

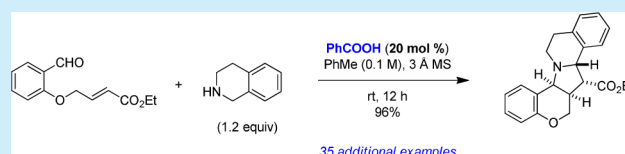
Intramolecular [3 + 2]-Cycloadditions of Azomethine Ylides Derived from Secondary Amines via Redox-Neutral C–H Functionalization

Kempegowda Mantelingu, Yingfu Lin, and Daniel Seidel*

Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08854, United States

S Supporting Information

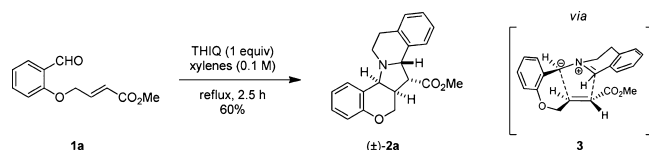
ABSTRACT: Azomethine ylides are accessed under mild conditions via benzoic acid catalyzed condensations of 1,2,3,4-tetrahydroisoquinolines or tryptolines with aldehydes bearing a pendent dipolarophile. These intermediates undergo intramolecular [3 + 2]-cycloadditions in a highly diastereoselective fashion to form polycyclic amines with four new stereogenic centers. Challenging substrates such as piperidine, morpholine, and thiomorpholine undergo the corresponding reactions at elevated temperatures.



[3 + 2]-Cycloadditions of azomethine ylides, in particular when performed in an intramolecular setting, are ideally suited for the purpose of rapidly constructing highly substituted polycyclic amines.¹ Among the methods that are available to generate nonstabilized azomethine ylides in situ, these dipolar species are most frequently prepared via decarboxylative condensation of aldehydes with amino acids such as proline and sarcosine.¹ Examples of azomethine ylide formation from simple, unfunctionalized cyclic amines and their subsequent dipolar cycloadditions remain rare and require relatively high reaction temperatures for even the most activated amines such as 1,2,3,4-tetrahydroisoquinoline (THIQ). Here we report a method to access azomethine ylides from a range of simple secondary amines and their application to intramolecular [3 + 2]-cycloadditions.

Given our continuing interest in developing methods for the redox-neutral α -C–H bond functionalization of amines,^{2–6} we were inspired by seminal studies of Grigg et al., who showed that THIQ reacts with aldehyde **1a** to form polycyclic amine **2a** via nonstabilized azomethine ylide **3** (Scheme 1).^{7,8} Although

Scheme 1. Pioneering Work by Grigg and Co-workers



this transformation requires relatively high reaction temperatures (reflux in xylenes), product **2a** was obtained as a single diastereomer. The rate limiting step of this reaction is thought to be the generation of the azomethine ylide **3**.⁷ If conditions could be identified that would allow for the generation of the required azomethine ylide under milder conditions, the scope and applicability of such transformations could be expanded

dramatically, possibly paving the way for the development of asymmetric variants.

We set out to identify the mildest conditions possible under which the reaction of aldehyde **1b** with THIQ would proceed with a synthetically useful rate (Table 1). A reaction conducted

Table 1. Evaluation of Reaction Conditions^a

entry	PhCOOH (mol %)	molecular sieves	temp [°C]	time [h]	2b , yield (%)
1	—	—	reflux	24	63
2	20	—	reflux	2	84
3	20	—	100	2	72
4	20	—	80	3	75
5	20	—	60	24	82
6	20	—	50	24	NR
7	—	3 Å	reflux	16	67
8	—	3 Å	70	24	65
9	—	3 Å	60	24	NR
10	20	3 Å	60	2	91
11	20	4 Å	60	2	89
12	20	3 Å	50	3	92
13	20	3 Å	rt	12	96
14	10	3 Å	rt	18	68
15	50	3 Å	rt	8	94

^aReactions were performed with 0.5 mmol of **1b** and 1.2 equiv of THIQ. Yields are isolated yields of chromatographically purified compounds.

