Study on Phase-Transfer Catalytic Asymmetric Transformations of Esters using a Water and Alcohols as a Nucleophile

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Study on Phase-Transfer Catalytic Asymmetric Transformations of Esters using a Water and Alcohols as a Nucleophile

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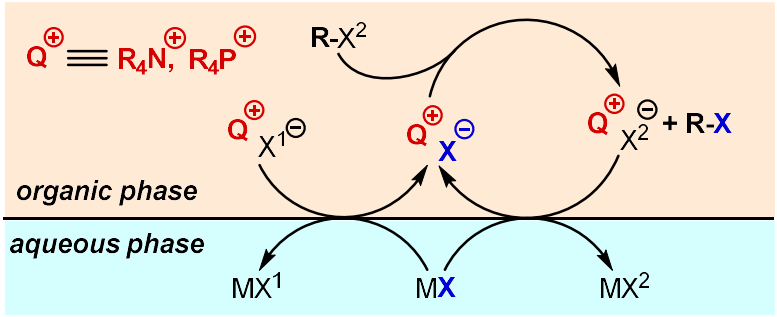
Chapter 1. General Introduction

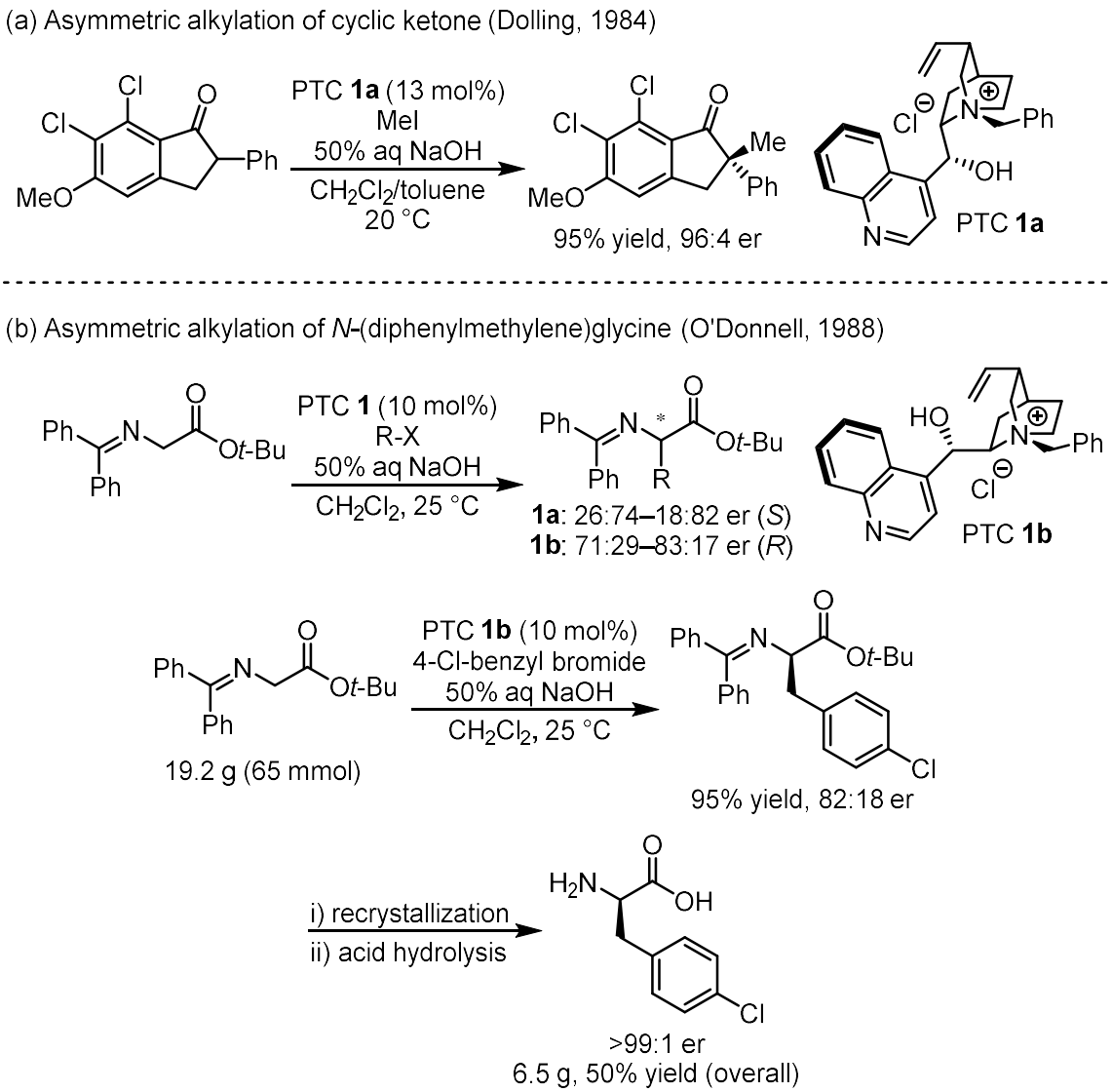
1.1. Phase-Transfer Catalysis in Asymmetric Organic Reactions

Phase-transfer catalysis is one of the powerful methods for the asymmetric organic synthesis in both industry and laboratory, because of its synthetic advantages such as operational simplicity, mild reaction conditions, and environmentally friendly nature of the biphasic reaction system.[1] In 1971, the term "phase-transfer catalysis" was defined by Starks in order to explain the role of tetraalkylammonium or phosphonium salts (Q^+X^-).[2] For instance, the S_N2 reaction of 1-chlorooctane with aq NaCN is significantly accelerated by the addition of hexadecyltributylphosphonium bromide. The most commonly used catalysts are quaternary ammonium or phosphonium salts, and their key role is the extraction of the anion from the aqueous phase into the organic phase via the formation of an ion pair.[3] The extracted anion, once in the organic phase, reacts with an organic substrate (Scheme 1).



Scheme 1. General reaction mechanism of phase-transfer catalysis under organic solvent-aqueous media biphasic system.

Owing to its usefulness in this organic synthesis, the phase-transfer reaction has become to be applied to asymmetric reactions using a chiral PTC. In 1975, asymmetric alkylation of cyclic *β*-keto ester or *β*-diketone was described by Fiaud as an attempt of the asymmetric phase-transfer catalysis.[4] After the early work on asymmetric reaction with a chiral quaternary ammonium salt, Dolling[5] and O'Donnell[6] separately reported the phase-transfer catalytic asymmetric alkylation using PTC derived from *cinchona* alkaloids (Scheme 2). Especially, asymmetric alkylation of *N*-(diphenylmethylene)glycine ester has been attracted much attention, because of the synthetic utility for the preparation of enantioenriched α-chiral amino acid.[1, 7]

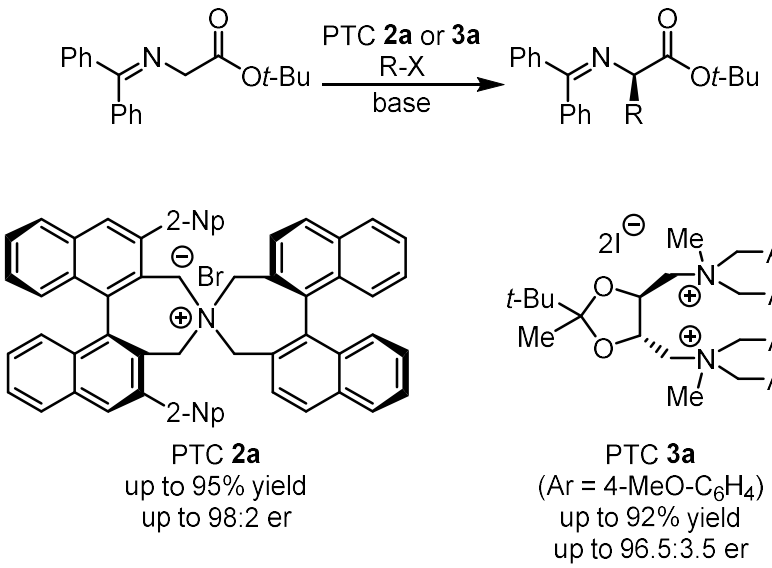


Scheme 2. Initial works on asymmetric alkylation using PTCs derived from *cinchona* alkaloids and the synthetic utility for the preparation of enantioenriched α-amino acid.

Corey[8] and Lygo[9] groups independently reported asymmetric alkylation reaction using a *cinchona* alkaloid derived PTC baring 9-anthyryl group or *O*-allylated quaternized cinchonidine with improvement from the previous results in terms of enantioselectivity. However, almost all of the successful chiral phase-transfer catalysts reported limited to *cinchona* alkaloid derivatives, which has a difficulty in rationally designing and fine-tuning.

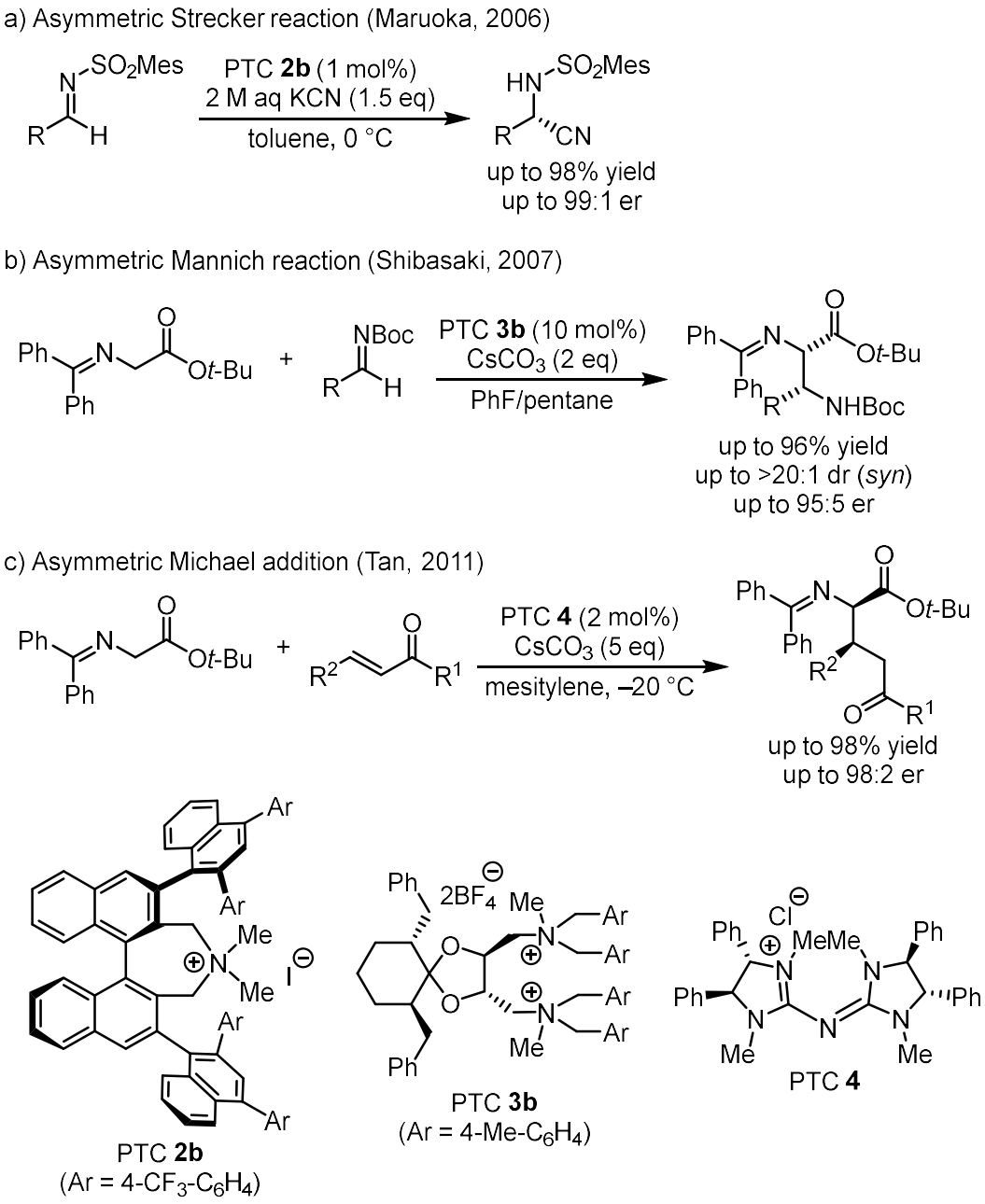
Maruoka and co-workers described a new *N*-spiro chiral quaternary ammonium salt (so-called Maruoka catalyst) and its successful application to the highly efficient catalytic enantioselective alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester.[10] In 2002, Shibasaki group developed dicationic chiral quaternary ammonium salts derived from a tartaric acid as new phase-transfer

catalysts, and applied in asymmetric alkylation (Scheme 3).[11]

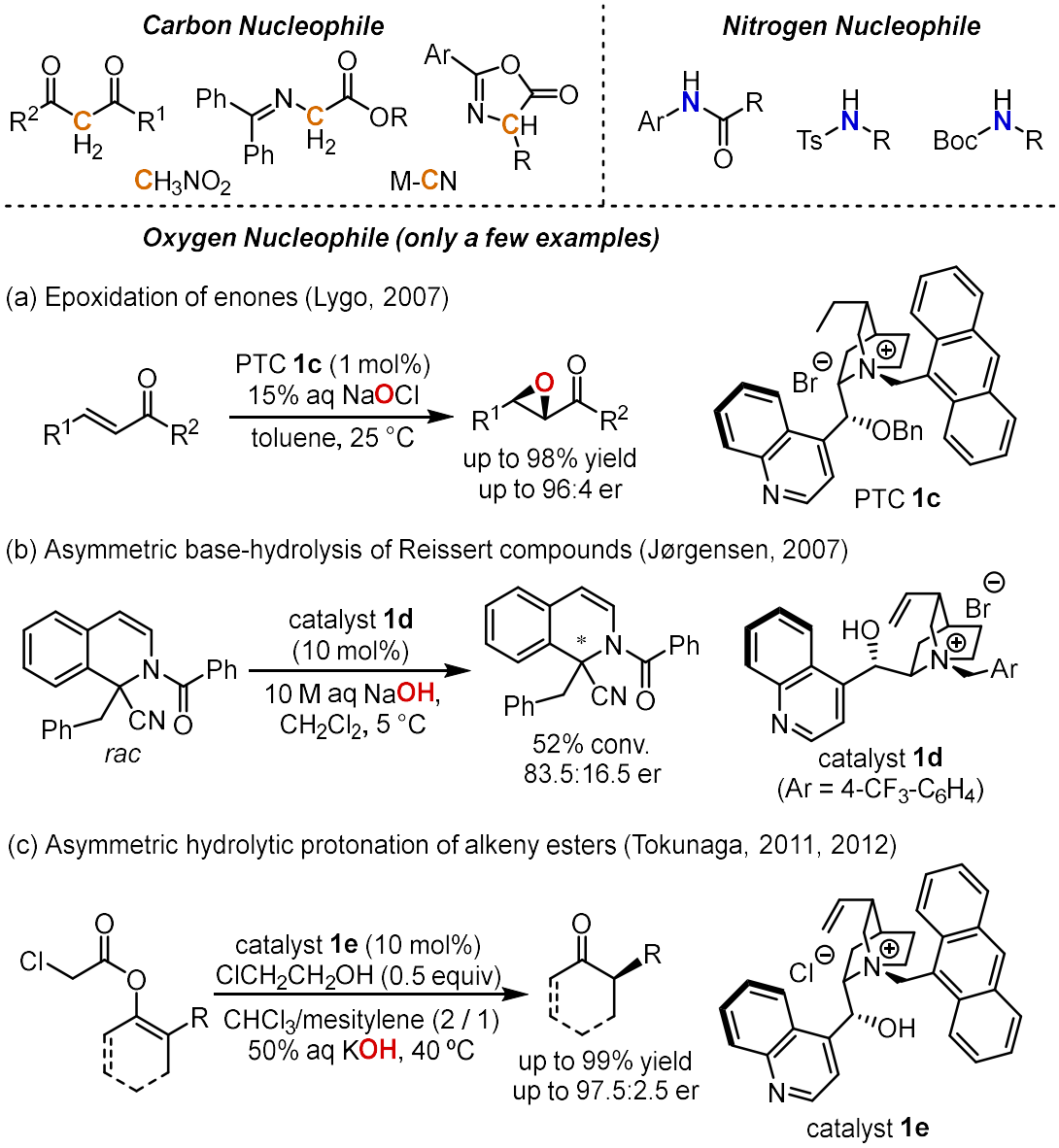


Scheme 3. Asymmetric alkylation with PTCs other than cinchona alkaloid derived catalysts.

In addition to the emergence of chiral PTCs with new structures, the phase-transfer catalysis has been studied not only in alkylation reactions but also in a wide variety of other organic reactions. For example, cyanation of *N*-protected imines[12] (Strecker reaction), Mannich reaction,[13] and Michael addition[14] were reported (Scheme 4). From the synthetic point of view, the availability of various nucleophiles as reaction substrates or reagents is desirable; however, there are very few examples of asymmetric reactions using water or alcohol as a nucleophile. Lygo group presented the asymmetric oxidative epoxidation of α,β-unsaturated ketones with aqueous NaOCl with PTC derived from dihydrocinchonidine (Scheme 5a).[15] Furthermore, chiral phase-transfer catalytic base-hydrolysis of Reissert compound was reported by Jørgensen (Scheme 5b).[16] This is the first report of stereoselective phase-transfer catalytic reaction with hydroxide anion as a nucleophile. In 2011 and 2012, Yamamoto, Tokunaga and co-workers developed a hydrolytic asymmetric protonation of alkenyl esters via phase-transfer catalyst (Scheme 5c).[17]



Scheme 4. Selected examples of the PTC catalyzed asymmetric reactions.



Scheme 5. Typical examples of carbon and nitrogen nucleophiles used in phase-transfer catalytic asymmetric reaction, and examples of PTC catalyzed reaction with oxygen nucleophiles.

1.2. Conformational Search for Asymmetric Organocatalysis

In the field of asymmetric reactions, identification of the transition state (TS) structures is important to reveal the origin of stereoselectivity. Unlike transition metal catalysts, however, noncovalent interactions, such as hydrogen bonding interactions, van der Waals interactions, and electrostatic interactions play an important role in constructing TS structures of organocatalysts, substrates, and reagents. Density functional theory (DFT) methods have been shown to be a powerful strategy for the prediction of the TS structures and reactivity of organocatalysts.[18] Numerous

organocatalytic asymmetric reactions have been investigated with DFT calculations; however, the attempt is still challenging due to their conformational flexibility arising from the complex noncovalent interactions and generation of numerous TS candidates.[19] Therefore, exploring the most stable TS structures has been a daunting task on organocatalytic asymmetric reactions.

Yoshizawa and Kamachi developed a DFT-based conformational analysis for phase-transfer catalytic asymmetric benzylation of glycine Schiff-base using the Maruoka catalyst, in order to determine the most stable TS structures leading to *R*- and *S*- products, and reveal the origin of the enantioselectivity.[20a] They elucidated the lowest-energy conformers for the major and minor product, which can explain the experimentally observed enantioselectivity and substituent effects of the catalyst. After the successful conformational exploring method for determining the most stable TS structures, their group developed a new conformational search program "ConFinder".[20b] This program is a low-cost and rapid conformational search program with semiempirical quantum mechanical (SQM) method and molecular mechanics (MM). This program employs the PM6-DH+ SQM method[21] which is able to provide accurate description of noncovalent interactions that are essential in the organocatalytic asymmetric reactions. In addition, ConFinder is based on the low-mode method of Kolossváry and Guida[22] with SQM calculation, whereby an initial structure is perturbed along one of its eigenvectors following of low-frequency vibrational modes (typically < 250 cm^{-1}). The resultant perturbed initial structures are subsequently subjected to MM minimization with the TINKER program[23] to obtain reasonable structures which could potentially employ new conformations, and this process is repeated to find new structures (Figure 1).

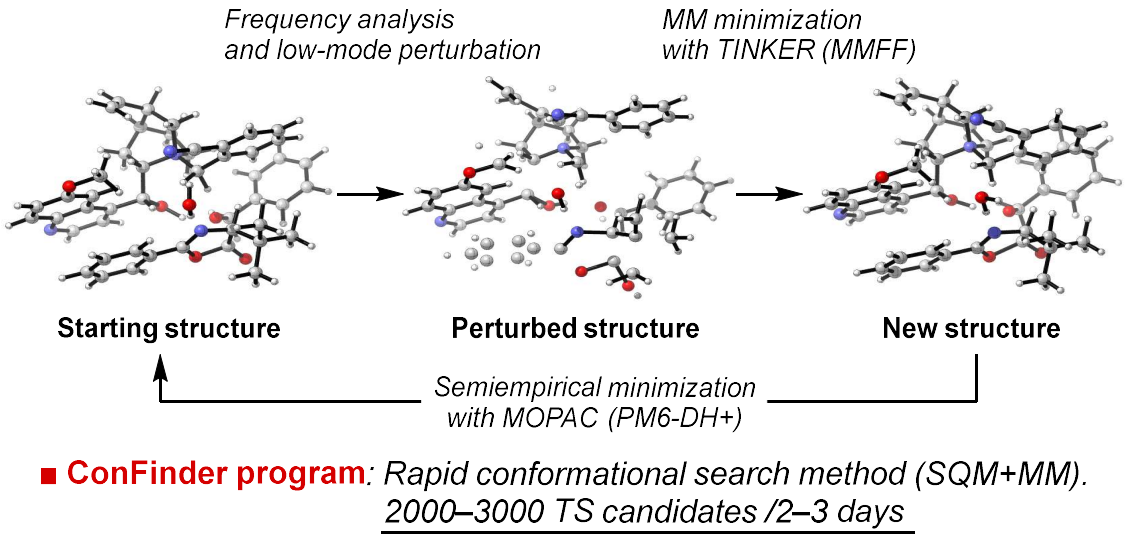


Figure 1. Schematic diagram of low-mode conformational search by ConFinder program.

Additionally, Kamachi and Yoshizawa developed a pseudo-transition state conformational search (PTSCS) using the ConFinder program, which is a potent calculation method for the theoretical investigation of TS structures for organocatalytic asymmetric reactions.[17b] PTSCS is a calculation method for exploring the most stable conformer of a TS analogue composed of reactants with an appropriate fixed length between the atoms involved in bond formation or dissociation.

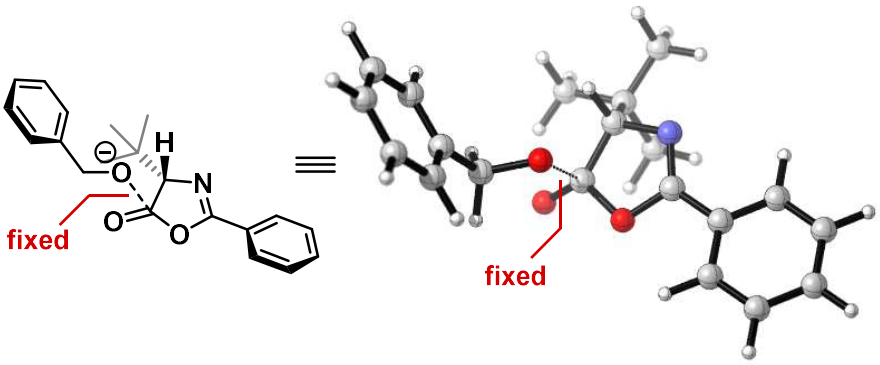
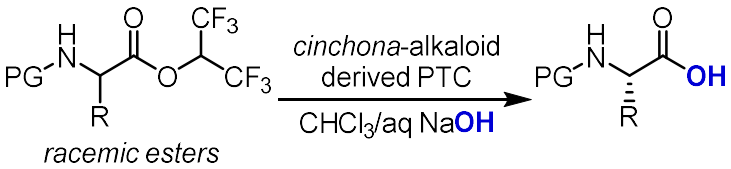


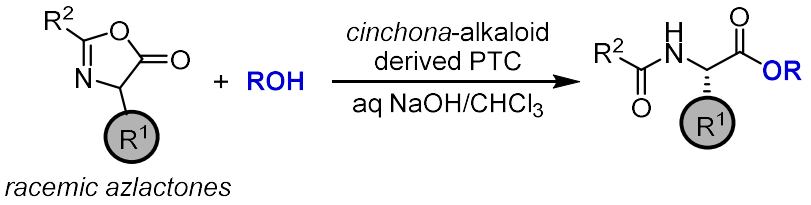
Figure 2. Pseudo-TS conformational search with bond fixing.

In this thesis, the author investigated phase-transfer catalytic asymmetric transformations using water and alcohols as an oxygen nucleophile. In chapter 2, dynamic kinetic resolution (DKR) of N-protected amino acid esters via phase-transfer catalytic base hydrolysis is described. Quaternary ammonium salts derived from quinine were used as chiral phase-transfer catalysts to promote the base hydrolysis of N-protected amino acid hexafluoroisopropyl esters in a $CHCl_3$/aq NaOH (Scheme 5).



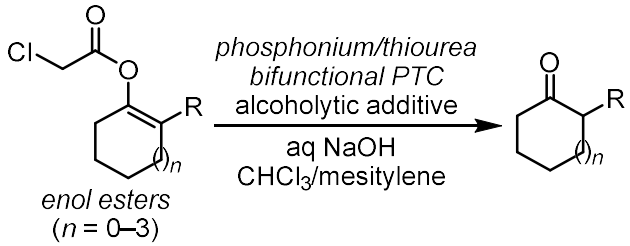
Scheme 5. Phase-transfer catalytic base-hydrolysis of N-protected amino acid esters.

Chapter 3 describes a phase-transfer catalytic asymmetric alcoholysis of azlactones via dynamic kinetic resolution, affording the corresponding α-chiral amino acid esters. In addition, synthetic applications and detailed mechanistic investigations are also shown (Scheme 6).



Scheme 6. Phase-transfer catalytic asymmetric alcoholysis of azlactones.

In Chapter 4, enantioselective protonation of enol esters with bifunctional phosphonium/thiourea PTCs derived from *t*-leucine is developed. The author clarified that bulky *t*-butyl group, phosphonium and thiourea moieties were necessary to achieve the high stereoselectivity by control experiments. In addition, mechanistic investigations indicated the PTC was converted to the corresponding betaine species, which served as a monomolecular catalyst (Scheme 7).



Scheme 7. Enantioselective protonation of enol esters with phosphonium/thiourea bifunctional PTCs.

4.5. References

[1] (a) Nelson, A. *Angew. Chem. Int. Ed.* **1999**, 38, 1583–1585. (b) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013–3028. (c) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506–517. (d) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518–525. (c) Ikunaka, M. *Org. Process Res. Dev.* **2008**, *12*, 698–709. (f) Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 4312–4348. (g) Tan, J.; Yasuda, N. *Org. Process Res. Dev.* **2015**, *19*, 1731–1746.

[2] Starks, C. M. *J. Am. Chem. Soc.* **1971**, 93, 195–199.

[3] Rabinovitz, M.; Cohen, Y.; Halpern, M. *Angew. Chem. Int. Ed.* **1986**, *25*, 960–970.

[4] Fiaud, J. C. *Tetrahedron Lett.* **1975**, *16*, 3495–3496.

[5] Dolling, U. H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446–447.

[6] O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353–2355.

[7] (a) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Keßeler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 788–824. (b) Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584–4671. (c) Larionov, V. A.; Stoletova, N. V.; Maleev, V. I. *Adv. Synth. Catal.* **2020**, *362*, 4325–

4367.

[8] Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595–8598.

[9] Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415.

[10] Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519–6520.

[11] Shibuguchi, T.; Fukuta, Y.; Akachi, Y.; Sekine, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 9539–9543.

[12] Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2548–2549.

[13] Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Ohshima, T.; Shibasaki, M. *Chem. Asian J.* **2007**, *2*, 794–801.

[14] Ma, T.; Fu, X.; Kee, C. W.; Zong, L.; Pan, Y.; Huang, K. W.; Tan, C. H. *J. Am. Chem. Soc.* **2011**, *133*, 2828–2831.

[15] Lygo, B.; Gardiner, S. D.; McLeod, M. C.; To, D. C. M. *Org. Biomol. Chem.* **2007**, *5*, 2283–2290.

[16] Frisch, K.; Jørgensen, K. A. *Org. Biomol. Chem.* **2007**, *5*, 2966–2974.

[17] (a) Yamamoto, E.; Nagai, A.; Hamasaki, A.; Tokunaga, M. *Chem. Eur. J.* **2011**, *17*, 7178–7182. (b) Yamamoto, E.; Gokuden, D.; Nagai, A.; Kamachi, T.; Yoshizawa, K.; Hamasaki, A.; Ishida, T.; Tokunaga, M. *Org. Lett.* **2012**, *14*, 6178–6181.

[18] (a) Cheong, P. H. Y.; Legault, C. Y.; Um, J. M.; Çelebi-Ölçüm, N.; Houk, K. N. *Chem. Rev.* **2011**, *111*, 5042–5137. (b) Hammar, P.; Marcelli, T.; Hiemstra, H.; Himo, F. *Adv. Synth. Catal.* **2007**, *349*, 2537–2548. (c) Çelebi-Ölçüm, N.; Aviyente, V.; Houk, K. N. *J. Org. Chem.* **2009**, *74*, 6944–6952. (d) Hirata, T.; Yamanaka, M. *Chem. Asian J.* **2011**, *6*, 510–516.

[19] (a) Odagi, M.; Furukori, K.; Yamamoto, Y.; Sato, M.; Iida, K.; Yamanaka, M.; Nagasawa, K. *J. Am. Chem. Soc.* **2015**, *137*, 1909–1915. (b) Trujillo, C.; Rozas, I.; Botte, A.; Connon, S. J. A *Chem. Commun.* **2017**, *53*, 8874–8877. (c) He, C. Q.; Simon, A.; Lam, Y. H.; Brunskill, A. P. J.; Yasuda, N.; Tan, J.; Hyde, A. M.; Sherer, E. C.; Houk, K. N. *J. Org. Chem.* **2017**, *82*, 8645–8650.

[20] (a) Kamachi, T.; Yoshizawa, K. *Org. Lett.* **2014**, *16*, 472–475. (b) Kamachi, T.; Yoshizawa, K. *J. Chem. Inf. Model.* **2016**, *56*, 347–353.

[21] Korth, M. *J. Chem. Theory Comput*. **2010**, *6*, 3808–3816.

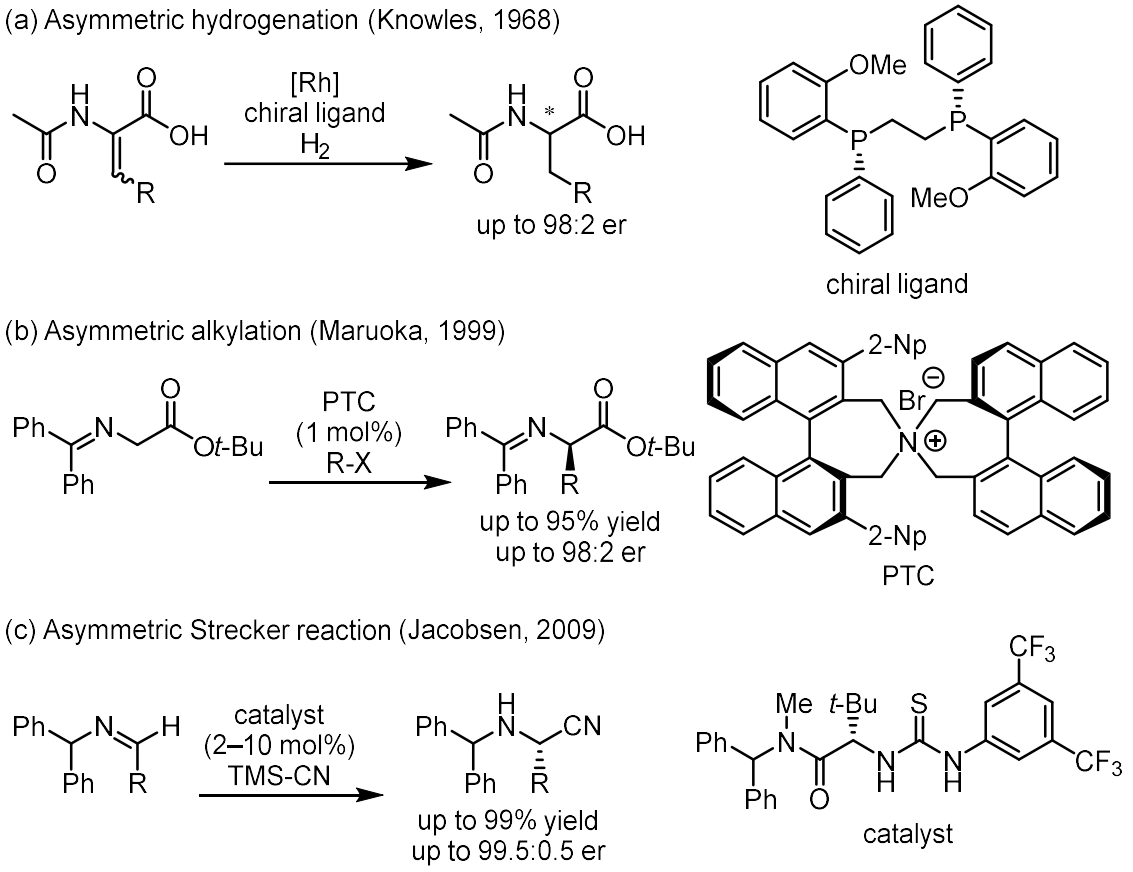
[22] Kolossváry, I.; Guida, W. C. *J. Am. Chem. Soc.* **1996**, *118*, 5011–5019.

[23] Ponder, J. W. *TINKER: Software Tools for Molecular Design*, version 7.1; Washington University School of Medicine: Saint Louis, MO,2015.

Chapter 2. Dynamic Kinetic Resolution of Amino Acid Esters via Phase-Transfer Catalytic Base-Hydrolysis

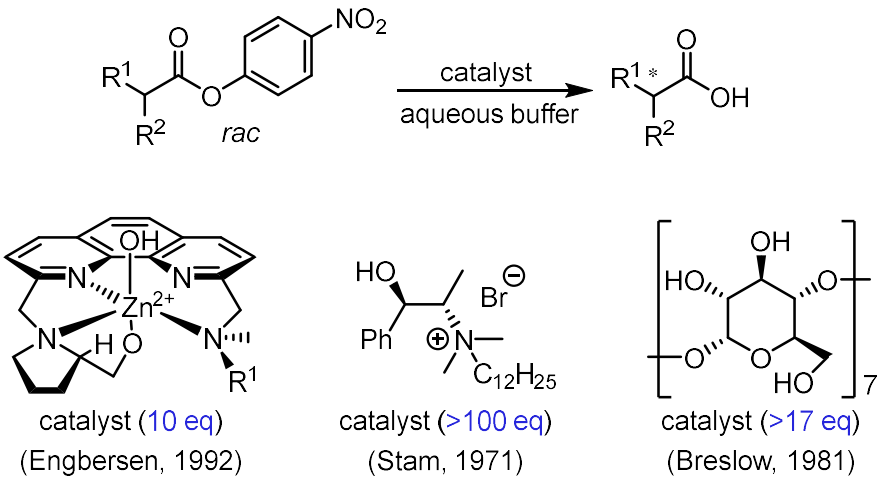
2.1. Introduction

Optically active amino acids are important building blocks of proteins and are widely used for the preparations of biologically active compounds and chiral catalysts.[1] Hence, numerous efficient asymmetric syntheses, such as asymmetric hydrogenation of amino acids,[2] alkylation of glycine derivatives[3], Strecker reactions[4] have been developed over the last few decades (Scheme 1).



Scheme 1. Asymmetric syntheses for optically active α-amino acids.

In addition, asymmetric hydrolysis of chiral esters is one of the most notable methods for the synthesis of optically active carboxylic acids in both laboratory and industrial scale.[5] Despite recent advances of asymmetric catalysis, however, only biocatalytic approaches achieved a high level of stereoselectivity in asymmetric ester hydrolysis. Indeed, synthetic catalysts such as metal complexes,[6] micellar catalysts,[7] and biomimetic catalysts[8] were reported, but they had limited to highly-reactive 4-nitropphhenyl esters as substrates, and required a large amount of catalyst loading (Scheme 2).



Scheme 2. Examples of synthetic catalysts for asymmetric ester hydrolysis.

Controlling the stereoselectivity of nucleophilic addition of water in ester hydrolysis with synthetic catalysts is a formidable challenge, probably because of the small size of water, formation of complex hydrogen bonding networks. The reaction mechanism of enzymatic asymmetric ester hydrolysis is generally ping-pong Bi-Bi reaction involving asymmetric transesterification and hydrolysis using the core Ser-His-Asp catalytic triad (Figure 1).[9]

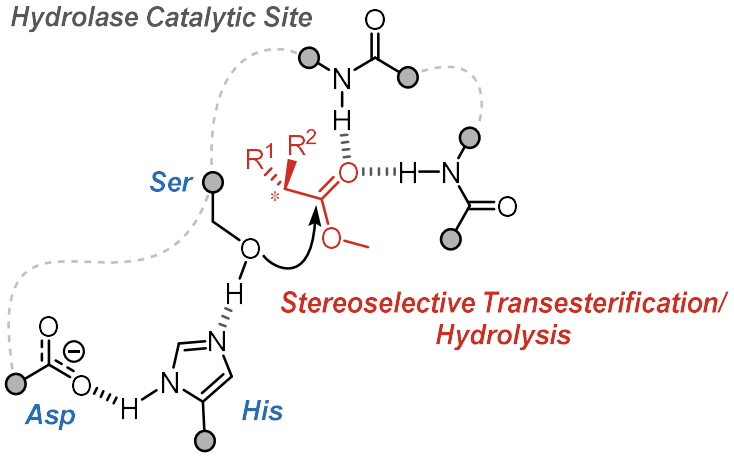
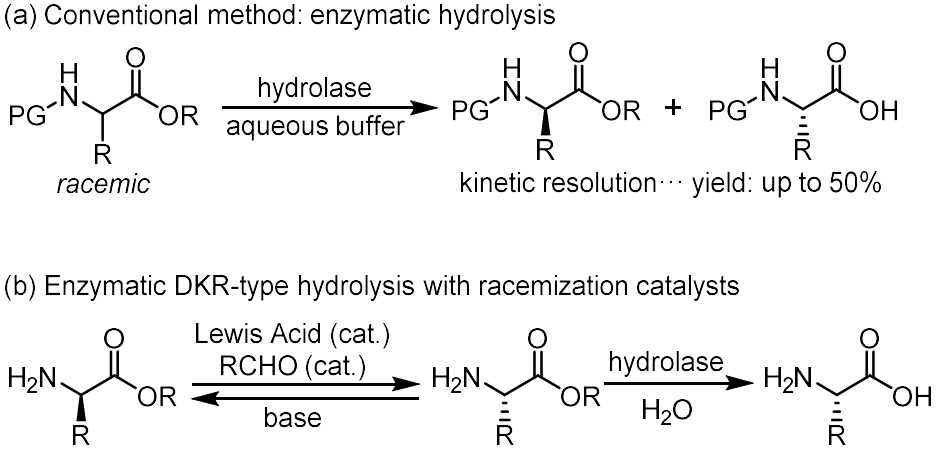


Figure 1. Asymmetric transesterification and hydrolysis using the core Ser-His-Asp catalytic triad.

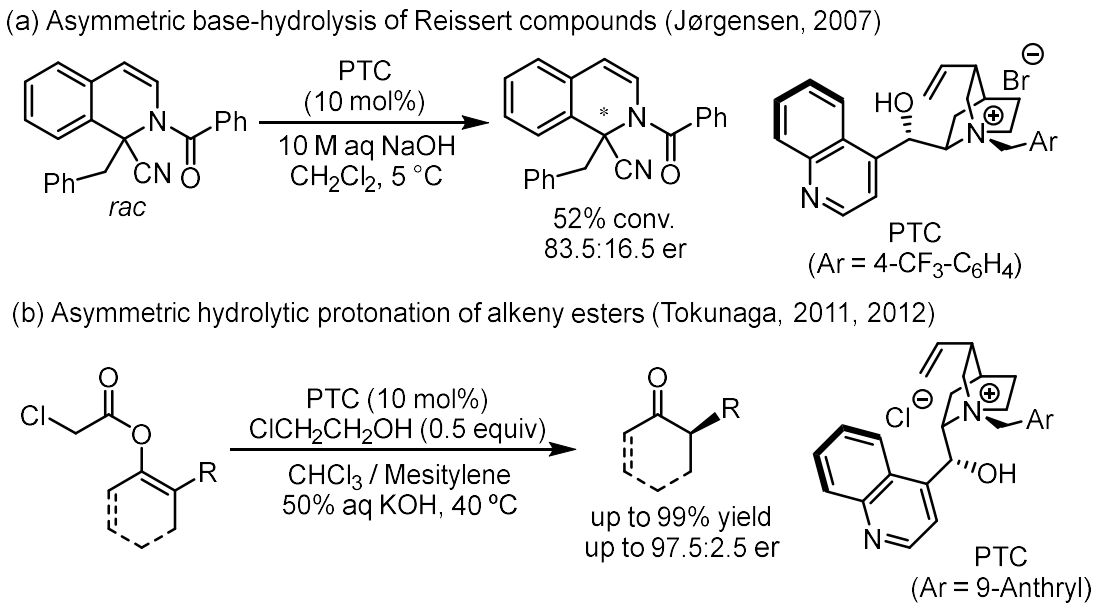
The actual stereodeterming step of enzymatic hydrolysis is the transesterification of the esters with serine residue, and therefore, even enzymes do not control stereoselectivity of nucleophilic addition of water. In addition, conventional enzymatic hydrolysis of amino acid esters[12] has been reported to involve kinetic resolution, which inherently has a theoretical maximum yield of 50%, and dynamic kinetic resolution-type enzymatic hydrolysis developed by Aron group requires additional

racemization catalysts and is limited to unprotected amino acid esters (Scheme 3).[11]



Scheme 3. (a) Conventional enzymatic and (b) enzymatic DKR-type asymmetric hydrolysis of amino acid esters.

Taking these problems into account, the author focused on the synthetic phase-transfer catalytic base-hydrolysis of esters via dynamic kinetic resolution. Previously, chiral phase-transfer catalytic base-hydrolysis of Reissert compound was reported[12] (Scheme 4a). Furthermore, Tokunaga and co-workers reported hydrolytic asymmetric protonation of alkenyl esters via phase-transfer catalyst (PTC)[13] (Scheme 4b). Encouraged by the successes of the phase-transfer catalytic base hydrolysis, the author envisioned that chiral quaternary ammonium hydroxide species could also discriminate the two enantiomers of the α-chiral esters in the nucleophilic attack of hydroxide on carbonyls (Scheme 4c).



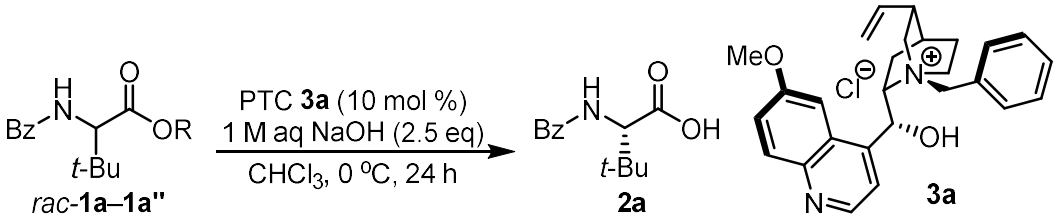
Scheme 4. Phase-transfer catalytic base-hydrolysis.

2.2. Results and Discussion

Optimization of the Reaction Conditions and Substrate Scope

Initially, phase-transfer catalytic asymmetric base-hydrolysis with *N*-benzoyl *tert*-leucine esters and PTC **3a** derived from quinine was examined (Table 1). Base-hydrolysis with methyl ester **1a′** afforded hydrolyzed product **2a** in quite low yield (entry 1). To improve the reactivity, reactions with 2,2,2-trifluoroethyl and hexafluoroisopropyl esters (**1a″** and **1a**, respectively) were examined, and resulted in a drastic increase in both the reactivity and stereoselectivity (entries 2 and 3).

Table 1. Effects of the ester moiety.

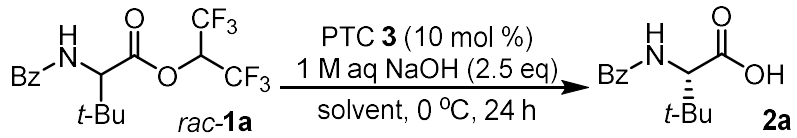


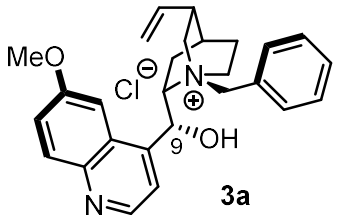
entry	substrate	R	yield[a] (%)	er
1	**1a'**	Me	6	–
2	**1a''**	CF_3CH_2	26	67:33
3	**1a**	$(CF_3)_2CH$	79	86.5:13.5

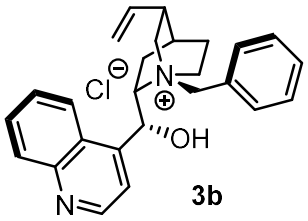
[a]Isolated yields are presented.

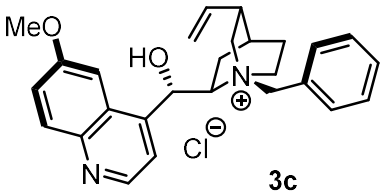
Next, the author carried out screening of chiral PTCs derived from *Cinchona* alkaloids (Table 2, entries 2−6). The reaction with PTC **3b** derived from cinchonidine or pseudoenantiomeric PTC **3c** gave lower selectivity and yield (entries 2 and 3). PTC **3d** having a 2-cyanobenzyl group showed the quantitative yield and high stereoselectivity (entry 4). The reaction with *O*-allylated PTC **3e** afforded only a trace amount of product (entry 5), and the use of PTC **3f** bearing a 2,6-dicyanobenzyl group resulted in a quite decrease in yield and with er (entry 6). These results suggested that the 9-OH group of the catalyst is crucial for reactivity and stereoselectivity, and that the reaction proceeded close to the 9-OH group. With the optimized catalyst **3d**, the other solvents were screened (entries 7−10). CH_2Cl_2 resulted in lower yield and stereoselectivity (entry 7), and other nonhalogenated solvents gave the product in significantly lower ers (entries 8–10).

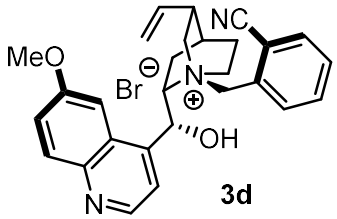
Table 2. Catalyst and solvent screening.

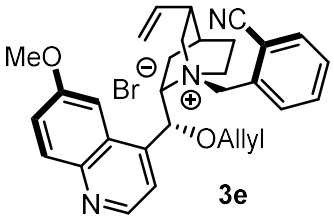


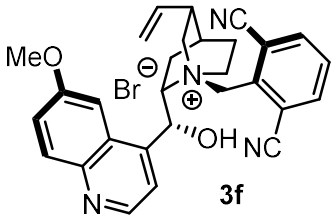










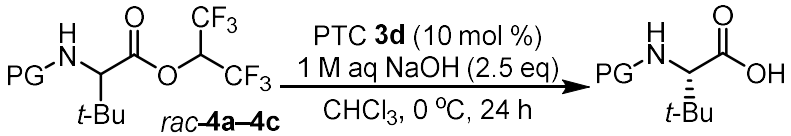


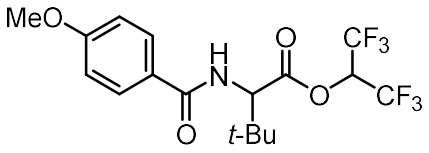
entry	PTC	solvent	yield[a] (%)	er
1[b]	**3a**	$CHCl_3$	79	86.5:13.5
2	**3b**	$CHCl_3$	14	80:20
3	**3c**	$CHCl_3$	17	27:73
4	**3d**	$CHCl_3$	>99	95:5
5	**3e**	$CHCl_3$	trace	–
6	**3f**	$CHCl_3$	5	47:53
7	**3d**	CH_2Cl_2	91	93:7
8	**3d**	toluene	31	61:39
9	**3d**	mesitylene	16	55.5:44.5
10	**3d**	Et_2O	56	56:44

[a]Isolated yields are presented. [b]The same result as entry 3 in Table 1.

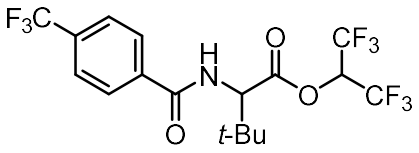
Next, the effect of N-protecting groups were explored (Table 3). Introduction an electron-rich or electron deficient substituent into the benzoyl group showed a loss of reactivity and stereoselectivity (**4a**, 23%,88:12 er; **4b**, 45%, 82.5:17.5 er). Protection with Boc group led to lower yield and er (**4c**, 52%, 64:36 er).

Table 3. Effect of the N-protecting group.

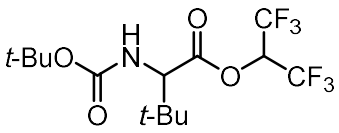




rac-**4a**, 23% yield, 88:12 er



rac-**4b**, 45% yield, 82.5:17.5 er

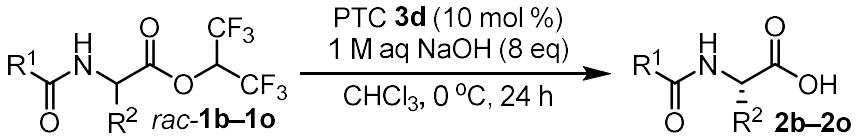


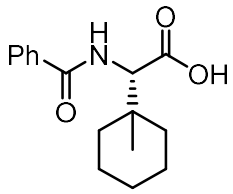
rac-**4c**, 52% yield, 64:36 er

Isolated yields are presented.

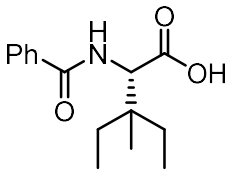
With the optimized reaction conditions, the author explored the scope of substrates (Table 4). Initially, the reaction with sterically hindered substrate **1b** was examined, and it provided product **2b** with good er, albeit in low yield (**2b**, 35%, 95:5 er). In order to improve the yield, the equivalent of aq NaOH was increased. As a result, the use of 8 equivalent of 1 M aq NaOH improved the yield significantly (78%, 96:4 er). Therefore, the reaction conditions were also applied to other substrates. Esters with sterically hindered substituents provided the corresponding *N*-benzoyl amino acids with good to high ers in moderate to excellent yields (**2c**, 53%, 94:6 er; **2d**, 58%, 93.5:6.5 er; **2e**, 65%, 86:14 er). Reactions with esters having secondary alkyl groups also showed good ers and moderate yields (**2f**, 41%, 86.5:13.5 er; **2g**, 89%, 92.5:7.5 er, **2h**, 85%, 86:14 er, **2i**, 94%, 83.5:16.5 er). The substrate having a phenyl group at the α-position also provided the corresponding product **2j** with good er in moderate yield (39%, 88.5:11.5 er). The reaction with substrates containing a primary alkyl group gave the desired products with significantly decreased stereoselectivity (**2k**, 90%, 57:43 er; **2l**, 51%, 51.5:48.5 er). *N*-Alloc and *N*-Boc aryl glycine HFIP esters were also examined. Substrate **1m** and **1n** provided the *N*-Alloc phenylglycine (**2m**) and (4-methoxyphenyl)glycine (**2n**) in good yield with moderate er (**2m**, 79%, 89:11 er; **2n,** 75%, 83.5:16.5 er), and *N*-Boc substrate **1o** provided the *N*-Boc phenylglycine in 35% yield with 90:10 er.

Table 4. Scope of *rac*-*N*-protected amino acid esters.

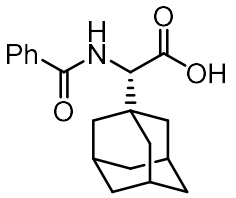




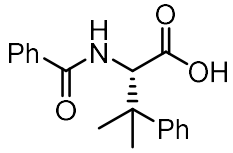
2b, 78%, 96:4 er (35%, 95:5 er[a])



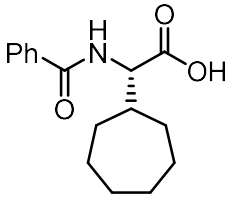
2c, 53%, 94:6 er



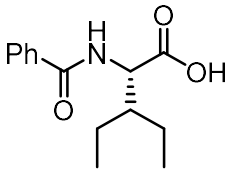
2d, 58%, 93.5:6.5 er



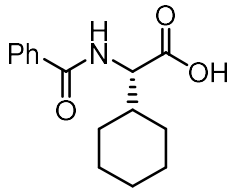
2e, 65%, 86:14 er



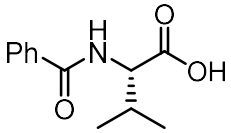
2f, 41%, 86.5:13.5 er



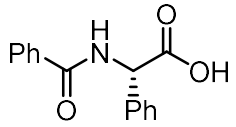
2g, 89%, 92.5:7.5 er



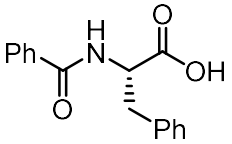
2h, 85%, 86:14 er



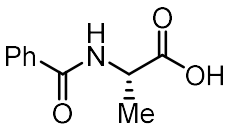
2i, 94%, 83.5:16.5 er



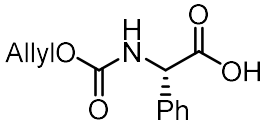
2j, 39%, 88.5:11.5 er[a]



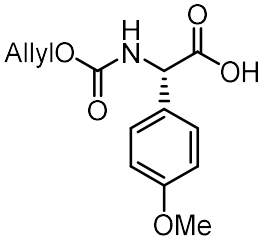
2k, 90%, 57:43 er[a]



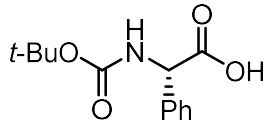
2l, 51%, 51.5:48.5 er[a]



2m, 79%, 89:11 er[a]



2n, 75%, 83.5:16.5 er[a]

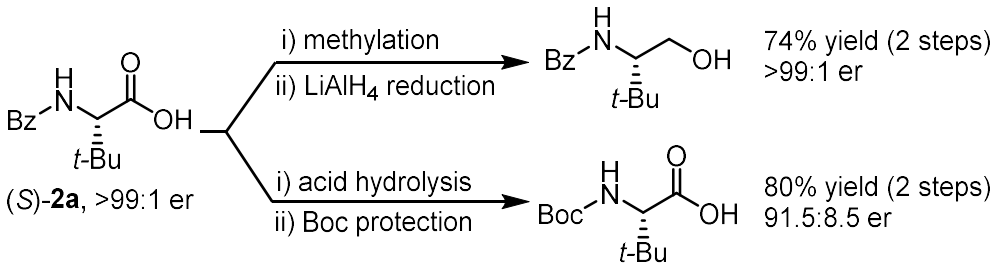


2o, 35%, 90:10 er[a]

Isolated yields are presented. [a]2.5 eq of 1 M NaOH (aq) (500 μL) was used.

Transformations of Hydrolyzed Product 2a

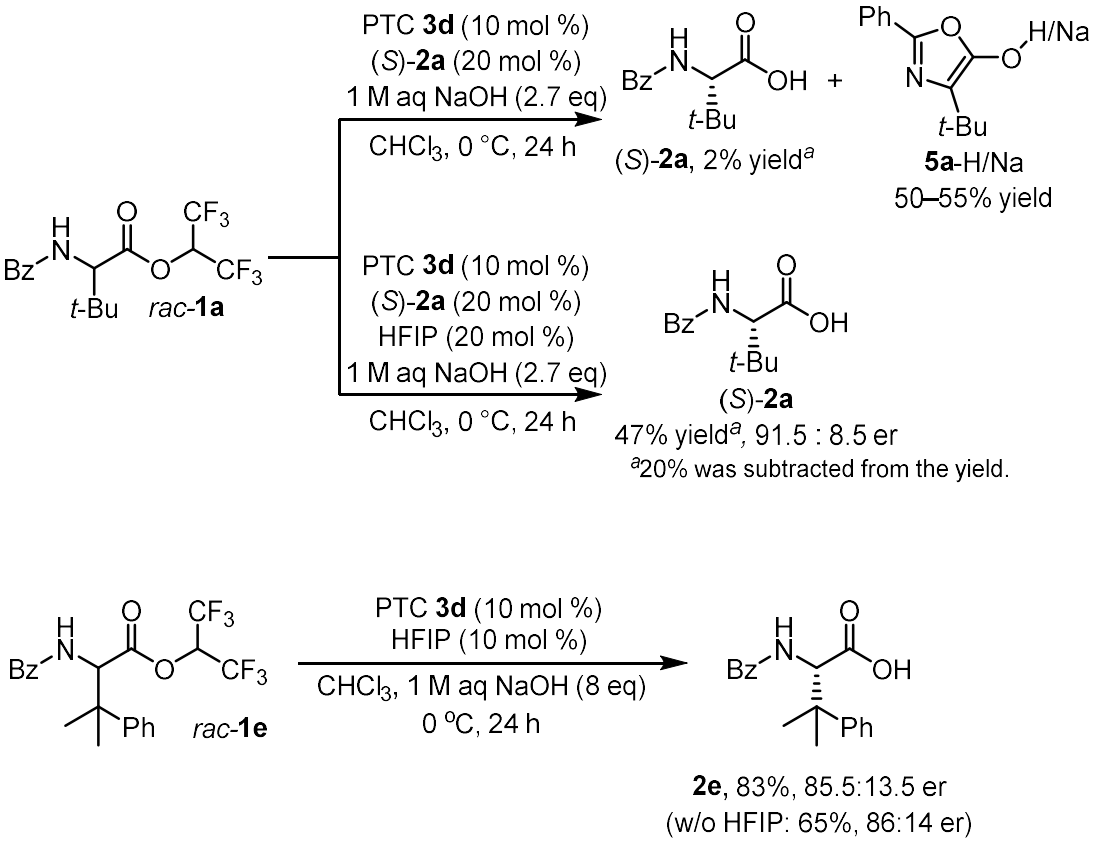
In order to demonstrate the practical utility of the asymmetric base-hydrolysis reaction, transformations of enantioenriched **2a** were examined (Scheme 5). Product **2a** was subjected to methylation/$LiAlH_4$ reduction reactions, which given the corresponding *N*-Bz-*tert*-leucinol in 74% yield without loss of the optical purity. The author also carried out acid hydrolysis and subsequent Boc protection, providing *N*-Boc-*tert*-leucine in 80% yield with 91.5:8.5 er.



Scheme 5. Transformations of hydrolyzed product **2a**.

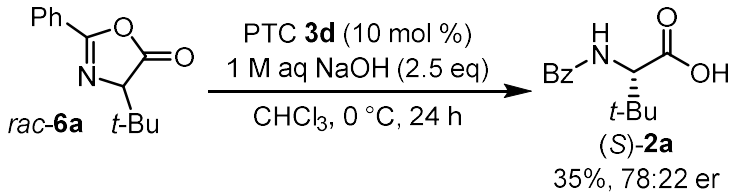
Mechanistic Investigation and Proposed Reaction Mechanism

As mentioned in the previous section, increasing the amount of 1 M aq NaOH from 2.5 equivalent to 8 equivalent improved the yield of **2b** (Table 4, 35% vs 78%). The author supposed that product inhibition by forming the ammonium carboxylate ion pair would occur. As expected, the addition of product (*S*)-**2a** (>99.5:0.5 er) gave the product in significantly low yield (2%), and 50–55% yield of hydroxyoxazole **5a**-H or the corresponding sodium salt **5a**-Na was observed (Scheme 5). Furthermore, the reaction of **1a** with a catalytic amount of hexafluoroisopropanol (HFIP) proceeded to provide the product **2a** in better yield (47%) in 91:9 er (Scheme 6). In addition, the reaction of substrate **1e** in the presence of a catalytic amount of HFIP was examined, and it afforded the corresponding hydrolyzed product **2e** in better yield without loss of stereoselectivity (83%, 85.5:14.5 er). These results indicate that the hydroxide anion or alkoxide anion derived from HFIP reduces the product inhibition effect. The formation of the byproduct **5a**-H/Na suggests the formation of an azlactone intermediate during the reaction, and dynamic kinetic resolution of the azlactone via base-hydrolysis would subsequently occur.



