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Nucleophilic addition of methyllithium to chiral oxime ethers: asymmetric preparation of 1-(aryl)ethylamines and application to a synthesis of calcimimetics (+)-NPS R-568 and its thio analogue

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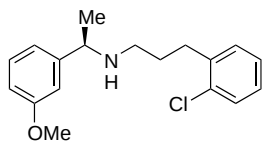
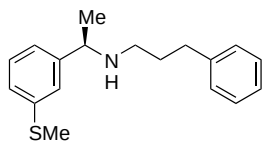
Abstract—Chiral (*E*)-arylaldehyde oxime ethers, prepared using (*R*)-1-phenyl-1,2-ethanediol as a chiral auxiliary, undergo nucleophilic addition with methyllithium to give diastereomerically enriched *O*-alkyl hydroxylamines which, after reductive N–O bond cleavage, lead to the corresponding (*R*)-1-(aryl)ethylamines. This methodology has been applied to the enantioselective synthesis of a new type of arylalkylamine calcimimetics (*R*)-(+)-NPS R-568 and its thio analogue.

Optically active primary amines are frequently encountered in naturally occurring products and pharmacologically active compounds and also could serve as chiral building blocks and chiral auxiliaries in asymmetric synthesis.[1] In this regard, the development of new and efficient methods for the asymmetric preparation of enantiopure primary amines and their derivatives is a matter of considerable significance.[1] One of the most widely used methods for the preparation of such compounds is nucleophilic addition of organometallic reagents to the C=N bond of chiral imines. In the chiral auxiliary based asymmetric synthesis, the use of chiral oxime ethers as substrates for the addition reaction of organometallic reagents is an attractive approach to primary amines because of the ease of removal of the chiral auxiliaries by N–O bond cleavage. However, despite numerous studies of imine addition, there have been only limited examples of this approach reported[2,3] mainly due to the low electrophilicity of the carbon atom of the C=N bond in oxime ethers in comparison with the corresponding imine carbon. To overcome this problem associated with the low electrophilicity, activation of oxime ethers by a Lewis acid such as boron trifluoride etherate is required,[3] which has restricted the synthetic application of this reaction because the Lewis acid activation is not compatible with substrates having acid-labile functional groups. In this paper we disclose a diastereoselective organometallic addition by activation of oxime ethers via intramolecular lithium chelation leading to 1,4-asymmetric induction to form optically active 1-(aryl)ethylamines. This methodology was applied to the enantioselective synthesis of (*R*)-(+)-NPS R-568 (**1**)[4,5] and its thio analogue, (*R*)-*N*-{1-[3-(methylsulfanyl)phenyl]ethyl}-3-phenyl-1-propanamime (**2**),[6] the former of which represents a new class of calcium receptor agonist (calcimimetics) with potent and selective activity and has been developed into drug candidates for the treatment of primary and secondary hyperparathyroidism.[4] The *R* enantiomer of **1** has been reported to be 10- to 100-fold more potent than the *S* enantiomer.[4] The latter compound **2** recently synthesized as a racemate has been proposed to be a potent calcium receptor modulating agent.[6]



(+)-NPS R-568 (**1**)



