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Stereoselective synthesis of nonracemic 1,3-amino alcohols from chiral 2-vinylaziridines by InI–Pd(0)-promoted metalation

Yoshiji Takemoto,* Miyuki Anzai, Reiko Yanada, Nobutaka Fujii, Hiroaki Ohno† and Toshiro Ibuka

Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan

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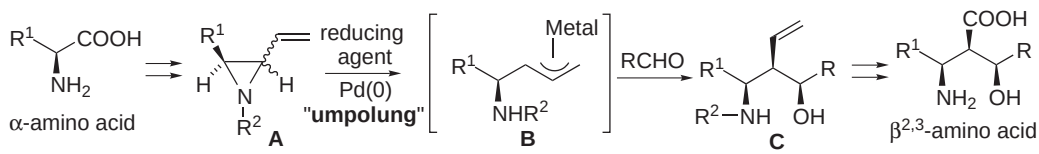
Abstract—Treatment of optically active 3-alkyl-2-vinylaziridines **1**, **8** and **9** and allylic acetates **10** and **11** with InI in the presence of $Pd(PPh_3)_4$ gives rise to chiral allylindiums bearing an amino group at the δ-position, which react with several aldehydes in highly regio- and stereoselective manner to afford the *syn*,*syn*-2-vinyl-1,3-amino alcohols **2a**, **5a**–**7a** and **12a**–**14a** possessing three contiguous chiral centers in good yields. © 2001 Elsevier Science Ltd. All rights reserved.

Over the past decade, allylmetallic reagents have been of increasing interest in organic synthesis.[1] In particular, diastereoselective addition of chiral allylmetals, possessing a stereogenic center at the δ-position with aldehyde, plays an important role in stereoselective synthesis since contiguous stereogenic centers can be created in a single operation and the resulting homoallylic alcohols can be used for further chemical transformation into various types of natural and synthetic compounds.[2,3] Although there are numerous reports concerning the preparation and utilization of 4-hydroxy- or 4-alkoxyallyl metals,[2] few reactions of chiral allylmetals bearing an amino group at the δ-position have been reported.[3] In order to establish an efficient synthetic method of chiral 4-amino allylmetal reagents **B**, we investigated the reducing agent and $Pd(PPh_3)_4$-promoted metalation of optically active 3-alkyl-2-vinylaziridines **A**[4] and the subsequent nucleophilic addition with several aldehydes.[5] If this reaction proceeds regio- and stereoselectively (**A**→**C**), β[2,3]-amino acid derivatives,[6] which are very important compounds as peptidomimetics, could easily be prepared from α-amino acids as shown in Scheme 1. In this communication, we describe an InI–Pd(0)-mediated allylation of aldehyde with the *N*-activated vinylaziridines **1** as well as the allylic acetate **10**, which proceeds with regio- and stereoselectivity irrespective of the chirality of the allylic carbon bearing a vinyl group, to provide the *syn*,*syn*-2-vinyl-1,3-amino alcohols **2a** in good yield.

We initially examined several reaction conditions for generating the desired allylmetal reagent from the known *N*-Mts-2-vinylaziridine *trans*-**1**.[4] The reactions of **1** and benzaldehyde (2 equiv.) were carried out at room temperature using various reducing agents (2–3 equiv.) and a catalytic amount of a Pd-catalyst under an argon atmosphere. As can be seen in Table 1, preparation and reactivity of the allylmetal reagent bearing an amino group at the δ-position are strongly affected by the reducing reagent employed. When



Scheme 1. General synthetic strategy of β[2,3]-amino acids from α-amino acids.

Keywords: indium and compounds; umpolung; amino alcohol; allylmetal; nucleophilic addition.

* Corresponding author.

† Current address: Graduate School of Pharmaceutical Sciences, Osaka University, Japan.

