Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 3385–3389
Tetrahedron Letters

Novel organic catalysts for the direct enantioselective α-oxidation of carbonyl compounds

Henrik Sundén, Nils Dahlin, Ismail Ibrahem, Hans Adolfsson* and Armando Córdova*

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden

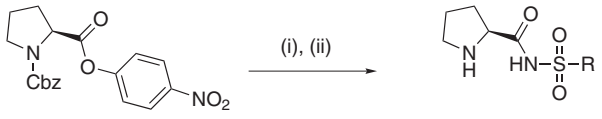
Received 26 December 2004; revised 9 March 2005; accepted 15 March 2005
Available online 2 April 2005

Abstract—The proline-derived *N*-sulfonylcarboxamide-catalyzed direct enantioselective α-oxidation of ketones and aldehydes with nitrosobenzene is presented. The reactions proceed smoothly furnishing the corresponding α-aminoxylated compounds in good yields with up to >99% ee. The proline-derived *N*-sulfonylcarboxamides were also found to be excellent catalysts for the direct enantioselective nitroso Diels–Alder-type reaction between nitrosobenzene and α,β-unsaturated cyclic ketones yielding the corresponding bicyclic Diels–Alder adduct products with up to >99% ee. The proline-derived *N*-sulfonylcarboxamides represent a readily available and highly modular novel type of organic catalyst.

Optically active α-hydroxy carbonyl moieties are common in numerous important natural products.[1,2] This has led to extensive research to find new diastereoselective and enantioselective routes for their syntheses.[3] One way of preparing these compounds is the asymmetric α-hydroxylation of enolates employing chiral auxiliaries or substrates.[4] Recently, Momiyama and Yamamoto reported an efficient catalytic system based on AgX/BINAP-complexes that mediate indirect α-oxidation of activated tin enolates with nitrosobenzene as the electrophile.[5]

Organocatalysis has experienced a renaissance in organic chemistry.[6] In this context, Zhong,[7c] MacMillan and co-workers,[7d] Hayashi et al.[7e,f,g] and ourselves[7a,b] have reported that amino acids and their derivatives catalyze Yamamoto-type α-aminoxylation reactions with excellent stereoselectivities.[7] These initial reports were later followed up by the excellent studies of Yamamoto and co-workers,[8] Blackmond and others.[9] Furthermore, we recently demonstrated that amino acids catalyze the biomimetic, asymmetric, aerobic α-oxidation of aldehydes and ketones.[10]

During studies on novel organic catalysts, we recently found that *N*-sulfonyl-2-aminomethylpyrrolidines were excellent catalysts for the direct enantioselective α-amination of aldehydes.[11] The organic catalysts furnished the desired products with good enantioselectivites, however, their preparation required five synthetic steps. In contrast, proline-derived *N*-sulfonylcarboxamides could be prepared in only two steps from commercially available *N*-Cbz protected *p*-nitrophenol proline esters (Scheme 1) and potentially could have similar activities as *N*-sulfonyl-2-aminomethylpyrrolidines. Based on these facts and our interest in the development of organocatalytic reactions,[12] we became interested in whether proline-derived *N*-sulfonylcarboxamides would be able to catalyze the direct, catalytic, enantioselective α-aminoxylation reaction. Herein, we disclose that proline-derived *N*-sulfonylcarboxamides are excellent catalysts for direct catalytic asymmetric α-oxidation and hetero Diels–Alder reactions of carbonyl compounds with nitrosobenzene, yielding the corresponding α-aminoxylated products with up to >99% ee.

