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# *N*-Tosylimidates in highly enantioselective organocatalytic Michael reactions

Antonio Massa, Naoto Utsumi, Carlos F. Barbas III *

*The Skaggs Institute for Chemical Biology and the Departments of Chemistry and Molecular Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, United States*

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ABSTRACT

*N*-Tosylimidates acted as nucleophiles in highly enantioselective organocatalytic Michael addition reactions to α,β-unsaturated aldehydes in the presence of a catalytic amount of trialkylsilyl-protected diarylprolinol. In particular, α-phenyl-substituted *N*-tosylimidates showed good reactivity. We also demonstrate that the kinetic acidity of the α-proton of α-phenyl *N*-tosylimidate as measured by proton/deuterium NMR exchange experiments is correlated with the potential of *N*-tosylimidates to act as nucleophiles in organocatalytic reactions.



The design and the use of new nucleophiles is an important challenge that must be addressed in order to expand the scope of direct organocatalytic reactions.[1] Typically, the in situ generation of effective nucleophiles based on reversible deprotonation and amine catalysts under mild organocatalytic reaction conditions requires p$K_a$ tuning since the proton to be abstracted must be removed by a relatively weak amine base.[2] For reactions using primary and secondary amine catalysts, the p$K_a$ barrier for nucleophile activation lies between the p$K_a$ values of 16 and 17. Simple esters, with a p$K_a$ of about 19, are inert in these organocatalytic reactions, whereas activated esters, like diethyl malonate with a p$K_a$ of 16.4, are widely used.[3]

Our recent studies demonstrated that simple trifluoroethyl thioesters were effective in enantioselective organocatalytic Michael addition reactions to α,β-unsaturated aldehydes in the presence of trialkylsilyl-protected diarylprolinol.[2] In the course of these analyses, we evaluated the kinetic acidity of the α-proton of a series of thioesters in proton/deuterium NMR exchange experiments. This led us to propose that this method could be used to determine the potential of molecules to act as nucleophiles in organocatalytic reactions.

Imidates, also known as imidoates, imidic acid esters, or imido esters, are important pharmacophores and useful synthetic building blocks.[4] Recent analyses of the transformations of imidates have increased interest in these molecules as functional groups.[5] In order to investigate the potential of imidates in enantioselective organocatalytic Michael addition reactions, we first evaluated the kinetic acidity of the α-proton of *N*-sulfonylimidate **1a**.

The results, shown in Figure 1, revealed a very rapid exchange with a $t_{1/2}$ of less than 10 min,[6] comparable to that determined for α-nitrophenyl trifluoroethyl thioester ($t_{1/2} < 5$ min) and significantly faster than that of the unsubstituted α-phenyl trifluoroethyl thioester ($t_{1/2} \sim 230$ min). These results suggest that *N*-sulfonylimidate **1a** should be an effective nucleophile under the iminium-based Michael reaction conditions previously that were used for trifluoroethyl thioesters.

We then tested the reactivity of *N*-tosylimidate **1a** in a model organocatalytic Michael addition to cinnamaldehyde in the presence of catalytic amount of racemic trialkylsilyl-protected diarylprolinol **3** and benzoic acid co-catalyst in a variety of reaction conditions (Scheme 1, Table 1). In this catalyst combination, diarylprolinol **3** performs dual roles as both the base and the iminium catalyst, whereas the benzoic acid acts as a catalyst of iminium formation.[2a] In the polar protic solvent methanol, the desired product was obtained after 16 h at room temperature with quantitative conversion and in 86% isolated yield (mixture of **4a** diastereomers) (Table 1, entries 1 and 2). Significant solvent effects were noted,

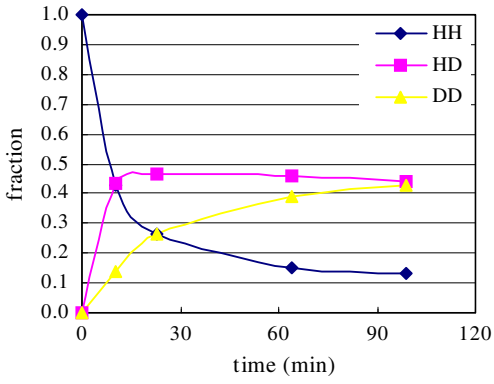


**Figure 1.** Proton/deuterium exchange experiment of **1a**: proton deuterium NMR exchange experiments performed in the presence of $CD_3OD$ and catalytic quantity of $Oct_3N$ were used to determine the rate of exchange of the α-proton of *N*-sulfonylimidate **1a**.

