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Enantioselective addition of organolithium reagents to a 2*H*-azirine

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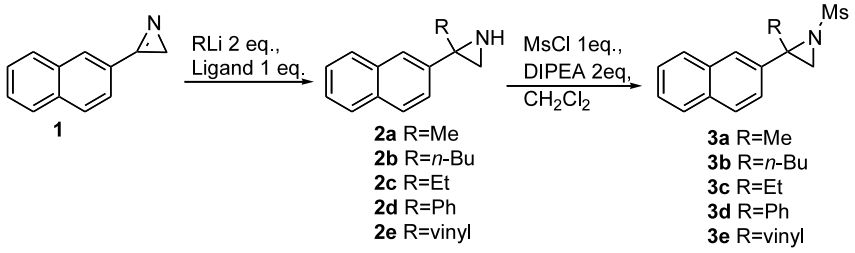
Abstract—3-(2-Naphthyl)-2*H*-azirine was used as a model substrate in the first enantioselective addition of organolithium reagents to an azirine. Various organolithium reagents have been used together with different chiral ligands.

The preparation of optically active amines is a field of growing interest. A useful synthetic route for the preparation of these target molecules is the enantioselective addition of *C*-nucleophiles to imines.[1–3] The first report concerning the asymmetric addition of organometallic reagents to an imine appeared in 1990, when it was observed that in the presence of chiral β-amino ethers organolithium compounds add to *N*-arylimines to give the corresponding amines in up to 77% ee.[4] Since this pioneering work, extensive efforts have been expended in this area.[5–9] To accomplish the addition of an organolithium reagent to the C=N bond at a reasonable rate, activation of the imine moiety is normally required. This can be achieved by Lewis acid activation,[6] or by using an electron-withdrawing *N*-alkyl or -aryl substituent.[4,5,8–14] The most commonly employed activation method has been to attach an *N*-*p*-methoxyphenyl group, although different aryl groups have been screened to investigate their influence on the enantioselectivity.[10]

We have investigated the possibility of using a 2*H*-azirine as the substrate in the asymmetric addition of organolithium reagents to C=N species to afford the corresponding aziridines (Scheme 1). The relief of ring strain associated with the conversion from azirine to aziridine was expected to provide sufficient driving force for the reaction and circumvent the need for activating groups.[15] Herein we detail our preliminary results.

Naphthyl azirine **1** was prepared according to known methods,[16] and was selected as a model substrate for the present study together with ligands **4**–**8** (Scheme 1 and Fig. 1), all of which have been used previously in enantioselective additions to imines. The addition of MeLi to **1** was performed in PhMe at −100±5°C, lower temperatures resulted in freezing, giving the aziridine **2**.

Compound **2a** was found to be unstable on alumina or silica gel and on our chiral HPLC column preventing chromatographic purification and ee determination.



Scheme 1.

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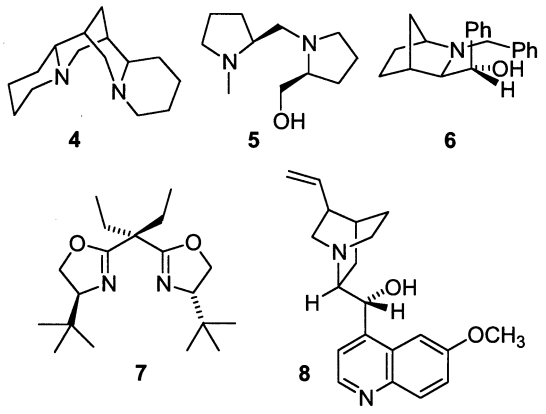
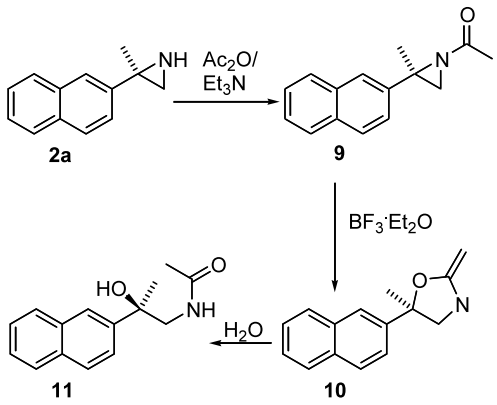


Figure 1. Chiral ligands used for enantioselective addition to azirine **1**.

Therefore aziridine **2a** was transformed into the mesylate **3a**, upon which yields and ee determinations are based. The alkylations were performed using two different procedures: in method A the organolithium reagent is added to a stirred, precooled mixture of **1** and the chiral ligand (entries 2, 3, 5, 8 and 9, Table 1),[5] while in method B a mixture of the organolithium reagent and the ligand is added to **1** (entries 1, 4, 6 and 7).[10] Of the ligands examined only **4** and **5** promoted the formation of aziridine **2**, albeit in modest yields and low ee (entries 1–4), while the use of ligands **6**–**8** resulted in decomposition of **1** and no detectable formation of **2** (entries 5–9). The highest ee in the MeLi case was obtained using ligand **5** together with **1** giving aziridine **3a** in 30% yield and 12% ee (entry 3) using method A. A comparable result was obtained when using method B, affording **3a** in 40% yield and 11% ee (entry 4). The absolute configuration of the major enantiomer of **2a** was determined to be (*R*) by conversion of the aziridine into the previously known *N*-acylamino alcohol **11** (Scheme 2).[17] Aziridine **2a** was acetylated, the obtained amide **9** rearranged into the corresponding oxazoline **10** using $BF_3{\cdot}Et_2O$, with retention of stereochemistry, followed by hydrolysis to give **11**.[18–20] Both ligands **4** and **5** were found to favor the formation of (*R*)-**2a**.



