An asymmetric organocatalytic approach towards allylic amines and β-keto amino compounds†

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Received (in Cambridge, UK) 29th July 2009, Accepted 22nd August 2009
First published as an Advance Article on the web 10th September 2009
DOI: 10.1039/b915439f

The enantioselective organocatalysed addition of β-keto benzothiazolesulfones to *N*-Boc-protected imines, leading to intermediates easily transformed into optically active allylic amines or β-keto amino compounds, is presented.

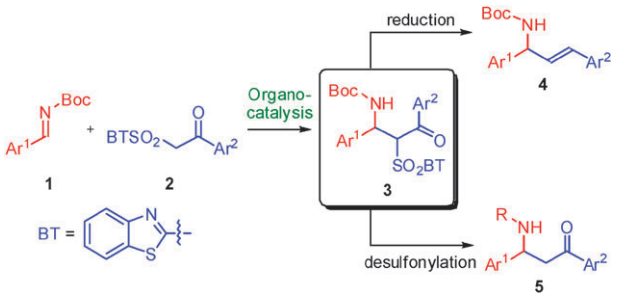
A major goal in chemistry is the development of novel transformations giving rise to enantioenriched products. The stereoselective formation of allylic amines and β-keto amino compounds are of special interest as these compounds are of high value for *e.g.* in the life-science industry and are readily transformed into a number of important products.

Traditionally, the task of forming optically active allylic amines in an enantioselective catalytic manner has been carried out by employing metal-catalysed allylic substitutions[1] or pre-activated boron-based nucleophiles.[2] The few existing enantioselective organocatalytic examples in general comprise alkenes adjacent to a conjugate electron-withdrawing substituent,[3] which limits the scope of compounds that can be synthesised. Thus, it is important to develop diverse procedures towards the allylic amine scaffold, giving access to products otherwise difficult to obtain with a stereoselective organocatalytic approach.

Accessing enantioenriched molecules containing the important β-keto amino functionality, by conducting organocatalytic Mannich reactions, have received great attention.[4] Given the usefulness of this functionality it is of interest to develop new versatile routes leading to new classes of optically active β-keto amino compounds.

Herein, we disclose a new type of organocatalytic approach towards synthetic applications of aryl imines, which may ease *e.g.* combinatorial studies and total synthesis procedures. Thus, the vision is to organocatalytically form a privileged key intermediate, which is easily transformed into various compounds based on a common carbon skeleton, otherwise difficult to access in a stereoselective organocatalytic manner.

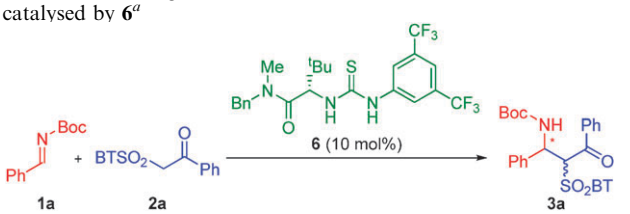
We envisioned that employing the heteroaryl β-ketosulfones **2**[5] to react with *N*-Boc-protected imines **1** under organocatalytic conditions would allow us to produce the enantioenriched key intermediate **3** (Scheme 1). Under mild reductive conditions, **3** can be transformed to optically active allylic amines **4** *via* a Smiles rearrangement,[5,6] while various desulfonylation reactions give the optically active Mannich products **5**. As previously described, accessing these acetophenone-derived Mannich products in an organocatalytic manner has been a difficult task, often leading to discouraging outcomes.[4] Therefore, an alternative protocol for the formation of these compounds is very attractive.



Scheme 1 Organocatalytic formation of optically active allylic amines and β-keto amino compounds (BT = benzothiazole).

Previous studies have shown that thiourea-based catalysts are prime specimens for conducting the activation of *N*-Boc-protected imines towards nucleophilic attack in a highly enantioselective manner.[7] Hence, we performed our initial screening (Table 1) using these catalysts.

Table 1 Screening results for the enantioselective addition of **2a** to **1a** catalysed by **6**[a]



Entry	Solvent	*T*/°C	Time/h	Conv.[b] (%)	ee[c] (%)
1	CH_2Cl_2	−30	18	Full	70
2	Toluene	−30	24	0	n.d.
3	Acetone	−30	48	Full	76
4	$CHCl_3$	−30	24	Full	37
5	CH_3CN	−30	42	80	67
6	THF	−30	24	Full	57
7	Et_2O	−30	24	Full	30
8	Propionitrile	−30	48	Full	83
9	Propionitrile	−40	72	Full	89
10[d]	Propionitrile	−40	54	Full	80

[a] All reactions performed on a 0.10 mmol scale (0.20 M) using **1a** (0.25 mmol), **2a** (0.10 mmol) and **6** (0.01 mmol). [b] Determined by ^{1}H NMR. [c] Determined by chiral stationary-phase HPLC after reduction with $NaBH_4$ (see ESI†). [d] Run as 0.40 M.

