

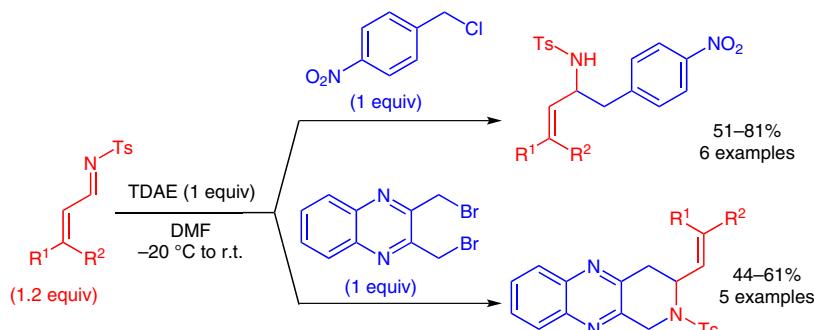
# Mild and Metal-Free Regioselective 1,2-Addition of Carbon Nucleophiles to $\alpha,\beta$ -Unsaturated Imines

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**Abstract** A mild and metal-free regioselective 1,2-addition of carbon nucleophiles to  $\alpha,\beta$ -unsaturated imines has been developed. Good yields and total regioselectivities were achieved by addition of *p*-nitrobenzyl chloride or 2,3-bis(bromomethyl)quinoxaline to  $\alpha,\beta$ -unsaturated tosylimines.

**Key words**  $\alpha,\beta$ -unsaturated tosylimines, regioselectivity, TDAE, addition, metal-free

Allylic amines represent an important structural motif in organic synthesis because of their high versatility in a wide range of organic transformations including asymmetric total syntheses.<sup>1</sup> Furthermore, allylic amine functionality is found in biologically active compounds.<sup>2</sup> Of the different methods available to construct the allylamine scaffold, adding organometallic reagents to  $\alpha,\beta$ -unsaturated imines is one of the most commonly used. When a nucleophile is added to  $\alpha,\beta$ -unsaturated tosylimines, it can lead to 1,2-addition or 1,4-addition. This is influenced by several factors, such as the nature of both organometallic species and substrates. As a general rule, organolithiums are by far the most popular reagents to promote 1,2-addition, whereas organocuprates predominantly promote conjugate addition.

Tetrakis(dimethylamino)ethylene (TDAE) is an organic reducing agent, that reacts with halogenated derivatives to generate a carbanion under mild conditions.<sup>3</sup> In particular, we have shown that from *o*- and *p*-nitrobenzyl chlorides, TDAE is able to generate a nitrobenzyl carbanion that can react with various electrophiles such as aromatic aldehydes,  $\alpha$ -ketoester, ketomalonate,  $\alpha$ -ketolactam, and imine derivatives.<sup>4</sup>

In this study we wished to determine how the carbanion generated by our metal-free conditions would react in the presence of  $\alpha,\beta$ -unsaturated imines. As part of our research program to develop new bioactive compounds,<sup>5</sup> we report herein the application of our TDAE methodology for the regioselective 1,2-addition of *p*-nitrobenzyl chloride (**1**) or 2,3-bis(bromomethyl)quinoxaline (**4**) to a variety of  $\alpha,\beta$ -unsaturated tosylimines **2**.

The reaction between *p*-nitrobenzyl chloride (**1**) and various  $\alpha,\beta$ -unsaturated *N*-tosylimines **2a-f** in the presence of TDAE at -20 °C for one hour, followed by two hours at room temperature, led to the corresponding allylamines<sup>6</sup> in good yields (51–81%) and with total 1,2-regioselectivity (Scheme 1). Reactions with both electron-poor and electron-rich imines produced good yields and complete regioselectivities. Interestingly, the heteroaromatic imine **2e** allowed the formation of the corresponding amine **3e** in good yield. Moreover, the more bulky  $\beta$ -disubstituted imine **2f** gave only the product of 1,2-addition **3f** in 69% yield.

The structure of amine **3a**, the only regioisomer formed by reaction of *p*-nitrobenzyl chloride (**1**) with imine **2a**, was determined by X-ray crystal structure analysis (Figure 1).<sup>7</sup>

