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Highly Enantioselective α-Aminoxylation of Aldehydes and Ketones with a Polymer-Supported Organocatalyst

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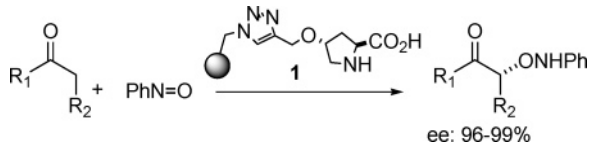
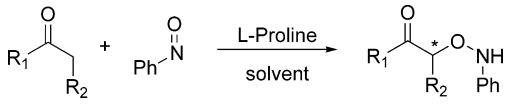
ABSTRACT



The first catalytic enantioselective α-aminoxylation of aldehydes and ketones using an insoluble, polymer-supported organocatalyst (1) derived from *trans*-4-hydroxyproline is reported (ee: 96–99%). Reaction rates in the aminoxylation of cyclic ketones with 1 are higher than those reported with L-proline. The insoluble nature of 1 simplifies workup conditions and allows catalyst recycling without an apparent decrease in enantioselectivity or yield.

Optically active α-hydroxycarbonyl compounds and 1,2-diols are interesting building blocks for the construction of biologically active products. As a consequence, a wide variety of diastereoselective and enantioselective methods for their preparation have been developed. Among these methods, the α-aminoxylation of carbonyl compounds has been the subject of much interest in recent times.[1] The first catalytic enantioselective introduction of an aminoxyl group at the α-position of ketones, involving nitrosobenzene as the electrophile, was reported in 2003 by Yamamoto using tin enolates and a silver complex as the catalyst.[2] Also in 2003, the direct proline-catalyzed α-aminoxylation of aldehydes with nitrosobenzene was independently reported by Zhong,[3] MacMillan,[4] and Hayashi.[5a] One year later, the scope of the proline-catalyzed reaction was extended to ketones simultaneously by the groups of Hayashi[5b] and Córdova.[6] After this initial breakthrough, however, little has been reported concerning the use of new organocatalysts[7] or substrates[8] in this process, and most additional effort has been devoted to the elucidation of the mechanism in the proline-catalyzed reaction (Scheme 1).[9]

Scheme 1. Proline-Mediated α-Aminoxylation of Carbonyl Compounds



Associated with this process but normally overlooked, the formation of azoxybenzene usually accompanies that of the

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(1) (a) Merino, P.; Tejero, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 2995. (b) Janey, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4292.
(2) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6038.
(3) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247.
(4) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808.
(5) (a) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293. (b) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1112.
(6) Bøgevig, A.; Sundén, H.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1109.

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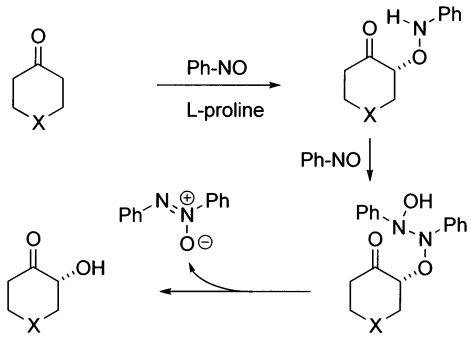
α-aminoxylation product.[5b] Barbas and co-workers proposed that azoxybenzene arises from the reaction of the α-aminoxylation product with nitrosobenzene.[10] Working with an excess of this reagent, these authors could perform aminoxylation and O−N bond heterolysis in a tandem manner for the direct, enantioselective α-hydroxylation of cyclohexanones (Scheme 2). From a practical perspective, it becomes

Scheme 2. Tandem Aminoxylation and O−N Bond Heterolysis of Cyclohexanones

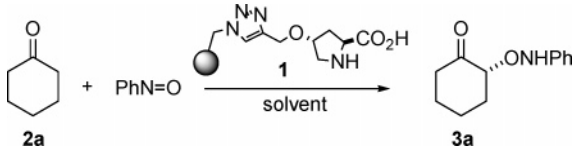


clear that the detection of azoxybenzene in aminoxylation reaction crudes is at the expense of α-aminoxylation yield.

Although organocatalysis incorporates important characteristics of environmentally benign practices through the avoidance of toxic metal contamination both in waste and in reaction products, the possibility of separating the catalyst by simple physical methods and even reusing it would represent an additional bonus in view of a potential large-scale operation. Thus, the development of polymer-supported organocatalysts suitable for work in a broad variety of solvents without deterioration of the catalytic performance of their monomeric counterparts is the subject of much current interest.[11] We have recently reported a new strategy for supporting *trans*-4-hydroxyproline onto Merrifield-type resins through Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition[12] (click chemistry) and have shown that the resulting resin (**1**) behaves as a highly active enantioselective and diastereoselective, yet reusable, organocatalyst for the direct aldol reaction in water.[13] Up to now, no reference can be found in the literature for the use of polymer-supported catalysts in the α-aminoxylation of carbonyl compounds.[14] We report here the first asymmetric α-aminoxylation of aldehydes and ketones using **1**, a readily available, recoverable, and reusable organocatalyst.

