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# Amine-Promoted, Organocatalytic Aziridination of Enones

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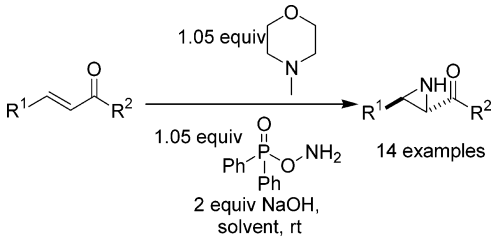
## ABSTRACT




**A novel method is presented using N–N ylides (prepared by in situ amination of a tertiary amine) for the aziridination of a range of enone systems. The amine may be used sub-stoichiometrically, and promising levels of enantioselectivity are observed with quinine as promoter.**

Aziridines are extremely important synthetic building blocks[1] that can be opened in a stereocontrolled manner with various nucleophiles,[2] providing access to a wide range of important nitrogen-containing products. However, they are less widely used in synthesis than their oxygen counterparts, the epoxides, partly because there are fewer efficient methods for alkene aziridination relative to epoxidation.[3] This is particularly true when enantioselective methods are considered.[4] Most of the catalytic methods involve transition metal nitrenoid species and are often inefficient, requiring the alkene substrate to be used in excess relative to the nitrogen source, and afford good yields and enantioselectivities only for a restricted range of alkenes. Additionally, many methods provide aziridines protected as *N*-tosyl derivatives, a protecting group that can prove difficult to remove. Currently, the rapidly developing area of organocatalysis[5] is revealing that small organic molecules can offer valuable alternatives to transition metal catalysts, often with the advantages that reactions can be performed without the need for rigorous exclusion of air or water. Progress in organocatalytic alkene aziridination has been limited to asymmetric phase-transfer catalysis, which provides acceptable results only for *tert*-butyl acrylate.[6] In considering possible novel organocatalytic methods, we were attracted to a report that bishydrazinium

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(1) For an overview of aziridine chemistry, see: Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247−258.

(2) For review of aziridine openings, see: (a) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701−2743. (b) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347−1365.

(3) For reviews on aziridine synthesis, see: (a) Halfen, J. A. *Curr. Org. Chem.* **2005**, *9*, 657−669. (b) Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905−2919. (c) Osborn, H. M. I.; Sweeney, J. B *Tetrahedron*: *Asymmetry* **1997**, *8*, 1693−1715.

(4) For recent examples of asymmetric metal-catalyzed chalcone aziridination see: (a) Ma, L. G.; Jiao, P.; Zhang, Q. H.; Xu, J. X. *Tetrahedron*: *Asymmetry* **2005**, *16*, 3718−3734. (b) Ma, L. G.; Du, D. M.; Xu, J. X. *J. Org. Chem.* **2005**, *70*, 10155−10158. (c) Xu, J. X.; Ma, L. G.; Jiao, P. *Chem. Commun.* **2004**, 1616−1617. For a two-step asymmetric aziridination of chalcones by using chiral rare-earth metal catalyzed Michael addition of hydroxylamines, see: (d) Jin, X. L.; Sugihara, H.; Daikai, K.; Tateishi, H.; Jin, Y. Z.; Furuno, H.; Inanaga, J. *Tetrahedron* **2002**, *58*, 8321−8329. (e) Sugihara, H.; Daikai, K.; Jin, X. L.; Furuno, H.; Inanaga, J. *Tetrahedron Lett.* **2002**, *43*, 2735−2739.

(5) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138−5175.

(6) (a) Murugan, E.; Siva, A. *Synthesis*, **2005**, 2022−2028. (b) Aires-de-Sousa, J.; Prabhakar, S.; Lobo, A. M.; Rosa, A. M.; Gomes, M. J. S.; Corvo, M. C.; Williams, D. J.; White, A. J. P. *Tetrahedron*: *Asymmetry* **2001**, *12*, 3349−3365. (c) Aires-de-Sousa, J.; Lobo, A. M.; Prabhakar, S. *Tetrahedron Lett.* **1996**, *37*, 3183−3186. (d) Pereira, M. M.; Santos, P. P. O.; Reis, L. V.; Lobo, A. M.; Prabhakar, S. *J. Chem. Soc., Chem. Commun.* **1993**, 38−40.