* Corresponding author. Tel.: +1 858 784 9098; fax: +1 858 784 2583.
*E-mail address:* carlos@scripps.edu (C. F. Barbas III).

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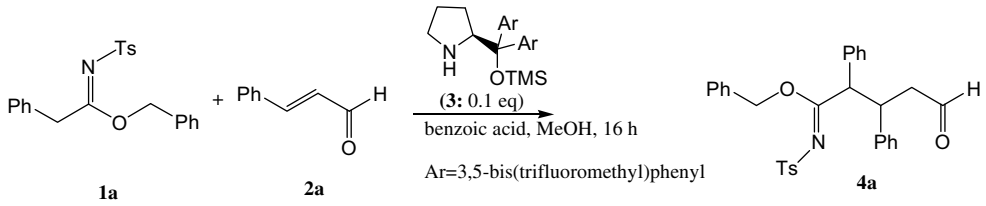



**Scheme 1.**

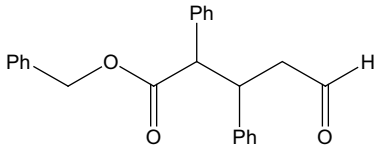
**Table 1**
Yields of organocatalytic Michael addition of **1a** to cinnamaldehyde **2a** using racemic catalyst **3** under various conditions

| Entry | Solvent | Time (h) | Conversion[a] (%) | Yield[b] | dr[a] |
|---|---|---|---|---|---|
| 1 | MeOH | 6 | 45 | 30 | 56/44 |
| 2 | MeOH | 16 | Quantitative | 86 | 55/45 |
| 3 | DMF | 16 | 40 | 28 | 57/43 |
| 4 | $Et_2O$ | 16 | 20 | n.d. | 55/45 |
| 5 | Hexane[c] | 16 | <10 | n.d. | n.d. |
| 6 | Toluene | 16 | <10 | n.d. | n.d. |

[a] Determined for crude reaction mixture by $^1$H NMR.
[b] Yields refer to the mixture of diastereomers.
[c] Compound **1a** was not very soluble in hexane.

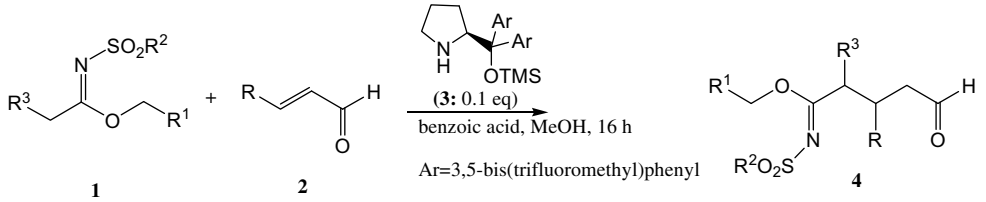
and the conversion decreased rapidly with decreasing polarity of the solvent used (Table 1, entries 3–6).

To optimize the reaction conditions, we studied the enantioselectivity of the process using enantiopure, protected diarylprolinol **3** (Scheme 2, Table 2). Our attempts to separate the two diastereomers of **4a** by chromatography failed, and we were able to isolate only the minor diastereomer in a 44% yield. The reaction, however, was highly enantioselective, and the isolated product was obtained with 98% ee (Table 2, entry 1). The by-product **5a** was isolated in 26% yield, suggesting that the major diastereomer may decompose during chromatography. Analysis of the mixed *syn/anti* products prior to chromatography indicated that the major diastereomer was also formed with high ee (Table 2, entry 2).