Scheme 6. Product inhibition experiment and the effect of the catalytic amount of HFIP.

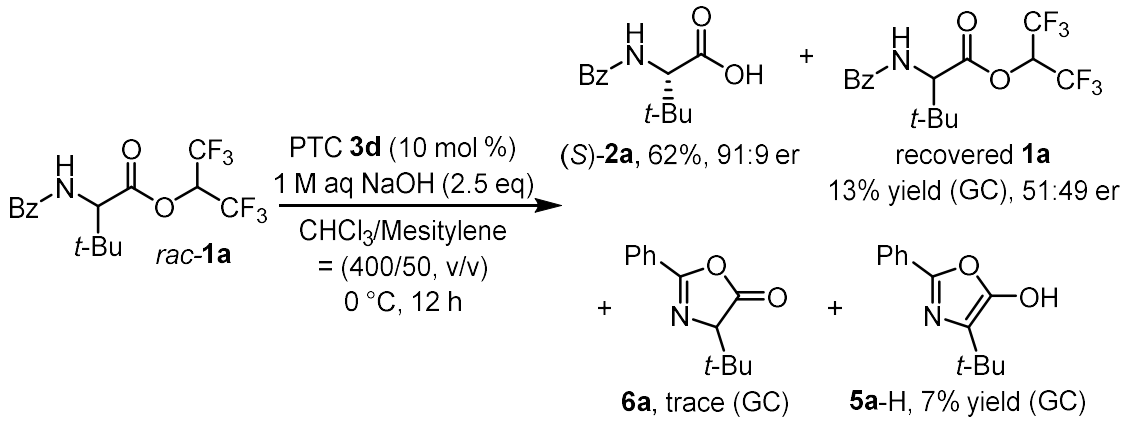
In order to estimate this hypothesis, the author performed the DKR-type base-hydrolysis reaction with azlactone **6a**, which provided the hydrolyzed product **2a** in quite low er compared to the reaction with HFIP ester **1a** (78:22 er, Scheme 7). Therefore, direct hydrolysis of the azlactone intermediate **6a** would be a minor pathway.



Scheme 7. Asymmetric base-hydrolysis of azlactone **6a**.

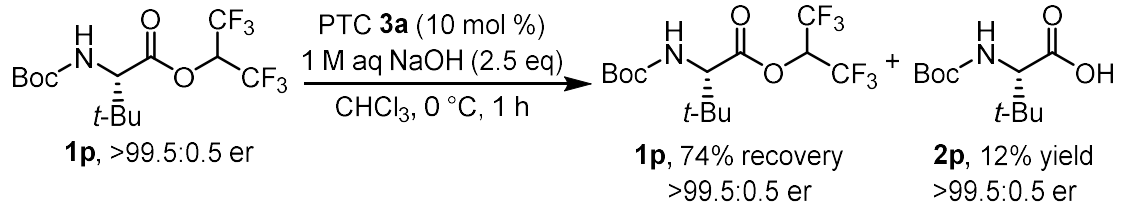
In addition, hydrolytic kinetic resolution of ester **1a** and following dynamic kinetic resolution of **6a** is a possible reaction pathway. Therefore, the author confirmed the er of recovered substrate **1a** under standard reaction conditions (Scheme 8). The recovered substrate **1a** was essentially racemic (13% yield, 51:49 er). Furthermore, two possible racemization/hydrolysis mechanistic pathways still exist; direct racemization via deprotonation/protonation of ester **1a** followed by base-hydrolysis of

ester **1a** (pathway A), or racemization via azlactone **6a** formation/ring-opening with HFIP followed by base-hydrolysis of ester **1a** (pathway B).



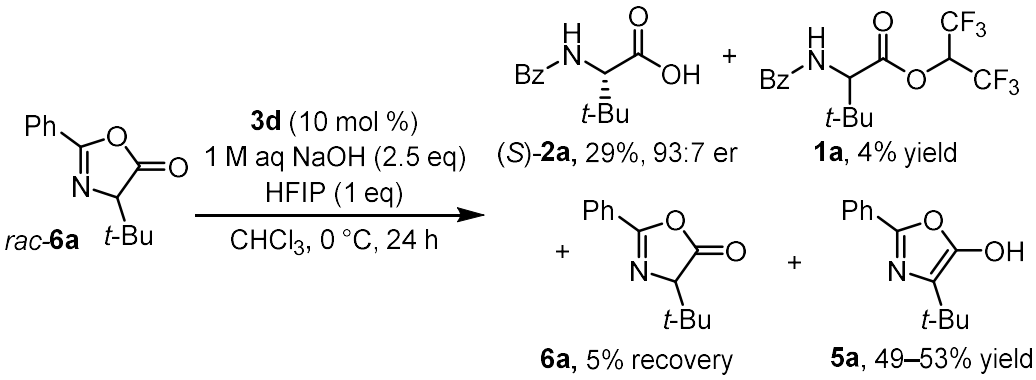
Scheme 8. Analysis of recovered substrate **1a**.

To evaluate the direct racemization of the HFIP esters via deprotonation of the α-proton, the reaction with enantiopure *N*-Boc substrate (*S*)-**1p** was examined (Scheme 9). The enantiopurity of the recovered substrate **1p** and hydrolyzed product **2p** were also >99.5:0.5 er, indicating that direct racemization of ester **1a** is unlikely under the reaction conditions.



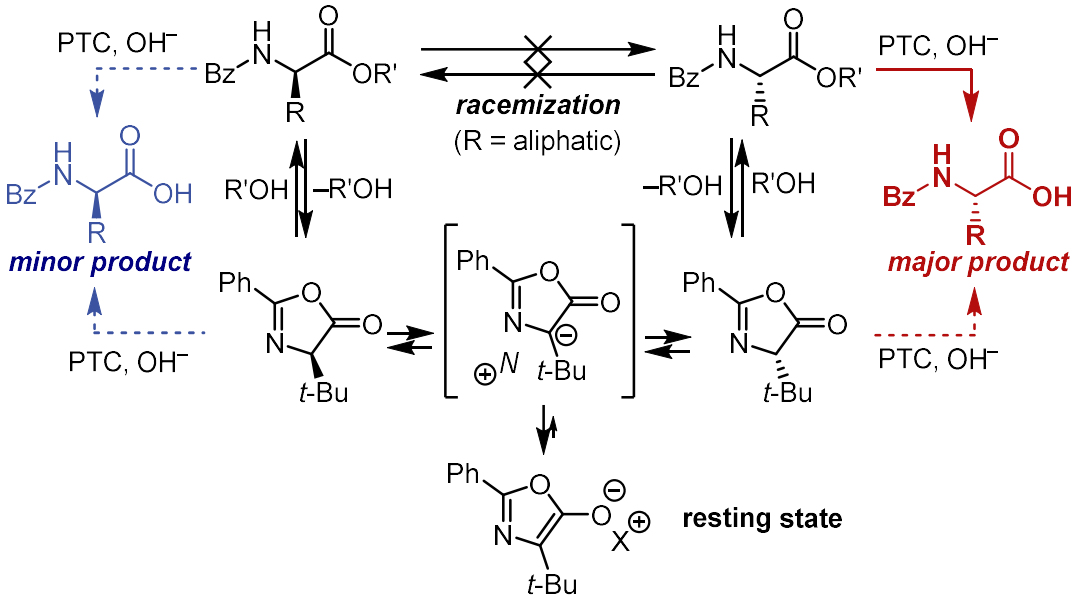
Scheme 9. Reaction with enantiopure ester **1p**.

Thus, the author carried out the reaction of azlactone intermediate **6a** in the presence of 1 equivalent of HFIP in order to investigate the possibility of the alcoholytic ring-opening of azlactone with HFIP, and it provided *N*-Bz tert-leucine HFIP ester **1a** (Scheme 10). This result shows that the ring-opening alcoholysis of azlactone **6a** would occur in the presence of the HFIP.



Scheme 10. Reaction with azlactone **6a** in the presence of HFIP.

These results support the racemization/hydrolysis pathway B. The base-hydrolysis of hydroxyoxazole **5a**-H was also explored, and the hydrolyzed product **2a** was not observed. On the basis of these results, the plausible reaction mechanism is shown in Scheme 11. The pathway affording the major enantiomer is likely to be the direct base hydrolysis of ester **1a** while both base-hydrolysis of **1a** and azlactone **6a** are possible for the pathways giving the minor enantiomer, and hydroxyoxazole **5a**-H is an inactive reaction intermediate.



Scheme 11. Plausible reaction mechanism.

Computational Studies

The author further performed a computational study to reveal the origin of the stereoselectivity of the asymmetric base-hydrolysis. The pseudo-transition state conformational search (PTSCS) was performed with the ConFinder program (introduced in Chapter 1.2.). At first, four initial structures of the substrate-catalyst complex **[3d′+1a]** was considered as a TS analogue, and they were classified by the stereochemistry of the enantiofaces attacked by the hydroxide and the ester's α-carbon center: *Re-R*, *Si-R*, *Re-S*, *Si-S* (Figure 2).

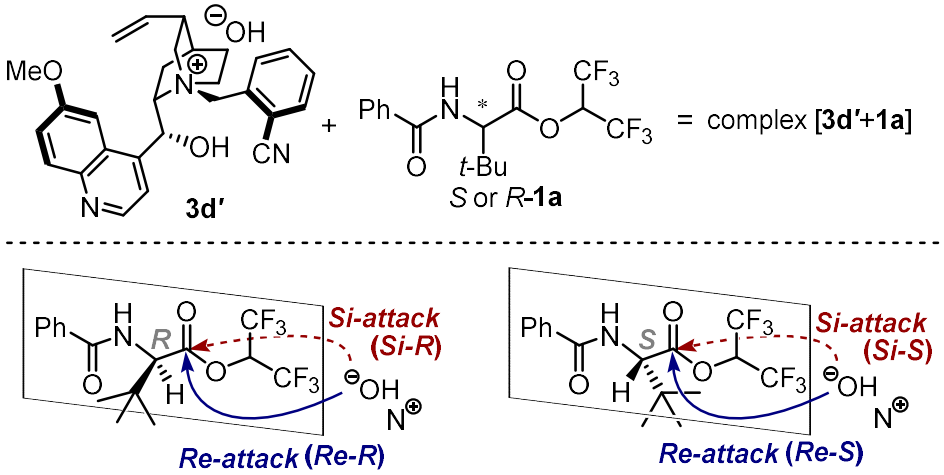


Figure 2. Calculated TS analogue [**3d′+1a**] and classification of pseudo-TS complexes by the enantiofaces and the stereochemistry.

During the conformational search with ConFinder, the C···O distance between the carbonyl carbon of the ester **1a** and oxygen atom of the hydroxide anion was fixed to 2.0 Å to keep the geometry close to the corresponding TS structures. The conformation search generated 2103 to 3275 conformations for each of the four complexes, and the energies for the obtained conformers were further assessed by single-point energy (SPE) calculations at the RI-B97D/SV(P) level of theory. After the refinement of the conformers, further partial optimization was carried out at the RI-B97D/SV(P) level of theory. The geometries of the TS structures were then optimized at the M06-2X/TZVP level of theory. The most stable TS structures leading to the *S*- or *R*-product were successfully obtained (Figure 3, TS-*Re-S* and TS-*Si-R*, respectively).

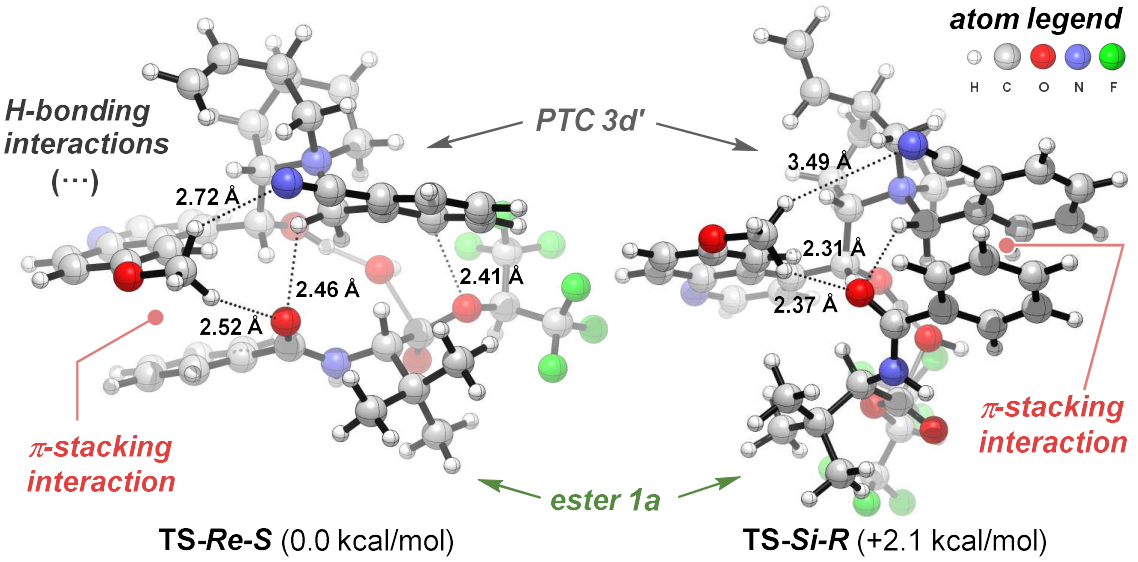


Figure 3. Calculated TS structures leading to each enantiomer at the M06-2X/TZVP level of calculation.

The difference in Gibbs free energy at 273.15 K between TS-*Re-S* and TS-*Si-R* is in good agreement with the *ΔΔG* values based on the experimental results [2.1 (calcd.) vs 1.6 (exptl.) kcal/mol]. In addition, both TS structures indicate the π-stacking between the quinoline ring or 2-cyanophenyl ring in **3d′** and Ph group in **1a** and H-bonding interactions between the hydrogen atoms in the MeO group or one of the benzylic protons in the 2-cyanobenzyl group and the oxygen atom in the Bz group (O–CH_2*H*···O=C and N^+*CH*H···O=C).[14] These noncovalent interactions would play key roles in stabilizing the TS structures. Furthermore, the H-bonding interaction between the hydrogen atom in the MeO group and the nitrogen atom in the cyano group having the PTC **3d′** was observed in the TS-*Re-S* structure, whereas the two groups were distant in the TS-*Si-R* structure (2.72 and 3.49 Å, respectively). Other TS structures without the H-bonding interaction (O–CH_2H···O=C) also resulted in a significant increase in energy (>3.8 kcal/mol), indicating the importance of the interactions. Furthermore, the favored TS-*Re-S* structure demonstrates the existence of a H-bonding interaction between the oxygen atom in the ester group and the *ortho*-hydrogen atom in the 2-cyanobenzyl group in PTC **3d′** (2.45 Å), which was not observed in the TS-*Si-R* structure. Thus, the lack of this H-bonding interaction would explain the energy differences between the TS structures.

2.3. Conclusion

In this study, the author developed a base-hydrolysis of N-protected α-chiral amino acid HFIP esters using *cinchona* alkaloid derived quaternary ammonium salts as phase-transfer catalysts. The

reaction proceeded via dynamic kinetic resolution process, providing the desired hydrolyzed products in moderate to good yields with up to 96:4 er. This strategy is useful for the synthesis of enantioenriched α-chiral amino acids bearing a bulky or aryl substituent. Detailed experimental studies revealed that the substrates are racemized via the formation of azlactone, and the stereodeterming step is the nucleophilic attack of the hydroxide on the carbonyl carbon in the ester substrate.

2.4. Experimental

General and Materials

Materials were obtained from commercial suppliers, and used as received unless otherwise noted. (Trimethylsilyl)diazomethane solution (2.0 M in Et_2O) was purchased from Sigma-Aldrich. Chloroform was purified prior to use following the guidelines of Perrin and Armarego.[15] CH_2Cl_2 (anhydrous) and THF (anhydrous, stabilizer free) were used as anhydrous solvents. *N*-Benzylquininium chloride (**3a**, TOKYO CHEMICAL INDUSTRYCO., LTD.), *N*-benzylcinchonidinium chloride (**3b**, TOKYO CHEMICAL INDUSTRYCO., LTD.) and *N*-benzylquinidinium chloride (**3c**, TOKYO CHEMICAL INDUSTRYCO., LTD.) were used as received. Catalyst **3e** was prepared according to the reported procedure.[16] ^{1}H NMR spectra were obtained in $CDCl_3$ or CD_3OD or DMSO-d_6 at 400 MHz or 600 MHz. Chemical shifts are reported in ppm and referenced to the $CHCl_3$ singlet at 7.26 ppm or the center peak of the CHD_2OD quintet at 3.31 ppm or the center peak of the DMSO-d_5 quintet at 2.50 ppm. ^{13}C NMR spectra were obtained in $CDCl_3$ or CD_3OD or DMSO-d_6 at 100 MHz or 600 MHz and referenced to the center peak of the $CDCl_3$ triplet at 77.16 ppm or the center peak of the CD_3OD septet at 49.00 ppm or the center peak of the DMSO-d_6 septet at 39.52 ppm. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sep (septet), m (multiplet), dd (doublet of doublets), br-s (broad singlet). The enantiomer ratios (ers) were determined by GC or HPLC analysis with a chiral stationary phase column specified in the individual experiment. GC analysis was carried out using Agilent GC 6850 series II equipped with InertCap CHIRAMIX Column (length 30 m, i.D. 0.25 mm, df. 0.25 μm) from GL Sciences Inc. using helium as a carrier gas. HPLC analysis was performed on a JASCO PU-2080 or HITACHI L-2130 equipped with a variable wavelength detector using chiral stationary columns (CHIRALPAK AD-H, AS-H, OP (+), CHIRALCEL OD-H, 0.46 cm x 25 cm) from Daicel. Specific optical rotations were measured on a JASCO DIP-1000 digital polarimeter. Column chromatography for the purification of chemicals was carried out with silica gel purchased from Kanto Chemicals (Silica gel 60N, spherical, neutral; particle size 40–100 μm). Abbreviations; aq = aqueous solution, eq = equivalent, Rt = retention time, pro = product, rt = room temperature, sub = substrate. NISSIN MAGNETIC STIRRER SW-800 was employed as a stirrer for the asymmetric base-hydrolysis. Elemental analyses were recorded at the Service Centre of the Elementary Analysis of Organic Compounds, Faculty of Science, Kyushu University. High resolution mass (HRMS) analyses were measured on JEOL JMS-700 mass spectrometer at Evaluation Center of Materials Properties and Function, Institute for Materials Chemistry and Engineering, Kyushu University.

General Experimental Procedures

General Procedure I: Catalytic Asymmetric Hydrolysis of N-Protected Amino Acid Esters

A chiral phase-transfer catalyst (PTC) (0.02 mmol, 10 mol %) was placed in a screw-capped test tube (diameter: 16 mm) under air. Then, $CHCl_3$ (600 μL) was added to the test tube followed by the addition of 1 M aq NaOH (500 or 1600 μL, 2.5 or 8 eq) under air. After stirred at 0 °C for 10 min, N-protected amino acid ester and $CHCl_3$ (200 μL) were added to the solution, and the resultant reaction mixture was further stirred for 24 h at 0 °C. Then, the organic phase of the reaction mixture was removed by extraction with EtOAc (2 mL x 3). The residual aqueous solution was acidified by 0.5 mL of 6 M aq HCl, then extracted by EtOAc (2 mL x 3). The latter extracts were corrected and concentrated by evaporation to give the corresponding N-protected amino acid. The enantiomer ratios of the products were analyzed by HPLC or chiral GC after methylation of the product by (trimethylsilyl)diazomethane in Et_2O at rt.

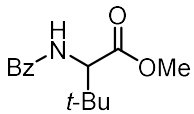
General Procedure II: Synthesis of N-Protected Amino Acid Esters

N-Protected amino acids (1 eq) was added to a mixture of DCC (1.5 eq), DMAP (10 mol %) and CH_2Cl_2 (0.1 M) at 0 ºC. The appropriate alcohol (2 eq) was slowly added at 0 ºC and the resultant mixture was vigorously stirred at the same temperature. The reaction was filtered through a short silica-gel column with Et_2O as an eluent. After removal of the solvent under reduced pressure, the crude products was purified by flash column chromatography to afford the N-protected amino acid esters.

Synthesis and Characterization of Substrates and Products

Synthesis of N-Protected Amino Acid Esters

Methyl 2-benzamido-3,3-dimethylbutanoate (1a′).[17]

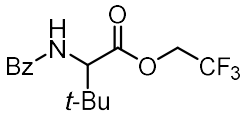


rac-**1a′**

To a stirred solution of *rac*-*N*-benzoyl-*tert*-leucine (118 mg, 0.500 mmol, 1 eq) in MeOH (0.5 mL) was added a drop of conc. H_2SO_4 at rt. The reaction mixture was heated to 70 ºC and stirred for 18 h. The resulting solution was neutralized with $NaHCO_3$ and extracted with Et_2O (1 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4 followed by filtration and evaporation. The crude product was further purified by silica-gel column chromatography with hexane/EtOAc (20:1 to 5:1) to give the title compound as a white solid (100 mg, 0.401 mmol, 80% yield). ^{1}H NMR was in agreement with the literature.[17] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.82–7.76 (m, 2H), 7.54–7.48 (m, 1H), 7.47–7.40 (m, 2H), 6.66 (d, *J* = 9.2 Hz, 1H), 4.70 (d, *J* = 9.6 Hz, 1H), 3.74 (s, 3H), 1.04 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.3 (*C*O),

167.2 (*C*O), 134.3 (*C*), 131.8 (*C*H), 128.7 (*C*H, 2C), 127.1 (*C*H, 2C), 60.3 (*C*H$_3$), 52.0 (*C*H), 35.3 (*C*), 26.7 (*C*H$_3$, 3C). Elemental Analysis: Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62;. Found: C, 67.63; H, 7.68; N, 5.57.

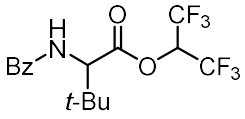
2,2,2-Trifluoroethyl 2-benzamido-3,3-dimethylbutanoate (**1a″**).



rac-**1a″**

Title compound was synthesized from *rac*-*N*-benzoyl-*tert*-leucine (340 mg, 1.45 mmol) according to General Procedure II (reaction time: 17 h, flash column chromatography eluent: hexane/EtOAc = 20/1 to 5/1) as a white solid in 32% yield (149 mg, 0.468 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81–7.74 (m, 2H), 7.52 (tt, *J* = 7.3, 1.7 Hz, 1H), 7.47–7.42 (m, 2H), 6.63 (d, *J* = 9.2 Hz, 1H), 4.76 (d, *J* = 9.2 Hz, 1H), 4.67 (dq, *J* = 12.7, 8.4 Hz, 1H), 4.39 (dq, *J* = 12.5, 8.5 Hz, 1H), 1.07 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.4 (*C*O), 167.4 (*C*O), 134.0 (*C*), 132.0 (*C*H), 128.8 (*C*H, 2C), 127.1 (*C*H, 2C), 122.8 (q, $J_{C\text{-}F}$ = 275.9 Hz, *C*F$_3$), 60.6 (q, $J_{C\text{-}F}$ = 36.6 Hz, *C*H), 60.4 (*C*H), 35.1 (*C*), 26.6 (*C*H$_3$, 3C). HRMS-FAB (*m/z*): $[M+H]^+$ calcd for $C_{15}H_{19}F_3NO_3$, 318.1312; found: 318.1318.

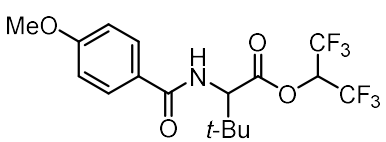
1,1,1,3,3,3-Hexafluoropropan-2-yl 2-benzamido-3,3-dimethylbutanoate (**1a**).



rac-**1a**

Title compound was synthesized from *rac*-*N*-benzoyl-*tert*-leucine (1176 mg, 5 mmol) according to General procedure II (reaction time: 26 h, flash column chromatography eluent: hexane/EtOAc = 50/1 to 20/1) as a white solid in 90% yield (1725 mg, 4.48 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81–7.75 (m, 2H), 7.55 (tt, *J* = 7.3, 1.4 Hz, 1H), 7.50–7.44 (m, 2H), 6.53 (d, *J* = 8.7 Hz, 1H), 5.81 (sep, *J* = 6.0 Hz, 1H), 4.82 (d, *J* = 8.7 Hz, 1H), 1.11 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.8 (*C*O), 167.5 (*C*O), 133.7 (*C*), 132.2 (*C*H), 128.9 (*C*H, 2C), 127.1 (*C*H, 2C), 124.8–116.0 (m, *C*F$_3$, 2C), 66.9 (sep, $J_{C\text{-}F}$ = 34.6 Hz, *C*H), 60.7 (*C*H), 35.0 (*C*), 26.6 (*C*H$_3$, 3C). HRMS-FAB (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{18}F_6NO_3$, 386.1185; found: 386.1191.

1,1,1,3,3,3-Hexafluoropropan-2-yl 2-(4-methoxybenzamido)-3,3-dimethylbutanoate (**4a**).

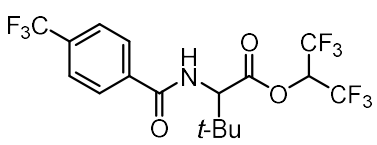


rac-**4a**

Title compound was prepared from *rac*-*N*-(4-methoxybenzoyl)-*tert*-leucine (106 mg, 0.400 mmol) according to General Procedure II (reaction time: 72 h, flash column chromatography eluent: hexane/EtOAc = 20/1 to 5/1) as a white solid in 84% yield (140 mg, 0.337 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77–7.72 (m, 2H), 6.97–6.92 (m, 2H), 6.45 (d, *J* = 8.7 Hz, 1H), 5.80 (sep, *J* = 6.0 Hz, 1H), 4.80 (d, *J* = 9.2 Hz, 1H), 3.85 (s, 3H), 1.10 (s, 9H). ^{13}C

NMR (100 MHz, $CDCl_3$) δ = 168.9 (*C*O), 166.9 (*C*O), 162.8 (*C*), 129.0 (*C*H, 2C), 125.9 (*C*), 124.9–116.0 (m, *C*F_3, 2C), 114.1 (*C*H, 2C), 66.9 (sep, $J_{C\text{-}F}$ = 34.3 Hz, *C*H), 60.7 (*C*H), 55.6 (*C*H_3), 35.0 (*C*), 26.6 (*C*H_3, 3C). Elemental Analysis: Calcd for $C_{17}H_{19}F_6NO_4$: C, 49.16; H, 4.61; N, 3.37;. Found: C, 49.63; H, 4.53; N, 3.43.

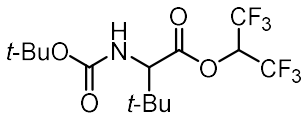
1,1,1,3,3,3-Hexafluoropropan-2-yl 3,3-dimethyl-2-[4-(trifluoromethyl)benzamido]butanoate (**4b**).



rac-**4b**

Title compound was prepared from *rac*-*N*-(4-trifluoromethyl)benzoyl-*tert*-leucine (607 mg, 2.00 mmol) according to General Procedure II (reaction time: 10 h, flash column chromatography eluent: hexane/EtOAc = 40/1 to 10/1) as a white solid in 78% yield (707 mg, 1.56 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.86 (d, *J* = 8.2 Hz, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 6.62 (d, *J* = 8.7 Hz, 1H), 5.81 (sep, *J* = 6.0 Hz, 1H), 4.80 (d, *J* = 8.7 Hz, 1H), 1.11 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.6 (*C*O), 166.4 (*C*O), 137.0 (*C*), 133.9 (q, $J_{C\text{-}F}$ = 32.7 Hz, *C*), 127.7 (*C*H, 2C), 125.9 (q, $J_{C\text{-}F}$ = 3.7 Hz, *C*H, 2C), 123.7 (q, $J_{C\text{-}F}$ = 271.3 Hz, *C*F_3), 124.8–116.0 (m, *C*F_3, 2C), 67.0 (sep, $J_{C\text{-}F}$ = 34.7 Hz, *C*H), 61.0 (*C*H), 35.0 (*C*), 26.6 (*C*H_3, 3C). Elemental Analysis: Calcd for $C_{17}H_{16}F_9NO_3$: C, 45.04; H, 3.56; N, 3.09;. Found: C, 45.19; H, 3.57; N, 3.14.

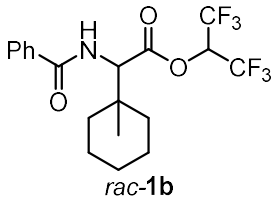
1,1,1,3,3,3-Hexafluoropropan-2-yl 2-[(*tert*-butoxycarbonyl)amino]-3,3-dimethylbutanoate (**4c**).



rac-**4c**

Title compound was synthesized from *rac*-*N*-Boc-*tert*-leucine (347 mg, 1.50 mmol) according to General procedure II (reaction time: 18 h, flash column chromatography eluent: hexane/EtOAc = 20/1) as a white solid in 94% yield (540 mg, 1.42 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.79 (sep, *J* = 6.0 Hz, 1H), 5.00 (d, *J* = 8.2 Hz, 1H), 4.24 (d, *J* = 9.2 Hz, 1H), 1.44 (s, 9H), 1.02 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.1 (*C*O), 155.4 (*C*O), 124.8–116.1 (m, *C*F_3, 2C), 80.6 (*C*), 66.7 (sep, $J_{C\text{-}F}$ = 34.6 Hz, *C*H), 62.2 (*C*H), 34.4 (*C*), 28.3 (*C*H_3, 3C), 26.5 (*C*H_3, 3C). HRMS-FAB (*m/z*): $[M+H]^+$ calcd for $C_{14}H_{22}F_6NO_4$, 382.1448; found: 382.1452.

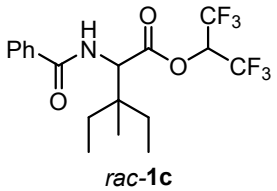
1,1,1,3,3,3-Hexafluoropropan-2-yl 2-benzamido-2-(1-methylcyclohexyl)acetate (1b).



rac-**1b**

Title compound was synthesized from *rac*-*N*-benzoyl-2-(1-methylcyclohexyl)glycine (932 mg, 3.38 mmol) according to General Procedure II (reaction time: 22 h, flash column chromatography eluent: hexane/EtOAc = 50/1 to 10/1) as a white solid in 64% yield (915 mg, 2.15 mmol). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.78 (d, *J* = 6.8 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 6.51 (d, *J* = 8.9 Hz, 1H), 5.80 (sep, *J* = 6.0 Hz, 1H), 5.00 (d, *J* = 8.9 Hz, 1H), 1.70–1.32 (m, 10H), 1.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.9 (*C*O), 167.5 (*C*O), 133.8 (*C*), 132.2 (*C*H), 128.9 (*C*H, 2C), 127.2 (*C*H, 2C), 124.8–116.0 (m, *C*F_3, 2C), 66.9 (sep, $J_{C\text{-}F}$ = 34.8 Hz, *C*H), 59.4 (*C*H), 37.7 (*C*), 35.0 (*C*H_2), 34.9 (*C*H_2), 25.8 (*C*H_2), 21.6 (*C*H_2), 21.5 (*C*H_2), 20.7 (*C*H_3, 2C). Elemental Analysis: Calcd for $C_{19}H_{21}F_6NO_3$: C, 53.65; H, 4.98; N, 3.29;. Found: C, 53.74; H, 4.96; N, 3.38.

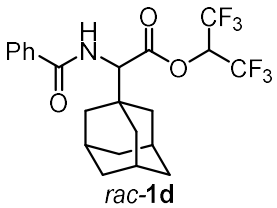
1,1,1,3,3,3-Hexafluoropropan-2-yl 2-benzamido-3-ethyl-3-methylpentanoate (1c).



rac-**1c**

Title compound was synthesized from *rac*-*N*-benzoyl-2-(1-ethylmethyl-1-propyl)glycine (294 mg, 1.11 mmol) according to General Procedure II (reaction time: 52 h, flash column chromatography eluent: hexane/EtOAc = 50/1 to 25/1) as a white solid in 66% yield (300 mg, 0.726 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80–7.74 (m, 2H), 7.57–7.51 (m, 1H), 7.49–7.42 (m, 2H), 6.51 (d, *J* = 8.7 Hz, 1H), 5.80 (sep, *J* = 6.0 Hz, 1H), 4.97 (d, *J* = 8.7 Hz, 1H), 1.55–1.35 (m, 4H), 1.00 (s, 3H), 0.93 (q, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.1 (*C*O), 167.4 (*C*O), 133.8 (*C*), 132.2 (*C*H), 128.9 (*C*H, 2C), 127.1 (*C*H, 2C), 124.8–116.0 (m, *C*F_3, 2C), 66.9 (sep, $J_{C\text{-}F}$ = 34.8 Hz, *C*H), 58.1 (*C*H), 40.1 (*C*), 28.4 (*C*H_2), 28.3 (*C*H_2), 20.4 (*C*H_3), 7.8 (*C*H_3, 2C). Elemental Analysis: Calcd for $C_{18}H_{21}F_6NO_3$: C, 52.30; H, 5.12; N, 3.39;. Found: C, 52.49; H, 5.22; N, 3.33.

1,1,1,3,3,3-Hexafluoropropan-2-yl 2-benzamido-2-(1-adamantyl)acetate (1d).

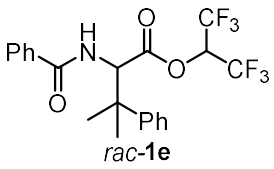


rac-**1d**

Title compound was prepared from *rac*-*N*-benzoyl-2-(1-adamantyl)glycine (150 mg, 0.478 mmol) according to General Procedure II (reaction time: 22 h, flash column chromatography eluent: hexane/EtOAc = 25/1 to 5/1) as a white solid in 72% yield (160 mg, 0.346 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.82–7.76 (m, 2H), 7.57–7.51 (m, 1H), 7.47 (t, *J* = 7.3 Hz, 2H), 6.58 (d, *J* = 8.7 Hz, 1H), 5.82 (sep, *J* = 6.0 Hz, 1H), 4.71 (d, *J* = 8.7 Hz, 1H), 2.05 (s, 3H), 1.78–1.60 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.3 (*C*O), 167.5 (*C*O), 133.8 (*C*), 132.2 (*C*H), 128.9 (*C*H, 2C), 127.2 (*C*H, 2C),

124.8–115.9 (m, *C*F_3, 2C), 66.9 (sep, $J_{C\text{-}F}$ = 34.8 Hz, *C*H), 61.4 (*C*H), 38.7 (*C*H_2, 3C), 36.9 (*C*), 36.6 (*C*H_2, 3C) , 28.3 (*C*H, 3C). Elemental Analysis: Calcd for $C_{22}H_{23}F_6NO_3$: C, 57.02; H, 5.00; N, 3.02;. Found: C, 57.07; H, 5.06; N, 3.00.

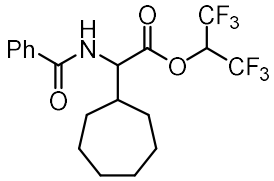
1,1,1,3,3,3-Hexafluoropropan-2-yl 2-benzamido-3-methyl-3-phenylbutanoate (1e).



rac-**1e**

Title compound was synthesized from *rac*-*N*-benzoyl-2-(2-phenyl-2-propyl)glycine (595 mg, 2.00 mmol) according to General Procedure II (reaction time: 16 h, flash column chromatography eluent: hexane/EtOAc = 50/1 to 25/1) as a white solid in 77% yield (691 mg, 1.54 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62–7.57 (m, 2H), 7.53–7.47 (m, 1H), 7.45–7.36 (m, 6H), 7.33–7.27 (m, 1H), 6.29 (d, *J* = 7.8 Hz, 1H), 5.76 (sep, *J* = 6.0 Hz, 1H), 5.15 (d, *J* = 7.8 Hz, 1H), 1.55 (d, *J* = 2.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.3 (*C*O), 167.4 (*C*O), 143.5 (*C*), 133.5 (*C*), 132.2 (*C*H), 128.9 (*C*H, 2C), 128.8 (*C*H, 2C), 127.5 (*C*H), 127.0 (*C*H, 2C), 126.2 (*C*H, 2C), 124.9–115.8 (m, *C*F_3, 2C), 67.0 (sep, $J_{C\text{-}F}$ = 34.8 Hz, *C*H), 61.1 (*C*H), 41.5 (*C*), 26.3 (*C*H_3), 24.8 (*C*H_3). Elemental Analysis: Calcd for $C_{21}H_{19}F_6NO_3$: C, 56.38; H, 4.28; N, 3.13;. Found: C, 56.56; H, 4.28; N, 3.15.

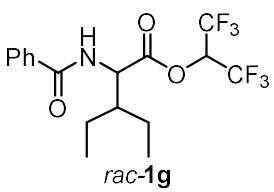
1,1,1,3,3,3-Hexafluoropropan-2-yl 2-benzamido-2-cycloheptylacetate (1f).



rac-**1f**

Title compound was prepared from *rac*-*N*-benzoyl-2-cycloheptylglycine (827 mg, 3.00 mmol) according to General Procedure II (reaction time: 38 h, flash column chromatography eluent: hexane/EtOAc = 20/1 to 10/1) as a white solid in 81% yield (1.04 g, 2.44 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81–7.74 (m, 2H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.46–7.38 (m, 2H), 6.69 (d, *J* = 8.7 Hz, 1H), 5.81 (sep, *J* = 6.0 Hz, 1H), 5.00 (dd, *J* = 4.6, 8.2 Hz, 1H), 2.24–2.10 (m, 1H), 1.90–1.79 (m, 1H), 1.78–1.32 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.4 (*C*O), 167.7 (*C*O), 133.7 (*C*), 132.1 (*C*H), 128.8 (*C*H, 2C), 127.2 (*C*H, 2C), 124.8–115.9 (m, *C*F_3, 2C), 67.0 (sep, $J_{C\text{-}F}$ = 34.8 Hz, *C*H), 57.8 (*C*H), 42.2 (*C*H), 31.4 (*C*H_2), 29.4 (*C*H_2), 28.0 (*C*H_2), 27.6 (*C*H_2), 26.6 (*C*H_2, 2C). Elemental Analysis: Calcd for $C_{19}H_{21}F_6NO_3$: C, 53.65; H, 4.98; N, 3.29;. Found: C, 53.72; H, 4.97; N, 3.35.

1,1,1,3,3,3-Hexafluoropropan-2-yl 2-benzamido-3-ethylpentanoate (**1g**).

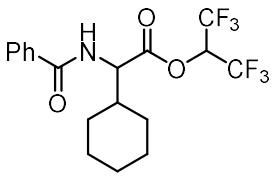


rac-**1g**

Title compound was synthesized from *rac*-*N*-benzoyl-2-(1-ethyl-1-propyl)glycine (190 mg, 0.762 mmol) according to General Procedure II (reaction time: 12 h, flash column chromatography eluent: hexane/EtOAc = 30/1 to 5/1) as a white solid in 95% yield (290 mg, 0.727 mmol). ^{1}H NMR

(400 MHz, $CDCl_3$) δ = 7.81–7.76 (m, 2H), 7.55 (tt, *J* = 7.3, 1.7 Hz, 1H), 7.50–7.43 (m, 2H), 6.43 (d, *J* = 8.7 Hz, 1H), 5.80 (sep, *J* = 6.0 Hz, 1H), 5.18 (dd, *J* = 8.7, 3.7 Hz, 1H), 1.87 (quintet of doublets, *J* = 6.4, 4.8 Hz, 1H), 1.57–1.44 (m, 1H), 1.44–1.29 (m, 3H), 1.04 (t, *J* = 7.3 Hz, 3H), 0.99 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.1 (*C*O), 167.6 (*C*O), 133.7 (*C*), 132.2 (*C*H), 128.9 (*C*H, 2C), 127.2 (*C*H, 2C), 120.5 (q, $J_{C\text{-}F}$ = 281.9 Hz, *C*F_3), 120.3 (q, $J_{C\text{-}F}$ = 281.6 Hz, *C*F_3), 67.1 (sep, $J_{C\text{-}F}$ = 34.6 Hz, *C*H), 54.1 (*C*H), 44.5 (*C*H), 22.9 (*C*H_2), 22.7 (*C*H_2), 11.8 (*C*H_3), 11.7 (*C*H_3). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{17}H_{19}F_6NO_3$, 399.1264; found: 399.1267.

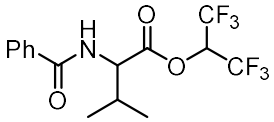
1,1,1,3,3,3-Hexafluoropropan-2-yl 2-benzamido-2-cyclohexylacetate (1h).



rac-**1h**

Title compound was prepared from *rac*-*N*-benzoyl-2-cyclohexylglycine (479 mg, 1.83 mmol) according to General Procedure II (reaction time: 18 h, flash column chromatography eluent: hexane/EtOAc = 20/1 to 10/1) as a white solid in 57% yield (428.4 mg, 1.04 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.82–7.75 (m, 2H), 7.55–7.49 (m, 1H), 7.48–7.40 (m, 2H), 6.65 (d, *J* = 8.3 Hz, 1H), 5.80 (sep, *J* = 6.0 Hz, 1H), 4.94 (dd, *J* = 8.2, 5.0 Hz, 1H), 2.02–1.92 (m, 1H), 1.84–1.73 (m, 3H), 1.72–1.61 (m, 2H), 1.38–1.03 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.3 (*C*O), 167.6 (*C*O), 133.7 (*C*), 132.1 (*C*H), 128.8 (*C*H, 2C), 127.2 (*C*H, 2C), 124.8–115.9 (m, *C*F_3, 2C), 67.0 (sep, $J_{C\text{-}F}$ = 34.8 Hz, *C*H), 57.1 (*C*H), 40.8 (*C*H), 29.5 (*C*H_2, C), 28.2 (*C*H_2, C), 25.9 (*C*H_2, 3C). Elemental Analysis: Calcd for $C_{18}H_{19}F_6NO_3$: C, 52.56; H, 4.66; N, 3.41;. Found: C, 52.77; H, 4.73; N, 3.47.

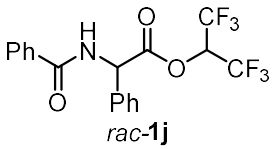
1,1,1,3,3,3-Hexafluoropropan-2-yl benzoylvalinate (1i).



rac-**1i**

Title compound was synthesized from *rac*-*N*-benzoylvaline (332 mg, 1.5 mmol) according to General Procedure II (reaction time: 96 h, flash column chromatography eluent: hexane/EtOAc = 8/1) as a white solid in 80% yield (445 mg, 1.20 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.82–7.75 (m, 2H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 6.61 (d, *J* = 6.9 Hz, 1H), 5.81 (sep, *J* = 6.0 Hz, 1H), 4.95 (dd, *J* = 8.7, 5.0 Hz, 1H), 2.42–2.29 (m, 1H), 1.06 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.4 (*C*O), 167.7 (*C*O), 133.7 (*C*), 132.2 (*C*H), 128.8 (*C*H, 2C), 127.2 (*C*H, 2C), 120.4 (q, $J_{C\text{-}F}$ = 277.8 Hz, *C*F_3), 120.3 (q, $J_{C\text{-}F}$ = 280.6 Hz, *C*F_3), 67.0 (sep, $J_{C\text{-}F}$ = 34.8 Hz, *C*H), 57.4 (*C*H), 31.2 (*C*H), 19.0 (*C*H_3), 17.6 (*C*H_3). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{15}H_{15}F_6NO_3$, 371.0951; found: 371.0958.

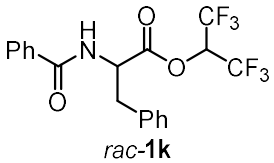
1,1,1,3,3,3-Hexafluoropropan-2-yl 2-benzamido-2-phenylacetate (1j).



rac-**1j**

Title compound was synthesized from *rac*-*N*-benzoylphenylglycine (697 mg, 2.73 mmol) according to General Procedure II (flash column chromatography eluent: hexane/EtOAc = 30/1 to 10/1) as a white solid in 82% yield (912 mg, 2.25 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83–7.77 (m, 2H), 7.53 (tt, *J* = 7.3, 1.5 Hz, 1H), 7.47–7.38 (m, 7H), 6.94 (d, *J* = 6.4 Hz, 1H), 5.87 (d, *J* = 6.4 Hz, 1H), 5.78 (sep, *J* = 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.4 (*C*O), 167.2 (*C*O), 134.0 (*C*), 133.1 (*C*), 132.3 (*C*H), 129.6 (*C*H), 129.5 (*C*H, 2C), 128.8 (*C*H, 2C), 127.6 (*C*H, 2C), 127.3 (*C*H, 2C), 120.3 (q, $J_{C\text{-}F}$ = 280.6 Hz, *C*F_3), 120.2 (q, $J_{C\text{-}F}$ = 279.7 Hz, *C*F_3), 67.4 (sep, $J_{C\text{-}F}$ = 34.8 Hz, *C*H), 57.2 (*C*H). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{18}H_{13}F_6NO_3$, 405.0794; found: 405.0802.

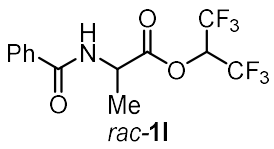
1,1,1,3,3,3-Hexafluoropropan-2-yl benzoylphenylalaninate (1k).



rac-**1k**

Title compound was synthesized from *rac*-*N*-benzoylphenylalanine (1347 mg, 5.00 mmol) according to General Procedure II (reaction time: 24 h, flash column chromatography eluent: hexane/EtOAc = 30/1 to 15/1) as a white solid in 60% yield (1254 mg, 2.99 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.72–7.64 (m, 2H), 7.53 (tt, *J* = 7.3, 1.5 Hz, 1H), 7.46–7.40 (m, 2H), 7.38–7.27 (m, 3H), 7.21–7.17 (m, 2H), 6.40 (d, *J* = 7.4 Hz, 1H), 5.80 (sep, *J* = 6.0 Hz, 1H), 5.21 (dt, *J* = 7.5, 6.3 Hz, 1H), 3.37 (dd, *J* = 14.2, 6.0 Hz, 1H), 3.23 (dd, *J* = 14.2, 6.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.1 (*C*O), 167.3 (*C*O), 134.7 (*C*), 133.3 (*C*), 132.2 (*C*H), 129.3 (*C*H, 2C), 129.1 (*C*H, 2C), 128.8 (*C*H, 2C), 127.8 (*C*H), 127.1 (*C*H, 2C), 120.4 (q, $J_{C\text{-}F}$ = 281.6 Hz, *C*F_3), 120.3 (q, $J_{C\text{-}F}$ = 281.0 Hz, *C*F_3), 67.3 (sep, $J_{C\text{-}F}$ = 34.8 Hz, *C*H), 53.3 (*C*H), 37.2 (*C*H_2). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{19}H_{15}F_6NO_3$, 419.0951; found: 419.0954.

1,1,1,3,3,3-Hexafluoropropan-2-yl benzoylalaninate (**1l**).

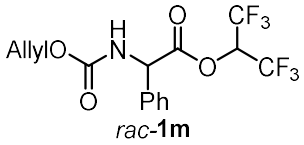


rac-**1l**

Title compound was synthesized from *rac*-*N*-benzoylalanine (966 mg, 5.00 mmol) according to General Procedure II (reaction time: 24 h, flash column chromatography eluent: hexane/EtOAc = 30/1 to 10/1) as a white solid in 86% yield (1481 mg, 4.31 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81–7.75 (m, 2H), 7.52 (tt, *J* = 7.3, 1.5 Hz, 1H), 7.46–7.39 (m, 2H), 6.74 (s, 1H), 5.78 (sep, *J* = 6.0 Hz, 1H), 4.92 (quin, *J* = 7.3 Hz, 1H), 1.58 (d, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.4 (*C*O), 167.4 (*C*O), 133.4 (*C*), 132.2 (*C*H), 128.8 (*C*H, 2C), 127.2 (*C*H, 2C), 120.4 (q, $J_{C\text{-}F}$ = 278.4 Hz, *C*F_3), 120.3 (q, $J_{C\text{-}F}$ = 281.0 Hz, *C*F_3), 67.2 (sep, $J_{C\text{-}F}$ = 34.8 Hz, *C*H), 48.4 (*C*H), 17.8 (*C*H_3). HRMS-EI (*m/z*): $[M]^+$ calcd for

$C_{13}H_{11}F_6NO_3$, 343.0638; found: 343.0640.

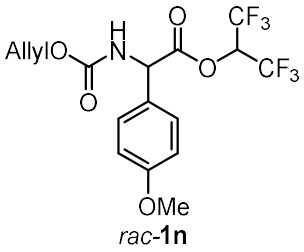
1,1,1,3,3,3-Hexafluoropropan-2-yl 2-{[(allyloxy)carbonyl]amino}-2-phenylacetate (**1m**).



rac-**1m**

Title compound was synthesized from *rac*-*N*-Alloc-phenylglycine (2100 mg, 8.93 mmol) according to General Procedure II (reaction time: 1 h, flash 37urbom chromatography eluent: hexane/EtOAc = 30/1 to 15/1) as a white solid in 75% yield (2586 mg, 6.71 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54–7.32 (m, 5H), 5.90 (ddt, *J* = 17.0, 10.6, 5.7 Hz, 1H), 5.74 (sep, *J* = 6.0 Hz, 1H), 5.70–5.60 (m, 1H), 5.53 (d, *J* = 6.8 Hz, 1H), 5.31 (d, *J* = 17.4 Hz, 1H), 5.22 (d, *J* = 10.1 Hz, 1H), 4.65–4.53 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.5 (*C*O), 155.3 (*C*O), 134.1 (*C*), 132.3 (*C*H), 129.6 (*C*H), 129.4 (*C*H, 2C), 127.4 (*C*H, 2C), 120.2 (q, $J_{C\text{-}F}$ = 281.3 Hz, *C*F_3), 120.1 (q, $J_{C\text{-}F}$ = 279.7 Hz, *C*F_3), 118.4 (*C*H_2), 67.4 (sep, $J_{C\text{-}F}$ = 34.8 Hz, *C*H), 66.4 (*C*H_2), 58.1 (*C*H). Elemental Analysis: Calcd for $C_{15}H_{13}F_6NO_4$: C, 46.76; H, 3.40; N, 3.64;. Found: C, 46.88; H, 3.44; N, 3.62.

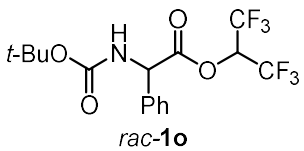
1,1,1,3,3,3-Hexafluoropropan-2-yl 2-{[(allyloxy)carbonyl]amino}-2-(4-methoxyphenyl)acetate (**1n**).



rac-**1n**

Title compound was synthesized from *rac*-*N*-Alloc-4-methoxyphenylglycine (1326 mg, 5.00 mmol) according to General Procedure II (reaction time: 11 h, flash column chromatography eluent: hexane/EtOAc = 10/1 to 3/1) as a yellow solid in 20% yield (416 mg, 1.00 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29–7.24 (m, 2H), 6.93–6.87 (m, 2H), 5.89 (ddt, *J* = 16.9, 11.0, 5.6 Hz, 1H), 5.73 (sep, *J* = 6.0 Hz, 1H), 5.59 (d, *J* = 6.4 Hz, 1H), 5.45 (d, *J* = 6.9 Hz, 1H), 5.30 (d, *J* = 17.4 Hz, 1H), 5.22 (dd, *J* = 1.1, 10.3 Hz, 1H), 4.64–4.53 (m, 2H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.6 (*C*O), 160.5 (*C*O), 155.3 (*C*), 132.4 (*C*H), 128.7 (*C*H, 2C), 126.0 (*C*), 120.3 (q, $J_{C\text{-}F}$ = 281.6 Hz, *C*F_3), 120.2 (q, $J_{C\text{-}F}$ = 279.7 Hz, *C*F_3), 118.3 (*C*H_2), 114.8 (*C*H, 2C), 67.3 (sep, $J_{C\text{-}F}$ = 34.7 Hz, *C*H), 66.4 (*C*H_2), 57.5 (*C*H) , 55.4 (*C*H_3). Elemental Analysis: Calcd for $C_{16}H_{15}F_6NO_5$: C, 46.28; H, 3.64; N, 3.37;. Found: C, 46.66; H, 3.68; N, 3.46.

1,1,1,3,3,3-Hexafluoropropan-2-yl 2-[(*tert*-butoxycarbonyl)amino]-2-phenylacetate (**1o**).



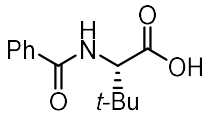
rac-**1o**

Title compound was synthesized from *rac*-*N*-Boc-phenylglycine (2160 mg, 8.60 mmol) according to General Procedure II (reaction time: 3 h, flash column chromatography eluent: hexane/EtOAc = 50/1 to 30/1) as

a white solid in 72% yield (2496 mg, 6.22 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42–7.31 (m, 5H), 5.74 (sep, *J* = 6.0 Hz, 1H), 5.46 (d, *J* = 6.4 Hz, 1H), 5.38 (br-s, 1H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.7 (*C*O), 154.8 (*C*O), 134.4 (*C*), 129.45 (*C*H), 129.39 (*C*H, 2C), 127.4 (*C*H, 2C), 120.3 (q, $J_{C\text{-}F}$ = 281.6 Hz, *C*F_3), 120.2 (q, $J_{C\text{-}F}$ = 279.0 Hz, *C*F_3), 81.0 (*C*H), 67.3 (sep, $J_{C\text{-}F}$ = 34.8 Hz, *C*H), 58.0 (*C*), 28.3 (*C*H_3, 3C). Elemental Analysis: Calcd for $C_{16}H_{17}F_6NO_4$: C, 47.89; H, 4.27; N, 3.49;. Found: C, 47.77; H, 4.22; N, 3.46.

Characterization of the Products

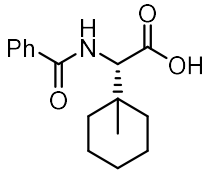
(*S*)-(+)-2-Benzamido-3,3-dimethylbutanoic acid (2a).[18]



(*S*)-**2a**

2.5 eq of 1 M aq NaOH was used. Title compound was obtained in >99% yield (20.9 mg, 0.889 mmol) as a white solid, 95:5 er. ^{1}H and ^{13}C NMR were in agreement with the literature.[18] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.82–7.76 (m, 2H), 7.56–7.50 (m, 1H), 7.48–7.42 (m, 2H), 6.70 (d, *J* = 9.2 Hz, 1H), 4.73 (d, *J* = 9.6 Hz, 1H), 1.10 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.8 (*C*O), 167.8 (*C*O), 134.0 (*C*), 132.1 (*C*H), 128.9 (*C*H, 2C), 127.2 (*C*H, 2C), 60.5 (*C*H), 35.2 (*C*H), 26.8 (3C). HRMS-FAB (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{18}NO_3$, 236.1281; found: 236.1287. In order to determine the enantiomer ratio (er) of the hydrolyzed product, **2a** was transformed to the corresponding methyl ester by the reaction with (trimethylsilyl)diazomethane solution 2.0 M in Et_2O at rt, and the er of the methyl ester was determined by HPLC analysis with CHIRALCEL OD column (conditions: hexane:2-propanol = 100:1, flow rate = 0.5 mL/min, rt, Rt (major) = 48.36 min, Rt (minor) = 38.20 min $[\alpha]_D^{24.7}$ = +10.2 (*c* 0.86, CH_3OH). The absolute configuration was determined by comparison of the HPLC retention time of (*S*)-(+)-2-benzamido-3,3-dimethylbutanoic acid methyl ester prepared from optically active (*S*)-2-amino-3,3-dimethylbutanoic acid.

(+)-2-Benzamido-2-(1-methylcyclohexyl)acetic acid (2b).

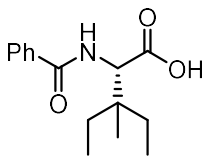


(+)-**2b**

8 eq of 1 M aq NaOH was used. Title compound was obtained in 78% yield (21.4 mg, 0.078 mmol) as a white solid, 96:4 er. ^{1}H NMR (400 MHz, CD_3OD) δ = 7.84–7.79 (m, 2H), 7.55 (tt, *J* = 7.3, 1.5 Hz, 1H), 7.50–7.44 (m, 2H), 4.79 (s, 1H), 1.74–1.33 (m, 10H), 1.08 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ = 174.4 (*C*O), 170.6 (*C*O), 135.7 (*C*), 132.8 (*C*H), 129.6 (*C*H, 2C), 128.5 (*C*H, 2C), 60.7 (*C*H), 38.0 (*C*), 36.5 (CH_2), 36.0 (CH_2), 27.1 (CH_2), 22.85 (CH_2), 22.79 (CH_2), 21.6 (CH_3). Elemental Analysis: Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09;. Found: C, 69.66; H, 7.74; N, 5.05. In order to determine the enantiomer ratio (er) of the hydrolyzed product, **2b** was transformed to the corresponding methyl ester

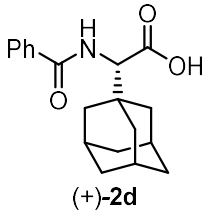
by the reaction with (trimethylsilyl)diazomethane solution 2.0 M in Et_2O at rt, and the er of the methyl ester was determined by HPLC analysis with CHIRALCEL OD-H column [conditions: hexane:2-propanol = 100:1, flow rate = 1 mL/min, rt, Rt (major) = 21.68 min, Rt (minor) = 18.05 min]. $[\alpha]_D^{21.0}$ = +66.9 (*c* 1.0, CH_3OH).

(+)-2-Benzamido-3-ethyl-3-methylpentanoic acid (2c).


(+)-**2c**

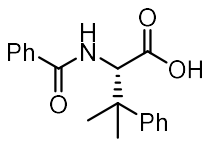
8 eq of 1 M aq NaOH was used. Title compound was obtained in 53% yield (28.1 mg, 0.107 mmol) as a white solid, 94:6 er. ^{1}H NMR (400 MHz, CD_3OD) δ = 7.84–7.76 (m, 2H), 7.58–7.51 (m, 1H), 7.50–7.43 (m, 2H), 4.78–4.73 (m, 1H), 1.59–1.40 (m, 4H), 1.02 (s, 3H), 0.92 (t, *J* = 7.8 Hz, 3H), 0.90 (t, *J* = 7.8 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ = 174.7 (*C*O), 170.6 (*C*O), 135.7 (*C*), 132.8 (*C*H), 129.6 (*C*H, 2C), 128.5 (*C*H, 2C), 59.3 (*C*H), 40.5 (*C*H), 29.4 (CH_2), 28.9 (CH_2), 20.9 (CH_3), 8.23 (CH_3), 8.18 (CH_3). Elemental Analysis: Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32;. Found: C, 68.27; H, 8.02; N, 5.26. In order to determine the enantiomer ratio (er) of the hydrolyzed product, **2c** was transformed to the corresponding methyl ester by the reaction with (trimethylsilyl)diazomethane solution 2.0 M in Et_2O at rt, and the er of the methyl ester was determined by HPLC analysis with CHIRALCEL OD-H column [conditions: hexane:2-propanol = 100:1, flow rate = 1 mL/min, rt, Rt (major) = 19.61 min, Rt (minor) = 17.44 min]. $[\alpha]_D^{20.8}$ = +82.4 (*c* 0.8, CH_3OH).

(+)-*N*-Benzoyl-2-(1-adamantyl)glycine (2d).


