

Synthesis of 3-Sulfonylamino Quinolines from 1-(2-Aminophenyl) Propargyl Alcohols through a Ag(I)-Catalyzed Hydroamination, (2 + 3) Cycloaddition, and an Unusual Strain-Driven Ring Expansion

Yalla Kiran Kumar,[†] Gadi Ranjith Kumar,^{†,||} Thota Jagadeshwar Reddy,[‡] Balasubramanian Sridhar,[§] and Maddi Sridhar Reddy^{*,†,||}

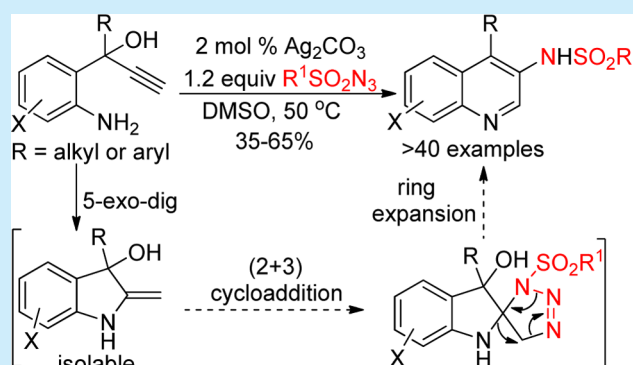
[†]Medicinal & Process Chemistry Division and [‡]SAIF Division, CSIR-Central Drug Research Institute, BS-10/1, Sector 10, Jankipuram Extension, Sitapur Road, Post Office Box 173, Lucknow 226031, India

[§]X-ray Crystallography Division, CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500007, India

^{||}Academy of Scientific and Innovative Research, New Delhi 110001, India

S Supporting Information

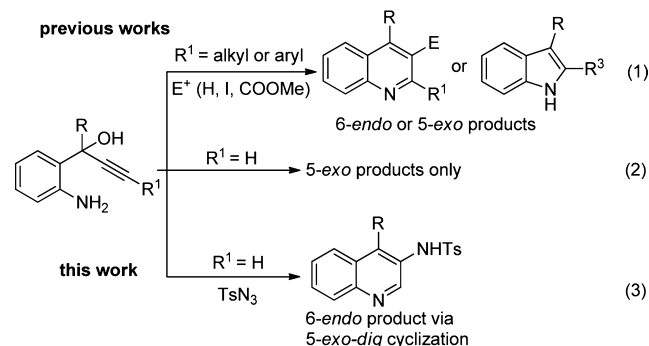
ABSTRACT: We describe herein a silver-catalyzed conversion of 1-(2-aminophenyl)-propargyl alcohols to 4-substituted 3-tosylaminoquinolines using TsN₃ as an amino surrogate. Controlled reactions reveal the pathway consisting of Ag(I)-catalyzed 5-*exo-dig* cyclization, catalyst-free (2 + 3) cycloaddition, and ring-expansive rearrangement via nitrogen expulsion. As a support study, we show that the cyclic enamines in similar conditions produce amidines via a C–C bond migration.



Aminoquinolines represent an important class of bioactive molecules that display a broad spectrum of pharmaceutical activities.¹ Although facile access is well-documented in the literature for the amino group insertion at C2 and C4 of quinoline² via nucleophilic displacement utilizing the electron deficiency at the respective positions, the synthesis of their C3 counterpart is highly underinvestigated because the same concept is unadoptable. This could have been one of the reasons for not undertaking the extensive evaluation of the biological activities of 3-aminoquinolines.³ As part of our ongoing program of unveiling the novel reactivities of alkynes activated by electrophiles,⁴ we herein present the synthesis of 4-substituted 3-tosylaminoquinolines from 1-(2-aminophenyl)-propargyl alcohols using TsN₃ as an amino surrogate.