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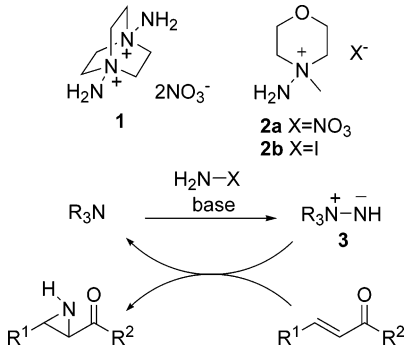
salt **1** (2 equiv), in the presence of NaH/*i*-PrOH as base, could effect aziridination of enones.[7] This salt was prepared by reaction of diazabicyclo[2.2.2]octane (DABCO) with hydroxylamine-*O*-sulfonic acid (HOSA) at elevated temperature. By analogy to an earlier study,[8] the aziridination reaction was assumed to proceed by deprotonation of **1** to give an N−N ylide (aminimine), which then effects aziridination by a Michael addition−ring closure mechanism. Recently, we have shown that the *N*-methylmorpholinium salts **2** effect aziridination of chalcones at room temperature.[9] Since the coproduct of the aziridination reaction is a tertiary amine, we reasoned that it should be possible to construct a catalytic system (Scheme 1), provided that the aminimine **3** could be

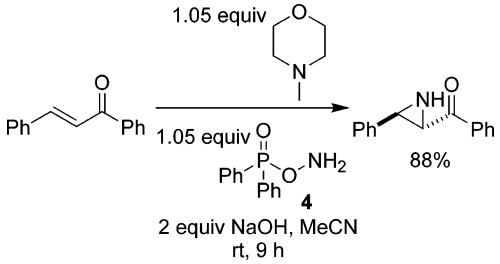
**Scheme 1.** Proposed Catalytic Cycle for Amine-Promoted Aziridination




prepared from a tertiary amine in the presence of the alkene substrate. A further exciting possibility was asymmetric induction if a chiral tertiary amine was employed. Here we describe our preliminary work demonstrating the feasibility of these aims.[10]

Our initial studies attempted to effect in situ aziridination of *E*-chalcone by reaction with *N*-methylmorpholine (NMM), HOSA, and various bases at room temperature. However, none of the desired aziridine product was obtained. In some cases, reduction of the chalcone was observed, presumably due to formation of diimide from the HOSA and base. The apparent failure to aminate the tertiary amine mediator at room temperature is perhaps not surprising given that HOSA generally requires elevated temperatures to accomplish this transformation. We reasoned that a neutral source of electrophilic nitrogen might give faster amination, and were pleased to accomplish our first in situ aziridination (Scheme 2) by using *O*-(diphenylphosphinyl)hydroxylamine (DppONH$_2$) **4**, which can be readily prepared in good yield in one step from commercial hydroxylamine hydrochloride and diphenylphosphinyl chloride.[11] Importantly, control experi-

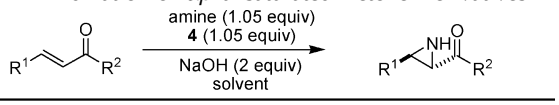
**Scheme 2.** Amine-Promoted Aziridination

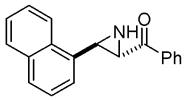
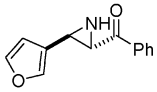
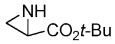
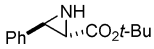



ments established that aziridination does not occur in the absence of the tertiary amine and that a secondary amine (morpholine) does not promote aziridination, lending support to the proposed aminimine pathway. A screen of several tertiary amines and solvents (see the Supporting Information) revealed NMM, *N*-methylpyrrolidine (NMP), and quinuclidine to be the most effective promoters, with fastest reactions in MeCN, $CH_2Cl_2$, or DMF.