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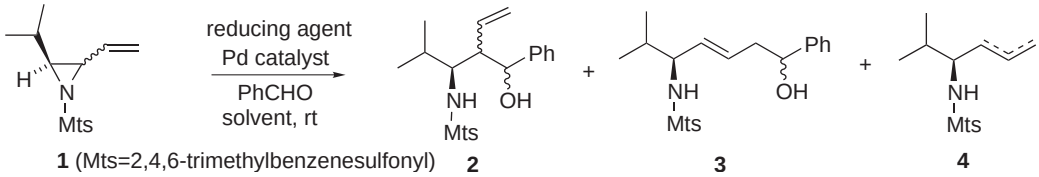
Table 1. Synthesis of 2-vinyl-1,3-amino alcohols **2** from 2-vinylaziridine **1** with various reducing agents[a]



1 (Mts=2,4,6-trimethylbenzenesulfonyl) **2** **3** **4**

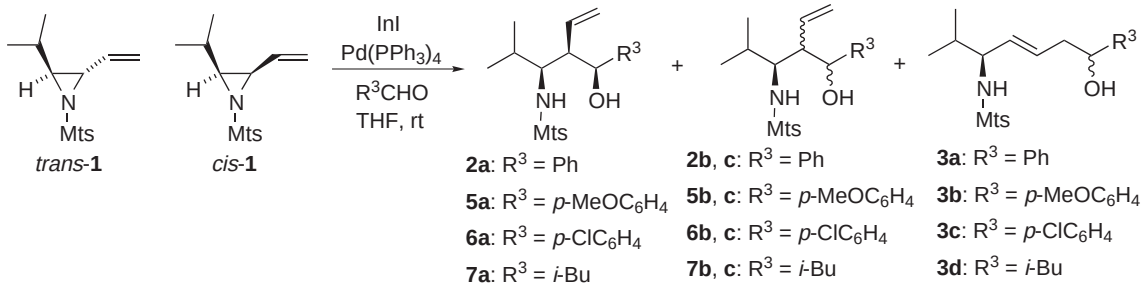
Entry	Reducing agent (equiv.)	Pd catalyst (mol%)	Solvent	Reaction time (h)	Yield[b] (%) (**2**:**3**:**4**)
1	Et_2Zn (2)	$Pd(PPh_3)_4$ (5)	THF	2	16:17:26
2	$SnCl_2$ (3)	$PdCl_2(CH_3CN)_2$ (2)	DMF/H_2O (3/1)	23	32:0:0
3	Et_3B (2)	$Pd(PPh_3)_4$ (5)	THF	8	Complex mixture
4	InI (2)	$Pd(PPh_3)_4$ (5)	THF	6	83:3:0

[a] All reactions were carried out with 2 equiv. of benzaldehyde in the presence of palladium catalyst and reducing agent at room temperature.
[b] Isolated yields.

Et_2Zn[7a] was used as a reducing agent (entry 1), the desired 1,3-amino alcohols **2** were obtained as minor products together with 1,5-amino alcohols **3** and reduction products **4**. A similar reaction of **1** with $SnCl_2$[7b] produced **2** without other products, but the yield of **2** was low due to decomposition of the starting material (entry 2). Although addition of Et_3B[7c] resulted in a complex mixture of products, the choice of InI[7d] as a reducing agent promoted the transmetalation and nucleophilic addition with benzaldehyde to give **2** in 83% yield (entries 3 and 4).

To next clarify the effect of the C-2 chirality of **1** on diastereoselectivity (**2a**/**2b**+**2c**), the 2,3-*cis*-2-vinylaziridine *cis*-**1** was treated with the InI–$Pd(PPh_3)_4$ reagent in the presence of several aldehydes. As shown

Table 2. The InI–Pd(0)-mediated allylation of 2-vinylaziridines **1**, **8**–**9** and allylic acetates **10**–**11** with various aldehydes[a]



Entry	Substrate	Aldehyde	Product	Yield[b] (%)	Ratio[c] (**a**:**b**+**c**:**3**)
1	*trans*-**1**	PhCHO	**2a–c**/**3a**	86	80:17:3
2	*cis*-**1**	PhCHO	**2a–c**/**3a**	98	81:15:4
3	*cis*-**1**	*p*-$MeOC_6H_4CHO$	**5a–c**/**3b**	91	85:13:2
4	*cis*-**1**	*p*-ClC_6H_4CHO	**6a–c**/**3c**	85	83:16:1
5	*cis*-**1**	*i*-BuCHO	**7a–c**/**3d**	97	85:12:3
6	**8**	PhCHO	**12a–c**/**3e**	58	79:9:12
7	**9**	PhCHO	**13a–c**/**3f**	70	71:13:16
8	**10**	PhCHO	**12a–c**/**3e**	93	91:6:3
9	**11**	PhCHO	**14a–c**/**3g**	65	52:17:31