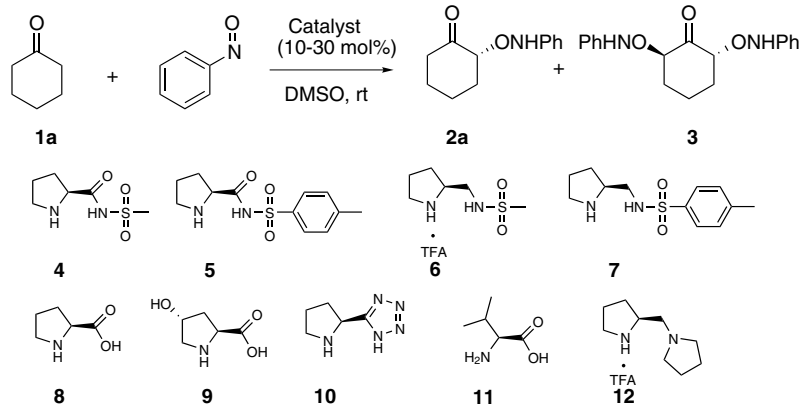


Scheme 1. Two-step synthesis of proline-derived *N*-sulfonylcarboxamides. Reagents and conditions: (i) 1.5 equiv NaH, 1.3 equiv $R–SO_2NH_2$, DMF, rt; (ii) Pd(C), H_2, MeOH.

Keywords: Proline-derived *N*-sulfonylcarboxamides; Asymmetric catalysis; Nitroso Diels–Alder; Ketones; Aldehydes.
* Corresponding authors. Tel.: +46 8 162479; fax: +46 8 154908; e-mail addresses: hansa@organ.su.se; acordova@organ.su.se; acordova1@netscape.net

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.03.085

Table 1. Catalyst screen for the direct catalytic asymmetric α-oxidations of **2a** with nitrosobenzene[a]



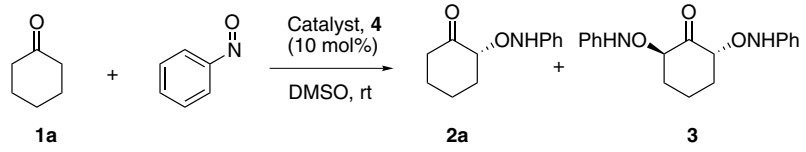
Entry	Cat.	Time (h)	Prod.	Yield (%)[b]	ee (%)[c]	Prod.	Yield (%)[b]	ee (%)[c]
1	**4**	2	**2a**	55	>99	**3**	27	>99
2	**5**	2	**2a**	52	98	**3**	21	99
3	**6**	16	**2a**	Traces	n.d.	**3**	—	—
4	**7**	18	**2a**	18	99	**3**	Traces	n.d.
5	**8**	3	**2a**	70	>99	**3**	22	>99
6	**9**	16	**2a**	67	>99	**3**	Traces	n.d.
7	**10**	3	**2a**	66	>99	**3**	20	>99
8	**11**	16	**2a**	Traces	n.d.	**3**	—	—
9	**12**	16	*ent*-**2a**	5	>99	*ent*-**3**	—	—

[a] To nitrosobenzene (1 mmol) in the presence of catalyst (10–30 mol %) in 2 mL of organic solvent was added ketone **1a** (2 mmol). After vigorous stirring at room temperature the reaction mixture was quenched by addition of brine and extraction with EtOAc. Subsequent purification utilizing silica-gel chromatography afforded the α-aminoxylated ketones **2a** and **3**.
[b] Yield of the isolated pure ketone.
[c] The ee as determined by chiral-phase HPLC analyses.

In an initial catalyst screen of amino acid derivatives **4**–**12**, we found that *N*-methylsulfonylcarboxamide **4** was an excellent catalyst for the reaction between cyclohexanone **1a** (3 mmol) and nitrosobenzene (1 mmol) and gave the corresponding α-aminoxylated ketone **2a** and α,α′-diaminoxylated ketone **3** in 55% and 27% yields with >99% ee's, respectively (Table 1).[13]

Furthermore, the novel sulfonylcarboxamides **4**, **5** and tetrazole **10** were the most reactive catalysts followed by proline.[14] In addition, hydroxyproline was a highly selective catalyst and furnished **2a** in 67% yield with >99% ee. To our surprise organic catalyst **6** provided only trace amounts of **2a**, which was probably due to the presence of TFA. This was further supported by the ability of our previously reported catalyst **7**, which did not have a TFA additive, to mediate the α-aminoxylation reaction to yield **2a** with >99% ee. Interestingly, diamine **12** provided **2a** with the opposite stereoselectivity as compared to all the other proline-derived catalysts. Encouraged by the discovery that the highly modular proline-derived *N*-alkyl- and arylsulfonylcarboxamide

Table 2. The direct asymmetric α-oxidations of **1** with sulfonylcarboxamide **4** as the catalyst[a]



Entry	Time (h)	Prod.	Yield (%)[b]	ee (%)[c]	Prod.	Yield (%)[b]	ee (%)[c]
1	2	**2a**	55	>99	**3**	27	>99
2	2	**2a**	80[d]	>99	**3**	Traces	n.d.
3	16[e]	**2a**	80[d]	98	**3**	Traces	n.d.

