Communication

Catalytic Asymmetric Synthesis of Chiral #-Amino Ketones via Umpolung Reactions of Imines

Lin Hu, Yongwei Wu, Zhe Li, and Li Deng

J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 22 Nov 2016

Catalytic Asymmetric Synthesis of Chiral γ-Amino Ketones via Umpolung Reactions of Imines

Lin Hu,† Yongwei Wu,† Zhe Li, and Li Deng*

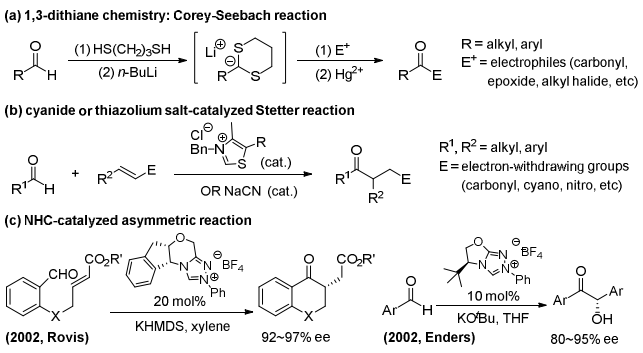
Department of Chemistry, Brandeis University, Waltham, Massachusetts 02454-9110, United States

Supporting Information Placeholder

ABSTRACT: The first direct catalytic asymmetric synthesis of γ-amino ketones was realized by the development of a highly diastereoselective and enantioselective C-C bond-forming umpolung reaction of imines and enones under the catalysis of a new cinchona alkaloid-derived phase-transfer catalyst. In a loading ranging from 0.02 to 2.5 mol%, the catalyst activates a broad range of trifluoromethyl imines and aldimines as nucleophiles to engage in chemo-, regio-, diastereo- and enantio-selective C-C bond-forming reactions with acyclic and cyclic enones, thereby converting these readily available prochiral starting materials into highly enantiomerically enriched chiral γ-amino ketones in synthetically useful yields. Enabled by this unprecedented umpolung reaction of imines, conceptually new and concise routes were developed for the asymmetric synthesis of nitrogen-heterocycles such as pyrrolidines and indolizidines.

The successful development of carbonyl umpolung reactions over the last forty years has greatly expanded the repertoire of organic synthesis.[1] For example, C-C bond-forming reactions with 1,3-dithianes [1a-c] and hydrazones [1d] as acyl anion equivalents have been widely used in natural product synthesis, although extra steps are required to implement these umpolung reactions (Scheme 1, a). An attractive strategy to implement carbonyl umpolung reactions is exemplified by the Stetter reaction,[1d] in which a catalyst activates a carbonyl compound directly as an acyl nucleophile for a C-C bond-forming reaction with an electrophile (Scheme 1, b). More recently, the power of carbonyl umpolung reactions was tapped for catalytic asymmetric synthesis through the discovery and development of efficient chiral NHC-carbene catalysts for enantioselective Stetter reactions and numerous other asymmetric reactions (Scheme 1, c).[2] In principle, the development of imine umpolung reactions should also provide an attractive strategy for the development of C-C bond-forming reactions of distinctive bond disconnections, thereby establishing strategically new approaches for the synthesis of nitrogen-containing compounds. In spite of such potential importance to organic synthesis, imine umpolung reactions remain underdeveloped in terms of not only the establishment of synthetically important transformations but also the development of general strategies for umpolung activation of imines.[3,4] We wish to describe here the development of effective new chiral catalysts to enable the realization of an unprecedented asymmetric umpolung reaction of imines for the direct and highly enantioselective generation of chiral γ-amino ketones from imines.