[a] All reactions were carried out with 2 equiv. of aldehyde in the presence of $Pd(PPh_3)_4$ (5 mol%) and InI (2 equiv.) in dry THF at room temperature.
[b] Total yields.
[c] Calculated from isolated yield.

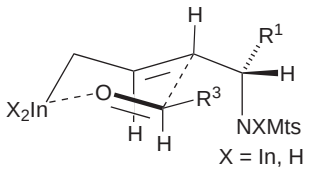


Figure 1. Transition state model (**A**).

in Table 2, both *trans*-**1** and *cis*-**1** gave the 1,3-amino alcohols **2a**–**c**[8] and 1,5-amino alcohols **3a** in a similar ratio (entries 1,2). In both cases, *syn*,*syn*-1,3-amino alcohol **2a** was predominantly produced. In addition, reaction of the allylindium reagent derived from *cis*-**1** with several aldehydes also proceeded in good yields to afford **5a**–**7a** as a major product among four possible diastereomers, irrespective of aromatic aldehydes having an electron-withdrawing or electron-donating group on the aromatic ring and aliphatic ones (entries 3–5). These results strongly suggest that diastereoselectivity of the InI-mediated allylation is independent of the chirality of the allylic carbon center of the substrates and the substituent (R^3) of the aldehydes. The latter result is in sharp contrast to that of allyltitanium reagents, where diastereoselectivity of the reaction with aryl aldehyde is very low.[3a] It would be desirable to employ a Boc group for protection of the amino moiety in place of the Mts group. Therefore, we next examined the umpolung of the *N*-Boc-aziridines **8** and **9** and *N*-Boc-allylic acetates **10** and **11** under identical transmetalation conditions. The reaction of **8** and **9** with benzaldehyde gave the corresponding *N*-Boc-1,3-amino alcohols **12a** and **13a** as a major product with similar diastereoselectivity to that of the *N*-Mts-aziridine **1**, but the chemical yields are low (entries 6 and 7). On the other hand, employing the allylic acetate **10** as a substrate, both the chemical yield and diastereoselectivity of **12a** were increased (entry 8).[9] From comparison with the diastereoselectivity obtained from the reactions of **9**, **10** and **11** (entries 7–9), it was revealed that bulkiness of the alkyl group (R^1) of the substrates would be crucial to achieve good diastereoselectivity. The good stereoselectivity attained in the allylation reaction can be explained by assuming that the reaction proceeds via the six-membered chair-like transition state (Fig. 1, **A**),[2c,10] which is the most favorable according to the Felkin–Ahn model, because the most sterically demanding alkyl moiety (R^1>NHR^2>H) is located at the *anti* position.

In conclusion, we have demonstrated a novel utility of *N*-activated 2-vinylaziridines as a precursor of chiral allylmetals by umpolung with an indium(I) salt. The allylindium reagents possessing a protected amino group (Mts and Boc) possess different characters from the reported allyltitanium[3a] and allenylindium reagents[5] in terms of stereochemistry of the major products (**2a** versus **2b**–**c**) and the stereodetermined chiral centers (C-2 versus C-3), respectively.

Acknowledgements

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8. Stereochemistry of **12a**–**14a** was confirmed by NOE analysis of tetrahydro-1,3-oxazin-2-ones prepared from **12a**–**14a** by treatment with NaH, and that of the others, **2a** and **5a**–**7a**, was deduced by comparison of their TLC behavior and ^1H NMR spectra.

9. The different outcome of **8** and **10** might be attributed to the corresponding allylindium intermediates bearing anionic and neutral species of the Boc group. The anionic species of the *N*-protecting groups tend to decrease the regio- and stereoselectivity (entries 1, 6, and 8).

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