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Paracyclophanes in Action: Asymmetric Catalytic Dialkylzinc Addition to Imines Using [2.2]Paracyclophane-based *N,O*-Ligands as Catalysts

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Abstract: The asymmetric addition of dibutylzinc to imines is achieved by employing [2.2]paracyclophane-based ketimine ligands with good to excellent enantioselectivities. A comparison to other organozinc reagent is made.

Keywords: amines · cyclophanes · zinc

Chiral amines represent one of the most actively investigated classes of compounds due to their importance as building blocks for biologically active compounds. Hence, the catalytic asymmetric preparation of amines by addition of organometallic reagents to C=N bonds is a field of considerable importance to 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 quite recently. In this context, the enantioselective addition of alkylzinc reagents to imines has attracted considerable interest in the last years. Two concepts can be distinguished: the addition of zinc reagents catalyzed by a transition metal complex other than zinc,[2–4] and the in situ formation of active catalyst based on the zinc complex of (usually) an *N,O*-ligand.[5]

Most of the studies reported so far are on the catalytic ethylation of imines using diethylzinc as readily available, reactive, and selective zinc reagent. Some studies have also given examples of, or been entirely focused on, dimethylzinc.[2d,4] Examples for the use of also commercially available dibutylzinc, however, are very rare.[2c,7] This is even more astonishing since the products, e.g., chiral phenyl pentylamine derivatives,[8,9] cannot easily been made by any other asymmetric catalytic method.

We have concentrated our efforts on the dibutylzinc addition using a class of [2.2]paracyclophane-based ketimine ligands **1** and **2** (Figure 1), which have already been successfully applied in related processes.[5a,b] These ligands, first reported by the Rozenberg group,[6] are readily available as both enantiomers in few steps. The catalytic reaction employing α-amido sulfones **3** as masked imine precursors[11] belongs to the latter class of solely zinc-mediated processes. We here report the first in-depth investigation on the asymmetric catalytic addition of butyl groups to imines.

The addition of dibutylzinc to α-amido sulfone **3a** proceeds via a two-step process (Table 1). Deprotonation of the sulfone by one equivalent of dibutylzinc generates the formyl imine **4a** in situ via elimination of the sulfinate. In a second step, the addition of another equivalent of zinc reagent takes place. In contrast to, for example, *tert*-butyl carbamate protected imines, which can be isolated and are employed in a variety of catalytic processes, formyl imines tend to be easily hydrolyzed to the corresponding

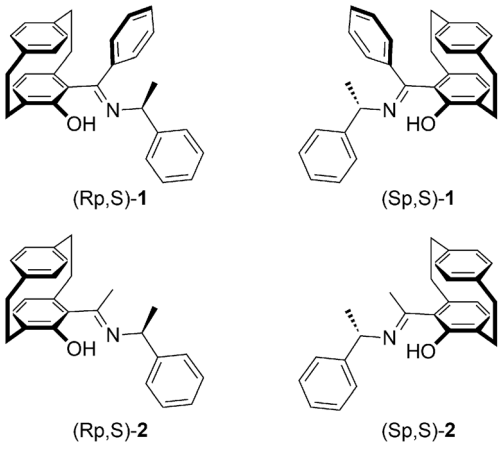

Figure 1. Ketimine ligands.

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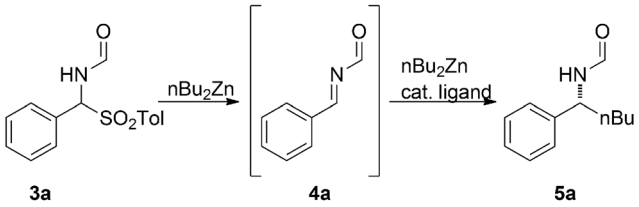
Table 1. Optimization of reaction conditions (selected examples).[a]



3a **4a** **5a**

Entry	Catalyst (mol%)	Conditions	conv.[b] (%)	*ee*[c] (%)
1	(R_p,*S*)-**2** (2)	RT, 16 h, heptane	>99	83 (*R*)
2	(R_p,*S*)-**2** (2)	10 °C, 16 h, heptane	98	84 (*R*)
3	(R_p,*S*)-**2** (2)	−20 °C, 16 h, heptane/toluene	85	84 (*R*)
4	(S_p,*S*)-**2** (2)	10 °C, 16 h, heptane	95	50 (*S*)
5	(S_p,*S*)-**1** (2)	10 °C, 16 h, heptane	94	68 (*S*)
6	(R_p,*S*)-**1** (2)	10 °C, 16 h, heptane	99	88 (*R*)
7	(R_p,*S*)-**1** (0.5)	10 °C, 16 h, heptane	88	66 (*R*)
8	(R_p,*S*)-**1** (1)	10 °C, 16 h, heptane	95	75 (*R*)
9	(R_p,*S*)-**1** (5)	10 °C, 16 h, heptane	>99	88 (*R*)
10	(R_p,*S*)-**2** (5)	10 °C, 16 h, heptane	>99	90 (*R*)

[a] Substrate **3a** (0.25 mmol), ligand, dibutylzinc (0.75 mmol). [b] Determined by GC and RP-HPLC. [c] Determined with chiral stationary phase HPLC (Chiralcel OD).

aldehydes. However, when formed in situ, they are excellent substrates for the catalytic addition of zinc reagents.

First results using our reference catalyst (R_p,*S*)-**2** indicated that a reaction temperature of 10 °C was optimal using a highly unpolar reaction medium such as heptane (entry 2). In fact, the reactions were run solely in the 1 molar dibutylzinc in heptane stock solution without adding more solvent. Previous studies had also shown that related addition processes can also be optimized for a different temperature window when more polar solvents such as toluene were used (entry 3).[5b] In this case the results in heptane were identical to the experiments in a heptane/toluene mixture at lower temperature. We therefore carried out a ligand screening with the experimentally simpler heptane protocol which, by comparison, also resulted in better reproducibility (deviation in repetitive runs <1% *ee*).