Received: October 2, 2014

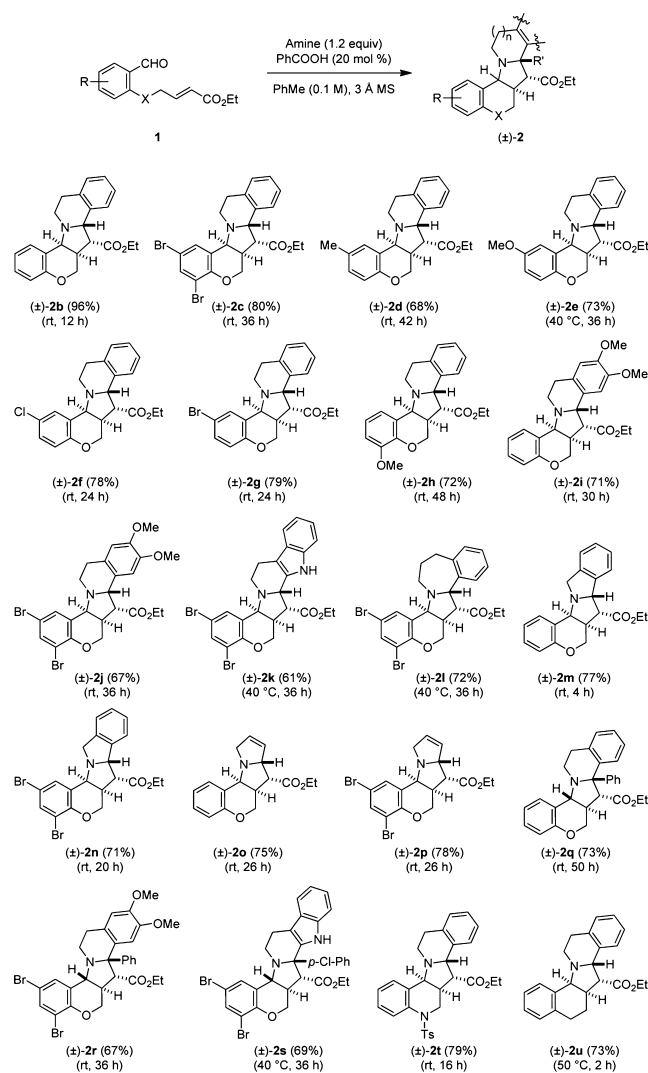
under reflux in toluene required 24 h to reach completion and provided [3 + 2]-cycloaddition product **2b** in 63% yield (Table 1, entry 1). This finding is in excellent agreement with the studies of Grigg and co-workers,⁷ with the increase in reaction time being fully expected based on the reduction in reaction temperature (138 vs 111 °C). As it has been shown that benzoic acid facilitates amine α -functionalization via intermediate azomethine ylides,^{2d} we tested this compound as an additive. Indeed, benzoic acid used at a 20 mol % loading led to marked rate acceleration with the reaction being completed after 2 h (Table 1, entry 2). In addition, **2b** was obtained with an increased yield of 84%. It was found that the reaction proceeded efficiently at temperatures down to 60 °C (Table 1, entries 3–5). However, little product formation was observed after 24 h in an experiment that was conducted at 50 °C (Table 1, entry 6).

In another set of experiments, we evaluated the effect of 3 Å molecular sieves (3 Å MS) on the reaction rate (Table 1, entries 7–9). Compared to the reaction without additives (Table 1, entry 1), addition of 3 Å MS resulted in a marked reduction of reaction time and a slight increase in yield (Table 1, entry 7). The reaction still progressed with a satisfactory rate down to 70 °C, but stalled at 60 °C (Table 1, entries 8, 9). A powerful cooperative effect was observed when the title reaction was conducted at 60 °C in the presence of both benzoic acid (20 mol %) and 3 Å MS. These conditions allowed for the isolation of **2b** in 91% yield after only 2 h (Table 1, entry 10, compare to entry 5). The use of 4 Å MS in an otherwise identical experiment gave very similar results (Table 1, entry 11). Remarkably, the reaction was found to proceed efficiently even at room temperature. In fact, the highest yield of **2b** (96%) was observed in this instance (Table 1, entry 13). A reduction in the loading of benzoic acid to 10 mol % had a negative effect on the yield of **2b** (Table 1, entry 14), whereas an increase to 50 mol % did not offer any significant advantages over the 20 mol % catalyst loading (Table 1, entry 15).⁹