1-(2-Aminophenyl)-propargyl alcohols have been identified as ready precursors for the synthesis of various benzo-fused six- or five-membered heterocycles (Scheme 1). When R¹ ≠ H (Scheme 1, eq 1), the substrates take a 6-*endo-dig*- or 5-*exo-dig*-cyclization pathway,⁵ depending on the N protection, reagent, and conditions, to give quinoline or indole derivatives, respectively. However, the substrates with R¹ = H (Scheme 1, eq 2) always undergo a 5-*exo-dig* cyclization⁶ to afford indole derivatives. Herein, we present a rare example of the conversion of substrates with R¹ = H (Scheme 1, eq 3) to 6-cyclized products, i.e., quinolines. The reaction is, however, identified to go through a 5-*exo-dig* cyclization followed by an unprecedented strain-driven ring-expansive rearrangement.

Scheme 1. Electrophilic Cyclizations of 1-(2-Aminophenyl) Propargyl Alcohols

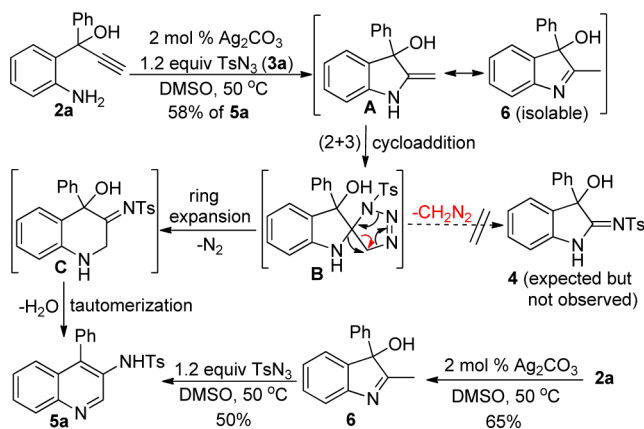


It was a serendipitous observation that occurred during an attempt at the outset for the conversion of **2a** (obtained by the addition of ethynylmagnesium bromide to 2-aminobenzophenone (**1a**)) to **4** via 5-*exo-dig* cyclization and (2 + 3) cycloaddition with TsN₃ (**3**) followed by a known diazo-methane expulsion.⁷ Intermediate **B** instead undertook a rare C–N bond migratory approach with the expulsion of nitrogen (Scheme 2). **C** subsequently underwent a tautomerization and