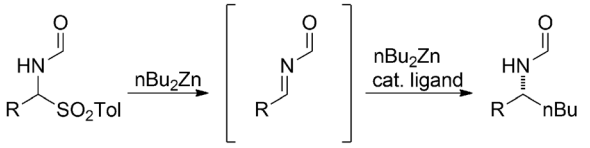
Ligand (R_p,*S*)-**1** gave slightly better results for the substrate **3a** than (R_p,*S*)-**2** when employed on a 2 mol% level (entry 8 vs. 2). When we optimized the ligand loading however, we obtained product **5a** in 90% *ee* with 5 mol% of (R_p,*S*)-**2** (entry 10) and in 88% *ee* with 5 mol% of (R_p,*S*)-**1** (entry 9). It must also be mentioned that the enantioselectivity of the process is highly dependent on the quality of the employed dibutylzinc. Commercially available dibutylzinc solutions of optically identical quality can result in differences in enantioselectivity of more than 20% *ee*. This is probably due to residual zinc salts in the solution, which can dramatically enhance undirected background reactions. In a previous work on the arylation of aldehydes, we have been able to counteract the effect of zinc salts by additives such as polyethylene glycol ethers (Di-MPEG)[12] or, in other cases, methane sulfonamide. However in the case of imine substrates, we have so far not been able to observe positive effects of additives on enantioselectivity.

Given the small difference in enantioselectivity for the ligands (R_p,*S*)-**2** and (R_p,*S*)-**1**, we chose to employ both ligands in a broader substrate screening (Table 2). In nearly all cases, excellent enantioselectivity could be achieved. All substituted phenyl substrates gave enantioselectivities of 90% *ee* or higher. Only the 1-naphthyl imine derivative (entries 11, 12) gave rise to somewhat lower enantioselectivity (68% *ee*). As expected however, neither of the two ligands gave the best *ee* for each substrate. Interestingly, ligand (R_p,*S*)-**2** seems to be superior for 4-substituted substrates (entries 2, 6, 10), while (R_p,*S*)-**1** consistently gave better results for 3-substituted imine precursors (entries 3 and 7). This was both true for electron-rich as well as electron-poor substrates. Clearly, the steric demand of substituent plays a more important role than its electronic properties, a fact often observed in diethylzinc addition reactions to aldehydes.

When compared to the results of the diethylzinc addition reactions,[5a] the catalysts showed somewhat lower selectivity. They have to be applied on a 5 mol% scale to achieve satisfactory enantioselectivity, while in the former case 2 mol% sufficed for most substrates. We attribute this behavior to a combination of the slightly lower reactivity and higher steric demand of the dibutylzinc reagent.

Representative reaction conditions for the synthesis of **5a**: Ligand (R_p,*S*)-**1** (5.4 mg, 5 mol%) and the imine substrate **3a** (69 mg, 0.25 mmol) were weighted into a 10 mL crimp vial and a magnetic stir bar was added. The vial

Table 2. Substrate scope[a]



3 4 5

Entry	Imine **3**, R =	Catalyst	Yield[b] (%)	*ee*[c] (%)
1	4-MeO-C_6H_4	(R_p,*S*)-**1**	81	92
2	4-MeO-C_6H_4	(R_p,*S*)-**2**	85	94
3	3-Cl-C_6H_4	(R_p,*S*)-**1**	91	97
4	3-Cl-C_6H_4	(R_p,*S*)-**2**	89	92
5	4-*t*Bu-C_6H_4	(R_p,*S*)-**1**	85	88
6	4-*t*Bu-C_6H_4	(R_p,*S*)-**2**	80	91
7	3-MeO-C_6H_4	(R_p,*S*)-**1**	85	97
8	3-MeO-C_6H_4	(R_p,*S*)-**2**	87	93
9	4-CO_2Me-C_6H_4	(R_p,*S*)-**1**	81	84
10	4-CO_2Me-C_6H_4	(R_p,*S*)-**2**	85	90
11	1-naphtyl	(R_p,*S*)-**1**	94	68
12	1-naphtyl	(R_p,*S*)-**2**	92	68

[a] Substrate (0.25 mmol), ligand (5 mol%), dibutylzinc (0.75 mmol), 16 h. Optimal reaction temperatures: 20 °C (entries 1, 2), 10 °C (entries 11, 12), 0 °C (entries 3–10). [b] Isolated yield. [c] Determined by HPLC with chiral stationary phase (Chiralcel OD). Absolute configuration established as (*R*) via Cbz-protected 1-phenyl pentylamine derived from **5a** by comparison with literature values.[10]

was closed and flushed with argon for several minutes. Subsequently, the vial was placed into a magnetically stirred reaction block and cooled to 10 °C. Dibutylzinc (0.75 mL, 1.0 molar solution in heptane, Fluka or Aldrich) was added and the heterogeneous mixture was stirred for 16 h. Aqueous workup and chromatography on silica afforded the desired product **5a** in 95% yield and 88% *ee* (Chiralcel OD, 1.0 mL min^{-1}. heptane/2-propanol 90/10).

In conclusion, we have reported the first study dedicated to the asymmetric catalytic addition of dibutylzinc to imine substrates giving rise to 1-aryl pentylamine derivatives in high yield and good to excellent enantioselectivity. In a collaborative project we are now working on a stereochemical rationale based on DFT calculations.[14]

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