Studies on Organocatalytic Reactions Utilizing Noncovalent Interaction

Keisuke Asano

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Contents

Abbreviations

Ac	acetyl	Me	methyl
ad	adamantly	mg	milligram(s)
aq	aqueous	MHz	megahertz
Ar	aryl	min	minute(s)
Bn	benzyl	mL	milliliter(s)
Boc	*tert*-butoxycarbonyl	mm	millimeter(s)
br	broad (spectral)	mmol	millimole(s)
br s	broad singlet (spectral)	mol	mole(s)
Bu	butyl	Mp.	melting point
˚C	degrees Celsius	MS4Å	molecular sieves 4Å
calcd	calculated	*n*	normal
cm	centimeter(s)	NBS	*N*-bromosuccinimide
Co.	company	nm	nanometer(s)
CPME	cyclopentyl methyl ether	NMR	nuclear magnetic resonance
Cy	cyclohexyl	*o*	ortho
δ	chemical shift in parts per million downfield from tetramethylsilane	*p*	para
		PG	protecting group
d	doublet (spectral)	Ph	phenyl
d	day(s)	ppm	parts per million (spectral)
DABCO	1,4-diazabicyclo[2.2.2]octane	Pr	propyl
DMAP	4-(dimethylamino)pyridine	*p*-Ts	*p*-toluenesulfonyl
DME	dimethoxyethane	q	quartet (spectral)
DMSO	dimethyl sulfoxide	quint	quintet (spectral)
dr	diastereomeric ratio	ref(s)	reference(s)
Ed(s).	editor(s)	R_f	retention factor (TLC)
E	*entgegen* (means "opposite")	rt	room temperature (25 ± 3 ˚C)
ee	enantiomeric excess	s	singlet (spectral)
equiv	equivalent(s)	*t* (*tert*)	tertiary
Et	ethyl	t	triplet (spectral)
g	gram(s)	TBME	*tert*-butyl methyl ether
h	hour(s)	TBS	*tert*-butyldimethylsilyl
HRMS	high-resolution mass spectrum	TEAI	tetraethylammonium iodide
Hz	hertz (s^{-1})	Tf	trifluoromethanesulfonyl
i	iso	TFA	trifluoroacetic acid
i.d.	internal diameter	THF	tetrahydrofuran
IR	infrared (spectral)	THP	tetrahydropyran
J	coupling constant (spectral)	TLC	thin-layer chromatography
m	multiplet (spectral)	TMS	trimethylsilyl
m	meta	UV	ultraviolet
M	molar (1 M = 1 mol dm^{-3})	Vol.	volume(s)
m-CPBA	*m*-chloroperoxybenzoic acid	*Z*	*zusammen* (means "together")

General Introduction

Recent significant advances of molecular catalysts, such as organocatalysts,[1] polymer catalysts,[2] supramolecular catalysts,[3] metal complex catalysts,[4] and so on, have made a great contribution to the development of highly selective organic synthesis. Those catalysts have been developed along with the discovery of the novel functions of various common organic groups. This fact suggests that new insights into latent functionalities of common organic frameworks would lead to further growth of catalyst development. In this thesis, the author initially focused on the functionalities of alkyl chains, which have often been regarded just as a "substituent" apparently without any function. He attempted to shed light on their utilities as a functional group for catalyst design. He also devoted his efforts to the demonstration of the demand of hydrogen bonding as the essential synthetic tool. Both of those topics are based on relatively weak *noncovalent interaction* in order to develop a highly efficient catalyst: the cooperation of weak interactions may have a considerable impact on the properties, and the employment of such weak forces is sometimes essential to give rise to unique functionalities as we can see in the activities of organisms. Based on such concepts, the author decided to discuss the above two subjects through the development of catalysts for selective reactions. First of all, he describes the perspective on these topics through the previous significant studies.

1. Long Alkyl Chains for Catalyst Design

The representative natures of long alkyl groups are hydrophobicity and softness. The former one has been applied to the design of amphiphilic catalysts for some organic reactions in aqueous media.[5] The use of amphiphilic catalysts in aqueous media leads to their aggregation to benefit the organic reactions. On the other hand, another nature, softness, has rarely been noted as an important functionality for the design of synthetic reagents. In this study, the author sought to exploit both of those natures in order to control the aggregation states of synthetic reagents. In this section, the author describes the potentials of alkyl chains through the significant previous

studies.

1.1. Organic Reactions Utilizing the Aggregation of Amphiphilic Catalysts

The use of water as a solvent for organic reactions has received considerable attention for some practical reasons, such as cost, safety, and environmental concerns.[6]   Moreover, water also benefits some organic reactions dynamically.   However, most organic reactions are difficult to perform in pure water under organic solvent free conditions.   One of the reasons is the instability of reaction components, such as substrates, intermediates, transition states, and so on, in the presence of water.   Therefore, as an efficient method to generate unstable chemical species in water, surfactant-type catalysts were employed.[5]   The aggregation of amphiphilic catalysts in water provides hydrophobic reaction media to enable the aqueous organic reactions by excluding water molecules outside the aggregates (Scheme 1).

Scheme 1.
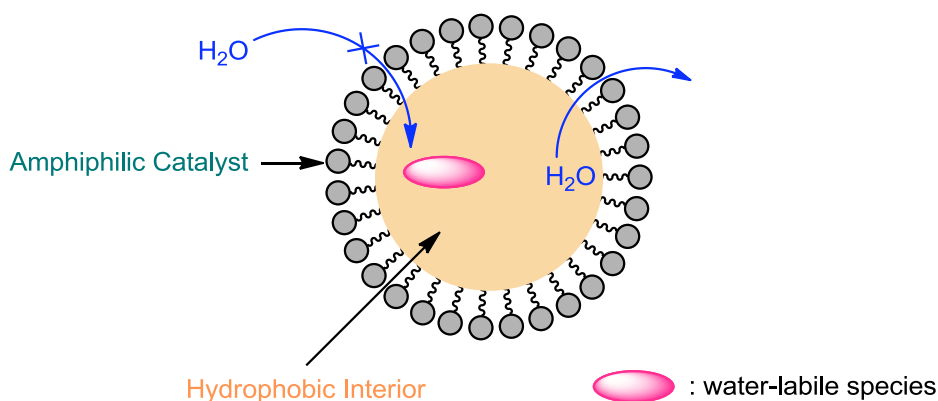
As a representative example, Kobayashi developed Lewis acid–surfactant-combined catalyst (LASC) (Scheme 2), which allows some Lewis acid-catalyzed reactions in the presence of water without any organic solvent.[7]   Even when the substrates are water-labile, stable colloidal dispersions formed by the catalyst enable the reactions of those substrates in water.

Scheme 2.
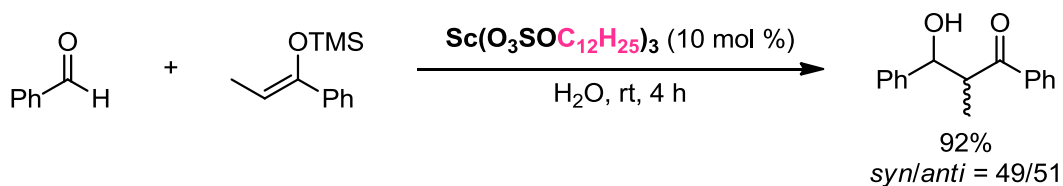
Scheme 3.

Meanwhile, Kotsuki reported the amphiphilic DMAP-related organic base catalyst.[8]   This catalyst mediates the Michael addition reactions of β-ketoesters in water (Scheme 3).   The reaction mixture becomes an emulsion system, which prevents the deactivation of the catalyst or the anionic intermediates even in water.
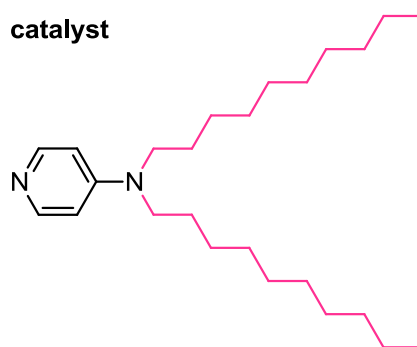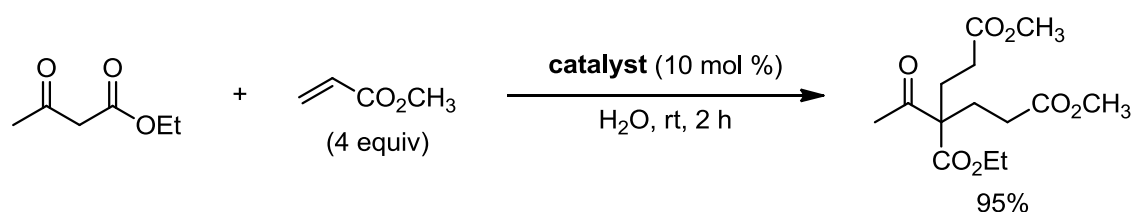
Long alkyl chains were also introduced into asymmetric organocatalysts for enantioselective reactions in water.[9-11]   For example, Barbas reported proline-derived organocatalyst carrying long alkyl chains for direct asymmetric aldol reactions in water (Scheme 4).[9]   Hayashi also developed combined proline-surfactant organocatalyst for aqueous direct cross-aldol reactions of aldehydes (Scheme 5).[10]   Those catalysts maintain the desired transition states even in the
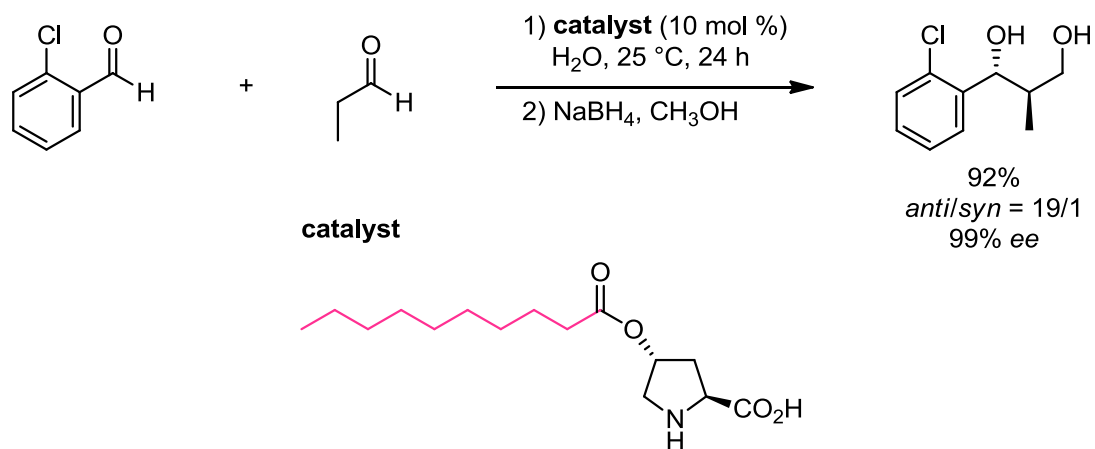
presence of water, which would disturb them without the amphiphilicity of the catalyst by interrupting the critical ionic interactions or the hydrogen bonds.

Scheme 4.

99%
anti/*syn* = 89/11
94% *ee*

Scheme 5.

92%
anti/*syn* = 19/1
99% *ee*
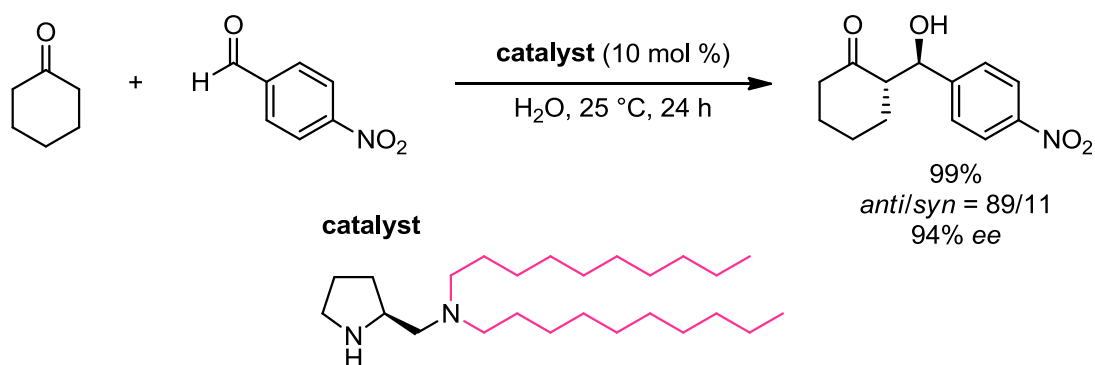
Further, Nagasawa demonstrated asymmetric Henry reactions by guanidine-thiourea catalyst containing a long alkyl chain (Scheme 6).[12]   This reaction prceeds in toluene/water system, and they proposed that a particular asymmetric environment is formed at the interface of the biphasic system by the self-assembly of the chiral amphiphilic catalysts, which was supported by the observation of (+)-nonlinear effect between *ee* of the catalyst and that of the product.   In this case, the aggregation of the catalysts not only prevents the inhibition by water but also assists

more efficient transition state than that generated by one molecule of the catalyst.

Scheme 6.
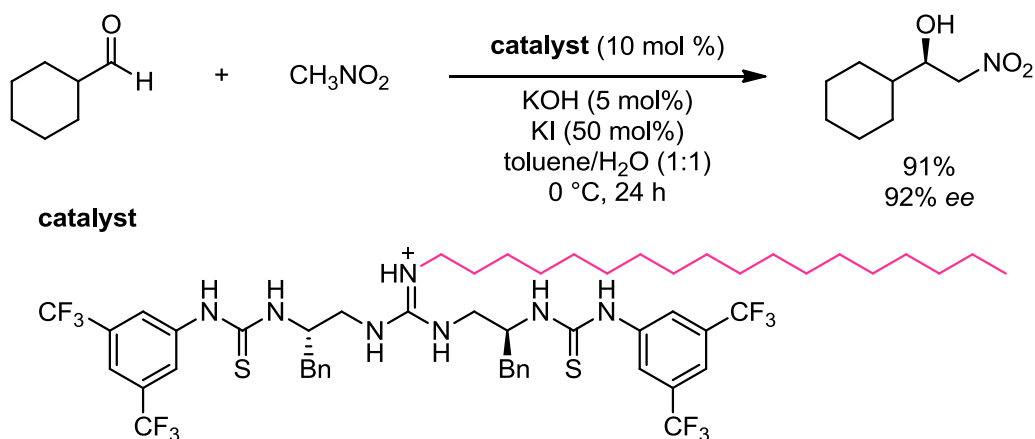
These examples show that the amphiphilic catalysts have advantages for organic reactions in aqueous media by preventing water from spoiling the important but water-labile species.   These studies have clearly disclosed the utility of long alkyl chains as a hydrophobic group for catalyst design.   Inspired by these examples, the author also sought to exploit the hydrophobic nature of long alkyl chains in the development of a novel amphiphilic catalyst to allow aqueous organic reactions via water-labile intermediates.

1.2.   Flexibility of Alkyl Chains Leading to a Steric Effect

The role of alkyl chains as a hydrophobic group has been discussed to some degree as described in the former section, but the flexibility has rarely been utilized actively for the design of synthetic reagents.   Meanwhile, in the field of supramolecular chemistry, some studies focused on the flexibility of alkyl chains.[13]   According to those studies, although normal alkyl groups ordinarily have an extended form with all *anti* configurations as their stable shape, they can readily change their conformations in a host molecule to an unusual one, such as coiled, folded, or U-shaped, to adjust to the cavity size (Scheme 7).
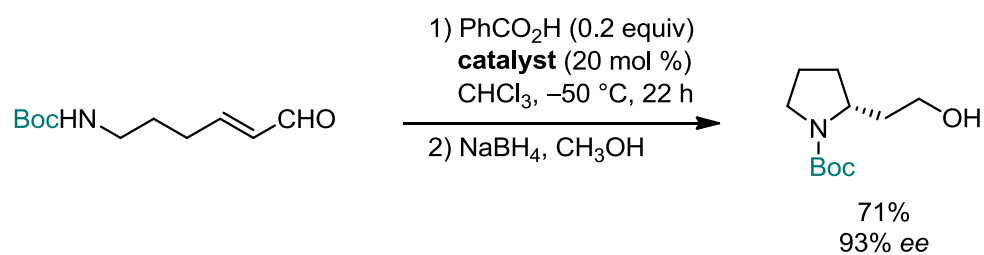
Scheme 7.
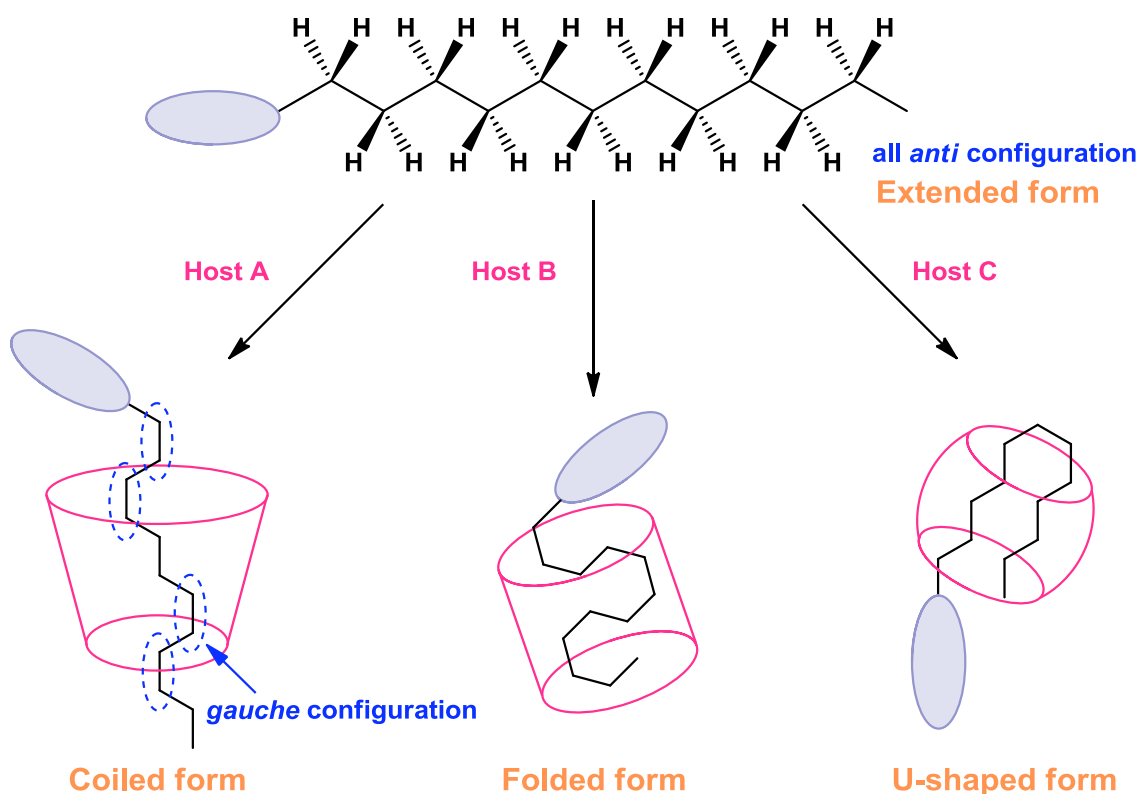
The behaviors which can change their shapes freely to fit the adjacent molecules may generate effective properties in the design of catalysts. While alkyl chains in amphiphiles generate an attracting force in water, they would also give rise to a repulsion force by their steric effect under a certain condition, and the steric effect by flexible alkyl chains may have some advantages over that derived from rigid frameworks. On the basis of such a viewpoint, the author sought to utilize the latent functionalities of normal alkyl groups in the design of a ligand for a transition metal catalyst. To demonstrate the steric effect by an alkyl chain, he decided to investigate the ligand effects for copper-catalyzed transformations of terminal alkynes via copper-acetylide intermediates: those reactions may be accelerated by bulky ligands to avoid the aggregation of the intermediates.[14]
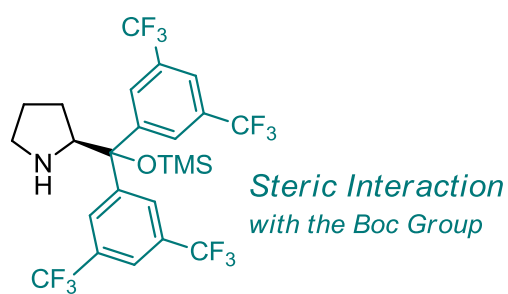
2. Asymmetric Oxycyclization Reactions by Bifunctional Organocatalysts Based on Hydrogen Bonding

Cyclization from unsaturated substrates bearing a pendant nucleophilic oxygen atom is a straightforward strategy for the synthesis of chiral oxacyclic compounds.   However, asymmetric oxycyclization reaction has been challenging due to the difficulty in installing a suitable chiral environment in a rapid intramolecular process.   On the other hand, successful asymmetric azacyclizations by proline-derived catalyst (Scheme 8)[15] and by chiral phase-transfer-catalyst (Scheme 9)[16] were reported.   The enantioselection of those azacyclizations is largely controlled by the effects of the substituents on the nitrogen atom through steric repulsion or π-interaction. Meanwhile, as the substrates for oxycyclization reactions lack such a substituent on the oxygen atom, those strategies cannot be applied for this transformation.   Therefore, another strategy should be developed in order to achieve an enantioselective oxycyclization.   The promising interaction to control the behavior of a pendant OH group is hydrogen bonding; thus the use of organocatalysts based on hydrogen bonding[17] would be essential for enantioselective oxycyclizations (Scheme 10).   Moreover, the multipoint recognition by asymmetric catalyst would be favorable to allow an effective transfer of the chiral information in the cyclization event (Scheme 10).
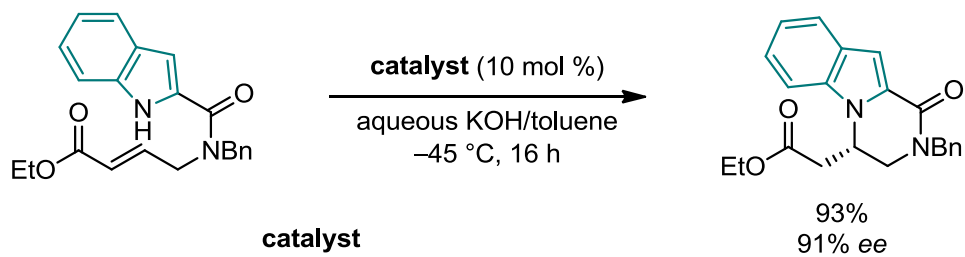
Scheme 8.

BocHN–CH₂–CH₂–CH₂–CH=CH–CHO

$\xrightarrow[\text{2) NaBH}_4, \text{CH}_3\text{OH}]{\substack{\text{1) PhCO}_2\text{H (0.2 equiv)}\\ \textbf{catalyst}\text{ (20 mol \%)}\\ \text{CHCl}_3, -50\ °\text{C, 22 h}}}$

71%
93% ee

catalyst

Steric Interaction
with the Boc Group

Scheme 9.

$\xrightarrow[\substack{\text{aqueous KOH/toluene}\\ -45\ °\text{C, 16 h}}]{\textbf{catalyst}\text{ (10 mol \%)}}$

93%
91% ee

catalyst

π-Interaction
with the Indolyl Group
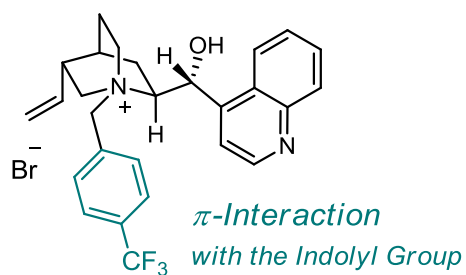
Scheme 10.

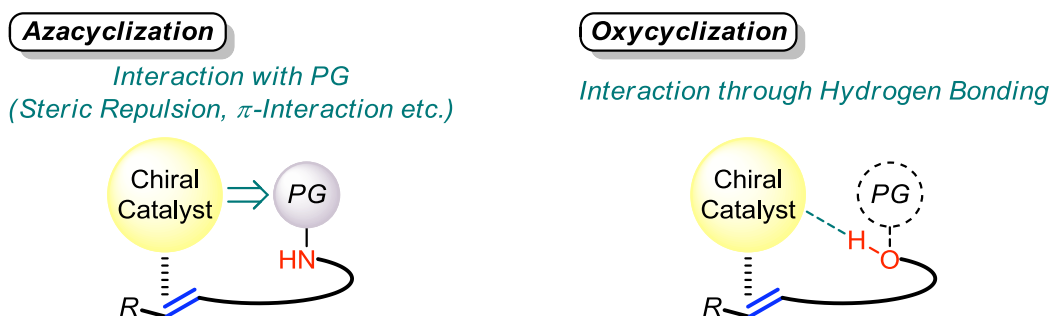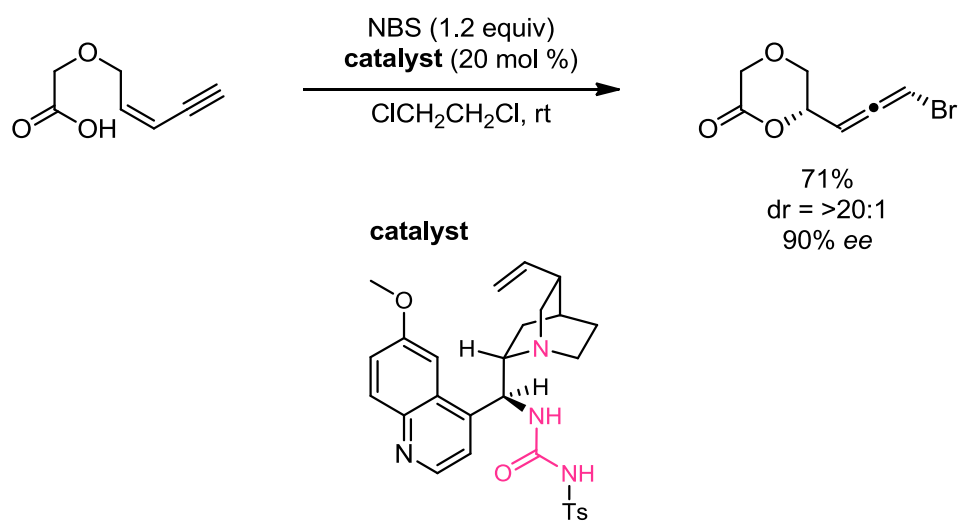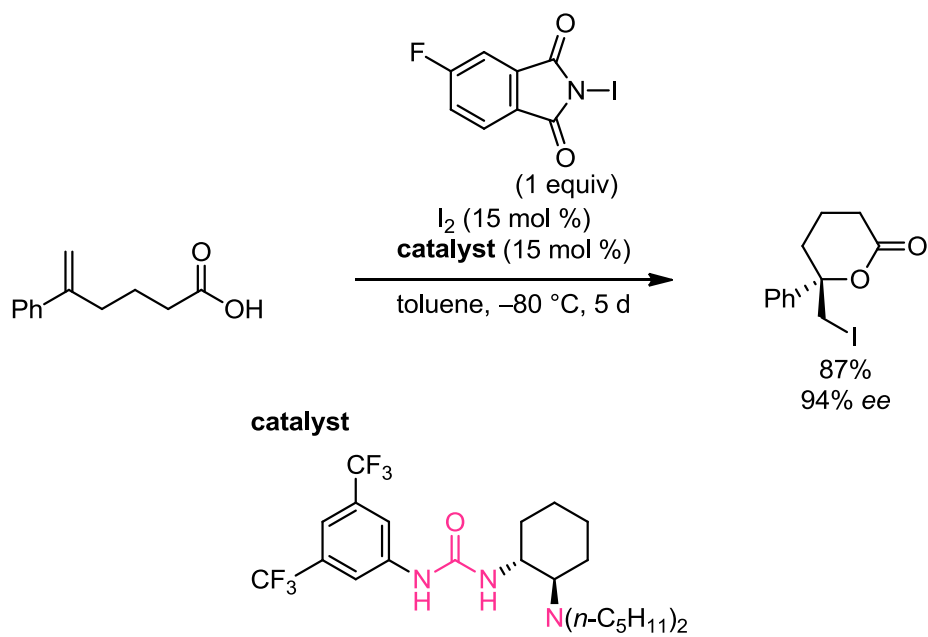The efficiency of this concept can be found in some recent reports. In 2010, several catalytic asymmetric halolactonizations were reported.[18–21] Some of them employed bifunctional organocatalysts, allowing multipoint interactions with the transition states, one of which is the hydrogen bonding interaction with the pendant carboxyl group. Tang demonstrated catalytic enantioselective bromolactonization of conjugated (Z)-enynes (Scheme 11).[19] The high enantioselectivity is provided by the bifunctionality of the catalyst containing a quinuclidine nitrogen and an urea group. Jacobsen also disclosed tertiary aminourea-catalyzed enantioselective iodolactonization (Scheme 12).[20] They proposed the reaction mechanism supported by preliminary computational studies as outlined in Scheme 13. The *N*-iodo complex **A**, formed by the aminourea catalyst and *N*-iodoimide, induces the formation of the iodonium ion **B** from the alkenoic acid. The iodonium ion complex **B** maintains a tertiary amino-iodonium ion interaction, and simultaneously the urea-bound phthalimide serves as the base to deprotonate from the carboxylic acid in the enantiodetermining cyclization step. Furthermore, Yeung developed asymmetric bromolactonization using amino-thiocarbamate catalyst (Scheme 14).[21] As the proposed mechanism depicted in Scheme 15, the thiocarbamate moiety of the catalyst activates *N*-bromosuccinimide, and at the same time, the quinuclidine moiety can interact with the carboxylic acid. Those simultaneous interactions support the suitable transition-state to attain high enantioselectivity.

Scheme 11.

NBS (1.2 equiv)
catalyst (20 mol %)

ClCH₂CH₂Cl, rt

71%
dr = >20:1
90% *ee*

catalyst

Scheme 12.

(1 equiv)
I₂ (15 mol %)
catalyst (15 mol %)

toluene, –80 °C, 5 d

87%
94% *ee*

catalyst

Scheme 13.

Scheme 14.

NBS (1.2 equiv)
NsNH$_2$ (0.5 equiv)
catalyst (10 mol %)

CHCl$_3$/toluene (1:2)
−78 °C, 40 h

98%
90% *ee*

catalyst
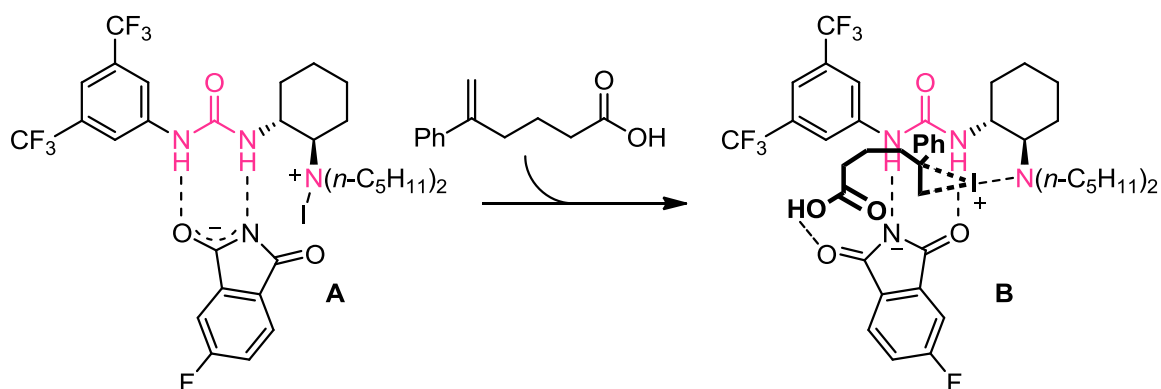
Scheme 15.

As an example of intramolecular oxy-Michael addition reaction, Scheidt disclosed enantioselective conjugate addition reaction from α-substituted chalcones using bifunctional aminothiourea catalyst (Scheme 16).[22]   Both of the tertiary amine and the thiourea functional groups exist in the same molecule to deliver the high stereoselectivity: the thiourea invokes the β-ketoester and the quinuclidine nitrogen interacts with the phenol moiety.   In addition, Falck reported enantioselective oxy-Michael addition to γ-hydroxy-α,β-unsaturated ketones via the formation of boronic acid hemiesters (Scheme 17).[23]   In this case, they proposed that the aminothiourea catalyst plays as a push/pull type catalyst: the thiourea binds with the carbonyl group and the tertiary nitrogen atom coordinates to the boron atom (Scheme 18), but the possibility that the tertiary amine may interact with the boronate oxygen through hydrogen bonding cannot be ruled out.

Scheme 16.

85%
dr = >20:1
92% *ee*
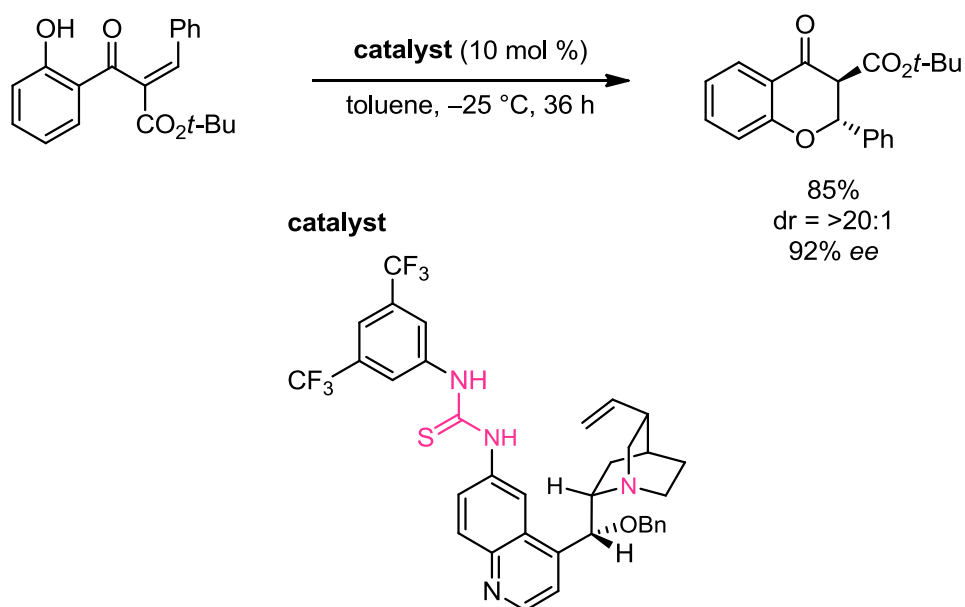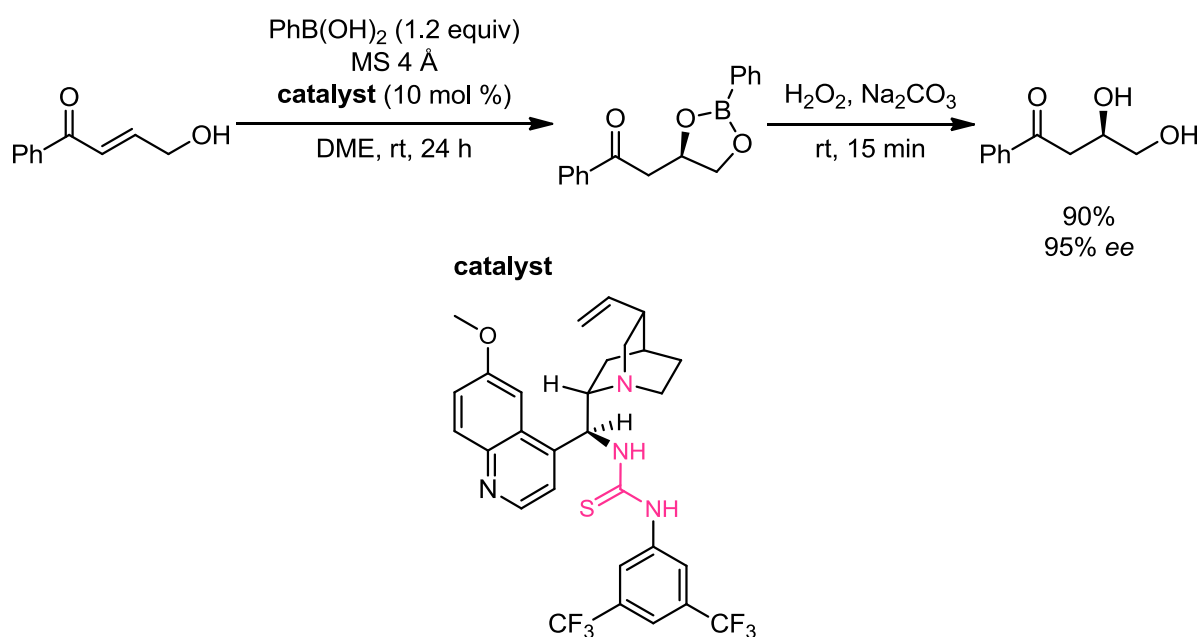
Scheme 17.

catalyst

Scheme 18.
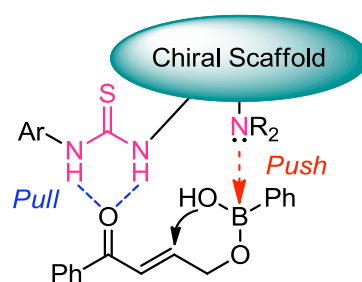
These examples suggest that the prospective strategy for enantioselective oxycyclizations is the asymmetric catalysis in which a bifunctional organocatalyst interacts with the important transition state at multiple points, one of which is the pendant OH group thorough hydrogen bonding. To consolidate this concept, the author investigated asymmetric cycloetherifications leading to some other oxacyclic compounds by bifunctional organocatalysts based on hydrogen bonding.

3. Overview of This Thesis

3.1. Catalyst Design Utilizing Long Alkyl Chains (Chapters 1–4)

To demonstrate the potentials of alkyl chains for catalyst design, imidazole derivatives carrying a long alkyl chain is employed as a nucleophilic organocatalyst or as a ligand for metal catalyst.   In Chapters 1 and 2, the efficiency of amphiphilic nucleophilic catalysts for organic reactions in the presence of water is described.   In Chapters 3 and 4, the effects of imidazole ligands bearing a long alkyl chain for copper-catalyzed transformations of terminal alkynes are presented.   These works totally suggest a new aspect that alkyl chains are interesting functional groups that can generate both an attracting force and a repulsive force depending on the situations.

3.1.1. Organic Reactions Mediated by Amphiphilic Imidazole Catalysts in Water (Chapters 1 and 2)

The author developed an amphiphilic nucleophilic catalyst, which consists of a hydrophilic imidazole moiety and a hydrophobic long alkyl chain (Scheme 19).[24]   The catalyst is expected to aggregate and construct some hydrophobic space in water due to its amphiphilicity.   He applied the catalyst to two organic reactions initiated by nucleophilic catalysts.   Although these reactions proceed via water-labile ionic intermediates, they were maintained by virtue of the amphiphilic catalysts.

Scheme 19.
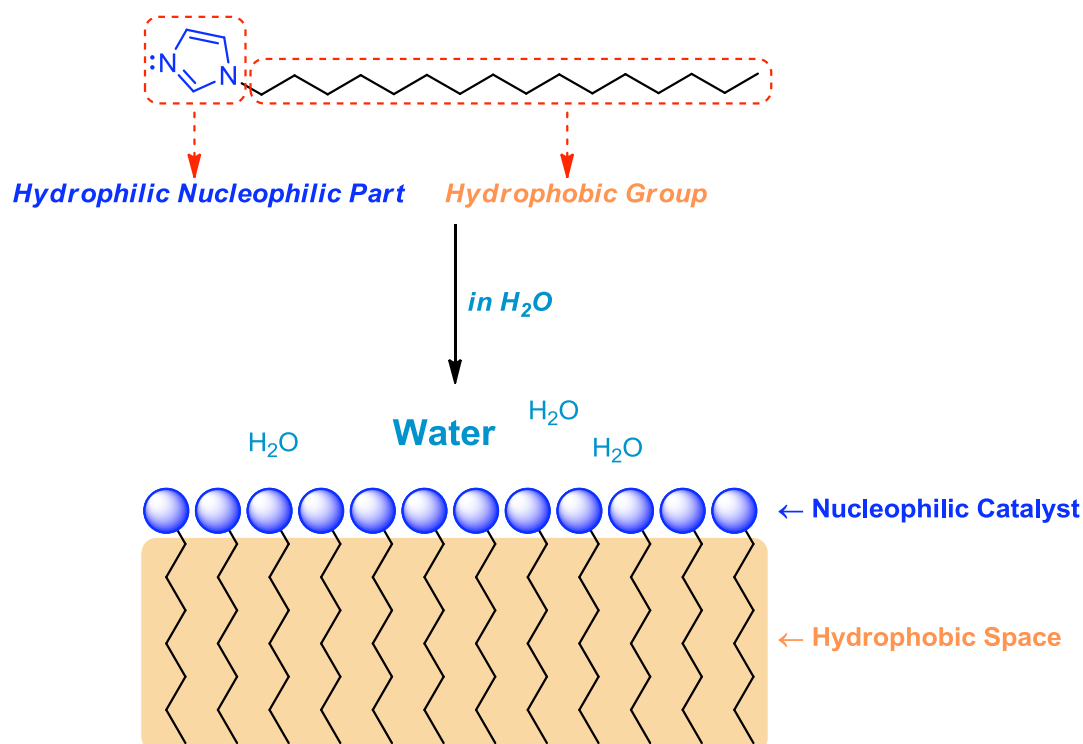
3.1.1.1. Morita–Baylis–Hillman Reaction on Water without Organic Solvent, Assisted by a 'Catalytic' Amount of Amphiphilic Imidazole Derivatives (Chapter 1)

The Morita–Baylis–Hillman (MBH) reaction is a useful method of C–C bond formation, but this reaction is notoriously slow.   To solve this problem, the author focused on the use of water as a polar solvent to stabilize the ionic intermediate of the reaction.   However, the addition of water may just protonate the ionic intermediate and may depress the nucleophilicity of the amine catalyst.   To avoid these inhibitions, organic co-solvents or excess amount of amines have been used.   In this study, the author found that the accelerating effect by water was obtained by the use of the amphiphilic imidazoles as a catalyst even in the absence of any organic solvent (Scheme 20).[25]   1,4-Diazabicyclo[2.2.2]octane and 4-(dimethylamino)pyridine were also examined under the author's conditions, and neither of them were effective catalysts (<1% and 6% yield, respectively).   These results show that nucleophiles should be endowed with

amphiphilicity for obtaining the acceleration. In addition, interestingly stirring was not necessary to carry out this reaction if there was sufficient surface area where the water and organic phase were contiguous; this reaction can be classified as one of the reactions *on water*.
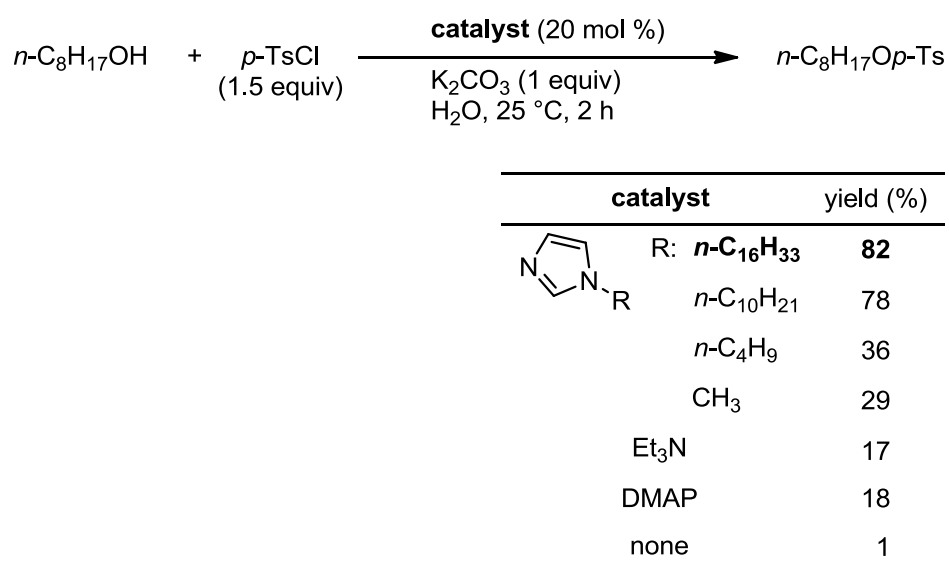
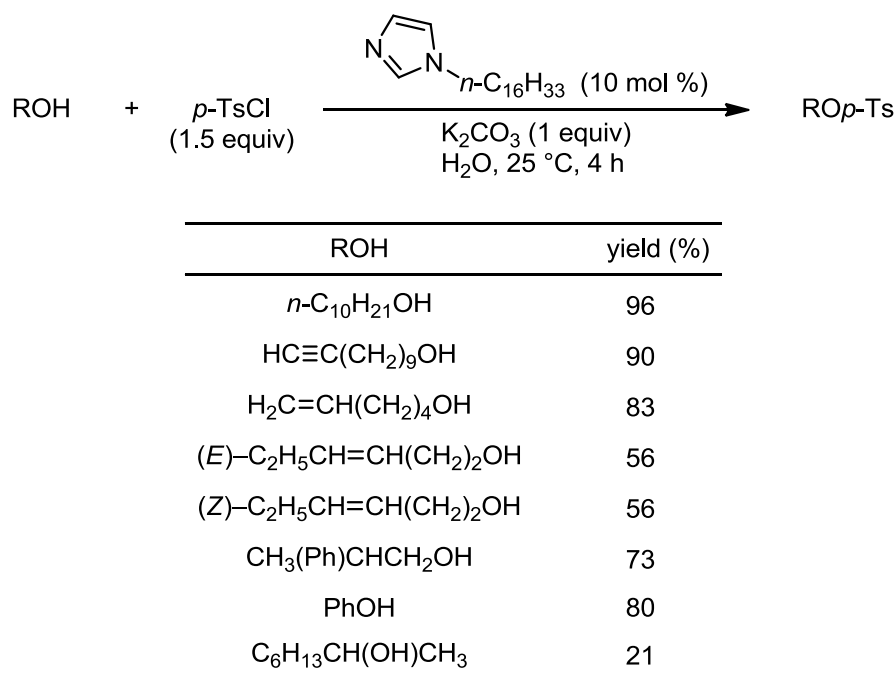**Scheme 20.**

67%
(without H$_2$O; 37%)
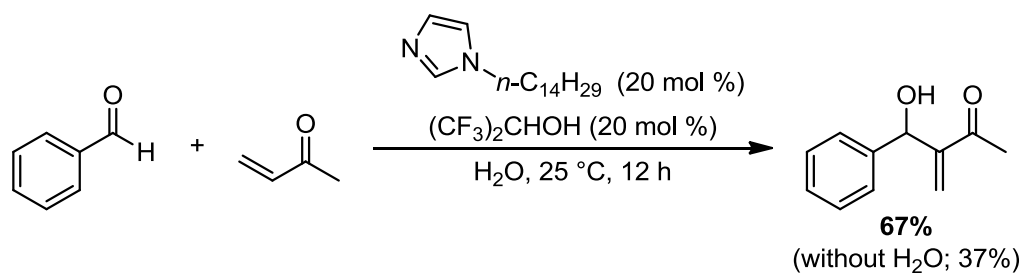
3.1.1.2. Amphiphilic Organocatalyst for Schotten–Baumann-Type Tosylation of Alcohols under Organic Solvent Free Condition (Chapter 2)

The tosylation of alcohols was conventionally performed by the treatment of alcohols with tosyl chloride and a stoichiometric amount of amine. Meanwhile, the Schotten–Baumann method using an inorganic base with a catalytic amine in aqueous media has been evaluated from the economical and environmental superiority.   However, it still requires an organic solvent, and if it is conducted in pure water, the control of pH and the slow addition of tosyl chloride were necessary to prevent the hydrolysis of tosyl chloride.[26]   It might be because the sulfonylammonium intermediate, which forms in the activation of tosyl chloride by an amine catalyst, is incredibly unstable in water.   In this study, the author disclosed that the Schotten–Baumann-type tosylation of alcohols with tosyl chloride and potassium carbonate could be performed in water without any organic solvent by using an *N*-alkylimidazole as a catalyst.[27] The *N*-alkylimidazole bearing a longer alkyl chain proved more efficient in the case of the tosylation of 1-octanol (Scheme 21).   The author supposes that the aggregation of amphiphilic molecules prevented tosyl chloride from undergoing hydrolysis.

Scheme 21.

$$n\text{-}C_8H_{17}OH \quad + \quad \underset{(1.5 \text{ equiv})}{p\text{-TsCl}} \quad \xrightarrow[\substack{K_2CO_3 \,(1 \text{ equiv}) \\ H_2O,\, 25\,°C,\, 2\,h}]{\textbf{catalyst} \,(20 \text{ mol \%})} \quad n\text{-}C_8H_{17}Op\text{-}Ts$$

catalyst		yield (%)
R: $n\text{-}\textbf{C}_{16}\textbf{H}_{33}$		**82**
$n\text{-}C_{10}H_{21}$		78
$n\text{-}C_4H_9$		36
CH_3		29
Et_3N		17
DMAP		18
none		1

Scheme 22.

$$ROH \quad + \quad \underset{(1.5 \text{ equiv})}{p\text{-TsCl}} \quad \xrightarrow[\substack{K_2CO_3 \,(1 \text{ equiv}) \\ H_2O,\, 25\,°C,\, 4\,h}]{n\text{-}C_{16}H_{33} \,(10 \text{ mol \%})} \quad ROp\text{-}Ts$$

| ROH	yield (%)
$n\text{-}C_{10}H_{21}OH$	96
$HC{\equiv}C(CH_2)_9OH$	90
$H_2C{=}CH(CH_2)_4OH$	83
$(E)\text{--}C_2H_5CH{=}CH(CH_2)_2OH$	56
$(Z)\text{--}C_2H_5CH{=}CH(CH_2)_2OH$	56
$CH_3(Ph)CHCH_2OH$	73
PhOH	80
$C_6H_{13}CH(OH)CH_3$	21

The Schotten–Baumann method could also be applied to other substrates (Scheme 22). In the course of these investigations, an interesting dependence of reactivities on the substrate structures was also observed: in the case of unsaturated substrates, the position of the double

bond determined the reaction conversion.[28] The affinity of the substrate structure to the particular reaction media formed by the catalyst seems to play an important role. The method may be extended to a tosylation that accompanies a molecular recognition.

3.1.2. Organic Reactions Utilizing a Steric Effect of a Flexible Alkyl Chain on a Ligand (Chapters 3 and 4)

The author subsequently investigated the use of *N*-alkylimidazoles as a ligand for copper catalyst. He found that the alkyl chain provides a sufficient steric effect to accelerate the copper-catalyzed transformations of terminal alkynes while allowing a creation of a flexible environment around a Cu center, which can accommodate even bulky substrates (Scheme 23).
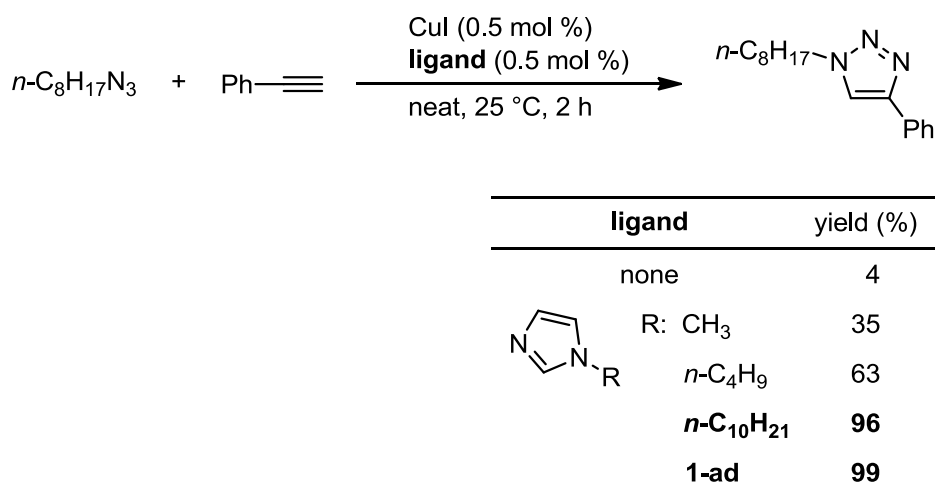
Scheme 23.
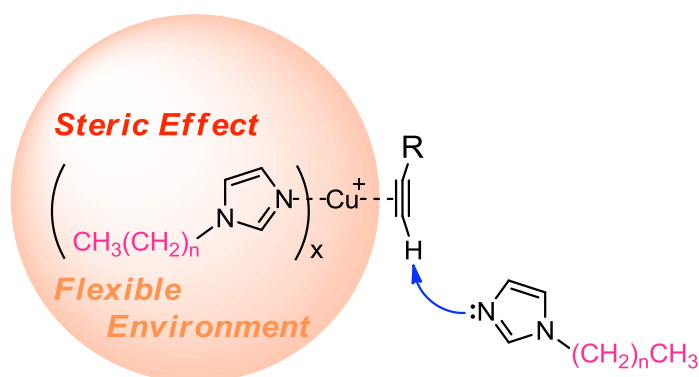
### 3.1.2.1. Effects of a Flexible Alkyl Chain on a Ligand for CuAAC Reaction (Chapter 3)

In Chapter 3, the author describes the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction using *N*-alkylimidazoles as a ligand.[29] The previous instances of CuAAC reaction suggest that bulky ligands are desirable for the efficient catalysis. Indeed, 1-(1-adamantyl)imidazole proved to be excellent as a ligand, and 1-decylimidazole also showed a good result in the CuAAC reaction of phenylacetylene (Scheme 24). These results suggest that the alkyl chain on the imidazole ligand has a steric effect to benefit the reaction. Further, the

N-alkylimidazole was also effective in various organic solvent and even in the presence of water, which leads to an efficient click catalyst useful for a wide range of substrates.

