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Organocatalytic Asymmetric Formal [3 + 2] Cycloaddition with in Situ-Generated *N*-Carbamoyl Nitrones

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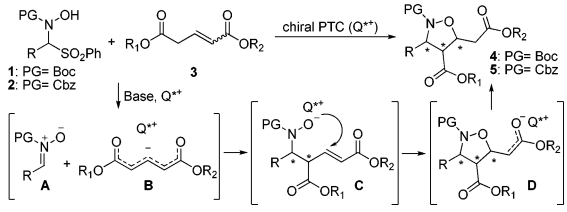
The [3 + 2] cycloaddition of nitrones and alkenes is one of the most versatile reactions in organic synthesis.[1] It offers the possibility of generating isoxazolidines with up to three new contiguous stereocenters, which are precursors of broadly useful compounds such as 1,3-aminoalcohols, amino acids, azasugars, and alkaloids.[2] Although several catalytic asymmetric versions of this powerful cycloaddition reaction have been developed,[3] all of them invariably involve *N*-benzyl- and *N*-aryl-substituted nitrones and thus yield isoxazolidines bearing nitrogen protecting groups that are very difficult to remove without concomitant cleavage of the N−O bond.[4] The unfeasibility of the preparation of unprotected isoxazolidines for further elaborations is a significant limitation of these otherwise exceptional methods, given the biological interest in these heterocycles.[5] On the other hand, a few contributions in the literature have reported nitrones bearing easily removable electron-withdrawing groups at nitrogen that can be generated in situ for use in nonasymmetric 1,3-cycloadditions,[6] overcoming the troublesome isolation of these unstable dipoles.

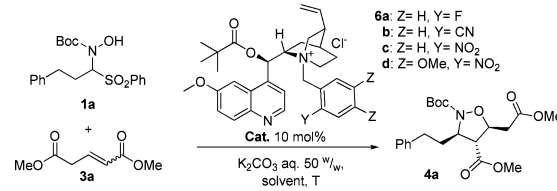
On the basis of the recently reported in situ generation of *N*-carbamoyl imines by means of phase-transfer catalysis (PTC),[7] we envisioned a novel asymmetric formal [3 + 2] nitrone cycloaddition reaction[8] using *N*-Boc- and *N*-Cbz-protected *N*-hydroxy-α-amido sulfones[6c] (**1** and **2**, respectively) as nitrone precursors (Scheme 1). Glutaconates **3** were selected as suitable reaction partners for the formation of formal anionic dipolarophiles. We expected that highly reactive *N*-carbamoyl nitrones **A** could be formed in situ and undergo an enantioselective Mannich addition by the chiral quaternary ammonium enolate **B**. The resulting anionic adducts **C** should then directly cyclize intramolecularly to the cycloadducts **D**, possibly diastereoselectively, affording isoxazolidines **4** and **5**.

Scheme 1. Reaction Pathway



Preliminary experiments on the reaction between sulfone **1a** and dimethyl glutaconate **3a** using *Cinchona* alkaloid-derived ammonium salts revealed that alkylation or acylation at the alcoholic moiety of the catalyst had a very positive effect on the observed asymmetric induction.[9] In particular, useful enantioselectivities could be obtained by using quinine-derived catalysts such as **6a**−**d** (Table 1), which bear an ortho-substituted benzyl group at the quinuclidinic nitrogen[10] and the hindered pivaloyl ester at C9.[11] *Remarkably, the cycloadduct* **4a** *was always obtained as a single diastereoisomer.* As shown in Table 1, when the reaction was performed in 10:1 toluene/CH_2Cl_2 at −30 °C with aqueous K_2CO_3 as the base, catalyst **6c** was identified as the best one, giving the cycloadduct **4a** with modest enantioselectivity (entries 1−4). A beneficial effect on the asymmetric induction was obtained by increasing the amount of CH_2Cl_2 and adding TBME (entries 5 and 6). Whereas the larger amount of CH_2Cl_2 markedly increased the solubility of catalyst **6c**, TBME facilitated solubilization of sulfone **1a** in the mixture. Finally, lowering the temperature to −42 °C and diluting the reaction led to a further improvement in the enantioselectivity (entry 7).