(+)-**2d**

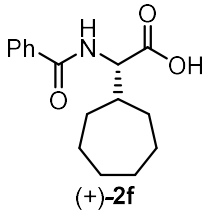
8 eq of 1 M aq NaOH was used. Title compound was obtained in 58% yield (36.2 mg, 0.116 mmol), 93.5:6.5 er. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.82–7.77 (m, 2H), 7.55–7.49 (m, 1H), 7.48–7.42 (m, 2H), 6.75 (d, *J* = 9.2 Hz, 1H), 4.64–4.60 (m, 1H), 2.06–1.98 (m, 3H), 1.76–1.60 (m, 12H). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 175.0 (*C*O), 167.9 (*C*O), 134.1 (*C*), 132.1 (*C*H), 128.8 (*C*H, 2C), 127.3 (*C*H, 2C), 61.4 (*C*H), 38.9 (CH_2, 3C), 37.0 (*C*), 36.7 (CH_2, 3C), 28.4 (*C*H, 3C). Elemental Analysis: Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47;. Found: C, 72.62; H, 7.44; N, 4.43. In order to determine the enantiomer ratio (er) of the hydrolyzed product, **2d** was transformed to the corresponding methyl ester by the reaction with (trimethylsilyl)diazomethane solution 2.0 M in Et_2O at rt, and the er of the methyl ester was determined by HPLC analysis with CHIRALCEL OD-H column [conditions: hexane:2-propanol = 100:1, flow rate = 1 mL/min, rt, Rt (major) = 24.69 min, Rt (minor) = 21.09 min]. $[\alpha]_D^{20.6}$ = +7.8 (*c* 1.0, CH_3OH).

(+)-2-Benzamido-3-methyl-3-phenylbutanoic acid (2e).


(+)-**2e**

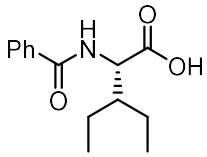
8 eq of 1 M aq NaOH was used. Title compound was obtained in 65% yield (38.6 mg, 0.130 mmol) as a white solid, 86:14 er. ^{1}H NMR (400 MHz, CD_3OD) δ = 7.60–7.53 (m, 2H), 7.52–7.45 (m, 3H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 1H), 5.04 (s, 1H), 1.55 (s, 3H), 1.52 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ = 173.9 (*C*O), 170.3 (*C*O), 147.0 (*C*), 135.6 (*C*), 132.7 (*C*H), 129.4 (*C*H, 2C), 129.2 (*C*H, 2C), 128.3 (*C*H, 2C), 127.5 (*C*H), 127.4 (*C*H, 2C), 62.4 (*C*H), 42.3 (*C*), 27.1 (CH_3), 25.0 (CH_3). Elemental Analysis: Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71;. Found: C, 72.59; H, 6.48; N, 4.64. In order to determine the enantiomer ratio (er) of the hydrolyzed product, **2e** was transformed to the corresponding methyl ester by the reaction with (trimethylsilyl)diazomethane solution 2.0 M in Et_2O at rt, and the er of the methyl ester was determined by HPLC analysis with CHIRALCEL OD-H column [conditions, hexane:2-propanol = 100:1, flow rate = 1 mL/min, rt, Rt (major) = 43.57 min, Rt (minor) = 29.47 min]. $[\alpha]_D^{17.7}$ = +88.2 (*c* 1.0, CH_3OH).

(+)-2-Benzamido-2-cycloheptylacetic acid (2f).


(+)-**2f**

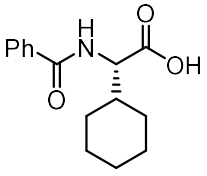
8 eq of 1 M aq NaOH was used. Title compound was obtained in 41% yield (22.4 mg, 0.081 mmol) as a white solid, 86.5:13.5 er. ^{1}H NMR (400 MHz, CD_3OD) δ = 7.85–7.80 (m, 2H), 7.57–7.50 (m, 1H), 7.49–7.42 (m, 2H), 4.60 (dd, *J* = 6.2, 3.0 Hz, 1H), 2.23–2.12 (m, 1H), 1.87–1.68 (m, 4H), 1.67–1.36 (m, 8H). ^{13}C NMR (100 MHz, CD_3OD) δ = 175.0 (*C*O), 170.7 (*C*O), 135.5 (*C*), 132.8 (*C*H), 129.5 (*C*H, 2C), 128.5 (*C*H, 2C), 59.7 (*C*H), 42.8 (*C*H), 32.4 (CH_2), 31.0 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 27.7 (CH_2), 27.6 (CH_2). Elemental Analysis: Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09;. Found: C, 69.43; H, 7.72; N, 4.95. In order to determine the enantiomer ratio (er) of the hydrolyzed product, **2f** was transformed to the corresponding methyl ester by the reaction with (trimethylsilyl)diazomethane solution 2.0 M in Et_2O at rt, and the er of the methyl ester was determined by HPLC analysis with CHIRALCEL OD-H column [conditions: hexane:2-propanol = 100:1, flow rate = 1 mL/min, rt, Rt (major) = 37.41 min, Rt (minor) = 29.08 min]. $[\alpha]_D^{18.4}$ = +23.5 (*c* 1.0, CH_3OH).

(+)-2-Benzamido-3-ethylpentanoic acid (2g).


(+)-**2g**

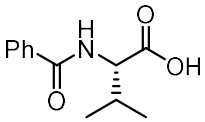
8 eq of 1 M aq NaOH was used. Title compound was obtained in 89% yield (44.5 mg, 0.178 mmol) as a white solid, 92.5:7.5 er. ^{1}H NMR (400 MHz, CD_3OD) δ = 7.86–7.79 (m, 2H), 7.57–7.51 (m, 1H), 7.50–7.42 (m, 2H), 4.82 (d, *J* = 5.5 Hz, 1H), 1.93–1.82 (m, 1H), 1.61–1.34 (m, 4H), 1.00 (t, *J* = 7.6 Hz, 3H), 0.97 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ = 175.5 (*C*O), 170.7 (*C*O), 135.6 (*C*), 132.8 (*C*H), 129.5 (*C*H, 2C), 128.5 (*C*H, 2C), 55.8 (*C*H), 44.9 (*C*H), 23.6 (CH_2), 23.4 (CH_2), 11.9 (CH_3), 11.8 (CH_3). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{14}H_{19}NO_3$, 249.1359; found: 249.1362. In order to determine the enantiomer ratio (er) of the hydrolyzed product, **2g** was transformed to the corresponding methyl ester by the reaction with (trimethylsilyl)diazomethane solution 2.0 M in Et_2O at rt, and the er of the methyl ester was determined by HPLC analysis with CHIRALCEL OD-H column [conditions: hexane:2-propanol = 100:1, flow rate = 0.5 mL/min, rt, Rt (major) = 38.36 min, Rt (minor) = 24.64 min]. $[\alpha]_D^{20.5}$ = +13.9 (*c* 1.0, CH_3OH).

(*S*)-(+)-2-Benzamido-2-cyclohexylacetic acid (2h).[19]


(*S*)-**2h**

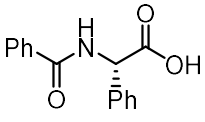
8 eq of 1 M aq NaOH was used. Title compound was obtained in 85% yield (44.2 mg, 0.169 mmol), 86:14 er. ^{1}H NMR (400 MHz, CD_3OD) δ = 7.86–7.80 (m, 2H), 7.57–7.50 (m, 1H), 7.49–7.42 (m, 2H), 4.50 (d, *J* = 6.9 Hz, 1H), 2.00–1.89 (m, 1H), 1.85–1.73 (m, 4H), 1.73–1.62 (m, 1H), 1.39–1.10 (m, 5H). ^{13}C NMR (100 MHz, CD_3OD) δ = 175.0 (*C*O), 170.6 (*C*O), 135.4 (*C*), 132.8 (*C*H), 129.5 (*C*H, 2C), 128.5 (*C*H, 2C), 59.4 (*C*H), 41.2 (*C*H), 31.0 (CH_2, C), 30.1 (CH_2, C), 27.2 (CH_2, C), 27.1 (CH_2, 2C). Elemental Analysis: Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36;. Found: C, 68.83; H, 7.19; N, 5.32. In order to determine the enantiomer ratio (er) of the hydrolyzed product, **2h** was transformed to the corresponding methyl ester by the reaction with (trimethylsilyl)diazomethane solution 2.0 M in Et_2O at rt, and the er of the methyl ester was determined by HPLC analysis with CHIRALCEL OD-H column [conditions: hexane:2-propanol = 100:1, flow rate = 1 mL/min, rt, Rt (major) = 49.95 min, Rt (minor) = 35.96 min]. $[\alpha]_D^{21.6}$ = +11.4 (*c* 1.0, CH_3OH). The absolute configuration was established by comparison of the specific optical rotation to the literature value for (*S*)-(+)-2-benzamido-2-cyclohexylacetic acid[20]: $[\alpha]_D^{25}$ = +8.7 (*c* 0.03, CH_3OH).

(*S*)-(+)-*N*-Benzoylvaline (2i).[21]


(*S*)-**2i**

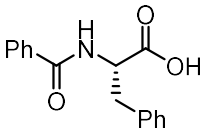
8 eq of 1 M aq NaOH was used. Title compound was obtained in 94% yield (41.7 mg, 0.188 mmol) as a white solid, 83.5:16.5 er. ^{1}H NMR was in agreement with the literature.[21] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.86–7.75 (m, 2H), 7.56–7.50 (m, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 6.68 (d, *J* = 8.7 Hz, 1H), 4.81 (dd, *J* = 8.7, 5.0 Hz, 1H), 2.44–2.30 (m, 1H), 1.06 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.1 (*C*O), 168.0 (*C*O), 133.9 (*C*), 132.1 (*C*H), 128.8 (*C*H, 2C), 127.2 (*C*H, 2C), 57.6 (*C*H), 31.4 (*C*H), 19.2 (CH_3), 18.0 (CH_3). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{12}H_{15}NO_3$, 221.1046; found: 221.1051. In order to determine the enantiomer ratio (er) of the hydrolyzed product, **2i** was transformed to the corresponding methyl ester by the reaction with (trimethylsilyl)diazomethane solution 2.0 M in Et_2O at rt, and the er of the methyl ester was determined by HPLC analysis with CHIRALPAK AD-H column [conditions: hexane:2-propanol = 90:1, flow rate = 1 mL/min, rt, Rt (major) = 66.05 min, Rt (minor) = 43.69 min]. $[\alpha]_D^{20.3}$ = +15.1 (*c* 1.0, CH_3OH). The absolute configuration was established by comparison of the specific optical rotation to the literature value for (*S*)-(+)-benzoylvaline[22]: $[\alpha]_D^{20}$ = +10 (*c* 1.03, CH_3OH).

(+)-2-Benzamido-2-phenylacetic acid (2j).[23]


(+)-**2j**

2.5 eq of 1 M aq NaOH was used. Title compound was obtained in 39% yield (19.8 mg, 0.078 mmol) as a white solid, 88.5:11.5 er. A small amount of impurity could not be removed by the work-up process. ^{1}H and ^{13}C NMR were in agreement with the literature.[23] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.09–7.99 (m, 1H), 7.87–7.72 (m, 2H), 7.68–7.37 (m, 5H), 7.68–7.37 (m, 2H), 5.70 (d, *J* = 2.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.8 (*C*O), 167.1 (*C*O), 136.8 (*C*), 134.9 (*C*), 132.0 (*C*H), 130.3 (*C*H), 130.0 (*C*H), 129.0 (*C*H), 128.9 (*C*H), 128.7 (*C*H), 128.6 (*C*H), 128.4 (*C*H), 127.4 (*C*H), 127.2 (*C*H), 56.9 (*C*H). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{15}H_{13}NO_3$, 255.0890; found: 255.0893. In order to determine the enantiomer ratio (er) of the hydrolyzed product, **2j** was transformed to the corresponding methyl ester by the reaction with (trimethylsilyl)diazomethane solution 2.0 M in Et_2O at rt, and the er of the methyl ester was determined by HPLC analysis with CHIRALCEL OD-H column [conditions: hexane:2-propanol = 20:1, flow rate = 1 mL/min, rt, Rt (major) = 31.62 min, Rt (minor) = 24.86 min]. $[\alpha]_D^{25.7}$ = +51.5 (*c* 1.0, CH_3OH).

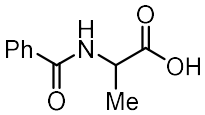
(*S*)-(+)-Benzoylphenylalanine (2k).[24]



(*S*)-**2k**

2.5 eq of 1 M aq NaOH was used. Title compound was obtained in 90% yield (48.3 mg, 0.179 mmol) as a white solid, 57:43 er. ^{1}H and ^{13}C NMR were in agreement with the literature.[24] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.72 (d, J = 8.2 Hz, 1H), 7.83–7.78 (m, 2H), 7.55–7.49 (m, 1H), 7.48–7.42 (m, 2H), 7.35–7.30 (m, 2H), 7.27 (t, J = 7.3 Hz, 2H), 7.21–7.15 (m, 1H), 4.64 (ddd, J = 10.6, 8.1, 4.2 Hz, 1H), 3.21 (dd, J = 13.7, 4.6 Hz, 1H), 3.09 (dd, J = 13.8, 11.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 173.3 (*C*O), 166.4 (*C*O), 138.3 (*C*), 134.0 (*C*), 131.4 (*C*H), 129.1 (*C*H, 2C), 128.3 (*C*H, 2C), 128.2 (*C*H, 2C), 127.4 (*C*H, 2C), 126.4 (*C*H), 54.3 (*C*H), 36.3 (*C*H$_2$). HRMS-EI (*m/z*): [M]$^+$ calcd for $C_{16}H_{15}NO_3$, 269.1046; found: 269.1052. In order to determine the enantiomer ratio (er) of the hydrolyzed product, **2k** was transformed to the corresponding methyl ester by the reaction with (trimethylsilyl)diazomethane solution 2.0 M in Et_2O at rt, and the er of the methyl ester was determined by HPLC analysis with CHIRALCEL OD-H column [conditions: hexane:2-propanol = 20:1, flow rate = 1 mL/min, rt, Rt (major) = 21.72 min, Rt (minor) = 30.38 min]. $[\alpha]_D^{25.5}$ = +4.7 (*c* 1.0, CH_3OH). The absolute configuration was established by comparison of the specific optical rotation to the literature value for (*S*)-(+)-benzoylphenylalanine[25]: $[\alpha]_D^{24}$ = +20 (*c* 0.1, CH_3OH).

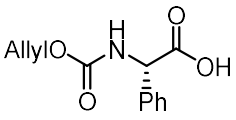
***N*-Benzoylalanine (2l).[26]**



2l

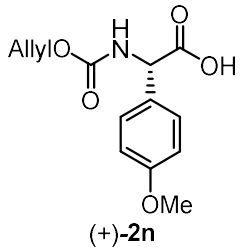
2.5 eq of 1 M aq NaOH was used. Title compound was obtained in 51% yield (19.8 mg, 0.102 mmol), 51.5:48.5 er. ^{1}H NMR (400 MHz, CD_3OD) δ = 7.88–7.82 (m, 2H), 7.54 (tt, J = 7.6, 2.5 Hz, 1H), 7.49–7.43 (m, 2H), 4.60 (q, J = 7.3 Hz, 1H), 1.52 (d, J = 7.8 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ = 176.2 (*C*O), 170.1 (*C*O), 135.3 (*C*), 132.8 (*C*H), 129.5 (*C*H, 2C), 128.5 (*C*H, 2C), 49.9 (*C*H), 17.5 (*C*H$_3$). HRMS-EI (*m/z*): [M]$^+$ calcd for $C_{10}H_{11}NO_3$, 193.0733; found: 193.0743. In order to determine the enantiomer ratio (er) of the hydrolyzed product, **2l** was transformed to the corresponding methyl ester by the reaction with (trimethylsilyl)diazomethane solution 2.0 M in Et_2O at rt, and the er of the methyl ester was determined by HPLC analysis with CHIRALCEL OD column [conditions, hexane:2-propanol = 20:1, flow rate = 1 mL/min, rt, Rt (major) = 20.02 min, Rt (minor) = 28.17 min].

(+)-2-{[(Allyloxy)carbonyl]amino}-2-phenylacetic acid (2m).


(+)-**2m**

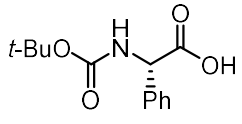
2.5 eq of 1 M aq NaOH was used. Title compound was obtained in 79% yield (37.2 mg, 0.158 mmol) as a white solid, 89:11 er. ^{1}H NMR (400 MHz, CD_3OD) δ = 7.44–7.39 (m, 2H), 7.38–7.29 (m, 3H), 5.93 (ddt, *J* = 17.0, 10.6, 5.6 Hz, 1H), 5.31 (d, *J* = 16.7 Hz, 1H), 5.24 (s, 1H), 5.18 (d, *J* = 10.6 Hz, 1H), 4.55 (dd, *J* = 5.4, 1.4 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ = 173.9 (*C*O), 157.9 (*C*O), 138.3 (*C*), 134.1 (*C*H), 129.7 (*C*H, 2C), 129.3 (*C*H), 128.5 (*C*H, 2C), 117.7 (CH_2), 66.7 (CH_2), 59.5 (*C*H). Elemental Analysis: Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95;. Found: C, 61.36; H, 5.55; N, 5.85. In order to determine the enantiomer ratio (er) of the hydrolyzed product, **2m** was transformed to the corresponding methyl ester by the reaction with (trimethylsilyl)diazomethane solution 2.0 M in Et_2O at rt, and the er of the methyl ester was determined by HPLC analysis with CHIRALPAK OP(+) column [conditions: hexane:2-propanol = 90:1, flow rate = 0.25 mL/min, rt, Rt (major) = 73.24 min, Rt (minor) = 68.95 min]. $[\alpha]_D^{20.2}$ = +78.5 (*c* 1.0, CH_3OH).

(+)-2-{[(Allyloxy)carbonyl]amino}-2-(4-methoxyphenyl)acetic acid (2n).


(+)-**2n**

2.5 eq of 1 M aq NaOH was used. Title compound was obtained in 75% yield (39.6 mg, 0.149 mmol) as a pale-yellow solid, 83.5:16.5 er. ^{1}H NMR (400 MHz, CD_3OD) δ = 7.32 (dt, *J* = 8.7, 2.4 Hz, 2H), 6.90 (dt, *J* = 8.7, 2.5 Hz, 2H), 5.93 (ddt, *J* = 17.0, 11.0, 5.6 Hz, 1H), 5.30 (d, *J* = 17.4 Hz, 1H), 5.17 (d, *J* = 8.4 Hz, 1H), 5.16 (s, 1H), 4.54 (d, *J* = 5.5 Hz, 2H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ = 174.4 (*C*O), 161.1 (*C*O), 157.8 (*C*), 134.2 (*C*H), 130.2 (*C*), 129.8 (*C*H, 2C), 117.7 (CH_2), 115.1 (*C*H, 2C), 66.6 (CH_2), 59.0 (*C*H), 55.7 (CH_3). Elemental Analysis: Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28;. Found: C, 58.77; H, 5.78; N, 5.16. In order to determine the enantiomer ratio (er) of the hydrolyzed product, **2n** was transformed to the corresponding methyl ester by the reaction with (trimethylsilyl)diazomethane solution 2.0 M in Et_2O at rt, and the er of the methyl ester was determined by HPLC analysis with CHIRALPAK OP(+) column [conditions, hexane:2-propanol = 100:1, flow rate = 1 mL/min, rt, Rt (major) = 25.93 min, Rt (minor) = 23.91 min]. $[\alpha]_D^{20.7}$ = +91.4 (*c* 1.0, CH_3OH).

(+)-2-[(*tert*-Butoxycarbonyl)amino]-2-phenylacetic acid (2o).[27]

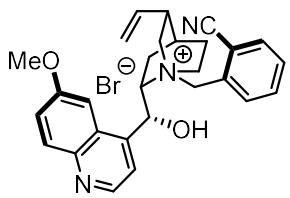

(+)-**2o**

2.5 eq of 1 M aq NaOH was used. Title compound was obtained in 35% yield (17.6 mg, 0.070 mmol) as a white solid, 90:10 er. ^{1}H NMR (400 MHz, CD_3OD, *indicate minor rotamer) δ = 7.43–7.38 (m, 2H), 7.37–7.26 (m, 3H), 5.22 (s,

1H), 1.44 (s, 7.4H), 1.37* (s, 1.6H). ^{13}C NMR (100 MHz, CD_3OD, *indicate minor rotamer) δ = 174.1 (*C*O), 157.3 (*C*O), 156.8* (*C*O), 138.5 (*C*), 129.7 (*C*H, 2C), 129.2 (*C*H), 128.5 (*C*H, 2C), 81.6* (*C*), 80.8 (*C*), 60.4* (*C*H), 59.1 (*C*H), 28.7 (*C*H_3, 3C), 28.5* (*C*H_3, 3C). Elemental Analysis: Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57;. Found: C, 62.21; H, 6.78; N, 5.50. In order to determine the enantiomer ratio (er) of the hydrolyzed product, **2o** was transformed to the corresponding methyl ester by the reaction with (trimethylsilyl)diazomethane solution 2.0 M in Et_2O at rt, and the er of the methyl ester was determined by HPLC analysis with CHIRALPAK AD-H column [conditions, hexane:2-propanol = 25:1, flow rate = 0.5 mL/min, rt, Rt (major) = 32.53 min, Rt (minor) = 30.80 min]. $[\alpha]_D^{20.2}$ = +84.4 (*c* 1.0, CH_3OH).

Synthesis and Characterization of Catalyst 3d and 3f

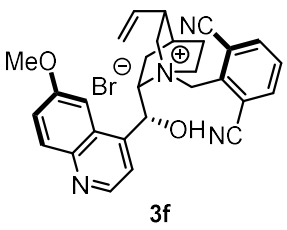
***N*-(2-Cyanobenzyl)quninium bromide (3d)**.



3d

Quinine (649 mg, 2.00 mmol) and 2-cyanobenzyl bromide (431 mg, 2.20 mmol) were added to a mixture of THF (1.8 mL), ethanol (1.5 mL), and chloroform (0.6 mL), and the reaction mixture was stirred at 100 ºC for 3 h under N_2. After cooled to rt, the crude material was concentrated under reduced pressure and purified by silica-gel column chromatography (CH_2Cl_2/MeOH = 50/1 to 20/1) to afford the title compound as a yellow solid in 68% yield (708 mg, 1.36 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.82 (d, *J* = 4.6 Hz, 1H), 8.62 (d, *J* = 7.4 Hz, 1H), 8.08 (d, *J* = 9.2 Hz, 1H), 7.91–7.80 (m, 3H), 7.69 (td, *J* = 7.8, 0.9 Hz, 1H), 7.41 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.09–6.98 (m, 2H), 6.75 (d, *J* = 6.9 Hz, 1H), 6.55 (d, *J* = 6.9 Hz, 1H), 5.61 (ddd, *J* = 17.1, 10.4, 6.5 Hz, 1H), 5.40–5.28 (m, 1H), 5.12 (dd, *J* = 10.5, 1.4 Hz, 1H), 5.08 (dd, *J* = 17.4, 1.4 Hz, 1H), 4.60 (d, *J* = 12.4 Hz, 1H), 4.02 (s, 3H), 3.80 (dd, *J* = 10.3, 6.7 Hz, 1H), 3.43–3.26 (m, 2H), 3.20 (td, *J* = 11.2, 6.7 Hz, 1H), 2.69–2.58 (m, 1H), 2.52–2.40 (m, 1H), 2.39–2.27 (m, 1H), 2.11 (d, *J* = 2.3 Hz, 1H), 1.94–1.66 (m, 1H), 1.57–1.45 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.6, 147.8, 144.4, 142.5, 136.3, 136.0, 134.5, 133.7, 132.6, 131.6, 130.2, 125.5, 122.2, 120.8, 118.3, 118.1, 116.0, 99.7, 71.9, 63.4, 61.6, 61.4, 56.1, 51.4, 37.9, 26.3, 24.8, 21.8. HRMS-FAB (*m/z*): $[M–Br^–]^+$ calcd for $C_{28}H_{30}N_3O_2$, 440.2333; found: 440.2338.

***N*-(2,6-Dicyanobenzyl)quininium bromide (3f).**

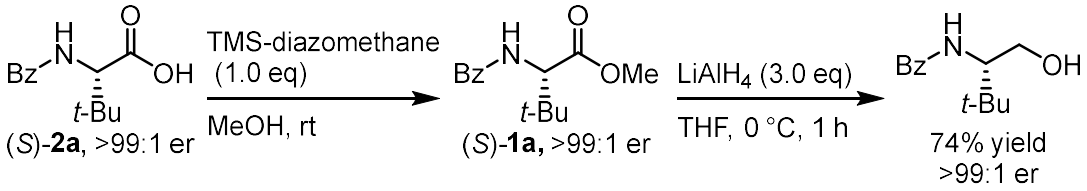


3f

Quinine (649 mg, 2.00 mmol) and 2,6-dicyanobenzyl bromide (559.0 mg, 2.20 mmol) were added to a mixture of THF (1.8 mL), ethanol (1.5 mL), and chloroform (0.6 mL), and the reaction mixture was stirred at 100 ºC for 3 h under N_2. After cooled to rt, the crude material was concentrated under reduced pressure and purified by silica-gel column chromatography (EtOAc/MeOH = 30/1 to 5/1) to afford the title compound as an orange solid in 42% yield (460 mg, 0.843 mmol). ^{1}H NMR (400 MHz, CD_3OD): δ = 8.80 (d, *J* = 4.6 Hz, 1H), 8.36 (d, *J* = 8.2 Hz, 2H), 8.05–7.98 (m, 2H), 7.94 (d, *J* = 4.6 Hz, 1H), 7.49 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.38 (d, *J* = 2.8 Hz, 1H), 6.76 (s, 1H), 5.76 (ddd, *J* = 17.0, 10.8, 6.0 Hz, 1H), 5.71 (d, *J* = 14.2 Hz, 1H), 5.24 (d, *J* = 13.8 Hz, 1H), 5.16 (d, *J* = 17.4, 1H), 5.07 (dd, *J* = 10.6, 0.9 Hz, 1H), 4.94–4.84 (m, 2H), 4.17–4.09 (m, 4H), 3.93 (dt, *J* = 12.4, 3.7 Hz, 1H), 3.78 (t, *J* = 11.2 Hz, 1H), 3.66 (td, *J* = 11.1, 3.7 Hz, 1H), 2.88–2.77 (m, 1H), 2.34–2.22 (m, 2H), 2.18–2.12 (m, 1H), 2.05–1.94 (m, 1H), 1.44–1.27 (m, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ = 160.3, 148.3, 145.3, 144.7, 139.9, 138.7, 134.4, 134.0, 131.9, 127.1, 124.2, 121.4, 119.9, 118.2, 117.0, 101.1, 79.5, 71.0, 66.8, 62.7, 62.1, 57.0, 54.6, 39.0, 26.9, 26.0, 23.1. HRMS-FAB (*m/z*): $[M–Br^–]^+$ calcd for $C_{29}H_{29}N_4O_2$, 465.2285; found: 465.2293.

Procedures for Transformations of Hydrolyzed Product 2a (Scheme 5)

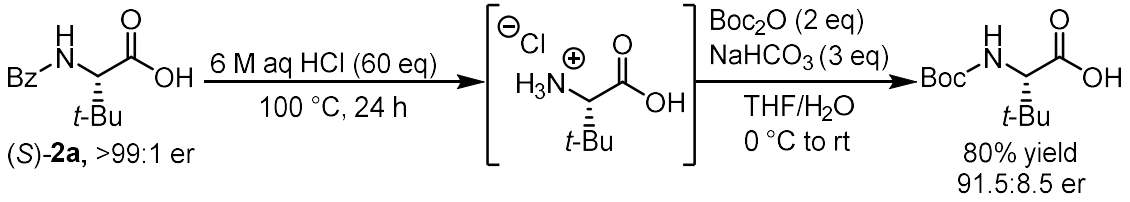
Methylation/Reduction Sequence of 2a



(*S*)-(+)-*N*-benzoyl-*tert*-leucine (**2a**) (>99:1 er, 234.5 mg, 0.997 mmol, 1.0 eq) was dissolved to MeOH (0.5 mL). TMS-diazomethane (2 M in Et_2O, 0.5 mL, 1.0 eq) was added dropwise to the solution until yellow color persists. The solution was purified by silica-gel column chromatography with hexane/Et_2O (2:1). Methyl 2-benzamido-3,3-dimethylbutanoate (**1a**) was obtained in 99% yield as colorless oil (247.6 mg, 0.993 mmol). A solution of methyl 2-benzamido-3,3-dimethylbutanoate (**1a**) (>99:1 er, 95.5 mg, 0.406 mmol, 1.0 eq) in dry THF (0.5 mL) was dropped to a stirred solution of lithium aluminum hydride (50.2 mg, 92% purity, 1.22 mmol, 3.0 eq) in dry THF (0.5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, and quenched by H_2O (2 mL). 15 % aq NaOH (3 mL) and H_2O (1 mL) was added to the reaction mixture at rt. Then, EtOAc (10 mL) was added to the mixture, and the resultant solution was filtrated. H_2O (5 mL) was added to the filtrate, and the mixture was

extracted with EtOAc (10 mL x 2). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The (*S*)-*N*-Bz-*tert*-leucinol was obtained in 74% yield (66.9 mg, 0.302 mmol) with >99:1 er as a white solid. ^{1}H NMR was in agreement with the literature.[28] ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 8.4 Hz, 2H), 7.51–7.46 (m, 1H), 7.44–7.38 (m, 2H), 6.39 (br-s, 1H), 4.04 (ddd, *J* = 9.6, 7.8, 3.6 Hz, 1H), 3.94–3.89 (m, 1H), 3.67 (dd, *J* = 11.4, 7.8 Hz, 1H), 2.89 (br-s, 1H), 1.00 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.9 (*C*O), 134.7 (*C*), 131.7 (*C*H), 128.7 (*C*H, 2C), 127.1 (*C*H, 2C), 63.2 (CH_2), 59.9 (*C*H), 34.1 (*C*), 27.2 (CH_3, 3C). Enantiomer ratio (er) was determined by HPLC with CHIRALPAK AD-H column [conditions: hexane:2-propanol = 70:30, flow rate = 0.5 mL/min, rt, Rt (major) = 8.04 min, Rt (minor) = 9.61 min] HRMS-EI (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{20}NO_2$, 222.1489; found: 222.1495. $[\alpha]_D^{17.2}$ = +107.4 (*c* 1.0, CH_3OH).

Acid-Hydrolysis/Boc-Protection Sequence of (*S*)-2a

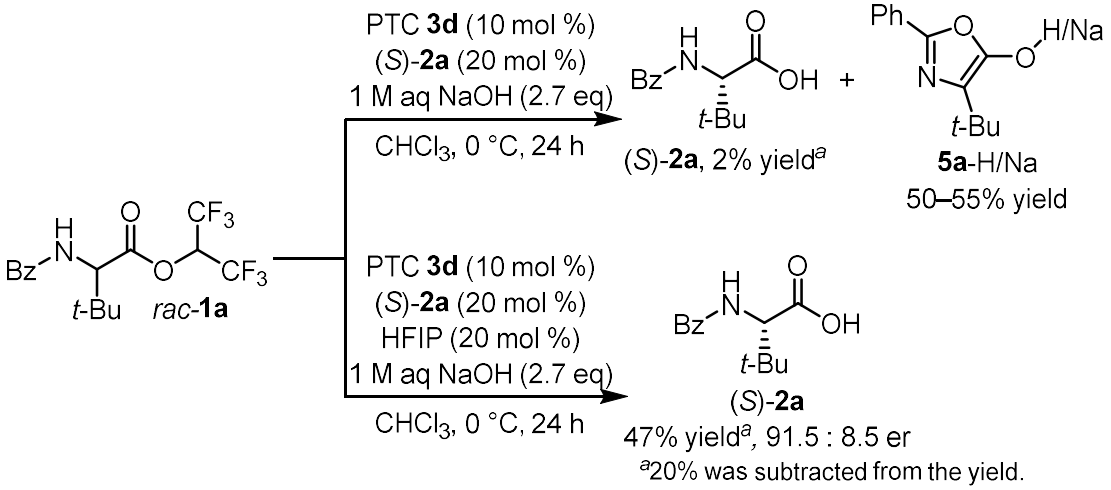


6 M aq HCl (5.0 mL, 60 eq) was added to (*S*)-2-benzamido-3,3-dimethylbutanoic acid (117.2 mg, 0.498 mmol, 1.0 eq), and the resulting mixture was stirred at 100 °C for 24 h. The reaction mixture was cooled to rt, and washed with Et_2O (5 mL x 3). The aqueous layer was heated to 100 °C under reduced pressure to remove H_2O, and the crude mixture was subjected to next Boc-protection without further purification. $NaHCO_3$ (127.5 mg, 1.52 mmol 3 eq), H_2O (2.5 mL) and THF (1.0 mL) was added to the crude mixture. The mixture was cooled to 0 °C, then Boc_2O (217.4 μL, 1.0 mmol, 2 eq) was added dropwise to the reaction mixture. The resultant mixture was warmed to rt, and stirred for 40 h. The progress of the reaction was checked by TLC. After the reaction was complete, the reaction mixture was washed with Et_2O (10 mL x 3), then acidified with 3 M aq HCl (pH<1). The aqueous layer was extracted with EtOAc (10 mL x 3), and dried over Na_2SO_4. The combined organic extracts were concentrated under reduced pressure to give the *N*-Boc-*tert*-leucine in 80% yield with 91.5:8.5 er (92.3 mg, 0.399 mmol) as a white solid. ^{1}H NMR was in agreement with the literature.[29] ^{1}H NMR (400 MHz, $CDCl_3$, *indicate minor rotamer) δ = 10.95 (br-s, 1H,), 6.16* (d, *J* = 4.8 Hz, 0.27H), 5.11 (d, 0.73H, *J* = 9.6 Hz), 4.12 (d, *J* = 9.6 Hz, 0.74H), 3.88* (d, *J* = 5.2 Hz, 0.26H), 1.44 (s, 9H), 1.01 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, *indicate minor rotamer) δ = 177.0 (*C*O), 156.8* (*C*O), 155.8 (*C*O), 81.7* (*C*), 80.2 (*C*), 63.7* (*C*H), 61.8 (*C*H), 34.6 (*C*), 34.2* (*C*), 28.5 (CH_3, 3C), 26.7 (CH_3, 3C). Elemental Analysis: Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found: C, 57.42; H, 9.16; N,

6.10. Enantiomer ratio (er) was determined by GC with InertCap CHIRAMIX column [conditions: starting temperature: 35 °C (hold 5 min), 1st rate of temperature increase: 10 °C/min up to 120 °C (hold 30 min), 2nd rate of temperature increase: 20 °C/min up to 180 °C (hold 10 min) Rt (major) = 46.23 min, Rt (minor) = 45.92 min] $[\alpha]_D^{18.9} = -13.0$ (*c* 1.0, CH_3OH).

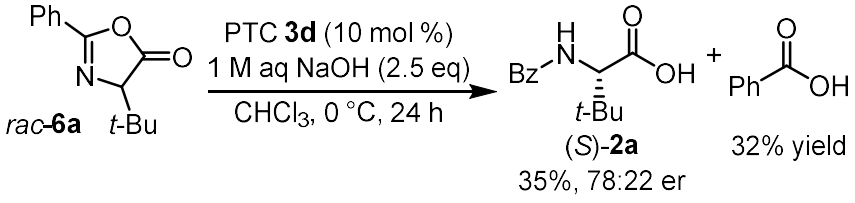
Mechanistic Investigation and Proposed Reaction Mechanism

Product Inhibition Experiment (Scheme 6)



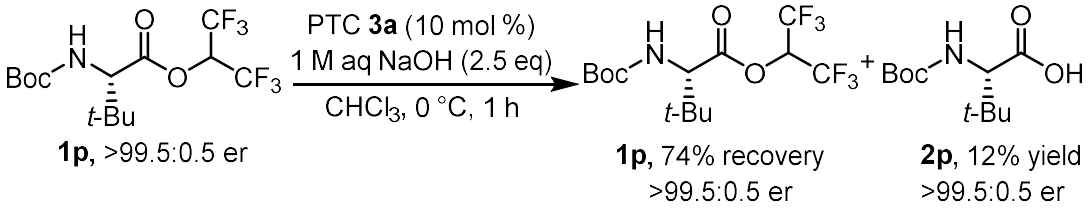
(*S*)-**2a** (4.7 mg, 0.02 mmol, >99:1 er) and 1 M aq NaOH (20 μL, 20 mol %) were placed in a screw-capped test tube (diameter: 16 mm) under air and the mixture was stirred for 10 min at rt. Then, **3d** (0.01 mmol, 10 mol %) and $CHCl_3$ (300 μL) were added to the test tube followed by the addition of 1 M aq NaOH (250 μL, 2.5 eq). After stirred at 0 °C for 10 min, **1a** (38.5 mg, 0.1 mmol) and $CHCl_3$ (100 μL) were added to the solution, and the resultant reaction mixture was further stirred for 24 h at 0 °C. Then, the reaction mixture was washed with EtOAc (2 mL x 3). The residual aqueous solution was acidified by 0.5 mL of 6 M aq HCl, then extracted by EtOAc (2 mL x 3). The latter extracts were corrected and concentrated to give (*S*)-**2a** (5.2 mg, 0.022 mmol) in 22% yield. The former crude extracts were concentrated and purified by silica-gel column chromatography with hexane/EtOAc (40:1 to 3:1) to give the byproduct **5a**-H/Na as a white solid (12.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.56 (s, 1H), 7.77–7.72 (m, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 1.33 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.3 (*C*), 166.4 (*C*), 134.0 (*C*), 133.0 (*C*H), 129.0 (*C*H, 2C), 127.8 (*C*H, 2C), 40.9 (*C*), 27.3 (CH_3, 3C). Elemental Analysis: Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45;. Found: C, 69.92; H, 7.50; N, 6.50. The found elemental analysis values were not in agreement with the calculated values since the **5a** is easily hydrolyzed.

Reaction with Azlactone 6a (Scheme 7)



Azlactone **6a** was prepared according to the reported procedure.[30] PTC **3d** (0.01 mmol, 10 mol %) was placed in a screw-capped test tube (diameter: 16 mm) under air. Then, $CHCl_3$ (300 μL) was added to the test tube followed by the addition of 1 M aq NaOH (250 μL, 2.5 eq) under air. After stirred at 0 °C for 10 min, **6a** (21.7 mg, 0.1 mmol) and $CHCl_3$ (100 μL) were added to the solution, and the resultant reaction mixture was further stirred for 24 h at 0 °C. Then, the organic phase of the reaction mixture was removed by extraction with EtOAc (2 mL x 3). The residual aqueous solution was acidified by 0.5 mL of 6 M aq HCl, then extracted by EtOAc (2 mL x 3). The latter extracts were corrected and concentrated to give the mixture of (*S*)-**2a** and benzoic acid (35 and 32% yield, respectively, total 12.1 mg). The yields were determined by ^{1}H NMR analysis. Er of the product **2a** was 78:22.

Reaction with Enantiopure Ester 1p (Scheme 9)



PTC **3d** (0.01 mmol, 10 mol %) was placed in a screw-capped test tube (diameter: 16 mm) under air. Then, $CHCl_3$ (300 μL) was added to the test tube followed by the addition of 1 M aq NaOH (250 μL, 2.5 eq) under air. After stirred at 0 °C for 10 min, enantiopure ester **1p (**38.1 mg, 0.1 mmol, >99.5:0.5 er) and $CHCl_3$ (100 μL) were added to the solution, and the resultant reaction mixture was further stirred for 1 h at 0 °C. Then, the organic phase of the reaction mixture was removed by extraction with EtOAc (2 mL x 3). The residual aqueous solution was acidified by 0.5 mL of 6 M aq HCl, then extracted by EtOAc (2 mL x 3). The latter extracts were corrected and concentrated to give the corresponding amino acid (2.8 mg, 0.012 mmol) in 12% yield. The former crude extracts were combined and concentrated under reduced pressure. Then, the crude mixture was purified by silica-gel column chromatography with hexane/Et_2O (20:1) to give **2p** (28.4 mg, 0.074 mmol) in 74% yield. The enantiomer ratio of the recovered substrate was analyzed by chiral GC with InertCap CHIRAMIX column [conditions: starting temperature: 35 °C (hold 5 min), 1st rate of temperature increase: 10 °C/min up to 120 °C (hold 30 min), 2nd rate of temperature increase: 20 °C/min up to 180 °C (hold 10 min) Rt (major) = 25.63 min, Rt (minor) = 25.14 min].

Details of the Pseudo-TS Conformational Search

Pseudo-TS conformational search was performed with ConFinder program[31] on a Linux PC (Core i7 4770K 3.5 GHz). ConFinder consists of molecular mechanics (MM) and semiempirical quantum mechanical (SQM) with low-mode algorithm of Kolossváry and Guida to generate new structures.[32] OPLS 2005 force field[33] with the TINKER program[34] and PM6-DH+[35] implemented in the MOPAC program[36] were employed as MM and SQM calculation in the conformational search with ConFinder, respectively. The PTSCS provided 2103 to 3275 of pseudo-TS conformers (*Re-S*: 2546 conformers, *Si-S*: 3275 conformers, *Re-R*: 2165 conformers, *Si-R*: 2103 conformers). The conformers were further subjected to DFT single-point energy (SPE) calculation at RI-B97-D[37]/SV(P)[38] level of theory with Turbomole program[39] in order to reevaluate the energies in a more accurate method. Table 5 shows the top 10 each stable TS candidates after the reevaluation by the SPE (Pseudo-TS-*Re-R*, Pseudo-TS-*Si-R*, Pseudo-TS-*Re-S*, Pseudo-TS-*Si-S*). The Pseudo-TS structures in Table 5 are visualized using Maestro 10.2 (Figure 4, 5, 6 and 7). Partial geometry optimization of the top 10 conformers was further performed to assess the validity of the energies obtained after SPE (Table 6). Pseudo-TS conformers (***Re-S*1**, ***Re-S*2**, ***Re-S*4**, ***Si-S*1**, ***Si-S*2**, ***Si-S*5**, ***Re-R*1**, ***Re-R*2**, ***Re-R*5**, ***Si-R*1**, ***Si-R*2**, ***Si-R*3**) were subjected to the following TS calculation described in the next section.

Table 5. Energies of pseudo-TS conformers after pseudo-TS conformational search and SPE calculation at RI-B97-D/SV(P) level of theory using Turbomole program.[a]

	Pseudo-TS-*Re-S*	Pseudo-TS-*Si-S*	Pseudo-TS-*Re-R*	Pseudo-TS-*Si-R*
Entry	Energy (*E*, kcal/mol) [**Structure Name**]			
1	0.0 [***Re-S*1**]	1.3 [***Si-S*1**]	3.8 [***Re-R*1**]	5.0 [***Si-R*1**]
2	0.6 [***Re-S*2**]	2.5 [***Si-S*2**]	4.4 [***Re-R*1**]	6.3 [***Si-R*2**]
3	1.3 [***Re-S*1**]	4.4 [***Si-S*3**]	5.0 [***Re-R*2**]	6.9 [***Si-R*3**]
4	1.3 [***Re-S*3**]	5.6 [***Si-S*4**]	5.6 [***Re-R*2**]	7.5 [***Si-R*4**]
5	1.3 [***Re-S*1**]	6.3 [***Si-S*5**]	6.3 [***Re-R*2**]	7.5 [***Si-R*5**]
6	1.3 [***Re-S*1**]	6.3 [***Si-S*6**]	6.9 [***Re-R*3**]	7.5 [***Si-R*6**]
7	3.8 [***Re-S*4**]	7.5 [***Si-S*7**]	6.9 [***Re-R*4**]	8.2 [***Si-R*7**]
8	4.4 [***Re-S*5**]	7.5 [***Si-S*8**]	7.5 [***Re-R*5**]	8.2 [***Si-R*8**]
9	4.4 [***Re-S*4**]	7.5 [***Si-S*9**]	7.5 [***Re-R*6**]	8.8 [***Si-R*9**]
10	5.0 [***Re-S*5**]	8.2 [***Si-S*7**]	7.5 [***Re-R*7**]	9.4 [***Si-R*10**]

[a]Similar structures are represented by the same Structure Name.

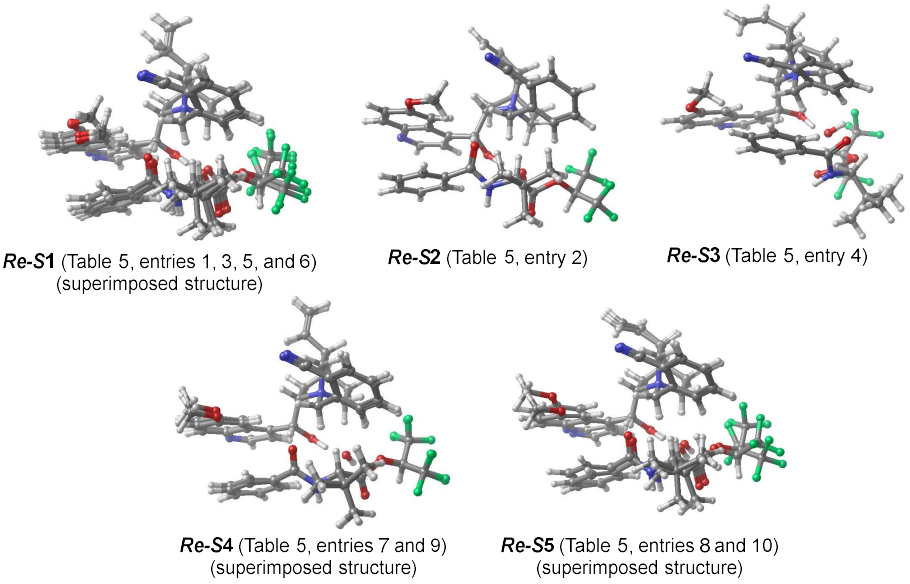


Figure 4. Pseudo-TS-*Re*-*S* conformers visualized using Maestro 10.2.

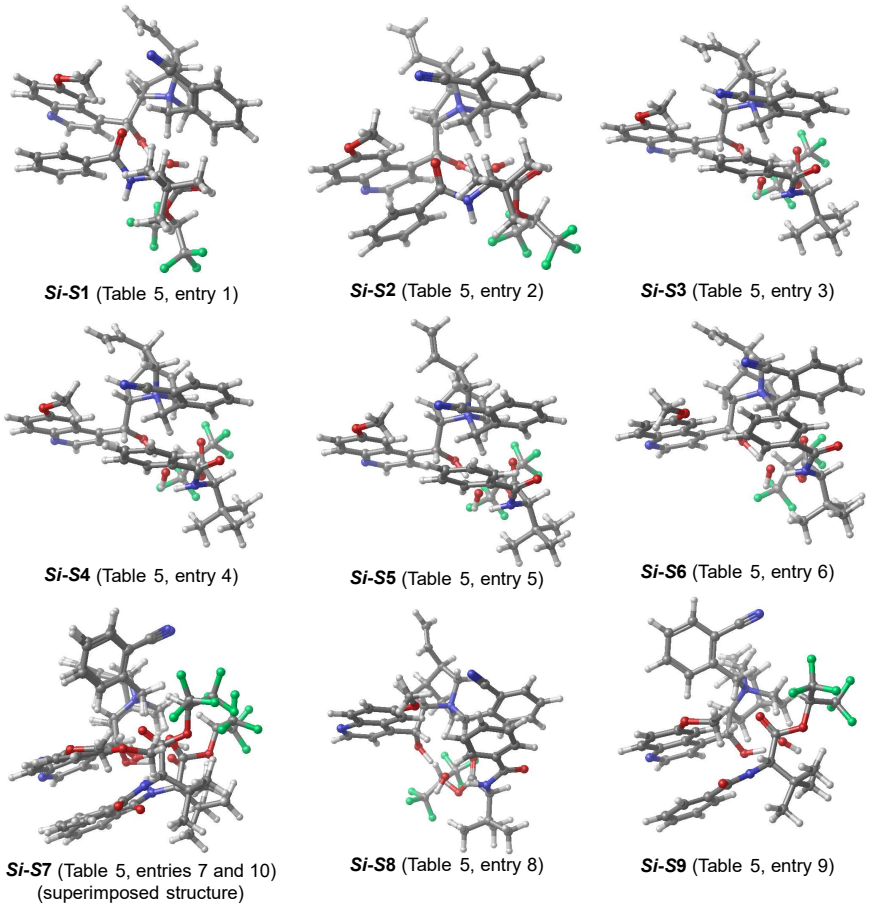


Figure 5. Pseudo-TS-*Si*-*S* conformers visualized using Maestro 10.2.

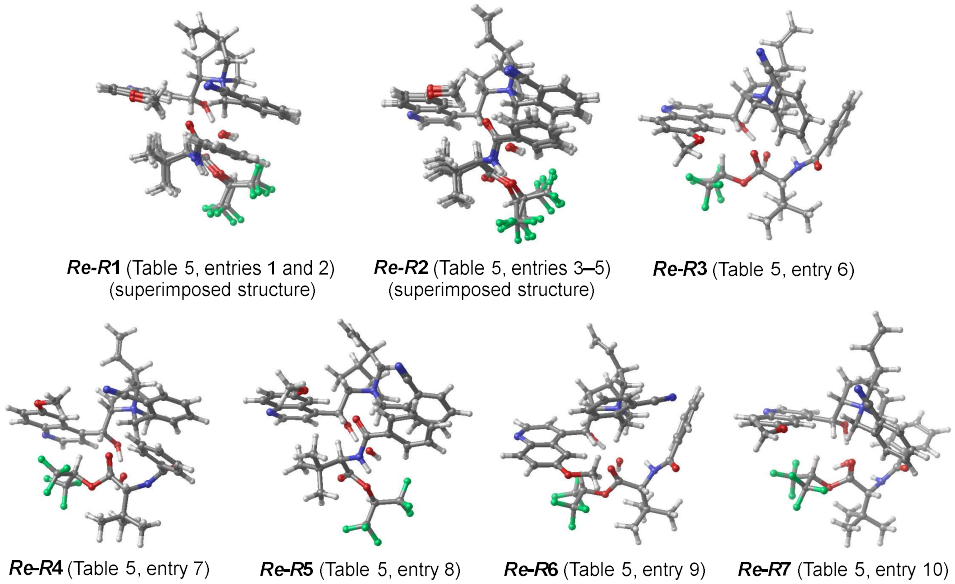


Figure 6. Pseudo-TS-*Re-R* conformers visualized using Maestro 10.2.

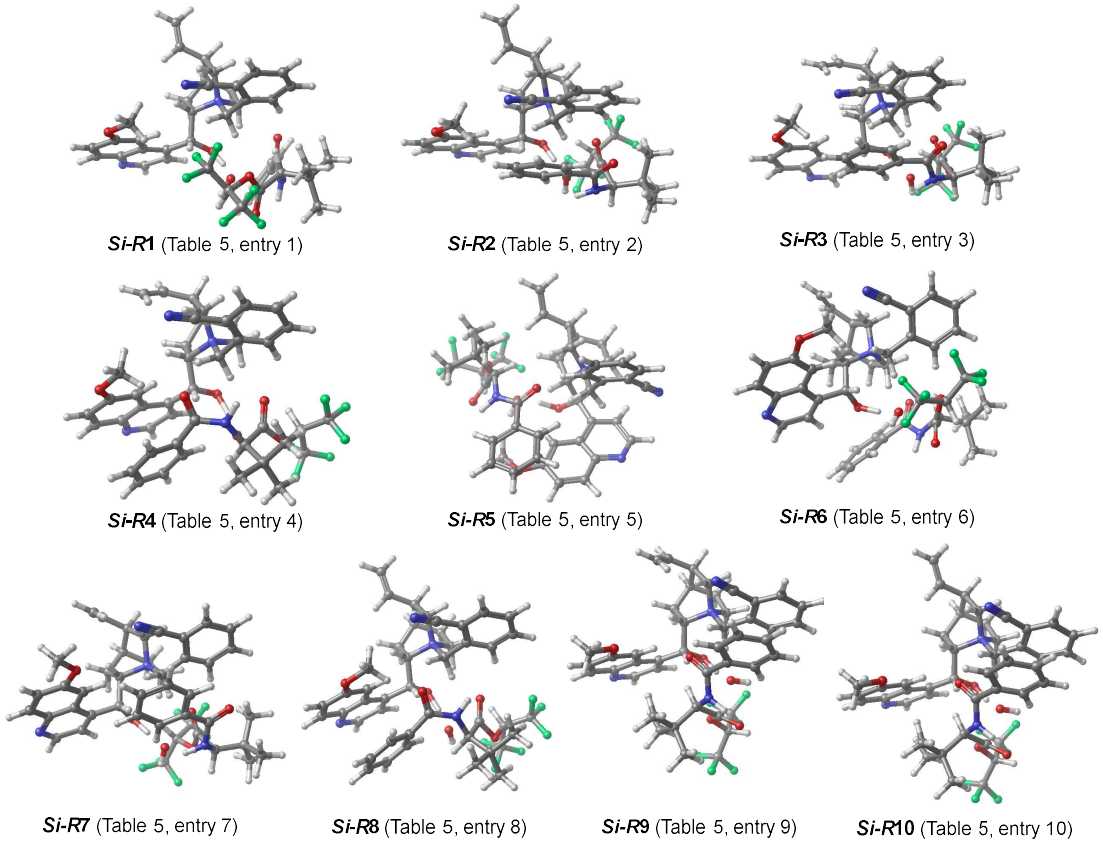


Figure 7. Pseudo-TS-*Si-R* conformers visualized using Maestro 10.2.

Table 6. Energies of pseudo-TS conformers after partial geometry optimization at RI-B97-D/SV(P) level of theory using Turbomole program.[a]

Entry	Pseudo-TS-*Re*-*S*	Pseudo-TS-*Si*-*S*	Pseudo-TS-*Re*-*R*	Pseudo-TS-*Si*-*R*
	Energy (*E,* kcal/mol) [Ranking in ConFinder output, **Structure Name**]			
1	0.0 [***Re*-*S*1**]	0.1 [***Si*-*S*1**]	1.4 [***Re*-*R*1**]	9.9 [***Si*-*R*1**]
2	–0.6 [***Re*-*S*2**]	1.1 [***Si*-*S*2**]		5.5 [***Si*-*R*2**]
3		–0.1 [***Si*-*S*3**]	2.3 [***Re*-*R*2**]	4.3 [***Si*-*R*3**]
4	0.2 [***Re*-*S*3**]	1.5 [***Si*-*S*4**]		5.9 [***Si*-*R*4**]
5		2.6 [***Si*-*S*5**]		11.7 [***Si*-*R*5**]
6		3.5 [***Si*-*S*6**]	5.1 [***Re*-*R*3**]	6.4 [***Si*-*R*6**]
7	5.3 [***Re*-*S*4**]	4.9 [***Si*-*S*7**]	5.8 [***Re*-*R*4**]	6.8 [***Si*-*R*7**]
8	5.0 [***Re*-*S*5**]	7.0 [***Si*-*S*8**]	9.5 [***Re*-*R*5**]	7.2 [***Si*-*R*8**]
9		6.5 [***Si*-*S*9**]	8.9 [***Re*-*R*6**]	7.8 [***Si*-*R*9**]
10			5.1 [***Re*-*R*7**]	8.4[***Si*-*R*10**]

[a]The partial geometry optimizations of the conformers at RI-B97-D/SV(P) level of theory were performed with the distance between the oxygen atom of the hydroxide and the carbon atom of the ester group fixed to 2.0 A. Conformers which have the same structure name were not subjected to the partial geometry optimization.

TS Calculations

Structures of TS candidates located by pseudo-TS conformation search were further used as initial structures to investigate the favorable TS structures determining the stereoselectivity. Transition state calculations were performed with Gaussian 16,[40] and figures presented in the manuscript were generated with CYLview.[41] All the geometry optimization were performed at the M06-2X[42]/TZVP[43] level of theory at 298.15 K at 1.0 atm in the gas phase followed by frequency calculations to confirm that the optimized structures have only one imaginary frequency mode. SPE calculations on the optimized geometries were conducted using M06-2X/TZVP at 273.15 K at 1.0 atm in the gas phase. The $\Delta\Delta G$ values are summarized in Table 7, and the TS-structures are shown in Figure 8–11. The most stable TS structures leading to the corresponding *S*- and *R*-product shown in the manuscript (**TS-*Re-S*** and **TS-*Si-R***) are **TS-*Re-S*2** and **TS-*Si-R*3**, respectively (Table 7).

TS calculation of ***Re-S*4**, ***Si-S*5**, ***Re-R*5** were performed to assess the importance of the H-bonding interaction between hydrogen atom in the MeO group of the catalyst **3d** and the carbonyl oxygen atom in the Bz group of the substrate **1a**. The loss of the H-bonding interaction results in significant increase of the energies (Figure 8 and 11, **TS-*Re-S*1** vs **TS-*Re-S*4**, $\Delta\Delta G$ = 3.8 kcal/mol; **TS-*Re-R*1** vs **TS-*Re-R*5**, $\Delta\Delta G$ = 4.2 kcal/mol). In the case of comparison of **TS-*Si-S*1** and **TS-*Si-S*5**, the energy difference is small ($\Delta\Delta G$ = 0.7 kcal/mol). This is probably due to the large difference of the TS structures and forming different type H-bonding interactions between α-proton of the quaternary ammonium moiety and carbonyl oxygen of the ester group.

Table 7. *ΔΔG* values of TS-complexes (273.15 K and 298.15 K).[a]

Entry	Structure Name	*ΔΔG* (kcal/mol) (273.15 K)	*ΔΔG* (kcal/mol) (298.15 K)
1	**TS-*Re*-*S*2**	0.0	0.0
2	**TS-*Re*-*S*1**	0.7	0.7
3	**TS-*Re*-*S*4**	4.6	4.5
4	**TS-*Si*-*S*1**	0.2	0.1
5	**TS-*Si*-*S*2**	0.3	0.2
6	**TS-*Si*-*S*5**	0.8	0.8
7	**TS-*Si*-*R*3**	2.2	2.1
8	**TS-*Si*-*R*2**	4.4	4.5
9	**TS-*Si*-*R*1**	5.1	5.2
10	**TS-*Re*-*R*1**	2.6	2.5
11	**TS-*Re*-*R*2**	3.1	2.9
12	**TS-*Re*-*R*3**	6.8	6.7

[a] *ΔΔG* values were calculated at M06-2X/TZVP level of theory, and free energy corrections at 1.0 atm in the gas phase.

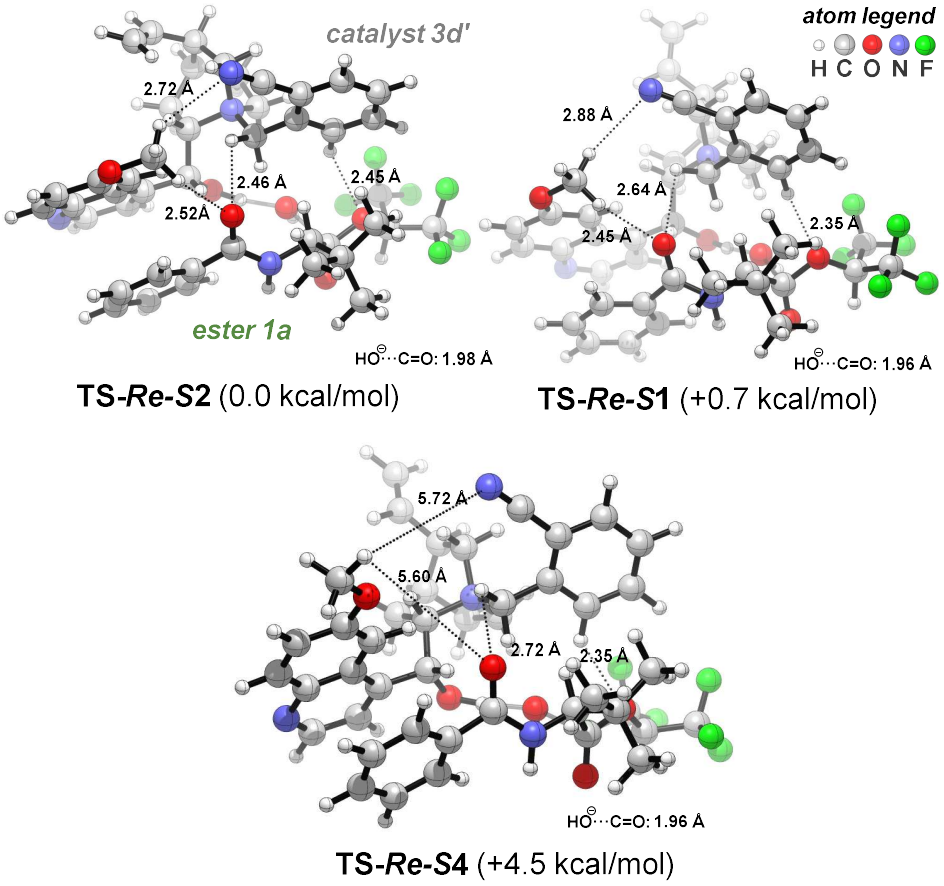


Figure 8. **TS-*Re*-*S*** structures at M06-2X/TZVP level calculation. *ΔΔG* values at 298.15 K, 1 atm in the gas phase are presented in parentheses.