Reactions of THIQ with a range of aldehydes derived from differently substituted salicylaldehydes were evaluated under the optimized conditions (Scheme 2). In all cases, products were obtained in good yields at room temperature or slightly elevated temperatures (products **2b–h**). Importantly, other benzylic amines including 6,7-dimethoxy-THIQ, tryptoline, isindoline, and 3-pyrroline also underwent the title reaction under equally mild conditions. Interestingly, even sterically demanding 1-aryl THIQ's and a 1-aryl-tryptoline readily participated in the reaction sequence to generate polycyclic amines containing tetrasubstituted carbon centers (products **2q–s**). Finally, the oxygen linker present in all products discussed so far could be replaced with nitrogen or carbon linkers (e.g., products **2t** and **2u**). Notably, in all cases, products were isolated as single diastereomers.

The scope of the [3 + 2]-cycloaddition could be readily expanded to nonbenzylic amines (Scheme 3). Not surprisingly, higher reaction temperatures were found to be required for these more challenging substrates. While pyrrolidine was sufficiently reactive at reflux temperature in toluene,¹⁰ superior results were obtained under microwave conditions. Following a reaction time of 30 min at 160 °C, product **4a** was obtained in 82% yield. Under similar conditions, piperidine, azepane, morpholine, thiomorpholine, and indoline²¹ also underwent the corresponding [3 + 2]-cycloadditions. Other aldehydes including those with nitrogen or carbon linkers also participated in efficient product formation.

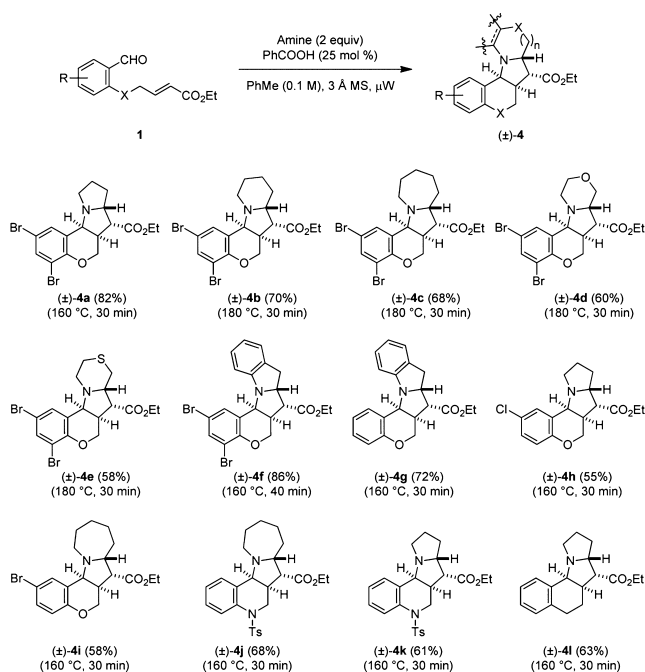
Scheme 2. Substrate Scope for the [3 + 2]-Cycloaddition with Benzylic Amines



