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COMMUNICATIONS

Published on Web 05/01/2002

The Asymmetric Dialkylzinc Addition to Imines Catalyzed by [2.2]Paracyclophane-Based *N,O*-Ligands

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Received February 6, 2002

The catalytic asymmetric preparation of amines by addition of organometallic reagents to C=N bonds is one of the most important reactions in homogeneous catalysis.[1] While there have been numerous efforts to control the stereoselectivity of this reaction either by chiral auxiliaries[1a,b] or (stoichiometric) chiral ligands,[1d] the catalytic asymmetric addition of simple alkylmetals has only been achieved very recently. Tomioka et al. described the dialkylzinc addition to *N*-sulfonyl imines in the presence of chiral amidophosphine copper(II) complexes with high levels of enantioselectivity (up to 94% ee).[2] At the same time, Hoveyda, Snapper, et al. reported a zirconium-catalyzed variant using peptidic Schiff-base ligands which were optimized in a combinatorial fashion (up to 97% ee were obtained for certain *N*-aryl imines).[3] However, both methods rely on metal complexes of specific ligands and therefore may complicate the extension to other zinc species or the use of other ligands. Additionally, preparation of the starting materials and deprotection of the obtained products is sometimes difficult.

The lack of a simple method employing only a catalytic amount of an *N,O*-ligand[4] and no additional central metal (other than zinc itself) is in sharp contrast to the asymmetric alkylation of aldehydes with organozinc reagents, which has become one of the most extensively studied catalytic reactions in organic synthesis.[5]

This apparent lack is not to be ascribed to selectivity problems in the addition reaction, but rather to the (un)reactivity of many imine substrates or precursors toward alkylzinc reagents. Additionally, reactive imine derivatives or their addition products tend to coordinate to the catalytically active zinc complexes and therefore prevent the formation of a catalytic cycle.

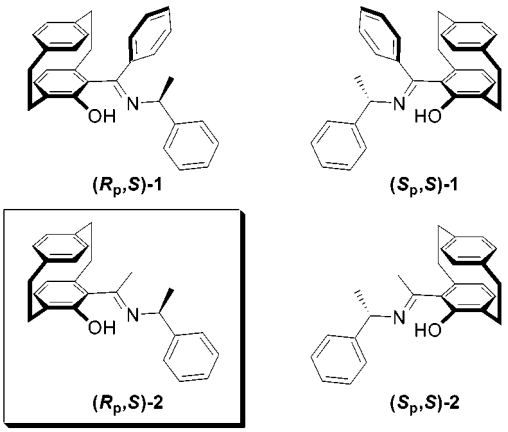
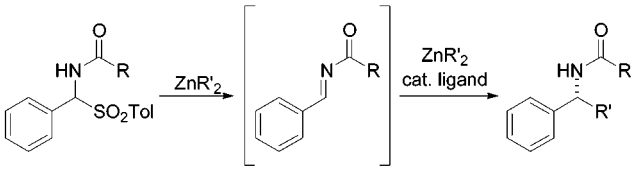


Figure 1. [2.2]-Paracyclophane-based ketimine ligands.

