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Synthesis and Catalytic Activity of New Chiral Ligands Based on a 1,3-Cyclopentanediamine

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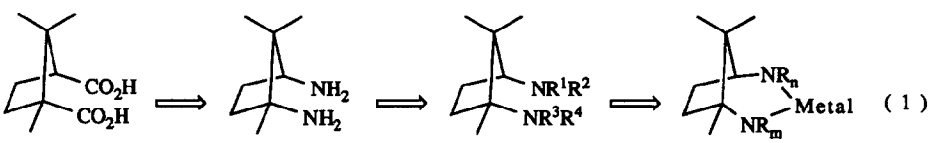
Abstract: (1*R*,3*S*)-1,2,2-Trimethyl-1,3-cyclopentanediamine and its derivatives have been prepared and utilized as chiral ligands for asymmetric addition reactions of organometallics to aldehydes.

Since recent progress on catalytic asymmetric synthesis depends on discovery of a large number of efficient chiral catalysts,[1a] this area should call for more kinds of new catalysts which will broaden the applicability of this practical method of synthesis. As far as amine ligands are concerned, a variety of 1,2-diamines and their derivatives are known and successfully used, but 1,3-diamines have been under limited investigation[1] although the latter would exhibit some different reactivities from the former. We wish to report here preparation of a new chiral 1,3-cyclopentanediamine and its derivatives and to disclose their certain catalytic activity in asymmetric synthesis as well.

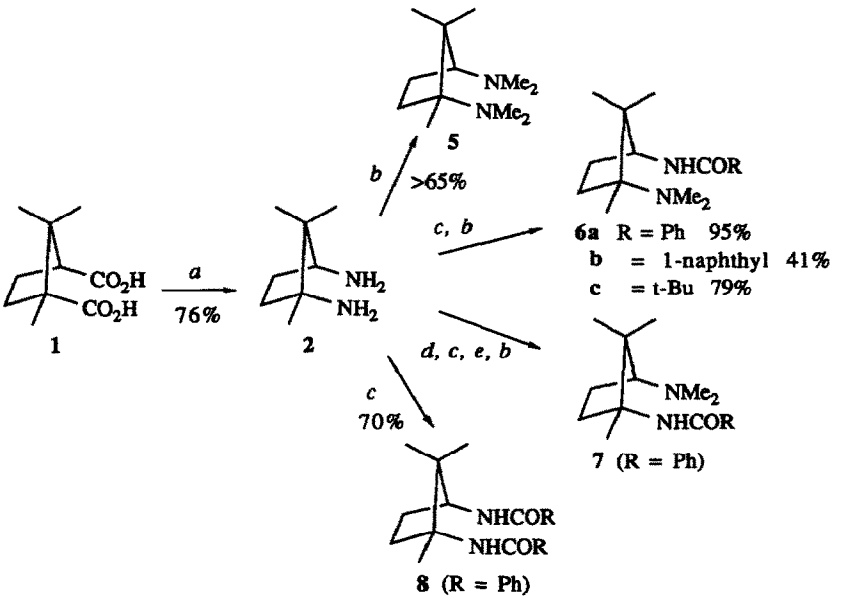
Among 1,3-diamines, we conceived that (1*R*, 3*S*)-1,2,2-trimethyl-1,3-cyclopentanediamine **2**[2] is a most versatile one as it is or as a starting material for ligands, chiral auxiliaries, etc. because of the following few characteristic features (eq 1): i) **2** could be readily prepared by the Schmidt reaction[3] from (+)-camphoric acid ((1*R*, 3*S*)-1,2,2-trimethyl-1,3-cyclopentanedicarboxylic acid, **1**)[4] without loss of its enantiomeric purity; ii) the different steric circumstances between the two amino groups of **2** should basically permit introduction of four different groups R^1--R^4 including hydrogen, alkyl, acyl, or sulfonyl which serve to adjust the chemical reactivity as well as catalytic activity of the derivative **3**; iii) in the case where **3** is used as a ligand, a conformationally rigid structure of the metal-chelated **4** would be able to allow a good degree of chirality transfer from itself to the product.



1 ⟹ **2** ⟹ **3** ⟹ **4** n, m = 1, 2 (1)

Scheme 1 shows the first two of our expectations are, in fact, correct. The Schmidt reaction[3] of **1** afforded **2**[5] in 76% yield. The (1*R*, 3*S*)-structure assigned to **2** stems from i) the well-precedent retention of configuration of the carbon initially bearing the carboxy group in the Schmidt reaction and ii) the formation of the cyclic urea on treatment with $ClCO_2Me$. Enantiomeric homogeneity of **2** (>95% ee) was verified by ^1H nmr analysis of the salt derived from **5** and (+)-/(-)-mandelic acid.[6] The derivatives **5**,[5] **6**, **7**, and **8** have been prepared in a

Scheme 1. Preparation of the Chiral Diamine **2** and Its Derivatives



[a]NaN_3, H_2SO_4; $CHCl_3$, 55-65°C, 1 hr (ref 3). [b]aq. HCHO-HCOOH; refl., 20 hr (ref 7). [c]RCOCl (1 equiv for **6** and **7**, 2.5 equiv for **8**), NEt_3; CH_2Cl_2, -78°C; r.t. [d]$PhCH_2OCOCl$ (1.1 equiv), NEt_3. [e]H_2, Pd/C.

straightforward manner as shown in Scheme 1. The preparation of **6a**[5] achieved in 95% yield clearly demonstrates the selective mono-acylation of the less hindered amino group of **2**.