Scheme 2.

Next, various organolithium reagents were evaluated (Table 2). (−)-Sparteine **4** was chosen as the ligand due to its broad spectrum of application with different organolithium reagents in imine alkylations.[5,8] The highest enantioselectivities were found in the addition of vinyllithium giving **3e** in 7% yield and 17% ee (entry 12), *n*-BuLi yielding **3b** in 15% yield and 16% ee (entry 2) and PhLi that gave **3d** in 30% yield and 15% ee (entry 6). Addition of EtLi afforded **3c** in low ee (entries 8 and 9). The mass balance of these additions indicated losses of approximately 30% of the crude product upon purification, as shown by reference reactions in the absence of a ligand (Table 2, entries 1, 4 and 7). All reference reactions gave clean conversions without the formation of side products according to TLC and ^{1}H NMR spectroscopic analysis of the crude reaction mixtures. The crude yield of **3b** (88%) decreased to 56% after Al_2O_3 chromatography (entry 1) and the same was found for **3d** (95–29% yield, entry 4) and **3c** (80–55% yield, entry 7). Reference reactions with MeLi (Table 1, entry 10) and vinylLi (Table 2,

Table 1. Addition of MeLi to azirine **1** with various ligands

Entry	Method[a]	Ligand	Product[d]	Yield (%)[e]	Ee (%)[f]
1	B	**4**	**3a**	28	9
2	A	**4**	**3a**	42	6
3	A	**5**	**3a**	30	12
4	B	**5**	**3a**	40	11
5	A	**6**		–	
6	B	**7**		–	
7	A	**7**		–	
8	B	**8**		–	
9[c]	A	**8**		–	
10[b]	R	–	**3a**	44	0

[a] Reactions were completed using two methods: **Method A**, where a mixture of azirine (1 equiv.) and ligand (1 equiv.) dissolved in PhMe was added to a precooled (−100±5°C) MeLi (2 equiv.) solution in PhMe and **Method B**, where the azirine (1 equiv.) dissolved in PhMe was added to a precooled (−100±5°C) solution of MeLi (2 equiv.) and ligand (1 equiv.) in PhMe.

[b] A reference reaction (R) was run where MeLi (2 equiv.) was added to azirine (1 equiv.) dissolved in PhMe at −78°C in the absence of ligand.

[c] Reaction was completed in Et_2O.

[d] Aziridine **2a** was mesylated giving **3a** prior to purification and analysis.

[e] Purity >85% according to ^{1}H NMR spectroscopy.

[f] Determined on a Chiralcel OD-H column.

Table 2. Addition of various organolithium reagents to azirine **1**

Entry	Method[a]	Nucleophile (equiv.)	Product[c]	Yield (%)	Ee (%)[g]
1[b]	R	*n*-BuLi, 2	**3b**	56[e], 88[f]	0
2	A	*n*-BuLi, 2	**3b**	15[d]	16
3	B	*n*-BuLi, 2	**3b**	38[d]	0
4[b]	R	PhLi, 2	**3d**	29[e], 95[f]	0
5	A	PhLi, 2	**3d**	20[d]	5
6	B	PhLi, 2	**3d**	30[d]	15
7[b]	R	EtLi, 2	**3c**	55[e], 80[f]	0
8	A	EtLi, 2	**3c**	47[d]	2
9	B	EtLi, 2	**3c**	7[d]	5
10[b]	R	VinylLi, 2	**3e**	18[d]	0
11	A	VinylLi, 2	**3e**	9[d]	7
12	B	VinylLi, 2	**3e**	7[d]	17

[a] Reactions were completed using two methods: **Method A**, where a RLi (2 equiv.) solution in PhMe was added to a precooled mixture of azirine (1 equiv.) and (−)-sparteine (1 equiv.) dissolved in PhMe and **Method B**, where a solution of RLi (2 equiv.) and (−)-sparteine (1 equiv.) in PhMe was added to a precooled solution of the azirine (1 equiv.) dissolved in PhMe.
[b] A reference reaction (R) was run where RLi (2 equiv.) was added to the azirine (1 equiv.) dissolved in PhMe at −78°C in absence of ligand.
[c] Aziridine **2** was mesylated giving **3** prior to purification and analysis.
[d] Purity >85% according to ^{1}H NMR spectroscopy.
[e] Pure aziridines after chromatography.
[f] Crude yield with a purity >85% according to ^{1}H NMR spectroscopy.
[g] Determined on a Chiralcel OD-H column.

entry 10) were not as clean and yields could not be determined on the crude reaction mixtures.

So far only low enantioselectivities have been obtained in the addition of various organolithium compounds to azirine **1** in the presence of chiral ligands, furnishing aziridine **2** and, on mesylation, **3**. No systematic variation in yield and product ee can be detected at this time.

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