Table 1. Substrate Screening and Optimization of Reaction Conditions



3a R = O*t*Bu
b R = Me
c R = H

4a-c **5a-c**

entry	R =	ligand (mol %)	reaction conditions[a]	yield [%][b] (ee [%][c])
1	Me	(***R***$_p$,***S***)−**2** (6)	$ZnMe_2$, hexane, 0 → 20 °C	57 (79)[d]
2	Me	(***R***$_p$,***S***)−**2** (6)	$ZnMe_2$, toulene, 0 → 20 °C	99 (47)[d]
3	Me	(***R***$_p$,***S***)−**2** (6)	$ZnMe_2$, CH_2Cl_2, 0 → 20 °C	95 (34)[d]
4	Me	(***R***$_p$,***S***)−**2** (6)	$ZnMe_2$, THF, 0 → 20 °C	77 (0)[d]
5	Me	(***R***$_p$,***S***)−**2** (2)	$ZnEt_2$, hexane, 10 °C	50 (80, *R*)[e]
6	Me	(***R***$_p$,***S***)−**2** (2)	$ZnEt_2$, hexane, 20 °C	92 (63, *R*)[e]
7	H	(***R***$_p$,***S***)−**1** (1)	$ZnEt_2$, hexane, 10 °C, 36 h	92 (95, *R*)[e]
8	H	(***S***$_p$,***S***)−**1** (1)	$ZnEt_2$, hexane, 10 °C, 36 h	90 (92, *R*)[e]
9	H	(***R***$_p$,***S***)−**2** (1)	$ZnEt_2$, hexane, 10 °C, 36 h	93 (93, *R*)[e]
10	H	(***S***$_p$,***S***)−**2** (1)	$ZnEt_2$, hexane, 10 °C, 36 h	92 (61, *S*)[e]

[a] Reaction time 16 h unless otherwise stated. [b] Determined by GC analysis of the crude reaction mixture. See Supporting Information. [c] Determined by GC_{CSP} or HPLC. See Supporting Information. [d] 2 equiv of $ZnMe_2$ as a 1 M solution in toluene. [e] 3 equiv $ZnEt_2$ as a 1 M solution in hexane.

We document here our results in the addition of dialkylzinc to imines in the presence of catalytic amounts of [2.2]paracyclophane-based *N,O*-ligands **1**,**2** (Figure 1).[6]

At the outset of our study, we examined the reactivity of *N*-(*tert*-butyloxycarbonyl)-α-(*p*-tolylsulfonyl)benzylamine **3a** which is successfully applied as *N*-acyl imine precursor and is readily available in a one-pot-synthesis from benzaldehyde, amide, and *p*-tolylsulfinic acid.[7] The reaction proceeds via deprotonation of the carbamate **3a**, upon which elimination of the sulfinate takes place to form the *N*-acyl imine **4a**.[8] Although the compounds showed reactivity in the reaction with dialkylzinc, only complex mixtures of products could be obtained. Some of the products could be identified by GC−MS analysis, indicating that the addition to the imine bond had occurred. Attack of the dialkylzinc on the carbonyl group of the carbamate led to the formation of byproducts.[9]

We reasoned that replacing the carbamate for an amide would prevent the complexation of zinc species to the protecting group, thus avoiding the attack on the carbonyl group. We therefore used the *N*-acetyl derivative **3b**.[10]

With this substrate, the addition reaction was achieved cleanly, giving the alkylated *N*-acetyl amine **5b** as the only product. A solvent screening indicated that hexane was the solvent of choice, giving up to 79% ee in the presence of 6 mol % of (***R***$_p$,***S***)-**2**

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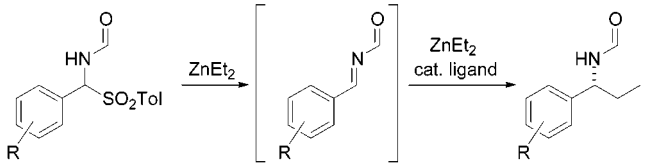
10.1021/ja025831e CCC: $22.00

Table 2. Scope and Limitation; Substrate Spectrum of the Diethylzinc Addition to Imines[a]



