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Cu(II)–Aza(bisoxazoline)-Catalyzed Asymmetric Benzoylations

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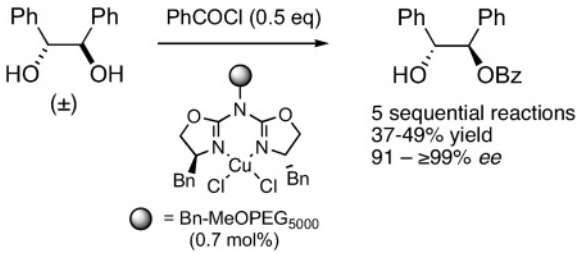
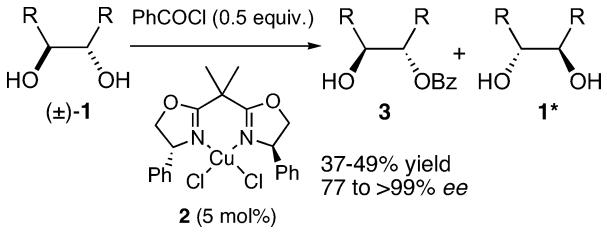
ABSTRACT



Racemic 1,2-diols and α-hydroxy carbonyl compounds can be asymmetrically benzoylated in a kinetic resolution in the presence of various Cu(II)–aza(bisoxazoline) catalysts. A novel bisbenzyl-substituted aza(bisoxazoline) ligand proved to be especially effective when immobilized on MeOPEG$_{5000}$, giving from 91 to ≥99% ee in 37–49% yield for each of five sequential reactions.

Enzyme-catalyzed asymmetric acylation reactions are powerful tools for the kinetic resolution or desymmetrization of alcohols.[1] Likewise, a number of efficient metal- and organocatalysts have been developed to effect this and related transformations.[2] We were especially intrigued by a report of Matsumura and co-workers[3] who recently reported the asymmetric benzoylation of 1,2-diols (±-**1**) with the Cu(II)−bis(oxazoline) **2** in high yields and excellent selectivities (Scheme 1).

Scheme 1. Cu(II)-Catalyzed Asymmetric Benzoylation by Matsumura and Co-workers



We recently introduced aza(bisoxazolines) **6a**−**c** and **7a**−**c** (Scheme 2) as chiral ligands for asymmetric catalysis,[4] which are readily synthesized by condensation of **4** and **5**, being both conveniently available[5] from the chiral pool in either enantiomeric form. An attractive feature of these ligands is their facile attachment to organic and inorganic supports through alkylation of the central nitrogen, thus, arriving at recyclable catalysts. Moreover, since aza(bisoxazolines) are considerably more electron rich than the corresponding bis(oxazolines), metal complexes of the former but not of the latter can also be immobilized in ionic liquids[6] and on Nafion or clays by ion exchange and employed as catalysts.[7] On the other hand, metal−aza(bisoxazoline) complexes display a reduced Lewis acidity compared to their bis(oxazoline)

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(2) (a) Brunner, H.; Obermann, U.; Wimmer, P. *Organometallics* **1989**, *8*, 821. (b) Vedejs, E.; Daugulis, O.; Tuttle, N. *J. Org. Chem.* **2004**, *69*, 1389. (c) Mizuta, S.; Sadamori, M.; Fujimoto, T.; Yamamoto, I. *Angew. Chem., Int. Ed.* **2003**, *42*, 3383. (d) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542. (e) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601.

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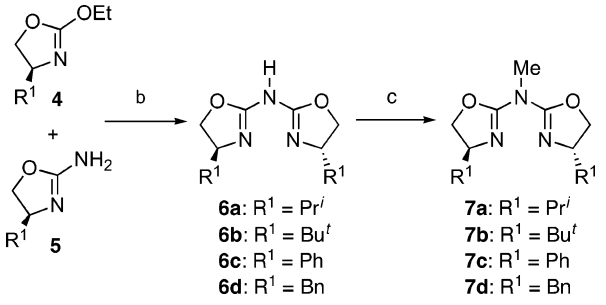
Scheme 2. Synthesis of Aza(bisoxazoline) Ligands[a]