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† Electronic supplementary information (ESI) available: Experimental details and spectroscopic data. See DOI: 10.1039/b915439f

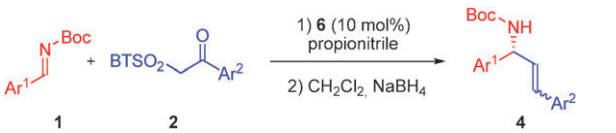
Preliminary results showed that catalyst **6** was superior in conducting the enantioselective reaction between the *N*-Boc-protected imine **1a** and the β-keto benzothiazole-based nucleophile **2a** (see ESI† for additional screening results). A survey of the reaction parameters was performed, leading to the finding that pre-dried propionitrile was the solvent of choice, as full conversion was achieved and the enantiomeric excess was superior to that obtained in other solvents (Table 1, entries 1–8). Lowering the reaction temperature further increased the enantioselectivity and the addition intermediate **3a** was formed in 89% ee (entry 9). Increasing the concentration led to a shorter reaction time, however, the enantioselectivity was also slightly decreased to 80% ee (entry 10).

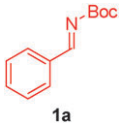
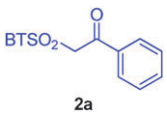
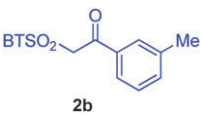
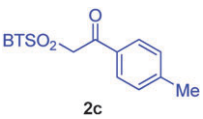
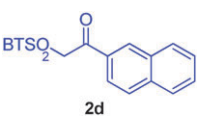
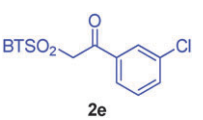
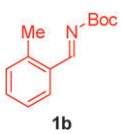
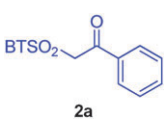
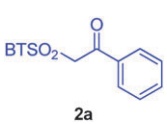
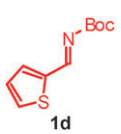
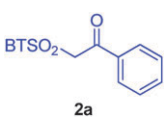
With these optimised reaction conditions in hand, we investigated the possible transformations of the privileged key intermediate **3**. As predicted, mild reductive conditions provided the formation of the allylic amines **4** in a one-pot procedure (Table 2). It was found that a change of solvent to CH_2Cl_2 between the organocatalytic step and the reduction was necessary in order to obtain the allylic amines **4** with excellent *E*–*Z*-selectivity (See ESI†).

Employing nucleophiles **2a–c** showed that the outcome of the reactions was reasonably independent of aromatic substitution pattern and the optically active allylic amines **4a–c** were formed in good yields and enantioselectivities (Table 2, entries 1–3). However, *ortho*-substituted nucleophiles proved to be unreactive in the present catalytic system, unless the temperature was increased significantly leading to inferior enantioselectivity. The ring-expanded naphthyl-based nucleophile **2d** also gave rise to the corresponding allylic amine **4d** (entry 4) in good yield and enantioselectivity. Interestingly, nucleophiles having electron-deficient aromatic moieties can be employed as shown by the utilisation of *meta*-chloro-substituted substrate **2e** (entry 5). Employment of the more electron rich *ortho*-substituted imine **1b** improved the enantioselectivity of the allylic amine **4f** to an excellent 96% ee (entry 6 *vs.* entry 1) with a 61% yield. Importantly, imines bearing an electron-deficient aromatic moiety can also be employed as shown with *ortho*-bromo imine **1c**, which gives rise to **4g**, formed exclusively as the *E*-isomer, in moderate yield and high enantioselectivity (entry 7). Finally, the reaction can also be performed with heteroaromatic imines and the thiophene-based imine **1d** gave rise to its corresponding allylic amine **4h** in good yield albeit with moderate enantioselectivity (entry 8). It should be noted that in all cases good to excellent *E*–*Z*-selectivities were obtained. It was found that alkyl-based β-ketosulfones **2** were unreactive under the given conditions.

