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Direct Asymmetric Amination of α-Branched Cyclic Ketones Catalyzed by a Chiral Phosphoric Acid

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Abstract

Here we report the direct asymmetric amination of α-substituted cyclic ketones catalyzed by a chiral phosphoric acid, yielding products with a N-containing quaternary stereocenter in high yields and excellent enantioselectivities. Kinetic resolution of the starting ketone was also found to occur on some of the substrates under milder conditions, providing enantio-enriched α-branched ketones, another important building block in organic synthesis. The utility of this methodology was demonstrated in the short synthesis of (*S*)-ketamine, the more active enantiomer of this versatile pharmaceutical.

α-Amino cyclic ketones with a N-containing quaternary stereocenter are important building blocks in organic synthesis and versatile precursors to physiologically active compounds such as ketamine[1] and tiletamine (Figure 1a).[2] Additionally, β-amino alcohols, which are derivatives of α-amino cyclic ketones, are widely used as chiral ligands in asymmetric catalysis.[3] The past decade has witnessed the development of direct asymmetric α-amination of carbonyl compounds as a useful method for the preparation of chiral amine-containing structures.[4] Despite these advances, the majority of reported reactions rely on activated carbonyl compounds, such as 1,3-dicarbonyls, 2-oxindoles, α-cyanoacetates, and other reactive substrates.[4,5] For carbonyl compounds with lower reactivity, enamine catalysis has been employed in the highly enantioselective amination of aldehydes[6,7] and ketones[8] without substitution at the α-position.[9] Alternatively, chiral α-amino ketones have been accessed via asymmetric amination of preactivated unsubstituted ketone equivalents, such as silyl enol ethers,[10] metal enolates,[11] and enamides.[12] Terada's chiral organosuperbase-catalyzed amination of 2-alkyl-substituted cyclic aromatic ketones (Figure 1c)[13] and Yamamoto's silver-catalyzed amination of the tin enolate of 2-phenylcyclohexanone (Figure 1b)[11b] stand as rare example of enantioselective amination to produce N-containing quaternary stereocenters.

Recently, our group reported the asymmetric fluorination of α-branched cyclic ketones enabled by a combination of chiral anion phase-transfer catalysis and enamine catalysis,[14] a

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The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

Experimental details and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

rare example of asymmetric functionalization of α-branched cyclic ketones to construct chiral quaternary stereocenters.[15] Continuing our interest in the asymmetric functionalization of α-branched cyclic ketones, here we report the direct asymmetric amination of α-branched cyclic ketones with azodicarboxylates catalyzed by a chiral phosphoric acid.[16]

We selected 2-phenylcyclohexanone as a model substrate and di-*tert*-butyl azodicarboxylate as the nitrogen source, which is widely used in asymmetric amination processes (Table 1). Reaction of these two components, catalyzed by (*S*)-TRIP (10 mol%) in xylenes (0.1 M) at 45 °C for 60 h, produced a minor amount of the desired product; substantial starting ketone remained unreacted (entry 1). Other chiral phosphoric acids (TCYP, H_8-TCYP, and C_8-TCYP) were also tested, and after reaction for 60 h at 45 °C, the highest enantioselectivity (97% ee) was generated with (*R*)-C_8-TCYP as catalyst, albeit with low conversion (38% yield, entry 4). In an attempt to improve the conversion, the reaction mixture was heated at 60 °C for 60 h; a higher yield of the product was isolated (57% yield), but with a decrease in enantioselectivity (91% ee, entry 5). A less sterically demanding electrophile, diethyl azodicarboxylate, was also employed in this reaction, providing a higher yield (60%) but a similar decrease in enantioselectivity (89% ee, entry 6). Utilizing a higher concentration (0.4 M) at 45 °C improved the conversion (52% yield) after 60 h with unchanged enantio-selectivity (entry 7). Finally, we found that running the reaction under “neat” conditions (via removal of the small amount of DCM after all the reagents were dissolved) gave almost full conversion after 60 h, and the desired product was obtained in 97% yield with 99% ee (entry 8).[17] Surprisingly, the regioselectivity of this reaction was excellent; no 6-amination or 2,6-diamination products were isolated.