Scheme 1. Carbonyl umpolung reactions



Bearing two of the most versatile functionalities, γ-amino ketones are versatile chiral building blocks for the asymmetric synthesis of chiral amino compounds. For example, they provide valuable synthons toward chiral nitrogen-heterocycles such as pyrrolidines (**7**) and azabicyclic compounds (**8**) (Figure 1, b), which are prevalent in numerous biologically active synthetic compounds and natural products.[5] However, an enantioselective and direct transformation of readily available prochiral precursors into highly enantiomerically enriched γ-amino ketones has, to our knowledge, not yet been disclosed. We envisaged that the development of catalytic asymmetric imine umpolung reactions of **1** and enones **5** could provide the first catalytic asymmetric method to access optically active γ-amino ketones. Recently, we discovered that chiral phase-transfer catalysts such as **11a** and **11b** could promote the deprotonation of *N*-benzyl imines to form 2-azaallyl anions **2** and then enable **2** to react in a chemo-, regio-, diastereo- and enantio-selective fashion in C-C bond-forming reactions with enals, a class of highly active electrophiles.[6] These results prompted us to explore whether this new catalytic strategy of activating imines as nucleophilic 2-azaallylanions could be applied to the development of imine umpolung reactions with enones as the electrophiles.

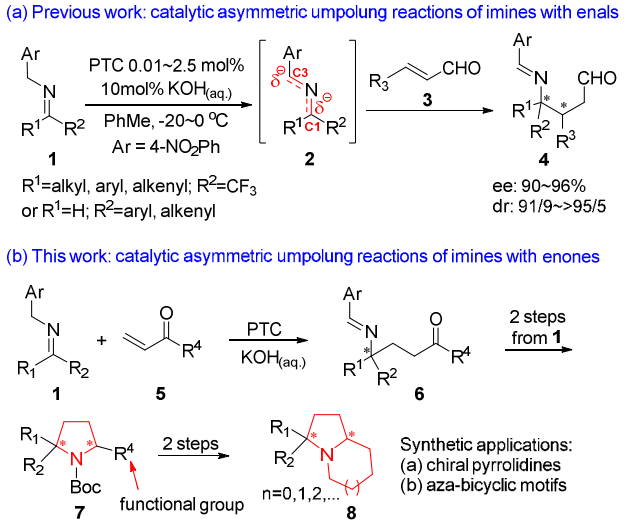
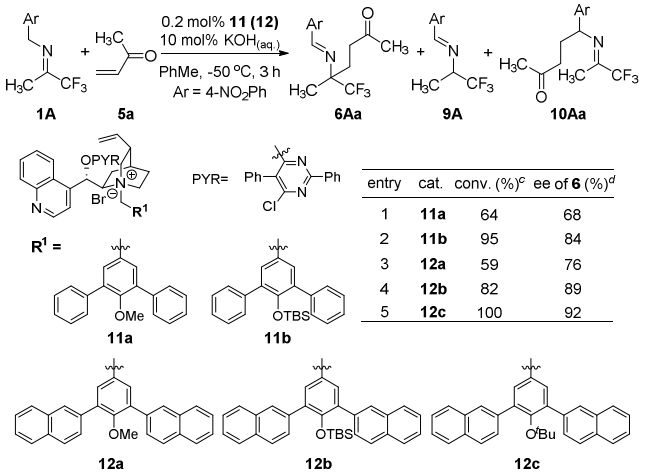


Figure 1. Development of catalytic asymmetric umpolung reactions of imines and important synthetic applications.

Compared to enals, enones **5** are significantly less active as electrophiles and structurally distinct. Consequently, the search of an effective catalyst became the focus of our initial investigations. The umpolung reaction of trifluoromethyl imine **1A** with methyl vinyl ketone (MVK, **5a**) was selected as the model reaction for our catalyst development studies (Table 1). Cinchonium salt **11a** was shown previously to be a highly effective catalyst for the asymmetric umpolung reaction of **1A** with acrolein, which afforded the desirable chiral amine in 92% ee.[6] However, the imine umpolung reaction of **1A** with **5a** mediated by **11a** proceeded in only modest enantioselectivity, affording the desired γ-amino ketone **6Aa** in only 68% ee (entry 1, Table 1). We next investigated cinchonium salt **11b** with the expectation that the presense of the bulky OTBS group would hamper the bond rotations between the phenyl groups. This in turn should render the terphenyl motif conformationally more defined, thereby more effectively engaging in π-π interaction with the 2-azallylanion **2**. Indeed, **11b** demonstrated improved activity and enantioselectivity over those by **11a** to furnished **6Aa** in 84% ee (entry 2, Scheme 2). These initial results, while encouraging, clearly indicated that further catalyst development was required in order to achieve an umpolung reaction of **1A** with an enone in excellent enantioselectivity.