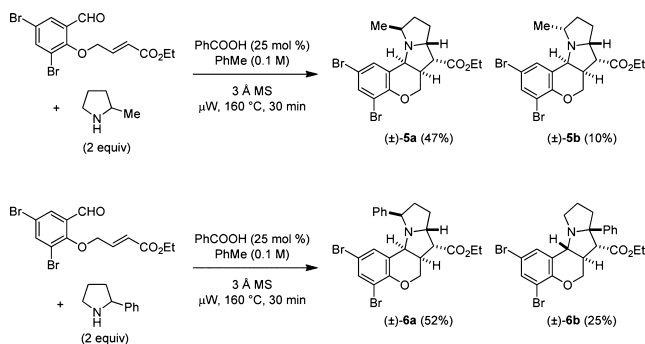
In order to explore the regioselectivity of the dipolar cycloaddition with nonsymmetrical amines, the reaction was conducted with 2-substituted pyrrolidines (Scheme 4). A reaction with 2-methylpyrrolidine resulted in the formation of the two diastereomeric products **5a** and **5b** in an approximately 5:1 ratio. Interestingly, no regioisomeric product was observed that would have resulted from the functionalization of the C–H bond α to the methyl group in 2-methylpyrrolidine. This preference for the functionalization of a secondary over an electronically favorable tertiary C–H bond is presumably due to steric reasons. Slightly higher overall yields were observed in the related reaction with 2-phenylpyrrolidine. Here, two regioisomeric products **6a** and **6b** were obtained in 52% and 25% yield, respectively, amounting to a 2-fold preference for the functionalization of a secondary over an electronically favorable tertiary benzylic C–H bond.

Lastly, we wanted to establish whether a stereospecific [3 + 2]-cycloaddition could be accomplished with a chiral non-racemic amine substrate, as this would add further value to this type of transformation. To this end, enantioenriched (*S*)-3-isopropyl-THIQ (88% ee)¹¹ was allowed to react with aldehyde **1b** (Scheme 5). In the event, product **7** was isolated as a single

Scheme 3. Substrate Scope for the [3 + 2]-Cycloaddition with Less Reactive Amines

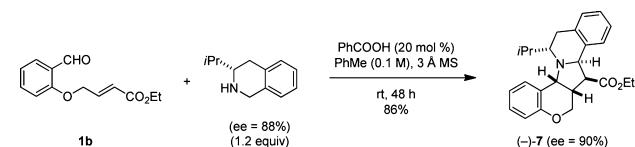


Scheme 4. Regioselectivity in the [3 + 2]-Cycloaddition with Nonsymmetrical Amines



diastereomer in 86% yield and with 90% ee, illustrating the feasibility of the asymmetric approach.

Scheme 5. Asymmetric Variant of the [3 + 2]-Cycloaddition



In conclusion, we have demonstrated that simple cyclic amines engage in reaction cascades with aldehydes bearing a pendent dipolarophile to provide polycyclic products via amine α -C–H bond functionalization. The key step is a highly diastereoselective [3 + 2]-cycloaddition of in situ generated azomethines ylides. The overall process is facilitated by the combined action of benzoic acid and molecular sieves. This approach provides a valuable alternative to the widely used decarboxylative versions of these transformations, in particular in those instances where the corresponding amino acids are not readily available.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data, including X-ray crystal structures of products **2g**, **2q**, **4a**, and **5a** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: seidel@rutchem.rutgers.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the NIH–NIGMS (R01GM101389-01) is gratefully acknowledged. K.M. acknowledges UGC, New Delhi for a Raman Postdoctoral Fellowship. We thank Dr. Tom Emge (Rutgers University) for crystallographic analysis.