Received: March 21, 2015

Published: April 15, 2015

Scheme 2. Conversion of 2a to Amino Quinoline 5a via 6



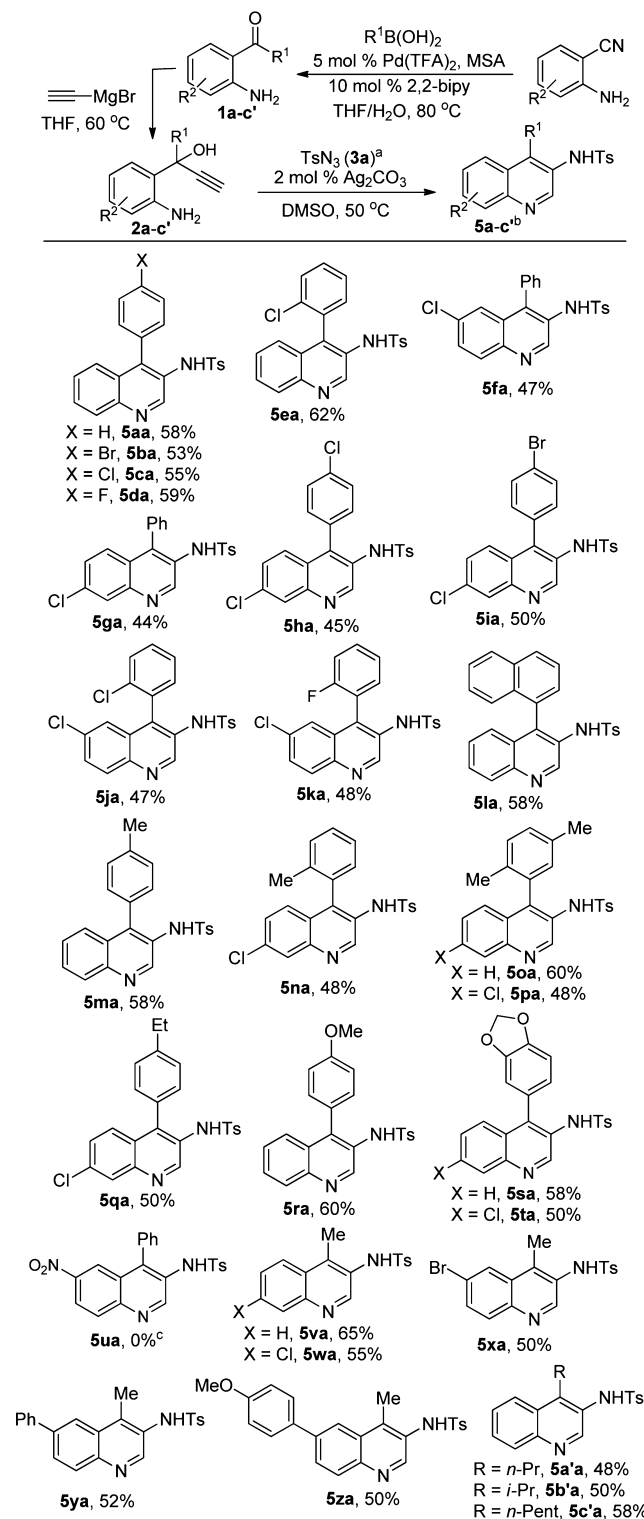
dehydration processes to reveal 4-phenyl-3-tosylamino quinoline (5a). The formation of 5-*exo* adduct A and its slow conversion to the product was clearly observed by TLC.

In the absence of TsN₃, tautomerized adduct (6) of 5-*exo* adduct A was exclusively isolated. To clearly establish the pathway, intermediate 6 was separately treated with TsN₃ in DMSO in the absence of silver catalyst. As expected, 6 was cleanly converted to product 5a, demonstrating that the reaction is going through a cascade involving Ag-catalyzed 5-*exo-dig* cyclization, catalyst-free (2 + 3) cycloaddition, and C–N bond migration. Although the yield of the product was moderate, no other considerable byproduct formation was observed. We attribute this to the unstable nature of A (or 6).

Considering the underdevelopment of 3-amino quinolines synthesis,³ we immediately turned to explore the generality of this new reaction. A variety of 2-aminophenyl propargyl alcohols (2) were synthesized (few from readily available 2-aminophenyl ketones (1) and others from 2-amino benzonitriles,⁸ see Supporting Information for details) and subjected to the standard reaction conditions (see the Supporting Information for optimization studies). As evident from Schemes 3 and 4, the reaction is applicable over a wide range of substrates to produce the products in moderate to good yields. Initially, we synthesized various C4-aryl adducts using this cascade process. Halogen groups like Br, Cl, and F were tolerated on the C4-aryl group as well as on the quinoline nucleus as in case of the products 5ba–ka. Products with halogen on the quinoline core were obtained with slightly lower yields (44–50% compared to 53–62%). A naphthyl group could also be introduced at C4 of aminoquinoline (5la) with the equal ease. Electron-rich substrates with methyl/ethyl (2m–q), methoxy (2r), and methylenedioxy (2s–t) substituents afforded the products in slightly better yield, whereas electron-deficient, nitro-substituted substrate 2u did not yield any product (starting material recovered after 24 h). We then focused on introducing alkyl groups at C4 of aminoquinoline adducts using substrates obtained from 2-aminophenyl alkyl ketones. Thus, 2v–z with a methyl group and 2a'–c' with *n*-propyl, *i*-propyl, and *n*-pentyl groups, respectively, along with a variety of other substitutions were successfully converted to the corresponding products (5va–c'a) in moderate to good yields (48–65%). In these cases, formation of traces (5–10%) of amidine byproducts relevant to 4 was observed.