In cognizant of the significant difference between the respective transition states of the reactions of **2** with enals and enones, we suspected that the terphenyl moiety in cinchonium salts **11**, tailored for achieving optimal catalysis for the reaction of **2** with enals **3**, might not be ideal for the reaction with enones **5.** These considerations directed us to explore catalyst **12a**, which was designed to present a spatially more extended aryl moiety by replacing the side phenyl groups of the terphenyl moiety in **11a** with napthyl groups.[7] To our delight, **12a** was found to be more enantioselective than **11a** (entry 3 vs 1, Table 1), although the enantioselectivity was still far from ideal. In order to make the extended aryl moiety in cinchonium salt **12** conformationally more rigid as a means to improve catalytic efficiency, we next replaced the 4-methoxy in **12a** with a more bulky 4-OTBS group to form catalyst **12b**. Subsequently, we found that **12b** was indeed superior to not only **12a** but also **11b** in enantioselectivity. We next investigated catalyst **12c**, which was derived by replacing the 4-OTBS group with the 4-O^{t}Bu group. At a loading of 0.2 mol%, **12c** afforded a complete reaction in 3 h to deliver the chiral γ-amino ketone **6Aa** in 92% ee.

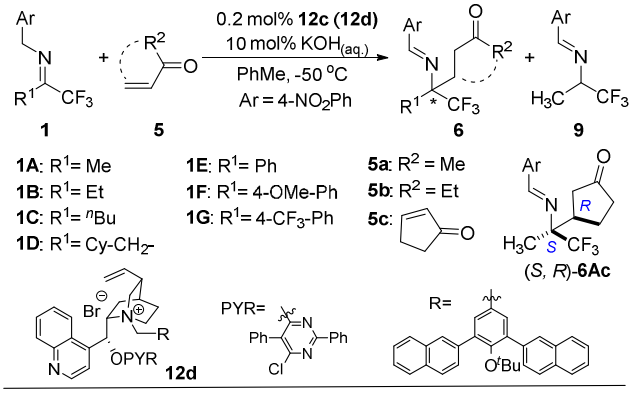
Table 1. Development of phase-transfer catalysts[a, b]



entry	cat.	conv. (%)[c]	ee of **6** (%)[d]
1	**11a**	64	68
2	**11b**	95	84
3	**12a**	59	76
4	**12b**	82	89
5	**12c**	100	92

[a]Unless noted, reactions were performed with **1A** (0.10 mmol), **5a** (0.20 mmol) and aqueous KOH (1.1 μL, 50 wt%, 10 mol%) in toluene (1.0 mL) with catalyst **11** or **12** (0.2 mol%). [b]**6Aa**/**9A** > 95:5 and **6Aa**/**10Aa** > 95:5 were determined for all reactions by ^{1}H and ^{19}F NMR analysis. [c]Conversion was determined by ^{19}F NMR analysis. [d]Determined by HPLC analysis.

Table 2. Substrate scope for umpolung reactions of trifluoromethyl imines with enones[a, b]



Entry	Imine	Enone	t (h)	**6**/**9**[c]	yield of **6** (%)[d]	ee of **6** (%)[e,f]
1	**1A**	**5a**	3(3)	>95:5(>95:5)	94(86)	92(-88)
2[g]	**1A**	**5a**	24	>95:5	82	91
3	**1B**	**5a**	3	>95:5	91	91
4	**1C**	**5a**	3(3)	>95:5(>95:5)	94(91)	91(-88)
5	**1D**	**5a**	24	>95:5	96	90
6	**1E**	**5a**	24(24)	93:7(>95:5)	89(88)	91(-81)
7	**1F**	**5a**	24	86:14	75	90
8	**1G**	**5a**	24	88:12	85	90
9	**1A**	**5b**	5	>95:5	90	78
10[h]	**1A**	**5c**	3(18)	>95:5(>95:5)	95(88)	99(-98)
11[h,i]	**1A**	**5c**	5	>95:5	94	99