With the optimized conditions in hand, we explored the substrate scope of the reaction (Table 2). A range of substituted aryl groups[18] were tolerated at the α-position of cyclohexanone, including electron-neutral, electron-donating, and electron-withdrawing arenes (**2b–2h**). Surprisingly, substrates with ortho substitution (**2i**, **2j**), which were previously reported to be unsuitable for enantioselective construction of quaternary centers due to steric hindrance,[14,15c] also worked well. Additionally, the cyclopentanone analogue (**2k**) gave the desired amination product in high yield and with excellent enantio-selectivity. Substrates bearing heteroatoms at the 4-position of the cyclohexanone ring (**2l**, **2m**) were also amenable to enantioselective amination, extending this methodology to potentially useful heterocyclic compounds.

Cyclic ketone substrates containing alkenyl substitution at the α-position were also explored (Table 3).[19] The reaction proceeded well with several types of substrates, including *trans*-1,2 (**2n**), *cis*-1,2 (**2p**, **2q**), cyclic alkenyl (**2r**), and simple vinyl substitution (**2o**). Substitution at the 4-positon of the cyclo-hexanone ring also gave high yield and excellent enantio-selectivity for products **2s** and **2t**. A cyclopentanone analogue yielded product **2v**, whose absolute (*S*)-configuration was determined by X-ray crystallography. Seven-membered analogue **2u** formed slowly under the conditions and was obtained with lower enantioselectivity (72% ee). α-Phenylethynyl-substituted **1w** gave the product with lower yield (33% yield, 93% ee) due to some decomposition of substrate under the standard conditions. Surprisingly, 2-methylcyclohexanone (**1x**) also exclusively yielded the more

substituted addition product, albeit with a slightly diminished enantioselectivity (86% ee). Increasing the size of the alkyl substituent (**1y**) furnished the adduct with high enantioselectivity (99% ee).

Initially, we envisioned a mechanism in which the phosphoric acid only mediated the enantioselective amination of the enol form of the ketone. Given that the chiral center of the starting ketone is destroyed in the keto/enol tautomerization, it seemed likely that this reaction was a simple dynamic kinetic asymmetric transformation; however, careful monitoring of the reaction showed that, in some cases, the reaction rate slowed when the conversion reached >50%. Therefore, milder reaction conditions (e.g., room temperature and lower concentration of 0.1 or 1 M) resulted in a good to excellent kinetic resolution of the starting ketones (Table 4).[20] For example, using ketone **1z**, the desired product was obtained in 55% yield with 93% ee, and the ketone was recovered in 45% yield with 96% ee after 60 h stirring at rt (*s*-factor of 32).[21] *trans*-Styrene-substituted substrates **1n** and **1t** also gave good to excellent kinetic resolution, affording the recovered ketones with 99% ee and 97% ee, respectively. This method provides an entry to chiral α-heteroaryl- and alkenyl-substituted cyclic ketones, which are very useful building blocks in organic synthesis but difficult to prepare enantiomerically enriched.[22]

On the basis of these observations, we propose that, in addition to mediating the enantioselective amination, the phosphoric acid also catalyzes the enantioselective activation (enolization) of chiral ketones.[23] While phosphoric acid protonation of carbonyl groups is a well-established mode of activation toward nucleophilic addition,[24] enolization has rarely been considered. These observations suggest that it is possible to achieve the kinetic resolution of the ketone substrates with phosphoric acid catalysts, provided the rate of the electrophilic addition (amination) step is faster than that of the enolization process.