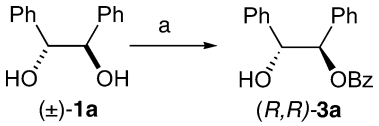


[a] Reagents and conditions: For synthesis of **6a**−**c** and **7a**−**c**, see ref 4b. For synthesis of **6d**/**7d**: (b) **4d** (1.2 equiv), **5d** (1 equiv), *p*-TSA, toluene, reflux, 24 h, 35%; (c) (i) *n*-BuLi, THF, −78 °C; (ii) MeI, −78 °C to rt, 98%.

counterparts, as reflected, for example, in the inability of Cu(II)−aza(bisoxazoline) complexes to catalyze [4 + 2]-cycloadditions in sharp contrast[8] to their bis(oxazoline) analogues. Nevertheless, we report here that Cu(II)−aza(bisoxazoline) complexes are not only good catalysts for the asymmetric benzoylation but, moreover, can be repeatedly used for this transformation and subsequently recovered after being immobilized on a poly(ethyleneglycol) support.[9]

Following the protocol developed by Matsumura and co-workers,[3a] we tested ligands **6** and **7** for the asymmetric benzoylation of (±)-**1a**. Initial optimization studies with the previously reported[4] **6a**−**c**, performed with the complete consumption of benzoyl chloride, assuming an identical degree of completion,[11] revealed that phenyl substitution (**6c**) gave the best results with respect to selectivity and yield for the benzoylated product **3a** (Table 1, entries 1−3). Matsumura and co-workers also found phenyl substitution, i.e., bis(oxazoline) **2**, to be most effective (>99% ee (s > 645) for **3a**). Methylation of the central nitrogen in **6** further improved the selectivity of this process from 87 to 93% ee (Table 1, entries 3 vs 5 (ligands **6c** vs **7c**)). The apparent beneficial effect of aryl substituents on the ligand prompted us to subsequently prepare the new bis(benzylated) aza(bisoxazoline) ligands **6d** and **7d** following our general strategy outlined in Scheme 2.[12] We were pleased to find that both of these ligands again considerably improved the selectivity for the formation of **3a** using the standard 5 mol % catalyst (Table 1, entries 4 and 6) and that especially **7d** was found to be highly efficient even at a catalyst concentration of 0.5 mol % (Table 1, entry 7).

Table 1. Cu(II)-Catalyzed Benzoylation of (±)-**1a** in the Presence of Various Aza(bisoxazoline) Ligands

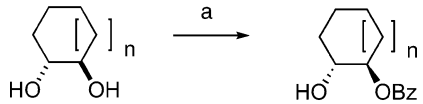


		monobenzoylated product **3a**			
entry	ligand	yield (%)	ee (%)[g]	configuration	selectivity (s)[h]
1[b]	**6a**	38	68	*R*,*R*	7.8
2	**6b**	49	33	*R*,*R*	2.6
3	(*ent*)-**6c**	48	87	*S*,*S*	35
4[c]	**6d**	45[e]	97	*R*,*R*	160
5	(*ent*)-**7c**	46	93	*S*,*S*	66
6[c]	**7d**	45[f]	99	*R*,*R*	501
7[c,d]	**7d**	**49**	**99**	***R*,*R***	**751**

[a] Reagents and conditions: 5 mol % $CuCl_2$, 5 mol % ligand, 0.5 equiv of PhCOCl, CH_2Cl_2, 3 h, 0 °C. [b] Reaction time = 2.5 h. [c] Reaction time = 2 h. [d] Performed with 0.5 mol % $CuCl_2$, 0.5 mol % ligand. [e] (*S*,*S*)-**1a** was isolated in 42% yield and 83% ee. [f] (*S*,*S*)-**1a** was isolated in 54% yield and 87% ee. [g] Determined by chiral GC. [h] Determined according to ref 10.

Racemic cyclohexene and cycloheptene diols **1b** and **1c**, respectively, were also benzoylated in good yields but with generally lower selectivities (Table 2). Moreover, the non-alkylated aza(bisoxazoline) **6c** proved to be best for **1b** (Table 2, entry 3), while for **1c** the nonalkylated aza(bisoxazoline) **6a** was most selective (Table 2, entry 7).