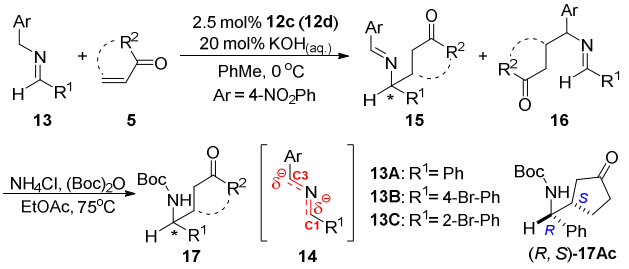
[a]Unless noted, reactions were performed with **1** (0.10 mmol), **5** (0.20 mmol) and aqueous KOH (1.1 μL, 50 wt%, 10 mol%) in toluene (1.0 mL) with catalyst **12c** (0.2 mol%). [b]Results in parentheses were obtained from reactions with **1** (0.20 mmol), **5** (0.40 mmol) and aqueous KOH (2.2 μL, 50 wt%, 10

mol%) in toluene (2.0 mL) with catalyst **12d** (0.2 mol%). [c]Determined by ^{19}F NMR analysis. [d]Isolated yields of **6**. [e]Determined by HPLC analysis. [f]The absolute configuration of **6Ac** obtained from the **12c**-catalyzed reaction was determined to be the *S, R* enantiomer, see the Supporting Information for details. [g]The reaction was performed with **1A** (0.20 mmol), **5a** (0.40 mmol) and aqueous KOH (2.2 μL, 50 wt%, 10 mol%) in toluene (2.0 mL) with catalyst **12c** (0.02 mol%). [h]Single diastereomer was obtained. [i]The reaction was performed with **1A** (0.20 mmol), **5c** (0.40 mmol) and aqueous KOH (2.2 μL, 50 wt%, 10 mol%) in toluene (2.0 mL) with catalyst **12c** (0.05 mol%) at -20 °C.

Having achieved the highly chemo-, regio-, and enantioselective umpolung reaction of **1A** and MVK (**5a**) with the newly developed catalyst **12c**, we next probed the substrate scope of this new imine umpolung reaction. As summarized in Table 2, catalyst **12c** showed consistently high activitity and selectivities for umpolung reactions of a range of aliphatic trifluoromethyl imines, including those presenting unbranched alkyl chains in various length (**1A-C**) and branched alkyl group (**1D**), which afforded the corresponding γ-amino ketones **6** in excellent yields and 90-92% ee (Table 2, entries 1, 3-5). Sterically more hindered trifluoromethylated imine such as **1D** reacted relatively slower (Table 2, entry 5 vs entries 1, 3-4). It is noteworthy that the amino ketones **6** are sufficiently stable on deactivated silica gel and could be isolated by chromatographic separation. Notably, with a catalyst loading of 0.02 mol%, the reaction still proceeded to completion within 24 hours to afford the corresponding γ-amino ketone in good yield without compromising the chemo-, regio-, and enantio-selectivity (Table 2, entry 2). Highly enantioselective umpolung reactions in synthetically useful yields could also be realized with aryl trifluoromethyl imines bearing either electron-rich or -deficient aryl rings. (Table 2, entries 6-8), although the reaction time became longer and the isomerized imine **9** could be detected as a minor product in these reactions. On the other hand, replacing the methyl group in enone **5a** with ethyl resulted in reduced enantioselectivity (Table 2, entry 9). Interestingly, the umpolung reaction of **1A** with cyclic pentenone **5c** was found to proceed in extraordinarily high diastereoselectivity and enantioselectivity, providing the desired amino ketone **6Ac** as a single diastereomer in 99% ee and 95% yield (Table 2, entry 10). Furthermore, the remarkably high diastereoselectivity and enantioselectivity were not compromised even when the catalyst loading was decreased to 0.05 mol% (Table 2, entry 11).