Derivatization of the enantioenriched amination products was also investigated (Scheme 1). Deprotection of Boc groups with TFA, followed by cleavage of the hydrazine bond using Raney Ni and H_2, afforded the β-amino alcohol, which was then protected to afford benzamide **3a** in 64% yield, preserving the enantio-purity, over three steps. To further demonstrate the utility of this method, a short synthetic route to (*S*)-ketamine was developed. Ketamine, which is on the World Health Organization's List of Essential Medicines, is a drug with multiple applications, including for general anesthesia, as a pain killer, and for treatment of bronchospasm and bipolar depression.[1] Normally pharmaceutical preparations of ketamine are racemic, although reports indicate that (*S*)-ketamine is 4 times more active than its (*R*) isomer.[25] Recently, commercial preparations obtain (*S*)-ketamine via resolution of the tartaric acid salt, leaving the undesired (*R*) isomer as the byproduct. To our knowledge, only one asymmetric synthesis of (*S*)-ketamine, requiring nine steps, has been reported.[26] After deprotection of the Boc of **2j**, cleavage of the hydrazine bond with Zn/HOAc furnished norketamine (**4j**) in 74% yield; monomethylation under reductive amination conditions provided the (*S*)-ketamine in 52% yield with >99% ee.

In summary, we have developed a chiral phosphoric acid-catalyzed asymmetric amination of α-substituted cyclic ketones which generates a N-containing quaternary stereocenter. The reaction tolerates a range of aryl, alkenyl, alkynyl, and alkyl substitutions at the α-position,

different ring sizes, and modifications of the cyclohexanone ring. Kinetic resolution of the starting ketone was observed for some substrates under milder conditions, providing enantioenriched α-branched ketones. A short synthetic route to enantioenriched (*S*)-ketamine was developed starting with amination product **2j**, demonstrating the power of this methodology. More encouragingly, using similar conditions, a highly enantioselective Mannich reaction of α-branched cyclic ketone was also achieved, creating an all-carbon quaternary center, which would broaden the application of this strategy.[27]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Ketamine is included as a general medicine in the 14th WHO model list of essential medicines: WHO Expert Committee on Drug Dependence. Critical review of ketamine, ECDD 34th report, WHO Technical Report Series 942, 2006.
2. Klockgether T, Turski L, Schwarz M, Sontag K-H, Lehmann J. Brain Res. 1988; 461:343. [PubMed: 2846121]
3. (a) Ager DJ, Prakash I, Schaad DR. Chem Rev. 1996; 96:835. [PubMed: 11848773] (b) Ianni JC, Annamalai V, Phuan PW, Panda M, Kozlowski MC. Angew Chem, Int Ed. 2006; 45:5502.
4. For reviews of asymmetric amination of carbonyl compounds, see: Vallribera A, Sebastián RM, Shafir A. Curr Org Chem. 2011; 15:2539.Vilaivan T, Bhanthumnavin W. Molecules. 2010; 15:917. [PubMed: 20335955] Smith AMR, Hii KK. Chem Rev. 2010; 111:1637. [PubMed: 20954710] Zhou F, Liao F-M, Yu J-S, Zhou J. Synthesis. 2014:2983.
5. (a) Xu C, Zhang L, Luo S. Angew Chem, Int Ed. 2014; 53:4149.(b) Zhang T, Cheng L, Liu L, Wang D, Chen YJ. Tetrahedron: Asymmetry. 2010; 21:2800.(c) Terada M, Amagai K, Ando K, Kwon E, Ube H. Chem—Eur J. 2011; 17:9037. [PubMed: 21751266] (d) Zhou F, Ding M, Liu YL, Wang CH, Ji CB, Zhang YY, Zhou J. Adv Syn Catal. 2011; 353:2945.(e) Yang Z, Wang Z, Bai S, Liu X, Lin L, Feng X. Org Lett. 2011; 13:596. [PubMed: 21214254] (f) Nelson HM, Patel JS, Shunatona HP, Toste FD. Chem Sci. 2015; 6:170. [PubMed: 25485073]
6. (a) Bøgevig A, Juhl K, Kumaragurubaran N, Zhuang W, Jørgensen KA. Angew Chem, Int Ed. 2002; 41:1790.(b) List B. J Am Chem Soc. 2002; 124:5656. [PubMed: 12010036]
7. (a) Vogt H, Vanderheiden S, Bräse S. Chem Commun. 2003:2448.(b) Baumann T, Vogt H, Bräse S. Eur J Org Chem. 2007:266.(c) Desmarchelier A, Yalgin H, Coeffard V, Moreau X, Greck C. Tetrahedron Lett. 2011; 52:4430.(d) Theodorou A, Papadopoulos GN, Kokotos CG. Tetrahedron. 2013; 69:5438.(e) Fu JY, Yang QC, Wang QL, Ming JN, Wang FY, Xu XY, Wang LX. J Org Chem. 2011; 76:4661. [PubMed: 21517112]
8. (a) Kumaragurubaran N, Juhl K, Zhuang W, Bøgevig A, Jørgensen KA. J Am Chem Soc. 2002; 124:6254. [PubMed: 12033850] (b) Liu TY, Cui HL, Zhang Y, Jiang K, Du W, He ZQ, Chen YC. Org Lett. 2007; 9:3671. [PubMed: 17691800] (c) Hayashi Y, Aratake S, Imai Y, Hibino K, Chen QY, Yamaguchi J, Uchimaru T. Chem—Asian J. 2008; 3:225. [PubMed: 18165948]
9. Only ketones with no α-substitution gave high enantioselectivities in the α-hydrazonation with α-diazoesters catalyzed by an *N*,*N*′-dioxide–scandium complex: Li W, Liu X, Hao X, Hu X, Chu Y, Cao W, Qin S, Hu C, Lin L, Feng X. J Am Chem Soc. 2011; 133:15268. [PubMed: 21882861]