Next, we evaluated the scope of the reaction with respect to sulfonyl azides. Like toluenesulfonyl azide, unsubstituted and halosubstituted phenyl sulfonyl azides also participated well in

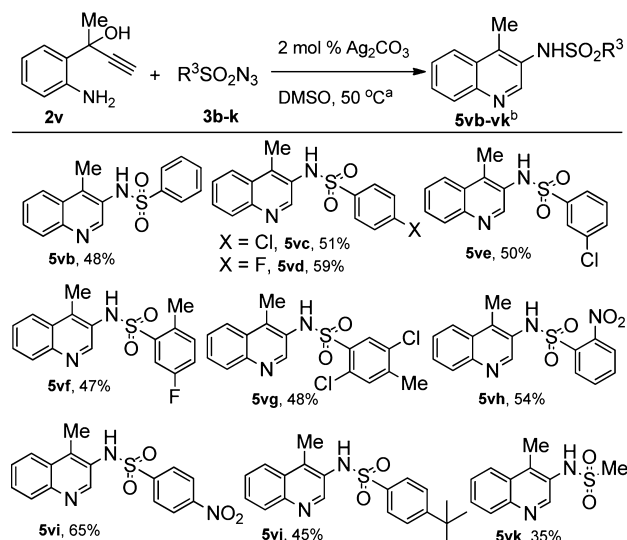
Scheme 3. Synthesis of 3-Tosylaminoquinolines (5) from Various Aminophenyl Propargyl Alcohols (2)



^aReaction conditions: TsN₃ (1.2 mmol), 2 (1.0 mmol), Ag₂CO₃ (0.02 mmol), DMSO (4 mL), 50 °C, open air. ^bIsolated yield. ^cStarting material recovered.

the reaction with 2v to produce corresponding products 5vb–vg in practically considerable yields (47–59%). Electronic variation in the phenyl group of sulfonyl azides (electron-poor nitrophenyl sulfonyl azides 3h–i and electron-rich *t*-butylphen-

Scheme 4. Scope of Sulfonyl Azides



^aReaction conditions: $R^3SO_2N_3$ (1.2 mmol), **2v** (1.0 mmol), Ag_2CO_3 (0.02 mmol), DMSO (4 mL), 50 °C, open air. ^bIsolated yield.

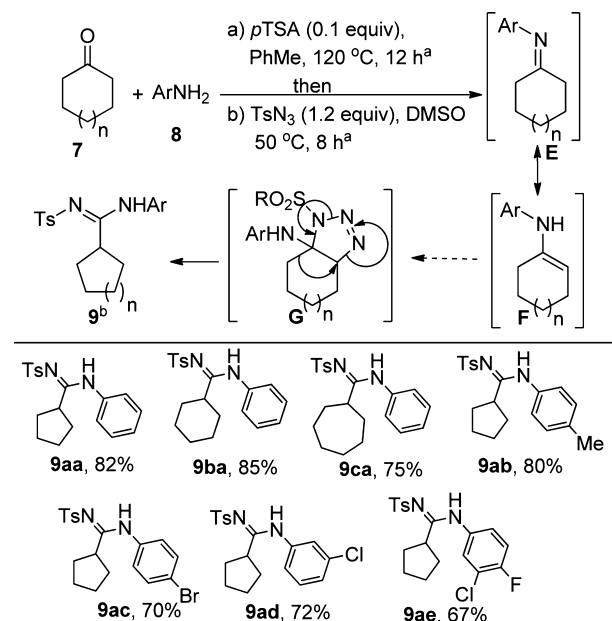
yl sulfonyl azide **3j**) did not show any impact on the reaction, producing the products in almost similar yields (45–65%). Unlike aryl azide, methane sulfonyl azide led to corresponding product **5vk** in moderate yield of 35%.

