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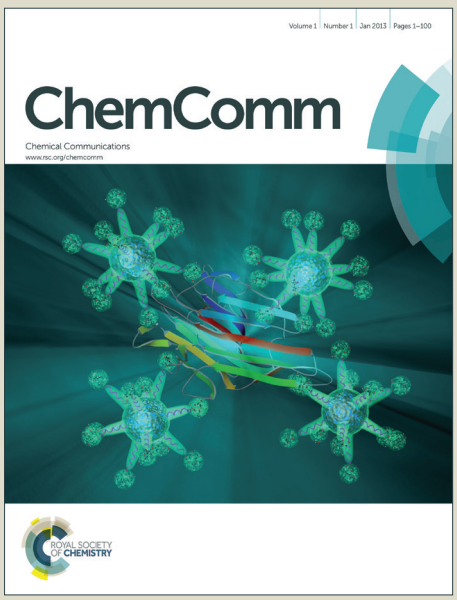

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The enantioselective Diels–Alder reaction of 1,2-dihydropyridines with α-acyloxyacroleins catalyzed by chiral primary ammonium salt†

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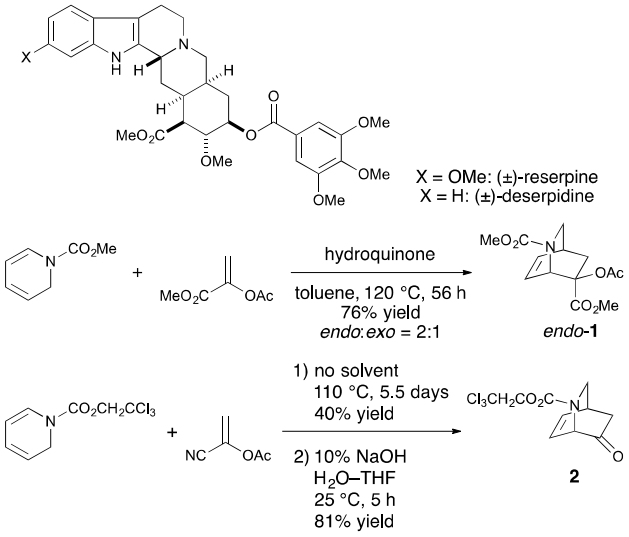
The first enantioselective Diels–Alder reaction of 1,2-dihydropyridines with α-acyloxyacroleins catalyzed by chiral primary ammonium salt has been developed and offers more efficient routes to key synthetic intermediates of alkaloids, for which the direct preparations were unavailable before. The asymmetric induction can be understood through the optimized geometry of iminium salt aqua complex derived from the catalyst and the dienophile.

The isoquinuclidine skeleton is found in a wide range of alkaloids, and optically active functionalized isoquinuclidines, as chiral synthons, can be transformed to versatile alkaloids.[1] The enantioselective Diels–Alder reaction of 1,2-dihydropyridines with acryloyl derivatives is one of the most straightforward methods for the construction of optically active isoquinuclidines.

For example, in 1980, Wender *et al*. achieved the total synthesis of (±)-reserpine from (±)-*endo*-Diels–Alder adduct **1** of *N*-methoxycarbonyl-1,2-dihrdropyridine with methyl α-acetoxyacrylate (Scheme 1).[2] In 1990, Mariano *et al*. achieved



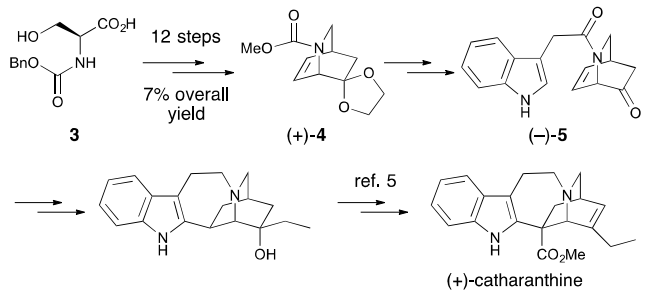
Scheme 1 Total synthesis of (±)-reserpine[2] and (±)-deserpidine.[3]

the formal total synthesis of (±)-deserpidine from (±)-Diels–Alder adduct **2** of *N*-(2,2,2-trichloroethoxycarbonyl)-1,2-dihydropyridine with α-acetoxyacrylonitrile. However, these Diels–Alder reactions were very slow and the *endo*-selectivity was low (Scheme 1).[3]

In 2006, Doris *et al.* reported the formal synthesis of (+)-catharanthine using optically active isoquinuclidine **4** as a key intermediate, which was derived from *N*-benzyloxycarbonyl-L-serine (**3**) in 7% overall yield over 12 steps (Scheme 2).[4,5]

