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Alkylation of nonstabilized aziridinylmagnesiums catalyzed by Cu(I) iodide: a new synthesis of amines, including optically active form, bearing a quaternary chiral center

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Abstract

A high-yield alkylation of aziridinylmagnesiums, which were generated from sulfinylaziridines with EtMgBr by sulfoxide–magnesium exchange, with primary alkyl halides in the presence of Cu(I) iodide as a catalyst, was realized. The alkylated aziridines were converted in quantitative yield to amines bearing a quaternary chiral center by hydrogenation with $Pd(OH)_2$. A synthesis of the optically active amines, bearing a quaternary chiral center, was realized, starting from optically active (*R*)-chloromethyl *p*-tolyl sulfoxide, in good overall yield by the presented method.

Keywords: aziridinyl anion; aziridinylmagnesium; quaternary chiral center; optically active amine.

Asymmetric synthesis of compounds having a quaternary chiral center has been a formidable but quite interesting challenge in synthetic organic chemistry.[1] In the chemistry of amines, optically active amines bearing a chiral quaternary center, including quaternary α- and β-amino acids,[2] are important as biologically active compounds, pharmaceuticals, catalysts, etc. However, few methods have so far reported the construction of these optically active amines bearing a chiral quaternary center.[3]

In our previous papers, we reported a new method for the generation of nonstabilized aziridinyl anions **3**[4] by the sulfoxide–metal exchange reaction[5] of sulfinylaziridines **2**, which were synthesized from 1-chloroalkyl *p*-tolyl sulfoxides **1** with imines.[6] In continuation of our study for the generation of nonstabilized aziridinyl anions and their application to the development of new synthetic methods, herein we report a new method for the synthesis of amines bearing a quaternary chiral center **5** from sulfinylaziridine **2**. The key step of this method is the generation of the aziridinylmagnesium **3** and alkylation of **3** with alkyl halides, using Cu(I) iodide as a

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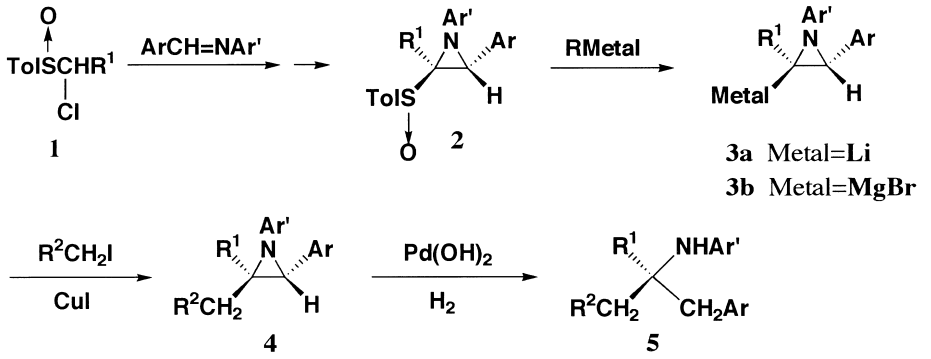
catalyst. We also report a new chiral synthesis of optically pure amines having a quaternary chiral center **5** starting from (*R*)-chloromethyl *p*-tolyl sulfoxide (**1**, $R^1 = H$) (Scheme 1).

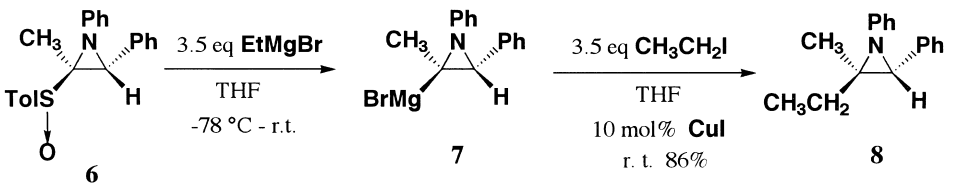


Scheme 1.