Scheme 24.

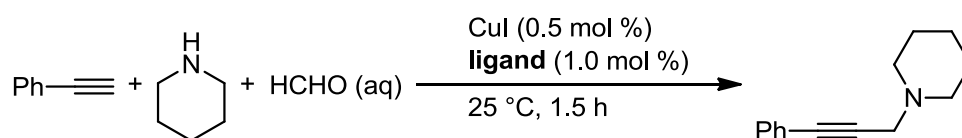| ligand	yield (%)
none	4
R: CH$_3$	35
n-C$_4$H$_9$	63
***n*-C$_{10}$H$_{21}$**	**96**
1-ad	**99**
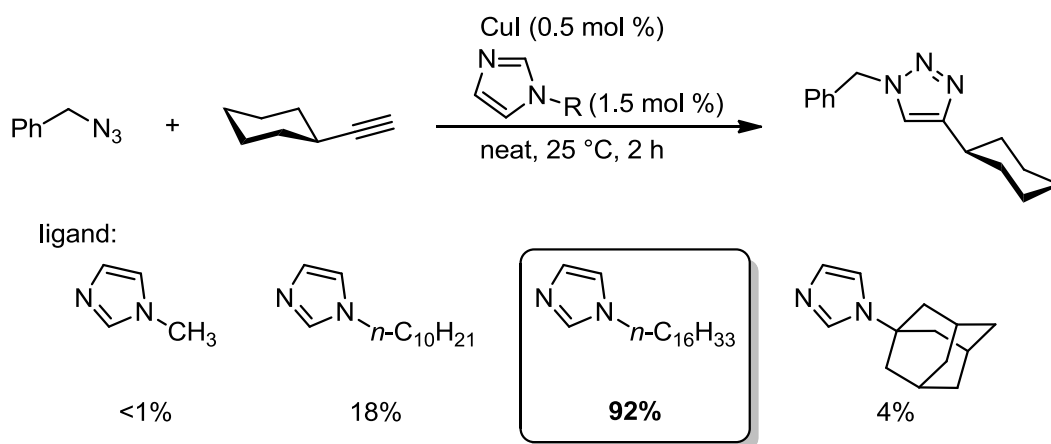
Scheme 25.

In addition, the imidazole ligand carrying a flexible long alkyl chain allowed a rapid CuAAC reaction of even a bulky alkyne, which has been difficult to perform under conventional conditions (Scheme 25). Notably, the rigid backbone of 1-(1-adamantyl)imidazole also disturbed the reaction despite its sufficient steric effect, indicating that the flexible alkyl chain has
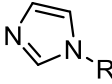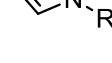
an advantage over rigid frameworks as a substituent of a ligand especially for the reaction of bulky substrates.

3.1.2.2. Effects of a Flexible Alkyl Chain on an Imidazole Ligand for Copper-Catalyzed Mannich Reaction of Terminal Alkynes (Chapter 4)

The results described in Chapter 3 motivated the author to expand the utility of the ligand to another copper-catalyzed transformation of terminal alkynes. In Chapter 4, he describes the efficiency of the imidazole ligand carrying a long alkyl chain to enhance the Mannich reactions of terminal alkynes mediated by copper catalyst.[30] Copper-catalyzed Mannich reactions of terminal alkynes procced via copper-acetylide intermediates, and they are known to aggregate easily to become an inactive polymeric form.[14] To promote the generation of active monomeric or oligomeric copper-acetylide species, sterically assisted ligands seem to be efficient. Thus, the author investigated the use of N-alkylimidazole ligands for this reaction, and the imidazole ligands showed the accelerating effects similar to those obtained in the CuAAC reaction described in Chapter 3 (Scheme 26). Also in this case, the imidazole ligand bearing a flexible alkyl chain was more efficient in the reaction of bulky alkynes than 1-(1-adamantyl)imidazole.

Scheme 26.

ligand		yield (%)
none		30
	R: CH$_3$	12
	n-C$_4$H$_9$	57
	n-C$_{10}$H$_{21}$	52
	n-C$_{16}$H$_{33}$	97
	1-ad	99

3.2. Asymmetric Cycloetherifications by Bifunctional Organocatalysts Based on Hydrogen Bonding (Chapters 5 and 6)

To demonstrate the utility of the catalysis by hydrogen bonding, the author decided to investigate asymmetric catalytic cycloetherifications mediated by bifunctional organocatalysts on the basis of the above concept. Although a few examples of asymmetric oxycyclization reactions were achieved by bifunctional organocatalysts as mentioned above, most of them are cyclolactonizations, and the examples of cycloetherifications are still limited.   Enantioselective cycloetherifications, especially the catalytic variants, are more challenging because of the higher nucleophilicity of hydroxy groups than that of carboxyl groups.   Indeed, several previous cycloetherifications have suffered from moderate enantioselectivity, which results from the unignorable background racemic reactions even at low temperature, and eventually they required a stoichiometric or a high loading of chiral mediators to reduce them.[31]   In this study, the author planed an intramolecular oxy-Michael addition reaction by bifunctional aminothiourea catalysts, which utilize hydrogen bonding at both catalytic sites, with the expectation that the mild character of hydrogen bonding may be reasonable to maintain the concerted catalysis critical for the multiple recognition even with the highly reactive substrates (Scheme 27).   Indeed, he disclosed that this method is useful for the asymmetric cyclotherification leading to the oxacycles, such as THFs, THP, and 1,3-dioxolanes.   These approaches open a new avenue for the synthesis of chiral oxacyclic compounds with asymmetric catalysis based on hydrogen bonding.

Scheme 27.
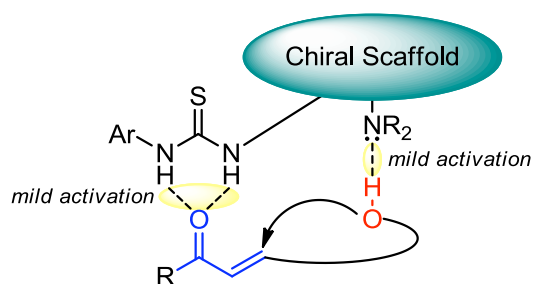
3.2.1. Asymmetric Catalytic Cycloetherification Mediated by Bifunctional Organocatalysts (Chapter 5)

In Chapter 5, the author presents a highly enantioselective catalytic cycloetherification method for the synthesis of 2-substituted THFs and THP.[32]   The cycloetherifications via intramolecular oxy-Michael addition reaction from ε- or ζ-hydroxy-α,β-unsaturated ketones could be performed in high enantioselective fashion by using cinchona-alkaloid-thiourea-based bifunctional organocatalysts (Scheme 28).   The catalytic loading could be lowered to 1 mol % while still giving excellent enantioselectivity.   This catalytic process represents a highly practical cycloetherification method that provides excellent enantioselectivities, even with low catalyst loadings at ambient temperature.
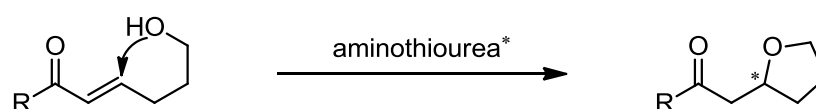
Scheme 28.
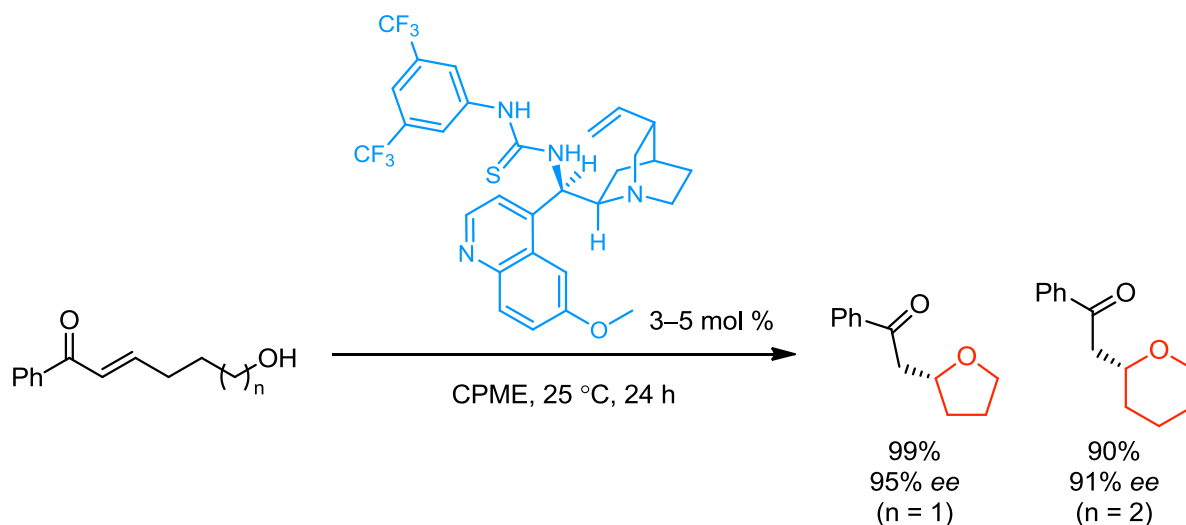
3.2.2. Asymmetric Synthesis of 1,3-Dioxolanes by Organocatalytic Formal [3+2] Cycloaddition via Hemiacetal Intermediates (Chapter 6)

In Chapter 6, the author describes a novel catalytic asymmetric formal [3+2] cycloaddition reaction for the synthesis of chiral 1,3-dioxolanes.[33]   Chiral cyclic acetals are valuable compounds, however, their enantioselective synthesis methods have been limited.   Especially, a

cycloaddition method has remained underdeveloped despite its advantage in terms of the ability to construct multiple bonds in a single step, thereby leading to divergent synthesis. So, the results described in Chapter 5 stimulated him to exploit this efficient cyclization route in the development of a formal cycloaddition reaction starting from γ-hydroxy-α,β-unsaturated ketones with aldehydes or ketones via the formation of hemiacetal intermediates (Scheme 29).
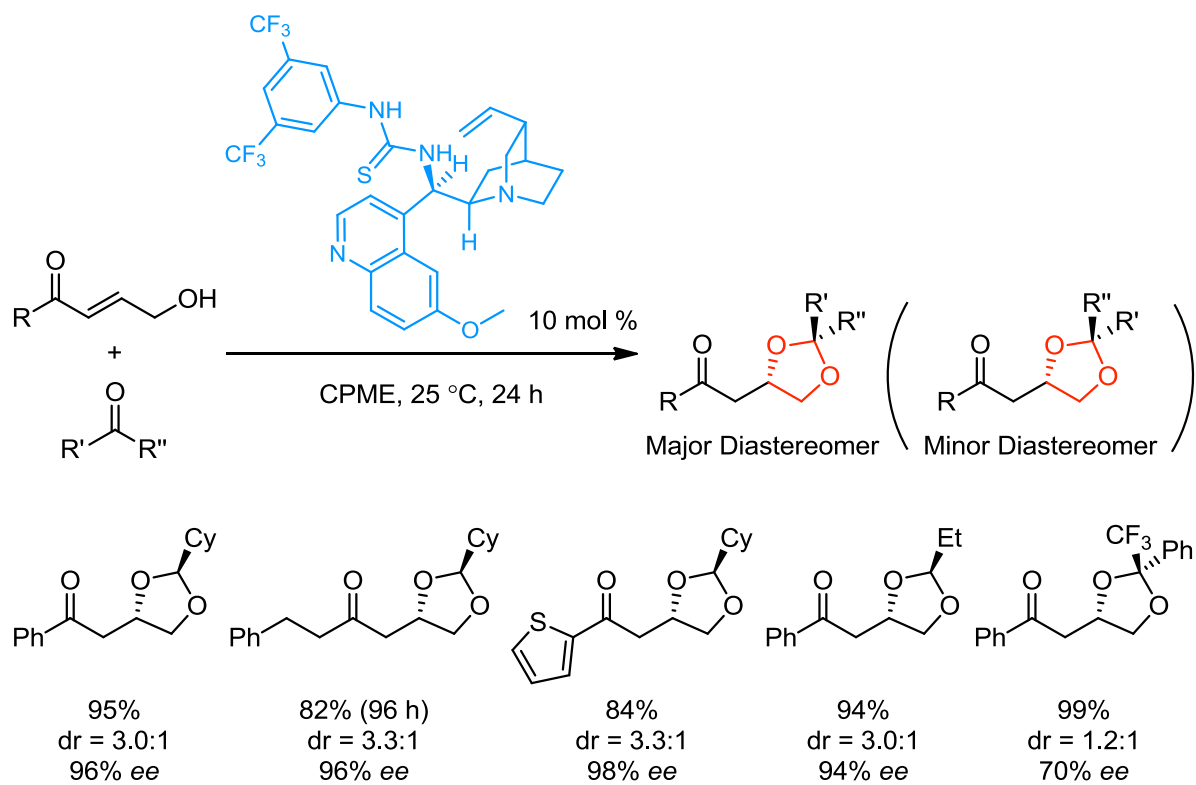
Scheme 29.

Cyclization (Chapter 5)

[3+2] Cycloaddition (Chapter 6)

Hemiacetal Intermediate
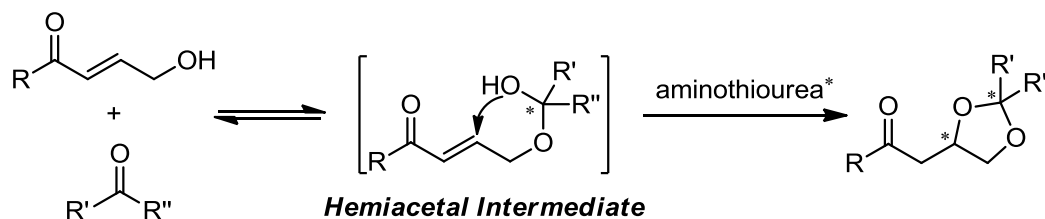
1,3-Dioxolanes were obtained stereoselectively by the formal cycloaddition reaction using cinchona-alkaloid-thiourea-based bifunctional organocatalysts (Scheme 30). The mechanistic considerations suggest that the enantioselectivity of this reaction can be attributed largely to the step comprising oxy-Michael addition from the hemiacetal intermediates. This synthetic route provides efficient access to a range of chiral cyclic acetals.

Scheme 30.

95%
dr = 3.0:1
96% *ee*

82% (96 h)
dr = 3.3:1
96% *ee*

84%
dr = 3.3:1
98% *ee*

94%
dr = 3.0:1
94% *ee*

99%
dr = 1.2:1
70% *ee*

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Instrumental and Materials

^{1}H and ^{13}C Nuclear magnetic resonance spectra were taken on a Varian UNITY INOVA 500 (^{1}H, 500 MHz; ^{13}C, 125.7 MHz) spectrometer or a Varian Mercury 200 (^{1}H, 300 MHz) spectrometer using tetramethylsilane as an internal standard for ^{1}H NMR (δ = 0 ppm) and CDCl$_3$ as an internal standard for ^{13}C NMR (δ = 77.0 ppm). Unless otherwise noted, ^{1}H NMR spectra were measured on a Varian UNITY INOVA 500 (500 MHz) spectrometer. When a ^{13}C NMR spectrum was measured using D$_2$O as a solvent, CD$_3$OD was used as an internal standard (δ = 49.0 ppm). When a ^{13}C NMR spectrum was measured using C$_6$D$_6$ as a solvent, C$_6$D$_6$ was used as an internal standard (δ = 128.06 ppm). ^{19}F NMR spectra were measured on a Varian Mercury 200 (^{19}F, 188 MHz) spectrometer with hexafluorobenzene as an internal standard (δ = 0 ppm). GC-MS analyses and High-resolution mass spectra were obtained with a JEOL JMS-700 spectrometer by electron ionization at 70 eV. High performance liquid chromatography (HPLC) was performed with a SHIMADZU Prominence chromatograph. Infrared (IR) spectra were determined on a SHIMADZU IR Affinity-1 spectrometer. Melting points were determined using a YANAKO MP-500D. Optical rotations were measured on a HORIBA SEPA-200 polarimeter. X-ray data were taken on a Bruker Smart APEX X-Ray diffractometer equipped with a large area CCD detector. The structures were solved with the program system SHELXS-97 and refined with SHELXL-97 package from Bruker. TLC analyses were performed by means of Merck Kieselgel 60 F$_{254}$ (0.25 mm) Plates. Visualization was accomplished with UV light (254 nm) and/or such as an aqueous alkaline KMnO$_4$ solution followed by heating. Flash column chromatography was carried out using Kanto Chemical silica gel (spherical, 40–50 μm). Preparative thin-layer chromatography (PTLC) was carried out using Merck Silica gel 60 F$_{254}$ (2 mm) Plates. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Distilled water and CPME were purchased from Wako Pure Chemical Co., stored under argon, and used as they are.

Chapter 1

Morita–Baylis–Hillman Reaction on Water without Organic Solvent, Assisted by a 'Catalytic' Amount of Amphiphilic Imidazole Derivatives

Morita–Baylis–Hillman (MBH) reaction using water as a solvent without any organic solvent can be performed by using an amphiphilic *N*-alkylimidazole.   This reaction is accelerated by the addition of water and is the first example of a 'catalytic' MBH reaction without any organic solvent in the presence of water.

Chapter 1

Introduction

The use of water as a solvent for organic reactions has been important since the pioneering work by Breslow.[1]   Some practical reasons, such as cost, safety, and environmental concerns, can be mentioned specially.   Moreover, water as a solvent often benefits the organic reaction itself dynamically.[2]   The high polarity of water may stabilize an ionic intermediate.[3]   In addition, the hydrophobicity of an organic compound will give rise to cohesion of substrates, which often enhances the reaction rate.[4]   The use of water as a solvent has been expanded even to the areas of organometallic chemistry, which include air- and watersensitive species.[5]   As the chemistry of organocatalytic reactions has been developed in recent years, the arguments about the contribution of water to these reactions have been rekindled.[6,7]   In the reaction with an organocatalyst, an ionic intermediate is inevitable, so the use of water may be effective.[6,7,8d]

The Morita–Baylis–Hillman (MBH) reaction is a useful method of C–C bond formation using an organocatalyst.[8–10]   The reaction is, however, notoriously slow and there have been many attempts to accelerate the reaction, some of which have used water.[7h–l,8d,9,10]   The reaction is initiated by an amine or phosphine (Scheme 1), and the formation of a betaine intermediate **1** is a crucial step.   In order to stabilize such an ionic intermediate, one can use water as a solvent. However, the addition of water may just protonate the ionic intermediate and may depress the nucleophilicity of the amine.   Actually, the reported methods that show rate enhancements for MBH reactions in the presence of water used an excess amount of nucleophilic mediator, and organic solvents were also often used as a co-solvent.[7h–l,8d]   To solve this contradiction, the author designed an imidazole[11] carrying a hydrophobic group,[6,7j,9] because the aggregation of the amphiphilic compounds in water will form a hydrophobic phase, which may work as a protection for the ionic intermediates and the nucleophilic catalyst from deactivation by water.

Scheme 1. Schematic Morita–Baylis–Hillman Reaction Catalyzed by an Amine.
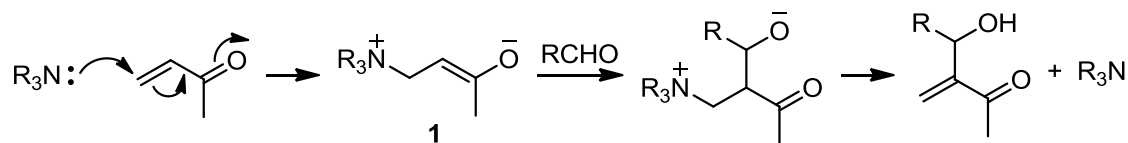

Results and Discussion

The author examined the reaction between benzaldehyde (**2a**) and methyl vinyl ketone (**3**) using a stoichiometric amount of an imidazole derivative and water as a solvent (Scheme 2). Although *N*-methylimidazole **5a** afforded only a trace amount of the product **4a**, *N*-tetradecylimidazole **5b** gave **4a** in 37% yield.   This suggests that the introduction of a tetradecyl group to an imidazole will make the reaction using water possible.

Scheme 2. MBH Reaction between Benzaldehyde (**2a**) and Methyl Vinyl Ketone (**3**) Using a Stoichiometric Amount of Imidazole Derivatives in the Presence of Water.

catalyst	yield of **4a** (%)
(5a)	<1
(5b)	37
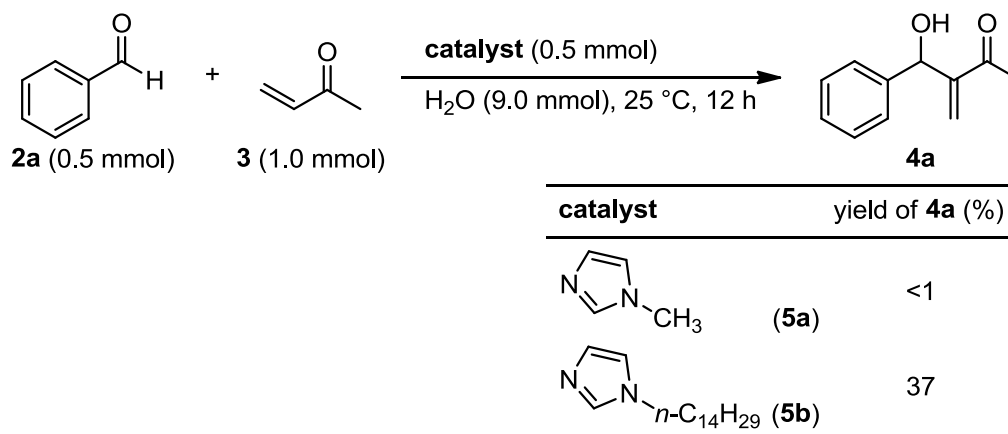
To improve the yield, the author examined the addition of a catalytic amount of Brønsted acid. As shown in Table 1, Brønsted acids whose pKa values are around 9 were effective in promoting this reaction (Table 1, entries 4–6, 8–10).   The added acid should activate methyl vinyl ketone without deactivation of the imidazole derivative.   Among them,

1,1,1,3,3,3-hexafluoropropan-2-ol (**6**) gave the best result (Table 1, entry 5).   The amount of acid was also optimized, and the results revealed that 20 mol % was sufficient for the reaction (Table 1, entries 5, 8–10).

   The author also tried to decrease the stoichiometric amount of the imidazole derivative to a catalytic amount (Table 2).   The use of 20 mol % of *N*-alkylimidazole **5b** was shown to give a reasonable yield of the product (Table 2, entry 5).

Table 1. MBH Reaction between Benzaldehyde (**2a**) and Methyl Vinyl Ketone (**3**) in the Presence of Brønsted Acid.[a]
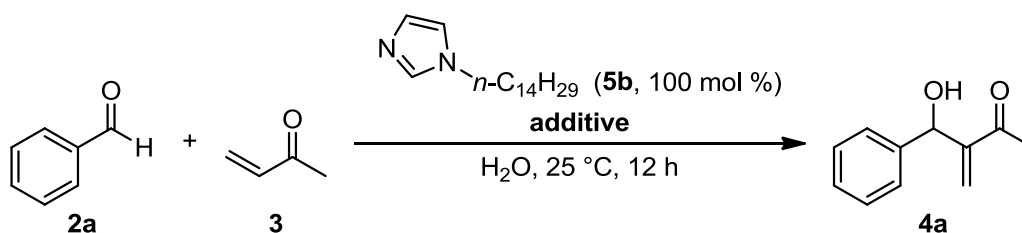
entry	**additive** (mol %)	pKa in H_2O	yield (%)[b]
1	TFA (20)	−0.25	39
2	Cl_3CCO_2H (20)	0.65	49
3	BzOH (20)	4.2	37
4	4-$NO_2C_6H_4OH$ (20)	7.1	51
5	$(CF_3)_2CHOH$ (**6**) (20)	9.3	54
6	PhOH (20)	10	52
7	CF_3CH_2OH (20)	12	46
8	$(CF_3)_2CHOH$ (**6**) (40)	9.3	61
9	$(CF_3)_2CHOH$ (**6**) (60)	9.3	64
10	$(CF_3)_2CHOH$ (**6**) (100)	9.3	63

[a] Reactions were run using benzaldehyde (**2a**, 0.5 mmol), methyl vinyl ketone (**3**, 1.0 mmol), *N*-tetradecylimidazole (**5b**, 0.5 mmol), the additive, and H_2O (9.0 mmol).   [b] Isolated yields.

Table 2. MBH Reaction between Benzaldehyde (**2a**) and Methyl Vinyl Ketone (**3**) Using a Catalytic Amount of **5b**.[a]
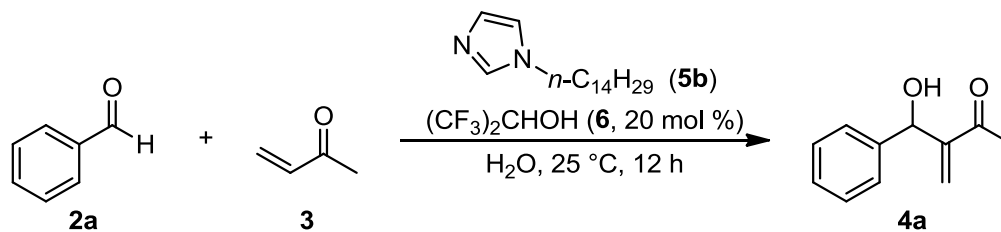
entry	catalyst loading (mol %)	yield (%)[b]
1	100	54
2	50	53
3	40	55
4	30	57
5	20	65
6	10	41

[a] Reactions were run using benzaldehyde (**2a**, 0.5 mmol), methyl vinyl ketone (**3**, 1.0 mmol), N-tetradecylimidazole (**5b**), 1,1,1,3,3,3-hexafluoropropan-2-ol (**6**, 0.1 mmol), and H_2O (9.0 mmol). [b] Isolated yields.
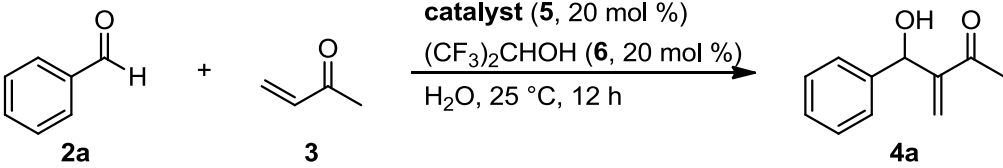
The amount of water was optimized under catalytic conditions using 20 mol % of N-alkylimidazole **5b** (Table 3). It is noteworthy that without water the yield decreased to 37%, while the reaction using 2.5 mmol of water afforded **4a** in 67% yield (Table 3, entries 1 and 2). The amount of water did not have a reasonable influence on the yield, and in any case, water worked for the acceleration of the reaction (Table 3, entries 2–10). Although a stoichiometric amount of nucleophile was required for acceleration by water in reported MBH reactions,[7h–l,8d] the author could construct a 'catalytic MBH reaction' in the presence of water by using N-alkylimidazole **5b**. This can be attributed to its aggregation in water. The aggregation makes a hydrophobic space by the tetradecyl groups, in which nucleophilic species are protected from deactivation by water, such as protonation. In addition, the aggregation may also help the

reaction by placing organic substrates in close proximity. 1,4-Diazabicyclo[2.2.2]octane and 4-(dimethylamino)pyridine, which have been regarded as efficient for MBH reactions, were also examined under the author's conditions; neither of them were effective catalysts (Scheme 3). Nucleophiles should be endowed with amphiphilicity for MBH reactions using water.

Table 3. Optimization of the Amount of Water for MBH Reaction between Benzaldehyde (**2a**) and Methyl Vinyl Ketone (**3**) Catalyzed by **5b**.[a]
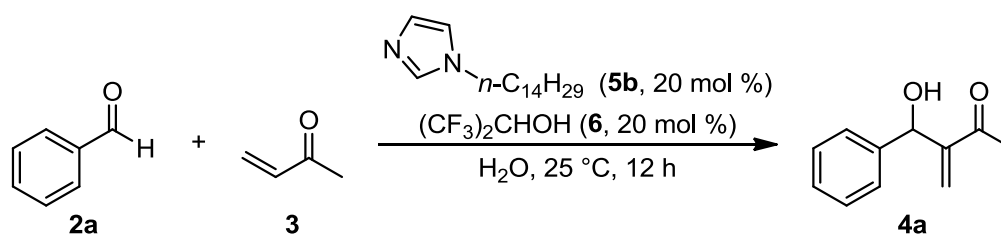
entry	H$_2$O (mmol)	yield (%)[b]
1	0	37
2	2.5	67
3	5.0	64
4	7.5	61
5	8.0	65
6	8.5	62
7	9.0	63
8	9.5	62
9	10	61
10	56 (1mL)	61

[a] Reactions were run using benzaldehyde (**2a**, 0.5 mmol), methyl vinyl ketone (**3**, 1.0 mmol), *N*-tetradecylimidazole (**5b**, 0.1 mmol), 1,1,1,3,3,3-hexafluoropropan-2-ol (**6**, 0.1 mmol), and H$_2$O. [b] Isolated yields.

Scheme 3. MBH Reaction between Benzaldehyde (**2a**) and Methyl Vinyl Ketone (**3**) Using DABCO and DMAP in the Presence of Water.
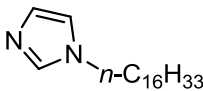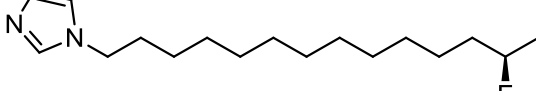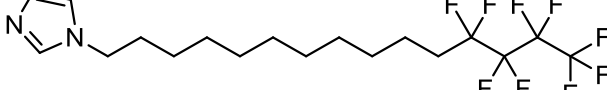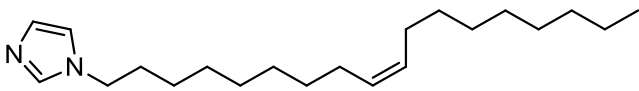

catalyst: DABCO   <1%
DMAP   6%
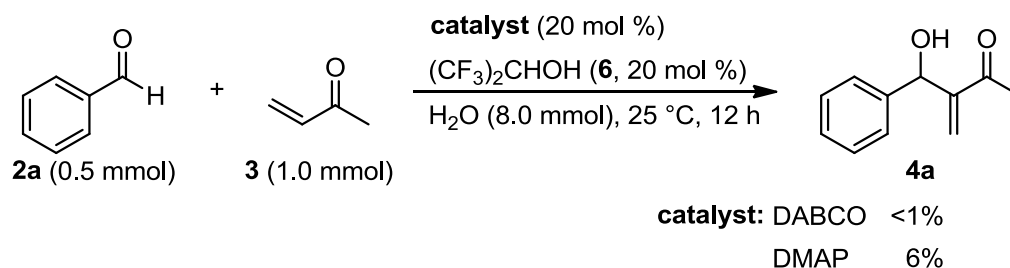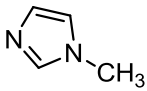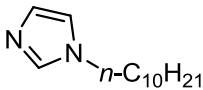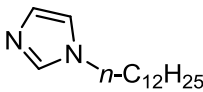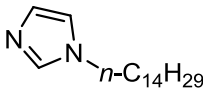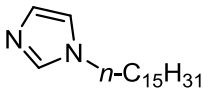
Then the author examined the effect created by modification of the hydrophobic groups in the catalyst (Table 4).   The lengths of carbon chains were arranged from C1 to C16 (Table 4, **5a–f**, entries 1–6).   Imidazoles with alkyl groups more than C10 showed acceptable yields.   No reasonable differences concerning the yield were observed among these cases (Table 4, entries 2–6).   The author also introduced fluorine atoms on the carbon chain,[12] and it resulted in only a slight increase in the yield (Table 4, **5g** and **5h**, entries 7 and 8).   The author also tried an unsaturated carbon chain, but the introduction of a (*Z*)-olefinic group in the middle of the chain did not create any remarkable effect (Table 4, **5i**, entry 9).

In these reactions, vigorous stirring was not necessary, although many reported reactions using water as a solvent required it for the formation of emulsions or fine oil drops.[6d,13]   As shown in Scheme 4, the reactions of benzaldehyde (**2a**, 0.5 mmol) and methyl vinyl ketone (**3**, 1.0 mmol) in the presence of *N*-hexadecylimidazole (**5f**, 0.1 mmol), 1,1,1,3,3,3-hexafluoropropan-2-ol (**6**, 0.1 mmol), and water (8.0 mmol) were examined both with and without stirring.   The non-stirred reaction in a wider vial (i.d. 20 mm) gave the same yield of **4a** as the vigorous stirred reaction.   However, if the non-stirred reaction was performed in a narrower vial (i.d. 5 mm), the yield of **4a** decreased to 50%.

Table 4. MBH Reaction between Benzaldehyde (**2a**) and Methyl Vinyl Ketone (**3**) Catalyzed by Imidazole Derivatives **5** Having Various Hydrophobic Groups.[a]
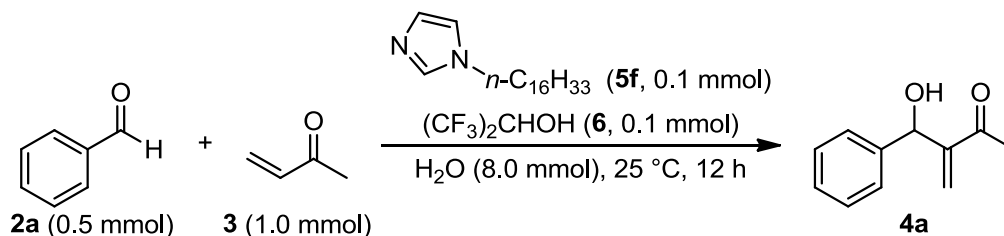

entry	catalyst	5	yield (%)[b]
1		**5a**	16
2		**5c**	63
3		**5d**	61
4		**5b**	65
5		**5e**	64
6		**5f**	64
7		**5g**	65
8		**5h**	66
9		**5i**	62

[a] Reactions were run using benzaldehyde (**2a**, 0.5 mmol), methyl vinyl ketone (**3**, 1.0 mmol), 1,1,1,3,3,3-hexafluoropropan-2-ol (**6**, 0.1 mmol), the catalyst **5** (0.1 mmol), and H_2O (8.0 mmol).
[b] Isolated yields.

Scheme 4. MBH Reaction between Benzaldehyde (**2a**) and Methyl Vinyl Ketone (**3**) with/without Stirring.

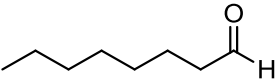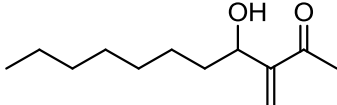|		
Stirred vigorously	No stirring in a vial (i.d. = 20 mm)	No stirring in a vial (i.d. = 5 mm)
	Contact area = ~ 22 cm^2/mL	Contact area = 1.4 cm^2/mL
12 h	12 h	12 h
64% yield	64% yield	50% yield
Reaction in emulsion	Reaction *on water*	Reaction *on water*

These results showed that stirring was not necessary to carry out the reaction under our conditions if there was sufficient surface area where the water and organic phase were contiguous. It seems to be important that the reaction proceeded in the range of the organic phase that is close to the surface of the water. In other words, this reaction can be classified as one of the reactions on water.[14] The author could utilize the potential of water to promote an organic reaction by forming a hydrophobic field for the reaction near the boundary between water and organic compounds, not by forming emulsions.

Table 5. MBH Reaction between Various Aldehydes **2** and Methyl Vinyl Ketone (**3**) Catalyzed by **5f** on Water without Organic Solvent.[a]
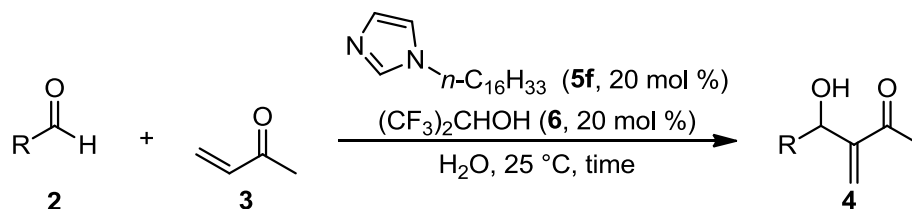
entry	substrate	2	product	4	time (h)	yield (%)[b]
1		2a		4a	12	64
2		2b		4b	12	37
3		2c		4c	12	67
4		2d		4d	12	64
5		2e		4e	12	61
6		2f		4f	12	65
7		2g		4g	24	62

Table 5. (Continued)

| 8 | | **2h** | | **4h** | 24 | 63 |

^a Reactions were run using the aldehyde **2** (0.5 mmol), methyl vinyl ketone (**3**, 1.0 mmol), *N*-hexadecylimidazole (**5f**, 0.1 mmol), 1,1,1,3,3,3-hexafluoropropan-2-ol (**6**, 0.1 mmol), and H_2O (8.0 mmol).   ^b Isolated yields.

Under the optimized conditions, the author examined MBH reactions of methyl vinyl ketone (**3**) with various aldehydes **2** (Table 5).   The use of aryl aldehydes **2c–e** carrying electron-withdrawing groups did not affect the yield (Table 5, entries 3–5).   Although the yields were not excellent, the author can show the possibility of MBH reactions that are catalyzed by imidazole derivatives carrying a hydrophobic group; such reactions are also accelerated by water.

Conclusion

In conclusion, the author has shown that some Morita–Baylis–Hillman reactions in the presence of water are initiated by a 'catalytic' amount of *N*-alkylimidazoles; in this reaction, the addition of water accelerated the reaction.   The 'catalytic' reaction promoted by water was realized by the amphiphilic imidazole derivatives carrying a hydrophobic group.   The amphiphilic catalyst forms a hydrophobic field for an organic reaction near the boundary between the water and the organic compounds by self-assembly.   These results show that such a reaction field constructed by an amphiphilic organocatalyst near the surface of water may be widely effective for the acceleration of organocatalytic reactions.

Experimental Section

Materials

Unless otherwise noted, commercially available reagents were used without purification.

Chapter 1

All aldehydes listed in Chapter 1 were commercially available.

General procedure for MBH reaction between aldehydes 2 and methyl vinyl ketone (3)

To a 5-mL vial were added sequentially aldehyde **2** (0.5 mmol), methyl vinyl ketone (**3**, 1.0 mmol), imidazole derivative **5** (0.1 mmol), 1,1,1,3,3,3-hexafluoropropan-2-ol (**6**, 0.1 mmol), and H_2O (0.14 mL, 8.0 mmol).   The mixture was stirred in an oil bath maintained at 25 °C for 12 h. The reaction mixture was subsequently diluted with Et_2O, dried over Na_2SO_4, and concentrated in vacuo.   Purification by flash silica gel column chromatography using hexane/EtOAc as an eluent afforded the corresponding product **4**.

General procedure for preparation of *N*-alkylimidazoles 5b, 5c, 5d, 5e, and 5f

A mixture of imidazole (0.75 g, 11 mmol) and alkyl bromide (11 mmol) in toluene (20 mL) in the presence of TEAI (0.57 g, 2.2 mmol) and NaOH (1.3 g, 33 mmol) was refluxed for 10 h. The resulting mixture was cooled to ambient temperature, H_2O was added, and the mixture was extracted with EtOAc.   The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo.   Purification by flash silica gel column chromatography using EtOAc as an eluent gave the corresponding *N*-alkylimidazole **5** in 64–78% yield.   The NMR results (^{1}H, ^{13}C) are as below.
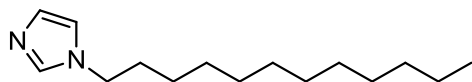
1-Decyl-1*H*-imidazole (5c): CAS RN [33529-02-1].
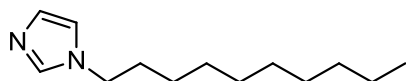
Yellow oil; yield: 64%.

^{1}H NMR ($CDCl_3$) δ 7.45 (s, 1 H), 7.05 (t, *J* = 1.0 Hz, 1 H), 6.90 (t, *J* = 1.0 Hz, 1 H), 3.92 (t, *J* = 7.5 Hz, 2 H), 1.76 (tt, *J* = 7.0, 7.0 Hz, 2 H), 1.34–1.20 (m, 14 H), 0.87 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$) δ 137.1, 129.4, 118.7, 47.0, 31.8, 31.1, 29.5, 29.4, 29.2, 29.0, 26.5, 22.6, 14.1.
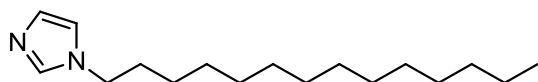
1-Dodecyl-1*H*-imidazole (5d): CAS RN [4303-67-7].

Orange oil; yield: 66%.

^{1}H NMR (CDCl$_3$) δ 7.45 (s, 1 H), 7.04 (t, *J* = 1.0 Hz, 1 H), 6.89 (t, *J* = 1.0 Hz, 1 H), 3.91 (t, *J* = 7.0 Hz, 2 H), 1.76 (tt, *J* = 7.0, 7.0 Hz, 2 H), 1.32–1.20 (m, 18 H), 0.87 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR (CDCl$_3$) δ 137.0, 129.3, 118.7, 47.0, 31.9, 31.1, 29.6, 29.5, 29.4, 29.3, 29.0, 26.5, 22.6, 14.1.
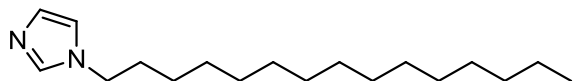
1-Tetradecyl-1*H*-imidazole (5b): CAS RN [54004-47-6].
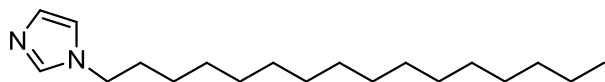

Pale yellow solid; yield: 68%.

^{1}H NMR (CDCl$_3$) δ 7.45 (s, 1 H), 7.05 (t, *J* = 1.0 Hz, 1 H), 6.90 (t, *J* = 1.0 Hz, 1 H), 3.91 (t, *J* = 7.5 Hz, 2 H), 1.76 (tt, *J* = 7.0, 7.0 Hz, 2 H), 1.34–1.20 (m, 22 H), 0.88 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR (CDCl$_3$) δ 137.1, 129.4, 118.7, 47.0, 31.9, 31.1, 29.7, 29.62, 29.58, 29.50, 29.4, 29.3, 29.1, 26.5, 22.7, 14.1.

1-Pentadecyl-1*H*-imidazole (5e): CAS RN [130482-55-2].

Pale yellow solid; yield: 70%.

^{1}H NMR (CDCl$_3$) δ 7.45 (s, 1 H), 7.05 (t, *J* = 1.0 Hz, 1 H), 6.90 (t, *J* = 1.0 Hz, 1 H), 3.91 (t, *J* = 7.0 Hz, 2 H), 1.76 (tt, *J* = 7.0, 7.0 Hz, 2 H), 1.34–1.20 (m, 24 H), 0.87 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR (CDCl$_3$) δ 137.1, 129.4, 118.7, 47.0, 31.9, 31.1, 29.66, 29.65, 29.63, 29.62, 29.58, 29.50, 29.4, 29.3, 29.1, 26.5, 22.7, 14.1.

1-Hexadecyl-1*H*-imidazole (5f): CAS RN [58175-55-6].

White solid; yield: 78%.

^{1}H NMR (CDCl$_3$) δ 7.45 (s, 1 H), 7.05 (t, *J* = 1.0 Hz, 1 H), 6.90 (t, *J* = 1.0 Hz, 1 H), 3.92 (t, *J* = 7.5 Hz, 2 H), 1.76 (tt, *J* = 7.0, 7.0 Hz, 2 H), 1.34–1.20 (m, 26 H), 0.87 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR (CDCl$_3$) δ 137.1, 129.4, 118.7, 47.0, 31.9, 31.1, 29.67, 29.66, 29.65, 29.64, 29.62, 29.58, 29.50, 29.4, 29.3, 29.1, 26.5, 22.7, 14.1.

Procedure for preparation of (*R*)-1-(13-fluorotetradecyl)-1*H*-imidazole (5g)[16]

NaH (60%, 0.066 g, 1.65 mmol) was washed with hexane, and THF (2 mL) was added. To the solution, a solution of imidazole (0.10 g, 1.5 mmol) in THF (2 mL) was added slowly at 0 °C. The mixture was stirred at room temperature for 45 min, then a solution of (*R*)-1-bromo-13-fluorotetradecane (0.44 g, 1.5 mmol) in THF (1 mL) was added slowly to the mixture, and it was stirred for 7 d. The mixture was filtered, and the filtrate was concentrated in vacuo. Purification by flash silica gel column chromatography using EtOAc as an eluent gave **5g** (0.30 g, 72% yield).

**(*R*)-1-(13-Fluorotetradecyl)-1*H*-imidazole (5g)**.
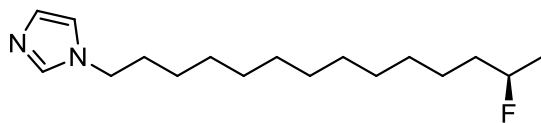
White solid.

[α]$_D^{28}$ –6.7 (*c* 4.46, CHCl$_3$). ^{1}H NMR (CDCl$_3$) δ 7.45 (s, 1 H), 7.05 (t, *J* = 1.0 Hz, 1 H), 6.90 (t, *J* = 1.0 Hz, 1 H), 4.64 (m, 1 H), 3.92 (t, *J* = 7.5 Hz, 2 H), 1.76 (m, 2 H), 1.65 (m, 1 H), 1.56–1.38 (m, 2 H), 1.33 (t, *J* = 6.0 Hz, 3 H), 1.36–1.22 (m, 17 H). ^{13}C NMR (CDCl$_3$) δ 137.1, 129.4, 118.7, 91.1 (d, *J* = 164.2 Hz), 47.0, 36.9 (d, *J* = 20.6 Hz), 31.1, 29.52, 29.48, 29.47, 29.42, 29.40, 29.1, 26.5, 25.1, 25.0, 21.0 (d, *J* = 23.0 Hz). ^{19}F NMR (CDCl$_3$) δ –10.3. Mp. 32.6–32.8 °C.

TLC: R_f 0.10 (EtOAc).   IR (KBr): 2930, 2849, 2359, 1512, 1471, 1385, 1283, 1231, 1132, 1107, 1082, 1057, 1036, 1007, 907, 837, 816, 750, 731, 665, 623 cm^{-1}.   HRMS Calcd for C$_{17}$H$_{31}$FN$_2$: M$^+$, 282.2471. Found: m/z 282.2472.

Procedure for preparation of 1-(12,12,13,13,14,14,15,15,15-nonafluoropentadecyl)-1H-imidazole (5h)[16]

NaH (60%, 0.15 g, 3.7 mmol) was washed with hexane, and THF (3 mL) was added.   To the solution, a solution of imidazole (0.23 g, 3.4 mmol) in THF (3 mL) was added slowly at 0 °C. The mixture was stirred at room temperature for 15 min.   Then a solution of 1-bromo-12,12,13,13,14,14,15,15,15-nonafluoropentadecane (1.5 g, 3.3 mmol) in THF (4 mL) was added slowly to the mixture, and it was stirred for 7 d.   The mixture was filtered, and the filtrate was concentrated in vacuo.   Purification by flash silica gel column chromatography using EtOAc as an eluent gave **5h** (1.1 g, 79% yield).

1-(12,12,13,13,14,14,15,15,15-Nonafluoropentadecyl)-1H-imidazole (5h).
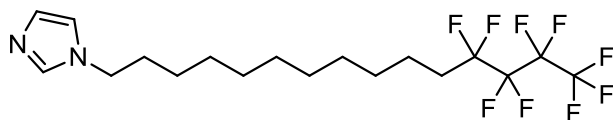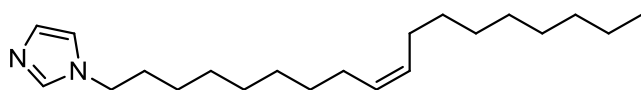

Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.46 (s, 1 H), 7.05 (t, J = 1.0 Hz, 1 H), 6.90 (t, J = 1.0 Hz, 1 H), 3.92 (t, J = 7.5 Hz, 2 H), 2.04 (m, 2 H), 1.76 (tt, J = 7.0, 7.0 Hz, 2 H), 1.59 (m, 2 H), 1.39–1.24 (m, 14 H). ^{19}F NMR (CDCl$_3$) δ 80.2 (3 F), 46.9 (2 F), 37.0 (2 F), 35.5 (2 F).   TLC: R_f 0.10 (EtOAc).   IR (neat): 2930, 2857, 1508, 1468, 1356, 1233, 1132, 1076, 1032, 907, 880, 847, 812, 733, 719, 664, 625, 592, 532 cm^{-1}.   HRMS Calcd for C$_{18}$H$_{25}$F$_9$N$_2$: M$^+$, 440.1874. Found: m/z 440.1874.

Procedure for preparation of (Z)-1-(octadec-9-enyl)-1H-imidazole (5i)[15]

A mixture of imidazole (0.34 g, 5.0 mmol) and (Z)-1-bromooctadec- 9-ene (1.7 g, 5.0 mmol) in toluene (10 mL) in the presence of TEAI (0.26 g, 1.0 mmol) and NaOH (0.60 g, 15 mmol) was

refluxed for 18.5 h.   The resulting mixture was cooled to ambient temperature, H_2O was added, and the mixture was extracted with EtOAc.   The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo.   Purification by flash silica gel column chromatography using EtOAc as an eluent gave **5i** (1.2 g, 75% yield).

**(Z)-1-(Octadec-9-enyl)-1H-imidazole (5i)**: CAS RN [90343-81-0].

Yellow oil.

^{1}H NMR (CDCl$_3$) δ 7.45 (s, 1 H), 7.05 (t, J = 1.0 Hz, 1 H), 6.90 (t, J = 1.0 Hz, 1 H), 5.34 (m, 2 H), 3.91 (t, J = 7.0 Hz, 2 H), 2.00 (dt, J = 6.0, 7.0 Hz, 4 H), 1.76 (tt, J = 7.0, 7.0 Hz, 2 H), 1.36–1.22 (m, 22 H), 0.88 (t, J = 7.5 Hz, 3 H). ^{13}C NMR (CDCl$_3$) δ 137.1, 130.0, 129.7, 129.4, 118.7, 47.0, 31.9, 31.1, 29.73, 29.66, 29.5, 29.4, 29.3, 29.1, 29.03, 29.01, 27.2, 27.1, 26.5, 22.7, 14.1.
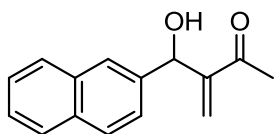
Characterization Data of Products

4-Hydroxy-3-methylene-4-phenylbutan-2-one (4a): CAS RN [73255-39-7].
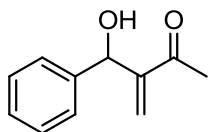
Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.37–7.25 (m, 5 H), 6.20 (s, 1 H), 5.98 (d, J = 1.0 Hz, 1 H), 5.62 (d, J = 5.0 Hz, 1 H), 3.13 (d, J = 5.0 Hz, 1 H), 2.34 (s, 3 H). ^{13}C NMR (CDCl$_3$) δ 200.4, 149.9, 141.4, 128.4, 127.7, 126.7, 126.5, 72.9, 26.5.
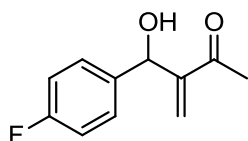
4-Hydroxy-3-methylene-4-(2-naphthyl)butan-2-one (4b): CAS RN [849900-45-4].

Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.86–7.79 (m, 4 H), 7.50–7.40 (m, 3 H), 6.23 (s, 1 H), 6.01 (d, J = 1.5 Hz, 1 H), 5.80 (d, J = 5.0 Hz, 1 H), 3.25 (dd, J = 5.0, 1.0 Hz, 1 H), 2.36 (s, 3 H). ^{13}C NMR (CDCl$_3$) δ 200.4, 149.8, 138.8, 133.2, 132.9, 128.12, 128.07, 127.6, 127.0, 126.1, 126.0, 125.4, 124.5, 72.9, 26.5.
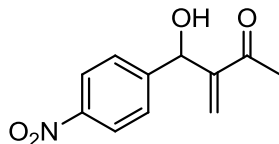
4-(4-Fluorophenyl)-4-hydroxy-3-methylenebutan-2-one (4c): CAS RN [888966-21-0].

Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.37–7.33 (m, 2 H), 7.06–7.01 (m, 2 H), 6.22 (d, J = 0.5 Hz, 1 H), 5.99 (d, J = 1.5 Hz, 1 H), 5.61 (d, J = 5.0 Hz, 1 H), 3.10 (d, J = 5.0 Hz, 1 H), 2.36 (s, 3 H). ^{13}C NMR (CDCl$_3$) δ 200.3, 162.2 (d, J = 245.7 Hz), 149.8, 137.2, 128.2 (d, J = 7.7 Hz), 126.8, 115.2 (d, J = 21.6 Hz), 72.3, 26.5. ^{19}F NMR (CDCl$_3$) δ 46.6.

4-Hydroxy-3-methylene-4-(4-nitrophenyl)butan-2-one (4d): CAS RN [203111-49-3].
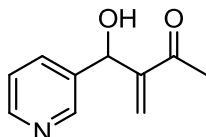

Colorless oil.

^{1}H NMR (CDCl$_3$) δ 8.20 (dt, J = 9.0, 2.0 Hz, 2 H), 7.55 (ddt, J = 9.0, 0.5, 2.0 Hz, 2 H), 6.27 (s, 1 H), 6.03 (d, J = 1.5 Hz, 1 H), 5.68 (d, J = 5.5 Hz, 1 H), 3.29 (d, J = 5.5 Hz, 1 H), 2.36 (s, 3 H).

^{13}C NMR (CDCl$_3$) δ 200.1, 148.93, 148.86, 147.3, 127.8, 127.2, 123.6, 72.3, 26.4.