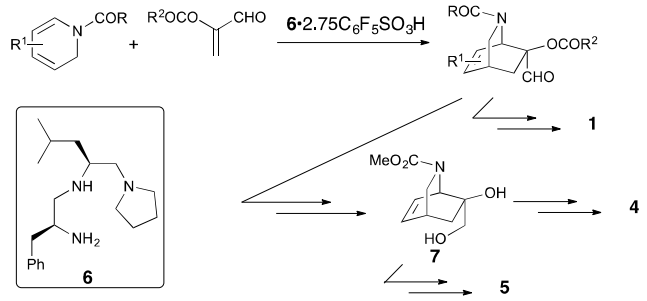
In 2002, Rawal *et al.* reported the first catalytic enantioselective Diels–Alder reaction of 1,2-dihydropyridine with *N*-acryloyloxazolidinone.[6a] Since then, Nakano *et al.* have intensively studied on the development of an asymmetric catalysis.[6b–k] In 2005, Fukuyama *et al.* reported that MacMillan's catalyst[7] was also effective for the enantioselective Diels–Alder reaction of *N*-benzyloxycarbonyl-1,2-dihrdropyridine with acrolein to give

optically active isoquinuclidine, and achieved the total synthesis of (–)-oseltamivir phosphate from the isoquinoline.[8]



Scheme 2 Doris's Formal Total Synthesis of (+)-Catharanthine.[4]

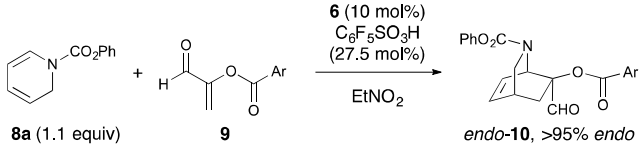
Against this backgroud, we expected that we could prepare optically active synthons **1**, **2** and **4** through the enantioselective Diels–Alder reaction of 1,2-dihydropyridines with α-acyloxyacroleins as a key step. However, there have been no reports on the highly enantioselective Diels–Alder reaction of dihydropyridines with α-substituted acryloyl derivatives.[9] Along these lines, we have developed the enantioselective Diels–Alder reaction of simple dienes with α-heterosubstituted acroleins catalyzed by chiral primary ammonium salts.[10] In this report we describe the enantioselective Diels–Alder reaction of 1,2-dihydropyridines with α-acyloxyacroleins catalyzed by **6**•2.75$C_6F_5SO_3H$, and derivatization of Diels–Alder adducts to *endo*-**1**, **7**, **4**, and **5** (Scheme 3).



Scheme 3 This work.

First, the Diels–Alder reaction of *N*-phenoxycarbonyl-1,2-dihydropyridine (**8a**, 0.11 mmol) with α-(benzoyloxy)acrolein (**9a**, 0.1 mmol) was examined in the presence of 10 mol% of **6**•2.75$C_6F_5SO_3H$ in nitroethane. The reaction temperature was gradually increased from –78 °C to 0 °C, and the reaction mixture was further stirred at 0 °C for 3 days. The desired isoquinuclidine **10aa** was obtained in 58% yield with >95% *endo*-selectivity. The enantioselectivity of *endo*-**10aa** was 88% ee (entry 1). Since a hydrogen-bonding interaction between an α-acyl moiety of **9** and an ammonium proton of the catalyst was expected, α-(*p*-methoxybenzoyloxy)acrolein (**9b**) was examined as a dienophile under the same conditions. Interestingly, **9b** was much more reactive than **9a**. *Endo*-**10ab** was obtained in 88% yield with 91% ee (entry 2). When the reaction was started at 0 °C, the enantioselectivity was reduced to 69% ee (entry 3). Actually, the reaction proceeded slowly even at –20 °C, and the enantioselectivity was 95% ee (entry 4). The reaction of **8a** with **9b** was scalable, and could be increased up to 2.4 mmol scale without reducing chemical yield and enantioselectivity of **10ab** (entry 5).

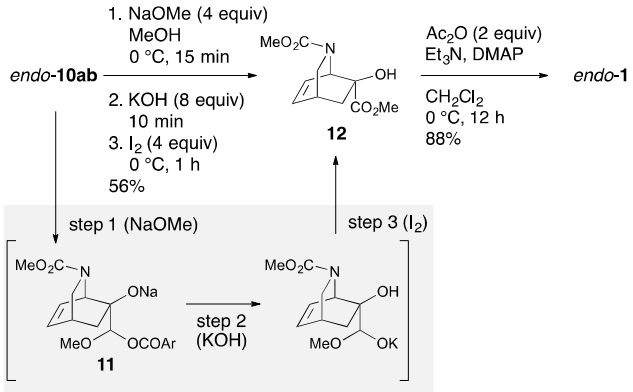
Table 1 Enantioselective Diels–Alder Reaction of **8a** with **9**[a]



entry	**9** (Ar)	conditions	**10** yield (%)	**10** ee (%)[b]
1[c]	**9a** (Ph)	–78 °C, 5 min to 0 °C, 3 days	**10aa**, 58	88
2[c]	**9b** (C_6H_4(OMe)-*p*)	–78 °C, 5 min to 0 °C, 1.5 days	**10ab**, 88	91
3[c]	**9b**	0 °C, 12 h	**10ab**, 88	69
4[d]	**9b**	–78 °C, 5 min to –20 °C, 4 days	**10ab**, 61	95
5[e]	**9b**	–20 °C, 5 min to 0 °C, 2.5 days	**10ab**, 81	92