Our initial goal in this study was the optimization of the reaction conditions for the suppression of azoxybenzene formation in the α-aminoxylation of ketones using the supported catalyst **1** and cyclohexanone (**2a**) as a model substrate (Table 1). It must be pointed out here that, although

Table 1. α-Aminoxylation of Cyclohexanone (**2a**) with Polymer-Supported Catalyst **1**[a]



entry	solvent	addition time (h)	yield (%)[b]	ee (%)[c]
1	$CHCl_3$	0[d]	21[e]	nd
2	$CHCl_3$	0[f]	0[g]	nd
3	DMF	0[h]	25	96
4	DMF	5[i]	48	98
5	DMF	3[i]	60 (74)[e]	98

[a] Reaction conditions: resin **1** (0.05 mmol; f: 0.6 mmol/g); 1 mL of solvent; variable amounts of **2a** and nitrosobenzene depending on the experiment; 23 °C. [b] Isolated yield of **3a**. [c] Determined by HPLC; see Supporting Information. [d] **1** (10 mol %); **2a** (10 equiv); nitrosobenzene (1 equiv); 2 h. [e] Estimated by ^{1}H NMR with mesitylene as the internal standard. [f] **1** (20 mol %); **2a** (1 equiv); nitrosobenzene (3 equiv); 24 h; 4 °C. [g] A 1:3.3 mixture of 2-hydroxycyclohexanone and azoxybenzene was formed in low yield. [h] **1** (20 mol %); **2a** (10 equiv); nitrosobenzene (1 equiv); 2 h. [i] **1** (20 mol %), **2a** (2 equiv); nitrosobenzene (1 equiv; 0.5 M solution).

most of the work reported on this reaction uses L-proline as the catalyst, very different reaction conditions have been used, which is somewhat intriguing.[15]

Thus, a clear difference exists between Hayashi's procedure which involves reaction at low temperature (0 °C) and slow addition of nitrosobenzene to an excess of ketone as key features to suppress undesired α,α′-bisaminoxylation and azoxybenzene formation[5b] and that of Córdova,[6] who reported reactions at room temperature in chloroform with addition of the reactants in one portion, without the observation of any side reaction. We first checked the addition of reactants at once to the suspension of resin **1**, and because resin swelling is critical for the successful use of insoluble polymer-supported catalysts, we paid attention to identify solvents with good swelling properties for **1**. When the reaction was conducted in chloroform, at room temperature

(7) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Sumiya, T.; Urushima, T.; Shoji, M.; Hashizume, D.; Koshino, H. *Adv. Synth. Catal.* **2004**, *346*, 1435.
(8) Kim, S.-G.; Park, T.-H. *Tetrahedron Lett.* **2006**, *47*, 9067.
(9) Mechanistic studies: (a) Cheong, P. H.-Y.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 13912. (b) Mathew, S. P.; Iwamura, H.; Blackmond, D. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3317. (c) Mathew, S. P.; Klussmann, M.; Wells, D. H., Jr.; Armstrong, A.; Blackmond, D. G. *Chem. Commun.* **2006**, 4291.
(10) Ramachary, D. B.; Barbas, C. F., III. *Org. Lett.* **2005**, *7*, 1577.
(11) For reviews on immobilized organocatalysts, see: (a) Benaglia, M.; Puglisi, A.; Cozzi, F. *Chem. Rev.* **2003**, *103*, 3401. (b) Cozzi, F. *Adv. Synth. Catal.* **2006**, *348*, 1367. For approaches to proline immobilization, see: (c) Benaglia, M.; Cinquini, M.; Cozzi, F.; Puglisi, A.; Celentano, G. *Adv. Synth. Catal.* **2002**, *344*, 533. (d) Benaglia, M.; Cinquini, M.; Cozzi, F.; Puglisi, A.; Celentano, G. *J. Mol. Catal. A: Chem.* **2003**, *204*−*205*, 157. (e) Kondo, K.; Yamano, T.; Takemoto, K. *Makromol. Chem.* **1985**, *186*, 1781. (f) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F. *J. Am. Chem. Soc.* **2001**, *123*, 5260.
(12) (a) Rostovtsed, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.
(13) Font, D.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2006**, *8*, 4653.
(14) For a different strategy towards catalyst recovery in this reaction, involving the use of ionic liquids, see: (a) Guo, H.-M.; Niu, H.-Y.; Xue, M.-X.; Guo, Q.-X.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Wang, J.-J. *Green Chem.* **2006**, *8*, 682. (b) Huang, K.; Huang, Z.-Z.; Li, X.-L. *J. Org. Chem.* **2006**, *71*, 8320.
(15) For a comment on this discrepancy, see: Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Hibino, K.; Shoji, M. *J. Org. Chem.* **2004**, *69*, 5966.