4-Hydroxy-3-methylene-4-(3-pyridyl)butan-2-one (4e): CAS RN [223393-88-2].

White solid.

^{1}H NMR (CDCl$_3$) δ 8.54 (d, *J* = 2.0 Hz, 1 H), 8.47 (dd, *J* = 5.0, 1.5 Hz, 1 H), 7.72 (ddd, *J* = 8.0, 1.5, 0.5 Hz, 1 H), 7.26 (ddd, *J* = 8.0, 5.0, 0.5 Hz, 1 H), 6.25 (d, *J* = 0.5 Hz, 1 H), 6.08 (d, *J* = 1.5 Hz, 1 H), 5.64 (s, 1 H), 3.79 (br, 1 H), 2.35 (s, 3 H). ^{13}C NMR (CDCl$_3$) δ 200.0, 149.3, 148.8, 148.3, 137.3, 134.3, 127.1, 123.3, 70.7, 26.4.
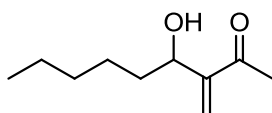
4-Hydroxy-3-methylene-6-phenylhexan-2-one (4f): CAS RN [108762-30-7].
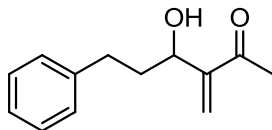
Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.30–7.26 (m, 2 H), 7.22–7.16 (m, 3 H), 6.11 (s, 1 H), 6.01 (d, *J* = 1.0 Hz, 1 H), 4.45 (ddd, *J* = 6.5, 6.5, 6.5 Hz, 1 H), 2.82 (m, 1 H), 2.74 (d, *J* = 6.5 Hz, 1 H), 2.68 (m, 1 H), 2.35 (s, 3 H), 1.93 (m, 2 H). ^{13}C NMR (CDCl$_3$) δ 200.9, 150.0, 141.7, 128.5, 128.4, 125.9, 125.8, 71.0, 37.7, 32.1, 26.5.

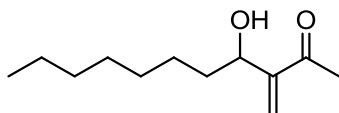**4-Hydroxy-3-methylenenonan-2-one (4g)**: CAS RN [108762-27-2].

Colorless oil.

^{1}H NMR (CDCl$_3$) δ 6.10 (s, 1 H), 5.99 (d, *J* = 1.0 Hz, 1 H), 4.40 (ddd, *J* = 6.5, 6.5, 6.5 Hz, 1 H),

2.63 (d, *J* = 6.5 Hz, 1 H), 2.36 (s, 3 H), 1.59 (m, 2 H), 1.42 (m, 1 H), 1.34–1.23 (m, 5 H), 0.88 (t,

J = 7.0 Hz, 3 H). ^{13}C NMR (CDCl$_3$) δ 200.8, 150.3, 125.6, 71.6, 36.2, 31.6, 26.5, 25.6, 22.6,

14.0.

4-Hydroxy-3-methyleneundecan-2-one (4h): CAS RN [108762-27-2].

Colorless oil.

^{1}H NMR (CDCl$_3$) δ 6.10 (s, 1 H), 5.99 (d, *J* = 0.5 Hz, 1 H), 4.40 (ddd, *J* = 6.5, 6.5, 6.5 Hz, 1 H),

2.63 (d, *J* = 6.5 Hz, 1 H), 2.36 (s, 3 H), 1.59 (tt, *J* = 7.0, 7.0 Hz, 2 H), 1.42 (m, 1 H), 1.35–1.20

(m, 9 H), 0.87 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR (CDCl$_3$) δ 200.8, 150.3, 125.6, 71.6, 36.3, 31.8,

29.4, 29.2, 26.5, 25.9, 22.6, 14.1.

Chapter 1

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Chapter 2

Amphiphilic Organocatalyst for Schotten–Baumann-Type Tosylation of Alcohols under Organic Solvent Free Condition

The tosylations of alcohols with p-toluenesulfonyl chloride were performed effectively using N-hexadecylimidazole as a catalyst in water containing K_2CO_3. The aggregation of the catalyst carrying a hydrophobic methylene chain worked as a substitute for organic solvent.
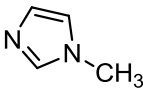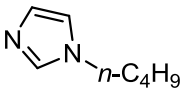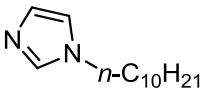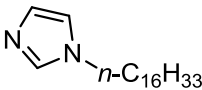
Introduction

Tosylation has long been recognized as a method of converting alcohols into reactive electrophiles.[1]   While the treatment of alcohols with tosyl chloride and an amine in an organic solvent is a conventional method to prepare the tosylates, the Schotten–Baumann method,[2] which is performed with tosyl chloride and an inorganic base such as potassium carbonate in an organic solvent[3] or in a biphase system consisting of water and an organic solvent,[4] has also been developed.   As the Schotten–Baumann reaction can avoid the use of a stoichiometric amount of amine, the procedures have been evaluated from the economical and environmental superiority. Even though the method was well planned, it still requires an organic solvent.   Tanabe reported an organic solvent free Schotten–Baumann-type tosylation in water, but it requires the control of the pH of water and the slow addition of tosyl chloride to prevent the hydrolysis of the chloride.[5] It might be because the sulfonylammonium intermediate formed in the activation of tosyl chloride with an amine catalyst is incredibly unstable in water.   The procedure reported by Kazemi without water and any organic solvent seems to be attractive, but it should be performed under harsh conditions to use inorganic bases without water.[6]   The author supposed that the use of an *N*-alkylimidazole as a nucleophilic catalyst with a hydrophobic group[7] for Schotten–Baumann-type tosylation might realize an organic solvent-free condition, because the aggregation of the amphiphilic compounds in water will form a hydrophobic phase, which may work as a substitute for an organic solvent.[8,9]   It will prevent tosyl chloride and the product from undergoing hydrolysis.
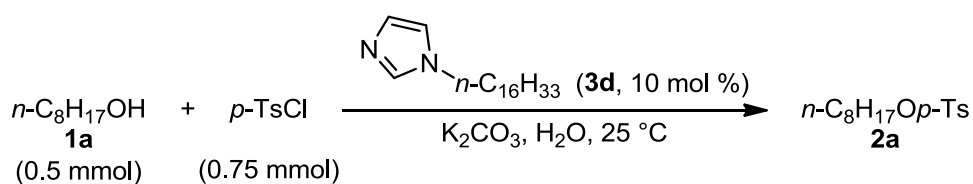
Results and Discussion

As shown in Table 1, 1-octanol (0.5 mmol) was treated with *p*-toluenesulfonyl chloride (0.75 mmol) and potassium carbonate (0.5 mmol) in the presence of *N*-alkylimidazole (0.1 mmol) and water (10 mmol) at 25 °C for 2 h.   The length of the alkyl chain on the imidazole determined the

efficiency of the reaction.   While *N*-methylimidazole (**3a**) or *N*-butylimidazole (**3b**) afforded the corresponding tosylate **2a** in poor yield, *N*-hexadecylimidazole (**3d**) gave the product **2a** in 82% yield.   Further optimization with **3d** as a catalyst showed that the reaction using 5.0 mmol of water improved the yield of tosylate **2a** to almost quantitatively (Table 2, entries 1–5).   In the absence of water, the yield of tosylate **2a** was decreased to 43% (Table 2, entry 6).   Potassium carbonate was also essential for this reaction (Table 2, entry 7).

Table 1. Organic Solvent Free Schotten–Baumann-Type Tosylation of 1-Octanol with Various Amines as Catalyst.[a]

$$n\text{-C}_8\text{H}_{17}\text{OH} + p\text{-TsCl} \xrightarrow[\substack{\text{K}_2\text{CO}_3 \ (0.5 \ \text{mmol}) \\ \text{H}_2\text{O} \ (10 \ \text{mmol}), \ 25 \ °\text{C}, \ 2 \ \text{h}}]{\text{catalyst} \ (20 \ \text{mol} \ \%)} n\text{-C}_8\text{H}_{17}\text{O}p\text{-Ts}$$

1a (0.5 mmol)   **p-TsCl** (0.75 mmol)   **2a**

entry	catalyst		yield (%)[b]
1	Et$_3$N		17
2	DMAP		18
3	[imidazole]–CH$_3$	**3a**	29
4	[imidazole]–n-C$_4$H$_9$	**3b**	36
5	[imidazole]–n-C$_{10}$H$_{21}$	**3c**	78
6	[imidazole]–n-C$_{16}$H$_{33}$	**3d**	82

[a]   Reactions were run using 1-octaol (**1a**, 0.5 mmol), *p*-toluenesulfonyl chloride (0.75 mmol), potassium carbonate (0.5 mmol), the catalyst (0.1 mmol), and H$_2$O (10 mmol).   [b] Yields were determined by ^{1}H NMR.
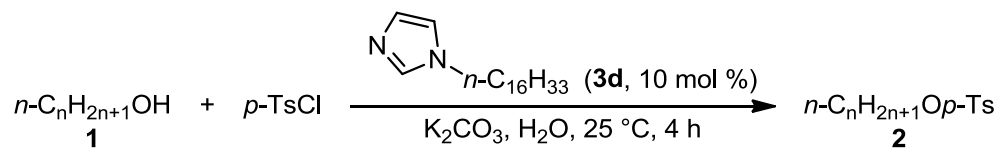
Table 2. Optimization of Conditions with **3d** as Catalyst.[a]

$$n\text{-}C_8H_{17}OH \quad + \quad p\text{-TsCl} \quad \xrightarrow[\text{K}_2\text{CO}_3,\ \text{H}_2\text{O, 25 °C}]{n\text{-}C_{16}H_{33}\ (\textbf{3d},\ 10\ \text{mol \%})} \quad n\text{-}C_8H_{17}Op\text{-Ts}$$

1a (0.5 mmol)   (0.75 mmol)   **2a**

entry	condition	yield (%)[b]
1[c]	H_2O 10 mmol, K_2CO_3 0.5 mmol, 2 h	82
2	H_2O 5 mmol, K_2CO_3 0.5 mmol, 3 h	87
3	H_2O 5 mmol, K_2CO_3 0.5 mmol, 4 h	99 (95[d])
4	H_2O 10 mmol, K_2CO_3 0.5 mmol, 4 h	86
5	H_2O 15 mmol, K_2CO_3 0.5 mmol, 4 h	65
6[c]	neat, K_2CO_3 0.5 mmol, 2 h	43
7	H_2O 5 mmol, without K_2CO_3, 4 h	12

[a] Reactions were run using 1-octaol (**1a**, 0.5 mmol), p-toluenesulfonyl chloride (0.75 mmol), potassium carbonate, N-hexadecylimidazole (**3d**, 0.05 mmol), and H_2O. [b] Yields were determined by ^{1}H NMR. [c] Reaction was run using 20 mol % of **3d**. [d] Isolated yield.

Under this organic solvent-free condition, various 1-alkanols were converted into the corresponding tosylates. As shown in Table 3, n-alkanols from C1 to C10 were examined. Although methanol (**1b**), ethanol (**1c**), and 1-propanol (**1d**) gave unsatisfactory results probably as they are too soluble in water to be tosylated (Table 3, entries 1–3), 1-alkanols **1a**, **1e**–**1j** with longer alkyl chains afforded the corresponding tosylates in high yields (Table 3, entries 4–10).

Table 3. Organic Solvent Free Schotten–Baumann-Type Tosylation of 1-Alkanols with **3d** as Catalyst.[a]

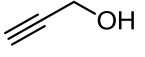$$n\text{-}C_nH_{2n+1}OH \quad + \quad p\text{-TsCl} \xrightarrow[\text{K}_2\text{CO}_3, \text{H}_2\text{O}, 25\,°\text{C}, 4\,\text{h}]{\overset{\displaystyle N \diagdown N - n\text{-}C_{16}H_{33} \;\; (\textbf{3d}, 10\text{ mol }\%)}{}} n\text{-}C_nH_{2n+1}O p\text{-Ts}$$

| | **1** | | | **2** |

entry	$n\text{-}C_nH_{2n+1}$	**1**	yield (%)[b]
1	CH_3	**1b**	35
2	C_2H_5	**1c**	35
3	$n\text{-}C_3H_7$	**1d**	52
4	$n\text{-}C_4H_9$	**1e**	71
5	$n\text{-}C_5H_{11}$	**1f**	82
6	$n\text{-}C_6H_{13}$	**1g**	88
7	$n\text{-}C_7H_{15}$	**1h**	90
8	$n\text{-}C_8H_{17}$	**1a**	95
9	$n\text{-}C_9H_{19}$	**1i**	89
10	$n\text{-}C_{10}H_{21}$	**1j**	96

[a] Reactions were run using the 1-alkanol **1** (0.5 mmol), *p*-toluenesulfonyl chloride (0.75 mmol), potassium carbonate (0.5 mmol), *N*-hexadecylimidazole (**3d**, 0.05 mmol), and H_2O (5 mmol). [b] Isolated yields.

Table 4. Organic Solvent Free Schotten–Baumann-Type Tosylation of Various Alcohols with **3d** as Catalyst.[a]

$$\text{ROH} + p\text{-TsCl} \xrightarrow[\text{K}_2\text{CO}_3, \text{H}_2\text{O}, 25\,°\text{C}, 4\,\text{h}]{n\text{-C}_{16}\text{H}_{33}\ (\textbf{3d}, 10\ \text{mol \%})} \text{RO}p\text{-Ts}$$
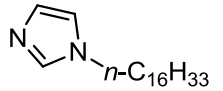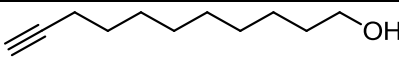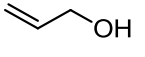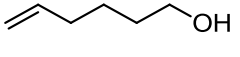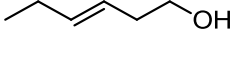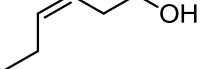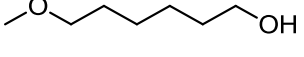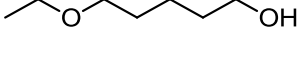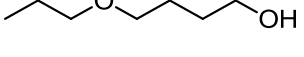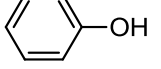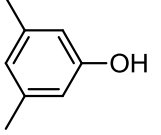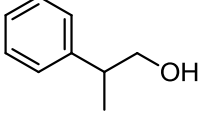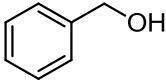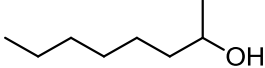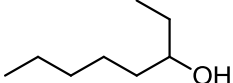
entry	ROH	1	yield (%)[b]
1		**1k**	90
2		**1l**	79
3		**1m**	70
4		**1n**	44
5		**1o**	83
6		**1p**	56
7		**1q**	56
8		**1r**	61
9		**1s**	66
10		**1t**	54
11		**1u**	80
12		**1v**	50
13	CF_3CH_2OH	**1w**	75
14		**1x**	73

Table 4. (Continued)

15		**1y**	34
16		**1z**	21
17		**1aa**	24

[a] Reactions were run using the alcohol **1** (0.5 mmol), *p*-toluenesulfonyl chloride (0.75 mmol), potassium carbonate (0.5 mmol), *N*-hexadecylimidazole (**3d**, 0.05 mmol), and H_2O (5 mmol).   [b] Isolated yields.

Reactions starting from alcohols other than 1-alkanols were also examined (Table 4).   The existence of a C–C triple bond in the substrate did not disturb the reaction (Table 4, entries 1–3). Allyl alcohol (**1n**) gave the product in 44% yield (Table 4, entry 4).   In the cases of hexenols **1o–1q**, the position of C–C double bond was significant for the reaction to proceed efficiently (Table 4, entries 5–7).[10]   Alcohols **1r–1t** with etherial moieties afforded the tosylates **2r–2t** in lower yields than 1-alkanols shown in Table 3 (Table 4, entries 8–10).   Phenol (**1u**) was also converted into the corresponding tosylate **2u**, although the bulkier derivative **1v** resulted in lower yield (Table 4, entries 11 and 12).   2,2,2-Trifluoroethanol (**1w**) resulted in good yield in contrast to the reaction of ethanol (**1c**) in Table 3 (Table 4, entry 13).   2-Phenylpropan-1-ol (**1x**) was a suitable substrate, however, the conversions of benzyl alcohol (**1y**) and secondary alcohols **1z**, **1aa** were not high (Table 1, entries 16 and 17).

The low conversion of 3-hexenols (**1p**, **1q**) (Table 4, entries 6 and 7) into the corresponding tosylates compared to 5-hexenol (**1o**) (Table 4, entry 5) may be explained as follows: the author suppose that *N*-alkylimidazole molecules align along the interface between water and organic compounds (Figure 1).[7a–b,9,11]   The imidazolium species, which are formed from tosyl chloride and the *N*-alkylimidazole, may also work as an efficient surfactant.   Alkoxides, which are also formed by the inorganic base in water, can also work as a surfactant.   The *N*-alkylimidazoles,

the imidazoliums, and the alkoxides are aligned in close proximity and react to give the tosylates efficiently.   Thus, the alignment of alkoxides, which keeps the right orientation in the *N*-alkylimidazolium phase, will lead to high conversion; the bent carbon chain skeleton such as 3-hexenol might be unfavorable for the reaction.   Similarly, the low conversion of 3,5-dimethylphenol (**1v**), benzyl alcohol (**1y**) and secondary alcohols **1z**, **1aa** may be explained (Table 4, entries 12, 15–17).
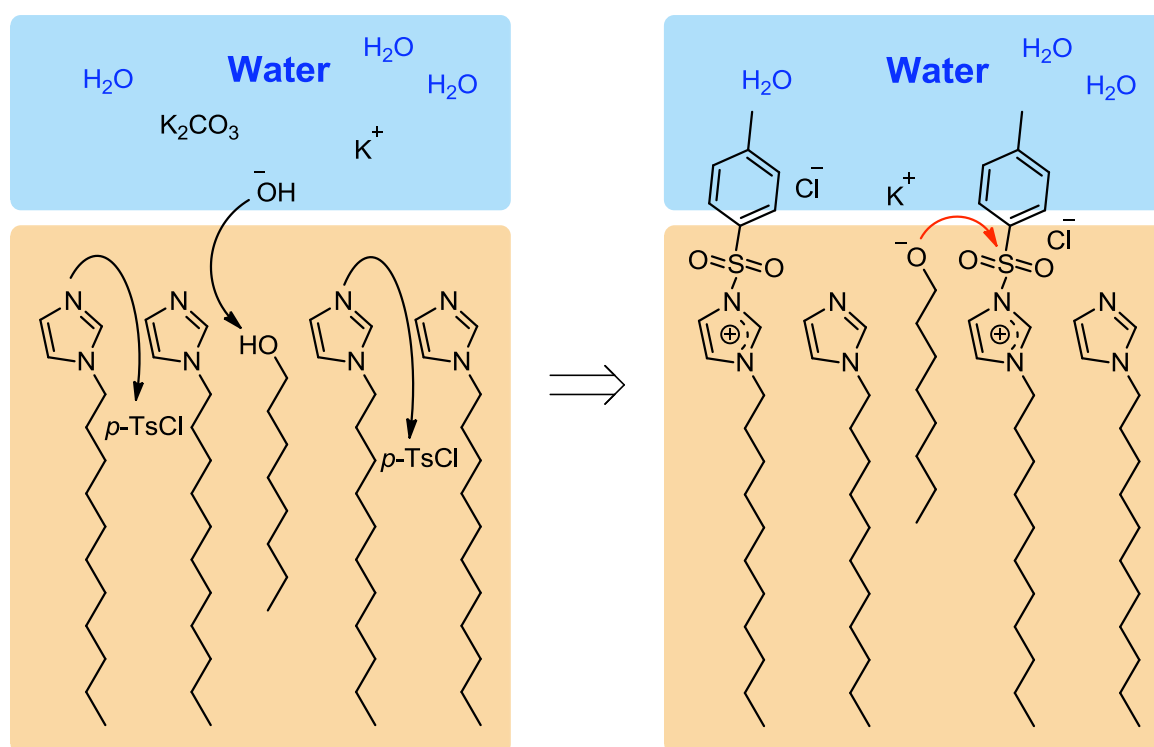

Figure 1. Role of the Alkyl Chain in the Catalyst.

This organic solvent-free method was also perfomed on a practical scale, as shown in Scheme 1: to a 100-mL glass vessel, 1-octanol (**1a**, 6.5 g, 50 mmol), *N*-hexadecylimidazole (**3d**, 1.5 g, 5.0 mmol), *p*-toluenesulfonyl chloride (14 g, 75 mmol), potassium carbonate (6.9 g, 50 mmol) and water (9 mL, 500 mmol) were added sequentially.   The mixture was stirred for 4 h in an oil bath maintained at 25 °C.   The mixture was then diluted with ethyl acetate and dried over anhydrous magnesium sulfate.   The organic solution was concentrated in vacuo.   After purification with

flash silica gel column chromatography using hexane/ethyl acetate (v/v = 30/1) as an eluent, 12 g

of **3a** (41.5 mmol) was isolated in 83% yield.

Scheme 1. Tosylation of 1-Octanol (**1a**) in Water on Semi-Large Scale.
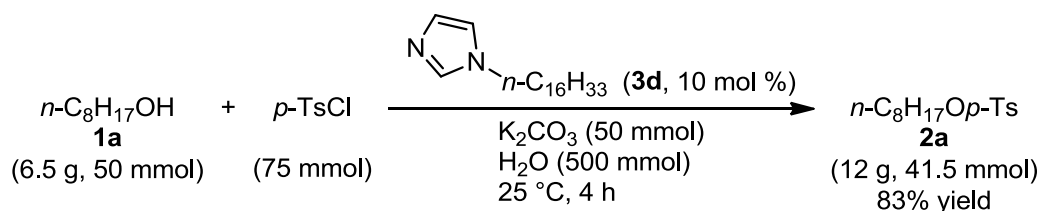
Conclusion

The author showed a novel organic solvent-free Schotten–Baumann-type tosylation of various

alcohols. In this method, the reaction proceeds efficiently by using a combination of the

N-alkylimidazole and water without any organic solvent. The affinity of the substrate to the

hydrophobic part of the catalyst plays an important role, and the method could be extended to a

tosylation that accompanies a molecular recognition.

Experimental Section

Materials

Unless otherwise noted, commercially available reagents were used without purification.

All alcohols listed in Chapter 2 were commercially available. *N*-Alkylimidazoles (**3c**, **3d**) were

prepared by the method descreibed in Chapter 1. *N*-Methylimidazole (**3a**) and *N*-butylimidazole

(**3b**) were commercially available.

General procedure for organic solvent free Schotten–Baumann-type tosylation of alcohols 1 (0.5 mmol scale)

To a 5-mL vial were added subsequently alcohol **1** (0.5 mmol), *N*-hexadecylimidazole (**3d**, 0.05 mmol), 4-toluenesulfonyl chloride (0.75 mmol), potassium carbonate (0.5 mmol), and water (0.09 mL, 5.0 mmol).   The mixture was stirred in an oil bath maintained at 25 °C for 4 h.   The reaction mixture was subsequently diluted with EtOAc, dried over Na_2SO_4, and concentrated in vacuo.   Purification by flash silica gel column chromatography afforded the corresponding tosylate **2**.

Procedure for organic solvent free Schotten–Baumann-type tosylation of 1-octanol (1a) on semi-large scale

To a 100-mL glass vessel were added subsequently 1-octanol (**1a**, 6.5 g, 50 mmol), *N*-hexadecylimidazole (**3d**, 1.5 g, 5 mmol), 4-toluenesulfonyl chloride (14 g, 75 mmol), potassium carbonate (6.9 g, 50 mmol), and water (9 mL, 500 mmol).   The mixture was stirred in an oil bath maintained at 25 °C for 4 h.   The reaction mixture was subsequently diluted with EtOAc and dried over $MgSO_4$.   After it was filtered, the filtrate was concentrated in vacuo. After purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 30/1) as an eluent, 12 g of **3a** was obtained (83% yield).

Characterization Data of Products

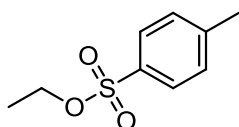**Methyl 4-methylbenzenesulfonate (2b)**: CAS RN [80-48-8].
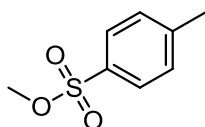
Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.79 (dt, *J* = 8.5 Hz, 2.0 Hz, 2H), 7.35 (m, 2H), 3.74 (s, 3H) 2.45 (s, 3H).

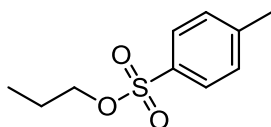^{13}C NMR (CDCl$_3$) δ 144.9, 132.2, 129.8, 128.0, 56.1, 21.6.

Ethyl 4-methylbenzenesulfonate (2c): CAS RN [80-40-0].

Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.79 (dt, J = 8.5 Hz, 2.0 Hz, 2H), 7.34 (m, 2H), 4.10 (q, J = 7.0 Hz, 2H), 2.45 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 144.6, 133.3, 129.8, 127.8, 66.8, 21.6, 14.7.
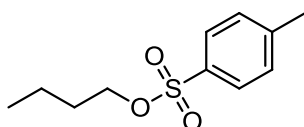
Propyl 4-methylbenzenesulfonate (2d): CAS RN [599-91-7].

Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.79 (d, J =8.5 Hz, 2H), 7.34 (m, 2H), 3.99 (dt, J = 0.5 Hz, 6.5 Hz, 2H), 2.45 (s, 3H), 1.67 (sext, J = 7.0 Hz, 2H), 0.90 (t, J = 7.5 Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 144.6, 133.2, 129.8, 127.9, 72.1, 22.3, 21.6, 9.9.

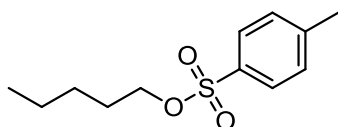**Butyl 4-methylbenzenesulfonate (2e)**: CAS RN [778-28-9].

Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.79 (d, J = 8.0 Hz, 2H), 7.34 (m, 2H), 4.03 (t, J = 6.5 Hz, 2H), 2.45 (s, 3H), 1.62 (dt, J = 1.5 Hz, 6.5 Hz, 2H), 1.34 (sext, J = 7.5 Hz, 2H), 0.86 (t, J = 7.5 Hz, 3H). ^{13}C NMR

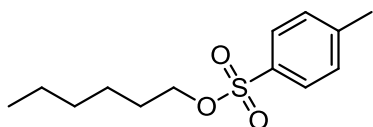(CDCl$_3$) δ 144.6, 133.2, 129.8, 127.9, 70.4, 30.8, 21.6, 18.6, 13.4.

Pentyl 4-methylbenzenesulfonate (2f): CAS RN [4450-76-4].

Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.79 (dt, *J* = 8.5 Hz, 2.0 Hz, 2H), 7.34 (m, 2H), 4.02 (t, *J* = 6.5 Hz, 2H), 2.45 (s, 3H), 1.64 (m, 2H), 1.27 (m, 4H), 0.85 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 144.6, 133.3, 129.8, 127.9,70.7, 28.5, 27.4, 22.0, 21.6, 13.8.
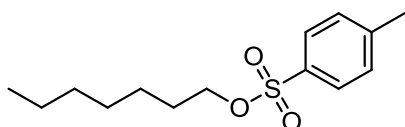
Hexyl 4-methylbenzenesulfonate (2g): CAS RN [3839-35-8].

Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.79 (dt, *J* = 8.5 Hz, 2.0 Hz, 2H), 7.34 (m, 2H), 4.02 (t, *J* = 6.5 Hz, 2H), 2.45 (s, 3H), 1.63 (dt, *J* = 1.0 Hz, 6.5 Hz, 2H), 1.32–1.16 (m, 6H), 0.85 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 144.6, 133.2, 129.8, 127.9, 70.7, 31.1, 28.8, 25.0, 22.4, 21.6, 13.9.

Heptyl 4-methylbenzenesulfonate (2h): CAS RN [24767-82-6].
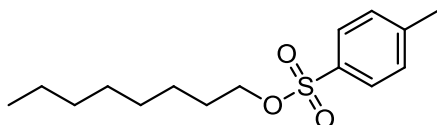

Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.79 (dt, *J* = 8.0 Hz, 2.0 Hz, 2H), 7.34 (m, 2H), 4.02 (t, *J* = 6.5 Hz, 2H), 2.45 (s, 3H), 1.63 (dt, *J* = 1.5 Hz, 6.5 Hz, 2H), 1.31–1.19 (m, 8H), 0.86 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR

(CDCl$_3$) δ 144.6, 133.3, 129.8, 127.9, 70.7, 31.6, 28.8, 28.6, 25.3, 22.5, 21.6, 14.0.
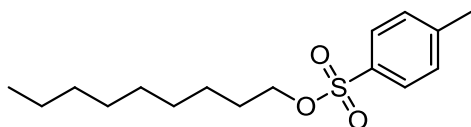
Octyl 4-methylbenzenesulfonate (2a): CAS RN [3386-35-4].

Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.79 (dt, J = 8.5 Hz, 2.0 Hz, 2H), 7.34 (m, 2H), 4.02 (t, J = 6.5 Hz, 2H), 2.45 (s, 3H), 1.63 (dt, J = 1.5 Hz, 6.5 Hz, 2H), 1.31–1.19 (m, 10H), 0.87 (t, J = 7.0 Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 144.6, 133.3, 129.8, 127.9, 70.7, 31.7, 29.0, 28.9, 28.8, 25.3, 22.6, 21.6, 14.0.
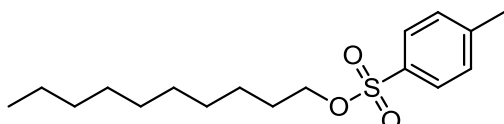
Nonyl 4-methylbenzenesulfonate (2i): CAS RN [67334-34-3].

Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.79 (dt, J = 8.0 Hz, 2.0 Hz, 2H), 7.34 (m, 2H), 4.02 (t, J = 6.5 Hz, 2H), 2.45 (s, 3H), 1.63 (dt, J = 1.5 Hz, 6.5 Hz, 2H), 1.31–1.19 (m, 12H), 0.87 (t, J = 7.5 Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 144.6, 133.2, 129.8, 127.9, 70.7, 31.8, 29.3, 29.1, 28.9, 28.8, 25.3, 22.6, 21.6, 14.1.
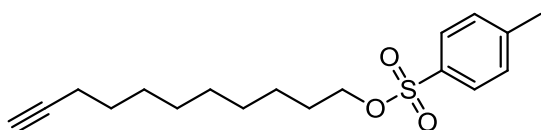
Decyl 4-methylbenzenesulfonate (2j): CAS RN [5509-08-0].

Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.79 (dt, J = 8.0 Hz, 2.0 Hz, 2H), 7.34 (m, 2H), 4.02 (t, J = 6.5 Hz, 2H), 2.45

(s, 3H), 1.63 (dt, J = 1.5 Hz, 6.5 Hz, 2H), 1.31–1.19 (m, 14H), 0.88 (t, J = 7.0 Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 144.6, 133.3, 129.8, 127.9, 70.7, 31.8, 29.43, 29.36, 29.2, 28.9, 28.8, 25.3, 22.6, 21.6, 14.1.
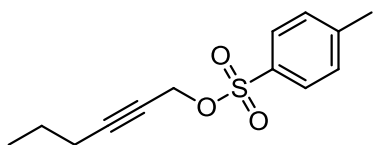
Undec-10-ynyl 4-methylbenzenesulfonate (2k): CAS RN [89329-65-7].

Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.79 (dt, J = 8.0 Hz, 2.0 Hz, 2H), 7.34 (m, 2H), 4.02 (t, J = 6.5 Hz, 2H), 2.45 (s, 3H), 2.17 (dt, J = 2.5 Hz, 7.0 Hz, 2H), 1.93 (t, J = 2.5 Hz, 1H), 1.63 (dt, J = 1.5 Hz, 6.5 Hz, 2H), 1.50 (m, 2H), 1.36 (m, 2H), 1.33–1.20 (m, 8H). ^{13}C NMR (CDCl$_3$) δ 144.6, 133.3, 129.8, 127.9, 84.7, 70.6, 68.1, 29.2, 28.9, 28.83, 28.79, 28.6, 28.4, 25.3, 21.6, 18.4.
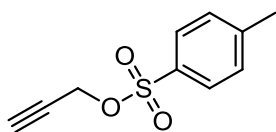
Hex-2-ynyl 4-methylbenzenesulfonate (2l): CAS RN [154659-33-3].

Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.81 (m, 2H), 7.34 (m, 2H), 4.70 (m, 2H), 2.44 (s, 3H), 2.05 (m, 2H), 1.41 (dsext, J = 1.5 Hz, 7.5 Hz, 2H), 0.89 (dt, J = 1.5 Hz, 7.5 Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 144.8, 133.5, 129.7, 128.1, 90.4, 72.0, 58.8, 21.6, 21.5, 20.6, 13.3.
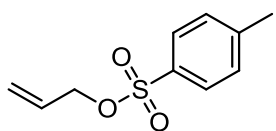
Prop-2-ynyl 4-methylbenzenesulfonate (2m): CAS RN [6165-76-0].

Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.82 (dt, J = 8.5 Hz, 2.0 Hz, 2H), 7.35 (m, 2H), 4.70 (d, J = 2.5 Hz, 2H), 2.47 (t, J = 2.5 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (CDCl$_3$) δ 145.2, 132.9, 129.9, 128.1, 77.3, 75.3, 57.3, 21.7.

Prop-2-enyl 4-methylbenzenesulfonate (2n): CAS RN [4873-09-0].

Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.80 (dt, J = 8.0 Hz, 2.0 Hz, 2H), 7.34 (m, 2H), 5.82 (ddt, J = 17.0 Hz, 10.5 Hz, 6.0 Hz, 1H), 5.31 (dq, J = 17.0 Hz, 1.5 Hz, 1H), 5.25 (dq, J = 10.5 Hz, 1.0 Hz, 1H), 4.53 (dt, J = 6.0 Hz, 1.5 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (CDCl$_3$) δ 144.8, 133.2, 130.2, 129.8, 127.9, 120.3, 70.7, 21.6.

Hex-5-enyl 4-methylbenzenesulfonate (2o): CAS RN [18922-06-0].

Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.79 (dt, J = 8.0 Hz, 2.0 Hz, 2H), 7.34 (m, 2H), 5.72 (ddt, J = 17.0 Hz, 10.0 Hz, 7.0 Hz, 1H), 4.98–4.92 (m, 2H), 4.03 (t, J = 6.5 Hz, 2H), 2.45 (s, 3H), 2.00 (m, 2H), 1.65 (m, 2H), 1.41 (m, 2H). ^{13}C NMR (CDCl$_3$) δ 144.7, 137.9, 133.2, 129.8, 127.9, 115.0, 70.4, 32.9,
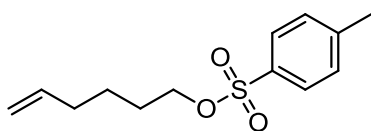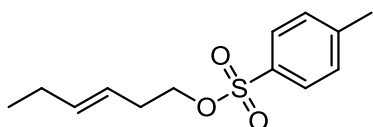
28.2, 24.5, 21.6.

(*E*)-Hex-3-enyl 4-methylbenzenesulfonate (2p): CAS RN [60470-33-9].

Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.78 (dt, *J* = 8.5 Hz, 2.0 Hz, 2H), 7.34 (m, 2H), 5.51 (dtt, *J* = 15.5 Hz, 6.0 Hz, 1.5 Hz, 1H), 5.23 (dtt, *J* = 15.5 Hz, 7.0 Hz, 1.5 Hz, 1H), 4.01 (t, *J* = 7.0 Hz, 2H), 2.45 (s, 3H), 2.32 (qq, *J* = 7.0 Hz, 1.5 Hz, 2H), 1.96 (m, 2H), 0.92 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 144.6, 136.1, 133.2, 129.8, 127.9, 122.5, 70.1, 32.0, 25.5, 21.6, 13.5.

(*Z*)-Hex-3-enyl 4-methylbenzenesulfonate (2q): CAS RN [34019-85-7].
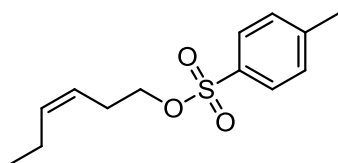
Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.79 (dt, *J* = 8.5 Hz, 2.0 Hz, 2H), 7.34 (m, 2H), 5.48 (dtt, *J* = 10.5 Hz, 7.5 Hz, 1.5 Hz, 1H), 5.18 (dtt, *J* = 10.5 Hz, 7.5 Hz, 1.5 Hz, 1H), 4.00 (t, *J* = 7.5 Hz, 2H), 2.45 (s, 3H), 2.39 (m, 2H), 1.98 (m, 2H), 0.92 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 144.7, 135.5, 133.1, 129.8, 127.9, 122.0, 69.8, 26.9, 21.6, 20.6, 14.1.

7-Oxaoctyl 4-methylbenzenesulfonate (2r): CAS RN [74366-48-6].

Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.78 (dt, J = 8.0 Hz, 2.0 Hz, 2H), 7.34 (m, 2H), 4.01 (t, J = 6.5 Hz, 2H), 3.32 (t, J = 6.5 Hz, 2H), 3.31 (s, 3H), 2.45 (s, 3H), 1.64 (m, 2H), 1.51 (m, 2H), 1.30 (m, 4H). ^{13}C NMR (CDCl$_3$) δ 144.6, 133.1, 129.8, 127.9, 72.5, 70.5, 58.5, 29.4, 28.8, 25.5, 25.2, 21.6.

6-Oxaoctyl 4-methylbenzenesulfonate (2s): CAS RN [131178-96-6].

Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.78 (dt, J = 8.5 Hz, 2.0 Hz, 2H), 7.34 (m, 2H), 4.02 (t, J = 6.5 Hz, 2H), 3.43 (q, J = 7.0 Hz, 2H), 3.35 (t, J = 6.5 Hz, 2H), 2.44 (s, 3H), 1.66 (m, 2H), 1.52 (m, 2H), 1.37 (m, 2H), 1.17 (t, J = 7.0 Hz, 2H). ^{13}C NMR (CDCl$_3$) δ 144.6, 133.1, 129.8, 127.9, 70.5, 70.1, 66.1, 29.1, 28.7, 22.2, 21.6, 15.2.

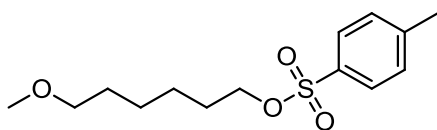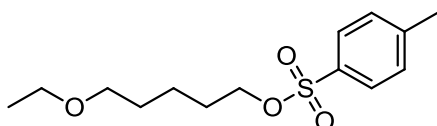**5-Oxaoctyl 4-methylbenzenesulfonate (2t)**: CAS RN [137963-85-0].

Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.79 (dt, J = 8.0 Hz, 2.0 Hz, 2H), 7.34 (m, 2H), 4.05 (t, J = 6.5 Hz, 2H), 3.35 (t, J = 6.5 Hz, 2H), 3.30 (t, J = 6.5 Hz, 2H), 2.45 (s, 3H), 1.74 (m, 2H), 1.61–1.50 (m, 4H), 0.88 (t, J = 7.5 Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 144.6, 133.1, 129.8, 127.9, 72.6, 70.5, 69.6, 25.9, 25.7, 22.8, 21.6, 10.5.

Phenyl 4-methylbenzenesulfonate (2u): CAS RN [640-60-8].

White solid.

^{1}H NMR (CDCl$_3$) δ 7.70 (dt, J = 8.0 Hz, 2.0 Hz, 2H), 7.32–7.22 (m, 5H), 6.98 (m, 2H), 2.45 (s, 3H). ^{13}C NMR (CDCl$_3$) δ 149.6, 145.3, 132.4, 129.7, 129.6, 128.5, 127.1, 122.4, 21.7.

3, 5-Dimethylphenyl 4-methylbenzenesulfonate (2v): CAS RN [95127-25-6].
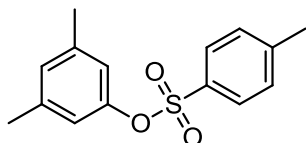
White solid.

^{1}H NMR (CDCl$_3$) δ7.73 (dt, J = 8.0 Hz, 2.0 Hz, 2H), 7.32 (m, 2H), 6.86 (m, 1H), 6.60 (m, 2H), 2.45 (s, 3H), 2.23 (q, J = 0.5 Hz, 6H). ^{13}C NMR (CDCl$_3$) δ 149.5, 145.1, 139.4, 132.7, 129.6, 128.7, 128.5, 119.8, 21.7, 21.1.
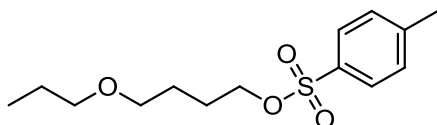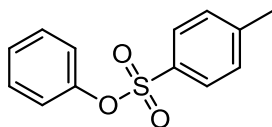
2, 2, 2-Trifluoroethyl 4-methylbenzenesulfonate (2w): CAS RN [433-06-7].
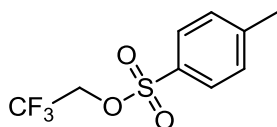
Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.82 (dt, J = 8.5 Hz, 2.0 Hz, 2H), 7.39 (m, 2H), 4.35 (q, J = 8.0 Hz, 2H), 2.47 (s, 3H). ^{13}C NMR (CDCl$_3$) δ 145.9, 131.8, 130.1, 128.1, 121.9 (d, J = 277.9 Hz), 64.5 (q, J = 38.0 Hz), 21.7. ^{19}F NMR (CDCl$_3$) δ 87.3.

2-Phenylpropyl 4-methylbenzenesulfonate (2x): CAS RN [23430-41-3].
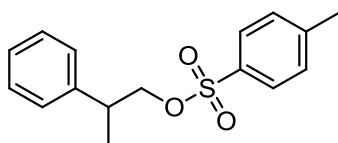
Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.67 (dt, *J* = 8.5 Hz, 2.0 Hz, 2H), 7.30–7.20 (m, 5H), 7.11 (m, 2H), 4.09 (dd, *J* = 9.5 Hz, 6.5 Hz, 1H), 4.03 (dd, *J* = 9.5 Hz, 7.5 Hz, 1H), 3.09 (sext, *J* = 7.0 Hz, 1H), 2.43 (s, 3H), 1.28 (d, *J* = 7.5 Hz, 3H).   ^{13}C NMR (CDCl$_3$) δ 144.6, 141.6, 132.9, 129.7, 128.6, 127.8. 127.2, 127.0, 74.8, 39.1, 21.6, 17.5.

Benzyl 4-methylbenzenesulfonate (2y): CAS RN [1024-41-5].
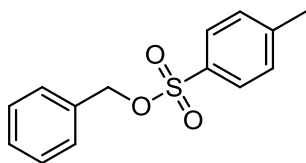
Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.80 (dt, *J* = 8.5 Hz, 2.0 Hz, 2H), 7.35–7.29 (m, 5H), 7.25 (m, 2H), 5.06 (s, 2H), 2.45 (s, 3H).   ^{13}C NMR (CDCl$_3$) δ 144.8, 133.3, 133.2, 129.8, 129.0, 128.6, 128.5, 127.9, 71.9, 21.6.

Octan-2-yl 4-methylbenzenesulfonate (2z): CAS RN [1028-12-2].
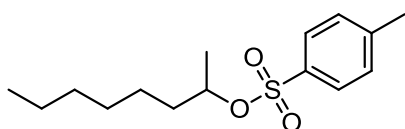
Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.79 (m, 2H), 7.33 (m, 2H), 4.60 (m, 1H), 2.44 (s, 3H), 1.60 (m, 1H), 1.47 (m, 1H), 1.26 (d, *J* = 6.5 Hz, 3H), 1.26–1.10 (m, 8H), 0.85 (t, *J* = 7.5 Hz, 3H).   ^{13}C NMR (CDCl$_3$) δ 144.3, 134.7, 129.7, 127.7, 80.7, 36.5, 31.6, 28.8, 24.8, 22.5, 21.6, 20.8, 14.0.

Octan-3-yl 4-methylbenzenesulfonate (2aa): CAS RN [4883-87-8].
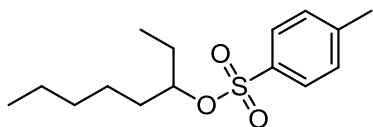
Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.79 (dt, J = 8.0 Hz, 2.0 Hz, 2H), 7.32 (m, 2H), 4.50 (m, 1H), 2.44 (s, 3H), 1.66–1.50 (m, 4H), 1.25–1.10 (m, 6H), 0.82 (m, 6H).   ^{13}C NMR (CDCl$_3$) δ 144.3, 134.7, 129.6, 127.7, 85.6, 33.5, 31.4, 27.1, 24.3, 22.4, 21.6, 13.9, 9.0.

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Chapter 3

Effects of a Flexible Alkyl Chain on a Ligand for CuAAC Reaction

Imidazole derivatives substituted by a normal alkyl group are shown to be efficient as a ligand for the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction. An alkyl chain on the imidazole ligands shows an efficient steric effect and benefits the reaction. Such functionalities of an alkyl chain allow a rapid CuAAC reaction of even a bulky alkyne, which has been difficult to perform under conventional conditions.
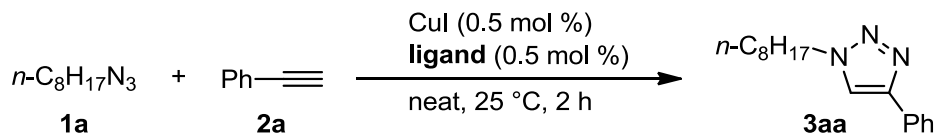
Chapter 3

Introduction

An alkyl chain is a part of many amphiphiles or other organic materials and plays an important role in determining their properties.[1]   Although it ordinarily has an extended form with all *anti* configurations as its stable shape, it can readily change its conformation in a host molecule to an unusual one, such as coiled, folded, or U-shaped, to adjust its volume to the cavity size.[2]   However, such a flexible nature of an alkyl chain has rarely been noted as a special functionality for synthetic reagents.[3,4]   In addition, a normal alkyl group with a variety of conformations may have an appreciable steric effect.   On the basis of such a viewpoint, the author sought to utilize the latent functionalities of a normal alkyl group in the design of a ligand for a transition metal catalyst.   In Chapter 3, the author describes the efficiency of imidazoles carrying a long alkyl chain[5,6] as a ligand for the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction.[7]

Results and Discussion

The CuAAC reaction[7] has been a representative of click chemistry[8] that has been utilized in various areas,[9] and there are a few examples where the reaction was accelerated by a ligand.[10–12] Polydentate ligands, such as tris(benzyltriazolylmethyl)amine (TBTA),[10a,b] are well-balanced to stabilize Cu(I) and to accelerate the reaction.[10]   Monodentate ligands with rigid backbones, such as an NHC (ICy or SIMes) or a phosphoramidite, were also shown to have a high accelerating effect.[11]   These previous instances suggest that bulky ligands are desirable for an efficient catalyst.   Indeed, during the author's initial investigations of the CuAAC reaction between 1-azidooctane (**1a**) and phenylacetylene (**2a**) under the conditions in Table 1, bulky 1-(1-adamantyl)imidazole (**4b**) was shown to be excellent as a ligand and much more efficient than 1-methylimidazole (**4a**) (Table 1, entries 1-8).   1,2-Dimethylimidazole (**5**) and

Table 1. CuAAC Reaction between 1-Azidooctane (**1a**) and Phenylacetylene (**2a**) with Various Ligands.[a]

$n\text{-}C_8H_{17}N_3$ + Ph$\equiv$ $\xrightarrow[\text{neat, 25 °C, 2 h}]{\substack{\text{CuI (0.5 mol \%)} \\ \textbf{ligand} \text{ (0.5 mol \%)}}}$ $n\text{-}C_8H_{17}\text{-}N\diagdown\overset{N}{\underset{N}{\diagup}}$

1a   **2a**   **3aa**   Ph

entry	ligand	yield (%)[b]
1	none	4
2	Et$_3$N	15
3	n-Bu$_3$N	37
4	EtNi-Pr$_2$	18
5	2,6-lutidine	6
6	DMAP	29
7	**4a** (R = CH$_3$)	35
8	**4b** (R = 1-ad)	99
9	**5**	61
10	**6**	51
11	**4c** (R = n-C$_4$H$_9$)	63
12	**4d** (R = n-C$_{10}$H$_{21}$)	99 (96[c])

[a] Reactions were run using 1-azidooctane (**1a**, 1.0 mmol), phenylacetylene (**2a**, 1.05 mmol), CuI (0.005 mmol), and the ligand (0.005 mmol). [b] Yields were determined by determined by ^{1}H NMR. [c] Isolated yield.

Imidazole Ligands

4a (R = CH$_3$)
4b (R = 1-ad)
4c (R = n-C$_4$H$_9$)
4d (R = n-C$_{10}$H$_{21}$)

5

6
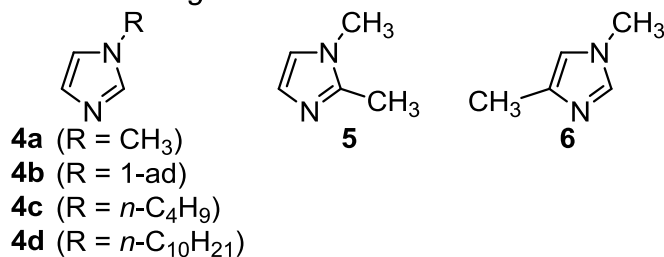
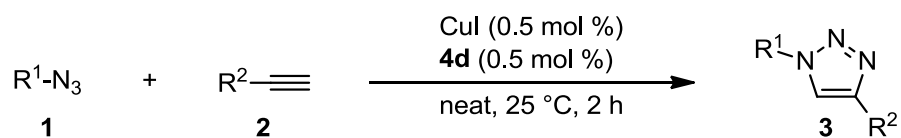1,4-dimethylimidazole (**6**) also gave **3aa** in higher yields than the case of **4a**, but they are not up to **4b** (Table 1, entries 9 and 10).[6d]   The author then investigated the efficiency of imidazoles substituted by a normal alkyl group in hopes of finding its steric effect.   As expected, they proved to be effective, and especially 1-decylimidazole (**4d**) showed as good a result as **4b** (Table 1, entries 11 and 12).[13]   With **4d**, the author also replaced CuI by some other Cu sources, and CuI was shown to be the best among them (Table 2).

Table 2. CuAAC Reaction using 1-Decylimidazole (**4d**) with Various Cu Sources.[a]
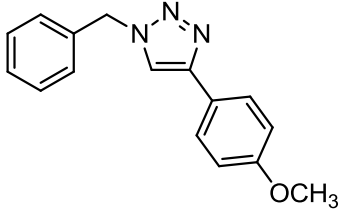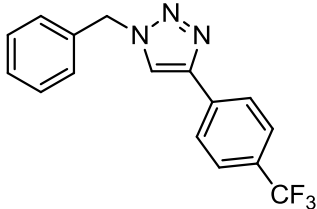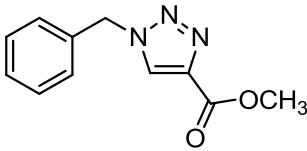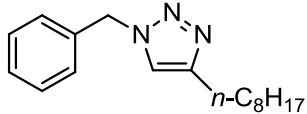
entry	*Cu*	yield (%)[b]
1	CuI	96
2	CuBr	63
3	CuCl	38
4	CuCN	54
5	$Cu(CH_3CN)_4PF_6$	31
6[c]	$CuSO_4$ with Na ascorbate	34

[a]   Reactions were run using 1-azidooctane (**1a**, 1.0 mmol), phenylacetylene (**2a**, 1.05 mmol), the Cu salt (0.005 mmol), and *N*-decylimidazole (**4d**, 0.005 mmol).   [b] Yields were determined by ^{1}H NMR.   [c] 0.025 mmol (2.5 mol %) of Na ascorbate was used.

CuAAC Reaction with 1-Decylimidazole (37).[a]

$$R^1\text{-}N_3 \quad + \quad R^2\text{---} \quad \xrightarrow[\text{neat, 25 °C, 2 h}]{\substack{\text{CuI (0.5 mol \%)} \\ \textbf{4d} \text{ (0.5 mol \%)}}} \quad R^1\text{-triazole-}R^2$$

entry	R^1	R^2	product	yield (%)[b]
1	$n\text{-}C_8H_{17}$	Ph		96
2	$PhCH_2$	Ph		99
3	$4\text{-}CH_3OC_6H_4CH_2$	Ph		99
4	$4\text{-}CF_3C_6H_4CH_2$	Ph		99
5	$t\text{-}BuOCOCH_2$	Ph		97
6	cyclohexyl	Ph		99

Table 3. (Continued)

7	PhCH$_2$	**1b**	4-CH$_3$OC$_6$H$_4$	**2b**		**3bb**	99
8	PhCH$_2$	**1b**	4-CF$_3$C$_6$H$_4$	**2c**		**3bc**	99
9	PhCH$_2$	**1b**	CH$_3$OCO	**2d**		**3bd**	97
10	PhCH$_2$	**1b**	n-C$_8$H$_{17}$	**2e**		**3be**	99

[a] Reactions were run using the azide **1** (1.0 mmol), the alkyne **2** (1.05 mmol), CuI (0.005 mmol), and 1-decylimidazole (**4d**, 0.005 mmol).   [b] Isolated yields.

The author then applied the condition with 0.5 mol % of CuI and 0.5 mol % of **4d** to some other azides and alkynes (Table 3).   Reactions with various substrates afforded excellent yields. Azides with benzyl groups (**1b**, **1c**, **1d**), an ester group (**1e**), and a cyclohexyl group (**1f**) showed rapid reactions (Table 3, entries 1–5).   Acetylenes with phenyl groups (**2b**, **2c**), an ester group (**2d**), and a primary alkyl group (**2e**) were also applicable (Table 3, entries 6–9).