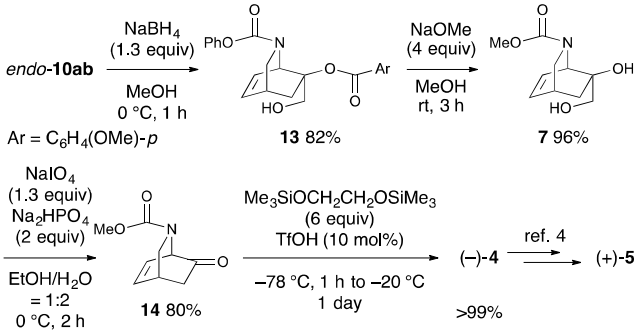
[a] See the experimental section in detail. [b] Ee of *endo*-**10**. [c] 0.1 mmol scale of **9** (0.8 *M*) in $EtNO_2$. [d] 0.1 mmol scale of **9b** (0.4 *M*) in $EtNO_2$. 1.5 equiv of **8a** was used. [e] 2.4 mmol scale of **9b** (0.8 *M*) in $EtNO_2$.

Endo-**10ab** was transformed to **12** in 56% yield under basic oxidation conditions (Scheme 4). This is a one-pot 3-step sequence of the three different functional groups.[11] Deprotection of the *p*-methoxybenzoyl group of **10ab** was promoted by the adjacent oxyanion (Step 1).[12] The generation of **11** was detected by ^{1}H NMR analysis. The subsequent acetylation of **12** gave *endo*-**1** in 88% yield.



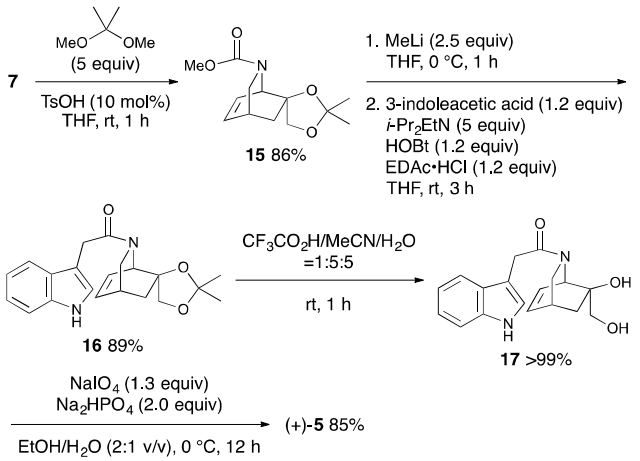
Scheme 4 Derivatization of *endo*-**10ab** to *endo*-**1**.

Endo-adduct **10ab** (91% ee) was converted to a key synthetic intermediate **4** of (+)-catharanthine in good yield by selective reduction of the formyl group of **10ab**, selective methanolysis of the ester moiety of **13**, oxidative cleavage of the vicinal diol moiety of **7**, and acetalization of **14** (Scheme 5).[13] The absolute configuration of **4** was determined to be (–)-(1*R*,4*R*) by comparison of its optical rotation (91% ee, $[\alpha]_D^{26}$ = –65 (*c* = 0.4, MeOH).[4] Spiroacetal **4** can be transformed to 2-(2-(1*H*-indol-3-yl)acetyl)-2-azabicyclo[2.2.2]oct-7-en-6-one (**5**) by Doris's synthetic method (Scheme 2).[4] Thus, (+)-(1*R*,4*R*)-**5** can be synthesized from **7** in 49% yield over 5 steps.



Scheme 5 Derivatization of *Endo*-**10ab** to (–)-**4**.

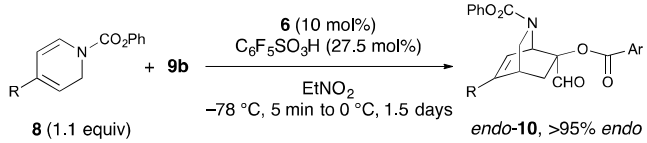
As a new and more concise synthetic route to (+)-(1*R*,4*R*)-**5**, we developed a 4-step sequence from diol **7** which included the acetalization of **7**, the *N*-deprotection/acylation of **15**, the hydrolysis of **16**, and the oxidative cleavage of **17** (Scheme 6). The overall yield of (+)-**5** (91% ee, $[\alpha]_D^{24}$ = +88 (*c* = 1.2, $CHCl_3$) from **7** was 65%.[4]



Scheme 6 Derivatization of **7** to (+)-**5**.