Table 2. Cu(II)-Catalyzed Benzoylation of Aliphatic Cyclic Diols in the Presence of Various Aza(bisoxazoline) Ligands



(±)-**1b** (n=1)
(±)-**1c** (n=2)

3b (n=1)
3c (n=2)

			monobenzoylated product **3**			
entry	ligand	diol	yield (%)	ee (%)[e]	configuration	s[f]
1	**6a**	**1b**	44	67	*R*,*R*	8.4
2[b]	**6b**	**1b**	43	27	*R*,*R*	2.1
3[c]	(***ent***)-**6c**	**1b**	**46**	**83**	***S*,*S***	**22**
4	**6d**	**1b**	41	70	*R*,*R*	9.1
5[d]	(*ent*)-**7c**	**1b**	47	52	*S*,*S*	4.9
6	**7d**	**1b**	45	73	*R*,*R*	11
7	**6a**	**1c**	**46**	**82**	***R*,*R***	**21**
8	**6b**	**1c**	43	32	*R*,*R*	2.4
9	(*ent*)-**6c**	**1c**	44	79	*S*,*S*	16
10	**6d**	**1c**	38	80	*R*,*R*	15
11[c]	(*ent*)-**7c**	**1c**	50	76	*S*,*S*	17
12	**7d**	**1c**	41	80	*R*,*R*	16

[a] Reagents and conditions: 5 mol % $CuCl_2$, 5 mol % ligand, 0.5 equiv of PhCOCl, 3 h, CH_2Cl_2, 0 °C. [b] Reaction time = 5 h. [c] Reaction time = 2 h. [d] Reaction time = 2.5 h. [e] Determined by chiral GC (**3b**) or chiral HPLC (**3c**). [f] Determined according to ref 10.

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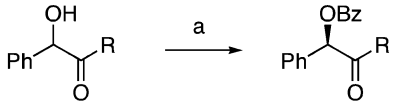
(7) (a) Fraile, J. M.; Garcia, J. I.; Harmer, M. A.; Herrerias, C. I.; Mayoral, J. A.; Reiser, O.; Werner, H. *J. Mater. Chem.* **2002**, *12*, 3290. (b) Fraile, J. M.; García, J. I.; Herrerías, C. I.; Mayoral, A.; Reiser, O.; Socuéllamos, A.; Werner, H. *Chem. Eur. J.* **2004**, *10*, 2997.

(8) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559.

We next investigated if the range of substrates can be extended from 1,2-diols. While 1,3-diols proved to be completely unreactive in the title transformation, α-hydroxycarbonyl compounds were amenable to this process. Thus, benzoin (±)-**8** could be benzoylated using **6a** with up to 79% ee (Table 3, entry 1). It was most striking to note that the

Table 3. Cu(II)-Catalyzed Benzoylation of α-Hydroxycarbonyl Compounds in the Presence of Various Aza(bisoxazoline) Ligands



