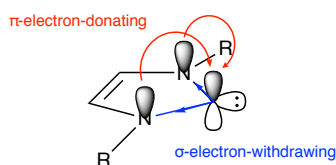


Figure 1.3 Ground-state Electronic Structure of NHC

Commonly used classes of NHCs are thiazolyldenes, imidazolinylidenes, imidazolyldenes, and triazolyldenes (Figure 1.4). In the majority of cases, the carbene is generated from deprotonation of the corresponding cationic heterocyclic azolium salts.

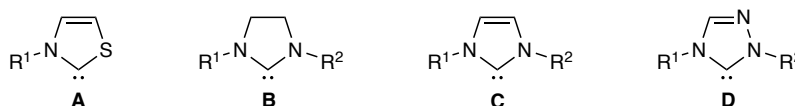


Figure 1.4 General types of N-heterocyclic carbenes.

The majority of applications of N-heterocyclic carbenes involve their coordination to transition metals (Figure 1.5), mainly owing to the inherent σ -donor ability of NHCs. After the pioneering study by Herrmann and co-workers, in which NHC was used as a ligand in a palladium-catalyzed Heck reaction,⁸ a wide range of applications of NHC complexes with various transition metals have been developed.⁹

Another major application of NHCs is their use as organocatalysts (Figure 1.5). The largest and most diverse type of NHC-catalyzed reactions involves nucleophilic attack of NHCs on carbon-electrophiles. On the other hand, the high Brønsted basicity of NHCs also facilitates hydrogen bond formation with alcohols, activating their nucleophilicity.

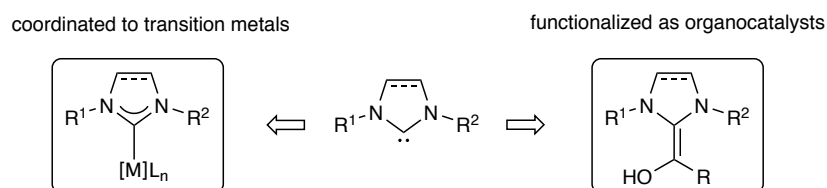


Figure 1.5 Major Applications of NHCs

With the development of NHCs in transition-metal catalysis and organocatalysis, many different types of carbenes with various substitution patterns have been synthesized. Several representative chiral azolium precatalysts are listed in Figure 1.6. At an early stage, NHC organocatalysis was dominated by thiazolium-based carbenes, since Sheehan reported the first asymmetric benzoin reaction using a chiral thiazolium salt in 1966.¹⁰ As the field has progressed, imidazolium, triazolium, and imidazolynium scaffolds have also become popular, owing to work by Herrmann,¹¹ Enders,¹² Leeper,¹³ Rovis,¹⁴ and Tomioka.¹⁵

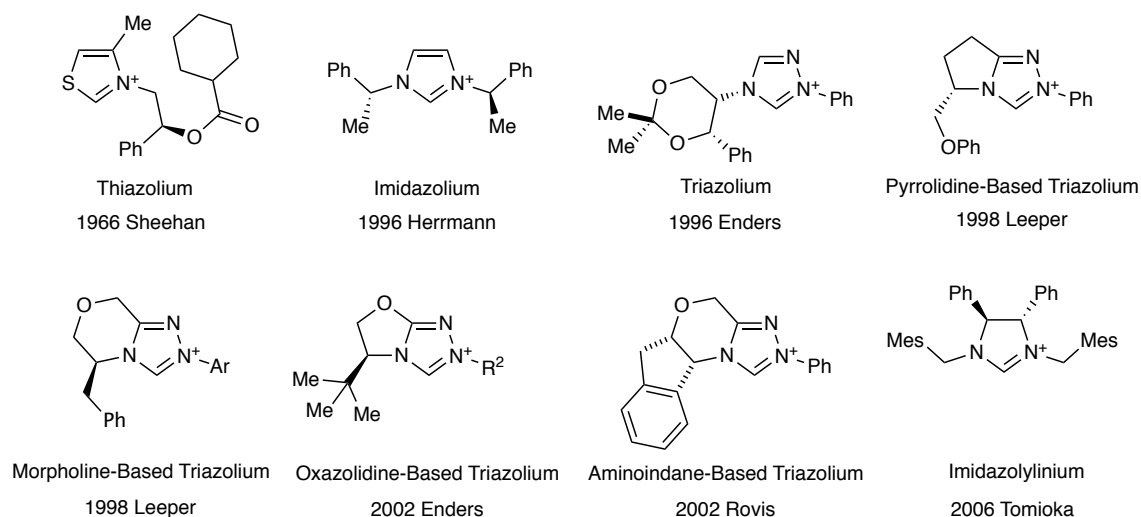


Figure 1.6 Representative Structures of Chiral Carbene Precursors.

1.2. Catalysis Involving Umpolung Process

Umpolung, also called “polarity inversion,” involves chemical modification of a functional group with the aim of the reversal of its inherent polarity.

Seebach and Corey (1975)

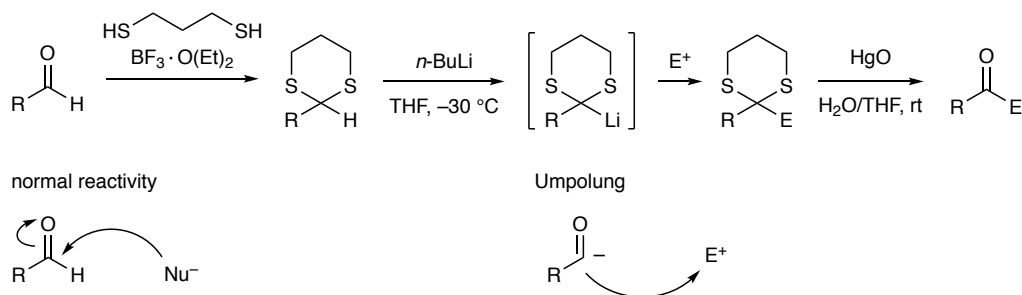


Figure 1.7 Corey-Seebach Umpolung

The concept was introduced by D. Seebach and E. J. Corey in a reaction that allows a reversal of the normal reactivity of acyl carbon atoms by temporary conversion to 1,3-dithiane (Figure 1.7).¹⁶ In this reaction, the lithiated 1,3-dithiane can be viewed as a masked acyl anion that is able to react with various electrophiles. Indeed, the evolution of umpolung catalysis dates back to the original discovery of the cyanide-catalyzed benzoin reaction in 1832.¹⁷ The proposed reaction mechanism was as follows: addition of the cyanide ion to benzaldehyde affords a cyanohydrin anion. The electrophilic aldehyde carbon becomes nucleophilic after proton transfer, and reacts with another benzaldehyde to give benzoin and a regenerated cyanide ion (Figure 1.8).

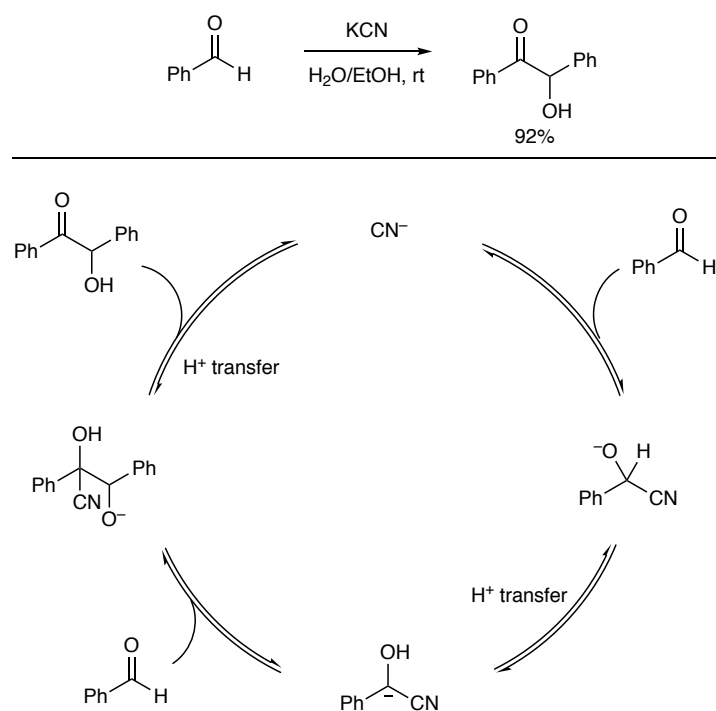
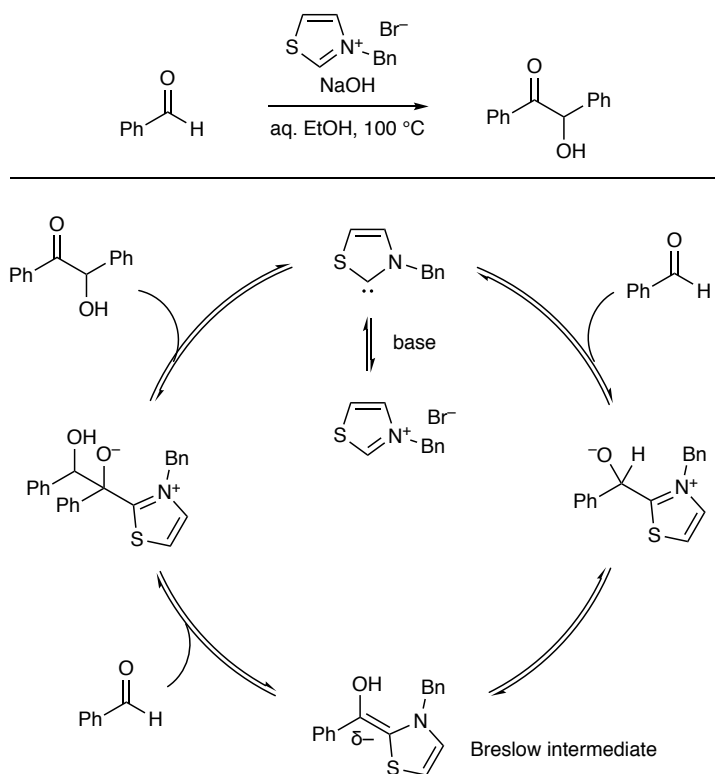


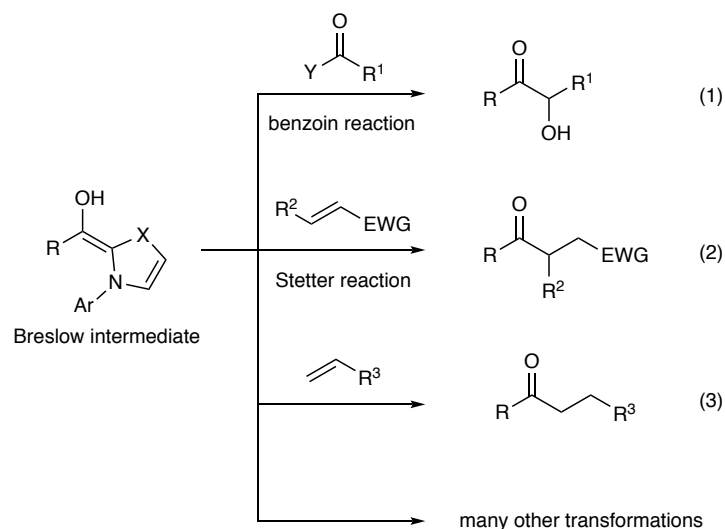
Figure 1.8 Cyanide-catalyzed Benzoin Reaction

NHCs mediate a wide range of organic transformations, mostly involving Umpolung processes. One of the most-studied NHC organocatalytic reactions results from the umpolung of aldehydes (d^1 Umpolung). The first example of this kind of transformation dates back to 1943, when Ukai and co-workers reported the homodimerization of aldehydes to benzoin catalyzed by a thiazolium salt by chance¹⁸ (Scheme 1.1).



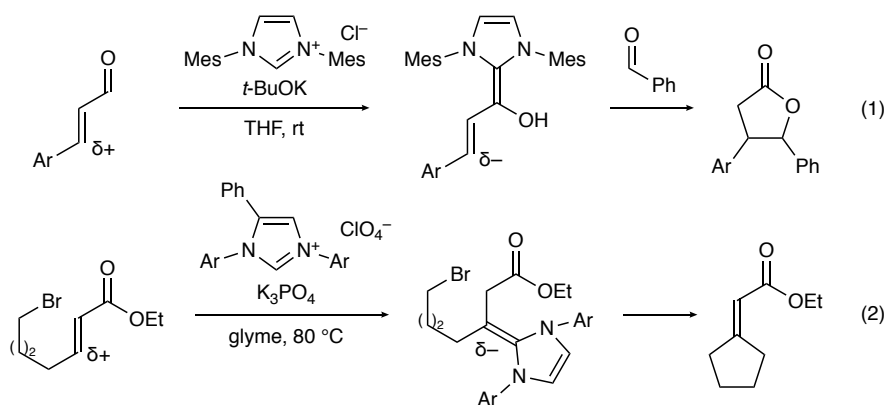
Scheme 1.1 NHC-catalyzed Benzoin Reaction (d¹ Umpolung)

Subsequently, based on the reported cyanide-catalyzed benzoin reaction (Figure 1), Breslow proposed the following mechanism for this process in 1958:¹⁹ NHC is generated from the thiazolium salt and NaOH *in situ*. Initial nucleophilic attack of NHC on the aldehyde leads to the tetrahedral intermediate, which undergoes proton transfer to the enamine-like “Breslow intermediate,” which is nucleophilic at carbon as a result of π -donation from the ring heteroatoms. The Breslow intermediate then undergoes addition to another molecule of aldehyde, giving rise to benzoin. Today, this acyl-anion-equivalent “Breslow intermediate” has been employed in many transformations, involving addition to a variety of carbonyl compounds (benzoin reaction, Scheme 1.2, eq 1),²⁰ Michael acceptors (Stetter reaction, Scheme 1.2, eq 2),²¹ and even unpolarized carbon–carbon multiple bonds (Scheme 1.2, eq 3).²²



Scheme 1.2 Reactions of Breslow Intermediate

Moreover, NHCs are employed for the conjugate umpolung of enals (d^3 Umpolung) to generate homoenolate equivalents, where the nucleophile is generated at the β -position, leading to annulated products (Scheme 1.3 eq 1). This kind of transformation was first reported by Glorius.²³ In 2006, Fu and co-workers extended the umpolung concept to Michael acceptors for the synthesis of cyclic α,β -unsaturated esters by an intramolecular β -alkylation (Scheme 1.3 eq 2).²⁴ NHC-catalyzed Umpolung of Michael acceptors was also used in other transformations by other groups.²⁵ In the majority of cases, Umpolung using NHCs is limited to carbonyl compounds.



Scheme 1.3 NHC-catalyzed d^3 Umpolung Reaction

1.3. Catalysis Involving Acylazolium Intermediates

Acylation is the process of introducing an acyl group to a compound. The acyl group donor is called an acylating agent. Acyl halides and anhydrides are commonly used acylating agents. In addition, acylazolium (Figure 1.7 A) has gradually become an important acylating agent in chemical sciences. Acylazoliums are known to be important intermediates in biological reactions, and Townsend and co-workers have reported that thiamine diphosphate (vitamin B1)-derived α,β -unsaturated acylazolium ion (Figure 1.7 B) is the key intermediate in clavulanic acid biosynthesis.²⁶

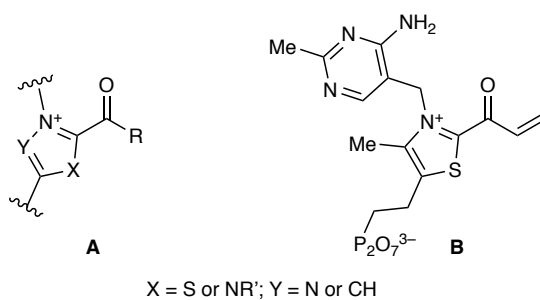
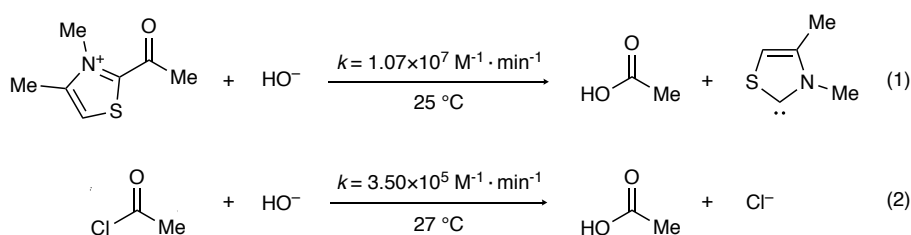


Figure 1.9 Acylazoliums

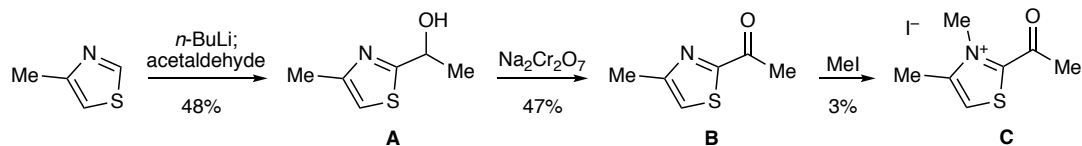
Acylazolium is a powerful acylating agent, and the reported rate constants of hydrolysis indicate that acylazolium²⁷ is more reactive than the corresponding acyl chloride (Scheme 1.4).²⁸



Scheme 1.4 Acylating Ability

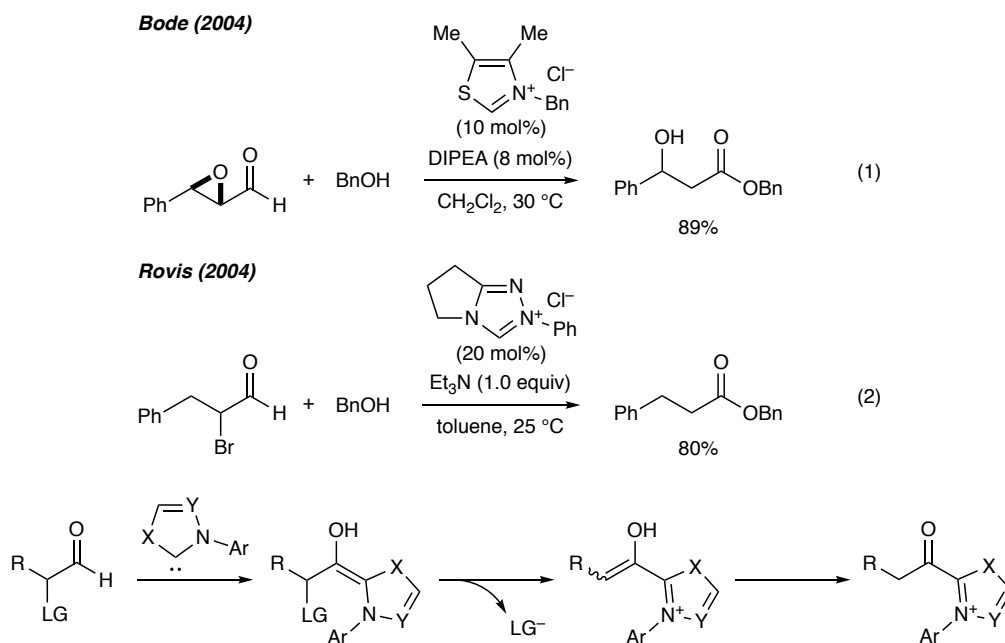
Despite this remarkable reactivity of acylazolium in acylation, there were only a few reports on acylazolium for a long time following the first report by Lienhard in 1966.²⁹ This may have been because preparation of acylazolium was tedious. Lienhard prepared acetylthiazolium salt using the method reported by Daigo,³⁰ which is shown in Scheme 1.5. Deprotonation of thiazole by *n*-BuLi and the following addition to acetaldehyde gave alcohol **A**. Then, oxidation of the

alcohol followed by methylation of the resulting ketone provided acylazolium salt **C** in extremely low yields.



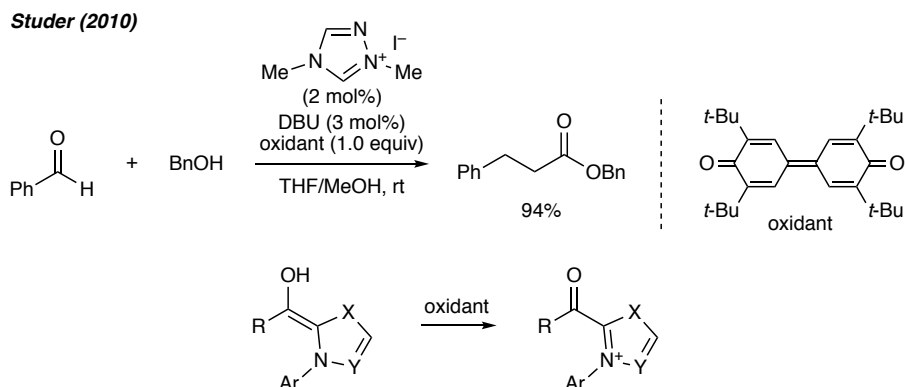
Scheme 1.5 Acylazolium Synthesis under Stoichiometric Conditions

Acyl azoliums have attracted increasing research attention since Bode's and Rovis's groups independently reported their catalytic *in situ* generation from α -oxidized aldehydes in 2004.³¹ Bode and co-workers described the thiazolylidene-catalyzed acylation of benzylalcohol using epoxy aldehydes to generate β -hydroxy amino ester (Scheme 1.6, eq 1). Rovis and co-workers reported the triazolylidene-catalyzed conversion of α -bromo aldehydes to aliphatic esters (Scheme 1.6, eq 2). Their methods involved nucleophilic addition of NHC to the α -substituted aldehydes, proton transfer to give Breslow intermediates, elimination of the leaving group situated in the α -position, and a final tautomerization to generate acyl azolium salts.



Scheme 1.6 Catalytically Acylazolium Generation from α -oxidized aldehydes

Another way to generate acylazolium is to use an oxidant. This approach was first reported by Studer in 2010, who described how an *in situ* oxidation of the Breslow intermediate to the corresponding acylazolium species could be accomplished with an external organic oxidant (Scheme 1.7).³¹



Scheme 1.7 Oxidative Formation of Acylazolium from Breslow intermediate

Our group also contributed to acylazolium chemistry using NCS as an oxidant. In this reaction, NCS oxidized aldehyde to α -chloro-aldehyde, which followed Bode's and Rovis' chemistry to give an acylazolium intermediate.³² Notably, depending on the NHC catalyst used, the amides and esters were formed selectively.

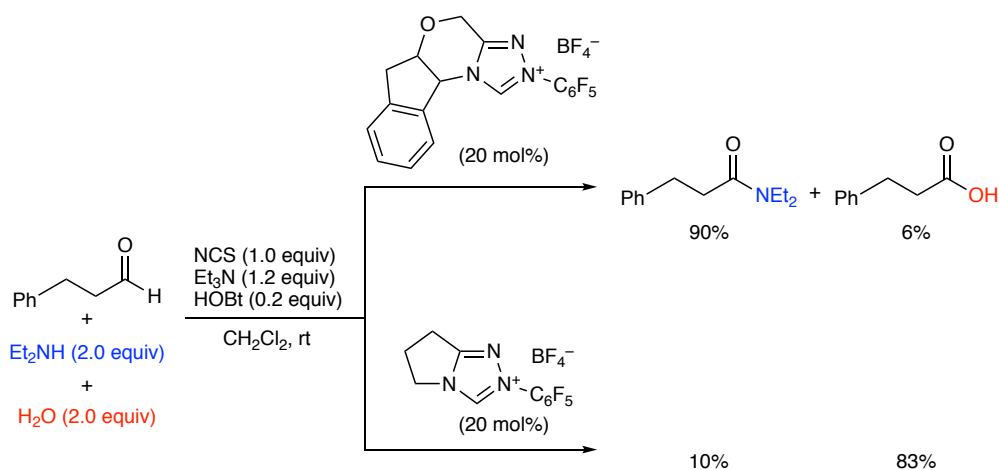
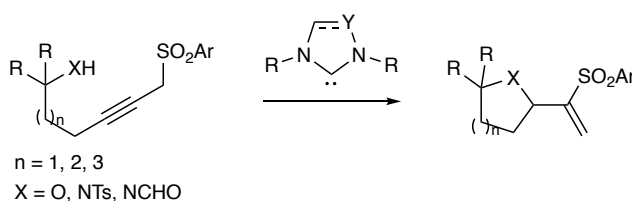


Figure 1.10 Reported *in situ* Generation of Acylazolium and Chemoselective Generation of Amides and Esters

1.4. Contents of This Thesis

Oxa- and Azacycle-formation via Migrative Cyclization of Sulfonylalkynol and Sulfonylalkynamide (Chapter 2)

Chapter 2 described how NHC promotes cyclization of sulfonylalkynols and sulfonylalkynamides in an a^4 Umpolung-type bond formation process that accompanied 1,2-migration of the sulfonyl groups. This reaction provides a novel access to oxa- and azacycles possessing a pendant vinyl sulfone functionality, which in turn is amenable to further transformations (Scheme 1.5).

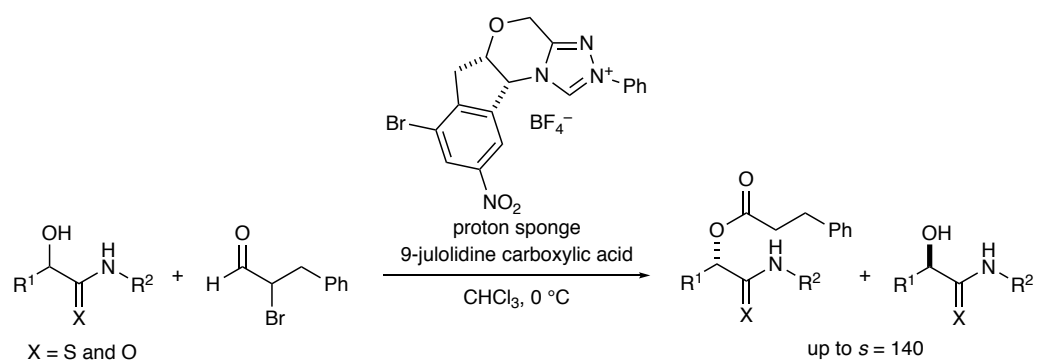


Scheme 1.8 Oxa- and Azacycle-formation via Migrative Cyclization of Sulfonylalkynol and Sulfonylalkynamide with NHC

During research on this migrative cyclization, mechanism studies indicated that nucleophiles other than NHCs might also induce this transformation. Further investigations showed that a catalytic amount of phosphine or 4-(*N,N*-dimethylamino)pyridine (DMAP) also promoted migrative cyclization in an a^4 Umpolung manner similarly. Furthermore, asymmetric induction was observed when a chiral DMAP derivative was used in the reaction.

Kinetic Resolution of α -Hydroxy Carboxylic Acid Derivatives Based on Chiral Recognition of Substrate–Cocatalyst Complex (Chapter 3)

During research on this migrative cyclization, mechanism studies indicated that nucleophiles other than NHCs might also induce this transformation. Further investigations showed that a catalytic amount of phosphine or DMAP also promoted migrative cyclization in an a^4 Umpolung manner similarly. Furthermore, asymmetric induction was observed when a chiral DMAP derivative was used in the reaction.



Scheme 1.9 Kinetic Resolution of α -Hydroxy Carboxylic Acid Derivatives

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2. Oxa- and Azacycle-formation via Migrative Cyclization of Sulfonylalkynol and Sulfonylalkynamide

2.1. NHC-Initiated Migrative Cyclization of Sulfonylalkynol and Sulfonylalkynamide

2.1.1. Introduction

Oxygen- or nitrogen-containing heterocycles are important moieties in natural compounds and products of biological or industrial importance.¹ Consequently, developing new synthetic approaches to access new families of oxa- and azacycles is highly desirable. Over the past several years, our laboratory has employed N-heterocyclic carbene catalysis as a platform for developing new methodologies to construct useful organic compounds.² The majority of NHC catalysis currently involves activation of carbonyl compounds, while that involving activation of other functional groups has rarely been described.³ As discussed in **1.3**, in the realm of NHC-catalyzed Umpolung reactions, although transformations involving polarity inversion of carbonyl carbon (d^1 Umpolung) and β -carbon (d^3 Umpolung) have been widely investigated, no other Umpolung mode has yet been accessed. In this study, I have developed a new activation process of NHC: NHC-promoted cyclization of sulfonylalkynols and sulfonylalkynamides in a d^4 Umpolung mode, accompanying 1,2-migration of the sulfonyl groups.

Catalytic a d^4 Umpolung reaction of activated allenes and acetylenes was first reported by Trost in 1994.^{4a, 4b} Cyclization of hydroxy-2-alkynoates was catalyzed by dppp (dppp = 1,3-bis(diphenylphosphino)propane) to generate saturated oxygen heterocycles (Figure 2.1).^{4b} A plausible pathway of this cyclization was suggested as follows: the reaction is triggered by nucleophilic addition of the phosphine to the alkynoate. Tautomerization is followed by the intramolecular addition to the olefin activated by the phosphonium cation. Elimination of the phosphine from the resulting intermediate gives the corresponding product. The acetic acid assists proton transfer in the overall catalysis. Fu and coworkers developed an asymmetric version of this Trost cyclization using a chiral phosphine with good enantiomeric excesses.⁵

Trost (1994)

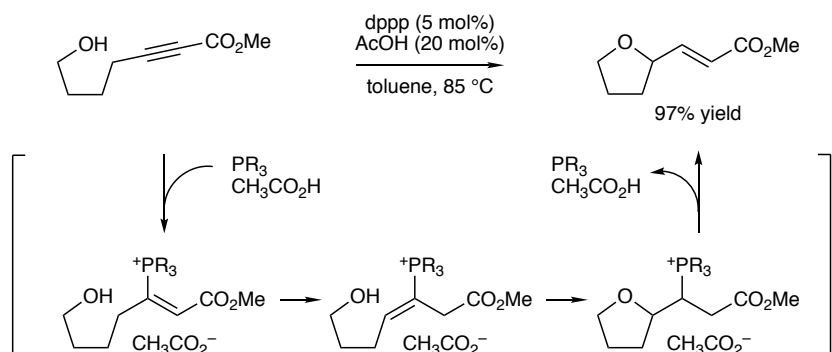
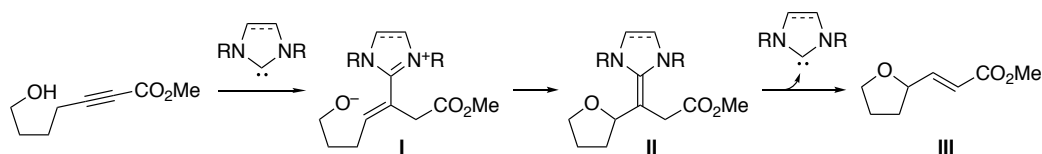


Figure 2.1 Reported Phosphine-catalyzed Intramolecular γ -Umpolung Addition of Oxygen Nucleophile

Based on the proposed mechanism of the phosphine-catalyzed α^4 Umpolung addition^{4b} and the NHC-catalyzed reactions of α,β -unsaturated esters (Scheme 1.1, eq 3),^{19,20} in chapter 1 the NHC-catalyzed α^4 Umpolung cyclization of alkynoates was envisaged as described in Scheme 2.1. Conjugate addition of NHC to alkynoate and the following proton transfer would provide intermediate **I**. Subsequent intramolecular conjugate addition and tautomerization could give rise to NHC-bearing heterocycle **II**, which undergoes elimination of NHC to produce oxacycle **III**.



Scheme 2.1 Expected α^4 Umpolung Reaction by NHC Catalysis

Initial evaluations using several NHC precatalysts were conducted in our group, but no expected product was formed, and the alkynoate was recovered (Figure 2.2). I rationalized that the electrophilicity of alkynoate might be insufficient for the nucleophilic addition of NHC. With this in mind, I turned my attention to the highly electrophilic Michael acceptor alkynyl sulfone.

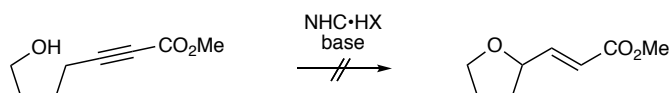
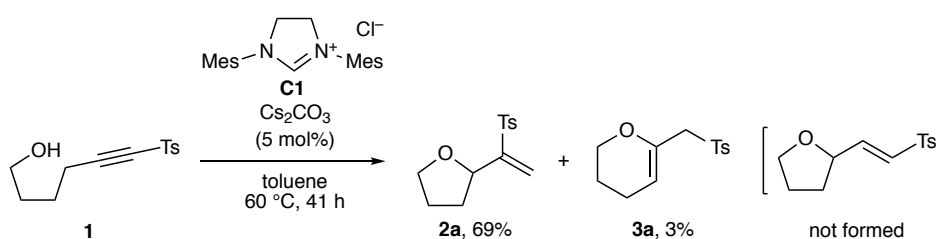


Figure 2.2 Initial Investigation

2.1.2. Migrative Cyclization of Sulfonylalkynol

The sulfone group is strongly electron-withdrawing and has the ability to stabilize an α -carbanion. Thus, alkynyl sulfones are known to undergo a variety of reactions via conjugate addition processes.⁶ First, alkynyl sulfone **1**, 5 mol% of SIMes·HCl (**C1**), and Cs₂CO₃ were heated at 60 °C in toluene (Scheme 2.2). After 41 h, however, the expected product was not detected by ¹H-NMR. Tetrahydrofuran **2a** bearing a vinyl sulfone group formed unexpectedly in 69% yield, along with a small amount of dihydropyran **3a**. The major product **2a** indicated that bond formation with the internal O-nucleophile had occurred at the γ -position of alkynyl sulfone (a⁴ Umpolung) with 1,2-sulfonyl migration. This interesting reaction mode led me to undertake further investigations.



Scheme 2.2 NHC-catalyzed Migrative Cyclization of Alkynyl Sulfone

2.1.3. Mechanism Consideration

A plausible reaction pathway to produce **2a** is shown in Scheme 2.3. Alkynyl sulfones reversibly isomerize to the corresponding allenyl sulfones and propargyl sulfones under basic conditions (Figure 2.3),⁷ and the reaction probably proceeds via allenyl sulfone intermediate **4** generated *in situ* from alkynyl sulfone **1**. Conjugate addition of NHC to allenyl sulfone **4**, followed by internal proton transfer, produces intermediate **VI**. Then, **VI** undergoes an intramolecular S_N2' reaction to give cationic compound **VII** and *p*-toluenesulfinate anion (Ts⁻) (Scheme 2.3, initiation step) rather than the initially expected conjugate addition. The liberation of Ts⁻ triggers the productive cycle as follows: formation of **VIII** by the addition of Ts⁻ to **4** and the following S_N2' cyclization result in the production of **2a** and the regeneration of Ts⁻ (Scheme 2.3, productive cycle).