Table 1. Optimization of Reaction Conditions: Representative Results[a]



entry	cat.	solvent	*T* (°C)	conv. (%)[b]	ee (%)[c]
1	**6a**	10:1 Tol/CH_2Cl_2	−30	90	70
2	**6b**	10:1 Tol/CH_2Cl_2	−30	90	75
3	**6c**	10:1 Tol/CH_2Cl_2	−30	90	76
4	**6d**	10:1 Tol/CH_2Cl_2	−30	90	70
5	**6c**	7:3 Tol/CH_2Cl_2	−30	65	82
6	**6c**	3.5:3.5:3 Tol/TBME/CH_2Cl_2	−30	>95	83
7[d]	**6c**	3.5:3.5:3 Tol/TBME/CH_2Cl_2	−42	>95	91

[a] Reactions were performed on a 0.10 mmol scale using 2 equiv of **3a**, 10 mol % **6**, and 5 equiv of 50% (w/w) K_2CO_3(aq) in 1.0 mL of the solvent for 21−24 h. [b] Determined by ^{1}H NMR analysis. [c] Determined by chiral HPLC analysis after Boc deprotection and Cbz derivatization. [d] Using 2 mL of the solvent.

With these conditions in hand, we evaluated the scope of the formal [3 + 2] cycloaddition (Table 2).[12] Several *N*-Boc sulfones **1a**−**j** derived from aliphatic aldehydes reacted well with glutaconate **3a** to give the cycloadducts **4a**−**j** with good results (entries 1−10), even on a preparative scale (entries 1 and 9). Because of the low efficiency of the available preparations of *N*-hydroxy-α-amido sulfones from aromatic aldehydes,[6c,13] only the two sulfones **1k** and **1l** were tested, giving the corresponding products **4k** and **4l** with moderate enantioselectivities (entries 11 and 12). Variation of the dipolarophile using glutaconates **3b**−**f** in combination with sulfone **1a** showed a considerable sensitivity of the reaction to the sterics of the diester used. In particular, while a simple increase in reaction time was sufficient for obtaining the cycloadducts **4m**−**o** with good results (entries 13−15), the more hindered di-*tert*-butyl derivative **3e** did not react with sulfone **1a**, even at 0 °C (entry 16). To differentiate the two ester groups in the cycloadducts through a regioselective, sterically controlled Mannich reaction (Scheme 1), *tert*-butyl methyl glutaconate **3f** was reacted with **1a**, but this gave **4q** in poor yield, only at 0 °C, and with a surprising lack of regioselectivity (entry 17).[14]

Finally this methodology was tested with Cbz as the protecting group, affording **5a**−**d** with good results (entries 18−21). The

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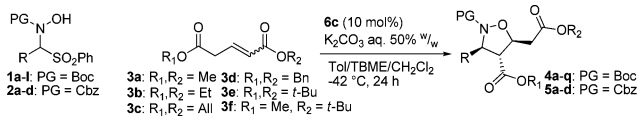
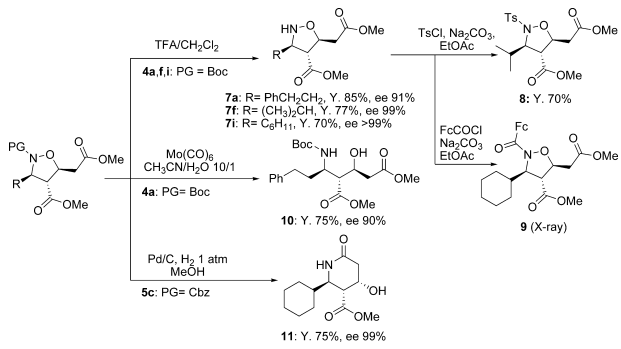
Table 2. Scope of the Catalytic Reaction[a]