[a] Nitrosobenzene (1 mmol) in DMSO (1 mL) was slowly added via a syringe-pump to a solution of ketone **1a** (2 mmol) in the presence of catalyst **4** (10 mol %) in DMSO (1 mL). After vigorous stirring at room temperature the reaction mixture was quenched by addition of brine and extraction with EtOAc. Subsequent purification utilizing silica-gel chromatography afforded the α-aminoxylated ketones **2a** and **3**.
[b] Yield of the isolated pure ketone.
[c] The ee as determined by chiral-phase HPLC analyses.
[d] Slow addition of the nitrosobenzene.
[e] The reaction was performed in DMF at 4 °C.

were excellent catalysts for the direct catalytic α-aminoxylation reaction, we decided to optimize the yield of **2a** using **4** as the catalyst (Table 2).

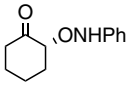
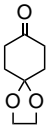
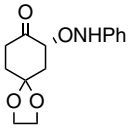
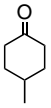
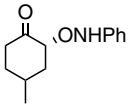
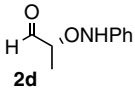
We found that the yield of **2a** was increased by slow addition of the electrophile using a syringe pump to the reaction mixture. For example, the reaction was completed within 2 h in DMSO and **2a** was isolated in 80% yield with >99% ee and only trace amounts of ketone **3**. The methylsulfonylcarboxamide **4** also mediated the α-oxidation reaction with excellent results in DMF.

Next, we investigated the α-aminoxylation reaction with a variety of ketones and aldehydes (Table 3).

The reactions proceeded smoothly and α-aminoxylated ketones **2a–c** were isolated in good yield with excellent enantioselectivity (entries 1–3). The methylsulfonylcarboxamide **4** was also able to mediate the direct enantioselective α-oxidation of aldehydes. For example, the sulfonylcarboxamide **4**-catalyzed reaction between propionaldehyde and nitrosobenzene furnished the corresponding α-aminoxylated product **2d** (entry 4), which was reduced in situ with excess $NaBH_4$ to the corresponding alcohol, which was isolated in 66% yield with >99% ee. We also investigated whether 2-cyclohexen-1-ones could be α-oxidized with nitrosobenzene using organic catalysts (Table 4).[8b,15] The reaction was successful and sulfonylcarboxamides, proline and tetrazole **10** were able to catalyze the reaction between cyclohexenone **1e** and nitrosobenzene to yield the corresponding bicyclic product **2e** with excellent stereoselectivity. Methylsulfonylcarboxamide **4**-catalyzed the tandem α-aminoxylation/Michael reaction with the highest stereoselectivity and enantiomerically pure **2e** was obtained (entry 1). However, tetrazole catalyst **10** furnished **2e** in a higher yield as compared to catalyst **4** with 99% ee (entry 3). The reaction was also run on a gram scale with L-proline as the catalyst without decreasing the enantioselectivity of the reaction.

The stereochemical outcome of the α-oxidations and tandem α-aminoxylation/Michael reactions of ketones and aldehydes utilizing sulfonylcarboxamide catalysis was the same as for L-proline catalysis.[7] Thus, organocatalysts **4** and **5** catalyzed the formation of (2*R*)-aminoxylated products. We therefore believe that the nitrosobenzene approaches the *si*-face of the chiral enamine-intermediate via transition state **I**, which is similar to our and Houk's previous density functional theory (DFT)-calculations of the transition state **II** of the proline-catalyzed α-aminoxylation reaction.[7b,9]

Table 3. The direct asymmetric α-oxidations of ketones and aldehydes with sulfonylcarboxamide **4** as the catalyst[a]