We next focused our attention on the umpolung reactions of simple imines with the goal of allowing the umpolung strategy to provide asymmetric access to optically active γ-amino ketones **15** (Table 3). At the outset of our investigation we were uncertain if catalyst **12c** would be able to promote the formation of the much less stable 2-azaallyl anions **14** derived from the deprotonation of simple aldimines **13** while effectively addressing the chemo-, regio- and enantioselectivity issues associated with the coupling of **14** with the enone electrophiles. We are particularly concerned about whether the catalyst could direct the C-C bond-forming reaction to occur with the desired sense of regioselectivity, namely selectively toward C1 in **14** (Table 3). To our delight, phenyl aldimine **13A** smoothly reacted with enone **5a** at o °C in the presence of 2.5 mol% of **12c** to afford the desired regioisomer **15Aa** as the dominating regioisomer (Table 3, entry 1). Thus, the umpolung reaction allowed the asymmetric synthesis of the *N*-Boc γ-aminoketone **17Aa** in 50% yield and 82% ee in two steps from aldimines **13A**. Catalyst **12c** afforded higher regio- and enantio-selectivity for the umpolung reaction of **13A** with cyclic enone **5c**, furnishing product **17Ac** as a single diastereomer in 91% ee (Table 3, entry 2). Similar regio-, enantio- and diastereoselectivities were also obtained in the umpolung reactions of 4-bromo-phenyl aldimine **13B** (Table 3, entries 3-4). Notably, the umpolung reaction with the sterically more hindered 2-bromo phenyl aldimine **13C** afforded the desired product with significantly higher regioselectivity (entry 5 vs entries 1 and 3, Table 3). The reaction of **13C** with ethyl vinyl ketone (EVK, **5b**) readily proceeded to completion in synthetically useful enantioselectivity (Table 3, entry 6). Finally, cinchonidine-derived catalyst **12d**, a pseudo enantiomer of catalyst **12c**, was found to afford similar activity and selectivities with an opposite sense of asymmetric induction, thereby allowing this umpolung reactions to provide access to either enantiomer of chiral γ-aminoketones **6** and **15** (Tables 2 and 3).

Table 3. Substrate scope for umpolung reactions of aldimines with enones[a, b]



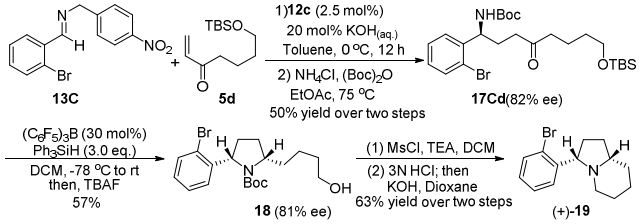
Entry	Aldimine	Enone	t (h)	15/16[c]	yield of 17 (%)[d]	ee of 17 (%)[e,f]
1	**13A**	**5a**	12(12)	2.5:1(2:1)	50(45)	82(-80)
2[g]	**13A**	**5c**	1(1)	5:1(4:1)	60(58)	91(-85)
3	**13B**	**5a**	8(8)	3:1(2.2:1)	52(46)	83(-81)
4[g]	**13B**	**5c**	1(1)	5:1(4:1)	56(53)	94(-93)
5	**13C**	**5a**	5(5)	15:1(12:1)	69(61)	89(-86)
6	**13C**	**5b**	12(12)	3:1(4:1)	47(50)	82(-80)

[a]Unless noted, reactions were performed with **13** (0.20 mmol), **5** (0.40 mmol) and aqueous KOH (4.4 μL, 50 wt%, 20 mol%) in toluene (2.0 mL) with catalyst **12c** (2.5 mol%) under N_2 atmosphere. [b]Results in parentheses were obtained with **12d** catalyst. [c]Determined by ^{1}H NMR analysis. [d]Isolated yields of **17**. [e]Determined by HPLC analysis. [f]The absolute configuration of **17Aa** obtained from the **12d**-catalyzed reaction was determined to be *R*. The absolute configuration of **17Ac** obtained from the **12d**-catalyzed reaction was determined to be the *R, S* enantiomer, see the Supporting Information for details. [g]Reaction was carried out at room temperature.