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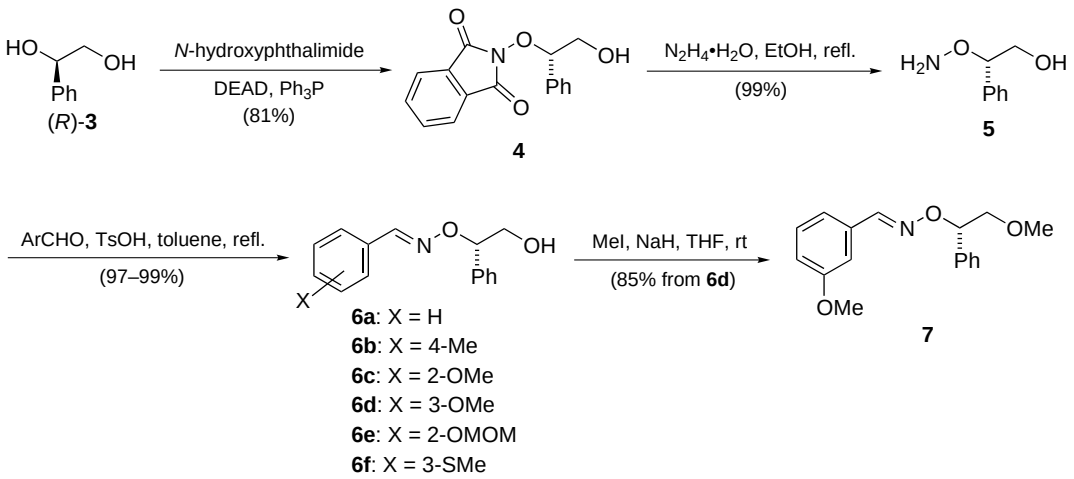
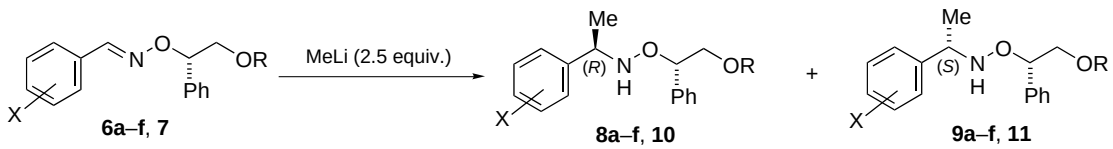
The chiral oxime ethers **6a–f** were readily prepared using commercially available 1-phenyl-1,2-ethanediol (**3**) as a chiral auxiliary (Scheme 1). Thus, the Mitsunobu reaction of (*R*)-**3** with *N*-hydroxyphthalimide occurred regioselectively at C-1 of (*R*)-**3** due to its benzylic nature, affording the alkoxyphthalimide **4** with clean inversion of the stereochemistry.[7] When the free (*S*)-alkoxylamine **5**, generated from **4** under standard conditions with hydrazine hydrate, was condensed with the aryl aldehydes (toluene, reflux) in the presence of a trace amount of TsOH, the reactions were completed in 15–20 min to form the corresponding oxime ethers **6a–f** as the *E* isomers in excellent yields.[8] The oxime ether **6d** was converted to the *O*-methyl derivative **7** by treatment with iodomethane and sodium hydride.

With the oxime ethers **6a–f** and **7** in hand, diastereoselective addition with methyllithium (1.14 M solution in diethyl ether) was investigated. Thus, after treatment of a THF solution of **6a** with 1 equiv. of methyllithium at 0°C for 5 min, another 1.5 equiv. of methyllithium was added, and the mixture was stirred at 0°C for 25 min; however, during the reaction extensive decomposition was observed without formation of the desired methyl adduct as seen from Table 1 (entry 1). On the other hand, when **6a** was submitted to the above reaction conditions, but using diethyl ether instead of THF as the solvent, the desired methyl adducts **8a** and **9a** were obtained in 64% total yield in a 9.8:1 ratio (entry 2) in favor of the 1′*R* isomer **8a**, along with some decomposition of the starting material. In the latter case changing



Scheme 1.

Table 1. Nucleophilic addition of methyllithium to chiral oxime ethers[a]



Entry	Oxime ether	R	X	Solvent	Temp. (°C)	Product	Yield (%)[b]	1*R*:1*S*[c]
1	**6a**	H	H	THF	0	–	0	–
2	**6a**	H	H	Et_2O	0	**8a**/**9a**	64	9.8:1
3	**6a**	H	H	Toluene	0	**8a**/**9a**	80	9.8:1
4	**6a**	H	H	Toluene	−20	**8a**/**9a**	78 (10)	14.0:1
5	**6b**	H	4-Me	Toluene	0	**8b**/**9b**	79	8.4:1
6	**6b**	H	4-Me	Toluene	−20	**8b**/**9b**	76 (11)	11.6:1
7	**6c**	H	2-OMe	Toluene	0	**8c**/**9c**	84	5.1:1
8	**6c**	H	2-OMe	Toluene	−20	**8c**/**9c**	81 (10)	7.6:1
9	**6d**	H	3-OMe	Et_2O	0	**8d**/**9d**	65	7.4:1
10	**6d**	H	3-OMe	Toluene	0	**8d**/**9d**	85	7.6:1
11	**6d**	H	3-OMe	Toluene	−20	**8d**/**9d**	79 (12)	8.1:1
12	**6e**	H	2-OMOM	Toluene	−20	**8e**/**9e**	74 (8)	7.5:1
13	**6f**	H	3-SMe	Toluene	−20	**8f**/**9f**	77 (10)	7.1:1
14	**7**	Me	3-OMe	Toluene	0	**10**/**11**	28	3.0:1

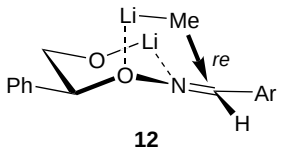
[a] All the reactions in this table were carried out using 1.5 equiv. of MeLi (1.14 M in Et_2O) for 25 min after treatment with 1 equiv. of MeLi (1.14 M in Et_2O) at 0°C for 5 min.