entry	1/2	R	3	4/5	yield (%)[b]	ee (%)[c]
1[d]	**1a**	$PhCH_2CH_2$	**3a**	**4a**	86 (86)	91 (60)[e]
2[f]	**1b**	CH_3	**3a**	**4b**	53	60[e]
3	**1c**	CH_3CH_2	**3a**	**4c**	80	88[e]
4	**1d**	$CH_3(CH_2)_3$	**3a**	**4d**	70	92[e]
5	**1e**	$CH_3(CH_2)_5$	**3a**	**4e**	72	94[e]
6	**1f**	$(CH_3)_2CH$	**3a**	**4f**	93 (87)	99 (80)[e]
7	**1g**	$(CH_3)_2CHCH_2$	**3a**	**4g**	97 (83)	98 (57)[e]
8	**1h**	*c*-C_5H_9	**3a**	**4h**	97	99[e]
9[g]	**1i**	*c*-C_6H_{11}	**3a**	**4i**	>99 (98)	>99 (83)[e]
10	**1j**	$PhCH_2$	**3a**	**4j**	81	95[e]
11[h]	**1k**	Ph	**3a**	**4k**	>99	67
12	**1l**	4-BrC_6H_4	**3a**	**4l**	63	60
13[i]	**1a**	$PhCH_2CH_2$	**3b**	**4m**	60	91
14[i]	**1a**	$PhCH_2CH_2$	**3c**	**4n**	76	94
15[i]	**1a**	$PhCH_2CH_2$	**3d**	**4o**	73	95
16[i,j]	**1a**	$PhCH_2CH_2$	**3e**	**4p**	<10	–
17[i,j]	**1a**	$PhCH_2CH_2$	**3f**	**4q**	25[k]	73[l]
18	**2a**	$(CH_3)_2CHCH_2$	**3a**	**5a**	60	75
19	**2b**	$(CH_3)_2CH$	**3a**	**5b**	72	80
20	**2c**	*c*-C_6H_{11}	**3a**	**5c**	>99	94
21	**2d**	*c*-C_5H_9	**3a**	**5d**	68	85

[a] Reactions were performed with 0.10 mmol of **1a**−**l** or **2a**−**d**, 0.20 mmol of **3a**−**f**, 0.01 mmol of **6c**, and 0.50 mmol of 50% (w/w) K_2CO_3(aq) in 3.5:3.5:3 Tol/TBME/CH_2Cl_2 (0.05 M) for 24 h. Results in parentheses refer to the opposite enantiomer, obtained using **QD-6c** as the catalyst. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] On a 1.0 mmol scale. [e] Determined after Boc deprotection and Cbz derivatization. [f] Using 4.5:4.5:1 Tol/TBME/CH_2Cl_2 (0.10 M) for 48 h. [g] On a 5.0 mmol scale. [h] Using 10:1 Tol/CH_2Cl_2. [i] For 96 h. [j] At 0 °C. [k] Regioisomeric ratio: 60:40 (^{1}H NMR analysis). [l] For the major regioisomer.

Scheme 2. Elaboration of the Cycloadducts



quasi-enantiomeric quinidine catalyst **QD**−**6c** gave access to the opposite enantiomer of the products, though with lower selectivities (values in parentheses in entries 1, 6, 7, and 9).[15]

The synthetic utility of the obtained isoxazolidines was first demonstrated by chemoselectively performing Boc deprotection and N−O cleavage. In fact, we were able to isolate the non-*N*-protected isoxazolidines **7a**, **7f**, and **7i** in good yields by treatment with trifluoroacetic acid (TFA) in CH_2Cl_2 (Scheme 2, top) and the *N*-Boc-protected 1,3-aminoalcohol **10** using $Mo(CO)_6$ as the reducing agent[16] (Scheme 2, middle). The highly substituted δ-lactam **11** could instead be obtained by hydrogenolysis of **5c**, giving simultaneous *N*-Cbz deprotection and N−O cleavage, followed by a spontaneous lactamization (Scheme 2, bottom).

The relative and absolute configurations of the cycloadducts were determined by nuclear Overhauser effect NMR experiments and by theoretical calculations of the ECD spectra and $[\alpha]_D$ values using time-dependent density functional theory performed on the tosyl derivative **8**.[17] X-ray analysis of the ferrocenoyl derivative **9** confirmed the correctness of this assignment (see the Supporting Information).

In summary, we have developed a novel organocatalytic process that uses simple reaction conditions and an inexpensive, readily available catalyst and gives access to *N*-Boc- and *N*-Cbz-protected isoxazolidines in generally good yields and enatioselectivities.

