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TETRAHEDRON: *ASYMMETRY*

Enantioselective synthesis of 2-substituted-*N*-Boc-Δ-4,5-piperidines

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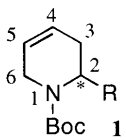
Abstract

The title compounds were prepared through a synthetic sequence involving: (i) a reaction of the condensation product between an enantiopure β-amino alcohol and an aldehyde with allylmagnesium chloride; (ii) an *N*-allylation of the resulting secondary amine; (iii) a chemoselective cleavage of the β-amino alcohol residue; and (iv) a protection of the secondary amine followed by a ring closing metathesis. The advantageous use of (1*R*,2*S*)-norephedrine was demonstrated in these syntheses. © 2001 Elsevier Science Ltd. All rights reserved.

Piperidine-derived heterocycles are ubiquitous substructures in natural molecules and a huge amount of work has been devoted towards the asymmetric synthesis of diversely substituted piperidinic compounds.[1] However, to our knowledge, a general and reliable method for the synthesis of enantioenriched 2-substituted-*N*-Boc-Δ-4,5-piperidines such as **1** still remains to be found.[2]



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Our interest in this unsaturated piperidinic core especially lies in the possibility of further functionalization of the C-4 or C-6 position of the heterocycle using Beak's methodology.[3] Our synthetic plan to reach these target molecules is depicted in Scheme 1.

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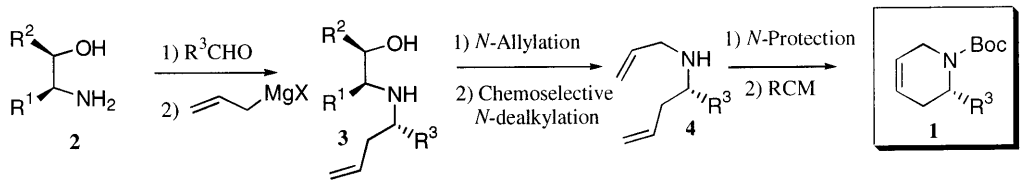
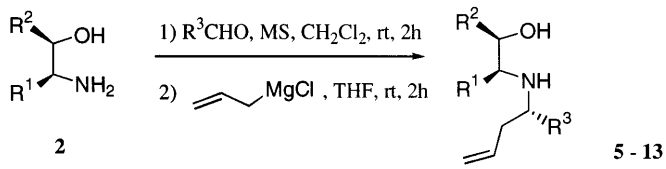


Scheme 1.

Reaction of an allyl Grignard reagent with the reaction product resulting from the condensation between an enantiopure β-amino alcohol **2** and an aldehyde accounts for the diastereoselective formation of the homoallylic amino alcohol **3**. *N*-Allylation, followed by a chemoselective *N*-dealkylation of the amino alcohol residue then gives diolefinic amine **4**. The last steps of this method consist in an *N*-protection by a Boc group followed by ring closing metathesis (RCM). We report herein our preliminary results of this synthetic scheme and delineate the scope.

As regards the first step of this synthesis, addition of Grignard reagents,[4] as well as lithium[5] or cerium[6] organometallics onto the reaction product[7] resulting from the condensation between an aldehyde and an enantiopure β-amino alcohol is a well-established methodology for the preparation of enantioenriched α-substituted amines. This simple reaction of predictable stereochemical outcome was therefore chosen to set the stereocenter in our target molecules. Two enantiopure β-amino alcohols, namely (1*R*,2*S*)-norephedrine (**2**: $R^1=Me$, $R^2=Ph$) and (*S*)-phenylglycinol (**2**: $R^1=Ph$, $R^2=H$) were used as chiral sources and were condensed with various aldehydes. Allylation was effected on the crude condensation product using 3 equiv. of allylmagnesium chloride in THF. The results are gathered in Table 1.

