Chiral Zirconium-Catalyzed Asymmetric Mannich-Type Reactions Using Acylhydrazones as Imine Equivalents

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In the presence of a catalytic amount of a new zirconium catalyst, prepared from zirconium(IV) *t*-butoxide and (*R*)-3,3'-dibromo-1,1'-bi-2-naphthol, 4-trifluoromethylbenzoylhydrazones reacted with silyl enolates to afford the corresponding adducts, β-*N*'-acylhydrazinocarbonyl compounds, in good yields with high enantiomeric excesses. Reductive cleavage of the nitrogen-nitrogen bond of the hydrazino compound using samarium diiodide gave a chiral β-aminocarbonyl compound. In addition, the hydrazino compound was also successfully converted to chiral β-lactam and pyrazolidinone derivatives.

Catalytic asymmetric Mannich-type reactions provide one of the most efficient methods for the synthesis of chiral nitrogen-containing compounds such as β-amino esters, β-lactams, β-amino alcohols, etc.[1] While much progress has been made in this decade in catalytic asymmetric aldol and Diels-Alder reactions,[2] less progress has been made in catalytic asymmetric versions of Mannich-type reactions.[3] In the course of our investigations to develop catalytic asymmetric carbon-carbon bond-forming reactions, we have recently developed catalytic enantioselective Mannich-type reactions of the imines derived from aldehydes and 2-aminophenol with silyl enolates using a novel chiral zirconium catalyst.[4] Optically active β-amino esters, β-amino alcohols, etc. were obtained in high enantiomeric excesses according to these reactions. On the other hand, novel Mannich-type reactions using acylhydrazones as imine equivalents (achiral reactions) have also been developed.[5] These reactions have some advantages over conventional Mannich-type reactions. For example, most acylhydrazones including those derived from aromatic, α,β-unsaturated, and even aliphatic aldehydes are stable crystals, easy to handle at room temperature, and the adducts are readily converted to several nitrogen-containing compounds. Herein we report the first catalytic asymmetric version of these acylhydrazone-based Mannich-type reactions.[6]

We chose the reaction of 4-trifluoromethylbenzoylhydrazone derived from 3-phenylpropionealdehyde (**1a**, $R^1 = Ph(CH_2)_2$) with the silyl enolate of methyl isobutyrate (**2a**, R^2 = Me, R^3 = OMe) as a model, and several reaction conditions were examined (Table 1). The reaction did not proceed at all in the presence of a zirconium compound, prepared from zirconium(IV) *t*-butoxide ($Zr(O^tBu)_4$), 2.0 eq. of (*R*)-6,6'-dibromo-1,1'-bi-2-naphthol ((*R*)-6,6'-BrBINOL), and 3.0 eq. of 1-methylimidazole, which was effective in catalytic enantioselective Mannich-type reactions of imines (entry 1).[4a,b] On the other hand, the desired product (**3**) was obtained in a 38% yield when a catalyst prepared from $Zr(O^tBu)_4$ and 2.0 eq. of (*R*)-6,6'-BrBINOL (without 1-methylimidazole) was used, but no chiral induction was observed (entry 2). We then examined several ligands. It was exciting to find that **3** was obtained in a 66% yield with a 66% ee when (*R*)-3,3'-dibromo-1,1'-bi-2-naphthol ((*R*)-3,3'-BrBINOL)[7] was used as a chiral source (entry 3). The enantiomeric excess was further improved when toluene was used as a solvent instead of

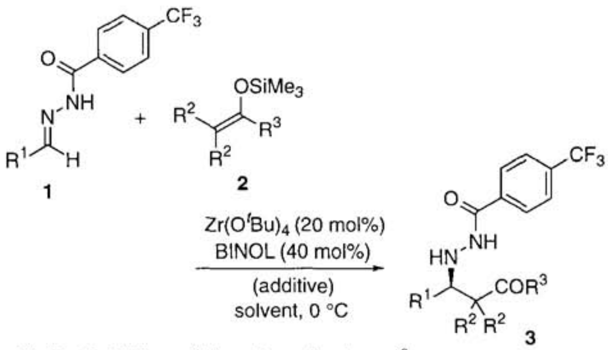
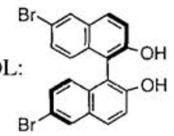


Table 1. Effect of ligands and solvents[a]

Entry	BINOL	Solvent	Yield/%	ee/%
1[b]	6,6'-BrBINOL	CH_2Cl_2	0	—
2	6,6'-BrBINOL	CH_2Cl_2	38	0
3	3,3'-BrBINOL	CH_2Cl_2	66	66
4	3,3'-BrBINOL	THF	11	17
5[c]	3,3'-BrBINOL	CH_3CN	74	76
6	3,3'-BrBINOL	Toluene	66	86

6,6'-BrBINOL:


3,3'-BrBINOL:


[a] $R^1 = Ph(CH_2)_2$, R^2 = Me, R^3 = OMe. [b] Sixty mol% of 1-methylimidazole was used as an additive. [c] The catalyst was prepared in CH_2Cl_2.