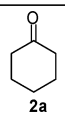
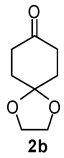
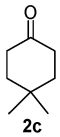
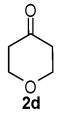
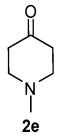
for 2 h, with a large excess of **2a** (10 equiv) relative to nitrosobenzene, the desired α-aminoxylation product **3a** was obtained in only 21% yield, along with 2-hydroxycyclohexanone (12%) and azoxybenzene (entry 1). In an attempt to improve the selectivity of the reaction and, hence, to increase the yield, we used an excess of nitrosobenzene with respect to the ketone (3:1). In this manner, we expected to induce the O−N bond heterolysis after the aminoxylation step (see Scheme 2) as reported by Barbas.[10] Indeed, a mixture of 2-hydroxycyclohexanone and azoxybenzene (1:3.3 ratio) was exclusively detected in the reaction crude by ^{1}H NMR spectroscopy, although conversion was very low (entry 2). In view of the negative results recorded with chloroform, we turned our attention to DMF. In this solvent, when nitrosobenzene was added to the reaction mixture in one portion (entry 3), **3a** was obtained in 25% yield and 96% ee (entry 3).[16] The effect of slow addition of nitrosobenzene to the reaction mixture was next investigated.[5b] To our delight, both the yield and enantioselectivity of the reaction were significantly improved with this modification (entries 4 and 5).

The reaction worked most nicely when nitrosobenzene was added over a 3 h period to a mixture of **2a** and **1** in DMF, providing the desired **3a** in 74% yield and 98% ee. Very interestingly, the insoluble nature of **1** allowed for a highly simplified product isolation by filtration of the resin followed by removal of solvents and unreacted **2a** under reduced pressure (see Supporting Information). Neither the α,α′-bisaminoxylation product nor 2-hydroxycyclohexanone was observed in the crude product, which was of satisfactory purity for synthetic purposes. Analytically pure **3a** could be isolated by flash column chromatography, but at the expense of some yield decrease (60%, entry 5), because the chromatographic process induced always partial O−N cleavage.

To assess the performance of **1**, the optimized reaction conditions were then applied to a set of six-membered ring cyclic ketones. In analogy with what is observed for **2a**, excellent enantioselectivities were recorded with substrates **2b**−**e**, as shown in Table 2. Yields were generally high, although with tetrahydro-4*H*-pyran-4-one (**2d**) and 1-methyl-4-piperidone (**2e**) they were somewhat lower (entries 4 and 5). A similar behavior has been reported with L-proline.[5]

It is interesting to note that **1**, in spite of its heterogeneous nature, is able to promote faster reactions than proline.[5] As an additional bonus derived from its insoluble nature, the α-aminoxylated ketone (**3a**) can be converted to the corresponding α-hydroxy ketone through a greatly simplified procedure involving filtration of the catalyst (what effectively stops the α-aminoxylation process) and addition of excess nitrosobenzene to the reaction mixture to selectively cleave the O−N bond (see Supporting Information).[10] In this manner, the two steps involved in the enantioselective conversion of a ketone substrate into the corresponding α-hydroxyketone can be separated in time, with an important gain in chemoselectivity.

Table 2. α-Aminoxylation of Ketones with the Polymer-Supported Catalyst **1**[a]

entry	ketone	product	yield (%)[b]	ee (%)[c]
1	 **2a**	**3a**	74 (60)	98
2	 **2b**	**3b**	75	99
3	 **2c**	**3c**	67 (58)	98
4	 **2d**	**3d**	61 (55)	97
5	 **2e**	**3e**	49 (43)	99

[a] Reaction conditions: catalyst **1** (20 mol %; f: 0.6 mmol/g); 1 mL of DMF; ketone (0.5 mmol); nitrosobenzene (0.25 mmol); 0.5 M in DMF; addition, 3 h; 23 °C. [b] Calculated by ^{1}H NMR with mesitylene as the internal standard. In parentheses: isolated yield. [c] Determined by chiral HPLC (see Supporting Information).