10. (a) Evans DA, Johnson DS. Org Lett. 1999; 1:595. [PubMed: 10823188] (b) Yamashita Y, Ishitani H, Kobayashi S. Can J Chem. 2000; 78:666.(c) Liang JL, Yu XQ, Che CM. Chem Commun. 2002:124.(d) Mizar P, Wirth T. Angew Chem, Int Ed. 2014; 53:5993.
11. Yanagisawa A, Miyake R, Yoshida K. Org Biomol Chem. 2014; 12:1935. [PubMed: 24526286] Silver-catalyzed amination of the tin enolate of 2-phenyl cyclohexanone gave the aminated product in 77% ee: Momiyama N, Yamamoto H. J Am Chem Soc. 2004; 126:5360. [PubMed: 15113198]
12. (a) Chang L, Kuang Y, Qin B, Zhou X, Liu X, Lin L, Feng X. Org Lett. 2010; 12:2214. [PubMed: 20402479] (b) Drouet F, Lalli C, Liu H, Masson G, Zhu J. Org Lett. 2011; 13:94. [PubMed: 21121643]
13. Takeda T, Terada M. J Am Chem Soc. 2013; 135:15306. [PubMed: 24074350]
14. Yang X, Phipps RJ, Toste FD. J Am Chem Soc. 2014; 136:5225. [PubMed: 24684209]
15. (a) Dong XQ, Teng HL, Tong MC, Huang H, Tao HY, Wang CJ. Chem Commun. 2010; 46:6840. (b) Kang JY, Carter RG. Org Lett. 2012; 14:3178. [PubMed: 22668200] (c) Kano T, Hayashi Y, Maruoka K. J Am Chem Soc. 2013; 135:7134. [PubMed: 23634801]
16. For chiral phosphoric acid-catalyzed asymmetric aminations, see: Zhang Z, Antilla JC. Angew Chem, Int Ed. 2012; 51:11778.Wang SG, Yin Q, Zhuo C-X, You SL. Angew Chem, Int Ed. 2015; 54:647.For chiral phosphoric acid-catalyzed asymmetric transformation of unactivated ketones, see: Pousse G, Le Cavelier F, Humphreys L, Rouden J, Blanchet J. Org Lett. 2010; 12:3582. [PubMed: 20704398] Felker I, Pupo G, Kraft P, List B. Angew Chem, Int Ed. 2015; 54:1960.
17. A larger scale (2.0 mmol) asymmetric amination of **1a** gave the desired product in 96% yield and 99% ee, with recovery of 35% of the catalyst (see Supporting Information).
18. Several heteroarylketones were unstable to the reactions conditions. For example, subjecting compound **1z** to the standard conditions led to partial decomposition of the starting material and therefore low yield of the desired product. On the other hand, **1z** showed excellent kinetic resolution under milder conditions.
19. Under the standard conditions, α-tetralone gave the amination product in low yield and enantioselectivity (7% yield, 36% ee), and acyclic ketones failed to give the desired product.
20. For examples of kinetic resolution of α-substituted ketones, see: Zhou L, Liu X, Ji J, Zhang Y, Hu X, Lin L, Feng X. J Am Chem Soc. 2012; 134:17023. [PubMed: 23020516] Reetz MT, Wu S. J Am Chem Soc. 2009; 131:15424. [PubMed: 19807086] Kim H, Kawasaki H, Nakajima M, Koga K. Tetrahedron Lett. 1989; 30:6537.
21. Kagan HB, Fiaud JC. Top Stereochem. 1988; 18:249. The s factor was calculated on the basis of the ee of the recovered starting material.
22. (a) Enders D, Whitehouse DL. Synthesis. 1996:621.(b) Huang Z, Lim LH, Chen Z, Li Y, Zhou F, Su H, Zhou J. Angew Chem, Int Ed. 2013; 52:4906.
23. The enantioselective enolization can be viewed as the microscopic reverse of the catalytic enantioselective protonation: Cheon CH, Yamamoto H. J Am Chem Soc. 2008; 130:9246. [PubMed: 18582053]
24. Rueping M, Kuenkel A, Atodiresei I. Chem Soc Rev. 2011; 40:4539. [PubMed: 21614342]
25. Adams HA, Werner C. Anaesthesist. 1997; 46:1026. [PubMed: 9451486]
26. Yokoyama R, Matsumoto S, Nomura S, Higaki T, Yokoyama T, Kiyooka S. Tetrahedron. 2009; 65:5181.
27. Mannich reaction of **1n** and *N*-Boc benzaldimine gave the product in 72% yield, >25:1 dr, and 96% ee (see Supporting Information).