**5a**

With the methyl *N*-sulfonylimidate **1b**, we observed a good conversion; again the major diastereomer of **4b** was unstable to chromatography. The minor diastereomer was readily isolated with high ee (Table 2, entry 3). The imidate **1c**, with a strong electron-withdrawing group in *para* position, showed a good reactivity,




**Scheme 2.**

**Table 2**
Organocatalyzed Michael addition of imidates **1** to α,β-unsaturated aldehydes **2**

| Entry | Aldehyde (R) | $R^1$ | $R^2$ | $R^3$ | Conversion (%)[a] | Yield (%) | dr[a] | ee[b] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | **2a** Ph | **1a** Ph | 4-$CH_3C_6H_4$ | Ph | Quantitative | **4a** 44[c] | 55/45 | 98[d] |
| 2 | **2a** Ph | **1a** Ph | 4-$CH_3C_6H_4$ | Ph | Quantitative | **4a** 85[e] | 55/45 | 97/98[f] |
| 3 | **2a** Ph | **1b** H | 4-$CH_3C_6H_4$ | Ph | 80 | **4b** 38[c] | 55/45 | 93[d] |
| 4 | **2a** Ph | **1c** Ph | 4-$CH_3C_6H_4$ | 4-$CF_3C_6H_4$ | Quantitative | **4c** 87[e] | 60/40 | 87/94[f] |
| 5 | **2a** Ph | **1d** Ph | 4-$CH_3C_6H_4$ | 4-$CH_3C_6H_4$ | 60 | **4d** 50[e] | 57/43 | 95/94[f] |
| 6 | **2a** Ph | **1e** Ph | 4-$CH_3C_6H_4$ | 4-$CH_3OC_6H_4$ | 50 | **4e** 50[e] | 57/43 | –[g] |
| 7 | **2a** Ph | **1f** Ph | 4-$CH_3C_6H_4$ | $CH_3OCH_2$ | 0 | – | – | – |
| 8 | **2a** Ph | **1g** Ph | $CH_3$ | Ph | 50 | n.d.[g] | 57/43 | n.d. |
| 9[h] | **2b** $CH_3$ | **1a** Ph | 4-$CH_3C_6H_4$ | Ph | 70 | **4f** 38/28[i] | 58/42 | 52/45 |
| 10 | **2c** H | **1a** Ph | 4-$CH_3C_6H_4$ | Ph | 0 | – | – | – |
| 11[h] | **2c** H | **1a** Ph | 4-$CH_3C_6H_4$ | Ph | 10 | n.d. | n.d. | n.d. |

[a] Determined for crude product by $^1$H NMR.
[b] Determined by chiral-phase HPLC.
[c] Isolated yield of the minor diastereomer. The major diastereomer decomposed during chromatography.
[d] The ee of minor diastereomer.
[e] Yields refer to the isolated mixture of diastereomers.
[f] The ee was determined prior to chromatography.
[g] The mixture of diastereomers was not stable.
[h] Reaction solvent was DMF.
[i] Isolated yields of major and minor diastereomers, respectively.

which was comparable to that of **1a** (entry 4). The imidates **1d** and **1e** were less reactive, presumably due to an electronic effect of their *para* electron-releasing methyl and methoxy groups, respectively, that decreased the acidity of the α proton (entries 5 and 6). Low stability of the major diastereomer was a common feature for the imidates studied (entries 4–6). Product **4e** was unusually unstable and decomposed within in a few hours after purification (entry 6). Imidate **1f** was completely non-reactive, and at the end of the standard reaction time it was quantitatively recovered (entry 7). The lower reactivity of **1f** may be due to the absence of an aromatic group in the α position; this group may be needed to confer sufficient acidity to the imidate under these mild conditions. The methyl imine imidate was relatively non-reactive and the products formed were unstable (entry 8).