Table 1



Entry	Amino alcohol	R^3	Product	Yield[a]	De[b]
1	(1*R*,2*S*)-Norephedrine	Ph	**5**	75	>80
2	–	n-C_9H_{20}	**6**	90	20
3	–	n-C_3H_7	**7**	91	76
4		(*E*)-CH=CHPh	**8**	79	>95
5	(*S*)-Phenylglycinol	Ph	**9**	58	>95
6	–	n-C_9H_{20}	**10**	50	54
7	–	(*E*)-CH=CHPh	**11**	65	81
8	–	(*E*)-CH=CHC_6H_{13}	**12**	57	>95
9	–	*i*-Pr	**13**	67	67

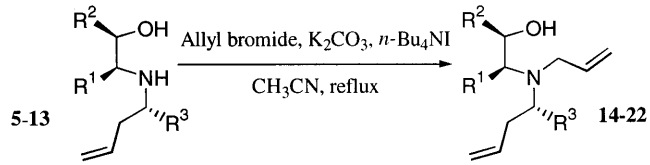
[a] Yield of isolated product.

[b] Determined by ^1H NMR. For all compounds, the diastereoisomeric excesses were ca. the same before and after purification by chromatography. In the case of compound **5**, the de was difficult to determine due to the presence of several minor impurities (GC purity of **5**: 95%).

The above results deserve some comments. First, the diastereoisomeric excesses obtained in these reactions dramatically depend upon the nature of the starting aldehyde. No minor stereoisomer, except in the case of the previously reported compound **11**,[8] could be detected in the reaction product when enals were used (entries 4, 7 and 8). Furthermore, in these cases, no competitive 1,4- versus 1,2-addition was detectable. Very good de's were also reached when benzaldehyde was used, but in the case of compound **5** (entry 1) accurate determination of the de was difficult (see Table 1). On the other hand, the diastereoselectivity dropped considerably when aliphatic aldehydes, and especially long chain aldehydes, were used (entries 2, 3, 6 and 9).

As regards the starting β-amino alcohol, the use of norephedrine instead of phenylglycinol was beneficial when cinnamaldehyde was used as the starting aldehyde. Indeed, compound **8** was obtained with better yield and de than **11** (compare entries 4 and 7).

Having in hand some allylic amino alcohols, the next step of the synthesis was studied. It consisted of an *N*-allylation of the secondary α,α′-disubstituted amine. The best conditions to achieve this reaction were reacting the amine with 4 equiv. of allyl bromide in refluxing acetonitrile for 12–24 h in the presence of K_2CO_3 and of a stoichiometric amount of tetrabutylammonium iodide (Scheme 2).



Norephedrine-derived amino alcohols	R^3	Yield
14 (from **5**)	Ph	57
15 (from **6**)	n-C_9H_{20}	not realized
16 (from **7**)	n-C_3H_7	95[a]
17 (from **8**)	(*E*)-CH=CHPh	66

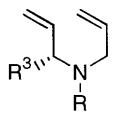
Phenylglycinol-derived amino alcohols	R^3	Yield
18 (from **9**)	Ph	22
19 (from **10**)	n-C_9H_{20}	40
20 (from **11**)	(*E*)-CH=CHPh	31
21 (from **12**)	(*E*)-CH=CHC_6H_{13}	75
22 (from **13**)	*i*-Pr	<10

a. de: 80% after purification by flash chromatography.

Scheme 2.

The above results clearly show that the success of this reaction depends on the steric crowding around the amine. Much better yields were obtained with norephedrine-derived amino alcohols (R^1 = Me) than with phenylglycinol-derived substrates (R^1 = Ph): compare the yields for **14** and **18** or **17** and **20**. This again highlights the advantageous use of norephedrine rather than phenylglycinol in this synthesis.

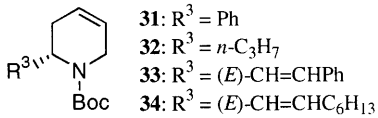
Chemoselective *N*-dealkylation was then effected on substrates **14**, **16**, **17** (derived from norephedrine) and **21** (derived from phenylglycinol). This procedure[9] consists of treatment of the β-amino alcohol with thionyl chloride in THF, followed by reaction with an excess of KCN in a mixture of DMSO/THF for 72 h. Following this two-step dealkylation procedure, diolefinic amines **23**–**26** were obtained with modest to fair yields, as shown below; these amines were then protected in quantitative yields as an *N*-Boc group by treatment with $(Boc)_2O$ in refluxing ethyl acetate to give compounds **27**–**30** (Fig. 1).