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Supporting Information Available: Assignment of the relative and absolute configurations of **4**, X-ray data for **9**, optimization results, experimental procedures, spectral data, and copies of ^{1}H and ^{13}C NMR spectra for compounds **4**, **5**, **6c**, **QD-6c**, and **7**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For a recent review, see: Merino, P. In *Science of Synthesis*, Vol. 27; Padwa, A., Ed.; Thieme: Stuttgart, Germany, 2004; p 511.
(2) Fredrickson, M. *Tetrahedron* **1997**, *53*, 403.
(3) For a review, see: (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Commun.* **2000**, 1449. For recent examples, see: (b) Palomo, C.; Oiarbide, M.; Arceo, E.; García, J. M.; López, R.; González, A.; Linden, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6187. (c) Evans, D. A.; Song, H.-J.; Fandrick, K. R. *Org. Lett.* **2006**, *8*, 3351. (d) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 718. (e) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 11926. (f) Jiao, P.; Nakashima, D.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2411.
(4) For an oxidatively removable *N*-diphenylmethyl group, see: (a) Hashimoto, T.; Omote, M.; Kano, T.; Maruoka, K. *Org. Lett.* **2007**, *9*, 4805. For carbohydrate derivatives as hydrolytically removable chiral auxiliaries, see: (b) Vasella, A. *Helv. Chim. Acta* **1977**, *60*, 1273.
(5) (a) Chiacchio, U.; Balestrieri, E.; Macchi, B.; Iannazzo, D.; Piperno, A.; Rescifina, A.; Romeo, R.; Saglimbeni, M.; Sciortino, M. T.; Valveri, V.; Mastino, A.; Romeo, G. *J. Med. Chem.* **2005**, *48*, 1389. (b) Rowe, S. P.; Casey, R. J.; Brennan, B. B.; Buhrlage, S. J.; Mapp, A. K. *J. Am. Chem. Soc.* **2007**, *129*, 10654.
(6) (a) Hussain, S. A.; Sharma, A. H.; Perkins, M. J.; Griller, D. *J. Chem. Soc., Chem. Commun.* **1979**, 289. (b) Partridge, K. M.; Anzovino, M. E.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 2920. (c) Guinchard, X.; Vallée, Y.; Denis, J.-N. *Org. Lett.* **2005**, *7*, 5147.
(7) (a) Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7975. (b) Palomo, C.; Oiarbide, M.; Laso, A.; López, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622.
(8) For organocatalytic cycloadditions of nitrones, see: (a) [3 + 3]: Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2416. (b) [3 + 2]: Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874.
(9) For example, a catalyst related to **6d** (Table 1) but bearing the free OH gave the product with 15% ee (see the Supporting Information).
(10) Yoo, M.-S.; Jeong, B.-S.; Lee, J.-H.; Park, H.-g.; Jew, S.-S. *Org. Lett.* **2005**, *7*, 1129.
(11) Poulsen, T. B.; Bernardi, L.; Bell, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6551.
(12) In every case, a single diastereoisomer was observed by ^{1}H NMR analysis of the crude mixture.
(13) **1k** and **1l** were prepared in low (<20%) yield according to ref 6c. Use of this method ($PhSO_2Na$, HCOOH, H_2O/MeOH or THF) or other procedures effective for α-amido sulfones (CH_2Cl_2, $PhSO_2H$; $PhSO_2Na$, HCOOH, MeOH/H_2O, 70 °C), other aromatic aldehydes (2-bromobenzaldehyde, anisaldehyde), or a tertiary aliphatic aldehyde (pivalaldehyde) failed to give the expected *N*-hydroxy-α-amido sulfones.
(14) This result seems to suggest that the two ester groups are not as independent as assumed in the simplified two-step pathway depicted in Scheme 1, although ^{1}H NMR analysis of the crude products **4b**−**e** revealed the presence of small amounts (<7 mol %) of the linear non-cyclized products (adduct **C** in Scheme 1).
(15) Other catalysts related to **QD-6c** gave similar or worse results (see the Supporting Information). For a recent example of a PTC reaction where quasi-enantiomeric *Cinchona* catalysts display very different behavior, see: Mizuta, S.; Shibata, N.; Goto, Y.; Furukawa, T.; Nakamura, S.; Toru, T. *J. Am. Chem. Soc.* **2007**, *129*, 6394.
(16) Kudoh, T.; Ishikawa, T.; Shimizu, Y.; Saito, S. *Org. Lett.* **2003**, *5*, 3875.
(17) For a review of the use of this method to assign the absolute configurations of organic molecules, see: Bringmann, G.; Bruhn, T.; Maksimenka, K.; Hemberger, Y. *Eur. J. Org. Chem.* **2009**, 2717. For leading references, see the Supporting Information.

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