To get insight into the intriguing rearrangement in the above cascade, we wanted to conduct some experiments where sulfonyl azide similarly adds on to enamine but the enamine now with the nonstrained C–N bond. For that, we prepared a Schiff base (**E**, from cyclohexanone aniline in refluxing toluene) which can in situ tautomerise to **F** during the reaction process. Unlike in the case of intermediate **B** in Scheme 2, where the C–N bond is part of a spirocyclic system, the $NHAr$ would be freely flanking outside of the probable bicyclic triazole **G** from enamine **F** and thus may not receive the same force to migrate. Thus, as expected, when **F** was treated (in the same RB flask after removal of toluene) with TsN_3 in DMSO at 50 °C, the C–C bond in **G** migrated in preference to a C–N bond to produce amidine **9** with ring-contracted cycle.⁹ To the best of our knowledge, this catalyst/reagent-free in situ cycloaddition and rearrangement is hitherto not reported in the literature. For this reason and because of the importance of amidine products in medicinal and biological fields,¹⁰ we aimed to explore its generality. Thus, cyclohexanone, cycloheptanone, and cyclooctanone (with aniline) furnished the corresponding amidine products in excellent yields (75–85%). The scope of the reaction with respect to aniline was also verified with variety of substituted anilines to obtain products **9ab–ae** in good to excellent yields (67–80%).

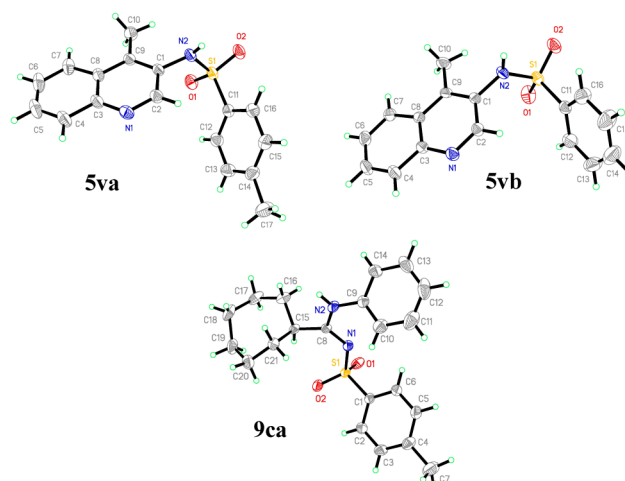
A structure from each category of compounds (**5va**, **5vb**, and **9ca** from Schemes 3–5, respectively) was unambiguously confirmed by X-ray crystallography, as depicted in Figure 1.

In summary, an efficient synthesis of hitherto formidable 3-amino quinoline derivatives from readily accessible 2-amino-phenyl propargylic alcohols is described. The reaction offers a rare 6-*endo-dig* product via common 5-*exo-dig* cyclization and an unusual rearrangement. A very catalytic amount of Ag_2CO_3 is sufficient to execute this cascade, and the reaction is found to have a broad substrate scope with respect to both the propargyl alcohols and the sulfonyl azides. Furthermore, we also

Scheme 5. Synthesis of N-Tosylamidines from Enamines



^aReaction conditions: (a) **7** (2 mmol), **8** (2 mmol), PhMe (2 mL), 120 °C, 12 h. (b) TsN_3 (1.2 mmol), DMSO (4 mL), 50 °C, 8 h, open air. ^bIsolated yield.

Figure 1. X-ray crystal structures of **5va**, **5vb**, and **9ca**.

demonstrated the catalyst/reagent-free and effective conversion of cycloalkanones to cycloalkyl amidines (with the reduced ring size) via another cascade involving enamine formation, regioselective (2 + 3) cycloaddition, and C–C bond migration.