6 **7** **8**

entry	R =	ligand (mol %)	temp [°C]	time [h]	yield [%][b]	ee [%][c]
1	H	(**R**$_p$,**S**)−**2** (2)	10	36	>99	95 (*R*)
2	H	(**R**$_p$,**S**)−**2** (2)	20	16	>99	93 (*R*)[d]
3	4-Cl	(**R**$_p$,**S**)−**2** (2)	20	3	>99	89 (*R*)
4	4-Cl	(**R**$_p$,**S**)−**2** (5)	20	16	97	90 (*R*)
5	4-OMe	(**R**$_p$,**S**)−**2** (2)	20	16	97	95 (*R*)
6	4-CO_2Me	(**R**$_p$,**S**)−**2** (2)	0	36	90	94 (*R*)
7	2,6-Cl_2	(**R**$_p$,**S**)−**2** (2)	0	36	98	95 (*R*)
8	4-*t*Bu	(**R**$_p$,**S**)−**2** (2)	0	24	>99	75 (*R*)
9	4-Me	(**R**$_p$,**S**)−**2** (2)	10	24	>99	95 (*R*)
10	3-Cl	(**R**$_p$,**S**)−**2** (2)	0	24	94	84 (*R*)
11	3-Cl	(**R**$_p$,**S**)−**2** (5)	0	24	99	93 (*R*)
12	3-Me	(**R**$_p$,**S**)−**2** (2)	−10	24	>99	70 (*R*)
13	3-Me	(**R**$_p$,**S**)−**2** (5)	−15	24	97	91 (*R*)

[a] 0.5 mmol imine precursor **6**, 3 equiv $ZnEt_2$, hexane. [b] Determined by GC analysis of the crude reaction mixture. See Supporting Information. [c] Determined by GC_{CSP} or HPLC. See Supporting Information. [d] 5 mmol.

(Table 1, entries 1−4). More polar solvents improved the yield while diminishing the enantioselectivity. In THF, only racemic product was obtained. By employing 3 equiv of diethylzinc at 10 °C, the ee could be improved to 80% (entry 5). At 20 °C, the ee dropped to 63%, indicating a narrow temperature window for the reaction.

To further improve the reaction conditions, we used the *N*-formyl derivative **3c** and submitted it to a ligand screening, employing the four [2.2]paracyclophane-based *N*,*O*-ligands depicted in Figure 1. Although we had somehow expected an attack of the zinc species on the formyl group, the reaction proceeded cleanly to give the *N*-(1-phenylpropyl)formamide **5c** in 61−95% ee in the presence of 1 mol % of ligand (entries 7−10). For further investigations, **(*R*$_p$,*S*)-2** was chosen because its broader substrate tolerance was known from previous work.[6b]

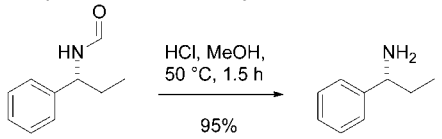
Functionalized substrates are usually well tolerated in dialkylzinc additions. Electron-rich (Table 2, entry 5) and electron-poor (entries 3,4,6,7) substrates gave comparably high ee's of 90−95%. Ortho and para substituents do not influence the selectivity of the catalysis (exception: entry 8), and even hindered imines were recognized on a very high level of enantioselectivity (entry 7). For meta substituted substrates however, ligand **(*R*$_p$,*S*)-1** gave superior results (entries 11,13). A scale-up to 5 mmol of substrate (entry 2) gave identical results as obtained on 0.5 mmol scale.

Although the substrate tolerance is very broad, each precursor has a relatively small temperature window for optimal enantioselectivity. As the solubility of the starting materials in hexane is very low, the deprotonation of the *N*-formyl sulfone **6** to give the *N*-formyl imine **7** is the rate-limiting step. The addition reaction itself is fast and proceeds even in the absence of a catalyst. The amount of available imine **7** is thus controlled by careful choice of the temperature. Higher temperatures liberate the imine too fast and thus decrease the ee due to the fast uncatalyzed background reaction. Lower temperatures *freeze* the reaction due to the diminished solubility of the starting material.

Although the mechanism is not yet fully understood, some experimental details are striking. In the dialkylylzinc addition to imines, the products of opposite absolute configuration are obtained (compared to the addition to aldehydes).[6] This and the higher enantioselectivity of the ligands[11] hint at a bidentate coordination of the imine to the catalytically active zinc species.[12]

The deprotection of *N*-formyl amine products **8a** was uneventful and furnished the (*R*)-phenylpropylamine **9a** racemization free and in nearly quantitative yield (Scheme 1).