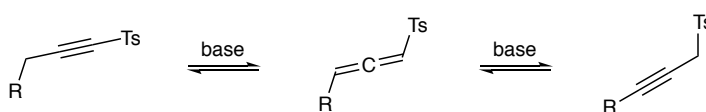
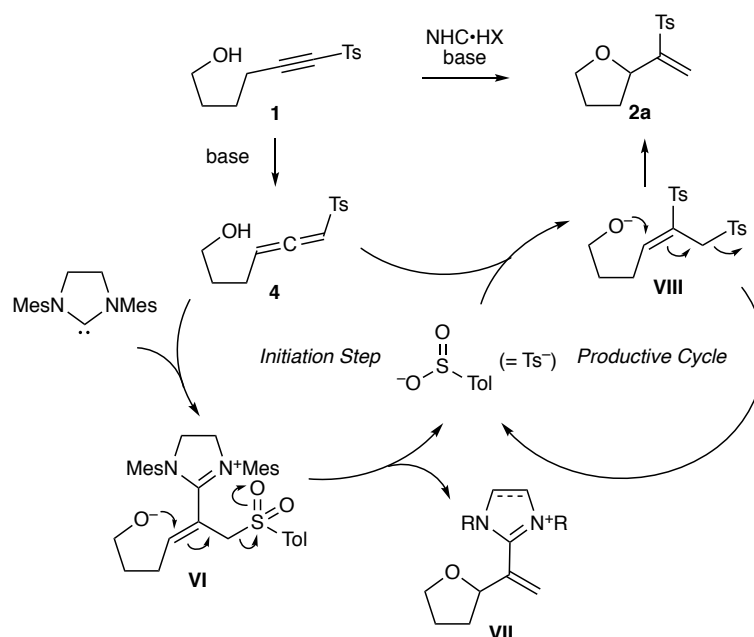


Figure 2.3 Isomerization between Alkynyl-, Allenyl-, and Propargyl-sulfones under Basic Conditions



Scheme 2.3 Proposed Mechanism for Migrative Cyclization

There is another possible pathway for the initiation step (Figure 2.3): Conjugate addition of NHC to alkynyl sulfone **1** followed by olefin isomerization and internal proton transfer would also produce intermediate **VI**. However, this pathway is less plausible, as a similar sulfone-migration reaction of allenyl sulfone was reported as shown below.⁸

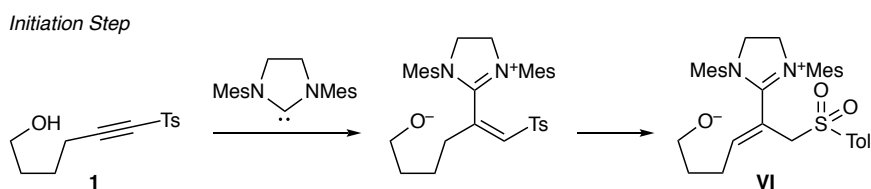


Figure 2.3 Another Possible Pathway to Intermediate **VI**

In 1988, Padwa and co-workers reported that the reaction of **5** and **6** gave mainly **8** along with **7**.^{8a} The proposed mechanism is as follows: conjugate addition of bis-(phenylsulfonyl)methane **5** to allenyl sulfone **6** resulted in compound **7**, which underwent S_N2' reaction with **5**, produced compound **9**, and eliminated phenylsulfinate anion. Addition of the phenylsulfinate anion to allenyl sulfone **6** generated intermediate **10**, which joined the productive cycle to provide the trisulfone **8** via addition and elimination of the phenylsulfinate anion.

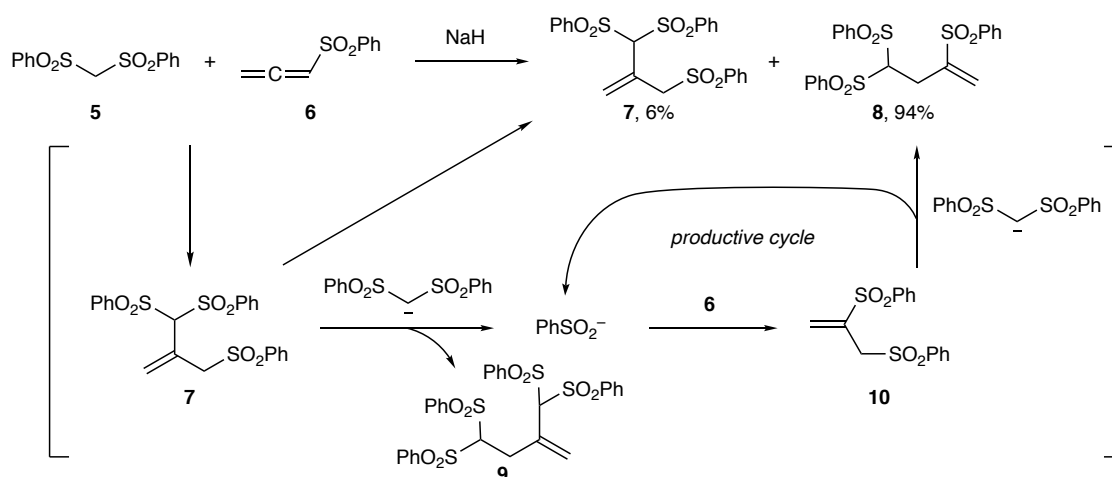
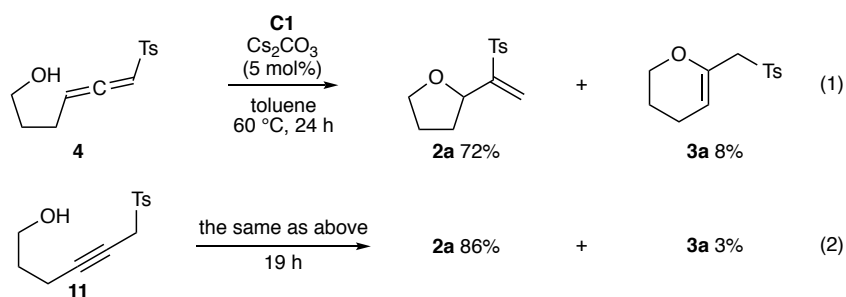


Figure 2.5 Sulfonyl Migration Reported by Padwa

Based on the pathway in Scheme 2.3, reactions using isomers of alkynyl sulfone **1** were tested (Scheme 2.4). Heating allenyl sulfone **4** at 60 °C in toluene in the presence of **C1** and Cs₂CO₃ (5 mol % each) produced **2a** in 72% yield (eq 1). The corresponding propargyl sulfone **11** gave **2a** in a much higher yield (86%) than the other isomers (eq 2). Thus, propargyl sulfone was considered the most suitable substrate in this reaction and was used in extensive further investigations.



Scheme 2.4 Migrative Cyclization of Allenyl Sulfone and Propargyl Sulfone

2.1.4. Optimization of Conditions

Optimization of the reaction conditions started with base screening. Among the tested bases, Cs_2CO_3 was the most suitable for this reaction (Table 2.1, entries 1 and 3–6). DBU gave the dihydropyran **3a** in a higher yield (18%, entry 6). Since generation of NHC from the precursor and base is reversible, the surplus highly basic DBU ($\text{p}K_{\text{a}} \sim 12$, value for protonated form)⁹ may cause deprotonation of alcohol, accelerating the competing intramolecular Michael addition (Figure 2.6). Other NHC precursors **C2**–**C6** were tested in the reaction. The more acidic NHC precursors (**C2**–**C4** and **C6**) prevented the formation of **3a** without dramatic erosion of the yield of **2a** (entries 7–9 and 11), although the reaction with **C5** was not fruitful and produced a significant amount of **3a** (8%, entry 10).

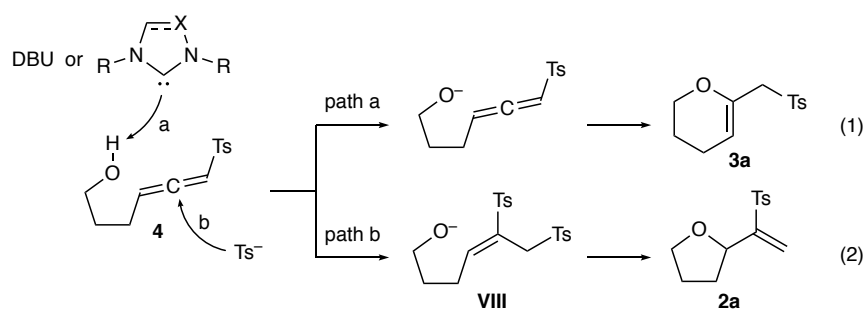


Figure 2.6 Competition of Michael Addition and Migrative Cyclization

As mentioned in **1.2**, NHCs can act as Brønsted bases to form hydrogen bonds with alcohols, which is activated for a nucleophilic attack. In this reaction, in the presence of highly basic NHC, the allenyl sulfone **4** generated *in situ* may undergo competing deprotonation of alcohol by NHC, and the following Michael addition provides dihydropyran **3a** (Figure 2.6, path a). Thus, the more acidic NHC precursors generated less-basic NHC, meaning that the conjugate addition of the sulfinate anion to allenyl sulfone **4** (Figure 2.6, path b) would be faster than the competing alcohol deprotonation. Interestingly, in the absence of NHC, the production of **2a** was also observed in 2% yield, along with **3a** in 70% yield (entry 2). The formation of **2a** could be rationalized as follows: the alcohol moiety of **11** could undergo conjugate addition to **11** instead of NHC in the initiation step, resulting in sulfinate elimination, which would promote the productive cycle to afford **2a**. The reaction was much slower in tetrahydrofuran (THF) or dichloroethane and proceeded most smoothly in toluene (entries 12–13, and 1). The use of 2 mol% **C2** was sufficient for the reaction to give **2a** in 91% yield (entry 14), although further efforts to reduce the amount of **C2** failed to provide satisfactory outcomes (entry 15).

Table 2.1 Optimization of Conditions

$\text{11a} \xrightarrow[60\text{ }^\circ\text{C}]{\text{NHC}\cdot\text{HX, base}} \text{2a} + \text{3a}$

C1

C2

C3

C4 R = Mes
C5 R = Ph
C6 R = C₆F₅

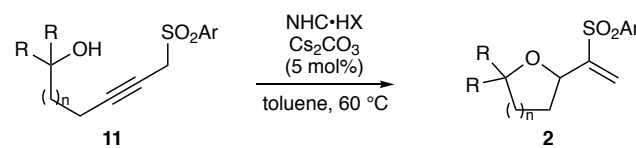
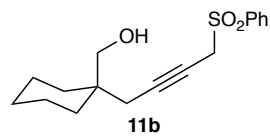
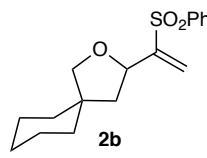
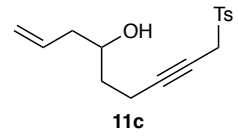
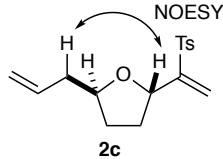
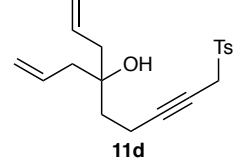
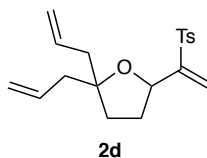
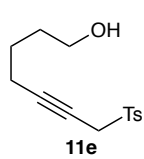
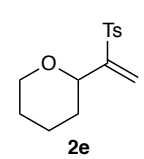
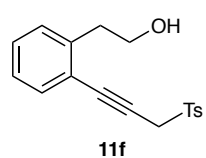
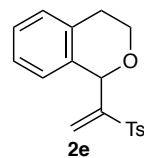
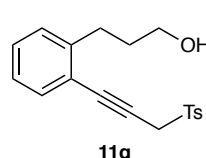
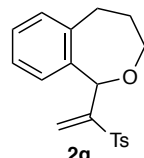
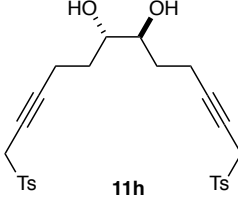
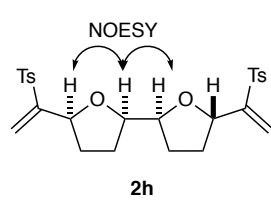
entry	NHC·HX (mol%)	base (mol%)	solvent	time (h)	2a (% yield)	3a (% yield)	11a (% recovery)
1	C1 (5)	Cs ₂ CO ₃ (5)	toluene	19	86	3	0
2	none	Cs ₂ CO ₃ (5)	toluene	12	2	70	0
3	C1 (5)	K ₂ CO ₃ (5)	toluene	26	0	0	89
4	C1 (5)	Na ₂ CO ₃ (5)	toluene	26	0	0	84
5	C1 (5)	Et ₃ N (5)	toluene	26	9	0	73
6	C1 (5)	DBU (5)	toluene	9	53	18	0
7	C2 (5)	Cs ₂ CO ₃ (5)	toluene	6	79	0	0
8	C3 (5)	Cs ₂ CO ₃ (5)	toluene	19	64	0	0
9	C4 (5)	Cs ₂ CO ₃ (5)	toluene	7.5	73	0	0
10	C5 (5)	Cs ₂ CO ₃ (5)	toluene	24	49	8	38
11	C6 (5)	Cs ₂ CO ₃ (5)	toluene	26	62	0	0
12	C2 (5)	Cs ₂ CO ₃ (5)	THF	26	3	0	83
13	C2 (5)	Cs ₂ CO ₃ (5)	(CH ₂ Cl) ₂	26	40	0	55
14	C2 (2)	Cs ₂ CO ₃ (2)	toluene	10	91	0	0
15	C2 (1)	Cs ₂ CO ₃ (1)	toluene	16	74	0	0

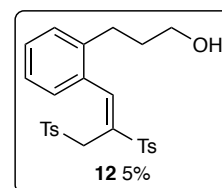
2.1.5. Scope of Migrative Cyclization of Sulfonylalkynols

With the optimized conditions in hand, the substrate scope of the migrative cyclization of sulfonylalkynol **11** was explored (Table 2.2). Propargyl sulfone **11b**, bearing vicinal substituents, showed good performance in this reaction, successfully forming **2b** in 83% yield (entry 2). Secondary alcohol **11c** (entry 3) and tertiary alcohol **11d** (entry 4) also led to formation of the tetrahydrofurans **2c** and **2d** in 81% and 70% yields, respectively. The relative configuration of **2c** was determined by NOESY correlation. For formation of the six-membered ring, the more basic carbene derived from **C1** promoted the reaction more smoothly than **C2**. Cyclization of **11e** was completed in refluxing toluene in 13 h, and tetrahydropyran **2e** was isolated in 68% yield (entry 5). Isochromane **2f** was produced in 58% yield (entry 6). Unfortunately, the reaction was not suitable for the formation of a seven-membered ring, even

when the reaction mixture was heated in refluxing toluene. In this reaction, cyclization intermediate disulfone **12** was formed in 5% yield, along with the oxepane **2g** in 5% yield. The isolation of **12** strongly supports the existence of intermediate **VIII** and, hence, the reaction pathway shown in Scheme 2.3. The reaction of C_2 -symmetric diol **11h** afforded a diastereomixture of bi-THF with **2h** as a major isomer in 88% yield, and the relative configuration was determined by NOESY correlation (entry 8). Notably, the reaction proceeded in 1.6 g scale without any problem to give **2a** in comparable yield (entry 1).

Table 2.2 Migrative Cyclization of Sulfonylalkynols

					
entry	11	NHC·HX	time	2	yield
1 ^a	11a	C2	10 h	2a	81%
2 ^b	 11b	C2	6.5 h	 2b	83%
3 ^c	 11c	C2	15 h	 2c	81%
4	 11d	C2	11 h	 2d	70%
5 ^d	 11e	C1	13 h	 2e	68%
6 ^d	 11f	C1	8 h	 2e	58%
7 ^d	 11g	C1	8 h	 2g	5%
8 ^e	 11h	C2	4 h	 2h	88%



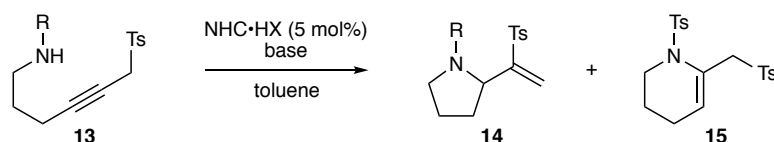
^aThe reaction was performed using 1.6 g of **2a**. ^bThe reaction was performed at 80 °C.

^cdr 3:2. ^dThe reaction was performed in refluxing toluene. ^edr 3:2:2.

2.1.6. Migrative Cyclization of Sulfonylalkynamide

Azacycle pyrrolidines are prevalent in many biologically active natural products as mentioned above, and are widely used in organic synthesis as organocatalysts and ligands.¹⁰ Thus, pyrrolidine scaffold has been the target of numerous synthetic efforts. Next, the reaction was applied to the formation of a pyrrolidine scaffold (Table 2.3). The standard conditions for alcohols (entry 1) converted *N*-*p*-toluenesulfonamide **13a** into the expected product **14a** in only 7% yield, mainly providing tetrahydropyridine **15a** in 77% yield. **15a** was formed in the same way as **3a** as described in Figure 2.6 (path a). Owing to the deprotonation of *N*-*p*-toluenesulfonamide by NHC or Cs₂CO₃, conjugate addition of the resulting sulfonamide anion rather than the sulfinate anion took place. Actually, treatment of **13a** with Cs₂CO₃ in the absence of NHC precatalyst afforded the Michael adduct **15a** in 98% (entry 2). Thus, a more acidic NHC precursor and a bulky strong base were used to suppress the undesired deprotonation of the sulfonamide. The use of **C4** and a proton sponge successfully suppressed the generation of **15a** and improved the yield of **14a** up to 75%. By contrast, the less-acidic formamide **13b** was smoothly converted to **14b** in 74% yield under the standard conditions for alcohols. Comparing the p*K*_a values of formamide (p*K*_a of CHONH₂ is 23.5 in DMSO)⁹ and tosylamide (p*K*_a of TsNH₂ is 16 in DMSO),⁹ deprotonation of **13b** is estimated to be much less favorable than that of **13a**.

Table 2.3 Migrative Cyclization of Sulfonylalkynes

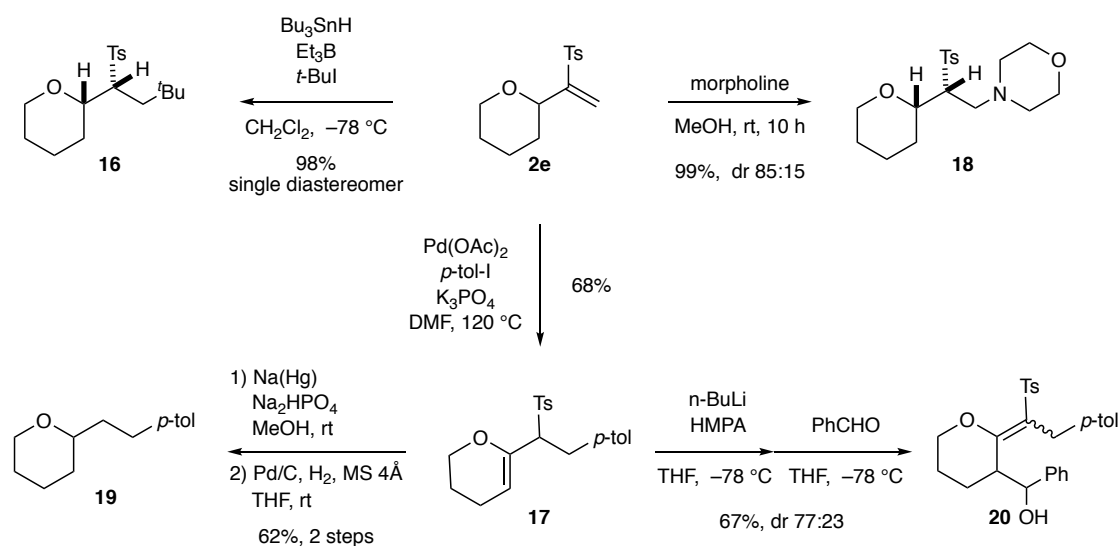


entry	13	R	NHC·HX	base (x mol%)	temp	time (h)	yield (%)	
							14	15
1	13a	Ts	C2	Cs ₂ CO ₃ (5)	60 °C	17	7	77
2			–	Cs ₂ CO ₃ (5)	60 °C	0.5	0	98
3			C4	proton sponge (10)	reflux	48	75	5
4	13b	CHO	C2	Cs ₂ CO ₃ (5)	60 °C	14	74	0

2.1.7. Further Transformation of the Product.

In view of the easily modified vinyl sulfone moiety¹¹ on the migrative cyclization products, transformation of the product was explored. Nucleophiles were introduced at the terminal carbon atom of vinyl sulfone **2e** (Scheme 2.5). Carbonucleophiles were introduced using a radical addition reaction and a Heck reaction, producing **16** and **17**, respectively. Notably, **16**

was quantitatively formed as a single diastereomer. Introduction of an N-nucleophile was also possible; conjugate addition of morpholine to **2e** quantitatively gave **18** with 85:15 diastereoselectivity. The stereochemistry of **16** and the major isomer of **18** were unequivocally determined by X-ray crystallography. Desulfonation of **17** with sodium amalgam, followed by hydrogenation of the dihydropyran moiety, gave **19** in 62% yield over two steps, whereas investigation of Julia–Lythgoe olefination using the Heck product **17** gave rise to compound **20** in 67% as a 77:23 diastereomixture. Interestingly, 1,2-addition of the carbanion to benzaldehyde occurred at the γ -position of the sulfonyl group instead of the α -position. The stereochemistry of **20** was not determined.



Scheme 2.5 Manipulation of the Vinyl Sulfone Moiety on Tetrahydropyran

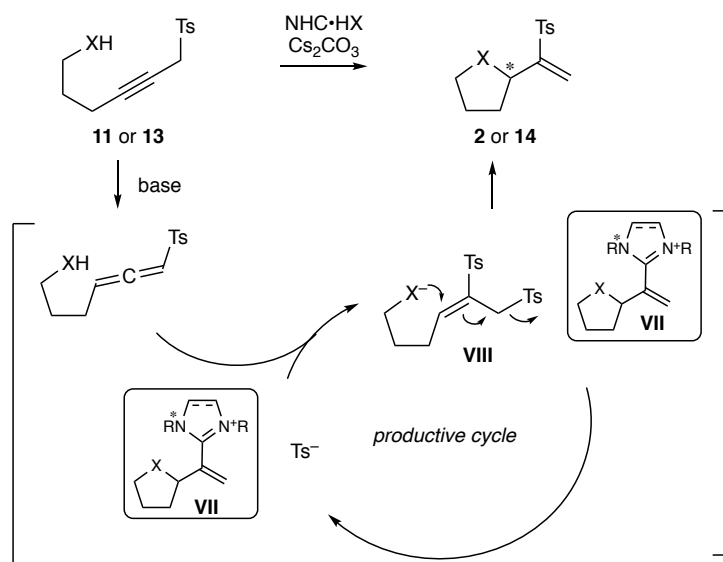
2.1.8. Conclusion

In summary, in the course of attempts to achieve NHC-catalyzed α^4 Umpolung-type bond formation, an unanticipated NHC-promoted oxa- and azacycle-forming reaction of sulfonylalkynols and sulfonylalkynamides with 1,2-sulfonyl migration was discovered. A possible mechanism was proposed, involving isomerization from propargyl sulfone to allenyl sulfone, NHC-triggered sulfinate generation, and sulfinate mediated $\text{S}_{\text{N}}2'$ cyclization as key steps. The reaction provides facile access to a series of vinyl sulfone-bearing heterocycles, which have functionality for further bond formation and may have medicinal and materials applications. Further investigations of this strategy are discussed in 2.2.

2.2 Migrative Cyclization of Sulfonylalkynol and Sulfonylalkynamide Initiated by N- and P-Nucleophiles

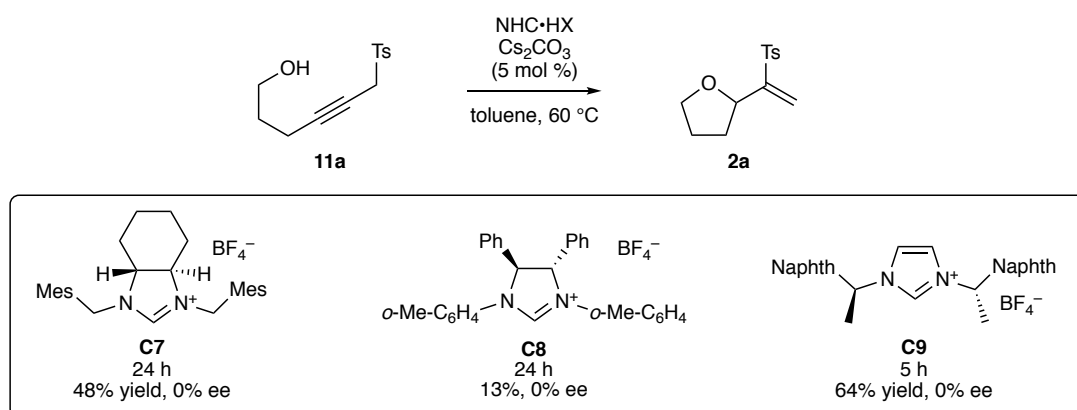
2.2.1. Introduction

In the previous section, the development of the oxa- and azacycle-forming reaction of sulfonylalkynols and sulfonylalkynamides utilizing an NHC was described. Based on the proposed mechanism, I hypothesized that an asymmetric version of this transformation might be realized by using a chiral NHC (Scheme 2.6). When a chiral NHC is used in the reaction, the initiation step should produce cation **VII**, possessing chirality. If the cation functions as a chiral counter ion of **VIII**, the S_N2' cyclization of **VIII** could proceed under the control of the chirality, and enantiomerically enriched **2** or **14** would be produced.



Scheme 2.6 Expected Asymmetric Induction by *In situ* Generated Cation from Chiral NHC

Initial evaluations using several chiral NHCs under the standard conditions were described in Scheme 2.7. Unfortunately, no asymmetric induction was observed.



Scheme 2.7 Asymmetric Attempt with Chiral NHCs

This was probably because the formation of NHC from its precursor requires an additional base (Figure 2.7). Achiral cationic species, such as a metal ion or ammonium ion, derived from the added achiral base, could also act as a counter cation of intermediate **VIII**, promoting the undesired achiral process. Thus, nucleophiles that induce the initiation step (Scheme 2.3) and do not generate any cationic species other than that derived from themselves were explored.

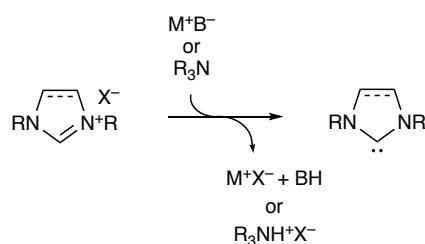


Figure 2.7 Undesired Achiral Cation Species Derived from Base

2.2.2. Investigation of Other Nucleophilic Initiators

A survey of several nucleophilic catalysts¹² was undertaken in the reaction of **11a** in refluxing toluene (Table 2.4).

Table 2.4 Reactions with P- or N- nucleophiles

The reaction scheme shows the conversion of **11a** (a 6-membered ring with an OH group and a propargyl group with a Ts substituent) to **2a** (a tetrahydrofuran derivative) and **3a** (a Michael adduct) using a nucleophile (5 mol%) in toluene at reflux.

entry	nucleophile	time (h)	2a yield (%)	3a yield (%)	11a recovery (%)
1	Ph ₃ P	18	81	0	0
2	Bu ₃ P	24	37	0	12
3	DMAP	2	71	12	0
4	DABCO	19	0	80	0

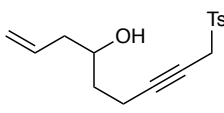
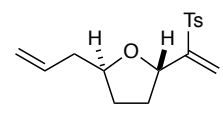
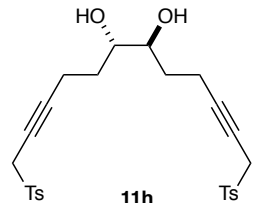
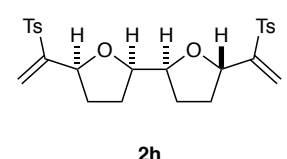
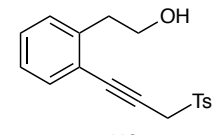
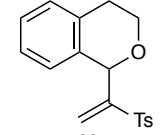
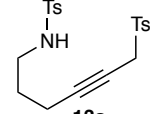
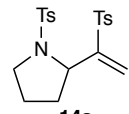
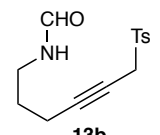
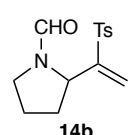
Triphenylphosphine promoted the migrative cyclization to produce the desired tetrahydrofuran **2a** in 81% yield after 18 h. Formation of **3a** was not observed (entry 1). More nucleophilic tributylphosphine led to less satisfactory results than triphenylphosphine, giving **2a** in 37% yield after 24 h, and **11a** was recovered in 12% yield (entry 2), probably owing to its lability with respect to autoxidation.¹³ No tributylphosphine was observed, but tributylphosphine oxide was detected by ¹H NMR of the crude materials. This indicates that the phosphine is required for the isomerization of **11a** to **4**. Production of **2a** indicates the formation of sulfinate anion in the reaction mixture; once this forms, it promotes the production of **2a** in the absence of phosphine for as long as **4** is also formed. Thus, the recovery of **11a** showed that the isomerization became much slower after the tributylphosphine was completely oxidized, and further indicated that the phosphines promoted this reaction, not only as initiating nucleophiles but also as bases to isomerize **11a** into **4**.

An sp²-N-nucleophile, DMAP also promoted the reaction to give **2a** in 71% yield, although Michael adduct **3a** was also produced in 12% yield (entry 3). An sp³-N-nucleophile, DABCO, only promoted the intramolecular Michael addition to give **3a** in 80% yield without any production of the desired Umpolung adduct **2a** (entry 4).

2.2.3. Phosphine-Promoted Migrative Cyclization

With the triphenylphosphine-promoted migrative cyclization conditions in hand, several other propargyl sulfones were tested (Table 2.5). Secondary alcohol **11c** failed to lead to tetrahydrofuran **2c** formation in the absence of additional base, but addition of 1 mol% Cs₂CO₃ resulted in full conversion of **11c**, and **2c** was produced in 71% yield with diastereomeric ratio (dr 5:4, entry 1), similar to that previously observed with NHC (dr 3:2). The requirement of additional base could have been because the slower S_N2' cyclization in the initiation step with secondary alcohol led to full consumption of triphenylphosphine before sulfinate anion generation. C₂-symmetric diol **11h** afforded bi-THF **2h** as a mixture of diastereomers in 82% yield (entry 2). The diastereomeric ratio (dr 5:3:2) was almost the same as that observed in the reaction with NHC (dr 3:2:2) (Table 2.2). Tetrahydropyran formation also proceeded smoothly under standard conditions, and isochromane **2f** was produced in 51% yield (entry 3). *N*-*p*-Toluenesulfonamide **13a** was also able, under this standard condition, to provide the corresponding pyrrolidine product in good isolated yield (entry 4). In the presence of Cs₂CO₃, formamide **13b** was smoothly converted to **14b** in 68% yield (entry 5) although the reaction failed to proceed without base. Thus, in general, the performance of the reaction with triphenylphosphine was comparable with that using NHC, and additional base was not required in most cases.

Table 2.5 Phosphine-Promoted Migrative Cyclization

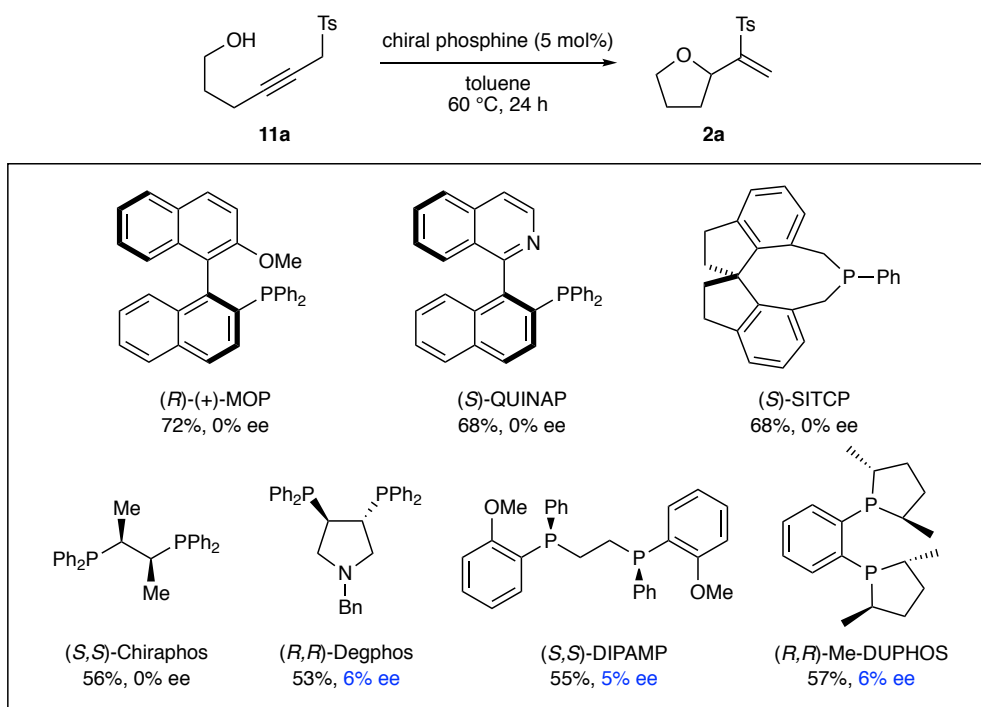
$ \begin{array}{ccc} \begin{array}{c} \text{R} \\ \\ \text{R}-\text{C}-\text{XH} \\ \\ (\text{CH}_2)_n \\ \\ \text{C}\equiv\text{C}-\text{Ts} \end{array} & \xrightarrow[\text{toluene, reflux}]{\text{Ph}_3\text{P (5 mol\%)}} & \begin{array}{c} \text{R} \\ \\ \text{R}-\text{C}-\text{X} \\ \\ (\text{CH}_2)_n \\ \\ \text{C}=\text{C}-\text{Ts} \end{array} \\ \text{11 or 13} & & \text{2 or 14} \end{array} $				
entry	11 or 13	time (h)	2 or 14	yield (%)
1 ^{a, b}	 11c	12	 2c	71
2	 11h	3	 2h	82
3	 11f	16	 2f	51
4	 13a	3	 14a	77 ^d
5 ^a	 13b	16	 14b	68

^aThe reaction was performed using 1 mol% of Cs₂CO₃. ^bdr 5:4. ^cdr 5:3:2.

^dMichael adduct **15a** formed in 16% yield.

