Asymmetric Catalysis

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Enantioselective Organocatalytic Construction of Spiroindane Derivatives by Intramolecular Friedel–Crafts-Type 1,4-Addition

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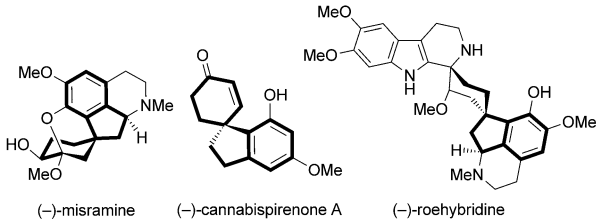
Abstract: *The highly enantioselective organocatalytic construction of spiroindanes containing an all-carbon quaternary stereocenter by intramolecular Friedel–Crafts-type 1,4-addition is described. The reaction was catalyzed by a cinchonidine-based primary amine and accelerated by water and p-bromophenol. A variety of spiro compounds containing quaternary stereocenters were obtained with excellent enantioselectivity (up to 95 % ee). The reaction was applied to the asymmetric formal synthesis of the spirocyclic natural products (−)-cannabispirenones A and B.*

The development of methods for the construction of spiro rings is important for the synthesis of bioactive natural products and medicines. Such ring systems, which are connected through one atom, are a unique kind of structure in organic compounds. Therefore, methods for spiro-ring formation have attracted intense interest. The most common method for constructing tetrasubstituted carbon centers in spiro compounds is ketal formation, which is often used in the total synthesis of natural products.[1] The dearomatization of phenol derivatives with a hypervalent iodine compound, followed by nucleophilic attack by an alcohol, carboxylic acid, or amide, has also been reported.[2] High enantioselectivity was possible in these reactions with chiral phosphoric acid,[3] thiourea,[4] and hypervalent iodine[5] organocatalysts. There have been many studies of the asymmetric organocatalytic construction of all-carbon quaternary stereocenters. However, there are fewer reports of organocatalytic reactions for the formation of spiro rings containing all-carbon quaternary centers than for spiro rings containing heteroatoms. To address this problem, a number of methods have been developed on the basis of the semipinacol rearrangement,[6] Diels–Alder reaction, and 1,4-addition followed by condensation in the presence of various organocatalysts.[7] The enantioselective construction of tertiary and tetrasubstituted carbon centers has been achieved by asymmetric Friedel–Crafts-type 1,4-addition.[8] In these reactions, electron-rich compounds, such as indoles,[9] pyrroles,[10] and phenol derivatives,[11] are often used as substrates. However, there are few examples of the highly enantioselective (> 90 % *ee*) organocatalytic construction of quaternary centers by Friedel–Crafts-type 1,4-addition. Akiyama and co-workers reported a highly enantioselective method for the synthesis of indole derivatives with a chiral phosphoric acid catalyst.[12] However, to the best of our knowledge, no such method for the synthesis of spiroindane compounds has yet been reported. A number of natural products, such as (−)-misramine,[13] (−)-cannabispirenone A,[14] and (−)-roehybridine,[15] contain the spiroindane skeleton (Scheme 1), and the structure has also been used in medicinal chemistry. Therefore, an effective asymmetric method for constructing spiroindane compounds is needed. We report herein the first enantioselective organocatalytic construction of spiroindane compounds containing a quaternary stereocenter by intramolecular Friedel–Crafts-type 1,4-addition. We have applied the reaction to the formal synthesis of (−)-cannabispirenones A and B.



Scheme 1. Natural products containing the chiral spiroindane skeleton.

Initially, we chose compound **1a** as a standard substrate (Table 1).[16] Catalyst screening began with chiral Brønsted acid catalysts. Treatment of **1a** with the chiral phosphoric acid **3**[17] (20 mol %) at room temperature did not lead to the formation of spiro product **2a** (Table 1, entry 1). The chiral sulfonic acid catalyst **4**[18] gave only a small amount of **2a**, and no enantioselectivity was observed (Table 1, entry 2). L-Proline (**5**) did not catalyze the reaction (entry 3). Eventually, we found that chiral primary amine catalysts **6**–**9** derived from various cinchona alkaloids were effective. These amines are superior catalysts for a variety of asymmetric reactions and undergo imine–enamine formation with ketones or aldehydes.[19] With *epi*-cinchonidine amine **6** (20 mol %) and trifluoroacetic acid (TFA; 40 mol %) as a cocatalyst to promote the formation of the iminium ion, compound **2a** was obtained in 60 % yield with moderate enantioselectivity (60 % *ee*; Table 1, entry 4). The use of catalysts **7**–**9** under the same conditions led to lower yields and enantioselectivity (entries 5–7). Next, we investigated the optimal amount of the TFA cocatalyst for this reaction. An increase in the amount of TFA from 40 to 200 mol % led to an increase in the yield to 75 %; however, the product was formed with only 7 % *ee* (Table 1, entry 8). This result suggests that excess strong acid