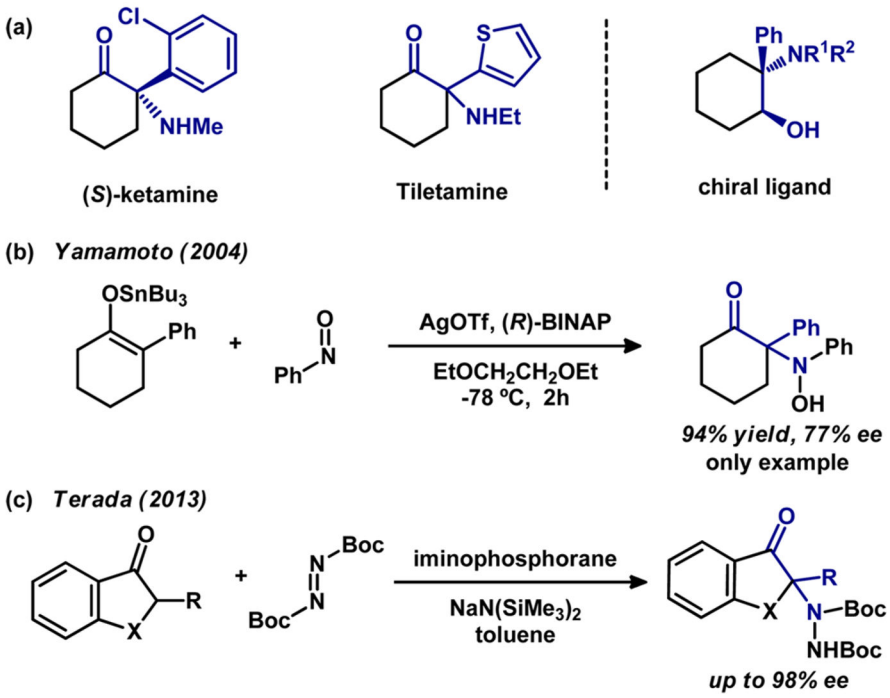
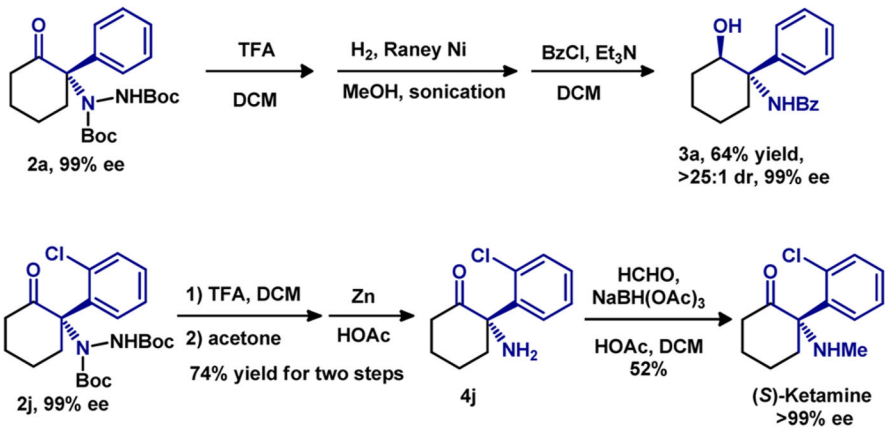