Entry	1	Time (h)	Prod.	Yield (%)[b]	ee (%)[c]
1	 **1a**	2	 **2a**	80	>99
2	 **1b**	5	 **2b**	74	98
3	 **1c**	3	 **2c**	54[d]	>99
4	 **1d**	2	 **2d**	66[e,f]	>99[e,g]

[a] Nitrosobenzene (1 mmol) in DMSO (1 mL) was slowly added with syringe-pump to a solution of ketone or aldehyde **1** (2 mmol) in the presence of catalyst **4** (10 mol %) in DMSO (1 mL). After vigorous stirring at room temperature the reaction mixture was quenched by addition of brine and extraction with EtOAc. Subsequent purification utilizing silica-gel chromatography afforded the α-aminoxylated product **2**.

[b] Yield of the isolated pure product.

[c] The ee as determined by chiral-phase HPLC analyses.

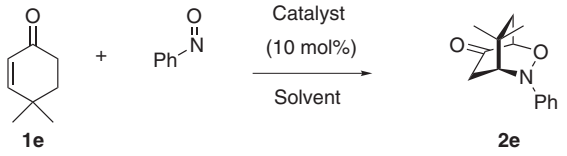
[d] Dr = 1:1 (*anti*:*syn*).

[e] The reaction was performed by simple mix and stirring.

[f] The yield of the isolated pure alcohol obtained by in situ reduction of **2d** with $NaBH_4$ at 0 °C.

[g] ee determined by chiral HPLC-analyses of the α-aminoxylated alcohol derived from **2d**.

Table 4. Amine-catalyzed direct enantioselective reactions with 2-cyclohexen-1-ones[a]



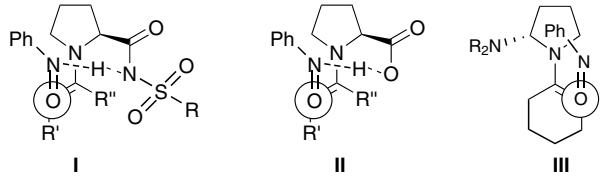
Entry	Catalyst	*T* (°C)	Solvent	Time (h)	Prod.	Yield (%)[b]	ee (%)[c]
1	**4**	40	MeCN	15	**2e**	22	>99
2	**4**	Rt	DMSO	12	**2e**	23	96
3	L-Proline	40	MeCN	16	**2e**	21	99
4	**10**	40	MeCN	15	**2e**	65	99

[a] A mixture of nitrosobenzene (1 mmol), ketone **1** (2 mmol) and catalyst (10 mol %) in DMSO (2 mL) was vigorously stirred at room temperature or 40 °C. The reaction mixture was quenched by addition of brine and extraction with EtOAc. Subsequent purification of the crude product by silica-gel chromatography afforded the Diels–Alder product **2**.

[b] Yield of the isolated pure product.

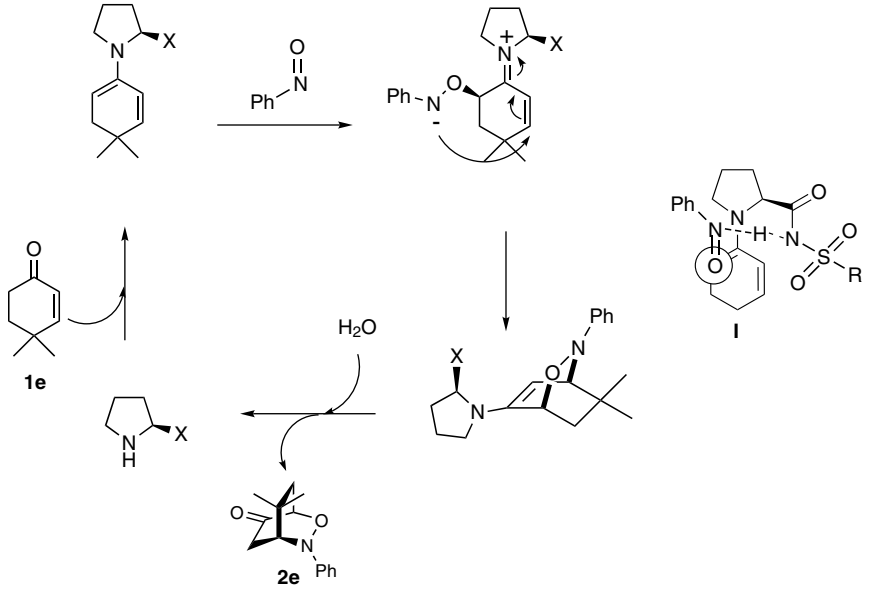
[c] The ee as determined by chiral-phase HPLC analyses.