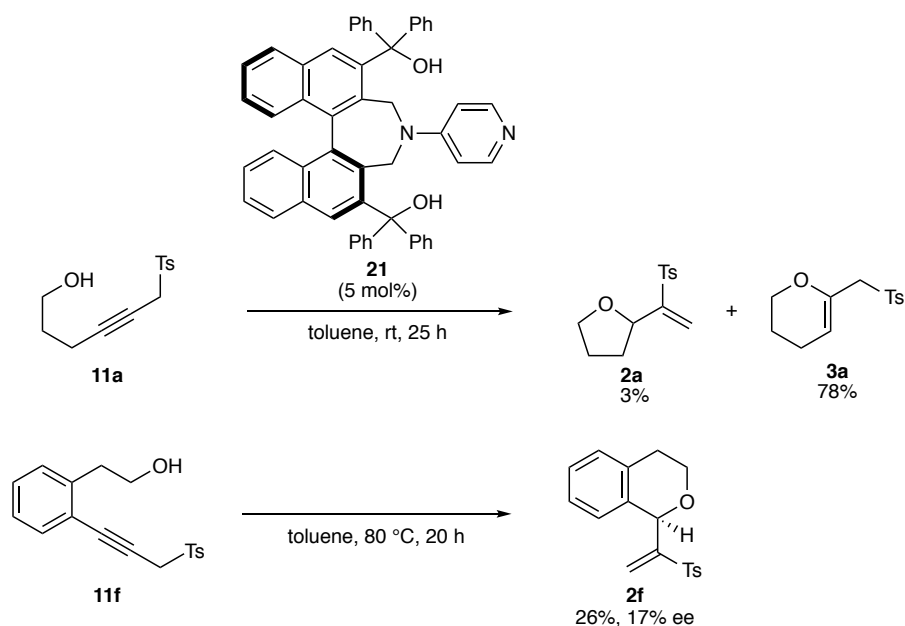
2.2.4. Attempts to Develop Asymmetric Version with Chiral Nucleophiles

Having assessed the practicability of this phosphine-initiated migrative cyclization, an asymmetric variant of this transformation was examined. As mentioned in Section 2.2.1, when a chiral phosphine is used in the reaction, the initiation step should produce chiral cation **VII** (a phosphine-based species), which could act as a chiral counter ion of **VIII** to influence the subsequent S_N2' cyclization. As shown in Scheme 2.8, slight asymmetric induction (5–6% ee) was observed in the reaction of **11a** after screening of the chiral phosphines.



Scheme 2.8 Asymmetric Version Attempts with Chiral Phosphines

Further attempts employing Suga's binaphthyl-based DMAP derivative **21**¹⁴ were carried out (Scheme 2.9). When **11a** was subjected to the reaction with **21** at room temperature, the desired tetrahydrofuran **2a** was obtained in only 3% yield, with the formation of dihydropyran **3a** in 78% yield.



Scheme 2.9 Asymmetric Version Attempts with Chiral DMAP

This could have been because the competition between the deprotonation of the hydroxyl group (Figure 2.9, a) with 1,4-addition of **21** to the allenyl sulfone (Figure 2.9, b) determined the ratio of **3a** and **2a**. The highly basic and bulky **21** preferred path a and was less effective for 1,4-addition to allenyl sulfone.

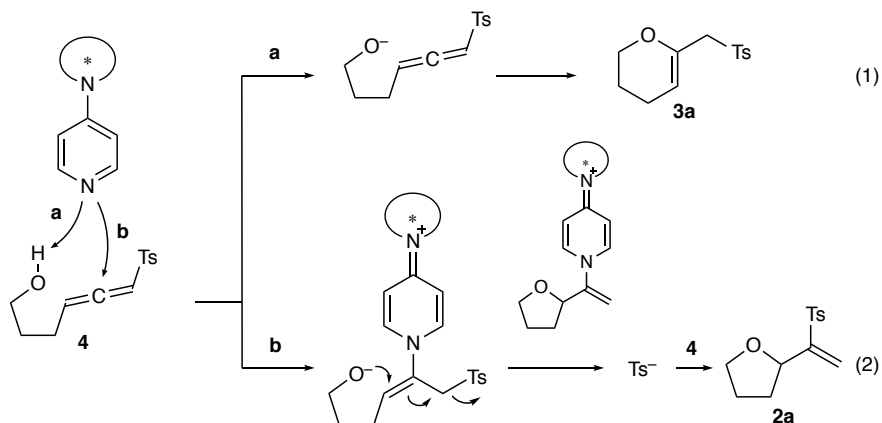


Figure 2.8 Competition of Deprotonation and Conjugate Addition of Chiral DMAP

In order to evaluate this binaphthyl-based DMAP derivative **21** in terms of its ability to asymmetrically induce this reaction, the propargyl sulfone **11f**, which is resistant to intramolecular Michael addition owing to the large entropic and enthalpic cost in seven-membered ring formation, was employed. A slightly enantioselective reaction was

observed by heating the reaction mixture in toluene at 80 °C, and **2f** was obtained in 17% ee (Scheme 2.9).

2.2.5. Conclusion

In conclusion, several P- and N-nucleophiles were tested as initiators of the migrative oxa- and azacycle-forming reaction of sulfonylalkynols and sulfonylalkynamides. Although a higher temperature was required for the reaction to proceed, the result obtained with triphenylphosphine was almost comparable with those of with NHCs. Fortunately, the possibility of enantio control of this reaction was indicated by the use of chiral phosphine and binaphthyl-based chiral DMAP. Further efforts to develop an efficient enantioselective variant are currently in progress in this laboratory.

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3. Kinetic Resolution of α -Hydroxy Carboxylic Acid Derivatives Based on Chiral Recognition of Substrate–Cocatalyst Complex

3.1. Introduction

3.1.1. Kinetic Resolution

Kinetic resolution is the oldest method¹ of preparing enantiomerically enriched compounds, and is defined as “The achievement of partial or complete resolution by virtue of unequal rates of reaction of the enantiomers in a racemate with a chiral agent (reagent, catalyst, solvent, etc.)” according to the 1996 IUPAC. The history of kinetic resolution can be traced back to 1858, when Pasteur observed that fermentation of racemic ammonium tartrate with *Penicillium glaucum* selectively destroyed the dextrorotatory isomer, leaving an excess of (*S,S*)-tartrate.¹ Today, kinetic resolution has grown into one of the most powerful tools in asymmetric catalysis, owing to progress made in the development of chiral catalysts for asymmetric reactions.

In a kinetic resolution, the two enantiomers of a racemic substrate interact with a chiral reagent to generate two diastereomeric transition states with different energies, which define the difference in rate constants of the substrate enantiomers. In a catalytic kinetic resolution, the relative reaction rates of the two enantiomers are typically expressed as selectivity factor (*s*) or k_{rel} , which is defined as $k_{\text{fast}}/k_{\text{slow}}$. Here, k_{fast} is the rate constant of the reaction of the enantiomer that has the lower activation energy in the selectivity-determining step, whereas k_{slow} represents the rate constant of the other enantiomer, with higher activation energy.

In a kinetic resolution experiment, the ee values of the product and unreacted substrate change as a function of conversion. Therefore, the *s* is generally used to evaluate the efficiency of the resolution process, and can be calculated with eq. 1 (based on ee of the recovered substrate) or eq. 2 (based on ee of the product) in cases where the product is also chiral (Figure 3.1).

$$s = \ln[(1-C)(1-ee)] / \ln[(1-C)(1+ee)] \quad (1)$$

$$s = \ln[(1-C)(1+ee)] / \ln[(1-C)(1-ee)] \quad (2)$$

s: selectivity factor
C: conversion
ee: enantiomeric excess of the recovered substrate
ee': enantiomeric excess of the product

Figure 3.1 Relative Rate Constants in Kinetic Resolution

Although kinetic resolution suffers from the disadvantage that the desired enantiomer can

only be obtained in 50% yield at most, it has been recognized as an attractive method to produce enantio-enriched compounds from a synthetic point of view, since the unreacted substrate can be recovered in enantiopure form even if the *s* is not very high, simply by carrying the reaction to a high enough conversion.

3.1.2. α -Hydroxy Carboxylic Acid Derivatives

α -Hydroxy carboxylic acid derivatives are present in a variety of compounds with biological activity (Figure 3.2),² and are versatile intermediates in the preparation of a wide range of chiral compounds. They can also serve as chiral ligands,³ as monomers in polymerization reactions,⁴ and as building blocks for unnatural peptides and depsipeptides.⁵

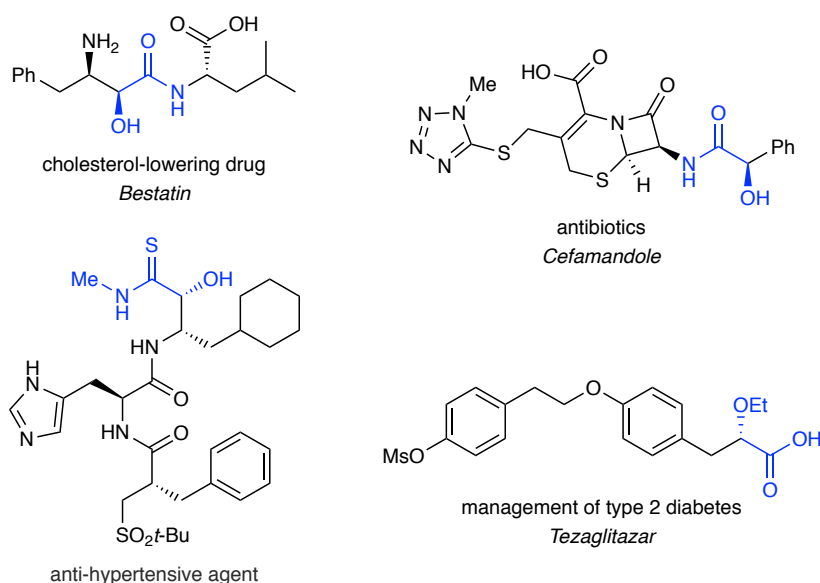
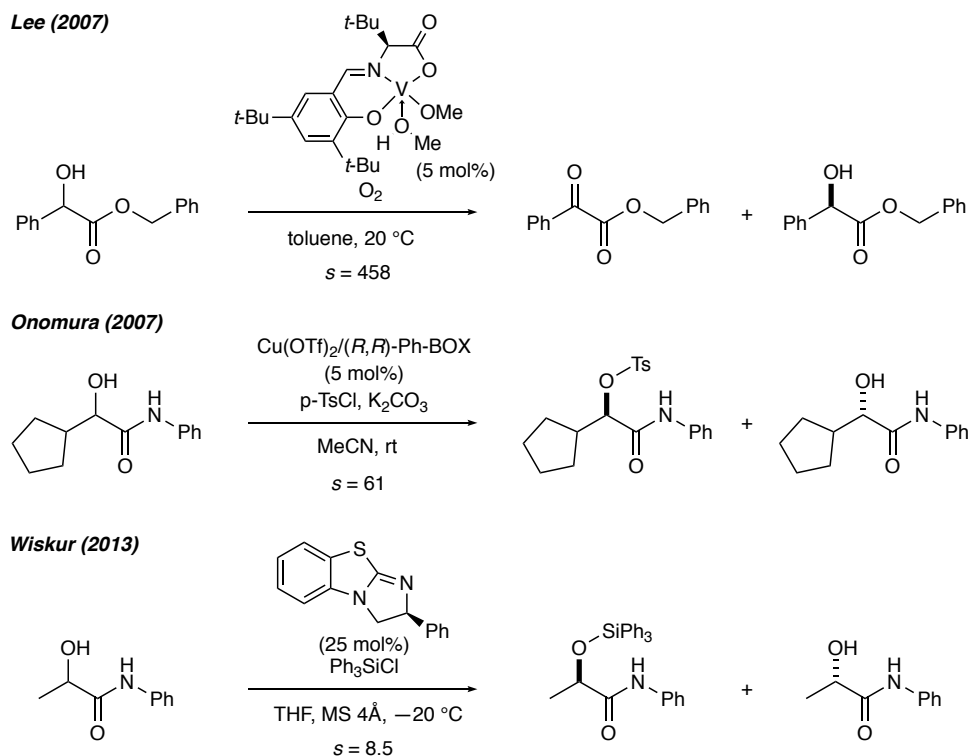


Figure 3.2 Biologically active α -Hydroxy Carboxylic Acid Derivatives

Owing to the importance of enantiomerically pure α -hydroxy carboxylic acid derivatives, tremendous efforts have been made to establish enantioselective routes for their production. Among these strategies, several highly efficient kinetic resolutions have been achieved using metal complexes (Scheme 3.1). In 2007, Lee and coworkers reported oxidation of an α -hydroxy ester with *s* exceeding 450, using a chiral vanadium complex under oxygen atmosphere.⁶ An (*R,R*)-Ph-BOX-Cu catalyzed tosylation of α -hydroxy amide was reported by Onomura's group, providing *s* values up to 61.⁷ Despite this progress, only one kinetic resolution using an organocatalyst has so far been achieved. Wiskur's group developed a silylation of an α -hydroxy amide. However, a 25 mol% chiral benzotetramisole catalyst was required, and the *s* was

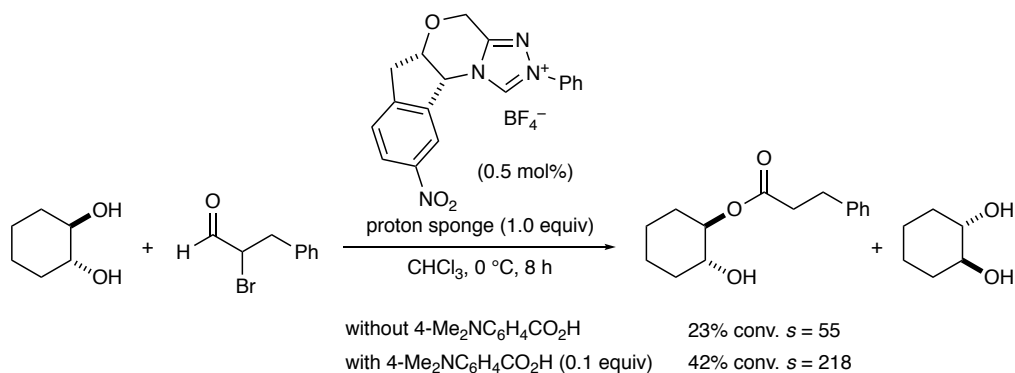
limited to 8.5.⁸ The development of a practical enantioselective synthetic route fulfilling the requirements of low catalyst loading, mild reaction conditions, and satisfactory yield and enantioselectivity is thus highly desirable.



Scheme 3.1 Reported Kinetic Resolutions of α -Hydroxy Carboxylic Acid Derivatives

3.1.3. Chiral Recognition of Substrate–Cocatalyst Complex Strategy

The development of ideal catalytic enantioselective reactions is an ongoing pursuit of synthetic organic chemists. Numerous efforts have been devoted to achieving low catalyst loading and high turnover number along with satisfied yield and enantioselectivity. The introduction of a suitable additive is a powerful tool to improve the efficiency of the catalytic system in many cases.⁹ Although there has been tremendous progress in asymmetric organocatalysis in recent years, the development of additive cooperating catalysis has yet to be synthetically investigated.¹⁰ Brønsted bases have been discussed as additives in several organocatalytic asymmetric reactions, where they have mainly functioned to assist proton transfer¹¹ or acted as acid scavengers.¹² In most of these cases, stoichiometric quantities of additives are necessary. Developing Brønsted bases as cocatalysts to improve organocatalytic asymmetric reactions may bring new perspectives to organocatalysis.



Scheme 3.2 Kinetic Resolution of Racemic 1,2-*trans*-cycloalkane diols through Acylation Catalyzed by a Chiral NHC

Our research group has focused on chiral recognition of the substrate–cocatalyst complex as a platform for catalytic asymmetric synthesis. Recently, a kinetic resolution of 1,2-*trans*-cycloalkanediols by chiral NHC-catalyzed asymmetric acylation was reported by this laboratory (Scheme 3.2).¹³ In this reaction, the addition of 10 mol% of 4-dimethylaminobenzoic acid not only significantly increased the 8-h conversion from 23% to 42%, but also increased the *s* value from 55 to 218.

The added carboxylic acid ($pK_a = 5.04$) should function as a carboxylate in the presence of a stoichiometric strong base proton sponge ($pK_a = 12.0$ for protonated form).¹⁴ DFT calculations showed that the hydrogen bond formation between carboxylate and diol stabilizes the transition state of this reaction. The geometries of the possible transition states TS_{major} and TS_{minor} with (*S,S*)-diol and (*R,R*)-diol, respectively, were calculated at the B3LYP/6-31G** level of theory and were shown in Figure 3.3. The carboxylate formed a double H-bond motif with the diol, and the interaction between acylazolium with the resulting diol–carboxylate complex was reinforced by the electrostatic stabilization. In TS_{major}, the distance between the middle of two oxygen atoms of carboxylate and the acylazolium ring was 3.3 Å, shorter than that in TS_{minor} (3.8 Å), leading to the minor enantiomer. Since the intensity of the interaction between the diol–carboxylate complex and acylazolium is inversely proportional to the second power of this distance, the intensity in TS_{minor} accounts for 75% of that in TS_{major}. Quantifying free energies of the two TSs results in an energy difference of 2.55 kcal/mol, favoring TS_{major}. This difference should derive from not only the steric difference of the two enantiomers of the diol, but also the difference of intensity in electrostatic stabilization.

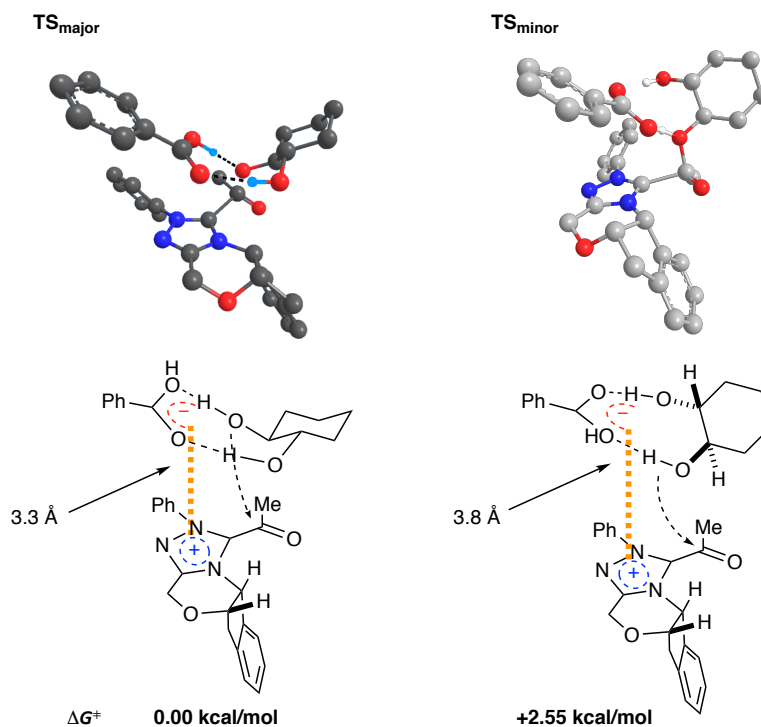


Figure 3.3 Calculated Transition State Structures of two enantiomers.

In this reaction, chiral acylazolium recognized the chirality of the diol in a diol-carboxylate complex; that is, chiral recognition of the substrate-cocatalyst complex occurred, as illustrated in Figure 3.4. This chiral recognition methodology is based not only on the steric interaction between the chiral catalyst and the substrate, but also on the electrostatic interaction between the chiral catalyst and the cocatalyst carboxylate anion, which may be important for high enantioselectivity.

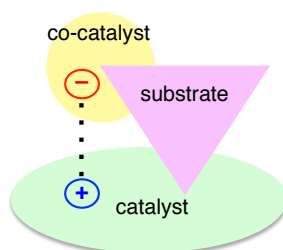


Figure 3.4 Chiral Recognition of Substrate-Cocatalyst Complex

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As a continuation of the research on the development of chiral recognition of substrate-cocatalyst complexes, an application of this strategy to achieve kinetic resolution of α -hydroxy

carboxylic acid derivatives bearing adjacent hydrogen bond donor groups is planned. As mentioned in 3.1.2, chiral α -hydroxy carboxylic acid derivatives are important building blocks in synthetic chemistry. The formation of hydrogen bonds with carboxylate could also have a role in controlling the conformation of α -hydroxy carboxylic acid derivatives. The expected transition state for the fast-reacting enantiomer is shown in Figure 3.5.

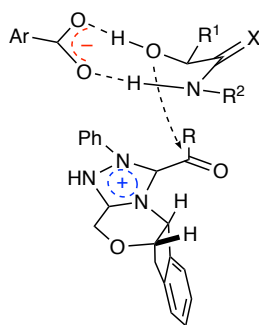
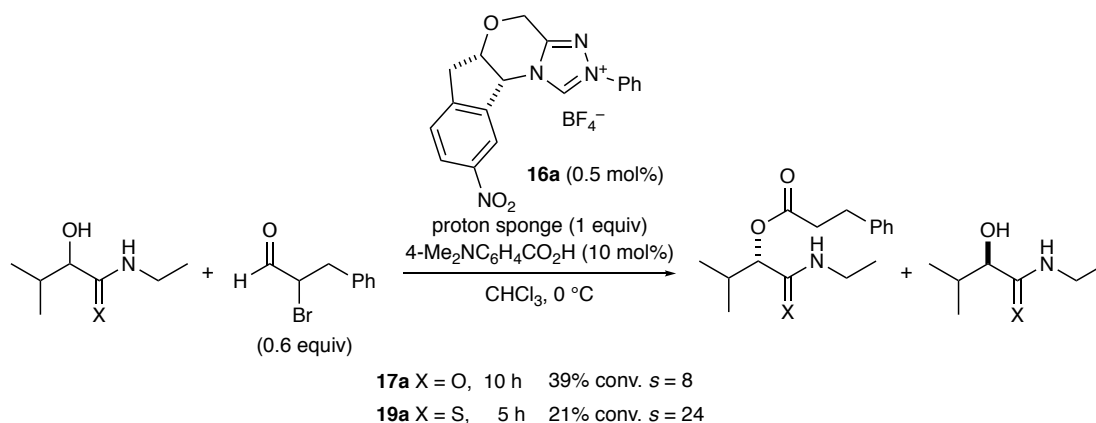


Figure 3.5 Expected Transition State of Kinetic Resolution of α -Hydroxyl Thioamide

3.2. Chiral NHC-Catalyzed Kinetic Resolution of α -Hydroxy Thioamides

3.2.1. Initial Investigations

As an initial study, the reactions of α -hydroxy ethylamide **17a** and thioamide **19a** were investigated under NHC and carboxylate catalysis (Scheme 3.3). The reaction with 2-bromo-3-phenylpropanal in the presence of NHC precursor **16a**, 4-dimethylaminobenzoic acid, and proton sponge proceeded with 39% conversion after 10 h and resulted in an s value of 8. The kinetic resolution of α -hydroxy ethylthioamide **19a** under the same conditions gave a significantly higher value ($s = 24$).



Scheme 3.3 Kinetic Resolutions of α -Hydroxy Amide and Thioamide

It could be rationalized that the innate lower pK_a value¹⁴ and higher H-bond donor ability of the NH on thioamides (Figure 3.6)¹⁵ could facilitate the hydrogen bond formation with carboxylate (Figure 3.5) in the transition state. Direct access to α -hydroxy thioamide motifs in a catalytic enantioselective manner has not been achieved, despite their prevalence as building blocks for bioactive natural products and pharmaceutically relevant compounds,¹⁶ and as important heterocyclic compounds.¹⁷ Encouraged by the above results, we explored the first kinetic resolution of α -hydroxy thioamide.

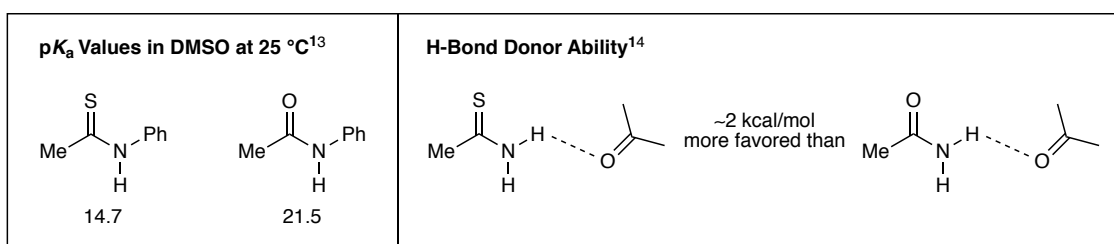


Figure 3.6 Comparison of Property between Amide and Thioamide

3.2.2. Investigation of Substituent on Thioamide Group

The study commenced with examination of the N-substituent on the thioamide. This may greatly affect the strength of the hydrogen bond with carboxylate, as well as the sterical interaction with chiral acylazolium in the transition state. α -Hydroxy thioamides **19** bearing different aromatic and aliphatic groups were treated with 2-bromo-3-phenylpropanal (0.6 equiv) and NHC precursor **16a** (0.5 mol%) in the presence of 4-dimethylaminobenzoic acid (10 mol%) and proton sponge (1.0 equiv) in chloroform at 0 °C (Table 3.1). **19a**, which bears a *p*-methoxyphenyl group, gave a synthetically useful *s* value (entry 1), similar to that of thioanilide **19b** (entry 2). However, introduction of electron-deficient 3,5-bis(trifluoromethyl)phenyl and trifluoroethyl groups, intended to strengthen the hydrogen bond with carboxylate, resulted in a dramatic decrease in the selectivity. **19c** and **19d** were acylated with *s* values of 2 and 5, respectively (entries 3 and 4). It could be reasoned that the introduction of the highly electron-withdrawing substituent would result in too-acidic NH, and that deprotonation of NH by the proton sponge or NHC would suppress the formation of hydrogen bonds between substrate and carboxylate. On the other hand, the electron-donating aliphatic groups showed better performance. The increased steric demand of the substituents led

to better enantioselectivity without significant negative effects on reactivity (entries 5–7). The *tert*-butyl thioamide gave the best results, with 26% conversion and an *s* value of 70 after 7 h.

Table 3.1 Effect of Substituent on Thioamide Group

Reaction scheme showing the conversion of thioamide **(±)-19** and bromoaldehyde (0.6 equiv) to cyclic thioamide **(S)-20** and recovered thioamide **(R)-19**. Conditions: **16a** (0.5 mol%), proton sponge (1 equiv), 4-Me₂NC₆H₄CO₂H (10 mol%), CHCl₃, 0 °C.

entry	(±)-19	R	time	20	recovered 19	<i>s</i>
1	19a		5 h	(S)-20a 21%, 81% ee	(R)-19a 79%, 22% ee	12
2	19b		5 h	(S)-20b 26%, 79% ee	(R)-19b 74%, 27% ee	11
3	19c		5 h	(S)-20c 37%, 21% ee	(R)-19c 63%, 12% ee	2
4	19d		5 h	(S)-20d 39%, 56% ee	(R)-19d 61%, 36% ee	5
5	19e		5 h	(S)-20d 21%, 90% ee	(R)-19d 79%, 24% ee	24
6	19f		7 h	(S)-20e 33%, 89% ee	(R)-19e 67%, 44% ee	26
7	19g		7 h	(S)-20f 26%, 96% ee	(R)-19f 74%, 34% ee	70

3.2.3. Influence of NHC Precatalysts and Carboxylic Acid Cocatalysts

NHC precatalysts were evaluated next (Table 3.2). It was hypothesized that lowering the electron density of acylazolium might increase the electrostatic interaction between the cationic acylazolium and the anionic α -hydroxy thioamide–carboxylate complex (Figure 3.5). On the basis of this hypothesis, a more electron-deficient pentafluorophenyl group was introduced to

the triazole moiety (entry 2). However, significant decreases in reactivity and enantioselectivity were observed. The acylation proceeded with 8% conversion after 7 h and resulted in an *s* value of 18. In our previous study on kinetic resolution of 1,2-diols with chiral NHC, electron tuning of the remote indane moiety resulted in greatly improved reaction rate and enantioselectivity.¹³ Thus, investigation of the substituent effect on the indane moiety was carried out. Introduction of a bromine atom to the nitro-substituted indane provided NHC precursor **16e**, which gave outstanding reactivity (39% conversion) and selectivity (*s* = 94) (entry 5). By contrast, the NHC precursors (**16c** and **16d**) bearing less-electron-deficient indane moieties showed lower reactivity, and the selectivity values also dropped to 15 and 18, as expected (entries 3–4).

Table 3.2 Evaluation of NHC Precatalysts

entry	NHC·HX	conv. (%)	ee of (<i>S</i>)- 20g (%)	ee of (<i>R</i>)- 19g (%)	<i>s</i>
electron tuning of N-substituent on triazole moiety					
1	 16a : Ar = Ph	26	96	34	70
2	 16b : Ar = C ₆ F ₅	8	89	8	18
electron tuning on indane moiety					
3	 16c : X = H, Y = H	3	87	3	15
4	 16d : X = H, Y = Br	8	94	8	18
5	 16e : X = Br, Y = NO ₂	39	96	61	94

Another attempt to enhance the electrostatic interaction between the acylazolium and the α -hydroxy thioamide–carboxylate complex was carried out by increasing the electron density of the carboxylate, as the more basic carboxylate could tighten the hydrogen bond with α -hydroxy thioamide. Based on this hypothesis, carboxylic acids, which are less acidic than 4-dimethylaminobenzoic acid, were tested (Table 3.3). By mixing ($\pm$)-**19g**, NHC precursor **16e**, and proton sponge with 4-pyrrolidinybenzoic acid as a cocatalyst¹⁸, (*S*)-**20g** was observed in

15% yield after 7 h with improved *s* value of 103 (entry 4). Addition of less-acidic 9-julolidinecarboxylic acid¹⁹ led to a significantly increased *s* value (124; entry 5). As expected, the more-acidic benzoic acid was less effective in this reaction, which provided (*S*)-**20** in 22% yield with an *s* value of 5 (entry 2). In the absence of a carboxylic acid cocatalyst, the acylation proceeded with moderate reactivity and selectivity (entry 1).

$(\pm)\text{-19g} + \text{H-C(=O)-CH(Br)-CH}_2\text{-Ph} \xrightarrow[\text{CHCl}_3, 0\text{ }^\circ\text{C}, 7\text{ h}]{\text{16e (0.5 mol\%), proton sponge (1 equiv), carboxylic acid (10 mol\%)}}$
 $(S)\text{-20g} + (R)\text{-19g}$

entry	carboxylic acid	p <i>K</i> _a	conv. (%)	ee of (<i>S</i>)- 20g (%)	ee of (<i>R</i>)- 19g (%)	<i>s</i>
1	none	–	10	95	10	44
2		4.21	22	64	18	5
3		5.04	39	96	61	94
4		5.11 ^a	15	98	17	103
5		5.18 ^a	28	98	37	124

^aCalculated using the Hammett equation^{18, 19}

3.2.4. Substrate Scope

Having assessed the efficiency of the catalytic system, the scope of the reaction was investigated (Table 3.4). Substrate **19h** bearing no β-substituent gave a lower selectivity (*s* = 7; entry 1) than the substrate (**19i**) with a isobutyl group (*s* = 29; entry 2). β-dimethyl thioamide **19g** showed good conversion and excellent ee (28% conv, *s* = 124; entry 3), whereas the corresponding β-diphenyl thioamide **19j** was formed with moderate conversion and selectivity (14% conversion, *s* = 16; entry 4), presumably owing to the subtle increased acidity of alcohol that results in deprotonation under this condition, suppressing the formation of hydrogen bonds

with carboxylate. Moreover, hydrogen bond formation might also have been impeded by steric repulsion of the diphenyl group and carboxylate. Cyclopropyl-substituted thioamide **19k** was acylated smoothly under this condition and was resolved with good selectivity ($s = 54$; entry 5). Cyclohexyl-substituted thioamide **19l** performed excellently, giving the corresponding ester with $s = 140$ (entry 6). The reaction rate was lower using a sterically hindered substrate bearing *tert*-butyl group on the α -position (entry 7), and 18% conversion with $s = 29$ was observed after 48 h by treating **19m** under this condition at room temperature. Unfortunately, the s value for kinetic resolution using α -phenyl thioamide **19n** was limited to 3 (entry 8).

Table 3.4 Substrate Scope of Kinetic Resolution through Acylation

$(\pm)\text{-19} + \text{H}-\text{C}(=\text{O})-\text{CH}(\text{Br})-\text{CH}_2-\text{Ph} \xrightarrow[\text{CHCl}_3, 0\text{ }^\circ\text{C}]{\begin{smallmatrix} \mathbf{16e} \text{ (0.5 mol\%)} \\ \text{proton sponge (1 equiv)} \\ \text{9-Julolidinecarboxylic acid (10 mol\%)} \end{smallmatrix}} \begin{matrix} \text{(S)-20} \\ \text{(R)-19} \end{matrix}$

entry	($\pm$)- 19	R	time	20	recovered 19	s
1 ^a	19h	Me	15 h	(<i>S</i>)- 20h 50%, 58% ee	(<i>R</i>)- 19h 50%, 57% ee	7
2	19i		24 h	(<i>S</i>)- 20i 31%, 90% ee	(<i>R</i>)- 19i 69%, 41% ee	29
3	19g		7 h	(<i>S</i>)- 20g 28%, 98% ee	(<i>R</i>)- 19g 72%, 37% ee	124
4	19j		24 h	(<i>S</i>)- 20j 14%, 86% ee	(<i>R</i>)- 19j 86%, 15% ee	16
5 ^b	19k		18 h	(<i>S</i>)- 20k 50%, 89% ee	(<i>R</i>)- 19k 50%, 91% ee	54
6	19l		7 h	(<i>S</i>)- 20l 31%, 98% ee	(<i>R</i>)- 19l 69%, 44% ee	140
7	19m	<i>t</i> -Bu	48 h	(<i>S</i>)- 20m 18%, 92% ee	(<i>R</i>)- 19m 82%, 20% ee	28
8	19n	Ph	20 h	(<i>S</i>)- 20n 32%, 41% ee	(<i>R</i>)- 19n 68%, 20% ee	3

^aUsing 1 mol% of **16e**, 20 mol% of carboxylic acid and 1.5 equiv of 2-bromo-3-phenylpropanal.

^b The reaction was performed at room temperature.