The efficiency of the catalyst for click chemistry should stay relatively constant in a wide range of reaction media.[8]   As shown in Table 4, **4d** was also useful in the reactions using a variety of solvents, and the effect of the long alkyl chain on **4d** was observed in almost solvents. **4d** was much more effective than **4a** in hexane (Table 4, entry 1), and the efficiency of **4d** was also seen in CHCl$_3$ and DMSO (Table 4, entries 2 and 4).   In CH$_2$Cl$_2$ or CH$_3$CN, **4d** and **4a** gave similarly good results (Table 4, entries 3 and 5).[14,15]   Although alcoholic solvents retarded the

reaction, the accelerating effect of **4d** was still available (Table 4, entries 6 and 7). In addition, **4d** maintained the activity even in the presence of water, and its large accelerating effect was observed (Table 4, entry 8).[16]

Table 4. CuAAC Reaction Using 1-Decylimidazole (**4d**) and 1-Methylimidazole (**4a**) with Various Solvents.[a]

entry	solvent	yield (%)[b]	
		with **4d**	with **4a**
1	Hexane	71	2
2	CHCl$_3$	85	46
3	CH$_2$Cl$_2$	99	99
4	DMSO	53	23
5	CH$_3$CN	85	82
6	CH$_3$OH	26	7
7	*t*-BuOH	40	10
8	H$_2$O	97	34

[a] Reactions were run using 1-azidooctane (**1a**, 1.0 mmol), phenylacetylene (**2a**, 1.05 mmol), CuI (0.005 mmol), the *N*-alkylimidazole **4** (0.005 mmol), and the solvent (0.5 mL). [b] Yields were determined by ^{1}H NMR.

Such a broad utility of the ligand expands the scope of substrates. For example, although the substrates having a hydroxyl group (**1g**, **2f**) showed a significant inhibition of the reaction under the neat condition, the author could perform their reactions efficiently in the presence of water, which may interrupt the coordination of a hydroxyl group to a Cu catalyst (Scheme 1, **3ga**

and **3bf**). A similar enhancement by water was also seen in the reaction of methyl propargyl ether (**2g**) (Scheme 1, **3bg**), and even the glucosyl azide without any protection of hydroxyl groups (**1h**) could also be used for the reaction by using a mixture of water and *t*-BuOH as a solvent (Scheme 1, **3ha**).[10h,17]

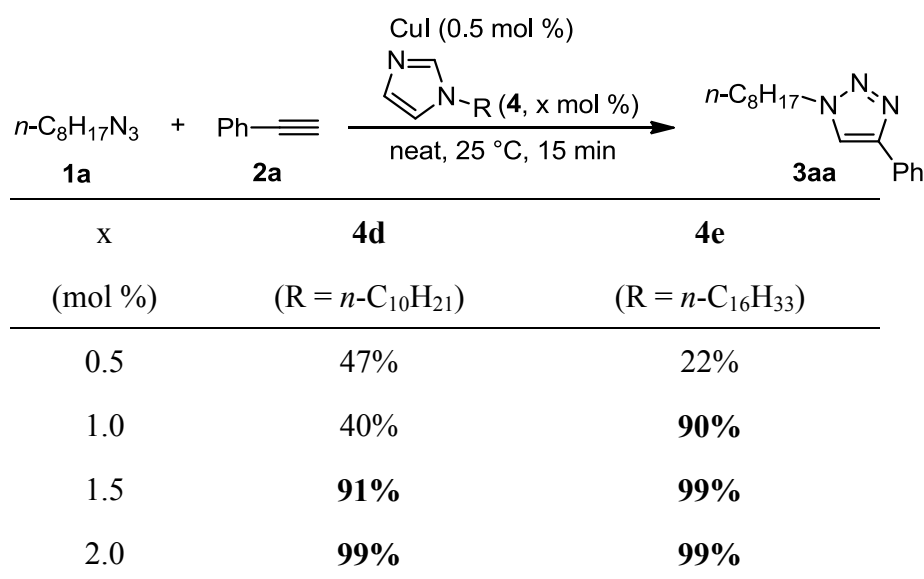**Scheme 1.** CuAAC Reaction in the Presence of Water.[a]
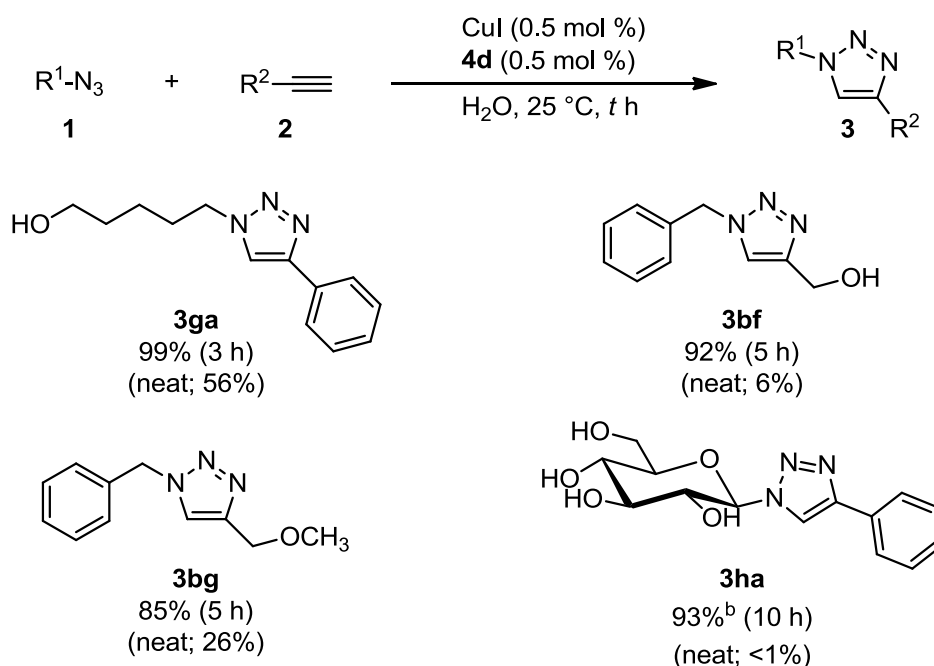
[a] Reactions were run using the azide **1** (1.0 mmol), the alkyne **2** (1.05 mmol), CuI (0.005 mmol), *N*-decylimidazole (**4d**, 0.005 mmol), and H_2O (0.5 mL). [b] Run in the presence of H_2O (0.1 mL) and *t*-BuOH (0.4 mL).

The author further investigated the reaction between **1a** and **2a** with various amounts of imidazole derivatives in a shorter reaction time (Scheme 2).[18] As a result, the use of more than 1.5 mol % of **4d** brought about a further acceleration, and the reaction using 2.0 mol % of **4d** proceeded to completion within only 15 min. Furthermore, with 1-hexadecylimidazole (**4e**), carrying an even longer alkyl chain, only 1.0 mol % was enough to gain a similar acceleration. The additional drastic acceleration can be attributed to the effect of free imidazole molecules not coordinating to a Cu catalyst and working as a base to deprotonate from a terminal alkyne in

forming a copper-acetylide intermediate.[7a,14]   The longer alkyl chain probably has a larger steric

effect to repulse the multiple coordination of **4e**, and released **4e** might work as a base (Scheme

3).

Scheme 2. CuAAC Reaction between 1-Azidooctane (**1a**) and Phenylacetylene (**2a**) with Various

Amounts of 1-Decylimidazole (**4d**) and 1-Hexadecylimidazole (**4e**).[a]

x	**4d**	**4e**
(mol %)	(R = n-$C_{10}H_{21}$)	(R = n-$C_{16}H_{33}$)
0.5	47%	22%
1.0	40%	**90%**
1.5	**91%**	**99%**
2.0	**99%**	**99%**

[a] Reactions were run using 1-azidooctane (**1a**, 1.0 mmol), phenylacetylene (**2a**, 1.05 mmol), CuI
(0.005 mmol), and the N-alkylimidazole **4**.

Scheme 3. Proposed Pathway of the Acceleration by **4e**.
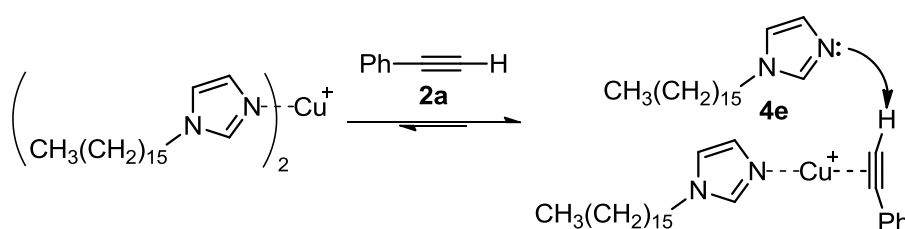
   The imidazole ligands with a long alkyl chain in particular were efficient for the reactions of

bulky alkynes.   A bulky alkyne is a relatively unfavorable substrate in the CuAAC reaction

under mild conditions.   Actually the reactions of *tert*-butylacetylene (**2h**) or cyclohexylacetylene

(**2i**) with **1b** under the condition using 0.5 mol % of **4d** as in Table 3 resulted in low yields (6%

and 0%, respectively),[19] and the previous research also suggests that such reactions should be performed under harsher conditions.[10f,20] This may be caused by the difficulty of a bulky alkyne to form a stable π-complex due to its steric hindrance, which would lead to a higher pKa of its terminal proton than in the other cases;[14] thus a base catalyst would be required for a rapid reaction. However, the use of a large amount of a small amine will saturate the coordination spaces of a Cu catalyst and suppress the catalytic activity.[5b,10a] Meanwhile, with 1.5 mol % of **4d** or **4e**, carrying a long alkyl chain, the reaction of even **2h** could be performed smoothly to give **3bh** in high yields, and the use of the same amount of **4a** or even **4b** was less efficient (Scheme 4). Besides, more noteworthy is that in the case of **2i**, only **4e** gave a prominent result (Scheme 4). These results suggest that the steric effect of **4e** might leave a free imidazole acting as a base while keeping a coordinatively unsaturated Cu catalyst.[21] In addition, the fact that the rigid backbone of **4b** also disturbed the reaction despite its sufficient steric effect indicates that the flexible alkyl chain must be present to create a favorable environment around a Cu center, even for a bulky substrate (Figure 1).[22]

Scheme 4. CuAAC Reaction of Acetylenes with Bulky Substituents.[a]

2 (t h)	4a	4d	4e	4b
	(R = CH$_3$)	(R = n-C$_{10}$H$_{12}$)	(R = n-C$_{16}$H$_{33}$)	(R = 1-ad)
2h (3 h)	4%	**99%**	**93%**	79%
2i (2 h)	<1%	18%	**92%**	4%

[a] Reactions were run using benzylazide **1b** (1.0 mmol), the alkyne **2** (1.05 mmol), CuI (0.005 mmol), and the N-alkylimidazole **4** (0.015 mmol).
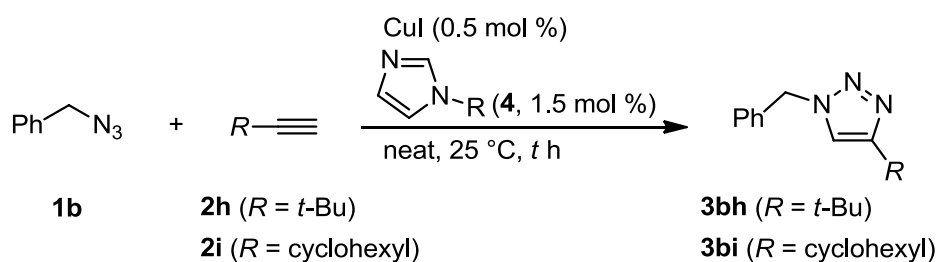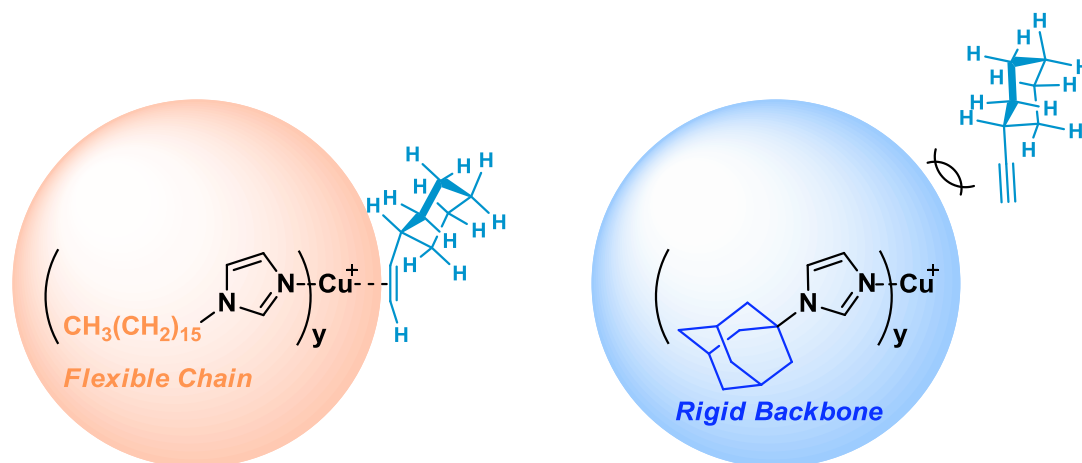
Figure 1. Steric Effect by the Flexible Alkyl Chain.

Conclusion

In summary, the author has showed the efficiency of *N*-alkylimidazoles as a ligand to achieve a rapid CuAAC reaction.   The alkyl chain gave an efficient steric effect, and imidazoles worked not only as a ligand but also as a base.   Furthermore, the flexible alkyl chain could provide a favorable environment around a Cu center for a variety of substrates.   These results suggest a new concept for an efficient ligand of transition metal catalysis.   Although a precise understanding of the role of the alkyl chain awaits further studies, this methodology could also be applied to other catalytic processes.

Experimental Section

Materials

Unless otherwise noted, commercially available reagents were used without purification. All alkynes listed in Chapter 3 were commercially available.   *N*-Alkylimidazoles (**4d**, **4e**) were prepared by the method descreibed in Chapter 1.   *N*-Methylimidazole (**4a**), *N*-butylimidazole (**4c**), and 1,2-dimethyl-1*H*-imidazole (**5**) were commercially available.

General procedure for CuAAC reaction

To a 5-mL vial were added sequentially azide **1** (1.0 mmol), alkyne **2** (1.05 mmol), *N*-decylimidazole (**4d**, 0.005 mmol), and CuI (0.005 mmol).   The mixture was stirred in an oil bath maintained at 25 °C for 2 h.   When the product was a solid with low solubility in H_2O, it was simply filtered and washed with H_2O (200 mL).   Otherwise, the reaction mixture was diluted with EtOAc or CH_3OH, dried over Na_2SO_4, concentrated in vacuo, and purified by flash silica gel column chromatography.

Procedure for preparation of 1-(1-adamantyl)-1*H*-imidazole (4b)

A mixture of imidazole (1.7 g, 25 mmol) and 1-bromoadamantane (4.3 g, 20 mmol) was heated at 200 °C for 9 h.   The resulting mixture was cooled to ambient temperature, diluted with $CHCl_3$, and washed with H_2O followed by brine.   The organic layer was dried over Na_2SO_4 and concentrated in vacuo.   To the residue was then added Hexane (150 mL).   The mixture was heated at 75 °C for a while and filtered off, and the filtrate was concentrated in vacuo.   Purification by flash silica gel column chromatography using EtOAc as an eluent gave **4b** (0.73 g, 18% yield).

1-(1-Adamantyl)-1*H*-imidazole (4b): CAS RN [69380-11-6].
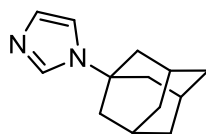
White solid.

^{1}H NMR ($CDCl_3$) δ 7.64 (s, 1H), 7.07 (s, 1H), 7.06 (s, 1H), 2.23 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 1.80 (m, 1H), 1.78 (m, 2H), 1.76 (m, 2H), 1.73 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 133.6, 128.8, 115.3, 55.0, 43.8, 36.0, 29.5.

Procedure for preparation of 1,4-dimethyl-1*H*-imidazole (6)[23]

Aqueous formaldehyde (37%, 2.5 mL, 32 mmol) was added to a mixture of copper(II) acetate (5.4 g, 30 mmol) and aqueous ammonia (28%, 20 mL). Aqueous methylamine (40%, 4.7 mL, 60 mmol), aqueous HCl (1M, 60 mL), and then acetol (1.9 mL, 28 mmol) were added to the mixture, which was stirred at 100 °C for 20 min. The resulting mixture was cooled to ambient temperature and extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by kugel distillation gave **6** (0.76 g, 28% yield).

**1,4-Dimethyl-1*H*-imidazole (6)**: CAS RN [6338-45-0].
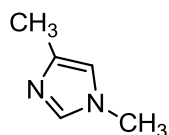
Pale yellow oil.

^{1}H NMR (CDCl$_3$) δ 7.28 (s, 1H), 6.56 (s, 1H), 3.59 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (CDCl$_3$) δ 138.5, 136.9, 116.5, 33.1, 13.6.

General procedure for preparation of azides 1a, 1b, 1c, 1d, 1f, and 1g[24]

Sodium azide (1.5 equiv) was added into a solution of bromide or chloride (1.0 equiv) in DMSO (0.67 M). The resulting suspension was stirred at room temperature for hours. H_2O was then added to quench the reaction, and the mixture became warm. After the mixture was cooled to ambient temperature, it was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The obtained oil was diluted with hexane, and the solution was filtered with a short silica gel column. Concentration of the filtered solution gave the corresponding azide **1** in 50–98% yield. The NMR results (^{1}H, ^{13}C) are as below.
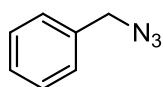
1-Azidooctane (1a): CAS RN [7438-05-3].
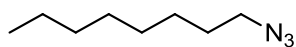
Colorless oil; the reaction time was 8.5 h; yield: 98% from 50 mmol of 1-bromooctane.

^{1}H NMR (CDCl$_3$) δ 3.25 (t, J = 7.0 Hz, 2H), 1.60 (tt, J = 7.0, 7.0 Hz, 2H), 1.43–1.22 (m, 10H), 0.88 (t, J = 7.0 Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 51.5, 31.7, 29.13, 29.11, 28.8, 26.7, 22.6, 14.1.
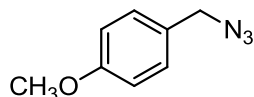
(Azidomethyl)benzene (1b): CAS RN [622-79-7].

Colorless oil; the reaction time was 10 h; yield: 93% from 30 mmol of (bromomethyl)benzene.

^{1}H NMR (CDCl$_3$) δ 7.40 (m, 2H), 7.37–7.32 (m, 3H), 7.35 (s, 2H). ^{13}C NMR (CDCl$_3$) δ 135.4, 128.8, 128.3, 128.2, 54.8.
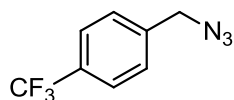
1-(Azidomethyl)-4-methoxybenzene (1c): CAS RN [70978-37-9].

Colorless oil; the reaction time was 18 h; yield: 50% from 10 mmol of 1-(chloromethyl)-4-methoxybenzene.

^{1}H NMR (CDCl$_3$) δ 7.25 (m, 2H), 6.91 (m, 2H), 4.27 (s, 2H), 3.82 (s, 2H). ^{13}C NMR (CDCl$_3$) δ 159.6, 129.7, 127.4, 114.2, 55.3, 54.4.

1-(Azidomethyl)-4-(trifluoromethyl)benzene (1d): CAS RN [222716-19-0].

Colorless oil; the reaction time was 21 h; yield: 80% from 5 mmol of 1-(bromomethyl)-4-(trifluoromethyl)benzene.

^{1}H NMR (CDCl$_3$) δ 7.65 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 4.43 (s, 2H). ^{13}C NMR

(CDCl$_3$) δ 139.4, 130.5 (q, J = 32.2 Hz), 128.3, 125.8 (q, J = 3.7 Hz), 123.9 (q, J = 272.1 Hz), 54.1. ^{19}F NMR (CDCl$_3$): δ 98.4.
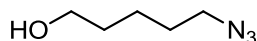

Azidocyclohexane (1f): CAS RN [19573-22-9].

Colorless oil; in this case the reaction mixture was refluxed for 29 h; yield: 80% from 10 mmol of bromocyclohexane.

^{1}H NMR (CDCl$_3$) δ 3.33 (m, 1H), 1.90 (m, 2H), 1.76 (m, 2H), 1.57 (m, 1H), 1.46–1.18 (m, 5H).

^{13}C NMR (CDCl$_3$) δ 59.9, 31.6, 25.3, 24.2.

5-Azidopentan-1-ol (1g): CAS RN [170220-11-8].

Colorless oil; the reaction time was 4 d; yield: 80% from 20 mmol of 5-bromopentan-1-ol.

^{1}H NMR (CDCl$_3$) δ 3.66 (m, 2H), 3.29 (t, J = 7.0 Hz, 2H), 1.67–1.57 (m, 4H), 1.49–143 (m, 2H).

^{13}C NMR (CDCl$_3$) δ 62.6, 51.4, 32.2, 28.6, 23.0.

Procedure for preparation of *tert*-butyl 2-azidoacetate (1e)[11c]

A solution of *tert*-butyl 2-bromoacetate (3.9 g, 20 mmol) and sodium azide (2.0 g, 30 mmol) in a mixture of acetone (12 mL) and H$_2$O (8 mL) was refluxed for 22 h.   After the mixture was cooled to ambient temperature, it was concentrated to remove acetone.   The remainder was then extracted with Et$_2$O.   The combined organic layers were washed with brine and dried over Na$_2$SO$_4$.   Concentration of the organic layers gave **1e** (2.8 g, 90% yield), and it was enough pure to be used for the CuAAC reaction without further purification.

Chapter 3

***tert*-Butyl 2-azidoacetate (1e)**: CAS RN [6367-36-8].
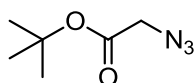

Colorless oil.

^{1}H NMR (CDCl$_3$) δ 3.75 (s, 2H), 1.50 (s, 9H). ^{13}C NMR (CDCl$_3$) δ 167.4, 83.1, 51.0, 28.0.

Procedure for preparation of *β*-D-glucopyranosyl azide (1h)[25,26]

To a suspension of *α*-D-glucose (2.9 g, 16 mmol) and sodium azide (10 g, 0.15 mol) in DMF (90 mL) was added triphenylphosphine (8.3 g, 32 mmol).   After the mixture was stirred for a few minutes, a solution of carbon tetrabromide (10 g, 32 mmol) in DMF (25 mL) was added. The resulting mixture was stirred at room temperature for 71 h.   CH$_3$OH (60 mL) was then poured, and the mixture was filtered.   After the filtrate was concentrated in vacuo, H$_2$O (200 mL) and toluene (200 mL) were added.   To the mixture was added EtOAc dropwise until it became clear.   The aqueous layer was then separated, and the organic layer was extracted with H$_2$O (100mL×3).   The combined aqueous layers were concentrated in vacuo, and the residue was dissolved in a mixture of pyridine (200 mL) and acetic anhydride (200 mL).   After stirring at room temperature for 12 h, the mixture was concentrated in vacuo, and the residue was dissolved in EtOAc (200 mL).   The solution was washed with H$_2$O (200 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo.   Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 2/1) as an eluent gave 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl azide (**1h'**) (2.4 g, 40% yield).

To a suspension of **1h'** (1.5 g, 4.0 mmol) in CH$_3$OH (6 mL) was added a solution of KOH (1.0 g, 18 mmol) in H$_2$O (1.5 mL).   After the mixture was stirred at room temperature, it was concentrated in vacuo.   Purification by flash silica gel column chromatography using CH$_2$Cl$_2$/EtOH (v/v = 7/3) as an eluent gave **1h** (0.73 g, 89% yield).   The NMR results (^{1}H, ^{13}C) are as below.

2,3,4,6-Tetra-*O*-acetyl-*β*-D-glucopyranosyl azide (1h'): CAS RN [13992-25-1].
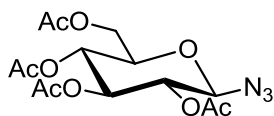
White solid.

^{1}H NMR (CDCl$_3$) δ 5.22 (dd, *J* = 9.5 Hz, 9.0 Hz, 1H), 5.11 (dd, *J* = 10.5 Hz, 9.0 Hz, 1H), 4.96 (dd, *J* = 9.5 Hz, 9.0 Hz, 1H), 4.65 (d, *J* = 9.0 Hz, 1H), 4.27 (dd, *J* = 12.5 Hz, 5.0 Hz, 1H), 4.17 (dd, *J* = 12.5 Hz, 2.0 Hz, 1H), 3.80 (ddd, *J* = 10.5 Hz, 5.0 Hz, 2.0 Hz, 1H), 2.10 (s, 3H), 2.08 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (CDCl$_3$) δ 170.6, 170.1, 169.3, 169.2, 87.9, 74.1, 72.7, 70.7, 68.0, 61.7, 20.7, 20.5, 20.5.

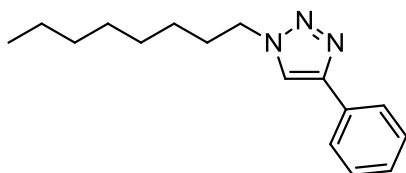**_β_-D-Glucopyranosyl azide (1h)**: CAS RN [20379-59-3].
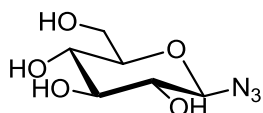
Pale yellow oil.

^{1}H NMR (D$_2$O, 300MHz) δ 4.75 (d, *J* = 8.7 Hz, 1H), 3.92 (dd, *J* = 12.3, 2.1 Hz, 1H), 3.75 (dd, *J* = 12.3, 5.4 Hz, 1H), 3.58–3.39 (m, 3H), 3.27 (t, *J* = 9.0 Hz, 1H). ^{13}C NMR (D$_2$O) δ 90.9, 78.7, 76.6, 73.7, 70.1, 61.5.

Characterization Data of Products

**1-Octyl-4-phenyl-1*H*-1,2,3-triazole (3aa)**: CAS RN [853052-50-3].

White solid.

^{1}H NMR (CDCl$_3$) δ 7.83 (m, 2H), 7.74 (s, 1H), 7.42 (m, 2H), 7.33 (tt, *J* = 7.5, 1.5 Hz, 1H), 4.40 (t, *J* = 7.0 Hz, 2H), 1.95 (tt, *J* = 7.0, 7.0 Hz, 2H), 1.40–1.31 (m, 4H), 1.31–1.20 (m, 6H), 0.87 (t, *J*

= 7.0 Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 147.7, 130.8, 128.8, 128.1, 125.7, 119.3, 50.4, 31.7, 30.3, 29.03, 28.97, 26.5, 22.6, 14.0. Mp. 76.0–76.5 °C. HRMS Calcd for C$_{16}$H$_{23}$N$_3$: M$^+$, 257.1892. Found: *m/z* 257.1893.
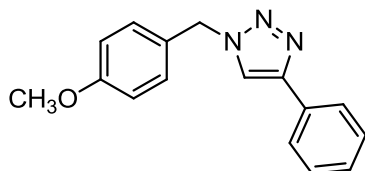
1-Benzyl-4-phenyl-1*H*-1,2,3-triazole (3ba): CAS RN [108717-96-0].
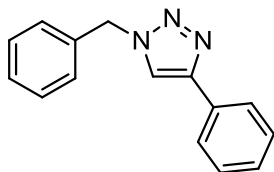
White solid.

^{1}H NMR (CDCl$_3$) δ 7.80 (m, 2H), 7.66 (s, 1H), 7.42–7.35 (m, 5H), 7.33–7.30 (m, 3H), 5.58 (s, 2H). ^{13}C NMR (CDCl$_3$) δ 148.3, 134.7, 130.6, 129.2, 128.8, 128.2, 128.1, 125.7, 119.4, 109.8, 54.2. Mp. 127.5–128.0 °C. HRMS Calcd for C$_{15}$H$_{13}$N$_3$: M$^+$, 235.1110. Found: *m/z* 235.1107.

1-(4-Methoxybenzyl)-4-phenyl-1*H*-1,2,3-triazole (3ca): CAS RN [126800-00-8].

White solid.

^{1}H NMR (CDCl$_3$) δ 7.79 (m, 2H), 7.62 (s, 1H), 7.39 (m, 2H), 7.33–7.26 (m, 3H), 6.91 (m, 2H), 5.51 (s, 2H), 3.81 (s, 3H). ^{13}C NMR (CDCl$_3$) δ 160.0, 148.2, 130.6, 129.7, 128.8, 128.1, 126.6, 125.7, 119.2, 114.5, 55.3, 53.8. Mp. 136.0–136.3 °C. HRMS Calcd for C$_{16}$H$_{15}$N$_3$O: M$^+$, 265.1215. Found: *m/z* 265.1215.

4-Phenyl-1-(4-(trifluoromethyl)benzyl)-1*H*-1,2,3-triazole (3da).
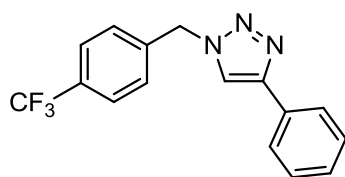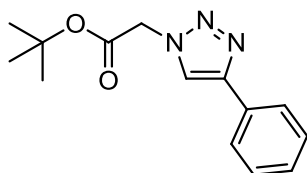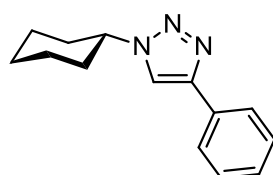

White solid.

¹H NMR (CDCl₃) δ 7.81 (m, 2H), 7.70 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.43–7.39 (m, 4H), 7.33 (m, 1H), 5.65 (s, 2H).   ¹³C NMR (CDCl₃) δ 148.6, 138.6, 131.1 (q, *J* = 32.6 Hz), 130.3, 128.9, 128.4, 128.2, 126.1 (q, *J* = 3.8 Hz), 125.7, 123.8 (q, *J* = 272.1 Hz), 119.5, 53.5.   ¹⁹F NMR (CDCl₃): δ 98.3.   Mp. 131.9–132.3 °C.   IR (KBr): 1330, 1165, 1125, 1069, 1017, 823, 767, 696 cm⁻¹.   HRMS Calcd for C₁₆H₁₂F₃N₃: M⁺, 303.0983. Found: *m/z* 303.0972.

tert-Butyl 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetate (3ea).

White solid.

¹H NMR (CDCl₃) δ 7.91 (s, 1H), 7.84 (m, 2H), 7.43 (m, 2H), 7.34 (m, 1H), 5.11 (s, 2H), 1.50 (s, 9H).   ¹³C NMR (CDCl₃) δ 165.3, 148.2, 130.5, 128.8, 128.2, 125.8, 120.9, 83.9, 51.6, 28.0.   Mp. 112.8–113.0 °C.   IR (KBr): 3448, 2998, 2930, 2361, 1741, 1471, 1381, 1244, 1164, 1077, 1052, 862, 800, 765, 699 cm⁻¹.   HRMS Calcd for C₁₄H₁₇N₃O₂: M⁺, 259.1321. Found: *m/z* 259.1318.

1-Cyclohexyl-4-phenyl-1*H*-1,2,3-triazole (3fa): CAS RN [116436-13-6].

White solid.

93

^{1}H NMR (CDCl$_3$) δ 7.83 (m, 2H), 7.76 (s, 1H), 7.42 (m, 2H), 7.32 (m, 1H), 4.50 (tt, J = 12.0, 4.0 Hz, 1H), 2.26 (m, 2H), 1.95 (m, 2H), 1.83–1.75 (m, 3H), 1.48 (m, 2H), 1.32 (tt, J = 12.5, 3.5 Hz, 1H).　^{13}C NMR (CDCl$_3$) δ 147.3, 130.9, 128.8, 127.9, 125.6, 117.2, 60.1, 33.6, 25.2, 25.1.　Mp. 104.0–104.5 °C.　HRMS Calcd for C$_{14}$H$_{17}$N$_3$: M$^+$, 227.1423. Found: m/z 227.1420.

1-Benzyl-4-(4-methoxyphenyl)-1H-1,2,3-triazole (3bb): CAS RN [116557-81-4].
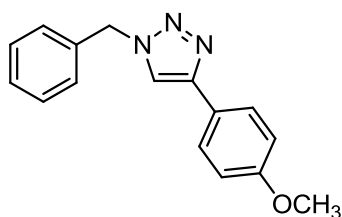
White solid.

^{1}H NMR (CDCl$_3$) δ 7.72 (m, 2H), 7.57 (s, 1H), 7.41–7.35 (m, 3H), 7.31 (m, 2H), 6.93 (dt, J = 9.5, 2.5 Hz, 2H), 5.56 (s, 2H), 3.83 (s, 3H).　^{13}C NMR (CDCl$_3$) δ 159.6, 148.1, 134.8, 129.1, 128.7, 128.0, 127.0, 123.3, 118.6, 114.2, 55.3, 54.2.　Mp. 142.7–143.0 °C.　HRMS Calcd for C$_{16}$H$_{15}$N$_3$O: M$^+$, 265.1215. Found: m/z 265.1215.

1-Benzyl-4-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole (3bc).
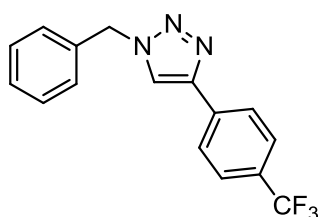
White solid.

^{1}H NMR (CDCl$_3$) δ 7.91 (m, 2H), 7.74 (s, 1H), 7.65 (m, 2H), 7.43–7.37 (m, 3H), 7.32 (m, 2H), 5.60 (s, 2H).　^{13}C NMR (CDCl$_3$) δ 146.9, 134.4, 134.0, 130.0 (q, J = 32.2 Hz), 129.2, 128.9, 128.1, 125.81, 125.79 (q, J = 3.9 Hz), 124.1 (q, J = 272.1 Hz), 120.2, 54.4.　^{19}F NMR (CDCl$_3$): δ 98.5.　Mp. 137.8–138.0 °C.　IR (KBr): 3448, 3109, 2361, 1623, 1460, 1415, 1331, 1229, 1155, 1126, 1066, 978, 847, 720, 699, 600 cm^{-1}.　HRMS Calcd for C$_{16}$H$_{12}$F$_3$N$_3$: M$^+$, 303.0983.

Found: *m/z* 303.0979.

Methyl 1-benzyl-1*H*-1,2,3-triazole-4-carboxylate (3bd): CAS RN [76003-76-4].
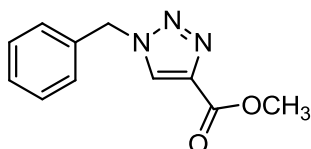
White solid.

^{1}H NMR (CDCl$_3$) δ 7.97 (s, 1H), 7.42–7.37 (m, 3H), 7.29 (m, 2H), 5.58 (s, 2H), 3.92 (s, 3H). ^{13}C NMR (CDCl$_3$) δ 161.1, 140.3, 133.6, 129.3, 129.2, 128.3, 127.3, 54.5, 52.2. Mp. 100.5–101.0 °C. HRMS Calcd for C$_{11}$H$_{11}$N$_3$O$_2$: M$^+$, 217.0851. Found: *m/z* 217.0846.

1-Benzyl-4-octyl-1*H*-1,2,3-triazole (3be): CAS RN [478555-29-2].
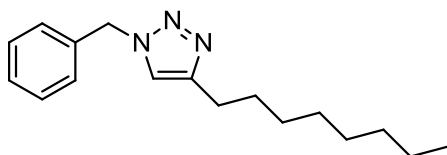
White solid.

^{1}H NMR (CDCl$_3$) δ 7.39–7.32 (m, 3H), 7.25 (m, 2H), 7.17 (s, 1H), 5.49 (s, 2H), 2.68 (t, *J* = 7.5 Hz, 2H), 1.63 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.35–1.19 (m, 10H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 149.0, 135.0, 129.0, 128.6, 127.9, 120.4, 54.0, 31.8, 29.4, 29.3, 29.24, 29.17, 25.7, 22.6, 14.1. Mp. 61.8–62.0 °C. HRMS Calcd for C$_{17}$H$_{25}$N$_3$: M$^+$, 271.2049. Found: *m/z* 271.2046.

5-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)pentan-1-ol (3ga).
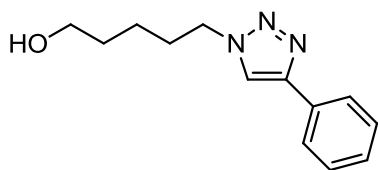
White solid, purified by flash silica gel column chromatography using EtOAc as an eluent.

^{1}H NMR (CDCl$_3$) δ 7.83 (m, 2H), 7.75 (s, 1H), 7.42 (m, 2H), 7.33 (m, 1H), 4.42 (t, J = 7.5 Hz, 2H), 3.66 (dt, J = 5.0, 6.5 Hz, 2H), 2.00 (m, 2H), 1.63 (m, 2H), 1.48–1.42 (m, 3H). ^{13}C NMR (CDCl$_3$) δ 147.8, 130.7, 128.8, 128.1, 125.7, 119.4, 62.4, 50.3, 31.9, 30.1, 22.8.   Mp. 82.5–82.7 °C.   IR (KBr): 3311, 3122, 2935, 2863, 1462, 1357, 1218, 1191, 1078, 1056, 1021, 977, 839, 763, 696, 527 cm^{-1}.   HRMS Calcd for C$_{13}$H$_{17}$N$_3$O: M$^+$, 231.1372. Found: m/z 231.1380.

(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methanol (3bf): CAS RN [28798-81-4].
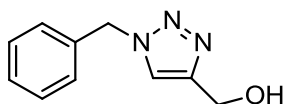
White solid, purified by flash silica gel column chromatography using EtOAc as an eluent.

^{1}H NMR (CDCl$_3$) δ 7.44 (s, 1H), 7.39–7.33 (m, 3H), 7.27 (m, 2H), 5.51 (s, 2H), 4.76 (d, J = 4.0 Hz, 2H), 2.65 (t, J = 4.0 Hz, 1H). ^{13}C NMR (CDCl$_3$) δ 148.1, 134.5, 129.1, 128.8, 128.1, 121.6, 56.6, 54.2.   Mp. 75.0–75.2 °C.   HRMS Calcd for C$_{10}$H$_{11}$N$_3$O: M$^+$, 189.0902. Found: m/z 189.0905.

1-Benzyl-4-(methoxymethyl)-1*H*-1,2,3-triazole (3bg).
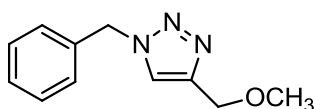
Pale yellow oil, purified by flash silica gel column chromatography using hexane/EtOAc (v/v = 1/1) as an eluent.

^{1}H NMR (CDCl$_3$) δ 7.43 (s, 1H), 7.39–7.35 (m, 3H), 7.27 (m, 2H), 5.52 (s, 2H), 4.56 (s, 2H), 3.39 (s, 3H). ^{13}C NMR (CDCl$_3$) δ 145.5, 134.5, 129.1, 128.8, 128.1, 122.2, 66.0, 58.3, 54.2.   IR (neat): 3467, 3137, 3090, 2929, 1498, 1456, 1333, 1222, 1193, 1095, 1050, 955, 908, 820, 763, 721, 482 cm^{-1}.   HRMS Calcd for C$_{11}$H$_{13}$N$_3$O: M$^+$, 203.1059. Found: m/z 203.1059.

1-(*β*-D-Glucopyranosyl)-4-phenyl-1*H*-1,2,3-triazole (3ha): CAS RN [26295-49-8].
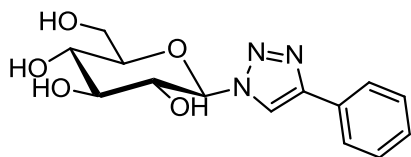
White solid, purified by flash silica gel column chromatography using CH_2Cl_2/EtOH (v/v = 8/2) as an eluent.

^{1}H NMR (CD$_3$OD, 300 MHz) δ 8.86 (s, 1H), 7.84 (m, 2H), 7.44 (m, 2H), 7.35 (m, 1H), 5.66 (d, *J* = 9.3 Hz, 1H), 3.99–3.88 (m, 2H), 3.74 (dd, *J* = 12.6 Hz, 4.8 Hz, 1H), 3.66–3.50 (m, 3H). ^{13}C NMR (CD$_3$OD) δ 148.9, 131.6, 130.0, 129.4, 126.7, 121.4, 89.8, 81.2, 78.6, 74.1, 70.9, 62.5. Mp. 233.8–234.0 °C.   HRMS Calcd for $C_{22}H_{25}N_3O_9$: $[M+H]^+$, 308.1241. Found: *m/z* 308.1241.

1-Benzyl-4-(*tert*-butyl)-1*H*-1,2,3-triazole (3bh): CAS RN [871689-96-2].
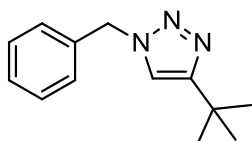
White solid.

^{1}H NMR (CDCl$_3$) δ 7.39–7.32 (m, 3H), 7.26 (m, 2H), 7.15 (s, 1H), 5.48 (s, 2H), 1.32 (s, 9H). ^{13}C NMR (CDCl$_3$) δ 158.2, 135.1, 129.0, 128.5, 128.0, 118.3, 53.9, 30.8, 30.3.   Mp. 79.5–80.0 °C.   HRMS Calcd for $C_{13}H_{17}N_3$: $[M+H]^+$, 216.1495. Found: *m/z* 216.1493.

1-Benzyl-4-cyclohexyl-1*H*-1,2,3-triazole (3bi): CAS RN [1062294-02-3].
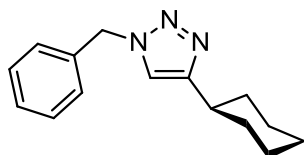
White solid.

^{1}H NMR (CDCl$_3$) δ 7.39–7.32 (m, 3H), 7.25 (m, 2H), 7.14 (s, 1H), 5.48 (s, 2H), 2.73 (m, 1H), 2.03 (m, 2H), 1.77 (m, 2H), 1.70 (m, 1H), 1.37 (m, 4H), 1.22 (m, 1H). ^{13}C NMR (CDCl$_3$) δ

154.2, 135.0, 129.0, 128.5, 128.0, 119.1, 54.0, 35.3, 33.0, 26.1, 26.0.   Mp. 105.1–105.3 °C.

HRMS Calcd for $C_{15}H_{19}N_3$: M^+, 241.1579. Found: m/z 241.1579.

Table S1. CuAAC Reaction between 1-Azidooctane (**1a**) and Phenylacetylene (**2a**) with Various Ligands in the Presence of Water.[a]
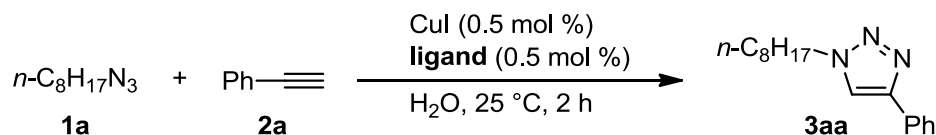
entry	ligand	yield (%)[b]
1	none	4
2	Et_3N	7
3	n-Bu_3N	3
4	EtN^iPr_2	6
5	2,6-lutidine	3
6	DMAP	65
7	**4a** (R = CH_3)	34
8	**4b** (R = 1-ad)	93
9	**5**	17
10	**6**	18
11	**4c** (R = n-C_4H_9)	51
12	**4d** (R = n-$C_{10}H_{21}$)	99 (97[c])

[a] Reactions were run using 1-azidooctane (**1a**, 1.0 mmol), phenylacetylene (**2a**, 1.05 mmol), CuI (0.005 mmol), and the ligand (0.005 mmol), and H_2O (0.5 mL). [b] Yields were determined by ^1H NMR. [c] Isolated yield.

Imidazole Ligands

4a (R = CH_3)
4b (R = 1-ad)
4c (R = n-C_4H_9)
4d (R = n-$C_{10}H_{21}$)

5

6
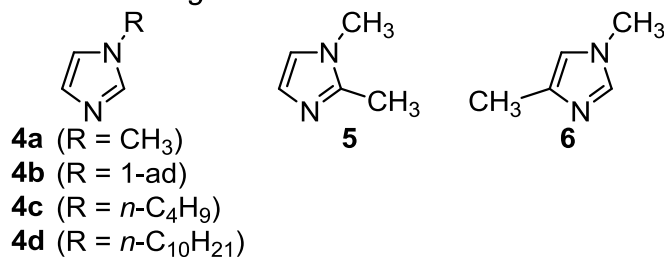
Scheme S1. CuAAC Reaction of Substrates Having a Hydroxyl or Methoxy Group in the Presence/Absence of Water.
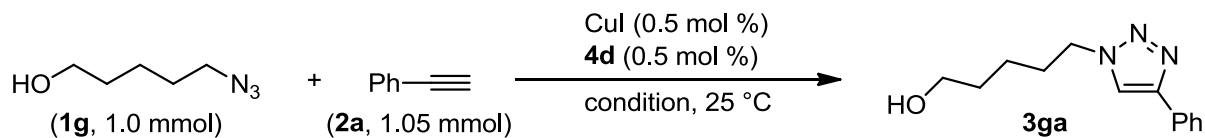
entry	condition	yield (%)[a]
1	neat, 4 h	56
2	with H_2O (0.5 mL), 2 h	86
3	with H_2O (0.5 mL), 3 h	99[b]

[a] Yields were determined by ^1H NMR.　　[b] Isolated yield.
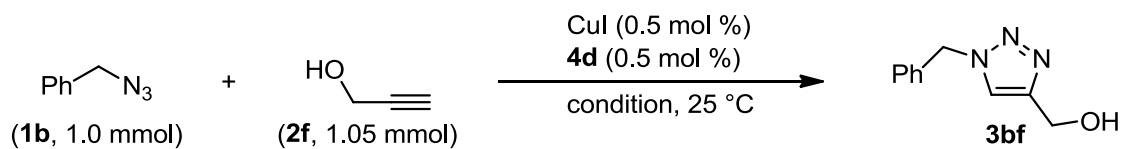
entry	condition	yield (%)[a]
1	neat, 5 h	6
2	with H_2O (0.5 mL), 2 h	56
3	with H_2O (0.5 mL), 5 h	92[b]

[a] Yields were determined by ^1H NMR.　　[b] Isolated yield.

Ph–CH2–N3 (**1b**, 1.0 mmol) + CH3O–CH2–C≡CH (**2g**, 1.05 mmol) → [CuI (0.5 mol %), **4d** (0.5 mol %), condition, 25 °C] → **3bg** (Ph–CH2–triazole–CH2–OCH3)
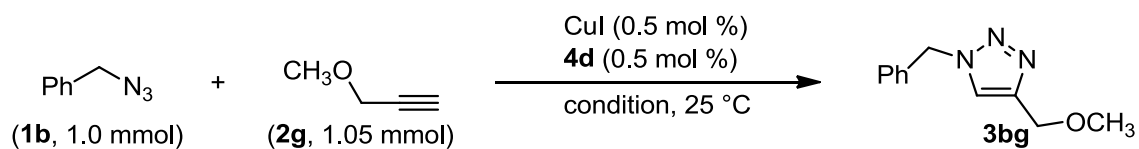
entry	condition	yield (%)^a
1	neat, 5 h	26
2	with H$_2$O (0.5 mL), 2 h	74
3	with H$_2$O (0.5 mL), 5 h	85^b

^{a} Yields were determined by ^{1}H NMR. ^{b} Isolated yield.

Glucosyl azide (**1h**, 1.0 mmol) + Ph–C≡CH (**2a**, 1.05 mmol) → [CuI (0.5 mol %), **4d** (0.5 mol %), condition, 25 °C] → **3ha**
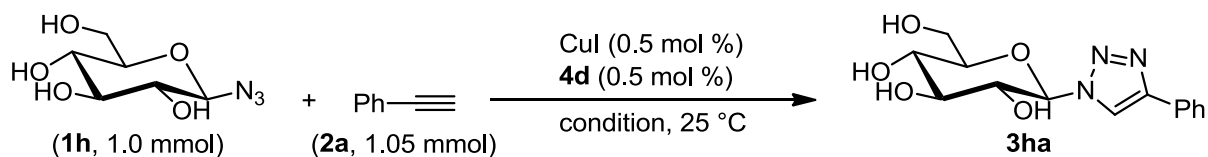
entry	condition	yield (%)^a
1	neat, 10 h	<1%
2	with H$_2$O (0.5 mL), 5 h	<1%
3	with H$_2$O (0.1 mL)/t-BuOH(0.4 mL), 5 h	58
4	with H$_2$O (0.1 mL)/t-BuOH(0.4 mL), 10 h	93^b

^{a} Yields were determined by ^{1}H NMR. ^{b} Isolated yield.

Scheme S2. CuAAC Reaction between 1-Azidooctane (**1a**) and Phenylacetylene (**2a**) with Various Amounts of Imidazole Derivatives.[a]
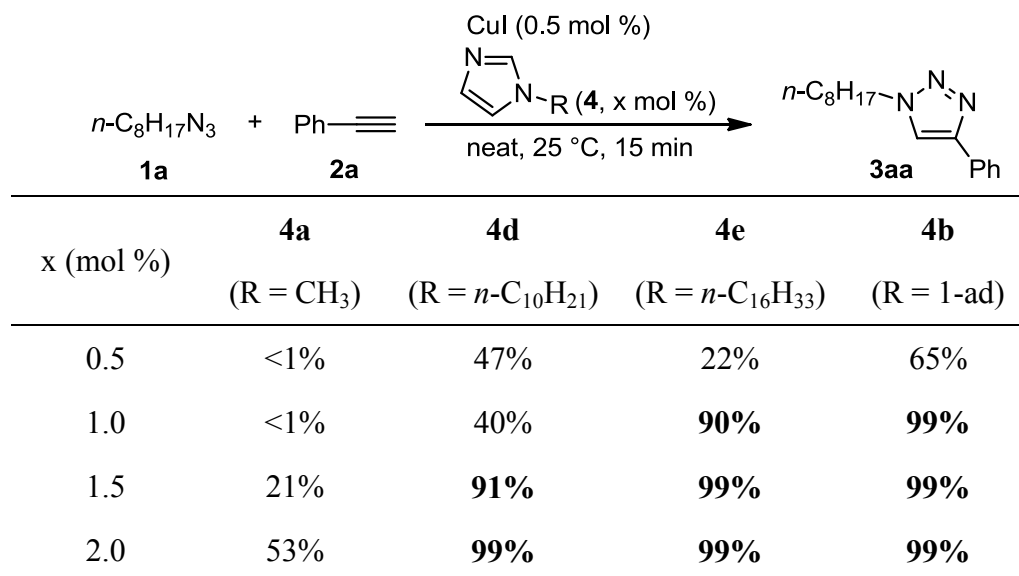
x (mol %)	**4a** (R = CH$_3$)	**4d** (R = n-C$_{10}$H$_{21}$)	**4e** (R = n-C$_{16}$H$_{33}$)	**4b** (R = 1-ad)
0.5	<1%	47%	22%	65%
1.0	<1%	40%	**90%**	**99%**
1.5	21%	**91%**	**99%**	**99%**
2.0	53%	**99%**	**99%**	**99%**

[a] Reactions were run using 1-azidooctane (**1a**, 1.0 mmol), phenylacetylene (**2a**, 1.05 mmol), CuI (0.005 mmol), and the *N*-alkylimidazole **4** (0.005 mmol).

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16. As for the reaction in the presence of water, further investigations corresponding to Table 1 were also performed; see Table S1 in Experimental Section for details.

17. See Scheme S1 in Experimental Section for more details.

18. Similar investigations were also performed with **4a** and **4b**; see Scheme S2 in Experimental Section for details.

19. The use of CH₃CN or CH₂Cl₂ as a solvent was also not effective for those reactions.

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Chapter 4

Effects of a Flexible Alkyl Chain on an Imidazole Ligand for Copper-Catalyzed Mannich Reaction of Terminal Alkynes

Copper-catalyzed Mannich reactions of terminal alkynes and secondary amines with aqueous formaldehyde can be accelerated by the use of a catalytic amount of an imidazole ligand carrying a long alkyl chain.   The alkyl chain shows an efficient steric effect and helps the reaction.   This imidazole ligand is efficient for various substrates, including even bulky alkynes.

Chapter 4

Introduction

An alkyl chain is an important group included in many amphiphiles or other organic materials; it helps to determine their properties.[1]   In Chapter 3, the author described that the imidazole ligand with a long alkyl chain accelerates the copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) reaction.[2]   The ligand with a flexible alkyl chain shows an efficient steric effect, allowing a creation of a favorable environment around a Cu center, which can accommodate even bulky substrates.[3]   Additionally, this ligand is also useful in aqueous media.   On the basis of this work, he sought to expand the utility of the ligand to another copper-catalyzed transformation of terminal alkynes.   In Chapter 4, the author describes the efficiency of an imidazole carrying a long alkyl chain[2,4–6] as a ligand to enhance the Mannich reactions of terminal alkynes mediated by a copper catalyst.[7]

Propargylamines are important compounds because of their biological activity or their utility as synthetic intermediates.[8,9]   Although the classical Mannich reaction between terminal alkynes and secondary amines with formaldehyde is a useful method to provide propargylamines, it is applicable only to aryl acetylenes.[7a]   The development of copper-catalyzed processes removed many limitations,[7,10,11] but the processes still suffer from harsh conditions, moderate yields, or complex procedures.   The harsh conditions employed in many procedures may be necessary not only for the formation but also for the activation of copper-acetylide intermediates; otherwise they are known to aggregate readily to become an inactive polymeric form.[12]   If a certain ligand realizes the activation of copper-acetylides under mild conditions, this copper catalyzed reaction will be more practical.   To promote the generation of active monomeric or oligomeric copperacetylide species, sterically assisted ligands seem to be efficient.[13]   In addition, the capability of using an aqueous formaldehyde solution would also contribute to the efficiency due to the easiness of handing and the stability even at room temperature.[14,15]

Results and Discussion

The author initially examined the reaction between phenylacetylene (**1a**, 1.0 mmol), piperidine (**2a**, 1.0 mmol), and aqueous formaldehyde (37% solution, 1.2 mmol) with 0.5 mol % of CuI and 1.0 mol % of various amine ligands without any organic solvent at 25 °C (Table 1). The reaction without any ligand gave the product **3aa** in only 30% yield (Table 1, entry 1), and the effects of pyridine derivatives, tertiary amines, or imidazole derivatives substituted by methyl groups (**4a**, **5**, **6**; Figure 1)[4d] as a ligand were also not satisfactory (Table 1, entries 2–10). On the other hand, 1-(1-adamantyl)imidazole (**4b**) was shown to be excellent as a ligand probably because its steric effect was sufficient (Table 1, entry 11). The author then investigated the efficiency of imidazoles substituted by a normal alkyl group in hopes of finding a steric effect. As expected, imidazole derivatives with normal alkyl groups (**4c–e**) were efficient, and especially 1-hexadecylimidazole (**4e**), with the longest alkyl chain among them, showed as good a result as **4b** (Table 1, entries 12–14). With **4e**, the author also investigated some other copper sources, and CuI was shown to be the best among them (Table 2).

