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Catalytic Asymmetric α-Amination of α-Branched Ketones via Enol Catalysis

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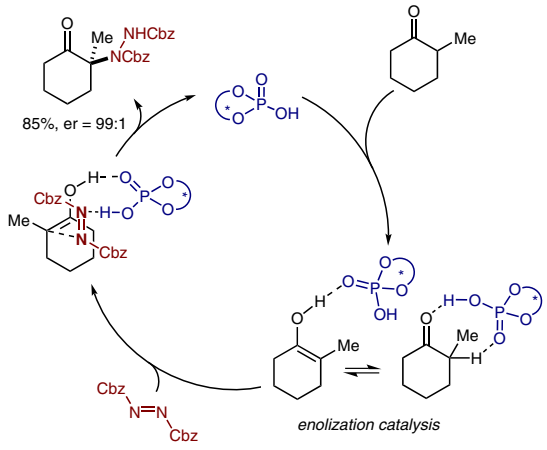

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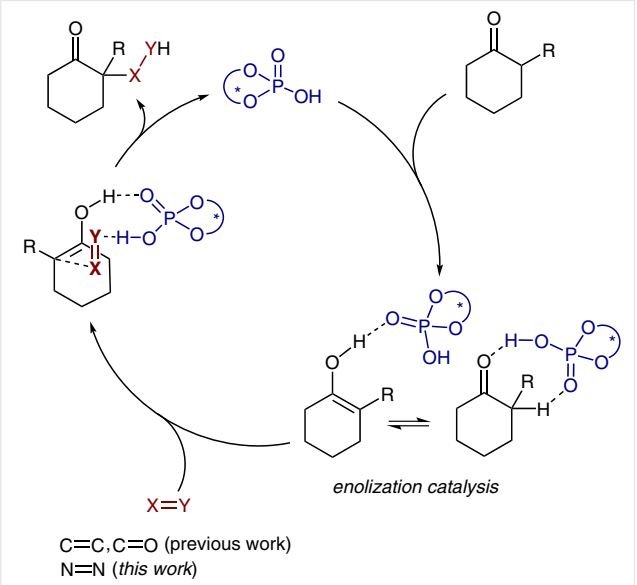
Abstract We report a highly enantioselective α-amination of α-branched ketones catalyzed by a chiral phosphoric acid employing azodicarboxylates as reagents. The desired products were obtained in good to excellent yields and enantioselectivities.

Key words asymmetric synthesis, Brønsted acid catalysis, electrophilic amination, α-branched ketones, enol catalysis, azodicarboxylates

Enantiomerically pure α-amino ketones and α-amino alcohols are important substructures of natural products and pharmaceuticals.[1] For example, ketamine is used as an anesthetic and currently under investigation for the treatment of depression.[2] Recent studies revealed that its (*S*)-isomer is four times more active than its enantiomer, making new asymmetric methodologies for the synthesis of ketamine even more relevant.[3] Recently, catalytic asymmetric electrophilic amination reactions of carbonyl compounds have been developed. The reported protocols employ azodicarboxylates, *N*-hydroxycarbamates, and nitrosobenzene as amination reagents.[4] Several activation modes have successfully been applied and typically take advantage of highly reactive starting materials, such as β-keto esters, α-cyano carbonyls, α-fluorinated ketones, nitroacetates, or oxindoles.[4,5] The direct amination of unactivated carbonyl compounds has been successfully achieved with both aldehydes and ketones by enamine catalysis.[6] However, when α-branched ketones are employed, chiral amine catalysts give poor results because of the sterically constrained enamine intermediate. Furthermore, aminocatalysis preferentially forms the kinetic enamine, thus restricting access to valuable enantioenriched ketones bearing a quaternary stereocenter. One of the rare examples which afford these compounds from unactivated α-alkyl ketones was reported by Terada and co-workers by employing tetralone derivatives as substrates and a chiral organosuperbase as catalyst.[7]