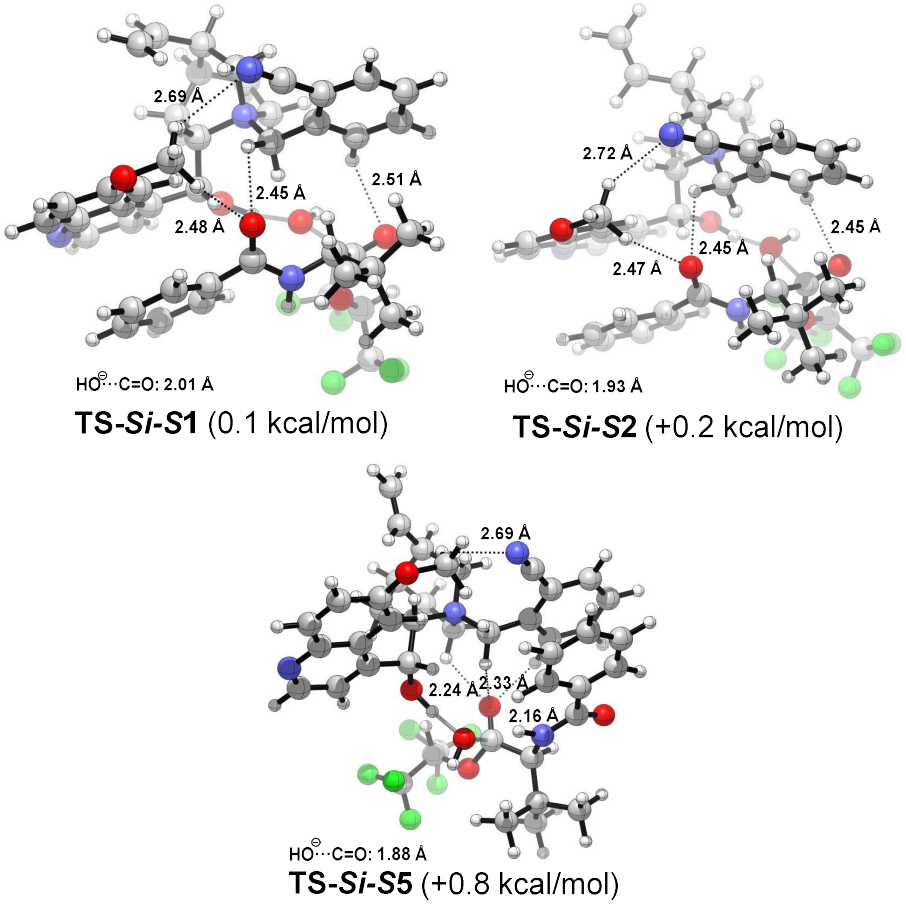


Figure 9. **TS-*Si-S*** structures at M06-2X/TZVP level calculation. *ΔΔG* values at 298.15 K, 1 atm in the gas phase are presented in parentheses.

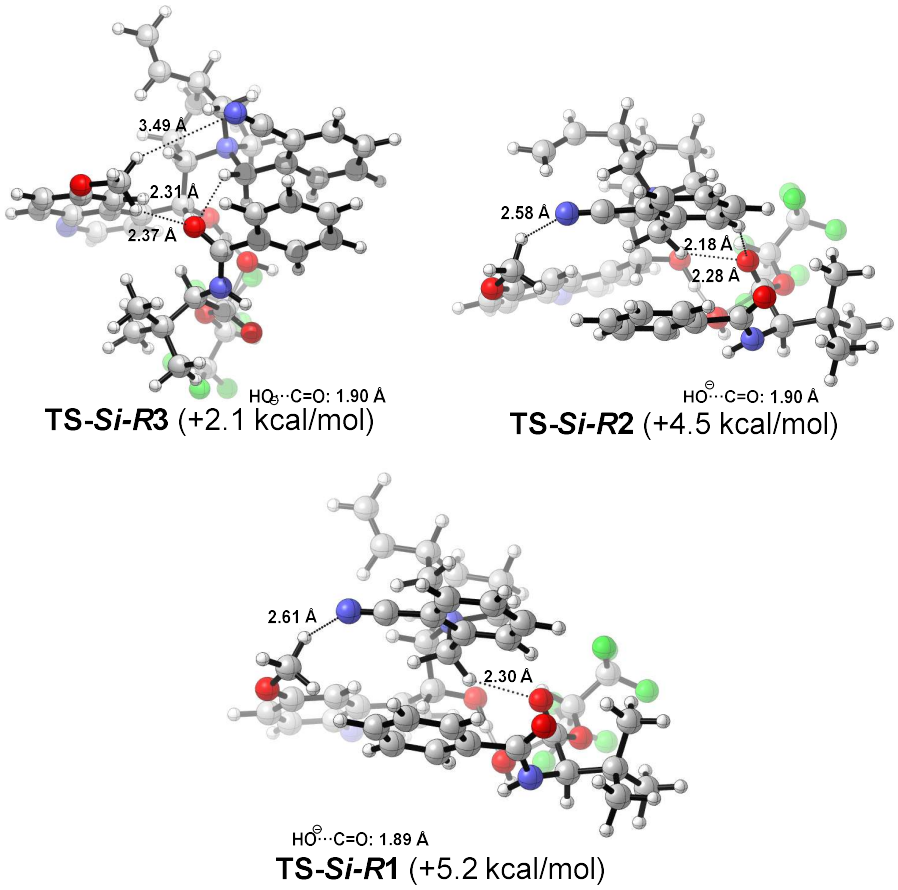


Figure 10. **TS-*Si-R*** structures at M06-2X/TZVP level calculation. *ΔΔG* values at 298.15 K, 1 atm in the gas phase are presented in parentheses.

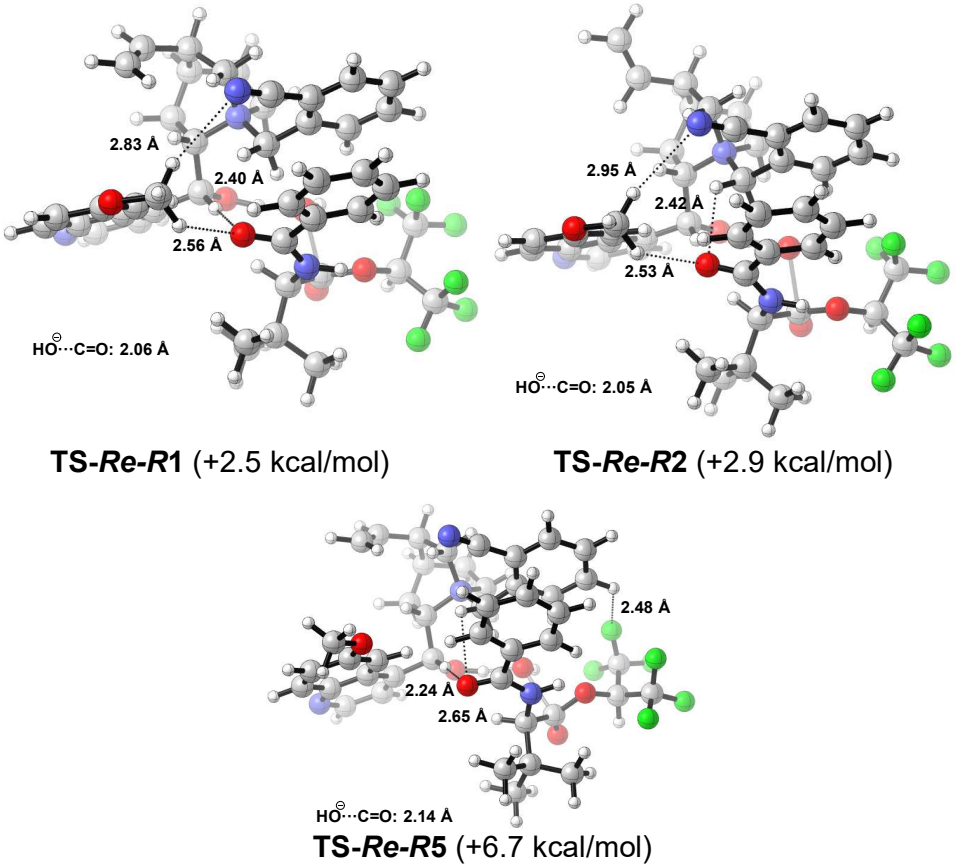


Figure 11. **TS-*Re-R*** structures at M06-2X/TZVP level calculation. *ΔΔG* values at 298.15 K, 1 atm in the gas phase are presented in parentheses.

2.5 References

[1] (a) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Keßeler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 788–824. (b) Nájera, C.; Sansano, J. M. *Chem. Rev*. **2007**, *107*, 4584–4671. (c) Larionov, V. A.; Stoletova, N. V.; Maleev, V. I. *Adv. Synth. Catal.* **2020**, *362*, 4325–4367.

[2] (a) Knowles, W. S.; Sabacky, M. J. *J. Chem. Soc., Chem. Commun.* **1968**, 1445–1446. (b) Horner, L.; Siegel, H.; Büthe, H. *Angew. Chem., Int. Ed.* **1968**, *7*, 942. (c) Dang, T. P.; Kagan, H. B. *J. Chem. Soc., Chem. Commun.* **1971**, 481. (d) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 2567–2568. (c) Noyori, R.; Ohkuma, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 40–73. (f) Jäkel, C.; Paciello, R. *Chem. Rev.* **2006**, *106*, 2912–2942.

[3] (a) Nelson, A. *Angew. Chem. Int. Ed.* **1999**, 38, 1583–1585. (b) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013–3028. (c) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506–517. (d) Lygo,

B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518–525. (c) Ikunaka, M. *Org. Process Res. Dev.* **2008**, *12*, 698–709. (f) Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 4312–4348. (g) Tan, J.; Yasuda, N. *Org. Process Res. Dev.* **2015**, *19*, 1731–1746.

[4] (a) Harada, K. *Nature* **1963**, *200*, 1201. (b) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2000**, *39*, 1279–1281. (c) Gröger, H. *Chem. Rev.* **2003**, *103*, 2795–2827. (d) Merino, P.; Marqués-López, E.; Tejero, T.; Herrera, R. P. *Tetrahedron* **2009**, *65*, 1219–1234. (c) Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. *Nature* **2009**, *461*, 968–971.

[5] (a) Straathof, A. J. J.; Panke, S.; Schmid, A. *Curr. Opin. Biotechnol.* **2002**, *13*, 548–556. (b) Wohlgemuth, R. *In Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*, 2nd Ed.; Blaser, H.-U.

[6] (a) Murakami, M.; Itatani, H.; Takahashi, K.; Kang, J.; Suzuki, K. *Mem. Inst. Sci. Ind. Res. Osaka Univ.* **1963**, *20*, 95. (b) Hix Jr., J. E.; Jones, M. M. *J. Am. Chem. Soc.* **1968**, *90*, 1723–1728. (c) Weijnen, J. G. J.; Koudijs, A.; Engbersen, J. F. J. *J. Org. Chem.* **1992**, *57*, 7258–7265.

[7] (a) Bunton, C. A.; Robinson, L.; Stam, M. F. *Tetrahedron Lett.* **1971**, 121–124. (b) Yamada, K.; Shosenji, H.; Ihara, H. *Chem. Lett.* **1979**, *8*, 491–494. (c) Ueoka, R.; Matsumoto, Y.; Moss, R. A.; Swarup, S.; Sugii, A.; Harada, K.; Kikuchi, J.; Murakami, Y. *J. Am. Chem. Soc.* **1988**, *110*, 1588–1595. (d) Ihara, Y.; Igata, Y.; Okubo, Y.; Nango, M. *J. Chem. Soc., Chem. Commun.* **1989**, 1900–1902. (c) Cleij, M. C.; Drenth, W.; Nolte, R. J. M. *J. Org. Chem.* **1991**, *56*, 3883–3891. (f) Kida, T.; Kajihara, K.; Isogawa, K.; Zhang, W.; Nakatsuji, Y.; Ikeda, I.; Akashi, M. *Langmuir* **2004**, *20*, 8504–8509.

[8] (a) Trainor, G. L.; Breslow, R. *J. Am. Chem. Soc.* **1981**, *103*, 154–158. (b) Breslow, R.; Trainor, G. L.; Ueno, A. *J. Am. Chem. Soc.* **1983**, *105*, 2739–2744. (c) Davies, R. R.; Distefano, M. D. *J. Am. Chem. Soc.* **1997**, *119*, 11643–11652.

[9] Rauwerdink, A.; Kazlauskas, R. J. *ACS Catal.* **2015**, *5*, 6153–6176.

[10] Agosta, E.; Caligiuri, A.; D'Arrigo, P.; Servi, S.; Tessaro, D.; Canevotti, R. *Tetrahedron: Asymmetry* **2006**, *17*, 1995–1999.

[11] Felten, A. E.; Zhu, G.; Aron, Z. D. *Org. Lett.* **2010**, *12*, 1916–1919.

[12] Frisch, K.; Jørgensen, K. A. *Org. Biomol. Chem.* **2007**, *5*, 2966–2974.

[13] (a) Yamamoto, E.; Nagai, A.; Hamasaki, A.; Tokunaga, M. *Chem. Eur. J.* **2011**, *17,* 7178–7182. (b) Yamamoto, E.; Gokuden, D.; Nagai, A.; Kamachi, T.; Yoshizawa, K.; Hamasaki, A.; Ishida, T.; Tokunaga, M. *Org. Lett.* **2012**, *14*, 6178–6181.

[14] Yang, H.; Wong, M. W. *J. Am. Chem. Soc.* **2013**, *135*, 5808–5818.

[15] Perrin, D. D.; Armarego, W. L. F.; Purification of Laboratory Chemicals; 3rd ed., Pergamon

Press, Oxford, 1988

[16] Matsushita, M.; Yoshida, K.; Yamamoto, N.; Wirsching, P.; Lerner, R. A.; Janda, K. D. *Angew. Chem. Int. Ed.* **2003**, *42*, 5984–5987.

[17] Bretschneider, T.; Miltz, W.; Münster, P.; Steglich, W. *Tetrahedron* **1988**, *44*, 5403–5414.

[18] Emder, D.; Del-Signore, G.; Raabe, G. *Turk. J. Chem.*, **2013**, *37*, 492–518.

[19] Chu, L.; Wang, X. C.; Moore, C. E.; Rheingold, A. L.; Yu, J. Q. *J. Am. Chem. Soc.* **2013**, *135*, 16344–16347.

[20] Bautista, F. M.; Campelo, J. M.; Garcìa, A.; Luna, D.; Marinas, J. M. *Amino Acids* **1992**, *2*, 87–95.

[21] Moon, N. G.; Harned, A. M. *Tetrahedron Lett.* **2013**, *54*, 2960–2963.

[22] Gómez, E. D.; Duddeck, H. *Magn. Reson. Chem*. **2009**, *47*, 222–227.

[23] Almansa, R.; Collados, J. F.; Guijarro, D.; Yus, M. *Tetrahedron:Asymmetry* **2010**, *21*, 1421–1431.

[24] Skogh, A.; Friis, S. D.; Skrydstrup, T.; Sandström, A. *Org. Lett.* **2017**, *19*, 2873–2876.

[25] Gűnay, M. E.; Richards, C. J. *Organometallics* **2009**, *28*, 5833–5836.

[26] Li, S.; Zhu, W.; Gao, F.; Li, C.; Wang, J.; Liu, H. *J. Org. Chem.* **2017**, *82*, 126–134.

[27] Arosio, D.; Caligiuri, A.; D'Arrigo, P.; Pedrocchi-Fantoni, G.; Rossi, C.; Saraceno, C.; Servi, S.; Tessaro, D. *Adv. Synth. Catal.* **2007**, *349*, 1345–1348.

[28] Chen, C. T.; Kuo, J. H.; Pawar, V. D.; Munot, Y. S.; Weng, S. S.; Ku, C. H.; Liu, C. Y. *J. Org. Chem*. **2005**, *70*, 1188–1197.

[29] Yu, M.; Lim, N. H.; Ellis, S.; Nagase, H.; Triccas, J. A.; Rutledge, P. J.; Todd, M. H. *ChemistryOpen* **2013**, *2*, 99–105.

[30] Finkbeiner, P.; Weckenmann, N. M.; Nachtsheim, B. J. *Org. Lett.* **2014**, *16*, 1326–1329.

[31] (a) Kamachi, T.; Yoshizawa, K. *Org. Lett.* **2014**, *16*, 472–475. (b) Kamachi, T.; Yoshizawa, K. *J. Chem. Inf. Model.* **2016**, *56*, 347–353.

[32] Kolossváry, I.; Guida, W. C. *J. Am. Chem. Soc.* **1996**, *118*, 5011–5019.

[33] Banks, J. L.; Beard, H. S.; Cao, Y.; Cho, A. E.; Damm, W.; Farid, R.; Felts, A. K.; Halgren, T. A.; Mainz, D. T.; Maple, J. R.; Murphy, R.; Philipp, D. M.; Repasky, M. P.; Zhang, L. Y.; Berne, B. J.; Friesner, R. A.; Gallicchio, E.; Levy, R. M. *J. Comput. Chem.* **2005**, *26*, 1752−1780.

[34] Ponder, J. W. TINKER: Software Tools for Molecular Design, version 7.1; Washington University School of Medicine: Saint Louis, MO, 2015.

[35] Korth, M. *J. Chem. Theory Comput.* **2010**, *6*, 3808−3816.

[36] Stewart, J. J. P. MOPAC2012, version 15.063; Stewart Computational Chemistry: Colorado

Springs, CO, 2012.

[37] Grimme, S. *J. Comput. Chem.* **2006**, *27*, 1787−1799.

[38] Schäfer, A.; Horn, H.; Ahlrichs, R. *J. Chem. Phys.* **1992**, *97*, 2571−2577.

[39] TURBOMOLE V7.0 2015, a development of University of Karlsruhe and Forschungszentrum Karlsruhe GmbH, 1989-2007, TURBOMOLE GmbH, since 2007; available from http://www.turbomole.com.

[40] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B. and Fox, D. J. Gaussian 16, Revision A.03; Gaussian, Inc.; Wallingford CT, 2016.

[41] CYLview, 1.0b; Legault, C. Y., Université de Sherbrooke, 2009. (http://www.cylview.org)

[42] (a) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215−241. (b) Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157−167.

[43] Schäfer, A.; Huber, C.; Ahlrichs, R. *J. Chem. Phys.* **1994**, *100*, 5829−5835.

Chapter 3. Dynamic Kinetic Resolution of Azlactones via Phase-Transfer Catalytic Alcoholysis

3.1. Introduction

α-Chiral amino acid esters are useful building blocks for the synthesis of amino alcohols, unprotected amino acids, and bioactive heterocyclic molecules.[1] Furthermore, enantioenriched amino acid derivatives bearing tertiary alkyl α-substituents have been employed as useful chiral building blocks for the synthesis of chiral ligands for metal-catalysis or organocatalysts.[2] In addition to their synthetic utility, amino acid-based structural motifs, including amino acid esters, are often found in drugs and drug candidates, and are thus greatly important in pharmaceutical applications[3] (Figure 1).

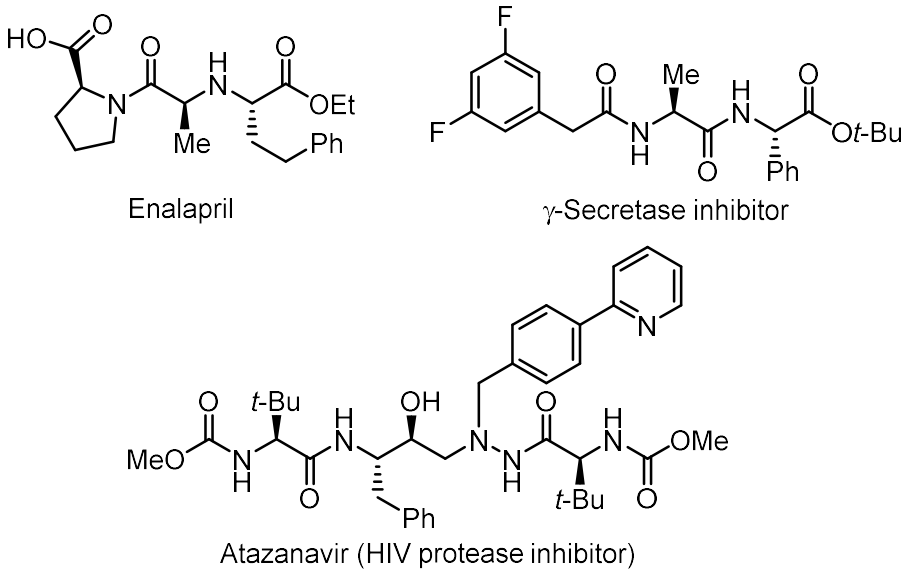
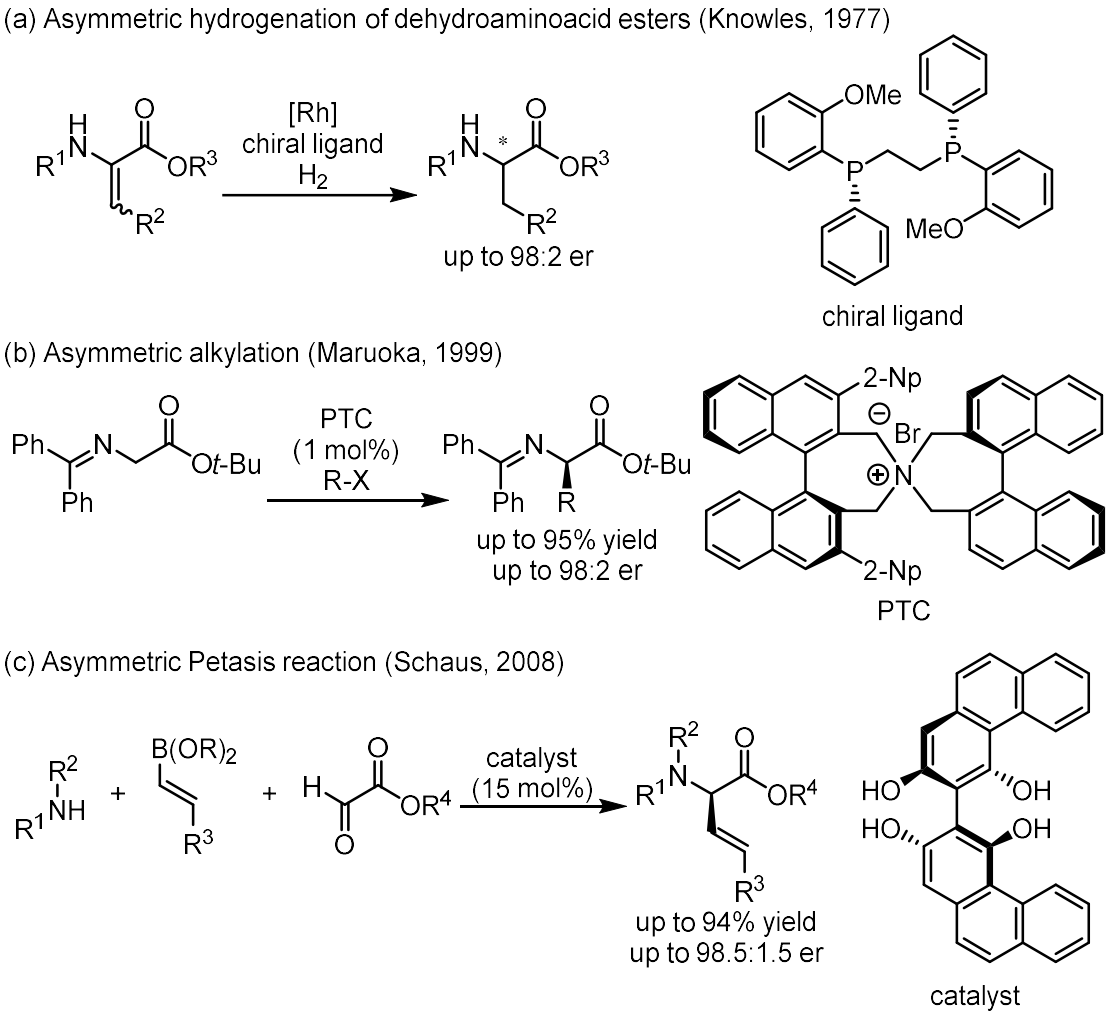


Figure 1. Selected examples of optically active amino acid derived bioactive molecules.

For the preparation of optically active α-chiral amino acid esters, straightforward asymmetric catalytic strategies providing amino acid esters are desirable, in order to avoid complex synthetic routes and racemization of the α-chiral center during multiple transformations. So far, numerous noble catalytic approaches have been achieved, such as hydrogenation of dehydroamino acid esters,[4] asymmetric alkylation,[5] and asymmetric Petasis reactions,[6] but these strategies are not suitable for synthesizing amino acid esters bearing tertiary alkyl α-substituents (Scheme 1).



Scheme 1. Asymmetric catalysis for the preparation of optically active α-amino acids esters.

The dynamic kinetic resolution (DKR) of azlactones via catalytic alcoholysis is a potent and straightforward method to access enantioenriched α-chiral amino acid esters.[7] Recently, efficient organocatalysts for the alcoholytic DKR of azlactones, such as acid-base,[8] Brønsted acid,[9] and nucleophilic[10] catalysts, have been developed (Figure 2a–c).

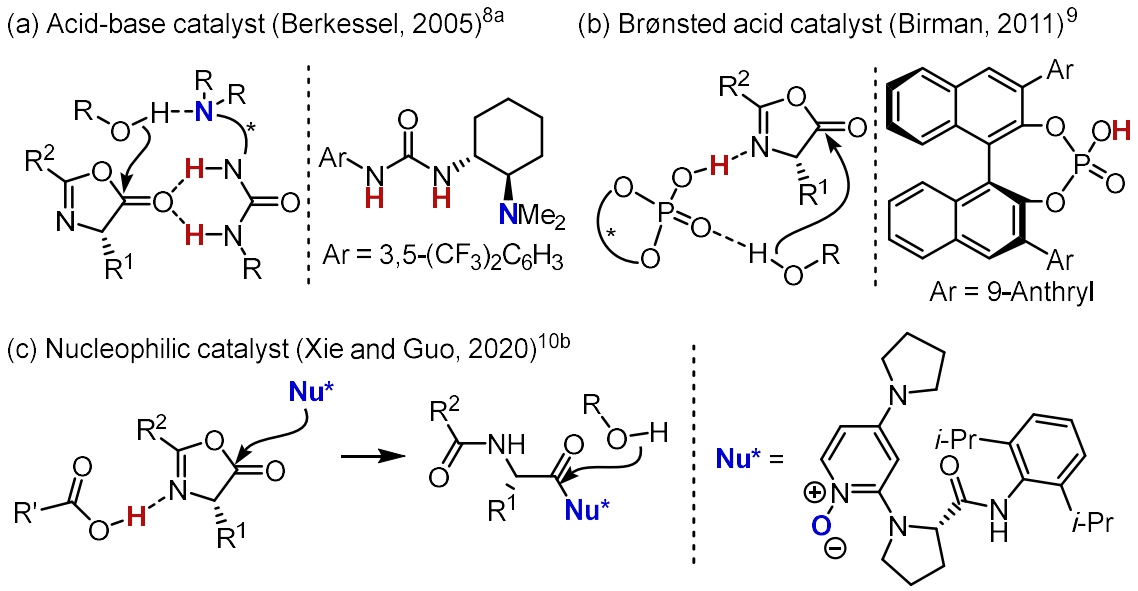
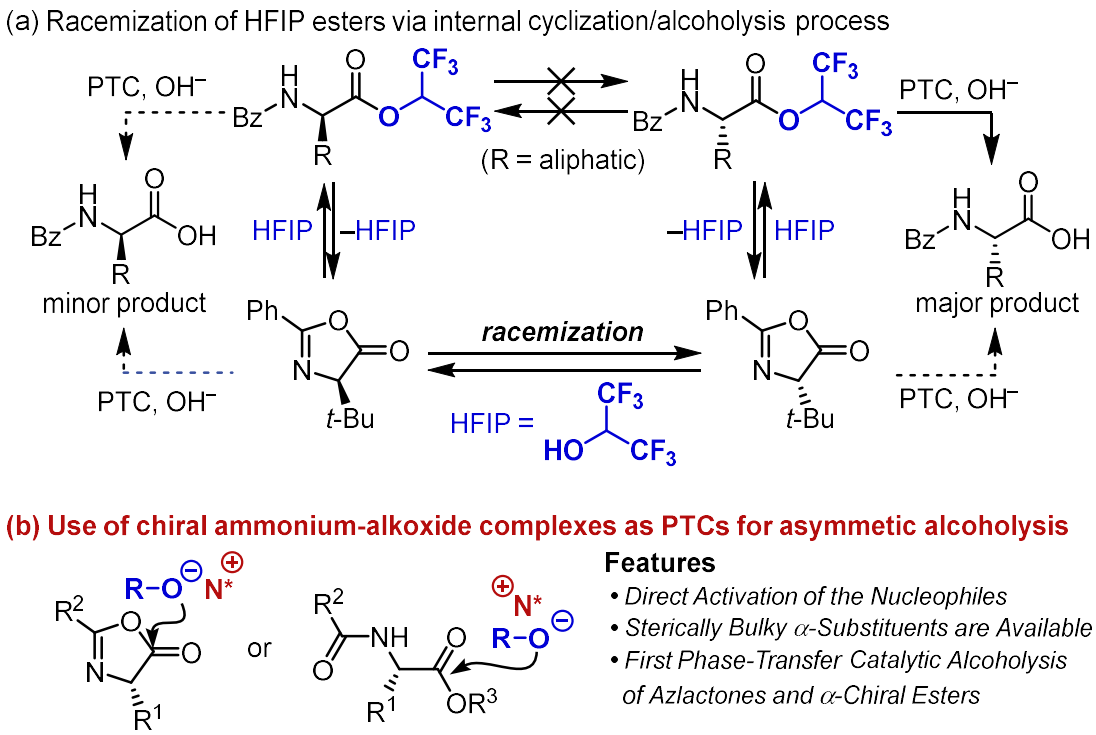


Figure 2. Examples of organocatalytic asymmetric alcoholysis of azlactones and N-protected amino acid esters.

However, current organocatalytic strategies have a limited scope for alcohols, and there are only a few methods that can use sterically hindered azlactone substrates with a high level of reactivity.[8a] Furthermore, as far as the author knows, the alcoholytic DKR of α-chiral amino acid esters has not been reported.[11]

Tokunaga group previously reported the hydrolytic enantioselective protonation of enol esters,[12] and the author described a base-hydrolytic DKR of N-protected amino acid esters using phase-transfer catalysts (PTCs)[13] in the previous chapter.[14] In the study on base-hydrolysis of amino acid esters, the author proposed that the DKR-type hydrolysis process proceeds via internal cyclization of esters, racemization/ring opening alcoholysis of azlactones (Scheme 2a). Based on these mechanistic insights, the addition of alcohols to the phase-transfer catalysis system under basic conditions would generate a chiral ammonium alkoxide complex, which would lead to a new stereoselective alcoholysis reaction for the preparation of enantioenriched α-chiral amino acid esters (Scheme 2b).



Scheme 2. (a) Racemization of amino acid HFIP esters via cyclization/ring-opening alcoholysis process. (b) Use of chiral ammonium-alkoxide complexes as PTCs for asymmetric alcoholysis of amino acid derivatives.

In this chapter, a phase-transfer catalytic asymmetric alcoholysis of azlactones, affording the corresponding enantioenriched α-chiral amino acid esters with excellent stereoselectivity (up to 99:1 er) is described. In addition, synthetic applications and computational studies with a pseudo-transition state conformational search (PTSCS) using the ConFinder program for searching the low-energy conformations of stereodetermining TS structures and density functional theory (DFT) calculations were performed to elucidate the origin of the stereoselectivity.

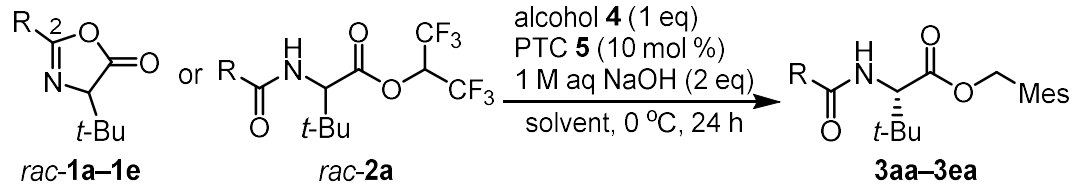
3.2. Results and Discussion

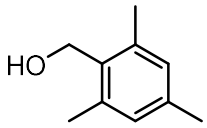
Optimization of the Reaction Conditions and Substrate Scope

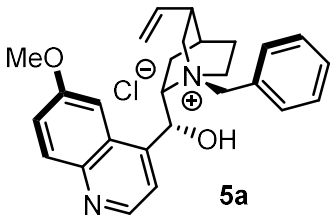
Initial screening for the reaction conditions showed that the ring-opening alcoholytic DKR with an azlactone prepared from *N*-benzoyl *tert*-leucine (**1a**), 2,4,6-trimethylbenzyl alcohol (**4**), and PTC **5a** afforded the corresponding ester **3aa** in low yield, albeit with excellent stereoselectivity (Table 1, entry 1). The reaction with PTC **5b** or pseudo-enantiomeric PTC **5c** resulted in moderate to low yields, though the stereoselectivity was also excellent (entries 2 and 3). The use of PTC **5d** bearing a 2-cyanobenzyl group, which showed the highest stereoselectivity in the previous base-hydrolytic DKR

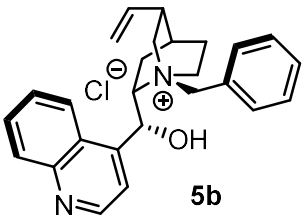
of esters,[14] gave the product in high yield without significant loss of stereoselectivity (entry 4). Varying the electron-withdrawing group on the PTC **5** from 2-cyano to 2-trifluoromethyl resulted in a lower yield and no significant influence on the stereoselectivity (entry 5). The use of dichloromethane, diethyl ether, and toluene as the solvent did not lead to an increase in the yield and stereoselectivity (entries 6–8). Next, to examine the effect of the C(2)-substituents on the DKR with alcohol **4**, various C(2) aryl- or alkyl-substituted azlactones were employed (entries 9–12). Introducing an electron-donating or electron-withdrawing group on the phenyl ring decreased the stereoselectivity from 94:6 er (**3ba**) to 84.5:15.5 er (**3ca**). The reaction with azlactone **1d** bearing a 3,5-dimethylphenyl group at the C(2) position provided the desired amino acid ester **3da** in high yield with a slightly lower er. Furthermore, changing the aryl substituent to a cyclohexyl ring (**3ea**) decreased the reactivity and stereoselectivity. These results indicate that C(2)-substituents of azlactones affect the stereodetermining transition state conformations. When *N*-benzoyl *tert*-leucine hexafluoroisopropyl (HFIP) ester **2a** was employed as a substrate instead of azlactone **1a**, the corresponding ester **3aa** was obtained in good yield with high stereoselectivity (entry 13). It is worth noting that this is the first example of an alcoholytic DKR of an α-chiral amino acid ester.

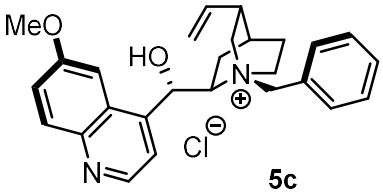
Table 1. Optimization of the reaction conditions.

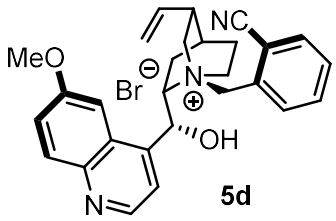


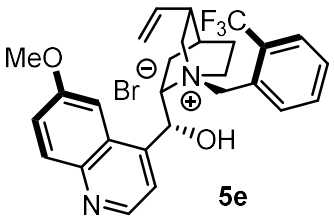

alcohol **4**


5a


5b


5c


5d

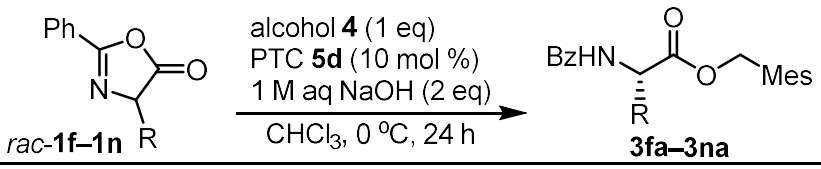

5e

entry	sub.	R	PTC	solvent	yield[a] (%)	er
1	**1a**	Ph	**5a**	$CHCl_3$	37	99:1
2	**1a**	Ph	**5b**	$CHCl_3$	50	99:1
3	**1a**	Ph	**5c**	$CHCl_3$	19	2:98
4	**1a**	Ph	**5d**	$CHCl_3$	87	98.5:1.5
5	**1a**	Ph	**5e**	$CHCl_3$	63	98:2
6	**1a**	Ph	**5d**	CH_2Cl_2	73	97.5:2.5
7	**1a**	Ph	**5d**	Et_2O	16	96:4
8	**1a**	Ph	**5d**	toluene	51	91.5:8.5
9	**1b**	4-MeO-C_6H_4	**5d**	$CHCl_3$	79	94:6
10	**1c**	4-CF_3-C_6H_4	**5d**	$CHCl_3$	59	84.5:15.5
11	**1d**	3,5-Me_2-C_6H_3	**5d**	$CHCl_3$	86	96.5:3.5
12	**1e**	Cy	**5d**	$CHCl_3$	50	87:13
13	**2a**	Ph	**5d**	$CHCl_3$	71	98:2

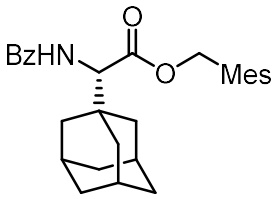
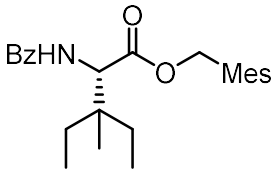
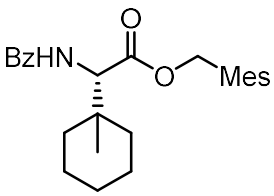
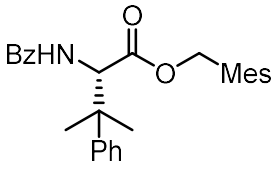
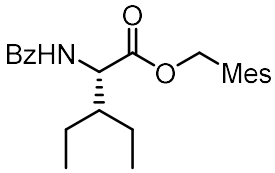
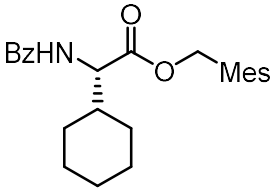
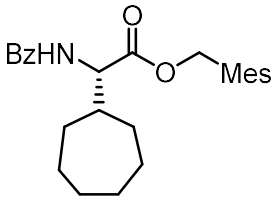
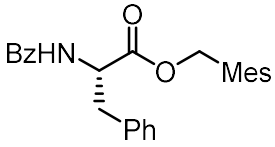
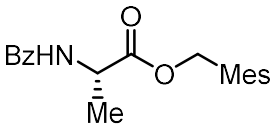
[a]Isolated yields are presented.

With the optimal reaction conditions in hand, the author examined the reaction of azlactones having different substituents at the α-position with 2,4,6-trimethybenzyl alcohol (**4**) (Table 2). Azlactones with sterically hindered substituents provided the corresponding esters with good to excellent enantiomeric ratios in good to high yields. Reactions with azlactones having secondary or primary alkyl groups showed lower yields and stereoselectivities.

Table 2. Scope of *rac*-Azlactones **1**[a]



rac-**1f–1n** → **3fa–3na**

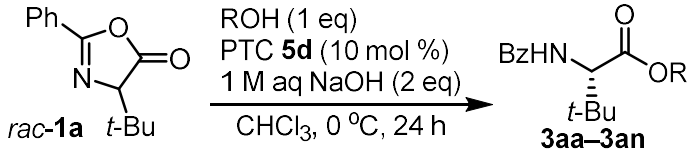
		
3fa	**3ga**	**3ha**
79%, 98:2 er	61%, 98.5:1.5 er	79%, 97.5:2.5 er
		
3ia	**3ja**	**3ka**
80%, 94:6 er	54%, 79:21 er	27%, 73:27 er
		
3la	**3ma**	**3na**
26%, 60:40 er	55%, 75.5:24.5 er	38%, 72.5:27.5 er

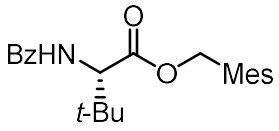
[a]Isolated yields are presented.

Then, the alcohol scope for the alcoholytic DKR of azlactone **1a** under $CHCl_3$/aqueous NaOH biphasic conditions was explored (Table 3). The reaction with alcohol **4** and azlactone **1a** at a 0.2 mmol scale afforded **3aa** in high yield with excellent stereoselectivity; however, an unsubstituted benzyl alcohol provided the desired product **3ab** with lower stereoselectivity. Additional exploration of the reaction conditions elucidated that the reaction with PTC **5b** improved the stereoselectivity

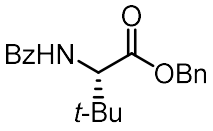
(footnote b). The alcoholytic DKR of several other alkyl-substituted benzyl alcohols provided the corresponding N-protected amino acid esters in 75–82% yields with high ers (**3ac**–**3af**). Benzylic alcohols containing an electron-donating substituent (**3ag** and **3ah**) resulted in a high yield with high er, whereas a 4-trifluoromethylbenzyl alcohol (**3ai**) showed low stereoselectivity. Furthermore, halogen substituents on the aromatic ring of the benzyl alcohol were also tolerated, though the stereoselectivities were only good to moderate (**3aj**–**l**). 3-Methyl-2-buten-1-ol (prenol) was employed for the alcoholysis of azlactone, which gave the corresponding ester **3am** in 56% yield with 98:2 er. The yield of allyl alcohol (**3an**) was lower than other alcohols, probably because of a competing hydrolysis reaction caused by its water solubility.

Table 3. Substrate Scope of Alcohols.[a]

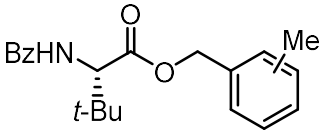




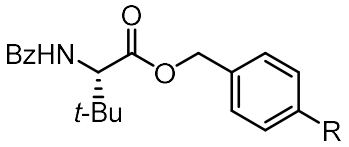
3aa
78%, 98.5:1.5 er



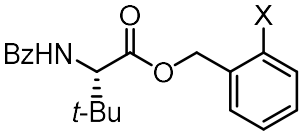
3ab
82%, 93.5:6.5 er
(69%, 95.5:4.5 er[b])



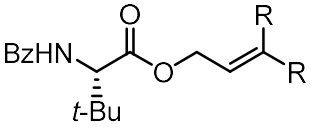
3ac: 2-Me, 75%, 97:3 er
3ad[b]: 3-Me, 76%, 97.5:2.5 er
3ae[b]: 4-Me, 82%, 96.5:3.5 er



3af[b]: R = *t*-Bu, 79%, 97:3 er
3ag[b]: R = OMe, 83%, 96.5:3.5 er
3ah[b]: R = OTBS, 81%, 98:2 er
3ai: R = CF_3, 88%, 79.5:20.5 er



3aj[b]: X = Cl, 89%, 92.5:7.5 er
3ak: X = Br, 94%, 91:9 er
3al: X = I, 98%, 89:11 er

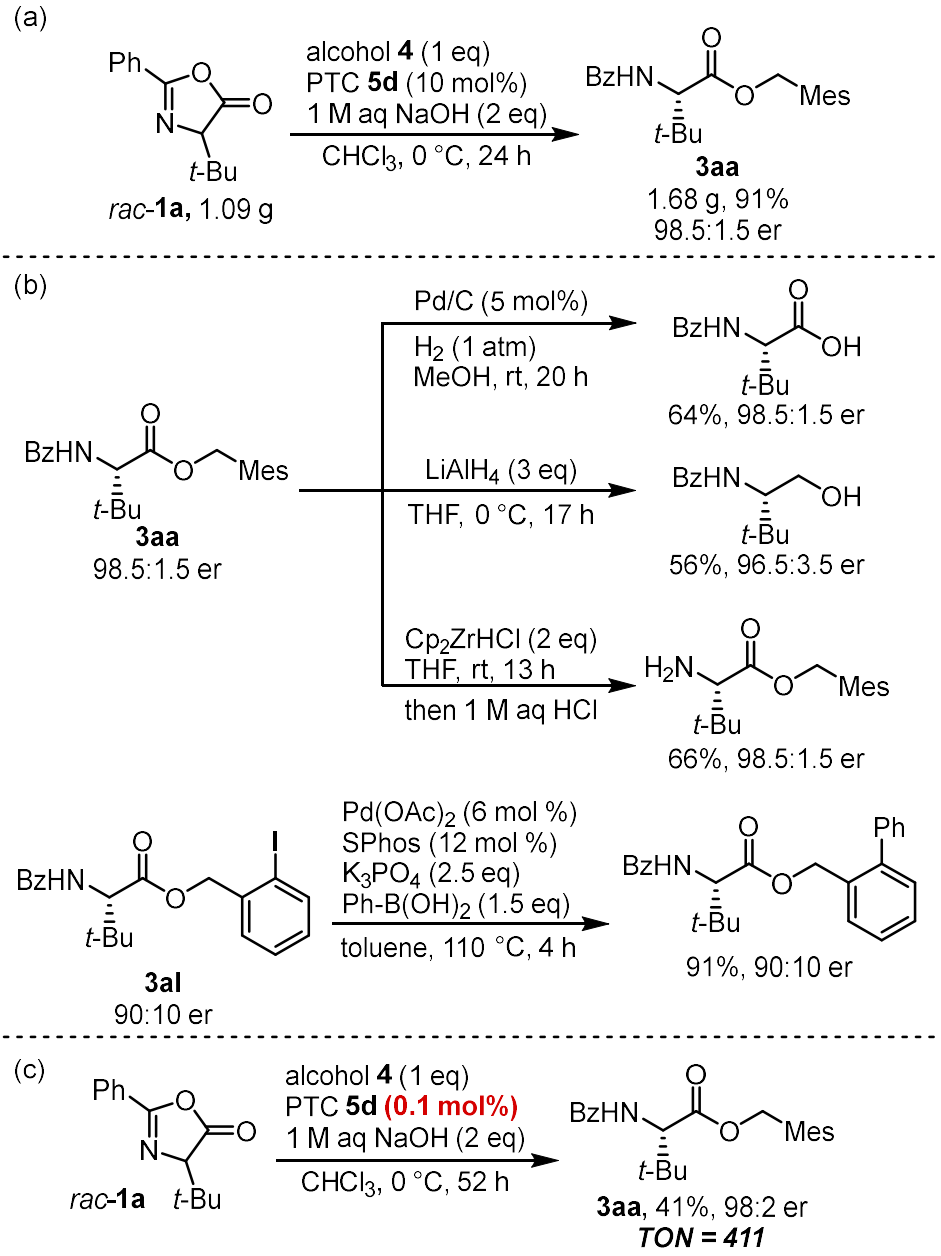


3am[b]: R = Me, 56%, 98:2 er
3an: R = H, 45%, 96.5:3.5 er

[a]Isolated yields are presented. [b]PTC **5b** was used.

In order to demonstrate the synthetic advantages of the alcoholytic DKR of azlactones, the author carried out a gram-scale reaction (Scheme 3a). Reaction with azlactone **1a** (1.09 g, 5 mmol) under the optimized conditions afforded product **3aa** in high yield without loss of the excellent stereoselectivity. Next, exposure of **3aa** to hydrogenolysis conditions gave *N*-benzoyl *tert*-leucine in 64% yield without any loss of optical purity. Ester **3aa** was also subjected to $LiAlH_4$ reduction,

providing *N*-benzoyl *tert*-leucinol in 56% yield with 96.5:3.5 er. Bz group of the enantioenriched product **3aa** was successfully removed without racemization by the treatment with Schwartz reagent and acid-hydrolysis. Suzuki-Miyaura cross-coupling of enantioenriched product **3al** was also carried out, which provided the corresponding phenyl-substituted product in 91% yield without any erosion of optical purity (Scheme 3b). Finally, the author tried to reduce the catalyst loading and found that the amount of the PTC **5d** could be reduced to 0.1 mol % without significant loss of stereoselectivity, and the reaction achieved a high turnover number (Scheme 3c, TON = 411).



Scheme 3. (a) Gram-scale reaction, (b) Transformations of enantioenriched products **3aa** and **3al** and (c) Reaction with low-catalyst loading.

Computational Study

In order to obtain mechanistic insights into the observed stereoselectivity, the author conducted a pseudo-transition state conformational search (PTSCS) using the ConFinder program and DFT calculations for the TS analogues composed of the ammonium alkoxide active species **5d′** derived from PTC **5d**, *S*- or *R*-**1a**, and H_2O or BnOH as the catalytically active species–substrate complexes for this asymmetric alcoholysis reaction (Figure 3).

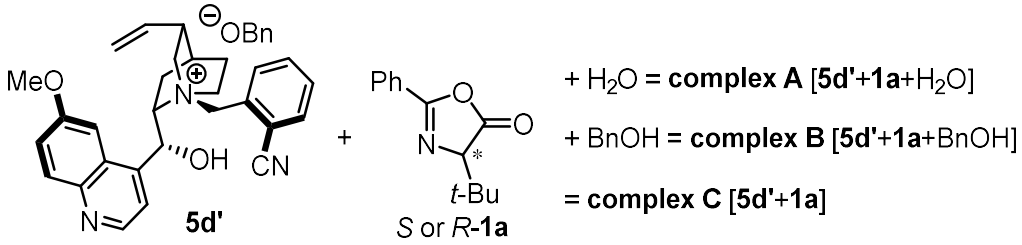


Figure 3. Calculated TS analogue **complex A**, **B** and **C**.

Initially, the structures of **complex A** [**5d′**+**1a**+H_2O] were classified by the stereochemistry of the enantiofaces attacked by the alkoxide anion and the α-carbon center of the azlactone **1a** (*Re*-*R*, *Si*-*S*). The C···O distance between the carbonyl carbon of **1a** and the oxygen atom of the benzyl alkoxide was fixed at 1.8 Å during the conformational search to keep the geometry close to the corresponding TS structures. The conformational search using ConFinder provided approximately 2000 structures for each of the complexes. The energies for the obtained conformers were further assessed by single-point energy (SPE) calculations at the RI-B97D/SV(P) level of theory. After the conformational search and SPE calculations, additional partial optimization was carried out for six conformations the energy of which were within 8.3 kcal/mol at the RI-B97D/TZVP level of theory. The lowest-energy TS structures leading to the major (*S*) and minor (*R*) products were successfully obtained for **complex A**, as shown in Figure 4 (TS-*Si*-*S*-H_2O and TS-*Re*-*R*-H_2O, respectively).

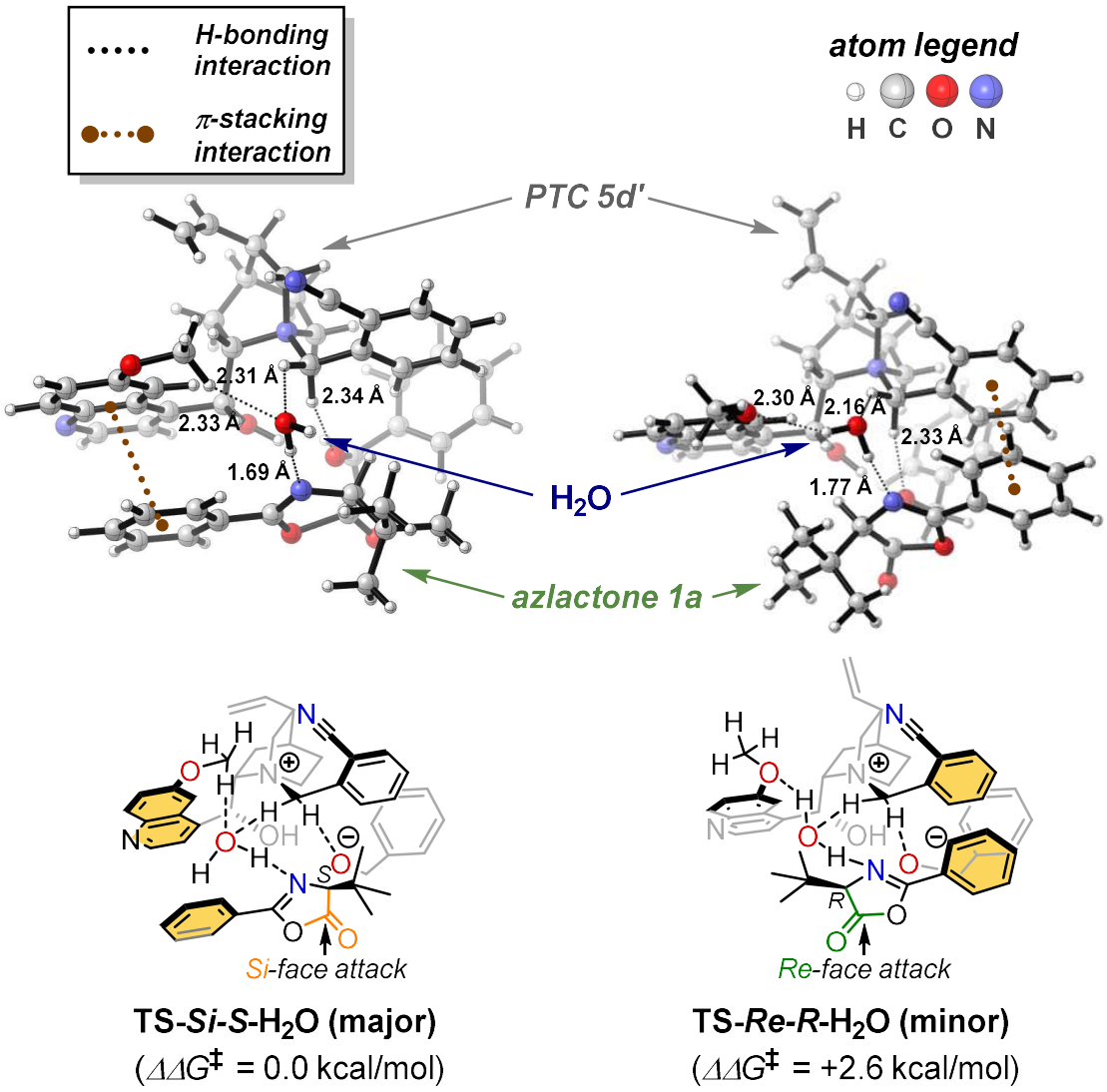


Figure 4. Calculated TS structures at the B97D/TZVP level leading to each enantiomer of **complex A**.

The major TS is more stable than the minor TS by 2.6 kcal/mol for TS calculations performed for 273.15 K in chloroform, which is in reasonable agreement with the experimentally observed stereoselectivity [2.6 (calcd.) vs 2.1 (exptl.) kcal/mol]. It is noteworthy that a PTSCS using the ConFinder program successfully reduced the laborious efforts typically needed to locate the appropriate positions for the H_2O molecule, which can form complicated H-bonding interactions. In addition, independent gradient model (IGM) analysis[15] was carried out to investigate the detailed intermolecular attractive interactions (Figure 5).

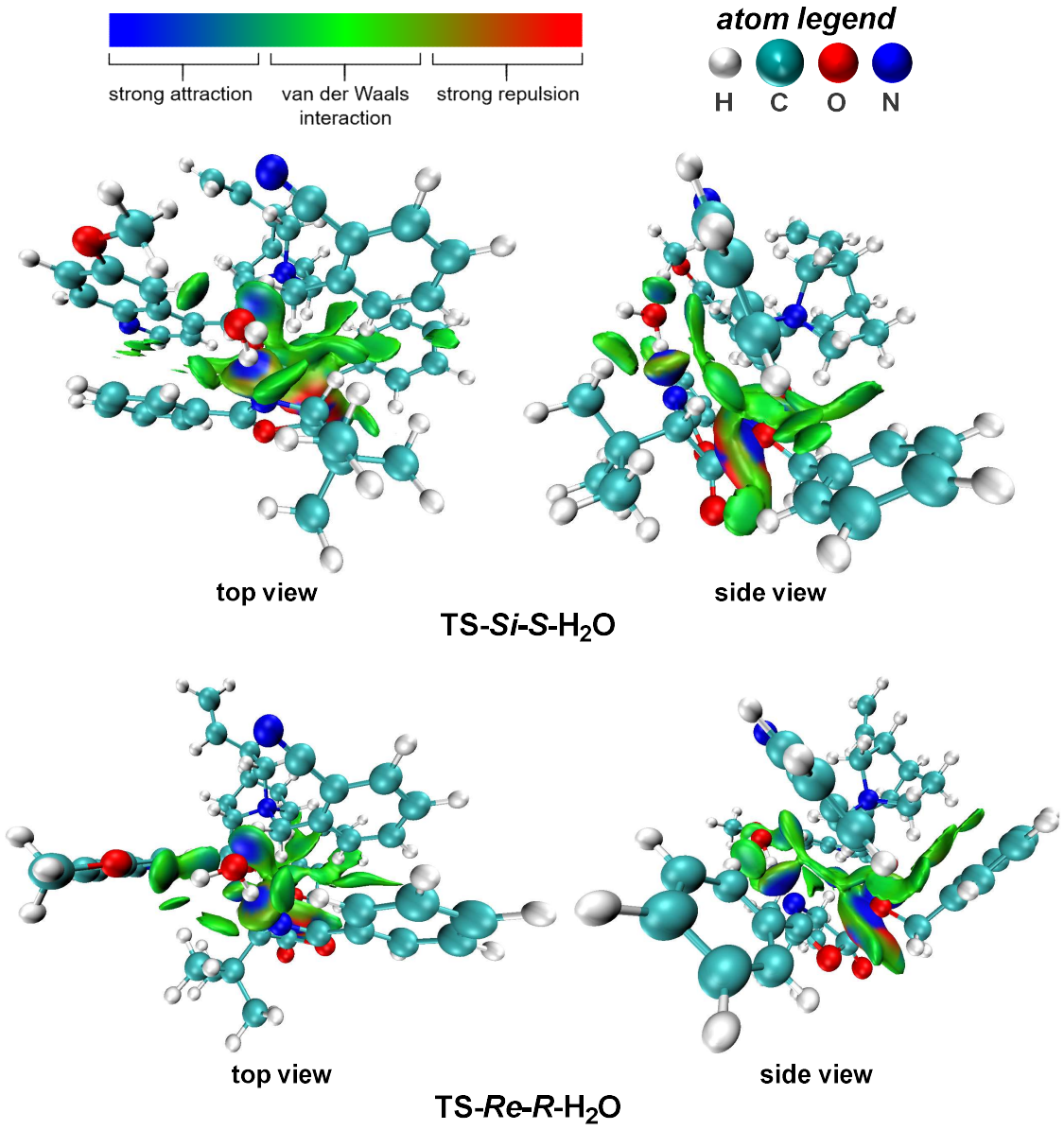
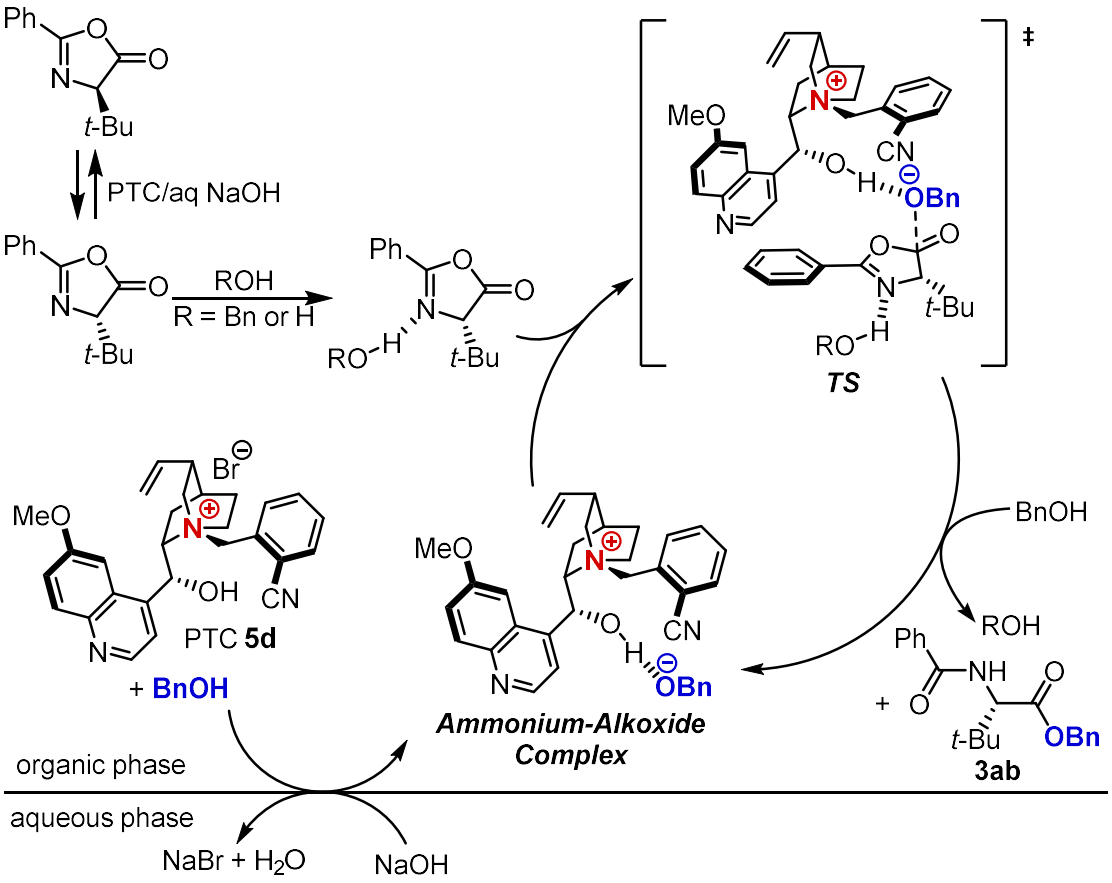


Figure 5. IGM analysis (isovalue = 0.01) of the optimized TS structures.

