ORGANIC LETTERS

2008
Vol. 10, No. 6
1235−1237

Highly Enantioselective Aryl Transfer to Aldehydes: A Remarkable Effect of Sulfur Substitution in Amino Thioacetate Ligands

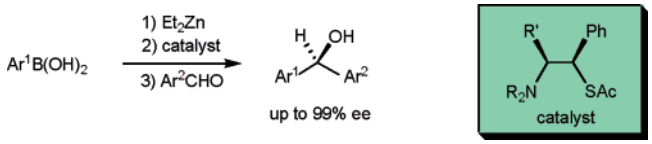
Myung-Jong Jin,* Shaheen M. Sarkar, Dong-Hwan Lee, and Huili Qiu

School of Chemical Science and Engineering, Inha University, Incheon 402-751, South Korea

mjjin@inha.ac.kr

Received January 18, 2008

ABSTRACT



Chiral amino thioacetate ligands were prepared from the corresponding amino alcohols and used as catalysts for enantioselective aryl transfer reaction. The amino thioacetates were remarkably superior to the corresponding amino alcohols. Low catalyst loadings of only 1–2.5 mol % were sufficient to achieve excellent enantioselectivity as well as high conversion in short reaction time. The results reveal that the thioacetoxy moiety of the amino thioacetates has a surprisingly beneficial effect in enhancing the asymmetric induction.

Catalytic enantioselective addition of organozinc to aldehydes has been widely studied as one of the most important methods for the synthesis of optically active secondary alcohols.[1] In contrast to the asymmetric alkyl transfer to aldehydes, the aryl transfer has been the subject of relatively few reports.[2] In 1997, Fu reported chiral ligand **1** for the addition of diphenylzinc to 4-chlorobenzaldehyde.[3] Despite this modest enantioselectivity, this initial report was the starting point for the growing field of this asymmetric catalysis. Soon after, Pu and Bolm developed highly enantioselective catalysts **2**[4] and **3**[5] for the phenyl transfer with diphenylzinc, respectively (Figure 1). Further, Bolm introduced the Ph_2Zn-Et_2Zn mixture[6] and the arylboronic acid−Et_2Zn mixture[7] as aryl sources to improve the performance of the aryl transfer. Since the discovery, chiral ligands such

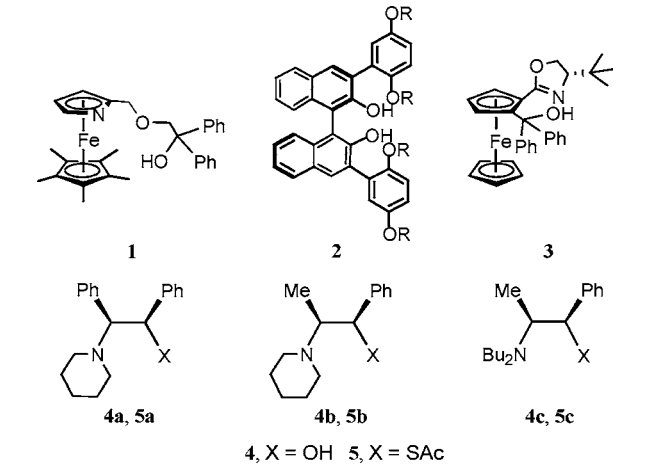


Figure 1. Asymmetric aryl transfer catalysts.

* To whom correspondence should be addressed. Tel: 82-32-860-7469. Fax: 82-32-872-0959.

(1) (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed.* **1991**, *30*, 49. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 883. (c) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757. (d) Walsh, P. J. *Acc. Chem. Res.* **2003**, *36*, 739.

(2) (a) Bolm, C.; Hildebrand, J. P.; Muniz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284. (b) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. *Chem. Soc. Rev.* **2006**, *35*, 454.

(3) Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444.

(4) (a) Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 4222. (b) Huang, W.-S.; Pu, L. *Tetrahedron Lett.* **2000**, *41*, 145.

(5) Bolm, C.; Muniz, K. *Chem. Commun.* **1999**, 1295.