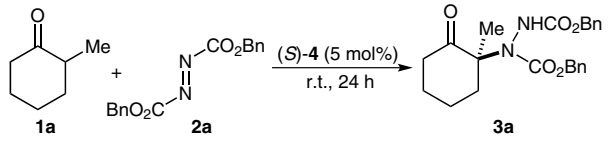
Recently, our group proposed a solution to this limitation of aminocatalysis by shifting to enol catalysis with the development of a chiral phosphoric acid catalyzed asymmetric Michael reaction of α-branched ketones with enones.[8] This approach directly suggests the use of various other electrophiles (X=Y; Scheme 1). Brønsted acid catalyzed α-aminations of aromatic nucleophiles have been reported but, the direct amination of α-branched ketones has been completely unknown.[9,10] Here, we report a chiral phosphoric acid catalyzed α-amination of α-branched cyclic ketones using azodicarboxylates as the electrophilic nitrogen source.[11]

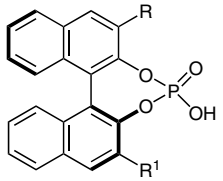
We began our studies by employing 2-methyl cyclohexanone (**1a**) as the model substrate and dibenzyl azodicarboxylate (DBAD; **2a**) as the electrophile (Table 1). When (*S*)-TRIP (**4a**) was used as catalyst, **3a** was obtained in excellent enantioselectivity; however. only poor conversion was observed (Table 1, entry 1). After screening several phosphoric acids bearing different substituents in the 3,3′-positions, catalyst **4c** proved to be superior, in terms of both reactivity and selectivity (Table 1, entry 3). Switching the solvent from dichloromethane to acetonitrile and raising the concentration of the substrate to 1 M led to a slight increase of the enantiomeric ratio and a beneficial effect on the conversion (Table 1, entry 4). The optimized reaction conditions, found by further increasing the concentration to 2 M and decreasing the amount of **2a** to 1.2 equivalents, afforded the desired product **3a** in 85% isolated yield and an enan-



Scheme 1 Proposed catalytic cycle for the α-functionalization of ketones by enol catalysis

Table 1 Optimization of the Brønsted Acid Catalyzed α-Amination of α-Branched Ketones[a]