Figure 1.

Previous work on the catalytic asymmetric synthesis of 2-aminocyclohexanone bearing a quaternary stereocenter.



Scheme 1.

Further Transformations of the α-Amino Ketone Products and Facile Synthesis of (*S*)-Ketamine

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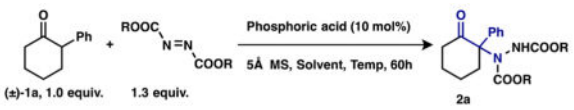
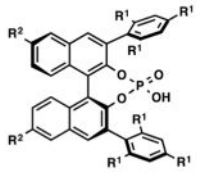
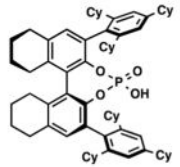
Table 1

Investigation of Asymmetric Amination of 2-Phenylcyclohexanone Catalyzed by Chiral Phosphoric Acids





TRIP, R^1= iPr, R^2= H;
TCYP, R^1= Cy, R^2= H;
C_8-TCYP, R^1= Cy, R^2= nC_8H_{17};



H_8-TCYP

entry	R	phosphoric acid	temp (°C)	solvent	conc (M)	conv (%)[a]	ee (%)[b]
1	*t*Bu	(*S*)-TRIP	45	xylenes	0.1	18 (18)	−88
2	*t*Bu	(*R*)-TCYP	45	xylenes	0.1	31 (31)	96
3	*t*Bu	(*R*)-H_8-TCYP	45	xylenes	0.1	26 (25)	97
4	*t*Bu	(*R*)-C_8-TCYP	45	xylenes	0.1	39 (38)	97
5	*t*Bu	(*R*)-C_8-TCYP	60	xylenes	0.1	70 (57)	91
6	Et	(*R*)-C_8-TCYP	45	xylenes	0.1	68 (60)	89
7	*t*Bu	(*R*)-C_8-TCYP	45	xylenes	0.4	53 (52)	97
8[c]	*t*Bu	(*R*)-C_8-TCYP	45	–	neat	97	99

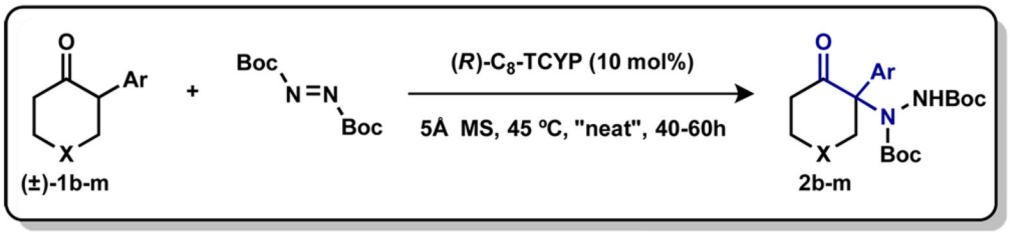
[a] Conversions calculated based on isolated yield of recovered starting material. Number in parentheses is isolated yields after chromatography.

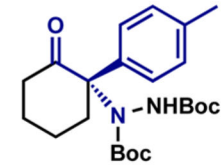
[b] Determined by chiral HPLC analysis of isolated products.

