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Umpolung of Chiral 2-Ethynylaziridines: Indium(I)-Mediated Stereoselective Synthesis of Nonracemic 1,3-Amino Alcohols Bearing Three Chiral Centers, Catalyzed by Palladium(0)

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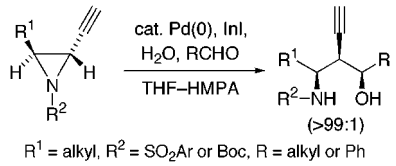
ABSTRACT



R^1 = alkyl, R^2 = SO_2Ar or Boc, R = alkyl or Ph

Treatment of 3-alkyl-2-ethynylaziridines with InI in the presence of $Pd(PPh_3)_4$ and H_2O gave allenylindium reagents bearing a protected amino group in high yields. Stereoselective addition of the allenylindium to aldehydes affords 2-ethynyl-1,3-amino alcohols bearing three chiral centers in good yields.

The N-activated or N-unactivated aziridines form a peculiar class of strained azacyclic compounds, with remarkable synthetic potential.[1−6] Currently, aziridines bearing an alkenyl[7,8] or ethynyl[9] group on one of the aziridine-ring carbon atoms have proven to be extremely useful intermediates for preparation of various types of natural and synthetic compounds. However, they serve only as electrophiles for carbon−carbon bond-forming reactions, except for aziridinyl anion reagents.[10] One might expect that, if the ethynylaziridines **1** could be converted into a nucleophilic species such as **A** in Scheme 1, they would become more valuable

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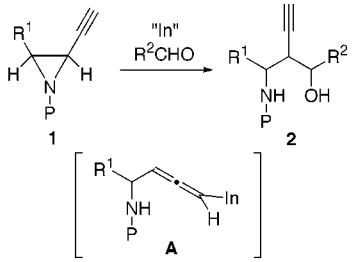
Scheme 1

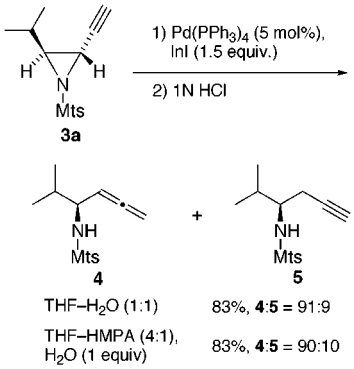


intermediates, e.g., for the synthesis of amino alcohols **2** bearing three chiral centers.

Recently, Marshall and co-workers reported pioneering work on chiral allenylindium reagents.[11] Thus, treatment of propargylic mesylates with InI and aldehydes in the presence of catalytic palladium(0) affords ethynyl alcohols in good to excellent stereoselectivities (45:55−95:5), via allenylindium reagents. However, it is a matter of interest to investigate the utility of ethynylaziridines as a precursor of an allenylindium reagent, the stability and reactivity of the allenylindium bearing an amino group, and regio- and stereoselectivity in both the reagent formation and addition to aldehydes. In this communication, we describe a highly stereoselective synthesis of 2-ethynyl-1,3-amino alcohols **2** by umpolung of ethynylaziridines **1** with indium(I) and a catalytic amount of palladium(0) (Scheme 1).

We initiated our study by forming the allenylindium reagent from the known 2,3-*trans*-2-ethynylaziridine **3a** (Scheme 2).[12] The desired indium reagent could not be

Scheme 2



prepared using indium powder under various reaction conditions in the presence or absence of a palladium catalyst.

(10) Aziridinyl anions are known to be effective precursors of highly substituted aziridines. (a) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303. (b) Vedejs, E.; Kendall, J. *J. Am. Chem. Soc.* **1997**, *119*, 6941. (c) Alezra, V.; Bonin, M.; Micouin, L.; Husson, H.-P. *Tetrahedron Lett.* **2000**, *41*, 651. See also, Almena, J.; Foubelo, F.; Yus, M. *J. Org. Chem.* **1994**, *59*, 3210.