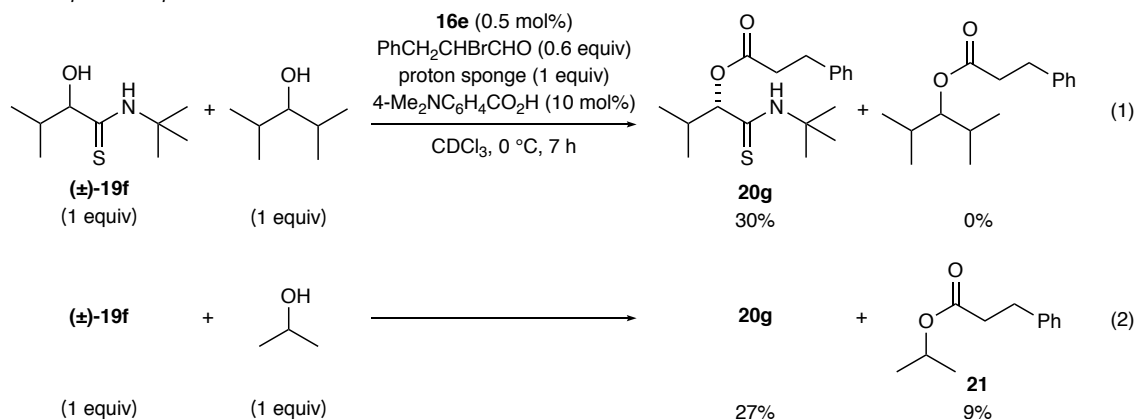
3.2.5. Investigation on the Hydrogen-bond Complex Formation

Mechanistic aspects of the chiral NHC-catalyzed kinetic resolution of α -hydroxy thioamide were also explored. In the described reaction mode of this carboxylate-assisted chiral acylation, the reaction rate acceleration and selectivity enhancement were interpreted in terms of the reversible complexation of substrate and carboxylate, which enhances the energy difference between the transition states of acylation, as well as stabilizing the transition states. The experiments described in the preceding paragraphs shed light on the details of this chiral recognition mode.

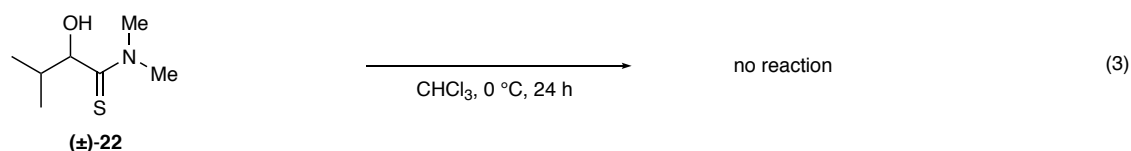
i). Effect of Adjacent H-Bond Donor Group on the Reaction Rate.

Competition experiments were carried out to evaluate the ability of NHC derived from **16e** to distinguish between alcohol substrates with and without an adjacent H-bond donor group, with the aid of carboxylate. By treating the same amount of α -hydroxy thioamide **19g** and 2,4-dimethyl-3-pentanol of similar steric hindrance with 2-bromo-3-phenylpropanal in the presence of NHC precursor **16e**, 4-dimethylaminobenzoic acid, and proton sponge, α -hydroxy thioamide **19f** was selectively acylated in 30% yield after 7 h (Scheme 3.6, eq 1). In a competition experiment between α -hydroxy thioamide **19f** and the much-less-sterically hindered 2-propanol, a 3:1 ratio favoring acylation of the α -hydroxy thioamide **19f** was observed (eq 2). The control experiment using N-methylated α -hydroxy thioamide **22**, resulting in no reaction, also indicated the importance of the adjacent H-bond donor group on the substrate in this carboxylate-assisted chiral acylation (eq 3).

A. competition experiments



B. control experiment using *N*-Me α -Hydroxy thioamide **22**



Scheme 3.4 Effect of NH Group on the Reaction Rate

ii). NMR Study

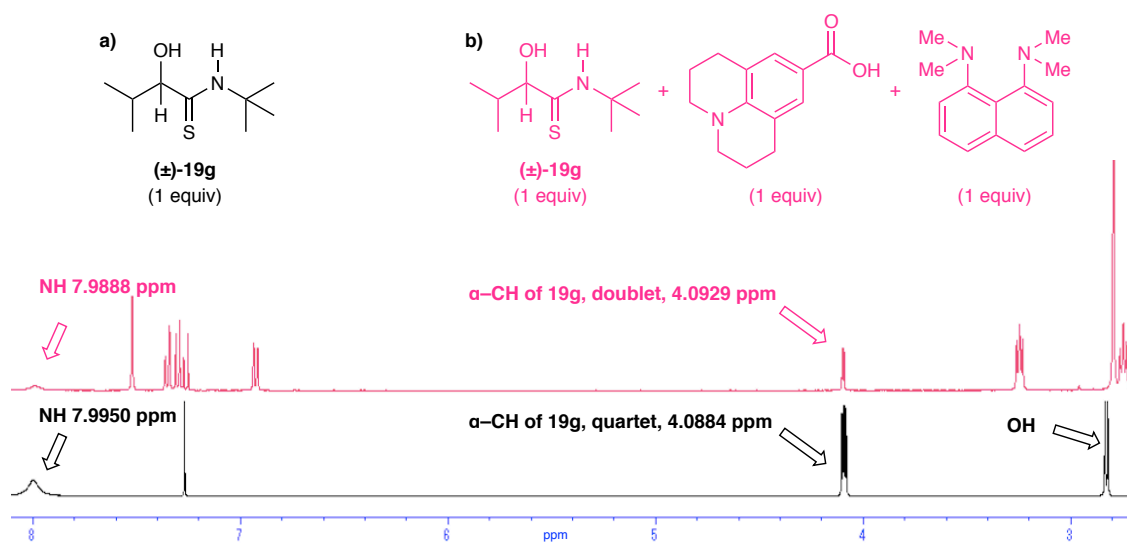


Figure 3.7 Partial ^1H -NMR Spectra in CDCl_3 (0.1 M) (a) $\mathbf{19g}$ (b) 1:1:1 mixture of $\mathbf{19g}$, 9-julolidine carboxylic acid and proton sponge

The interaction of α -hydroxy thioamide and carboxylate was probed by ^1H -NMR spectroscopy. When 1 equivalent of carboxylic acid and proton sponge were added to a solution of $\mathbf{19g}$ in CDCl_3 (Figure 3.7, b), a slight upfield shift of the NH signal and downfield shift of the

α -H signal of **19g** were observed (Figure 3.7, pink). On the other hand, the α -H of **19g** presented in doublet in this mixture (pink), whereas it was a double doublet in the absence of carboxylic acid and proton sponge (black). The proton of the OH group also disappeared in this mixture (Figure 3.7, b). These observations indicated the existence of an interaction between α -hydroxy thioamide and carboxylate.

iii). *Estimation of the Association Constant by UV Spectra*

To gain more insight into the formation of the hydrogen-bonded complex, ultraviolet (UV) spectra were recorded to determine the hydrogen-bonding ability of α -hydroxy thioamide **19f** with 9-julolidinecarboxylate.

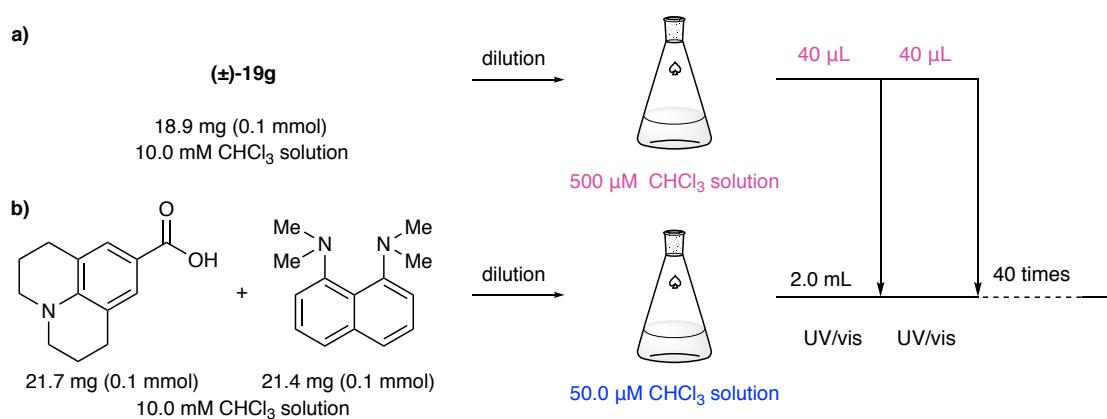


Figure 3.8 Titration of α -Hydroxy Thioamide with Carboxylate

Titration of substrate **19g** to the solution of 9-julolidinecarboxylic acid and proton sponge was conducted as follows (Figure 3.8). The UV absorbance (200–500 nm) of a 2.0 mL mixture of 9-julolidinecarboxylic acid and proton sponge (50.0 μ M each in CHCl₃) was measured. Then, 40 μ L each of 500 μ M solution of **19g** in CHCl₃ was added to this solution for 40 times. The UV absorbance was measured after every addition. The absorption at 330 nm was the most dramatically changed with the addition of **19g** (Figure 3.9).

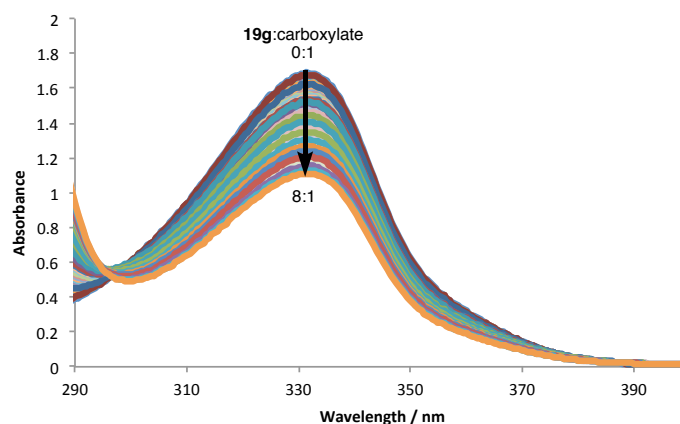


Figure 3.9 UV/vis Absorption Spectra for Titration, Arrow shows the change of intensity at increasing **19g** concentration.

The black × symbols in Figure 3.10 indicate the observed absorbance values at 330 nm as the ratio of **19g** to carboxylate was increased from 0:1 to 8:1. The blue curve shows the calculated absorbance values under the conditions where **19g** and carboxylate have no interaction, which are clearly different from the observed value (Figure 3.10, ×). Assuming a 1:1 association of **19g** and carboxylate, the association constant K_a and the absorption coefficient of the 1:1 complex were determined by the least-square method to give the calculated absorbance, shown as a red curve in Figure 3.10.

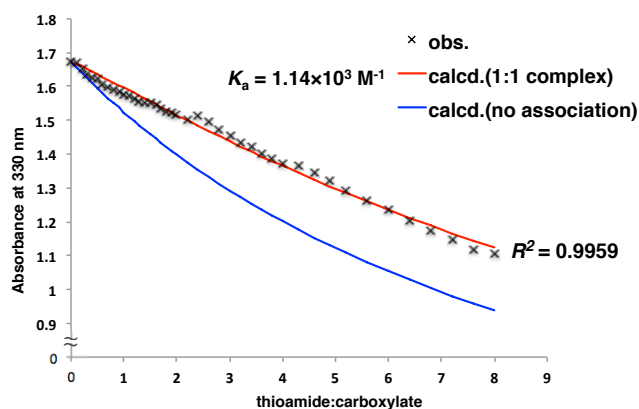


Figure 3.10 Absorbance Curves at 330 nm for (1) observed absorbance values; (2) calculated absorbance values for 1:1 complex; (3) calculated absorbance values for no complexation

The association constant K_a between 9-julolidinecarboxylate and **19g** was estimated as $1.14 \times 10^3 \text{ M}^{-1}$. The decision coefficient was 0.9959, indicating that the calculated curve fits well with the observed values. The acylation reactions in Table 3.4 were conducted using 250 μmol **19g**, 25 μmol 9-julolidinecarboxylic acid, and 250 μmol proton sponge. Based on the pK_a values, the

carboxylic acid should be totally deprotonated by the proton sponge, giving 25 μmol carboxylate (Figure 3.11, initial). The estimated K_a indicates that almost all the carboxylate was associated with **19g** (Figure 3.11, equilibrated).

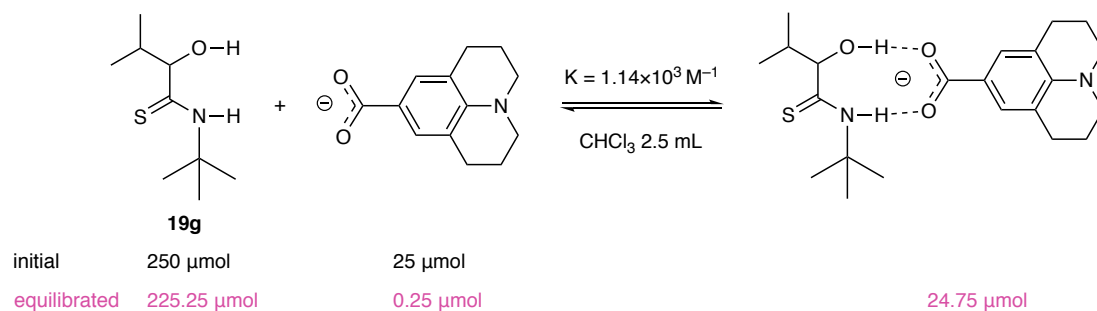
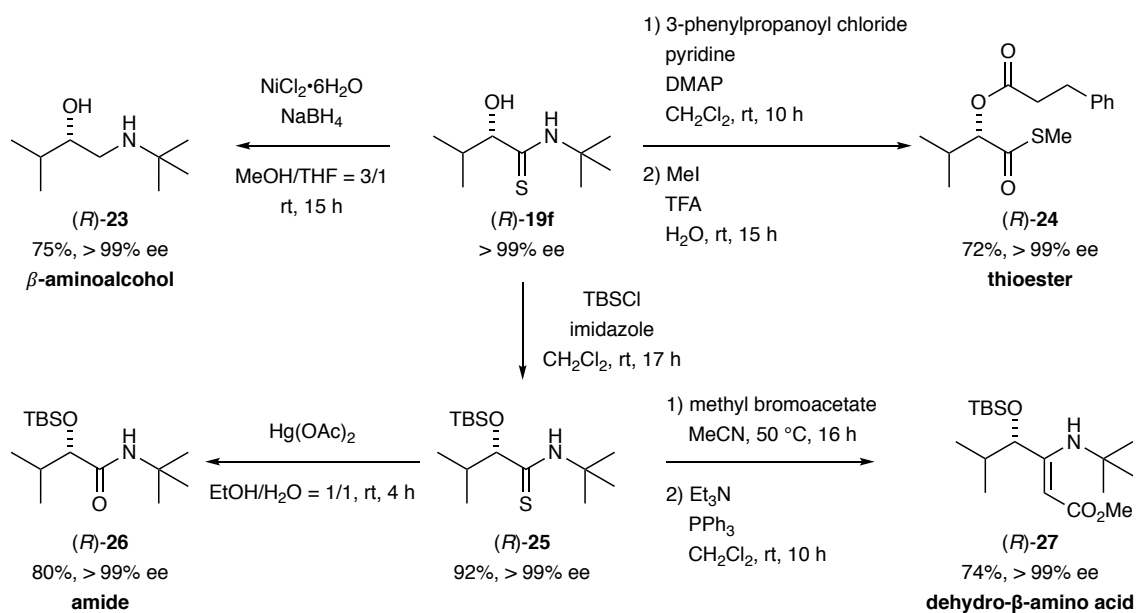


Figure 3.11 Hydrogen-bond Complex Formation under the Acylation Conditions

3.2.6. Further Transformation

The resulting enantiopure α -hydroxy thioamide could be readily converted to other compounds through established protocols, which are outlined in Scheme 3.8. The α -hydroxy thioamide (*R*)-**19g** was easily reduced to β -amino alcohol **23** by treating with $\text{NiCl}_2 \cdot \text{H}_2\text{O}$ and NaBH_4 . The β -amino alcohols are common structural units in pharmaceutical agents²⁰ and useful ligands for metal catalysts.²¹ Acylated thioamide was smoothly converted to the corresponding thioester **24** through S-methylation of the thioamide functionality and subsequent hydrolysis. Thioesters can be transformed to divergent carboxylic acid derivatives, such as aldehydes²² and amides²³. A sequence of hydroxy group protection with TBS, thiocarbonyl group activation with $\text{Hg}(\text{OAc})_2$, and hydrolysis afforded amide **26** in 80% yield. Dehydro- β -amino acid **27** was also obtained in 74% yield as a single diastereomer through Eschenmoser sulfide contraction. All the transformations were achieved in satisfactory yields without any erosion of enantiopurity.



Scheme 3.5 Further Functionalization of Enantiopure α-Hydroxy Thioamide

3.3 Chiral NHC-Catalyzed Kinetic Resolution of α -Hydroxy Amide

3.3.1. Introduction

As described in Figure 3.4, the more acidic proton of thioamide compared with that of amide tightened the hydrogen bond with carboxylate (also see Figure 3.12 A), resulting in higher selectivity in this reaction. This indicates that introduction of an electron-withdrawing group (R^2) as an N-substituent of the amide may enhance the acidity of NH, leading to more efficient hydrogen bond formation between amide and carboxylate (Figure 3.12 B), and thus more effective kinetic resolution.

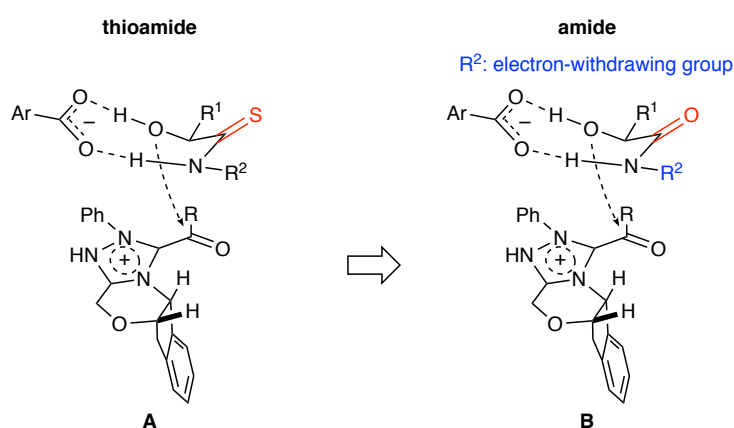
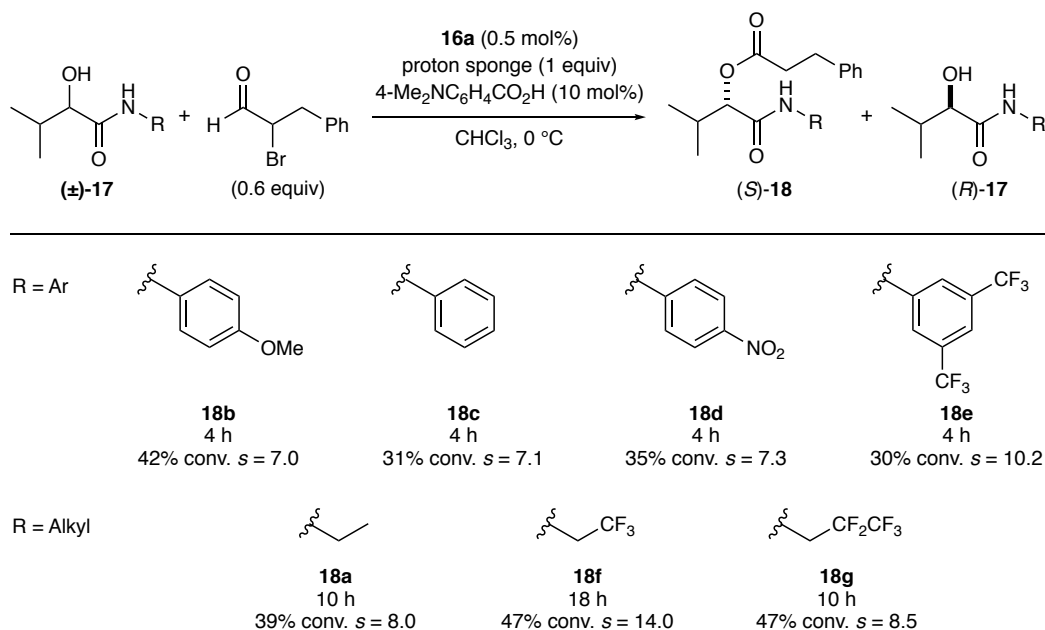


Figure 3.12 Expected Good Performance of Electron Deficient Amides

3.3.2. Investigation of Electron Deficient Amides

Following the identification of a suitably reactive catalyst system, we then investigated the effects of a substituent R on the amide substrate (Scheme 3.9).



Scheme 3.9 Effect of Substituent on Amide Group

Treating several aromatic amides (**17b** to **17e**) with 2-bromo-3-phenylpropanal (0.6 equivalent) in the presence of NHC pre-catalyst **16a** (0.5 mol%), 4-dimethylaminobenzoic acid (0.1 equivalent), and proton sponge (1.0 equivalent) in chloroform at 0°C , **17e** bearing electron-withdrawing substituents showed higher selectivity. Upon investigation of aliphatic amides, it was observed that trifluoroethyl amide **17f** performed with higher selectivity than ethyl amide **17a**, giving an *s* value of 14.0. Further attempts employing the more-electron-deficient pentafluoropropyl amide **17g** failed to provide any improvement. This may have been because deprotonation of NH proceeded in the reaction using the amides bearing the highly electron-withdrawing substituent, and so hydrogen bond formation with the carboxylate was suppressed. On the other hand, since fluorine is known to function as a hydrogen bond acceptor, the possibility of intramolecular hydrogen bond formation in **17g** (Figure 3.12) may have a negative effect on the formation of the intermolecular substrate–carboxylate complex. Further investigations to develop a more efficient catalytic system for kinetic resolution of α -hydroxy amides are underway in this laboratory.

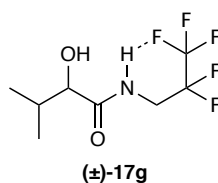


Figure 3.12 Effect of Substituent on Amide Group

3.5. Conclusion

This chapter describes a detailed investigation into chiral recognition of substrate–carboxylate complex methodology using chiral NHC-catalyzed acylation. The first kinetic resolution of α -hydroxy thioamide was achieved with this strategy, using the novel chiral NHC precatalyst **16e** and weakly acidic 9-julolidinecarboxylic acid. Mechanistic experiments provided strong support for the complexation of substrate and carboxylate in this process, and enabled the estimation of the substrate–carboxylate association constant. The resulting chiral α -hydroxy thioamides acted as synthetic intermediates in the preparation of α -hydroxy carboxylic acid derivatives and other multiple optically active compounds. This method would facilitate the synthesis of a wide variety of enantiomerically enriched hydroxy-substituted structures and enable the preparation of novel pharmaceutical compounds.

This mode of catalysis has been extended to the kinetic resolution of α -hydroxy amides, notably, aliphatic ones bearing electron-withdrawing substituents that have never been accessed before.

These results may provide a useful starting point for efforts toward identifying novel catalysis systems based on chiral recognition of substrate–cocatalyst complexes, and encourage applications of this methodology to stereocontrol of more complex substrates.

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Chapter 4. Conclusion

In this thesis, the author developed a new oxa- and azacycle forming reaction using sulfonylalkynol and sulfonylalkynamide in the presence of a substoichiometric amount of NHC. This reaction proceeded in a ⁴-Umpolung-type bond formation process that accompanied 1,2-migration of the sulfonyl groups. Investigation of the reaction mechanism showed that other nucleophiles may also promote this reaction instead of NHC. Actually, the triphenylphosphine was found to give similar results with NHC. The possibility of enantiocontrol of this reaction was indicated by the use of chiral phosphine and binaphthyl-based chiral DMAP. Further investigation on developing an efficient enantioselective variant is currently in progress in this laboratory.

In addition, the author developed the first kinetic resolution of α -hydroxy thioamide using a new aminoindane-based triazolium salt and low acidic carboxylic acid cocatalyst. The *in situ* generated carboxylate was found to associate with α -hydroxy thioamide through hydrogen bond formation, which was recognized by chiral NHC during the acylation process. Further extension of this method to α -hydroxy amides is also described.

Experimental Section

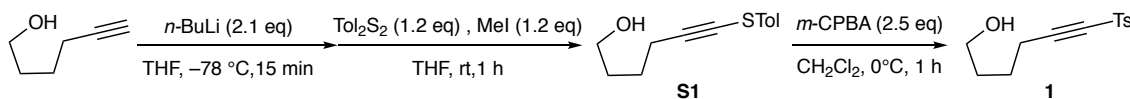
General Remarks

All non-aqueous reactions were carried out under a positive atmosphere of argon in dried glassware. Dehydrated solvents were purchased for the reactions and used without further desiccation. Reagents were purchased and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on Merck TLC silica gel 60 F₂₅₄. Column chromatography was performed using Kanto Chem. Co. Silica Gel 60N (particle size 0.040–0.050 mm). Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-ECA 500 instrument and a Bruker AV-400N instrument. The ¹H chemical shifts were calibrated with internal tetramethylsilane (TMS, 0 ppm) in deuterated organic solvents. The ¹³C chemical shifts are reported relative to CDCl₃ (77.0 ppm), DMSO-*d*₆ (39.5 ppm), acetone-*d*₆ (206.7 and 30.4 ppm). The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Low-resolution mass spectra (LRMS) were recorded on a SHIMADZU GCMS-QP2010 SE spectrometer (EI) or a JEOL MS700 spectrometer (FAB). High-resolution mass spectra (HRMS) were recorded on a JEOL MS700 spectrometer (FAB) or a SHIMADZU LCMS-IT-TOF fitted with an ESI. IR experiments were recorded on a SHIMADZU IRAffinity-1 spectrometer. The wave numbers of maximum absorption peaks of IR spectroscopy are presented in cm⁻¹. All melting points were determined using a Yamato MP-21 melting point apparatus and are uncorrected. Optical rotations were obtained on a JASCO P-1030 polarimeter. X-ray diffraction data were recorded on a RIGAKU R-Axis RAPID system. High performance liquid chromatography (HPLC) analyses were performed on a SHIMADZU analytical system equipped with two LC-20AT pumps.

The ¹H NMR data of **3a**,¹ **14a**,² and **S49**³ corresponds to those reported in literature.

Chapter 1

1. Preparation of substrate



Compound S1

To a solution of hex-5-yn-1-ol (2.1 mL, 20 mmol) in anhydrous THF (60 mL) cooled at $-78\text{ }^{\circ}\text{C}$ under argon atmosphere, was added a 1.6 M hexane solution of *n*-BuLi (26 mL, 42 mmol), and the mixture was stirred for 15 min. A solution of *p*-ditolyl disulfide (5.9 g, 24 mmol) and MeI (1.5 mL, 24 mmol) in anhydrous THF (80 mL), which had been stirred for 1 h, was added dropwise. The cooling bath was removed, and the whole was stirred for 1 h. After addition of saturated aqueous NH_4Cl , the organic layer was separated. The aqueous layer was extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. The residue was purified by column chromatography (hexane to hexane/EtOAc 4:1) to give **S1** (4.41 g, quant) as a colorless oil

^1H NMR (500 MHz, CDCl_3) δ 7.30 (d, $J = 8.0$, 2H), 7.14 (d, $J = 8.0$, 2H), 3.70 (q, $J = 6.0$, 2H), 2.49 (t, $J = 6.5$, 2H), 2.33 (s, 3H), 1.75–1.66 (m, 4H) ppm.

^{13}C NMR (125 MHz, CDCl_3) δ 136.1 (C), 129.8 (CH), 129.7 (C), 126.1 (CH), 98.7 (C), 65.6 (C), 62.2 (CH_2), 31.7 (CH_2), 24.9 (CH_2), 20.9 (CH_3), 20.0 (CH_2) ppm.

LRMS (ESI) m/z 221(M + H).

HRMS (ESI) m/z : [M + H] $^+$ calcd for $\text{C}_{13}\text{H}_{17}\text{OS}$, 221.0995; found, 221.0995.

IR 3344, 2939, 1493, 1053, 910, 802, 737.

Compound 1

To a solution of **S1** (220 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) cooled in an ice–water bath, was added *m*-CPBA (0.57 g, 2.5 mmol), and the mixture was stirred for 30 min. After addition of saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (25 mL), the cooling bath was removed, and the mixture was stirred for 2 h. To the mixture, was added saturated aqueous NaHCO_3 , and the organic layer was separated. The aqueous layer was extracted 3 times with CHCl_3 . The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 2:1) to give compound **1** (209 mg, 83%) as a colorless oil.

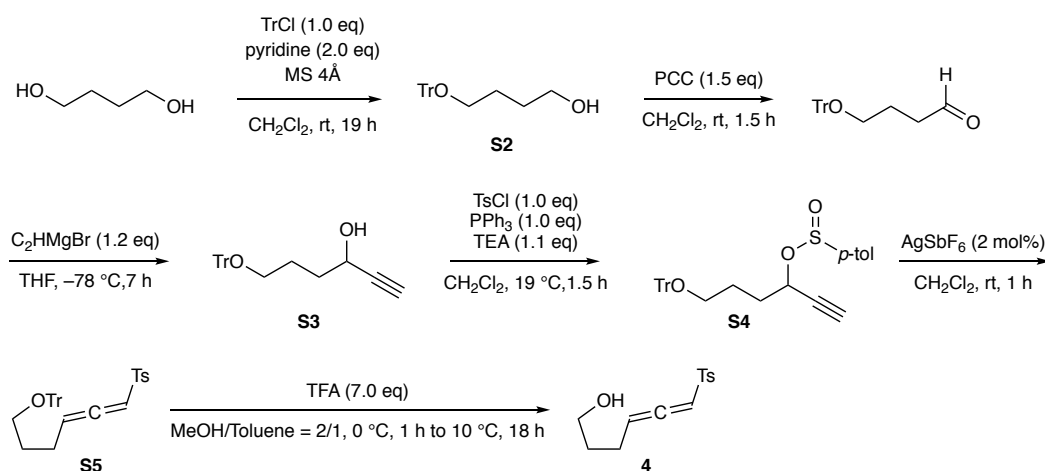
¹H NMR (500 MHz, CDCl₃) δ 7.88 (d, *J* = 8.5, 2H), 7.37 (d, *J* = 8.5, 2H), 3.64 (t, *J* = 6.0, 2H), 2.47 (s, 3H), 2.42 (t, *J* = 7.0, 2H), 1.70–1.59 (m, 4H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 145.2 (C), 138.9 (C), 129.9 (CH), 127.2 (CH), 96.9 (C), 78.4 (C), 61.7 (CH₂), 31.4 (CH₂), 23.4 (CH₂), 21.6 (CH₃), 18.7 (CH₂) ppm.

LRMS (ESI) *m/z* 253 (M + H).

HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₁₃H₁₇O₃S, 253.0893; found, 253.0893.

IR 3557, 2199, 1323, 1153, 1088, 814.



Compound S2

To a solution of butane-1,4-diol (25.0 g, 277 mmol) in anhydrous CH₂Cl₂ (280 mL) under an argon atmosphere were added TrCl (19 g, 69 mmol), pyridine (11 mL, 0.14 mol), and MS4 Å (100 g), and the mixture was stirred at rt for 19 h. After dilution with CH₂Cl₂, the mixture was filtered through a pad of Celite and concentrated in vacuo. The crude product was purified by column chromatography (hexane/EtOAc 2:1) to give **S2** (23.0 g, quant) as white solids.

¹H NMR (500 MHz, CDCl₃) δ 7.44 (d, *J* = 7.5, 6H), 7.30 (t, *J* = 7.5, 6H), 7.25–7.22 (m, 3H), 3.64 (q, *J* = 5.0, 2H), 3.12 (t, *J* = 5.5, 2H), 1.71–1.65 (m, 4H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 144.1 (C), 128.5 (CH), 127.7 (CH), 126.8 (CH), 86.5 (C), 63.4 (CH₂), 62.6 (CH₂), 29.7 (CH₂), 26.4 (CH₂) ppm.

LRMS (ESI) *m/z* 355 (M + Na).

HRMS (ESI) *m/z*: [M + Na]⁺ calcd for C₂₃H₂₄NaO₂, 355.1669; found, 355.1667.

IR 3365, 2940, 1447, 1219, 1061, 907, 729.

mp 52–58 °C.

Compound S3

To a solution of **S1** (12.6 g, 38.0 mmol) in anhydrous CH_2Cl_2 (190 mL) were added PCC (12 g, 57 mmol) and Celite (20 g), and the mixture was stirred at rt for 1.5 h. After dilution with Et_2O , the mixture was filtered through a pad of SiO_2 and concentrated in vacuo to give 4-trityloxybutanal as a colorless solid (12.3 g), which was used in the next reaction without further purification.

To a solution of the above aldehyde (12.3 g) in anhydrous THF (88 mL) cooled at $-78\text{ }^\circ\text{C}$ under an argon atmosphere was added a 0.5 M THF solution of ethynylmagnesium bromide (91 mL, 46 mmol), and the mixture was stirred for 7 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl , and the organic layer was separated. The aqueous layer was extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 2:1) to give **S3** (9.52 g, 69% for 2 steps) as a colorless oil.

^1H NMR (500 MHz, CDCl_3) δ 7.44 (d, $J = 7.5$, 6H), 7.30 (dd, $J = 7.5$, 7.0, 6H), 7.23 (d, $J = 7.0$, 3H), 4.39 (m, 1H), 3.15 (m, 1H), 3.10 (m, 1H), 2.47 (d, $J = 2.0$, 1H), 2.28 (d, $J = 6.0$, 1H), 1.88–1.77 (m, 4H) ppm.

^{13}C NMR (125 MHz, CDCl_3) δ 144.1 (C), 128.6 (CH), 127.8 (CH), 126.9 (CH), 86.7 (C), 84.8 (C), 72.9 (CH), 63.2 (CH_2), 62.0 (CH), 34.9 (CH_2), 25.6 (CH_2) ppm.

LRMS (ESI) m/z 379 ($\text{M} + \text{Na}$).

HRMS (ESI) m/z : [$\text{M} + \text{Na}$] calcd for $\text{C}_{25}\text{H}_{24}\text{NaO}_2$, 379.1669; found, 379.1668.

IR 3302, 3021, 1728, 1489, 1446, 1219, 1072, 1029, 748.

Compound S4

To a solution of TsCl (1.0 g, 5.4 mmol) and Et_3N (0.84 mL, 6.0 mmol) in anhydrous CH_2Cl_2 (14 mL) under an argon atmosphere were added a solution of **S3** (1.92 g, 5.40 mmol) and PPh_2 (1.4 g, 5.4 mmol) in anhydrous CH_2Cl_2 (14 mL) dropwise at $19\text{ }^\circ\text{C}$ over 10 min. The mixture was stirred at the same temperature for 1.5 h, then filtered through a short pad of SiO_2 to remove $\text{Et}_3\text{N}\cdot\text{HCl}$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/ EtOAc 9:1) to give a 1:1 diastereomer mixture of **S4** (2.31 g, 85%) as a colorless oil

^1H NMR (500 MHz, CDCl_3) δ 7.61 (d, $J = 8.0$, 2H), 7.44–7.38 (m, 6H), 7.32–7.25 (m, 8H), 7.25–7.20 (m, 3H), 4.92–4.86 (m, 1H), 3.10–3.07 (m, 1H), 3.06–3.03 (m, 1H), 2.65 (d, $J = 1.0$, 0.5H), 2.42 (s, 1.5H), 2.41 (s, 1.5H), 2.37 (d, $J = 1.4$, 0.5H), 1.98–1.88 (m, 2H), 1.82–1.71 (m,

2H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 144.2 (C), 142.91 (C), 142.86 (C), 142.3 (C), 141.6 (C), 129.7 (CH), 128.61 (CH), 128.59 (CH), 127.9 (CH), 127.7 (CH), 126.9 (CH), 125.3 (CH), 125.0 (CH), 106.7 (C), 86.4 (CH), 75.9 (C), 74.0 (C), 62.7 (CH₂), 33.2 (CH₂), 25.4 (CH₂), 21.5 (CH₂) ppm.

