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Catalytic asymmetric intramolecular hydroamination of aminoalkenes

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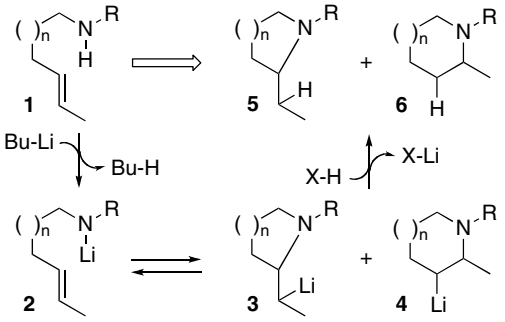
Abstract—Asymmetric intramolecular cyclization of aminoalkenes was catalyzed by a catalytic amount of *n*-butyllithium, diisopropylamine, and a newly designed chiral bisoxazoline in toluene to produce kinetically controlled *exo*-cyclized amines with up to 91% ee quantitatively.

Nitrogen containing chiral compounds are of importance and interest from the view points of biological activity[1] as well as utility in synthetic chemistry.[2] Asymmetric synthesis of these compounds has been the target of considerable enthusiastic efforts. Although brilliant successes have been reported by using the methodologies of asymmetric alkylation and hydrogenation of C–N double bonds,[3,4] approaches toward catalytic asymmetric amination of C–C double bonds has just been started recently. Of these approaches, asymmetric conjugate amination of C–C double bonds that are activated by an electron-withdrawing group has met some successes as has been shown by the reaction of lithium amide as a nitrogen nucleophile.[5,6] On the other hand, direct amination[7,8] of simple C–C double bonds that are not activated and extension to an asymmetric reaction[9] have remained in relatively undeveloped stage. We have already reported the chiral ligand-controlled asymmetric conjugate amination reaction of lithium amides with enoates.[10] As a next generation of the studies, we describe the lithium-catalyzed asymmetric intramolecular amination of aminoalkenes.

The reaction of lithium amide **2** derived from aminoalkene **1** by lithiation gives **3** and **4** via *exo*-and *endo*-cyclization, respectively (Scheme 1). Protonation of **3** and **4** completes the hydroamination of **1** to give **5** and **6**. A chiral ligand for lithium offers a chance to realize the asymmetric conversion of **2** to **3** and **4**. This scheme, however, involves some problems in that stoichiometric conversion of **1** to **2** suggests no agents present for protonation of **3** and **4**. Another problem is difficulty in the conversion of N–Li **2** to C–Li **3** and **4** due to unfavorable acid–base equilibrium.



Scheme 1. Intramolecular hydroamination via lithium amide.

We began our studies by treating **1a** with 1.2 equiv of *n*-butyllithium in the presence of 1.5 equiv of established *i*-PrBox ligand **7a** in toluene at −60 °C for 5 h (Scheme 2, Fig. 1, Table 1, entry 1). The product **5a** was obtained in 6% yield along with recovery of **1a** unchanged. Although the yield was poor as we had expected, the enantioselectivity was as fair as 54% ee. This low conversion problem was partially solved by using catalytic amounts of butyllithium and **7a** to give **5a** with 74% ee in 22% yield at −60 °C, and with 63% ee quantitatively at room temperature (entries 2 and 3). Then, we

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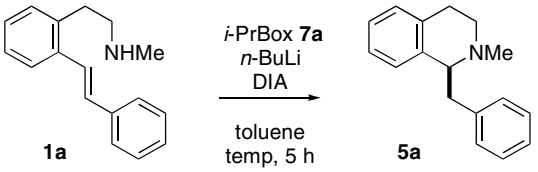


Scheme 2. Intramolecular hydroamination of **1a** via lithium amide.

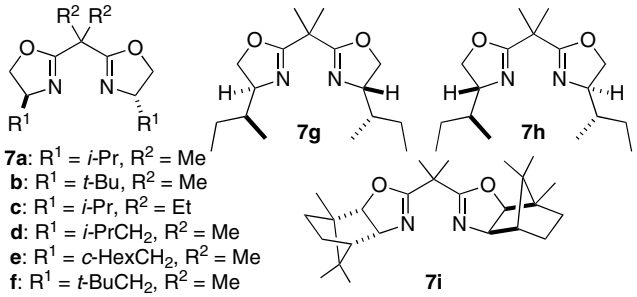


Figure 1. Chiral bisoxazolines (Box) **7**.

Table 1. Intramolecular amination of **1a** giving (*S*)-**5a**

Entry	BuLi (equiv)	DIA (equiv)	**7a** (equiv)	Temperature (°C)	Yield (%)	ee (%)
1	1.2	0	1.5	−60	6	54
2	0.2	0	0.4	−60	22	74
3	0.1	0	0.2	rt	99	63
4	0.2	0.2	0	−60	0	
5	0.2	0.2	0.4	−60	99	71

examined effect of diisopropylamine (DIA) as an external protonating agent. The reaction with 0.2 equiv of butyllithium and 0.2 equiv of DIA did not proceed at −60 °C for 5 h, resulting in recovery of **1a** (entry 4). However, further addition of 0.4 equiv of **7a** promoted the reaction to give (*S*)-**5a** with 71% ee quantitatively (entry 5). This indicates that protonation of **3** or **4** is required to proceed the reaction, and a coordinating agent for lithium activates lithium amide **2** to afford **3** or **4**. Regioselective production of *exo*-cyclized six-membered **5a** suggests the kinetically controlled *exo*-cyclization to give **3** in preference to *endo*-attack.