We next examined the scope of this novel aziridination procedure. We were pleased to find that the chemistry was

**Table 1.** Aziridination of $\alpha\beta$-unsaturated Ketone Derivatives[a]




| entry | aziridine | amine; solvent | time (h) | yield (%)[b] |
|---|---|---|---|---|
| 1 | $R^1 = m$-$NO_2$Ph | NMM; MeCN | 10 | 75 |
| 2 | $R^1 = p$-CNPh | NMM; MeCN | 10 | 62 |
| 3 | $R^1 = p$-MePh | NMM; MeCN | 10 | 78 |
| 4 | $R^1 = p$-OMePh | NMP; $CH_2Cl_2$ | 24 | 79 |
| 5 | $R^2 = p$-ClPh | NMM; MeCN | 10 | 90 |
| 6 | $R^2 = p$-MePh | NMM; MeCN | 24 | 86 |
| 7 | $R^2 = p$-OMePh | NMM; MeCN | 24 | 97 |
| 8 |  | NMP; $CH_2Cl_2$ | 24 | 67 |
| 9 |  | NMM; MeCN | 6 | 90 |
| 10 | $R^1 = n$-Bu | NMM; $CH_2Cl_2$ | 22 | 83 |
| 11 | $R^1 = i$-Bu | NMM; $CH_2Cl_2$ | 22 | 78 |
| 12 | $R^1 = CH_2CH_2Ph$ | NMM; $CH_2Cl_2$ | 16 | 62 |
| 13 |  | NMM; $CH_2Cl_2$ | 10 | 80 |
| 14 |  | NMM; $CH_2Cl_2$[c] | 40 | 32 |

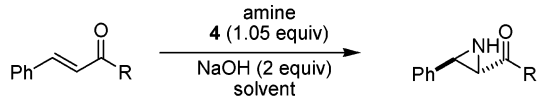
[a] Reaction performed on a 0.240 mmol scale. See the Supporting Information for details. [b] Isolated yields after column chromatography. [c] Reaction performed on a 0.120 mmol scale. NMM = *N*-methylmorpholine. NMP = *N*-methylpyrrolidine.

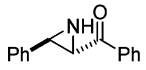
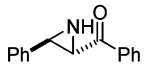
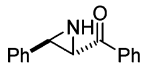
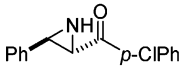
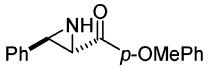
(7) Xu, J.; Jiao, P. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1491−1493.
(8) Ikeda, I.; Machii, Y.; Okahara, M. *Synthesis* **1980**, 650−651.
(9) Armstrong, A.; Carbery, D. R.; Lamont, S. G.; Pape, A. R.; Wincewicz, R. *Synlett* **2006**, 2504−2506.
(10) After initial submission of this work, we became aware of closely related results by Shi and co-workers: Shen, Y.-M.; Zhao, M.-X.; Xu, J.; Shi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 8005−8008.
(11) Colvin, E. W.; Kirby, G. W.; Wilson, A. C. *Tetrahedron Lett.* **1982**, *23*, 3835−3836.

successful for a range of aromatic enones (Table 1). In all cases, the product was obtained exclusively (>95:5) as the *trans*-aziridine. It is especially noteworthy that high yields were obtained for both electron-rich (entries 4 and 7) and electron-poor enones (e.g., entries 1, 2, and 5), since the isolated hydrazinium nitrate salt derived from NMM (**2a**) was restricted to the electron-poor substrates.[9] While the aryl aziridine products in Table 1 are of high synthetic value,[12] the successful extension to alkyl enones is gratifying (entries 10−12), as is the demonstration for the first time that α,β-unsaturated esters can be successfully aziridinated by using this chemistry (entries 13 and 14). Overall, the in situ chemistry appears to have considerably higher scope than the use of isolated hydrazinium salts, as well as being more convenient. An advantage of the method is that it affords *N*-unsubstituted aziridines, which allows flexibility in further functionalizing the nitrogen with a choice of activating group.