In order to show further possible transformations, the key intermediate **3** (Scheme 1) was subjected to different desulfonylation reaction conditions, obtaining two classes of highly valuable Mannich-type products (Scheme 2). Treating **3** with sodium ethanethiolate furnished the *N*-Boc-protected β-keto amines **5a–c** in generally good to excellent yields (Scheme 2, upper reaction). Importantly, the enantioselectivities of **5a–c** were only slightly reduced compared to the enantioselectivities of the allylic amines **4**. To the best of our knowledge, this process constitutes the most efficient and general procedure for making these *N*-Boc-protected acetophenone-derived Mannich products with an organocatalytic approach, in terms of yield, enantioselectivity or catalyst loading.[4a–c,f]

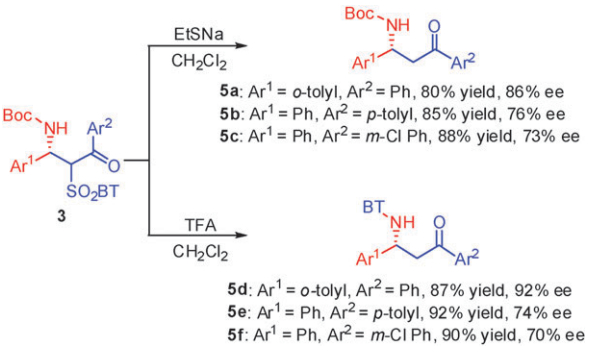
Table 2 Scope of the one-pot formation of allylic amines **4**[a]



Entry	Imine **1**	Sulfone **2**	Yield (%)	*E* : *Z*[b]	ee[c] (%)
1	 **1a**	 **2a**	**4a**-63	9 : 1	89
2	 **1a**	 **2b**	**4b**-65	12 : 1	90
3[d]	 **1a**	 **2c**	**4c**-61	13 : 1	84
4[d]	 **1a**	 **2d**	**4d**-65	9 : 1	85
5	 **1a**	 **2e**	**4e**-54	10 : 1	82
6	 **1b**	 **2a**	**4f**-61	10 : 1	96
7[e]	 **1c**	 **2a**	**4g**-42	>20 : 1	87
8[d]	 **1d**	 **2a**	**4h**-65	n.d.[f]	58

[a] All reactions performed on a 0.10 mmol scale (0.20 M in propionitrile) using **1** (0.25 mmol), **2** (0.10 mmol) and **6** (0.01 mmol) at −40 °C. [b] Determined by ^{1}H NMR. [c] Determined by chiral stationary-phase HPLC. [d] Reactions performed at −30 °C. [e] Reaction performed at 0 °C. [f] In both NMR and GC, the signals overlapped.

Treating the intermediate **3** with TFA resulted in *N*-Boc-deprotection, after which an intramolecular nitrogen-based Smiles rearrangement between the BT-group and the primary amine is proposed to occur, leading to the β-keto amino compounds **5d–f** (Scheme 2, lower reaction). These products contain the highly valuable 2-aminobenzothiazole moiety,[8] often present in biologically active compounds.[9] The



Scheme 2 Transformation of intermediate **3** into optically active β-keto amino compounds **5**.

products **5d–f** were obtained in good to excellent yields and enantiomeric excess. Moreover, both desulfonylation methods presented here represent, to the best of our knowledge, the first reactions of this type performed in an organomediated manner.[10]

The absolute configurations of the products **4** and **5** were correlated to the absolute configuration of **5b**, which was determined to be *R* by comparison with the literature.[11]

In conclusion, we have reported a new enantioselective organocatalytic addition of β-keto benzothiazolesulfones to *N*-Boc-protected imines. The resultant key intermediate can easily be transformed into optically active *trans*-allylic amines, absent of a conjugate electron-withdrawing substituent, or optically active β-keto amino compounds in good yields and enantioselectivities.

This work was made possible by a grant from The Danish National Research Foundation, OChemSchool and Carlsberg Foundation. D.M. thanks the "Ministerio de Ciencia e Innovación" of Spain for a postdoctoral fellowship.