Asymmetric amination of **1a** was further examined under the catalysis of known chiral bisoxazolines **7a**–**e** (Fig. 1, Table 2). It became apparent that **7b** bearing a bulkier *t*-Bu group, in place of *i*-Pr, on the oxazoline ring worst effected the amination to need higher temperature to complete the reaction, giving **5a** with poor 31% ee (entry 1). Replacement of dimethyl group (R^2) with diethyl group, **7c**, did not realize higher selectivity as well as reactivity (entry 2). It is interesting to find that one methylene interval between oxazoline skeleton and bulky appendage (**7d,e**) is important to effect higher enantioselectivity of 84% and 78% ee (entries 3 and 4). New chiral Box **7f** bearing a neopentyl group on the oxazoline, however, gave **5a** with decreased 75% ee (entry 5).

Table 2. Catalytic asymmetric amination of **1a** giving **5a**[a]

Entry	**7**	Temperature (°C)	Time (h)	Yield (%)	ee (%)	*R*/*S*
1	**b**	rt	5	99	31	*S*
2	**c**	−60	27	99	62	*S*
3	**d**	−60	5	97	84	*S*
4	**e**	−60	5	92	78	*S*
5	**f**	−60	5	90	75	*S*
6	**g**	−60	5	25	81	*S*
7	**h**	−60	15	91	60	*R*
8	**i**	−60	22	54	62	*R*

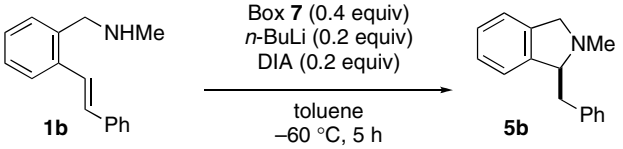
[a] The reaction was conducted with 0.4 equiv of **7**, 0.2–0.4 equiv of butyllithium and 0.2 equiv of DIA at −60 °C.

Further approach toward the better Box ligand was the modification of *i*-Pr group of **7a**. Among two new Box ligands prepared, **7g** was better than **7h** to give **5a** with 81% ee (entries 6 and 7). New ligand **7i** of much more rigid skeleton gave **5a** with 62% ee (entry 8). The stereochemistry of **7** and the absolute configurations of **5a** produced by the action of the corresponding **7** are in good relationships without any exception.

Under the established conditions of 0.2 equiv each of butyllithium and DIA, and 0.4 equiv of **7**, the catalytic asymmetric amination of **1b** was examined (Table 3). *exo*-Cyclized five-membered **5b** was obtained regioselectively and % ee reached to 91% by using newly designed **7h** (entry 8). It is noteworthy that the reaction was catalyzed by 0.05 equiv each of butyllithium, DIA, and 0.1 equiv of **7h** to give (*R*)-**5b** with 91% ee quantitatively (entry 9). It is also important to note that only *exo*-cyclized five-membered **5b** was obtained without any detection of *endo*-cyclized six-membered **6b**.

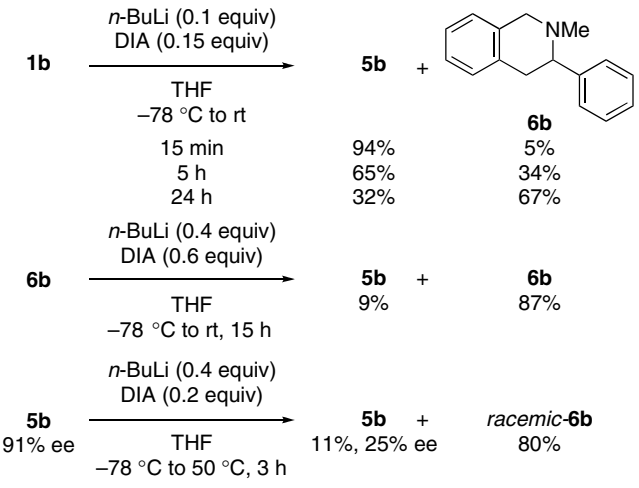
Contrary to the selective formation of *exo*-product **5b** under asymmetric reaction conditions in toluene, a mixture of **5b** and *endo*-cyclized **6b** was obtained in 94% and 5% isolated yields, respectively, when the reaction was conducted in THF for 15 min (Scheme 3). The same reaction gave **5b** and **6b** in 64% and 34% yields after 5 h. The reaction for 24 h gave **5b** and **6b** in the reversed

Table 3. Catalytic asymmetric intramolecular amination of **1b**



Entry	**7**	Yield (%)	ee (%)	*R*/*S*
1	**a**	99	84	*S*
2	**b**	89	19	*S*
3	**c**	99	84	*S*
4	**d**	99	79	*S*
5	**e**	99	76	*S*
6	**f**	99	71	*S*
7	**g**	99	66	*S*
8	**h**	98	91	*R*
9[a]	**h**	99	91	*R*
10	**i**	98	86	*R*

[a] The reaction was carried out using 0.1 equiv of **7h**, 0.05 equiv each of butyllithium and DIA.



Scheme 3. Hydroamination of **1b** and equilibrium in THF.

ratio of 32% and 67% yields. This indicates that **5b** is kinetic product and **6b** is thermodynamic product. In fact, treatment of **6b** under the amination conditions in THF gave **5b** in 9% yield along with recovery of **6b**. Similarly, treatment of **5b** with 91% ee gave **5b** with decreased 25% ee in 11% yield and *racemic*-**6b** in 80% yield. Attempted isomerization of racemic **5b** under the asymmetric conditions in toluene gave back **5b** unchanged probably because of difficulty in lithiation. This indicates clearly that kinetic control is operative in the catalytic asymmetric reaction in toluene.

In conclusion, we have developed lithium-catalyzed asymmetric hydroamination of aminoalkenes by using a chiral external Box ligand. Kinetically controlled reaction is operative in preference to thermodynamic equilibrium. Since the present procedure is simple, further application is promisingly broad.

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