Conformational Control in Proton Sources for Enantioselective Protonation of Samarium Enolate Derived from α-Methoxy-Substituted Ketones

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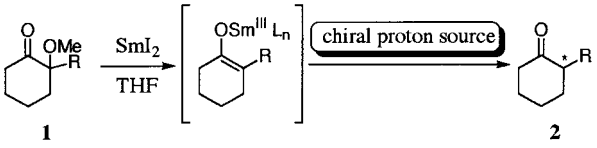
Abstract: High enantioselectivity is achieved in the asymmetric protonation of samarium enolate, regioselectively generated by SmI_2-mediated reduction of 2-methoxy-substituted cyclohexanones using achiral diamine- or pro-atropisomeric 2,2'-biphenol-derived chiral diols as proton sources by virtue of the conformational control.

Enantioselective protonations of metal enolates with chiral proton sources such as alcohols, phenols and metal complexes thereof are a useful method to synthesize chiral carbonyl compounds or carboxylic acid derivatives bearing a stereogenic center at the α-position.[1,2] We have reported the enantioselective protonation of samarium enolates which are regioselectively generated by SmI_2-mediated reaction[3] of the α-hetero-substituted cyclohexanones (**1**) bearing an α-aryl substituent, using a **chiral** binaphthol-derived C_2-symmetric diol as a proton source.[4,5,] We now wish to report that chiral diol proton sources derived from **achiral** diamine or **pro-atropisomeric** biphenol are quite effective by virtue of their conformational control in enantioselective protonation of samarium enolate generated from the α-methoxy-substituted ketones (Scheme 1).



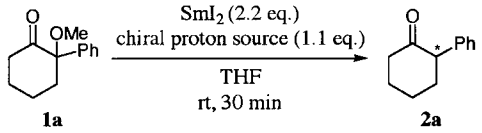
1 **2**

Scheme 1

Typical experimental procedure is as follows: To a solution of α-alkoxyketone in dry tetrahydrofuran was added a solution of SmI_2 in tetrahydrofuran. To the reaction mixture was added a chiral proton source.[6] After stirring for 30 min, usual work-up followed by purification by silica-gel column chromatography afforded the ketone in 80-90% yield. The enantiomeric excess of the ketone is determined by chiral HPLC analysis (DAICEL CHIRALCEL OD-H). The results thus obtained were summarized in Tables 1-3.

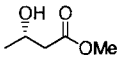
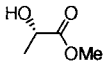
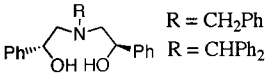
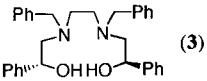
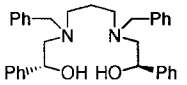
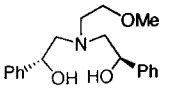
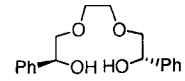
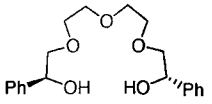
Inspection of Table 1 reveals the characteristic features of the present asymmetric protonation. 5-Membered chelate with samarium is better than the 6-membered counterpart in terms of the enantioselectivity (entries 1 *vs.* 2). Such rigid 5-membered chelate structure and sterically demanding substituent at the carbinol carbon is preferable to give high enantioselectivity. Therefore, pantoyl lactone provides higher selectivity (entries 2 *vs.* 3). Tridentate ligand to form bicyclic 5,5-members provides an improved selectivity up to 67% ee (entry 4). Furthermore, a tetradentate proton source to form 5,5,5-tricyclic chelates provides further increased selectivity than similar tetradentate proton sources to form 6,5,5-chelates or facial-type chelates (entries 6 *vs.* 7 and 8). However, pentacoordinated proton source is less effective than the tetradentate proton source (entries 9 *vs.* 10).

We have further found that short reaction time within 30 min is the key to obtain the higher enantioselectivity with diol (**3**) or pantoyl lactone (Table 2). Unfortunately however, the diol (**3**) does not work well as a chiral proton source at low temperature (entries 6 *vs.* 15).[6] The ketone



1a **2a**

Table 1. Conformational control in enantioselective protonation of samarium enolate prepared from 2-methoxy-2-phenylcyclohexanone

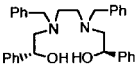
entry	chiral proton source	% yield[a]	% ee[b]	config.[c]
1		80	11	*R*
2		92	23	*R*
3		95	54	*S*
4	 R = CH_2Ph	78	67	*S*
5	R = $CHPh_2$	89	13	*S*
6	 (**3**)	91	73	*S*
7		80	59	*S*
8		85	60	*S*
9		83	58	*R*
10		89	40	*R*

[a] Isolated yield. [b] Determined by chiral HPLC analysis (DAICEL CHIRALCEL OD-H). [c] Assigned by optical rotation. See Ref 9

product in the mixture undergoes racemization over more than 30 min at room temperature (entries 6 and 13 *vs.* 14), presumably because of a samarium alkoxide even in the case with pantoyl lactone (entries 3 *vs.* 11).