Notes and references

1 For reviews on allylic amination see *e.g.*: (*a*) M. Johannsen and K. A. Jørgensen, *Chem. Rev.*, 1998, **98**, 1689; (*b*) B. M. Trost and M. L. Crawley, *Chem. Rev.*, 2003, **103**, 2921.
2 For recent examples see *e.g.*: (*a*) S. Lou and S. E. Schaus, *J. Am. Chem. Soc.*, 2008, **130**, 6922; (*b*) J. A. Bishop, S. Lou and S. E. Schaus, *Angew. Chem., Int. Ed.*, 2009, **48**, 4337; (*c*) K. Brak and J. A. Ellman, *J. Am. Chem. Soc.*, 2009, **131**, 3850.
3 (*a*) T. B. Poulsen, C. Alemparte and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 11614; (*b*) S. Bertelsen, M. Marigo, S. Brandes, P. Dinér and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2006, **128**, 12973; (*c*) S. Kobbelgaard, S. Brandes and K. A. Jørgensen, *Chem.–Eur. J.*, 2008, **14**, 1464; (*d*) C. Cassani, L. Bernadi, F. Fini and A. Ricci, *Angew. Chem., Int. Ed.*, 2009, **48**, 5694; (*e*) G. Ma, S. Cao and M. Shi, *Tetrahedron: Asymmetry*, 2009, **20**, 1086; (*f*) T. Zhang, L. Dai and X. Hou, *Tetrahedron: Asymmetry*, 2007, **18**, 1990; (*g*) Z. Wang, X. Ye, S. Wei, P. Wu, A. Zang and J. Sun, *Org. Lett.*, 2006, **8**, 999.
4 For recent reviews see: (*a*) M. M. B. Marques, *Angew. Chem., Int. Ed.*, 2006, **45**, 348; (*b*) A. Ting and S. E. Schaus, *Eur. J. Org. Chem.*, 2007, 5797; (*c*) J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg and F. P. J. T. Rutjes, *Chem. Soc. Rev.*, 2008, **37**, 29; For selected recent examples see: (*d*) M. Terada, K. Machioka and K. Sorimachi, *Angew. Chem., Int. Ed.*, 2006, **45**, 2254; (*e*) N. S. Chowdari, M. Ahmad, K. Albertshofer, F. Tanaka and C. F. Barbas III, *Org. Lett.*, 2006, **8**, 2839; (*f*) A. L. Tillman and D. J. Dixon, *Org. Biomol. Chem.*, 2007, **5**, 606; (*g*) M. Rueping, E. Sugiono and F. Schoepke, *Synlett*, 2007, 1441; (*h*) D. Uraguchi, Y. Ueki and T. Ooi, *J. Am. Chem. Soc*, 2008, **130**, 14088; (*i*) J. W. Yang, C. Chandler, M. Stadler, D. Kampen and B. List, *Nature*, 2008, **452**, 453; (*j*) H. Yang and R. G. Carter, *J. Org. Chem.*, 2009, **74**, 2246; (*k*) P. Dziedzic, P. Schyman, M. Kullberg and A. Cordova, *Chem.–Eur. J.*, 2009, **15**, 4044.
5 M. Nielsen, C. B. Jacobsen, M. W. Paixão, N. Holub and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2009, **131**, 10581.
6 C. Aïssa, *Eur. J. Org. Chem.*, 2009, 1831.
7 For recent reviews see *e.g.*: (*a*) A. G. Doyle and E. N. Jacobsen, *Chem. Rev.*, 2007, **107**, 5713; (*b*) Z. Zhang and P. R. Schreiner, *Chem. Soc. Rev.*, 2009, **38**, 1187.
8 For a recent article concerning the synthesis of compounds containing this moiety see: G. W. Stewart, C. A. Baxter, E. Cleator and F. J. Sheen, *J. Org. Chem.*, 2009, **74**, 3229.
9 For a few recent examples see: As HIV-1 protease inhibitors: (*a*) D. L. N. G. Surleraux, H. A. Kock, W. G. Verschueren, G. M. E. Pille, L. J. R. Maes, A. Peeters, S. Vendeville, S. D. Meyer, H. Azijn, R. Pauwels, M. Bethune, N. M. King, M. Prabu-Jeyabalan, C. A. Schiffer and P. B. T. P. Wigerinck, *J. Med. Chem.*, 2005, **48**, 1965; As vanilloid receptor-1 antagonists: (*b*) E. M. Doherty, C. Fotsch, A. W. Bannon, Y. Bo, N. Chen, C. Dominguez, J. Falsey, N. R. Gavva, J. Katon, T. Nixey, V. I. Ognyanov, L. Pettus, R. M. Rzasa, M. Stec, S. Surapaneni, R. Tamir, J. Zhu, J. J. S. Treanor and M. H. Norman, *J. Med. Chem.*, 2007, **50**, 3515; As c-Src kinase and nitric oxide synthase inhibitors: (*c*) X. Cao, Q. You, Z. Li, Q. Guo, J. Shang, M. Yan, J. Chernc and M. Chenc, *Bioorg. Med. Chem.*, 2008, **16**, 5890; As CYP26 inhibitors see: (*d*) M. S. Gomaa, J. L. Armstrong, B. Bobillon, G. J. Veal, A. Brancale, C. P. F. Redfern and C. Simons, *Bioorg. Med. Chem.*, 2008, **16**, 8301.
10 For a review on desulfonylation reactions see: C. Nájera and M. Yus, *Tetrahedron*, 1999, **55**, 10547.
11 The absolute configuration was determined to be *R* by comparison of the specific rotation of **5b** with the literature: A. L. Tillman and D. J. Dixon, *Org. Biomol. Chem.*, 2007, **5**, 606.