■ ASSOCIATED CONTENT

§ Supporting Information

Experimental details and copies of 1H and ^{13}C spectra for compounds **2**, **5**, **6**, and **9**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: msreddy@cdri.res.in.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Y.K.K. and G.R.K. thank CSIR for the fellowships. We thank SAIF division CSIR-CDRI for the analytical support. We gratefully acknowledge the financial support by CSIR-Network project BSC0104 (CSIR-CDRI-SPLENDID) and by DST under Fast Track Proposal Scheme for Young Scientists (SB/FT/CS-102/2012). CDRI Communication No. 8957.

REFERENCES

- (1) (a) Videnovic, M.; Opsenica, D. M.; Burnett, J. C.; Gomba, L.; Nuss, J. E.; Selakovic, Z.; Konstantinovic, J.; Krstic, M.; Segan, S.; Zlatovic, M.; Sciotti, R. J.; Bavari, S.; Solaja, B. A. *J. Med. Chem.* **2014**, *57*, 4134–4153. (b) Singh, K.; Kaur, H.; Smith, P.; de Kock, C.; Chibale, K.; Balzarini, J. *J. Med. Chem.* **2014**, *57*, 435–448. (c) Opsenica, I. M.; Tot, M.; Gomba, L.; Nuss, J. E.; Sciotti, R. J.; Bavari, S.; Burnett, J. C.; Solaja, B. A. *J. Med. Chem.* **2013**, *56*, 5860–5871. (d) Cornut, D.; Lemoine, H.; Kanishchev, O.; Okada, E.; Albrieux, F.; Beavogui, A. H.; Bienvenu, A. L.; Picot, S.; Bouillon, J. P.; Medebielle, M. *J. Med. Chem.* **2013**, *56*, 73–83. (e) Kaur, K.; Jain, M.; Reddy, R. P.; Jain, R. *Eur. J. Med. Chem.* **2010**, *45*, 3245–3264. (f) Bawa, S.; Kumar, S.; Drabu, S.; Kumar, R. *J. Pharm. BioAllied Sci.* **2010**, *2*, 64–71. (g) Inglis, S. R.; Jones, R. K.; Booker, G. W.; Pyke, S. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 387–390. (h) Inglis, S.; Jones, R.; Fritz, D.; Booker, G.; Pyke, S. *Org. Biomol. Chem.* **2005**, *3*, 2543–2257. (i) Campbell, S. F.; Hardstone, J. D.; Palmer, M. J. *J. Med. Chem.* **1988**, *31*, 1031–1035. (j) Alhaider, A. A.; Abdelkader, M. A.; Lien, E. *J. J. Med. Chem.* **1985**, *28*, 1394–1398.
- (2) (a) Zhang, L.; Zheng, L.; Guo, B.; Hua, R. *J. Org. Chem.* **2014**, *79*, 11541–11548. (b) Aillerie, A.; Pellegrini, S.; Bousquet, T.; Pelinski, L. *New J. Chem.* **2014**, *38*, 1389–1391. (c) Liu, B.; Gao, H.; Yu, Y.; Wu, W.; Jiang, H. *J. Org. Chem.* **2013**, *78*, 10319–10328. (d) Tomioka, T.; Takahashi, Y.; Maejima, T. *Org. Biomol. Chem.* **2012**, *10*, 5113–5118. (e) Hwang, A. H.; Park, S. H.; Choi, E. B.; Pak, C. S.; Lee, H. K. *Tetrahedron* **2008**, *64*, 6698–6704. (f) Li, J.-S.; Chen, F.-X.; Shikiya, R.; Marky, L. A.; Gold, B. *J. Am. Chem. Soc.* **2005**, *127*, 12657–12665. (g) Sanchez-Martin, R.; Campos, J. M.; Conejo-Garcia, A.; Cruz-Lopez, O.; Banez-Coronel, M.; Rodriguez-Gonzalez, A.; Gallo, M. A.; Lacal, J. C.; Espinosa, A. *J. Med. Chem.* **2005**, *48*, 3354–3363. (h) Inglis, S. R.; Stojkoski, C.; Branson, K. M.; Cawthray, J. F.; Fritz, D.; Wiadrowski, E.; Pyke, S. M.; Booker, G. W. *J. Med. Chem.* **2004**, *47*, 5405–5417.