Scheme 1. Deprotection of *N*-Formyl Amines



8a 93% *ee* **9a** 93% *ee*

In summary, we have demonstrated the first highly enantioselective dialkylzinc addition to imines in the presence of catalytic amounts of *N*,*O*-ligands. The extension of this methodology to other organozinc reagents is under current investigation. Due to the simplicity of the process and the good availability of the imine precursors **6** from the corresponding aldehydes, a broad applicability of the reported catalytic reaction can be anticipated.

Acknowledgment. We gratefully acknowledge financial support from the *Deutsche Forschungsgemeinschaft* (SFB 380, BR1750-1) and the *Fonds der Chemischen Industrie*.

Supporting Information Available: General experimental procedure and analytical data for the products **8** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For reviews on (catalytic) asymmetric additions to imines, see: (a) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895−1946. (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438. (c) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069−1094. (d) Denmark, S. E.; Nicaise, O. J.-C. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; pp 924−958.
(2) Fujihara, H.; Nagai, K.; Tomioka, K. *J. Am. Chem. Soc.* **2000**, *122*, 12055−12056.
(3) (a) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 984−985. The methodology was recently extended to aliphatic substrates: (b) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409−10410.
(4) The number of available *N*,*O*-ligands is very high due to the success of the alkylzinc addition to aldehydes. In a recent review [ref 5a] the catalytic properties of approximately 600 ligands were summarized.
(5) For reviews, see: (a) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757−824. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833−856.
(6) The [2.2]paracyclophane-based *N*,*O*-ligands have previously been employed in the dialkylzinc addition to aldehydes: (a) Dahmen, S.; Bräse, S. *Chem. Commun.* **2002**, 26−27, and the alkenylzinc addition to aldehydes: (b) Dahmen, S.; Bräse, S. *Org. Lett.* **2001**, *3*, 4119−4122. For the synthesis of the compounds **1**,**2**, see: (c) Rozenberg, V.; Danilova, T.; Sergeeva, E.; Vorontsov, E.; Starikova, Z.; Lysenko, K.; Belokon, Y. *Eur. J. Org. Chem.* **2000**, 3295.
(7) (a) Schunk, S.; Enders, D. *Org. Lett.* **2001**, *3*, 3177−3180. (b) Palomo, C.; Oiarbide, M.; González-Rego, C.; Sharma, A. K.; Garia, J. M.; González, A.; Landa, C.; Linden A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1063−1065. (c) Mecozzi, T.; Petrini, M. *Tetrahedron Lett.* **2000**, *41*, 2709−2712. (d) Ballini, R.; Petrini, M. *Tetrahedron Lett.* **1999**, *40*, 4449−4452. (e) Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, *64*, 8970−8972. (f) Kanazawa, A. M.; Denis, J.-N.; Greene, A. E. *J. Org. Chem.* **1994**, *59*, 1238−1240.
(8) A related method using benzotriazole-masked *N*-acyl imines was published earlier. However, low temperatures and stoichiometric amounts of ligand had to be applied: Katritzky, A. R.; Harris, P. A. *Tetrahedron: Asymmetry* **1992**, *3*, 437−442.
(9) Interestingly, the carbamoyl group in these substrates is reported to be not affected by organomagnesium and alkynyllithium reagents: ref 7e.
(10) Sisko, J.; Mellinger, M.; Sheldrake, P. W.; Baine, N. H. *Tetrahedron Lett.* **1996**, *37*, 8113−8116.
(11) In the diethylzinc addition to benzaldehyde, ligand **(*R*$_p$,*S*)-2** produces the (*S*)-product in 82% ee. See ref 6a.
(12) As also pointed out by one of the reviewers, changing only the planar chirality of the ligand was the factor influencing the selectivity (*R* or *S*) when aldehydes were used (ref 6a). This is also observed with ligands **2** (Table 1, entries 9, 10), but not with ligands **1** (Table 1, entries 7, 8). We account this for a change in the mechanism of the reaction using **(*S*$_p$,*S*)-1** which may be due to interactions of the two phenyl substituents in the ligand side chain and a bidentate coordinated imine. A detailed mechanistic study is underway.

JA025831E