First, sulfinylaziridine **6**[6b] was treated with 3.5 equiv. of EtMgBr at –78°C and the temperature of the reaction mixture was allowed to warm to room temperature to give the aziridinylmagnesium **7** in quantitative yield. The carbanion **7** was found to be stable at room temperature for several hours. It was also found that the reactivity of **7** was quite low. For example, **7** reacted only with acetaldehyde but neither ketones nor iodomethane reacted with **7**.[6b]

We further investigated the alkylation of **7** with iodoalkanes in the presence of metal catalysts and finally found that copper(I) iodide worked excellently.[7] For instance, aziridinylmagnesium **7** was treated with 3.5 equiv. of iodoethane and 10 mol% of Cu(I) iodide in THF at room temperature for 30 min to give the ethylated aziridine **8** in 86% yield, as a single isomer (Scheme 2).

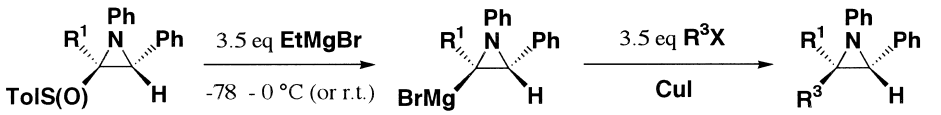
The stereochemistry of product **8** was investigated with the ^{1}H NMR NOESY spectrum. As the NOE between the hydrogen on the aziridine ring and the methyl group of the ethyl substituent was observed, the structure of **8** was unambiguously determined to be *E*. From this result, it was found that the stereochemistry of the carbon bearing the sulfinyl group of **6** was retained throughout the whole sequence.



Scheme 2.

Representative results for the alkylation of the aziridinylmagnesiums with alkyl halides are summarized in Table 1. As shown in the table, both the aziridinylmagnesiums having a methyl and decyl group gave quite good results with primary alkyl iodides (entries 1–3 and 8–10). Allyl bromide and benzyl bromide show much higher reactivity than other primary alkyl iodides in this reaction (entries 4, 5, 11, and 12). However, secondary alkyl iodide (2-iodopropane) and aryl iodide (iodobenzene) did not react at all (entries 6 and 13). Although the TBDMS ether of 2-iodoethanol reacted less vigorously, it gave the desired product in moderate yield (entry 14). In

Table 1
Generation of aziridinylmagnesiums and alkylation with alkyl halides



Entry	R^1	R^3X	CuI/mol%	Conditions °C (min)	Yield / %[a]
1	CH_3	CH_3I	10	r.t. (30)	87
2	CH_3	$C_5H_{11}I$	10	r.t. (30)	87
3	CH_3	$C_{10}H_{21}I$	10	r.t. (30)	94
4	CH_3	CH_2=$CHCH_2Br$	10	0 (5)	92
5	CH_3	$PhCH_2Br$	10	0 (5)	87
6	CH_3	$(CH_3)_2CHI$	40	0 (120)	-[b]
7	CH_3	$NCCH_2I$	40	0 (120)	-[b]
8	$C_{10}H_{21}$	CH_3I	10	r.t. (15)	96
9	$C_{10}H_{21}$	$C_5H_{11}I$	10	r.t. (30)	88
10	$C_{10}H_{21}$	$C_{10}H_{21}I$	10	r.t. (20)	83
11	$C_{10}H_{21}$	CH_2=$CHCH_2Br$	10	r.t. (35)	91
12	$C_{10}H_{21}$	$PhCH_2Br$	10	r.t. (10)	94
13	$C_{10}H_{21}$	PhI	10	r.t. (10)	-[c]
14	$C_{10}H_{21}$	$TBDMSOCH_2CH_2I$	40	r.t. (180)	66[d]
15	$C_{10}H_{21}$	$EtOCOCH_2I$	10	r.t. (15)	-[e]

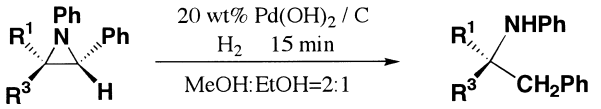
a) Isolated yield after silica gel column chromatography. All the products were fully characterized by IR, ^{1}H NMR, MS (low and high-resolution). b) A complex mixture. c) Main product was the aziridine having H as R^3. d) This product was isolated after deprotection of the TBDMS group by treatment of the initial product with TBAF. e) The product is the reduced aziridine (R^1=$C_{10}H_{21}$, R^3=H)

an attempt to synthesize β-amino acids, the aziridinylmagnesium was reacted with iodoacetonitrile and ethyl iodoacetate (entries 7 and 15); however, the reaction gave either a complex mixture or desulfinylated aziridine.