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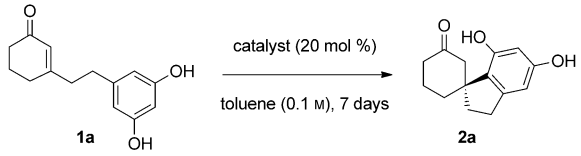
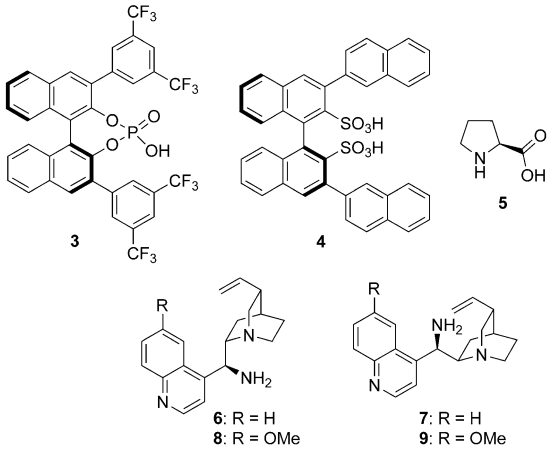
Table 1: Catalyst screening for the Friedel–Crafts-type 1,4-addition.



Entry	Catalyst	*T* [°C]	Yield [%][a]	*ee* of **2a** [%][b]
1[c]	**3**	RT	no reaction	–
2[c]	**4**	RT	15	0
3	**5**	65	no reaction	–
4	**6** + TFA (40 mol %)	65	60	60
5	**7** + TFA (40 mol %)	65	34	−51
6	**8** + TFA (40 mol %)	65	40	51
7	**9** + TFA (40 mol %)	65	18	−26
8	**6** + TFA (200 mol %)	65	75	7
9	**6**	65	36	90
10[d]	**6**	65	47	94

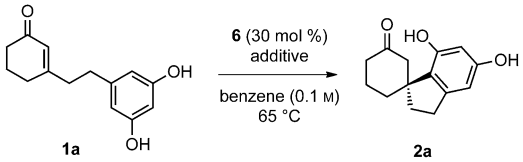
[a] Yield of the isolated product. [b] The *ee* value was determined by HPLC analysis on a chiral stationary phase. [c] CH_2Cl_2 was used as the solvent. [d] Benzene was used as the solvent.



promoted a non-amine-catalyzed cyclization reaction. Finally, we found that the desired reaction proceeded without an acid cocatalyst to afford **2a** with excellent enantioselectivity (90% *ee*), thus indicating that the phenolic hydroxy groups in the substrate serve as a proton source for activating the imine (Table 1, entry 9). When benzene was used as the solvent, the yield was improved, as was the enantioselectivity (94% *ee*; entry 10). We selected benzene as the optimal solvent.

Although we had identified conditions for high enantioselectivity, the moderate yield (47%) and long reaction time (7 days) were still problematic. We examined a variety of additives to tackle these problems (Table 2). The addition of activated 3 or 4 Å molecular sieves as water scavengers resulted in low yields (Table 2, entries 2 and 3). A base was also ineffective (entry 4). However, the addition of water (1 equiv) accelerated the reaction, and product **2a** was obtained in 63% yield with 94% *ee* (entry 5). By extending the reaction time to 14 days, the yield was improved to 73% (entry 6). We expected that the addition of a weak acid, such as silica gel, would decrease the reaction time. Under these conditions, product **2a** was obtained in good yield (82%); however, the enantioselectivity was decreased (Table 2, entry 7). Considering that the phenolic hydroxy groups in **1a** may protonate the imine, we expected that phenol derivatives would serve as effective additives. The addition of *p*- or *m*-nitrophenol (1 equiv) decreased the reaction time to 5 days, and **2a** was obtained in good yield with good enantioselectivity (Table 2, entries 8 and 9). We found that the combination of H_2O (1 equiv) and *p*-bromophenol (1 equiv) gave **2a** in excellent yield without a decrease in the *ee* value (Table 2, entry 10). In the absence of H_2O, a lower yield was observed (entry 11). When catalyst **7**, pseudoenantiomer of **6**, was examined under the same conditions, the enantiomer of **2a** was obtained with 90% *ee* (Table 2, entry 12). We determined the absolute configuration of the spiro carbon atom in **2a** as *R* by comparing the optical rotation after converting **2a** into a known compound, whose absolute configuration had been determined.[20]

