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LETTERS

Trifluoromethylated amino alcohols as chiral ligands for highly enantioselective Reformatsky reaction☆

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Abstract—The enantioselective Reformatsky reaction of PhCHO was achieved by the use of trifluoromethylated amino alcohols as chiral ligands to afford the corresponding optically active β-hydroxy ester with up to 90% ee.

The Reformatsky reaction is a fundamental reaction in organic syntheses.[1,2] Attainment of high stereoselectivity of the reaction would be a key issue for further extension of its applicability. Until now, the selectivities of stereoselective Reformatsky reactions using a chiral ligand remained moderate.[3–5] The best record of the reaction of PhCHO with haloacetate is 75% ee, which was attained by the use of (*R*)-DPMPM, an amino alcohol derived from proline.[3a]

Recently, we revealed that the origin of the stereochemical interaction of a trifluoromethyl group arises from its negatively charged nature.[6] Therefore, trifluoromethylated ligands would be effective for stereoselective alkylation with a carbanion species. Moreover, we have found that a trifluoromethylated ligand (CF_3-C*H-(OH)-CH_2-NR_2) promoted association of an organozinc species; in this instance, the association of the organozinc species seemed to play a crucial role in stereoselective Et_2Zn alkylation of PhCHO.[7] Furthermore, a structural study on the Reformatsky reagents suggested a key role of such aggregation of the reagent.[8] These findings encouraged us to attempt the enantioselctive Reformatsky reaction using chiral trifluoromethylated amino alcohol ligands.

Trifluoromethylated amino alcohols **1a**–**f** and **2a**–**b** were used as the chiral ligand for stereoselective Reformatsky reaction of PhCHO.[9] The results are summarized in Table 1. Among the examined amino alcohols, *tert*-amino alcohols, **1c** and **1d**, were found effective (entries 3 and 4); the fluorinated amino alcohol **1d** was superior to non-fluorinated analog **3**, which result is similar to that in the reaction of Et_2Zn with PhCHO.[7] Further modification of the amino moieties (entries 3, 4, and 6) gave a better result, 81% ee, with **1c**. This selectivity is as high as the best record which has been attained.[3] Contrary to the result of Andres' reports,[3f,h,j] double-headed amino alcohols, **2a** and **2b**, were not effective.

Among the solvents examined, THF was found to be the best for this reaction. Other ethereal solvents, such as Et_2O and DME (entries 10 and 11) led to moderate stereoselectivity of the reaction. The much polar DMF resulted in no reaction (entry 12) and nonpolar toluene (entry 13) gave the product in high yield with low stereoselectivity.

A time course study of the reaction showed that the reaction was completed within a minute under THF reflux conditions. Thus, we considered that better selectivity would be attained under milder conditions. Instead of ethyl bromoacetate, utilization of ethyl iodoacetate enabled us to carry out the reaction smoothly even at 20°C; the reaction gave the product with 89% ee (entry 3, Table 2). Further elaboration of the conditions improved the stereoselectivity of the reaction up to 90% ee (entry 6).

Further application of these trifluoromethylated ligands for enantioselective alkylation with carbanions is under investigation and will be reported in due course.

Keywords: trifluoromethylated amino alcohol; chiral ligand; enantioselective Reformatsky reaction.

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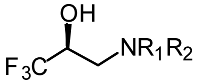
Table 1. Stereoselective Reformatsky reaction of PhCHO conducted by trifluoromethylated chiral ligands, **1** and **2**



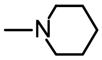
1

—NR_1R_2

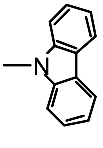
a; —NH_2

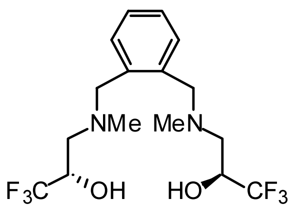
b; —NHEt

c; —NMe_2

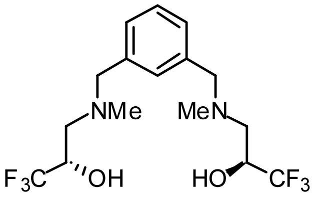
d; 

e; —$NiPr_2$

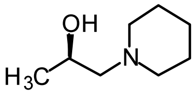
f; 



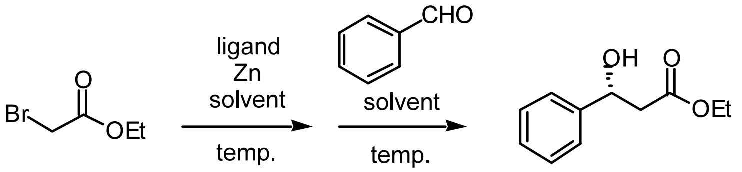
2a



2b



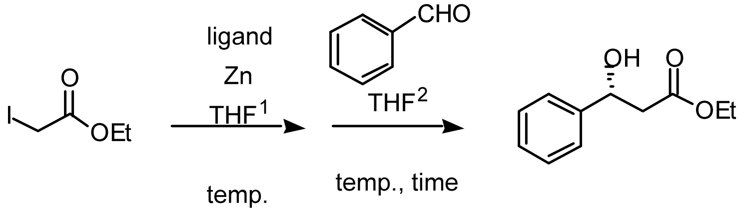
3



entry[a]	ligand	solvent	temp.	yield [%]	ee [%][c]
1	**1a**	THF	reflux	94	27
2	**1b**			52	56
3	**1c**			80	81
4	**1d**			68	78
5	**3**			78	23
6	**1e**			44	67
7	**1f**			68	4
8[b]	**2a**			49	4
9[b]	**2b**			74	68
10	**1d**	Et_2O	reflux	67	54
11	**1d**	DME	60 °C	60	56
12	**1d**	DMF	80 °C	no reaction	-
13	**1d**	toluene	80 °C	87	24
14	**1d**	CH_2Cl_2	reflux	64	65

a) Reaction was carried out with **PhCHO : Zn : ligand : $BrCH_2CO_2Et$ = 1.0 : 4.0 : 1.2 : 2.5.** b) Reaction was carried out with **PhCHO : Zn : ligand : $BrCH_2CO_2Et$ = 1.0 : 4.0 : 0.5 : 2.5.** c) Determined by HPLC analysis using a Daicel Chiralcel OD-H (hexane : iPrOH = 7 : 1).

Table 2. Elaboration of the reaction conditions in stereoselective Reformatsky reaction using **1c** or **1d**



Entry[a]	Ligand	Temp. (°C)	Time	THF^1 (ml)/THF^2 (ml)	Yield (%)	Ee (%)[b]
1	**1c**	Reflux	30 min	2.0/1.0	69	28
2	**1c**	50	Overnight	4.0/2.0	46	81
3	**1c**	20	3 h	6.0/6.0	61	89
4	**1c**	10	Overnight	6.0/6.0	8	82
5	**1c**	0	Overnight	6.0/6.0	No reaction	–
6	**1d**	30	3 h	6.0/6.0	68	90

[a] Reaction was carried out with PhCHO (1 mmol):Zn:ligand:ICH_2CO_2Et = 1.0:5.0:1.5:2.6.

[b] Determined by HPLC analysis using a Daicel Chiralcel OD-H (hexane:*i*PrOH = 7:1).

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