In TS-*Si*-*S*-H_2O, π–π stacking was formed between the quinoline ring of **5d′** and the Ph group in **1a**, while TS-*Re*-*R*-H_2O showed π-stacking interactions between the 2-cyanophenyl ring in **5d′** and the Ph group in **1a**. Furthermore, both TS structures indicated hydrogen-bonding interactions between the MeO group in **5d′** and a water molecule [O–$CH_2H\cdots OH_2$ (*S*) or $H_3CO\cdots H$–OH (*R*)], one of the benzylic protons in **5d′** and the oxygen atom of water, another benzylic proton in the 2-cyanobenzyl group and the oxygen atom in the alkoxide anion ($N^+CHH\cdots OH_2$ and $N^+CHH\cdots {}^-OPh$),[16] or the

nitrogen atom in the azlactone ring and water (N···H–OH). Next, to confirm the importance of the proton source for activating the azlactone by a hydrogen-bonding interaction, additional calculations for **complex B** [**5d′**+**1a**+BnOH] and **complex C** [**5d′**+**1a**] were conducted. For **complex B**, the conformational search and TS calculations gave TS structures leading to the major (*S*) and minor (*R*) products (TS-*Si*-*S*-BnOH and TS-*Re*-*R*-BnOH, respectively). The *S*-isomer is more stable than the *R*-isomer by 1.5 kcal/mol. The calculated energy difference is in reasonable agreement with the experimentally observed stereoselectivity [1.5 (calcd.) vs 2.1 (exptl.) kcal/mol]. For **complex C**, the PTSCS provided pseudo-TS structures for each of the conformers (*S*: 482 conformers, *R*: 1162 conformers). However, the difference in energies between pseudo-TS-*Si*-*S* and pseudo-TS-*Re*-*R* did not agree with the $\Delta\Delta G$ values from the experimental results [0.0 (calcd.) vs 2.1 (exptl.) kcal/mol]. In addition, the TS calculations for these conformers did not converge. This inconsistency indicates that the alcoholysis reaction proceeds via activation of the azlactone substrate by a proton source such as water or alcohol.

The plausible reaction mechanism is proposed in Scheme 4. Initially, the bromide anion of PTC **5d** is exchanged for the hydroxide anion in the aqueous phase, and then the deprotonation of the benzyl alcohol generates the ammonium-alkoxide complex as the catalytic active species. Azlactone substrate is activated via hydrogen-bonding interactions with water or alcohol molecules, and the stereoselective carbonyl nucleophilic attack of the alkoxide anion provides the corresponding N-protected amino acid ester **3ab**, and regenerates the catalytic active species.



Scheme 4. Plausible reaction mechanism.

3.4. Conclusion

In conclusion, the DKR-type asymmetric alcoholysis of azlactones using PTCs afforded a wide variety of corresponding amino acid esters in up to 98% yield and up to 99:1 er. The α-chiral amino acid HFIP ester was also an acceptable substrate. A PTC loading of only 0.1 mol% was able to catalyze this reaction without significant loss of stereoselectivity, and a high turnover number was achieved. Detailed computational studies using a pseudo-TS conformational search with ConFinder and DFT calculations elucidated the essential non-covalent interactions between the substrate and the catalyst.

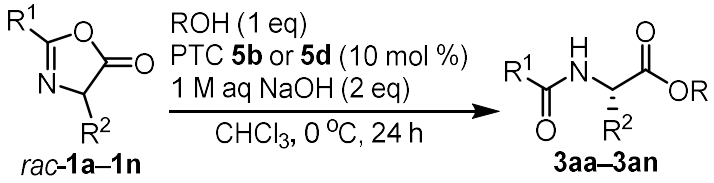
3.5. Experimental

General and Materials

Materials were purchased from commercial suppliers and used directly without further purification unless otherwise noted. Chloroform ($CHCl_3$) was purified prior to use following the guidelines of Perrin and Armarego.[17] *N*-Benzylquininium chloride (**5a**, TOKYO CHEMICAL INDUSTRY CO., LTD.), *N*-benzylcinchonidinium chloride (**5b**, TOKYO CHEMICAL INDUSTRY CO., LTD.), and *N*-benzylquinidinium chloride (**5c**, TOKYO CHEMICAL INDUSTRY CO., LTD.) were used as received. Catalyst **5d** and **5e** were prepared according to the slightly modified procedures of the literature.[14, 18] ^1H, ^{13}C, and ^{19}F NMR spectra were obtained on JEOL JNM-ECS400 (^1H NMR at 400 MHz, ^{13}C NMR at 100 MHz, and ^{19}F NMR at 376 MHz) spectrometers in $CDCl_3$. Chemical shifts for ^1H, ^{13}C, and ^{19}F NMR are reported in ppm and referenced to tetramethylsilane (at 0 ppm for ^1H and ^{13}C NMR) or benzotrifluoride (at –63.72 ppm for ^{19}F NMR). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sext (sextet), sep (septet), m (multiplet), br (broad). The enantiomer ratios (ers) were determined by HPLC analysis with a chiral stationary phase column specified in the individual experiment. HPLC analysis was performed on a JASCO PU-2080 equipped with a variable wavelength detector or HITACHI Chromaster 5110 equipped with a diode array detector using chiral stationary columns (DAICEL CHIRALPAK AD-H, DAICEL CHIRALCEL OD-H, OD-3, 0.46 cm x 25 cm). Preparative gel permeation chromatography (GPC) was performed on a LaboACE LC-5060 (Japan Analytical Industry Co., Ltd.) equipped with a UV-Vis 4ch 800LA detector. GPC columns used were JAIGEL-1HR and JAIGEL-2HR (Japan Analytical Industry Co., Ltd.). Specific optical rotations were measured on a JASCO DIP-1000 digital polarimeter. Column chromatography for the purification of chemicals was carried out with silica gel purchased from FUJIFILM Wako Pure Chemical Corporation (Wakosil HC-N, spherical; particle size 35–63 μm). Elemental analyses were recorded at the Service Centre of the Elementary Analysis of Organic Compounds, Faculty of Science, Kyushu University. High resolution mass (HRMS) analyses were measured on JEOL JMS-700 mass spectrometer at Evaluation Center of Materials Properties and Function, Institute for Materials Chemistry and Engineering, Kyushu University. Abbreviations; aq = aqueous solution, eq = equivalent, Rt = retention time, rt = room temperature, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl, HFIP = hexafluoroisopropyl.

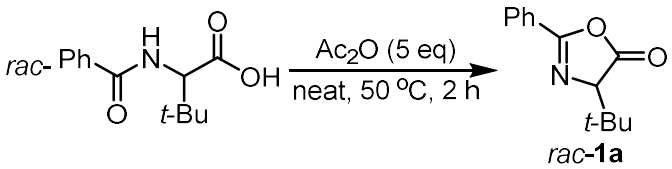
General Experimental Procedures

General Procedure I: Phase-Transfer Catalytic Asymmetric Alcoholysis of Azlactones 1



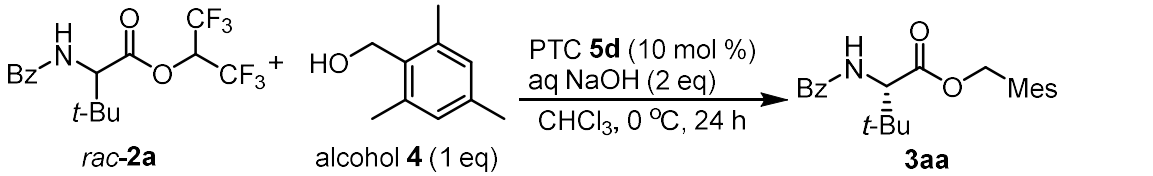
A chiral phase-transfer catalyst (PTC) (0.02 mmol, 10 mol %) was placed in a screw-capped test tube (diameter: 16 mm) under air. Then, alcohol (0.2 mmol, 1 eq) and $CHCl_3$ (1.6 mL) were added to the test tube followed by the addition of 1 M aq NaOH (400 μL, 2 eq). After stirred at 0 °C and 200 rpm for 10 min, azlactone (0.2 mmol, 1 eq) was added to the solution, and the resultant reaction mixture was further stirred for 24 h at 0 °C. The organic phase was filtered through a short silica-gel column with Et_2O as an eluent. After removal of the solvent under reduced pressure, the crude products were purified by flash column chromatography to afford the corresponding α-chiral N-protected amino acid esters. The enantiomer ratios of the products were analyzed by chiral HPLC.

General Procedure II: Representative Synthetic Procedure of Azlactones 1



N-Benzoyl-*tert*-leucine (3.40 g, 14.5 mmol, 1 eq) was mixed in a 30 mL round-bottom flask with anhydrous acetic anhydride (7.2 mL, 75 mmol, 5 eq), and heated to 50 °C for 2 h. After total consumption of the starting material, the acetic acid/anhydride were removed under reduced pressure. The crude products were purified by flash column chromatography (eluent: hexane/Et_2O = 50/1 to 10/1) to afford the corresponding azlactone substrate **1a** as a white solid (2.89 g, 92% yield).

Procedure for Phase-Transfer Catalytic Asymmetric Alcoholysis of *N*-Benzoyl *tert*-Leucine HFIP Ester 2a (Table 1, entry 13)



PTC **5d** (0.01 mmol, 10 mol %) was placed in a screw-capped test tube (diameter: 16 mm) under air. Then, alcohol **4** (15.0 mg, 0.1 mmol, 1 eq) and $CHCl_3$ (800 μL) were added to the test tube followed

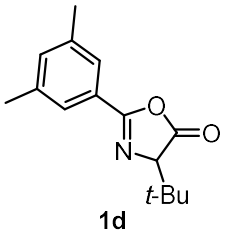
by the addition of 1 M aq NaOH (200 μL, 2 eq). After stirred at 0 °C and 200 rpm for 10 min, HFIP ester **2a** (0.1 mmol, 1 eq) was added to the solution, and the resultant reaction mixture was further stirred for 24 h at 0 °C. The organic phase was filtered through a short silica-gel column with Et_2O as an eluent. After removal of the solvent under reduced pressure, the crude products were purified by flash column chromatography (eluent: hexane/EtOAc = 7/1) to afford the corresponding ester **3aa** as a colorless oil in 71% yield with 98:2 er. In addition, when the use of 0.25 M aq NaOH, the ester **3aa** was obtained in 60% yield with 98.5:1.5 er.

Synthesis and Characterization of Substrates and Products

Synthesis of Substrates 1d, 1e, 1g–1j, and 1l

The following substrates **1a**–**1c**,[19–21] **1f**,[22] **1k**[23], **1m**[24], **1n**[24], **2a**[14] are known compounds. Thus, the analyses data for unknown substrates, including **1d**, **1e**, **1g**–**1j**, and **1l** were given.

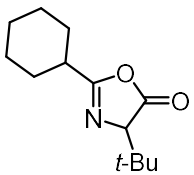
4-(*tert*-Butyl)-2-(3,5-dimethylphenyl)oxazol-5(4*H*)-one (1d).



1d

Title compound was synthesized from *N*-(3,5-dimethylbenzoyl)-*tert*-leucine (527 mg, 2.00 mmol) according to General Procedure II (reaction time: 4 h, flash column chromatography eluent: hexane/Et_2O = 50/1 to 20/1) as a white solid in 91% yield (447 mg, 1.82 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 (s, 2H), 7.20 (s, 1H), 4.06 (s, 1H), 2.38 (s, 6H), 1.14 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.1 (*C*O), 161.6 (*C*), 138.5 (*C*, 2C), 134.4 (*C*H), 125.7 (*C*), 125.6 (*C*H, 2C), 74.0 (*C*H), 35.9 (*C*), 26.2 (*C*H_3, 3C), 21.2 (*C*H_3, 2C). Elemental Analysis: Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.39; H, 7.80; N, 5.58.

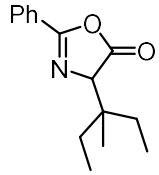
4-(*tert*-Butyl)-2-cyclohexyloxazol-5(4*H*)-one (1e).



1e

Title compound was synthesized from 2-(cyclohexanecarboxamido)-3,3-dimethylbutanoic acid (483 mg, 2.00 mmol) according to General Procedure II (reaction time: 91 h, flash column chromatography eluent: hexane/Et_2O = 20/1 to 10/1) as a white solid in 86% yield (384 mg, 1.72 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.82 (d, *J* = 1.6 Hz, 1H), 2.50 (ttd, *J* = 11.4, 3.6, 1.6 Hz, 1H), 2.02–1.91 (m, 2H), 1.88–1.75 (m, 2H), 1.73–1.63 (m, 1H), 1.60–1.43 (m, 2H), 1.41–1.20 (m, 3H), 1.06 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.5 (*C*O), 168.5 (*C*), 73.1 (*C*H), 38.2 (*C*H), 35.2 (*C*), 29.0 (*C*H_2), 28.9 (*C*H_2), 26.0 (*C*H_3, 3C), 25.6 (*C*H_2), 25.3 (*C*H_2), 25.2 (*C*H_2). Elemental Analysis: Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.77; H, 9.43; N, 6.08.

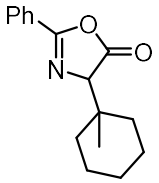
4-(3-Methylpentan-3-yl)-2-phenyloxazol-5(4*H*)-one (**1g**).



1g

Title compound was synthesized from *N*-benzoyl-2-(1-ethylmethyl-1-propyl)glycine (527 mg, 2.00 mmol) according to General Procedure II (reaction time: 11 h, flash column chromatography eluent: hexane/Et_2O = 60/1 to 30/1) as a white solid in 76% yield (373 mg, 1.52 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.04–7.97 (m, 2H), 7.56 (tt, *J* = 7.4, 1.6 Hz, 1H), 7.52–7.43 (m, 2H), 4.26 (s, 1H), 1.73–1.50 (m, 4H), 0.97 (s, 3H), 0.92 (t, *J* = 7.4 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.7 (*C*O), 161.1 (*C*), 132.5 (*C*H), 128.7 (*C*H, 2C), 127.8 (*C*H, 2C), 126.1 (*C*), 71.1 (*C*H), 41.4 (*C*), 27.9 (CH_2), 27.5 (CH_2), 20.0 (CH_3), 7.9 (CH_3, 2C). Elemental Analysis: Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.29; H, 7.84; N, 5.71.

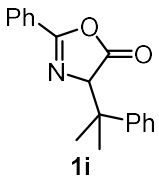
4-(1-Methylcyclohexyl)-2-phenyloxazol-5(4*H*)-one (**1h**).



1h

Title compound was synthesized from *N*-benzoyl-2-(1-methylcyclohexyl)glycine (277 mg, 1.01 mmol) according to General Procedure II (reaction time: 16 h, flash column chromatography eluent: hexane/Et_2O = 40/1 to 15/1) as a white solid in 35% yield (91 mg, 0.35 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.05–7.97 (m, 2H), 7.57 (tt, *J* = 7.2, 1.7 Hz, 1H), 7.52–7.43 (m, 2H), 4.27 (s, 1H), 1.87–1.69 (m, 2H), 1.68–1.28 (m, 8H), 0.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.3 (*C*O), 161.2 (*C*), 132.6 (*C*H), 128.7 (*C*H, 2C), 127.9 (*C*H, 2C), 126.0 (*C*), 72.6 (*C*H), 38.9 (*C*), 34.4 (CH_2), 33.8 (CH_2), 25.9 (CH_2), 21.7 (CH_2), 21.6 (CH_2), 20.4 (CH_3). Elemental Analysis: Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.58; H, 7.40; N, 5.38.

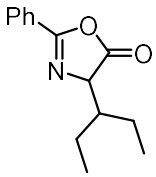
2-Phenyl-4-(2-phenylpropan-2-yl)oxazol-5(4H)-one (**1i**).



1i

Title compound was synthesized from *N*-benzoyl-2-(2-phenyl-2-propyl)glycine (595 mg, 2.00 mmol) according to General Procedure II (reaction time: 18 h, flash column chromatography eluent: hexane/Et_2O = 20/1 to 5/1) as a white solid in 43% yield (238 mg, 0.850 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94–7.87 (m, 2H), 7.54 (tt, *J* = 7.4, 1.5 Hz, 1H), 7.48–7.36 (m, 4H), 7.32–7.23 (m, 2H), 7.20 (tt, *J* = 7.2, 1.7 Hz, 1H), 4.48 (s, 1H), 1.66 (s, 3H), 1.63 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.2 (*C*O), 161.4 (*C*), 143.3 (*C*), 132.6 (*C*H), 128.7 (*C*H, 2C), 128.1 (*C*H, 2C), 127.8 (*C*H, 2C), 126.8 (*C*H), 126.4 (*C*H, 2C), 125.8 (*C*), 74.2 (*C*H), 42.2 (*C*), 26.1 (CH_3), 25.0 (CH_3). Elemental Analysis: Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.41; H, 6.15; N, 4.99.

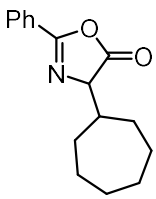
4-(Pentan-3-yl)-2-phenyloxazol-5(4H)-one (**1j**).



1j

Title compound was synthesized from *N*-benzoyl-2-(3-pentyl)glycine (500 mg, 2.00 mmol) according to General Procedure II (reaction time: 8 h, flash column chromatography eluent: hexane/Et_2O = 100/1 to 30/1) as a white solid in 90% yield (418 mg, 1.81 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.04–7.97 (m, 2H), 7.57 (tt, *J* = 7.4, 1.5 Hz, 1H), 7.53–7.44 (m, 2H), 4.51 (d, *J* = 4.0 Hz, 1H), 1.93 (dquint, *J* = 6.8, 3.8 Hz, 1H), 1.62–1.48 (m, 2H), 1.47–1.32 (m, 2H), 1.02 (t, *J* = 7.2 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 178.7 (*C*O), 161.5 (*C*), 132.6 (*C*H), 128.8 (*C*H, 2C), 127.9 (*C*H, 2C), 126.0 (*C*), 67.4 (*C*H), 44.4 (*C*H), 23.1 (*C*H_2), 22.5 (*C*H_2), 11.8 (*C*H_3, 2C). Elemental Analysis: Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.55; H, 7.41; N, 6.15.

4-Cycloheptyl-2-phenyloxazol-5(4H)-one (**1l**).



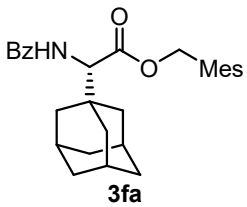
1l

Title compound was synthesized from *N*-benzoyl 2-cycloheptylglycine (275 mg, 1.00 mmol) according to General Procedure II (reaction time: 8 h, flash column chromatography eluent: hexane/Et_2O = 30/1 to 10/1) as a white solid in 70% yield (180 mg, 0.698 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.04–7.97 (m, 2H), 7.57 (tt, *J* = 7.2, 1.7 Hz, 1H), 7.53–7.44 (m, 2H), 4.34 (d, *J* = 4.0 Hz, 1H), 2.32–2.18 (m, 1H), 1.91–1.38 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 178.0 (*C*O), 161.5 (*C*), 132.6 (*C*H), 128.8 (*C*H, 2C), 127.9 (*C*H, 2C), 126.0 (*C*), 71.4 (*C*H), 42.1 (*C*H), 31.1 (*C*H_2), 29.8 (*C*H_2), 27.9 (*C*H_2, 2C), 26.6 (*C*H_2), 26.4 (*C*H_2). Elemental Analysis: Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.72; H, 7.39; N, 5.34.

Characterization of Products 3

Asymmetric alcoholysis reactions in Table 1–3 were performed according to the General Procedure I. All the N-protected amino acid esters were purified by a flash column chromatography (eluent: hexane/EtOAc).

(+)-2,4,6-Trimethylbenzyl 2-(adamantan-1-yl)-2-benzamidoacetate (**3fa**).

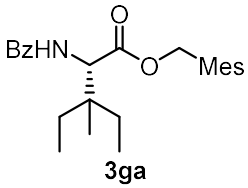


3fa

Title compound was obtained according to General Procedure I (PTC **5d**, flash column chromatography eluent: hexane/EtOAc = 20/1 to 10/1) as a colorless oil in 79% yield (70.7 mg, 0.159 mmol) with 98:2 er. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.84–7.74 (m, 2H), 7.52 (tt, *J* = 7.4, 1.7 Hz, 1H), 7.48–7.40 (m, 2H), 6.88 (s, 2H), 6.68 (br-d, *J* = 9.2 Hz, 1H), 5.24 (s, 2H), 4.57 (d, *J* = 9.6 Hz, 1H), 2.36 (s, 6H),

2.28 (s, 3H), 1.98 (br-s, 3H), 1.74–1.52 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.4 (*C*O), 167.1 (*C*O), 138.7 (*C*), 138.2 (*C*, 2C), 134.2 (*C*), 131.7 (*C*H), 129.1 (*C*H, 2C), 128.6 (*C*H, 2C), 128.4 (*C*), 127.0 (*C*H, 2C), 61.7 (CH_2), 61.1 (*C*H), 38.8 (CH_2, 3C), 37.1 (*C*), 36.6 (CH_2, 3C), 28.2 (*C*H, 3C), 21.0 (CH_3), 19.6 (CH_3, 2C). Elemental Analysis: Calcd for $C_{29}H_{35}NO_3$: C, 78.17; H, 7.92; N, 3.14. Found: C, 78.09; H, 8.02; N, 3.09. HPLC analysis: CHIRALCEL OD-3 column [conditions, hexane:2-propanol = 95:5, flow rate = 1 mL/min, rt, Rt (major) = 20.087 min, Rt (minor) = 6.853 min]. $[\alpha]_D^{22.0}$ = +29.0 (*c* = 1.2, $CHCl_3$).

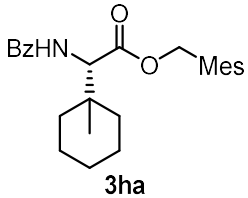
(+)-2,4,6-Trimethylbenzyl 2-benzamido-3-ethyl-3-methylpentanoate (**3ga**).



3ga

Title compound was obtained according to General Procedure I (PTC **5d**, flash column chromatography eluent: hexane/EtOAc = 7/1) as a white solid in 61% yield (48.3 mg, 0.122 mmol) with 98.5:1.5 er. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80–7.73 (m, 2H), 7.51 (tt, *J* = 7.2, 1.7 Hz, 1H), 7.47–7.39 (m, 2H), 6.87 (s, 2H), 6.60 (br-d, *J* = 9.6 Hz, 1H), 5.25 (A of AB, J_{AB} = 12.0 Hz, 1H), 5.21 (B of AB, J_{AB} = 12.0 Hz, 1H), 4.86 (d, *J* = 9.2 Hz, 1H), 2.34 (s, 6H), 2.28 (s, 3H), 1.49–1.23 (m, 4H), 0.93 (s, 6H), 0.86 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.2 (*C*O), 167.0 (*C*O), 138.6 (*C*), 138.2 (*C*, 2C), 134.3 (*C*), 131.7 (*C*H), 129.0 (*C*H, 2C), 128.6 (*C*H, 2C), 128.4 (*C*), 127.0 (*C*H, 2C), 61.6 (CH_2), 57.5 (*C*H), 40.3 (*C*), 28.3 (CH_2), 28.0 (CH_2), 21.0 (CH_3), 20.4 (CH_3), 19.5 (CH_3, 2C), 7.9 (CH_3), 7.8 (CH_3). Elemental Analysis: Calcd for $C_{25}H_{33}NO_3$: C, 75.91; H, 8.41; N, 3.54. Found: C, 75.83; H, 8.37; N, 3.46. HPLC analysis: CHIRALCEL OD-H column [conditions, hexane:2-propanol = 95:5, flow rate = 1 mL/min, rt, Rt (major) = 14.44 min, Rt (minor) = 10.44 min]. $[\alpha]_D^{23.1}$ = +55.4 (*c* = 1.4, $CHCl_3$).

(+)-2,4,6-Trimethylbenzyl 2-benzamido-2-(1-methylcyclohexyl)acetate (**3ha**).

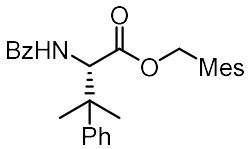


3ha

Title compound was obtained according to General Procedure I (PTC **5d**, flash column chromatography eluent: hexane/EtOAc = 7/1) as a white solid in 79% yield (64.8 mg, 0.159 mmol) with 97.5:2.5 er. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83–7.72 (m, 2H), 7.51 (tt, *J* = 7.2, 1.7 Hz, 1H), 7.47–7.39 (m, 2H), 6.87 (s, 2H), 6.64 (br-d, *J* = 9.6 Hz, 1H), 5.25 (A of AB, J_{AB} = 12.0 Hz, 1H), 5.21 (B of AB, J_{AB} = 12.0 Hz, 1H), 4.85 (d, *J* = 9.2 Hz, 1H), 2.34 (s, 6H), 2.28 (s, 3H), 1.67–1.17 (m, 10H), 0.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.9 (*C*O), 167.1 (*C*O), 138.7 (*C*), 138.2 (*C*, 2C), 134.3 (*C*), 131.7 (*C*H), 129.1 (*C*H, 2C), 128.6 (*C*H, 2C), 128.4 (*C*), 127.0 (*C*H, 2C), 61.6 (CH_2), 59.2 (*C*H), 37.9 (*C*), 35.0 (CH_2), 34.8 (CH_2), 25.9 (CH_2), 21.61 (CH_2), 21.56 (CH_2), 21.1 (CH_3), 20.6 (CH_3), 19.6 (CH_3,

2C). Elemental Analysis: Calcd for $C_{26}H_{33}NO_3$: C, 76.62; H, 8.16; N, 3.44. Found: C, 76.59; H, 8.24; N, 3.40. HPLC analysis: CHIRALCEL OD-3 column [conditions, hexane:2-propanol = 95:5, flow rate = 1 mL/min, rt, Rt (major) = 9.000 min, Rt (minor) = 5.733 min]. $[\alpha]_D^{20.5}$ = +65.5 (*c* = 1.0, $CHCl_3$).

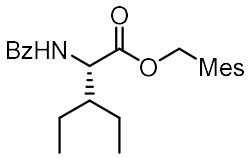
(+)-2,4,6-Trimethylbenzyl 2-benzamido-3-methyl-3-phenylbutanoate (**3ia**).



3ia

Title compound was obtained according to General Procedure I (PTC **5d**, flash column chromatography eluent: hexane/EtOAc = 6/1) as a white solid in 80% yield (68.9 mg, 0.160 mmol) with 94:6 er. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69–7.62 (m, 2H), 7.49 (tt, *J* = 7.2, 1.7 Hz, 1H), 7.44–7.36 (m, 2H), 7.36–7.29 (m, 2H), 7.29–7.22 (m, 2H), 7.18 (tt, *J* = 7.4, 1.6 Hz, 1H), 6.83 (s, 2H), 6.47 (br-d, *J* = 8.8 Hz, 1H), 5.13 (A of AB, J_{AB} = 12.0 Hz, 1H), 5.08 (B of AB, J_{AB} = 11.6 Hz, 1H), 5.05 (d, *J* = 9.2 Hz, 1H), 2.27 (s, 3H), 2.23 (s, 6H), 1.48 (s, 3H), 1.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.1 (*C*O), 167.0 (*C*O), 144.3 (*C*), 138.5 (*C*), 138.3 (*C*, 2C), 134.1 (*C*), 131.7 (*C*H), 129.0 (*C*H, 2C), 128.6 (*C*H, 2C), 128.34 (*C*), 128.25 (*C*H, 2C), 127.0 (*C*H, 2C), 126.7 (*C*H), 126.2 (*C*H, 2C), 61.5 (CH_2), 60.7 (*C*H), 42.0 (*C*), 25.9 (CH_3), 25.4 (CH_3), 21.0 (CH_3), 19.5 (CH_3, 2C). Elemental Analysis: Calcd for $C_{28}H_{31}NO_3$: C, 78.29; H, 7.27; N, 3.26. Found: C, 78.15; H, 7.27; N, 3.22. HPLC analysis: CHIRALCEL OD-3 column [conditions, hexane:2-propanol = 95:5, flow rate = 1 mL/min, rt, Rt (major) = 19.713 min, Rt (minor) = 8.067 min]. $[\alpha]_D^{21.2}$ = +30.8 (*c* = 1.2, $CHCl_3$).

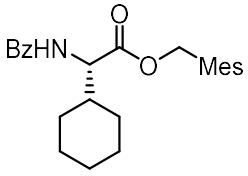
(+)-2,4,6-Trimethylbenzyl 2-benzamido-3-ethylpentanoate (**3ja**).



3ja

Title compound was obtained according to General Procedure I (PTC **5d**, flash column chromatography eluent: hexane/EtOAc = 7/1) as a white solid in 54% yield (41.2 mg, 0.108 mmol) with 79:21 er. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81–7.75 (m, 2H), 7.52 (tt, *J* = 7.4, 1.6 Hz, 1H), 7.48–7.40 (m, 2H), 6.89 (s, 2H), 6.56 (br-d, *J* = 8.8 Hz, 1H), 5.26 (A of AB, J_{AB} = 12.0 Hz, 1H), 5.22 (B of AB, J_{AB} = 11.6 Hz, 1H), 5.00 (dd, *J* = 8.8, 4.0 Hz, 1H), 2.35 (s, 6H), 2.28 (s, 3H), 1.84–1.73 (m, 1H), 1.46–1.23 (m, 4H), 0.98 (t, *J* = 7.2 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.0 (*C*O), 167.3 (*C*O), 138.7 (*C*), 138.3 (*C*, 2C), 134.3 (*C*), 131.7 (*C*H), 129.1 (*C*H, 2C), 128.6 (*C*H, 2C), 128.4 (*C*), 127.0 (*C*H, 2C), 62.1 (CH_2), 54.2 (*C*H), 44.9 (*C*H), 23.0 (CH_2), 22.7 (CH_2), 21.1 (CH_3), 19.5 (CH_3, 2C), 11.8 (CH_3), 11.7 (CH_3). Elemental Analysis: Calcd for $C_{24}H_{31}NO_3$: C, 75.56; H, 8.19; N, 3.67. Found: C, 75.39; H, 8.18; N, 3.68. HPLC analysis: CHIRALCEL OD-3 column [conditions, hexane:2-propanol = 95:5, flow rate = 1 mL/min, rt, Rt (major) = 16.887 min, Rt (minor) = 8.667 min]. $[\alpha]_D^{23.2}$ = +39.2 (*c* = 0.9, $CHCl_3$).

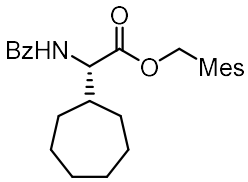
(+)-2,4,6-Trimethylbenzyl 2-benzamido-2-cyclohexylacetate (**3ka**).



3ka

Title compound was prepared according to General Procedure I (PTC **5d**, flash column chromatography eluent: hexane/EtOAc = 7/1). Further purification by gel permeation chromatography gave the **3ka** as a white solid in 27% yield (21.0 mg, 0.053 mmol) with 73:27 er. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83–7.76 (m, 2H), 7.52 (tt, *J* = 7.6, 1.5 Hz, 1H), 7.48–7.40 (m, 2H), 6.89 (s, 2H), 6.66 (br-d, *J* = 8.8 Hz, 1H), 5.237 (s, 1H), 5.235 (s, 1H), 4.80 (dd, *J* = 8.8, 4.4 Hz, 1H), 2.35 (s, 6H), 2.28 (s, 3H), 1.98–1.85 (m, 1H), 1.82–1.68 (m, 3H), 1.67–1.52 (m, 2H), 1.35–0.99 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.4 (*C*O), 167.2 (*C*O), 138.8 (*C*), 138.2 (*C*, 2C), 134.2 (*C*), 131.7 (*C*H), 129.1 (*C*H, 2C), 128.6 (*C*H, 2C), 128.3 (*C*), 127.0 (*C*H, 2C), 62.1 (CH_2), 57.1 (*C*H), 41.5 (*C*H), 29.6 (CH_2), 28.1 (CH_2), 25.9 (CH_2, 3C), 21.1 (CH_3), 19.5 (CH_3, 2C). Elemental Analysis: Calcd for $C_{25}H_{31}NO_3$: C, 76.30; H, 7.94; N, 3.56. Found: C, 76.02; H, 8.01; N, 3.39. HPLC analysis: CHIRALCEL OD-3 column [conditions, hexane:2-propanol = 95:5, flow rate = 1 mL/min, rt, Rt (major) = 11.827 min, Rt (minor) = 6.340 min]. $[\alpha]_D^{23.1}$ = +14.3 (*c* = 1.1, $CHCl_3$).

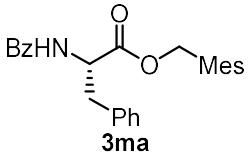
(+)-2,4,6-Trimethylbenzyl 2-benzamido-2-cycloheptylacetate (**3la**).



3la

Title compound was prepared according to General Procedure I (PTC **5d**, flash column chromatography eluent: hexane/EtOAc = 7/1). Further purification with gel permeation chromatography gave the **3la** as a white solid in 26% yield (20.8 mg, 0.051 mmol) with 60:40 er. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.84–7.74 (m, 2H), 7.52 (tt, *J* = 7.4, 1.7 Hz, 1H), 7.48–7.40 (m, 2H), 6.89 (s, 2H), 6.66 (br-d, *J* = 8.4 Hz, 1H), 5.23 (s, 2H), 4.84 (dd, *J* = 8.8, 4.4 Hz, 1H), 2.35 (s, 6H), 2.28 (s, 3H), 2.17–2.03 (m, 1H), 1.88–1.75 (m, 1H), 1.74–1.19 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.5 (*C*O), 167.3 (*C*O), 138.8 (*C*), 138.2 (*C*, 2C), 134.2 (*C*), 131.7 (*C*H), 129.1 (*C*H, 2C), 128.6 (*C*H, 2C), 128.3 (*C*), 127.0 (*C*H, 2C), 62.1 (CH_2), 57.8 (*C*H), 42.8 (*C*H), 31.3 (CH_2), 29.5 (CH_2), 28.0 (CH_2), 27.7 (CH_2), 26.51 (CH_2), 26.46 (CH_2), 21.1 (CH_3), 19.5 (CH_3, 2C). Elemental Analysis: Calcd for $C_{26}H_{33}NO_3$: C, 76.62; H, 8.16; N, 3.44. Found: C, 76.60; H, 8.28; N, 3.34. HPLC analysis: CHIRALCEL OD-3 column [conditions, hexane:2-propanol = 95:5, flow rate = 1 mL/min, rt, Rt (major) = 17.927 min, Rt (minor) = 8.173 min]. $[\alpha]_D^{22.6}$ = +12.5 (*c* = 1.4, $CHCl_3$).

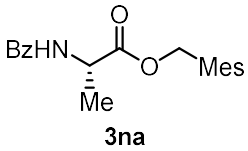
(–)-2,4,6-Trimethylbenzyl 2-benzamido-3-phenylpropanoate (**3ma**).



3ma

Title compound was obtained according to General Procedure I (PTC **5d**, flash column chromatography eluent: hexane/EtOAc = 7/1) as a white solid in 55% yield (44.5 mg, 0.111 mmol) with 75.5:24.5 er. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73–7.67 (m, 2H), 7.50 (tt, *J* = 7.4, 1.5 Hz, 1H), 7.45–7.37 (m, 2H), 7.24–7.16 (m, 3H), 7.03–6.96 (m, 2H), 6.90 (s, 2H), 6.56 (br-d, *J* = 8.0 Hz, 1H), 5.31 (A of AB, J_{AB} = 12.0 Hz, 1H), 5.24 (B of AB, J_{AB} = 12.0 Hz, 1H), 5.08 (dt, *J* = 8.0, 5.5 Hz, 1H), 3.27 (dd, *J* = 13.6, 6.0 Hz, 1H), 3.16 (dd, *J* = 13.8, 5.0 Hz, 1H), 2.34 (s, 6H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.6 (*C*O), 166.8(*C*O), 138.9 (*C*), 138.3 (*C*, 2C), 135.7 (*C*), 134.0 (*C*), 131.7 (*C*H), 129.4 (*C*H, 2C), 129.2 (*C*H, 2C), 128.6 (*C*H, 2C), 128.5 (*C*H, 2C), 128.4 (*C*), 127.1 (*C*H), 127.0 (*C*H, 2C), 62.2 (CH_2), 53.5 (*C*H), 37.8 (CH_2), 21.0 (CH_3), 19.6 (CH_3, 2C). Elemental Analysis: Calcd for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49;. Found: C, 77.78; H, 7.00; N, 3.23. HPLC analysis: CHIRALCEL OD-3 column [conditions, hexane:2-propanol = 95:5, flow rate = 1 mL/min, rt, Rt (major) = 10.367 min, Rt (minor) = 14.140 min]. $[\alpha]_D^{30.1}$ = –11.1 (*c* = 1.0, $CHCl_3$).

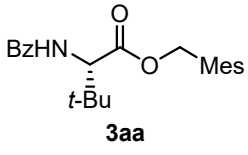
(–)-2,4,6-Trimethylbenzyl 2-benzamidopropanoate (**3na**).



3na

Title compound was obtained according to General Procedure I (PTC **5d**, flash column chromatography eluent: hexane/EtOAc = 7/1 to 5/1) as a white solid in 38% yield (24.7 mg, 0.076 mmol) with 72.5:27.5 er. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.82–7.76 (m, 2H), 7.50 (tt, *J* = 7.2, 1.7 Hz, 1H), 7.46–7.39 (m, 2H), 6.89 (s, 2H), 6.79 (br-d, *J* = 6.8 Hz, 1H), 5.27 (s, 2H), 4.79 (qd, *J* = 7.1, 7.0 Hz, 1H), 2.35 (s, 6H), 2.28 (s, 3H), 1.50 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.4 (*C*O), 166.8 (*C*O), 138.8 (*C*), 138.3 (*C*, 2C), 134.0 (*C*), 131.7 (*C*H), 129.2 (*C*H, 2C), 128.6 (*C*H, 2C), 128.4 (*C*), 127.0 (*C*H, 2C), 62.3 (CH_2), 48.6 (*C*H), 21.0 (CH_3), 19.5 (CH_3, 2C), 18.8 (CH_3). Elemental Analysis: Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30;. Found: C, 73.83; H, 7.18; N, 4.26. HPLC analysis: CHIRALCEL OD-3 column [conditions, hexane:2-propanol = 95:5, flow rate = 1 mL/min, rt, Rt (major) = 11.167 min, Rt (minor) = 15.280 min]. $[\alpha]_D^{30.3}$ = –16.1 (*c* = 1.0, $CHCl_3$).

(*S*)-(+)-2,4,6-Trimethylbenzyl *N*-benzoyl-*tert*-leucinate (**3aa**).

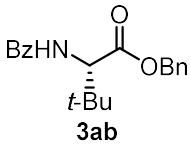


3aa

Title compound was obtained according to General Procedure I (PTC **5d**, flash column chromatography eluent: hexane/EtOAc = 20/1 to 7/1) as a colorless oil in 78% yield (57.0 mg, 0.155 mmol) with 98.5:1.5 er. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83–7.72 (m, 2H), 7.51 (tt, *J* = 7.2, 1.7 Hz, 1H), 7.47–7.37 (m, 2H), 6.87 (s,

2H), 6.68 (br-d, J = 9.6 Hz, 1H), 5.24 (s, 2H), 4.69 (d, J = 9.2 Hz, 1H), 2.35 (s, 6H), 2.27 (s, 3H), 1.02 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.9 (*C*O), 167.1 (*C*O), 138.7 (*C*), 138.2 (*C*, 2C), 134.3 (*C*), 131.7 (*C*H), 129.1 (*C*H, 2C), 128.6 (*C*H, 2C), 128.3 (*C*), 127.0 (*C*H, 2C), 61.7 (CH_2), 60.3 (*C*H), 35.3 (*C*), 26.7 (CH_3, 3C), 21.0 (CH_3), 19.6 (CH_3, 2C). Elemental Analysis: Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 74.91; H, 7.95; N, 3.71. HPLC analysis: CHIRALCEL OD-3 column [conditions, hexane:2-propanol = 95:5, flow rate = 1 mL/min, rt, Rt (major) = 8.293 min, Rt (minor) = 6.300 min]. $[\alpha]_D^{24.5}$ = +72.9 (c = 1.7, $CHCl_3$).

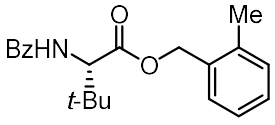
(+)-Benzyl *N*-benzoyl-*tert*-leucinate (3ab).



3ab

Title compound was obtained according to General Procedure I (PTC **5b**, flash column chromatography eluent: hexane/EtOAc = 7/1) as a colorless oil in 69% yield (45.2 mg, 0.139 mmol) with 95.5:4.5 er. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.84–7.73 (m, 2H), 7.51 (tt, J = 7.2, 1.8 Hz, 1H), 7.47–7.41 (m, 2H), 7.40–7.28 (m, 5H), 6.69 (br-d, J = 9.2 Hz, 1H), 5.22 (A of AB, J_{AB} = 12.4 Hz, 1H), 5.15 (B of AB, J_{AB} = 12.4 Hz, 1H), 4.75 (d, J = 9.6 Hz, 1H), 1.03 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.6 (*C*O), 167.1 (*C*O), 135.1 (*C*), 134.2 (*C*), 131.7 (*C*H), 128.63 (*C*H, 2C), 128.59 (*C*H, 2C), 128.52 (*C*H, 2C), 128.47 (*C*H), 127.0 (*C*H, 2C), 67.0 (CH_2), 60.2 (*C*H), 35.4 (*C*), 26.7 (CH_3, 3C). Elemental Analysis: Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.64; H, 7.12; N, 4.21. HPLC analysis: CHIRALCEL OD-3 column [conditions, hexane:2-propanol = 95:5, flow rate = 1 mL/min, rt, Rt (major) = 9.793 min, Rt (minor) = 8.693 min]. $[\alpha]_D^{24.5}$ = +44.0 (c = 1.0, $CHCl_3$).

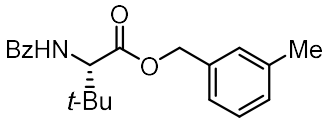
(+)-2-Methylbenzyl *N*-benzoyl-*tert*-leucinate (3ac).



3ac

Title compound was obtained according to General Procedure I (PTC **5d**, flash column chromatography eluent: hexane/EtOAc = 20/1 to 5/1) as a white solid in 75% yield (51.1 mg, 0.151 mmol) with 97:3 er. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85–7.73 (m, 2H), 7.52 (tt, J = 7.4, 1.6 Hz, 1H), 7.48–7.40 (m, 2H), 7.38–7.31 (m, 1H), 7.28–7.13 (m, 3H), 6.68 (br-d, J = 9.6 Hz, 1H), 5.21 (s, 2H), 4.74 (d, J = 9.2 Hz, 1H), 2.37 (s, 3H), 1.03 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.7 (*C*O), 167.1 (*C*O), 137.1 (*C*), 134.2 (*C*), 133.1 (*C*), 131.7 (*C*H), 130.4 (*C*H), 129.7 (*C*H), 128.8 (*C*H), 128.6 (*C*H, 2C), 127.0 (*C*H, 2C), 126.1 (*C*H), 65.3 (CH_2), 60.3 (*C*H), 35.4 (*C*), 26.7 (CH_3, 3C), 19.0 (CH_3). Elemental Analysis: Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.23; H, 7.46; N, 4.08. HPLC analysis: CHIRALCEL OD-3 column [conditions, hexane:2-propanol = 95:5, flow rate = 1 mL/min, rt, Rt (major) = 13.253 min, Rt (minor) = 9.453 min]. $[\alpha]_D^{24.5}$ = +46.2 (c = 1.0, $CHCl_3$).

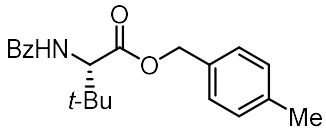
(+)-3-Methylbenzyl *N*-benzoyl-*tert*-leucinate (3ad).



3ad

Title compound was obtained according to General Procedure I (PTC **5b**, flash column chromatography eluent: hexane/EtOAc = 7/1) as a colorless oil in 76% yield (51.5 mg, 0.152 mmol) with 97.5:2.5 er. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85–7.74 (m, 2H), 7.51 (tt, *J* = 7.4, 1.7 Hz, 1H), 7.47–7.39 (m, 2H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.20–7.08 (m, 3H), 6.69 (br-d, *J* = 9.6 Hz, 1H), 5.18 (A of AB, J_{AB} = 12.0 Hz, 1H), 5.12 (B of AB, J_{AB} = 12.0 Hz, 1H), 4.76 (d, *J* = 9.6 Hz, 1H), 2.35 (s, 3H), 1.04 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.6 (*C*O), 167.1 (*C*O), 138.3 (*C*), 135.1 (*C*), 134.3 (*C*), 131.7 (*C*H), 129.2 (*C*H, 2C), 128.6 (*C*H, 2C), 128.5 (*C*H), 127.0 (*C*H, 2C), 125.5 (*C*H), 67.1 (CH_2), 60.3 (*C*H), 35.4 (*C*), 26.7 (CH_3, 3C), 21.3 (CH_3). Elemental Analysis: Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.30; H, 7.45; N, 4.06. HPLC analysis: CHIRALPAK AD-H column [conditions, hexane:2-propanol = 95:5, flow rate = 1 mL/min, rt, Rt (major) = 19.760 min, Rt (minor) = 15.560 min]. $[\alpha]_D^{24.6}$ = +42.7 (*c* = 1.0, $CHCl_3$).

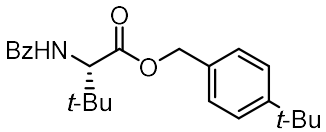
(+)-4-Methylbenzyl *N*-benzoyl-*tert*-leucinate (3ae).



3ae

Title compound was obtained according to General Procedure I (PTC **5b**, flash column chromatography eluent: hexane/EtOAc = 7/1) as a white solid in 82% yield (55.8 mg, 0.164 mmol) with 96.5:3.5 er. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.84–7.73 (m, 2H), 7.51 (tt, *J* = 7.4, 1.7 Hz, 1H), 7.47–7.39 (m, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.68 (br-d, *J* = 9.2 Hz, 1H), 5.18 (A of AB, J_{AB} = 12.0 Hz, 1H), 5.10 (B of AB, J_{AB} = 12.0 Hz, 1H), 4.74 (d, *J* = 9.2 Hz, 1H), 2.35 (s, 3H), 1.02 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.7 (*C*O), 167.1 (*C*O), 138.3 (*C*), 134.3 (*C*), 132.2 (*C*), 131.7 (*C*H), 129.3 (*C*H, 2C), 128.7 (*C*H, 2C), 128.6 (*C*H, 2C), 127.0 (*C*H, 2C), 67.0 (CH_2), 60.2 (*C*H), 35.4 (*C*), 26.7 (CH_3, 3C), 21.2 (CH_3). Elemental Analysis: Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.02; H, 7.48; N, 4.08. HPLC analysis: CHIRALCEL OD-3 column [conditions, hexane:2-propanol = 95:5, flow rate = 1 mL/min, rt, Rt (major) = 8.347 min, Rt (minor) = 7.340 min]. $[\alpha]_D^{24.7}$ = +38.1 (*c* = 1.1, $CHCl_3$).

(+)-4-(*tert*-Butyl)benzyl *N*-benzoyl-*tert*-leucinate (3af).

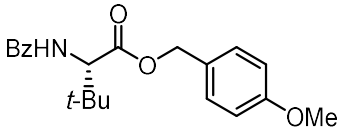


3af

Title compound was obtained according to General Procedure I (PTC **5b**, flash column chromatography eluent: hexane/EtOAc = 10/1) as a colorless oil in 79% yield (60.3 mg, 0.158 mmol) with 97:3 er. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83–7.76 (m, 2H), 7.51 (tt, *J* = 7.4, 1.7 Hz, 1H), 7.47–7.41 (m, 2H),

7.41–7.35 (m, 2H), 7.33–7.26 (m, 2H), 6.70 (br-d, J = 9.2 Hz, 1H), 5.18 (A of AB, J_{AB} = 12.4 Hz, 1H), 5.14 (B of AB, J_{AB} = 12.0 Hz, 1H), 4.75 (d, J = 9.6 Hz, 1H), 1.32 (s, 9H), 1.04 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.7 (*C*O), 167.1 (*C*O), 151.5 (*C*), 134.3 (*C*), 132.1 (*C*), 131.7 (*C*H), 128.6 (*C*H, 2C), 128.3 (*C*H, 2C), 127.0 (*C*H, 2C), 125.5 (*C*H, 2C), 66.9 (CH_2), 60.2 (*C*H), 35.4 (*C*), 34.6 (*C*), 31.3 (CH_3, 3C), 26.7 (CH_3, 3C). Elemental Analysis: Calcd for $C_{24}H_{31}NO_3$: C, 75.56; H, 8.19; N, 3.67. Found: C, 75.41; H, 8.19; N, 3.62. HPLC analysis: CHIRALCEL OD-3 column [conditions, hexane:2-propanol = 95:5, flow rate = 1 mL/min, rt, Rt (major) = 6.840 min, Rt (minor) = 6.313 min]. $[\alpha]_D^{24.6}$ = +41.7 (c = 1.0, $CHCl_3$).

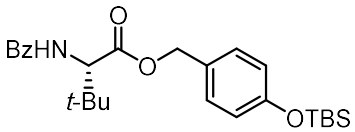
(+)-4-Methoxybenzyl *N*-benzoyl-*tert*-leucinate (3ag).



3ag

Title compound was obtained according to General Procedure I (PTC **5b**, flash column chromatography eluent: hexane/EtOAc = 7/1 to 5/1) as a colorless oil in 83% yield (59.2 mg, 0.167 mmol) with 96.5:3.5 er. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.82–7.75 (m, 2H), 7.51 (tt, J = 7.2, 1.7 Hz, 1H), 7.48–7.39 (m, 2H), 7.34–7.27 (m, 2H), 6.94–6.82 (m, 2H), 6.68 (br-d, J = 9.2 Hz, 1H), 5.17 (A of AB, J_{AB} = 11.6 Hz, 1H), 5.07 (B of AB, J_{AB} = 11.6 Hz, 1H), 4.72 (d, J = 9.2 Hz, 1H), 3.80 (s, 3H), 1.01 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.7 (*C*O), 167.1 (*C*O), 159.7 (*C*), 134.3 (*C*), 131.7 (*C*H), 130.4 (*C*H, 2C), 128.6 (*C*H, 2C), 127.3 (*C*), 127.0 (*C*H, 2C), 113.9 (*C*H, 2C), 66.9 (CH_2), 60.2 (*C*H), 55.3 (CH_3), 35.4 (*C*), 26.7 (CH_3, 3C). Elemental Analysis: Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.84; H, 7.12; N, 3.82. HPLC analysis: CHIRALCEL OD-3 column [conditions, hexane:2-propanol = 95:5, flow rate = 1 mL/min, rt, Rt (major) = 11.240 min, Rt (minor) = 9.913 min]. $[\alpha]_D^{24.7}$ = +24.6 (c = 1.0, $CHCl_3$).

(+)-4-[(*tert*-Butyldimethylsilyl)oxy]benzyl *N*-benzoyl-*tert*-leucinate (3ah).

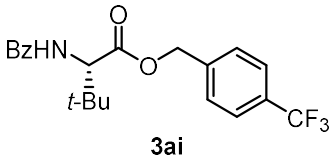


3ah

Title compound was obtained according to General Procedure I (PTC **5b**, flash column chromatography eluent: hexane/EtOAc = 10/1 to 5/1) as a colorless oil in 81% yield (73.8 mg, 0.162 mmol) with 98:2 er. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81–7.77 (m, 2H), 7.52 (tt, J = 7.4, 1.5 Hz, 1H), 7.48–7.42 (m, 2H), 7.26–7.23 (m, 2H), 6.82 (dt, J = 8.4, 2.4 Hz, 2H), 6.66 (br-d, J = 9.6 Hz, 1H), 5.17 (A of AB, J_{AB} = 11.6 Hz, 1H), 5.06 (B of AB, J_{AB} = 12.0 Hz, 1H), 4.72 (d, J = 9.6 Hz, 1H), 1.00 (s, 9H), 0.98 (s, 9H), 0.19 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.7 (*C*O), 167.1 (*C*O), 156.0 (*C*), 134.3 (*C*), 131.7 (*C*H), 130.4 (*C*H, 2C), 128.6 (*C*H, 2C), 128.0 (*C*), 127.0 (*C*H, 2C), 120.2 (*C*H, 2C), 66.9 (CH_2), 60.2 (*C*H), 35.5 (*C*), 26.7 (CH_3, 3C), 25.7 (CH_3, 3C), 18.2 (*C*), –4.4 (CH_3, 2C). Elemental

Analysis: Calcd for $C_{26}H_{37}NO_4Si$: C, 68.53; H, 8.18; N, 3.07. Found: C, 68.32; H, 8.17; N, 2.91. HPLC analysis: CHIRALPAK AD-H column [conditions, hexane:2-propanol = 97:3, flow rate = 1 mL/min, rt, Rt (major) = 13.320 min, Rt (minor) = 9.553 min]. $[\alpha]_D^{21.8}$ = +21.0 (*c* = 1.2, $CHCl_3$).

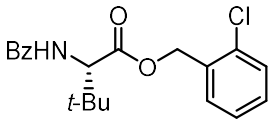
(+)-4-Trifluoromethylbenzyl *N*-benzoyl-*tert*-leucinate (3ai).



3ai

Title compound was obtained according to General Procedure I (PTC **5d**, flash column chromatography eluent: hexane/EtOAc = 10/1 to 5/1) as a white solid in 88% yield (69.1 mg, 0.176 mmol) with 79.5:20.5 er. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83–7.76 (m, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.55–7.40 (m, 5H), 6.67 (br-d, *J* = 9.2 Hz, 1H), 5.25 (A of AB, J_{AB} = 12.8 Hz, 1H), 5.22 (B of AB, J_{AB} = 12.8 Hz, 1H), 4.76 (d, *J* = 9.2 Hz, 1H), 1.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.6 (*C*O), 167.2 (*C*O), 139.1 (*C*), 134.1 (*C*), 131.9 (*C*H), 130.6 (q, $J_{C\text{-}F}$ = 32.4 Hz, *C*), 128.7 (*C*H, 2C), 128.5 (*C*H, 2C), 127.0 (*C*H, 2C), 125.6 (q, $J_{C\text{-}F}$ = 3.8 Hz, *C*H, 2C), 124.0 (q, $J_{C\text{-}F}$ = 270.8 Hz, *C*F_3), 66.0 (*C*H_2), 60.3 (*C*H), 35.2 (*C*), 26.7 (*C*H_3, 3C). ^{19}F NMR (376 MHz, $CDCl_3$) δ = –62.7. Elemental Analysis: Calcd for $C_{21}H_{22}F_3NO_3$: C, 64.11; H, 5.64; N, 3.56. Found: C, 63.97; H, 5.68; N, 3.51. HPLC analysis: CHIRALCEL OD-3 column [conditions, hexane:2-propanol = 95:5, flow rate = 1 mL/min, rt, Rt (major) = 10.900 min, Rt (minor) = 9.627 min]. $[\alpha]_D^{24.7}$ = +18.5 (*c* = 1.1, $CHCl_3$).

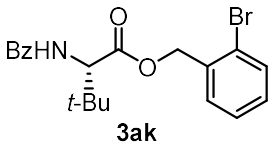
(+)-2-Chlorobenzyl *N*-benzoyl-*tert*-leucinate (3aj).



3aj

Title compound was obtained according to General Procedure I (PTC **5b**, flash column chromatography eluent: hexane/EtOAc = 7/1) as a colorless oil in 89% yield (64.4 mg, 0.179 mmol) with 92.5:7.5 er. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83–7.76 (m, 2H), 7.53 (tt, *J* = 6.6, 1.7 Hz, 1H), 7.49–7.42 (m, 3H), 7.42–7.36 (m, 1H), 7.32–7.24 (m, 2H), 6.67 (br-d, *J* = 9.2 Hz, 1H), 5.32 (A of AB, J_{AB} = 12.8 Hz, 1H), 5.27 (B of AB, J_{AB} = 12.4 Hz, 1H), 4.78 (d, *J* = 9.6 Hz, 1H), 1.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.5 (*C*O), 167.2 (*C*O), 134.2 (*C*), 133.9 (*C*), 132.9 (*C*), 131.8 (*C*H), 130.4 (*C*H), 129.9 (*C*H), 129.6 (*C*H), 128.7 (*C*H, 2C), 127.03 (*C*H, 2C), 126.99 (*C*H), 64.3 (*C*H_2), 60.3 (*C*H), 35.3 (*C*), 26.7 (*C*H_3, 3C). Elemental Analysis: Calcd for $C_{20}H_{22}ClNO_3$: C, 66.76; H, 6.16; N, 3.89. Found: C, 66.77; H, 6.24; N, 3.79. HPLC analysis: CHIRALCEL OD-3 column [conditions, hexane:2-propanol = 95:5, flow rate = 1 mL/min, rt, Rt (major) = 9.533 min, Rt (minor) = 7.893 min]. $[\alpha]_D^{24.6}$ = +27.9 (*c* = 1.0, $CHCl_3$).