10.1021/ol8001249 CCC: $40.75
Published on Web 02/21/2008

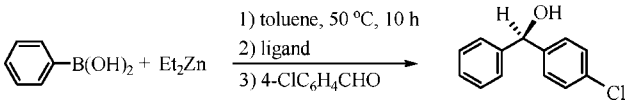
as aminonaphthol,[8] piperidinoethanol,[9] pyrrolidinylmethanol,[10] thiazolidine,[11] dialkylnorephedrine,[12] and MIB[13] have been emerged along this line. However, high catalyst loadings of 10−20 mol % were sometimes required to achieve satisfactory enantioselectivity without additives. Both accessibility of chiral catalysts and their high efficiency of asymmetric induction would be necessary for the practical asymmetric catalysis. Therefore, the search of truly valuable catalysts is a field of continuous interest for the catalytic aryl transfer reaction.

Previously, amino thioacetates were found to be highly enantioselective catalysts for the addition of diethylzinc to aldehydes.[14] We envisioned that amino thioacetates **5** would be applicable to the aryl transfer to aldehyde. In fact, outstanding results were obtained in the aryl transfer. Moreover, the reaction was performed well with low loadings of the catalysts. Most of the prominent catalysts are based on protic ligands with hydroxy group. It should be of interest to explore the catalytic ability of the aprotic ligands **5** in the aryl transfer. In this context, we report a surprisingly beneficial effect of the SAc moiety in the amino acetate ligands on the enantioselectivity in the aryl transfer to aldehydes.

The (−)-*N*,*N*-dialkylamino thioacetates **5a**−**c** were readily prepared by mesylation of the corresponding (−)-*N*,*N*-dialkylamino alcohols **4a**−**c** with methanesulfonyl chloride and triethylamine in methylene chloride, followed by subsequent displacement with an excess of potassium thioacetate in aqueous ethanol, respectively. At first, the phenyl transfer to 4-chlorobenzaldehyde using phenylboronic acid−Et_2Zn mixture was attempted in the presence of optically active amino alcohols **4a**−**c** (Table 1). The amino alcohols have proven to be excellent chiral ligands for the addition of diethylzinc to aldehydes.[15] However, the data in Table 1 reveal that the amino alcohols have very weak enantiocontolling ability in the phenyl transfer (entries 1−7). Although good chemical yields were obtained, the ee's were very low in each case. When the catalyst loading was decreased to 1 mol %, catalysts **4** afforded virtually no asymmetric induction (entries 2, 3, and 6). Next, we examined the catalytic behavior of the corresponding amino thioacetates **5** in the same phenyl transfer reaction. The initial trial with 10 mol % of **5a** gave a remarkable result of 99% ee (entry 8). The reaction could be completed within a short time at 10 °C affording optically pure (*R*)-product. Unexpectedly, reducing the catalyst loading to 2.5−5.0 mol % has only a little influence on the enantioselectivity (entries 9−12). The catalyst loading could be decreased to 1 mol % to still furnish a high ee of 90% (entry 13). These results came as a surprise since the serious effect of catalyst loading has been observed in most of the previous studies. The reaction gave a slightly higher ee when the reaction temperature was decreased from 20 to 10 °C. (−)-Norephedrine-derived ligands **5b** and **5c** were also examined for the phenyl transfer to 4-chlorobenzaldehyde (entries 14−21). The reaction proceeded very well with 91−98% ee in high yields. It is worthy that the phenyl transfer employing catalyst loading as low as 0.5 mol % afforded the product in 91% ee (entry 19). Until now, this level of enantioselectivity has scarcely been achieved without additives at such low catalyst loadings. The results show that the amino thioacetates are remarkably superior to the corresponding amino alcohols.

Encouraged by the high efficiency of the amino thioacetates, phenyl transfer to different aromatic aldehydes was performed in the presence of 2.5 or 5.0 mol % of **5** (Table 2). Amino alcohol **4b** gave poor ee's in the phenyl transfer to 2-chlorobenzaldehyde and 4-methoxybenzaldehyde (en-