LRMS (ESI) *m/z* 533 (M + K)..

HRMS (ESI) *m/z*: [M + K]⁺ calcd for C₃₂H₃₀KO₃S, 533.1547; found, 533.1547.

IR 1597, 1493, 1447, 1134, 1076, 748.

Compound S5

To AgSbF₆ (60 mg, 0.17 mmol) under an argon atmosphere was added a solution of **S4** (4.20 g, 8.50 mmol) in anhydrous CH₂Cl₂ (17 mL) dropwise at rt over 10 min. The mixture was stirred for 1 h, diluted with Et₂O (5 mL), filtered through a pad of SiO₂, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 5:1) to give **S5** (2.45 g, 57%) as a colorless oil.

¹H NMR (500 MHz, CDCl₃) δ 7.76 (d, *J* = 8.0, 2H), 7.40 (d, *J* = 7.0, 6H), 7.31–7.27 (m, 8H), 7.23 (t, *J* = 7.0, 3H), 6.11 (dt, *J* = 5.5, 3.0, 1H), 5.82 (td, *J* = 7.0, 5.5, 1H), 3.07 (m, 2H), 2.41 (s, 3H), 2.25 (m, 2H), 1.69 (m, 2H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 205.3 (C), 144.2 (C), 144.0 (C), 138.3 (C), 129.6 (CH), 128.5 (CH), 127.6 (CH), 127.5 (CH), 126.8 (CH), 101.5 (CH), 100.7 (CH), 86.3 (C), 62.2 (CH₂), 28.6 (CH₂), 24.6 (CH₂), 21.5 (CH₃) ppm.

LRMS (ESI) *m/z* 533 (M + K).

HRMS (ESI) *m/z*: [M + K]⁺ calcd for C₃₂H₃₀KO₃S, 533.1547; found, 533.1547.

IR 1956, 1597, 1446, 1319, 1146, 1084, 748.

Compound 4

To a solution of **S5** (315 mg, 0.640 mmol) in a 2:1 mixture of MeOH and toluene (6.4 mL) cooled in an ice–water bath was added TFA (0.34 mL, 4.5 mmol), and the mixture was stirred for 1 h. Then, the mixture was allowed to warm to 10 °C and stirred for 18 h. The reaction was quenched by the addition of saturated aqueous NaHCO₃, and the organic layer was separated. The aqueous layer was extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 4:1 to 1:2) to give **1a** (70.1 mg, 43%) as a colorless oil.

¹H NMR (500 MHz, CDCl₃) δ 7.78 (d, *J* = 8.5, 2H), 7.34 (d, *J* = 8.5, 2H), 6.18 (dt, *J* = 5.5, 3.0,

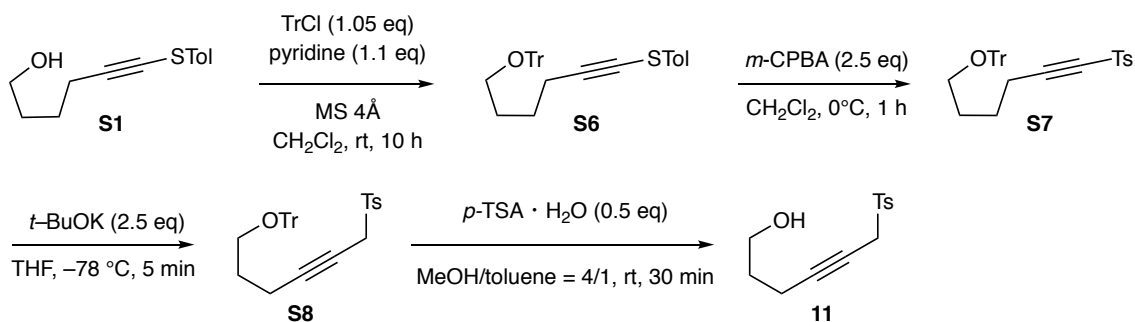
1H), 5.89 (td, $J = 7.5, 5.5$, 1H), 3.73 (t, $J = 4.0$, 2H), 2.45 (s, 3H), 2.30 (m, 2H), 1.82 (br s, 1H), 1.74 (m, 1H), 1.68 (m, 1H) ppm.

^{13}C NMR (125 MHz, CDCl_3) δ 205.5 (C), 144.5 (C), 138.4 (C), 129.8 (CH), 127.5 (CH), 101.3 (CH), 100.8 (CH), 61.4 (CH_2), 30.8 (CH_2), 24.4 (CH_2), 21.6 (CH_3) ppm.

LRMS (ESI) m/z 291 (M + K).

HRMS (ESI) m/z : $[\text{M} + \text{K}]^+$ calcd for $\text{C}_{13}\text{H}_{16}\text{KO}_3\text{S}$, 291.0452; found, 291.0448.

IR 3476, 3021, 1956, 1315, 1215, 1142, 748.



Compound S6

To a solution of 2a-1 (4.41g, 20.0 mmol) in anhydrous CH_2Cl_2 (50 mL) under an argon atmosphere were added TrCl (5.9 g, 21 mmol), pyridine (1.8 mL, 22 mmol), and MS4Å (20 g), and the mixture was stirred at rt for 10 h. After dilution with EtOAc, the mixture was filtered through a pad of Celite and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 20:1) to give **S6** (9.25 g, quant) as a yellow oil.

^1H NMR (500 MHz, CDCl_3) δ 7.44 (d, $J = 7.5$, 6H), 7.31–7.28 (m, 8H), 7.22 (t, $J = 7.5$, 3H), 7.11 (d, $J = 8.0$, 2H), 3.09 (t, $J = 6.0$, 2H), 2.41 (t, $J = 6.5$, 2H), 2.31 (s, 3H), 1.76 (m, 2H), 1.71 (m, 2H) ppm.

^{13}C NMR (125 MHz, CDCl_3) δ 144.3 (C), 136.1 (C), 129.8 (CH), 128.6 (CH), 127.9 (C), 127.7 (CH), 126.8 (CH), 126.1 (CH), 99.0 (C), 86.3 (C), 65.5 (C), 62.9 (CH_2), 29.2 (CH_2), 25.6 (CH_2), 20.9 (CH_3), 20.1 (CH_2) ppm.

LRMS (ESI) m/z 501 (M + K).

HRMS (ESI) m/z : $[\text{M} + \text{K}]^+$ calcd for $\text{C}_{32}\text{H}_{30}\text{KOS}$, 501.1649; found, 501.1648.

IR 2940, 1493, 1447, 1076, 910, 802, 764.

Compound S7

To a solution of **S6** (9.24 g, 20.0 mmol) in CH₂Cl₂ (200 mL) cooled in an ice–water bath was added *m*-CPBA (12 g, 50 mmol), and the mixture was stirred for 1 h. After addition of saturated aqueous Na₂S₂O₃ (50 mL), the cooling bath was removed, and the mixture was stirred for 2 h. To the mixture was added saturated aqueous NaHCO₃, and the organic layer was separated. The aqueous layer was extracted 3 times with CHCl₃. The combined organic layers were washed with brine, dried over Na₂SO₃, and concentrated in vacuo. The residue was recrystallized from hexane–EtOAc (6:1) to give **S7** (6.92 g, 70%) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ 7.87(d, *J* = 8.0, 2H), 7.40 (d, *J* = 7.5, 6H), 7.34 (d, *J* = 8.0, 2H), 7.30–7.26 (m, 6H), 7.23 (t, *J* = 7.0, 3H), 3.04 (t, *J* = 5.5, 2H), 2.43 (s, 3H), 2.33 (t, *J* = 6.5, 2H), 1.68–1.62 (m, 4H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 145.0 (C), 144.1 (C), 139.1 (C), 129.9 (CH), 128.6 (CH), 127.7 (CH), 127.2 (CH), 126.9 (CH), 97.0 (C), 86.4 (C), 78.5 (C), 62.4 (CH₂), 28.9 (CH₂), 24.1 (CH₂), 21.7 (CH₃), 18.7 (CH₂) ppm.

LRMS (ESI) *m/z* 533 (M + K).

HRMS (ESI) *m/z*: [M + K]⁺ calcd for C₃₂H₃₀KO₃S, 533.1547; found, 533.1547.

IR 3024, 2936, 2199, 1447, 1327, 1157, 1088, 752.

mp 114–117 °C.

Compound S8

A 1 M THF solution of *t*-BuOK (17 mL, 17 mmol) was diluted with anhydrous THF (30 mL) under an argon atmosphere and cooled at –78 °C. To the solution, was added **S7** (3.36g, 6.80 mmol) in THF (40 mL) dropwise over 15 min, and the mixture was stirred for 5 min. The reaction was quenched by the addition of a 1 M THF solution of AcOH (15 mL), and the cooling bath was removed. After addition of saturated aqueous NaHCO₃, the organic layer was separated. The aqueous layer was extracted 3 times with Et₂O. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (hexane/ EtOAc 5:1) to give **S8** (3.06 g, 91%) as light brown oil.

¹H NMR (500 MHz, CDCl₃) δ 7.79 (d, *J* = 8.5, 2H), 7.39 (d, *J* = 8.5, 6H), 7.31–7.26 (m, 8H), 7.24–7.21 (m, 3H), 3.84 (t, *J* = 2.5, 2H), 3.07 (t, *J* = 6.0, 2H), 2.42 (s, 3H), 2.31 (tt, *J* = 7.0, 2.5, 2H), 1.71 (tt, *J* = 7.0, 6.0, 2H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 145.0 (C), 144.1 (C), 134.8 (C), 129.5 (CH), 128.8 (CH), 128.6 (CH), 127.7 (CH), 126.9 (CH), 88.2 (C), 86.3 (C), 67.8 (C), 61.7 (CH₂), 49.0 (CH₂), 28.8 (CH₂), 21.7 (CH₃), 15.9 (CH₂) ppm.

LRMS (ESI) *m/z* 533 (M + K).

HRMS (ESI) *m/z*: [M + K]⁺ calcd for C₃₂H₃₀KO₃S, 533.1547; found, 533.1547.

IR 1447, 1319, 1134, 1069, 748.

Compound 11a

To a solution of **S8** (8.11 g, 16.4 mmol) in a 4:1 mixture of MeOH and toluene (160 mL) was added TsOH·H₂O (1.4 g, 8.2 mmol), and the mixture was stirred for 30 min at rt. To the mixture were added EtOAc and saturated aqueous NaHCO₃, and the organic layer was separated. The aqueous layer was extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 1:1) to give **11a** (3.18 g, 77%) as a light yellow oil.

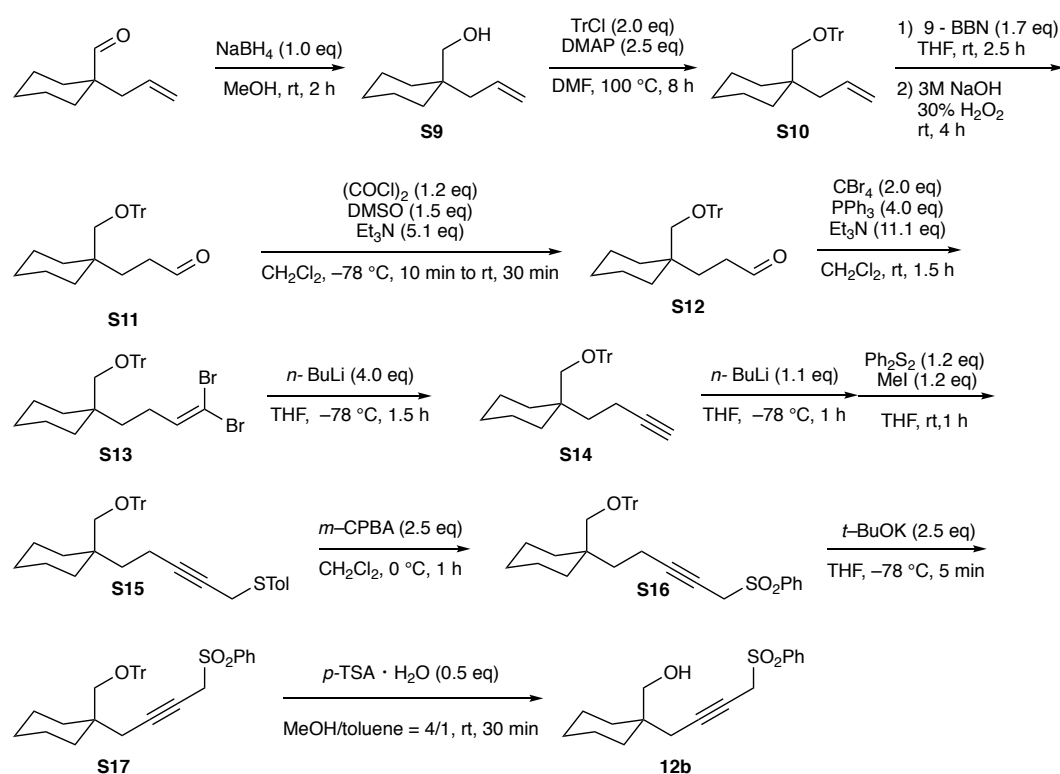
¹H NMR (500 MHz, CDCl₃) δ 7.85 (d, *J* = 8.0, 2H), 7.37 (d, *J* = 8.0, 2H), 3.91 (br s, 2H), 3.67 (br td, *J* = 6.0, 3.5, 2H), 2.47 (s, 3H), 2.30 (br t, *J* = 7.0, 2H), 1.71 (tt, *J* = 7.0, 6.0, 2H), 1.35 (br s, 1H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 145.2 (C), 134.8 (C), 129.7 (CH), 128.7 (CH), 87.9 (C), 68.1 (C), 61.2 (CH₂), 49.0 (CH₂), 30.7 (CH₂), 21.7 (CH₃), 15.2 (CH₂) ppm.

LRMS (ESI) *m/z* 291 (M + K).

HRMS (ESI) *m/z*: [M + K]⁺ calcd for C₁₃H₁₆KO₃S, 291.0452; found, 291.0452.

IR 3522, 2947, 1597, 1319, 1134, 1084, 748.



Compound **S9**

To a solution of 1-allylcyclohexane-1-carbaldehyde (4.26 g, 28.0 mmol) in MeOH (56 mL) was added NaBH₄ (1.1 g, 28 mmol), and the mixture was stirred at rt for 2 h. The reaction was quenched by the addition of water, and after dilution with EtOAc, the organic layer was separated. The aqueous layer was extracted 5 times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 9:1) to give **S9** (3.58 g, 83%) as colorless oil.

¹H NMR (500 MHz, CDCl₃) δ 5.87 (m, 1H), 5.10–5.00 (m, 2H), 3.42 (s, 2H), 2.12 (d, $J = 7.5$, 2H), 1.51–1.40 (m, 5H), 1.36–1.29 (m, 5H). ppm.

¹³C NMR (125 MHz, CDCl₃) δ 135.3 (CH), 117.0 (CH₂), 68.8 (CH₂), 40.0 (CH₂), 37.8 (C), 32.3 (CH₂), 26.3 (CH₂), 21.4 (CH₂) ppm.

ESIMS m/z 155 ($M + H$).

IR 3383, 3075, 2924, 1636, 1454, 1385, 1030, 910.

Compound S10

To a solution of the above **S9** (3.24 g, 21.0 mmol) in DMF (42 mL) were added DMAP (6.4 g, 53 mmol) and TrCl (12 g, 42 mmol), and the mixture was stirred for 8 h at 100 °C and then cooled to rt. After addition of water and Et₂O, the organic layer was separated. The aqueous layer was extracted 5 times with Et₂O. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (hexane/ toluene 9:1) to give **S10** (6.41 g, 77%) as brown oil.

¹H NMR (500 MHz, CDCl₃) δ 7.45 (d, *J* = 7.5, 6H), 7.29–7.26 (m, 6H), 7.23–7.19 (m, 3H), 5.53 (ddt, *J* = 16.5, 10.0, 7.5, 1H), 4.93 (dd, *J* = 16.5, 2.0, 1H), 4.86 (dd, *J* = 10.0, 2.0, 1H), 2.87 (s, 2H), 2.24 (d, *J* = 7.5, 2H), 1.40–1.21 (m, 10H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 144.4 (C), 135.1 (CH), 128.9 (CH), 127.6 (CH), 126.8 (CH), 116.7 (CH₂), 85.8 (C), 67.5 (CH₂), 40.3 (CH₂), 37.4 (CH₂), 33.2 (CH₂), 26.3 (CH₂), 21.5 (CH₂) ppm.

LRMS (ESI) *m/z* 435 (M + K)..

HRMS (ESI) *m/z*: [M + K]⁺ calcd for C₂₉H₃₂KO, 435.2085; found, 435.2085..

IR 2924, 2855, 1489, 1447, 1215, 1069, 752.

Compound S11

To a solution of **S10** (416 mg, 1.05 mmol) in anhydrous THF (25 mL) cooled in an ice–water bath was added a 0.5 M THF solution of 9-BBN (3.4 mL, 1.7 mmol) dropwise over 1 min. The cooling bath was removed, and the mixture was stirred for 2.5 h. Then, 3 M aqueous NaOH (3.3 mL) and 30% aqueous H₂O₂ (3.3 mL) were added slowly, and the resulting solution was stirred for 4 h. After addition of water and Et₂O, the organic layer was separated. The aqueous layer was extracted 3 times with Et₂O. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (hexane/ Et₂O 2:1) to give **S11** (357 mg, 82%) as a colorless oil.

¹H NMR (500 MHz, CDCl₃) δ 7.45 (d, *J* = 7.5, 6H), 7.29 (t, *J* = 7.5, 6H), 7.22 (t, *J* = 7.5, 3H), 3.51 (t, *J* = 6.5, 2H), 2.88 (s, 2H), 1.49–1.46 (m, 2H), 1.41–1.28 (m, 10H), 1.17–1.10 (m, 2H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 144.3 (C), 128.8 (CH), 127.6 (CH), 126.8 (CH), 85.7 (C), 67.0 (CH₂), 63.9 (CH₂), 36.6 (C), 33.5 (CH₂), 27.4 (CH₂), 26.4 (CH₂), 26.2 (CH₂), 21.5 (CH₂) ppm.

LRMS (ESI) *m/z* 437 (M + Na).

HRMS (ESI) *m/z*: [M + Na] calcd for C₂₉H₃₄NaO₂, 437.2451; found, 437.2452.

IR 3352, 2924, 1447, 1215, 1065, 752.

Compound S12

To a mixture of DMSO (0.34 mL, 4.8 mmol) and anhydrous CH₂Cl₂ (7 mL) cooled at -78 °C under an argon atmosphere was added a solution of (COCl)₂ (0.33 mL, 3.8 mmol) in anhydrous CH₂Cl₂ (5 mL) dropwise over 5 min. Then, a solution of **S11** (1.29 g, 3.12 mmol) in anhydrous CH₂Cl₂ (4 mL) was added dropwise over 15 min. After 15 min, Et₃N (2.2 mL, 16 mmol) was added over 3 min with vigorous stirring. After 10 min, the cooling bath was removed, and the mixture was stirred for 30 min. After addition of saturated aqueous NH₄Cl, the organic layer was separated. The aqueous layer was extracted 3 times with CHCl₃. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 20:1) to give **S12** (940 mg, 73%) as a light brown oil.

¹H NMR (500 MHz, CDCl₃) δ 9.63 (s, 1H), 7.44 (d, *J* = 7.5, 6H), 7.30 (t, *J* = 7.5, 6H), 7.23 (t, *J* = 7.5, 3H), 2.88 (s, 2H), 1.97 (t, *J* = 8.5, 2H), 1.76 (t, *J* = 8.5, 2H), 1.42–1.30 (m, 10H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 203.2 (CH), 144.0 (C), 128.7 (CH), 127.7 (CH), 126.9 (CH), 85.9 (C), 81.2 (CH₂), 38.1 (CH₂), 36.4 (C), 33.5 (CH₂), 30.0 (CH₂), 26.3 (CH₂), 21.5 (CH₂) ppm.

ESIMS *m/z* 413 (M + H).

IR 2924, 1721, 1447, 1065, 756.

Compound S13

To a solution of CBr₄ (2.9 g, 8.6 mmol) and PPh₃ (4.5 g, 17 mmol) in anhydrous CH₂Cl₂ (16 mL) cooled at -78 °C under an argon atmosphere were sequentially added Et₃N (4.8 mL, 35 mmol) and a solution of the **S12** (1.78 g, 4.30 mmol) in anhydrous CH₂Cl₂ (0.7 mL). After 1.5 h, hexane was added, and the cooling bath was removed. The mixture was filtered and concentrated in vacuo. The residue was purified by column chromatography (hexane/toluene 20:1) to give **S13** (1.64 g, 67%) as yellow oil.

¹H NMR (500 MHz, CDCl₃) δ 7.44 (d, *J* = 7.5, 6H), 7.29 (t, *J* = 7.5, 6H), 7.24–7.21 (m, 3H), 6.31 (t, *J* = 7.0, 1H), 2.87 (s, 2H), 1.75–1.71 (m, 2H), 1.57–1.54 (m, 2H), 1.39–1.26 (m, 10H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 144.2 (C), 139.5 (CH), 128.8 (CH), 128.2 (C), 127.7 (CH), 126.9 (CH), 85.9 (C), 67.1 (CH₂), 36.9 (CH), 33.5 (CH₂), 27.1 (C), 26.3 (CH₂), 26.3 (CH₂), 21.5 (CH₂) ppm.

IR 1477, 1435, 1215, 1088, 1069, 907, 741.

Compound S14

To a solution of the above dibromide **S13** (1.59 g, 2.80 mmol) in anhydrous THF (17 mL) cooled at -78 °C under an argon atmosphere was added a 1.6 M hexane solution of *n*-BuLi (7.0 mL, 11 mmol), and the mixture was stirred for 1.5 h. After dilution with Et₂O, the reaction was quenched by the addition of saturated aqueous NH₄Cl. The organic layer was separated, and the aqueous layer was extracted 3 times with Et₂O. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (hexane/toluene 10:1) to give **S14** (980 mg, 86%) as a yellow oil.

¹H NMR (500 MHz, CDCl₃) δ 7.47–7.44 (m, 6H), 7.32–7.28 (m, 6H), 7.25–7.21 (m, 3H), 2.83 (s, 2H), 1.90 (t, *J* = 2.5, 1H), 1.82–1.76 (m, 4H), 1.40–1.25 (m, 10H). ppm.

¹³C NMR (125 MHz, CDCl₃) δ 144.2 (C), 128.8 (CH), 127.7 (CH), 126.8 (CH), 85.9 (CH), 85.7 (C), 67.5 (CH₂), 66.9 (C), 36.8 (C), 34.8 (CH₂), 33.2 (CH₂), 26.3 (CH₂), 21.5 (CH₂), 12.5 (CH₂) ppm.

LRMS (ESI) *m/z* 447 (M + K)..

HRMS (ESI) *m/z*: [M + K]⁺ calcd for C₃₀H₃₂KO, 447.2085; found, 447.2083.

IR 2928, 1450, 1215, 1065, 748.

Compound S16

To a solution of **S14** (172 mg, 0.420 mmol) in anhydrous THF (1.4 mL) cooled at -78 °C under an argon atmosphere was added a 1.6 M hexane solution of BuLi (0.29 mL, 0.46 mmol), and the mixture was stirred for 15 min. A mixture of (PhS)₂ (0.11 g, 0.50 mmol) and MeI (0.03 mL, 0.5 mmol) in anhydrous THF (1.6 mL), which had been stirred for 1 h, was added dropwise, and the cooling bath was removed. After 1 h, the reaction was quenched by the addition of saturated aqueous NH₄Cl, and the organic layer was separated. The aqueous layer was extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was passed through a short SiO₂ plug, which was rinsed with hexane to remove MeSPh and then with (hexane/toluene 10:1) to give crude **S15** (210 mg), which was used in the next reaction without further purification.

To a solution of the crude sulfide (210 mg) in CH₂Cl₂ (4 mL) cooled in an ice–water bath was added *m*-CPBA (0.25 g, 1.1 mmol), and the mixture was stirred for 1 h. After addition of saturated aqueous Na₂S₂O₃ (1 mL), the cooling bath was removed. After 2 h, saturated aqueous NaHCO₃ was added, and the organic layer was separated. The aqueous layer was extracted 3 times with CHCl₃. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo to give crude 1-(4-benzenesulfonylbut-3-ynyl)-1-trityloxymethylcyclohexane as yellow oil (266 mg), which was used in the next reaction without further purification.

Compound S17

A 1 M THF solution of *t*-BuOK (1.0 mL, 1.0 mmol) was diluted with anhydrous THF (3 mL) under an argon atmosphere. To the solution cooled at –78 °C was added a solution of the crude alkynyl sulfone **S16** (266 mg) in anhydrous THF (1 mL) dropwise over 1 min, and the mixture was stirred for 5 min. The reaction was quenched by the addition of a 1 M THF solution of AcOH (1.0 mL), and the cooling bath was removed. After addition of saturated aqueous NaHCO₃, the organic layer was separated. The aqueous layer was extracted 3 times with CHCl₃. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 5:1) to give **S17** (131 mg, 57% for 3 steps) as light brown oil.

¹H NMR (500 MHz, CDCl₃) δ 7.90 (d, *J* = 7.5, 2H), 7.60 (d, *J* = 7.5, 1H), 7.49 (t, *J* = 7.5, 2H), 7.39 (d, *J* = 7.0, 6H), 7.28–7.25 (m, 6H), 7.23–7.20 (m, 3H), 3.83 (t, *J* = 2.5, 2H), 2.86 (s, 2H), 2.36 (t, *J* = 2.5, 2H), 1.30–1.15 (m, 10H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 144.1 (C), 137.8 (C), 133.9 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 127.6 (CH), 126.8 (CH), 86.6 (C), 85.8 (C), 69.0 (C), 66.6 (CH₂), 48.9 (CH₂), 37.7 (C), 32.5 (CH₂), 26.5 (CH₂), 26.0 (CH₂), 21.5 (CH₂) ppm.

LRMS (ESI) *m/z* 571 (M + Na).

HRMS (ESI) *m/z*: [M + Na]⁺ calcd for C₃₆H₃₆NaO₂S, 571.2277; found, 571.2276.

IR 2924, 2855, 2199, 1447, 1327, 1161, 1088, 1065, 752.

Compound 11b

To a solution of **S17** (198 mg, 0.360 mmol) in a 4:1 mixture of MeOH and toluene (1.4 mL) was added TsOH·H₂O (31 mg, 0.18 mmol), and the mixture was stirred at rt for 30 min. After

addition of EtOAc and saturated aqueous NaHCO₃, the organic layer was separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 5:1) to give **11b** (65.1 mg, 59%) as light yellow oil.

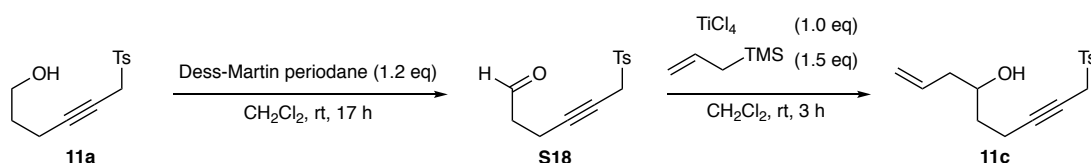
¹H NMR (500 MHz, CDCl₃) δ 7.98 (d, *J* = 8.0, 2H), 7.69 (t, *J* = 7.5, 1H), 7.59 (dd, *J* = 8.0, 7.5, 2H), 3.98 (br s, 2H), 3.42 (d, *J* = 5.0, 2H), 2.23 (br s, 2H), 1.44–1.31 (m, 10H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 137.9 (C), 134.1 (CH), 129.1 (CH), 128.7 (CH), 86.4 (C), 69.4 (C), 68.3 (CH₂), 49.0 (CH₂), 37.9 (C), 31.8 (CH₂), 29.7 (CH₂), 26.0 (CH₂), 21.5 (CH₂) ppm.

LRMS (FAB) *m/z* 329 (M + Na).

HRMS (ESI) *m/z*: [M + Na]⁺ calculated for C₁₇H₂₂NaO₃S 329.1182; found, 329.1179.

IR 3537, 2924, 1447, 1312, 1134, 1084, 744.



Compound S18

To a solution of **11a** (252 mg, 1.00 mmol) in anhydrous CH₂Cl₂ (5 mL) cooled in an ice–water bath was added Dess–Martin periodinane (0.51 g, 1.2 mmol). Then, the cooling bath was removed, and the whole was stirred for 17 h. The mixture was filtered through filter paper, and the filtrate was washed with saturated aqueous NaHCO₃ and brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 2:1) to give **S18** (225 mg, 90%) as a light yellow oil.

¹H NMR (500 MHz, CDCl₃) δ 9.73 (s, 1H), 7.83 (d, *J* = 8.0, 2H), 7.38 (d, *J* = 8.0, 2H), 3.90 (t, *J* = 2.5, 2H), 2.62 (t, *J* = 7.0, 2H), 2.50–2.47 (m, 2H), 2.48 (s, 3H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 199.8 (CH), 145.2 (C), 134.6 (C), 129.6 (CH), 128.6 (CH), 86.3 (C), 68.6 (C), 48.7 (CH₃), 41.8 (CH₂), 21.6 (CH₃), 11.8 (CH₃) ppm.

LRMS (FAB) *m/z* 273 (M + Na).

IR 2920, 1724, 1319, 1134, 1084, 748.

Compound 11c

To a solution of **S18** (175 mg, 0.700 mmol) in anhydrous CH₂Cl₂ (7 mL) under an argon atmosphere was added a 1.0 M CH₂Cl₂ solution of TiCl₄ (0.70 mL, 0.70 mmol), and the mixture was stirred at rt for 5 min. Then, allyltrimethylsilane (0.19 mL, 1.1 mmol) was added, and the

whole was stirred at rt for 3 h. To the mixture were added Et₂O and saturated aqueous NaHCO₃, and the organic layer was separated. The aqueous layer was extracted 3 times with Et₂O. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 5:1) to give **11c** (163 mg, 80%) as light yellow oil.

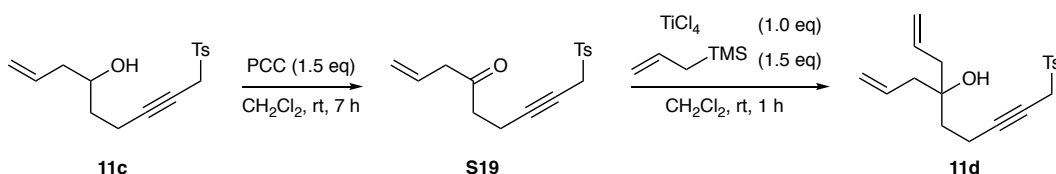
¹H NMR (500 MHz, CDCl₃) δ 7.84 (d, *J* = 8.0, 2H), 7.37 (d, *J* = 8.0, 2H), 5.80 (m, 1H), 5.17–5.13 (m, 2H), 3.92 (br s, 2H), 3.68 (m, 1H), 2.47 (s, 3H), 2.37–2.31 (m, 2H), 2.27 (m, 1H), 2.14 (m, 1H), 1.67 (m, 1H), 1.62 (m, 1H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 145.1 (C), 134.9 (C), 134.3 (CH), 129.6 (CH), 128.8 (CH), 118.4 (CH₂), 88.1 (C), 69.1 (CH), 68.1 (C), 49.0 (CH₂), 41.8 (CH₂), 34.8 (CH₂), 21.6 (CH₃), 15.3 (CH₂) ppm.

LRMS (FAB) *m/z* 315 (M + Na).

HRMS (ESI) *m/z*: [M + Na]⁺ calcd for C₁₆H₂₀NaO₂S, 315.1025; found, 315.1022.

IR 3522, 2920, 1319, 1134, 1084, 748.



Compound S19

To a solution of **11c** (84.8 mg, 0.290 mmol) in anhydrous CH₂Cl₂ (1.4 mL) was added PCC (94 mg, 0.44 mmol) and Celite (200 mg), and the mixture was stirred at rt for 7 h. After dilution with Et₂O, the mixture was filtered through a pad of SiO₂, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 5:1) to give **S19** (73.3 mg, 87%) as white solids.

¹H NMR (500 MHz, CDCl₃) δ 7.83 (d, *J* = 8.0, 2H), 7.37 (d, *J* = 8.0, 2H), 5.90 (ddt, *J* = 17.0, 10.0, 6.5, 1H), 5.21 (d, *J* = 10.0, 1H), 5.16 (d, *J* = 17.0, 1H), 3.89 (br s, 2H), 3.17 (d, *J* = 6.5, 2H), 2.63 (t, *J* = 7.0, 2H), 2.47 (s, 3H), 2.43 (br t, *J* = 7.0, 2H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 206.0 (C), 145.1 (C), 134.8 (C), 130.0 (CH), 129.6 (CH), 128.7 (CH), 119.2 (CH₂), 86.9 (C), 68.2 (C), 48.9 (CH₂), 47.6 (CH₂), 40.4 (CH₂), 21.6 (CH₃), 13.1 (CH₂) ppm.

LRMS (ESI) *m/z* 329 (M + K).

HRMS (ESI) m/z : $[M + K]^+$ calcd for $C_{16}H_{18}KO_3S$, 329.0608; found, 329.0609.

IR 2913, 1713, 1319, 1134, 1084, 748.

mp 55–59 °C.

Compound 11d

To a solution of **S19** (29.0 mg, 0.100 mmol) in anhydrous CH_2Cl_2 (1 mL) under an argon atmosphere was added a 1.0 M CH_2Cl_2 solution of $TiCl_4$ (0.10 mL, 0.10 mmol), and the mixture was stirred at rt for 5 min. Then, allyltrimethylsilane (0.03 mL, 0.2 mmol) was added, and the whole was stirred for 1 h at rt. To the mixture were added Et_2O and saturated aqueous $NaHCO_3$, and the organic layer was separated. The aqueous layer was extracted 3 times with Et_2O . The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. The residue was purified by column chromatography (hexane/ $EtOAc$ 2:1) to give **11d** (26.6 mg, 80%) as a white solid.

1H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 8.0, 2H), 7.37 (d, J = 8.0, 2H), 5.80 (ddt, J = 17.0, 10.0, 7.0, 2H), 5.17 (d, J = 10.0, 2H), 5.13 (d, J = 17.0, 2H), 3.91 (br s, 2H), 2.47 (s, 3H), 2.27 (brt, J = 8.0, 2H), 2.19 (d, J = 7.0, 4H), 1.64 (t, J = 8.0, 2H) ppm.

