Asymmetric Cycloaddition of 1,2-Dihydropyridine Derivatives in the Presence of Lewis Acids

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Asymmetric cycloaddition of 1-phenoxycarbonyl- (**1**) or 1-methoxycarbonyl-1,2-dihydropyridine (**2**) with *N*-acryloyl-(1*S*)-2,10-camphorsultam (**3**) produced chiral isoquinuclidine **4a** or **5a** in good yields with excellent diastereoselectivity in the presence of a Lewis acid such as titanium tetrachloride, zirconium tetrachloride, or hafnium tetrachloride. The absolute stereochemistry assignment of endo-cycloaddition products **4a** and **5a** has been established to be 1S, 4R, and 7S.

The isoquinuclidine ring system, azabicyclo[2.2.2]octane, is common to Iboga-type indole alkaloids of which (+)-catharanthine attracts special interest because of its eminent role as a biogenetic as well as a synthetic precursor of vinblastine and related antileukemic bisindole alkaloids (Figure 1).[1] Furthermore, isoquinuclidines are valuable intermediates in the synthesis of other alkaloids[2] and in medicinal chemistry.[3] The Diels–Alder reaction of 1,2-dihydropyridines with dienophiles is a well-established route to the synthesis of the azabicyclo-[2.2.2]octane ring system. For the asymmetric synthesis of isoquinuclidines, diastereoselective cycloadditions of 1,2-dihydropyridines with dienophiles having a chiral auxiliary have been reported.[4] Recently, the catalytic enantioselective synthesis of isoquinuclidines has also been reported.[5]

We selected 1,2-dihydropyridine derivative **1** or **2**[6] as the diene and *N*-acryloyl-(1*S*)-2,10-camphorsultam (**3**)[7] as the dienophile and investigated their asymmetric Diels–Alder cycloaddition. The both enantiomers of (1*S*)- and (1*R*)-2,10-camphorsultam are easily available and our plan is the stereoselective synthesis of both enantiomers of isoquinuclidine such as (+)-catharanthine and (−)-ibogamine. We report herein an effective asymmetric cycloaddition of diene **1** or **2** with dienophile **3** in the presence of a Lewis acid to produce chiral isoquinuclidines in good yields with high endo-diastereoselectivity.

We first examined the cycloaddition of 1-phenoxycarbonyl-1,2-dihydropyridine (**1**) (2 mmol) with *N*-acryloyl-(1*S*)-2,10-camphorsultam (**3**) (1 mmol). The reaction was carried out in refluxing toluene and the corresponding cycloaddition products *endo*-**4a** and *exo*-**4b** (endo/exo = 57/43) were obtained in 82% total yield (Table 1, Entry 6). However, the diastereomeric excess (d.e.) of the endo-cycloaddition product **4a** was 38%. Then, the cycloaddition reaction was carried out in the presence of a Lewis acid (Scheme 1) and the results are summarized in Table 1. As a result, the cycloaddition of **1** (2 mmol) with (1*S*)-**3** (1 mmol) in the presence of titanium tetrachloride (1.3 mmol) in CH_2Cl_2 (10 mL) at −78 °C for 24 h mainly produced the endo-cycloaddition product **4a** (endo/exo = 96/4) in 99% chemical yield with 94% d.e. (Table 1, Entry 1).[8]

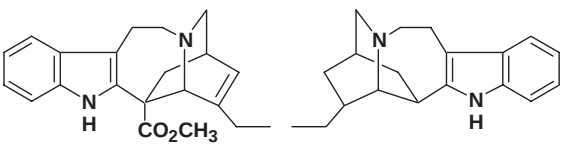
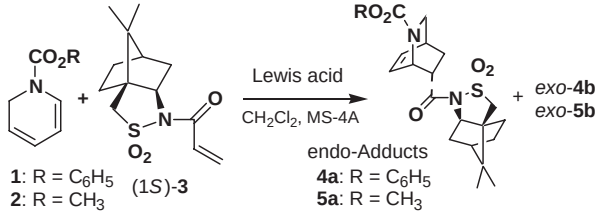


Figure 1. (+)-Catharanthine and (−)-ibogamine.



Scheme 1. Asymmetric cycloaddition of 1,2-dihydropyridine **1** or **2** with (1*S*)-**3**.

The reactivity of several Lewis acids for the asymmetric cycloaddition of 1-phenoxycarbonyl-1,2-dihydropyridine (**1**) with (1*S*)-**3** was also investigated.[9] In the presence of a Lewis acid such as zirconium tetrachloride or hafnium tetrachloride, this cycloaddition produced **4a** in good yields, and the diastereoselectivity of the endo-cycloaddition product **4a** was excellent as shown in Table 1; for example, $TiCl_4$ (94% d.e.) (Entry 1), $ZrCl_4$ (96% d.e.) (Entry 2), and $HfCl_4$ (97% d.e.) (Entry 3). Titanium tetrachloride[10] was highly reactive as a Lewis acid, so it needed low-temperature reaction conditions (Table 1, Entry 1). When zirconium tetrachloride was used, dropwise addition of diene **1** gave better result (Table 1, Entry 2). Hafnium tetrachloride was the most useful Lewis acid and the cycloaddition reaction proceeded smoothly at room temperature (Table 1, Entry 3).