(±)-**8**: R=Ph
(±)-**9**: R=OEt

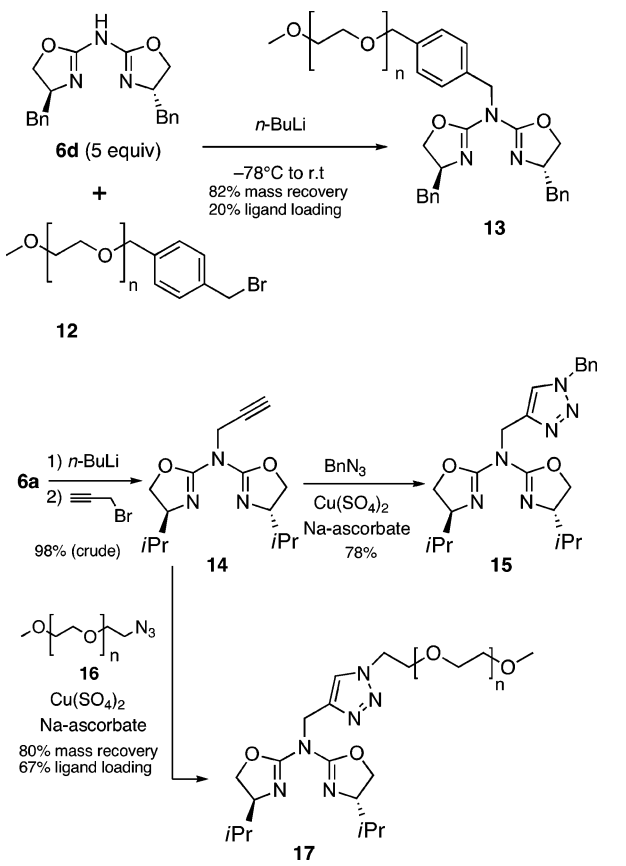
10: R=Ph
11: R=OEt

			benzoylated products **10** or **11**			
entry	ligand	substrate	yield (%)	ee (%)[c]	configuration	*s*[e]
1	**6a**	**8**	**43**	**79**[d]	***R***	**16**
2	**6b**	**8**	36	10	*R*	1.3
3	(*ent*)-**6c**	**8**	45	39	*S*	3.1
4	**6d**	**8**	32	77	*R*	11
5	(*ent*)-**7c**	**8**	0			
6	**7d**	**8**	32	27	*R*	2.0
7[b]	**6a**	**9**	**45**	**75**	***R***	**13**
8[b]	**6d**	**9**	49	53	*R*	5.3

[a] Reagents and conditions: 5 mol % $CuCl_2$, 5 mol % ligand, 0.5 equiv of PhCOCl, 4 h, CH_2Cl_2, 0 °C. [b] Reaction time = 3 h. [c] Determined by chiral HPLC. [d] (*S*)-**8** was isolated in 38% yield and 81% ee. [e] Determined according to ref 10.

previously successful phenyl-substituted ligands **6c** and **7c** performed very poorly with this substrate (Table 3, entries 3 and 5). Moreover, alkylation of the central nitrogen in the aza(box) ligands was also not tolerated any longer (Table 3, entries 5 and 6) in contrast to the previously discussed reactions with 1,2-diols **1a**−**c**. Although we have not yet addressed these results in mechanistic studies, it is worth noting that **6** and **7** differ in that the former can be an anionic ligand while the latter cannot. The resulting Cu(II) complexes of these ligands should therefore have significantly different electronic properties. We have noted previously in the cobalt(II)-catalyzed conjugate reduction of α,β-unsaturated carbonyl compounds that there are profound differences in catalytic activity upon switching from nonalkylated aza(bisoxazolines) **6** to the alkylated counterparts **7**.[13]

Scheme 3. Attachment of Aza(bisoxazoline) Ligands to $MeOPEG_{5000}$



The central nitrogen bridge in the aza(bisoxazoline) ligands can be functionalized by alkylation and therefore offers a convenient possibility for immobilization via attachment to a polymeric support. Thus, by deprotonation with *n*-BuLi, **6d** could be connected with the benzyl-modified poly(ethyleneglycol) $MeOPEG_{5000}$ **12** to give **13**. However, only 20% ligand loading onto the polymer could be achieved even when employing 5 equiv of **6d**. We envisioned a more effective immobilization strategy by using the copper-catalyzed[14] azide−alkyne cycloaddition[15] (CuAAC) reaction, which has proven to be very powerful for ligating functional molecules to supporting scaffolds or to each other. Propargylation of **6a** was readily performed to yield **14** in nearly quantitative yield, which was tested for coupling with benzyl azide. Aza(bisoxazolines) are strongly coordinating ligands for copper ions, thus greatly reducing their Lewis acidity to the point that they are ineffective in the catalysis of Diels−Alder reactions.[16] Nevertheless, **17** could be obtained in 78% yield in the presence of substoichiometric amounts of copper-

(9) Reviews on (polymer-supported) bis(oxazoline) ligands: (a) Rechavi, D.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 3467. (b) McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151.

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(11) For selected examples (Table 1, entries 4 and 6; Table 3, entry 1), also the starting materials were recovered and analyzed for their optical purity, which corresponded well with the predicted values.

(12) Benzyl-substituted bis(oxazolines) were also successfully employed in the benzoylation of *meso*-1,2,3-triols for the synthesis of phosphatidylinositol-3,5-biphosphate: Hamaguchi A.; Nishikawa A.; Shirai, R. *Book of Abstracts, 19th International Congress of Heterocyclic Chemistry*; Elsevier: New York, 2003; p 96.