Table 1. Asymmetric Phenyl Transfer to 4-Chlorobenzaldehyde in the Presence of Chiral Ligands **4** and **5**[a]



entry	ligand (mol %)	time (h)	*T* (°C)	yield[b] (%)	ee[c] (%)
1	**4a** (0.05)	4	20	85	48 (*R*)
2	**4a** (0.01)	6	20	76	2
3	**4a** (0.01)	8	10	70	3
4	**4b** (0.05)	4	20	87	32 (*R*)
5	**4b** (0.025)	6	10	83	17
6	**4b** (0.01)	8	20	74	1
7	**4c** (0.05)	4	20	83	29 (*R*)
8	**5a** (0.1)	3	10	95	99 (*R*)
9	**5a** (0.05)	2	20	96	96
10	**5a** (0.05)	2	10	92	97
11	**5a** (0.05)	4	0	83	97
12	**5a** (0.025)	2	10	94	96
13	**5a** (0.01)	2	10	91	90
14	**5b** (0.1)	2	10	97	98 (*R*)
15	**5b** (0.05)	2	20	92	96
16	**5b** (0.05)	3	10	90	98
17	**5b** (0.025)	3	10	91	95
18	**5b** (0.01)	4	10	90	94
19	**5b** (0.005)	4	10	83	91
20	**5c** (0.05)	2	10	94	96 (*R*)
21	**5c** (0.025)	3	10	92	94

[a] Reactions were performed with 2 equiv of phenylboronic acid and 6 equiv of Et_2Zn in toluene. [b] Yield of isolated product. [c] Enantiomeric excess determined by chiral HPLC on a Chiralcel OB-H column. Absolute configuration is determined by comparison of the HPLC elution order with the literature data.[7]

(6) (a) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Nuniz, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3465. (b) Bolm, C.; Kesselgruber, M.; Hermanns, N.; Hildebrand, J. P. *Angew. Chem., Int. Ed.* **2001**, *39*, 1488.

(7) (a) Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850. (b) Rudolph, J.; Hermanns, N.; C. Bolm, *J. Org. Chem.* **2004**, *69*, 3997.

(8) Ji, J.-X.; Wu, J.; Au-Yeung, T. T.-L.; Yip, C.-W.; Haynes, R. K.; Chan, A. S. *J. Org. Chem.* **2005**, *70*, 1093.

(9) (a) Braga, A. L.; Lüdtke, D. S.; Vargas, F.; Paixão, M. W. *Chem. Commun.* **2005**, 2512. (b) Jimeno, C.; Sayalero, S.; Fjermestad, T.; Colet, G.; Maseras, F.; Pericàs, M. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 1098.

(10) Braga, A. L.; Lüdtke, D. S.; Schneider, P. H.; Vargas, F.; Schneider, A.; Wessjohann, L. A.; Paixão, M. W. *Tetrahedron Lett.* **2005**, *46*, 7827.

(11) Braga, A. L.; Milani, P.; Vargas, F.; Paixão, M. W.; Sehnem, J. A. *Tetrahedron: Asymmetry* **2006**, *17*, 2793.

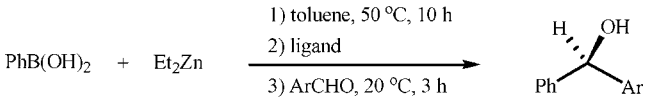
(12) Paixão, M. W.; Godoi, M.; Rhoden, C. R. B.; Westermann, B.; Wessjohann, L.; Lüdtke, D. S.; Braga, A. L. *J. Mol. Catal. A* **2007**, *261*, 120.

(13) Kim, J. G.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4175.

(14) (a) Jin, M.-J.; Ahn, S.-J.; Lee, K.-S. *Tetrahedron Lett.* **1996**, *37*, 8767. (b) Wipf, P.; Kendall, C. *Chem. Eur. J.* **2002**, *8*, 1779.

(15) Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, *56*, 4264.

Table 2. Asymmetric Phenyl Transfer to Aldehydes[a]



entry	Ar	ligand (mol %)	yield[b] (%)	ee[c] (%)
1	2-ClC_6H_4	**4b** (0.05)	83	15 (*R*)
2	2-ClC_6H_4	**4b** (0.025)	80	7
3	4-$MeOC_6H_4$	**4b** (0.025)	85	8 (*R*)
4	2-ClC_6H_4	**5a** (0.05)	97	98 (*R*)
5	2-ClC_6H_4	**5b** (0.05)	97	98
6	2-ClC_6H_4	**5b** (0.025)	93	90
7	4-$MeOC_6H_4$	**5b** (0.025)	98	93 (*R*)
8	2-$MeOC_6H_4$	**5b** (0.025)	93	91 (*R*)
9	4-MeC_6H_4	**5b** (0.025)	94	94 (*R*)
10	2-$C_{10}H_8$	**5b** (0.025)	91	94 (*R*)