■ REFERENCES

- (1) Selected reviews on azomethine ylides: (a) Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*, Vol. 1; Wiley: New York, N.Y., 1984. (b) Padwa, A.; Ed. *1,3-Dipolar Cycloaddition Chemistry*, Vol. 2; Wiley: New York, N.Y., 1984. (c) Padwa, A.; Pearson, W. H. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Wiley: Chichester, U.K., 2002; Vol. 59. (d) Najera, C.; Sansano, J. M. *Curr. Org. Chem.* **2003**, 7, 1105. (e) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, 105, 2765. (f) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, 106, 4484. (g) Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2006**, 2873. (h) Bonin, M.; Chauveau, A.; Micouin, L. *Synlett* **2006**, 2349. (i) Nair, V.; Suja, T. D. *Tetrahedron* **2007**, 63, 12247. (j) Najera, C.; Sansano, J. M. *Top. Heterocycl. Chem.* **2008**, 12, 117. (k) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, 108, 2887. (l) Nyerges, M.; Toth, J.; Groundwater, P. W. *Synlett* **2008**, 1269. (m) Pineiro, M.; Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2009**, 5287. (n) Burrell, A. J. M.; Coldham, I. *Curr. Org. Synth.* **2010**, 7, 312. (o) Anac, O.; Gungor, F. S. *Tetrahedron* **2010**, 66, 5931. (p) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2011**, 47, 6784.
- (2) Selected examples from our laboratory: (a) Zhang, C.; De, C. K.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, 130, 416. (b) Deb, I.; Seidel, D. *Tetrahedron Lett.* **2010**, 51, 2945. (c) Zhang, C.; Das, D.; Seidel, D. *Chem. Sci.* **2011**, 2, 233. (d) Deb, I.; Das, D.; Seidel, D. *Org. Lett.* **2011**, 13, 812. (e) Ma, L.; Chen, W.; Seidel, D. *J. Am. Chem. Soc.* **2012**, 134, 15305. (f) Das, D.; Sun, A. X.; Seidel, D. *Angew. Chem., Int. Ed.* **2013**, 52, 3765. (g) Das, D.; Seidel, D. *Org. Lett.* **2013**, 15, 4358. (h) Dieckmann, A.; Richers, M. T.; Platonova, A. Y.; Zhang, C.; Seidel, D.; Houk, K. N. *J. Org. Chem.* **2013**, 78, 4132. (i) Richers, M. T.; Deb, I.; Platonova, A. Y.; Zhang, C.; Seidel, D. *Synthesis* **2013**, 45, 1730. (j) Chen, W.; Wilde, R. G.; Seidel, D. *Org. Lett.* **2014**, 16, 730. (k) Seidel, D. *Org. Chem. Front.* **2014**, 1, 426. (l) Chen, W.; Kang, Y.; Wilde, R. G.; Seidel, D. *Angew. Chem., Int. Ed.* **2014**, 53, 5179. (m) Richers, M. T.; Breugst, M.; Platonova, A. Y.; Ullrich, A.; Dieckmann, A.; Houk, K. N.; Seidel, D. *J. Am. Chem. Soc.* **2014**, 136, 6123. (n) Chen, W.; Seidel, D. *Org. Lett.* **2014**, 16, 3158. (o) Jarvis, C. L.; Richers, M. T.; Breugst, M.; Houk, K. N.; Seidel, D. *Org. Lett.* **2014**, 3556.
- (3) Reviews on redox economy: (a) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, 48, 2854. (b) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, 38, 3010. (c) Ketcham, J. M.; Shin, I.; Montgomery, T. P.; Krische, M. J. *Angew. Chem., Int. Ed.* **2014**, 53, 9142.
- (4) Selected reviews on amine α -functionalization, including redox-neutral approaches: (a) Murahashi, S.-I. *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 2443. (b) Matyus, P.; Elias, O.; Tapolcsanyi, P.; Polonka-Balint, A.; Halasz-Dajka, B. *Synthesis* **2006**, 2625. (c) Campos, K. R.

Chem. Soc. Rev. **2007**, 36, 1069. (d) Li, C.-J. *Acc. Chem. Res.* **2009**, 42, 335. (e) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, 16, 2654. (f) Jones, K. M.; Klusmann, M. *Synlett* **2012**, 23, 159. (g) Pan, S. C. *Beilstein J. Org. Chem.* **2012**, 8, 1374. (h) Mitchell, E. A.; Peschiulli, A.; Lefevre, N.; Meerpoel, L.; Maes, B. U. W. *Chem.—Eur. J.* **2012**, 18, 10092. (i) Platonova, A. Y.; Glukhareva, T. V.; Zimovets, O. A.; Morzherin, Y. Y. *Chem. Heterocycl. Compd.* **2013**, 49, 357. (j) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, 113, 5322. (k) Peng, B.; Maulide, N. *Chem.—Eur. J.* **2013**, 19, 13274. (l) Qin, Y.; Lv, J.; Luo, S. *Tetrahedron Lett.* **2014**, 55, 551. (m) Wang, L.; Xiao, J. *Adv. Synth. Catal.* **2014**, 356, 1137. (n) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, 53, 74. (o) Vo, C.-V. T.; Bode, J. W. *J. Org. Chem.* **2014**, 79, 2809. (p) Haibach, M. C.; Seidel, D. *Angew. Chem., Int. Ed.* **2014**, 53, 5010.