Favourable coloumbic interactions between nitrosobenzene and the pyrrolidine ring of catalyst **12** in transition state **III** may explain why *ent*-**2a** was obtained.



In the case, of the sulfonylcarboxamide-catalyzed nitroso reactions of α,β-unsaturated cyclic ketones we believe that the reaction proceeds via a potential step-wise mechanism (Scheme 2). Accordingly, the tandem α-aminoxylation/Michael reaction starts by reaction of the unsaturated ketone with the organic catalyst to yield the chiral enamine. Next, the electrophile approaches the *si*-face of the chiral enamine intermediate via transition state **I** to furnish the activated iminium salt. The chiral-activated iminium salts undergoes a subsequent stereospecific intermolecular Michael-addition, which results in the bicyclic enamine intermediate. Hydrolysis of this chiral enamine intermediate provides the desired bicycle **2e** and free organic catalyst.

In summary, we have shown that proline-derived sulfonylcarboxamides are excellent catalysts for the direct enantioselective α-oxidation of ketones and aldehydes. The alkyl and arylsulfonylcarboxamides furnished the corresponding α-aminoxylated products in good yield with up to >99% ee. The novel organic catalysts are readily prepared in two steps and allows for the generation of catalyst libraries. Furthermore, proline-derived sulfonylcarboxamides are able to catalyze nitroso reactions that proceed via a tandem α-aminoxylation–Michael reaction



Scheme 2. Potential catalytic mechanism of the amine-catalyzed tandem α-aminoxylation/Michael reaction and plausible transition state **I** of the initial **4**-catalyzed α-aminoxylation of ketone **1e**.

to yield the desired bicyclic adducts with up to >99% ee. The high modularity in the synthesis of proline-derived carboxamides makes the likelihood of finding highly enantioselective reactions mediated by this class of catalysts a real possibility. Efforts in this area are in progress.

Acknowledgements

A.C. and H.A. thank the Swedish Research Council and Wenner-Gren Foundation for financial support.