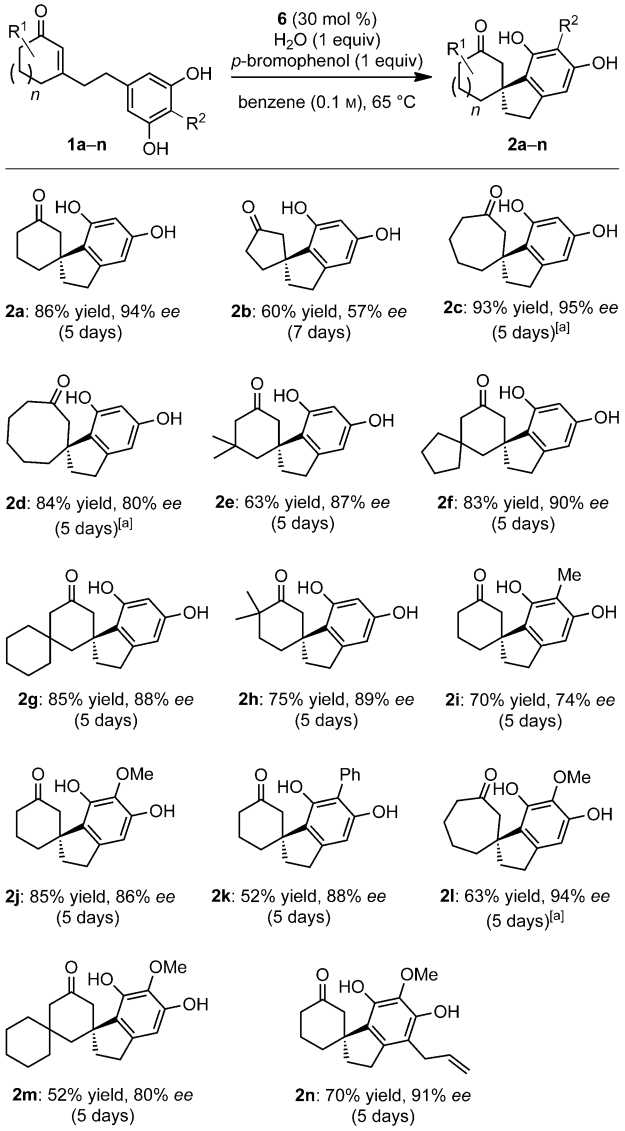
Table 2: Additive screening for the Friedel–Crafts-type 1,4-addition.



Entry	Additive	*t* [days]	Yield [%][a]	*ee* of **2a** [%][b]
1	none	7	47	94
2	MS3A	7	23	94
3	MS4A	7	25	94
4	Cs_2CO_3	7	40	84
5	H_2O	7	63	94
6	H_2O	14	73	94
7	silica gel	7	82	69
8	*p*-nitrophenol + H_2O	5	83	83
9	*m*-nitrophenol + H_2O	5	63	90
10	*p*-bromophenol + H_2O	5	86	94
11	*p*-bromophenol	5	67	94
12[c]	*p*-bromophenol + H_2O	5	86	−90

[a] Yield of the isolated product. [b] The *ee* value was determined by HPLC analysis on a chiral stationary phase. [c] Amine **7** was used as the catalyst.

To expand the scope of this reaction, we explored the use of various substrates (Scheme 2).[16] Compounds with different sized enone rings were treated under the optimized conditions to afford spiro compounds (products **2a–d**). Compounds **2a** and **2c** were obtained in high yields with high enantioselectivity. Products **2e** and **2h** bearing a dimethyl group at the 5- or 6-position of the cyclohexanone ring were obtained in moderate yields with good enantioselectivity. For the formation of **2f** and **2g**, which contain another spiro ring at the 5-position of the cyclohexanone ring, good yields and high enantioselectivity were also observed. Various substituents (Me, Ph, OMe) at the 4-position of the aromatic ring were examined (products **2i–m**). Although **2i** was formed with slightly decreased enantioselectivity, **2j–m** had high *ee* values. Furthermore, this catalytic system was effective for a bulky substrate bearing a pentasubstituted benzene ring (product **2n**). These results demonstrate that this reaction can