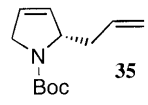
R = H	R = *t*-Boc
23: R^3 = Ph (45% from **14**)	**27**
24: R^3 = *n*-C_3H_7 (47% from **16**)	**28**
25: R^3 = (*E*)-CH=CHPh (56% from **17**)	**29**
26: R^3 = (*E*)-CH=CHC_6H_{13} (53% from **21**)	**30**

Figure 1.

Finally, these *N*-Boc amines were subjected to ring closing metathesis in refluxing dichloromethane (1 h) in the presence of the Grubbs catalyst (3% molar ratio). Under these conditions, compounds **27** and **28** gave the expected cyclized piperidines **31** and **32** in respective yields of 98 and 73%. On the other hand, using substrates **29** and **30**, a problem of chemoselectivity arises from the presence of an olefinic moiety in R^3. As a matter of fact, piperidine **34** was isolated pure from minor by-products in 57% yield when **30** was used in this reaction, but piperidine **33** resulting from the metathesis of **29** could not be obtained free of pyrrolidine **35**,[10] resulting from a metathesis reaction between the styrenic substituent and the *N*-allyl group (ratio **33**/**35**: 88/12, yield 82%).



31: R^3 = Ph
32: R^3 = *n*-C_3H_7
33: R^3 = (*E*)-CH=CHPh
34: R^3 = (*E*)-CH=CHC_6H_{13}



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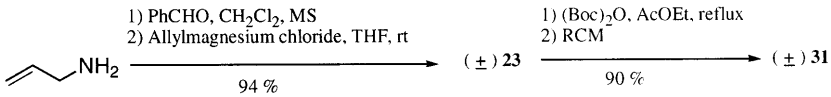
Since the *N*-dealkylation procedure used above was proved not to alter the stereochemical integrity of the released amine,[11] the enantiomeric excesses of the target compounds correspond to the diastereoisomeric ratio of their allylated precursor and are 80,[12] >95 and >95% for **32**, **33**, and **34**, respectively. Since some imprecision persisted in the determination of the enantiomeric excess of **31** (vide supra), racemic **31** was prepared as depicted in Scheme 3.



Scheme 3.

Chiral GC analysis (Supelco β-DEX-120) of *N*-Boc deprotected (TFA, CH_2Cl_2, 0°C, 1 h) racemic and enantioenriched **31** then allowed accurate determination of its ee that was found to be 87%.

In conclusion, this work delineates the scope of an enantioselective synthesis of 2-substituted-*N*-Boc-Δ-4,5-piperidines in which the advantageous use of norephedrine as chiral inductor was demonstrated. Further studies towards the subsequent functionalization of these unsaturated piperidines are in progress.

Acknowledgements

Marie Roger and Minh-Thu Dinh are thanked for their technical assistance.

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10. The nature of the minor compound **35** was determined by GC–MS analysis. All new compounds gave satisfactory analytical data. Selected data: Compound **34**: R_f (ether/petroleum ether: 5/95): 0.35; $[\alpha]_D^{20}$ −25 (*c* 0.7, $CHCl_3$); oil; ^{1}H NMR: 0.87 (t, $J=7$ Hz, 3H), 1.25–1.28 (m, 8H), 1.47 (bs, 9H), 1.9–2.1 (m, 3H), 2.45 (dd, $J=2.2$ and 17 Hz, 1H), 3.5 (d, $J=18$ Hz, 1H), 4.11 (d, $J=18$ Hz, 1H), 4.88 (very broad singlet, 1H), 5.41 (dd, $J=16$ and 5.8 Hz, 1H), 5.49–5.72 (m, 3H); ^{13}C NMR: 14.5, 23.0, 28.9, 29.1, 29.6, 32.1, 32.7, 40.8, 49.9, 79.8, 123.1, 124.1, 128.5, 132.4, 155.5; anal. calcd for $C_{18}H_{31}NO_2$: C, 73.67; H, 10.64; N, 4.77%. Found: C, 73.65; H, 10.61; N, 4.69%.
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