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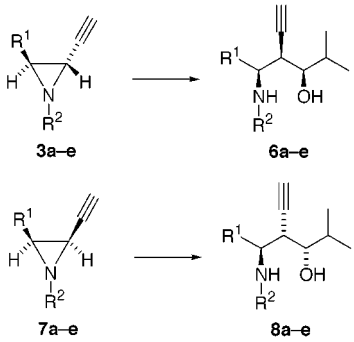
Scheme 3



a: R^1 = *i*-Pr, R^2 = Mts
b: R^1 = Bn, R^2 = Mts
c: R^1 = Bn, R^2 = Mtr
d: R^1 = $TBSOCH_2$, R^2 = Mts
e: R^1 = *i*-Pr, R^2 = Boc

Attempted formation of allenylindium could not be realized even using one of Marshall's conditions [InI, $Pd(PPh_3)_4$, THF−HMPA].[11] After considerable experimentation using InI in various solvents such as DMF, MeOH, or THF, we found that the desired reagent can be formed using InI and a catalytic amount of $Pd(PPh_3)_4$ in THF−H_2O (1:1), yielding an inseparable mixture of **4** and **5** after hydrolysis (**4**:**5** = 91:9, 83%). A similar result was obtained using THF−HMPA (4:1) in the presence of 1 equiv of H_2O. It was found that H_2O is essential for the formation of the allenylindium bearing a protected amino group from 2-ethynylaziridine **3a**.

Next, the reaction of the indium reagents prepared from 2,3-*trans*-2-ethynylaziridines **3a**−**e**[12] with isobutyraldehyde was investigated. As shown in Scheme 3 and Table 1, the aziridines **3a** and **3b** were treated with InI (1.3 equiv) and the aldehyde (1.5 equiv) in the presence of $Pd(PPh_3)_4$ (5 mol %) and H_2O (1 equiv) in THF−HMPA (4:1), affording the desired amino alcohols **6a** and **6b**, respectively (entries 1 and 2). In both cases, the *syn*,*syn*-adduct was the only isomer

Table 1. Synthesis of 2-Ethynyl-1,3-amino Alcohols from 2-Ethynylaziridines[a]

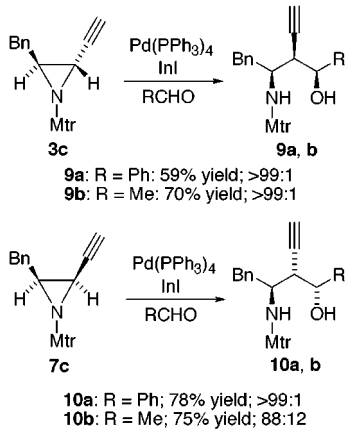
entry	aziridine	Pd[b]	solvent	product	yield[c]
1	**3a**	A	THF−HMPA	**6a**	42%
2	**3b**	A	THF−HMPA	**6b**	62%
3	**3b**	A	THF	**6b**	53%
4	**3b**	A	THF−H_2O (10:1)	**6b**	46%
5	**3b**	A	THF−H_2O (1:1)	**6b**	48%
6	**3b**	B	THF−HMPA	**6b**	61%
7	**3c**	A	THF−HMPA	**6c**	57%
8	**3d**	A	THF−HMPA	**6d**	68%
9	**3e**	A	THF−HMPA	**6e**	43%
10	**7a**	A	THF−HMPA	**8a**	59%
11	**7c**	A	THF−HMPA	**8c**	62%
12	**7d**	A	THF−HMPA	**8d**	70%
13	**7e**	A	THF−HMPA	**8e**	45%

[a] All reactions were carried out at room temperature using palladium catalyst (5 mol %), InI (1.3 equiv), H_2O (1 equiv), and isobutyraldehyde (1.5 equiv). [b] A: $Pd(PPh_3)_4$; B: $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$. [c] Isolated yields.

isolated. Unfortunately, THF or a mixed solvent of THF−H_2O was less effective for the addition reaction toward the aldehyde (entries 3−5). Both $Pd(PPh_3)_4$ and Pd(dppf)-Cl_2·CH_2Cl_2 can be used for the present transformation (compare entries 2 and 6). Similarly, 2,3-*trans*-aziridines **3c**−**3e** also gave *syn*,*syn*-adducts **6c**−**6e** exclusively (entries 7−9). In contrast, it was found that 2,3-*cis*-2-ethynylaziridines **7a**, **7c**, **7d**, and **7e** gave *anti*,*syn*-adducts **8a**, **8c**, **8d**, and **8e** in >99% selectivities under identical reaction conditions (entries 10−13, Table 2). It should be noted that the allenylindium from 2,3-*trans*-2-ethynylaziridines **3a** and **3e** bearing a bulky isopropyl group showed lower reactivities toward the aldehyde, giving the corresponding amino alcohols **6a** and **6e** in relatively low yields (entries 1 and 9).