(13) Geiger, C.; Kreitmeier, P.; Reiser, O. *Adv. Synth. Catal.* **2005**, *347*, 249.

(14) (a) Rostovtsev, 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. (c) Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 3192. (d) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128.

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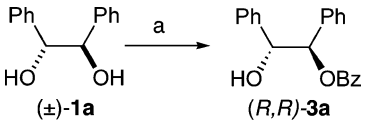
Table 4. Cu(II)-Catalyzed Benzoylation of (±)-**1a** in the Presence of Various PEG-Bound Aza(bisoxazoline) Ligands



(±)-**1a** (*R,R*)-**3a**

				3a		
entry	ligand (mol %)	cycle	time (h)	yield (%)	ee (%)[b]	*s*[c]
1	**15** (5)	n/a	3	38	66	7.2
2	**17** (1.3)	1	6	28	63	5.6
3	**17** (1.3)	2	6	25	56	4.2
4	**7d** (0.5)	n/a	2	49	99	751
5	**13** (0.7)	1	2	41	>99	>411
6	**13** (0.7)	2	2	38	98.5	245
7	**13** (0.7)	3	2	37	97	117
8	**13** (0.7)	4	2	49	91	61
9	**13** (0.7)	5	2	41	98	203

[a] Reagents and conditions: $CuCl_2$, ligand, 0.5 equiv of PhCOCl, CH_2Cl_2, 0 °C. [b] Determined by chiral GC. [c] Determined according to ref 10.

(II)chloride (0.5 equiv) and ascorbic acid (0.6 equiv), followed by removal of copper from the product by several extraction cycles with aqueous EDTA solution. Likewise, ligation to MeOPEG-N_3 **16** could be achieved[17] in a much improved manner: employing only 1.5 equiv of **14**, 67% ligand loading onto MeOPEG was achieved. Both MeOPEG-bound ligands **13** and **17** were employed in the copper-catalyzed benzoylation of (±)-**1**, being almost as enantioselective as their nonimmobilized counterparts (Table 4). However, the reaction rate with **17** was considerably slower than with **15**, requiring longer reaction times and resulting in lower yields (entries 1−3) of **3a**. Nevertheless, almost quantitative recovery (≥95% by mass) and subsequent reuse of Cu(II)·**17** was possible (entries 2 and 3). In contrast, excellent results in the benzoylation of **1a** were achieved with **13**, allowing multiple runs at only 0.7 mol % catalyst concentration (entries 5−9) with very comparable results with respect to the nonimmobilized Cu(II)·**7d** (entry 4).

In conclusion, we were able to demonstrate that aza(bisoxazolines) are capable ligands for the copper(II)-catalyzed asymmetric benzoylation of 1,2-diols and α-hydroxycarbonyl compounds. However, success with these substrates greatly depends on the type of aza(bisoxazolines) being employed, i.e., being alkylated or nonalkylated at the central nitrogen bridge. Finally, it was demonstrated that immobilized catalysts can be employed for the title reaction, allowing facile catalyst recovery and multiple reusability.

Acknowledgment. This work was supported by the Bavarian California Technology Center (BACATEC), the Fonds der Chemischen Industrie, and EU-COST D29/005 *Sustainable/Green Chemistry and Chemical Technology* and through generous chemical gifts by Degussa Eva Zocher is acknowledged for carrying out initial studies toward the synthesis of **15**.

Note Added after ASAP Publication. The substituents on the oxazolines in structures **14**, **15**, and **17** were incorrectly shown as Bn instead of *i*Pr in Scheme 3 in the version published ASAP on May 10, 2005. The corrected version was published ASAP on May 13, 2005.

Supporting Information Available: Experimental and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Comparative measurements of reaction rates showed that **14** and other aza(bisoxazoline) ligands are not strong accelerators of the azide−alkyne cycloaddition reaction.

(17) Thermal azide cycloadditions with **16** have been reported: Garanti, L.; Molteni, G. *Tetrahedron Lett.* **2003**, *44*, 1133.