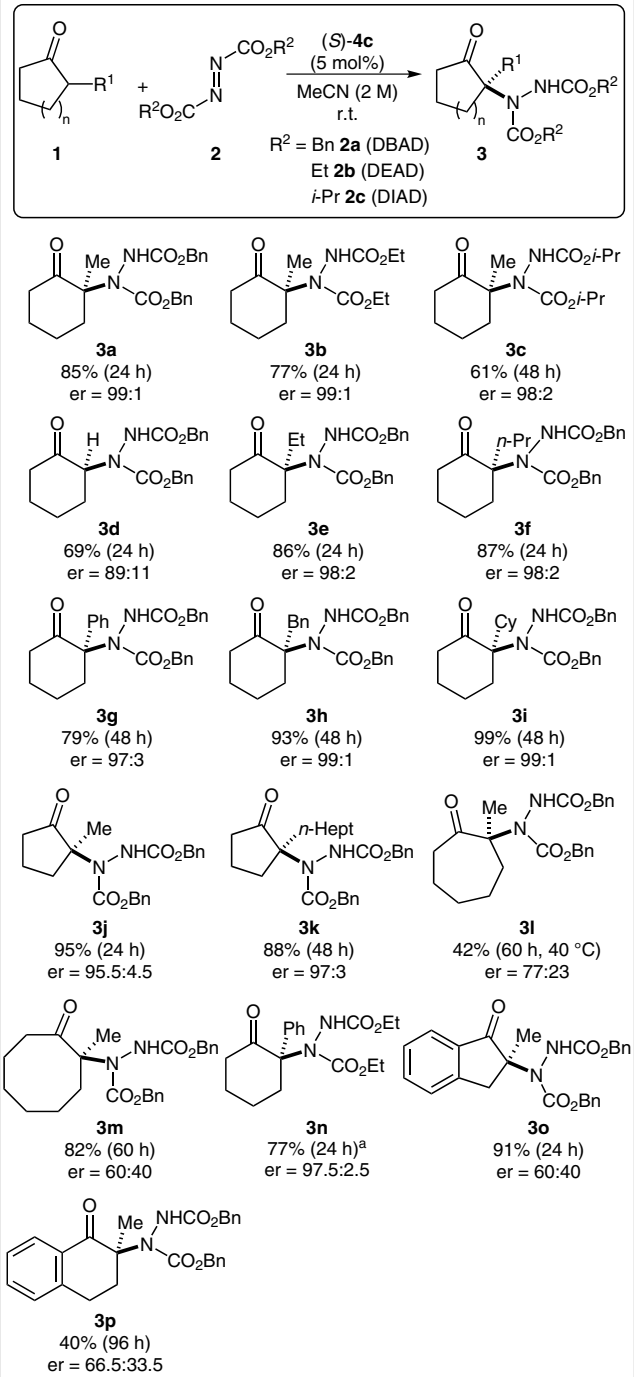




R = 2,4,6-*i*-Pr$_3$C$_5$H$_2$ (**4a**)
2,4,6-Cy$_3$C$_5$H$_2$ (**4b**)
9-anthracenyl (**4c**)

Entry	Catalyst	Solvent	Conversion[b]	er[c]
1	**4a**	CH_2Cl_2 (0.5 M)	21%	94:6
2	**4b**	CH_2Cl_2 (0.5 M)	39%	93:7
3	**4c**	CH_2Cl_2 (0.5 M)	96%	98:2
4	**4c**	MeCN (1.0 M)	93%	98.5:1.5
5[d,e]	**4c**	MeCN (2.0 M)	(85%)	99:1

[a] Reaction conditions: **1a** (0.05 mmol), **2** (0.1 mmol), **4** (5 mol%), solvent (0.1 mL), r.t., 24 h.
[b] Determined by ^{1}H NMR using triphenylmethane as an internal standard, with isolated yield given in parentheses.
[c] Determined by HPLC on a chiral stationary phase.
[e] Amount of **2** used was 0.06 mmol.
[f] Reaction was carried out on a 0.2-mmol scale.



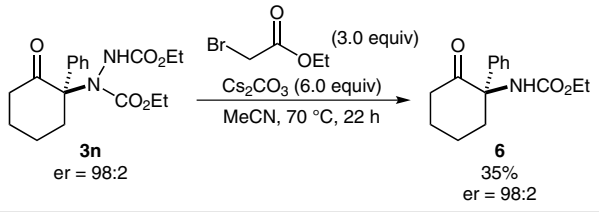
Scheme 2 Substrate scope of the Brønsted acid catalyzed asymmetric α-amination of α-branched ketones. Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), **4c** (5 mol%), MeCN (0.1 mL), r.t. or 40 °C, 24–60 h.
[a] Reaction was carried out on a 1.0 mmol scale.

tiomeric ratio of 99:1 (Table 1, entry 5). Interestingly, decreasing the catalyst loading to 1 mol% had no influence on enantioselectivity, but lower conversions were obtained. When neat conditions were employed, a strong increase of

reactivity was observed, albeit the enantioselectivity was diminished (for the full optimization, see the Supporting Information).

With the optimal reaction conditions in hand, we focused our attention on the scope of the Brønsted acid catalyzed α-amination of α-branched ketones (Scheme 2). The reaction proved to be rather general; in addition to DBAD (**2a**), DEAD (**2b**) and DIAD (**2c**) could also be used as electrophilic aminating reagents, giving the corresponding α-hydrazino ketones in moderate to good yields and excellent enantioselectivities (**3a**–**c** in Scheme 2). To our delight, a large variety of substituents in the 2-position were tolerated under the reaction conditions, affording in all cases the desired products in good yields and excellent enantioselectivities (**3d–i**). Interestingly, when cyclohexanone itself was used as a starting material, the monoaminated product **3d** was obtained, and no racemization occurred under the reaction conditions, further supporting the generality of enol catalysis. 2-Alkyl-substituted cyclopentanones also reacted smoothly (**3j**,**k**). When the ring size of the cyclic ketones was increased, a lower reactivities and enantioselectivities were observed, presumably due to a slow and hindered enolization (**3l**,**m**). The scalability of the reaction was proven by reacting 2-phenylcyclohexanone (**1c**) and DEAD (**2b**) on a 1.0 mmol scale to give product **3n** in 77% yield and an enantiomeric ratio of 97.5:2.5. 1-Indanone- and 1-tetralone-derived substrates represent a current limitation of the methodology as only low reactivity and enantioselectivity were observed (**3o** and **3p**). The absolute configuration of the products was assigned based on known compound **3d**.[12]

To further prove the utility of our transformation, preliminary attempts to cleave the N–N bond by employing a slightly modified literature procedure[13] afforded the desired product **6** in 35% yield and without any loss of enantiopurity (Scheme 3).