[b] Total yield of the chromatographically separated diastereomers. Yields in parentheses are for recovered starting material.

[c] Determined by ^1H NMR of the product mixture.

the solvent from diethyl ether to a very weakly polar toluene led to an improved total yield of 80% with the same diastereoselectivity (entry 3). When the addition to **6a** in toluene was employed at lower temperature of −20°C the diastereomeric ratio increased significantly to 14.0:1 (entry 4). Similar trends in the diastereoselective addition with methyllithium were observed for other oxime ethers **6b**–**f** (entries 5–13).

It is interesting to note that the methyl addition to the methoxy oxime ether **7** in toluene resulted in only poor yield (28%) and low diastereoselectivity (entry 14), suggesting that the formation of the lithium salt of the primary alcohol is important in promoting the diastereoselective methyl additions to the oxime ethers **6a**–**f**. A mechanistic rationale based on a six-membered chair-like chelate structure **12** is thus proposed as an intermediate for the observed *R* selectivity. In this structure, one molecule of methyllithium would be consumed for the initial formation of the lithium alkoxide followed by coordination of the lithium atom to the nitrogen atom of the oxime ether[9] which is activated toward nucleophilic attack. A second molecule of methyllithium coordinated to the oxygen atom might occupy an axial position to avoid 1,3-allylic strain,[10] and a subsequent internal delivery of the methyl group would occur to the *re* face of the imino group. The use of a non-coordinating solvent such as toluene favors intramolecular chelation phenomenon associated with the oxime activation, providing improved yield of the methyl adducts.



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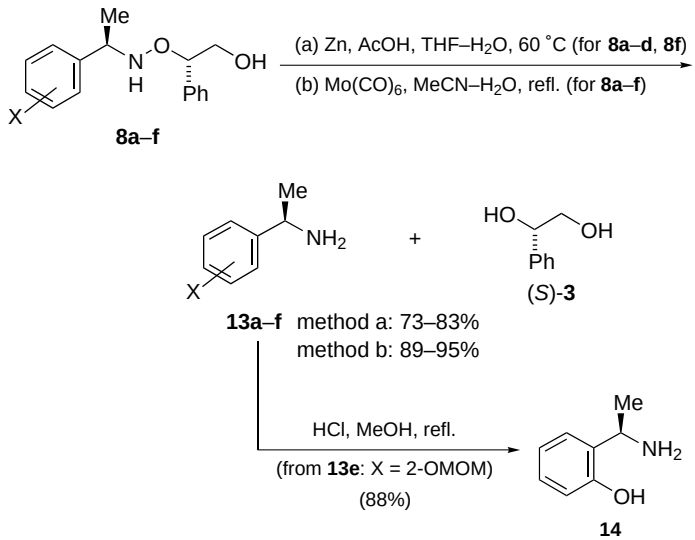
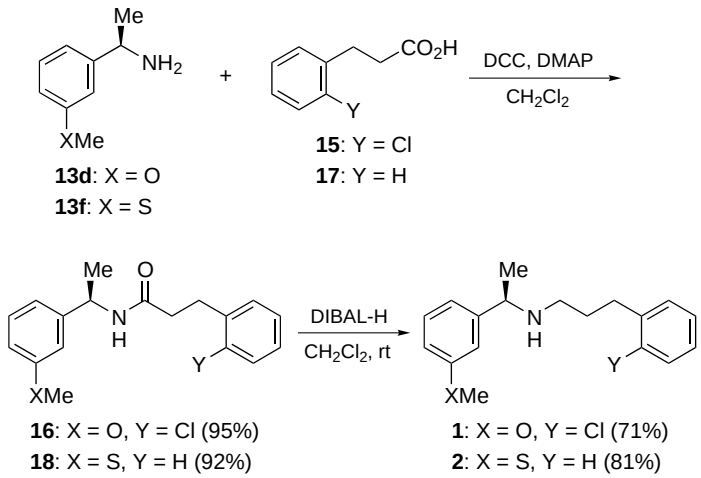
When reductive N–O bond cleavage was carried out with **8a**–**d** and **8f** by using Zn–AcOH (method a), the corresponding (*R*)-1-(aryl)ethylamines **13a**–**d**[11] and **13f**[11] were obtained in 73–83% yield with recovery of the antipodal chiral auxiliary (*S*)-**3**, which can be utilized as a chiral auxiliary for the preparation of *ent*-**13a**–**f**. The use of molybdenum hexacarbonyl[12] (method b) for the reductive N–O bond cleavage was effective for **8a**–**f**, and in each case the yield of corresponding **13a**–**f** was noticeably improved to 89–95% (Scheme 2). The 1-(aryl)ethylamines **13e** (X = 2-OMOM)[11] obtained was subjected to deprotection of the MOM group (HCl, MeOH, reflux) to give (1*R*)-1-(2-hydroxyphenyl)ethylamine (**14**),[13] which, together with its (1*S*)-enantiomer, was previously demonstrated by us to be a useful chiral auxiliary in the enantioselective synthesis of natural alkaloids.[14]