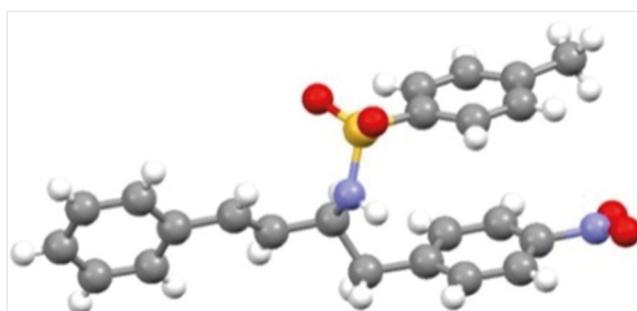
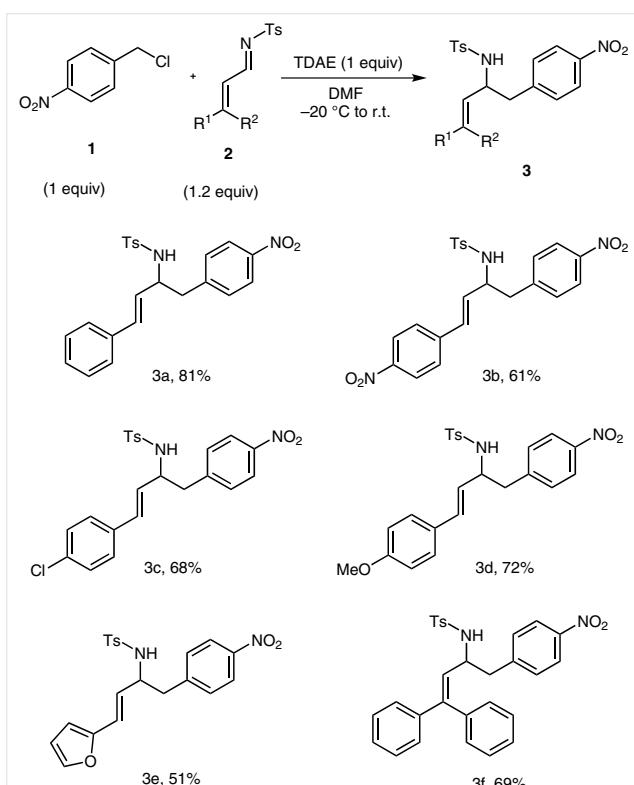
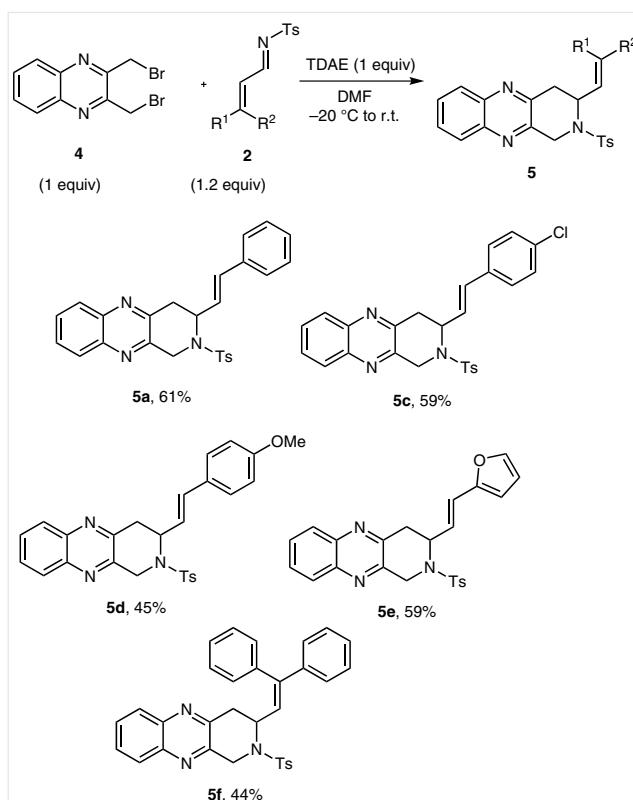


Figure 1 X-ray crystal structure of **3a**



**Scheme 1** Regioselective 1,2-addition of *p*-nitrobenzyl chloride (**1**) to  $\alpha,\beta$ -unsaturated tosylimines **2** using the TDAE strategy. *Reagents and conditions:* **1** (0.2 mmol), **2** (0.24 mmol), and TDAE (0.2 mmol) in anhydrous DMF stirred at  $-20\text{ }^{\circ}\text{C}$  for 1 h and then maintained at r.t. for 2 h; yields are isolated yields after purification by chromatography.



**Scheme 2** Regioselective 1,2-addition of 2,3-bis(bromomethyl)quinoxaline (**4**) to  $\alpha,\beta$ -unsaturated tosylimines **2** using the TDAE strategy. *Reagents and conditions:* **1** (0.2 mmol), **2** (0.24 mmol), and TDAE (0.2 mmol) in anhydrous DMF stirred at  $-20\text{ }^{\circ}\text{C}$  for 1 h and then maintained at r.t. for 2 h; yields are isolated yields after purification by chromatography.

Since 2003, we have introduced a new program directed toward the development of original synthetic methods using TDAE methodology in medicinal chemistry.<sup>8</sup> In this context, we recently described the synthesis of quinoxaline derivatives which could offer very interesting biological properties.<sup>9</sup> Thus, we describe herein the metal-free synthesis of five new substituted pyrido[3,4-*b*]quinoxalines using TDAE in the presence of 2,3-bis(bromomethyl)quinoxaline (**4**) and various  $\alpha,\beta$ -unsaturated *N*-tosylimines **2** (Scheme 2).