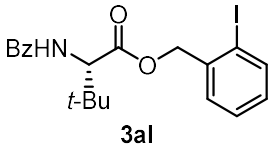
(+)-2-Bromobenzyl *N*-benzoyl-*tert*-leucinate (3ak).



3ak

Title compound was obtained according to General Procedure I (PTC **5d**, flash column chromatography eluent: hexane/EtOAc = 7/1) as a colorless oil in 94% yield (75.7 mg, 0.187 mmol) with 91:9 er. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83–7.76 (m, 2H), 7.58 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.52 (tt, *J* = 7.4, 1.7 Hz, 1H), 7.48–7.40 (m, 3H), 7.32 (td, *J* = 7.6, 1.1 Hz, 1H), 7.20 (td, *J* = 7.8, 1.7 Hz, 1H), 6.70 (br-d, *J* = 8.8 Hz, 1H), 5.28 (s, 2H), 4.79 (d, *J* = 8.8 Hz, 1H), 1.06 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.4 (*C*O), 167.2 (*C*O), 134.5 (*C*), 134.2 (*C*), 132.9 (*C*H), 131.7 (*C*H), 130.4 (*C*H), 130.0 (*C*H), 128.6 (*C*H, 2C), 127.6 (*C*H), 127.0 (*C*H, 2C), 123.6 (*C*), 66.5 (CH_2), 60.3 (*C*H), 35.3 (*C*), 26.7 (CH_3, 3C). Elemental Analysis: Calcd for $C_{20}H_{22}BrNO_3$: C, 59.42; H, 5.48; N, 3.46. Found: C, 59.52; H, 5.55; N, 3.39. HPLC analysis: CHIRALCEL OD-3 column [conditions, hexane:2-propanol = 95:5, flow rate = 1 mL/min, rt, Rt (major) = 9.487 min, Rt (minor) = 8.780 min]. $[\alpha]_D^{24.6}$ = +18.1 (*c* = 1.2, $CHCl_3$).

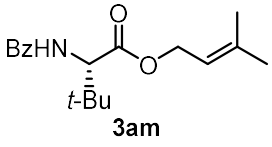
(+)-2-Iodobenzyl *N*-benzoyl-*tert*-leucinate (3al).



3al

Title compound was obtained according to General Procedure I (PTC **5d**, flash column chromatography eluent: hexane/EtOAc = 7/1) as a colorless oil in 98% yield (88.7 mg, 0.197 mmol) with 89:11 er. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.82–7.76 (m, 2H), 7.52 (tt, *J* = 7.4, 1.7 Hz, 1H), 7.48–7.40 (m, 3H), 7.35 (td, *J* = 7.5, 1.1 Hz, 1H), 7.03 (td, *J* = 7.6, 1.7 Hz, 1H), 6.70 (br-d, *J* = 9.6 Hz, 1H), 5.22 (s, 2H), 4.79 (d, *J* = 9.6 Hz, 1H), 1.06 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.3 (*C*O), 167.1 (*C*O), 139.5 (*C*H), 137.6 (*C*), 134.2 (*C*), 131.7 (*C*H), 130.1 (*C*H), 129.9 (*C*H), 128.6 (*C*H, 2C), 128.5 (*C*H), 127.0 (*C*H, 2C), 98.6 (*C*), 70.7 (CH_2), 60.4 (*C*H), 35.3 (*C*), 26.7 (CH_3, 3C). Elemental Analysis: Calcd for $C_{20}H_{22}INO_3$: C, 53.23; H, 4.91; N, 3.10. Found: C, 52.96; H, 4.87; N, 2.99. HPLC analysis: CHIRALPAK AD-H column [conditions, hexane:2-propanol = 95:5, flow rate = 1 mL/min, rt, Rt (major) = 29.413 min, Rt (minor) = 23.173 min]. $[\alpha]_D^{24.6}$ = +10.9 (*c* = 1.0, $CHCl_3$).

(+)-3-Methylbut-2-en-1-yl *N*-benzoyl-*tert*-leucinate (3am).

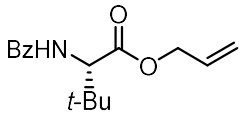


3am

Title compound was obtained according to General Procedure I (PTC **5b**, flash column chromatography eluent: hexane/EtOAc = 10/1 to 5/1) as a colorless oil in 56% yield (33.9 mg, 0.112 mmol) with 98:2 er. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.84–7.77 (m, 2H), 7.52 (tt, *J* = 7.4, 1.6 Hz, 1H), 7.48–7.41 (m, 2H), 6.68 (br-d, *J* = 9.2 Hz, 1H), 5.41–5.32 (m, 1H), 4.70 (d, *J* = 9.2 Hz, 1H), 4.68 (dd, *J* = 12.8, 7.2 Hz, 1H), 4.63 (dd, *J* = 12.2, 7.4 Hz, 1H), 1.76 (s, 3H), 1.72 (s, 3H), 1.05 (s, 9H). ^{13}C

NMR (100 MHz, $CDCl_3$) δ = 171.8 (*C*O), 167.1 (*C*O), 139.9 (*C*), 134.4 (*C*), 131.7 (*C*H), 128.6 (*C*H, 2C), 127.0 (*C*H, 2C), 118.0 (*C*H), 62.0 (CH_2), 60.2 (*C*H), 35.4 (*C*), 26.7 (CH_3, 3C), 25.7 (CH_3), 18.1 (CH_3). Elemental Analysis: Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.11; H, 8.25; N, 4.51. HPLC analysis: CHIRALPAK AD-H column [conditions, hexane:2-propanol = 97:3, flow rate = 1 mL/min, rt, Rt (major) = 18.000 min, Rt (minor) = 12.267 min]. $[\alpha]_D^{21.3}$ = +46.6 (*c* = 1.3, $CHCl_3$).

(*S*)-(+)-Allyl *N*-benzoyl-*tert*-leucinate (3an).[25]

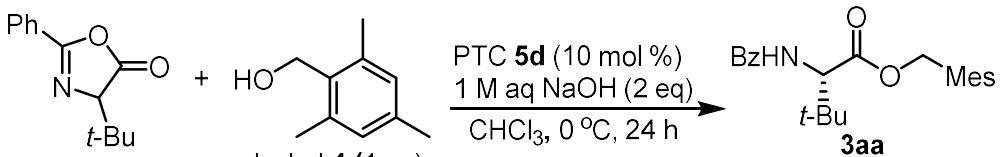


3an

Title compound was obtained according to General Procedure I (flash column chromatography eluent: hexane/EtOAc = 14/1 to 7/1) as a colorless oil in 45% yield (12.4 mg, 0.045 mmol) with 98:2 er. ^1H and ^{13}C NMR spectra were in good agreement with the literature.[26] ^1H NMR (400 MHz, $CDCl_3$) δ = 7.84–7.76 (m, 2H), 7.52 (tt, *J* = 7.4, 1.7 Hz, 1H), 7.49–7.40 (m, 2H), 6.66 (br-d, *J* = 9.2 Hz, 1H), 5.94 (ddt, *J* = 17.0, 9.1, 6.1 Hz, 1H), 5.37 (dq, *J* = 17.4, 1.5 Hz, 1H), 5.27 (dq, *J* = 10.6, 1.2 Hz, 1H), 4.73 (d, *J* = 9.6 Hz, 1H), 4.71–4.60 (m, 2H), 1.07 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.5 (*C*O), 167.1 (*C*O), 134.3 (*C*), 131.7 (*C*H), 131.5 (*C*H), 128.7 (*C*H, 2C), 127.0 (*C*H, 2C), 119.2 (CH_2), 65.9 (CH_2), 60.2 (*C*H), 35.3 (*C*), 26.7 (CH_3, 3C). Elemental Analysis: Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.49; H, 7.72; N, 4.92. HPLC analysis: CHIRALCEL OD-3 column [conditions, hexane:2-propanol = 95:5, flow rate = 1 mL/min, rt, Rt (major) = 8.453 min, Rt (minor) = 5.580 min]. $[\alpha]_D^{25.5}$ = +29.0 (*c* = 1.0, $CHCl_3$).

Procedures for the Synthetic Applications

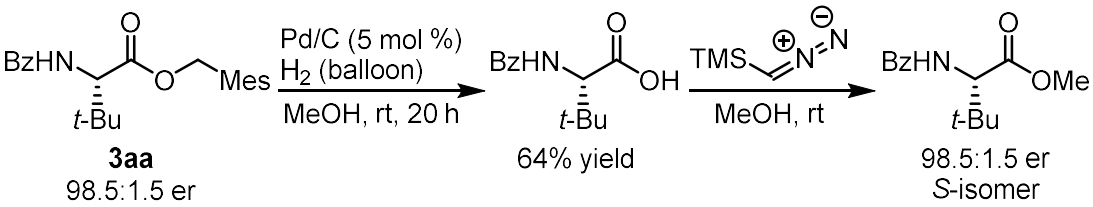
Gram-scale Reaction



A chiral PTC **5d** (260.2 mg, 0.5 mmol, 10 mol %) was placed in a 200 mL round bottom flask under air. Then, alcohol **4** (751 mg, 5 mmol, 1 eq) and $CHCl_3$ (40 mL) were added to the flask followed by the addition of 1 M aq NaOH (10 mL, 2 eq). After stirred at 0 °C and 200 rpm for 10 min, azlactone **1a** (1.09 g, 5 mmol, 1 eq) was added to the solution, and the resultant reaction mixture was further stirred for 24 h at 0 °C. The organic phase was filtered through a short silica-gel column with Et_2O as

an eluent. After removal of the solvent under reduced pressure, the crude products were purified by flash column chromatography (eluent: hexane/EtOAc = 7/1) to afford **3aa** as a colorless oil in 91% yield (1.68 g, 4.57 mmol) with 98.5:1.5 er. The enantiomer ratios of the products were analyzed by chiral HPLC with CHIRALCEL OD-3 column [conditions, hexane:2-propanol = 95:5, flow rate = 1 mL/min, rt, Rt (major) = 9.420 min, Rt (minor) = 7.013 min].

Deprotection of 2,4,6-Trimethylbenzyl Group and Determination of the Absolute Configuration of the Product 3aa



3aa
98.5:1.5 er

64% yield

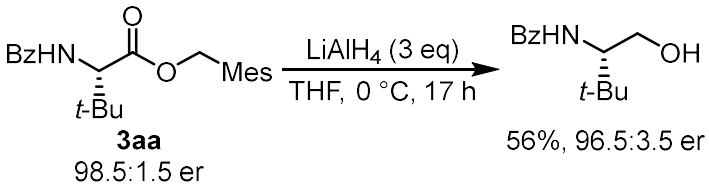
98.5:1.5 er
S-isomer

An enantioenriched product **3aa** (98.1:1.5 er, 373 mg, 1.01 mmol) was placed in a 50 mL two-neck round bottom flask under N_2 atmosphere. Then, Pd/C (10 wt %, 53.1 mg, 5 mol %) and dry MeOH (10 mL) were added to the flask, and the resultant reaction mixture was vigorously stirred at rt under ambient H_2 (balloon) atmosphere. After stirring for 20 h, the reaction mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure. and 0.25 M aq NaOH (10 mL) and EtOAc (10 mL) were added to the crude product. Then, the organic phase of the mixture was extracted with H_2O (5 mL x 4). The combined aqueous solution was acidified by 1 mL of 1 M aq HCl, then extracted by CH_2Cl_2 (5 mL x 4). The latter extracts were corrected and concentrated under reduced pressure to give the corresponding *N*-benzoyl *tert*-leucine as a white solid in 64% yield (152 mg, 0.646 mmol). ^{1}H and ^{13}C NMR were in agreement with the literature.[14] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83–7.75 (m, 2H), 7.52 (tt, *J* = 7.4, 1.6 Hz, 1H), 7.48–7.39 (m, 2H), 6.76 (br-d, *J* = 9.2 Hz, 1H), 4.71 (d, *J* = 9.2 Hz, 1H), 1.09 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.5 (*C*O), 167.8 (*C*O), 133.9 (*C*), 131.9 (*C*H), 128.7 (*C*H, 2C), 127.1 (*C*H, 2C), 60.4 (*C*H), 35.0 (*C*), 26.7 (*C*H$_3$, 3C). Elemental Analysis: Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.39; H, 7.24; N, 5.82. $[\alpha]_D^{22.3}$ = +24.7 (*c* = 1.0, CH_3OH). To determine the enantiomer ratio, the deprotected product was transformed to the corresponding methyl ester by the reaction with (trimethylsilyl)diazomethane solution 2.0 M in hexane at rt, and the er of the methyl ester was determined by HPLC analysis with CHIRALCEL OD-3 column, (conditions: hexane:2-propanol = 95:5, flow rate = 1 mL/min, rt, Rt (major) = 14.760 min, Rt (minor) = 10.460 min), 98.5:1.5 er.

The absolute configuration was determined by comparison of the HPLC retention time of (*S*)-(+)-*N*-benzoyl *tert*-leucine methyl ester prepared from optically active (*S*)-*tert*-leucine (conditions:

hexane:2-propanol = 95:5, flow rate = 1 mL/min, rt, Rt (*S*-isomer) = 14.947 min).

LAH Reduction of 3aa

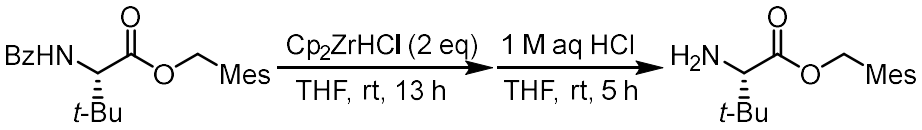


3aa
98.5:1.5 er

56%, 96.5:3.5 er

To a suspension of $LiAlH_4$ (114 mg, 3 mmol, 3 eq) in THF (1 mL) was added a solution of **3aa** (367 mg, 1.0 mmol) in THF (1 mL) at rt. After stirring at 0 °C for 17 h, the reaction mixture was quenched by H_2O (0.12 mL). 5 M aq NaOH (0.12 mL) and H_2O (0.4 mL). Then, the resultant mixture was filtered through a Celite pad with Et_2O, and the mixture was washed with H_2O (10 mL x 3). The aqueous layer was extracted with Et_2O (10 mL x 3), and the combined organic layer was dried over Na_2SO_4. After removal of the solvent, the crude products were purified by flash column chromatography (eluent: hexane/EtOAc = 1/2) to afford corresponding alcohol as a colorless oil in 56% yield (123 mg, 0.558 mmol) with 96.5:3.5 er. ^1H and ^{13}C NMR was in agreement with the literature.[26] ^1H NMR (400 MHz, $CDCl_3$) δ = 7.81–7.70 (m, 2H), 7.49 (tt, *J* = 7.4, 1.7 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 6.44 (br-d, *J* = 8.8 Hz, 1H), 4.04 (ddd, *J* = 10.2, 7.0, 2.6 Hz, 1H), 3.98–3.82 (m, 1H), 3.67 (ddd, *J* = 11.4, 7.4, 4.4 Hz, 1H), 3.06 (br-s, 1H), 1.02 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.8 (*C*O), 134.6 (*C*), 131.6 (*C*H), 128.6 (*C*H, 2C), 127.0 (*C*H, 2C), 62.9 (CH_2), 59.8 (*C*H), 34.0 (*C*), 27.1 (CH_3, 3C). Elemental Analysis: Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.31; H, 8.67; N, 6.29. Er was determined by HPLC with CHIRALPAK AD-H column [conditions: hexane:2-propanol = 70:30, flow rate = 1 mL/min, rt, Rt (major) = 9.940 min, Rt (minor) = 11.627 min]. $[\alpha]_D^{20.5}$ = –3.9 (*c* = 1.1, $CHCl_3$).

Deprotection of Benzoyl Group of the Product 3aa



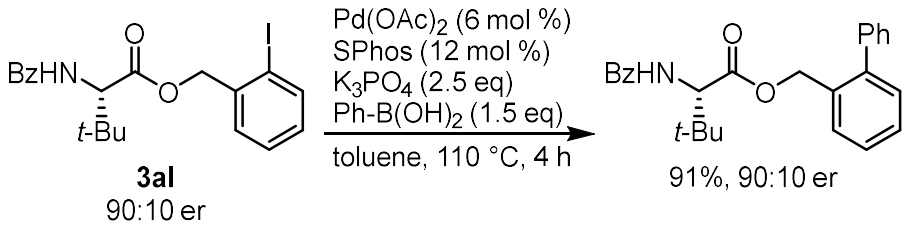
3aa
98.5:1.5 er

66% yield
98.5:1.5 er

(*S*)-**3aa** (64.7 mg, 0.18 mmol, 98.5:1.5 er) was dissolved in anhydrous THF and added dropwise to a suspension of Cp_2ZrHCl (94.6 mg, 0.35 mmol, 2 eq) in anhydrous THF at 0 °C under N_2 atmosphere. The reaction mixture was gradually warmed to rt and stirred for 13 h. 1 M aqueous HCl (0.5 mL) was added, and the resultant mixture was further stirred for 5 h. Saturated aqueous $NaHCO_3$

2 mL was added, and the mixture was extracted with Et_2O 1.5 mL x 3. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluent: hexane/EtOAc = 5/1 to 3/1) to afford the product as a pale-brown oil in 66% yield (30.8 mg, 0.12 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.88 (s, 2H), 5.24 (A of AB, J_{AB} = 11.6 Hz, 1H), 5.13 (B of AB, J_{AB} = 12.0 Hz, 1H), 3.15 (s, 1H), 2.35 (s, 6H), 2.28 (s, 3H), 0.95 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.3 (*C*O), 138.6 (*C*), 138.2 (*C*, 2C), 129.1 (*C*H, 2C), 128.8 (*C*), 63.5 (*C*H), 61.0 (*C*H_2), 34.4 (*C*), 26.3 (*C*H_3, 3C), 21.0 (*C*H_3), 19.6 (*C*H_3, 2C). Elemental Analysis: Calcd for $C_{16}H_{25}NO_2$: C, 72.97; H, 9.57; N, 5.32. Found: C, 72.84; H, 9.43; N, 5.12. $[\alpha]_D^{27.5}$ = +43.2 (*c* = 0.6, $CHCl_3$). To determine the enantiomer ratio, the deprotected product was transformed to the corresponding N-protected ester **3aa** by the reaction with Et_3N and benzoyl chloride in CH_2Cl_2 at rt, and the er of the Bz-protected product was determined by HPLC analysis with CHIRALCEL OD-3 column, (conditions: hexane:2-propanol = 95:5, flow rate = 1 mL/min, rt, Rt (major) = 7.813 min, Rt (minor) = 5.747 min), 98.5:1.5 er.

Suzuki-Miyaura Cross Coupling



Enantioenriched product **3al** (90:10 er, 389 mg, 0.86 mmol) and K_3PO_4 (297 mg, 2.15 mmol, 2.5 eq) was placed in a 20 mL Schlenk flask under N_2 atmosphere. Then, $Pd(OAc)_2$ (11.6 mg, 0.0516 mmol, 6 mol %), SPhos (42.4 mg, 0.103 mmol, 12 mol %) and toluene (degassed by three freeze-pump-thaw cycles) were added to the flask, and the resultant reaction mixture was vigorously stirred at rt. After an addition of phenylboronic acid (157 mg, 1.29 mmol, 1.5 eq), the reaction mixture was warmed to 110 °C and stirred for 4 h. Then, the resulting mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluent: hexane/EtOAc = 15/1 to 5/1) to afford the product as a pale-yellow oil in 91% yield (314 mg, 0.783 mmol) with 90:10 er. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.82–7.74 (m, 2H), 7.54–7.47 (m, 2H), 7.46–7.27 (m, 10H), 6.64 (br-d, *J* = 9.6 Hz, 1H), 5.16 (A of AB, J_{AB} = 12.4 Hz, 1H), 5.11 (B of AB, J_{AB} = 12.4 Hz, 1H), 4.72 (d, *J* = 8.8 Hz, 1H), 1.01 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.4 (*C*O), 167.0 (*C*O), 142.5 (*C*), 140.2 (*C*), 134.2 (*C*), 132.4 (*C*), 131.7 (*C*H), 130.2 (*C*H), 129.9 (*C*H), 129.1 (*C*H, 2C), 128.61 (*C*H, 2C), 128.56 (*C*H), 128.3 (*C*H, 2C), 127.6 (*C*H),

127.4 (*C*H), 127.0 (*C*H, 2C), 65.0 (*C*H$_2$), 60.3 (*C*H), 35.4 (*C*), 26.7 (*C*H$_3$, 3C). HRMS-FAB (*m/z*): [M+H]$^+$ calcd for $C_{26}H_{28}NO_3$, 402.2069; found: 402.2070. Er was determined by HPLC with CHIRALPAK AD-H column [conditions: hexane:2-propanol = 95:5, flow rate = 1 mL/min, rt, Rt (major) = 19.313 min, Rt (minor) = 16.113 min]. $[\alpha]_D^{24.6}$ = +13.9 (*c* = 1.2, $CHCl_3$).

Details of the Pseudo-TS Conformational Search

Pseudo-TS conformational search (PTSCS) was performed with ConFinder program[27] on a Linux PC (Core i7 4770K 3.5 GHz). OPLS 2005 force field[28] with the TINKER program[29] and PM6-DH+[30] implemented in the MOPAC program[31] were employed as molecular mechanics (MM) and semiempirical quantum mechanical (SQM) calculation in the conformational search with ConFinder, respectively. The PTSCS of two initial structures of complex classified by the stereochemistry of the azlactone's α-carbon center and the enantiofaces attacked by the alkoxide (Figure X, *Si-S, Re-R*) were performed. The C···O distance between the carbonyl carbon of the azlactone and the oxygen atom of the alkoxide was fixed to 1.8 Å in the conformational search to keep the geometry close to the corresponding TS structures. The conformational search provided pseudo-TS conformers, and the conformers were further subjected to DFT single-point energy (SPE) calculation at RI-B97-D[32]/SV(P)[33] level of theory with Turbomole program.[34] Partial geometry optimization was further performed to assess the validity of the energies obtained after SPE calculation. Conformers that have the same structure name were not subjected to the partial geometry optimization. Pseudo-TS conformers were subjected to the following TS calculation.

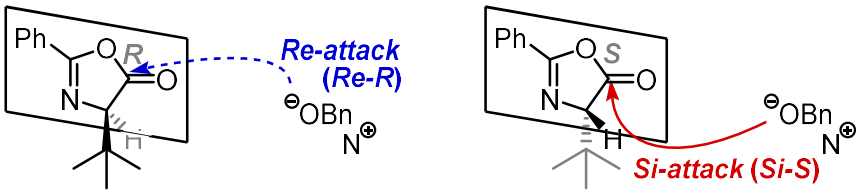


Figure 6. Classification of pseudo-TS complexes by the enantiofaces and the stereochemistry.

TS Calculations

Structures of TS candidates located by PTSCS were further used as initial structures to investigate the favorable TS structures determining the stereoselectivity. Transition state calculations were performed with Gaussian 16,[35] and figures presented in the manuscript were generated with CYLview.[36] All the geometry optimizations were performed at the B97-D/TZVP[37] level of theory at 298.15 K at 1.0 atm in the gas phase followed by frequency calculations to confirm that the optimized structures have only one imaginary frequency mode. In addition, quasi-intrinsic reaction coordinate

(quasi-IRC) calculations[38] with Turbomole program at RI-B97-D/TZVP were carried out to confirm an appropriate connection between the reactant complexes and product complexes. In the quasi-IRC calculation, the geometry of the TS was first slightly shifted by perturbing the geometries along the reaction coordinate, and then released for equilibrium optimization. After that, all of the conformers were further optimized in chloroform at 273.15 K while using the conductor-like polarized continuum model.[39] The IGM analyses[15] were performed using Multiwfn[40] and visualized by VMD program.[41]

Conformational Search and TS Calculation for Complex A [5d'+1a+H_2O]

The conformational search provided pseudo-TS conformers (*Si*-*S*-H_2O: 2236 conformers, *Re*-*R*-H_2O: 2003 conformers). Table S1 shows the top 3 of each stable (< 8.3 kcal/mol) pseudo-TS complexes after the reevaluation by the SPE (Pseudo-TS-*Re*-*R*-H_2O, Pseudo-TS-*Si*-*S*-H_2O). The pseudo-TS structures in Table 4 are presented in Figures 7 and 8.

Table 4. Energies of pseudo-TS conformers of **complex A** after pseudo-TS conformational search and SPE calculation at RI-B97-D/SV(P) level of theory using Turbomole program.[a]

	Pseudo-TS-*Si*-S-H_2O	Pseudo-TS-*Re*-*R*-H_2O
entry	energy (*E*, kcal/mol) [Ranking in ConFinder Output, **Structure Name**]	
1	0.0 [211, ***Si*-*S*1-H_2O**]	3.8 [1101, ***Re*-*R*1-H_2O**]
2	0.0 [487, ***Si*-*S*1-H_2O**]	8.2 [743, ***Re*-*R*2-H_2O**]
3	0.6 [521, ***Si*-*S*2-H_2O**]	8.2 [1132, ***Re*-*R*3-H_2O**]
4	6.3 [435, ***Si*-*S*3-H_2O**]	

[a]Similar structures are represented by the same Structure Name.

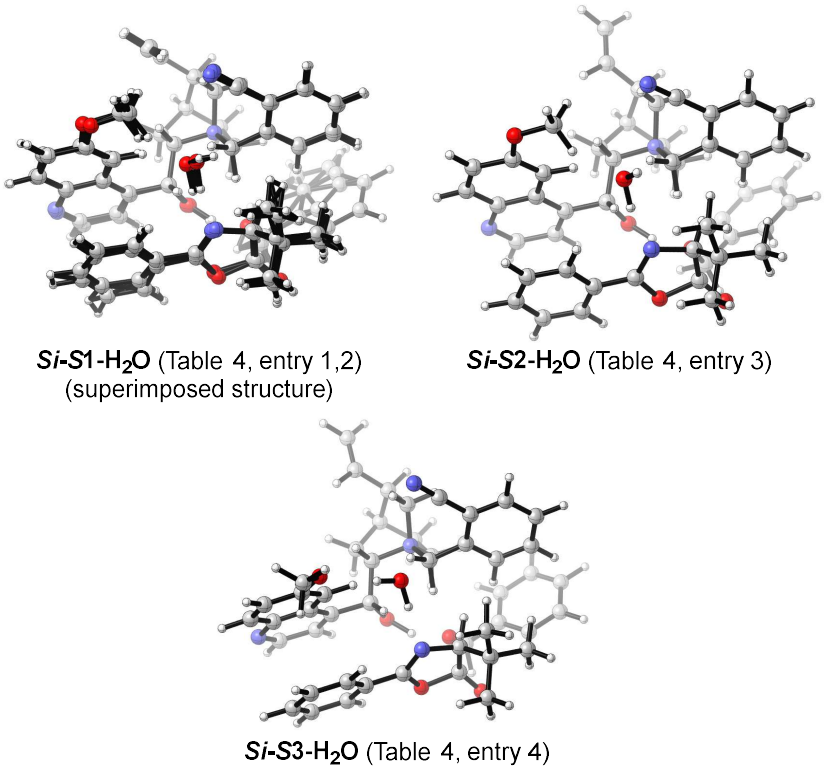


Figure 7. Pseudo-TS-*Si*-*S*-H_2O conformers provided by the PTSCS.

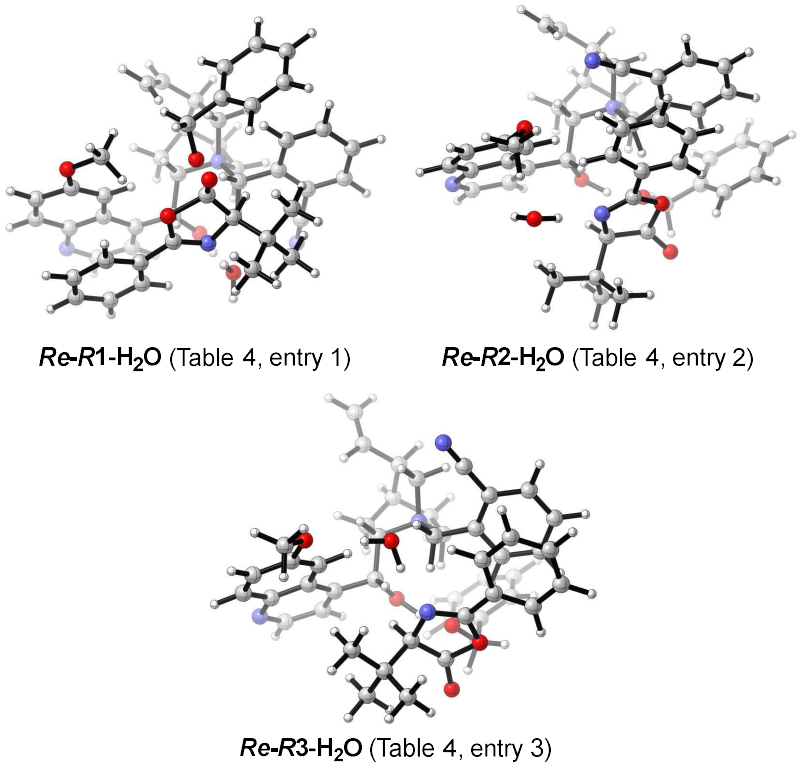


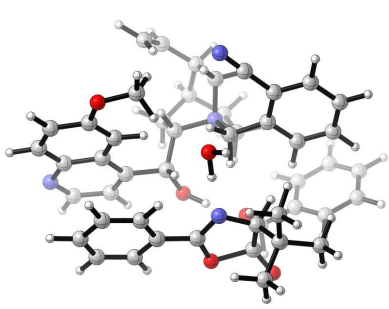
Figure 8. Pseudo-TS-*Re*-*R*-H_2O conformers provided by the PTSCS.

Partial geometry optimizations of the top 3 conformers at RI-B97-D/TZVP level of theory using Gaussian 16 were further performed to assess the validity of the energies obtained after SPE (Table 5). The Pseudo-TS structures in Table 5 are presented in Figures 9 and 10.

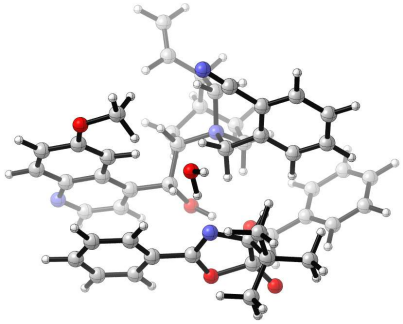
Table 5. Energies of pseudo-TS conformers of complex A after partial geometry optimization at RI-B97-D/TZVP level of theory using Gaussian 16.[a]

	Pseudo-TS-*Si*-*S*-H_2O	Pseudo-TS-*Re*-*R*-H_2O
entry	energy (*E*, kcal/mol) [Ranking in ConFinder Output, **Structure Name**]	
1	0.0 [211, ***Si*-*S*1-H_2O**]	4.1 [1101, ***Re*-*R*1-H_2O**]
2	---- [487, ***Si*-*S*1-H_2O**]	7.7 [743, ***Re*-*R*2-H_2O**]
3	0.4 [521, ***Si*-*S*2-H_2O**]	7.0 [1132, ***Re*-*R*3-H_2O**]
4	3.3 [435, ***Si*-*S*3-H_2O**]	

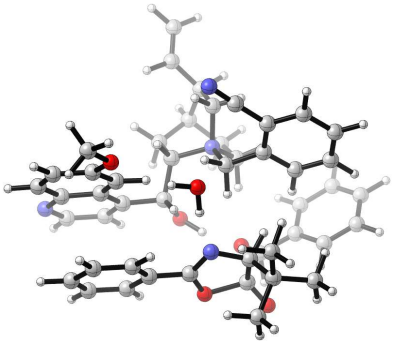
[a]The partial geometry optimizations of the conformers were performed with the distance between the oxygen atom of the alkoxide and the carbon atom of the azlactone fixed to 1.8 A.



***Si*-*S*1-H_2O** (Table 5, entry 1)

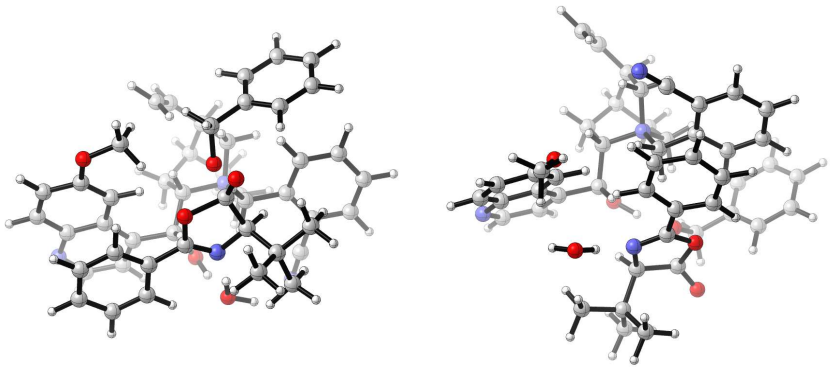


***Si*-*S*2-H_2O** (Table 5, entry 3)



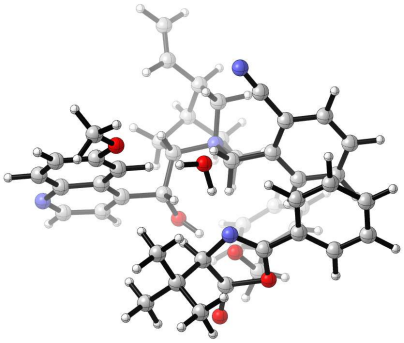
***Si*-*S*3-H_2O** (Table 5, entry 4)

Figure 9. Pseudo-TS-*Si*-*S*-H_2O conformers after partial optimization with Gaussian 16.



***Re-R*1-H_2O** (Table 5, entry 1)

***Re-R*2-H_2O** (Table 5, entry 2)



***Re-R*3-H_2O** (Table 5, entry 3)

Figure 10. Pseudo-TS-*Re*-*R*-H_2O conformers after partial optimization with Gaussian 16.

Transition state calculations for the pseudo-TS candidates were performed and the $\Delta G^{\ddagger}$ values are summarized in Table 6, and the TS structures are shown in Figures 11 and 12. The most stable TS structures leading to the corresponding *S*- and *R*-product has shown in the manuscript (TS-*Si*-*S*-H_2O and TS-*Re*-*R*-H_2O) are TS-*Si*-*S*1-H_2O and TS-*Re*-*R*3-H_2O, respectively (Table 6).

Table 6. $\Delta G^{\ddagger}$ values of TS-complexes of **complex A** in gas phase and chloroform.[a]

entry	Structure	$\Delta G^{\ddagger}$ (kcal/mol)			
		298.15 K in gas phase	298.15 K in chloroform	273.15 K in gas phase	273.15 K in chloroform
1	**TS-*Si*-*S*1-H_2O**	0.0	0.0	0.0	0.0
2	**TS-*Si*-*S*2-H_2O**	0.4	0.4	0.2	0.2
3	**TS-*Si*-*S*3-H_2O**	3.5	1.5	3.0	1.1
4	**TS-*Re*-*R*1-H_2O**	4.1	5.1	7.1	8.0
5	**TS-*Re*-*R*2-H_2O**	7.8	6.2	7.7	6.5
6	**TS-*Re*-*R*3-H_2O**	6.9	4.0	5.0	3.6

[a] $\Delta G^{\ddagger}$ values were calculated at B97-D/TZVP level of theory, and free energy corrections at 1.0 atm.

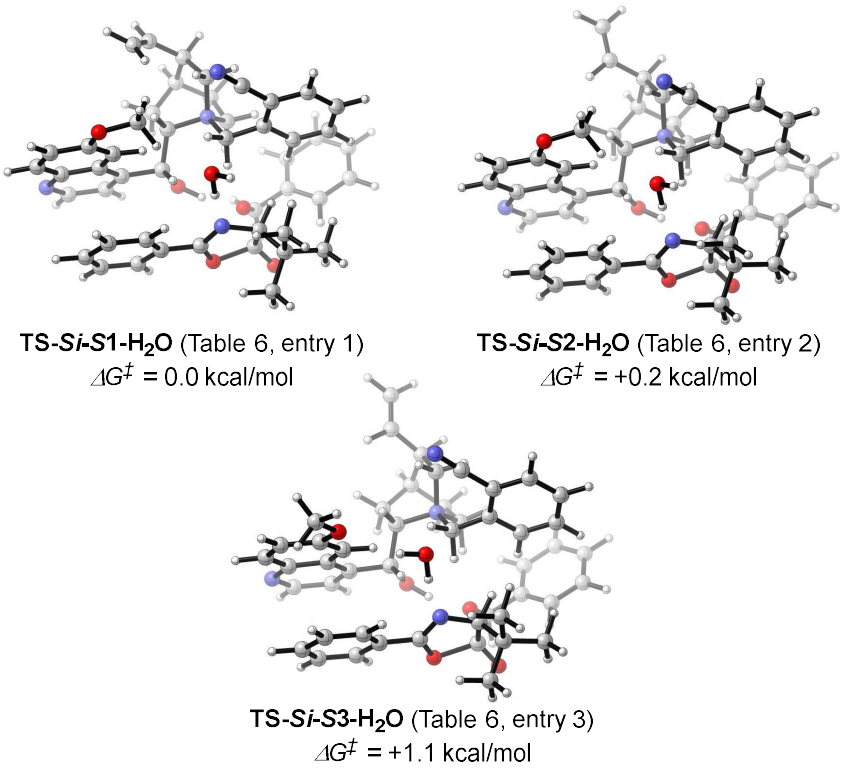


Figure 11. TS-*Si*-*S*-H_2O structures (273.15 K, 1 atm in the chloroform).

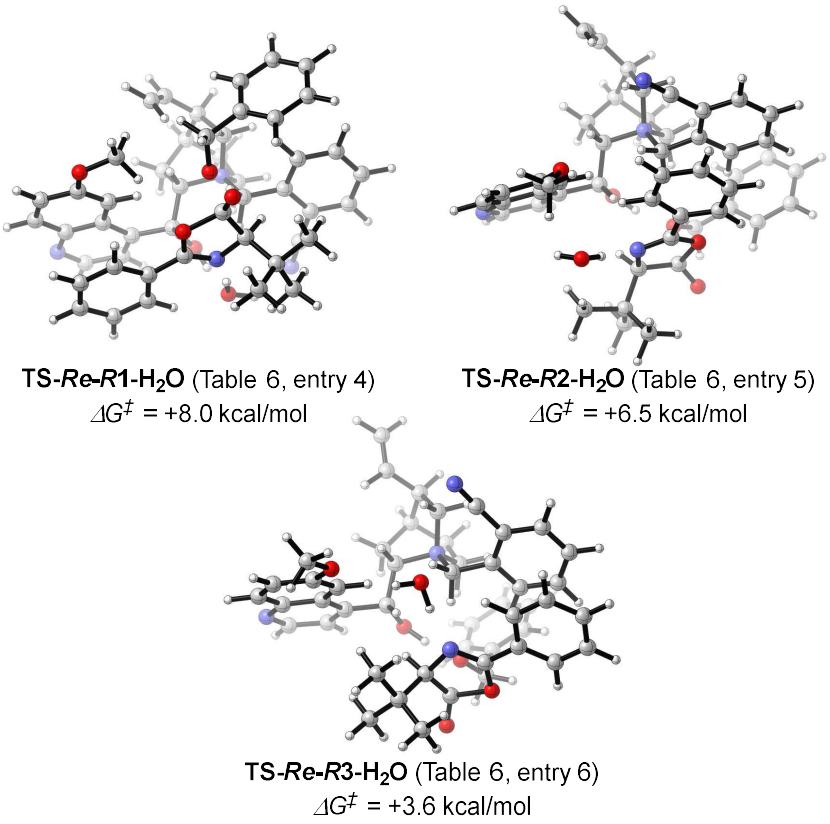


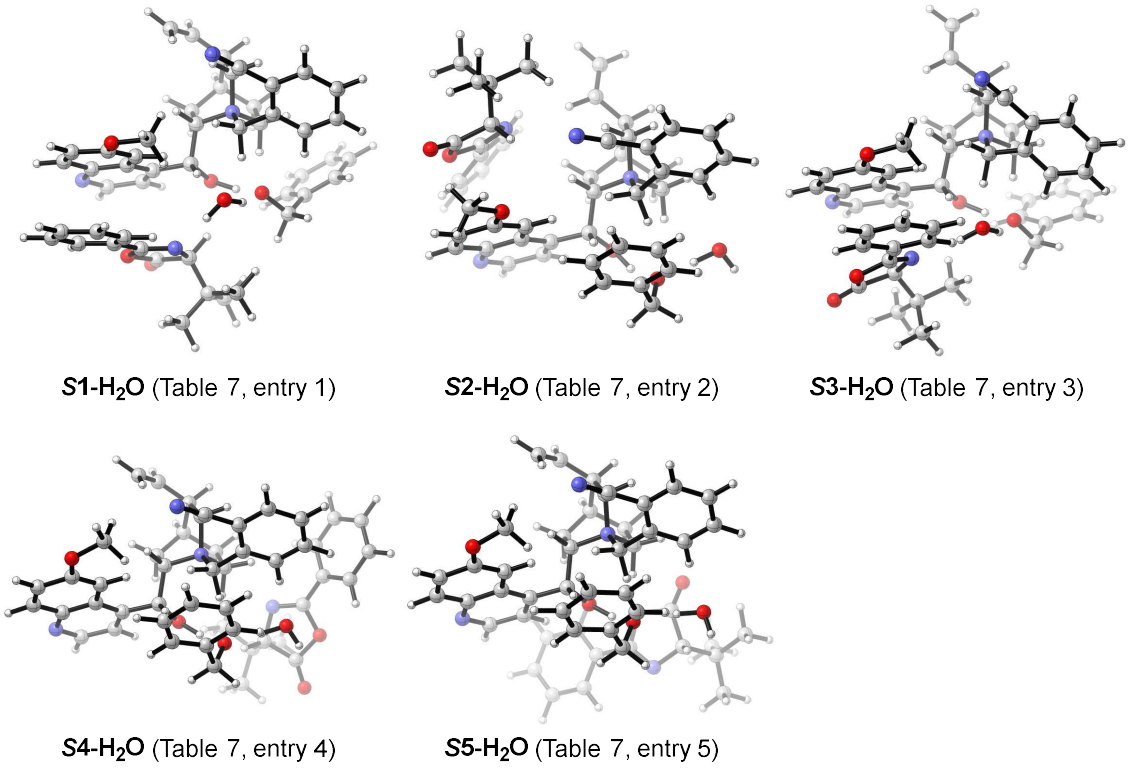
Figure 12. TS-*Re*-*R*-H_2O structures (273.15 K, 1 atm in the chloroform).

Conformational Search and Optimization for Reactant Complex A [5d'+1a+H_2O]

The conformational search provided reactant complexes (*S*: 9986 conformers, *R*: 9986 conformers). Table S4 shows the stable (< 3.0 kcal/mol) reactant complexes after the reevaluation by the SPE (reactant-*S*-H_2O, reactant-*R*-H_2O). The conformers in Table 7 are presented in Figures 13 and 14.

Table 7. Energies of reactant conformers of **complex A** after conformational search and SPE calculation at RI-B97-D/SV(P) level of theory using Turbomole program.

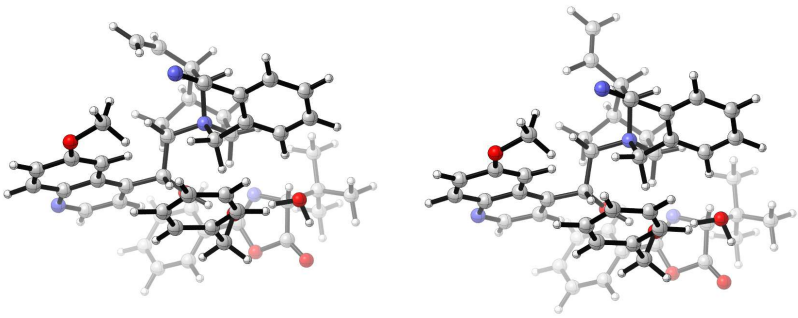
	reactant-*S*-H_2O	reactant-*R*-H_2O
entry	energy (*E*, kcal/mol) [Ranking in ConFinder Output, **Structure Name**]	
1	1.3 [953, ***S*1**]	0.0 [5562, ***R*1**]
2	1.9 [7812, ***S*2**]	1.3 [5482, ***R*2**]
3	2.5 [586, ***S*3**]	2.5 [1849, ***R*3**]
4	2.5 [6365, ***S*4**]	2.5 [2945, ***R*4**]
5	2.5 [6855, ***S*5**]	



***S*1-H_2O** (Table 7, entry 1) ***S*2-H_2O** (Table 7, entry 2) ***S*3-H_2O** (Table 7, entry 3)

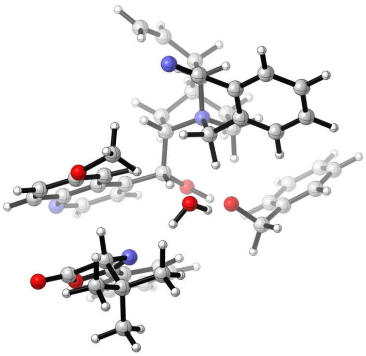
***S*4-H_2O** (Table 7, entry 4) ***S*5-H_2O** (Table 7, entry 5)

Figure 13. Reactant-*S*-H_2O conformers provided by the PTSCS.

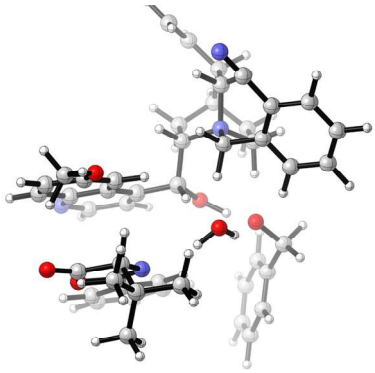


***R*1-H_2O** (Table 7, entry 1)

***R*2-H_2O** (Table 7, entry 2)



***R*3-H_2O** (Table 7, entry 3)



***R*4-H_2O** (Table 7, entry 4)

Figure 14. Reactant-*R*-H_2O conformers provided by the PTSCS.

Geometry optimizations were performed and the $\Delta G_{reactant}$ values are summarized in Table 8, and the structures of the reactant are shown in Figures 15 and 16.

Table 8. $\Delta G_{reactant}$ values of reactant complexes of **complex A** in gas phase or chloroform.[a]

entry	Structure	$\Delta G_{reactant}$ (kcal/mol)	
		298.15 K in gas phase	273.15 K in chloroform
1	***S*1-H_2O**	0.2	0.0
2	***S*2-H_2O**	1.0	2.1
3	***S*3-H_2O**	0.0	0.1
4	***S*4-H_2O**	0.8	1.6
5	***S*5-H_2O**	1.0	2.0
6	***R*1-H_2O**	0.3	1.0
7	***R*2-H_2O**	0.5	1.1
8	***R*3-H_2O**	1.9	2.2
9	***R*4-H_2O**	3.9	4.4

[a] $\Delta G_{reactant}$ values were calculated at B97-D/TZVP level of theory, and free energy corrections at 1.0 atm.

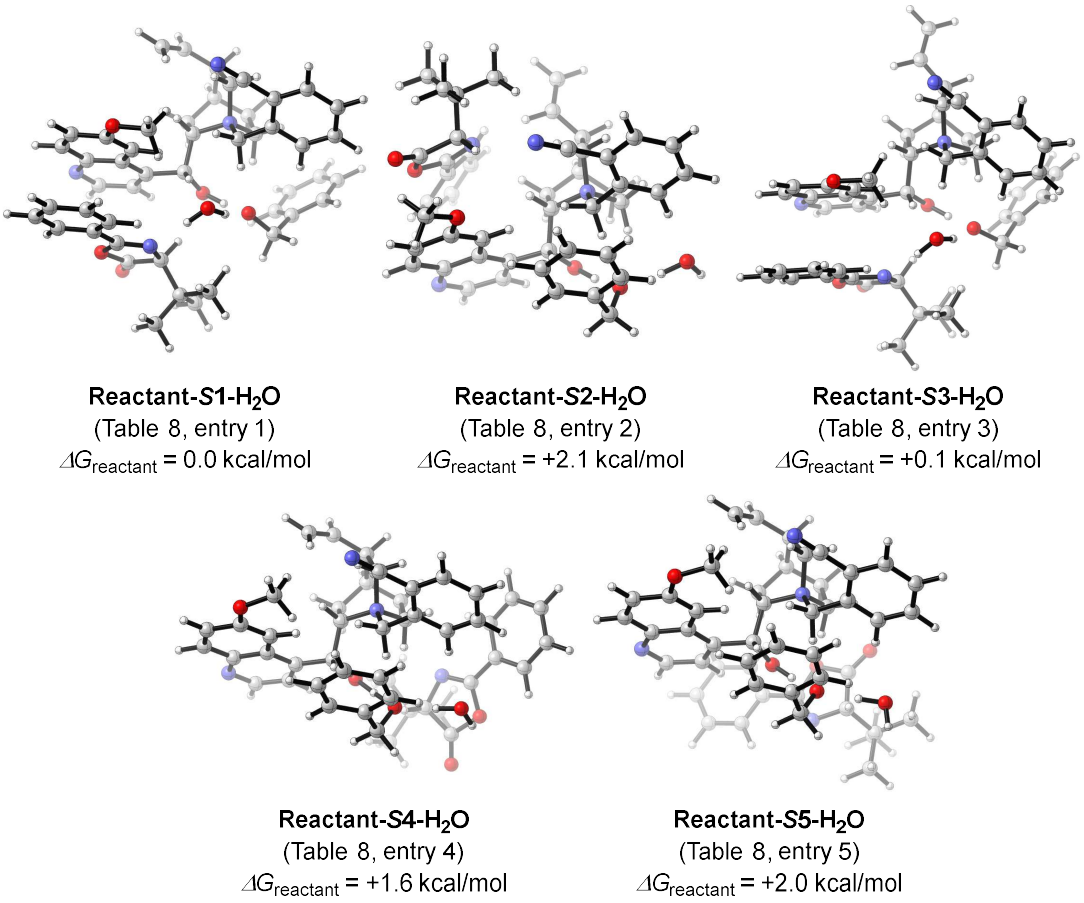


Figure 15. Reactant-*S*-H_2O structures (273.15 K, 1 atm in the chloroform).

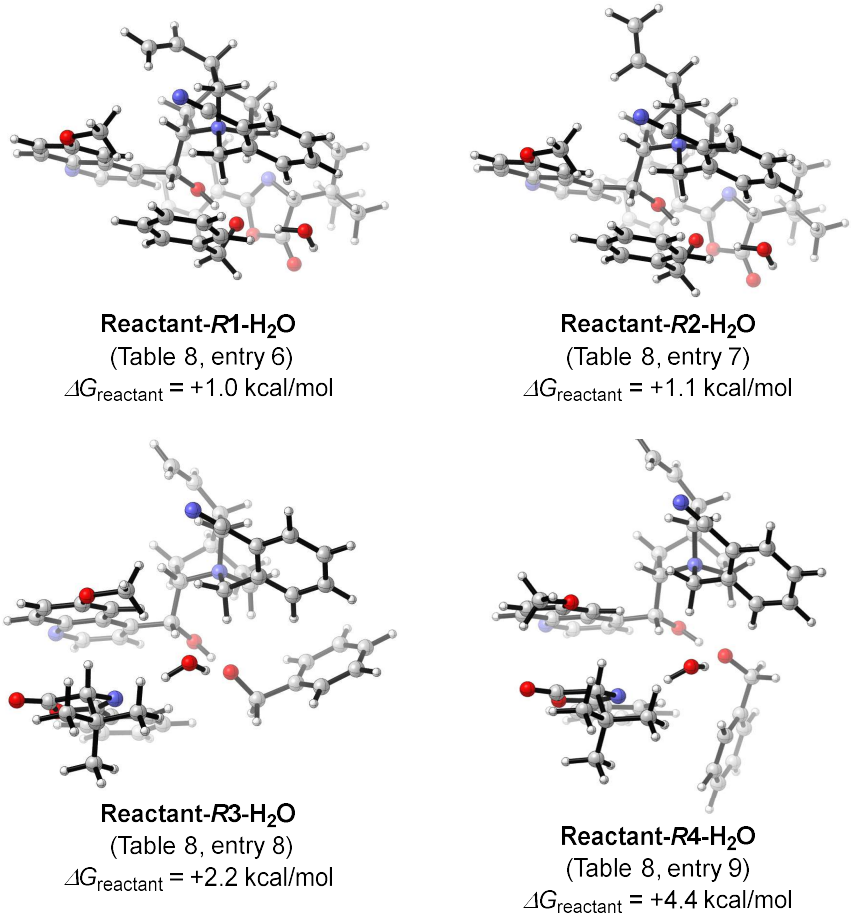


Figure 16. Reactant-*R*-H_2O structures (273.15 K, 1 atm in the chloroform).

Combining these results showed in Table 6 and 8 provided corresponding the $\Delta\Delta G^{\ddagger}$ values in the transition state (Table 9).

Table 9. $\Delta\Delta G^{\ddagger}$ values of each TS structures in chloroform at 273.15 K.[a]

entry	Structure	$\Delta\Delta G^{\ddagger}$ (kcal/mol) at 273.15 K in chloroform
1	**TS-*Si*-*S*1-H_2O**	**0.0**
2	**TS-*Si*-*S*2-H_2O**	0.2
3	**TS-*Si*-*S*3-H_2O**	1.1
4	**TS-*Re*-*R*1-H_2O**	7.1
5	**TS-*Re*-*R*2-H_2O**	5.6
6	**TS-*Re*-*R*3-H_2O**	**2.6**

[a] $\Delta\Delta G^{\ddagger}$ values were calculated at B97-D/TZVP level of theory, and free energy corrections at 1.0 atm.

Conformational Search and TS Calculation for Complex B [5d'+1a+BnOH]

The conformational search provided pseudo-TS conformers (*Si*-*S*: 3000 conformers, *Re*-*R*: 3000 conformers). Table 10 shows the top 5 of each stable pseudo-TS complexes after the reevaluation by the SPE (Pseudo-TS-*Re*-*R*-BnOH, Pseudo-TS-*Si*-*S*-BnOH). The Pseudo-TS structures in Table 10 are presented in Figures 17 and 18.

Table 10. Energies of pseudo-TS conformers of **complex B** after PTSCS and SPE calculation at RI-B97-D/SV(P) level of theory using Turbomole program.

	Pseudo-TS-*Si*-*S*-BnOH	Pseudo-TS-*Re*-*R*-BnOH
entry	energy (*E*, kcal/mol) [Ranking in ConFinder Output, **Structure Name**]	
1	0.0 [299, ***Si*-*S*1-BnOH**]	1.3 [2836, ***Re*-*R*1-BnOH**]
2	0.6 [1407, ***Si*-*S*2-BnOH**]	1.9 [1787, ***Re*-*R*2-BnOH**]
3	1.3 [338, ***Si*-*S*3-BnOH**]	2.5 [2972, ***Re*-*R*3-BnOH**]
4	1.9 [2199, ***Si*-*S*4-BnOH**]	5.0 [1612, ***Re*-*R*4-BnOH**]
5	3.1 [1447, ***Si*-*S*5-BnOH**]	5.0 [2589, ***Re*-*R*5-BnOH**]

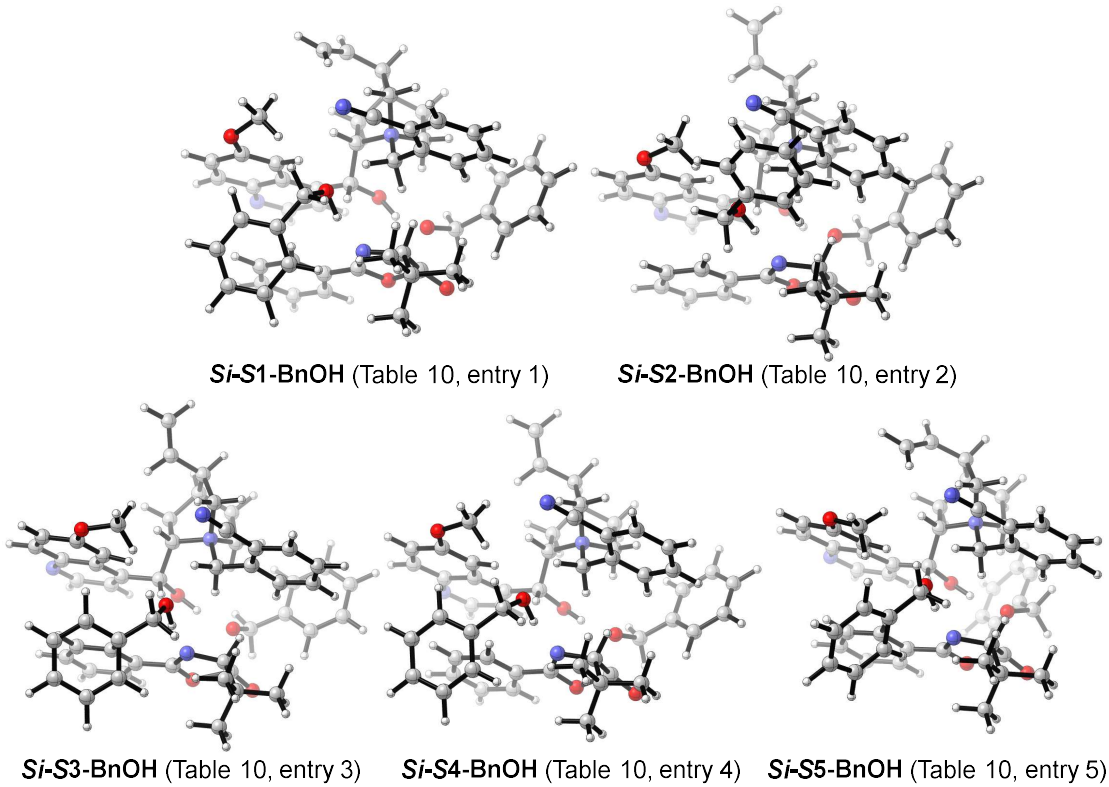
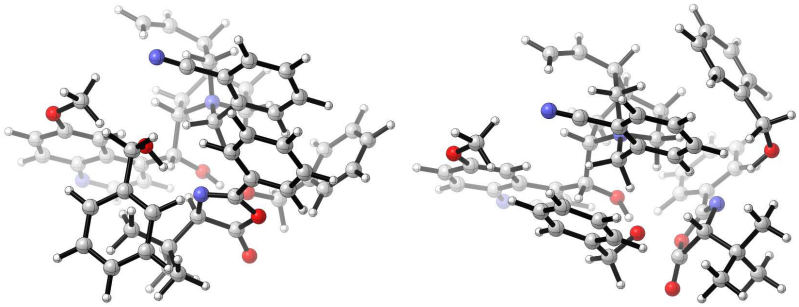
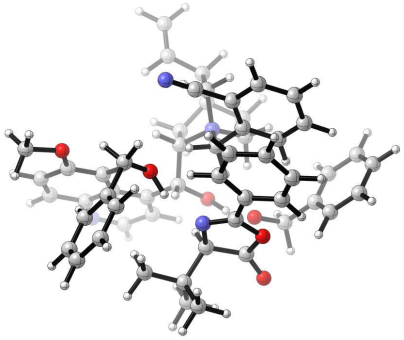


Figure 17. Pseudo-TS-*Si*-*S*-BnOH conformers provided by the PTSCS.