To demonstrate the synthetic potential of this new asymmetric transformation, we pursued the enantioselective synthesis of (+)-(3*S*, 8*S*)-3-(2-bromophenyl)octahydro-indolizine (**19**), a potent non-opiate antinociceptive agent for pain relief with an ED_{50} value of 7.9 mg/kg in the mouse abdominal constrictions test.[8] Interestingly, (+)-**19** is nearly three times more potent than (-)-**19**. However, optically active **19** was previously obtained by conventional resolution of racemic samples involving multiple recrystallizations.[8] We designed an enantioselective synthetic route featuring the **12c**-

catalyzed umpolung reaction of **13C** and enone **5d** as the asymmetric induction step (Scheme 2). The umpolung reaction proceeded to completion in 12 hours to afford γ-aminoketone **15Cd** as the major regioisomer and in 82% ee. Upon treatment of γ-amino ketone **15Cd** with Boc-anhydride and ammonium chloride, the *N*-Boc γ-aminoketone **17Cd** was obtained in 50% overall yield from imine **13C**. Amino ketone **17Cd** was transformed into *cis*-2-aryl-5-alkyl-pyrrolidine **18** in 57% yield via a one-pot protocol by first being exposed to triphenylsilane and $B(C_6F_5)_3$[9] and then to TBAF. This two-pot synthesis of optically active 2,5-disubstituted pyrrolidines from readily available prochiral imines and enones should provide an efficient and distinct synthetic strategy to complement existing strategies toward this important class of nitrogen-heterocycles.[10] We next converted the alcohol in **18** into the corresponding mesylate, and then found the subsequent removal of the *N*-Boc automatically triggered the cyclization to afford (+)-**19** in 63% overall yield from **18**.[11]

Scheme 2. Synthesis of (+)-(3*S*, 8*S*)-3-(2-bromophenyl)octahydroindolizine 19



In summary, we have developed an unprecedented catalytic asymmetric umpolung reaction of imines with enones as the electrophiles. Notably, enones as moderately active electrophiles presented a significant challenge to existing catalysts[6] for imine umpolung reactions. The discovery of an effective new catalyst proved to be critical to allow the realization of this new imine umpolung reaction. As the first highly enantioselective catalytic reaction directly generating optically active γ-amino ketones from readily available prochiral precursors, this new asymmetric transformation provides a new strategy for the construction of various chiral *N*-heterocycles and acyclic amine building blocks and their respective trifluoromethylated analogues.

ASSOCIATED CONTENT

Supporting Information

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

AUTHOR INFORMATION

Corresponding Author

*deng@brandeis.edu

Author Contributions

†L. H. and Y. W. contributed equally.

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We are grateful for financial support from National Institute of Health (Grant GM-61591) and the Keck Foundation.

REFERENCES

(1) For selected papers, see: (a) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231. (b) GrÖBel, B.-T.; Seebach, D. *Synthesis* **1977**, 357. (c) Smith, A. B.; Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365. (d) Brehme, R.; Enders, D.; Fernandez, R.; Lassaletta, J. M. *Eur. J. Org. Chem.* **2007**, 5629. (e) Stetter, H. *Angew. Chem. Int. Ed.* **1976**, *15*, 639.

(2) (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (b) Vora, H. U.; Rovis, T. *Aldrichim. Acta* **2011**, *44*, 3. (c) Cardinal-David, B.; Scheidt, K. A. *Top. Organomet. Chem.* **2013**, *44*, 233. (d) Mahatthananchai, J.; Bode, J. W. *Acc. Chem. Res.* **2014**, *47*, 696. (e) Cai, X.-H.; Xie, B. *Arkivoc* **2014**, *44*, 205. (f) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis. T. *Chem. Rev.* **2015**, *115*, 9307.

(3) For selected examples of activation of imines not conjugated with carbonyl functionalities as nucleophiles, see: (a) Reich, B. J. E.; Justice, A. K.; Beckstead, B. T.; Reibenspies, J. H.; Miller, S. A. *J. Org. Chem.* **2004**, *69*, 1357. (b) Ogle, J. W.; Zhang, J.; Reibenspies, J. H.; Abboud, K. A.; Miller, S. A. *Org. Lett.* **2008**, *10*, 3677. (c) Liu, X.; Gao, A.; Ding, L.; Xu, J.; Zhao, B. *Org. Lett.* **2014**, *16*, 2118. (d) Matsumoto, M.; Harada, M.; Yamashita, Y.; Kobayashi, S. *Chem. Commun.* **2014**, *50*, 13041. (e) Zhu, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2014**, *136*, 4500. (f) Qian, X.; Ji, P.; He, C.; Zirimwabagabo, J.-O.; Archibald, M. M.; Yeagley, A. A.; Chruma, J. J. *Org. Lett.* **2014**, *16*, 5228. (g) Xu, J.; Chen, J.; Yang, Q.; Ding, L.; Liu, X.; Xu, D.; Zhao, B. *Adv. Synth. Catal.* **2014**, *356*, 3219. (h) Wu, L.; Xie, C.; Mei, H.; Dai, Y.; Han, J.; Soloshonok, V. A.; Pa, Y. *J. Org. Chem.* **2015**, *80*, 3187. (i) Tang, S.; Park, J. Y.; Yeagley, A. A.; Sabat M.; Chruma, J. J. *Org. Lett.* **2015**, *17*, 2042.