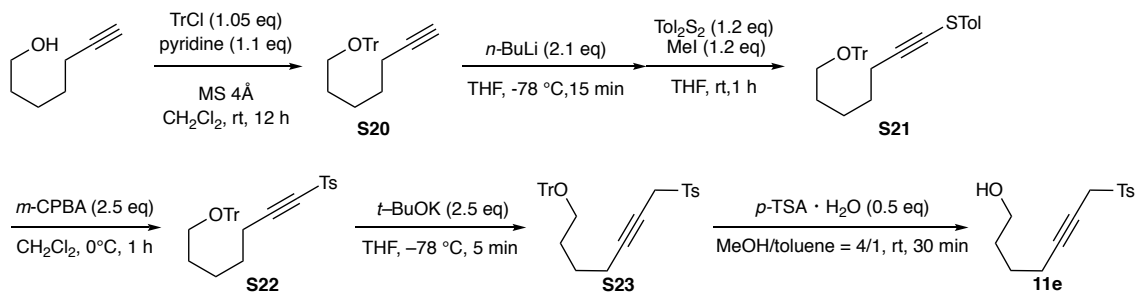
^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1 (C), 134.8 (CH), 133.1 (C), 129.6 (CH), 128.8 (CH), 119.1 (CH_2), 88.6 (C), 72.7 (C), 67.8 (C), 49.0 (CH_2), 43.4 (CH_2), 37.2 (CH_2), 21.7 (CH_3), 13.1 (CH_2) ppm.

LRMS (ESI) m/z 335 ($M + Na$).

HRMS (ESI) m/z : $[M + Na]^+$ calcd for $C_{19}H_{24}NaO_3S$, 355.1338; found, 355.1337.

IR 2974, 1639, 1597, 1315, 1138, 1045, 752.

mp 55–59 °C.



Compound S20

To a solution of hept-6-yn-1-ol (426 mg, 3.80 mmol) in anhydrous CH₂Cl₂ (50 mL) under an argon atmosphere were added TrCl (1.1 g, 4.0 mmol), pyridine (0.34 mL, 4.2 mmol), and MS4 Å (6 g), and the mixture was stirred at rt for 12 h. After dilution with EtOAc, the mixture was filtered through a pad of Celite and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 4:1) to give **S20** (1.33 g, 99%) as a colorless solid.

¹H NMR (500 MHz, CDCl₃) δ 7.44 (d, *J* = 8.5, 6H), 7.29 (dd, *J* = 8.0, 7.0, 6H), 7.23 (t, *J* = 7.0, 3H), 3.06 (t, *J* = 6.5, 2H), 2.18 (m, 2H), 1.93 (t, *J* = 2.5, 1H), 1.64 (quintet, *J* = 6.5, 2H), 1.52–1.47 (m, 4H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 144.4 (C), 128.6 (CH), 127.7 (CH), 126.8 (CH), 86.3 (C), 84.5 (C), 68.2 (CH), 63.3 (CH₂), 29.5 (CH₂), 28.3 (CH₂), 25.4 (CH₂), 18.3 (CH₂) ppm.

LRMS (ESI) *m/z* 393 (M + K).

HRMS (ESI) *m/z*: [M + K]⁺ calcd for C₂₆H₂₆KO, 393.1615; found, 393.1615.

IR 3294, 2936, 1489, 1447, 1072, 744.

mp 65–70 °C.

Compound S21

To a solution of **S20** (1.77 g, 5.00 mmol) in anhydrous THF (16 mL) cooled at –78 °C under an argon atmosphere was added a 1.6 M hexane solution of BuLi (3.8 mL, 6.0 mmol). After 15 min, a mixture of *p*-ditolyl disulfide (1.5 g, 6.0 mmol) and MeI (0.37 mL, 6.0 mmol) in anhydrous THF (20 mL), which had been stirred for 1 h, was added dropwise to the mixture. The cooling bath was removed, and the whole was stirred for 1 h. After addition of aqueous saturated NH₄Cl, the organic layer was separated. The aqueous layer was extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (hexane to hexane/EtOAc 5:1) to give **S21** (2.05 g, 86%) as colorless oil.

¹H NMR (500 MHz, CDCl₃) δ 7.44 (d, *J* = 8.0, 6H), 7.31–7.26 (m, 8H), 7.23–7.20 (m, 3H), 7.09 (d, *J* = 8.0, 2H), 3.07 (t, *J* = 6.5, 2H), 2.42 (t, *J* = 6.5, 2H), 2.30 (s, 3H), 1.65 (quintet, *J* = 6.5, 2H), 1.57–1.51 (m, 4H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 144.4 (C), 136.0 (C), 129.8 (CH), 128.6 (CH), 127.9 (C), 127.7 (CH), 126.8 (CH), 126.0 (CH), 99.1 (C), 86.3 (C), 65.3 (C), 63.4 (CH₂), 29.5 (CH₂), 28.5 (CH₂), 25.6 (CH₂), 20.9 (CH₃), 20.2 (CH₂) ppm.

LRMS (ESI) *m/z* 515 (M + K).

HRMS (ESI) m/z : $[M + K]^+$ calcd for $C_{33}H_{32}KOS$, 515.1805; found, 515.1803.

IR 2936, 1489, 1069, 802, 745.

Compound S22

To a solution of **S21** (1.62 g, 3.40 mmol) in CH_2Cl_2 (34 mL) cooled in an ice–water bath was added *m*-CPBA (2.0 g, 8.5 mmol), and the mixture was stirred for 1 h. After addition of saturated aqueous $Na_2S_2O_3$ (5 mL), the cooling bath was removed, and the mixture was stirred for 2 h. To the mixture was added saturated aqueous $NaHCO_3$, and the organic layer was separated. The aqueous layer was extracted 3 times with $CHCl_3$. The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. The residue was purified by column chromatography (toluene/ $CHCl_3$ 9:1) to give **S22** (1.54 g, 89%) as a white solid.

1H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 8.5, 2H), 7.42 (d, J = 7.0, 6H), 7.31–7.27 (m, 8H), 7.24–7.21 (m, 3H), 3.03 (t, J = 6.5, 2H), 2.42 (s, 3H), 2.32 (t, J = 7.0, 2H), 1.57 (m, 2H), 1.50 (m, 2H), 1.41 (m, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 145.0 (C), 144.3 (C), 139.1 (C), 129.8 (CH), 128.6 (CH), 127.7 (CH), 127.2 (CH), 126.9 (CH), 97.1 (C), 86.3 (C), 78.4 (C), 63.0 (CH_2), 29.3 (CH_2), 26.8 (CH_2), 25.6 (CH_2), 21.7 (CH_3), 18.9 (CH_2) ppm.

LRMS (ESI) m/z 531 ($M + Na$).

HRMS (ESI) m/z : $[M + Na]^+$ calcd for $C_{33}H_{32}NaO_3S$, 531.1964; found, 531.1965.

IR 2936, 2199, 1446, 1327, 1157, 1087, 748.

mp 103–107 °C.

Compound S23

A 1 M THF solution of *t*-BuOK (7.0 mL, 7.0 mmol) was diluted with anhydrous THF (15 mL) under an argon atmosphere and cooled at –78 °C. To the solution was added **S22** (1.42 g, 2.80 mmol) in anhydrous THF (13 mL) dropwise over 5 min, and the mixture was stirred for 5 min. The reaction was quenched by the addition of a 1 M THF solution of AcOH (7 mL), and the cooling bath was removed. After addition of saturated aqueous $NaHCO_3$, the organic layer was separated. The aqueous layer was extracted 3 times with Et_2O . The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. The residue was purified by column chromatography (hexane/ $EtOAc$ 5:1) to give **S23** (1.05 g, 74%) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ 7.81 (d, *J* = 8.0, 2H), 7.42 (d, *J* = 7.0, 6H), 7.31–7.28 (m, 8H), 7.23 (d, *J* = 7.0, 3H), 3.90 (br s, 2H), 3.03 (t, *J* = 6.0, 2H), 2.37 (s, 3H), 2.14 (br t, *J* = 6.5, 2H), 1.64–1.57 (m, 4H). ppm.

¹³C NMR (125 MHz, CDCl₃) δ 145.0 (C), 144.2 (C), 134.8 (C), 129.5 (CH), 128.7 (CH), 128.6 (CH), 127.7 (CH), 126.8 (CH), 88.4 (C), 86.3 (C), 67.8 (C), 62.7 (CH₂), 49.0 (CH₂), 29.0 (CH₂), 25.1 (CH₂), 21.6 (CH₂), 18.5 (CH₂) ppm.

LRMS (ESI) *m/z* 547 (M + K).

HRMS (ESI) *m/z*: [M + K]⁺ calcd for C₃₃H₃₂KO₃S, 547.1704; found, 547.1704.

IR 2947, 1489, 1447, 1327, 1134, 1069, 748.

mp 113–116 °C.

Compound 11e

To a solution of **S23** (916 mg, 1.80 mmol) in a 4:1 mixture of MeOH and toluene (18 mL) was added TsOH·H₂O (0.16 mg, 0.90 mmol), and the mixture was stirred at rt for 30 min. After addition of EtOAc and saturated aqueous NaHCO₃, the organic layer was separated. The aqueous layer was extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 1:1) to give **11e** (407 mg, 85%) as a light yellow oil.

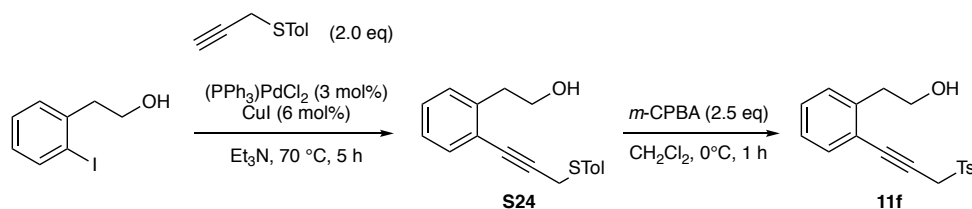
¹H NMR (500 MHz, CDCl₃) δ 7.84 (d, *J* = 8.0, 2H), 7.37 (d, *J* = 8.0, 2H), 3.92 (t, *J* = 2.0, 2H), 3.64 (br s, 2H), 2.47 (s, 3H), 2.21 (m, 2H), 1.61–1.53 (m, 4H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 145.1 (C), 134.7 (C), 129.6 (CH), 128.7 (CH), 88.3 (C), 67.8 (C), 61.9 (CH₂), 48.9 (CH₂), 31.5 (CH₂), 24.3 (CH₂), 21.6 (CH₃), 18.4 (CH₂). ppm.

LRMS (ESI) *m/z* 305 (M + K).

HRMS (ESI) *m/z*: [M + K]⁺ calcd for C₁₄H₁₈KO₃S, 305.0608; found, 305.0606.

IR 3367, 2936, 2199, 1597, 1323, 1153, 1088, 814.



Compound 11f

To a solution of 2-iodobenzeneethanol (248 mg, 1.00 mmol) in Et₃N (3 mL) under an argon atmosphere were added PdCl₂(PPh₃)₂ (21 mg, 0.030 mmol) and CuI (11 mg, 0.060 mmol), and the mixture was stirred at rt for 30 min. A solution of 3-p-tolylthiopropyne (0.33 g, 2.0 mmol) in Et₃N (1 mL) was added dropwise over 1 min. The mixture was stirred at 70 °C for 7 h, and then cooled to rt. After dilution with CHCl₃, the reaction was quenched by the addition of water, and the organic layer was separated. The aqueous layer was extracted 3 times with CHCl₃. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo to give crude **S24** as a yellow oil (278 mg), which was used in the next reaction without further purification.

To a solution of the crude sulfide (278 mg) in CH₂Cl₂ (10 mL) cooled in an ice–water bath was added *m*-CPBA (0.58 mg, 2.5 mmol), and the mixture was stirred for 30 min. After addition of saturated aqueous Na₂S₂O₃ (1 mL), the cooling bath was removed. After 2 h, saturated aqueous NaHCO₃ was added, and the organic layer was separated. The aqueous layer was extracted 3 times with CHCl₃. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 3:2) to give **11f** (116 mg, 37% over 2 steps) as brown oil.

¹H NMR (500 MHz, CDCl₃) δ 7.89 (d, *J* = 8.0, 2H), 7.39 (d, *J* = 8.0, 2H), 7.34 (d, *J* = 7.5, 1H), 7.30 (t, *J* = 7.5, 1H), 7.25 (d, *J* = 7.5, 1H), 7.18 (t, *J* = 7.5, 1H), 4.23 (s, 2H), 3.82 (t, *J* = 7.0, 2H), 3.00 (t, *J* = 7.0, 2H), 2.47 (s, 3H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 145.4 (C), 141.3 (C), 135.0 (C), 132.4 (CH), 129.9 (CH), 129.6 (CH), 129.2 (CH), 128.6 (CH), 126.3 (CH), 121.6 (C), 86.3 (C), 80.0 (C), 63.0 (CH₂), 49.6 (CH₂), 38.1 (CH₂), 21.7 (CH₃) ppm.

LRMS (ESI) *m/z* 353 (M + K).

HRMS (ESI) *m/z*: [M + K]⁺ calcd for C₁₈H₁₈KO₃S, 353.0608; found, 353.0608.

IR 1597, 1319, 1134, 1084, 1018, 756.

Compound 11f

Prepared from commercially available 2-iodobenzenepropanol using analogous procedure to that for **11f** gave the title compound (2.87g, 68%, 2 steps) as white solids.

¹H NMR (500 MHz, CDCl₃) δ 7.88 (d, *J* = 8.0, 2H), 7.37 (d, *J* = 8.0, 2H), 7.32 (d, *J* = 7.5, 1H), 7.29 (dd, *J* = 7.5, 6.5, 1H), 7.21 (d, *J* = 6.5, 1H), 7.15 (t, *J* = 7.5, 1H), 4.22 (s, 2H), 3.67 (t, *J* = 6.0, 2H), 2.83 (t, *J* = 8.0, 2H), 2.47 (s, 3H), 1.86 (tt, *J* = 8.0, 6.0, 2H) ppm.

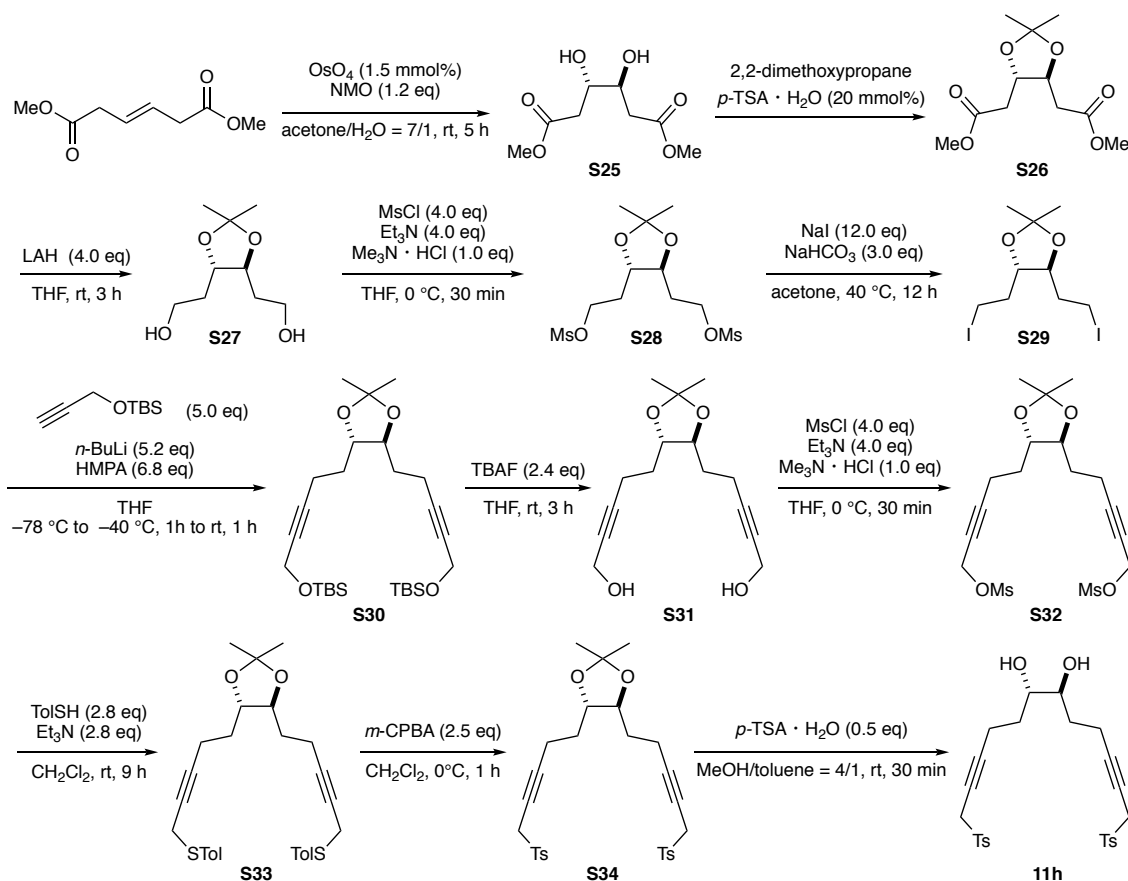
^{13}C NMR (125 MHz, CDCl_3) δ 145.4 (C), 144.9 (C), 134.9 (C), 132.4 (CH), 129.8 (CH), 129.2 (CH), 128.9 (CH), 128.6 (CH), 125.8 (CH), 121.0 (C), 86.3 (C), 79.9 (C), 62.1 (CH_2), 49.6 (CH_2), 33.8 (CH_2), 30.9 (CH_2), 21.6 (CH_3) ppm.

LRMS (ESI) m/z 351 ($\text{M} + \text{Na}$).

HRMS (ESI) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{20}\text{NaO}_3\text{S}$, 351.1025; found, 351.1025

IR 3526, 2936, 1597, 1315, 1134, 1084, 752.

mp 88–92 °C.



Compound S25

To a solution of dimethyl (E)-hex-3-enedioate (31.8 mL, 203 mmol) in a 7:1 mixture of acetone and water (615 mL) were added N-methylmorpholine-N-oxide (29 g, 244 mmol) and 4% aqueous OsO₄ (19 mL, 3.1 mmol), and the mixture was stirred at rt for 5 h. The reaction was quenched by the addition of NaHSO₃ (20 g), and the mixture was filtered through a pad of Celite. The filtrate was acidified with 3 N HCl and concentrated in vacuo. The residual solids were recrystallized from hexane–EtOAc (5:1) to give dimethyl **S25** (20.3 g, 48%) as white solids.

¹H NMR (500 MHz, CDCl₃) δ 3.99 (br s, 2H), 3.73 (s, 6H), 3.15 (br s, 2H), 2.68 (dd, *J* = 16.5, 8.5, 2H), 2.59 (dd, *J* = 16.5, 3.5, 2H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 173.0 (C), 69.8 (CH₃), 52.0 (CH₃), 37.8 (CH₃) ppm.

LRMS (ESI) *m/z* 229 (M + Na).

HRMS (ESI) *m/z*: [M + Na]⁺ calcd for C₈H₁₄NaO₆, 229.0683; found, 229.0681.

IR 3298, 1782, 1732, 1435, 1369, 1153, 1057, 768.

mp 72–76 °C.

Compound S26

To a solution of **S25** (20.1 g, 97.6 mmol) in 2,2-dimethoxypropane (485 mL) was added TsOH·H₂O (3.4 g, 20 mmol), and the mixture was stirred at rt for 12 h. The reaction was quenched by the addition of saturated aqueous NaHCO₃, and the organic layer was separated. The aqueous layer was extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 5:1) to give **S26** (19.7 g, 82%) as white solids.

¹H NMR (500 MHz, CDCl₃) δ 4.18–4.14 (m, 2H), 3.71 (s, 6H), 2.69–2.63 (m, 4H), 1.40 (s, 6H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 170.9 (C), 109.1 (C), 76.6 (CH₂), 51.8 (CH₃), 37.8 (CH₃), 27.0 (CH₂) ppm.

LRMS (ESI) *m/z* 269 (M + Na).

HRMS (ESI) *m/z*: [M + Na]⁺ calcd for C₁₁H₁₈NaO₆, 269.0996; found, 269.0997.

IR 2990, 1736, 1439, 1381, 1169, 1057, 841.

mp 37–41 °C.

Compound S27

To a suspension of LiAlH₄ (12 g, 0.32 mol) in anhydrous THF (270 mL) cooled in an ice–water bath was added a solution of **S26** (19.7 g, 79.9 mmol) in anhydrous THF (50 mL) dropwise over 20 min. The cooling bath was removed, and the mixture was stirred at rt for 3 h. Then, the mixture was cooled in an ice–water bath, and the reaction was quenched by the slow addition of saturated aqueous Rochelle salt (100 mL). After 1 h, the whole was diluted with Et₂O, and the organic layer was separated. The aqueous layer was extracted 3 times with Et₂O, and the combined organic layers were washed with brine, dried over Na₂SO₃, and concentrated in vacuo.

The residue was purified by column chromatography (hexane/EtOAc 1:2) to give **S27** (9.73 g, 64%) as colorless oil.

¹H NMR (500 MHz, CDCl₃) δ 3.87–3.85 (m, 2H), 3.85–3.81 (m, 4H), 2.32 (br s, 2H), 1.87–1.83 (m, 2H), 1.81–1.74 (m, 2H), 1.41 (s, 6H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 108.6 (C), 79.3 (CH), 60.1 (CH₂), 34.4 (CH₂), 27.1 (CH₃) ppm.

LRMS (ESI) *m/z* 213 (M + Na).

HRMS (ESI) *m/z*: [M + Na]⁺ calcd for C₉H₁₈NaO₄ 213.1097, found 213.1098.

IR 3360, 2936, 1373, 1219, 1045, 872.

Compound S31

To a solution of **S27** (9.42 g, 49.6 mmol), Et₃N (28 mL, 0.20 mol), and Me₃N·HCl (4.7 g, 50 mmol) in anhydrous THF (165 mL) cooled in an ice–water bath was added MsCl (15 mL, 0.20 mol) dropwise over 10 min, and the mixture was stirred for 30 min. The reaction was quenched by the addition of saturated aqueous NH₄Cl, and the organic layer was separated. The aqueous layer was extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo to give crude **S28** as yellow oil (18.1 g), which was used in the next reaction without further purification.

To a solution of the crude mesylate (18.1 g) in anhydrous acetone (500 mL) were added NaI (89 g, 0.60 mol) and NaHCO₃ (13 g, 0.15 mol), and the mixture was stirred at 40 °C in the dark for 12 h. After addition of saturated aqueous Na₂S₂O₃ (100 mL), the organic layer was separated. The aqueous layer was extracted 3 times with Et₂O. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo to give crude **S29** as a brown oil (20.9 g), which was used in the next reaction without further purification.

To a solution of **S29** (42 g, 0.25 mol) and HMPA (59 mL, 0.34 mol) in anhydrous THF (81 mL) cooled at –78 °C under an argon atmosphere was added a 1.6 M hexane solution of *n*-BuLi (0.16 L, 0.26 mol). After slowly warmed up to –40 °C, the mixture was stirred for 1 h. Then, the mixture was cooled to –78 °C, and a solution of the crude iodide (20.9 g) in anhydrous THF (80 mL) was added dropwise for 25 min. The cooling bath was removed, and the whole was stirred for 1 h. The reaction was quenched by the addition of saturated aqueous NH₄Cl, and the organic layer was separated. The aqueous layer was extracted 3 times with Et₂O. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was filtered through a short SiO₂ plug, which was rinsed with hexane. Concentration of the

combined filtrate gave crude **S30** as brown oil (61.2 g), which was used in the next reaction without further purification.

To a solution of the crude alkyne (61.2 g) in anhydrous THF (350 mL) was added a 1.0 M THF solution of TBAF (0.25 L, 0.25 mol), and the mixture was stirred for 3 h. The reaction was quenched by addition of saturated aqueous NH_4Cl , and the organic layer was separated. The aqueous layer was extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 2:1) to give **S31** (5.11 g, 39% over 4 steps) as colorless oil.

^1H NMR (500 MHz, CDCl_3) δ 4.26 (t, J = 2.0, 4H), 3.80–3.78 (m, 2H), 2.48–2.41 (m, 2H), 2.39–2.33 (m, 2H), 1.81–1.75 (m, 4H), 1.38 (s, 6H) ppm.

^{13}C NMR (125 MHz, CDCl_3) δ 108.5 (C), 85.4 (C), 79.2 (CH), 79.0 (C), 51.2 (CH_2), 31.8 (CH_2), 27.3 (CH_3), 15.5 (CH_2) ppm.

LRMS (ESI) m/z 289 ($\text{M} + \text{Na}$).

HRMS (ESI) m/z : [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{15}\text{H}_{22}\text{NaO}_4$ 289.1410, found 289.1410.

IR 3356, 2932, 1377, 1219, 1065, 1011, 864.

Compound S32

To a solution of **S31** (4.08 g, 15.3 mmol), Et_3N (8.6 mL, 61 mmol), and $\text{Me}_3\text{N}\cdot\text{HCl}$ (1.5 g, 15 mmol) in anhydrous THF (150 mL) cooled in an ice–water bath was added MsCl (4.8 mL, 61 mmol) dropwise over 10 min, and the mixture was stirred for 30 min. The reaction was quenched by addition of saturated aqueous NH_4Cl , and the organic layer was separated. The aqueous layer was extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 2:1) to give **S32** (5.69 g, 88%) as a brown oil.

^1H NMR (500 MHz, CDCl_3) δ 4.85 (s, 4H), 3.73–3.72 (m, 2H), 3.11 (s, 6H), 2.50–2.38 (m, 4H), 1.81–1.73 (m, 4H), 1.37 (s, 6H) ppm.

^{13}C NMR (125 MHz, CDCl_3) δ 108.6 (C), 89.7 (C), 78.9 (CH), 72.8 (C), 58.2 (CH_2), 38.8 (CH_3), 31.4 (CH_2), 27.2 (CH_3), 15.5 (CH_2) ppm.

LRMS (ESI) m/z 445 ($\text{M} + \text{Na}$).

HRMS (ESI) m/z : [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{17}\text{H}_{26}\text{NaO}_8\text{S}_2$ 445.0961, found 445.0960.

IR 3028, 1354, 1173, 934, 748.

Compound 11h

To a solution of p-thiocresol (4.7 g, 38 mmol) and Et₃N (5.3 mL, 38 mmol) in anhydrous CH₂Cl₂ (100 mL) under an argon atmosphere was added a solution of **S32** (5.66 g, 13.4 mmol) in anhydrous CH₂Cl₂ (30 mL) dropwise over 10 min. After 9 h, the solvent was removed in vacuo and the residue was dissolved in anhydrous CH₂Cl₂ (80 mL). To the solution cooled in an ice–water bath was added *m*-CPBA (15 g, 67 mmol), and the mixture was stirred for 30 min. After addition of saturated aqueous Na₂S₂O₃ (30 mL), the cooling bath was removed, and the mixture was stirred for 2 h. To the mixture was added saturated aqueous NaHCO₃, and the organic layer was separated. The aqueous layer was extracted 3 times with CHCl₃. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo to give crude **S33** as a yellow oil (6.80 g), which was used in the next reaction without further purification.

To a solution of the crude sulfone (6.80 g) in MeOH (110 mL) was added TsOH·H₂O (0.23 g, 1.3 mmol). After being heated under reflux for 5 h, the mixture was cooled to rt, and the reaction was quenched by the addition of water and saturated aqueous NaHCO₃. After dilution with EtOAc, the organic layer was separated. The aqueous layer was extracted 3 times with EtOAc. The combined organic layers were washed with water and brine, dried over Na₂SO₄, and concentrated in vacuo. The residual solids were recrystallized from hexane–EtOAc (2:1) to give 11h (2.35 g, 35% over 3 steps) as white solids.

¹H NMR (500 MHz, CDCl₃) δ 7.84 (d, *J* = 8.0, 4H), 7.38 (d, *J* = 8.0, 4H), 3.92 (t, *J* = 2.5, 4H), 3.57–3.52 (m, 2H) 2.47 (s, 6H), 2.36 (tt, *J* = 7.0, 2.5, 4H), 2.30 (d, *J* = 5.5, 2H), 1.66 (td, *J* = 7.0, 6.0, 4H) ppm.

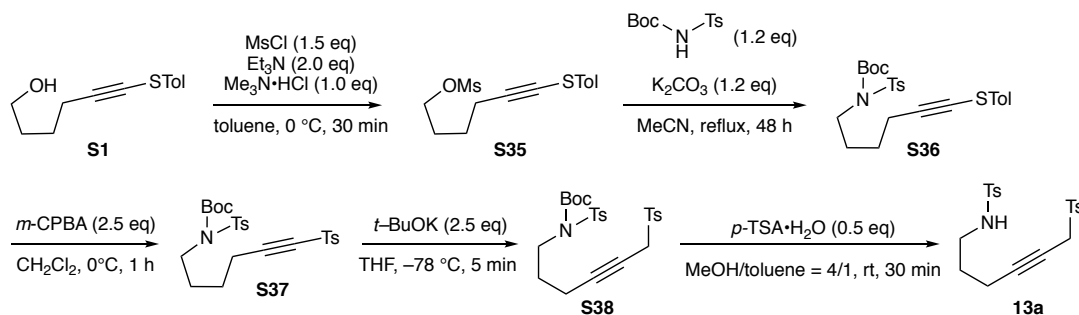
¹³C NMR (125 MHz, CDCl₃) δ 145.3 (C), 134.9 (C), 129.8 (CH), 128.7 (CH), 88.1 (C), 72.8 (CH), 68.3 (C), 49.0 (CH₂), 31.8 (CH₂), 21.7 (CH₃), 15.3 (CH₂) ppm.

LRMS (ESI) *m/z* 525 (M + Na).

HRMS (ESI) *m/z*: [M + Na]⁺ calcd for C₂₆H₃₀NaO₆S₂, 525.1376, found 525.1377.

IR 3495, 3318, 2920, 1597, 1304, 1142, 1083, 729.

mp 125–128 °C.



Compound S35

To a solution of **S1** (375 mg, 1.70 mmol), Et₃N (0.47 mL, 3.4 mmol), and Me₃N·HCl (0.16 g, 1.7 mmol) in anhydrous toluene (1.7 mL) cooled in an ice–water bath was added MsCl (0.20 mL, 2.5 mmol) dropwise over 1 min. After 30 min, the reaction was quenched by the addition of saturated aqueous NH₄Cl, and the organic layer was separated. The aqueous layer was extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (toluene/CHCl₃ 1:1) to give **S35** (477 mg, 94%) as a brown oil.

¹H NMR (500 MHz, CDCl₃) δ 7.29 (d, *J* = 8.0, 2H), 7.14 (d, *J* = 8.0, 2H), 4.28 (t, *J* = 6.5, 2H), 3.01 (s, 3H), 2.51 (t, *J* = 7.0, 2H), 2.33 (s, 3H), 1.91 (m, 2H), 1.72 (m, 2H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 136.3 (C), 129.9 (CH), 129.5 (C), 126.2 (CH), 97.7 (C), 69.3 (CH₂), 66.5 (C), 37.4 (CH₃), 28.2 (CH₂), 24.5 (CH₂), 20.9 (CH₃), 19.7 (CH₂) ppm.

LRMS (ESI) *m/z* 321 (*M* + Na).

HRMS (ESI) *m/z*: [*M* + Na]⁺ calcd for C₁₄H₁₈NaO₃S₂, 321.0590, found 321.0582

IR 2959, 1493, 1350, 1173, 930, 806, 733.

Compound S36

To a solution of **S35** (95.4 mg, 0.320 mmol) in anhydrous MeCN (16 mL) were added K₂CO₃ (54 mg, 0.39 mmol) and BocTsNH (0.11 g, 0.39 mmol). After being heated under reflux for 48 h, the mixture was cooled to rt. The reaction was quenched by the addition of water, and the organic layer was separated. The aqueous layer was extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 10:1) to give **S36** (1.45 g, 96%) as yellow oil.

¹H NMR (500 MHz, CDCl₃) δ 7.78 (d, *J* = 8.5, 2H), 7.31–7.28 (m, 4H), 7.13 (d, *J* = 8.0, 2H), 3.87 (t, *J* = 7.5, 2H), 2.51 (t, *J* = 7.0, 2H), 2.43 (s, 3H), 2.31 (s, 3H), 1.91 (m, 2H), 1.66 (m, 2H),

1.33 (s, 9H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 150.9 (C), 144.0 (C), 137.4 (C), 136.1 (C), 129.9 (CH), 129.7 (C), 129.2 (CH), 127.8 (CH), 126.1 (CH), 98.5 (C), 84.2(C), 65.9 (C), 46.5 (CH₂), 29.4 (CH₂), 27.8 (CH₃), 25.8 (CH₂), 21.6 (CH₃), 21.0 (CH₃), 20.0 (CH₂) ppm.

LRMS (ESI) *m/z* 496 (M + Na).

HRMS (ESI) *m/z*: [M + Na]⁺ calcd for C₂₅H₃₁NNaO₄S₂, 496.1587; found, 496.1588.

IR 3291, 2920, 1493, 1408, 1231, 1092, 1018, 806, 733.

Compound S37

To a solution of **S36** (5.02 g, 10.6 mmol) in CH₂Cl₂ (100 mL) cooled in an ice–water bath was added *m*-CPBA (6.1 g, 27 mmol), and the mixture was stirred for 30 min. After addition of saturated aqueous Na₂S₂O₃ (25 mL), the cooling bath was removed, and the mixture was stirred for 2 h. To the mixture was added saturated aqueous NaHCO₃, and the organic layer was separated. The aqueous layer was extracted 3 times with CHCl₃. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (hexane/ EtOAc 5:1) to give **S37** (5.09 g, 95%) as yellow oil.

¹H NMR (500 MHz, CDCl₃) δ 7.88 (d, *J* = 8.5, 2H), 7.76 (d, *J* = 8.5, 2H), 7.36 (d, *J* = 8.0, 2H), 7.32 (d, *J* = 8.0, 2H), 3.81 (t, *J* = 7.5, 2H), 2.45 (s, 3H), 2.44 (s, 3H), 1.81 (m, 2H), 1.63 (m, 2H), 1.33 (s, 9H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 150.8 (C), 145.1 (C), 144.2 (C), 138.9 (C), 137.1 (C), 129.9 (CH), 129.3 (CH), 127.7 (CH), 127.2 (CH), 96.3 (C), 84.3 (C), 78.7 (C), 46.1 (CH₂), 29.2 (CH₂), 27.8 (CH₃), 24.1 (CH₂), 21.7 (CH₃), 21.6 (CH₃), 18.6 (CH₂) ppm.

LRMS (ESI) *m/z* 528 (M + Na).

HRMS (ESI) *m/z*: [M + Na]⁺ calcd for C₂₅H₃₁NNaO₆S₂, 528.1485; found, 528.1487.

IR 2978, 2199, 1724, 1331, 1153, 1088, 999, 813, 756.