References and notes

1. (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; (b) Noyori, R. *Asymmetric Catalysis in Asymmetric Organic Synthesis*; John Wiley & Sons: New York, 1994; (c) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed., 2nd ed.; Wiley-VCH: New York, 2000.
2. (a) Davis, F. A.; Chen, B. C. In Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Houben-Weyl: Methods of Organic Chemistry; Georg Thieme: Stuttgart, 1995; Vol. E 21, p 4497; (b) Enders, D.; Reinhold, U. *Liebigs Ann.* **1996**, 11; (c) Enders, D.; Reinhold, U. *Synlett* **1994**, 792.
3. (a) Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919, and references cited therein; (b) Lohray, B. B.; Enders, D. *Helv. Chim. Acta* **1989**, *72*, 980.
4. Paquette, L. A.; Hartung, R. E.; Hofferberth, J. E.; Vilotijevic, I.; Yang, J. *J. Org. Chem.* **2004**, *69*, 2454, and references cited therein.
5. Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6038.
6. (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726; (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138; (c) List, B. *Tetrahedron* **2002**, *58*, 5573; (d) Merino, P.; Tejero, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 2995; For α-aminations see: (e) Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790; (f) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656; (g) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254; For α-chlorinations of ketones see: (h) Marigo, M.; Bachmann, S.; Halland, N.; Braunton, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5507; For amine-catalyzed epoxidations see: (i) Bohe, L.; Hanquet, M.; Lusinchi, M.; Lusinchi, X. *Tetrahedron Lett.* **1993**, *34*, 7271; (j) Adamo, M. F. A.; Aggarwal, V. K.; Sage, M. A. *J. Am. Chem. Soc.* **2000**, *122*, 8317; (k) Armstrong, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1460, and references cited therein.
7. (a) Bøgevig, A.; Sundén, H.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1109; (b) Córdova, A.; Sundén, H.; Bøgevig, A.; Johansson, M.; Himo, F. *Chem. Eur. J.* **2004**, *10*, 3673; (c) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247; (d) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808; (e) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293; (f) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Angew. Chem., Int Ed.* **2004**, *43*, 1112; (g) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Hibino, K.; Shoji, M. *J. Org. Chem.* **2004**, *69*, 5966.
8. (a) Momiyama, N.; Torii, H.; Saito, S.; Yamamoto, H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5374; (b) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962.
9. (a) Mathew, S. P.; Iwamura, H.; Blackmond, D. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3317; (b) Wang, W.; Wang, J.; Hao; Li; Liao, L. *Tetrahedron Lett.* **2004**, *45*, 7235; (c) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Sumiya, T.; Urushima, T.; Shoji, M.; Hashizume, D.; Koshino, H. *Adv. Synth. Catal.* **2004**, *346*, 1435. For density functional calculations see: Ref. 7b and (d) Cheong, P. H.-Y.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *43*, 13912.
10. (a) Córdova, A.; Sundén, H.; Engqvist, M.; Ibrahem, I.; Casas, J. *J. Am. Chem. Soc.* **2004**, *126*, 8914; (b) Sundén, H.; Engqvist, M.; Casas, J.; Ibrahem, I.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6532.
11. (a) Dahlin, N.; Bøgevig, A.; Adolfsson, H. *Adv. Synth. Catal.* **2004**, *346*, 1101; During the preparation of this manuscript Berkessel and co-workers reported that arylsulfonylcarboxamides catalyze the direct catalytic asymmetric aldol reaction with excellent stereoselectivity see: (b) Berkessel, A.; Koch, B.; Lex, J. *Adv. Synth. Catal.* **2004**, *346*, 1141.
12. (a) Casas, J.; Persson, P. V.; Iversen, T.; Córdova, A. *Adv. Synth. Catal.* **2004**, *346*, 1087; (b) Córdova, A. *Tetrahedron Lett.* **2004**, *45*, 3949; (c) Casas, J.; Sundén, H.; Córdova, A. *Tetrahedron Lett.* **2004**, *45*, 6117; (d) Ibrahem, I.; Casas, J.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6528; (e) Córdova *Acc. Chem. Res.* **2004**, *37*, 102; (f) Córdova, A.; Notz, W.; Barbas, C. F., III. *J. Org. Chem.* **2002**, *67*, 301; (g) Córdova, A. *Chem. Eur. J.* **2004**, *10*, 1987; (h) Córdova *Synlett* **2003**, 1651, and references cited therein.
13. In a typical experiment, the ketone **1a** (2 mmol) was added to a mixture of nitrosobenzene (1 mmol) in DMSO (4 mL) and organic catalyst (10–30 mol %). After vigorous stirring at room temperature the reaction mixtures were quenched by addition of brine followed by extraction with EtOAc to furnish the corresponding α-aminoxylated ketone **2a**. Pure **2a** was isolated by silica-gel column chromatography (EtOAc/pentane-1:4) and the ee was determined by chiral-phase HPLC-analysis (see Ref. 7b).
14. For previous use of catalyst **10** see: Ref. 8a,8b,10, and (a) Cobb, A. J. A.; Shaw, D. M.; Ley, S. V. *Synlett* **2004**, 558; (b) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983; (c) Hartikaa, A.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2004**, *15*, 1831.
15. In a typical experiment, the ketone **1e** (2 mmol) was added to nitrosobenzene (1 mmol) and catalyst (10 mol %) in organic solvent (2 mL) and the reaction mixture was vigorously stirred. After 14–16 h the reaction mixture was quenched by addition of brine followed by extraction with EtOAc to give the bicyclic adduct **2e**. Pure **2e** was isolated by silica-gel column chromatography (EtOAc/pentane-1:10) and the ee was determined by chiral-phase HPLC-analysis. HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 97:3, flow rate 0.5 mL/min, $\lambda = 254$ nm): major isomer: $t_R = 25.72$ min; minor isomer: $t_R = 19.81$ min; $[\alpha]_D^{23}$ −80.1 (*c* 0.5, $CHCl_3$).