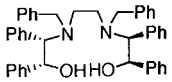
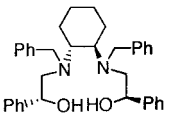
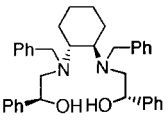
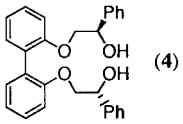
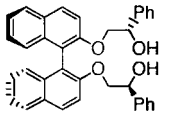
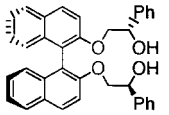
Further examination of similar meridional-type chelating proton sources highlights the conformational control over the **achiral** diamine tether in **3** for enantioselective protonation (Figure 1). Co-operative effect of the sterically demanding *N*-benzyl group and the phenyl substituent at the carbinol carbon would be operative for the high level of enantioselectivity (**B** over **C**) in view of the low enantioselectivity obtained with a tetraphenyl proton source to fix the *N*-benzyl conformation (**D**) because of the Pitzer strain[7] (entries 17 and 9 *vs.* 6). This conformational control could be further extented to **achiral** but **pro-atropisomeric** 2,2'-biphenol[8] tether in **4** for enantioselective protonation (**B'** and **E**).

Table 2. The Optimization of the Reaction Conditions

entry	chiral proton source	reaction temp. (°C)	reaction time (min.)	% yield[a]	% ee[b]	config.[c]
11		r.t.	120	78	45	*S*
12		-40	120	84	61	*S*
13		r.t.	5	80	71	*S*
14		r.t.	120	80	53	*S*
15		-40	120	79	35	*S*
16[d]		-40	120	82	46	*S*

[a] Isolated yield. [b] Determined by chiral HPLC analysis (DAICEL CHIRALCEL OD-H). [c] Assigned by optical rotation. [d] The reaction was carried out using 2.0 mol *equiv*. of chiral proton source

Table 3. Conformational control in enantioselective protonation of samarium enolate prepared from 2-methoxycyclohexanones

entry	chiral proton source	% yield[a]	% ee[b]	config.[c]
17		69	2	*S*
18		77	2	*R*
19		80	41	*R*
20[d]	 (**4**)	88	85	*S*
21[d,e]		72	81	*S*
22		85	34	*R*
23[d,f]		70	87	*R*
24[d,e]		70	80	*R*

[a] Isolated yield. [b] Determined by chiral HPLC analysis (DAICEL CHIRALCEL OD-H). [c] Assigned by optical rotation. [d] The reactions were carried out using 2.0 mol *equiv*. of the chiral proton source at -45 °C. [e] 2-benzyl-2-methoxycyclohexanone was employed instead of 2-phenyl-2-methoxycyclohexanone. [f] Ref 4

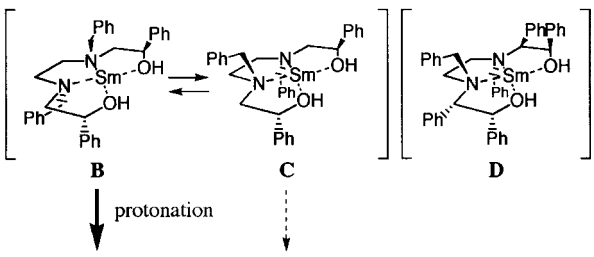


Figure 1

Pro-atropisomeric biphenol-derived proton source (**4**) is quite effective to give an equally high level of enantioselectivity to that obtained by using a (*R*)-binaphthol-derived C_2-symmetric diol proton source (entries 20 and 21 *vs*. 23 and 24) and much higher than with (*S*)-binaphthol-derived C_2-symmetric diol (entries 20 *vs*. 22).

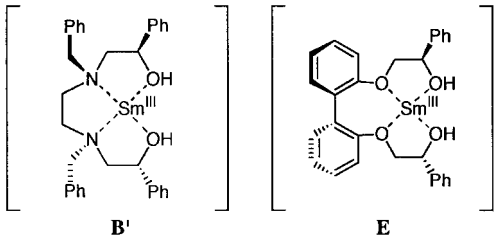


Figure 2

In summary, we have disclosed herein that high enantioselectivity is achieved in the asymmetric protonation of samarium enolate, regioselectively generated by SmI_2-mediated reduction of 2-methoxy-substituted cyclohexanones using achiral diamine- or pro-atropisomeric biphenol-derived chiral diols as proton sources by virtue of the conformational control.

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6. When the reaction was carried out at low temperature, a chiral proton source was added to the reaction mixture prior to the preparation of the samarium enolate. Upon addition of a chiral proton source to the solution of the samarium enolate at –45 °C, the enantiomeric excess of the product was lower than that obtained at room temperature.
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