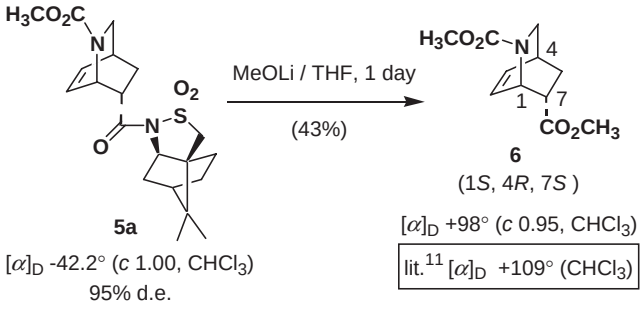
The cycloaddition reaction of 1-methoxycarbonyl-1,2-dihydropyridine (**2**) (3 mmol) and (1*S*)-**3** (1 mmol) was carried out in refluxing toluene and the corresponding cycloaddition products *endo*-**5a** and *exo*-**5b** (endo/exo = 84/16) were obtained in 89% yield (Table 1, Entry 7). However, the d.e. of the *endo*-**5a** was 63%. The cycloaddition of **2** with (1*S*)-**3** in the presence of titanium tetrachloride at −78 °C selectively produced the *endo*-**5a** (endo/exo = 100/0) in 63% chemical yield with 95% d.e. (Table 1, Entry 4). The cycloaddition of **2** (2 mmol) with (1*S*)-**3** (1 mmol) in the presence of hafnium tetrachloride (2 mmol) also selectively produced the *endo*-**5a** (endo/exo = 100/0) in 87% chemical yield with 96% d.e. (Table 1, Entry 5).

In order to determine the absolute stereochemistry of cycloaddition products, the assignment of *endo*-**5a** was carried out as follows (Scheme 2). For the assignment of **5a** (Table 1, Entry 4), **5a** was converted into the known (1*S*,4*R*,7*S*)-methyl ester **6**.[11]

Table 1. Diastereoselective cycloaddition of 1,2-dihydropyridine **1** or **2** with dienophile (1*S*)-**3**

Entry	Diene (molar equiv)	Dienophile (molar equiv)	Lewis acid (molar equiv)	Temp /°C	Time /h	Product	Yield[a] /%	endo/exo[b]	% d.e.[c] of endo adduct
1	**1** (2)	(1*S*)-**3** (1)	$TiCl_4$ (1.3)	−78	24	**4a**/**4b**	99	96/4	94
2[d]	**1** (2)	(1*S*)-**3** (1)	$ZrCl_4$ (2)	rt	24	**4a**/**4b**	78 (15)	98/2	96
3	**1** (2)	(1*S*)-**3** (1)	$HfCl_4$ (2)	rt	24	**4a**/**4b**	89 (6)	98/2	97
4	**2** (2.2)	(1*S*)-**3** (1)	$TiCl_4$ (1.5)	−78	24	**5a**/**5b**	63 (31)	100/0	95[e]
5	**2** (2)	(1*S*)-**3** (1)	$HfCl_4$ (2)	rt	24	**5a**/**5b**	87 (12)	100/0	96[e]
6	**1** (2)	(1*S*)-**3** (1)	—	reflux[f]	48	**4a**/**4b**	82	57/43	38
7	**2** (3)	(1*S*)-**3** (1)	—	reflux[f]	24	**5a**/**5b**	89	84/16	63[e]

[a]Isolated yield. Recovery of (1*S*)-**3** is shown in parentheses. [b]The ratio of endo/exo was determined by HPLC analysis using a TOSOH TSK-GEL Silica-60. [c]The % d.e. of endo isomer was determined by HPLC analysis using a TOSOH TSK-GEL Silica-60; 1% EtOH/hexane; flow rate; 1 mL/min, $Rt = 45$ min (minor), 49 min (major). [d]Dropwise addition of 1. [e]The % d.e. of endo isomer was determined by HPLC analysis using a TOSOH TSK-GELSilica-60; 1% EtOH/hexane; flow rate; 1 mL/min, $Rt = 60$ min (minor), 63 min (major). [f]Reaction in refluxing toluene.



Scheme 2. Absolute configuration of Diels–Alder adduct **5a**.

Thus, the reaction of **5a** (95% d.e.) with lithium methoxide in THF afforded (7*S*)-methyl ester **6** in moderate yield. According to the stereochemistry of (7*S*)-**6** as shown in Scheme 2, the chiral isoquinuclidine **4a** which was obtained from the reaction of 1-phenoxycarbonyl-1,2-dihydropyridine (**1**) with *N*-acryloyl-(1*S*)-2,10-camphorsultam (**3**) (Table 1, Entry 1), has also been established to be 1S, 4R, and 7S.

The stability and reactivity of 1,2-dihydropyridines are different in the presence of a Lewis acid. 1-Phenoxycarbonyl-1,2-dihydropyridine (**1**) and 1-methoxycarbonyl-1,2-dihydropyridine (**2**) are stable and its cycloaddition with (1*S*)-**3** proceeded in the presence of a Lewis acid. Though thermal cycloaddition of 1-*tert*-butoxycarbonyl-1,2-dihydropyridine with (1*S*)-**3** has been reported, unfortunately attempts to promote an enantioselective cycloaddition of 1-*tert*-butoxycarbonyl-1,2-dihydropyridine with (1*S*)-**3** failed in the presence of a Lewis acid.[9]

In summary, we have developed a highly diastereoselective cycloaddition of 1,2-dihydropyridine as diene with dienophile (1*S*)-**3** that provides an efficient methodology for obtaining pharmacologically important chiral isoquinuclidines. In the reaction, the combination of a Lewis acid and dienophile (1*S*)-**3** is effective, affording the corresponding chiral isoquinuclidines endo-adduct **4a** and endo-adduct **5a** having 94–97% d.e. with a very high endo selectivity of 96–100%.

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