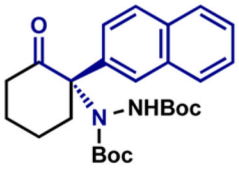
[c] Reagents were dissolved in DCM; after removal of the solvent, the mixture was heated at 45 °C for 60 h. In the absence of 5 Å MS, **2a** was formed in 87% yield and 99% ee.

Table 2

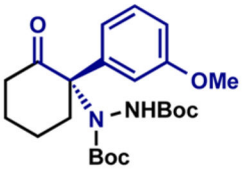
Substrate Scope of the Asymmetric Amination of 2-Aryl Cyclic Ketones[a]

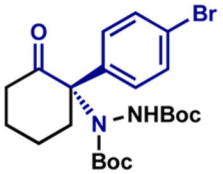


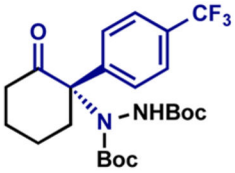

2b, 97% yield, 99% ee

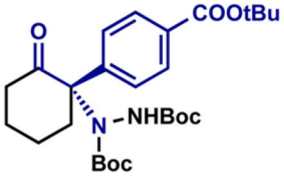

2c, 90% yield, 97% ee

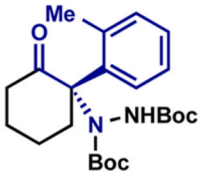

2d, 80% yield, 98% ee

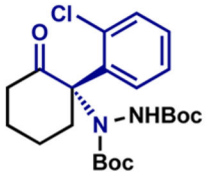

2e, 88% yield, 98% ee

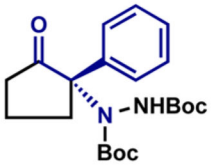

2f, 94% yield, 98% ee

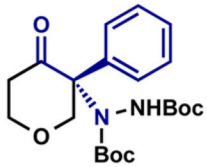

2g, 71% yield, 98% ee

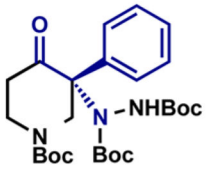

2h, 76% yield, 97% ee


2i, 93% yield, 99% ee


2j, 78% yield, 99% ee


2k, 92% yield, >95% ee

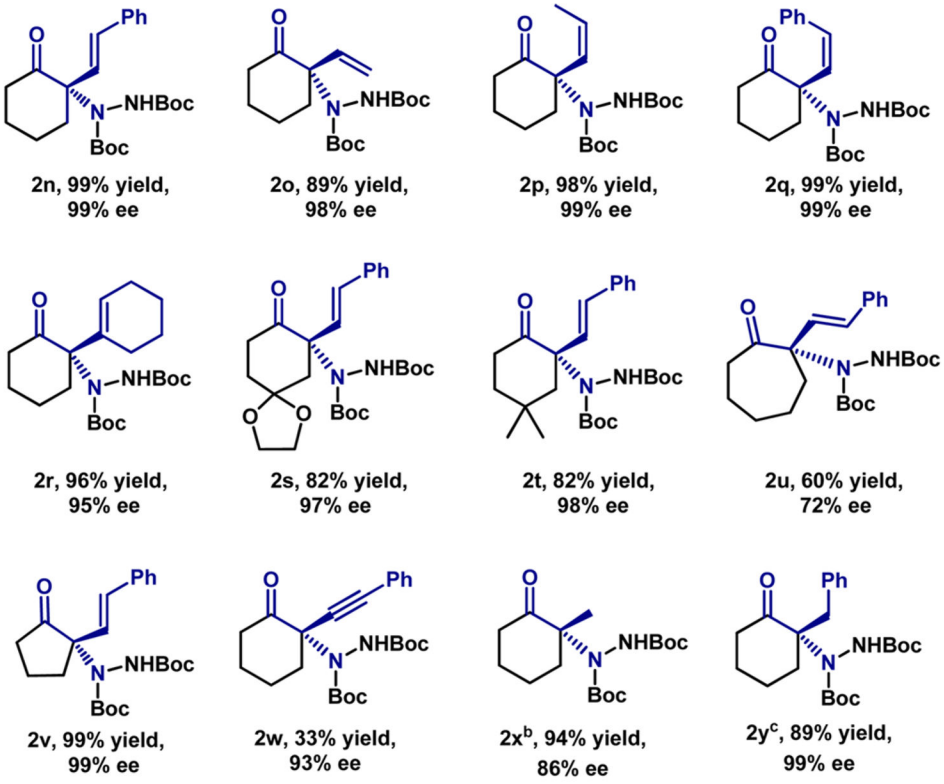

2l, 97% yield, 99% ee


2m, 79% yield, 96% ee