He then examined the effect of the amount of imidazole ligands (Scheme 1). When the amount of **4e** was decreased to 0.5 mol %, the yield considerably dropped, while the reactions with larger amounts of **4e** gave high yields. In contrast, such a drastic change in the yield was not observed by using **4a** as a ligand in any case.[16] The acceleration obtained by the use of an excess amount of **4e** to a Cu catalyst can be attributed to the effect of free **4e**, which does not coordinate to a Cu catalyst and works as a base to deprotonate from a terminal alkyne in forming a copper-acetylide intermediate. Thus, the steric effect of the long alkyl chain on **4e** might also play a role in repulsing the multiple coordination of **4e** on a Cu center and releasing free **4e** working as a base.[2,17]

Table 1. Mannich Reaction between Phenylacetylene (**1a**), Piperidine (**2a**), and Formaldehyde with Various Ligands.[a]

entry	**ligand**	yield (%)[b]
1	none	30
2	pyridine	44
3	2,6-lutidine	10
4	DMAP	29
5	Et$_3$N	26
6	n-Bu$_3$N	11
7	EtNi-Pr$_2$	19
8	**4a** (R = CH$_3$)	12
9	**5**	31
10	**6**	40
11	**4b** (R = 1-ad)	99
12	**4c** (R = n-C$_4$H$_9$)	57
13	**4d** (R = n-C$_{10}$H$_{21}$)	52
14	**4e** (R = n-C$_{16}$H$_{33}$)	97

[a] Reactions were run using phenylacetylene (**1a**, 1.0 mmol), piperidine (**2a**, 1.0 mmol), formaldehyde (37% aqueous solution, 1.2 mmol), CuI (0.005 mmol), and the ligand (0.01 mmol). [b] Yields were determined by ^{1}H NMR.
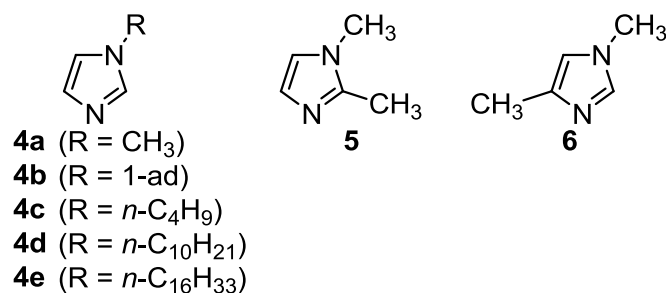
4a (R = CH$_3$)
4b (R = 1-ad)
4c (R = *n*-C$_4$H$_9$)
4d (R = *n*-C$_{10}$H$_{21}$)
4e (R = *n*-C$_{16}$H$_{33}$)

Figure 1. Imidazole Ligands.

Table 2. Mannich Reaction using 1-Hexadecylimidazole (**4e**) with Various Cu Sources.[a]

entry	*Cu*	yield (%)[b]
1	CuI	97
2	CuBr	26
3	CuCl	32
4	CuCN	47
5	(CuOTf)$_2$·benzene	23
6	Cu(MeCN)$_4$PF$_6$	46

[a] Reactions were run using phenylacetylene (**1a**, 1.0 mmol), piperidine (**2a**, 1.0 mmol), formaldehyde (37% aqueous solution, 1.2 mmol), the Cu salt (0.005 mmol), and *N*-hexadecylimidazole (**4e**, 0.01 mmol). [b] Yields were determined by ^{1}H NMR.
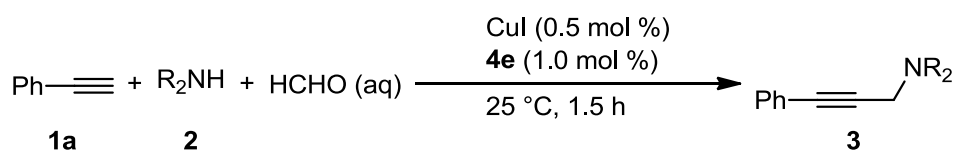
Scheme 1. Mannich Reaction between Phenylacetylene (**1a**), Piperidine (**2a**), and Formaldehyde with Various Amounts of 1-Methylimidazole (**4a**) and 1-Hexadecylimidazole (**4e**).[a]
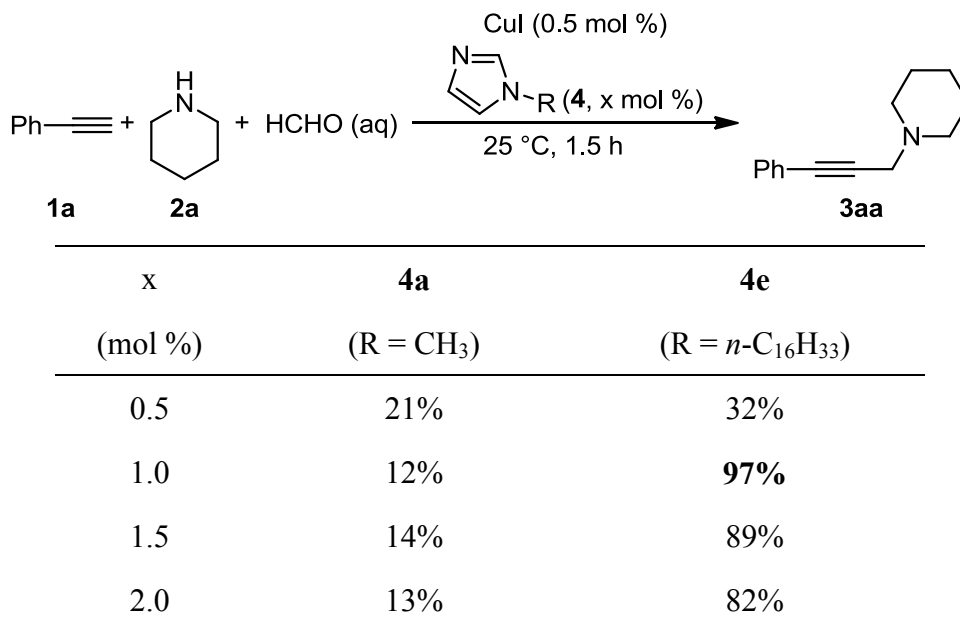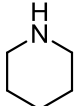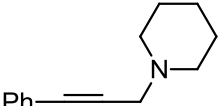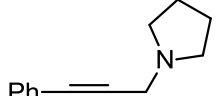

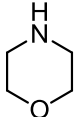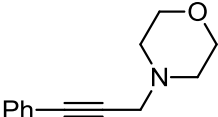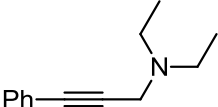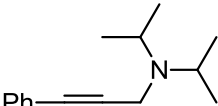| x	**4a**	**4e**
(mol %)	(R = CH$_3$)	(R = n-C$_{16}$H$_{33}$)
0.5	21%	32%
1.0	12%	**97%**
1.5	14%	89%
2.0	13%	82%

[a] Reactions were run using phenylacetylene (**1a**, 1.0 mmol), piperidine (**2a**, 1.0 mmol), formaldehyde (37% aqueous solution, 1.2 mmol), CuI (0.005 mmol) and the *N*-alkylimidazole **4**.

The author also applied the conditions using **4e** as a ligand to some other secondary amines (Table 3). Some cyclic and acyclic secondary amines were also available, and the ligand effect of **4e** could be observed.[18] Especially in the case of pyrrolidine (**2b**), the product **3ab** was obtained quantitatively, and a large ligand effect was observed (Table 3, entry 2).

The author then investigated the reactions with some other alkynes (Table 4). The reactions of various alkynes could be performed, and **4e** accelerated those reactions. 4-Trifluoromethylphenylacetylene (**1b**) showed a rapid reaction due to the use of **4e** (Table 4, entry 1). In the slower reactions with 4-methoxylphenylacetylene (**1c**) and 2-methylphenylacetylene (**1d**), **4e** improved the rates to an acceptable degree (Table 4, entries 2 and 3). Although the reactions of the acetylenes with aliphatic groups (**1e–g**) required higher temperatures, the effect of **4e** was observed in these cases also (Table 4, entries 4–6).

Table 3. Mannich Reaction of Various Secondary Amines **2** with 1-Hexadecylimidazole (**4e**).[a]

entry	R$_2$NH	2	product	3	yield with **4e** (%)[c]	yield without **4e** (%)[c]
1		2a		3aa	97	30
2[b]		2b		3ab	99	42
3		2c		3ac	34	7
4	Et$_2$NH	2d		3ad	70	58
5	*i*-Pr$_2$NH	2e		3ae	43	32

[a] Reactions were run using phenylacetylene (**1a**, 1.0 mmol), the secondary amine **2** (1.0 mmol), formaldehyde (37% aqueous solution, 1.2 mmol), CuI (0.005 mmol), and *N*-hexadecylimidazole (**4e**, 0.01 mmol). [b] CuI and **4e** were added after stirring the mixture of the other components for 1 h. [c] Yields were determined by ^{1}H NMR.

Table 4. Mannich Reaction of Various Alkynes **1** with 1-Hexadecylimidazole (**4e**).[a]


entry	R	1	product	3	T (°C)	yield with 4e (%)[b]	yield without 4e (%)[b]
1	4-CF$_3$C$_6$H$_4$	**1b**		**3ba**	25	92	61
2	4-CH$_3$OC$_6$H$_4$	**1c**		**3ca**	25	47	27
3	2-CH$_3$C$_6$H$_4$	**1d**		**3da**	25	74	22
4	n-C$_8$H$_{17}$	**1e**		**3ea**	80	97	44
5	n-C$_4$H$_9$	**1f**		**3fa**	80	84	55
6	HO(CH$_2$)$_4$	**1g**		**3ga**	50	65	42

[a] Reactions were run using the alkyne **1** (1.0 mmol), piperidine (**2a**, 1.0 mmol), formaldehyde (37% aqueous solution, 1.2 mmol), CuI (0.005 mmol), and *N*-hexadecylimidazole (**4e**, 0.01 mmol).   [b] Yields were determined by ^{1}H NMR.

Notably with **4e**, the reactions of even bulky alkynes (**1h**, **1i**) could be performed efficiently (Scheme 2).   In these instances, the yields of the reactions with **4e** were even better than those of the reactions using **4b** as a ligand.   This suggests that the flexible alkyl chain has an advantage in the creation of a favorable environment around a Cu center for bulky substrates.

Scheme 2. Mannich Reaction of Acetylenes with Bulky Substituents.[a]
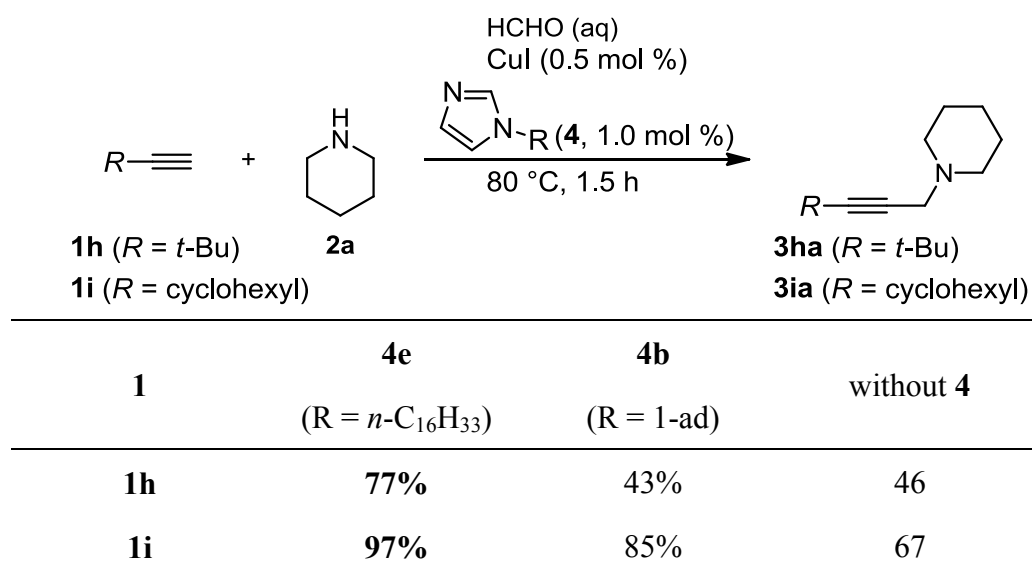
1	4e	4b	without 4
	(R = n-C$_{16}$H$_{33}$)	(R = 1-ad)	
1h	**77%**	43%	46
1i	**97%**	85%	67

[a] Reactions were run using the alkyne **1** (1.0 mmol), piperidine (**2a**, 1.0 mmol), formaldehyde (37% aqueous solution, 1.2 mmol), CuI (0.005 mmol), and the *N*-alkylimidazole **4** (0.01 mmol).

Conclusion

In summary, the author has shown the efficiency of an imidazole carrying a long alkyl chain as a ligand to enhance the copper-catalyzed Mannich reactions of terminal alkynes, secondary amines, and aqueous formaldehyde.   The alkyl chain gave an efficient steric effect, and the imidazole benefited the reaction not only as a ligand but also as a base catalyst.   Furthermore, the flexible alkyl chain could provide a favorable environment around a copper center for a variety of substrates.   These results suggest a new concept for an efficient ligand of transition-metal catalysis.   This methodology could also be further applied to other catalytic processes.

Chapter 4

**Experimental Section**

Materials

Unless otherwise noted, commercially available reagents were used without purification. All alkynes listed in Chapter 4 were commercially available. *N*-Alkylimidazoles (**4d**, **4e**) were prepared by the method descreibed in Chapter 1. *N*-Adamantylimidazole (**4b**) and 1,4-dimethyl-1*H*-imidazole (**6**) were prepared by the method descreibed in Chapter 3. *N*-Methylimidazole (**4a**), *N*-butylimidazole (**4c**), and 1,2-dimethyl-1*H*-imidazole (**5**) were commercially available.

General procedure for Mannich Reaction of Terminal Alkynes 1 and Secondary Amines 2 with Formaldehyde

To a 5-mL vial were added sequentially terminal alkyne **1** (1.0 mmol), secondary amine **2** (1.0 mmol), formaldehyde (37% aqueous solution, 1.2 mmol), *N*-hexadecylimidazole (**4e**, 0.01 mmol), and CuI (0.005 mmol). The mixture was stirred in an oil bath maintained at 25 °C for 1.5 h. The mixture was diluted with EtOAc, dried over Na$_2$SO$_4$, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 1/1) as an eluent afforded the corresponding propargylamine **3**.

Characterization Data of Products

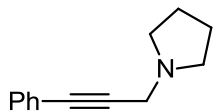**1-(3-Phenylprop-2-yn-1-yl)piperidine (3aa)**: CAS RN [2658-57-2].
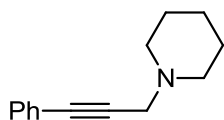
Orange oil.

^{1}H NMR (CDCl$_3$) δ 7.43 (m, 2H), 7.30–7.27 (m, 3H), 3.48 (s, 2H), 2.57 (br, 4H), 1.64 (tt, *J* = 6.0, 5.5 Hz, 4H), 1.45 (br, 2H). ^{13}C NMR (CDCl$_3$) δ 131.7, 128.2, 127.9, 123.3, 85.1, 84.9, 53.5,
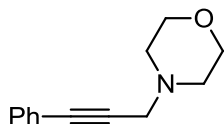
48.5, 26.0, 23.9.

1-(3-Phenylprop-2-yn-1-yl)pyrrolidine (3ab): CAS RN [1015-02-7].

Orange oil.

^{1}H NMR (CDCl$_3$) δ 7.43 (m, 2H), 7.30–7.27 (m, 3H), 2.69 (m, 4H) , 1.83 (m, 4H). ^{13}C NMR (CDCl$_3$) δ 131.7, 128.2, 127.9, 123.3, 85.4, 84.3, 52.7, 43.8, 23.8.
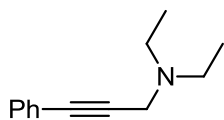
4-(3-Phenylprop-2-yn-1-yl)morpholine (3ac): CAS RN [1017-73-8].

Pale yellow oil.

^{1}H NMR (CDCl$_3$) δ 7.43 (m, 2H), 7.32–7.29 (m, 3H), 3.78 (t, J = 4.5 Hz, 4H), 3.51 (s, 2H), 2.65 (t, J = 4.5 Hz, 4H). ^{13}C NMR (CDCl$_3$) δ 131.6, 128.2, 128.1, 123.0, 85.5, 84.0, 66.9, 52.4, 48.0.
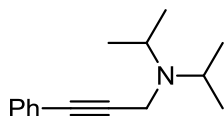
***N*,*N*-Diethyl-3-phenylprop-2-yn-1-amine (3ad)**: CAS RN [22396-72-1].

Pale yellow oil.

^{1}H NMR (CDCl$_3$) δ 7.43 (m, 2H), 7.31–7.27 (m, 3H), 3.65 (s, 2H), 2.64 (q, J = 7.0 Hz, 4H), 1.13 (t, J = 7.0 Hz, 6H). ^{13}C NMR (CDCl$_3$) δ 131.6, 128.1, 127.8, 123.3, 84.8, 84.3, 47.2, 51.4, 12.5.
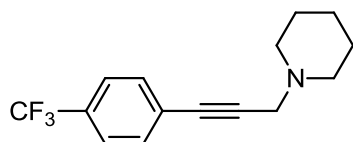
***N*,*N*-Diisopropyl-3-phenylprop-2-yn-1-amine (3ae)**: CAS RN [90733-18-9].

Pale yellow oil.

^{1}H NMR (CDCl$_3$) δ 7.39 (m, 2H), 7.30–7.27 (m, 3H), 3.66 (s, 2H), 3.26 (sept, J = 6.5 Hz, 2H), 1.16 (d, J = 6.5 Hz, 12H). ^{13}C NMR (CDCl$_3$) δ 131.4, 128.2, 127.7, 123.8, 89.1, 83.4, 48.5, 34.8, 20.7.

1-(3-(4-(Trifluoromethyl)phenyl)prop-2-yn-1-yl)piperidine (3ba).

Pale yellow oil.

^{1}H NMR (CDCl$_3$) δ 7.55–7.49 (m, 4H), 3.47 (s, 2H), 2.55 (br, 4H), 1.64 (tt, J = 6.0, 5.5 Hz, 4H), 1.44 (br, 2H). ^{13}C NMR (CDCl$_3$) δ 131.9, 129.7 (q, J = 32.7 Hz), 127.1, 125.1 (q, J = 3.8 Hz), 123.9 (q, J = 272.0 Hz), 87.9, 83.7, 53.5, 48.4, 25.9, 23.9. ^{19}F NMR (CDCl$_3$): δ 98.3.   IR (neat): 2937, 2797, 2234, 1617, 1453, 1323, 1128, 1068, 1018, 842, 466 cm^{-1}.   HRMS Calcd for C$_{15}$H$_{15}$F$_3$N: [M–H]$^+$, 266.1146. Found: m/z 266.1159.
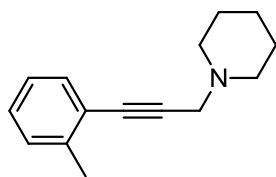
1-(3-(4-Methoxyphenyl)prop-2-yn-1-yl)piperidine (3ca): CAS RN [500140-87-4].
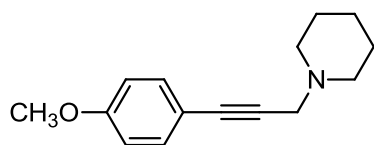
Orange oil.

^{1}H NMR (CDCl$_3$) δ 7.37 (dt, J = 9.0, 2.5 Hz, 2H), 6.82 (dt, J = 9.0, 2.5 Hz, 2H), 3.80 (s, 3H), 3.45 (s, 2H), 2.56 (br, 4H), 1.64 (tt, J = 5.5, 5.5 Hz, 4H), 1.44 (br, 2H). ^{13}C NMR (CDCl$_3$) δ 159.4, 133.1, 1155, 113.8, 84.8, 83.5, 55.3, 53.5, 48.5, 26.0, 24.0.
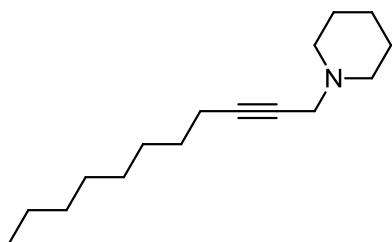
1-(3-(2-Tolyl)prop-2-yn-1-yl)piperidine (3da): CAS RN [500140-85-2].

Pale yellow oil.

^{1}H NMR (CDCl$_3$) δ 7.40 (d, J = 7.0 Hz, 1H), 7.21–7.17 (m, 2H), 7.11 (m, 1H), 3.55 (s, 2H), 2.59 (br, 4H), 2.44 (s, 3H), 1.65 (tt, J = 5.5, 5.5 Hz, 4H), 1.45 (br, 2H).   ^{13}C NMR (CDCl$_3$) δ 144.0, 132.0, 129.3, 127.8, 125.4, 123.2, 88.8, 83.9, 53.3, 48.6, 26.0, 23.9, 20.9.

1-(Undec-2-yn-1-yl)piperidine (3ea): CAS RN [19699-16-2].

Orange oil.

^{1}H NMR (CDCl$_3$) δ 3.20 (t, J = 2.0 Hz, 2H), 2.46 (br, 4H), 2.17 (tt, J = 7.0, 1.0 Hz, 2H), 1.60 (tt, J = 6.0, 5.5 Hz, 4H), 1.48 (tt, J = 7.5, 7.0 Hz, 2H), 1.44–1.33 (m, 4H), 1.32–1.20 (m, 8H), 0.87 (t, J = 7.0 Hz, 3H).   ^{13}C NMR (CDCl$_3$) δ 85.1, 75.3, 53.4, 48.1, 31.8, 29.2, 29.1, 28.9, 25.9, 24.0, 22.6, 18.7, 14.1.
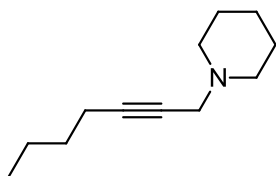
1-(Hept-2-yn-1-yl)piperidine (3fa): CAS RN [19699-12-8].
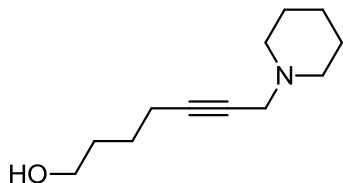

Pale yellow oil.

^{1}H NMR (CDCl$_3$) δ 3.20 (t, J = 2.0 Hz, 2H), 2.46 (br, 4H), 2.19 (tt, J = 7.0, 2.0 Hz, 2H), 1.60 (tt, J = 5.5, 6.0 Hz, 4H), 1.51–1.36 (m, 6H), 0.90 (t, J = 7.0 Hz, 3H).   ^{13}C NMR (CDCl$_3$) δ 85.0,

75.3, 53.4, 48.1, 31.0, 25.9, 25.1, 24.0, 18.5, 13.6.

7-(Piperidin-1-yl)hept-5-yn-1-ol (3ga).

Pale yellow oil.

^{1}H NMR (CDCl$_3$) δ 3.67 (t, J = 6.5 Hz, 2H), 3.20 (t, J = 2.0 Hz, 2H), 2.47 (br, 4H), 2.25 (tt, J = 7.0, 2.0 Hz, 2H), 1.67 (m, 2H), 1.63–1.56 (m, 6H), 1.42 (br, 2H). ^{13}C NMR (CDCl$_3$) δ 84.6, 75.8, 62.4, 53.4, 48.1, 31.9, 25.9, 25.1, 24.0, 18.5. IR (neat): 3321, 2804, 2935, 2231, 1653, 1454, 1341, 1156, 1102, 1067, 991, 859, 782, 471 cm^{-1}. HRMS Calcd for C$_{12}$H$_{20}$NO: [M–H]$^+$, 194.1545. Found: m/z 194.1536.

1-(4,4-Dimethylpent-2-yn-1-yl)piperidine (3ha): CAS RN [60948-82-5].
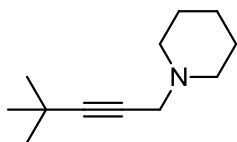
Pale yellow oil.

^{1}H NMR (CDCl$_3$) δ 3.21 (s, 2H), 2.46 (br, 4H), 1.61 (tt, J = 5.5, 6.0 Hz, 4H), 1.42 (br, 2H), 1.22 (s, 9H). ^{13}C NMR (CDCl$_3$) δ 93.7, 73.5, 53.3, 48.0, 31.2, 27.4, 25.9, 24.1.

1-(3-Cyclohexylprop-2-yn-1-yl)piperidine (3ia).
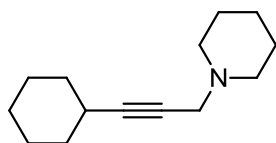
Pale yellow oil.

^{1}H NMR (CDCl$_3$) δ 3.20 (d, J = 2.5 Hz, 2H), 2.45 (br, 4H), 1.59 (tt, J = 6.0, 5.5 Hz, 2H), 1.48 (m,

1H), 1.40 (m, 4H), 1.27 (m, 3H). ^{13}C NMR (CDCl$_3$) δ 89.2, 74.9, 53.1, 48.0, 32.8, 29.0, 25.8, 24.8, 23.9. IR (neat): 2931, 2795, 2237, 1450, 1341, 1158, 1107, 994, 860, 782, 490 cm^{-1}. HRMS Calcd for C$_{14}$H$_{22}$N: [M–H]$^+$, 204.1752. Found: m/z 204.1760.

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16. Similar investigations corresponding to Table 3 were also performed with **4c** and **4d**, which carry alkyl chains of other lengths; also in those cases, a drastic acceleration such as occurred in the case of **4e** was not observed.

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18. The reactions of dibutylamine and dicyclohexylamine could be performed to afford the corresponding products quantitatively even without any ligand.

Chapter 5

Asymmetric Catalytic Cycloetherification Mediated by Bifunctional Organocatalysts

Oxacyclic structures such as tetrahydrofuran (THF) rings are commonly found in many bioactive compounds, and this has led to several efforts toward their stereoselective syntheses. However, the process of catalytic asymmetric cycloetherification for their straightforward synthesis has remained a challenge. In Chapter 5, the author demonstrates a novel asymmetric synthesis method for THF via the catalytic cycloetherification of ε-hydroxy-α,β-unsaturated ketones mediated by cinchona-alkaloid-thiourea-based bifunctional organocatalysts. This catalytic process represents a highly practical cycloetherification method that provides excellent enantioselectivities, even with low catalyst loadings at ambient temperature.

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Chapter 5

Introduction

The prevalence of oxacyclic frameworks such as tetrahydrofuran (THF) rings in a broad array of natural products and biologically active agents has resulted in the development of a number of methods for their stereoselective synthesis.[1,2] Among these methods, cycloetherification offers straightforward ring construction and has been successfully employed in the synthesis of 2-substituted oxacyclic compounds. However, catalytic enantioselective cycloetherification has remained a challenge despite significant advances in asymmetric catalysis.[3] This challenge is due to the difficulty in achieving a suitable chiral environment and the rapidity of the intramolecular processes involved in the catalysis.[4,5]
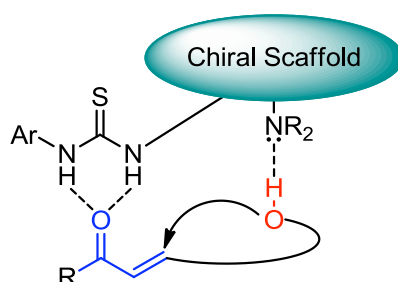

Figure 1. Asymmetric Cycloetherification via Intramolecular Oxy-Michael Addition Reaction Mediated by Bifunctional Organocatalyst.

Over the past decade, the process of asymmetric catalysis based on hydrogen bonding has seen continuous progress in the field of synthetic chemistry,[6,7] and the use of bifunctional organocatalysts that include a thiourea group and a tertiary amino group has made a significant contribution.[7] In this class of catalysts, the thiourea and tertiary amino groups function cooperatively as hydrogen bond donors and acceptors, respectively; this enables the simultaneous activation of a nucleophile and an electrophile in a suitable reaction direction, thereby leading to the desired stereochemical yields.[6,7] The efficiency of bifunctional organocatalysts stimulated the author to exploit the concerted catalysis in order to develop a catalytic asymmetric

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cycloetherification for THF synthesis via an intramolecular oxy-Michael addition reaction (Figure 1).[8] In Chapter 5, he present a highly enantioselective catalytic cycloetherification method for the synthesis of 2-substituted THFs from ε-hydroxy-α,β-unsaturated ketones mediated by cinchona-alkaloid-thiourea-based bifunctional organocatalysts.

Results and Discussion

The author initiated his investigations using (*E*)-6-hydroxy-1-phenylhex-2-en-1-one (**1a**) and 3 mol % of quinidine-derived bifunctional catalyst **3a** in CH$_2$Cl$_2$ at 25 °C. As expected, the THF product **2a** was obtained quantitatively and enantioselectively (Table 1, entry 1). The solvent optimization process identified cyclopentyl methyl ether (CPME) as the most suitable solvent for enantioselectivity (Table 1, entries 1–5). Moreover, the catalytic loading could even be lowered to 1 mol % at ambient temperature while still giving excellent yield and enantioselectivity (Table 1, entry 6), thereby showing that this reaction mode allows a highly practical cycloetherification. The screening of catalysts further showed that **3c** is an efficient catalyst for obtaining the opposite enantiomer of **2a** in excellent yield and enantioselectivity (Table 1, entry 8).

Subsequently, the author explored the substrate scope using 3 mol % of **3a** as a catalyst. Good to excellent yields and enantioselectivities were obtained with both electron-rich and electron-poor enones (Table 2, entries 2 and 3). In addition, substrates bearing naphthyl, *p*-tolyl, or *p*-bromophenyl groups afforded THF products in excellent yields with high enantioselectivities (Table 2, entries 4–6). An enone substituted by an alkyl group also underwent this reaction and yielded a THF product (Table 2, entry 7). In addition, the obtained THF product **2b** could be further transformed into the corresponding ester **4** by means of Baeyer–Villiger oxidation with *m*-CPBA and TFA in 92% yield without any loss of optical purity (Scheme 1). This transformation allows further transformations, such as the subsequent reduction of **4** with lithium aluminum hydride that yielded (*R*)-2-(tetrahydrofuran-2-yl)ethanol (**5**); the product **5** is a

valuable synthetic intermediate (Scheme 1).[9]   The absolute configuration of **2b** was determined by comparing the optical rotation of **5** derived from **2b** with the literature value[9a] (see Experimental Section for details), and the configurations for all other examples were assigned analogously.

Table 1. Optimization of Conditions.[a]

entry	catalyst	solvent	yield (%)[b]	ee (%)
1	**3a**	CH_2Cl_2	99	92
2	**3a**	benzene	97	94
3	**3a**	THF	73	90
4	**3a**	Et_2O	99	94
5	**3a**	CPME	99	95
6[c]	**3a**	CPME	95	96
7	**3b**	CPME	99	89
8	**3c**	CPME	99	−96
9	**3d**	CPME	99	−94

[a] Reactions were run using ε-hydroxy-α,β-unsaturated ketone **1a** (0.25 mmol) and the catalyst **3** (0.0075 mmol) in the solvent (0.5 mL).   [b] Isolated yields.
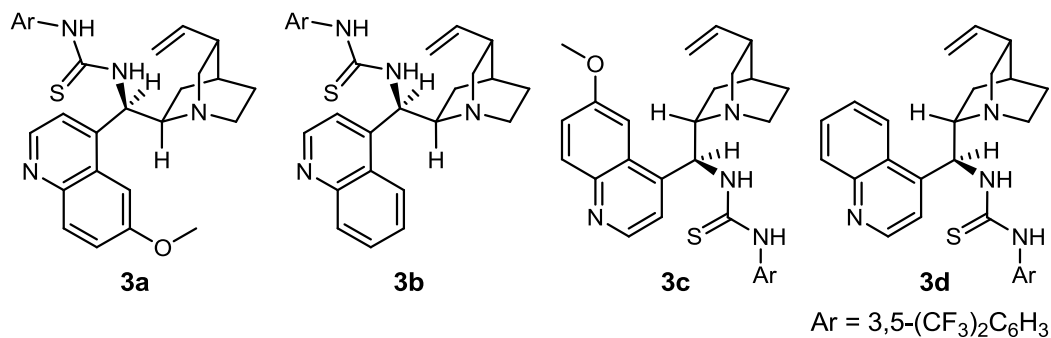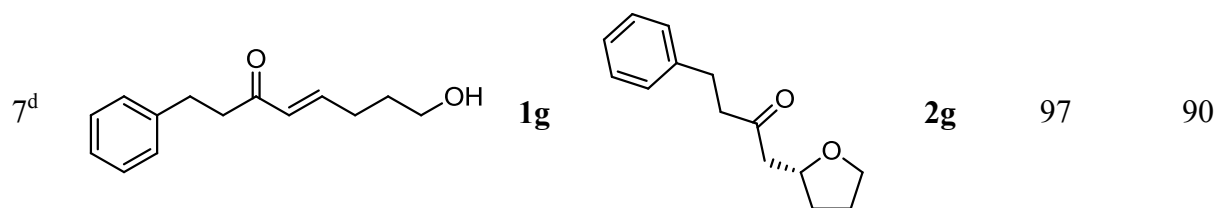[c] Reaction was run using 1 mol % of **3a** (0.0025 mmol).

3a   **3b**   **3c**   **3d**

$Ar = 3,5\text{-}(CF_3)_2C_6H_3$

Table 2. Substrate Scope with **3a** as Catalyst.[a]

entry	substrate	1	product	2	yield (%)[b]	ee (%)
1		**1a**		**2a**	99	95
2		**1b**		**2b**	99	94
3[c]		**1c**		**2c**	93	85
4		**1d**		**2d**	98	91
5		**1e**		**2e**	99	93
6		**1f**		**2f**	99	92

Table 2. (Continued)

7[d]	**1g**	**2g**	97	90

[a] Reactions were run using the ε-hydroxy-α,β-unsaturated ketone **1** (0.25 mmol) and catalyst **3a** (0.0075 mmol) in CPME (0.5 mL). [b] Isolated yields. [c] Reaction was run starting from 0.125 mmol of **1c**. [d] Reaction was run for 120 h.

Scheme 1. Transformation of **2b**.
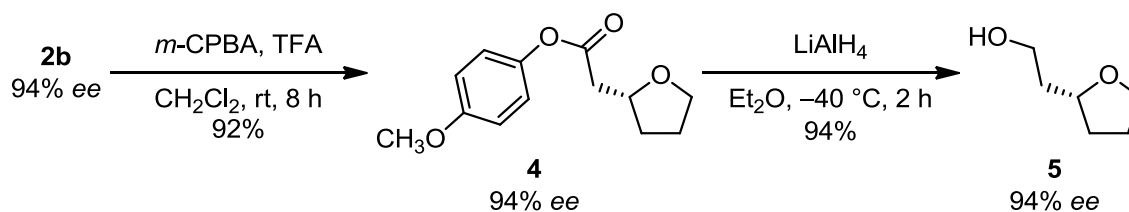
Furthermore, this protocol can also be applied to the asymmetric synthesis of 2-substituted tetrahydropyran (THP) (Scheme 2). Preliminary studies showed that the reaction of ζ-hydroxy-α,β-unsaturated ketone **6** using **3a** as a catalyst afforded the THP product **7** in good yield and high enantioselectivity.

Scheme 2. Asymmetric Synthesis of 2-Substituted Tetrahydropyran **7**.

Conclusion

In summary, the author has demonstrated a novel asymmetric cycloetherification for the synthesis of 2-substituted THFs by utilizing synergistic activations due to bifunctional organocatalysts.   This reaction is highly practical in the sense that the products were obtained in excellent enantioselectivities at ambient temperature, even under low catalyst loading conditions. Furthermore, this approach opens a new avenue for heterocycle synthesis with asymmetric catalysis based on hydrogen bonding.

Experimental Section

Materials

Unless otherwise noted, commercially available reagents were used without purification.

General procedure for asymmetric cycloetherification of *ε*-hydroxy-*α,β*-unsaturated ketones 1

To a 5-mL vial were added sequentially *ε*-hydroxy-*α,β*-unsaturated ketone **1** (0.25 mmol), cyclopentyl methyl ether (CPME, 0.5 mL), and quinidine-derived bifunctional catalyst **3a** (0.0075 mmol).   The mixture was stirred in an oil bath maintained at 25 °C for 24 h.   The reaction mixture was subsequently diluted with hexane/EtOAc (v/v = 1/1), passed through a short silica gel pad to remove **3a**, and concentrated in vacuo.   Purification of the reaction mixture by flash silica gel column chromatography using hexane/EtOAc (v/v = 3/1) as an eluent afforded the corresponding 2-substituted tetrahydrofuran **2**.   Racemic compounds were prepared using *p*-toluenesulfonic acid as a catalyst.

Procedure for asymmetric cycloetherification of *ζ*-hydroxy-*α,β*-unsaturated ketone 6

To a 5-mL vial were added sequentially *ζ*-hydroxy-*α,β*-unsaturated ketone **6** (0.030 g, 0.15

mmol), cyclopentyl methyl ether (CPME, 0.3 mL), and quinidine-derived bifunctional catalyst **3a** (0.0045 g, 0.0075 mmol).   The mixture was stirred in an oil bath maintained at 25 °C for 24 h. The reaction mixture was subsequently diluted with hexane/EtOAc (v/v = 1/1), passed through a short silica gel pad to remove **3a**, and concentrated in vacuo.   Purification of the reaction mixture by flash silica gel column chromatography using hexane/EtOAc (v/v = 3/1) as an eluent afforded tetrahydropyran **7** (0.027 g, 90% yield, 91% *ee*).

General procedure for preparation of bifunctional catalysts 3

Bifunctional organocatalysts **3** were prepared by the literature procedure.[7c]   A cinchona alkaloid (5 mmol) and triphenylphosphine (1.6 g, 6 mmol) were dissolved in THF (25 mL), and the solution was cooled to 0 °C.   Diethyl azodicarboxylate (1.0 g, 6 mmol) was subsequently added.   To the resulting solution was added dropwise the solution of diphenyl phosphoryl azide (1.3 mL, 6 mmol) in THF (10 mL) at 0 °C.   The mixture was allowed to warm to ambient temperature.   After being stirred for 24 h, it was heated to 50 °C and stirred for 10 h. Triphenylphosphine (1.7 g, 6.5 mmol) was added again, and the mixture was stirred at 50 °C for additional 15 h.   After the solution was cooled to ambient temperature, H_2O (0.5 mL) was added, and the solution was stirred for 24 h.   The solvents were removed in vacuo, and the residue was dissolved in CH_2Cl_2/10% aqueous HCl (25 mL/25 mL).   The aqueous phase was separated and washed with CH_2Cl_2 (25 mL × 4).   It was subsequently made alkaline with aqueous NH_3, and the aqueous phase was extracted with CH_2Cl_2 (25 mL × 4).   The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo.   Purification by flash silica gel column chromatography using EtOAc/CH_3OH (v/v = 9/1) then $CHCl_3$/CH_3OH (v/v = 8/2) as an eluent gave the corresponding 9-amino(9-deoxy)cinchona alkaloids.

Next, to the solution of the obtained 9-amino(9-deoxy)cinchona alkaloid in THF (6 mL) was slowly added a solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1 equiv) in THF (4 mL) at ambient temperature.   The mixture was stirred overnight, and the solvents were removed in vacuo.   Purification by flash silica gel column chromatography using EtOAc/CH_3OH (v/v =

95/5–97.5/2.5) or EtOAc as an eluent gave the corresponding bifunctional organocatalyst **3**. The characterization results are as below.
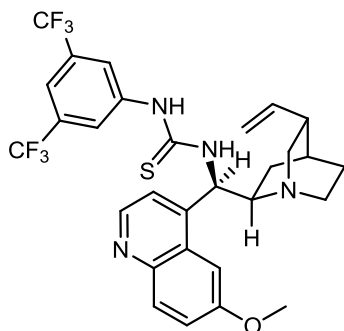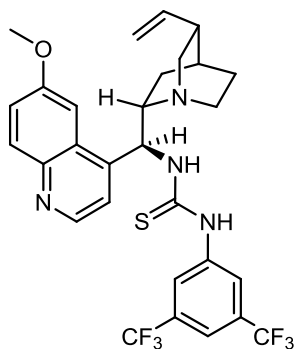

3a. White solid; 41% yield (for 2steps from quinidine). $[\alpha]_D^{23}$ +122.6 (*c* 1.33, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 8.65 (br s, 1H), 8.02 (d, *J* = 9.0 Hz, 1H), 7.86 (s, 2H), 7.67 (s, 1H), 7.59 (br s, 1H), 7.40 (d, *J* = 9.0 Hz, 1H), 7.23 (br s, 1H), 5.86 (br s, 2H), 5.19 (br s, 1H), 5.15 (d, *J* = 9.5 Hz, 1H), 3.97 (s, 3H), 3.22 (br s, 1H), 3.10 (br s, 1H), 3.03 (m, 2H), 2.94 (m, 1H), 2.38 (m, 1H), 1.70 (s, 1H), 1.61 (m, 2H), 1.27 (br s, 1H), 1.02 (m, 1H). ^{13}C NMR (CDCl$_3$) δ 181.0, 158.1, 147.3, 144.7, 144.5, 140.1, 139.6, 132.5 (q, *J* = 33.6 Hz), 131.6, 128.0, 123.5, 122.9 (q, *J* = 273.0 Hz), 122.3, 118.7, 115.3, 101.7, 61.4, 55.6, 48.5, 47.1, 38.7, 27.1, 26.1, 25.0.   Mp. 125.0–125.2 °C. IR (KBr): 3221, 2944, 2361, 1735, 1623, 1511, 1475, 1384, 1278, 1177, 1134, 1034, 959, 916, 884, 850, 826, 682 cm^{-1}.   HRMS Calcd for C$_{29}$H$_{28}$F$_6$N$_4$OS: [M+H]$^+$, 595.1966. Found: *m/z* 595.1961.
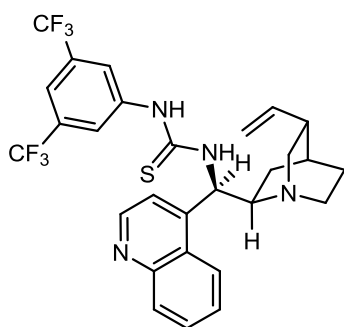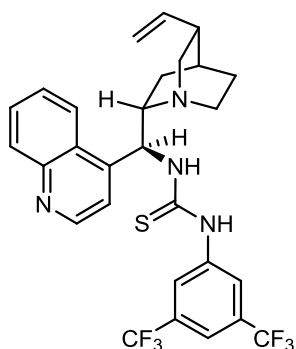

3b. White solid; 36% yield (for 2steps from cinchonine). $[\alpha]_D^{23}$ +163.3 (*c* 1.23, CH$_2$Cl$_2$). ^{1}H

NMR (CDCl$_3$) δ 8.83 (br s, 1H), 8.28 (br s, 1H), 8.15 (d, J = 8.5 Hz, 1H), 7.85 (br s, 2H), 7.56 (dd, J = 7.5, 7.5 Hz, 1H), 7.68 (s, 1H), 7.64 (dd, J = 7.5, 7.5 Hz, 1H), 7.29 (br s, 1H), 5.81 (br s, 2H), 5.14 (m, 2H), 3.21 (br s, 1H), 3.00 (m, 3H), 2.92 (br s, 1H), 2.36 (m, 1H), 1.66 (s, 1H), 1.59 (m, 2H), 1.22 (br s, 1H), 0.95 (m, 1H). ^{13}C NMR (CDCl$_3$) δ 181.3, 150.0, 148.6, 145.8, 140.2, 139.3, 132.5 (q, J = 33.6 Hz), 130.5, 129.5, 127.1, 126.7, 123.4, 122.9 (q, J = 273.1 Hz), 122.8, 119.0, 118.7, 115.5, 61.8, 55.7, 48.5, 47.0, 38.9, 27.3, 26.0, 24.9. Mp. 189.9–190.3 °C. IR (KBr): 3428, 3246, 2944, 2360, 1622, 1588, 1512, 1474, 1386, 1281, 1183, 1126, 960, 882, 848, 752, 682 cm^{-1}. HRMS Calcd for C$_{28}$H$_{26}$F$_6$N$_4$S: [M+H]$^+$, 565.1861. Found: m/z 565.1855.

3c. White solid; 27% yield (for 2steps from quinine). [α]$_D^{23}$ –99.0 (c 1.24, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 8.60 (br s, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.82 (br s, 2H), 7.68 (s, 1H), 7.62 (br s, 1H), 7.39 (d, J = 8.5 Hz, 1H), 7.18 (br s, 1H), 5.84 (br s, 1H), 5.70 (m, 1H), 5.01 (m, 2H), 3.96 (s, 3H), 3.37 (br s, 1H), 3.30 (br s, 1H), 3.18 (m, 1H), 2.79 (br s, 2H), 2.35 (br s, 1H), 1.72 (s, 1H), 1.68 (m, 2H), 1.41 (m, 1H), 0.92 (br s, 1H). ^{13}C NMR (CDCl$_3$) δ 181.0, 158.2, 147.4, 144.8, 144.0, 140.6, 140.0, 132.6 (q, J = 33.6 Hz), 131.8, 127.9, 123.6, 122.9 (q, J = 273.0 Hz), 122.0, 118.8, 115.1, 102.1, 61.2, 55.7, 54.9, 41.3, 39.0, 27.5, 27.1, 25.7. Mp. 121.0–121.5 °C. IR (KBr): 3220, 2946, 2360, 1623, 1510, 1475, 1384, 1279, 1180, 1134, 1032, 959, 917, 885, 850, 683 cm^{-1}. HRMS Calcd for C$_{29}$H$_{28}$F$_6$N$_4$OS: [M+H]$^+$, 595.1966. Found: m/z 595.1961.

3d. White solid; 44% yield (for 2steps from cinchonidine). $[\alpha]_D^{23}$ −101.0 (*c* 1.24, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 8.80 (br s, 1H), 8.35 (br s, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 7.80 (s, 2H), 7.74 (dd, *J* = 8.0, 7.5 Hz, 1H), 7.69 (s, 1H), 7.63 (dd, *J* = 8.0, 7.5 Hz, 1H), 7.27 (br s, 1H), 5.78 (br s, 1H), 5.67 (m, 1H), 4.98 (m, 2H), 3.26 (m, 1H), 3.20 (br s, 1H), 3.17 (dd, *J* = 13.5, 10.5 Hz, 1H), 2.78 (m, 2H), 2.33 (br s, 1H), 1.70 (m, 2H), 1.63 (m, 1H), 1.33 (m, 1H), 0.93 (br s, 1H). ^{13}C NMR (CDCl$_3$) δ 180.9, 149.9, 148.5, 145.9, 140.7, 139.9, 132.6 (q, *J* = 33.6 Hz), 130.4, 129.5, 127.0, 123.6, 122.9 (q, *J* = 273.0 Hz), 119.1, 118.9, 115.0, 61.5, 56.5, 54.9, 41.1, 39.2, 27.5, 27.1, 25.7. Mp. 122.8–123.1 °C. IR (KBr): 3240, 3081, 2946, 2366, 1510, 1473, 1384, 1281, 1181, 1135, 990, 958, 884, 849, 755, 683 cm^{-1}. HRMS Calcd for C$_{28}$H$_{26}$F$_6$N$_4$S: [M+H]$^+$, 565.1861. Found: *m/z* 565.1855.

General procedure for preparation of *ε*-hydroxy-*α,β*-unsaturated ketones 1

To a solution of 1,4-butanediol (5.0 g, 55 mmol) in THF (135 mL) was added *n*-BuLi (34 mL, 1.63 M in hexanes, 55 mmol) dropwise at 0 °C. After the mixture was stirred for 1 h, a solution of *tert*-butyldimethylsilyl chloride (7.5 g, 50 mmol) in THF (15 mL) was added, and the reaction was allowed to warm to ambient temperature. After being stirred for additional 14 h, the reaction was quenched with H$_2$O (15 mL), and the mixture was subsequently extracted with CH$_2$Cl$_2$. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 5/1) as an eluent gave 4-(*tert*-butyldimethylsilyloxy)butan-1-ol as a colorless oil (9.7 g, 94% yield); CAS RN [87184-99-4]. ^{1}H NMR (CDCl$_3$) δ 3.67 (t, *J* = 6.0 Hz,

2H), 3.66 (dt, J = 5.5, 6.0 Hz, 2H), 2.49 (t, J = 6.0 Hz, 1H), 1.64 (m, 4H), 0.90 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (CDCl$_3$) δ 63.3, 62.8, 30.2, 29.9, 25.9, 18.3, −5.4.

To a solution of oxalyl chloride (4.8 mL, 57 mmol) in CH$_2$Cl$_2$ (165 mL) was added DMSO (6.7 mL, 94 mmol) dropwise over 10 min at −50 °C.   The solution of 4-(*tert*-butyldimethylsilyloxy)butan-1-ol (9.7 g, 47 mmol) in CH$_2$Cl$_2$ (15 mL) was added to the mixture, and the resulting solution was stirred at −50 °C for 10 min.   Triethylamine (15 mL, 104 mmol) was subsequently added, and the mixture was stirred at −50 °C for 10 min.   The reaction was allowed to warm to ambient temperature gradually over 3 h.   H$_2$O (100 mL) was added to quench the reaction, and the mixture was extracted with CH$_2$Cl$_2$.   The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. 4-(*tert*-Butyldimethylsilyloxy)butanal was obtained as a pale yellow oil (10 g, 100% yield), which was used for the next step without further purification; CAS RN [87184-81-4]. ^{1}H NMR (CDCl$_3$) δ 9.79 (t, J = 2.0 Hz, 1H), 3.65 (t, J = 6.0 Hz, 2H), 2.50 (dt, J = 1.5, 7.0 Hz, 2H), 1.86 (tt, J = 7.0, 6.0 Hz, 2H), 0.88 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (CDCl$_3$) δ 202.5, 62.1, 40.8, 25.9, 25.5, 18.3, −5.

4-(*tert*-Butyldimethylsilyloxy)butanal (0.51 g, 2.5 mmol) and a stabilized ylide (3.0 mmol) were dissolved in THF (15 mL), and the solution was refluxed in an oil bath maintained at 90 °C overnight.   After the solution was cooled to ambient temperature, the solvents were removed in vacuo.   Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 10/1) as an eluent gave the corresponding (*E*)-6-(*tert*-butyldimethylsilyloxy)hex-2-en-1-one. Subsequently, it was dissolved in CH$_3$CN (5 mL), and 46–48% aqueous HF (0.1 mL) was added to the solution.   After being stirred for 5–10 min, the reaction was quenched with saturated aqueous NaHCO$_3$, and the mixture was subsequently extracted with EtOAc.   The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 1/1) as an eluent gave the corresponding ε-hydroxy-α,β-unsaturated ketone **1**.   Ylides commercially unavailable were prepared by the literature procedure.[10]   The characterization results of **1** are as
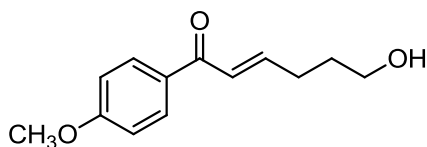
below.

(*E*)-6-Hydroxy-1-phenylhex-2-en-1-one (1a): CAS RN [1245719-57-6].
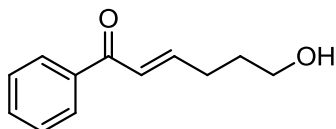
Colorless oil; 40% yield (for last 2steps).

^{1}H NMR (CDCl$_3$) δ 7.92 (m, 2H), 7.55 (m, 1H), 7.46 (m, 1H), 7.07 (dt, *J* = 15.5, 7.0 Hz, 1H), 6.92 (dt, *J* = 15.5, 1.5 Hz, 1H), 3.71 (t, *J* = 6.5 Hz, 2H), 2.43 (ddt, *J* = 7.0, 1.5, 7.0 Hz, 2H), 1.80 (tt, *J* = 7.0, 6.5 Hz, 2H), 1.65 (br s, 1H). ^{13}C NMR (CDCl$_3$) δ 190.8, 149.0, 137.9, 132.6, 128.5, 126.3, 62.0, 31.1, 29.1.

(*E*)-6-Hydroxy-1-(4-methoxyphenyl)hex-2-en-1-one (1b).

Colorless oil; 48% yield (for last 2steps).