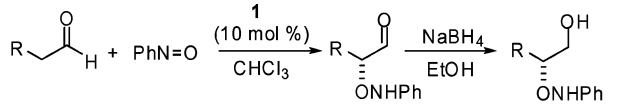
Because the reaction of aldehydes with nitrosobenzene is known to be faster than that of ketones, we reasoned that the balance between α-aminoxylation and the subsequent reaction of nitrosobenzene with the aminoxylated product would be even more favorable with these substrates. To test the suitability of **1** for this reaction, we simply mixed polymer-supported catalyst **1** (10 mol %) with nitrosobenzene and propanal (3 equiv), taken as a representative substrate, at low temperature in chloroform.[17] Under these conditions, propanal (**4a**) was α-aminoxylated in only 1.5 h, at 0−4 °C, with **5a** being isolated in 81% yield (Table 3, entry 1). Very interestingly, no aldol product could be detected in the reaction crude. So, it is clear that, in the presence of **1**, aldehydes react much faster with nitrosobenzene than with themselves[18] and also faster than ketones do. After this encouraging result, a representative set of aldehydes (**4b**−**h**) was also tested under these reaction conditions (addition of nitrosobenzene in one portion, 0−4 °C, 3 equiv of aldehyde, 10 mol % of catalyst). These results are collected in Table 3. Because the α-aminoxylated aldehydes are not stable,[3,4] they were isolated as the α-aminoxylated primary alcohols (**6a**−**h**) after in situ reduction with sodium boro-

(16) DMSO was also tried and afforded the aminoxylated ketone in 20% yield. It must be noted that the ^{1}H NMR spectra of the reaction crudes (in DMF and DMSO) showed small signals due to the formation of the α,α′-bisaminoxylation product which was not observed using chloroform.

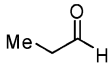
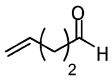
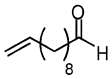
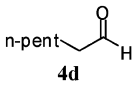
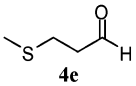
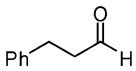
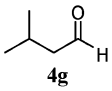
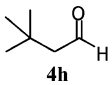
(17) An experiment in DMF with the conditions of entry 1 (Table 2) showed, after 7 h, no progress of the reaction.

(18) For examples of self-aldolization of aldehydes, see: Northrup, A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798.

Table 3. α-Aminoxylation of Aldehydes with Polymer-Supported Catalyst **1** (10 mol %)[a]



4a-4h **5a-5h** **6a-6h**

entry	aldehyde	time (h)	yield (%)[b]	ee (%)[c]
1	 **4a**	1.5	81	98
2	 **4b**	3	79	96
3	 **4c**	1	75	98
4	 **4d**	1	86[d]	98
5	 **4e**	15	83	99
6	 **4f**	2	50	99
7	 **4g**	1	80	97
8	 **4h**	1	35	98

[a] Reaction conditions: resin **1** (10 mol %; 77.8 mg; f: 0.6 mmol/g); aldehyde (3 equiv); nitrosobenzene (1 equiv); 2 mL of $CHCl_3$; 0−4 °C. [b] Yield of isolated product. [c] Determined by chiral HPLC (see Supporting Information). [d] Determined by ^1H NMR.

hydride. It is assumed that the reduction step takes place with quantitative yield and that the enantiomeric purity of **6** exactly reflects that of **5**.[1] As shown in Table 3, aldehydes **4a**−**h** are selectively converted within 1−3 h to the corresponding aminoxylated products **5a**−**h**. This correlates well with the higher reactivity expected for aldehydes than for ketones (compare Table 3 with Table 2). Aminoxylated primary alcohols (**6a**−**g**) are obtained generally in high yield and with high enantioselectivities (96−99%). The lower yield obtained for **4h** (entry 8) can be attributed to a decreased reactivity of the rather hindered, enamine intermediate (compare entries 1−7 with entry 8). Substrates containing olefinic double bonds or the thioether functionality can be also selectively aminoxylated (entries 2, 3, and 5).

Because one of the main advantages of using an insoluble catalyst is the possibility of its recycling and reuse, we explored the possibility of a repeated use of **1**. To this end, we filtered the resin after the aminoxylation reaction, washed it several times with dichloromethane, and dried it in vacuum before reuse. In this way, resin **1** could be recycled three times without an appreciable loss in enantioselectivity or yield (see Supporting Information).

In summary, we have developed suitable reaction conditions for the use of **1** in the highly enantioselective α-aminoxylation of aldehydes and ketones. To the best of our knowledge, this study reports the first example of an insoluble and recyclable catalyst which is operative for the considered reaction. Key to this behavior, resin **1** exhibits a high rate balance between the catalytic α-aminoxylation and the noncatalytic, subsequent reaction with nitrosobenzene leading to O−N cleavage. From a practical perspective, the use of **1** as a catalyst for the aminoxylation reaction allows for significantly simplified workup conditions, the product being obtained in most favorable cases after simple filtration of the catalyst and elimination of the solvents. Moreover, if the α-hydroxycarbonyl compound is the ultimate target of the reaction, the insoluble nature of **1** is again advantageous because the catalytic α-aminoxylation step and the noncatalytic O−N cleavage can be separated at will with the result of increased selectivity.

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Supporting Information Available: Experimental procedures, characterization of new aminoxylated products, and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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