Scheme 3 Application of the Brønsted acid catalyzed α-amination of α-branched ketones to the synthesis of carbamate-protected α-amino ketones

In summary, we have developed an asymmetric α-amination of α-branched cyclic ketones by enol catalysis.[14] Employing a chiral phosphoric acid as the catalyst and various azodicarboxylates, the desired carbamate-protected cyclic α-hydrazino ketones were obtained in good to excellent yields (40–99%) and enantioselectivities (enantiomeric ratios from 60:40 to 99:1). The feasibility of the N–N bond cleavage under mild redox neutral conditions was also proven. The current protocol expands the scope of enol catalysis, thus further opening new reaction pathways in asymmetric catalysis.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380680.

References and Notes

(1) (a) Carrol, F. I.; Blough, B. E.; Abraham, P.; Mills, A. C.; Holleman, J. A.; Wolchenhauer, S. A.; Decker, A. M.; Landavazo, A. K.; McElroy, T.; Navarro, H. A.; Gatch, M. B.; Forster, M. *J. Med. Chem.* **2009**, *52*, 6768. (b) Tapping, K. G. Eur. Patent EP0686629A3, **1999**. (c) Teall, M. R. US Patent US5627211, **1997**. (d) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835. (e) Klinger, F. D. *Acc. Chem. Res.* **2007**, *40*, 1367.

(2) (a) Ketamine is part of the 18th WHO model list of essential medicines. More information can be found on the website of the WHO: http://www.who.int (b) Reardon, S. *Nature (London)* **2015**, *517*, 130. (c) Morgan, C. J. A.; Curran, H. V. *Addiction* **2011**, *107*, 27. (d) Blonk, M. I.; Koder, B. G.; van den Bemt, P. M. L. A.; Huygen, F. J. P. M. *Eur. J. Pain* **2010**, *14*, 466.

(3) (a) Adams, H. A.; Werner, C. *Der Anaesthesist* **1997**, *46*, 1026. (b) Hempelmann, G.; Kuhn, D. F. M. *Der Anaesthesist* **1997**, *46*, S3.

(4) For recent reviews on catalytic asymmetric aminations of carbonyl compounds, see: (a) Janey, J. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4292. (b) Vilaivan, T.; Bhanthumnavin, W. *Molecules* **2010**, *15*, 917. (c) Smith, A. M. R.; Hii, K. K. *Chem. Rev.* **2011**, *111*, 1637. (d) Zhou, F.; Liao, F.-M.; Yu, J.-S.; Zhou, J. *Synthesis* **2014**, *46*, 2983.

(5) (a) Saaby, S.; Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120. (b) Xu, X.; Yabuta, T.; Yuan, P.; Takemoto, Y. *Synlett* **2006**, 137. (c) Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, *128*, 16044. (d) He, R.; Wang, X.; Hashimoto, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 9466. (e) Terada, M.; Tsushima, D.; Nakano, N. *Adv. Synth. Catal.* **2009**, *351*, 2817. (f) Han, X.; Zhong, F.; Lu, Y. *Adv. Synth. Catal.* **2010**, *352*, 2778. (g) Xu, C.; Zhang, L.; Luo, S. *Angew. Chem. Int. Ed.* **2014**, *53*, 4149. (h) Xu, C.; Zhang, L.; Luo, S. *J. Org. Chem.* **2014**, *79*, 11517. (i) Nelson, H. M.; Patel, J. S.; Shunatona, H. P.; Toste, F. D. *Chem. Sci.* **2015**, *6*, 170.