- (3) For a few available references, see (a) Vo, G. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 11049–11061. (b) Wang, Y. D.; Boschelli, D. H.; Johnson, S.; Honores, E. *Tetrahedron* **2004**, *60*, 2937–2942. (c) Khan, M. S.; LaMontagne, M. P. *J. Med. Chem.* **1979**, *22*, 1003–1005.
- (4) (a) Babu, M. H.; Dwivedi, V.; Kant, R.; Reddy, M. S. *Angew. Chem., Int. Ed.* **2015**, *54*, 3783–3786. (b) Puri, S.; Thirupathi, N.; Reddy, M. S. *Org. Lett.* **2014**, *16*, 5246–5249. (c) Thirupathi, N.; Babu, M. H.; Dwivedi, V.; Reddy, M. S. *Org. Lett.* **2014**, *16*, 2908–2911. (d) Kumar, Y. K.; Kumar, G. R.; Reddy, M. S. *J. Org. Chem.* **2014**, *79*, 823–828. (e) Thirupathi, N.; Kumar, Y. K.; Kant, R.; Reddy, M. S. *Adv. Synth. Catal.* **2014**, *356*, 1823–1834. (f) Kumar, G. R.; Kumar, Y. K.; Kant, R.; Reddy, M. S. *Beilstein J. Org. Chem.* **2014**, *10*, 1255–1260. (g) Reddy, M. S.; Thirupathi, N.; Babu, M. H.; Puri, S. *J. Org. Chem.* **2013**, *78*, 5878–5888. (h) Reddy, M. S.; Kumar, Y. K.; Thirupathi, N. *Org. Lett.* **2012**, *14*, 824–827. (i) Reddy, M. S.; Thirupathi, N.; Babu, M. H. *Eur. J. Org. Chem.* **2012**, 5803–5809. (j) Reddy, M. S.; Thirupathi, N.; Kumar, Y. K. *RSC Adv.* **2012**, *2*, 3986–3992.
- (5) (a) Dhiman, S.; Ramasastry, S. S. V. *Chem. Commun.* **2015**, 557–560. (b) Susanti, D.; Ru Ng, L. L.; Chan, P. W. H. *Adv. Synth. Catal.* **2014**, *356*, 353–358. (c) Susanti, D.; Koh, F.; Kusuma, J. A.; Kothandaraman, P.; Chan, P. W. H. *J. Org. Chem.* **2012**, *77*, 7166–7175. (d) Mothe, S. R.; Kothandaraman, P.; Lauw, S. J. L.; Chin, S. M.; Chan, P. W. H. *Chem.—Eur. J.* **2012**, *18*, 6133–6137. (e) Ali, S.; Zhu, H. T.; Xia, X. F.; Ji, K. G.; Yang, Y. F.; Song, X. R.; Liang, Y. M. *Org. Lett.* **2011**, *13*, 2598–2601. (f) Kothandaraman, P.; Rao, W.; Foo, S. J.; Chan, P. W. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 4619–4623. (g) Gabriele, B.; Mancuso, R.; Lupinacci, E.; Spina, R.; Salerno, G.; Veltri, L.; Dibeneditto, A. *Tetrahedron* **2009**, *65*, 8507–8512. (h) Gabriele, B.; Mancuso, R.; Salerno, G.; Lupinacci, E.; Ruffolo, G.; Costa, M. *J. Org. Chem.