As shown in Scheme 4, the reaction of the 2,3-*trans*- and 2,3-*cis*-2-ethynylaziridines **3c** and **7c** with benzaldehyde gave

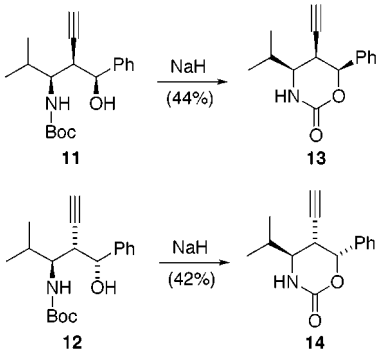
Scheme 4



9a and **10a** exclusively. When employing acetaldehyde as an electrophile, although the 2,3-*trans*-aziridine **3c** yielded only *anti*,*syn*-**9b** in 70% yield, the corresponding 2,3-*cis*-aziridine **7c** gave an inseparable mixture of the diastereomeric amino alcohols **10b** (88:12) in 75% yield.[13]

Stereochemical assignments for the synthesized diastereomeric amino alcohols were readily made by their transformation into tetrahydro-1,3-oxazin-2-one derivatives as shown in Scheme 5. The amino alcohols **11** and **12**, prepared by

Scheme 5



the reaction of the aziridine **3e** and **7e** with benzaldehyde, respectively, were treated with NaH to give the tetrahydro-1,3-oxazin-2-ones **13** and **14**. The stereochemistries of **13** and **14** were easily determined by NOE analyses.

One plausible mechanism for the present reductive coupling reaction is shown in Figure 1. Although the exact role

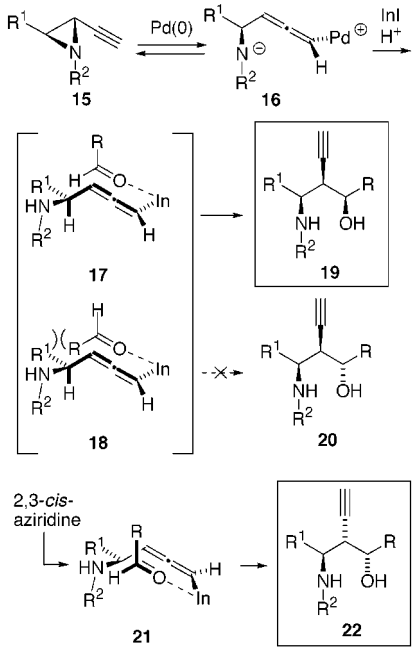


Figure 1.

of H_2O is unclear, protonation of the aza-anionic species **16** by H_2O is assumed to be an important factor for the effective formation of the allenylindium reagent bearing a protected amino group.

In conclusion, we have demonstrated a novel utility of 2-ethynylaziridines as a precursor of nucleophilic reagents by umpolung with indium(I). Allenylindium reagents bearing a protected amino group were effectively formed by treatment of 2-ethynylaziridines with InI, H_2O, and catalytic Pd(0). Subsequent reaction of the indium reagents, prepared from 2,3-*trans*-2-ethynylaziridines, with aldehydes afford *syn*,*syn*-2-ethynyl-1,3-amino alcohols exclusively, while the reagents from 2,3-*cis*-aziridines give *anti*,*syn*-isomers in high selectivities.

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Supporting Information Available: Selected experimental procedures and ^1H NMR spectra for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006089V

(13) Comparison of the NMR spectra of **9b** and both isomers of **10b** revealed that they are different from **9b**. Considering the mechanistic pathway shown in Figure 1, **10b** would be an epimeric mixture at the oxygenated carbon.