With (1*R*)-(+)-1-(3-methoxyphenyl)ethylamine (**13d**) (obtained in 93% yield from **8d** by method b) in hand, we next examined its conversion into (*R*)-(+)-NPS R-568 (**1**). Thus, coupling of **13d** and 2-chlorobenzenepropionic acid (**15**) was effected with DCC–DMAP (CH_2Cl_2, rt) to give the amide **16** in 95% yield. The DIBAL-H reduction (CH_2Cl_2, rt) of **16** yielded **1** (71%), $[\alpha]_D^{20}$ +41.9 (*c* 1.1, $CHCl_3$) (lit.[5b] $[\alpha]_D$ +38.6 (*c* 1.1, $CHCl_3$)). In a similar sequence, coupling of **13f** (obtained in 95% yield from **8f** by method b) with phenylpropionic acid (**17**) afforded the amide **18** (92%), which underwent DIBAL-H reduction to provide the thio analogue of **1**, (*R*)-*N*-{1-[3-(methylsulfanyl)-phenyl]ethyl}-3-phenyl-1-propanamime (**2**), $[\alpha]_D^{20} = +44.4$ (*c* 0.3, $CHCl_3$), in 81% yield (Scheme 3).

In summary, we have developed an enantioselective synthesis of 1-(aryl)ethylamines based on diastereoselective addition of methyllithium to the chiral oxime ethers via six-membered ring lithium chelation, which activates the substrate for the addition, leading to 1,4-asymmetric induction. The synthetic utility of this oxime ether-based methodology has been demonstrated by the application to the enantioselective synthesis of a new type of arylalkylamine calcimimetics (+)-NPS R-568 and its thio analogue.



Scheme 2.



Scheme 3.

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11. Optical rotation of corresponding 1-(aryl)ethylamines.
    13a (X = H): $[\alpha]_D^{20} = +34.5$ (*c* 1.0, $CHCl_3$), lit. (Chapman, D. T.; Crout, D. H. G.; Mahmoudian, M.; Scopes, D. I. C.; Smith, P. W. *Chem. Commun.* **1996**, 2415–2416) $[\alpha]_D = +32$ (*c* 0.3, $CHCl_3$).
    13b (X = 4-Me): $[\alpha]_D^{21} = +31.2$ (*c* 1.2, $CHCl_3$), lit. (Hose, D. R. J.; Mahon, M. F.; Molloy, K. C.; Raynham, T.; Wills, M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 691–703) $[\alpha]_D = +28.1$ (*c* 1.0, $CHCl_3$).
    13c (X = 2-OMe): $[\alpha]_D^{21} = +18.9$ (*c* 1.0, MeOH), lit. (Giardina, D.; Marrazzo, A.; Marucci, G.; Piloni, M. G.; Quaglia, W. *Farmaco* **1991**, *46*, 861–872) $[\alpha]_D^{20} = +18.2$ (*c* 1.0, MeOH).
    13d (X = 3-OMe): $[\alpha]_D^{20} = +23.6$ (*c* 0.8, MeOH), lit. (Sakai, K.; Hashimoto, Y.; Kinbara, K.; Saigo, K.; Murakami, H.; Nohira, H. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3414–3418) $[\alpha]_D^{20} = +17.6$ (*c* 2, MeOH).
    13e (X = 2-OMOM): $[\alpha]_D^{25} = +14.3$ (*c* 0.6, $CHCl_3$).
    13f (X = 3-SMe): $[\alpha]_D^{20} = +34.0$ (*c* 1.2, $CHCl_3$).
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