^{1}H NMR (CDCl$_3$) δ 7.93 (m, 2H), 7.04 (dt, *J* = 15.0, 7.0 Hz, 1H), 6.92 (m, 3H), 3.85 (s, 3H), 3.69 (t, *J* = 6.5 Hz, 2H), 2.40 (ddt, *J* = 7.0, 1.5, 7.0 Hz, 2H), 1.94 (br s, 1H), 1.78 (tt, *J* = 7.0, 6.5 Hz, 2H). ^{13}C NMR (CDCl$_3$) δ 189.0, 163.3, 147.9, 130.8, 130.7, 125.9, 113.7, 62.0, 55.4, 31.1, 29.0. TLC: R$_f$ 0.18 (hexane/EtOAc = 1:1).   IR (neat): 3406, 2937, 2362, 1665, 1599, 1511, 1457, 1421, 1341, 1308, 1262, 1173, 1059, 1027, 823, 499 cm^{-1}.   HRMS Calcd for C$_{13}$H$_{17}$O$_3$: [M+H]$^+$, 221.1178. Found: *m/z* 221.1172.

(*E*)-6-Hydroxy-1-(4-(trifluoromethyl)phenyl)hex-2-en-1-one (1c).
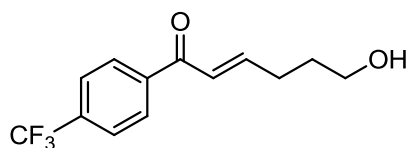
Pale yellow oil; 17% yield (for last 2steps).

^{1}H NMR (CDCl$_3$) δ 8.02 (dd, *J* = 8.5, 0.5 Hz, 2H), 7.75 (dd, *J* = 8.5, 0.5 Hz, 2H), 7.13 (dt, *J* = 15.5, 7.0 Hz, 1H), 6.91 (dt, *J* = 15.5, 1.5 Hz, 1H), 3.74 (t, *J* = 6.5 Hz, 2H), 2.48 (ddt, *J* = 7.0, 1.5, 7.5 Hz, 2H), 1.83 (tt, *J* = 7.5, 6.5 Hz, 2H), 1.35 (br s, 1H). ^{13}C NMR (CDCl$_3$) δ 189.8, 150.5, 134.0 (q, *J* = 33.1 Hz), 128.8, 128.6, 126.1, 125.6 (q, *J* = 3.8 Hz), 123.7 (q, *J* = 272.5 Hz), 62.0, 31.0, 29.2. ^{19}F NMR (CDCl$_3$) δ 98.0. TLC: R$_f$ 0.25 (hexane/EtOAc = 1:1). IR (neat): 3422, 3068, 2937, 2877, 2368, 1937, 1672, 1624, 1580, 1512, 1410, 1323, 1227, 1169, 1128, 1067, 1016, 920, 859, 820, 764, 456 cm^{-1}. HRMS Calcd for C$_{13}$H$_{14}$F$_3$O$_2$: [M+H]$^+$, 259.0946. Found: *m/z*.

(*E*)-6-Hydroxy-1-(naphthalen-2-yl)hex-2-en-1-one (1d).
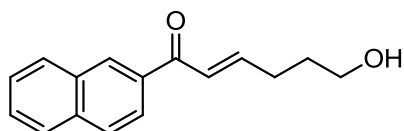
White solid; 32% yield (for last 2steps).

^{1}H NMR (CDCl$_3$) δ 8.45 (dd, *J* = 1.5, 0.5 Hz, 1H), 8.03 (dd, *J* = 9.0, 1.5 Hz, 1H), 7.97 (ddd, *J* = 8.0, 1.0, 0.5 Hz, 1H), 7.91 (dd, *J* = 9.0, 0.5 Hz, 1H), 7.89 (ddd, *J* = 8.0, 1.0, 0.5 Hz, 1H), 7.60 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.56 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.16 (dt, *J* = 15.5, 6.5 Hz, 1H), 7.10 (dt, *J* = 15.5, 0.5 Hz, 1H), 3.75 (dt, *J* = 5.0, 6.5 Hz, 2H), 2.49 (ddt, *J* = 6.5, 0.5, 7.0 Hz, 2H), 1.85 (tt, *J* = 7.0, 6.5 Hz, 2H), 1.37 (t, *J* = 5.0 Hz, 1H). ^{13}C NMR (CDCl$_3$) δ 190.5, 148.8, 135.5, 135.2, 132.5, 130.0, 129.5, 128.5, 128.3, 127.8, 126.7, 126.3, 124.5, 62.1, 31.2, 29.2. Mp. 62.5–63.0 °C. TLC: R$_f$ 0.21 (hexane/EtOAc = 1:1). IR (KBr): 3305, 3054, 2938, 2359, 1669, 1616, 1434, 1371, 1285, 1193, 1126, 1070, 1008, 974, 920, 823, 744, 692, 480 cm^{-1}. HRMS

Calcd for $C_{16}H_{17}O_2$: $[M+H]^+$, 241.1229. Found: m/z 241.1223.

(E)-6-Hydroxy-1-(4-methylphenyl)hex-2-en-1-one (1e).
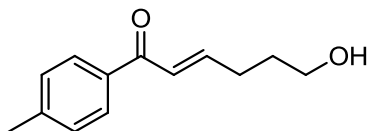
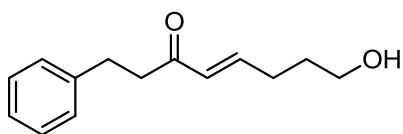
Colorless oil; 34% yield (for last 2steps).

^{1}H NMR (CDCl$_3$) δ 7.86 (m, 2H), 7.28 (m, 2H), 7.08 (dt, J = 15.5, 7.0 Hz, 1H), 6.94 (dt, J = 15.5, 1.5 Hz, 1H), 3.73 (dt, J = 4.0, 6.5 Hz, 2H), 2.44 (ddt, J = 7.0, 1.5, 6.5 Hz, 2H), 2.43 (s, 3H), 1.82 (tt, J = 6.5, 6.5 Hz, 2H), 1.43 (t, J = 4.0 Hz, 1H). ^{13}C NMR (CDCl$_3$) δ 190.2, 148.3, 143.5, 135.3, 129.2, 128.7, 126.3, 62.1, 31.1, 29.1, 21.6.   TLC: R_f 0.24 (hexane/EtOAc = 1:1).   IR (neat): 3421, 2935, 2870, 2362, 1668, 1619, 1570, 1446, 1408, 1338, 1292, 1234, 1182, 1060, 1009, 979, 924, 809, 782, 723, 492 cm^{-1}.   HRMS Calcd for $C_{13}H_{17}O_2$: $[M+H]^+$, 205.1229. Found: m/z 205.1223.

(E)-1-(4-Bromophenyl)-6-hydroxyhex-2-en-1-one (1f).
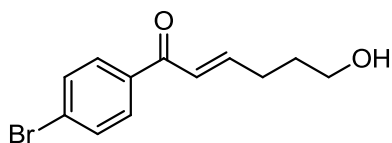
Colorless oil; 38% yield (for last 2steps).

^{1}H NMR (CDCl$_3$) δ 7.80 (dt, J = 9.0, 2.0 Hz, 2H), 7.61 (dt, J = 9.0, 2.0 Hz, 2H), 7.09 (dt, J = 15.5, 7.0 Hz, 1H), 6.88 (dt, J = 15.5, 1.5 Hz, 1H), 3.72 (dt, J = 5.0, 6.5 Hz, 2H), 2.44 (ddt, J = 7.0, 1.5, 7.0 Hz, 2H), 1.81 (tt, J = 7.0, 6.5 Hz, 2H), 1.33 (t, J = 5.0 Hz, 1H). ^{13}C NMR (CDCl$_3$) δ 189.6, 149.7, 136.6, 131.8, 130.0, 127.8, 125.8, 61.9, 31.0, 29.1.   TLC: R_f 0.20 (hexane/EtOAc = 1:1). IR (neat): 3422, 2937, 2874, 1668, 1618, 1585, 1483, 1397, 1336, 1297, 1225, 1178, 1071, 1009, 919, 847, 810, 728, 502 cm^{-1}.   HRMS Calcd for $C_{12}H_{14}BrO_2$: $[M+H]^+$, 269.0177. Found: m/z 269.0172.

**(*E*)-8-Hydroxy-1-phenyloct-4-en-3-one (1g)**.

Colorless oil; 26% yield (for last 2steps).

^{1}H NMR (CDCl$_3$) δ 7.28 (m, 2H), 7.19 (m, 3H), 6.84 (dt, J = 15.5, 7.0 Hz, 1H), 6.13 (dt, J = 15.5, 1.5 Hz, 1H), 3.67 (t, J = 6.5 Hz, 2H), 2.94 (m, 2H), 2.87 (m, 2H), 2.31 (m, 2H), 1.72 (m, 2H), 1.27 (br s, 1H). ^{13}C NMR (CDCl$_3$) δ 199.4, 146.7, 141.2, 130.6, 128.5, 128.3, 126.1, 62.0, 41.7, 30.7, 30.1, 28.8.   TLC: R$_f$ 0.30 (hexane/EtOAc = 1:1).   IR (neat): 3422, 3027, 2918, 2352, 1752, 1664, 1624, 1497, 1457, 1367, 1299, 1190, 1164, 1113, 1059, 979, 920, 748, 700, 463 cm^{-1}. HRMS Calcd for C$_{14}$H$_{19}$O$_2$: M$^+$, 218.1307. Found: m/z 218.1311.

Procedure for preparation of ζ-hydroxy-*α,β*-unsaturated ketone 6

To a solution of 3,4-dihydro-2*H*-pyran (2.7 mL, 30 mmol) in THF (30 mL) was added 1M aqueous HCl (6mL) at 0 °C.   After the mixture was stirred at ambient temperature for 4 h, 1 M aqueous NaOH was added to adjust the solution to pH ≈ 7, and the mixture was subsequently extracted with Et$_2$O.   The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo.   Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 1/1) as an eluent gave tetrahydro-2*H*-pyran-2-ol as a colorless oil (2.2 g, 70% yield); CAS RN [694-54-2]. ^{1}H NMR (CDCl$_3$) δ 4.90 (m, 1H), 4.01 (m, 1H), 3.53 (m, 1H), 2.89 (m, 1H), 1.86 (m, 1H), 1.80 (m, 1H), 1.58–1.46 (m, 4H). ^{13}C NMR (CDCl$_3$) δ 94.4, 63.8, 31.9, 25.2, 20.2.

Tetrahydro-2*H*-pyran-2-ol   (0.25   g,   2.5   mmol)   and 1-phenyl-2-(triphenylphosphoranylidene)ethanone (1.2 g, 3.0 mmol) were dissolved in CH$_2$Cl$_2$ (15 mL).   After the mixture was stirred at ambient temperature overnight, the solvents were removed in vacuo.   Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 2/1) as an eluent gave **6** (0.081 g, 16% yield).

**(*E*)-7-hydroxy-1-phenylhept-2-en-1-one (6)**.
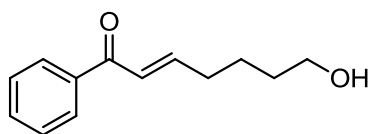
Colorless oil.

^{1}H NMR (C$_6$D$_6$) δ 7.92 (m, 2H), 7.13 (m, 1H), 7.08 (m, 3H), 6.70 (dt, *J* = 15.5, 1.5 Hz, 1H), 3.28 (m, 2H), 1.91 (m, 2H), 1.25 (m, 4H), 0.89 (br s, 1H). ^{13}C NMR (C$_6$D$_6$) δ 189.6, 149.0, 138.7, 132.4, 128.8, 128.7, 126.2, 62.3, 32.6, 32.5, 24.7.   TLC: R$_f$ 0.15 (hexane/EtOAc = 2:1).   IR (neat): 3422, 3060, 2935, 2862, 2368, 1669, 1620, 1578, 1449, 1347, 1297, 1227, 1180, 1159, 1061, 1003, 986, 929, 853, 767, 694, 664, 479 cm^{-1}.   HRMS Calcd for C$_{13}$H$_{17}$O$_2$: [M+H]$^+$, 205.1229. Found: *m/z* 205.1227.

Characterization Data of Products

1-Phenyl-2-(tetrahydrofuran-2-yl)ethanone (2a).
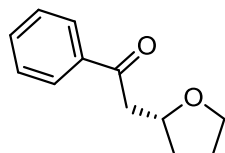
Colorless oil, 95% *ee*.

[α]$_D$^{23} −3.5 (*c* 4.98, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 7.97 (m, 2H), 7.56 (m, 1H), 7.46 (m, 2H), 4.41 (dddd, *J* = 7.0, 6.5, 6.5, 6.0 Hz, 1H), 3.89 (ddd, *J* = 8.5, 7.0, 6.5 Hz, 1H), 3.75 (m, 1H), 3.40 (dd, *J* = 16.0, 6.0 Hz, 1H), 3.06 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.20 (m, 1H), 1.93 (m, 2H), 1.57 (m, 1H). ^{13}C NMR (CDCl$_3$) δ 198.4, 137.1, 133.1, 128.6, 128.2, 75.4, 67.8, 44.7, 31.6, 25.6.   TLC: R$_f$ 0.26 (hexane/EtOAc = 3:1).   IR (neat): 3351, 2973, 2873, 1682, 1598, 1581, 1449, 1382, 1300, 1280, 1210, 1181, 1067, 1002, 928, 754, 691, 498 cm^{-1}.   HRMS Calcd for C$_{12}$H$_{15}$O$_2$: [M+H]$^+$, 191.1072. Found: *m/z* 191.1067.   HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 99.9/0.1, flow rate = 5.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 15.4 min, t_{major} = 17.1 min.

(*R*)-1-(4-Methoxyphenyl)-2-(tetrahydrofuran-2-yl)ethanone (2b).
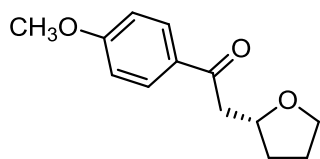
Colorless oil, 94% *ee*.

$[\alpha]_D^{23}$ –2.5 (*c* 4.02, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 7.95 (m, 2H), 6.93 (m, 2H), 4.38 (dddd, *J* = 7.0, 6.5, 6.5, 6.0 Hz, 1H), 3.89 (m, 1H), 3.86 (s, 3H), 3.74 (m, 1H), 3.35 (dd, *J* = 16.0, 6.0 Hz, 1H), 3.00 (dd, *J* = 16.0, 7.0 Hz, 1H), 2.18 (m, 1H), 1.92 (m, 2H), 1.56 (m, 1H). ^{13}C NMR (CDCl$_3$) δ 196.9, 163.5, 130.5, 130.3, 113.7, 75.6, 67.8, 55.4, 44.3, 31.6, 25.6.   TLC: R$_f$ 0.15 (hexane/EtOAc = 3:1).   IR (neat): 3474, 2957, 2872, 2360, 1677, 1601, 1576, 1510, 1458, 1419, 1381, 1309, 1261, 1216, 1170, 1066, 1030, 990, 847, 488 cm^{-1}.   HRMS Calcd for C$_{13}$H$_{17}$O$_3$: [M+H]$^+$, 221.1178. Found: *m/z* 221.1172.   HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 99.9/0.1, flow rate = 5.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 34.1 min, t_{major} = 41.1 min.

2-(Tetrahydrofuran-2-yl)-1-(4-(trifluoromethyl)phenyl)ethanone (2c).
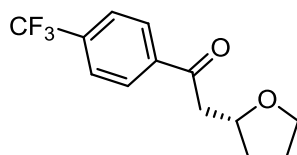
White solid, 85% *ee*.

$[\alpha]_D^{23}$ –7.1 (*c* 3.18, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 8.07 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H), 4.40 (dddd, *J* = 7.0, 6.5, 6.5, 6.0 Hz, 1H), 3.89 (ddd, *J* = 8.5, 7.0, 6.5 Hz, 1H), 3.76 (m, 1H), 3.39 (dd, *J* = 16.0, 6.5 Hz, 1H), 3.08 (dd, *J* = 16.0, 6.0 Hz, 1H), 2.21 (m, 1H), 1.94 (m, 2H), 1.58 (m, 1H). ^{13}C NMR (CDCl$_3$) δ 197.5, 139.7, 134.4 (q, *J* = 32.7 Hz), 128.5, 125.6 (q, *J* = 3.8 Hz), 123.6 (q, *J* = 272.6 Hz), 75.2, 67.9, 44.9, 31.6, 25.6. ^{19}F NMR (CDCl$_3$) δ 98.0.   Mp. 82.0–82.3 °C.   TLC: R$_f$ 0.30 (hexane/EtOAc = 3:1).   IR (KBr): 3428, 2987, 2881, 2366, 1685, 1513, 1411, 1387, 1330, 1209, 1159, 1127, 1110, 1060, 1017, 995, 830, 760, 687, 607, 511 cm^{-1}.   HRMS Calcd for C$_{13}$H$_{13}$F$_3$O$_2$: M$^+$, 258.0868. Found: *m/z* 258.0863.   HPLC (Daicel Chiralcel

OD-H, hexane/*i*-PrOH = 99/1, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 11.8 min, t_{major} = 13.6 min.

1-(Naphthalen-2-yl)-2-(tetrahydrofuran-2-yl)ethanone (2d).
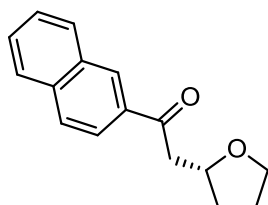
Colorless oil, 91% *ee*.

$[\alpha]_D^{23}$ −0.3 (*c* 7.36, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 8.49 (s, 1H), 8.04 (d, *J* = 9.0 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 9.0 Hz, 1H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.60 (dd, *J* = 8.0, 7.0 Hz, 1H), 7.56 (dd, *J* = 8.5, 7.0 Hz), 4.47 (dddd, *J* = 7.0, 6.5, 6.5, 6.0 Hz, 1H), 3.92 (m, 1H), 3.78 (m, 1H), 3.54 (dd, *J* = 16.0, 6.0 Hz, 1H), 3.19 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.23 (m, 1H), 1.95 (m, 2H), 1.63 (m, 1H). ^{13}C NMR (CDCl$_3$) δ 198.3, 135.6, 134.5, 132.5, 130.0, 129.6, 128.5, 128.4, 127.8, 126.7, 123.9, 75.6, 67.9, 44.8, 31.7, 25.7.   TLC: R_f 0.27 (hexane/EtOAc = 3:1).   IR (neat): 3058, 2971, 2871, 2368, 1681, 1628, 1597, 1469, 1385, 1359, 1297, 1279, 1210, 1186, 1126, 1065, 1026, 991, 943, 918, 865, 820, 754, 464 cm^{-1}.   HRMS Calcd for C$_{16}$H$_{16}$O$_2$: M$^+$, 240.1150. Found: *m/z* 240.1144.   HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 99/1, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 14.2 min, t_{minor} = 15.8 min.

1-(4-Methylphenyl)-2-(tetrahydrofuran-2-yl)ethanone (2e).
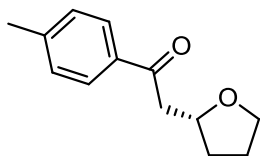
Colorless oil, 93% *ee*.

$[\alpha]_D^{23}$ −1.7 (*c* 5.75, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 7.86 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 4.39 (dddd, *J* = 7.0, 6.5, 6.5, 6.0 Hz, 1H), 3.89 (m, 1H), 3.75 (m, 1H), 3.37 (dd, *J* = 16.0, 5.0

Hz, 1H), 3.03 (dd, J = 16.0, 7.0 Hz, 1H), 2.41 (s, 3H), 2.19 (m, 1H), 1.92 (m, 2H), 1.56 (m, 1H).
^{13}C NMR (CDCl$_3$) δ 198.0, 143.9, 134.7, 129.2, 128.3, 75.5, 67.8, 44.6, 31.6, 25.7, 21.6.　TLC:
R$_f$ 0.29 (hexane/EtOAc = 3:1).　IR (neat): 3584, 2970, 2870, 2360, 1681, 1607, 1574, 1449,
1408, 1380, 1301, 1221, 1206, 1181, 1067, 1013, 844, 807, 761, 464 cm^{-1}.　HRMS Calcd for
C$_{13}$H$_{16}$O$_2$: M$^+$, 204.1150. Found: m/z 204.1154.　HPLC (Daicel Chiralcel OD-H, hexane/i-PrOH
= 99/1, flow rate = 0.5 mL/min, λ = 254 nm, 40 °C): t_{minor} = 29.7 min, t_{major} = 31.9 min.

1-(4-Bromophenyl)-2-(tetrahydrofuran-2-yl)ethanone (2f).
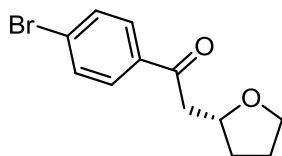
White solid, 92% *ee*.

[α]$_D^{28}$ –6.7 (c 6.39, CH$_2$Cl$_2$).　^{1}H NMR (CDCl$_3$) δ 7.83 (m, 2H), 7.60 (m, 2H), 4.38 (dddd, J =
7.0, 6.5, 6.5, 6.0 Hz, 1H), 3.88 (ddd, J = 8.0, 7.0, 6.5 Hz, 1H), 3.75 (ddd, J = 8.0, 7.5, 7.0, Hz 1H),
3.33 (dd, J = 16.0, 6.0 Hz, 1H), 3.02 (dd, J = 16.0, 6.5 Hz, 1H), 2.19 (m, 1H), 1.93 (m, 2H), 1.56
(m, 1H).　^{13}C NMR (CDCl$_3$) δ 197.4, 135.8, 131.9, 129.8, 128.3, 75.3, 67.9, 44.6, 31.6, 25.6.
Mp. 59.2–59.5 °C.　TLC: R$_f$ 0.29 (hexane/EtOAc = 3:1).　IR (KBr): 3459, 2928, 2878, 2366,
1679, 1587, 1485, 1397, 1343, 1301, 1209, 1179, 1062, 991, 814, 791, 668, 574 cm^{-1}.　HRMS
Calcd for C$_{12}$H$_{14}$BrO$_2$: [M+H]$^+$, 269.0177. Found: m/z 269.0172.　HPLC (Daicel Chiralcel
OD-H, hexane/i-PrOH = 99/1, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 7.9 min, t_{major}
= 9.1 min.

4-Phenyl-1-(tetrahydrofuran-2-yl)butan-2-one (2g).
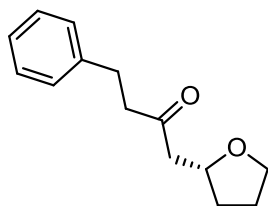
Colorless oil, 90% *ee*.

$[\alpha]_D^{28}$ −4.8 (*c* 6.14, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 7.27 (m, 2H), 7.18 (m, 3H), 4.21 (m, 1H), 3.84 (ddd, *J* = 8.5, 7.0, 7.0 Hz, 1H), 3.71 (ddd, *J* = 8.5, 7.0, 7.0 Hz, 1H), 2.90 (t, *J* = 8.0 Hz, 2H), 2.79 (m, 2H), 2.72 (dd, *J* = 16.0, 7.0 Hz, 1H), 2.51 (dd, *J* = 16.0, 6.0 Hz, 1H), 2.07 (m, 1H), 1.88 (m, 2H), 1.44 (m, 1H). ^{13}C NMR (CDCl$_3$) δ 208.3, 141.1, 128.5, 128.3, 126.0, 75.1, 67.8, 48.9, 45.0, 31.5, 29.5, 25.5.   TLC: R$_f$ 0.33 (hexane/EtOAc = 3:1).   IR (neat): 3027, 2955, 2870, 1713, 1604, 1498, 1453, 1409, 1383, 1296, 1182, 1126, 1056, 1017, 919, 749, 700, 492 cm^{-1}.   HRMS Calcd for C$_{14}$H$_{18}$O$_2$: M$^+$, 218.1307. Found: *m/z* 218.1304.   HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 99/1, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 10.6 min, t_{minor} = 15.5 min.

1-Phenyl-2-(tetrahydro-2*H*-pyran-2-yl)ethanone (7).
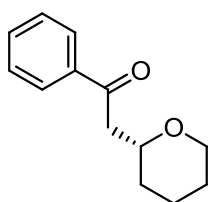
Colorless oil, 91% *ee*.

$[\alpha]_D^{26}$ +16.8 (*c* 2.53, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 7.97 (m, 2H), 7.56 (m, 1H), 7.46 (m, 2H), 3.96 (m, 2H), 3.48 (m, 1H), 3.29 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.92 (dd, *J* = 16.0, 5.5 Hz, 1H), 1.84 (m, 1H), 1.75 (m, 1H), 1.57 (m, 2H), 1.52 (m, 1H), 1.36 (m, 1H). ^{13}C NMR (CDCl$_3$) δ 198.4, 137.4, 133.0, 128.5, 128.3, 74.4, 68.7, 45.4, 32.0, 25.9, 23.4.   TLC: R$_f$ 0.45 (hexane/EtOAc = 3:1).   IR (neat): 3060, 2936, 2849, 1686, 1597, 1581, 1449, 1379, 1357, 1325, 1292, 1273, 1208,

1194, 1175, 1088, 1045, 1003, 971, 904, 810, 777, 751, 692, 661, 471 cm^{-1}. HRMS Calcd for C$_{13}$H$_{17}$O$_2$: [M+H]$^+$, 205.1229. Found: m/z 205.1227. HPLC (Daicel Chiralcel OD-H, hexane/i-PrOH = 99/1, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 6.1 min, t_{major} = 8.0 min.

Procedure for Baeyer–Villiger oxidation of 2b[11]

The mixture of **2b** (0.040 g, 0.18 mmol), m-CPBA (0.20 g, 77% purity, 0.9 mmol), and trifluoroacetic acid (0.014 mL, 0.18 mmol) in CH$_2$Cl$_2$ (1.5 mL) was stirred at room temperature for 8 h. Saturated aqueous Na$_2$S$_2$O$_3$ and saturated aqueous NaHCO$_3$ were added to quench the reaction, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 3/1) as an eluent gave **4** (0.039 g, 92% yield).

(R)-4-Methoxyphenyl 2-(tetrahydrofuran-2-yl)acetate (4).
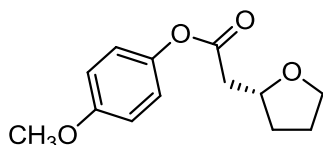
Colorless oil, 94% ee.

[α]$_D$^{23} −12.8 (c 3.91, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 7.03 (m, 2H), 6.89 (m, 2H), 4.38 (dddd, J = 7.0, 7.0, 6.5, 6.0 Hz, 1H), 3.95 (m, 1H), 3.810 (m, 1H), 3.806 (s, 3H), 2.83 (dd, J = 15.0, 7.0 Hz, 1H), 2.72 (dd, J = 15.0, 6.0 Hz, 1H), 2.18 (m, 1H), 1.97 (m, 2H), 1.67 (m, 1H). ^{13}C NMR (CDCl$_3$) δ 170.1, 157.2, 144.2, 122.3, 114.4, 75.2, 68.1, 55.6, 40.7, 31.3, 25.6. TLC: R$_f$ 0.24 (hexane/EtOAc = 3:1). IR (neat): 3491, 3056, 2956, 2874, 2352, 2053, 1755, 1597, 1506, 1466, 1443, 1385, 1360, 1298, 1249, 1195, 1144, 1102, 1064, 1033, 910, 842, 765, 702, 450 cm^{-1}. HRMS Calcd for C$_{13}$H$_{16}$O$_4$: M$^+$, 236.1049. Found: m/z 236.1045. HPLC (Daicel Chiralcel OD-H, hexane/i-PrOH = 98/2, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 11.8 min,

t_{minor} = 14.3 min.

Procedure for synthesis of 5[9d]

To a suspension of LiAlH$_4$ (0.015 g, 0.38 mmol) in Et$_2$O (1 mL) was added a solution of **4** (0.045 g, 0.19 mmol) in Et$_2$O (1 mL) at –40 °C, and the mixture was stirred at –40 °C for 2 h. To the solution were then added dropwise H$_2$O (0.015 mL), 15% aqueous NaOH (0.015 mL), and again H$_2$O (0.044 mL) sequentially.   After the mixture was stirred at room temperature for a while, it was filtered, and the filtrate was concentrated in vacuo.   Purification by flash silica gel column chromatography using hexane/Et$_2$O (v/v = 1/3) as an eluent gave **5** (0.021 g, 94% yield).

(*R*)-2-(Tetrahydrofuran-2-yl)ethanol (5): CAS RN [71884-84-9].
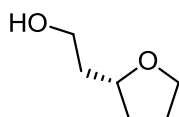
Colorless oil, 94% *ee*.

^{1}H NMR (CDCl$_3$) δ 4.02 (m, 1H), 3.89 (ddd, *J* = 8.5, 7.5, 6.5 Hz, 1H), 3.79 (m, 2H), 3.74 (ddd, *J* = 8.0, 8.0, 6.5 Hz, 1H), 2.77 (t, *J* = 5.0 Hz, 1H), 2.03 (m, 1H), 1.89 (m, 2H), 1.77 (m, 2H), 1.54 (m, 1H). ^{13}C NMR (CDCl$_3$) δ 79.3, 67.9, 61.7, 37.3, 31.7, 25.4.

The absolute configuration of **5** was assigned as (*R*) by comparing the optical rotation with the literature value.[9a]   The enantiomeric excess of **5** was determined by HPLC analysis after benzoylation.

[α]$_D^{26}$ –5.9 (*c* 2.96, EtOH) [lit.[9a] (*R*)-2-(tetrahydrofuran-2-yl)ethanol: [α]$_D^{25}$ –5.8 (*c* 1.0, EtOH)].

Procedure for benzoylation of 5

To a solution of **5** (0.012 g, 0.1 mmol) in CH$_2$Cl$_2$ (0.5 mL) were added benzoylchloride (0.029 mL, 0.25 mmol) and pyridine (0.041 mL, 0.5 mmol) at ambient temperature.   After the solution was stirred for 3 h, the reaction was quenched with H$_2$O, and the mixture was

subsequently extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 10/1) as an eluent gave (*R*)-2-(tetrahydrofuran-2-yl)ethyl benzoate (0.018 g, 83% yield).

(*R*)-2-(Tetrahydrofuran-2-yl)ethyl benzoate.
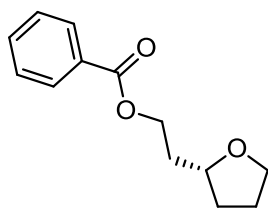
Colorless oil, 94% *ee*.

$[\alpha]_D^{26}$ −14.7 (*c* 2.21, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.04 (m, 2H), 7.55 (m, 1H), 7.44 (m, 2H), 4.44 (m, 2H), 4.01 (m, 1H), 3.89 (ddd, *J* = 8.5, 7.5, 6.0 Hz, 1H), 3.75 (ddd, *J* = 8.0, 8.0, 6.0 Hz, 1H), 2.10–1.85 (m, 5H), 1.56 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 166.6, 132.8, 130.5, 129.6, 128.3, 76.2, 67.7, 62.6, 34.8, 31.5, 25.7. TLC: R_f 0.13 (hexane/EtOAc = 10:1). IR (neat): 3064, 2964, 2870, 2368, 1721, 1603, 1585, 1452, 1382, 1315, 1276, 1177, 1113, 1071, 1026, 919, 712, 688, 676, 492 cm^{-1}. HRMS Calcd for $C_{13}H_{17}O_3$: [M+H]$^+$, 221.1178. Found: *m/z* 221.1170. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 99.9/0.1, flow rate = 1.1 mL/min, λ = 254 nm, 40 °C): t_{minor} = 13.3 min, t_{major} = 14.4 min.

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Chapter 6

Asymmetric Synthesis of 1,3-Dioxolanes by Organocatalytic Formal [3+2] Cycloaddition via Hemiacetal Intermediates
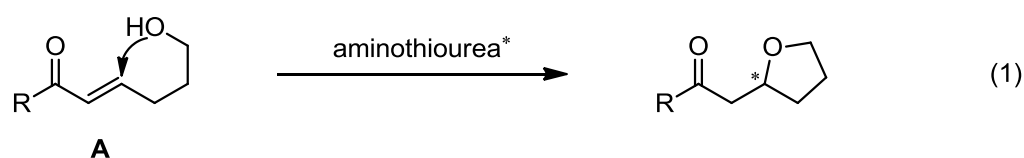
In Chapter 6, the author reports a novel asymmetric formal [3+2] cycloaddition reaction for the synthesis of 1,3-dioxolanes using cinchona-alkaloid-thiourea-based bifunctional organocatalysts. The reaction proceeds via the formation of hemiacetal intermediates between γ-hydroxy-α,β-unsaturated ketones and aldehydes.

Chapter 6

Introduction

Optically active cyclic acetals are important in various biologically active agents and natural products.[1]   They are also known as versatile intermediates for asymmetric synthesis:[2–4] they can be used as chiral auxiliaries to control the reaction of a proximal prochiral center,[2,3] and can also be used as chiral templates for stereospecific cleavage of their ring in the presence of nucleophiles and Lewis acid reagents.[2,4]   Therefore, asymmetric synthesis methods of chiral cyclic acetals would be particularly useful as approaches to various chiral building blocks. Nevertheless, optically active acetals are largely prepared from chiral starting materials or by the use of stoichiometric chiral reagents,[2–5] and there have been only a few examples of catalytic asymmetric syntheses.[6–8]   Moreover, catalytic asymmetric cycloaddition has remained underdeveloped despite its advantage in terms of the ability to construct multiple bonds in a single step, thereby leading to divergent synthesis.

Scheme 1. Asymmetric Cycloetherification by Bifunctional Aminothiourea Catalyst.

Cyclization (Chapter 5)

(1)

[3+2] Cycloaddition (Chapter 6)

(2)
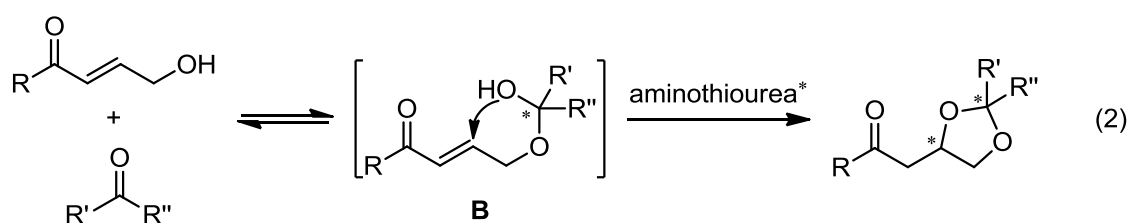
In Chapter 5, the author reported an asymmetric cycloetherification reaction of ε-hydroxy-α,β-unsaturated ketones **A** mediated by cinchona-alkaloid-thiourea-based bifunctional

organocatalysts (Scheme 1, eq. 1).[9]   In this reaction, concerted catalysis due to the bifunctional nature of the catalyst led to highly enantioselective cyclization, which afforded chiral oxacyclic compounds.   The results of the author's previous work motivated him to exploit this efficient cyclization route in the development of a formal cycloaddition reaction starting from γ-hydroxy-α,β-unsaturated ketones with aldehydes or ketones via hemiacetal intermediates **B** (Scheme 1, eq. 2).[10]   In Chapter 6, the author presents a novel catalytic asymmetric formal [3+2] cycloaddition reaction for the synthesis of chiral 1,3-dioxolanes using bifunctional organocatalysts derived from cinchona alkaloids.[11,12]

Results and Discussion

The author initiated his investigations using (*E*)-4-hydroxy-1-phenylbut-2-en-1-one (**1a**) and cyclohexanecarboxaldehyde (**2a**) with 10 mol % of quinidine-derived bifunctional catalyst **4a** in CH_2Cl_2 at 25 °C.   As expected, 1,3-dioxolane **3aa** was obtained stereoselectively in 83% yield (Table 1, entry 1).   Through a process of solvent optimization, ethereal solvents were identified as being efficient for stereoselectivity, and cyclopentyl methyl ether (CPME) was identified as the most suitable solvent from the viewpoints of both yield and enantioselectivity (Table 1, entries 1–6).   The use of 1.2 equivalent of **2a** further improved the yield without decreasing the stereoselectivity (Table 1, entry 7).   Catalyst screening identified **4c** also as an efficient catalyst for obtaining the opposite enantiomer of **3aa** in good yield with high enantioselectivity (Table 1, entry 9).

With the optimized conditions and using **4a** as a catalyst, the author next explored the substrate scope. γ-Hydroxy-α,β-unsaturated ketones **1** could be readily prepared from commercially available materials by Matsubara's reported procedure.[13]   Good to excellent yields and enantioselectivities were obtained with both electron-rich and electron-poor enones (Table 2, entries 2 and 3).   Substrates bearing *p*-bromophenyl, *o*-tolyl, and 1-naphthyl groups were tolerated (Table 2, entries 4–6).   Further, enones substituted by a heterocycle or an alkyl group

Table 1. Optimization of Conditions.[a]
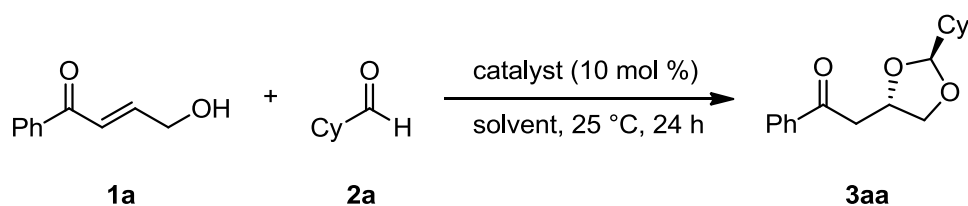
entry	catalyst	solvent	yield (%)[b]	dr[c]	ee (%)[d]
1	**4a**	CH$_2$Cl$_2$	83	2.9:1	93
2	**4a**	benzene	89	2.3:1	94
3	**4a**	THF	56	3.7:1	96
4	**4a**	Et$_2$O	85	2.4:1	95
5	**4a**	TBME	81	2.9:1	96
6	**4a**	CPME	86	3.0:1	96
7[e]	**4a**	CPME	95	3.0:1	96
8[e]	**4b**	CPME	88	2.7:1	95
9[e]	**4c**	CPME	91	4.0:1	–93
10[e]	**4d**	CPME	87	3.4:1	–93

[a] Reactions were run using γ-hydroxy-α,β-unsaturated ketone **1a** (0.25 mmol), cyclohexanecarboxaldehyde (**2a**, 0.25 mmol), and the catalyst **4** (0.025 mmol) in the solvent (0.5 mL). [b] Isolated yields. [c] Diastereomeric ratios were determined by ^{1}H NMR. [d] Values are for the major diastereomer of **3aa**. [e] Reactions were run using 0.3 mmol of **2a**.

Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$
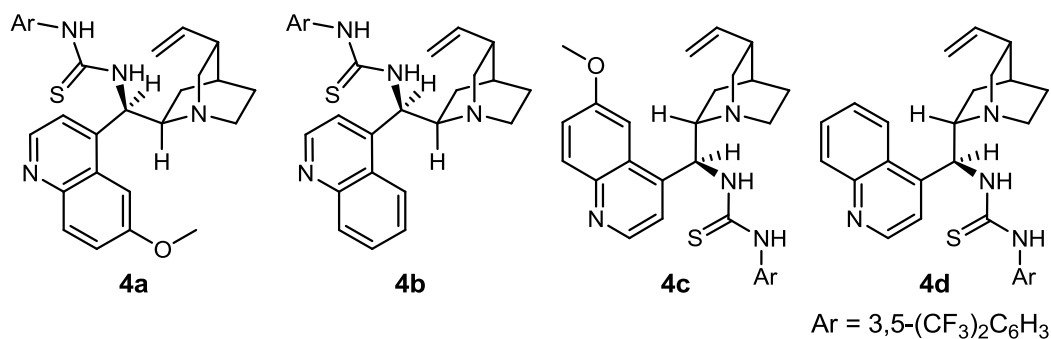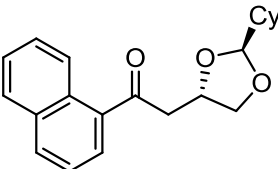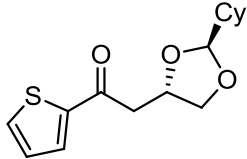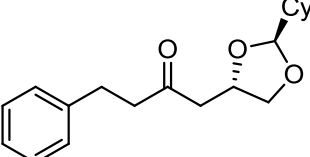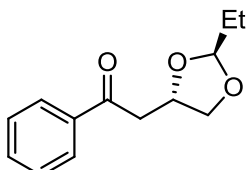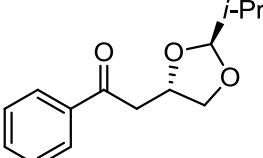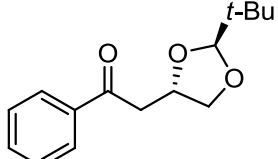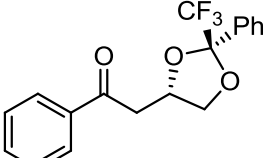
Table 2. Scope of Substrates.[a]

entry	R^1	1	R^2	R^3	2	product	3	yield (%)[b]	dr[c]	ee (%)[d]
1	Ph	1a	Cy	H	2a		3aa	95	3.0:1	96
2[e]	4-CH$_3$OC$_6$H$_4$	1b	Cy	H	2a		3ba	93	3.4:1	96
3	4-CF$_3$C$_6$H$_4$	1c	Cy	H	2a		3ca	83	2.5:1	95
4	4-BrC$_6$H$_4$	1d	Cy	H	2a		3da	88	4.7:1	96
5	2-CH$_3$C$_6$H$_4$	1e	Cy	H	2a		3ea	71	3.3:1	91

Table 2. (Continued)

#						structure				
6	1-naphthyl	**1f**	Cy	H	**2a**		**3fa**	82	2.9:1	90
7	2-thienyl	**1g**	Cy	H	**2a**		**3ga**	84	3.3:1	98
8[f]	PhCH$_2$CH$_2$	**1h**	Cy	H	**2a**		**3ha**	82	3.3:1	96
9	Ph	**1a**	Et	H	**2b**		**3ab**	94	3.0:1	94
10	Ph	**1a**	i-Pr	H	**2c**		**3ac**	92	2.7:1	93
11[g]	Ph	**1a**	t-Bu	H	**2d**		**3ad**	84	2.6:1	94
12	Ph	**1a**	CF$_3$	Ph	**2e**		**3ae**	99	1.2:1	70

[a] Reactions were run using the γ-hydroxy-α,β-unsaturated ketone **1** (0.25 mmol), the aldehyde or the ketone **2** (0.3 mmol), and catalyst **4a** (0.025 mmol) in CPME (0.5 mL). [b] Isolated yields. [c] Diastereomeric ratios were determined by ^{1}H NMR. [d] Values are for the major diastereomers of **3**. See Experimental Section for minor diastereomers. [e] Reaction was run for 48 h. [f] Reaction was run for 96 h. [g] Reaction was run for 120 h.

also gave 1,3-dioxolanes in good yields and high enantioselectivities (Table 2, entries 7 and 8). In addition, he could replace **2a** with propionaldehyde (**2b**), isobutyraldehyde (**2c**), and pivalaldehyde (**2d**) to obtain the corresponding cycloadducts in excellent enantioselectivities (Table 2, entries 9–11).[14]   Instead of an aldehyde, electron-deficient ketone **2e** could also be employed to furnish the cyclic acetal **3ae** with a chiral quaternary acetal carbon (Table 2, entry 12).   The absolute configurations of **3da** were determined by X-ray analysis for both diastereomers (see Experimental Section for details),[15] and the configurations of all other examples were assigned analogously.

To demonstrate the utility of the author's products as synthetic intermediates, he performed the transformation of **3aa**.   Reduction with lithium aluminum hydride in the presence of lithium iodide afforded the corresponding alcohol **5** in high diastereoselectivity, and subsequent de-acetalization gave optically active triol **6** (Scheme 2).   In addition, treatment of **3aa** with allyltrimethylsilane in the presence of titanium tetrachloride led to allylative ring cleavage to provide **7** in regio- and diastereoselective fashion while maintaining the optical purity (Scheme 3).[4b]

Scheme 2. Synthesis of Chiral Triol **6**.
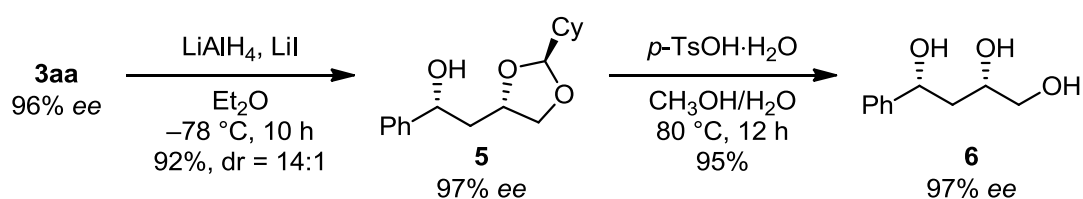
Scheme 3. Stereospecific Ring Cleavage of **3aa**.

To gain an insight into the enantiodetermining step, the author further investigated formal [3+2] cycloaddition reactions using formaldehyde (**2f**) and acetone (**2g**) with **1a** (Scheme 4).   He found that products **3af** and **3ag** were obtained enantioselectively regardless of the fact that the forming acetal carbon was achiral.   Although a precise understanding of the mechanism requires additional studies, from these results, the enantioselectivity of this reaction can be attributed largely to the step comprising oxy-Michael addition from the hemiacetal intermediates.[16]   This is in accordance with the consistent absolute configuration (the same (*S*)-configuration) at the *β*-position of the carbonyl group in both diastereomers of **3da**.[15]

Scheme 4. Formal [3+2] Cycloaddition with Formaldehyde (**2f**) and Acetone (**2g**).

R = H (**2f**)[a]
R = Me (**2g**)

4a (10 mol %)
CPME, 25 °C, 24 h

R = H (**3af**); 91%, 62% *ee*
R = Me (**3ag**); 4%, 98% *ee*

[a] Reaction was run using 37% aqueous solution of formaldehyde.

Conclusion

In summary, the author developed a novel organocatalytic formal [3+2] cycloaddition reaction leading to optically active 1,3-dioxolanes.   Bifunctional organocatalysts allowed cyclization from hemiacetals in high enantioselectivity.   This synthetic route provides efficient access to a range of chiral cyclic acetals.   In addition, the novel potential of bifunctional organocatalysts in chiral heterocycle synthesis was demonstrated.

Experimental Section

Materials

Unless otherwise noted, commercially available reagents were used without purification. All aldehydes and ketones **2** listed in Chapter 6 were commercially available. Bifunctional organocatalysts **4** were prepared by the method described in Chapter 5.

General procedure for asymmetric formal [3+2] cycloaddition reaction of γ-hydroxy-α,β-unsaturated ketones 1 with aldehydes or ketones 2

To a 5-mL vial were added sequentially γ-hydroxy-α,β-unsaturated ketone **1** (0.25 mmol), cyclopentyl methyl ether (CPME, 0.5mL), aldehyde or ketone **2** (0.3 mmol), and quinidine-derived bifunctional catalyst **4a** (0.025 mmol). The mixture was stirred in an oil bath maintained at 25 °C for 24 h. The reaction mixture was sequentially diluted with hexane/EtOAc (v/v = 1/1), passed through a short silica gel pad to remove **4a**, and concentrated in vacuo. Purification of the reaction mixture by flash silica gel column chromatography using hexane/EtOAc (v/v = 10/1) as an eluent afforded the corresponding 1,3-dioxolane **3** as a mixture of the diastereomers. Racemic compounds were prepared using triethylamine as a catalyst.

General procedure for preparation of γ-hydroxy-α,β-unsaturated ketones 1

γ-Hydroxy-α,β-unsaturated ketones **1** were prepared by Matsubara's reported procedure.[13] The characterization results of **1** are as below.

(*E*)-4-Hydroxy-1-phenylbut-2-en-1-one (1a): CAS RN [156386-82-2].
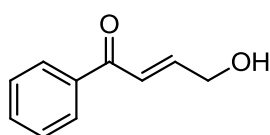
White solid.

^{1}H NMR (C$_6$D$_6$) δ 7.92 (m, 2H), 7.11 (m, 1H), 7.09 (dt, J = 15.5, 2.0 Hz, 1H), 7.04 (m, 2H), 6.99 (dt, J = 15.5, 3.5 Hz, 1H), 3.75 (br s, 2H). ^{13}C NMR (C$_6$D$_6$) δ 189.3, 147.3, 138.5, 132.6, 128.9, 128.7, 123.5, 62.1.

(*E*)-4-Hydroxy-1-(4-methoxyphenyl)but-2-en-1-one (1b): CAS RN [112533-12-7].
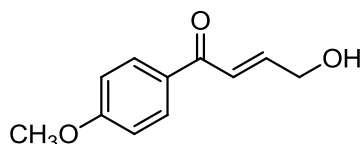
Pale yellow solid.

^{1}H NMR (C$_6$D$_6$) δ 8.00 (m, 2H), 7.15 (m, 1H), 7.07 (dt, J = 15.0, 3.5 Hz, 1H), 6.64 (m, 2H), 3.77 (m, 2H), 3.16 (s, 3H). ^{13}C NMR (C$_6$D$_6$) δ 188.6, 163.6, 146.3, 131.5, 131.2, 123.4, 114.1, 62.2, 54.9.

(*E*)-6-Hydroxy-1-(4-(trifluoromethyl)phenyl)but-2-en-1-one (1c): CAS RN [1158843-58-3].
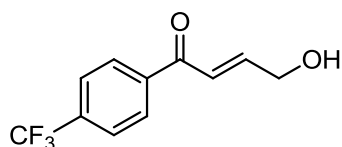
Colorless oil.

^{1}H NMR (C$_6$D$_6$) δ 7.66 (m, 2H), 7.26 (m, 2H), 6.98 (m, 1H), 6.93 (m, 1H), 3.82 (m, 2H), 1.58 (br s, 1H). ^{13}C NMR (C$_6$D$_6$) δ 188.8, 148.6, 141.0, 133.8 (q, J = 32.7 Hz), 129.0, 125.7 (q, J = 3.9 Hz), 124.4 (q, J = 272.5 Hz), 123.3, 62.0. ^{19}F NMR (C$_6$D$_6$) δ 99.4.

(*E*)-1-(4-Bromophenyl)-4-hydroxybut-2-en-1-one (1d): CAS RN [557085-43-5].
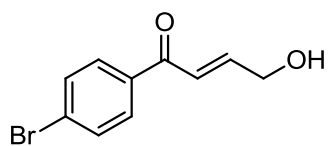
White solid.

^{1}H NMR (C$_6$D$_6$) δ 7.53 (m, 2H), 7.16 (m, 2H), 6.91 (m, 2H), 3.68 (m, 2H), 0.69 (t, J = 5.5 Hz, 1H). ^{13}C NMR (C$_6$D$_6$) δ 188.1, 147.6, 137.0, 132.0, 130.3, 128.4, 123.0, 62.0.

(*E*)-4-Hydroxy-1-(2-methylphenyl)but-2-en-1-one (1e).
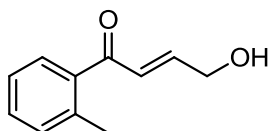
Pale yellow oil.

^{1}H NMR (C$_6$D$_6$) δ 7.31 (dd, J = 7.0, 1.5 Hz, 1H), 7.04 (ddd, J = 7.5, 7.5, 1.5 Hz, 1H), 6.94 (m, 2H), 6.72 (dt, J = 16.0, 2.0 Hz, 1H), 6.56 (dt, J = 16.0, 4.0 Hz, 1H), 3.66 (m, 2H), 2.41 (s, 3H), 0.87 (br s, 1H). ^{13}C NMR (C$_6$D$_6$) δ 194.8, 147.9, 139.5, 137.6, 131.6, 130.5, 128.6, 128.4, 125.6, 61.8, 20.5.   TLC: R$_f$ 0.36 (hexane/EtOAc = 1:1).   IR (neat): 3431, 3062, 3021, 2962, 2925, 1735, 1655, 1625, 1571, 1487, 1438, 1381, 1303, 1275, 1207, 1099, 1069, 1024, 963, 923, 859, 759, 735, 657, 474 cm^{-1}.   HRMS Calcd for C$_{11}$H$_{13}$O$_2$: [M+H]$^+$, 177.0916. Found: *m/z* 177.0908.

(*E*)-4-Hydroxy-1-(naphthalen-1-yl)but-2-en-1-one (1f).
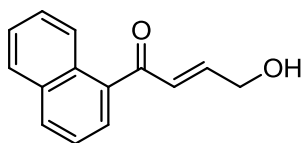
Pale yellow oil.

^{1}H NMR (C$_6$D$_6$) δ 8.64 (dd, J = 8.5, 1.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.56 (dd, J = 8.0, 1.5 Hz, 1H), 7.47 (dd, J = 7.0, 1.5 Hz, 1H), 7.29 (ddd, J = 8.5, 7.0, 1.5 Hz, 1H), 7.20 (ddd, J = 8.0, 7.0, 1,0 Hz, 1H), 7.07 (dd, J = 8.0, 7.0 Hz, 1H), 6.91 (m, 1H), 6.66 (dt, J = 15.5, 4.0 Hz, 1H), 3.75 (br s, 2H), 1.76 (br s, 1H). ^{13}C NMR (C$_6$D$_6$) δ 194.7, 148.7, 137.2, 134.3, 131.7, 131.2, 128.62, 128.59, 127.70, 127.67, 126.6, 126.4, 124.6, 61.9.   TLC: R$_f$ 0.33 (hexane/EtOAc = 1:1). IR (neat): 3438, 3050, 2916, 2849, 2366, 1735, 1646, 1508, 1437, 1397, 1371, 1343, 1286, 1254, 1198, 1177, 1136, 1110, 1095, 1021, 963, 922, 871, 802, 777, 477 cm^{-1}.   HRMS Calcd for

$C_{14}H_{13}O_2$: $[M+H]^+$, 213.0916. Found: *m/z* 213.0907.

(*E*)-4-Hydroxy-1-(thiophen-2-yl)but-2-en-1-one (1g): CAS RN [1191258-98-6].
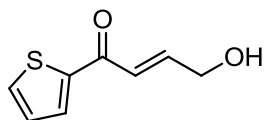
Pale yellow oil.