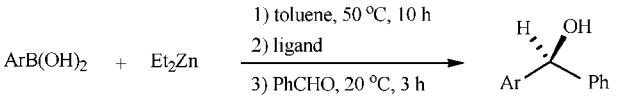
[a] Reactions were performed with 2 equiv of phenylboronic acid and 6 equiv of Et_2Zn in toluene. [b] Yield of isolated product. [c] Enantiomeric excess determined by chiral HPLC on a Chiralcel OB-H column. Absolute configuration is determined by comparison of the HPLC elution order.

tries 1−3), whereas amino thioacetates **5a** and **5b** gave high ee's up to 98% regardless of substituent on the aldehydes (entries 4−10).

In next step, we investigated the aryl transfer to benzaldehyde with substituted phenylboronic acids (Table 3). In cases of 4-substituted phenylboronic acids, very high ee's (≥90%) were obtained (entries 1−13). In contrast, 3- and 2-chlorophenylboronic acids lowered ee under the same conditions (entries 14 and 15). All of the ee values were slightly low compared with those of the phenyl transfer. From these results, the combination of phenylboronic acid and substituted benzaldehyde appears to be a better approach for the preparation of enantioenriched diarylmethanols. Our results show that replacement of the hydroxy group of the amino alcohols **4** with thioacetoxy group increases remarkably the enantioselectivity. The remarkable efficiency of ligands **5** may be explained by the fact which sulfur has stronger affinity toward Zn of arylzinc species[16] formed. This

(16) (a) Srebnik, M. *Tetrahdron Lett*. **1991**, *32*, 2449. (b) Langer, F.; Schwink, L.; Devasagayaraj, A.; Chavant, P.-Y.; Knochel, P. *J. Org. Chem*. **1996**, *61*, 8229. (c) Dahmen, S.; Bräse, S. *Org. Lett*. **2001**, *3*, 4119.

Table 3. Asymmetric Aryl Transfer to Benzaldehydes[a]



entry	Ar	ligand (mol %)	yield[b] (%)	ee[c] (%)
1	4-$MeOC_6H_4$	**5a** (0.05)	93	92 (*S*)
2	4-$MeOC_6H_4$	**5a** (0.025)	90	90
3	4-$MeOC_6H_4$	**5b** (0.05)	93	93
4	4-$MeOC_6H_4$	**5b** (0.025)	86	90
5	4-$MeOC_6H_4$	**5c** (0.025)	90	93
6	4-ClC_6H_4	**5a** (0.05)	91	95 (*S*)
7	4-ClC_6H_4	**5a** (0.025)	92	93
8	4-ClC_6H_4	**5b** (0.05)	96	94
9	4-ClC_6H_4	**5b** (0.025)	90	92
10	4-ClC_6H_4	**5c** (0.05)	92	95
11	4-ClC_6H_4	**5c** (0.025)	87	94
12	4-MeC_6H_4	**5a** (0.025)	90	92 (*S*)
13	4-MeC_6H_4	**5b** (0.025)	90	90
14	3-Cl C_6H_4	**5b** (0.025)	91	88 (*S*)
15	2-Cl C_6H_4	**5b** (0.025)	86	80 (*S*)

[a] Reactions were performed with 2 equiv of arylboronic acid and 6 equiv of Et_2Zn in toluene. [b] Yield of isolated product. [c] Enantiomeric excess determined by chiral HPLC on a Chiralcel OB-H column. Absolute configuration is determined by comparison of the HPLC elution order.

causes an increase in rigidity of the coordination sphere of the catalyst and leads to higher enantioselectivity.

In conclusion, amino thioacetate ligands **5** turned out to be highly efficient catalysts for the enantioselective aryl transfer reaction. The results indicate that the SAc moiety of the amino thioacetate has a surprisingly beneficial effect in enhancing the asymmetric induction.

Acknowledgment. This work was supported by Inha University Research Grant (INHA-2008).

Supporting Information Available: General experimental procedures, spectral data for **5a-c** and chiral HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8001249