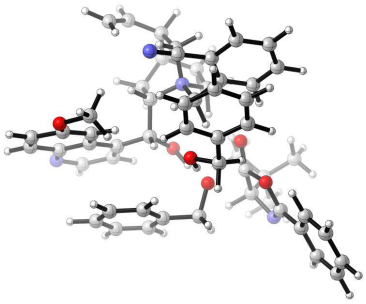


***Re-R*1-BnOH** (Table 10, entry 1)

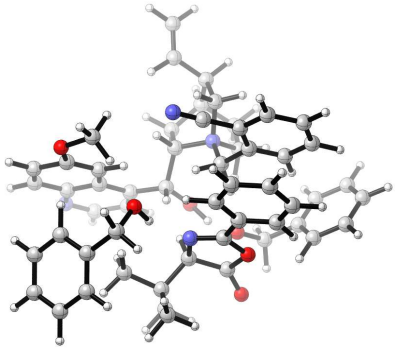
***Re-R*2-BnOH** (Table 10, entry 2)



***Re-R*3-BnOH** (Table 10, entry 3)



***Re-R*4-BnOH** (Table 10, entry 4)



***Re-R*5-BnOH** (Table 10, entry 5)

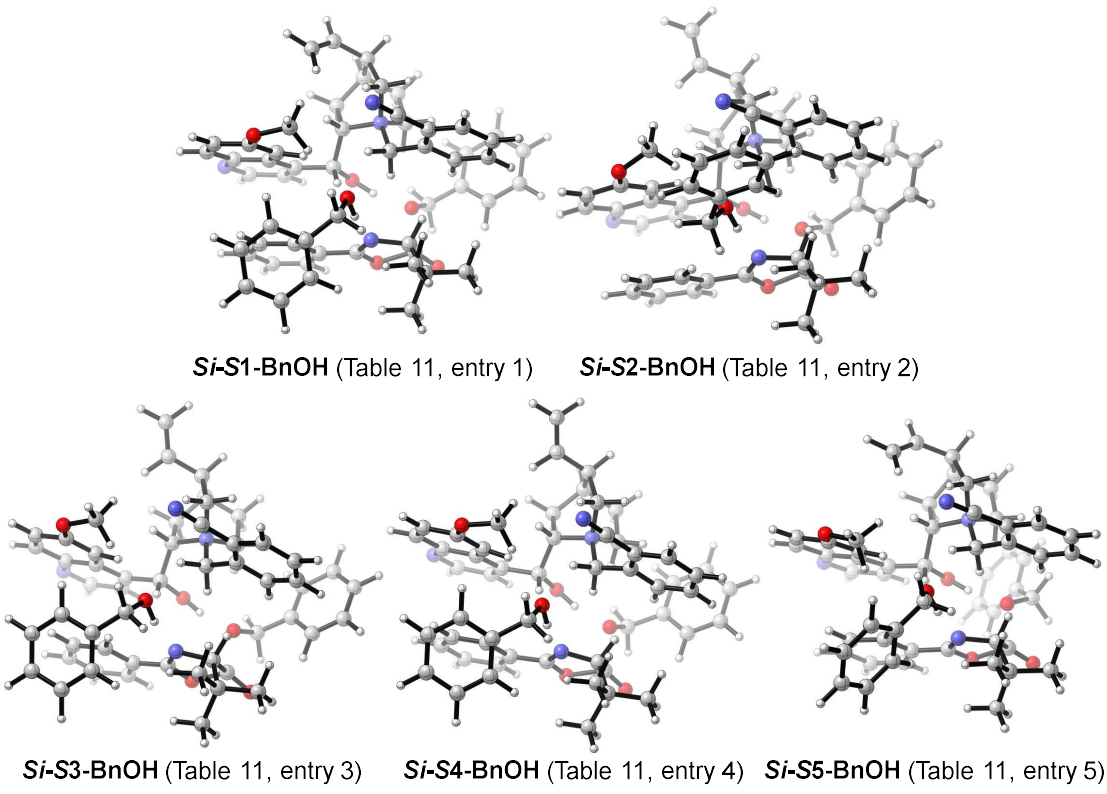
Figure 18. Pseudo-TS-*Re*-*R*-BnOH conformers provided by the PTSCS.

Partial geometry optimizations of the top 5 conformers were further performed to assess the validity of the energies obtained after SPE (Table 11). The Pseudo-TS structures in Table 11 are presented in Figures 19 and 20.

Table 11. Energies of pseudo-TS conformers of **complex B** after partial geometry optimization at RI-B97-D/TZVP level of theory using Gaussian 16.[a]

	Pseudo-TS-*Si*-*S*-BnOH	Pseudo-TS-*Re*-*R*-BnOH
entry	energy (*E,* kcal/mol) [Ranking in ConFinder Output, **Structure Name**]	
1	0.0 [299, ***Si*-*S*1-BnOH**]	4.6 [2836, ***Re*-*R*1-BnOH**]
2	1.5 [1407, ***Si*-*S*2-BnOH**]	2.6 [1787, ***Re*-*R*2-BnOH**]
3	0.1 [338, ***Si*-*S*3-BnOH**]	6.6 [2972, ***Re*-*R*3-BnOH**]
4	0.1 [2199, ***Si*-*S*4-BnOH**]	5.0 [1612, ***Re*-*R*4-BnOH**]
5	3.9 [1447, ***Si*-*S*5-BnOH**]	3.6 [2589, ***Re*-*R*5-BnOH**]

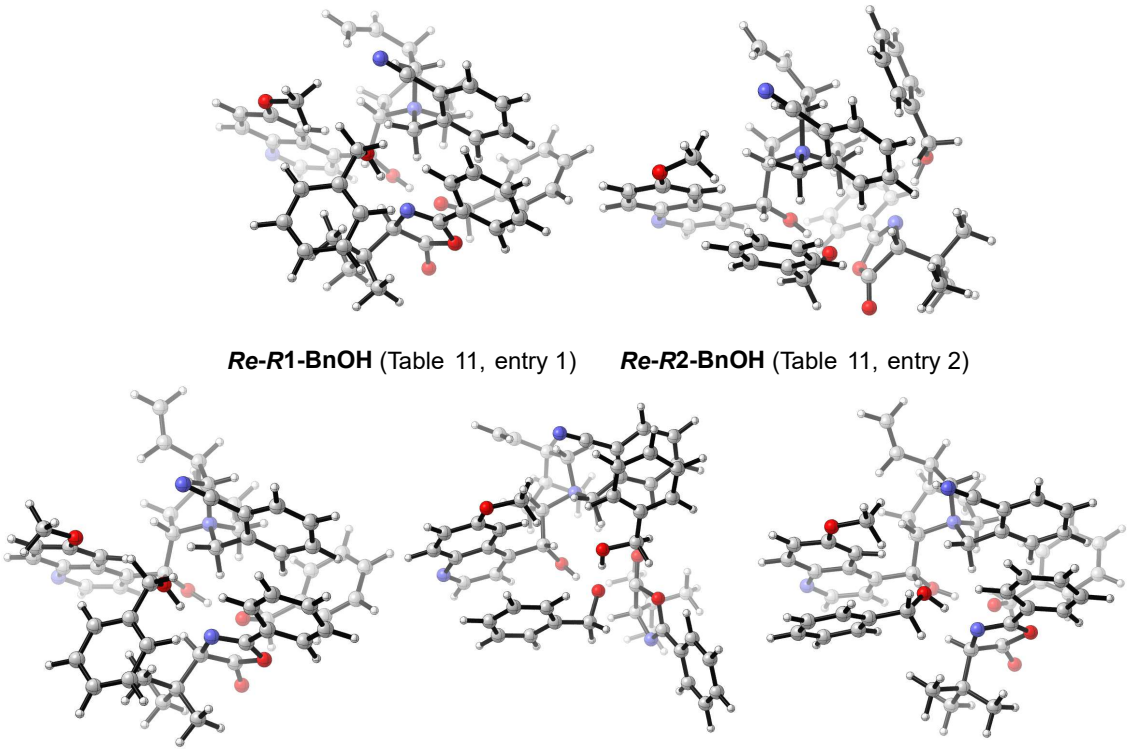
[a]The partial geometry optimizations of the conformers were performed with the distance between the oxygen atom of the alkoxide and the carbon atom of the azlactone fixed to 1.8 A.



***Si*-*S*1-BnOH** (Table 11, entry 1) ***Si*-*S*2-BnOH** (Table 11, entry 2)

***Si*-*S*3-BnOH** (Table 11, entry 3) ***Si*-*S*4-BnOH** (Table 11, entry 4) ***Si*-*S*5-BnOH** (Table 11, entry 5)

Figure 19. Pseudo-TS-*Si*-*S*-BnOH conformers after partial optimization.



***Re-R*1-BnOH** (Table 11, entry 1) ***Re-R*2-BnOH** (Table 11, entry 2)

***Re-R*3-BnOH** (Table 11, entry 3) ***Re-R*4-BnOH** (Table 11, entry 4) ***Re-R*5-BnOH** (Table 11, entry 5)

Figure 20. Pseudo-TS-*Re*-*R*-BnOH conformers after partial optimization.

Transition state calculations for the pseudo-TS candidates were performed and the $\Delta G^{\ddagger}$ values are summarized in Table 12, and the TS structures are shown in Figures 21 and 22. The TS calculation for the pseudo-TS-*Re*-*R*4-BnOH was not converged. Therefore, the value of free energy of the most stable structure obtained in the TS calculation is shown in parentheses (Table 12, entry 9).

Table 12. $\Delta G^{\ddagger}$ values of TS conformers of **complex B** in gas phase and chloroform.[a]

entry	Structure	$\Delta G^{\ddagger}$ (kcal/mol)	
		298.15 K in gas phase	273.15 K in chloroform
1	**TS-*Si*-*S*1-BnOH**	1.2	1.0
2	**TS-*Si*-*S*2-BnOH**	0.0	0.0
3	**TS-*Si*-*S*3-BnOH**	1.1	1.1
4	**TS-*Si*-*S*4-BnOH**	1.1	1.1
5	**TS-*Si*-*S*5-BnOH**	2.8	2.5
6	**TS-*Re*-*R*1-BnOH**	2.6	2.4
7	**TS-*Re*-*R*2-BnOH**	2.1	2.2
8	**TS-*Re*-*R*3-BnOH**	3.4	2.8
9	***Re*-*R*4-BnOH**	(2.6)	(4.3)
10	**TS-*Re*-*R*5-BnOH**	0.7	1.5

[a] $\Delta G^{\ddagger}$ values were calculated at B97-D/TZVP level of theory, and free energy corrections at 1.0 atm.

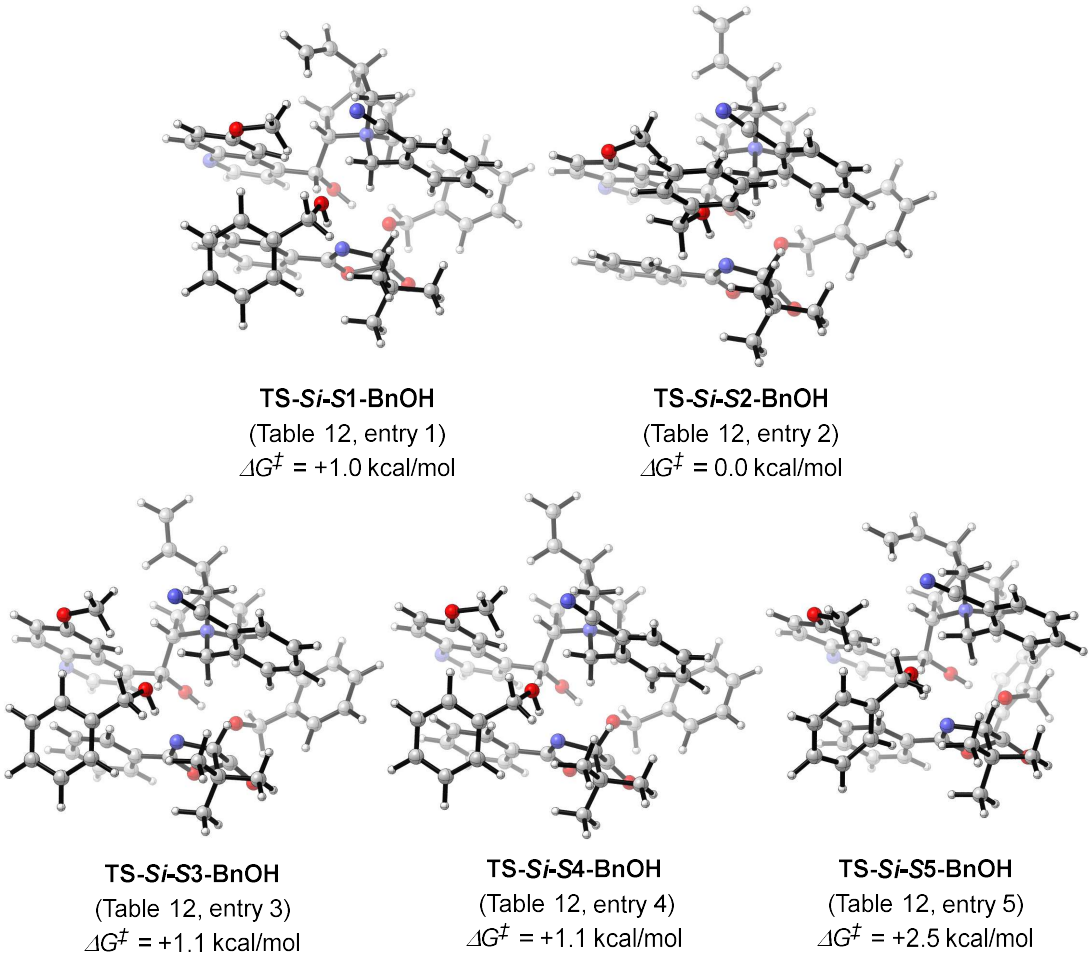


Figure 21. TS-*Si*-*S*-BnOH structures (273.15 K, 1 atm in the chloroform).

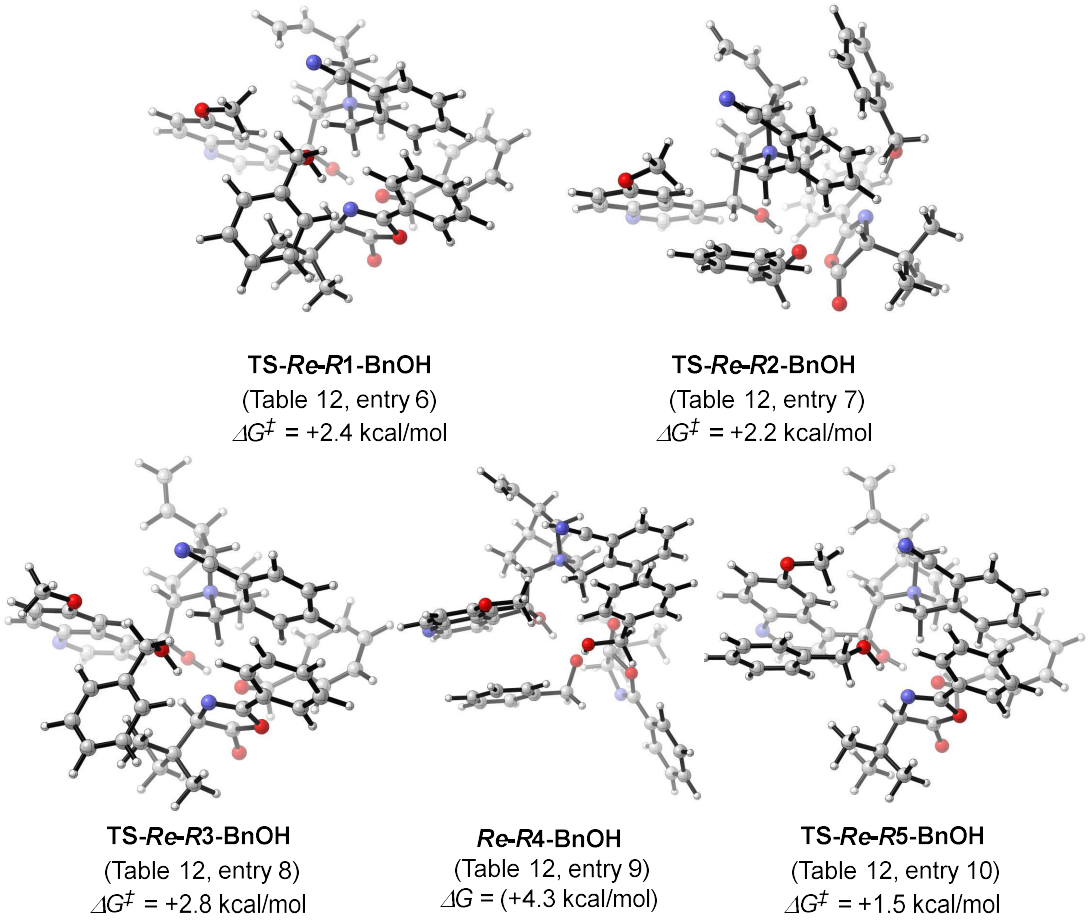


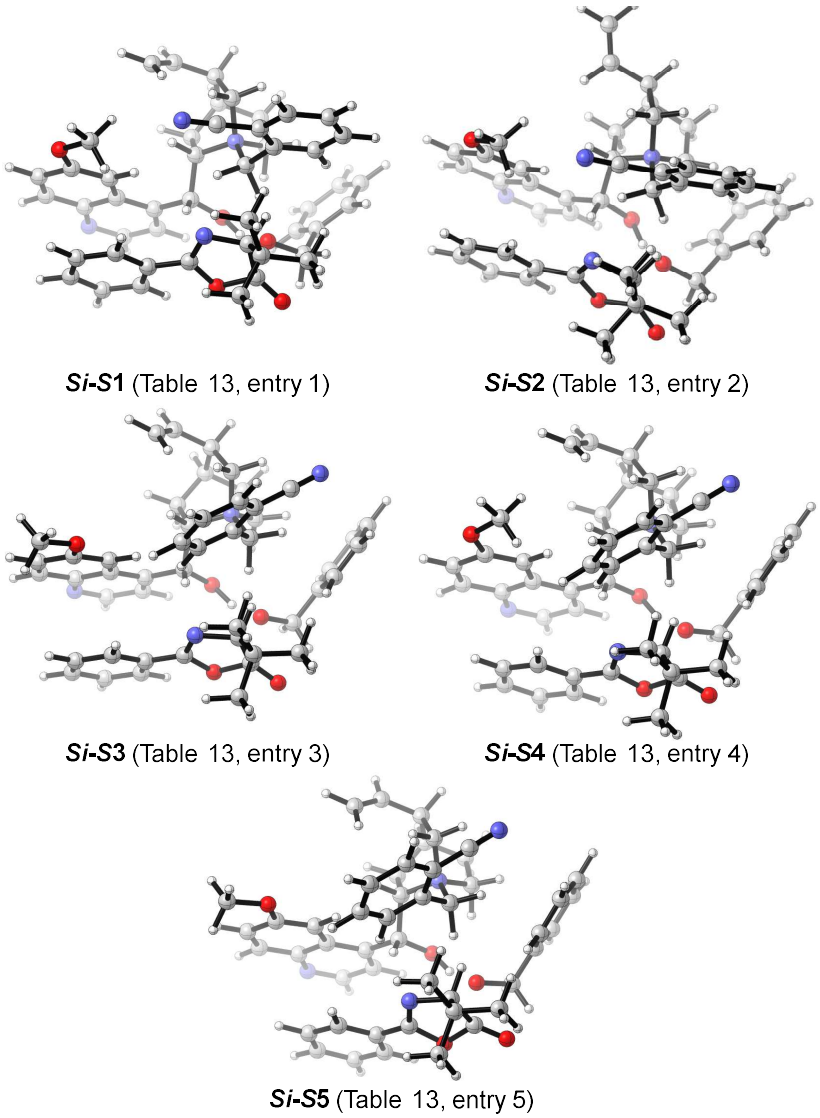
Figure 22. TS-*Re*-*R*-BnOH structures (273.15 K, 1 atm in the chloroform).

Conformational Search and TS Calculation for Complex C [5d'+1a]

The conformational search provided pseudo-TS conformers (*Si*-*S*: 482 conformers, *Re*-*R*: 1162 conformers). Table 13 shows the top 5 of each stable pseudo-TS complexes after the reevaluation by the SPE (Pseudo-TS-*Re*-*R*, Pseudo-TS-*Si*-*S*). The Pseudo-TS structures in Table 13 are presented in Figures 23 and 24.

Table 13. Energies of pseudo-TS conformers of **complex C** after pseudo-TS conformational search and SPE calculation at RI-B97-D/SV(P) level of theory using Turbomole program.

	Pseudo-TS-*Si*-*S*	Pseudo-TS-*Re*-*R*
entry	energy (*E*, kcal/mol) [Ranking in ConFinder Output, **Structure Name**]	
1	**0.0** [130, ***Si*-S1**]	**0.0** [786, ***Re*-R1**]
2	1.3 [160, ***Si*-S2**]	1.9 [763, ***Re*-R2**]
3	3.1 [212, ***Si*-S3**]	3.8 [334, ***Re*-R3**]
4	3.8 [227, ***Si*-S4**]	4.4 [619, ***Re*-R4**]
5	4.4 [401, ***Si*-S5**]	4.4 [11, ***Re*-R5**]



***Si*-S1** (Table 13, entry 1)

***Si*-S2** (Table 13, entry 2)

***Si*-S3** (Table 13, entry 3)

***Si*-S4** (Table 13, entry 4)

***Si*-S5** (Table 13, entry 5)

Figure 23. Pseudo-TS-*Si*-*S* conformers provided by the PTSCS.

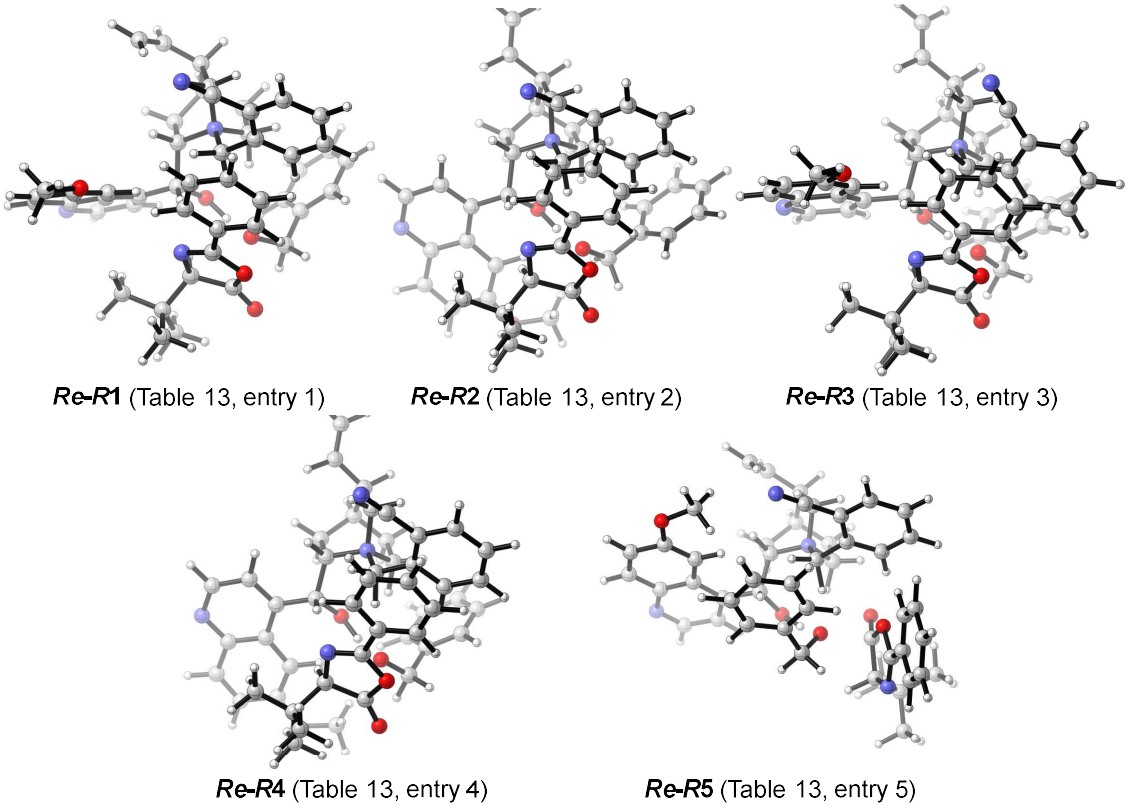


Figure 24. Pseudo-TS-*Re*-*R* conformers provided by the PTSCS.

The difference in activation energy between the most stable pseudo-TS-*Si*-*S* and pseudo-TS-*Re*-*R* is not agreed with the $\Delta\Delta G^{\ddagger}$ values based on the experimental results [0.0 (calcd.) vs 2.1 (exptl.) kcal/mol]. In addition, TS calculations for the conformers were not converged. This inconsistency might indicate that the alcoholysis reaction would proceed via activation of the azlactone substrate by a proton source such as water or alcohol.

3.5 References

[1] (a) Matsukawa, Y.; Isobe, M.; Kotsuki, H.; Ichikawa, Y. *J. Org. Chem.* **2005**, *70*, 5339–5341. (b) Tu, G.; Yan, Y.; Chen, X.; Lv, Q.; Wang, J.; Li, S. *Drug Discov. Ther.* **2013**, *7*, 58–65. (c) Zou, J.; Ni, G.; Tang, J.; Yu, J.; Jiang, L.; Ju, D.; Zhang, F.; Chen, S. *Eur. J. Org. Chem.* **2018**, *2018*, 5044–5053.

[2] (a) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336–345. (b) Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. *Nature* **2009**, *461*, 968–970.

[3] (a) Ohkanda, J.; Strickland, C. L.; Blaskovich, M. A.; Carrico, D.; Lockman, J. W.; Vogt, A.; Bucher, C. J.; Sun, J.; Qian, Y.; Knowles, D.; Pusateri, E. E.; Sebti, S. M.; Hamilton, A. D. *Org.*

Biomol. Chem. **2006**, *4*, 482–492. (b) Tsantrizos, Y. S. *Acc. Chem. Res.* **2008**, *41*, 1252–1263. (c) Wolfe, M. S. *J. Neurochem.* **2012**, *120*, 89–98.

[4] (a) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946–5952. (b) Kreuzfeld, H. J.; Döbler, C.; Krause, H. W.; Facklam, C. *Tetrahedron: Asymmetry* **1993**, *4*, 2047–2051. (c) Imamoto, T.; Tamura, K.; Zhang, Z.; Horiuchi, Y.; Sugiya, M.; Yoshida, K.; Yanagisawa, A.; Gridnev, I. D. *J. Am. Chem. Soc.* **2012**, *134*, 1754–1769. (d) Etayo, P.; Vidal-Ferran, A. *Chem. Soc. Rev.* **2013**, *42*, 728–754.

[5] (a) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353–2355. (b) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415. (c) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595–8598. (d) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519–6520. (c) Ooi, T.; Uematsu, Y.; Maruoka, K. *Tetrahedron Lett.* **2004**, *45*, 1675–1678.

[6] Lou, S.; Schaus, S. E. *J. Am. Chem. Soc.* **2008**, *130*, 6922–6923

[7] (a) de Castro, P. P.; Carpanez, A. G.; Amarante, G. W. *Chem. Eur. J.* **2016**, *22*, 10294–10318. (b) Yu, K.; Liu, X.; Lin, X.; Lin, L.; Feng, X. *Chem. Commun*. **2015**, *51*, 14897-14900. (c) Rodríguez-Docampo, Z.; Quigley, C.; Tallon, S.; Connon, S. J. *J. Org. Chem.* **2012**, *77*, 2407–2414. (d) Zhang, Y. C.; Yang, Q.; Yang, X.; Zhu, Q. N.; Shi, F. *Asian J. Org. Chem.* **2016**, *5*, 914–919. (c) Palacio, C.; Connon, S. J. *Eur. J. Org. Chem.* **2013**, 5398–5413. (f) Cronin, S. A.; Connon, S. J. *Org. Biomol. Chem.* **2021**, *19*, 7348–7352.

[8] (a) Berkessel, A.; Cleemann, F.; Mukherjee, S.; Müller, T. N.; Lex, J. *Angew. Chem. Int. Ed.* **2005**, *44*, 807–811. (b) Berkessel, A.; Mukherjee, S.; Cleemann, F.; Müller, T. N.; Lex, J. *Chem. Commun.* **2005**, 1898–1900. (c) Peschiulli, A.; Quigley, C.; Tallon, S.; Gun'ko, Y. K.; Connon, S. J. *J. Org. Chem.* **2008**, *73*, 6409–6412. (d) Lee, J. W.; Ryu, T. H.; Oh, J.S.; Bae, H. Y.; Jang, H. B.; Song, C. E. *Chem. Commun.* **2009**, 7224–7226. (c) Tallon, S.; Manoni, F.; Connon, S. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 813–817.

[9] Lu, G.; Birman, V. B. *Org. Lett.* **2011**, *13*, 356–358.

[10] (a) Mandai, H.; Hongo, K.; Fujiwara, T.; Fujii, K.; Mitsudo, K.; Suga, S. *Org. Lett.* **2018**, *20*, 4811–4814. (b) Xie, M. S.; Huang, B.; Li, N.; Tian, Y.; Wu, X. X.; Deng, Y.; Qu, G. R.; Guo, H. M. *J. Am. Chem. Soc.* **2020**, *142*, 19226–19238.

[11] Alcoholytic KR of α-chiral esters (transesterification) have been reported, see: Dro, C.; Bellemin-Laponnaz, S.; Welter, R.; Gade, L. H. *Angew. Chem. Int. Ed.* **2004**, *43*, 4479–4482.

[12] (a) Yamamoto, E.; Nagai, A.; Hamasaki, A.; Tokunaga, M. *Chem. Eur. J.* **2011**, *17*, 7178–7182. (b) Yamamoto, E.; Gokuden, D.; Nagai, A.; Kamachi, T.; Yoshizawa, K.; Hamasaki, A.; Ishida,

T.; Tokunaga, M. *Org. Lett.* **2012**, *14*, 6178–6181. (c) Yamamoto, E.; Wakafuji, K.; Mori, Y.; Teshima, G.; Hidani, Y.; Tokunaga, M. *Org. Lett.* **2019**, *21*, 4030–4034.

[13] (a) Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222–4266. (b) Brière, J. F.; Oudeyer, S.; Dalla, V.; Levacher, V. *Chem. Soc. Rev.* **2012**, *41*, 1696–1707. (c) Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 4312–4348. (d) Zong, L.; Tan, C. H. *Acc. Chem. Res.* **2017**, *50*, 842–856. (c) Qian, D.; Sun, J. *Chem. Eur. J.* **2019**, *25*, 3740–3751. (f) Frisch, K.; Jørgensen, K. A. *Org. Biomol. Chem.* **2007**, *5*, 2966–2974

[14] Yamamoto, E.; Wakafuji, K.; Furutachi, Y.; Kobayashi, K.; Kamachi, T.; Tokunaga, M. *ACS Catal.* **2018**, *8*, 5708–5713.

[15] Lefebvre, C.; Khartabil, H.; Boisson, J. C.; Contreras-García, J.; Piquemal, J. P.; Hénon, E. *ChemPhysChem* **2018**, *19*, 724–735.

[16] Yang, H.; Wong, M. W. *J. Am. Chem. Soc.* **2013**, *135*, 5808–5818.

[17] Perrin, D. D.; Armarego, W. L. F.; Purification of Laboratory Chemicals; 3rd ed., Pergamon Press, Oxford, 1988

[18] Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Fini, F.; Pettersen, D.; Ricci, A. *J. Org. Chem.* **2006**, *71*, 9869–9872.

[19] Turner, N. J.; Winterman, J. R.; McCague, R.; Parratt, J. S.; Taylor, S. J. C. *Tetrahedron Lett.* **1995**, *36*, 1113–1116.

[20] Wang, T.; Yu, Z.; Hoon, D. L.; Phee, C. Y.; Lan, Y.; Lu, Y. *J. Am. Chem. Soc.* **2016**, *138*, 265–271.

[21] Palacio, C.; Connon, S. J. *Eur. J. Org. Chem.* **2013**, 5398–5413.

[22] Commercially available from Aurora Fine Chemicals LLC (https://aurorafinechemicals.com/). Catalog number: A17.414.064

[23] Zhou, J.; Wang, M. L.; Gao, X.; Jiang, G. F.; Zhou, Y. G. *Chem. Commun.* **2017**, *53*, 3531–3534.

[24] De Mello, A. C.; Momo, P. B.; Burtoloso, A. C. B.; Amarante, G. W. *J. Org. Chem.* **2018**, *83*, 11399–11406.

[25] Lee, J. W.; Ryu, T. H.; Oh, J. S.; Bae, H. Y.; Jang, H. B.; Song, C. E. *Chem. Commun.* **2009**, 7224–7226.

[26] Menges, F.; Neuburger, M.; Pfaltz, A. *Org. Lett.* **2002**, *4*, 4713–4716.

[27] (a) Kamachi, T.; Yoshizawa, K. *Org. Lett.* **2014**, *16*, 472–475. (b) Kamachi, T.; Yoshizawa, K. *J. Chem. Inf. Model.* **2016**, *56*, 347–353.

[28] Banks, J. L.; Beard, H. S.; Cao, Y.; Cho, A. E.; Damm, W.; Farid, R.; Felts, A. K.; Halgren, T.

A.; Mainz, D. T.; Maple, J. R.; Murphy, R.; Philipp, D. M.; Repasky, M. P.; Zhang, L. Y.; Berne, B. J.; Friesner, R. A.; Gallicchio, E.; Levy, R. M. *J. Comput. Chem.* **2005**, *26*, 1752−1780.

[29] Ponder, J. W. TINKER: Software Tools for Molecular Design, version 7.1; Washington University School of Medicine: Saint Louis, MO, 2015.

[30] Korth, M. *J. Chem. Theory Comput.* **2010**, *6*, 3808−3816.

[31] Stewart, J. J. P. MOPAC2012, version 15.063; Stewart Computational Chemistry: Colorado Springs, CO, 2012.

[32] Grimme, S. *J. Comput. Chem.* **2006**, *27*, 1787−1799.

[33] Schäfer, A.; Horn, H.; Ahlrichs, R. Fully Optimized Contracted Gaussian Basis Sets for Atoms Li to Kr. *J. Chem. Phys.* **1992**, *97*, 2571−2577.

[34] TURBOMOLE V7.0 2015, a development of University of Karlsruhe and Forschungszentrum Karlsruhe GmbH, 1989-2007, TURBOMOLE GmbH, since 2007; available from http://www.turbomole.com.

[35] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B. and Fox, D. J. Gaussian 16, Revision A.03; Gaussian, Inc.; Wallingford CT, 2016.

[36] CYLview, 1.0b; Legault, C. Y., Université de Sherbrooke, 2009 (http://www.cylview.org)

[37] Schäfer, A.; Huber, C.; Ahlrichs, R. *J. Chem. Phys.* **1994**, *100*, 5829−5835.

[38] Hoshi, K.; Tahara, A.; Sunada, Y.; Tsutsumi, H.; Inoue, R.; Tanaka, H.; Shiota, Y.; Yoshizawa, K.; Nagashima, H. *Bull. Chem. Soc. Jpn.* **2017**, *90*, 613–626.

[39] (a) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995–2001. (b) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2003**, *24*, 669–681.

[40] Lu, T.; Chen, F. *J. Comput. Chem.* **2012**, *33*, 580–592.

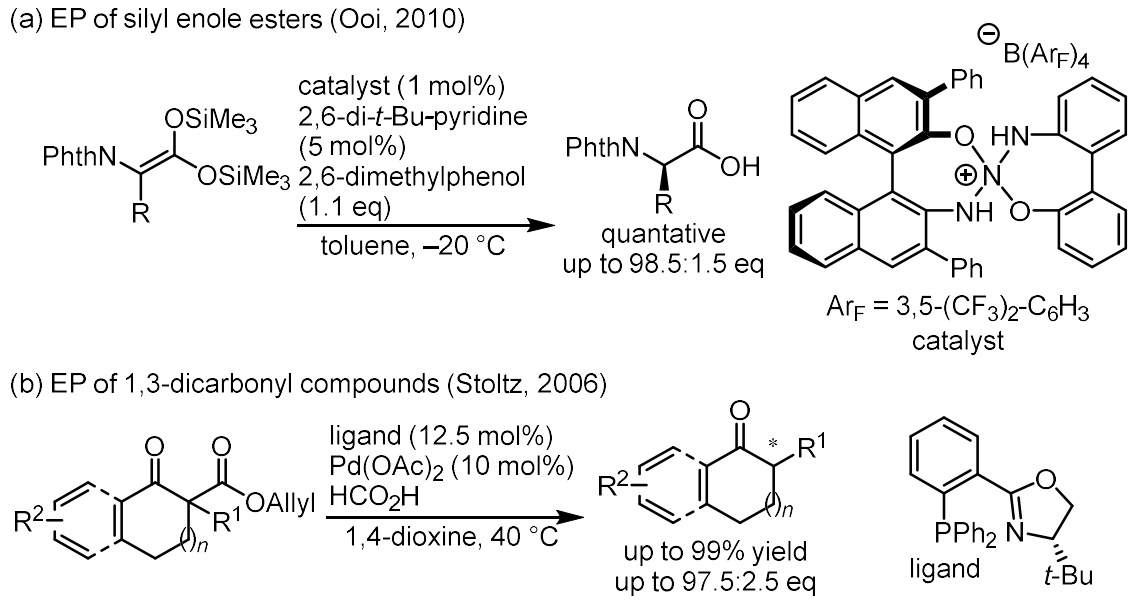
[41] Humphrey, W.; Dalke, A.; Schulten, K. *J. Mol. Graph.* **1996**, *14*, 33–38.

Chapter 4. Reaction Mechanism of Enantioselective Protonation of Enol Esters with Bifunctional Phosphonium/Thiourea Catalysts

4.1. Introduction

Carbonyl compounds having tertiary carbon center at the α-positions are broadly found in bioactive and natural molecules.[1] Enantioselective protonation (EP) of enolate derivatives is one of the straightforward and efficient access to carbonyl compounds having chiral tertiary α-carbon center. Although a large number of catalytic EP has been developed,[2] controlling the enantioselectivity of EP is a still challenging task, because the proton is the smallest electrophile and racemization of the products via fast proton exchange.

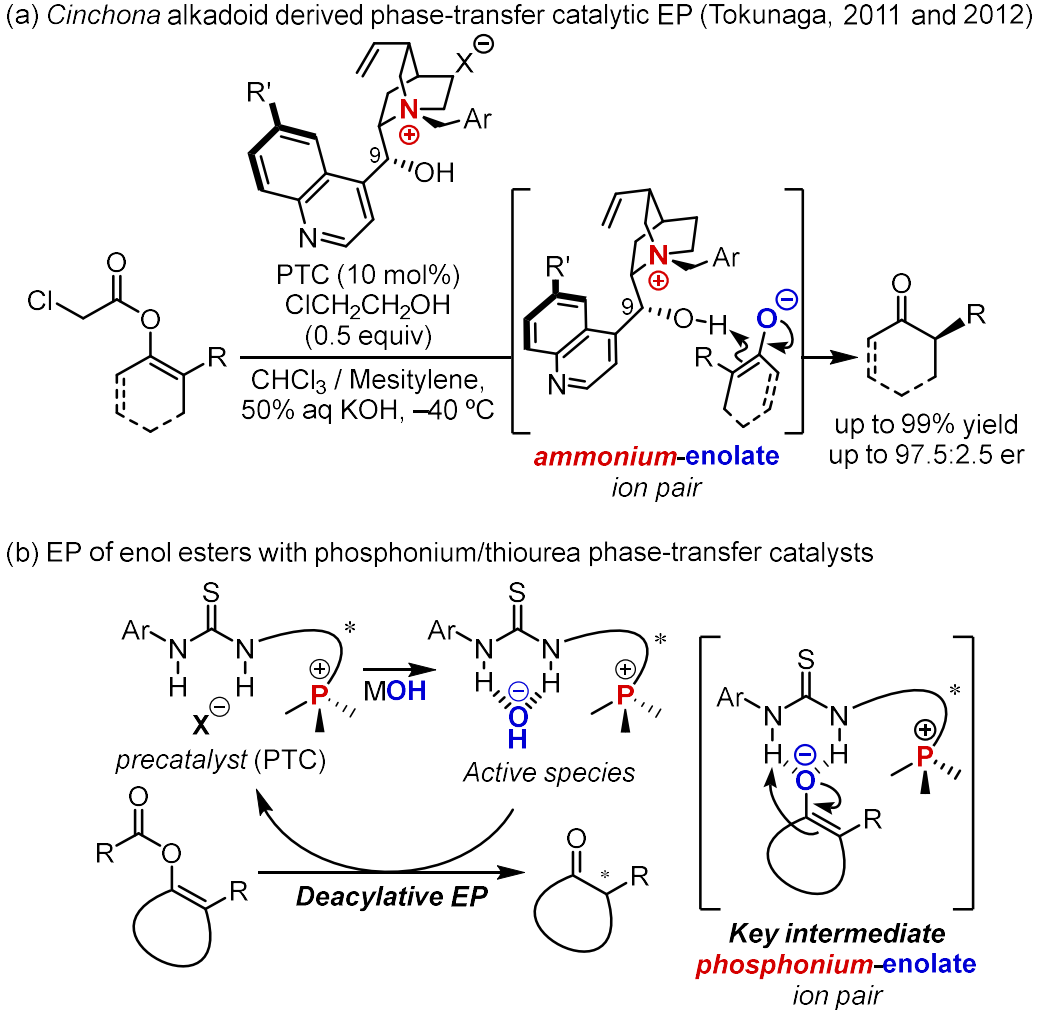
So far, novel catalytic EP has been developed such as silyl enol esters (Scheme 1a)[3] and 1,3-dicarbonyl compounds (Scheme 1b).[4] Enol esters (alkenyl esters) are useful for the EP as due to the stability and synthetic convenience because of their good synthetic accessibility and stability.[5] However, there are only a few reports of the EP that used the enol esters as substrates. In addition, the substrate scope of the reactions have room to further improvement.[6]



Scheme 1. Selected examples of EP.

In 2011 and 2012, Tokunaga and co-worker showed that the chiral phase-transfer catalysts (PTCs) also exhibited high enantioselectivities and catalytic activities for the EP of chloroacetyl enolates via base-hydrolysis (Scheme 2a).[7] Their experimental and theoretical mechanistic studies suggested that the comparatively high acidic 9-OH group of the *cinchona* alkaloid derived PTC worked as a chiral proton source in the EP reaction. Based on these mechanistic insights, the author and co-workers then focused on the use of quaternary phosphonium/thiourea catalysts because this motif includes the acidic hydrogen bond donor would be the proton source in the enantioselective step

and various accessible unique structures (Scheme 2b). In addition, the thiourea group would form a hydrogen bond with hydroxide, protecting the relatively fragile phosphonium moiety from decomposition via β-elimination by the strong hydroxide base. Considering the synthetic accessibility of the catalysts, phosphonium/thiourea catalysts derived from chiral α-amino acids were selected, which were first developed by Zhao's group.[8]



Scheme 2. Phase-transfer catalytic EP of enol esters.

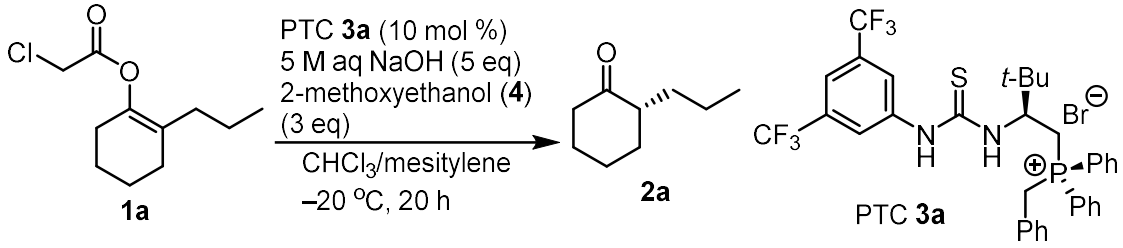
4.2. Results and Discussion

Optimization of the Reaction Conditions and Substrate Scope

Initially, the author and co-workers (Mr. Hidani, Mr. Teshima, and Mr. Mori) explored the optimal reaction conditions with chloroacetyl enolate **1a** using 5 M aq NaOH and 2-methoxyethanol (**4**) as an additive in $CHCl_3$/mesitylene solvent, and found that the corresponding α-chiral ketone **2a** was obtained in 92% yield with 95.5:4.5 er (Table 1, entry 1). For this catalytic system, addition of 3

equivalents of **4** is important from the viewpoint of the reactivity and enantioselectivity (entries 2–5). The reaction in the absence of **4** or with 2 equivalents of **4** provided the product in lower yield and er. Furthermore, an additive such as an aprotic polar compound (1,2-dimethoxyethane) or a sterically hindered alcohol (*tert*-butanol) significantly lowered the yields. The additive **4** promoted the decomposition of the substrate even in the absence of PTC **3a** (entry 6). These results indicate that the alcoholic additives work as a nucleophile and generate the enolate intermediate by the alcoholysis of the chloroacetyl enolate. The enantioselectivity decreased when the reactions were performed in $CHCl_3$ or mesitylene alone (entries 7 and 8) instead of a mixture of these solvents. Warming the reaction temperature lowered the enantioselectivity (entry 9).

Table 1. Optimization of the reaction conditions.

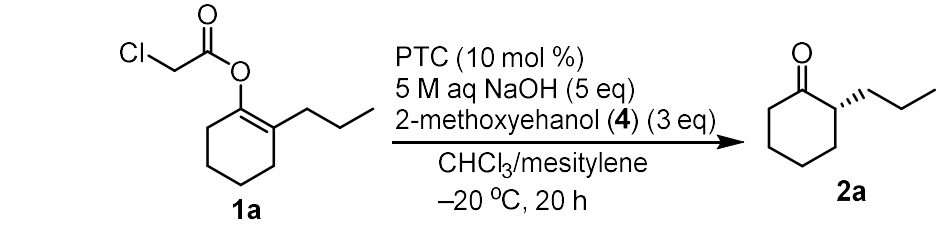


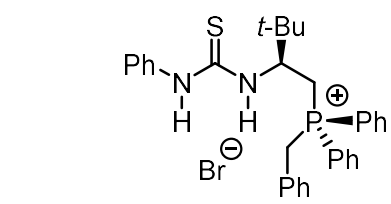
entry	deviation from standard conditions	yield[a] (%)	er
1	standard conditions	92	95.5:4.5
2	without **4**	18	86:14
3	2 eq of **4**	47	96:4
4	with 2 eq $MeOCH_2CH_2OMe$ instead of **4**	14	86.5:13.5
5	with 2 eq *t*-BuOH instead of **4**	28	88:12
6	without PTC **3a**	47	50:50
7	solvent: $CHCl_3$	65	94.5:5.5
8	solvent: mesitylene	79	79.5:20.5
9	reaction temp.: –10 °C	99	93.5:6.5

[a]GC yields are presented.

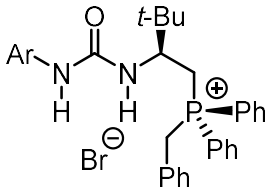
Next, the author and Mr. Mori examined chiral PTCs with different scaffolds and investigated the substituent effects of the phosphonium/thiourea catalysts (Scheme 3). The use of PTC **3b** with a phenyl group instead of the 3,5-(bistrifluoromethyl)phenyl group lowered the enantioselectivity, and

the replacement of the sulfur atom with an oxygen atom resulted in a low er (PTC **3c**). These results suggest that the high acidity of the proton of the thiourea moiety is indispensable to attain the high enantioselectivity. Finally, the catalysts **3d**–**3f** having different aryl groups on the phosphorous atom were investigated, and catalyst **3d** bearing 1-naphthyl group showed the highest yield and stereoselectivity (98%, 97.5:2.5 er). Furthermore, the 1 mmol scale reaction with the catalyst **3d** successfully proceeded without significant loss of the stereoselectivity (75%, 97:3 er).

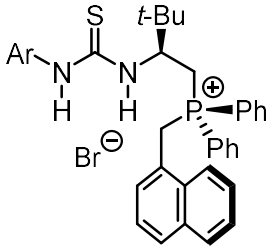




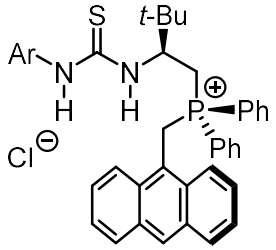
3b: 93% yield, 81:19 er



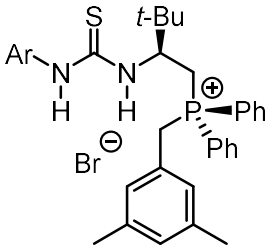
(Ar = 3,5-CF_3-C_6H_3)
3c: 95% yield, 69.5:30.5 er



(Ar = 3,5-CF_3-C_6H_3)
3d: 98% yield, 97.5:2.5 er
(1mmol scale: 75% yield, 97:3 er)



(Ar = 3,5-CF_3-C_6H_3)
3e: 92% yield, 85:15 er

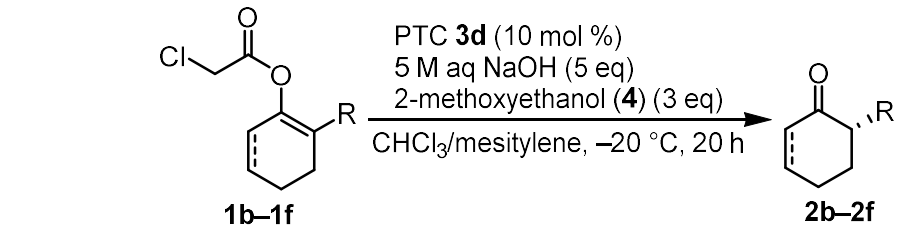


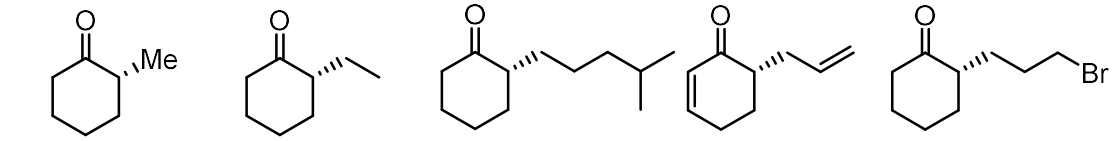
(Ar = 3,5-CF_3-C_6H_3)
3f: 89% yield, 95:5 er

[a]GC yields are presented.

Scheme 3. Catalyst screening.

With the optimized reaction conditions, the author expanded the substrate scope for the EP reaction (Scheme 4). Reactions with substrates bearing aliphatic substituents provided the corresponding α-chiral ketones in good yields with good to high enantioselectivities (**2b**: 70%, 89.5:10.5 er; **2c**: 79%, 94:6 er; **2d**, 76%, 93.5:6.5 er). It is worthy of note that product **2d** is the useful synthetic intermediate for ent-10-methyl-6-undecanolide.[9] Dienyl ester **1e** and enol ester **1f** having 3-bromopropyl group reacted to provide the corresponding ketones in moderate to good yields with good to high stereoselectivities (**2e**: 89%, 91.5:8.5 er; **2f**: 98%, 88.5:11.5 er).





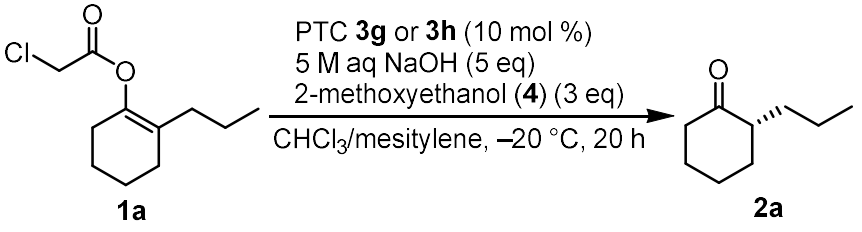
2b, 70% yield, 89.5:10.5 er | **2c**, 79% yield, 94:6 er | **2d**, 76% yield, 93.5:6.5 er | **2e**, 89% yield, 91.5:8.5 er | **2f**, 98% yield, 88.5:11.5 er

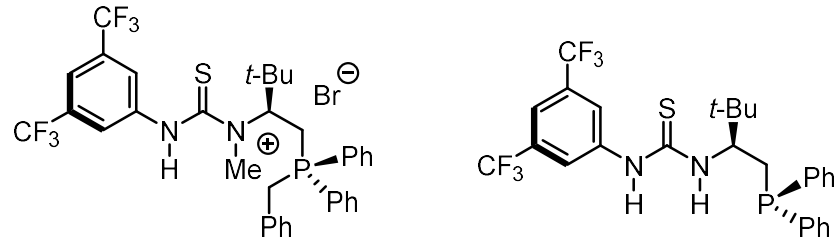
[a]Isolated yields are presented.

Scheme 4. Substrate scope of enol esters.

Mechanistic Studies

Based on the above experimental results, the author investigated the roles of the thiourea and phosphonium groups by the use of N-methylated catalyst PTC **3g** and thiourea-phosphine catalyst **3h** (Scheme 5). PTC **3g** provided the racemic **2a** under the standard reaction conditions, and the lack of quaternarization of the phosphorous atom retarded the selectivity (60:40 er). These results indicated that the hydrogen bonding donor and formation of the ion pairing of the catalyst both played important roles in the stereodetermining step.



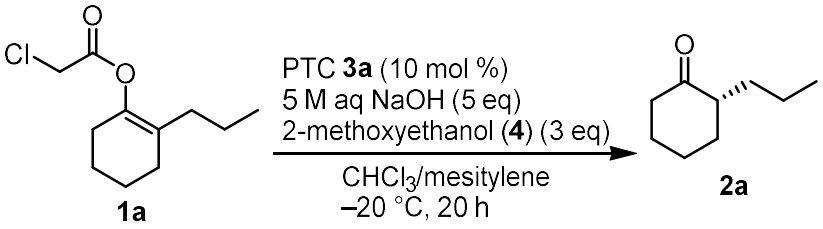


PTC **3g**: 68% yield, 50:50 er

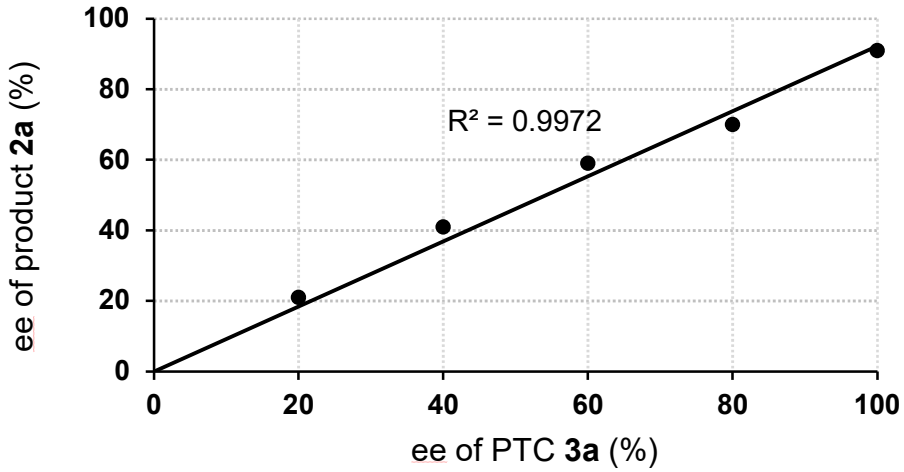
3h: 93% yield, 60:40 er

Scheme 5. Control experiments to investigate the substituent effects of the PTC **3g** and **3h**.

After the investigation of the role of the thiourea group of PTCs, the relationship between the enantiomeric excess (ee) value of the PTC **3a** and the product **2a** was explored (Scheme 6). Potentially, PTC **3** and the corresponding betaine species could work cooperatively because of the difference between the acidity of the corresponding N-H protons.[10] However, a clear linear linearity was observed, which indicates that the monomeric catalytic active species is involved in the enantioselective protonation step.



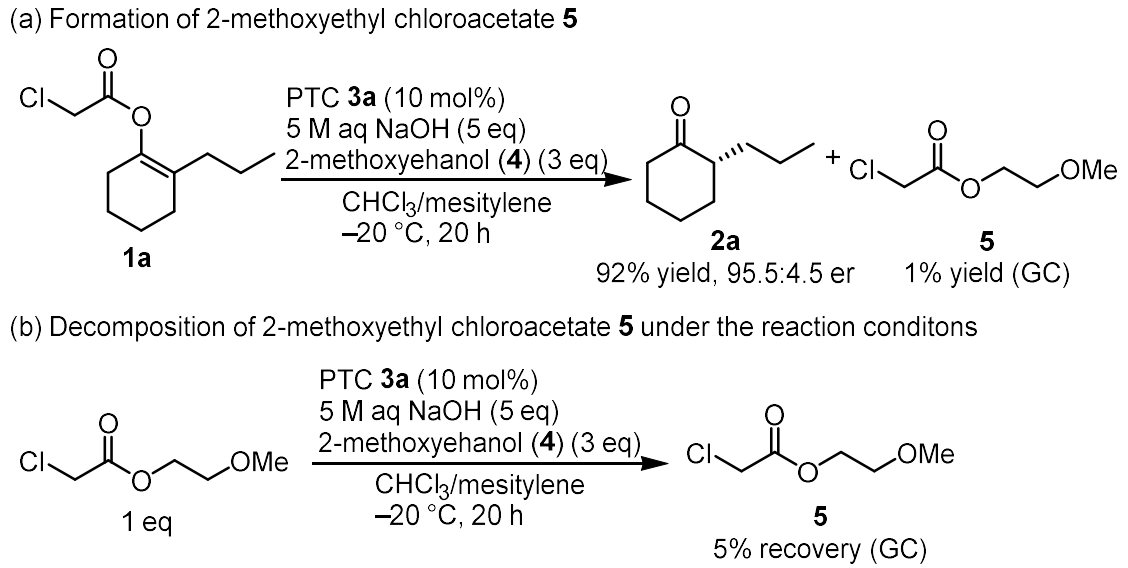
entry	ee of PTC **3a** (%)	yield (%)	ee of product (%)
1	80	95	70
2	60	70	59
3	40	96	41
4	20	91	21



Scheme 6. Non-linear effect study.

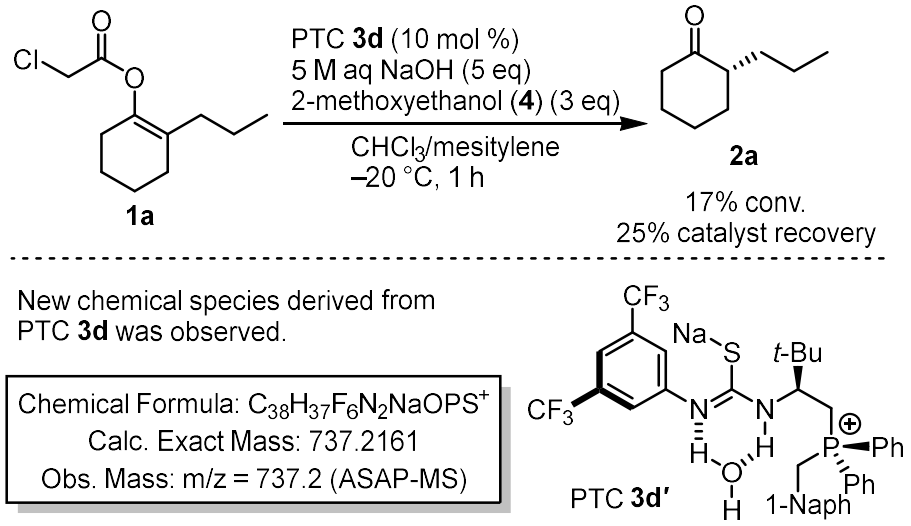
Next, the effort was directed towards elucidating the roles of the alcoholytic additives. The author hypothesized that 2-methoxyethanol **4** would play as a nucleophile instead of the hydroxide anion, and suppress the formation of the chloroacetic acid, which would be a potential achiral proton source. In order to probe this hypothesis, the formation of 2-methoxyethyl chloroacetate **5** under the

standard reaction conditions was investigated, and detected a small amount of **5** (Scheme 7a). Furthermore, **5** was found to quickly decompose under the reaction conditions (Scheme 7b). In the screening of the reaction conditions, additives such as sterically hindered alcohols or aprotic polar compounds significantly lowered the yields based on the preliminary screening of the additives. These results also support the above hypothesis.