(5) Examples of redox-neutral amine C–H functionalizations that likely involve azomethine ylides as intermediates: (a) Oda, M.; Fukuchi, Y.; Ito, S.; Thanh, N. C.; Kuroda, S. *Tetrahedron Lett.* **2007**, 48, 9159. (b) Zheng, L.; Yang, F.; Dang, Q.; Bai, X. *Org. Lett.* **2008**, 10, 889. (c) Pahadi, N. K.; Paley, M.; Jana, R.; Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2009**, 131, 16626. (d) Mao, H.; Xu, R.; Wan, J.; Jiang, Z.; Sun, C.; Pan, Y. *Chem.—Eur. J.* **2010**, 16, 13352. (e) Xue, X. S.; Yu, A.; Cai, Y.; Cheng, J. P. *Org. Lett.* **2011**, 13, 6054. (f) Zheng, Q.-H.; Meng, W.; Jiang, G.-J.; Yu, Z.-X. *Org. Lett.* **2013**, 15, 5928. (g) Lin, W.; Cao, T.; Fan, W.; Han, Y.; Kuang, J.; Luo, H.; Miao, B.; Tang, X.; Yu, Q.; Yuan, W.; Zhang, J.; Zhu, C.; Ma, S. *Angew. Chem., Int. Ed.* **2014**, 53, 277. (h) Haldar, S.; Mahato, S.; Jana, C. K. *Asian J. Org. Chem.* **2014**, 3, 44. (i) Li, J.; Wang, H.; Sun, J.; Yang, Y.; Liu, L. *Org. Biomol. Chem.* **2014**, 12, 2523.

(6) Other recent examples of redox-neutral amine C–H functionalizations: (a) Barluenga, J.; Fananas-Mastral, M.; Aznar, F.; Valdes, C. *Angew. Chem., Int. Ed.* **2008**, 47, 6594. (b) Polonka-Balint, A.; Saraceno, C.; Ludányi, K.; Bényei, A.; Matyus, P. *Synlett* **2008**, 2846. (c) Mori, K.; Ohshima, Y.; Ehara, K.; Akiyama, T. *Chem. Lett.* **2009**, 38, 524. (d) Ruble, J. C.; Hurd, A. R.; Johnson, T. A.; Sherry, D. A.; Barbachyn, M. R.; Toogood, P. L.; Bundy, G. L.; Graber, D. R.; Kamilar, G. M. *J. Am. Chem. Soc.* **2009**, 131, 3991. (e) Cui, L.; Peng, Y.; Zhang, L. *J. Am. Chem. Soc.* **2009**, 131, 8394. (f) Dunkel, P.; Turos, G.; Bényei, A.; Ludányi, K.; Matyus, P. *Tetrahedron* **2010**, 66, 2331. (g) Zhou, G.; Zhang, J. *Chem. Commun.* **2010**, 46, 6593. (h) Kang, Y. K.; Kim, S. M.; Kim, D. Y. *J. Am. Chem. Soc.* **2010**, 132, 11847. (i) Cao, W. D.; Liu, X. H.; Wang, W. T.; Lin, L. L.; Feng, X. M. *Org. Lett.* **2011**, 13, 600. (j) Mori, K.; Ehara, K.; Kurihara, K.; Akiyama, T. *J. Am. Chem. Soc.* **2011**, 133, 6166. (k) Barluenga, J.; Fananas-Mastral, M.; Fernandez, A.; Aznar, F. *Eur. J. Org. Chem.* **2011**, 1961. (l) Zhou, G. H.; Liu, F.; Zhang, J. L. *Chem.—Eur. J.* **2011**, 17, 3101. (m) He, Y. P.; Du, Y. L.; Luo, S. W.; Gong, L. Z. *Tetrahedron Lett.* **2011**, 52, 7064. (n) Jurberg, I. D.; Peng, B.; Woestefeld, E.; Wasserloos, M.; Maulide, N. *Angew. Chem., Int. Ed.* **2012**, 51, 1950. (o) Sugiishi, T.; Nakamura, H. *J. Am. Chem. Soc.* **2012**, 134, 2504. (p) Wang, Y.; Chi, Y.; Zhang, W. X.; Xi, Z. F. *J. Am. Chem. Soc.* **2012**, 134, 2926. (q) Han, Y. Y.; Han, W. Y.; Hou, X.; Zhang, X. M.; Yuan, W. C. *Org. Lett.* **2012**, 14, 4054. (r) Chen, L. J.; Zhang, L.; Lv, J.; Cheng, J. P.; Luo, S. Z. *Chem.—Eur. J.* **2012**, 18, 8891. (s) He, Y. P.; Wu, H.; Chen, D. F.; Yu, J.; Gong, L. Z. *Chem.—Eur. J.* **2013**, 19, 5232. (t) Kang, Y. K.; Kim, D. Y. *Chem. Commun.* **2014**, 50, 222. (u) Mori, K.; Kurihara, K.; Akiyama, T. *Chem. Commun.* **2014**, 50, 3729. (v) Mori, K.; Kurihara, K.; Yabe, S.; Yamanaka, M.; Akiyama, T. *J. Am. Chem. Soc.* **2014**, 136, 3744.