(6) (a) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656. (b) Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1790. (c) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254. (d) Vogt, H.; Vanderheiden, S.; Bräse, S. *Chem. Commun.* **2003**, 2448. (e) Hartmann, C.; Baumann, T.; Bächle, M.; Bräse, S. *Tetrahedron: Asymmetry* **2010**, *21*, 1341. (f) Fu, J.-Y.; Yang, Q.-C.; Wang, Q.-L.; Ming, J.-N.; Wang, F.-Y.; Xu, H.-Y.; Wang, L.-X. *J. Org. Chem.* **2011**, *76*, 4661. (g) Desmarchelier,

A.; Yalgin, H.; Coeffard, V.; Moreau, X.; Greck, X. *Tetrahedron Lett.* **2011**, *52*, 4430. (h) Liu, C.; Zhu, Q.; Huang, K.-W.; Lu, Y. *Org. Lett.* **2011**, *13*, 2638.

(7) Takeda, T.; Terada, M. *J. Am. Chem. Soc.* **2013**, *135*, 15306.

(8) Felker, I.; Pupo, G.; Kraft, P.; List, B. *Angew. Chem. Int. Ed.* **2015**, *54*, 1960.

(9) For Brønsted acid catalyzed asymmetric aminations of indoles and naphthols, see: (a) Zhang, Z.; Antilla, J. C. *Angew. Chem. Int. Ed.* **2012**, *51*, 11778. (b) Wang, S.-G.; Yin, Q.; Zhou, C.-X.; You, S.-L. *Angew. Chem. Int. Ed.* **2015**, *54*, 647.

(10) For Brønsted acid catalyzed asymmetric aldol reactions of β-keto esters, see: (a) Akiyama, T.; Katoh, T.; Mori, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 4226. (b) Yamakana, M.; Hoshino, M.; Katoh, T.; Mori, K.; Akiyama, T. *Eur. J. Org. Chem.* **2012**, *2012*, 4508. For Brønsted acid catalyzed asymmetric α-functionalization of unactivated ketones via enolization, see: (c) Guo, Q.-X.; Liu, H.; Guo, C.; Luo, S.-W.; Gu, Y.; Gong, L.-Z. *J. Am. Chem. Soc.* **2007**, *129*, 3790. (d) Pousse, G.; Le Cavalier, F.; Humphreys, L.; Rouden, J.; Blanchet, J. *Org. Lett.* **2010**, *12*, 3582.

(11) During the preparation of this manuscript the Toste group independently published a very similar approach for the synthesis of enantioenriched α-branched α-amino ketones. See: Yang, X.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3205.

(12) (a) Beattie, C.; North, M. *Molecules* **2011**, *16*, 3420. (b) Msutu, A.; Hunter, R. *Tetrahedron Lett.* **2014**, *55*, 2295.

(13) (a) Magnus, P.; Garizi, N.; Seibert, K.; Ornholt, A. *Org. Lett.* **2009**, *11*, 5646. (b) Magnus, P.; Brozell, A. *Org. Lett.* **2012**, *14*, 3952.

(14) **Representative Procedure**: To a solution of the catalyst (*S*)-**4c** (7.0 mg, 0.01 mmol, 5 mol%) and the ketone **1b** (24.3 µL, 0.2 mmol) in MeCN (0.1 mL) azodicarboxylate **2a** (74.6 mg, 96%, 0.24 mmol) was added and the resulting mixture was stirred at r.t. for 24 h. The crude reaction mixture was directly purified by silica gel column chromatography (CH_2Cl_2–MTBE = 0% to 5%) giving **3a** (69.6 mg, 85%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.01–7.42 (m, 10 H), 6.44–6.82 (m, 1 H), 4.79–5.19 (m, 4 H), 1.08–2.74 (m, 11 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.1, 156.7, 155.8, 135.6, 135.5, 128.6, 128.5, 128.4, 128.3, 128.1, 70.7, 69.7, 68.6, 68.4, 68.0, 67.8, 39.6, 39.0, 38.3, 29.7, 29.2, 26.5, 21.8, 21.8, 21.0, 19.8. HRMS (ESI, +ve): *m*/*z* [M + Na] calcd for $C_{23}H_{26}N_2NaO_5$: 433.1734; found: 433.1732. HPLC (Chiralcel OJ-3R, MeCN–H_2O = 50:50, flow rate: 1.0 mL/min, λ = 220 nm): $t_{R(major)}$ = 15.2 min, $t_{R(minor)}$ = 12.2 min.