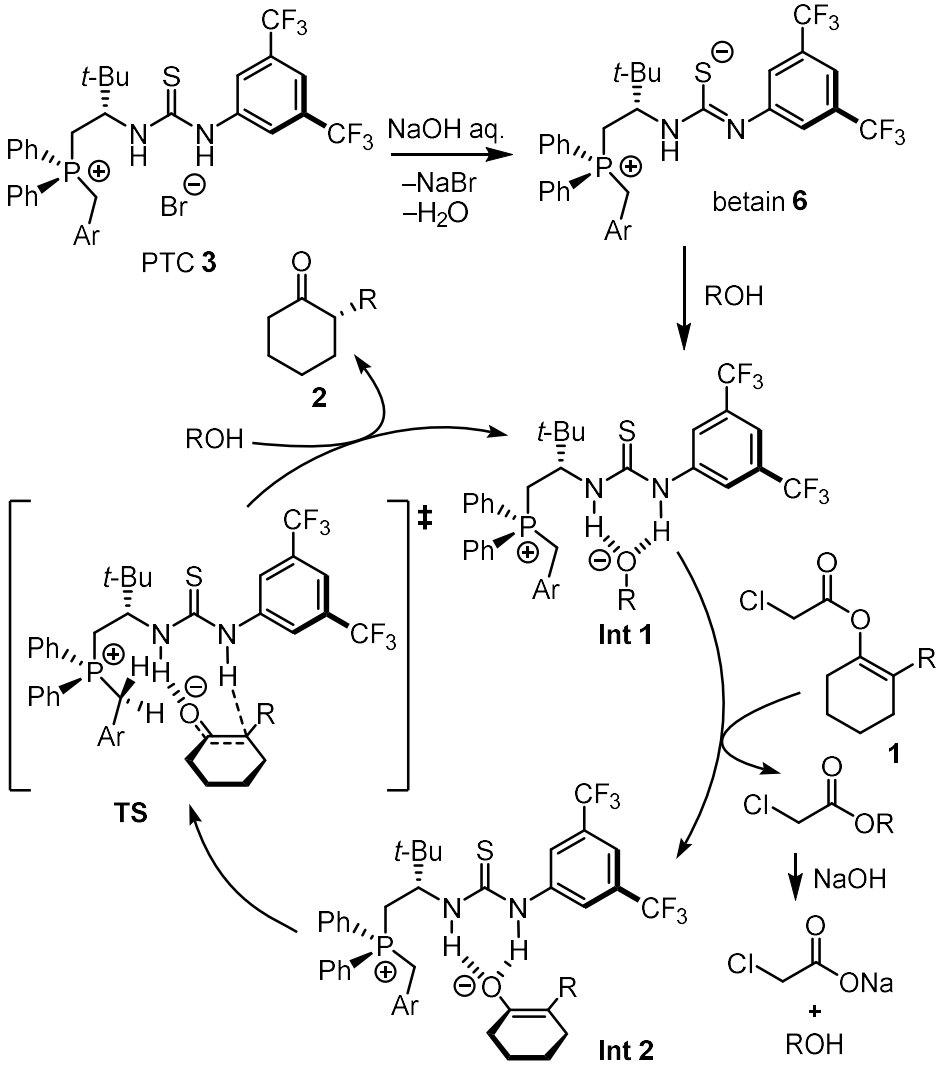
Scheme 7. Investigation of the role of the alcohol additives.

In order to gain further mechanistic insights, analyzing the reaction mixture under the standard reaction conditions was carried out (Scheme 8). ^{31}P NMR analysis of the chloroform extracts of the reaction mixtures under standard conditions observed new phosphorus compounds derived from **3d** formed after 1 h, although the conversion of the substrate was low (recovery of **3d**: 25%, substrate conv.: 17%). In addition, Atmospheric Pressure Solid Analysis Probe MS (ASAP-MS) analysis of the organic phase of the reaction mixture revealed a signal at m/z = 737.2 corresponding to a deprotonated hydrated sodium salt of PTC **3d** (Scheme 8, PTC **3d′**). These results indicated that PTC **3d** was initially deprotonated and formed betaine, which also catalyzed the alcoholytic or hydrolytic EP.



Scheme 8. ASAP-MS analysis of the reaction mixture under the standard reaction conditions.

Finally, based on the above mechanistic studies, the putative reaction mechanism is shown in Scheme 9. Initially, the halide anion of the PTC **3** is exchanged for the hydroxide anion in the basic aqueous phase, and **3** is deprotonated by the base to form the corresponding betaine **6**. Then, the phosphonium/thiourea-alkoxide complex **Int 1** was provided by the reaction with ROH. Taking the role of additives as nucleophile into consideration, this complex would undergo transesterification with enol ester **1**, providing the phosphonium-enolate complex **Int 2**. While the external EP pathways cannot be excluded, subsequent stereoselective internal EP by the acidic NH proton in the thiourea group would provide the corresponding ketones with high enantioselectivity.



Scheme 9. Proposed reaction mechanism.

4.3. Conclusion

In this chapter, an enantioselective protonation reaction of enol esters using phosphonium/thiourea bifunctional catalysts delivering enantioenriched α-chiral ketones with good to high er is described. Especially, the author focused on revealing this catalytic system via experimental mechanistic investigations, and elucidated the roles of the alcohol additive as a nucleophile and the phosphonium and thiourea moieties in the catalysts, which were essential to achieve the observed high enantioselectivity.

4.4. Experimental

General and Materials

Material Chloroform was purified prior to use following the guidelines of Perrin and Armarego.[11] All other chemical reagents were used in commercial grade and without further purification. Enol esters **1a**, **1c**, **1d**,[7a] **1e**[7b] and PTC **3a**,[8a] **3f**,[8d] **3h**[8e] were known compounds and prepared according to the reported procedures. $CDCl_3$ was used as solvent for NMR analyses. NMR spectra were recorded on a JEOL spectrometer ECS-400 or ECA-600. Data for ^{19}F and ^{31}P NMR spectra are referenced to benzotrifluoride at –63.72 ppm and 85% aqueous phosphoric acid at 0 ppm, respectively. Data for NMR spectra are described as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext =sextet, sep = septet, oct = octet, non = nonet, m = multiplet, dd = doublet of doublets, tt = triplet of triplets, td = triplet of doublets, dt = doublet of triplets, qd = quartet of doublets, qt = quartet of triplets, ap = apparent, br = broad), integration, coupling constant (Hz) and assignment. The enantiomer ratios were determined by GC or HPLC analysis employing a chiral stationary phase column specified in the individual experiment, by comparing the samples with the corresponding racemic mixtures. GC analyses were carried out using Agilent GC 6850 series II equipped with InertCap CHIRAMIX Column (length 30 m, i.D. 0.25 mm, df. 0.25 μm) from GL Sciences Inc. and CHIRASIL-DEX CB (length 25 m, i.D. 0.25 mm, df. 0.25 μm) from Varian using helium as a carrier gas. HPLC analysis was performed on a JASCO PU-2080 or HITACHI L-2130 equipped with a variable wavelength detector using chiral stationary columns (CHIRALPAK AD-H, AS-H, CHIRALCEL OD-H, OJ-H, 0.46 cm x 25 cm) from Daicel. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. Chromatography was performed on silica-gel (Kanto Chemical, Silica gel 60N, spherical, neutral; particle size 40–100 μm). Elemental analyses were recorded at the Service Centre of the Elementary Analysis of Organic Compounds, Faculty of Science, Kyushu University. High resolution mass (HRMS) analyses were measured on JEOL JMS-700 mass spectrometer at Evaluation Center of Materials Properties and Function, Institute for Materials Chemistry and Engineering, Kyushu University. Abbreviations; aq = aqueous solution, eq = equivalent, er = enantiomer ratio, ee = enantiomeric excess, Rt = retention time of HPLC or GC, pro = product, rt = room temperature, sub = substrate, AIBN = 2,2'-azodiisobutyronitrile.

General Experimental Procedures

Phase-Transfer Catalytic Enantioselective Protonation of Enol Esters

PTC **3** (0.025 mmol, 10 mol%) and 2-methoxyethanol (60 μL, 3 eq) were added to the $CHCl_3$/mesitylene (250 μL/250 μL) solution followed by the addition of 5 M aq NaOH (250 μL, 5 eq)

under air. After stirred at –20 °C for 10 min, enol ester **1** (0.25 mmol, 1 eq) was added and the resultant solution was further stirred for 20 h at –20 °C. The reaction mixture was filtered through a short silica-gel column with Et_2O as an eluent. After removal of the solvent under reduced pressure, the crude products were purified by flash column chromatography to afford the corresponding α-chiral ketones. The Enantiomer ratios of the products were analyzed by HPLC or chiral GC.

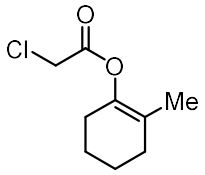
Synthesis of Enol Esters 1

Aqueous $HClO_4$ solution (60 wt%, 5 mol%) was added to a mixture of racemic ketones (1 eq) and chloroacetic acid anhydride (2 eq) in CCl_4 and CH_2Cl_2 (v/v = 1/1) under air at rt. After the reactions were completed determined by TLC analyses, saturated aq $NaHCO_3$ was added to the reaction mixtures and extracted with Et_2O × 3. The combined organic layers were dried with Na_2SO_4, and concentrated by evaporation. The resultant crude products were purified by silica-gel column chromatography (hexane/Et_2O) to give enol esters **1**.

Synthesis and Characterization of Substrates, Products and PTCs

Synthesis and Characterization of Enol Esters 1

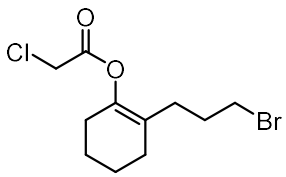
2-Methylcyclohex-1-en-1-yl 2-chloroacetate (1b).



1b

The title compound was synthesized according to the general procedure (reaction time: 2 h, flash column chromatography eluent: hexane/Et_2O = 40/1) as a colorless oil in 52% yield (494 mg, 2.62 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.11 (s, 2H), 2.12–2.05 (m, 2H), 2.05–1.98 (m, 2H), 1.73–1.64 (m, 2H), 1.63–1.55 (m, 2H), 1.52–1.48 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4 (*C*O), 141.9 (*C*), 121.2 (*C*), 40.8 (*C*H_2), 30.1 (*C*H_2), 26.8 (*C*H_2), 23.1 (*C*H_2), 22.4 (*C*H_2), 16.0 (*C*H_3). Elemental Analysis: Calcd for $C_9H_{13}ClO_2$: C, 57.30; H, 6.95; N, 0.00; Found: C, 57.02; H, 6.85; N, 0.00.

2-(3-Bromopropyl)cyclohex-1-en-1-yl 2-chloroacetate (1f)



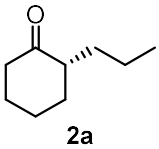
1f

The title compound was synthesized according to the general procedure (reaction time: 13 h, flash column chromatography eluent: hexane/Et_2O = 50/1 to 30/1) as a colorless oil in 72% yield (158.1 mg, 0.535 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.15 (s, 2H), 3.35 (t, *J* = 6.7 Hz, 2H), 2.17–2.01 (m, 6H), 1.89 (quint, *J* = 6.9 Hz, 2H), 1.74–1.66 (m, 2H), 1.65–1.57 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7 (*C*O), 143.4 (*C*), 123.5 (*C*), 41.0 (*C*H_2), 33.8 (*C*H_2), 30.4 (*C*H_2), 28.5 (*C*H_2), 28.0 (*C*H_2), 26.9 (*C*H_2), 23.0 (*C*H_2), 22.4 (*C*H_2). Elemental Analysis: Calcd

for $C_{11}H_{16}BrClO_2$: C, 44.70; H, 5.46; N, 0.00;. Found: C, 44.98; H, 5.54; N, 0.01.

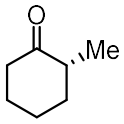
Characterization of Products 2

(*R*)-(–)-2-Propylcyclohexan-1-one (2a).[7a]


2a

The reaction was performed according to the general procedure (0.1 mmol scale). The title compound was purified by silica-gel chromatography (hexane/Et_2O). 98% isolated yield (13.8 mg, 0.098 mmol, colorless oil), 97.5:2.5 er. The ^1H and ^{13}C NMR spectra of the product were in agreement with the literature.[7a] ^1H NMR (400 MHz, $CDCl_3$): δ = 2.40–2.21 (m, 3H), 2.12–1.93 (m, 2H), 1.89–1.59 (m, 4H), 1.45–1.10 (m, 4H), 0.88 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 213.8 (*C*O), 50.6 (*C*H), 42.1 (*C*H_2), 33.9 (*C*H_2), 31.7 (*C*H_2), 28.2 (*C*H_2), 24.9 (*C*H_2), 20.4 (*C*H_2), 14.3 (*C*H_3). Elemental Analysis: Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50; N, 0.00; Found: C, 76.88; H, 11.48; N, 0.00. Enantiomer ratio (er) was determined by GC InertCap CHIRAMIX column [conditions, starting temperature: 40 °C, 1st rate of temperature increase: 3 °C/min up to 100 °C (hold 10 min), 2nd rate of temperature increase: 3 °C/min up to 120 °C (hold 15 min), 3rd rate of temperature increase: 3 °C/min up to 180 °C (hold 5 min). Rt (major) = 46.79 min, Rt (minor) = 45.78 min]. $[\alpha]_D^{22.1}$ = –73.7 (*c* 1.00, $CHCl_3$). The absolute configuration was determined by comparison of the specific optical rotation to the literature value for (*S*)-(+)-2-propylcyclohexan-1-one: $[\alpha]_D^{22.5}$ = +33.5 (*c* 1.0, $CHCl_3$).[7a]

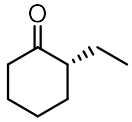
(*R*)-(–)2-Methylcyclohexan-1-one (2b).[4e]



2b

The reaction was performed according to the general procedure. The title compound was purified by silica-gel chromatography (hexane/Et_2O). 70% isolated yield (19.6 mg, 0.175 mmol, colorless oil), 89.5:10.5 er. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.37–2.16 (m, 3H), 2.07–1.93 (m, 2H), 1.81–1.70 (m, 1H), 1.67–1.50 (m, 2H), 1.29 (qd, *J* = 12.6, 3.8 Hz, 1H), 0.94 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 213.5 (*C*O), 45.3 (*C*H), 41.8 (*C*H_2), 36.2 (*C*H_2), 27.9 (*C*H_2), 25.2 (*C*H_2), 14.7 (*C*H_3). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_7H_{12}O$, 112.0883; found: 112.0847. Enantiomer ratio (er) was determined by GC with InertCap CHIRAMIX column [conditions, starting temperature: 40 °C, 1st rate of temperature increase: 3 °C/min up to 135 °C (hold 5 min). Rt (major) = 23.23 min, Rt (minor) = 23.09 min]. $[\alpha]_D^{22.8}$ = –11.0 (*c* 1.00, $CHCl_3$). The absolute configuration was established by comparison of the specific optical rotation to the literature value for (*R*)-**(–)**-2-methylcyclohexan-1-one: $[\alpha]_D^{26.2}$ = –6.2 (*c* 0.87, MeOH).[4e]

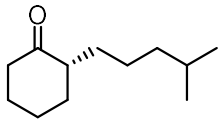
(*R*)-(–)2-Ethylcyclohexan-1-one (2c).[7a]



2c

The reaction was performed according to the general procedure. The title compound was purified by silica-gel chromatography (hexane/Et_2O). 79% isolated yield (24.9 mg, 0.197 mmol, colorless oil), 94:6 er. The ^1H and ^{13}C NMR spectra of the product were in agreement with the literature.[7a] ^1H NMR (400 MHz, $CDCl_3$): δ = 2.37–1.90 (m, 5H), 1.87–1.54 (m, 4H), 1.40–1.27 (m, 1H), 1.27–1.14 (m, 1H), 0.84 (td, *J* = 7.5, 2.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 213.5 (*C*O), 52.4 (*C*H), 42.1 (*C*H_2), 33.5 (*C*H_2), 28.1 (*C*H_2), 24.9 (*C*H_2), 22.5 (*C*H_2), 11.8 (*C*H_3). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_7H_{12}O$, 126.1039; found: 126.1043. Enantiomer ratio (er) was determined by GC with InertCap CHIRAMIX column [conditions, starting temperature: 40 °C, 1st rate of temperature increase: 3 °C/min up to 135 °C (hold 5 min). Rt (major) = 27.69 min, Rt (minor) = 27.59 min]. $[\alpha]_D^{23.0}$ = –41.4 (*c* 1.00, $CHCl_3$). The absolute configuration was established by comparison of the specific optical rotation to the literature value for (*S*)-(+)-2-ethylcyclohexan-1-one: $[\alpha]_D^{25.6}$ = +36.1 (*c* 0.5, $CHCl_3$).[7a]

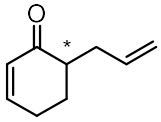
(*S*)-(–)-2-(4-Methylpentyl)cyclohexan-1-one (2d).[7a]



2d

The reaction was performed according to the general procedure. The title compound was purified by silica-gel chromatography (hexane/Et_2O). 76% isolated yield (34.6 mg, 0.19 mmol, colorless oil), 93.5:6.5 er. The ^1H and ^{13}C NMR spectra of the product were in agreement with the literature.[7a] ^1H NMR (400 MHz, $CDCl_3$): δ = 2.41–2.33 (m, 1H), 2.33–2.21 (m, 2H), 2.14–1.94 (m, 2H), 1.88–1.80 (m, 1H), 1.80–1.61 (m, 3H), 1.52 (non, *J* = 6.0 Hz, 1H), 1.43–1.32 (m, 1H), 1.30–1.08 (m, 5H), 0.85 (d, *J* = 6.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 213.8 (*C*O), 50.9 (*C*H), 42.1 (*C*H_2), 39.2 (*C*H_2), 34.0 (*C*H_2), 29.8 (*C*H_2), 28.2 (*C*H_2), 28.0 (*C*H), 25.1 (*C*H_2), 24.9 (*C*H_2), 22.8 (*C*H_3), 22.7 (*C*H_3). Elemental Analysis: Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16; N, 0.00; Found: C, 78.93; H, 11.92; N, 0.03. Enantiomer ratio (er) was determined by GC with CHIRASIL-DEX CB column [conditions, starting temperature: 60 °C (hold 10 min), 1st rate of temperature increase: 2 °C/min up to 120 °C (hold 20 min). Rt (major) = 53.10 min, Rt (minor) = 52.84 min]. $[\alpha]_D^{23.3}$ = –51.6 (*c* 1.00, $CHCl_3$). The absolute configuration was established by comparison of the specific optical rotation to the literature value for (*R*)-(+)-2-(4-methylpentyl)cyclohexan-1-one: $[\alpha]_D^{24.4}$ = +20.1 (*c* 1.0, $CHCl_3$).[7a]

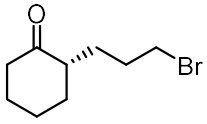
(–)-6-Allylcyclohex-2-en-1-one (2e).[7b]



2e

The reaction was performed according to the general procedure. The title compound was purified by silica-gel chromatography (hexane/Et_2O = 20/1). 89% isolated yield (30.3 mg, 0.222 mmol, colorless oil), 91.5:8.5 er. The ^1H and ^{13}C NMR spectra of the product were in agreement with the literature.[7b] ^1H NMR (400 MHz, $CDCl_3$): δ = 6.90–6.83 (m, 1H), 5.90 (dt, *J* = 10.1, 2.1 Hz, 1H), 5.76–5.63 (m, 1H), 5.02–4.93 (m, 2H), 2.58–2.49 (m, 1H), 2.39–2.22 (m, 3H), 2.11–1.98 (m, 2H), 1.70–1.58 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.7 (*C*O), 149.8 (*C*H), 136.0 (*C*H), 129.4 (*C*H), 116.7 (*C*H_2), 46.1 (*C*H), 33.6 (*C*H_2), 27.3 (*C*H_2), 25.2 (*C*H_2). Elemental Analysis: Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88; N, 0.00; Found: C, 79.13; H, 8.92; N, 0.00. Enantiomer ratio (er) was determined by HPLC with CHIRALPAK AD-H column [conditions, hexane:2-propanol = 100:1, flow rate = 0.5 mL/min, rt, Rt (major) = 30.73 min, Rt (minor) = 27.99 min]. $[\alpha]_D^{23.4}$ = –36.0 (*c* 1.00, $CHCl_3$).

(*S*)-(–)-2-(3-Bromopropyl)cyclohexan-1-one (2f).[12]

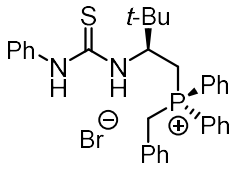


2f

The reaction was performed according to the general procedure. The title compound was purified by silica-gel chromatography (hexane/Et_2O). 98% isolated yield (53.7 mg, 0.245 mmol, pale yellow oil), 88.5:11.5 er. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.40–3.29 (m, 2H), 2.31–2.19 (m, 3H), 2.10–1.99 (m, 2H), 1.91–1.70 (m, 4H), 1.69–1.53 (m, 2H), 1.40–1.23 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.7 (*C*O), 49.9 (*C*H), 42.1 (*C*H_2), 34.1 (*C*H_2), 33.9 (*C*H_2), 30.5 (*C*H_2), 28.3 (*C*H_2), 28.0 (*C*H_2), 25.0 (*C*H_2). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_9H_{15}BrO$, 218.0301; found: 218.0307. $[\alpha]_D^{24.4}$ = –9.5 (*c* 1.00, $CHCl_3$). In order to determine the er of the product, **2f** was transformed to **2a**. The detailed procedures are described below. To the stirred solution of **2f** (21.9 mg, 0.1 mmol, 1 eq) in toluene (0.5 mL) was added *n*-Bu_3SnH (40 μL, 0.15 mmol, 1.5 eq) and AIBN (1.6 mg, 0.01 mmol, 10 mol%) followed by stirring at 110 °C for 16 h. After the substrate was completely converted, the reaction mixture was filtered through a short silica-gel column with Et_2O as an eluent. After removal of the solvent under reduced pressure, the crude products were purified by flash column chromatography (hexane/ Et_2O = 20/1) to afford **2a** (9.8 mg, 70% yield, colorless oil). Enantiomer ratio (er) of **2a** was determined by GC InertCap CHIRAMIX column [conditions, starting temperature: 40 °C, 1st rate of temperature increase: 3 °C/min up to 100 °C (hold 10 min), 2nd rate of temperature increase: 3 °C/min up to 120 °C (hold 15 min), 3rd rate of temperature increase: 3 °C/min up to 180 °C (hold 5 min). Rt (major) = 38.77 min, Rt (minor) = 38.43 min]. The absolute configuration was established by comparison of the Rt of GC analysis of **2a**.

Synthesis and Characterization of PTCs 3

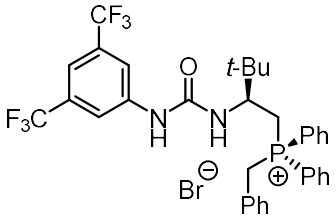
(*S*)-Benzyl[3,3-dimethyl-2-(3-phenylthioureido)butyl]diphenylphosphonium bromide (3b).



3b

To a solution of (*S*)-1-[1-(diphenylphosphaneyl)-3,3-dimethylbutan-2-yl]-3-phenylthiourea prepared according to reported procedures[8] (195.3 mg, 0.464 mmol, 1 eq) in toluene (2.8 mL) was added the benzyl bromide (75 μL, 0.631 mmol, 1.36 eq), and the mixture was stirred overnight at 110 °C. After the reactions were completed determined by TLC, the solution was cooled to room temperature and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (CH_2Cl_2/MeOH = 50/1 to 30/1). Title compound was obtained in 78% yield (213.2 mg, 0.360 mmol) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.50 (s, 1H), 9.30 (d, *J* = 10.1 Hz, 1H), 7.80–7.67 (m, 5H), 7.66–7.58 (m, 3H), 7.56–7.48 (m, 4H), 7.24–7.16 (m, 3H), 7.12 (t, *J* = 7.6 Hz, 2H), 7.04 (tt, *J* = 7.6, 1.1 Hz, 1H), 6.92 (dd, *J* = 7.3, 1.8 Hz, 2H), 5.09 (dt, *J* = 13.8, 12.0 Hz, 1H), 4.94 (t, *J* = 14.9 Hz, 1H), 4.77 (t, *J* = 14.9 Hz, 1H), 3.64 (dt, *J* = 15.1, 11.5 Hz, 1H), 2.65 (t, *J* = 14.2 Hz, 1H), 0.97 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.3 (*C*S), 139.3 (*C*), 135.1 (d, $J_{C\text{-}P}$ = 2.9 Hz, *C*H), 134.7 (d, $J_{C\text{-}P}$ = 2.9 Hz, *C*H), 133.6 (d, $J_{C\text{-}P}$ = 9.5 Hz, *C*H, 2C), 133.4 (d, $J_{C\text{-}P}$ = 9.5 Hz, *C*H, 2C), 130.5 (d, $J_{C\text{-}P}$ = 5.7 Hz, *C*H, 2C), 130.2 (d, $J_{C\text{-}P}$ = 11.4 Hz, *C*H, 2C), 130.1 (d, $J_{C\text{-}P}$ = 11.4 Hz, *C*H, 2C), 129.2 (d, $J_{C\text{-}P}$ = 2.9 Hz, *C*H, 2C), 128.6 (d, $J_{C\text{-}P}$ = 3.8 Hz, *C*H), 128.2 (*C*H, 2C), 127.2 (d, $J_{C\text{-}P}$ = 8.6 Hz, *C*), 124.7 (*C*H), 123.7 (*C*H, 2C), 118.2 (d, $J_{C\text{-}P}$ = 80.1 Hz, *C*), 117.4 (d, $J_{C\text{-}P}$ = 82.0 Hz, *C*), 55.5 (d, $J_{C\text{-}P}$ = 4.5 Hz, *C*H), 37.4 (d, $J_{C\text{-}P}$ = 11.4 Hz, *C*), 28.5 (d, $J_{C\text{-}P}$ = 43.9 Hz, *C*H_2), 26.3 (*C*H_3, 3C), 25.3 (d, $J_{C\text{-}P}$ = 50.5 Hz, *C*H_2). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 26.3. HRMS-FAB (*m/z*): $[M–Br^–]^+$ calcd for $C_{32}H_{36}N_2PS$, 511.2331; found: 511.2337. $[\alpha]_D^{24.7}$ = –71.4 (*c* 1.00, $CHCl_3$).

(*S*)-Benzyl(2-{3-[3,5-bis(trifluoromethyl)phenyl]ureido}-3,3-dimethylbutyl)diphenylphosphonium bromide (3c).

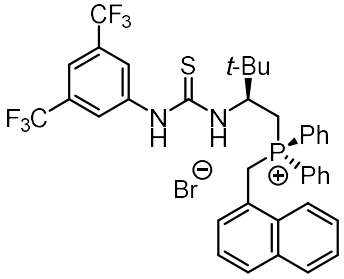


3c

To a solution of (*S*)-1-[3,5-bis(trifluoromethyl)phenyl]-3-(1-(diphenylphosphaneyl)-3,3-dimethylbutan-2-yl)urea prepared according to reported procedures[8] (162.3 mg, 0.300 mmol, 1 eq) in toluene (1.8 mL) was added the benzyl bromide (50 μL, 0.421 mmol, 1.4 eq), and the mixture was stirred for 13 h at 110 °C. After the reactions were completed determined by TLC, the solution was cooled to room temperature and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (CH_2Cl_2/MeOH = 50/1 to 30/1). Title compound was obtained in 73% yield (155.0 mg, 0.218 mmol) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.09 (s, 1H), 7.88 (d, *J* = 10.1

Hz, 1H), 7.81 (s, 2H), 7.69–7.52 (m, 8H), 7.51–7.45 (m, 2H), 7.37 (s, 1H), 7.25–7.20 (m, 1H), 7.16 (t, J = 7.6 Hz, 2H), 6.92 (dd, J = 7.5, 2.1 Hz, 2H), 4.65 (t, J = 14.7 Hz, 1H), 4.45 (t, J = 14.7 Hz, 1H), 4.11 (q, J = 2.7 Hz, 1H), 3.33 (dt, J = 15.6, 11.9 Hz, 1H), 2.75 (td, J = 14.4, 1.4 Hz, 1H), 0.97 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.2 (*C*O), 141.4 (*C*), 135.0 (d, $J_{C\text{-}P}$ = 2.9 Hz, *C*H), 134.8 (d, $J_{C\text{-}P}$ = 2.9 Hz, *C*H), 133.4 (d, $J_{C\text{-}P}$ = 6.7 Hz, *C*H, 2C), 133.3 (d, $J_{C\text{-}P}$ = 6.7 Hz, *C*H, 2C), 131.6 (q, $J_{C\text{-}F}$ = 32.7 Hz, *C*, 2C), 130.6 (d, $J_{C\text{-}P}$ = 5.7 Hz, *C*H, 2C), 130.3 (*C*H), 130.2 (*C*H, 2C), 130.1 (*C*H), 129.4 (d, $J_{C\text{-}P}$ = 2.9 Hz, *C*H, 2C), 129.0 (d, $J_{C\text{-}P}$ = 3.8 Hz, *C*H), 126.6 (d, $J_{C\text{-}P}$ = 8.6 Hz, *C*), 123.5 (q, $J_{C\text{-}F}$ = 271.4 Hz, *C*F_3, 2C), 117.99 (d, $J_{C\text{-}P}$ = 82.9 Hz, *C*), 117.95 (d, $J_{C\text{-}P}$ = 2.9 Hz, *C*H), 117.6 (d, $J_{C\text{-}P}$ = 82.9 Hz, *C*), 114.61 (d, $J_{C\text{-}P}$ = 3.8 Hz, *C*H), 114.57 (d, $J_{C\text{-}P}$ = 3.8 Hz, *C*H), 52.1 (d, $J_{C\text{-}P}$ = 4.8 Hz, *C*H), 36.7 (d, $J_{C\text{-}P}$ = 11.4 Hz, *C*), 29.6 (d, $J_{C\text{-}P}$ = 45.8 Hz, *C*H_2), 26.3 (*C*H_3, 3C), 24.1 (d, $J_{C\text{-}P}$ = 52.4 Hz, *C*H_2). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 25.0. Elemental Analysis: Calcd for $C_{34}H_{34}BrF_6N_2OP$: C, 57.39; H, 4.82; N, 3.94; Found: C, 57.52; H, 4.83; N, 3.85. $[\alpha]_D^{23.6}$ = –13.4 (*c* 1.50, $CHCl_3$).

(*S*)-(2-{3-[3,5-Bis(trifluoromethyl)phenyl]thioureido}-3,3-dimethylbutyl)(naphthalen-1-ylmethyl)diphenylphosphonium bromide (3d).

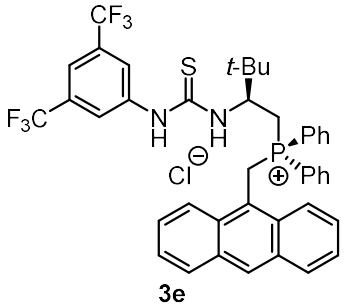


3d

To a solution of (*S*)-1-[3,5-bis(trifluoromethyl)phenyl]-3-(1-(diphenylphosphaneyl)-3,3-dimethylbutan-2-yl)thiourea prepared according to reported procedures[8] (1319 mg, 2.37 mmol, 1 eq) in toluene (15 mL) was added the 1-bromomethynaphthalene (722.3 mg, 3.27 mmol, 1.38 eq), and the mixture was stirred for 18 h at 140 °C. After the reactions were completed determined by TLC, the solution was cooled to room temperature and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (CH_2Cl_2/MeOH = 30/1 to 25/1). Title compound was obtained in 87% yield (1601.6 mg, 2.06 mmol) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.16 (s, 1H), 9.66 (d, J = 9.6 Hz, 1H), 8.15 (s, 2H), 7.80–7.65 (m, 6H), 7.52–7.40 (m, 8H), 7.37–7.27 (m, 3H), 7.18 (t, J = 8.2 Hz, 1H), 5.31–5.16 (m, 2H), 5.02 (t, J = 14.9 Hz, 1H), 3.51 (dt, J = 15.1, 11.7 Hz, 1H), 2.70 (t, J = 14.2 Hz, 1H), 0.96 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.2 (*C*S), 140.9 (*C*), 135.2 (d, $J_{C\text{-}P}$ = 2.9 Hz, *C*H), 134.7 (d, $J_{C\text{-}P}$ = 2.9 Hz, *C*H), 133.9 (d, $J_{C\text{-}P}$ = 2.9 Hz, *C*), 133.6 (d, $J_{C\text{-}P}$ = 9.5 Hz, *C*H, 2C), 133.4 (d, $J_{C\text{-}P}$ = 8.6 Hz, *C*H, 2C), 132.0 (d, $J_{C\text{-}P}$ = 4.8 Hz, *C*), 131.2 (q, $J_{C\text{-}F}$ = 33.1 Hz, *C*, 2C), 130.1 (*C*H), 130.02 (*C*H, 2C), 129.97 (*C*H), 129.91 (*C*H), 129.2 (d, $J_{C\text{-}P}$ = 6.7 Hz, *C*H), 128.9 (*C*H), 127.0 (*C*H), 126.4 (*C*H), 125.1 (d, $J_{C\text{-}P}$ = 3.8 Hz, *C*H), 123.5 (*C*H), 123.4 (q, $J_{C\text{-}F}$ = 271.1 Hz, *C*F_3, 2C), 123.0 (d, $J_{C\text{-}P}$ = 8.6 Hz, *C*), 122.4 (d, $J_{C\text{-}P}$ = 2.9 Hz, *C*H), 118.7 (d, $J_{C\text{-}P}$ = 83.0 Hz, *C*), 117.22 (d, $J_{C\text{-}P}$ = 3.8 Hz, *C*H), 117.19 (d, $J_{C\text{-}P}$ = 3.8 Hz, *C*H), 116.5 (d, $J_{C\text{-}P}$ = 82.9 Hz, *C*), 55.7 (d,

$J_{C\text{-}P}$ = 4.8 Hz, *C*H), 37.5 (d, $J_{C\text{-}P}$ = 11.4 Hz, *C*), 26.3 (*C*H$_3$, 3C), 25.5 (d, $J_{C\text{-}P}$ = 45.8 Hz, *C*H$_2$), 24.9 (d, $J_{C\text{-}P}$ = 51.5 Hz, *C*H$_2$). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 24.8. Elemental Analysis: Calcd for $C_{38}H_{36}BrF_6N_2PS$: C, 58.69; H, 4.67; N, 3.60; Found: C, 58.67; H, 4.81; N, 3.53. $[\alpha]_D^{22.4}$ = –18.6 (*c* 1.00, $CHCl_3$).

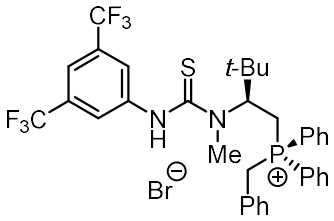
(*S*)-(Anthracen-9-ylmethyl)(2-{3-[3,5-bis(trifluoromethyl)phenyl]thioureido}-3,3-dimethylbutyl)diphenylphosphonium chloride (3e).



3e

To a solution of (*S*)-1-[3,5-bis(trifluoromethyl)phenyl]-3-(1-(diphenylphosphaneyl)-3,3-dimethylbutan-2-yl)thiourea prepared according to reported procedures[8] (89.9 mg, 0.162 mmol, 1 eq) in toluene (1.0 mL) was added the 9-chloromethyanthracene (46.1 mg, 0.203 mmol, 1.26 eq), and the mixture was stirred for 14 h at 110 °C. After the reactions were completed determined by TLC, the solution was cooled to room temperature and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (CH_2Cl_2/MeOH = 50/1 to 30/1). Title compound was obtained in 56% yield (70.1 mg, 0.0895 mmol) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.62 (s, 1H), 9.87 (d, *J* = 9.6 Hz, 1H), 8.38 (d, *J* = 3.7 Hz, 1H), 8.16 (s, 2H), 8.00 (br-s, 2H), 7.91 (d, *J* = 8.3 Hz, 2H), 7.73–7.65 (m, 2H), 7.50–7.23 (m, 9H), 7.19 (td, *J* = 8.0, 3.7 Hz, 2H), 7.10–7.02 (m, 2H), 5.70 (t, *J* = 15.1 Hz, 1H), 5.35–5.21 (m, 2H), 3.16 (dt, *J* = 15.1, 11.9 Hz, 1H), 2.56 (t, *J* = 14.0 Hz, 1H), 0.86 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.3 (*C*S), 141.1 (*C*), 134.6 (d, $J_{C\text{-}P}$ = 2.9 Hz, *C*H), 134.5 (d, $J_{C\text{-}P}$ = 1.9 Hz, *C*H), 133.8 (d, $J_{C\text{-}P}$ = 9.5 Hz, *C*H, 2C), 133.2 (d, $J_{C\text{-}P}$ = 9.5 Hz, *C*H, 2C), 131.2 (*C*, 2C), 131.0 (q, $J_{C\text{-}F}$ = 33.1 Hz, *C*, 2C), 130.9 (d, $J_{C\text{-}P}$ = 5.7 Hz, *C*, 2C), 129.8 (d, $J_{C\text{-}P}$ = 12.4 Hz, *C*H, 2C), 129.50 (d, $J_{C\text{-}P}$ = 9.5 Hz, *C*H, 2C), 129.46 (*C*H, 2C), 127.1 (*C*H, 2C), 125.4 (*C*H, 2C), 123.8 (*C*H, 2C), 123.4 (q, $J_{C\text{-}F}$ = 271.1 Hz, *C*F$_3$, 2C), 122.14 (d, $J_{C\text{-}P}$ = 2.9 Hz, *C*H, 2C), 119.3 (d, $J_{C\text{-}P}$ = 82.0 Hz, *C*), 117.9 (d, $J_{C\text{-}P}$ = 10.5 Hz, *C*), 116.78 (d, $J_{C\text{-}P}$ = 2.9 Hz, *C*H), 116.75 (d, $J_{C\text{-}P}$ = 3.8 Hz, *C*H), 116.0 (d, $J_{C\text{-}P}$ = 82.0 Hz, *C*), 55.9 (d, $J_{C\text{-}P}$ = 4.8 Hz, *C*H), 37.3 (d, $J_{C\text{-}P}$ = 11.5 Hz, *C*), 26.2 (*C*H$_3$, 3C), 25.7 (d, $J_{C\text{-}P}$ = 49.6 Hz, *C*H$_2$), 23.2 (d, $J_{C\text{-}P}$ = 54.4 Hz, *C*H$_2$). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 24.6. HRMS-FAB (*m/z*): $[M–Cl^–]^+$ calcd for $C_{42}H_{38}F_6N_2PS$, 747.2398; found: 747.2392. $[\alpha]_D^{22.8}$ = –32.3 (*c* 1.00, $CHCl_3$).

(*S*)-Benzyl(2-{3-[3,5-bis(trifluoromethyl)phenyl]-1-methylthioureido}-3,3-dimethylbutyl)diphenylphosphonium (3g).



3g

To a solution of (*S*)-3-[3,5-bis(trifluoromethyl)phenyl]-1-[1-(diphenylphosphaneyl)-3,3-dimethylbutan-2-yl]-1-methylthiourea prepared according to reported procedures[8] (105.4 mg, 0.185 mmol, 1 eq) in toluene (1.0 mL) was added the benzyl bromide (30 μL, 0.253 mmol, 1.37 eq), and the mixture was stirred for 16 h at 110 °C. After the reactions were completed determined by TLC, the solution was cooled to room temperature and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (CH_2Cl_2/MeOH = 50/1 to 10/1). The title compound was obtained in 85% yield (117.3 mg, 0.158 mmol) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.13 (s, 1H), 8.05–7.92 (m, 6H), 7.71 (t, *J* = 7.6 Hz, 2H), 7.58–7.48 (m, 5H), 7.27–7.21 (m, 1H), 7.16 (t, *J* = 7.6 Hz, 2H), 7.01 (d, *J* = 7.3 Hz, 2H), 6.30 (t, *J* = 11.9 Hz, 1H), 5.13 (t, *J* = 14.9 Hz, 1H), 4.95 (q, *J* = 13.3 Hz, 1H), 4.48 (t, *J* = 14.9 Hz, 1H), 3.05 (s, 3H), 2.66 (t, *J* = 15.1 Hz, 1H), 0.98 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.2 (*C*S), 141.6 (*C*), 135.0 (d, $J_{C\text{-}P}$ = 2.9 Hz, *C*H), 134.9 (d, $J_{C\text{-}P}$ = 2.9 Hz, *C*H), 133.7 (d, $J_{C\text{-}P}$ = 9.5 Hz, *C*H, 2C), 133.5 (d, $J_{C\text{-}P}$ = 9.5 Hz, *C*H, 2C), 130.7 (q, $J_{C\text{-}F}$ = 33.1 Hz, *C*, 2C), 130.4 (d, $J_{C\text{-}P}$ = 5.7 Hz, *C*H, 2C), 129.8 (d, $J_{C\text{-}P}$ = 12.4 Hz, *C*H, 2C), 129.6 (d, $J_{C\text{-}P}$ = 12.4 Hz, *C*H, 2C), 129.2 (d, $J_{C\text{-}P}$ = 1.9 Hz, *C*H, 2C), 128.9 (d, $J_{C\text{-}P}$ = 2.9 Hz, *C*H), 127.2 (*C*H, 2C), 127.1 (*C*), 123.5 (q, $J_{C\text{-}F}$ = 271.1 Hz, *C*F_3, 2C), 119.0 (d, $J_{C\text{-}P}$ = 86.8 Hz, *C*), 118.6 (*C*H), 118.0 (d, $J_{C\text{-}P}$ = 82.0 Hz, *C*), 61.2 (d, $J_{C\text{-}P}$ = 4.8 Hz, *C*H), 38.9 (d, $J_{C\text{-}P}$ = 12.4 Hz, *C*), 36.8 (*C*H_3), 30.2 (d, $J_{C\text{-}P}$ = 46.7 Hz, *C*H_2), 27.8 (*C*H_3, 3C), 19.4 (d, $J_{C\text{-}P}$ = 50.5 Hz, *C*H_2). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 23.5. Elemental Analysis: Calcd for $C_{35}H_{36}BrF_6N_2PS$: C, 56.69; H, 4.89; N, 3.78; Found: C, 56.84; H, 4.88; N, 3.50. $[\alpha]_D^{22.7}$ = –166.7 (*c* 1.00, $CHCl_3$).

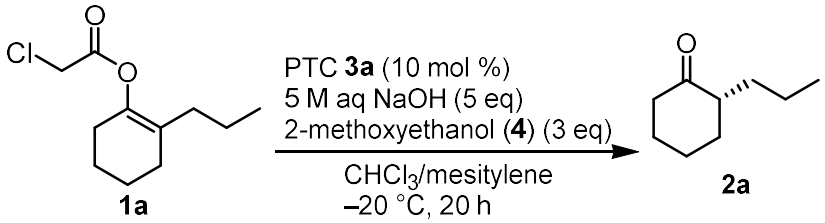
Enantioselective Protonation of 1a on 1 mmol Scale

PTC **3d** (77.8 mg, 0.1 mmol, 10 mol%) and 2-methoxyethanol (240 μL, 3 eq) were added to the $CHCl_3$/mesitylene (1 mL/1 mL) solution followed by the addition of 5 M aq NaOH (1 mL, 5 eq) under air. After stirred at –20 °C for 10 min, enol ester **1a** (216.7 mg, 1.0 mmol, 1 eq) was added and the resultant solution was further stirred for 20 h at –20 °C. The reaction mixture was filtered through a short silica-gel column with Et_2O as an eluent. After removal of the solvent under reduced pressure, the crude products were purified by flash column chromatography (hexane/ Et_2O = 20/1) to afford **3a** (104.5 mg, 75% yield, colorless oil), 97:3 er. Er was determined by GC InertCap CHIRAMIX column [conditions, starting temperature: 40 °C, 1st rate of temperature increase: 3 °C/min up to 100 °C (hold

10 min), 2nd rate of temperature increase: 3 °C/min up to 120 °C (hold 15 min), 3rd rate of temperature increase: 3 °C/min up to 180 °C (hold 5 min). Rt (major) = 38.59 min, Rt (minor) = 38.46 min].

Mechanistic Experiments

Non-Linear Effect Study (Scheme 6)

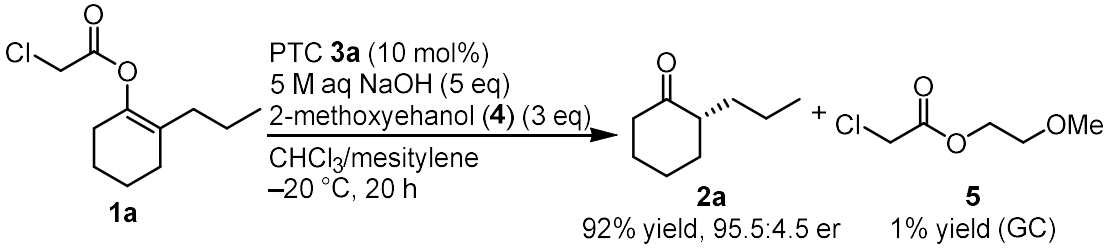


entry	ee of PTC **3a** (%)	yield (%)	ee of product (%)
1	80	95	70
2	60	70	59
3	40	96	41
4	20	91	21

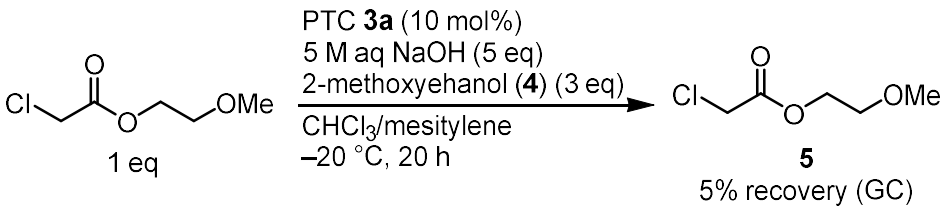
PTC **3a** (80–20% ee, 0.01 mmol, 10 mol%) and 2-methoxyethanol (24 μL, 3 eq) were added to the $CHCl_3$/mesitylene (200 μL/200 μL) solution followed by the addition of 5 M aq NaOH (100 μL, 5 eq) under air. **1a** (0.1 mmol) was added and the resultant solution was further stirred for 20 h at –20 °C. After that, the reaction mixture was filtered through a short silica-gel column with Et_2O as an eluent. The yield and enantiomeric excess (ee) of product **2a** was determined by GC analysis.

Investigation of the Role of Alcohol Additives (Scheme 7)

(a) Formation of 2-methoxyethyl chloroacetate **5**



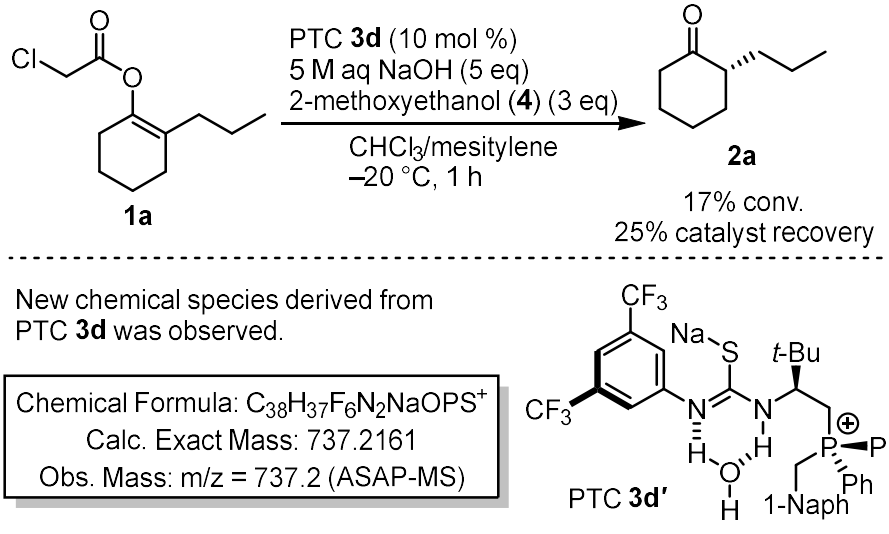
(b) Decomposition of 2-methoxyethyl chloroacetate **5** under the reaction conditons



PTC **3a** (0.01 mmol, 10 mol%) and 2-methoxyethanol (24 μL, 3 eq) were added to the $CHCl_3$/mesitylene (200 μL/200 μL) solution followed by the addition of 5 M aq NaOH (200 μL, 5 eq) under air. Enol ester **1a** (0.1 mmol) was added and the resultant solution was further stirred for 20 h at –20 °C. After that, the reaction mixture was filtered through a short silica-gel column with Et_2O as an eluent. The resultant solution was analyzed by GC. (b) PTC **3a** (0.025 mmol, 10 mol%) and 2-methoxyethanol (60 μL, 3 eq) were added to the $CHCl_3$/mesitylene (250 μL/250 μL) solution followed by the addition of 5 M aq NaOH (250 μL, 5 eq) under air. 2-Methoxyethyl chloroacetate (0.25 mmol, 1 eq) was added and the resultant solution was further stirred for 1 h at –20 °C. After that, the reaction mixture was filtered through a short silica-gel column with Et_2O as an eluent. The GC analysis showed that 5% of 2-methoxyethyl chloroacetate was recovered after 1 h.

^{31}P NMR and MS Analyses of the Reaction Mixture (Scheme 8)

PTC **3d** (0.025 mmol, 10 mol%) and 2-methoxyethanol (60 μL, 3 eq) were added to the $CHCl_3$/mesitylene (250 μL/250 μL) solution followed by the addition of 5 M aq NaOH (250 μL, 5 eq) under air. **1a** (0.25 mmol) was added and the resultant solution was further stirred for 1 h at –20 °C. After that, the reaction mixture was extracted with $CHCl_3$ (1 mL × 3). The organic extracts were combined and dried with Na_2SO_4 and concentrated by evaporation. Then, the crude mixture was analyzed by ^{31}P NMR and Atmospheric Pressure Solid Analysis Probe MS (ASAP-MS). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 28.2, 25.6, 25.0, 19.9, 9.3. ASAP-MS (*m/z*): calcd for $C_{38}H_{37}F_6N_2NaOPS^+$, 737.2161; found: 737.2. After the analyses, crude mixtures were purified by flash column chromatography to afford the substrate **1a** (45.1 mg, 83% recovery) and PTC **3d** (4.9 mg, 25% recovery).



4.5 References

[1] Poisson, T.; Kobayashi, S. *Asymmetric Protonation of Carbanions and Polar Double Bonds: Application to Total Syntheses* in *Stereoselective Synthesis of Drugs and Natural Products*, 1st ed.; Andrushko, V.; Andrushko, N. Eds.; Wiley: Hoboken, NJ, U.S.A.; 2013; vol. 2; pp 961–992.

[2] (a) Fehr, C. *Angew*. *Chem*. *Int*. *Ed*. **1996**, *35*, 2566; (b) Eames, J., Weerasooriya, N. *Tetrahedron Asymmetry* **2001**, *12*, 1. (c) Duhamel, L., Duhamel, P., Plaquevent, J. C. *Tetrahedron Asymmetry* **2004**, *15*, 3653. (d) Mohr, J. T.; Hong, A. Y.; Stoltz, B. M. *Nat. Chem.* **2009**, *1*, 359–369. (c) Oudeyer, S.; Brière, J.-F.; Levacher, V. *Eur. J. Org. Chem.* **2014**, 6103–6119.

[3] (a) Sugiura, M.; Nakai, T. *Angew. Chem. Int. Ed.* **1997**, *36*, 2366–2368. (b) Poisson, T.; Dalla, V.; Marsais, F.; Dupas, G.; Oudeyer, S.; Levacher, V. *Angew. Chem. Int. Ed.* **2007**, *46*, 7090–7093. (c) Poisson, T.; Oudeyer, S.; Dalla, V.; Marsais, F.; Levacher, V. *Synlett* **2008**, 2447–2450. (d) Morita, M.; Drouin, L.; Motoki, R.; Kimura, Y.; Fujimori, I.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 3858–3859. (c) Uraguchi, D.; Kinoshita, N.; Ooi, T. *J. Am. Chem. Soc.* **2010**, *132*, 12240–12242. (f) Beck, E. M.; Hyde, A. M.; Jacobsen, E. N. *Org. Lett.* **2011**, *13*, 4260–4263. (g) Claraz, A.; Landelle, G.; Oudeyer, S.; Levacher, V. *Eur. J. Org. Chem.* **2013**, *2013*, 7693–7696. (h) Paladhi, S.; Liu, Y.; Kumar, B. S.; Jung, M.-J.; Park, S. Y.; Yan, H.; Song, C. E. *Org. Lett.* **2017**, *19*, 3279–3282.

[4] (a) Marckwald, W. *Ber*. *Dtsch*. *Chem*. *Ges*. **1904**, *37*, 349–354. (b) Brunner, H.; Kurzwart, M. *Monatsh*. *Chem*. **1992**, *123*, 121–128. (c) Brunner, H.; Schmidt, P. *Eur*. *J*. *Org*. *Chem*. **2000**, *2000*, 2119–2133. (d) Rogers, L. M.-A.; Rouden, J.; Lecomte, L.; Lasne, M.-C. *Tetrahedron Lett*. **2003**, *44*, 3047–3050. (c) Mohr, J. T.; Nishimata, T.; Behenna, D. C.; Stoltz, B. M. *J*. *Am*. *Chem*. *Soc*. **2006**, *128*, 11348–11349. (f) Blanchet, J.; Baudoux, J.; Amere, M.; Lasne, M. C.; Rouden, J. *Eur*. *J*. *Org*. *Chem*. **2008**, *2008*, 5493–5506. (g) Nakamura, S. *Org*. *Biomol*. *Chem*. **2014**, *12*, 394–405.

[5] (a) Gall, M.; House, H. O. *Org*. *Synth*. **2003**, *52*, 39. (b) Matsumoto, K.; Tsutsumi, S.; Ihori, T.; Ohta, H. *J*. *Am*. *Chem*. *Soc*. **1990**, *112*, 9614–9619. (c) Isambert, N.; Cruz, M.; Arévalo, M. J.; Gómez, E.; Lavilla, R. *Org*. *Lett*. **2007**, *9*, 4199–4202. (d) Liu, J.; Mishra, S.; Aponick, A. *J*. *Am*. *Chem*. *Soc*. **2018**, *140*, 16152–16158.

[6] Claraz, A.; Leroy, J.; Oudeyer, S.; Levacher, V. *J*. *Org*. *Chem*. **2011**, *76*, 6457–6463.

[7] (a) Yamamoto, E.; Nagai, A.; Hamasaki, A.; Tokunaga, M. *Chem. Eur. J.* **2011**, *17*, 7178–7182. (b) Yamamoto, E.; Gokuden, D.; Nagai, A.; Kamachi, T.; Yoshizawa, K.; Hamasaki, A.; Ishida, T.; Tokunaga, M. *Org. Lett.* **2012**, *14*, 6178–6181.

[8] (a) Cao, D.; Chai, Z.; Zhang, J.; Ye, Z.; Xiao, H.; Wang, H.; Chen, J.; Wu, X.; Zhao, G. *Chem. Commun.* **2013**, *49*, 5972–5974. (b) Wu, X.; Liu, Q.; Liu, Y.; Wang, Q.; Zhang, Y.; Chen, J.; Cao, W.; Zhao, G. *Adv. Synth. Catal.* **2013**, *355*, 2701–2706. (c) Cao, D.; Zhang, J.; Wang, H.; Zhao, G. *Chem. Eur. J.* **2015**, *21*, 9998–10002. (d) Wang, H.; Wang, K.; Ren, Y.; Li, N.; Tang, B.; Zhao, G. *Adv. Synth. Catal.* **2017**, *359*, 1819–1824. (c) Ji, X.; Cao, W. G.; Zhao, G. *Tetrahedron* **2017**, *73*, 5983–5992.

[9] Stritzke, K.; Schulz, S.; Laatsch, H.; Helmke, E.; Beil, W. *J. Nat. Prod.* **2004**, *67*, 395–401.

[10] (a) Jones, C. R.; Pantoş, G. D.; Morrison, A. J.; Smith, M. D. *Angew. Chem. Int. Ed.* **2009**, *48*, 7391–7394. (b) Probst, N.; Madarász, Á.; Valkonen, A.; Pápai, I.; Rissanen, K.; Neuvonen, A.; Pihko, P. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 8495–8499. (c) Kennedy, C. R.; Lehnherr, D.; Rajapaksa, N. S.; Ford, D. D.; Park, Y.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2016**, *138*, 13525–13528. (d) Bécart, D.; Diemer, V.; Salaün, A.; Oiarbide, M.; Nelli, Y. R.; Kauffmann, B.; Fischer, L.; Palomo, C.; Guichard, G. *J. Am. Chem. Soc.* **2017**, *139*, 12524–12532. (c) Park, Y.; Harper, K. C.; Kuhl, N.; Kwan, E. E.; Liu, R. Y.; Jacobsen, E. N. *Science* **2017**, *355*, 162–166.

[11] Perrin, D. D.; Armarego, W. L. F.; Purification of Laboratory Chemicals; 3rd ed., Pergamon Press, Oxford, 1988.

[12] Crandall, J. K.; Magaha, H. S.; Henderson, M. A.; Widener, R. K.; Tharp, G. A. *J. Org. Chem.* **1982**, *47*, 5372–5380.

Concluding Remarks

In this thesis, three phase-transfer catalytic asymmetric transformations of esters using a water and alcohols as a nucleophile were developed.

In chapter 2, an asymmetric base-hydrolysis of N-protected amino acid esters using *cinchona* alkaloid derived quaternary ammonium salts as phase-transfer catalysts was performed. The reaction proceeded via dynamic kinetic resolution process, providing the desired hydrolyzed products in moderate to good yields with good to high er. Furthermore, the author carried out detailed experimental studies to reveal the racemization mechanism, and found that the HFIP esters are racemized via formation of azlactone. Computational studies using ConFinder conformational search and DFT calculations elucidated the essential non-covalent interactions between the substrate and the catalyst.

In the third section, a DKR-type asymmetric alcoholysis of azlactones using PTCs affording a wide variety of corresponding amino acid esters in up to 98% yield and up to 99:1 er is described. A gram-scale reaction and transformations of the enantioenriched products involving hydrogenolysis, LAH-reduction, deprotection of a benzoyl group, and Suzuki–Miyaura coupling reactions were successfully achieved. A PTC loading of only 0.1 mol% was able to catalyze this reaction without significant loss of stereoselectivity, and a high turnover number was achieved. Detailed computational studies using a pseudo-TS conformational search with ConFinder and DFT calculations elucidated the essential non-covalent interactions between the substrate and the catalyst.

In chapter 4, an enantioselective protonation reaction of enol esters using phosphonium/thiourea bifunctional catalysts was developed. This catalytic system delivered enantioenriched α-chiral ketones with good to high er values. The author conducted several experimental mechanistic investigations, suggesting the roles of the alcohol additive and the phosphonium and thiourea moieties in the catalysts.

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List of Publications

[1] Yamamoto, E.; Wakafuji, K.; Furutachi, Y.; Kobayashi, K.; Kamachi, T.; Tokunaga, M. Dynamic Kinetic Resolution of N-Protected Amino Acid Esters via Phase-Transfer Catalytic Base Hydrolysis. *ACS Catal.* **2018**, *8*, 5708–5713.

[2] Yamamoto, E.; Wakafuji, K.; Mori, Y.; Teshima, G.; Hidani, Y.; Tokunaga, M. Enantioselective Protonation of Enol Esters with Bifunctional Phosphonium/Thiourea Catalysts. *Org. Lett.* **2019**, *21*, 4030–4034.

[3] Wakafuji, K.; Iwasa, S.; Ouchida, K. N.; Cho, H.; Dohi, H.; Yamamoto, E.; Kamachi, T.; Tokunaga, M. Dynamic Kinetic Resolution of Azlactones via Phase-Transfer Catalytic Alcoholysis. *ACS Catal.* **2021**, *11*, 14067–14075.