We then investigated the regioselective cleavage of the produced aziridines by hydrogenation with a palladium catalyst to afford the amines bearing a quaternary chiral center. Usually, the hydrogenative cleavage of aziridines is conducted with $Pd(OH)_2$.[8] We also used $Pd(OH)_2$ as the catalyst for cleavage of the C–N bond, and the results are summarized in Table 2.

As shown in Table 2, the regioselective cleavage of the aziridines is quite effective, to afford the desired amines bearing a quaternary chiral center. However, the reaction required 100 to 300

Table 2
Hydrogenation of alkylated aziridines to the amines bearing a quaternary chiral center

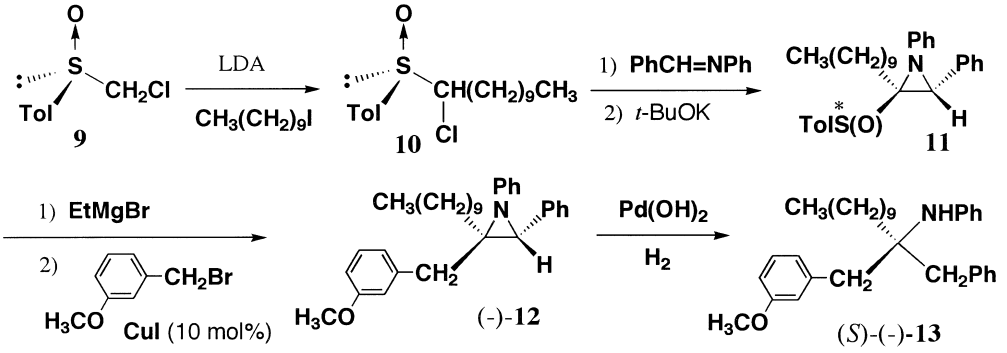


Entry	R^1	R^3	$\frac{Pd(OH)_2}{\text{weight \%}}$	Yield/%
1	CH_3	$C_{10}H_{21}$	200	99
2	$C_{10}H_{21}$	CH_3	120	93
3	$C_{10}H_{21}$	C_5H_{11}	300	98
4	$C_{10}H_{21}$	$PhCH_2$	300	97
5	$C_{10}H_{21}$	$HOCH_2CH_2$	200	95[a)]

a) Methanol was used as the solvent.

wt% of the $Pd(OH)_2$. When this reduction was conducted with less $Pd(OH)_2$, a considerable amount of the starting material remained. It is noted that the product in entry 5 is a γ,γ-disubstituted γ-amino alcohol.

Finally, we applied the presented procedure to an asymmetric synthesis of amines bearing a quaternary chiral center, starting from the chiral sulfoxide **9**[6b] (see Scheme 3). Optically active sulfinylaziridine **11** (over 98% ee)[6b] was treated with 3.5 equiv. of EtMgBr, followed by 3-methoxybenzyl bromide in the presence of 10 mol% of Cu(I) iodide, to give the optically active **12** ($[\alpha]_D^{26}$ –87.45° (c 0.27, acetone), 98% ee)[9] as a colorless oil in 98% yield. The catalytic hydrogenation of **12** with $Pd(OH)_2$ (200 wt%) in a mixture of MeOH:EtOH (2:1) as above, afforded the optically active amine bearing a quaternary chiral center (*S*)-(–)-**13** ($[\alpha]_D^{25}$ –2.2° (c 0.1, acetone)) as a colorless oil with over 97% ee[9] in quantitative yield.



Scheme 3. Asymmetric synthesis of the optically active amine (*S*)-**13** starting from (*R*)-chloromethyl *p*-tolyl sulfoxide **9**

Acknowledgements

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