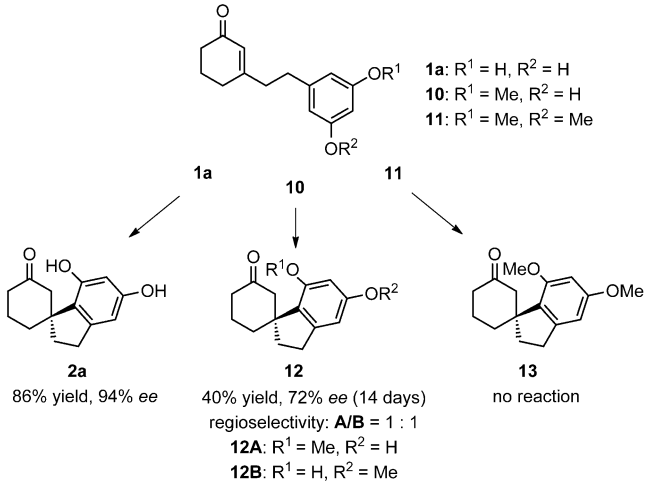


Scheme 2. Scope of the Friedel–Crafts-type 1,4-addition. [a] The reaction was carried out at 55 °C.

be used to form a variety of spiro compounds containing all-carbon quaternary stereocenters.

To investigate the role of the two phenolic hydroxy groups, we conducted control experiments with substrates **10** and **11**, in which one or both of the phenolic hydroxy groups were masked as methyl ethers (Scheme 3). The reaction of compound **10** bearing only one phenolic hydroxy group afforded a 1:1 mixture of regioisomers **12** in low yield, even though the reaction mixture was stirred for 14 days. Furthermore, the enantioselectivity was lower than for the reaction of **1a**. The reaction of dimethyl ether **11** gave no spiro product **13**. These results demonstrate that the two phenolic hydroxy groups in the substrate are crucial for both reactivity and enantioselectivity.

Based on these results, a possible reaction mechanism for the catalytic spirocyclization with amino catalyst **6** is shown in Scheme 4. First, imine **A** is formed from **1a** and **6**. After the imine is formed, the tertiary amine of **6** deprotonates the

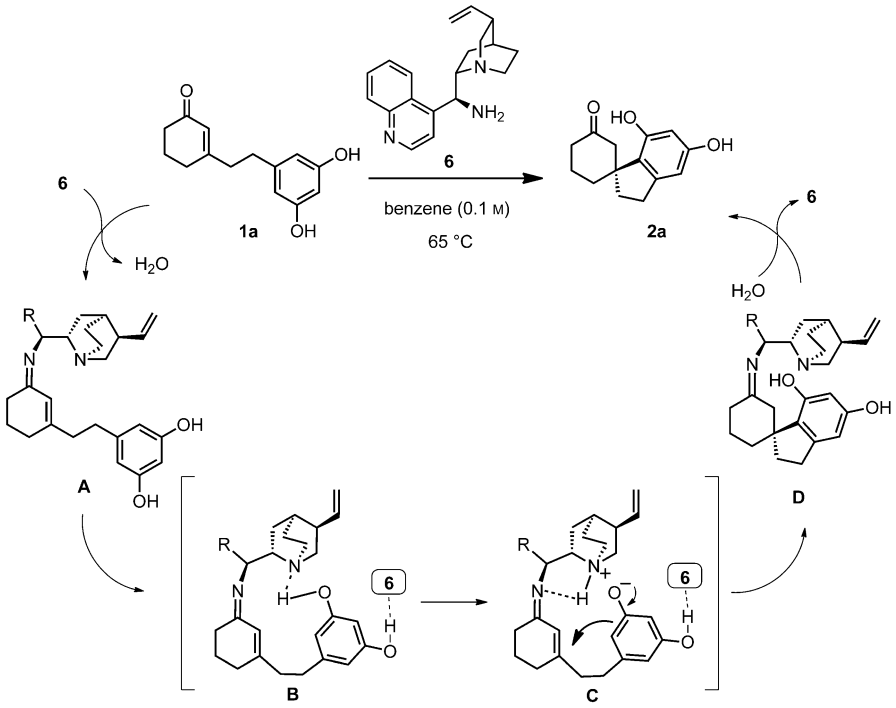


Scheme 3. Investigation of the role of phenolic hydroxy groups.

phenolic hydroxy group, and the imine is activated by protonation (**B**→**C**). The results in Scheme 3 and entry 4 of Table 2 suggest that another catalyst may deprotonate the other phenolic hydroxy group to increase the reactivity and form an advanced asymmetric reaction site. Intramolecular 1,4-addition of **C** proceeds to produce spiro compound **D**. Finally, hydrolysis of **D** gives product **2a**, and amino catalyst **6** is regenerated to complete the catalytic cycle. We expect that *p*-bromophenol participates in the hydrolysis process.