Modification of the Michael acceptor substrate to crotonaldehyde **2b** resulted in a stable product **4f**. We were able to resolve the two diastereomers by chromatography and analyze them independently. Unfortunately, as was the case for our previous studies using this Michael acceptor with trifluoroethyl thioester nucleophiles, the enantioselectivity was only moderate (entry 9). The increased stability of **4f** might be due to decreased steric hindrance relative to the bisaromatic products. Acrolein **2c** was not reactive as a Michael acceptor. In reactions performed in methanol and DMF, we recovered unreacted imidate **1a** almost quantitatively (entries 10 and 11).

In conclusion, we have developed a highly enantioselective organocatalytic Michael addition of *N*-tosylimidates to α,β-unsaturated aldehydes in the presence of catalytic amounts of trialkylsilyl-protected diarylprolinol. Significantly, the evaluation of the kinetic acidity of the α-proton of α-phenyl *N*-tosylimidate in proton/deuterium NMR exchange experiments indicated that rapid rates of α-proton exchange determined using this method are indicative of reactivity as a nucleophile in aminocatalytic reactions.

## Acknowledgments

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6. $t_{1/2}$ is approximated as the time at which the ratio of the imidate **1a** and α-mono-deuterated derivative of **1a** is 1.
   General procedure for the Michael addition of imidates to α,β -unsaturated aldehydes: To a solution of (*S*)-α,α -bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether (**3**) (10 mol %, 0.015 mmol) and benzoic acid (10 mol %, 0.015 mmol) in MeOH (0.20 mL) was added α,β-unsaturated aldehyde (1.3 equiv, 0.195 mmol). After the resulting mixture was stirred at room temperature for 15 min, a previously prepared (2–3 min before addition) MeOH (0.15 mL) solution of the imidate (0.15 mmol) was added dropwise, and the reaction mixture was stirred for 16 h (until the imidate disappeared as indicated by TLC). MeOH was then evaporated, and the conversion and the diastereomeric ratio (dr) was determined by $^1$H NMR of the crude product. The crude mixture was purified by flash chromatography (hexane/EtOAc mixtures) to afford Michael adducts. The enantiomeric purity was determined by chiral-phase HPLC analysis of the products.
   Minor diastereomer (**4a**): viscous oil, $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.39 (s, 3H, C*H*$_3$), 2.45 (ddd, *J* = 17.2, 4.0, 1.2 Hz, 1H, ½ C*H*$_2$CHO), 2.70 (ddd, *J* = 17.2, 10.4, 2.0 Hz, 1H, ½ C*H*$_2$CHO), 4.00 (td, *J* = 11.0, 4.0 Hz, 1H, CHC*H*CH$_2$), 4.68 (d, *J* = 12.0 Hz, 1H, ½PhC*H*$_2$O), 4.87 (d, *J* = 12.0 Hz, 1H, ½PhC*H*$_2$O), 5.44 (d, *J* = 11.0 Hz, 1H, C*H*C=N), 7.09 (d, *J* = 7.2 Hz, 2H, Ar*H*), 7.17 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.19–7.35 (m, 11H, Ar*H*), 7.53 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.63 (d, *J* = 6.8 Hz, 2H, Ar*H*), 9.36 (br s, 1H, C*H*O). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 21.5, 43.3, 48.3, 53.6, 70.7, 126.5, 127.3, 128.2, 128.4, 128.5, 128.6, 128.7, 128.8, 129.1, 129.2, 129.4, 134.2, 135.8, 138.5, 140.6, 143.1, 171.7, 200.2. HRMS: calcd for $C_{31}H_{29}NO_4S$ ($MH^+$) 512.1890, found 512.1896. The ee was determined by chiral HPLC analysis (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, $\lambda$ = 254 nm): $t_R$ (minor enantiomer) = 26.3 min, $t_R$ (major enantiomer) = 35.3 min. $[\alpha]_D^{25}$ − 29.0 (*c* 1.0, $CHCl_3$, 98% ee).