Compound 13a

A 1 M THF solution of *t*-BuOK (25 mL, 25 mmol) was diluted with anhydrous THF (50 mL) under an argon atmosphere and cooled at –78 °C. To the solution was added **S37** (5.05 g, 10.0 mmol) in THF (50 mL) dropwise over 20 min, and the mixture was stirred for 5 min. The reaction was quenched by the addition of a 1 M THF solution of AcOH (18 mL), and the cooling bath was removed. After addition of saturated aqueous NaHCO₂, the organic layer was

separated. The aqueous layer was extracted twice with Et₂O. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo to give crude **S38** as a brown amorphous solid (5.17 g), which was used in the next reaction without further purification.

To a solution of the crude propargyl sulfone (5.17 g) in CH₂Cl₂ (10 mL) was added TFA (0.5 mL, 5 mmol), and the mixture was stirred at rt for 10 h. The reaction was quenched by addition of saturated aqueous NaHCO₃, and the organic layer was separated. The aqueous layer was extracted 3 times with Et₂O. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (hexane/ EtOAc 3:2) to give **13a** (3.12 g, 77% over 2 steps) as white solids.

¹H NMR (500 MHz, CDCl₃) δ 7.82 (d, *J* = 8.5, 2H), 7.75(d, *J* = 7.5, 2H), 7.37 (d, *J* = 8.5, 2H), 7.32 (d, *J* = 7.5, 2H), 4.50 (brm, 1H), 3.88 (t, *J* = 2.5, 2H), 3.00 (q, *J* = 6.5, 2H), 2.47 (s, 3H), 2.43 (s, 3H), 2.23 (tt, *J* = 6.5, 2.5, 2H), 1.64 (quintet, *J* = 6.5, 2H) ppm.

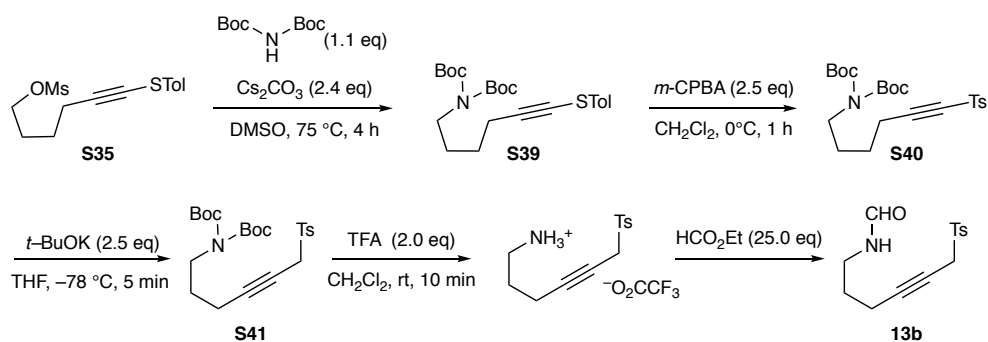
¹³C NMR (125 MHz, CDCl₃) δ 145.3 (C), 143.4 (C), 136.8 (C), 134.8 (C), 129.74 (CH), 129.72 (CH), 128.7 (CH), 127.0 (CH), 87.0 (C), 68.8 (C), 48.9 (CH₂), 41.9 (CH₂), 28.0 (CH₂), 21.7 (CH₃), 21.5 (CH₃), 16.0 (CH₂) ppm.

LRMS (ESI) *m/z* 444 (M + K).

HRMS (ESI) *m/z*: [M + K]⁺ calcd for C₂₀H₂₃KNO₄S₂, 444.0700; found, 444.0701

IR 3283, 2951, 1597, 1319, 1157, 1087, 752.

mp 91–96°C



Compound S39

To a solution of **S35** (1.22 g, 4.10 mmol) in anhydrous DMSO (21 mL) were added Cs₂CO₃ (3.2 g, 9.8 mmol) and Boc₂NH (0.98 g, 4.5 mmol). After being heated under reflux for 4 h, the mixture was cooled to rt, and water was added. The organic layer was separated, and the aqueous layer was extracted 3 times with EtOAc. The combined organic layers were washed

with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 10:1) to give **S39** (1.65 g, 96%) as yellow oil.

¹H NMR (500 MHz, CDCl₃) δ 7.28 (d, *J* = 8.0, 2H), 7.13 (d, *J* = 8.0, 2H), 3.60 (t, *J* = 8.0, 2H), 2.47 (t, *J* = 7.5, 2H), 2.32 (s, 3H), 1.72 (m, 2H), 1.60 (m, 2H), 1.501 (s, 9H), 1.498 (s, 9H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 152.4 (C), 135.8 (C), 129.7 (CH), 129.6 (C), 125.9 (CH), 98.4 (C), 81.9 (C), 65.5 (C), 45.6 (CH₂), 28.1 (CH₂), 27.8 (CH₃), 25.8 (CH₂), 20.7 (CH₃), 19.9 (CH₂) ppm.

LRMS (ESI) *m/z* 442 (M + Na).

HRMS (ESI) *m/z*: [M + Na]⁺ calcd for C₂₃H₃₃NNaO₄S, 442.2023; found, 442.2025.

IR 2978, 1744, 1694, 1366, 1250, 1134, 1111, 856, 802.

Compound S40

To a solution of **S39** (1.42 g, 3.40 mmol) in CH₂Cl₂ (34 mL) cooled in an ice–water bath was added *m*-CPBA (2.0 g, 8.5 mmol), and the mixture was stirred for 30 min. After addition of saturated aqueous Na₂S₂O₃ (5 mL), the cooling bath was removed, and the mixture was stirred for 2 h. To the mixture was added saturated aqueous NaHCO₃, and the organic layer was separated. The aqueous layer was extracted 3 times with CHCl₃. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (hexane/ EtOAc 5:1) to give **S40** (1.45 g, 94%) as yellow oil.

¹H NMR (500 MHz, CDCl₃) δ 7.87 (d, *J* = 8.0, 2H), 7.36 (d, *J* = 8.0, 2H), 3.54 (t, *J* = 7.0, 2H), 2.46 (s, 3H), 2.39 (t, *J* = 7.0, 2H), 1.62 (m, 2H), 1.56 (m, 2H), 1.49 (s, 18H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 152.6 (C), 145.1 (C), 139.0 (C), 129.9 (CH), 127.3 (CH), 96.5 (C), 82.4 (C), 78.6 (C), 45.3 (CH₂), 28.2 (CH₂), 28.0 (CH₃), 24.3 (CH₂), 21.7 (CH₃), 18.7 (CH₂) ppm.

LRMS (ESI) *m/z* 474 (M + Na)

HRMS (ESI) *m/z*: [M + Na]⁺ calcd for C₂₃H₃₃NNaO₆S, 474.1921; found, 474.1921.

IR 2203, 1732, 1694, 1366, 1331, 1134, 752.

Compound S41

A 1 M THF solution of *t*-BuOK (5.8 mL, 5.8 mmol) was diluted with anhydrous THF (10 mL) under an argon atmosphere and cooled at $-78\text{ }^{\circ}\text{C}$. To the solution was added **S40** (1.04 g, 2.30 mmol) in THF (13 mL) dropwise over 25 min, and the mixture was stirred for 5 min. The reaction was quenched by the addition of a 1 M THF solution of AcOH (5 mL), and the cooling bath was removed. After addition of saturated aqueous NaHCO_3 , the organic layer was separated. The aqueous layer was extracted twice with Et_2O . The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 3:1) to give **S41** (430 mg, 43%) as brown oil.

^1H NMR (500 MHz, CDCl_3) δ 7.84 (d, $J = 8.0$, 2H), 7.36 (d, $J = 8.0$, 2H), 3.90 (brs, 2H), 3.56 (t, $J = 7.0$, 2H), 2.46 (s, 3H), 2.19 (br t, $J = 7.0$, 2H), 1.72 (quintet, $J = 7.0$, 2H), 1.50 (s, 18H) ppm.

^{13}C NMR (125 MHz, CDCl_3) δ 152.5 (C), 145.1 (C), 134.9 (C), 129.7 (CH), 128.8 (CH), 87.6 (C), 82.3 (C), 68.0 (C), 49.0 (CH_2), 45.5 (CH_2), 28.0 (CH_3), 27.6 (CH_2), 21.7 (CH_3), 16.5 (CH_2) ppm.

LRMS (ESI) m/z 407 ($\text{M} + \text{Na}$).

HRMS (ESI) m/z : [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{23}\text{H}_{33}\text{NNaO}_6\text{S}$, 474.1921; found, 474.1925.

IR 3021, 2978, 1694, 1366, 1323, 1134, 748.

Compound 13b

To a solution of **S41** (452 mg, 1.00 mmol) in anhydrous CH_2Cl_2 (3 mL) was added TFA (0.15 mL, 2.0 mmol), and the mixture was stirred at rt for 10 min, and concentrated in vacuo. The residue was dissolved in CHCl_3 and washed with saturated aqueous NaHCO_3 , and the organic layer was separated. The aqueous layer was extracted 3 times with CHCl_3 . The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. The residue was dissolved in ethyl formate (2.2 mL, 25 mmol), and the mixture was heated under reflux for 22 h. After evaporation of ethyl formate in vacuo, the residue was purified by column chromatography (hexane/ EtOAc 1:3) to give **5b** (111 mg, 40% over 2 steps) as brown oil.

^1H NMR (500 MHz, CDCl_3) δ 8.20 (s, 1H), 7.83 (d, $J = 8.0$, 2H), 7.39 (d, $J = 8.0$, 2H), 5.99 (br m, 1H), 3.92 (br s, 2H), 3.38 (q, $J = 6.5$, 2H), 2.48 (s, 3H), 2.28 (t, $J = 6.5$, 2H), 1.74 (quintet, $J = 6.5$, 2H) ppm.

^{13}C NMR (125 MHz, CDCl_3) δ 161.6 (CH), 145.4 (C), 134.9 (C), 129.8 (CH), 128.5 (CH), 87.6 (C), 68.6 (C), 49.0 (CH_3), 37.4 (CH_3), 27.6 (CH_3), 21.7 (CH_3), 16.6 (CH_3) ppm.

LRMS (ESI) m/z 302 ($\text{M} + \text{Na}$).

HRMS (ESI) m/z : $[M + Na]^+$ calcd for $C_{14}H_{17}NNaO_3S$, 302.0821; found, 302.0821.

IR 3375, 3279, 2947, 1663, 1528, 1385, 1319, 1134, 1084, 748.

2. Migrative cyclization promoted by NHC (section 2.1)

General Procedure A. 2-(1-Tosylvinyl)tetrahydrofuran (**2a**). A 10 mL flame-dried test tube with a magnetic stirring bar was charged with **C2** (3.4 mg, 0.010 mmol) and Cs_2CO_3 (3.3 mg, 0.010 mmol). The test tube was filled with argon by the evacuation–refill process. After addition of toluene (0.6 mL), the mixture was stirred at 60 °C for 30 min. After the reaction mixture was allowed to cool to rt, a solution of **2a** (50.4 mg, 0.200 mmol) in toluene (0.4 mL) was added via cannula. The mixture was then stirred at 60 °C until TLC monitoring showed that **2a** was completely consumed. After dilution with EtOAc (2 mL), the organic layer was washed sequentially with aqueous 10% HCl, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4 , and concentrated. The residue was purified by column chromatography (hexane/EtOAc 5:2) to give **2a** (40.0 mg, 79%) as a colorless oil.

1H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.0, 2H), 7.33 (d, J = 8.0, 2H), 6.35 (d, J = 1.5, 1H), 6.05 (d, J = 1.5, 1H), 4.50 (t, J = 6.5, 1H), 3.92 (q, J = 8.0, 1H), 3.76 (q, J = 8.0, 1H), 2.44 (s, 3H), 2.21 (m, 1H), 1.92–1.83 (m, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7 (C), 144.5 (C), 136.5 (C), 129.8 (CH), 128.1 (CH), 122.9 (CH₂), 75.6 (CH), 68.6 (CH₂), 32.9 (CH₂), 25.6 (CH₂), 21.6 (CH₃) ppm.

Compound 2b

Procedure A, using **11b** (61.3 mg, 0.200 mmol) in place of **11a**, and purification by column chromatography (hexane/toluene 10:1) gave **2b** (50.9 mg, 83%) as a colorless oil.

1H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, J = 7.5, 2H), 7.63 (t, J = 7.5, 1H), 7.54 (t, J = 7.5, 2H), 6.35 (s, 1H), 6.14 (s, 1H), 4.55 (t, J = 8.0, 1H), 3.61 (d, J = 8.5, 1H), 3.57 (d, J = 8.5, 1H), 2.15 (dd, J = 13.0, 7.0, 1H), 1.56 (m, 1H), 1.42–1.40 (m, 10H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8 (C), 139.7 (C), 133.5 (CH), 129.2 (CH), 128.1 (CH), 123.0 (CH₂), 75.4 (CH₂), 44.5 (CH), 36.2 (CH₂), 35.0 (CH₂), 25.9 (C), 23.9 (CH₂), 23.3 (CH₂) ppm.

LRMS (ESI) m/z 345 (M + K).

HRMS (ESI) m/z : $[M + K]^+$ calcd for $C_{17}H_{22}KO_3S$, 345.0921; found, 345.0921.

IR 2920, 2851, 1447, 1308, 1142, 1057, 748.

Compound 2c

Procedure A, using **11c** (29.2 mg, 0.100 mmol) in place of **11a**, and purification by column chromatography (hexane/EtOAc 9:1) gave a 3:2 mixture of the title compounds (23.7 mg, 81%) as a colorless oil.

¹H NMR (500 MHz, CDCl₃) δ 7.74 (d, J = 8.0, 2H), 7.71 (d, J = 8.0, 2H), 6.34 (s, 1H), 6.05 (s, 1H), 5.81–5.70 (m, 1H), 5.10–5.02 (m, 2H), 4.62 (t, J = 7.0, 1H), 4.09 (quintet, J = 6.5, 1H), 2.43 (s, 3H), 2.31–2.25 (m, 2H), 2.23–2.16 (m, 1H), 2.05–1.99 (m, 1H), 1.89–1.81 (m, 1H), 1.63–1.56 (m, 1H); *cis* δ 7.74 (d, J = 8.0, 2H), 7.71 (d, J = 8.0, 2H), 6.36 (br s, 1H), 6.13 (br s, 1H), 5.81–5.70 (m, 1H), 5.10–5.02 (m, 2H), 4.48 (t, J = 7.0, 1H), 3.92 (quintet, J = 6.5, 1H), 2.43 (s, 3H), 2.38–2.31 (m, 1H), 2.31–2.25 (m, 2H), 2.23–2.16 (m, 1H), 1.99–1.94 (m, 1H), 1.63–1.56 (m, 1H) ppm.

¹³C NMR (125 MHz, CDCl₃) *trans* δ 152.74 (C), 144.48 (C), 136.7 (CH), 134.4 (C), 129.76 (CH), 128.2 (CH), 122.7 (CH₂), 117.1 (CH₂), 79.30 (CH), 75.8 (CH), 39.9 (CH₂), 33.2 (CH₂), 31.1 (CH₂), 21.6 (CH₃) ppm; *cis* δ 152.70 (C), 144.53 (C), 136.5 (CH), 134.4 (C), 129.79 (CH), 128.2 (CH), 123.1 (CH₂), 117.2 (CH₂), 79.25 (CH), 75.6 (CH), 39.9 (CH₂), 32.8 (CH₂), 30.3 (CH₂), 21.6 (CH₃). *cis* δ 152.8 (C), 139.7 (C), 133.5 (CH), 129.2 (CH), 128.1 (CH), 123.0 (CH₂), 75.4 (CH₂), 44.5 (CH), 36.2 (CH₂), 35.0 (CH₂), 25.9 (C), 23.9 (CH₂), 23.3 (CH₂) ppm.

LRMS (ESI) m/z 315 (M + Na).

HRMS (ESI) m/z : [M + Na]⁺ calcd for C₁₆H₂₀NaO₃S, 315.1025; found, 315.1025.

IR 2978, 2932, 1697, 1636, 1435.

The relative configuration was determined by NOESY correlation between the signals of the methine proton at the 5-position (4.62 ppm) and the allylic proton (2.31–2.25 ppm) for *trans*, and those of the methine protons at the 2- and 5-positions (3.92 and 4.48 ppm, respectively) for *cis*. The diastereomeric ratio was determined based on the integration area of ¹H NMR signals at 4.62 and 4.48 ppm.

Compound 2d

Procedure A, using **11d** (33.2 mg, 0.100 mmol) in place of **11a**, and purification by column chromatography (hexane/EtOAc 9:1) gave **2d** (23.3 mg, 70%) as a colorless oil.

¹H NMR (500 MHz, CDCl₃) δ 7.74 (d, J = 8.0, 2H), 7.32 (d, J = 8.0, 2H), 6.34 (s, 1H), 6.18 (s, 1H), 5.74 (m, 2H), 5.09–5.02 (m, 4H), 4.54 (t, J = 7.0, 1H), 2.44 (s, 3H), 2.27–2.23 (m, 5H), 1.82–1.71 (m, 3H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 152.6 (C), 144.5 (C), 136.5 (C), 133.9 (CH), 133.2 (CH), 129.8 (CH), 128.2 (CH), 122.9 (CH₂), 118.22 (CH₂), 118.17 (CH₂), 85.0 (C), 75.5 (CH), 44.0 (CH₂), 43.3 (CH₂), 34.2 (CH₂), 33.7 (CH₂), 21.6 (CH₃) ppm.

LRMS (ESI) *m/z* 355 (M + Na).

HRMS (ESI) *m/z*: [M + Na]⁺ calcd for C₁₉H₂₄NaO₃S, 355.1338; found, 355.1335.

IR 2974, 1639, 1597, 1315, 1138, 1045, 752.

Compound 2e

Procedure A, using **11e** (53.3 mg, 0.200 mmol) and C1 (3.4 mg, 0.010 mmol) in place of **11a** and C2, and purification by column chromatography (hexane/EtOAc 3:1) gave **2e** (36.2 mg, 68%) as colorless oil.

¹H and ¹³C NMR, IR, and MS were in good agreement with those reported.

Compound 2f

Procedure A, using **11f** (62.8 mg, 0.200 mmol) and C1 (3.4 mg, 0.010 mmol) in place of **11a** and C2, and purification by column chromatography (hexane/EtOAc 5:1) gave **2f** (36.5 mg, 58%) as colorless oil.

¹H NMR (500 MHz, CDCl₃) δ 7.85 (d, *J* = 8.0, 2H), 7.33 (d, *J* = 8.0, 2H), 7.19 (t, *J* = 7.5, 1H), 7.14 (t, *J* = 7.5, 1H), 7.09 (d, *J* = 7.5, 1H), 6.89 (d, *J* = 7.5, 1H), 6.67 (s, 1H), 5.81 (s, 1H), 5.55 (s, 1H), 3.44–3.36 (m, 2H), 2.85 (m, 1H), 2.61 (dt, *J* = 16.5, 3.5, 1H), 2.45 (s, 3H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 151.8 (C), 144.2 (C), 137.1 (C), 133.9 (C), 132.9 (C), 129.7 (CH₂), 129.5 (CH), 129.0 (CH), 128.5 (CH), 127.4 (CH), 126.8 (CH), 126.0 (CH), 72.2 (CH), 59.6 (CH₂), 27.7 (CH₂), 21.6 (CH₃) ppm.

LRMS (ESI) *m/z* 353 (M + K).

HRMS (ESI) *m/z*: [M + K]⁺ calcd for C₁₈H₁₈KO₃S, 353.0608; found, 353.0609.

IR 3021, 1315, 1215, 1134, 1080, 756.

Compound 2h

General Procedure B. A 10 mL flame-dried test tube with a magnetic stir bar was charged with C2 (3.4 mg, 0.010 mmol), Cs₂CO₃ (3.3 mg, 0.010 mmol), and **11h** (101 mg, 0.200 mmol). The flask was filled with argon by the evacuate–refill process. After addition of toluene (1.0 mL), the mixture was stirred at 60 °C until TLC monitoring showed the complete consumption of **11h**. After addition of EtOAc (2 mL), the organic layer was washed sequentially with 10%

aqueous HCl, saturated aqueous NaHCO₃, and brine, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography (toluene/Et₂O 2:1) to give a 3:2:2 mixture of **2h** (89.1 mg, 88%) as a yellow oil.

¹H NMR (500 MHz, CDCl₃) δ 7.71 (d, *J* = 8.0, 4H), 7.29 (d, *J* = 8.0, 4H), 6.34 (s, 3/7H, cis,trans), 6.32 (s, 8/7H, trans,trans and cis,cis), 6.28 (s, 3/7H, cis,trans), 6.07 (s, 10/7H, cis,trans and trans,trans), 6.03 (s, 4/7H, cis,cis), 4.58–4.46 (m, 2H), 4.03 (q, *J* = 7.0, 3/7H, cis,trans), 3.93 (m, 4/7H, trans,trans), 3.81 (m, 4/7H, cis,cis), 3.71 (q, *J* = 7.0, 3/7H, cis,trans), 2.33–2.15 (m, 4H), 2.03–1.80 (m, 4H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 152.33 (C), 152.29 (C), 152.22 (C), 152.20 (C), 144.61 (C), 144.57 (C), 144.55 (C), 136.5 (C), 136.3 (C), 129.79 (CH), 129.76 (CH), 128.17 (CH), 128.14 (CH), 123.4 (CH₂), 123.3 (CH₂), 123.1 (CH₂), 82.1 (CH), 81.9 (CH), 81.6 (CH), 76.6 (CH), 76.4 (CH), 75.9 (CH), 75.8 (CH), 33.7 (CH₂), 33.4 (CH₂), 32.7 (CH₂), 32.6 (CH₂), 28.7 (CH₂), 28.2 (CH₂), 27.6 (CH₂), 27.5 (CH₂), 21.6 (CH₂) ppm.

LRMS (ESI) *m/z* 525 (M + H).

HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₂₆H₃₀NaO₆S₂, 525.1376; found, 525.1375.

IR 1597, 1300, 1138, 1053, 752.

The relative configuration was determined by NOESY correlation between the signals of the methine protons at the 2- and 5-positions (4.03 and 4.48 ppm, respectively) for cis,trans, and those of the methine protons at the 2,2'- and 5,5'-positions (3.81 and 4.51 ppm, respectively) for cis,cis. The diastereomeric ratio was determined based on the integration area of ¹H NMR signals at 4.03 (cis,trans), 3.96–3.91 (trans,trans), and 3.83–3.78 ppm (cis,cis).

Compound 2g and Compound 12

Procedure B, using **11g** (65.7 mg, 0.200 mmol) and C1 (3.4 mg, 0.010 mmol) in place of **11h** and C2, and purification by column chromatography (hexane/ EtOAc 3:1) gave the title compounds as colorless oil (3.3 mg, 5%) and a yellow oil (5.8 mg, 6%), respectively.

2g:

¹H NMR (500 MHz, CDCl₃) δ 7.74 (d, *J* = 8.5, 2H), 7.28 (d, *J* = 8.5, 2H), 7.16–7.11 (m, 2H), 7.01 (dd, *J* = 7.5, 7.0, 1H), 6.90 (d, *J* = 7.5, 1H), 6.69 (s, 1H), 6.03 (s, 1H), 5.55 (s, 1H), 3.94 (dt, *J* = 12.5, 4.0, 1H), 3.58 (ddd, *J* = 12.5, 10.0, 3.5, 1H), 2.98 (m, 1H), 2.91 (m, 1H), 2.42 (s, 3H), 1.83–1.71 (m, 2H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 150.9 (C), 144.5 (C), 141.4 (C), 138.4 (C), 136.3 (C), 129.7 (CH₂), 129.6 (CH), 128.5 (CH), 128.14 (CH), 128.12 (CH), 127.5 (CH), 126.1 (CH), 78.3 (CH), 72.1 (CH₂), 34.0 (CH₂), 29.3 (CH₂), 21.6 (CH₃) ppm.

LRMS (ESI) *m/z* 367 (M + K).

HRMS (ESI) *m/z*: [M + K]⁺ calcd for C₁₉H₂₀KO₃S, 367.0765; found, 367.0766.

IR 2928, 1674, 1489, 1315, 1134, 1084, 756.

12:

¹H NMR (500 MHz, CDCl₃) δ 8.31 (s, 1H), 7.87 (d, *J* = 8.5, 2H), 7.51 (d, *J* = 8.5, 2H), 7.42 (d, *J* = 7.5, 1H), 7.37 (d, *J* = 8.5, 2H), 7.33 (d, *J* = 7.5, 1H), 7.27–7.22 (m, 4H), 4.42 (s, 2H), 3.63 (br m, 2H), 2.67 (t, *J* = 7.5, 2H), 2.46 (s, 3H), 2.41 (s, 3H), 1.79 (tt, *J* = 7.5, 6.5, 2H) ppm.

¹³C NMR (125 MHz, CDCl₃) δ 146.5 (CH), 144.84 (C), 144.75 (C), 141.4 (C), 136.9 (C), 136.1 (C), 133.4 (C), 131.6 (C), 130.1 (CH), 129.72 (CH), 129.67 (CH), 129.6 (CH), 128.7 (CH), 127.8 (CH), 127.6 (CH), 126.4 (CH), 61.6 (CH₂), 54.3 (CH₂), 33.1 (CH₂), 29.7 (CH₂), 21.64 (CH₃), 21.56 (CH₃) ppm.

LRMS (ESI) *m/z* 523 (M + K).

HRMS (ESI) *m/z*: [M + K]⁺ calcd for C₂₆H₂₈KO₅S₂, 523.1010; found, 523.1010.

IR 3534, 1597, 1304, 1146, 1084, 756.

The E-geometry was determined on the basis of the NOESY correlation between the protons at the 3-position of the benzenepropanol (7.42 ppm) and the allylic position (4.42 ppm).

Compound 14a and Compound 15a

Procedure A, using **13a** (81.1 mg, 0.200 mmol), C4 (3.3 mg, 0.010 mmol), and a proton sponge (4.3 mg, 0.020 mmol) under reflux, instead of **11a**, C2, and Cs₂CO₃ at 60 °C, and purification by column chromatography (hexane/Et₂O 2:3) gave a 15:1 mixture of the title compounds (66 mg, 75% and 5%, respectively) as a yellow oil.

¹H NMR (500 MHz, CDCl₃) **14a** δ 7.83 (d, *J* = 8.0, 2H), 7.44 (d, *J* = 8.0, 2H), 7.22–7.18 (m, 4H), 6.46 (s, 1H), 6.20 (s, 1H), 4.04 (dd, *J* = 7.5, 2.5, 1H), 3.58 (ddd, *J* = 9.5, 6.5, 3.5, 1H), 3.12 (td, *J* = 9.5, 6.5, 1H), 2.51 (s, 3H), 2.42 (s, 3H), 2.03 (m, 1H), 1.81–1.77 (m, 2H), 1.61 (m, 1H) ppm. **15a** δ 7.77 (d, *J* = 8.5, 2H), 7.63 (d, *J* = 8.5, 2H), 7.34 (d, *J* = 7.5, 2H), 7.29 (d, *J* = 7.5, 2H), 5.66 (t, *J* = 3.5, 1H), 4.45 (s, 2H), 3.22–3.20 (m, 2H), 2.46 (s, 3H), 2.43 (s, 3H), 1.96–1.94 (m, 2H), 1.31–1.29 (m, 2H).

¹³C NMR (125 MHz, CDCl₃) **14a** δ 151.4 (C), 144.8 (C), 143.8 (C), 135.7 (C), 133.1 (C), 129.8 (CH), 129.59 (CH), 128.6 (CH), 127.3 (CH), 125.0 (CH₂), 58.1 (CH), 49.5 (CH₂), 33.5 (CH₂), 23.3 (CH₂), 21.7 (CH₃), 21.50 (CH₃); **15a** δ 144.6 (C), 143.9 (C), 136.1 (C), 135.8 (C), 129.7 (CH), 129.56 (CH), 128.4 (CH), 127.4 (CH), 126.9 (C), 126.2 (CH), 61.7 (CH₂), 46.3 (CH₂), 22.6 (CH₂), 21.6 (CH₃), 21.55 (CH₃), 19.1 (CH₂). ppm.

LRMS (ESI) *m/z* 406 (M + H).

HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₂₀H₂₄NO₄S₂, 406.1141; found, 406.1140.

IR 2766, 2441, 1691, 1304, 1121, 756.

Compound 14b

Procedure A, using **13b** (55.9 mg, 0.200 mmol) under reflux, instead of **11a** at 60 °C, and purification by column chromatography (hexane/EtOAc 10:1) gave the title compound (41.4 mg, 74%) as a light yellow oil.

The two rotamers (ratio 2:1) were observed in ¹H and ¹³C NMR

¹H NMR (500 MHz, CDCl₃) major δ 7.78 (d, *J* = 8.0, 2H), 7.76 (s, 1H), 7.37 (d, *J* = 8.0, 2H), 6.43 (s, 1H), 5.78 (s, 1H), 4.57 (dd, *J* = 8.5, 2.5, 1H), 3.50 (t, *J* = 7.0, 2H), 2.46 (s, 3H), 2.21–2.15 (m, 1H), 2.01–1.96 (m, 1H), 1.93–1.86 (m, 2H); minor δ 8.11 (s, 1H), 7.80 (d, *J* = 7.5, 2H), 7.35 (d, *J* = 7.5, 2H), 6.37 (s, 1H), 5.73 (s, 1H), 4.54 (m, 1H), 3.60–3.56 (m, 2H), 2.44 (s, 3H), 2.33–2.24 (m, 1H), 2.21–2.15 (m, 1H), 2.01–1.96 (m, 1H), 1.93–1.86 (m, 2H).

¹³C NMR (125 MHz, CDCl₃) major δ 161.4 (CH), 153.3 (C), 145.3 (C), 135.4 (C), 130.2 (CH), 128.2 (CH), 124.1 (CH₂), 56.1 (CH), 44.0 (CH₂), 32.4 (CH₂), 22.0 (CH₂), 21.6 (CH₃); minor δ 160.4 (CH), 149.9 (C), 144.6 (C), 135.9 (C), 129.7 (CH), 128.1 (CH), 123.1 (CH₂), 54.8 (CH), 46.6 (CH₂), 32.2 (CH₂), 23.4 (CH₂), 21.6 (CH₃).

LRMS (ESI) *m/z* 302 (M + Na).

HRMS (ESI) *m/z*: [M + Na]⁺ calcd for C₁₄H₁₇NNaO₃S, 302.0821; found, 302.0821.

IR 1670, 1377, 1304, 1130, 1080, 814, 733

3. Transformation of vinyl sulfone into other functional groups

Compound 16

To a solution of **2e** (40.2 mg, 0.150 mmol) in anhydrous CH₂Cl₂ (15 mL) cooled at –78 °C under an argon atmosphere were added *t*-BuI (0.06 mL, 0.5 mmol), Et₃B (0.47 mL, 0.46 mmol), and Bu₃SnH (0.13 mL, 0.46 mmol), and the mixture was stirred for 6 h. Then, the mixture was

poured into saturated aqueous NaH_2PO_4 , and the organic layer was separated. The aqueous layer was extracted 3 times with Et_2O . The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. The residue was purified by column chromatography (hexane to hexane/ EtOAc 9:1) to give the title compound (47.7 mg, 98%) as white solids.

^1H NMR (500 MHz, CDCl_3) δ 7.77 (d, J = 8.5, 2H), 7.31 (d, J = 8.5, 2H), 3.86 (d, J = 11.0, 1H), 3.71 (dd, J = 11.0, 3.0, 1H), 3.23 (td, J = 11.0, 3.0, 1H), 2.96 (m, 1H), 2.43 (s, 3H), 1.86 (m, 1H), 1.81 (dd, J = 15.5, 4.0, 1H), 1.71 (dd, J = 15.5, 4.0, 1H), 1.52–1.42 (m, 5H), 0.89 (s, 9H).

^{13}C NMR (125 MHz, CDCl_3) δ 144.2 (C), 136.3 (C), 129.6 (CH), 129.2 (CH), 76.8 (CH), 68.5 (CH_2), 67.5 (CH), 36.1 (CH_2), 30.5 (C), 29.8 (CH_3), 29.4 (CH_2), 25.3 (CH_2), 23.7 (CH_2), 21.6 (CH_3).

LRMS (ESI) m/z 347 ($\text{M} + \text{Na}$).

HRMS (ESI) m/z : [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{18}\text{H}_{28}\text{NaO}_3\text{S}$, 347.1651; found, 347.1653.

IR 2951, 1288, 1130, 1084, 1045, 814, 756.

mp 88–89 °C

Compound 17

To a solution of **2e** (613 mg, 2.30 mmol) in anhydrous DMF (15 mL) under an argon atmosphere were added $\text{Pd}(\text{OAc})_2$ (52 mg, 0.23 mmol), 4-iodotoluene (1.3 g, 5.8 mmol), and K_3PO_4 (1.5 g, 6.9 mmol). After being heated at 120 °C for 24 h, the mixture was cooled to rt and diluted with EtOAc . After addition of water, the organic layer was separated. The aqueous layer was extracted 5 times with EtOAc . The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. The residue was purified by column chromatography (hexane/ EtOAc 3:1 and then hexane/toluene/ Et_2O = 5:3:2) to give the title compound (558 mg, 68%) as yellow oil.

^1H NMR (500 MHz, CDCl_3) δ 7.78 (d, J = 8.0, 2H), 7.32 (d, J = 8.0, 2H), 7.06–7.02 (m, 4H), 4.49 (t, J = 3.5, 1H), 3.83 (td, J = 10.0, 3.0, 1H), 3.73 (td, J = 10.0, 3.0, 1H), 3.61 (dd, J = 12.0, 3.0, 1H), 3.31 (dd, J = 13.5, 3.0, 1H), 3.13 (dd, J = 13.5, 12.0, 1H), 2.45 (s, 3H), 2.29 (s, 3H), 1.84–1.79 (m, 2H), 1.68–1.59 (m, 2H).

^{13}C NMR (125 MHz, CDCl_3) δ 144.9 (C), 144.3 (C), 135.9 (C), 134.7 (C), 133.8 (C), 129.1 (CH), 129.0 (CH), 128.9 (CH), 128.7 (CH), 105.3 (CH), 72.6 (CH), 66.1 (CH_2), 30.5 (CH_2), 21.47 (CH_2), 21.45 (CH_3), 20.9 (CH_2), 20.1 (CH_2).

LRMS (ESI) m/z 395 ($\text{M} + \text{K}$).

HRMS (ESI) m/z :

IR 1597, 1516, 1296, 1142, 1065, 748.

Compound 18

To a solution of **2e** (26.7 mg 0.100 mmol) in MeOH (2 mL) under an argon atmosphere was added morpholine (0.10 mL, 0.10 mmol), and the mixture was stirred at rt for 10 h. Then, the mixture was concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 2:1) to give an 85:15 mixture of the title compounds (35.0 mg, 99%) as white solids.