(7) Ardill, H.; Fontaine, X. L. R.; Grigg, R.; Henderson, D.; Montgomery, J.; Sridharan, V.; Surendrakumar, S. *Tetrahedron* **1990**, 46, 6449.

(8) Other examples for azomethine ylide formation/[3 + 2]-cycloaddition with secondary amines: (a) Ardill, H.; Grigg, R.; Sridharan, V.; Surendrakumar, S.; Thianpatanagul, S.; Kanajun, S. *J. Chem. Soc., Chem. Commun.* **1986**, 602. (b) Ardill, H.; Dorrity, M. J. R.; Grigg, R.; Leon-Ling, M. S.; Malone, J. F.; Sridharan, V.; Thianpatanagul, S. *Tetrahedron* **1990**, 46, 6433. (c) Wang, B.; Mertes, M. P.; Mertes, K. B.; Takusagawa, F. *Tetrahedron Lett.* **1990**, 31, 5543. (d) Wittland, C.; Arend, M.; Risch, N. *Synthesis* **1996**, 367.

(e) Marx, M. A.; Grillot, A.-L.; Louer, C. T.; Beaver, K. A.; Bartlett, P. A. *J. Am. Chem. Soc.* **1997**, 119, 6153. (f) Grigg, R.; Sridharan, V.; Thornton-Pett, M.; Wang, J.; Xu, J.; Zhang, J. *Tetrahedron* **2002**, 58, 2627. (g) Parmar, N. J.; Pansuriya, B. R.; Labana, B. M.; Kant, R.; Gupta, V. K. *RSC Adv.* **2013**, 3, 17527. (h) Rahman, M.; Bagdi, A. K.; Mishra, S.; Hajra, A. *Chem. Commun.* **2014**, 50, 2951.

(9) The reaction of **1b** with THIQ (1.2 equiv) and the benzoic acid catalyst (20 mol %) was also performed on a larger scale (1 g of **1b**). To avoid the use of large amounts of molecular sieves, the reaction was conducted under reflux in benzene (0.1 M) with a Dean–Stark trap. The reaction went to completion within 2 h and provided **2b** in 91% yield.

(10) Thus far, the highest yield for **4a** obtained under reflux conditions in toluene was 41%.

(11) García, D.; Foubelo, F.; Yus, M. *Eur. J. Org. Chem.* **2010**, 2893.