* **2008**, *73*, 4971–4977. (i) Gabriele, B.; Mancuso, R.; Salerno, G.; Costa, M. *J. Org. Chem.* **2007**, *72*, 9278–9282. (j) Knight, D. W.; Rost, H. C.; Sharland, C. M.; Singkhonrat, J. *Tetrahedron Lett.* **2007**, *48*, 7906–7910. (k) Gabriele, B.; Mancuso, R.; Salerno, G.; Ruffolo, G.; Plastina, P. *J. Org. Chem.* **2007**, *72*, 6873–6877. (l) Gabriele, B.; Mancuso, R.; Salerno, G.; Costa, M. *Adv. Synth. Catal.* **2006**, *348*, 1101–1109. (m) Hessian, K. O.; Flynn, B. L. *Org. Lett.* **2006**, *8*, 243–246. (n) Jiang, B.; Si, Y. G. *J. Org. Chem.* **2002**, *67*, 9449–9451. See also refs 4e, 4i, and 4j.
- (6) (a) Li, X.; Song, W.; Tang, W. *J. Am. Chem. Soc.* **2013**, *135*, 16797–16800. (b) Mancuso, R.; Gabriele, B. *Molecules* **2013**, *18*, 10901–10911. (c) Kothandaraman, P.; Lauw, S. J. L.; Chan, P. W. H. *Tetrahedron* **2013**, *69*, 7471–7480. (d) Kothandaraman, P.; Koh, B. Q.; Limpanuparb, T.; Hirao, H.; Chan, P. W. H. *Chem.—Eur. J.* **2013**, *19*, 1978–1985. (e) Chowdhury, C.; Das, B.; Mukherjee, S.; Achari, B. *J. Org. Chem.* **2012**, *77*, 5108–5119. (f) Kothandaraman, P.; Mothe, S. R.; Toh, S. S. M.; Chan, P. W. H. *J. Org. Chem.* **2011**, *76*, 7633–7640. (g) Gabriele, B.; Mancuso, R.; Salerno, G. *J. Org. Chem.* **2008**, *73*, 7336–7341. (h) Gabriele, B.; Mancuso, R.; Salerno, G.; Plastina, P. *J. Org. Chem.* **2008**, *73*, 756–759. (i) Henke, N.; Payne, L. J.; Parsons, P. J.; Hitchcock, P. B. *Synlett* **2006**, *4*, 654–656. See also ref 4c.
- (7) (a) Chang, S.; Lee, M.; Jung, D. Y.; Yoo, E. J.; Cho, S. H.; Han, S. K. *J. Am. Chem. Soc.* **2006**, *128*, 12366. (b) Gao, T.; Zhao, M.; Meng, X.; Li, C.; Chen, B. *Synlett* **2011**, 1281–1284.
- (8) Chen, J.; Ye, L.; Su, W. *Org. Biomol. Chem.* **2014**, *12*, 8204–8211.
- (9) Secondary enamines in similar conditions react with opposite regioselectivity; this may be due to the steric hindrance. For the literature, see (a) Ref 7b. (b) Continini, A.; Erba, E. *RSC Adv.* **2012**, *2*, 10652–10660.
- (10) (a) Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 2038–2039. (b) Caron, S.; Wei, L.; Douville, J.; Ghosh, A. *J. Org. Chem.* **2010**, *75*, 945–947. (c) Cortes-Salva, M.; Garvin, C.; Antilla, J. C. *J. Org. Chem.* **2011**, *76*, 1456–1459. (d) Harjani, J. R.; Liang, C.; Jessop, P. G. *J. Org. Chem.* **2011**, *76*, 1683–1691. (e) Wang, J.; Xu, F.; Cai, T.; Shen, Q. *Org. Lett.* **2008**, *10*, 445–448. (f) Chauhan, D. P.; Varma, S. J.; Vijeta, A.; Banerjee, P.; Talukdar, P. *Chem. Commun.* **2014**, *50*, 323–325. (g) Ref 4f.