^{1}H NMR (C_6D_6) δ 7.35 (dd, *J* = 4.0, 1.0 Hz, 1H), 7.04 (m, 2H), 6.88 (dd, *J* = 5.0, 1.0 Hz, 1H), 6.54 (dd, *J* = 5.0, 4.0 Hz, 1H), 3.80 (m, 2H), 1.59 (br s, 1H). ^{13}C NMR (C_6D_6) δ 181.7, 147.0, 145.9, 133.7, 132.0, 128.1, 123.3, 62.0.

(*E*)-6-Hydroxy-1-phenylhex-4-en-3-one (1h): CAS RN [1158843-60-7].
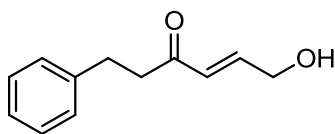
Colorless oil.

^{1}H NMR (C_6D_6) δ 7.12 (m, 2H), 7.03 (m, 3H), 6.41 (dt, *J* = 16.0, 4.0 Hz, 1H), 6.16 (dt, *J* = 16.0, 2.0 Hz, 1H), 3.62 (m, 2H), 2.87 (t, *J* = 8.0 Hz, 2H), 2.45 (t, *J* = 8.0 Hz, 2H), 0.91 (t, *J* = 6.5 Hz, 1H). ^{13}C NMR (C_6D_6) δ 197.8, 144.6, 141.9, 128.8, 128.7, 128.4, 126.3, 61.7, 42.4, 30.2.

Characterization Data of Products

2-(2-Cyclohexyl-1,3-dioxolan-4-yl)-1-phenylethanone (3aa).

The diastereomers were further separated by flash silica gel column chromatography using toluene as an eluent.

TLC: R_f 0.20 (hexane/EtOAc = 10:1).
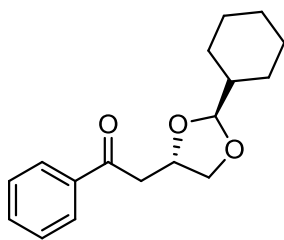
Major diastereomer: white solid, 96% *ee*.

$[\alpha]_D^{26}$ +29.3 (*c* 4.60, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 7.95 (m, 2H), 7.58 (m, 1H), 7.47 (m, 2H), 4.75 (d, *J* = 5.5 Hz, 1H), 4.59 (m, 1H), 4.37 (d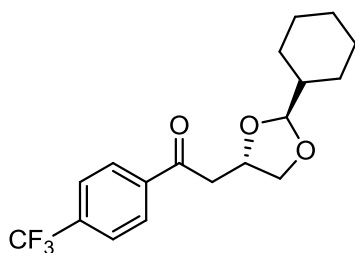d, *J* = 8.5, 6.0 Hz, 1H), 3.57 (dd, *J* = 17.5, 5.0 Hz, 1H), 3.54 (dd, *J* = 8.5, 7.0 Hz, 1H), 3.11 (dd, *J* = 17.5, 8.5 Hz, 1H), 1.81–1.72 (m, 4H), 1.66 (m, 1H), 1.54 (m, 1H), 1.28–1.13 (m, 3H), 1.07 (m, 2H). ^{13}C NMR (CDCl$_3$) δ 197.7, 136.7, 133.4, 128.7, 128.1, 107.1, 72.2, 70.9, 42.5, 41.9, 27.3, 27.1, 26.4, 25.7.   Mp. 68.5–68.9 °C.   IR (KBr): 3449, 2928, 2851, 2361, 1679, 1597, 1449, 1412, 1388, 1360, 1214, 1134, 1076, 986, 889, 753, 688, 577 cm^{-1}.   HRMS Calcd for C$_{17}$H$_{23}$O$_3$: [M+H]$^+$, 275.1647. Found: *m/z* 275.1632. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 98.5/1.5, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 3.9 min, t_{minor} = 5.2 min.
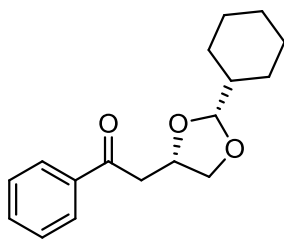
Minor diastereomer: white solid, 83% *ee*.

$[\alpha]_D^{26}$ +22.6 (*c* 1.33, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 7.96 (m, 2H), 7.59 (m, 1H), 7.48 (m, 2H), 4.65 (d, *J* = 5.0 Hz, 1H), 4.59 (m, 1H), 4.16 (dd, *J* = 8.5, 7.0 Hz, 1H), 3.64 (dd, *J* = 8.5, 5.5 Hz, 1H), 3.56 (dd, *J* = 17.5, 4.5 Hz, 1H), 3.11 (dd, *J* = 17.5, 8.0 Hz, 1H), 1.82–1.72 (m, 4H), 1.67 (m, 1H), 1.55 (m, 1H), 1.32–1.16 (m, 3H), 1.10 (m, 2H). ^{13}C NMR (CDCl$_3$) δ 197.8, 136.6, 133.4, 128.7, 128.1, 107.5, 72.4, 70.2, 43.3, 41.6, 27.4, 27.2, 26.4, 25.78, 25.75.   Mp. 66.0–66.5 °C. IR (KBr): 3448, 2929, 2852, 2367, 1672, 1598, 1449, 1408, 1382, 1352, 1241, 1213, 1139, 1061, 1000, 758, 689 cm^{-1}.   HRMS Calcd for C$_{17}$H$_{23}$O$_3$: [M+H]$^+$, 275.1647. Found: *m/z* 275.1632. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 98.5/1.5, flow rate = 2.0 mL/min, λ = 254 nm,

40 °C): t_{minor} = 3.5 min, t_{major} = 4.4 min.

2-(2-Cyclohexyl-1,3-dioxolan-4-yl)-1-(4-methoxyphenyl)ethanone (3ba).

The diastereomers were further separated by flash silica gel column chromatography using toluene/THF (v/v = 99/1) as an eluent.

TLC: R_f 0.18 (hexane/EtOAc = 10:1).
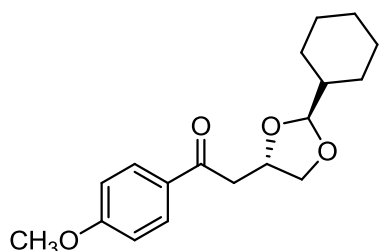
Major diastereomer: white solid, 96% *ee*.

$[\alpha]_D^{26}$ +33.8 (*c* 3.99, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 7.93 (m, 2H), 6.94 (m, 2H), 4.75 (d, *J* = 5.0 Hz, 1H), 4.57 (m, 1H), 4.36 (dd, *J* = 8.5, 6.0 Hz, 1H), 3.88 (s, 3H), 3.54 (dd, *J* = 8.5, 7.0 Hz, 1H), 3.52 (dd, *J* = 17.0, 5.0 Hz, 1H), 3.05 (dd, *J* = 17.0, 8.0 Hz, 1H), 1.82–1.72 (m, 4H), 1.67 (m, 1H), 1.54 (m, 1H), 1.28–1.14 (m, 3H), 1.08 (m, 2H). ^{13}C NMR (CDCl$_3$) δ 196.2, 163.8, 130.4, 129.9, 113.9, 107.1, 72.4, 71.0, 55.5, 42.2, 41.9, 27.4, 27.2, 26.4, 25.8.   Mp. 78.0–78.5 °C.   IR (KBr): 2924, 2850, 2361, 1669, 1604, 1578, 1511, 1451, 1420, 1387, 1356, 1313, 1262, 1219, 1183, 1139, 1080, 1035, 992, 837, 816, 604, 576 cm^{-1}.   HRMS Calcd for C$_{18}$H$_{25}$O$_4$: [M+H]$^+$, 305.1753. Found: *m/z* 305.1748.   HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 98/2, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 6.9 min, t_{major} = 10.1 min.
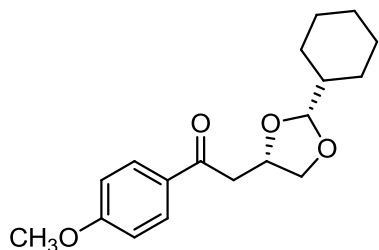
Minor diastereomer: white solid, 81% *ee*.

$[\alpha]_D^{26}$ −11.9 (*c* 0.21, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 7.94 (m, 2H), 6.94 (m, 2H), 4.64 (d, *J* = 5.0 Hz, 1H), 4.57 (m, 1H), 4.14 (dd, *J* = 8.5, 7.0 Hz, 1H), 3.88 (s, 3H), 3.63 (dd, *J* = 8.5, 5.5 Hz, 1H),

3.51 (dd, *J* = 17.0, 5.0 Hz, 1H), 3.05 (dd, *J* = 17.0, 8.5 Hz, 1H), 1.82–1.72 (m, 4H), 1.67 (m, 1H), 1.55 (m, 1H), 1.32–1.14 (m, 3H), 1.10 (m, 2H). ^{13}C NMR (CDCl$_3$) δ 196.3, 163.8, 130.4, 129.9, 113.8, 1107.5, 72.6, 70.2, 55.5, 42.9, 41.7, 27.4, 27.2, 26.4, 25.79, 25.76. Mp. 48.0–49.0 °C. IR (KBr): 2929, 2855, 2361, 1719, 1663, 1602, 1575, 1509, 1455, 1424, 1380, 1350, 1319, 1280, 1262, 1216, 1177, 1139, 1037, 990, 828, 604, 577 cm^{-1}. HRMS Calcd for C$_{18}$H$_{25}$O$_4$: [M+H]$^+$, 305.1753. Found: *m/z* 305.1748. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 98/2, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 5.7 min, t_{major} = 8.0 min.

**2-(2-Cyclohexyl-1,3-dioxolan-4-yl)-1-(4-(trifluoromethyl)phenyl)ethanone (3ca)**.

The diastereomers could not be separated.

White solid.

Mp. 64.5–66.0 °C. TLC: R$_f$ 0.30 (hexane/EtOAc = 10:1). IR (KBr): 2932, 2857, 2369, 1684, 1512, 1457, 1412, 1327, 1212, 1167, 1134, 1068, 990, 887, 831, 768, 604 cm^{-1}.

Major diastereomer: 95% *ee*.

^{1}H NMR (CDCl$_3$) δ 8.06 (m, 2H), 7.75 (m, 2H), 4.75 (d, *J* = 5.0 Hz, 1H), 4.59 (m, 1H), 4.37 (dd, *J* = 8.5, 6.0 Hz, 1H), 3.56 (dd, *J* = 17.5, 5.0 Hz, 1H), 3.55 (dd, *J* = 8.5, 6.5 Hz, 1H), 3.12 (dd, *J* = 17.5, 7.5 Hz, 1H), 1.81–1.72 (m, 4H), 1.67 (m, 1H), 1.55 (m, 1H), 1.28–1.13 (m, 3H), 1.08 (m, 2H). ^{13}C NMR (CDCl$_3$) δ 196.8, 139.1, 134.6 (q, *J* = 32.7 Hz), 128.4, 125.7, 123.5 (q, *J* = 272.5 Hz), 107.1, 71.9, 70.7, 42.7, 41.8, 27.2, 27.0, 26.3, 25.6. ^{19}F NMR (CDCl$_3$) δ 97.9. HRMS Calcd for C$_{18}$H$_{20}$F$_3$O$_3$: [M–H]$^-$, 341.1365. Found: *m/z* 341.1364. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 99.5/0.5, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 10.1 min, t_{major} = 21.1 min.
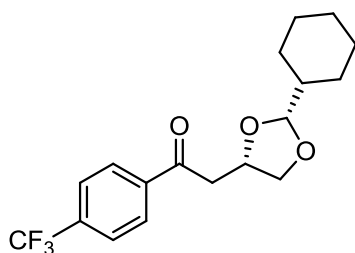
Minor diastereomer: 87% *ee*.

^{1}H NMR (CDCl$_3$) δ 8.07 (m, 2H), 7.75 (m, 2H), 4.64 (d, *J* = 5.0 Hz, 1H), 4.59 (m, 1H), 4.15 (dd, *J* = 8.5, 6.5 Hz, 1H), 3.66 (dd, *J* = 8.5, 5.5 Hz, 1H), 3.54 (dd, *J* = 17.5, 5.0 Hz, 1H), 3.12 (dd, *J* = 17.5, 7.5 Hz, 1H), 1.81–1.72 (m, 4H), 1.67 (m, 1H), 1.55 (m, 1H), 1.28–1.13 (m, 3H), 1.08 (m, 2H). ^{13}C NMR (CDCl$_3$) δ 196.9, 139.1, 134.6 (q, *J* = 32.7 Hz), 128.4, 125.7, 123.5 (q, *J* = 272.5 Hz), 107.6, 72.0, 69.9, 43.4, 41.5, 27.3, 27.1, 26.3, 25.6. ^{19}F NMR (CDCl$_3$) δ 97.9.   HRMS Calcd for C$_{18}$H$_{20}$F$_3$O$_3$: [M–H]$^-$, 341.1365. Found: *m/z* 341.1365.   HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 99.5/0.5, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 6.2 min, t_{major} = 11.5 min.

1-(4-Bromophenyl)-2-((2*S*,4*S*)-2-cyclohexyl-1,3-dioxolan-4-yl)ethanone (3da).

The diastereomers were further separated by flash silica gel column chromatography using toluene as an eluent.

TLC: R$_f$ 0.29 (hexane/EtOAc = 10:1).
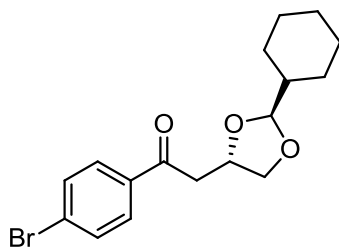
Major diastereomer: white solid, 96% *ee*.

[α]$_D^{26}$ +25.2 (*c* 4.96, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 7.81 (m, 2H), 7.62 (m, 2H), 4.74 (d, *J* = 5.0 Hz, 1H), 4.56 (m, 1H), 4.35 (dd, *J* = 8.5, 6.0 Hz, 1H), 3.53 (dd, *J* = 8.5, 7.0 Hz, 1H), 3.50 (dd, *J* = 17.0, 5.0 Hz, 1H), 3.06 (dd, *J* = 17.0, 7.5 Hz, 1H), 1.80–1.72 (m, 4H), 1.67 (m, 1H), 1.54 (m, 1H),

1.28–1.13 (m, 3H), 1.07 (m, 2H). ^{13}C NMR (CDCl$_3$) δ 196.8, 135.4, 132.0, 129.6, 128.7, 107.2, 72.1, 70.8, 42.4, 41.9, 27.3, 27.1, 26.4, 25.7.   Mp. 94.0–94.2 °C.   IR (KBr): 3458, 2925, 2853, 1679, 1587, 1486, 1451, 1398, 1316, 1212, 1138, 1075, 988, 888, 817, 571, 511, 454 cm^{-1}. HRMS Calcd for C$_{17}$H$_{22}$BrO$_3$: [M+H]$^+$, 353.0752. Found: *m/z* 353.0745.   HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 98/2, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 5.5 min, t_{major} = 9.5 min.
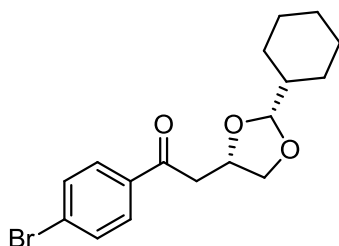
Minor diastereomer: white solid, 85% *ee*.

[α]$_D^{26}$ +25.0 (*c* 1.80, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 7.82 (m, 2H), 7.62 (m, 2H), 4.64 (d, *J* = 4.5 Hz, 1H), 4.56 (m, 1H), 4.13 (dd, *J* = 8.5, 6.0 Hz, 1H), 3.64 (dd, *J* = 8.5, 5.0 Hz, 1H), 3.49 (dd, *J* = 17.5, 5.0 Hz, 1H), 3.06 (dd, *J* = 17.5, 8.0 Hz, 1H), 1.82–1.71 (m, 4H), 1.67 (m, 1H), 1.54 (m, 1H), 1.32–1.12 (m, 3H), 1.10 (m, 2H). ^{13}C NMR (CDCl$_3$) δ 196.8, 135.4, 132.0, 129.6, 128.7, 107.6, 72.2, 70.0, 43.2, 41.6, 27.4, 27.2, 26.4, 25.74, 25.72.   Mp. 84.0–84.5 °C.   IR (KBr): 3453, 2934, 2858, 1674, 1585, 1458, 1417, 1398, 1375, 1341, 1288, 1207, 1167, 1135, 1068, 1033, 987, 887, 816, 569, 511, 458 cm^{-1}.   HRMS Calcd for C$_{17}$H$_{22}$BrO$_3$: [M+H]$^+$, 353.0752. Found: *m/z* 353.0745.   HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 98/2, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 4.1 min, t_{major} = 6.7 min.

**2-(2-Cyclohexyl-1,3-dioxolan-4-yl)-1-(2-methylphenyl)ethanone (3ea)**.

The diastereomers were further separated by preparative TLC using toluene/THF (v/v = 99/1) as an eluent.

TLC: R$_f$ 0.33 (hexane/EtOAc = 10:1).
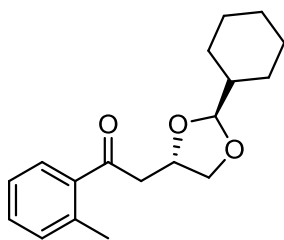
Major diastereomer: cololess oil, 91% *ee*.

$[\alpha]_D^{28}$ +14.3 (*c* 0.35, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 7.82 (d, *J* = 7.5 Hz, 1H), 7.53 (dd, *J* = 7.5, 7.0 Hz, 1H), 7.41 (m, 2H), 4.88 (d, *J* = 5.0 Hz, 1H), 4.70 (m, 1H), 4.47 (dd, *J* = 8.5, 6.0 Hz, 1H), 3.69 (dd, *J* = 8.5, 7.5 Hz, 1H), 3.60 (dd, *J* = 17.0, 5.5 Hz, 1H), 3.19 (dd, *J* = 17.0, 7.5 Hz, 1H), 2.65 (s, 3H), 1.95–1.86 (m, 4H), 1.81 (m, 1H), 1.67 (m, 1H), 1.42–1.27 (m, 3H), 1.21 (m, 2H). ^{13}C NMR (CDCl$_3$) δ 201.5, 138.5, 137.4, 132.1, 131.7, 128.8, 125.8, 107.1, 72.4, 70.8, 45.2, 41.9, 27.3, 27.2, 26.4, 25.7, 21.4.   IR (neat): 2926, 2854, 1681, 1601, 1570, 1487, 1452, 1410, 1382, 1347, 1288, 1213, 1153, 1134, 1073, 980, 888, 755, 719, 480 cm^{-1}.   HRMS Calcd for C$_{18}$H$_{25}$O$_3$: [M+H]$^+$, 289.1804. Found: *m/z* 289.1798.   HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 99/1, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 5.5 min, t_{major} = 7.8 min.
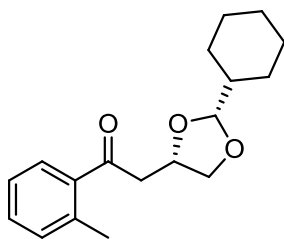
Minor diastereomer: colorless oil, 79% *ee*.

$[\alpha]_D^{28}$ +6.4 (*c* 0.78, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 7.69 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.39 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 7.27 (m, 2H), 4.64 (d, *J* = 5.0 Hz, 1H), 4.55 (m, 1H), 4.13 (dd, *J* = 8.5, 7.0 Hz, 1H), 3.64 (dd, *J* = 8.5, 5.5 Hz, 1H), 3.46 (dd, *J* = 17.0, 5.5 Hz, 1H), 3.05 (dd, *J* = 17.0, 7.5 Hz, 1H), 2.51 (s, 3H), 1.81–1.71 (m, 4H), 1.66 (m, 1H), 1.54 (m, 1H), 1.28–1.11 (m, 3H), 1.08 (m, 2H). ^{13}C NMR (CDCl$_3$) δ 201.5, 138.6, 137.0, 132.1, 131.7, 128.9, 125.8, 107.5, 72.5, 70.0, 45.8, 41.6, 27.3, 27.2, 26.4, 25.72, 25.70, 21.5.   IR (neat): 2925, 2853, 2368, 1679, 1601, 1570, 1487, 1452, 1412, 1381, 1347, 1287, 1214, 1134, 1069, 980, 888, 756, 719, 466 cm^{-1}.   HRMS Calcd for C$_{18}$H$_{25}$O$_3$: [M+H]$^+$, 289.1804. Found: *m/z* 289.1797.   HPLC (Daicel Chiralcel OD-H,

hexane/*i*-PrOH = 99/1, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 4.6 min, t_{major} = 7.2 min.

2-(2-Cyclohexyl-1,3-dioxolan-4-yl)-1-(naphthalen-1-yl)ethanone (3fa).

The diastereomers were further separated by preparative TLC using xylene/THF (v/v = 99/1) as an eluent.

TLC: R_f 0.20 (hexane/EtOAc = 10:1).
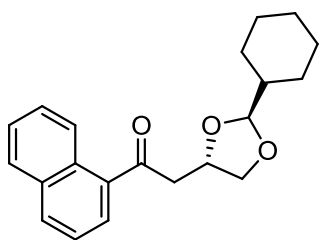
Major diastereomer: pale yellow oil, 90% *ee*.

$[\alpha]_D^{26}$ +18.9 (*c* 0.53, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 8.65 (dd, *J* = 8.5, 1.0 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.92 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.88 (ddd, *J* =8.0, 1.5, 0.5 Hz, 1H), 7.60 (ddd, *J* =8.5, 7.0, 1.5 Hz, 1H), 7.54 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.51 (dd, *J* = 8.0, 7.5 Hz, 1H), 4.77 (d, *J* = 5.0 Hz, 1H), 4.65 (m, 1H), 4.38 (dd, *J* = 8.5, 6.0 Hz, 1H), 3.63 (dd, *J* = 8.5, 1.5 Hz, 1H), 3.62 (dd, *J* = 17.0, 6.0 Hz, 1H), 3.20 (dd, *J* = 17.0, 7.5 Hz, 1H), 1.81–1.71 (m, 4H), 1.66 (m, 1H), 1.55 (m, 1H), 1.31–1.13 (m, 3H), 1.07 (m, 2H). ^{13}C NMR (CDCl$_3$) δ 201.7, 135.3, 134.0, 133.1, 130.1, 128.5, 128.13, 128.12, 126.6, 125.8, 124.3, 107.2, 72.5, 70.8, 45.7, 41.9, 27.3, 27.2, 26.4, 25.7. IR (neat): 3060, 2925, 2852, 2364, 1676, 1594, 1574, 1507, 1449, 1396, 1350, 1289, 1232, 1174, 1153, 1135, 1060, 983, 950, 889, 802, 775, 493 cm^{-1}.   HRMS Calcd for C$_{21}$H$_{25}$O$_3$: [M+H]$^+$, 325.1804. Found: *m/z* 325.1790.   HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 98/2, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 5.6 min, t_{major} = 6.6 min.
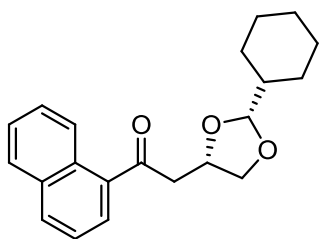
Minor diastereomer: pale yellow oil, 85% *ee*.

$[\alpha]_D^{26}$ +2.9 (*c* 0.87, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 8.68 (dd, *J* = 8.5, 1.0 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.95 (dd, *J* = 7.0, 1.5 Hz, 1H), 7.90 (ddd, *J* = 8.0, 1.5, 0.5 Hz, 1H), 7.62 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.56 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.53 (dd, *J* = 8.0, 7.0 Hz, 1H), 4.68 (d, *J* = 5.5 Hz, 1H), 4.67 (m, 1H), 4.19 (dd, *J* = 8.0, 7.0 Hz, 1H), 3.74 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.62 (dd, *J* = 17.0, 5.5 Hz, 1H), 3.22 (dd, *J* = 17.0, 7.5 Hz, 1H), 1.83–1.72 (m, 4H), 1.68 (m, 1H), 1.56 (m, 1H), 1.29–1.13 (m, 3H), 1.10 (m, 2H). ^{13}C NMR (CDCl$_3$) δ 201.8, 135.3, 134.0, 133.1, 130.1, 128.5, 128.2, 128.1, 126.5, 125.8, 124.3, 107.6, 72.7, 70.1, 46.4, 41.7, 27.3, 27.2, 26.4, 25.8, 25.7. IR (neat): 3050, 2925, 2853, 2360, 1676, 1594, 1574, 1507, 1452, 1396, 1379, 1350, 1288, 1232, 1174, 1153, 1134, 1065, 992, 949, 888, 802, 775, 496 cm^{-1}.   HRMS Calcd for C$_{21}$H$_{25}$O$_3$: [M+H]$^+$, 325.1804. Found: *m/z* 325.1789.   HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 98/2, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 5.3 min, t_{major} = 6.2 min.

2-(2-Cyclohexyl-1,3-dioxolan-4-yl)-1-(thiophen-2-yl)ethanone (3ga).

The diastereomers were further separated by preparative TLC using toluene/THF (v/v = 99/1) as an eluent.

TLC: R$_f$ 0.18 (hexane/EtOAc = 10:1).
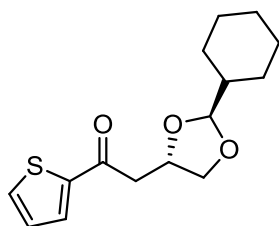
Major diastereomer: pale yellow oil, 98% *ee*.

$[\alpha]_D^{24}$ +19.0 (*c* 3.43, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 7.73 (dd, *J* = 3.5, 1.0 Hz, 1H), 7.66 (dd, *J* = 4.5, 1.0 Hz, 1H), 7.14 (dd, *J* = 4.5, 3.5 Hz, 1H), 4.76 (d, *J* = 5.0 Hz, 1H), 4.56 (m, 1H), 4.32 (dd, *J* = 8.5, 6.0 Hz, 1H), 3.58 (dd, *J* = 8.5, 6.5 Hz, 1H), 3.47 (dd, *J* = 16.5, 5.5 Hz, 1H), 3.03 (dd, *J* = 16.5, 7.5 Hz, 1H), 1.80–1.71 (m, 4H), 1.66 (m, 1H), 1.53 (m, 1H), 1.27–1.13 (m, 3H), 1.07 (m, 2H). ^{13}C NMR (CDCl$_3$) δ 190.4, 144.1, 134.1, 132.4, 128.2, 107.2, 72.1, 70.7, 43.1, 41.9, 27.3,

27.1, 26.4, 25.7. IR (neat): 3097, 2925, 2853, 1661, 1518, 1451, 1417, 1357, 1289, 1218, 1135, 1059, 982, 946, 888, 859, 772, 722, 485 cm^{-1}. HRMS Calcd for $C_{15}H_{21}O_3S$: [M+H]$^+$, 281.1211. Found: m/z 281.1197. HPLC (Daicel Chiralpak AD-H, hexane/i-PrOH = 99.7/0.3, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 40.6 min, t_{minor} = 50.0 min.
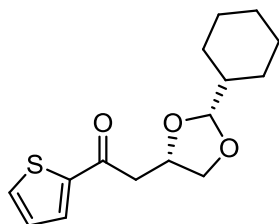
Minor diastereomer: pale yellow solid, 85% *ee*.

$[\alpha]_D^{24}$ +29.8 (*c* 0.84, CH_2Cl_2). ^{1}H NMR (CDCl$_3$) δ 7.74 (dd, *J* = 4.0, 1.5 Hz, 1H), 7.66 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.14 (dd, *J* = 5.0, 4.0 Hz, 1H), 4.64 (d, *J* = 4.5 Hz, 1H), 4.55 (m, 1H), 4.10 (dd, *J* = 8.0, 6.5 Hz, 1H), 3.68 (dd, *J* = 8.0, 5.5 Hz, 1H), 3.45 (dd, *J* = 16.5, 5.0 Hz, 1H), 3.03 (dd, *J* = 16.5, 7.5 Hz, 1H), 1.81–1.72 (m, 4H), 1.66 (m, 1H), 1.55 (m, 1H), 1.28–1.13 (m, 3H), 1.09 (m, 2H). ^{13}C NMR (CDCl$_3$) δ 190.4, 144.1, 134.1, 132.4, 128.2, 107.6, 72.2, 70.0, 43.8, 41.6, 27.4, 27.2, 26.4, 25.8, 25.7. Mp. 64.5–65.0 °C. IR (KBr): 3106, 2934, 2858, 1650, 1517, 1456, 1416, 1378, 1354, 1289, 1211, 1165, 1135, 1074, 1030, 995, 947, 887, 772, 727, 656, 588 cm^{-1}. HRMS Calcd for $C_{15}H_{21}O_3S$: [M+H]$^+$, 281.1211. Found: m/z 281.1196. HPLC (Daicel Chiralpak AD-H, hexane/i-PrOH = 99.7/0.3, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 24.2 min, t_{minor} = 29.2 min.

**1-(2-Cyclohexyl-1,3-dioxolan-4-yl)-4-phenylbutan-2-one (3ha)**.

The diastereomers were further separated by flash silica gel column chromatography using toluene/THF (v/v = 99/1) as an eluent.

TLC: R$_f$ 0.18 (hexane/EtOAc = 10:1).
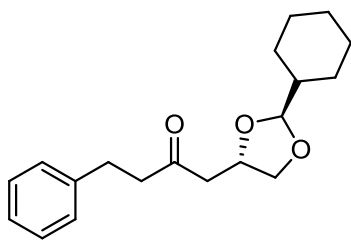
Major diastereomer: white solid, 96% *ee*.

$[\alpha]_D^{28}$ –9.2 (*c* 1.90, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.30 (m, 2H), 7.20 (m, 3H), 4.69 (d, *J* = 5.0 Hz, 1H), 4.39 (m, 1H), 4.22 (dd, *J* = 8.5, 6.0 Hz, 1H), 3.42 (dd, *J* = 8.5, 7.0 Hz, 1H), 2.92 (m, 2H), 2.89 (dd, *J* = 16.5, 6.5 Hz, 1H), 2.80 (m, 2H), 2.54 (dd, *J* = 16.5, 7.0 Hz, 1H), 1.76 (m, 4H), 1.67 (m, 1H), 1.51 (m, 1H), 1.21 (m, 3H), 1.06 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 207.6, 140.8, 128.5, 128.3, 126.2, 107.2, 71.7, 70.6, 46.5, 45.0, 41.9, 29.6, 27.3, 27.1, 26.4, 25.7.   Mp. 57.0–57.5 °C. IR (KBr): 3028, 2934, 2853, 1701, 1604, 1499, 1454, 1410, 1388, 1367, 1301, 1267, 1168, 1120, 1070, 990, 890, 842, 751, 698, 581, 512 cm^{-1}.   HRMS Calcd for $C_{19}H_{27}O_3$: $[M+H]^+$, 303.1960. Found: *m/z* 303.1946.   HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 9.2 min, t_{minor} = 11.3 min.
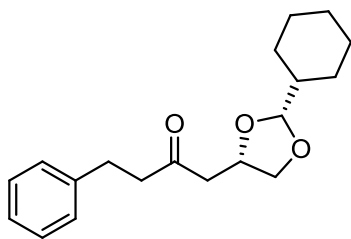
Minor diastereomer: colorless oil, 82% *ee*.

$[\alpha]_D^{28}$ +12.8 (*c* 0.39, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.28 (m, 2H), 7.19 (m, 3H), 4.59 (d, *J* = 4.5 Hz, 1H), 4.38 (m, 1H), 4.01 (dd, *J* = 8.0, 7.0 Hz, 1H), 3.49 (dd, *J* = 8.0, 6.0 Hz, 1H), 2.90 (m, 2H), 2.87 (dd, *J* = 17.0, 6.0 Hz, 1H), 2.78 (m, 2H), 2.54 (dd, *J* = 17.0, 7.0 Hz, 1H), 1.78–1.71 (m, 4H), 1.66 (m, 1H), 1.52 (m, 1H), 1.32–1.13 (m, 3H), 1.07 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 207.7, 140.8, 128.5, 128.3, 126.2, 107.6, 71.9, 69.8, 47.2, 44.9, 41.6, 29.5, 27.4, 27.1, 26.4, 25.8, 25.7.   IR (neat): 3027, 2925, 2854, 1715, 1604, 1542, 1497, 1452, 1412, 1383, 1262, 1133, 1065, 989, 888, 801, 749, 699, 490 cm^{-1}.   HRMS Calcd for $C_{19}H_{27}O_3$: $[M+H]^+$, 303.1960. Found: *m/z* 303.1946. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm,

40 °C): t_{major} = 5.4 min, t_{minor} = 7.5 min.

2-(2-Ethyl-1,3-dioxolan-4-yl)-1-phenylethanone (3ab).

The diastereomers could not be separated.

Pale yellow oil.

TLC: R_f 0.18 (hexane/EtOAc = 10:1).   IR (neat): 2973, 2935, 2881, 2368, 1735, 1685, 1598, 1450, 1379, 1355, 1283, 1240, 1213, 1160, 1118, 1087, 1044, 1001, 934, 756, 690, 485 cm^{-1}.
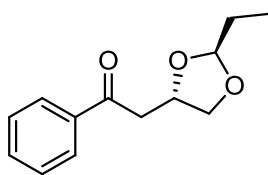
Major diastereomer: 94% *ee*.

^{1}H NMR (CDCl$_3$) δ 7.96 (m, 2H), 7.59 (m, 1H), 7.48 (m, 2H), 4.98 (t, *J* = 5.0 Hz, 1H), 4.64 (m, 1H), 4.41 (dd, *J* = 8.5, 6.5 Hz, 1H), 3.57 (dd, *J* = 17.0, 5.0 Hz, 1H), 3.56 (dd, *J* = 8.5, 7.0 Hz, 1H), 3.13 (dd, *J* = 17.0, 8.0 Hz, 1H), 1.68 (dt, *J* = 5.0, 7.5 Hz, 2H), 0.96 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 197.7, 136.5, 133.4, 128.6, 128.0, 104.8, 72.0, 70.9, 42.4, 27.1, 7.9.   HRMS Calcd for C$_{13}$H$_{17}$O$_3$: [M+H]$^+$, 221.1178. Found: *m/z* 221.1171.   HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 99.7/0.3, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 11.8 min, t_{major} = 16.4 min.
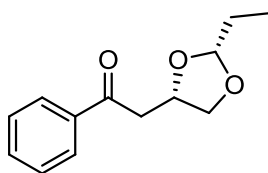
Minor diastereomer: 85% *ee*.

^{1}H NMR (CDCl$_3$) δ 7.96 (m, 2H), 7.59 (m, 1H), 7.48 (m, 2H), 4.87 (t, *J* = 4.5 Hz, 1H), 4.62 (m, 1H), 4.18 (dd, *J* = 8.5, 7.0 Hz, 1H), 3.68 (dd, *J* = 8.5, 5.5 Hz, 1H), 3.58 (dd, *J* = 17.5, 5.5 Hz, 1H), 3.13 (dd, *J* = 17.5, 8.5 Hz, 1H), 1.71 (dt, *J* = 4.5, 7.5 Hz, 2H), 0.97 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 197.7, 136.4, 133.4, 128.6, 128.0, 105.2, 72.4, 70.1, 43.3, 26.9, 7.9.   HRMS Calcd for C$_{13}$H$_{17}$O$_3$: [M+H]$^+$, 221.1178. Found: *m/z* 221.1171.   HPLC (Daicel Chiralcel OD-H,

hexane/*i*-PrOH = 99.7/0.3, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 10.1 min, t_{major} = 14.5 min.

2-(2-(2-Propyl)-1,3-dioxolan-4-yl)-1-phenylethanone (3ac).

The diastereomers were further separated by preparative TLC using toluene/THF (v/v = 99.5/0.5) as an eluent.

TLC: R_f 0.20 (hexane/EtOAc = 10:1).
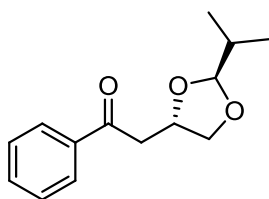
Major diastereomer: cololess oil, 93% *ee*.

$[\alpha]_D^{26}$ +18.0 (*c* 2.22, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 7.95 (m, 2H), 7.58 (m, 1H), 7.48 (m, 2H), 4.77 (d, *J* = 5.0 Hz, 1H), 4.61 (m, 1H), 4.39 (dd, *J* = 8.5, 6.0 Hz, 1H), 3.58 (dd, *J* = 17.0, 5.0 Hz, 1H), 3.56 (dd, *J* = 8.5, 7.0 Hz, 1H), 3.12 (dd, *J* = 17.0, 8.0 Hz, 1H), 1.83 (m, 1H), 0.95 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (CDCl$_3$) δ 197.8, 136.7, 133.4, 128.7, 128.1, 107.8, 72.4, 71.1, 42.5, 32.2, 16.8, 16.7.   IR (neat): 3061, 2963, 2932, 2875, 1682, 1598, 1582, 1474, 1450, 1410, 1388, 1353, 1317, 1293, 1212, 1191, 1090, 987, 949, 801, 755, 690, 491 cm^{-1}.   HRMS Calcd for C$_{14}$H$_{19}$O$_3$: [M+H]$^+$, 235.1334. Found: *m/z* 235.1326.   HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 98.5/1.5, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 3.8 min, t_{major} = 4.4 min.
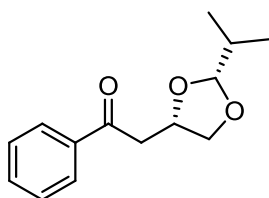
Minor diastereomer: cololess oil, 82% *ee*.

$[\alpha]_D^{26}$ +44.9 (*c* 0.39, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 7.96 (m, 2H), 7.59 (m, 1H), 7.48 (m, 2H), 4.67 (d, *J* = 5.0 Hz, 1H), 4.60 (m, 1H), 4.17 (dd, *J* = 8.5, 6.5 Hz, 1H), 3.65 (dd, *J* = 8.5, 5.5 Hz,

1H), 3.57 (dd, J = 17.5, 4.5 Hz, 1H), 3.11 (dd, J = 17.5, 8.0 Hz, 1H), 1.85 (m, 1H), 0.964 (d, J = 7.0 Hz, 3H), 0.963 (d, J = 6.5 Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 197.8, 136.7, 133.4, 128.7, 128.1, 108.2, 72.5, 70.3, 43.2, 31.9, 16.9, 16.7.   IR (neat): 3064, 2963, 2926, 2876, 2360, 1684, 1598, 1582, 1473, 1450, 1412, 1387, 1358, 1319, 1288, 1212, 1093, 989, 954, 802, 755, 690, 478 cm^{-1}. HRMS Calcd for C$_{14}$H$_{19}$O$_3$: [M+H]$^+$, 235.1334. Found: m/z 235.1326.   HPLC (Daicel Chiralcel OD-H, hexane/i-PrOH = 98.5/1.5, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 3.5 min, t_{major} = 4.2 min.

2-(2-(2-Methyl-2-propyl)-1,3-dioxolan-4-yl)-1-phenylethanone (3ad).

The diastereomers were further separated by flash silica gel column chromatography using toluene as an eluent.

TLC: R$_f$ 0.23 (hexane/EtOAc = 10:1).
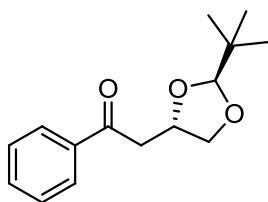
Major diastereomer: cololess oil, 94% ee.

[α]$_D^{26}$ +21.2 (c 3.42, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 7.95 (m, 2H), 7.58 (m, 1H), 7.47 (m, 2H), 4.66 (s, 1H), 4.58 (m, 1H), 4.39 (dd, J = 8.5, 6.0 Hz, 1H), 3.59 (dd, J = 17.0, 5.0 Hz, 1H), 3.55 (dd, J = 8.5, 7.0 Hz, 1H), 3.11 (dd, J = 17.0, 8.5 Hz, 1H), 0.92 (s, 9H). ^{13}C NMR (CDCl$_3$) δ 197.8, 136.5, 133.4, 128.7, 128.1, 109.7, 72.7, 71.3, 42.4, 34.7, 24.2.   IR (neat): 3352, 3061, 2958, 2907, 2870, 2364, 1683, 1598, 1582, 1482, 1450, 1402, 1457, 1317, 1294, 1212, 1181, 1107, 1037, 967, 805, 754, 690, 465 cm^{-1}.   HRMS Calcd for C$_{15}$H$_{21}$O$_3$: [M+H]$^+$, 249.1491. Found: m/z 249.1480.   HPLC (Daicel Chiralcel OD-H, hexane/i-PrOH = 98/2, flow rate = 0.3 mL/min, λ = 254 nm, 40 °C): t_{minor} = 19.1 min, t_{major} = 20.9 min.
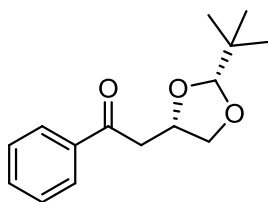
Minor diastereomer: cololess oil, 91% *ee*.

$[\alpha]_D^{26}$ +38.5 (*c* 1.30, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 7.96 (m, 2H), 7.59 (m, 1H), 7.48 (m, 2H), 4.60 (m, 1H), 4.56 (s, 1H), 4.18 (dd, *J* = 8.0, 6.5 Hz, 1H), 3.62 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.57 (dd, *J* = 17.0, 5.0 Hz, 1H), 3.09 (dd, *J* = 17.0, 8.0 Hz, 1H), 0.93 (s, 9H). ^{13}C NMR (CDCl$_3$) δ 197.9, 136.5, 133.5, 128.7, 128.1, 110.1, 72.5, 70.4, 43.0, 34.0, 24.3.   IR (neat): 3356, 3061, 2959, 2925, 2871, 2364, 1683, 1598, 1582, 1483, 1450, 1412, 1388, 1358, 1319, 1288, 1211, 1108, 1042, 972, 805, 756, 690, 427 cm^{-1}.   HRMS Calcd for C$_{15}$H$_{21}$O$_3$: [M+H]$^+$, 249.1491. Found: *m/z* 249.1481.   HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 98/2, flow rate = 0.3 mL/min, λ = 254 nm, 40 °C): t_{minor} = 18.3 min, t_{major} = 22.2 min.

1-Phenyl-2-(2-phenyl-2-(trifluoromethyl)-1,3-dioxolan-4-yl)ethanone (3ae).

The diastereomers could not be separated.

White solid.

Mp. 80.0–81.5 °C.   TLC: R$_f$ 0.20 (hexane/EtOAc = 10:1).   IR (KBr): 3451, 3069, 2916, 2368, 1688, 1596, 1581, 1452, 1388, 1361, 1335, 1301, 1241, 1184, 1107, 1052, 999, 956, 918, 763, 716, 691, 666, 501 cm^{-1}.
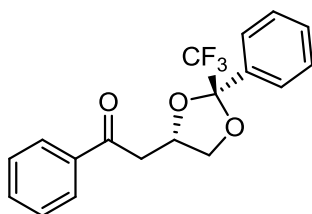
Major diastereomer: 70% *ee*.

^{1}H NMR (CDCl$_3$) δ 7.86 (m, 2H), 7.64–7.56 (m, 3H), 7.44 (m, 2H), 7.44–7.37 (m, 3H), 5.05 (m, 1H), 4.69 (dd, *J* = 8.5, 6.5 Hz, 1H), 3.78 (m, 1H), 3.66 (dd, *J* = 17.5, 4.5 Hz, 1H), 2.99 (dd, *J* =

17.5, 8.5 Hz, 1H). ^{13}C NMR (CDCl$_3$) δ 196.9, 136.0, 135.1, 133.6, 129.6. 128.7, 128.03, 128.01, 126.7, 122.8 (q, J = 289.4 Hz), 104.5 (q, J = 32.3 Hz), 74.3, 71.8, 42.4. ^{19}F NMR (CDCl$_3$) δ 79.5. HRMS Calcd for C$_{18}$H$_{16}$F$_3$O$_3$: [M+H]$^+$, 337.1052. Found: m/z 337.1046. HPLC (Daicel Chiralcel OJ-H, hexane/i-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 3.9 min, t_{minor} = 4.4 min.
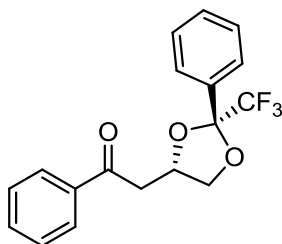
Minor diastereomer: 31% *ee*.

^{1}H NMR (CDCl$_3$) δ 7.98 (m, 2H), 7.64–7.56 (m, 3H), 7.50 (m, 2H), 7.44–7.37 (m, 3H), 4.71 (m, 1H), 4.51 (m, 1H), 3.93 (dd, J = 8.5, 7.5 Hz, 1H), 3.83 (dd, J = 18.0, 5.0 Hz, 1H), 3.29 (dd, J = 18.0, 8.5 Hz, 1H). ^{13}C NMR (CDCl$_3$) δ 196.8, 136.1, 134.6, 133.7, 129.7, 128.7, 128.1, 128.0, 126.9, 122.6 (q, J = 287.5 Hz), 104.5 (q, J = 32.3 Hz), 75.5, 71.9, 41.9. ^{19}F NMR (CDCl$_3$) δ 79.4. HRMS Calcd for C$_{18}$H$_{16}$F$_3$O$_3$: [M+H]$^+$, 337.1052. Found: m/z 337.1046. HPLC (Daicel Chiralcel OJ-H, hexane/i-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 5.1 min, t_{major} = 22.7 min.

2-(1,3-Dioxolan-4-yl)-1-phenylethanone (3af).
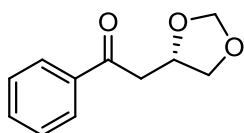
Pale yellow solid, 62% *ee*.

[α]$_D^{26}$ +28.6 (*c* 3.50, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 7.96 (m, 2H), 7.59 (m, 1H), 7.48 (m, 2H), 5.06 (s, 1H), 4.88 (s, 1H), 4.59 (m, 1H), 4.22 (dd, J = 8.5, 7.0 Hz, 1H), 3.61 (dd, J = 8.5, 6.0 Hz, 1H), 3.58 (dd, J = 17.5, 5.5 Hz, 1H), 3.14 (dd, J = 17.5, 8.0 Hz, 1H). ^{13}C NMR (CDCl$_3$) δ 197.6,

136.6, 133.5, 128.7, 128.1, 94.8, 72.1, 70.1, 42.6. Mp. 34.0–34.2 °C. TLC: R_f 0.10 (hexane/EtOAc = 10:1). IR (KBr): 4055, 3459, 3330, 2862, 2751, 1984, 1927, 1831, 1793, 1678, 1596, 1448, 1417, 1375, 1350, 1298, 1209, 1158, 1082, 1000, 937, 794, 759, 691, 636, 578, 497 cm^{-1}. HRMS Calcd for $C_{11}H_{13}O_3$: [M+H]$^+$, 193.0865. Found: m/z 193.0859. HPLC (Daicel Chiralcel OD-H, hexane/i-PrOH = 98/2, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 6.1 min, t_{major} = 7.4 min.

2-(2,2-Dimethyl-1,3-dioxolan-4-yl)-1-phenylethanone (3ag).
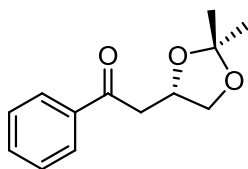
Cololess oil, 98% *ee.*

$[\alpha]_D^{26}$ +35.7 (c 0.42, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 7.96 (m, 2H), 7.58 (m, 1H), 7.48 (m, 2H), 4.66 (m, 1H), 4.32 (dd, J = 8.5, 6.5 Hz, 1H), 3.65 (dd, J = 8.5, 6.5 Hz, 1H), 3.56 (dd, J = 17.0, 5.0 Hz, 1H), 3.11 (dd, J = 17.0, 8.0 Hz, 1H), 1.44 (d, J = 1.0 Hz, 3H), 1.39 (d, J = 1.0 Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 197.8, 136.5, 133.5, 128.7, 128.1, 108.7, 72.1, 69.7, 43.2, 26.9, 25.4. TLC: R_f 0.19 (hexane/EtOAc = 10:1). IR (neat): 3064, 2987, 2934, 2364, 1683, 1598, 1582, 1450, 1412, 1379, 1353, 1298, 1256, 1211, 1157, 1063, 1001, 917, 863, 809, 755, 691, 417 cm^{-1}. HRMS Calcd for $C_{13}H_{17}O_3$: [M+H]$^+$, 221.1178. Found: m/z 221.1167. HPLC (Daicel Chiralcel OD-H, hexane/i-PrOH = 98/2, flow rate = 0.3 mL/min, λ = 254 nm, 40 °C): t_{minor} = 25.3 min, t_{major} = 28.8 min.

Procedure for synthesis of 5

To the mixture of **3aa** (single diastereomer, 0.049 g, 0.18 mmol) and LiI (0.072 g, 0.54 mmol) in Et$_2$O (3.5 mL) was added LiAlH$_4$ (0.0070 g, 0.18 mmol) in −78 °C, and the mixture was stirred at −78 °C for 10 h. 10% Aqueous NaOH were added to quench the reaction, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over

Na$_2$SO$_4$, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 5/1) as an eluent gave **5** (0.045 g, 92% yield, dr = 14:1). The diastereomers were further separated by flash silica gel column chromatography using toluene/THF (v/v = 99/1) as an eluent.

2-(2-Cyclohexyl-1,3-dioxolan-4-yl)-1-phenylethanol (5).
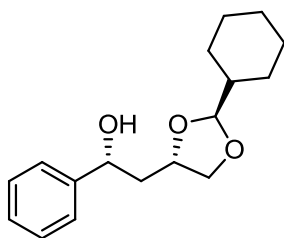
Colorless oil, 97% *ee*.

$[\alpha]_D^{23}$ +33.7 (*c* 3.12, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 7.37 (m, 4H), 7.28 (m, 1H), 4.96 (ddd, *J* = 9.5, 3.5, 1.5 Hz, 1H), 4.78 (d, *J* = 5.5 Hz, 1H), 4.23 (m, 1H), 4.14 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.48 (d, *J* = 1.5 Hz, 1H), 3.45 (dd, *J* = 8.0, 7.5 Hz, 1H), 1.98 (ddd, *J* = 14.0, 9.5, 9.5 Hz, 1H), 1.84 (ddd, *J* = 14.0, 3.5, 3.5 Hz, 1H), 1.82–1.73 (m, 4H), 1.67 (m, 1H), 1.56 (m, 1H), 1.29–1.14 (m, 3H), 1.08 (m, 2H). ^{13}C NMR (CDCl$_3$) δ 143.9, 128.4, 127.5, 125.7, 107.2, 75.5, 73.6, 70.7, 42.3, 41.7, 27.24, 27.18, 26.3, 25.6. TLC: R$_f$ 0.15 (hexane/EtOAc = 5:1). IR (neat): 3243, 2931, 2854, 1455, 1388, 1299, 1262, 1227, 1192, 1133, 1060, 1030, 1003, 966, 916, 889, 862, 780, 757, 701, 603, 555 cm^{-1}. HRMS Calcd for C$_{17}$H$_{24}$NaO$_3$: [M+Na]$^+$, 299.1623. Found: *m/z* 299.1620. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 99.9/0.1, flow rate = 5.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 11.1 min, t_{minor} = 15.0 min.

Procedure for synthesis of 6

The mixture of **5** (single diastereomer, 0.011 g, 0.039 mmol) and *p*-TsOH·H$_2$O (0.0037 g, 0.019 mmol) in CH$_3$OH (0.3 mL) and H$_2$O (0.3 mL) was was stirred at 80 °C for 12 h. The mixture was cooled to ambient temperature and concentrated in vacuo to remove CH$_3$OH. The residue was dissolved in CH$_2$Cl$_2$, dried over Na$_2$SO$_4$, and concentrated in vacuo. Purification by

flash silica gel column chromatography using EtOAc as an eluent gave **6** (0.0067 g, 95% yield).

4-Phenylbutane-1,2,4-triol (6): CAS RN [159974-69-3].
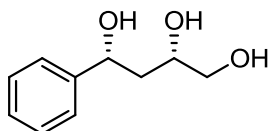
Colorless oil, 97% *ee*.

$[\alpha]_D^{23}$ +50.7 (*c* 1.38, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$) δ 7.37 (m, 4H), 7.29 (m, 1H), 5.01 (dd, *J* = 10.0, 3.0 Hz, 1H), 4.06 (m, 1H), 3.66 (ddd, *J* = 11.5, 6.0, 3.5 Hz, 1H), 3.52 (ddd, *J* = 11.5, 6.0, 5.5 Hz, 1H), 3.44 (d, *J* = 2.5 Hz, 1H), 2.91 (br s, 1H), 2.03 (t, *J* = 6.0 Hz, 1H), 1.95 (ddd, *J* = 14.5, 10.0, 10.0 Hz, 1H), 1.77 (ddd, *J* = 14.5, 3.0, 3.0 Hz, 1H). ^{13}C NMR (CDCl$_3$) δ 144.1, 128.6, 127.8, 125.6, 74.6, 72.3, 66.7, 41.4.   TLC: R$_f$ 0.27 (EtOAc).   IR (neat): 3355, 2919, 2874, 1727, 1686, 1599, 1540, 1494, 1454, 1417, 1287, 1207, 1105, 1051, 975, 916, 852, 758, 700, 483 cm^{-1}. HRMS Calcd for C$_{10}$H$_{14}$NaO$_3$: [M+Na]$^+$, 205.0841. Found: *m/z* 205.0833.   HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 95/5, flow rate = 3.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 19.2 min, t_{major} = 23.6 min.

The relative configuration of **6** was assigned as 1,3-*syn* by comparison of the NMR spectral data with those in the literature.[17]

Procedure for synthesis of 7[4b]

To a stirred solution of **3aa** (single diastereomer, 0.045 g, 0.16 mmol) and allyltrimethylsilane (0.096 mL, 0.60 mmol) in CH$_2$Cl$_2$ (3.5 mL) was added titanium tetrachloride (0.025 mL, 0.23 mmol) rapidly in −78 °C, and the mixture was stirred at −78 °C for 20 min.   CH$_3$OH (0.1 mL) was added to the solution, and the mixture was stirred at −78 °C for 30 min and subsequently warmed to ambient temperature.   H$_2$O was added to the solution, and the mixture was extracted with CH$_2$Cl$_2$.   The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and

concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 5/1) as an eluent gave **7** (0.050 g, 96% yield, dr = 4:1). The diastereomeric ratio was determined by HPLC analysis.