(4) For selected recent examples of activation of imines conjugated with carbonyl functionalities as enolate and enol nucleophiles, see: (a) Guo, C.; Song, J.; Gong, L.-Z. *Org. Lett.* **2013,** *15,* 2676. (b) Tian, L.; Hu, X.–Q.; Li, Y.–H.; Xu, P.-F. *Chem. Commun.* **2013,** *49,* 7213.

(5) (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139. (b) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556.

(6) Wu, Y.; Hu, L.; Li, Z.; Deng, L. *Nature* **2015,** 523, 445.

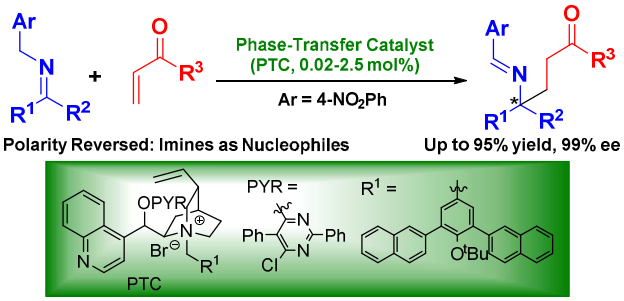
(7) Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030.

(8) Carson, J. R.; Carmosin, R. J.; Vaught, J. F.; Gardocki, J. F.; Costanzo, M. J.; Raffa, R. B.; Jr. H. R. Almond, *J. Med. Chem.* **1992**, *35*, 2855.

(9) Abels, F.; Lindemann, C.; Schneider. C. *Chem. Eur. J.* **2014**, *20*, 1964.

(10) For leading references for the synthesis of *cis*-2-aryl-5-alkyl or 2, 5-dialkyl-substituted pyrrolidines, see: (a) Haddad, M.; Imogaï, H.; Larchevêque, M. *J. Org. Chem.* **1998**, *63*, 5680. (b) Brenneman, J. B.; Martin. S. F. *Org. Lett.* **2004**, *6*, 1329. (c) van Esseveldt, B. C. J.; Vervoort, P. W. H.; van Delft, F. L.; Rutjes. F. P. J. T. *J. Org. Chem.* **2005**, *70*, 1791. (d) Zhang, S.; Xu, L.; Miao, L.; Shu, H.; Trudell, M. J. *J. Org. Chem.* **2007**, *72*, 3133. (e) Viso, A.; Lee, N. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 9373. (f) Redford, J. E.; McDonald, R. I.; Rigsby, M. L.; Wiensch, J. D.; Stahl. S. S. *Org. Lett.* **2012**, *14*, 1242. (g) Race, N. J.; Bower, J. F. *Org. Lett.* **2013**, *15*, 4616. (h) Wang, D.-S.; Ye, Z.-S.; Chen, Q.-A.; Zhou, Y.-G.; Yu, C.-B.; Fan, H.-J.; Duan, Y. *J. Am. Chem. Soc.* **2011**, *133*, 8866.

(11) Sibi, M. P.; Christensen. J. W. *J. Org. Chem.* **1999**, *64*, 6434.


Ar
N
R1
R2
+
O
R3
Phase-Transfer Catalyst
(PTC, 0.02-2.5 mol%)
Ar = 4-NO2Ph
Ar
N
O
R3
R1
R2
*
Polarity Reversed: Imines as Nucleophiles
Up to 95% yield, 99% ee
OPYR
N
Br
R1
PTC
PYR =
Ph
N
N
Ph
Cl
R1 =
OtBu