With an efficient one-pot aziridination procedure in hand, we now addressed the possibility of using substoichiometric quantities of the amine promoter. Using 50 mol % of NMM under the standard conditions of MeCN/NaOH, we found that a 75% yield of aziridine could be isolated (Table 2, entry 1). A solvent screen indicated that in general best results with substoichiometric amine are obtained in DMF (entries 3−5). These results are noteworthy as they demonstrate the feasibility of using substoichiometric amine as aziridination promoter. We believe that the key to further improvement in turnover is the discovery of a nitrogen source that is more stable to base, and this will be the subject of further optimization.

**Table 2.** Organocatalytic Aziridination of Chalcone Derivatives[a]

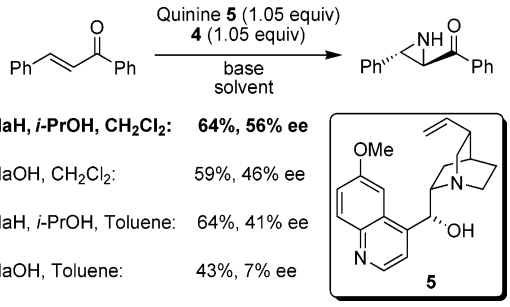



| entry | aziridine | amine (mol %) | solvent | convn (%)[b] | yield (%)[c] |
|---|---|---|---|---|---|
| 1 |  | NMM (50) | MeCN | - | 75 |
| 2 |  | NMM (25) | $CH_2Cl_2$ | - | 49 |
| 3 |  | NMP (25) | DMF | 90 | 66 |
| 4 |  | NMP (25) | DMF | >95 | 54 |
| 5 |  | NMP (25) | DMF | >95 | 61 |

[a] Reaction performed on a 0.120 mmol scale. See the Supporting Information for details. [b] Based on $^1$H NMR analysis of the crude reaction mixture. [c] Isolated yields after column chromatography. NMM = *N*-methylmorpholine. NMP = *N*-methylpyrrolidine.

As well as the use of substoichiometric amine, another important question is whether asymmetric induction is possible when a chiral tertiary amine is used. Building on the earlier successful use of quinuclidine as promoter, the readily available chiral analogue quinine was an attractive starting point. While rates and enantiomeric excesses are highly solvent dependent (see the Supporting Information), promising levels of asymmetric induction can be observed. In the best compromise of yield and enantioselectivity, *E*-chalcone can be aziridinated in 56% ee and 64% yield (Scheme 3).

**Scheme 3.** Quinine-Mediated Enantioselective Aziridination




In conclusion, we have demonstrated that tertiary amines can promote aziridination of enones using Dpp-$ONH_2$ **4** as the stoichiometric nitrogen source, believed to proceed via in situ formation of an N−N ylide (aminimine). We have demonstrated turnover, leading to an organocatalytic enone aziridination, and we have also shown that use of a chiral amine can lead to asymmetric induction. Although the levels of turnover and ee are moderate at present, the strong track record of chiral amines in asymmetric catalysis[13] and the large number of possibilities for screening suggest that a highly enantioselective catalytic system may well be attainable. Further efforts toward this goal along with mechanistic studies and synthetic applications of the aziridine products are underway. In addition to the highly synthetically valuable aziridination process, the demonstration that N−N ylides can be generated in situ from a substoichiometric amine may also have wider synthetic applications.

**Acknowledgment.** We thank the EPSRC (GR/S58508) and AstraZeneca (CASE award to R.W.) for their support of this work. We are grateful to Bristol-Myers Squibb and Merck Sharpe and Dohme for generous support of our research programs. We acknowledge Dr. D. R. Carbery for preliminary experiments on in situ aziridination.

**Supporting Information Available:** General experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Recent example: Xiong, C.; Wang, W.; Cai, C.; Hruby, V. J. *J. Org. Chem.* **2002**, *67*, 1399−1402.

(13) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985−3012.