[a]Reactions were carried out with ketone (0.3 mmol), BocN=NBoc (0.39 mmol), (*R*)-C8-TCYP (0.03 mmol), and 5 Å MS (50 mg) in DCM (0.3 mL). After removal of the solvent, the mixture was heated at 45 °C for 40–60 h. Yields are isolated yields after chromatography. Absolute configurations assigned by analogy with **2v** (determined by X-ray crystallography) and (*S*)-ketimine.

Table 3

Substrate Scope of the Asymmetric Amination of 2-Substituted Cyclic Ketones[a]



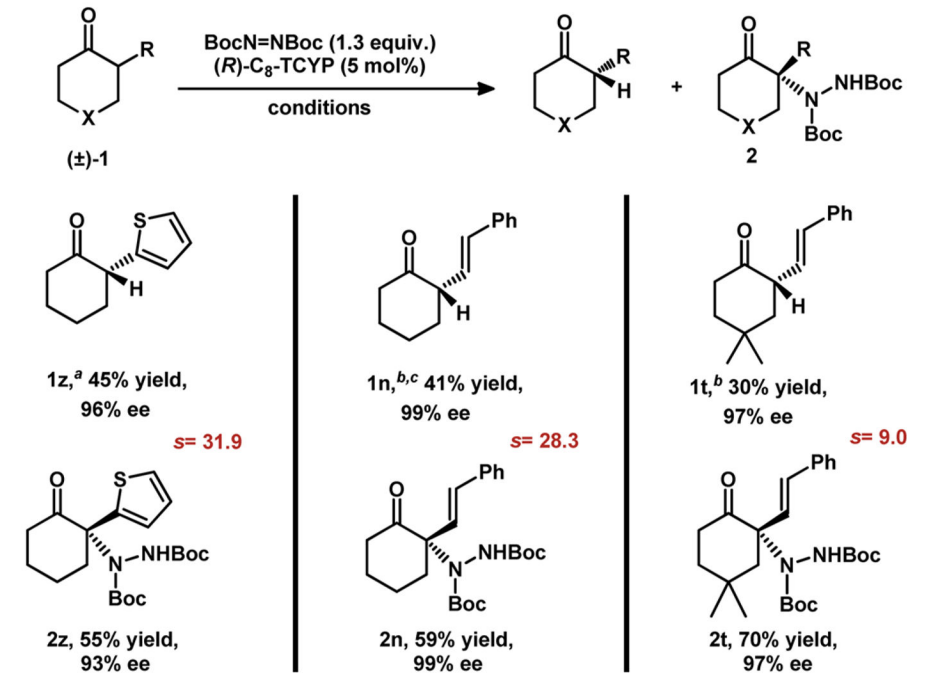
[a] Conditions as indicated in Table 2, except 5 mol% (*R*)-C8-TCYP was used.

[b] ee was determined after conversion to the benzamide derivative (see Supporting Information).

[c] 10% catalyst was used.

Table 4

Substrate Scope of Kinetic Resolution and Asymmetric Amination of *α*-Branched Cyclic Ketones



[a]Reactions were carried out with ketone (0.3 mmol), BocN=NBoc (0.39 mmol), (*R*)-C8-TCYP (0.03 mmol), and 5 Å MS (50 mg) in DCM (0.3 mL) for 60 h at rt.

[b]Conditions as indicated as above except 5 mol% (*R*)-C8-TCYP and DCM (3 mL) were used for 40 h at rt.

[c]Absolute configurations of recovered ketones was assigned by comparison of optical rotation of hydrogenated **1n** with the literature (see Supporting Information).