The substrate scope of the Diels–Alder reaction of 4-substituted *N*-phenoxycarbonyl-1,2-dihydropyridines (**8b–e**) with **9b** was investigated under the optimized conditions (entry 2 in Table 1). The results are shown in Table 2. The reactions proceeded smoothly at –20 ~ 0 °C to give desired *endo*-adducts **10** in good to high yield with high enantioselectivity.

Table 2 Enantioselective Diels–Alder reaction of **8** with **9b**[a]



entry	**8** (R)	**10**	
		yield (%)	ee (%)
1[b]	**8b** (Me)	**10bb**, 95	88
2	**8c** (*i*-Pr)	**10cb**, 86	80
3	**8d** ($OCOC_6H_4(OMe)$-*p*)	**10db**, 84	90
4[c]	**8d**	**10db**, 81	95
5[c]	**8e** (CH_2OSi*t*-$BuMe_2$)	**10eb**, 82	93

[a] See the experimental section in detail. [b] 2.2 equiv of **8** was used. [c] The reaction was carried out at –20 °C for 3 days.

To understand the reaction mechanism, the optimized geometry of iminium salt **18** prepared from **6**•3$C_6F_5SO_3H$ and **9a** was calculated using B3LYP/6-31G(d).[14,15] However, no reasonable geometries that could explain the enantioface selectivity were obtained. When a key intermediate was postulated to be an aqua complex **18**•H_2O, the desired optimized geometry was obtained as shown in Fig. 1. One water molecule stabilizes the (*Z*)-iminium geometry through three hydrogen bonds. In this geometry, the *re*-face of the dienophile is effectively shielded by the benzyl moiety of **6**•3$C_6F_5SO_3H$. Thus, 1,2-dihydropyridine can approach the *si*-face of the dienophile to give (1*R*,4*R*)-adduct enantioselectively. While this mechanism is plausible, it is not supported by any experimental evidence. Nevertheless, some water molecules may contribute to the construction of key intermediates or transition-state assemblies. Further mechanistic studies are in progress and will be reported in the near future.

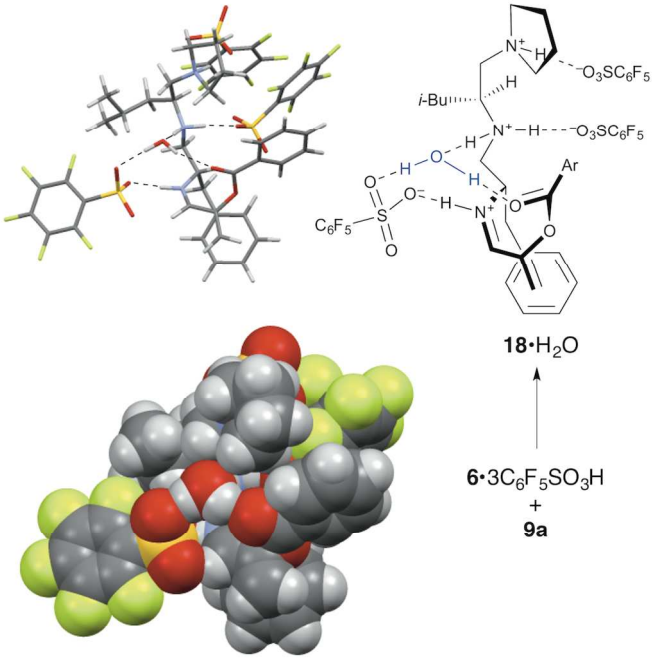


Fig. 1 Optimized geometry (B3LYP/6-31G(d)) of iminium salt **18**•H_2O prepared from **6**•3$C_6F_5SO_3H$ and **9a** *in situ*.

In summary, we have developed the first example of a catalytic and highly enantioselective Diels–Alder reaction of 1,2-dihydropyridines with α-acyloxyacroleins catalyzed by **6**•2.75$C_6F_5SO_3H$, and their derivatization to some key synthetic intermediates of biologically active compounds. Furthermore, a plausible mechanism via an aqua complex such as **18**•H_2O can explain all previous results with the use of **6**•$C_6F_5SO_3H$.[10]

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/c000000x/

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Graphical abstract

The enantioselective Diels–Alder reaction of 1,2-dihydropyridines with α-acyloxyacroleins catalyzed by chiral primary ammonium salt has been developed.