We demonstrated the utility of the Friedel–Crafts-type 1,4-addition by using the reaction in an asymmetric formal synthesis of (−)-cannabispirenones A and B (**18** and **19**; Scheme 5). Compounds **18** and **19** are spirocyclic natural products isolated from cannabis, and the two enantiomers occur in different plants.[14] Although racemic and asymmetric synthetic studies of cannabispirenones have been reported,[21] these compounds have not been synthesized with high enantiomeric purity (>90% *ee*). The synthesis began with the Friedel–Crafts-type 1,4-addition of **1a**. After recrystallization, product **2a** was obtained in almost enantiomerically pure form (99% *ee*). Methyl etherification of **2a** afforded dimethyl ether **13**, which was converted into α-hydroxyketone **14** by the Rubottom oxidation via a silyl enol ether. Other regio- and diastereoisomers were not detected. Protection of the hydroxy group in **14** as a TBS ether, followed by treatment with LHMDS and Tf_2NPh, furnished enol triflate **15**. Under palladium catalysis, **15** was reduced to **16**. Deprotection of **16** and subsequent oxidation of the resulting allylic alcohol finally provided (−)-*O*-methylcannabispirenone (**17**), the spectroscopic data of which were identical to those reported previously.[21a] The optical rotation ($[\alpha]_D = -175$) indicated the extremely high optical purity of synthetic **17** (Ref. [21e]: synthetic *ent*-**17** (84% *ee*): $[\alpha]_D = +142$). Transformations of **17** into cannabispirenones A (**18**) and B (**19**) have already been reported;[21a,b] thus, an asymmetric formal synthesis of these natural products was achieved.

In conclusion, we have developed a highly enantioselective organocatalytic method for constructing spiroindanes containing an all-carbon quaternary stereocenter. Asymmet-



Scheme 4. Proposed mechanism for the construction of spiroindanes by Friedel–Crafts-type 1,4-addition.

ric spiroindane formation by intramolecular Friedel–Crafts-type 1,4-addition under organocatalytic conditions has not been reported previously. The key feature of this reaction is its acceleration by additives (H_2O and *p*-bromophenol) and the two phenolic hydroxy groups on the substrate. Furthermore, we applied this reaction to the formal synthesis of (−)-cannabispirenones A and B. Our research group is currently working on the application of this reaction to the asymmetric total synthesis of other natural products with a spiroindane skeleton.

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Keywords: asymmetric catalysis · cyclization · natural products · organocatalysis · spiro compounds

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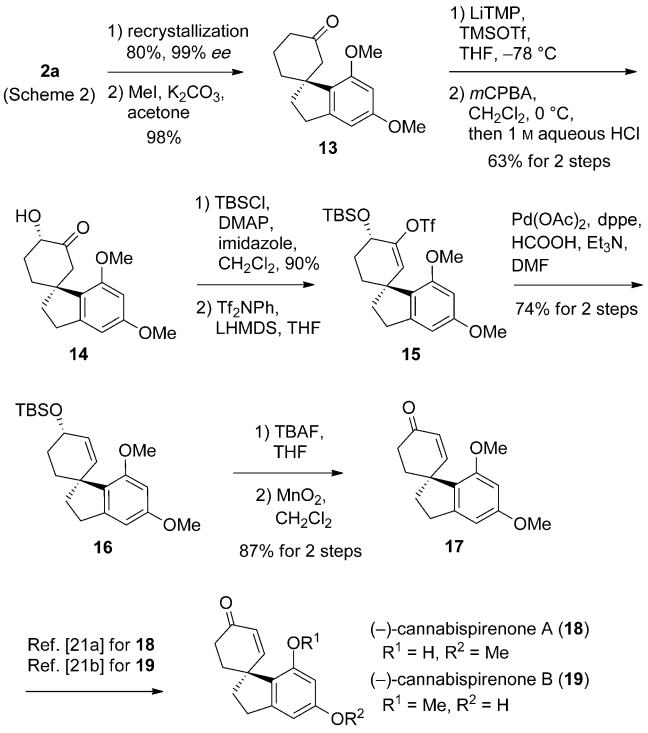

Scheme 5. Formal synthesis of (−)-cannabispirenones A and B. LiTMP = lithium 2,2,6,6-tetramethylpiperidide, TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl, *m*CPBA = *m*-chloroperoxybenzoic acid, TBS = *tert*-butyldimethylsilyl, DMAP = 4-(dimethylamino)pyridine, LHMDS = lithium bis(trimethylsilyl)amide, dppe = 1,2-bis(diphenylphosphino)ethane, DMF = *N*,*N*-dimethylformamide, TBAF = tetra-*n*-butylammonium fluoride.

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