Both electron-poor and electron-rich imines produced good yields and complete regioselectivities. Interestingly, the reaction conditions are tolerant with the formation of amine **5e** from heteroaromatic imine **2e**. Moreover, the more bulky  $\beta$ -disubstituted imine **2f** gave only the product of 1,2-addition **5f** in 44% yield. The mechanism could involve nucleophilic addition of carbanion formed by the action of TDAE with 2,3-bis(bromomethyl)quinoxaline on the imine group of sulfonimine **2** followed by an intramolecular nucleophilic substitution of the second bromomethyl group.<sup>9b</sup>

In conclusion, the regioselective addition of *p*-nitrobenzyl chloride (**1**) or 2,3-bis(bromomethyl)quinoxaline (**4**) to  $\alpha,\beta$ -unsaturated tosylimines using the TDAE strategy allowed the synthesis of allylamines in good yields and complete 1,2-regioselectivity. The tolerance of nitro groups and heteroaromatic nucleophiles such as quinoxaline derivatives suggests that this method is a good alternative to the use of organometallic reagents to prepare allylic amines. Further research is in progress to extend the scope to an asymmetric version using enantiopure  $\alpha,\beta$ -unsaturated *N*-sulfinimines.

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## Supporting Information

Supporting information for this article is available online at <http://dx.doi.org/10.1055/s-0035-1560574>.

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- (6) **General Procedure**  
 To a stirred solution of *p*-nitrobenzyl chloride (**1**) or 2,3-bis(bromomethyl)quinoxaline (**4**, 0.2 mmol) and *N*-tosylimine **2** (0.24 mmol) in DMF (1 mL) at -20 °C was added TDAE (0.2 mmol). The solution was vigorously stirred at -20 °C for 1 h and then maintained at r.t. for 2 h. Water (5 mL) was added, and the aqueous solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 15 mL). The combined organic layers were washed with H<sub>2</sub>O (20 mL) and dried over MgSO<sub>4</sub>. Filtration and evaporation of the solvent furnished the crude product. Purification by silica gel chromatography (PE-EtOAc from 8:2 to 7:3 depending on the polarity of substrate) afforded pure amine products **3** or **5**.
- (*E*)-4-Methyl-N-(1-(4-nitrophenyl)-4-phenylbut-3-en-2-yl)benzenesulfonamide (**3a**)  
 81% yield; yellow solid; mp 189–191 °C. <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>): δ = 8.04 (d, *J* = 8.5 Hz, 2 H), 7.60 (d, *J* = 8.1 Hz, 2 H), 7.26–7.12 (m, 9 H), 6.24 (d, *J* = 15.9 Hz, 1 H), 5.85 (dd, *J* = 15.9, 7.0 Hz, 1 H), 4.75 (d, *J* = 7.9 Hz, 1 H), 4.29–4.18 (m, 1 H), 3.03–2.98 (m, 2 H), 2.31 (s, 3 H). <sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>): δ = 147.0, 144.4, 143.8, 137.6, 135.8, 132.5, 130.5, 129.7, 128.7, 128.3, 127.4, 127.2, 126.6, 123.8, 56.9, 42.3, 21.5. ESI-HRMS: *m/z* [M + NH<sub>4</sub>]<sup>+</sup> calcd for [C<sub>23</sub>H<sub>26</sub>N<sub>3</sub>O<sub>4</sub>S]<sup>+</sup>: 440.1639; found: 440.1640.
- (*E*-3-Styryl-2-tosyl-1,2,3,4-tetrahydropyrido[3,4-*b*]quinoxaline (**5a**)  
 61% yield; yellow solid; mp 72–75 °C. <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>): δ = 8.02–7.95 (m, 2 H), 7.79 (d, *J* = 8.2 Hz, 2 H), 7.75–7.71 (m, 2 H), 7.22–7.16 (m, 5 H), 7.05–7.01 (m, 2 H), 6.38 (d, *J* = 16.1 Hz, 1 H), 5.86 (dd, *J* = 16.1, 5.5 Hz, 1 H), 5.32 (br s, 1 H), 5.12 (d, *J* = 17.6 Hz, 1 H), 4.50 (d, *J* = 17.6 Hz, 1 H), 3.55 (dd, *J* = 17.3, 5.9 Hz, 1 H), 3.38 (dd, *J* = 17.3, 2.0 Hz, 1 H), 2.34 (s, 3 H). <sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>): δ = 149.4, 148.0, 144.1, 141.9, 141.4, 136.3, 135.7, 134.2, 130.1, 130.0, 128.8, 128.7, 128.6, 128.3, 127.7, 126.6, 124.6, 53.4, 46.4, 36.9, 21.6 (one carbon missing due to overlap). ESI-HRMS: *m/z* [M + H]<sup>+</sup> calcd for [C<sub>26</sub>H<sub>24</sub>N<sub>3</sub>O<sub>2</sub>S]<sup>+</sup>: 442.1584; found: 442.1584.
- (7) CCDC 1413021 contains the supplementary crystallographic data of compound **3a** for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via [http://www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
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