Table 2. Catalytic asymmetric Mannich-type reactions[a]

Entry	R^1	R^2	R^3	Yield/%	ee/%
1	$Ph(CH_2)_2$	Me	OMe	66	86
2	$Ph(CH_2)_2$	H	SEt	42	88
3	C_6H_{13}	Me	OMe	60	96
4	C_6H_{13}	H	SEt	39	87
5	$C_{12}H_{25}$	Me	OMe	63	91
6[b]	Ph	Me	OMe	59	81
7	$ClCH_2$	Me	OMe	59	93

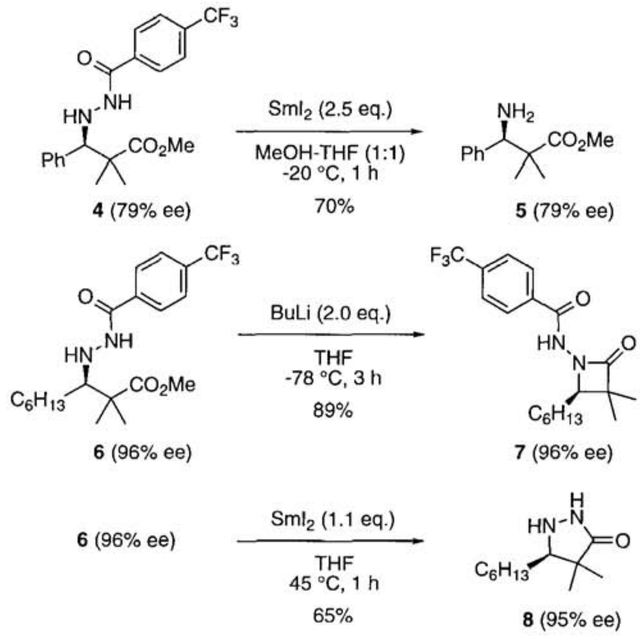
[a] BINOL = 3,3'-BrBINOL, solvent = toluene. [b] $Zr(O^tBu)_4$ (50 mol%) and 3,3'-BrBINOL (100 mol%) were used.

dichloromethane (entry 6).

Other substrates were then tested and the results are summarized in Table 2. As for silyl enolates, not only **2a** but also the silyl enolate derived from *S*-ethyl thioacetate (**2b**, R^2 = H, R^3 = SEt) worked well to afford the corresponding adducts in high enantiomeric excesses (entries 2 and 4). A variety of hydrazones derived from aliphatic, aromatic, and α-halogenated aldehydes were successfully used in the present reactions to produce the corresponding β-*N'*-acylhydrazinocarbonyl compounds in good yields with high enantiomeric excesses.[8] All hydrazino compounds obtained are crystalline and it was easy to purify by simple recrystallization. It is noteworthy that aliphatic aldehyde-derived acylhydrazones reacted smoothly to give the desired Mannich-type adducts in high enantiomeric excesses. In addition, the acylhydrazone derived from chloroacetaldehyde reacted with **2a** under these reaction conditions to afford the desired adduct, a synthetically useful β-*N'*-acylhydrazino-γ-chlorocarbonyl compound, in a 93% ee.

A typical experimental procedure is described for the reaction of 4-trifluoromethylbenzoylhydrazone derived from heptanal (**1b**, R^1 = C_6H_{13}) with **2a**: To a stirred solution of (*R*)-3,3'-BrBINOL (0.08 mmol) in toluene (1.0 ml) was added a toluene solution of $Zr(O^tBu)_4$ (0.04 mmol) at room temperature. The mixture was stirred for an hour at the same temperature. Hydrazone **1b** (0.20 mmol) and silyl enolate **2a** (0.27 mmol) in toluene (2.0 ml) were then added to the above catalyst solution at 0 °C, and the mixture was stirred for 7 h. After saturated aqueous $NaHCO_3$ was added to quench the reaction, the aqueous layer was extracted with dichloromethane. After a usual work-up, the crude product was purified by column chromatography on silica gel to afford methyl 2,2-dimethyl-3-[*N'*-(*p*-trifluoromethylbenzoyl)hydrazino]nonanate as white crystals in a 60% yield. Mp 96-97 °C. Enantiomeric excess was determined (96% ee) by HPLC analysis using a chiral column (Daicel Chiralcel OK, hexane/*i*-PrOH = 9/1).

Reductive cleavage of the nitrogen-nitrogen bond of the hydrazino compound (**4**) was successfully carried out using samarium diiodide (SmI_2) at -20 °C to afford amino ester **5**.[9] The absolute configuration of **4** was determined by comparison of its optical rotation with that reported in the literature.[10] In addition, it was found that β-lactam **7** was obtained by treatment of **6** with *n*-BuLi at -78 °C, pyrazolidinone **8** was produced in the presence of SmI_2 at 45 °C. No racemization occurred during this transformation (Scheme 1).



Scheme 1. Conversion to β-amino ester, β-lactam, and pyrazolidinone.

In summary, a new type of catalytic asymmetric Mannich-type reaction has been developed. Acylhydrazones have been successfully used as imine equivalents, and their reactions with silyl enolates proceeded smoothly in the presence of a catalytic amount of a novel zirconium compound to afford the corresponding adducts in good yields with high enantiomeric excesses. It is noted that aliphatic hydrazones were successfully employed, and that the adducts were readily converted to versatile nitrogen-contaning compounds with no loss of optical purity. Further investigations including application of these enantioselective reactions for the synthesis of natural biologically important compounds are now in progress.

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References and Notes

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