With chiral 1,3-diamine derivatives in hand, we then turned our attention to evaluate their catalytic activities in the reactions of benzaldehyde with organometallics, which are summarized in Table 1. Although **5** does not effect asymmetric additions of BuMgBr and BuLi to PhCHO (runs 1 and 2), it does in an organocopper version albeit in a moderate degree (runs 3 and 5) which was somewhat improved up to 38% op (optical purity) with the lithiated form of **6a** (run 4).[11] It is noteworthy that **5** catalyzed asymmetric 1,2-addition of organocopper reagents rather than that of organolithium or Grignard reagents. A larger ionic radius of Cu^+ as compared to that of Mg^{2+} or Li^+ may make the strained chelation **4** resulting from **5** (or lithiated **6a**) and the metal more feasible. The Et_2Zn-mediated alkylation (runs 6--10), in which the ethylzinc salt **10** or its complex with another Et_2Zn **10'** is the most likely active species,[8] successfully proceeded to show a maximum ee (enantiomeric excess) value of 93% with **6a**. This is the first example that a chiral carboxylic amide is an efficient catalyst for this process, while chiral amines, amino alcohols, and diols have been frequently used previously.[8] Interestingly, the more bulky amido group the ligand **6** has, the lower ee the product showed. Moreover, the structure for a high degree of chirality induction is so unique that neither **7** nor **8** worked well. The compound **6a** also catalyzed the reactions of

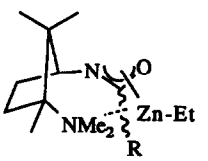
Table 1. Asymmetric Addition of Organometallics to PhCHO

PhCHO (0.5-0.8 equiv) + " R-M " (1 equiv) —Catalyst→ PhCH(OH)R **9**

Entry	"R-M"	Cat. (equiv to "R-M")	Conditions	Product (9) R	Yield[a] (%)	Ee[b] (%)	Op[c] (%)	Abs.[c] Config.
1	BuMgBr[d]	5 (1.2)	PhMe-Et_2O; -100°C; -78°C	Bu	89	--	8	*S*
2	BuLi[e]	" (")	hexane; -100°C	"	100	--	4	*S*
3	BuCu[f]	" (")	Et_2O; -20°C	"	95	--	17	*S*
4	"	Li-**6a**[g] (")	Et_2O; -78°C; -20°C	"	25	--	38	*S*
5	Bu_2CuLi[f]	5 (")	Et_2O; -100°C	"	41	--	35	*S*
6	Et_2Zn[h]	**6a** (0.04)	PhMe-hexane; 0°C	Et	81	93	90-95	*S*
7	"	**6b** (")	"	"	89	88	--	*S*
8	"	**6c** (")	"	"	32	4	--	*S*
9	"	**7** (")	"	"	55	5	--	*S*
10	"	**8** (")	"	"	24	--	13	*R*

[a]Isolated yields not necessarily optimized. [b]Determined by ^1H nmr after derivatization to the MTPA (α-methoxy-α-(trifluoromethyl)phenylacetyl) ester. [c]Determined based on the optical rotations for (*S*)-PhCH(OH)Et: $[\alpha]_D^{22}$ -47.6 (*c* 6.11, $CHCl_3$) (ref 8b) and for (*R*)-PhCH(OH)Bu: $[\alpha]_D$ 37.6° (*c* 3, C_6H_6) (ref 9b). [d]Ref 10. [e]Ref 9. [f]Prepared from BuLi and CuI. [g]Prepared from **6a** and BuLi (1:1) in Et_2O. [h]Ref 8.

other aldehydes with Et_2Zn under the same reaction conditions: *p*-$ClC_6H_4CH(OH)Et$ (91% yield, 92% ee, *S*)[8] from *p*-ClC_6H_4CHO; *p*-$MeOC_6H_4CH(OH)Et$ (73% yield, 94% ee, *S*)[8] from *p*-$MeOC_6H_4CHO$; $Ph(CH_2)_2CH(OH)Et$ (69% yield, 85% op, *S*)[8] from $Ph(CH_2)_2CHO$.



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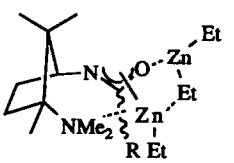

10'

In summary, we reported here new chiral ligands derived from a readily available 1,3-cyclopentanediamine and their application to asymmetric synthesis. Study towards developement of new asymmetric reactions characteristic of **4** and **5**--**8** is now in progress.

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4. (+)-Camphoric acid (**1**) is commercially available. Alternatively, both the (+)- and (-)-enantiomers are prepared by oxidation of (+)- and (-)-camphor, respectively: Aschan, O. *Annalen* **1901**, *316*, 196.
5. **2**: low-melting solid. $[\alpha]_D^{25}$ +35 (*c* 1.0, EtOH). **5**: bp 88--90 °C/0.6--0.7 mmHg. $[\alpha]_D^{25}$ +35.3 (*c* 1.0, EtOH). **6a**: mp 135--137°C (EtOAc-hexane). $[\alpha]_D^{25}$ +30 (*c* 0.6, $CHCl_3$).
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11. At our hands, a reaction of PhCHO and Bu_2CuLi in the presence of *N,N,N',N'*-tetramethyl-(*R*, *R*)-1,2-diphenylethylenediamine[6] gave the adduct of only 10% ee under similar reaction conditions as shown in entry 5, Table 1.