¹H NMR (500 MHz, CDCl₃) major δ 7.79 (d, *J* = 8.5, 2H), 7.30 (d, *J* = 8.5, 2H), 4.22 (d, *J* = 11.0, 1H), 3.90 (dd, *J* = 11.5, 1.5, 1H), 3.50–3.41 (m, 5H), 3.06 (br t, *J* = 5.0, 1H), 2.78 (dd, *J* = 14.0, 7.0, 1H), 2.72 (dd, *J* = 14.0, 5.0, 1H), 2.44 (s, 3H), 2.35–2.20 (m, 4H), 1.87 (m, 1H), 1.68 (ddd, *J* = 13.0, 11.0, 3.5, 1H), 1.45–1.52 (m, 4H); minor δ 7.78 (d, *J* = 8.5, 2H), 7.30 (d, *J* = 8.5, 2H), 4.10 (m, 1H), 3.90 (m, 1H), 3.40–3.39 (m, 2H), 3.36–3.32 (m, 2H), 3.31–3.17 (m, 2H), 2.97 (dd, *J* = 13.5, 9.0, 1H), 2.66 (dd, *J* = 13.5, 3.5, 1H), 2.44 (s, 3H), 2.35–2.20 (m, 4H), 1.90–1.85 (m, 1H), 1.72–1.64 (m, 1H), 1.57–1.54 (m, 4H).

¹³C NMR (125 MHz, CDCl₃) major δ 144.1 (C), 136.9 (C), 129.1 (CH), 128.99 (CH), 74.4 (CH), 68.4 (CH₂), 66.9 (CH), 66.6 (CH₂), 53.2 (CH₂), 53.1 (CH₂), 29.5 (CH₂), 25.3 (CH₂), 23.6 (CH₂), 21.5 (CH₃); minor δ 143.9 (C), 138.7 (C), 129.04 (CH), 128.4 (CH), 74.5 (CH), 69.1 (CH₂), 66.6 (CH), 66.4 (CH₂), 53.9 (CH₂), 53.0 (CH₂), 27.5 (CH₂), 25.7 (CH₂), 23.1 (CH₂), 21.5 (CH₃).

LRMS (ESI) *m/z* 354 (M + H).

HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₁₈H₂₈NO₄S 354.1734, found 354.1734.

IR 2940, 2851, 1454, 1142, 1115, 1084, 752.

mp 82–85 °C

Compound 19

To a suspension of 10% Na(Hg) (2.3 g, 10 mmol) and Na₂HPO₄ (0.57 mg, 4.0 mmol) in anhydrous MeOH (10 mL) cooled in an ice–water bath was added a solution of **17** (357 mg, 1.00 mmol) in anhydrous MeOH (3 mL), and the mixture was stirred at rt for 17 h. After addition of water and Et₂O, and the organic layer was separated. The aqueous layer was extracted 3 times with Et₂O. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. To the residue were added 10% Pd/C (containing ca. 55% water, 40 mg, 17 μmol), MS4 Å (300 mg), and anhydrous THF (10 mL), and the mixture was

stirred under a H₂ atmosphere at rt for 20 h. The mixture was filtered through a pad of Celite, which was washed successively with Et₂O. The combined filtrate was concentrated in vacuo, and the residue was purified by column chromatography (pentane/Et₂O 20:1) to give the title compound (127 mg, 62% over 2 steps) as a colorless oil

¹H NMR (500 MHz, CDCl₃) δ 7.09 (s, 4H), 4.00 (ddd, *J* = 11.0, 2.5, 2.0, 1H), 3.42 (td, *J* = 11.5, 2.0, 1H), 3.24 (m, 1H), 2.72 (ddd, *J* = 13.5, 10.0, 5.5, 1H), 2.62 (ddd, *J* = 13.5, 9.5, 7.0, 1H), 2.32 (s, 3H), 1.83–1.76 (m, 2H), 1.69–1.62 (m, 1H), 1.60 (m, 1H), 1.57–1.53 (m, 1H), 1.51–1.47 (m, 2H), 1.29 (qd, *J* = 12.5, 2.0, 1H).

¹³C NMR (125 MHz, CDCl₃) δ 139.2 (C), 134.9 (C), 128.9 (CH), 128.3 (CH), 76.8 (CH), 68.4 (CH₂), 38.4 (CH₂), 31.9 (CH₂), 31.2 (CH₂), 26.1 (CH₂), 23.5 (CH₂), 20.9 (CH₃).

LRMS (ESI) *m/z* 227 (M + Na).

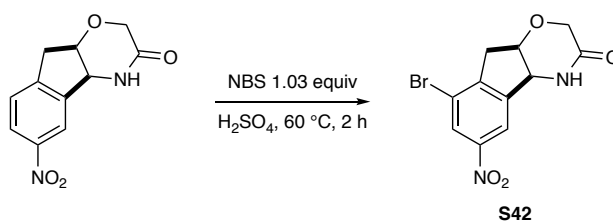
HRMS (ESI) *m/z*: [M + Na]⁺ calcd for C₁₄H₂₀NaO, 227.1406; found, 227.1392.

IR 2932, 2843, 1516, 1088, 1045, 810, 733.

Chapter 3

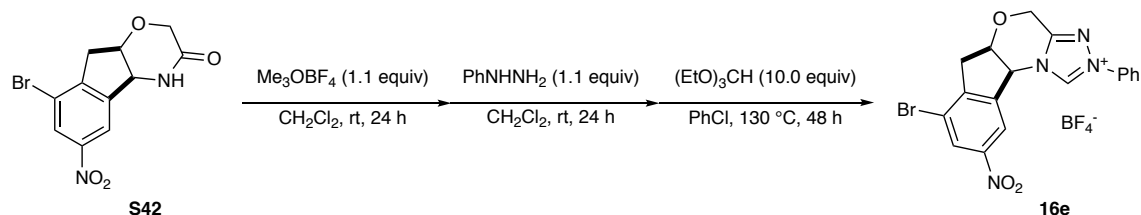
1. Preparation of NHC precursor

Compound S42



(4aR,9aS)-6-nitro-4,4a,9,9a-tetrahydroindeno[2,1-b][1,4]oxazin-2(3H)-one¹ (513.2 mg, 2.19 mmol) was dissolved in concd sulfuric acid (2.2 mL) and heated to 60 °C. N-Bromosuccinimide (401.7 mg, 2.26 mmol) was added in three portions over 30 min. The reaction mixture was stirred at 60 °C for an additional 2 h and then poured onto ice. The precipitate was filtered off and washed with cold water and hexane affording **S42** (636 mg, 93%) as white solids, which was used in the next step without further purification.

Compound 16e



To a solution of **S1** (997 mg, 3.2 mmol) in CH₂Cl₂ (64 mL) was added MeO₃BF₄ (545 mg, 3.5 mmol), and the mixture was stirred for 24 h at rt. PhNHNH₂ (0.35 mL, 3.5 mmol) was then added, and the mixture was stirred for another 24 h. The mixture was concentrated *in vacuo*, and the residue was dissolved in PhCl (32 mL) followed by addition of (EtO)₃CH (2.7 mL, 5.0 mmol). The mixture was heated at 130 °C for 24 h open to the atmosphere. (EtO)₃CH (2.7 mL, 5.0 mmol) was then added followed by continued stirring for 24 h. The whole mixture was concentrated *in vacuo* to remove the solvent. Column chromatography (CHCl₃:Acetone = 3:1 to 2:1) and recrystallization from EtOAc gave the title compound (817 mg, 51%) as light brown solids of mp

¹H NMR (400 MHz, acetone-d₆) δ 11.4 (s, 1H), 8.60 (s, 1H), 8.48 (s, 1H), 8.60-8.48 (m, 2H), 7.77-7.73 (m, 3H), 6.54 (s, 1H), 5.44 (d, *J* = 16.1, 1H), 5.33-5.29 (m, 2H), 3.73 (dd, *J* = 18.1, 5.5 Hz, 1H), 3.40 (d, *J* = 18.1 Hz, 1H) ppm.

¹³C NMR (100 MHz, acetone-d₆) δ 151.1 (C), 149.8 (C), 149.4 (C), 142.0 (CH), 140.0 (C), 136.4 (C), 132.0 (CH), 131.2 (CH), 128.7 (CH), 122.3 (CH), 120.9 (C), 120.6 (CH), 77.5 (CH), 63.0 (CH), 61.2 (CH₂), 39.8 (CH₂).

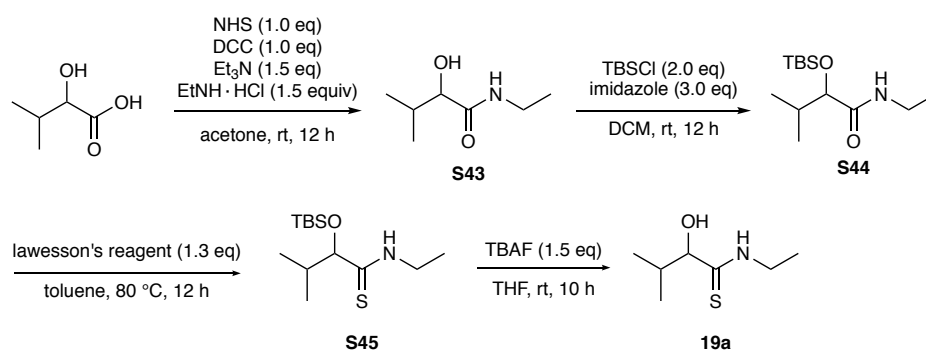
LRMS (ESI) *m/z* 413 (M)⁺.

HRMS (ESI) *m/z*: [M]⁺ calcd for C₁₈H₁₄BrN₄O₃, 413.0244; found, 413.0243.

IR 1589, 1531, 1350, 1061, 764.

mp 245 °C (decomp.)

2. General procedure for the preparation of α-hydroxy thioamide



Compound S43

To a solution of 2-hydroxy-3-methylbutanoic acid (2.15 g, 18.2 mmol) and N-hydroxysuccinimide (2.10 g, 18.2 mmol) in acetone (50 mL) was added *N,N'*-Dicyclohexylcarbodiimide (3.80 g, 18.2 mmol) at 0 °C under argon atmosphere. The mixture was stirred at this temperature for 2 h, then a solution of ethylamine hydrochloride (1.94 g, 27.3 mmol) and triethylamine (3.8 mL, 27.3 mmol) in acetone (5 mL) was added. The cooling bath was removed and the reaction mixture was stirred for 12 h. After filtration, the cake of dicyclohexylurea was washed with acetone (2 × 15 mL). The solvent was removed under reduced pressure, and the residue was dissolved with EtOAc. The solution was washed successively with saturated aqueous NaHCO₃, water, 1 M HCl, and brine, then dried over Na₂SO₄. The aqueous layer was extracted 3 times with EtOAc. The combined organic layers were dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 2:1) to give **S43** (1.29 g, 49%) as colorless solids.

¹H NMR (400 MHz, CDCl₃) δ 6.33 (s, 1H), 3.96 (dd, *J* = 4.9, 3.2, 1H), 3.40–3.31 (m, 2H), 2.37 (d, *J* = 4.9, 1H), 2.16 (septet d, *J* = 7.1, 3.2, 1H), 1.17 (t, *J* = 7.1, 3H), 1.03 (d, *J* = 7.1, 3H), 0.86 (d, *J* = 7.1, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 172.9 (C), 76.3 (CH), 34.0 (CH₂), 31.9 (CH), 19.2 (CH₃), 15.4 (CH₃), 14.9 (CH₃).

LRMS (ESI) *m/z* 146 (*M* + *H*).

HRMS (ESI) *m/z*: [*M* + *H*]⁺ calcd for C₇H₁₆NO₂ 146.1176, found 146.1177.

IR 3345, 2963, 1639, 1539, 1018, 1084, 752.

mp 87–88 °C

Compound 19a

tert-Butyldimethylsilyl chloride (1.08 g, 7.2 mmol), imidazole (520 mg, 7.6 mmol) and **S43** (760 mg, 4.8 mmol) were stirred in CH₂Cl₂ (100 mL) for 12 h at rt. The solution was diluted with water (20 mL) and the organic layer was separated. The aqueous layer was extracted 3 times with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, and concentrated in vacuo. Lawesson's reagent (3.52 g, 8.7 mmol) and toluene (110 mL) was added to the residue. This solution was stirred at 80 °C for 12 h under argon atmosphere. The reaction mixture was concentrated in vacuo and diluted with hexane/EtOAc = 20:1, then filtered through a silica gel pad to give crude **S45**, which was used in the next reaction without further purification.

To a solution of the crude **S45**, (1.58 g) in anhydrous THF (11 mL) was added a 1.0 M THF solution of TBAF (10.7 mL, 10.7 mmol), and the mixture was stirred for 3 h. The reaction was quenched by addition of saturated aqueous NH₄Cl, and the organic layer was separated. The aqueous layer was extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 5:1) to give **19a** (665 mg, 26% over 3 steps) as white solids.

¹H NMR (400 MHz, CDCl₃) δ 8.18 (br, s, 1H), 4.29 (d, *J* = 2.9, 1H), 3.81-3.68 (m, 2H), 2.54-2.47 (m, 1H), 1.30 (t, *J* = 7.4, 3H), 1.06 (d, *J* = 6.8, 3H), 0.78 (d, *J* = 6.8, 3H) ppm.

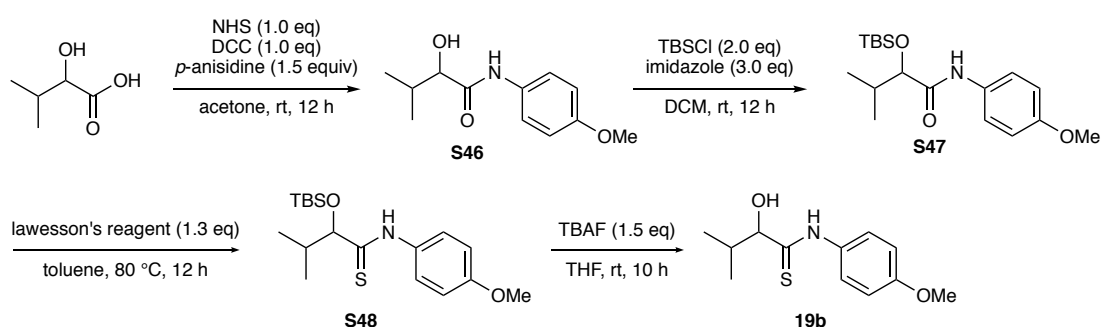
¹³C NMR (100 MHz, CDCl₃) δ 203.3 (C), 82.1 (CH), 40.0 (CH₂), 33.9 (CH), 19.9 (CH₃), 14.3 (CH₃), 13.2 (CH₃).

LRMS (ESI) *m/z* 162 (*M* + *H*).

HRMS (ESI) *m/z*: [*M* + *H*]⁺ calcd for C₇H₁₆NOS, 162.0947; found, 162.0949.

IR 3271, 2963, 1551, 1049, 1003, 937, 779.

mp 71–72 °C



Compound S46

To a solution of 2-hydroxy-3-methylbutanoic acid (2.36 g, 20.0 mmol) and N-hydroxysuccinimide (2.30 g, 20.0 mmol) in acetone (50 mL) was added *N,N'*-Dicyclohexylcarbodiimide (4.13 g, 20.0 mmol) at 0 °C under argon atmosphere. The mixture was stirred at this temperature for 2 h, then added *p*-Anisidine (3.70 g, 30 mmol). The cooling bath was removed and the reaction mixture was stirred for 12 h. After filtration, the cake of dicyclohexylurea was washed with acetone (2 × 15 mL). The solvent was removed under reduced pressure, and the residue was dissolved with EtOAc. The solution was washed successively with saturated aqueous NaHCO₃, water, 1 M HCl, and brine, then dried over Na₂SO₄. The aqueous layer was extracted 3 times with EtOAc. The combined organic layers were dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 2:1) to give brown solids, which were recrystallized from hexane–EtOAc (9:1) to give **S46** (3.48 g, 78%) as brown solids.

¹H NMR (400 MHz, CDCl₃) δ 8.19 (s, 1H), 7.48 (dt, *J* = 9.1, 3.2, 2H), 6.88 (dt, *J* = 9.1, 3.2, 2H), 4.12 (dd, *J* = 5.1, 3.2, 1H), 3.80 (s, 3H), 2.38 (d, *J* = 5.1, 1H), 2.32 (septet d, *J* = 6.9, 3.2, 1H), 1.08 (d, *J* = 6.9, 3H), 0.93 (d, *J* = 6.9, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 170.9 (C), 156.6 (C), 130.4 (C), 121.6 (CH), 114.2 (CH), 55.5 (CH), 55.5 (CH₃), 31.9 (CH), 19.2 (CH₃), 15.5 (CH₃).

LRMS (ESI) *m/z* 224 (M + H).

HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₁₂H₁₈NO₃, 224.1281, found 224.1283.

IR 3360, 2963, 2932, 1655, 1512, 1246, 1030, 829.

mp 105–106 °C

Compound 19b

Analogous procedure to that for **19a**, using **S46** (3.48 g, 15.6 mmol) in place of **S43**, and purification by column chromatography (hexane/ EtOAc 5:1) gave white solids, which were recrystallized from hexane–EtOAc (6:1) to give **19b** (896 mg, 24% over 3 steps) as colorless solids.

¹H NMR (400 MHz, CDCl₃) δ 9.72 (s, 1H), 7.67 (d, *J* = 8.8, 2H), 6.93 (d, *J* = 8.8, 2H), 4.44 (d, *J* = 3.2, 1H), 3.83 (s, 3H), 2.62 (septet d, *J* = 7.1, 3.2, 1H), 1.12 (d, *J* = 7.1, 3H), 0.87 (d, *J* = 7.1, 3H).

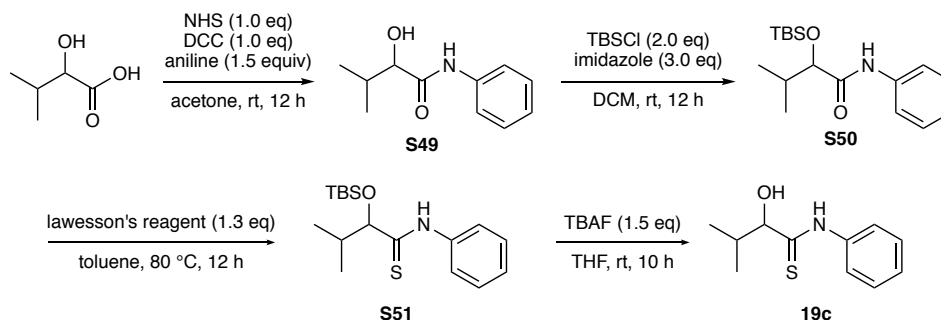
^{13}C NMR (100 MHz, CDCl_3) δ 201.7 (C), 158.2 (C), 130.9 (C), 124.9 (CH), 114.1 (CH), 83.0 (CH), 55.5 (CH_3), 34.3 (CH), 20.0 (CH_3), 14.0 (CH_3).

LRMS (ESI) m/z 240 ($\text{M} + \text{H}$).

HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{18}\text{NO}_2\text{S}$, 240.1053, found 240.1052.

IR 3267, 2963, 1512, 1381, 1246, 1011, 833, 748.

mp 121–123 $^\circ\text{C}$



Compound **S49**

Analogous procedure to that for **S49**, using aniline (2.74 mL, 30 mmol, 1.5 equiv) in place of *p*-Anisidine, and purification by column chromatography (hexane/ EtOAc 2:1) gave orange solids, which were recrystallized from hexane–EtOAc (5:1) to give **S49** (3.13 g, 81%) as white solids.

^1H NMR (400 MHz, CDCl_3) δ 8.31 (s, 1H), 7.58 (dd, J = 8.6, 1.0, 2H), 7.34 (t, J = 8.1, 2H), 7.13 (t, J = 7.5, 1H), 4.14 (dd, J = 5.1, 3.2, 1H), 2.37 (d, J = 5.1, 1H), 2.33 (septet d, J = 7.1, 3.2, 1H), 1.09 (d, J = 7.1, 3H), 0.93 (d, J = 7.1, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 171.1 (C), 137.2 (C), 129.1 (CH), 124.5 (CH), 119.8 (CH), 76.7 (CH), 32.0 (CH), 19.2 (CH_3), 15.5 (CH_3).

LRMS (ESI) m/z 194 ($\text{M} + \text{H}$).

HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{11}\text{H}_{16}\text{NO}_2$, 194.1176, found 194.1174.

IR 3356, 2928, 1659, 1531, 1443, 1315, 1022, 752.

mp 135–136 $^\circ\text{C}$

Compound **19c**

Analogous procedure to that for **19a**, using **S49** (3.13 g, 16.2 mmol) in place of **S43**, and purification by column chromatography (hexane/ EtOAc 5:1) gave white solids, which were recrystallized from hexane–EtOAc (9:1) to give **19c** (1.02 g, 30% over 3 steps) as yellow solids.

¹H NMR (400 MHz, CDCl₃) δ 9.83 (s, 1H), 7.81 (dd, *J* = 8.8, 1.2, 2H), 7.42 (t, *J* = 8.3, 2H), 7.28 (t, *J* = 7.6, 1H), 4.45 (d, *J* = 3.0, 1H), 2.64 (septet d, *J* = 6.8, 3.0, 1H), 1.13 (d, *J* = 6.8, 3H), 0.87 (d, *J* = 6.8, 3H).

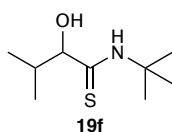
¹³C NMR (100 MHz, CDCl₃) δ 202.5 (C), 137.8 (C), 129.0 (CH), 127.1 (CH), 123.3 (CH), 83.0 (CH), 34.4 (CH), 20.1 (CH₃), 14.4 (CH₃).

LRMS (ESI) *m/z* 210 (M + H).

HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₁₁H₁₆NOS, 210.0947, found 210.0946.

IR 3264, 2963, 1520, 1381, 1007, 752.

mp 71–72 °C



Compound 19f

Analogous procedure to that for **19a**, using **S46** (3.48 g, 0.200 mmol) in place of **S43** and C2, and purification by column chromatography (hexane/ EtOAc 3:1) gave the title compounds as colorless oil (3.3 mg, 5%) and a yellow oil (5.8 mg, 6%), respectively.

gave the title compound.

¹H NMR (400 MHz, CDCl₃) δ 7.93 (br, s, 1H), 4.10 (d, *J* = 3.4, 1H), 2.46–2.38 (m, 1H), 1.60 (s, 9H), 0.78 (d, *J* = 6.9, 3H), 0.96 (d, *J* = 6.9, 3H) ppm.

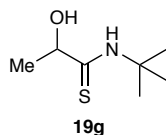
¹³C NMR (100 MHz, CDCl₃) δ 202.0 (C), 82.8 (CH), 55.4 (C), 34.0 (CH), 27.7 (CH₃), 19.9 (CH₃), 14.4 (CH₃).

LRMS (ESI) *m/z* 190 (M + H).

HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₉H₂₀NOS, 190.1260; found, 190.1261.

IR 3271, 2967, 1531, 1366, 1211, 1015, 957.

mp 96–97 °C



Compound 19g

Analogous procedure to that for **19a** gave the title compound.

¹H NMR (400 MHz, CDCl₃) δ 7.96 (br, s, 1H), 4.40 (q, *J* = 6.6, 1H), 1.57 (s, 1H), 1.51 (d, *J* = 6.6, 3H) ppm.

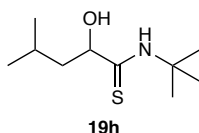
¹³C NMR (100 MHz, CDCl₃) δ 203.8 (C), 75.4 (CH), 55.3 (C), 27.7 (CH₃), 24.6 (CH₃).

LRMS (ESI) m/z 162 (M + H).

HRMS (ESI) m/z : [M + H]⁺ calcd for C₇H₁₆NOS, 162.0947; found, 162.0948.

IR 3252, 1539, 1420, 1366, 1215, 1057.

mp 100–101 °C



Compound 19h

Analogous procedure to that for **19a** gave the title compound.

¹H NMR (400 MHz, CDCl₃) δ 7.93 (br, s, 1H), 4.27 (dd, J = 10.3, 2.7, 1H), 2.76 (s, 1H), 1.88–1.77 (m, 2H), 1.57 (s, 9H), 1.52–1.45 (m, 1H), 0.99 (d, J = 6.4, 3H), 0.96 (d, J = 6.4, 3H) ppm.

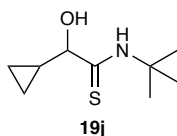
¹³C NMR (100 MHz, CDCl₃) δ 203.9 (C), 77.9 (CH), 55.3 (C), 47.1 (CH₂), 27.7 (CH₃), 25.0 (CH), 23.6 (CH₃), 21.4 (CH₃).

LRMS (ESI) m/z 204 (M + H).

HRMS (ESI) m/z : [M + H]⁺ calcd for C₁₀H₂₂NOS, 204.1417; found, 204.1416.

IR 3298, 2959, 1528, 1367, 1211, 1053, 968.

mp 50–51 °C



Compound 19j

Analogous procedure to that for **19a** gave the title compound.

¹H NMR (400 MHz, CDCl₃) δ 7.80 (br, s, 1H), 3.62 (d, J = 7.72, 1H), 1.58 (s, 9H), 1.51–1.07 (m, 1H), 0.71–0.64 (m, 1H), 0.60–0.53 (m, 2H), 0.51–0.48 (m, 2H) ppm.

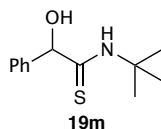
¹³C NMR (100 MHz, CDCl₃) δ 200.7 (C), 78.0 (CH), 53.5 (C), 25.7 (CH₃), 15.9 (CH), 1.6 (CH₂), 0.0 (CH₂).

LRMS (ESI) m/z 210 (M+Na).

HRMS (ESI) m/z : [M + Na]⁺ calcd for C₉H₁₇NNaOS, 210.0923; found, 210.0924.

IR 3298, 1528, 1211, 1022.

mp 58–59 °C



Compound 19m

Analogous procedure to that for **19a** gave the title compound.

¹H NMR (400 MHz, CDCl₃) δ 7.39–7.26 (m, 5H), 5.02 (d, *J* = 3.44, 1H), 4.27 (d, *J* = 3.64, 1H), 1.49 (s, 9H) ppm.

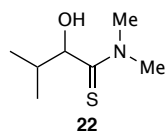
¹³C NMR (100 MHz, CDCl₃) δ 201.5 (C), 140.9 (C), 129.0 (CH), 128.8 (CH), 126.9 (CH), 79.0 (CH), 55.9 (C), 27.6 (CH₃).

LRMS (ESI) *m/z* 224 (M + H).

HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₁₂H₁₈NOS, 224.1104; found, 224.1106.

IR 3302, 2967, 1524, 1366, 1211, 1011.

mp 84–86 °C



Compound 22

Analogous procedure to that for **19a** gave the title compound.

¹H NMR (400 MHz, CDCl₃) δ 4.31 (dd, *J* = 8.8, 3.9, 1H), 4.09 (d, *J* = 8.5, 1H), 3.50 (s, 3H), 3.30 (s, 3H), 1.87–1.79 (m, 1H), 1.04 (d, *J* = 6.9, 3H), 0.90 (d, *J* = 6.9, 3H) ppm.

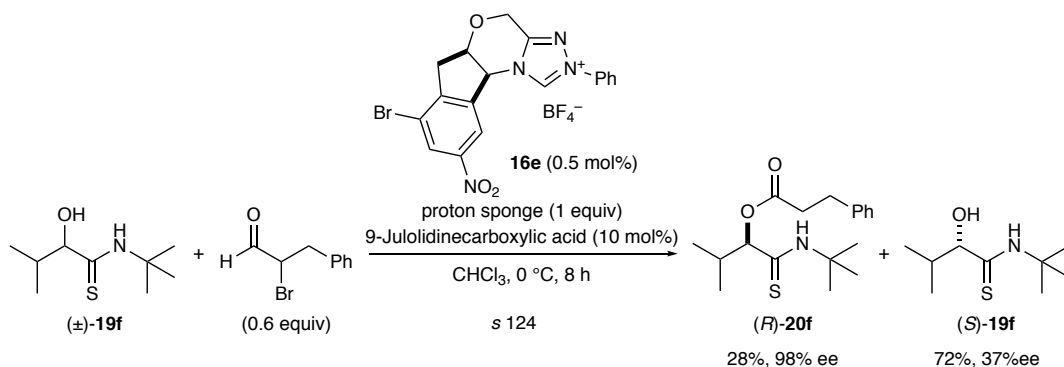
¹³C NMR (100 MHz, CDCl₃) δ 206.5 (C), 75.5 (CH), 45.0 (CH₃), 40.9 (CH₃), 33.7 (CH), 20.3 (CH₃), 15.6 (CH₃).

LRMS (ESI) *m/z* 162 (M + H).

HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₇H₁₆NOS, 162.0947; found, 162.0949.

IR 2963, 1528, 1381, 1269, 1138, 1026.

4. General procedure for kinetic resolution of α -hydroxy thioamide



Compound (*R*)-20f

A solution of **16e** (0.7 mg, 1 μmol), 9-Julolidinecarboxylic acid (5.5 mg, 0.025 mmol), 1,8-bis(dimethylamino)naphthalene (54 mg, 0.25 mmol, 1.0 equiv), and $(\pm)\text{-19f}$ (47 mg, 0.25 mmol) in CHCl_3 (2.5 mL) was stirred for 10 min at rt and cooled to 0 $^\circ\text{C}$. To the mixture, **3b** (25 μL , 0.15 mmol) was added, and the mixture was stirred for 8 h at 0 $^\circ\text{C}$. The whole mixture was directly purified by column chromatography (hexane/EtOAc 10:1 to 5:1) to give recovered **19f** with 37% ee (34 mg, 72% yield; $[\alpha]_{\text{D}}^{22}$ -39.8 (c 1.3, CHCl_3) as white solids and the title compound with 98% ee (23 mg, 28% yield) as yellow oil: $[\alpha]_{\text{D}}^{22}$ $+47.2$ (c 1.0, CHCl_3).

^1H NMR (400 MHz, CDCl_3) δ 7.32–7.28 (m, 2H), 7.23–7.20 (m, 3H), 5.28 (d, J = 3.9, 1H), 3.04–2.94 (m, 2H), 2.82–2.69 (m, 2H), 2.65–2.57 (m, 1H), 1.48 (s, 9H), 0.90 (d, J = 7.1, 3H), 0.81 (d, J = 7.1, 3H) ppm.

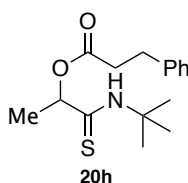
^{13}C NMR (100 MHz, CDCl_3) δ 198.1 (C), 171.1 (C), 140.1 (C), 129.3 (CH), 128.9 (CH), 127.8 (CH), 85.2 (CH), 55.1 (C), 36.7 (CH_2), 33.2 (CH), 31.3 (CH_2), 27.6 (CH_3), 19.4 (CH_3), 16.6 (CH_3).

LRMS (ESI) m/z 322 ($\text{M} + \text{H}$).

HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{28}\text{NO}_2\text{S}$, 322.1835; found, 322.1836.

IR 2967, 1744, 1520, 1420, 1126, 752.

The ee was determined by HPLC analysis (Daicel Chiralcel AD-3; hexane/*i*-PrOH 49:1; 0.5 mL/min; 254 nm; minor 11.2 min, major 14.8 min). The absolute configuration was based on that of the recovered **19f**.



Compound (*R*)-20h

The typical procedure except that ($\pm$)-**19h** (40 mg, 0.25 mmol) was used in place of ($\pm$)-**19f** gave recovered **19h** with 57% ee (20 mg, 50% yield; $[\alpha]_D^{26} +23.0$ (c 1.1, CHCl_3) as white solids and the title compound **20h** with 58% ee (37 mg, 50% yield) as colorless oil: $[\alpha]_D^{26} -11.1$ (c 1.0, CHCl_3).

^1H NMR (400 MHz, CDCl_3) δ 7.31–7.29 (m, 2H), 7.22–7.19 (m, 3H), 5.03 (d, $J = 8.1$, 1H), 3.01–2.97 (m, 2H), 2.80–2.69 (m, 2H), 1.48 (s, 9H), 1.03 (d, $J = 8.1$, 3H) ppm.

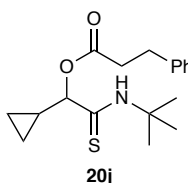
^{13}C NMR (100 MHz, CDCl_3) δ 196.0 (C), 170.9 (C), 140.1 (C), 128.6 (CH), 128.2 (CH), 126.5 (CH), 88.4 (CH), 55.5 (C), 35.7 (CH_2), 34.4 (CH_2), 30.7 (CH_3), 27.6 (CH_3).

LRMS (ESI) m/z 294 (M+H).

HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_2\text{S}^+$, 294.1522; found, 294.1524.

IR 2932, 1699, 1387, 1208, 1159, 949, 754.

The ee was determined by HPLC analysis (Daicel Chiralcel AD-3; hexane/*i*-PrOH 99:1; 1 mL/min; 254 nm; minor 7.2 min, major 15.5 min).



Compound (*R*)-20j

Analogous procedure to that for **20f** gave recovered **19j** with 91% ee (23 mg, 50% yield; $[\alpha]_D^{27} -36.4$ (c 1.5, CHCl_3)) as white solids and the title compound with 89% ee (40 mg, 50% yield) as colorless oil: $[\alpha]_D^{27} +38.2$ (c 1.0, CHCl_3).

^1H NMR (400 MHz, CDCl_3) δ 7.32–7.29 (m, 2H), 7.28–7.18 (m, 3H), 4.84 (d, $J = 8.1$, 1H), 2.99 (td, $J = 10.3, 4.1$, 2H), 2.79–2.70 (m, 2H), 1.58 (s, 9H), 0.71–0.64 (m, 1H), 0.60–0.49 (m, 2H), 0.45–0.39 (m, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3) δ 197.8 (C), 171.1 (C), 140.1 (C), 128.6 (CH), 128.3 (CH), 126.5 (CH), 84.1 (CH), 55.5 (C), 35.9 (CH_2), 30.8 (CH_2), 27.6 (CH_3), 15.8 (CH), 4.4 (CH_2), 3.3 (CH_2).

LRMS (ESI) m/z 320 (M+H).

HRMS (ESI) m/z : $[M + H]^+$ calcd for $C_{18}H_{26}NO_2S$, 320.1679; found, 320.1677.

IR 2927, 1740, 1420, 1207, 1142, 949

The ee was determined by HPLC analysis (Daicel Chiralcel AD-3; hexane/*i*-PrOH 49:1; 0.5 mL/min; 254 nm; minor 17.8 min, major 21.1 min).

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1. Edwards, G. L.; Muldoon, C. A.; Sinclair, D. J. *Tetrahedron* **1996**, 52, 7779.
2. Kang, S.-K.; Ko, B.-S.; Ha, Y.-H. *J. Org. Chem.* **2001**, 66, 3630.
3. Clark, R. W.; Deaton, T. M.; Zhang, Y.; Moore, M. I.; Wiskur, S. L. *Org. Lett.* **2013**, 15, 6132.