4-((1-Cyclohexylbut-3-en-1-yl)oxy)-3-hydroxy-1-phenylbutan-1-one (7).

The diastereomers could not be separated.

Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.97 (m, 2H), 7.58 (m, 1H), 7.48 (m, 2H), 5.89–5.78 (m, 1H), 5.11–5.01 (m, 2H), 4.37 (m, 1H), 3.61–3.56 (m, 1H), 3.54–3.49 (m, 1H), 3.25–3.16 (m, 2H), 3.14–3.09 (m, 2H), 2.33–2.21 (m, 2H), 1.79 (m, 1H), 1.73 (m, 2H), 1.65 (m, 2H), 1.50 (m, 1H), 1.25–1.09 (m, 3H), 1.01 (m, 2H). ^{13}C NMR (CDCl$_3$) δ 199.8, 199.7, 136.9, 135.64, 135.59, 133.4, 128.6, 128.1, 116.8, 84.3, 84.2, 73.1, 73.0, 67.4, 67.3, 42.0, 41.9, 41.1, 35.41, 35.37, 28.8, 28.7, 26.6, 26.3, 26.2. TLC: R$_f$ 0.20 (hexane/EtOAc = 5:1). IR (neat): 3454, 3071, 2925, 2852, 1685, 1598, 1581, 1449, 1355, 1279, 1211, 1181, 1110, 1002, 912, 753, 690, 464 cm^{-1}.
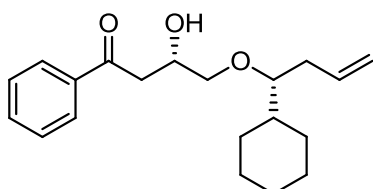
Major diastereomer: 97% *ee*.

HRMS Calcd for C$_{20}$H$_{28}$O$_3$: [M+H]$^+$, 317.2117. Found: *m/z* 317.2107. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 99/1, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 29.9 min, t_{major} = 38.8 min.
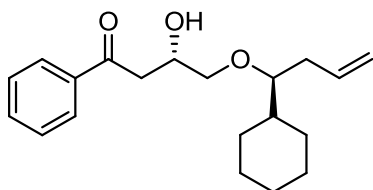
Minor diastereomer: 97% *ee*.

HRMS Calcd for $C_{20}H_{28}O_3$: $[M+H]^+$, 317.2117. Found: m/z 317.2107. HPLC (Daicel Chiralpak AD-H, hexane/i-PrOH = 99/1, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 27.9 min, t_{major} = 33.4 min.

ORTEP Drawing of 3da (major diastereomer)
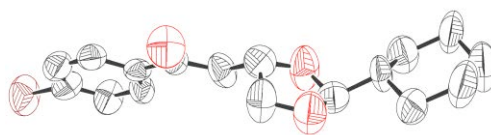
Identification code	**3da** (major diastereomer)
Empirical formula	$C_{17}H_{21}BrO_3$
Formula weight	353.25
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)
Unit cell dimensions	a = 5.710(5) Å α= 90°
	b = 33.88(3) Å β= 90.22(2)°
	c = 16.887(15) Å γ = 90°
Volume	3267(5) Å^3
Z	8
Density (calculated)	1.436 Mg/m^3
Absorption coefficient	2.524 mm^{-1}
F(000)	1456
Crystal size	0.50 x 0.30 x 0.20 mm^3
Theta range for data collection	1.21 to 27.43°.
Index ranges	-7<=h<=6, -43<=k<=38, -15<=l<=21
Reflections collected	18503
Independent reflections	12737 [R(int) = 0.1134]
Completeness to theta = 27.43°	94.5 %
Absorption correction	None
Max. and min. transmission	0.6323 and 0.3651
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	12737 / 1 / 757
Goodness-of-fit on F^2	0.709
Final R indices [I>2sigma(I)]	R1 = 0.0642, wR2 = 0.1349
R indices (all data)	R1 = 0.2420, wR2 = 0.1868
Absolute structure parameter	0.038(13)
Largest diff. peak and hole	0.408 and -0.331 e.Å^{-3}

ORTEP Drawing of 3da (minor diastereomer)
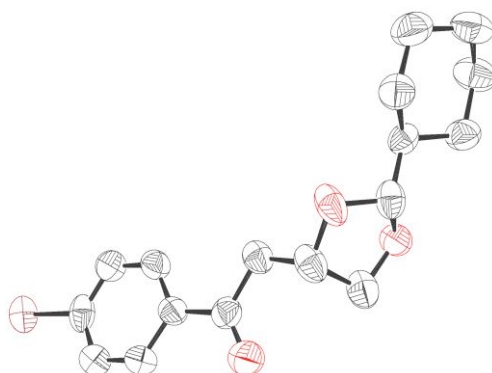
Identification code	**3da** (minor diastereomer)
Empirical formula	$C_{17}H_{21}BrO_3$
Formula weight	353.25
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)
Unit cell dimensions	a = 6.031(4) Å $\quad$ α= 90°
	b = 5.231(4) Å $\quad$ β= 91.551(12)°
	c = 25.812(18) Å $\quad$ γ = 90°
Volume	814.0(10) Å^3
Z	2
Density (calculated)	1.441 Mg/m^3
Absorption coefficient	2.532 mm^{-1}
F(000)	364
Crystal size	0.50 x 0.10 x 0.10 mm^3
Theta range for data collection	1.58 to 27.23°.
Index ranges	-3<=h<=7, -6<=k<=6, -33<=l<=32
Reflections collected	4931
Independent reflections	3447 [R(int) = 0.0329]
Completeness to theta = 27.23°	97.9 %
Absorption correction	None
Max. and min. transmission	0.7858 and 0.3641
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3447 / 1 / 190
Goodness-of-fit on F^2	0.941
Final R indices [I>2sigma(I)]	R1 = 0.0511, wR2 = 0.1258
R indices (all data)	R1 = 0.0784, wR2 = 0.1398
Absolute structure parameter	0.001(15)
Largest diff. peak and hole	0.507 and -0.410 e.Å^{-3}

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14. Aryl and alkenyl aldehydes proved to be much less reactive: reactions using benzaldehyde or cinnamaldehyde with **1a** gave the corresponding products in less than 10% yields, while electron-poor 4-(trifluoromethyl)benzaldehyde gave the acetal product in 70% yield with moderate stereoselectivities (dr = 0.9:1, 79% *ee* and 82% *ee*, respectively).

15. The absolute configuration of the minor diastereomer of **3da** was determined by X-ray analysis to be as follows;
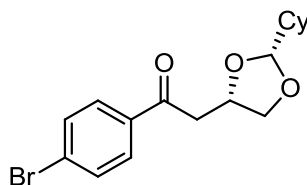
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Appendix

Design of Reaction Media for Nucleophilic Substitution Reactions by Using a Catalytic Amount of an Amphiphilic Imidazolium Salt in Water

Molecules of amphiphilic imidazolium salts assemble in water to form a hydrophobic membrane including an interface consisting of ammonium species.   Such an interface works as a reaction medium like an ionic liquid.   The author used the medium for nucleophilic substitution reactions between alkyl halides and anionic nucleophiles.   This procedure allowed the reactions to proceed efficiently in water without any organic solvent.

Appendix

Introduction

Reactions using ionic liquids as a solvent have received considerable attention.[1,2] The unique properties of ionic liquids, such as high polarity, non-coordinating nature, nonvolatility, and anisotropic aspects, provide several benefits for organic reactions, including reactions with polar organic compounds[3] or gases,[4,5b–d] organometallic reactions,[5] and even biocatalytic reactions.[2f,6] However, there are also some problems, which include the difficulty of isolating the product and the high cost for reaction media.[1]

To overcome such problems while keeping the merits, the author focused on the amphiphilicity of imidazolium salts with a hydrophobic long hydrocarbon chain.[7–9] The use of an amphiphilic imidazolium salt in water will align the molecules to construct an interface between water molecules and organic compounds efficiently, and the interface might be a practical reaction medium for the reactions mentioned above.[7–11] In this Chapter, the author describes nucleophilic substitutions performed in the medium constructed by a catalytic amount of imidazolium salts in water.[2]

Results and Discussion

The author examined the reaction between benzyl bromide (**1a**) and phthalimide potassium salt (**2a**) using 10 mol % of 1-hexadecyl-3-phenylmethyl-1*H*-imidazolium bromide (**4a**) in water (Scheme 1). The reaction gave *N*-benzylphthalimide (**3a**) in 96% yield. When the reaction was examined in the absence of **4a**, only a trace amount of the product was obtained. Water is also essential for this reaction: in the absence of water, the rate of the reaction became slower. The combination of **4a** and water was shown to be indispensable for the efficient reaction.

Scheme 1. Nucleophilic Substitution Reaction between Benzyl Bromide (**1a**) and Phthalimide Potassium Salt (**2a**).

1a (0.5 mmol)   2a (0.6 mmol)

(**4a**, 0.05 mmol)

H_2O (5 mmol), 25 °C, 2 h

3a
96%
without **4a**: trace
without H_2O: 72%
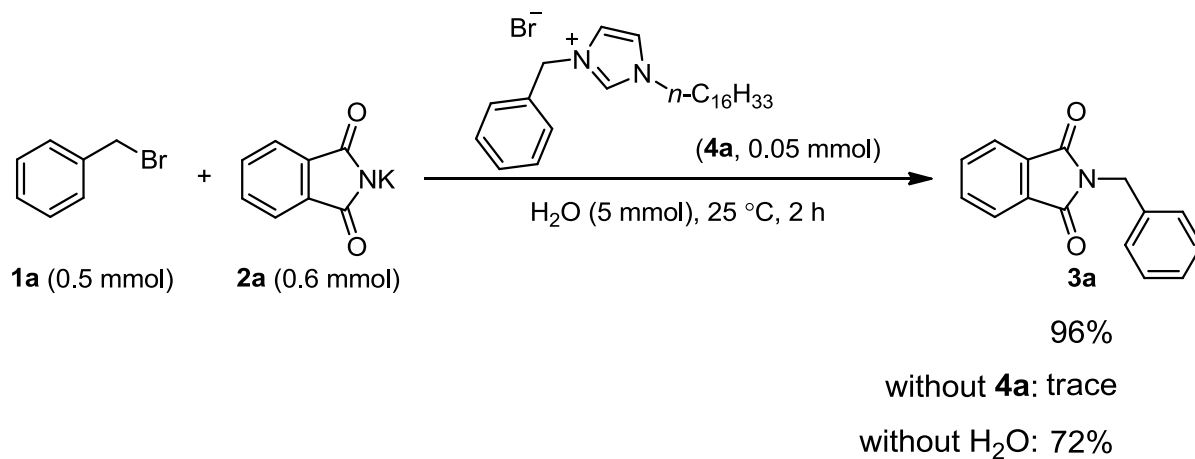
Table 1. Nucleophilic Substitution Reaction in Water between **1a** and **2a** in the Presence of Imidazolium Salts (**4**) Having Various Alkyl Chaina as Hydrophobic Group.[a]

1a   2a

(**4**, 10 mol %)

H_2O, 25 °C, 2 h

3a
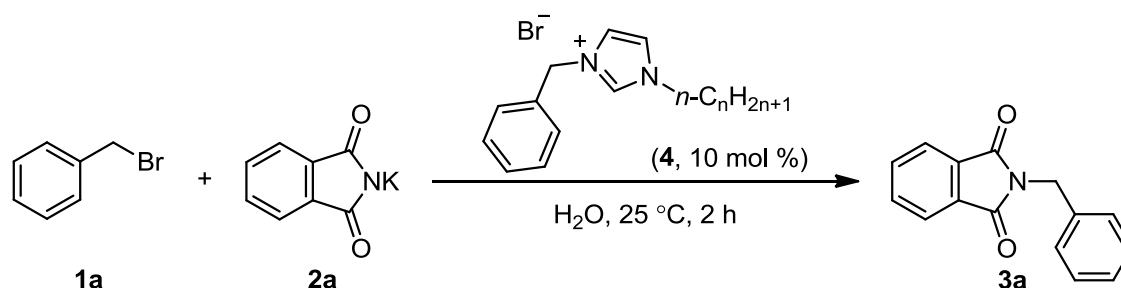
entry	n	4	yield (%)[b]
1	1	**4b**	18
2	4	**4c**	36
3	10	**4d**	96
4	16	**4a**	96

[a] Reactions were run using benzyl bromide (**1a**, 0.5 mmol), phthalimide potassium salt (**2a**, 0.6 mmol), the imidazolium salt **4** (0.05 mmol), and H_2O (5.0 mmol). [b] Yields were determined by ^{1}H NMR.

Appendix

The lengths of an alkyl chain on 1-alkyl-3-phenylmethyl-1*H*-imidazolium bromide **4** were arranged from C1 to C16 (Table 1).   Among them, imidazolium salts **4a** and **4d** with the long alkyl chain (C10 and C16) afforded the desired product **3a** in good yields (Table 1, entries 3 and 4).

Table 2. Effects of Substituents on Imidazolium Salts for the Nucleophilic Substitution Reaction in Water between **1a** and **2a**.[a]
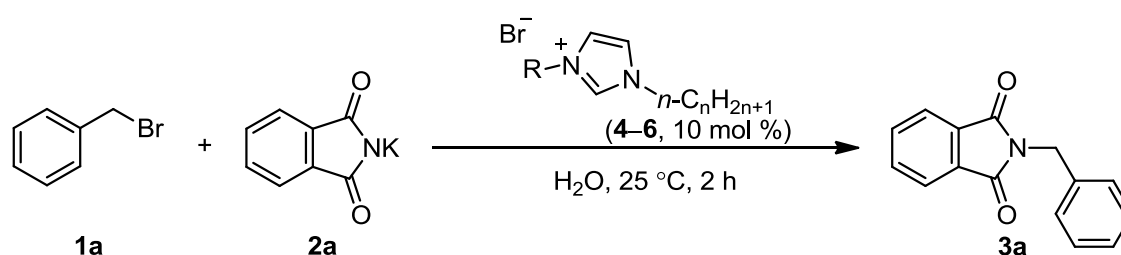
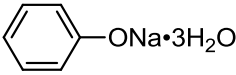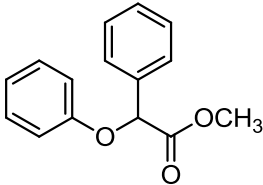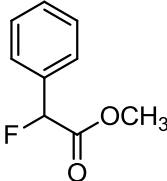| entry	imidazolium salt		yield (%)[b]
1		**4d**	96
2		**5**	96
3		**6a**	37
4		**6b**	44

[a] Reactions were run using benzyl bromide (**1a**, 0.5 mmol), phthalimide potassium salt (**2a**, 0.6 mmol), the imidazolium salt **4–6** (0.05 mmol), and H_2O (5.0 mmol).   [b] Yields were determined by ^1H NMR.

The author then examined the effect of the second substituent in the imidazolium salts (Table 2). 1-Decyl-3-cyclohexylmethyl-1*H*-imidazolium bromide (**5**) was effective for this reaction to the same degree as **4d** (Table 2, entries 1 and 2), but 1-decyl-3-methyl-1*H*-imidazolium bromide (**6a**) was less effective (Table 2, entry 3). Even when the alkyl chain was longer than that of **6a**, the yield was still low (**6b**, Table 2, entry 4). These results suggest that **4d** or **5** assembles in water to form an aggregation including a "hydrophobic cationic layer" in which the reaction proceeds (Scheme 2), but in the case of **6a** or **6b**, the imidazolium part may not be hydrophobic enough to perform an organic reaction of the substrate **1a**.

Scheme 2. Formation of Reaction Media by the Self-Assembly of **4d**.
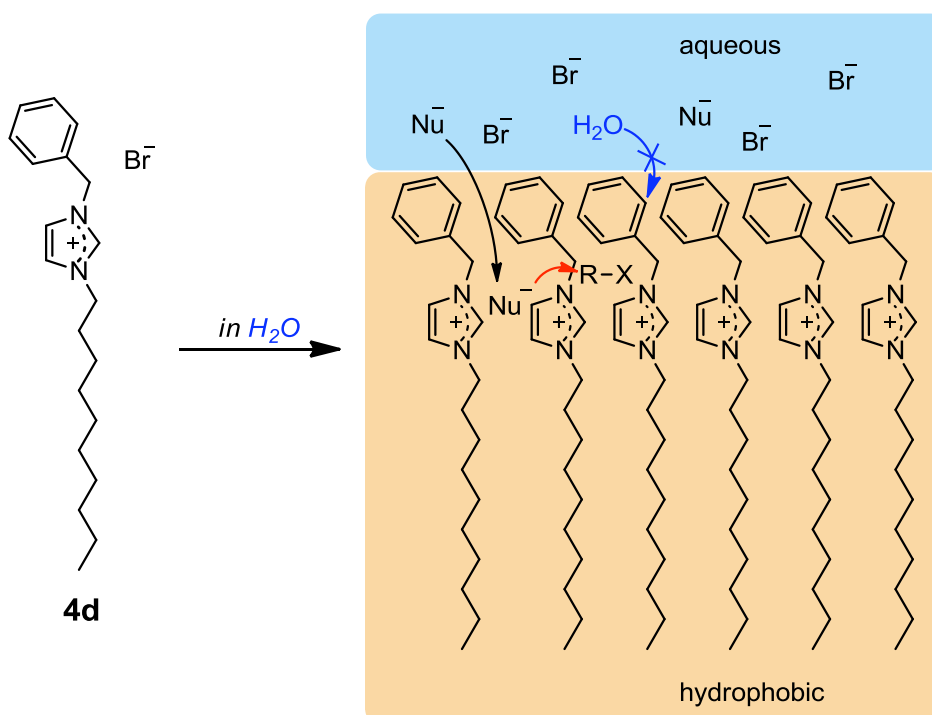
Appendix

The author also investigated the reactions of phthalimide potassium salt (**2a**) with the other electrophiles (**1b–1k**) by using **4d** (Table 3).   Allylic and propargylic bromides (**1b–1e**) underwent the reaction to give the corresponding products (**3b–3e**) in moderate to good yields (Table 3, entries 2–5), while a non-activated octyl bromide (**1f**) and mesylate (**1f'**) were poorly reactive (Table 3, entries 6 and 7).   Reactions with α-bromoesters (**1g–1k**) also took place efficiently to produce the corresponding α-amino acid derivatives (**3g–3k**, Table 3, entries 8–12).   Especially, *tert*-butyl bromoacetate (**1h**) was highly reactive under the condition to give a glycine derivative (**3h**) quantitatively (Table 3, entry 9).   In this case, the amount of **4d** could be decreased to only 1 mol % without any loss of the yield.   This low loading of **4d** seems to be achieved due to its self-assembly and due to the hydrophobic effect of organic compounds in water.[10]   As to secondary bromides, although α-bromopropionic acid esters (**1i**, **1j**) were poorly reactive (Table 3, entries 10 and 11), methyl α-bromophenylacetate (**1k**) gave a phenylglycine derivative (**3k**) in good yield (Table 3, entry 12).
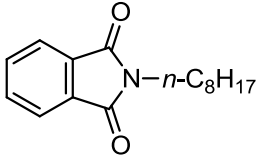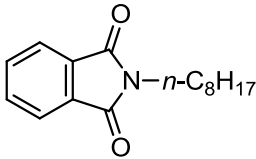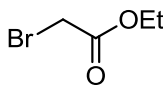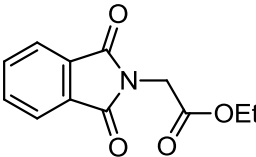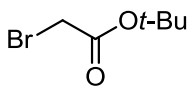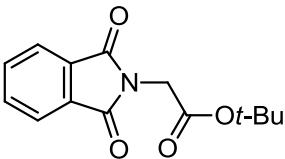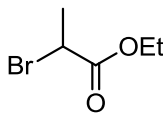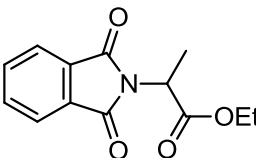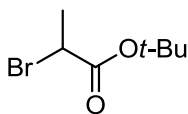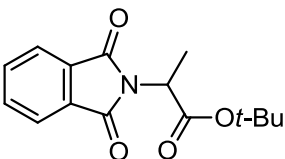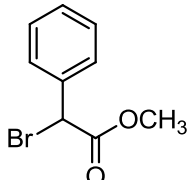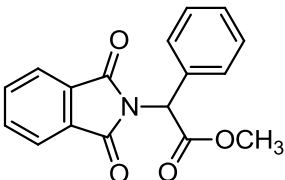
The author subsequently investigated the reactions of various water-soluble anionic nucleophiles (**2b–2e**) with α-bromoesters (**1h**, **1k**) by using **4d** (Table 4).   Sodium azide (**2b**) reacted with **1h** and **1k** to give the products **7a** and **7b** in excellent yields (Table 4, entries 1 and 2).   Sodium benzenethiolate (**2c**) and sodium phenoxide (**2d**) reacted with both **1h** and **1k** to afford the corresponding products (**7c–7f**) in moderate to good yields (Table 4, entries 3–6).   Although a harsher condition was required, a fluorination reaction of **1k** with cesium fluoride could also be performed to give the α-fluoroester (**7g**) in acceptable yield (Table 4, entry 7).

Table 3. Nucleophilic Substitution Reaction in Water between Various Electrophiles **1** and **2a** in the Presence of **4d**.[a]
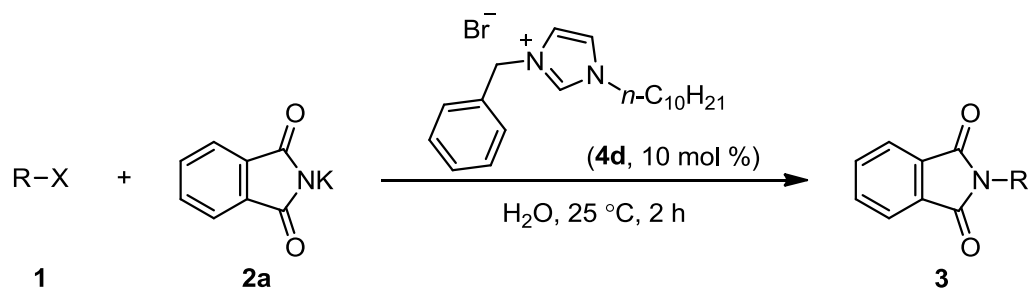
entry	R–X	1	product	3	yield (%)[b]
1		**1a**		**3a**	96
2		**1b**		**3b**	28
3		**1c**		**3c**	60
4		**1d**		**3d**	55
5		**1e**		**3e**	82

Table 3. (Continued)

6	n-C$_8$H$_{17}$Br	**1f**		**3f**	4
7	n-C$_8$H$_{17}$OMs	**1f'**		**3f**	16
8[c]		**1g**		**3g**	77
9		**1h**		**3h**	99
10		**1i**		**3i**	16
11		**1j**		**3j**	10
12		**1k**		**3k**	70

[a] Reactions were run using the electrophile **1** (0.5 mmol), phthalimide potassium salt (**2a**, 0.6 mmol), imidazolium salt **4d** (0.05 mmol), and H$_2$O (5.0 mmol). [b] Isolated yields. [c] Reaction was run using 1 mol % of **4d** (0.005 mmol).

Table 4. Nucleophilic Substitution Reaction in Water between α-Bromoesters (**1h**, **1k**) and Various Nucleophiles **2** in the Presence of **4d**.[a]
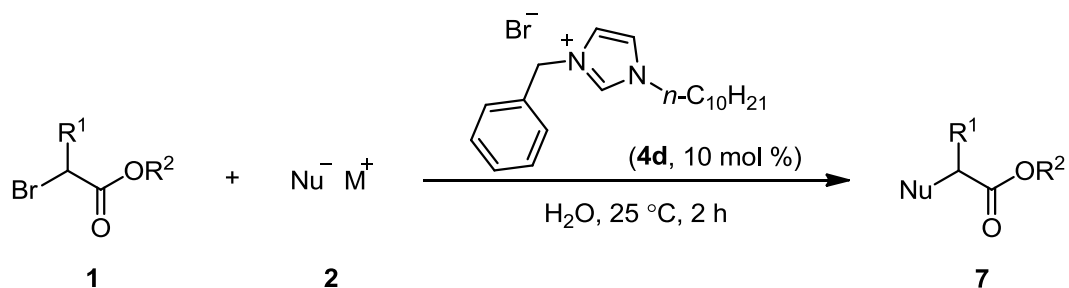
entry	nucleophile	2	R^1	R^2	1	product	7	yield (%)[b]
1	NaN$_3$	**2b**	H	t-Bu	**1h**		**7a**	99
2	NaN$_3$	**2b**	Ph	Me	**1k**		**7b**	92
3	—SNa	**2c**	H	t-Bu	**1h**		**7c**	47
4	—SNa	**2c**	Ph	Me	**1k**		**7d**	40
5	—ONa•3H$_2$O	**2d**	H	t-Bu	**1h**		**7e**	85

Table 4. (Continued)

6	Ph—ONa·3H₂O	**2d**	Ph	Me	**1k**		**7f**	93
7[c]	CsF	**2e**	Ph	Me	**1k**		**7g**	53

[a] Reactions were run using the α-bromoester **1** (0.5 mmol), the nucleophile **2** (0.6 mmol), imidazolium salt **4d** (0.05 mmol), and H_2O (5.0 mmol). [b] Isolated yields. [c] Reaction was performed at 100 °C for 3 h.

Conclusion

In conclusion, the author showed the usefulness of an imidazolium salt in water for construction of a reaction medium working as an ionic liquid. It assembled in water efficiently to form an interfacial medium in which nucleophilic substitution reactions took place. Furthermore, the hydrophobic effect of organic compounds might promote the reaction. These results suggest a new efficient reaction medium.

Experimental Section

Materials

Unless otherwise noted, commercially available reagents were used without purification.

General procedure for nucleophilic substitution reaction between alkyl halides 1 and anionic nucleophiles 2

To a 5-mL vial were added sequentially alkyl halides **1** (0.5 mmol), nucleophile **2** (0.6 mmol), imidazolium salt **4d** (0.05 mmol), and H$_2$O (0.09 mL, 5.0 mmol).   The mixture was stirred for 2 h in an oil bath maintained at 25 °C.   The reaction mixture was subsequently diluted with EtOAc, dried with anhydrous Na$_2$SO$_4$, and concentrated in vacuo.   Purification by flash silica gel column chromatography using hexane/EtOAc as an eluent afforded the corresponding product **3** or **7**.

Procedure for preparation of 1-hexadecyl-3-phenylmethyl-1*H*-imidazolium bromide (4a)

A mixture of 1-hexadecyl-1*H*-imidazole (0.015 g, 0.50 mmol) and benzyl bromide (0.071 mL, 0.60 mmol) was heated to 100 ºC for 2 h.   After the mixture was cooled to ambient temperature, the resulting solid was collected and washed with cooled Et$_2$O to give **4a** (0.23 g, 99% yield).

1-Hexadecyl-3-phenylmethyl-1*H*-imidazolium bromide (4a).
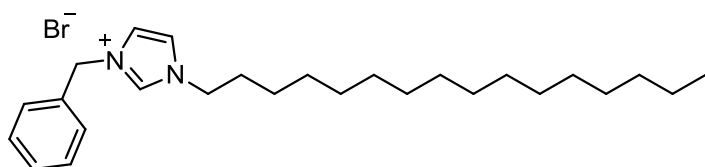
White solid.

^{1}H NMR (CDCl$_3$) δ 10.87 (m, 1H), 7.49 (m, 2H), 7.39 (m, 3H), 7.21 (m, 2H), 5.63 (s, 2H), 4.29 (t, *J* = 7.5 Hz, 2H), 1.91 (tt, *J* = 7.0 Hz, 7.0 Hz, 2H), 1.31 (m, 4H), 1.29–1.20 (m, 22H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 137.6, 132.9, 129.55, 129.47, 129.1, 121.5, 53.4, 50.3, 31.9, 30.2, 29.67, 29.66, 29.65, 29.62, 29.61, 29.55, 29.4, 29.3, 28.9, 26.3, 22.7, 14.1.   Mp. 74.5–75.1 °C.   IR (KBr): 3437, 3080, 2916, 2851, 1560, 1472, 1368, 1327, 1148, 837, 824, 735, 712, 679, 617 cm^{-1}.   HRMS Calcd for C$_{26}$H$_{43}$N$_2$: [2M+Br]$^+$, 845.6030. Found: *m/z* 845.6036. Anal. Calcd for C$_{26}$H$_{43}$BrN$_2$: C, 67.37; H, 9.35. Found: C, 67.29; H, 9.09.

Procedure for preparation of 1-methyl-3-phenylmethyl-1*H*-imidazolium bromide (4b)

A mixture of 1-methyl-1*H*-imidazole (0.16 g, 2.0 mmol) and benzyl bromide (0.25 mL, 2.1 mmol) was heated to 100 ºC for 2 h.   After the mixture was cooled to ambient temperature, Et₂O (2 mL) was added.   The mixture was subsequently refluxed, and the supernatant liquid was decanted off.   After these procedures were repeated several times, the residue was concentrated in vacuo to give **4b** (0.51 g, 100% yield).

1-Methyl-3-phenylmethyl-1*H*-imidazolium bromide (4b): CAS RN [65039-11-4].
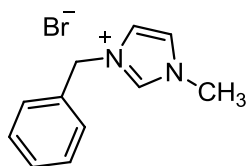
Purple oil.

^{1}H NMR (CDCl₃) δ 10.37 (s, 1H), 7.47 (m, 3H), 7.37–7.32 (m, 4H), 5.56 (s, 2H), 4.04 (s, 3H).

^{13}C NMR (CDCl₃) δ 137.3, 132.9, 129.5, 129.4, 129.0, 123.5, 121.8, 53.3, 36.7.

Procedure for preparation of 1-butyl-3-phenylmethyl-1*H*-imidazolium bromide (4c)

A mixture of 1-butyl-1*H*-imidazole (0.25 g, 2.0 mmol) and benzyl bromide (0.25 mL, 2.1 mmol) was heated to 100 ºC for 2 h.   After the mixture was cooled to ambient temperature, Et₂O (2 mL) was added.   The mixture was subsequently refluxed, and the supernatant liquid was decanted off.   After these procedures were repeated several times, the residue was concentrated in vacuo to give **4c** (0.61 g, 100% yield).

**1-Butyl-3-phenylmethyl-1*H*-imidazolium bromide (4c)**: CAS RN [642096-86-4].
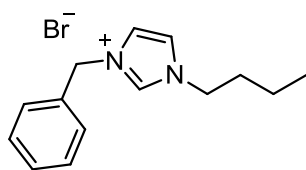
Orange oil.

^{1}H NMR (CDCl$_3$) δ 10.56 (s, 1H), 7.48 (m, 2H), 7.43 (t, *J* = 1.5 Hz, 1H), 7.39 (t, *J* = 1.5 Hz, 1H), 7.36–7.30 (m, 3H), 5.59 (s, 2H), 4.27 (t, *J* = 7.5 Hz, 2H), 1.86 (m, 2H), 1.33 (m, 2H), 0.90 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 136.8, 133.1, 129.4, 129.3, 128.9, 122.1, 121.9, 53.1, 49.8, 32.0, 19.4, 13.3.

Procedure for preparation of 1-decyl-3-phenylmethyl-1*H*-imidazolium bromide (4d)

A mixture of 1-decyl-1*H*-imidazole (0.25 g, 1.2 mmol) and benzyl bromide (0.16 mL, 1.3 mmol) was heated to 100 ºC for 2 h.   After the mixture was cooled to ambient temperature, Et$_2$O (2 mL) was added.   The mixture was subsequently refluxed, and the supernatant liquid was decanted off.   After these procedures were repeated several times, the residue was concentrated in vacuo to give **4d** (0.47 g, 100% yield).

1-Decyl-3-phenylmethyl-1*H*-imidazolium bromide (4d).
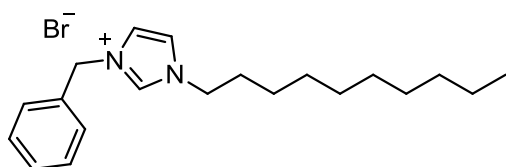
White solid.

^{1}H NMR (CDCl$_3$) δ 10.87 (s, 1H), 7.48 (m, 2H), 7.41–7.37 (m, 3H), 7.23 (m, 2H), 5.62 (s, 2H), 4.28 (t, *J* = 7.5 Hz, 2H), 1.90 (tt, *J* = 7.5 Hz, 7.5 Hz, 2H), 1.36–1.18 (m, 14H), 0.87 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 137.5, 132.9, 129.54, 129.45, 129.1, 121.5, 53.4, 50.3, 31.8, 30.2, 29.4, 29.3, 29.2, 28.9, 26.2, 22.6, 14.1.   Mp. 34–35 °C (deliquescent material).   IR (KBr): 3439, 3067, 2924, 2855, 1624, 1560, 1497, 1456, 1362, 1157, 712 cm^{-1}.   HRMS Calcd for C$_{20}$H$_{31}$N$_2$: [2M+Br]$^+$, 677.4152. Found: *m/z* 677.4144.

Procedure for preparation of 1-decyl-3-cyclohexylmethyl-1*H*-imidazolium bromide (5)

A mixture of 1-decyl-1*H*-imidazole (0.10 g, 0.5 mmol) and bromomethylcyclohexane (0.071 mL, 0.51 mmol) was heated to 100 ºC for 12 h.   After the mixture was cooled to ambient

temperature, Et$_2$O (2 mL) was added.   The mixture was subsequently refluxed, and the supernatant liquid was decanted off.   After these procedures were repeated several times, the residue was concentrated in vacuo to give **5** (0.20 g, 100% yield).

1-Decyl-3-cyclohexylmethyl-1*H*-imidazolium bromide (5).
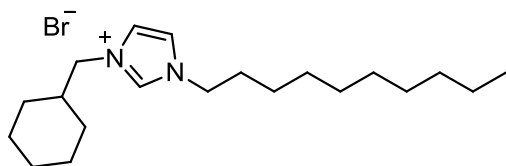
Colorless oil.

^{1}H NMR (CDCl$_3$) δ 10.74 (s, 1H), 7.27 (t, *J* = 2.0 Hz, 1H), 7.23 (t, *J* = 2.0 Hz, 1H), 4.36 (t, *J* = 7.5 Hz, 2H), 4.20 (d, *J* = 7.5 Hz, 2H), 1.95–1.81 (m, 3H), 1.75 (m, 2H), 1.67 (m, 2H), 1.62 (m, 2H), 1.32 (m, 4H), 1.29–1.11(m, 14H), 1.05 (dq, *J* = 3.0 Hz, 12.0 Hz, 2H), 0.86 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (CDCl$_3$) δ138.1, 122.0, 121.2, 55.9, 50.1, 38.5, 31.8, 30.3, 30.0, 29.4, 29.3, 29.2, 28.9, 26.2, 25.7, 25.3, 22.6, 14.1.   IR (neat): 3431, 3059, 2924, 2853, 1560, 1451, 1375, 1165, 779, 644 cm^{-1}.   HRMS Calcd for C$_{20}$H$_{37}$N$_2$: [2M+Br]$^+$, 689.5091. Found: *m/z* 689.5119.

Procedure for preparation of 1-decyl-3-methyl-1*H*-imidazolium bromide (6a)

A mixture of 1-methyl-1*H*-imidazole (0.17 mL, 2.1 mmol) and 1-boromodecane (0.44 g, 2.0 mmol) was heated to 100 ºC for 12 h.   After the mixture was cooled to ambient temperature, Et$_2$O (2 mL) was added.   The mixture was subsequently refluxed, and the supernatant liquid was decanted off.   After these procedures were repeated several times, the residue was concentrated in vacuo to give **6a** (0.61 g, 100% yield).

1-Decyl-3-methyl-1*H*-imidazolium bromide (6a): CAS RN [188589-32-4].
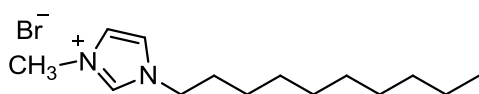
Colorless oil.

¹H NMR (CDCl₃) δ 10.39 (d, *J* = 6.5 Hz, 1H), 7.55 (m, 1H), 7.38 (m, 1H), 4.28 (t, *J* = 7.5 Hz, 2H), 4.10 (s, 3H), 1.88 (tt, *J* = 7.5 Hz, 7.5 Hz, 2H), 1.35–1.15 (m, 14H), 0.84 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (CDCl₃) δ 137.4, 123.5, 121.7, 50.1, 36.7, 31.7, 30.2, 29.33, 29.26, 29.1, 28.9, 26.2, 22.5, 14.0.

Procedure for preparation of 1-hexadecyl-3-methyl-1*H*-imidazolium bromide (6b)

A mixture of 1-methyl-1*H*-imidazole (0.84 mL, 11 mmol) and 1-boromohexadecane (3.1 g, 10 mmol) was heated to 100 ºC for 21 h.   Et₂O (10 mL) was added, and the resulting mixture was refluxed.   After the mixture was cooled to ambient temperature, the precipitate was collected and washed with cooled Et₂O to give **6b** (3.9 g, 100% yield).

1-Hexadecyl-3-methyl-1*H*-imidazolium bromide (6b): CAS RN [132361-22-9].
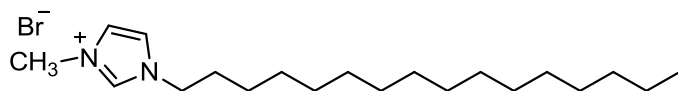
White solid.

¹H NMR (CDCl₃) δ 10.41 (s, 1H), 7.34 (t, *J* = 2.0 Hz, 1H), 7.25 (t, *J* = 2.0 Hz, 1H), 4.31 (t, *J* = 7.5 Hz, 2H), 4.12 (s, 3H), 1.90 (tt, *J* = 7.5 Hz, 7.5 Hz, 2H), 1.38–1.20 (m, 26H), 0.87 (t, *J* = 7.5 Hz, 3H).   ¹³C NMR (CDCl₃) δ 138.0, 123.1, 121.5, 50.3, 36.8, 31.9, 30.2, 29.7, 29.62, 29.61, 29.56, 29.5, 29.33, 29.32, 28.9, 26.2, 22.6, 14.1.   Mp. 62.0–63.0 °C.

Characterization Data of Products

2-(Phenylmethyl)-1*H*-isoindole-1,3(2*H*)-dione (3a): CAS RN [2142-01-0].
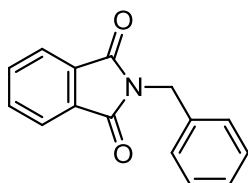
White solid.

^{1}H NMR (CDCl$_3$) δ 7.85 (m, 2H), 7.71 (m, 2H), 7.44 (m, 2H), 7.32 (m, 2H), 7.26 (m, 1H), 4.85 (s, 2H). ^{13}C NMR (CDCl$_3$) δ 168.0, 136.3, 134.0, 132.1, 128.7, 128.6, 127.8, 123.3, 41.6.   Mp. 114.7–115.2 °C.

2-(Prop-2-enyl)-1*H*-isoindole-1,3(2*H*)-dione (3b): CAS RN [5428-09-1].
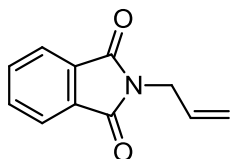
White solid.

^{1}H NMR (CDCl$_3$) δ 7.86 (m, 2H), 7.72 (m, 2H), 5.89 (ddt, *J* = 17.0 Hz, 10.5 Hz, 5.5 Hz, 1H), 5.25 (ddt, *J* = 17.0 Hz, 1.0 Hz, 1.5 Hz, 1H), 5.20 (ddt, *J* = 10.5 Hz, 1.0 Hz, 1.5 Hz, 1H), 4.30 (ddd, *J* = 5.5 Hz, 1.5 Hz, 1.5 Hz, 2H). ^{13}C NMR (CDCl$_3$) δ 167.9, 134.0, 132.1, 131.5, 123.3, 117.7, 40.0.   Mp. 64.8–65.1 °C.

2-[(2*E*)-3-phenylprop-2-enyl]-1*H*-isoindole-1,3(2*H*)-dione (3c): CAS RN [17480-07-8].
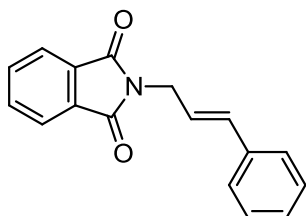
White solid.

^{1}H NMR (CDCl$_3$) δ 7.87 (m, 2H), 7.72 (m, 2H), 7.35 (m, 2H), 7.28 (m, 2H), 7.22 (m, 1H), 6.66 (d, *J* = 16.0 Hz, 1H), 6.26 (dt, *J* = 16.0 Hz, 6.5 Hz, 1H), 4.45 (dd, *J* = 6.5 Hz, 1.0 Hz, 2H). ^{13}C NMR (CDCl$_3$) δ 168.0, 136.3, 134.0, 133.8, 132.2, 128.5, 127.9, 126.5, 123.3, 122.7, 39.7.   Mp. 150.5–151.2 °C.

2-(Prop-2-ynyl)-1*H*-isoindole-1,3(2*H*)-dione (3d): CAS RN [7223-50-9].
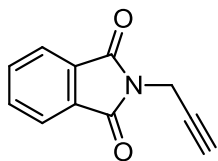
White solid.

^{1}H NMR (CDCl$_3$) δ 7.89 (m, 2H), 7.74 (m, 2H), 4.46 (d, *J* = 2.5 Hz, 2H), 2.22 (t, *J* = 2.5 Hz, 1H).

^{13}C NMR (CDCl$_3$) δ 167.0, 134.2, 132.0, 123.6, 77.2, 71.5, 27.0.   Mp. 149.0–149.9 °C.

2-(3-Phenylprop-2-ynyl)-1*H*-isoindole-1,3(2*H*)-dione (3e): CAS RN [4656-94-4].
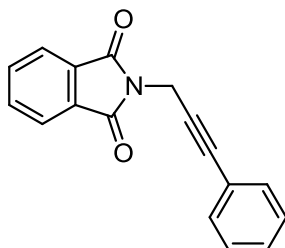
White solid.

^{1}H NMR (CDCl$_3$) δ 7.90 (m, 2H), 7.74 (m, 2H), 7.42 (m, 2H), 7.31–7.25 (m, 3H), 4.68 (s, 2H).

^{13}C NMR (CDCl$_3$) δ 167.1, 134.2, 132.1, 131.9, 128.5, 128.2, 123.5, 122.3, 83.0, 82.6, 27.9.

Mp. 149.0–150.0 °C.

2-Octyl-1*H*-isoindole-1,3(2*H*)-dione (3f): CAS RN [59333-62-9].
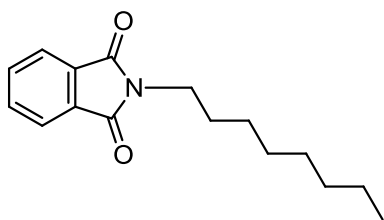
White solid.

^{1}H NMR (CDCl$_3$) δ 7.83 (m, 2H), 7.70 (m, 2H), 3.67 (t, *J* = 7.5 Hz, 1H), 1.66 (tt, *J* = 7.5 Hz, 7.5 Hz, 2H), 1.37–1.20 (m, 10H), 0.86 (t, *J* = 7.0 Hz, 3H).   ^{13}C NMR (CDCl$_3$) δ 168.5, 133.8, 132.2, 123.1, 38.1, 31.8, 29.1, 28.6, 26.9, 22.6, 14.0.   Mp. 45.5–46.0 °C.

Appendix

Ethyl 2-(1,3-dioxoisoindolin-2-yl)acetate (3g): CAS RN [6974-10-3].
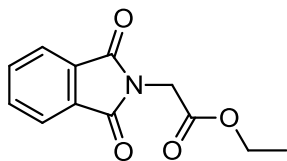
White solid.

^{1}H NMR (CDCl$_3$) δ 7.89 (m, 2H), 7.75 (m, 2H), 4.44 (s, 2H), 4.23 (q, J = 7.0 Hz, 2H), 1.29 (t, J = 7.0 Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 167.5, 167.2, 134.2, 132.0, 123.6, 61.9, 38.9, 14.1.   Mp. 112.0–112.5 °C.

tert-Butyl 2-(1,3-dioxoisoindolin-2-yl)acetate (3h): CAS RN [6297-93-4].
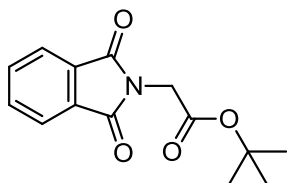
White solid.

^{1}H NMR (CDCl$_3$) δ 7.88 (m, 2H), 7.74 (m, 2H), 4.34 (s, 2H), 1.46 (s, 9H). ^{13}C NMR (CDCl$_3$) δ 167.6, 166.3, 134.1, 132.1, 123.5, 82.8, 39.7, 28.0.   Mp. 96.0–96.8 °C.

Ethyl 2-(1,3-dioxoisoindolin-2-yl)propanoate (3i): CAS RN [14380-86-0].
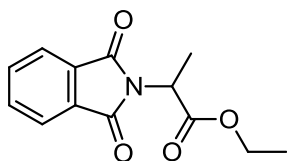
White solid.

^{1}H NMR (CDCl$_3$) δ 7.86 (m, 2H), 7.73 (m, 2H), 4.96 (q, J = 7.5 Hz, 1H), 4.20 (m, 2H), 1.69 (d, J = 7.5 Hz, 3H), 1.23 (t, J = 7.0 Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 169.7, 167.4, 134.1, 131.9, 123.4, 61.8, 47.5, 15.2, 14.1.   Mp. 61.5–62.5 °C.

tert-Butyl 2-(1,3-dioxoisoindolin-2-yl)propanoate (3j): CAS RN [76517-88-9].
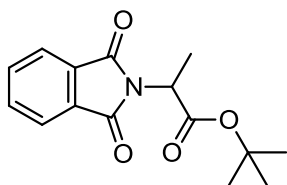
White solid.

^{1}H NMR (CDCl$_3$) δ 7.86 (m, 2H), 7.73 (m, 2H), 4.87 (q, _J_ = 7.5 Hz, 1H), 1.65 (d, _J_ = 7.5 Hz, 3H), 1.42 (s, 9H). ^{13}C NMR (CDCl$_3$) δ 168.7, 167.6, 134.0, 131.9, 123.4, 82.3, 48.3, 27.8, 15.3. Mp. 95.2–96.0 °C.

Methyl 2-(1,3-dioxoisoindolin-2-yl)-2-phenylacetate (3k): CAS RN [1082222-36-3].
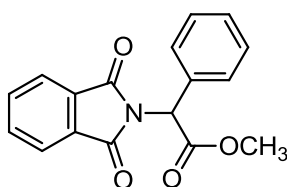
White solid.

^{1}H NMR (CDCl$_3$) δ 7.86 (m, 2H), 7.72 (m, 2H), 7.55 (m, 2H), 7.35 (m, 3H), 6.02 (s, 1H), 3.81(s, 3H). ^{13}C NMR (CDCl$_3$) δ 168.5, 167.1, 134.4, 134.2, 131.8, 129.7, 128.63, 128.56, 123.6, 55.8, 53.1.   Mp. 102.5–103.0 °C.

tert-Butyl 2-azidoacetate (7a): CAS RN [6367-36-8].
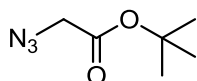
Colorless oil.

^{1}H NMR (CDCl$_3$) δ 3.75 (s, 2H), 1.50 (s, 9H). ^{13}C NMR (CDCl$_3$) δ 167.4, 83.1, 51.0, 28.0.

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Methyl 2-azido-2-phenylacetate (7b): CAS RN [409335-57-5].
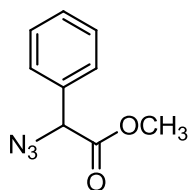
Pale yellow oil.

^{1}H NMR (CDCl$_3$) δ 7.41 (m, 5H), 4.98 (s, 1H), 3.78 (s, 3H). ^{13}C NMR (CDCl$_3$) δ 169.6, 133.8, 129.3, 129.1, 127.6, 65.3, 52.9.

tert-Butyl 2-(phenylthio)acetate (7c): CAS RN [63006-68-8].
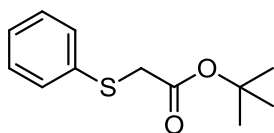
Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.95 (m, 2H), 7.68 (m, 1H), 7.58 (m, 2H), 4.04 (s, 2H), 1.36 (s, 9H). ^{13}C NMR (CDCl$_3$) δ 161.2, 139.0, 134.1, 129.1, 128.5, 83.6, 62.1, 27.7.

Methyl 2-phenyl-2-(phenylthio)acetate (7d): CAS RN [51256-38-3].
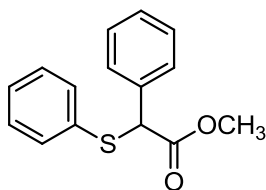
White solid.

^{1}H NMR (CDCl$_3$) δ 7.61 (m, 3H), 7.43 (m, 2H), 7.37 (m, 1H), 7.33 (m, 2H), 7.29 (m, 2H), 5.11 (s, 1H), 3.77 (s, 3H). ^{13}C NMR (CDCl$_3$) δ 165.3, 136.2, 134.2, 130.2, 129.9, 129.7, 128.6, 128.5, 127.8, 75.2, 53.2.   Mp. 108.0–109.0 °C.

tert-Butyl 2-phenoxyacetate (7e): CAS RN [36304-22-0].
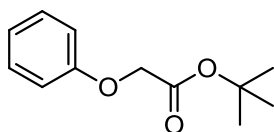
Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.29 (m, 2H), 6.98 (tt, J = 7.5 Hz, 1.0 Hz, 1H), 6.90 (m, 2H), 4.52 (s, 2H), 1.49 (s, 9H).   ^{13}C NMR (CDCl$_3$) δ 168.1, 157.9, 129.5, 121.5, 114.6, 82.3, 65.7, 28.0.

Methyl 2-phenoxy-2-phenylacetate (7f): CAS RN [32191-46-1].
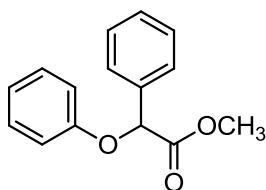
Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.58 (m, 2H), 7.39 (m, 3H), 7.28 (m, 2H), 6.98 (tt, J = 7.5 Hz, 1.0 Hz, 1H), 6.95 (m, 2H), 5.65 (s, 1H), 3.74 (s, 3H).   ^{13}C NMR (CDCl$_3$) δ 170.4, 157.3, 135.4, 129.6, 129.0, 128.8, 127.1, 121.8, 115.5, 78.6, 52.6.

Methyl 2-fluoro-2-phenylacetate (7g): CAS RN [17841-30-4].
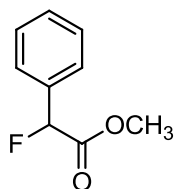
Colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.46 (m, 2H), 7.41 (m, 3H), 5.80 (d, J = 47.5 Hz, 1H), 3.79 (s, 3H).   ^{13}C NMR (CDCl$_3$) δ 169.0 (d, J = 27.8 Hz), 134.1 (d, J = 20.6 Hz), 129.7 (d, J = 2.0 Hz), 128.8, 126.7 (d, J = 6.2 Hz), 89.3 (d, J = 185.7 Hz), 52.6.   ^{19}F NMR (CDCl$_3$) δ −18.1.

Appendix

References and Notes

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Publication List

1. Parts of the present thesis have been published in the following journals.

Chapter 1 *N*-Alkylimidazole as Amphiphilic Organocatalyst: 'Catalytic' Morita–Baylis–Hillman Reaction on Water without Organic Solvent
Keisuke Asano and Seijiro Matsubara
Synlett **2009**, 35–38.

Morita–Baylis–Hillman Reaction on Water without Organic Solvent, Assisted by a 'Catalytic' Amount of Amphiphilic Imidazole Derivatives
Keisuke Asano and Seijiro Matsubara
Synthesis **2009**, 3219–3226.

Chapter 2 Amphiphilic Organocatalyst for Schotten–Baumann-Type Tosylation of Alcohols under Organic Solvent Free Condition
Keisuke Asano and Seijiro Matsubara
Org. Lett. **2009**, *11*, 1757–1759.

Chapter 3 Effects of a Flexible Alkyl Chain on a Ligand for CuAAC Reaction
Keisuke Asano and Seijiro Matsubara
Org. Lett. **2010**, *12*, 4988–4991.

Chapter 4 Effects of a Flexible Alkyl Chain on an Imidazole Ligand for Copper-Catalyzed Mannich Reactions of Terminal Alkynes
Takaaki Okamura, Keisuke Asano, and Seijiro Matsubara
Synlett, **2010**, 3053–3056.

Chapter 5 Asymmetric Catalytic Cycloetherification Mediated by Bifunctional Organocatalysts
Keisuke Asano and Seijiro Matsubara
J. Am. Chem. Soc. **2011**, *133*, 16711–16713.

2. Other publications not included in this thesis.

(1) C–H Bond Activation by Water on a Palladium or Platinum Metal Surface
Seijiro Matsubara, Keisuke Asano, Yuichi Kajita, and Mitsuru Yamamoto
Synthesis, **2007**, 2055–2059.

(2) Diastereoselective Nucleophilic Cyclopropanation of 1,2-Diketones and α-Ketoimines with Bis(iodozincio)methane
Kenichi Nomura, Keisuke Asano, Takuya Kurahashi, and Seijiro Matsubara
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(3) Stereoselective Preparation of 3-Alkanoylprop-2-en-1-ol Derivatives
Mutsumi Sada, Shizue Ueno, Keisuke Asano, Kenichi Nomura, and Seijiro Matsubara
Synlett, **2009**, 724–726.

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