Organocatalysis

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Organocatalytic Activation of the Leaving Group in the Intramolecular Asymmetric S_N2' Reaction**

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Abstract: *A Brønsted-acid-catalyzed intramolecular enantioselective S_N2' reaction was developed utilizing trichloroacetimidate as a leaving group. The findings indicated that dual activation of the substrates is operative. This metal-free allylic alkylation allows highly enantioselective access to 2-vinylpyrrolidines bearing various substituents.*

Nucleophilic allylic substitution is a fundamental and important reaction in organic synthesis.[1] Several catalytic enantioselective allylic substitutions have been developed. One major strategy is the activation of a nucleophile by a base (Figure 1 a). In this type of reaction, the enantiotopic face of the nucleophile, such as enol(ate)s, is discriminated by a chiral catalyst. Consequently, the stereogenic center of the products arises at the nucleophilic carbon atom of the nucleophiles.[2] An alternative major strategy is transition metal catalysis (Figure 1 b). For example, in the Tsuji–Trost reaction, an allylic substrate is activated by a chiral palladium(0) catalyst to give a chiral π-allyl palladium complex, which is attacked by a nucleophile.[3] Because the reaction is initiated by nucleophilic attack of a palladium(0) species with expulsion of the leaving group from the substrate, this type of allylic substitution can be regarded as nucleophilic catalysis.

Allylic substitution is also an important process in biological systems.[4,5] These processes are catalyzed by enzymes with simultaneous activation of a nucleophile and an electrophile.[6] On the other hand, it is well known that a chiral phosphoric acid realizes acid–base dual activation through H-bonds.[7] We also reported the kinetic resolution of chiral secondary alcohols by a chiral phosphoric acid-catalyzed acylation with acid anhydride.[8] In that reaction, the acid anhydride and the alcohols are likely activated through H-bonds with the P–OH and the P=O moieties of the catalyst, respectively. We envisioned that the chiral phosphoric acid could activate a leaving group as well as a nucleophile, which would accelerate the allylic substitution like the enzymatic S_N2' process (Figure 1 c). To the best of our knowledge, catalytic activation of a leaving group in a catalytic asymmetric S_N2' reaction has rarely been reported.[9–12] Herein, we describe the enantioselective intramolecular S_N2' reaction catalyzed by a chiral phosphoric acid providing chiral pyrrolidines.

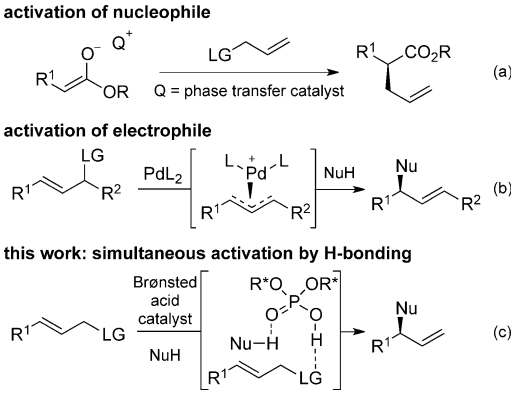
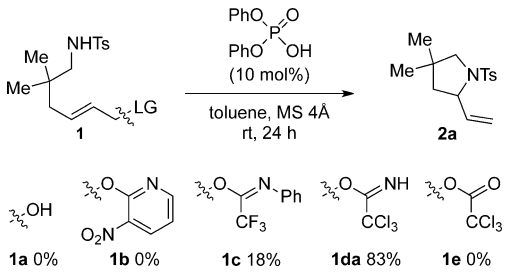


Figure 1. Strategies for an asymmetric S_N2' reaction.

Because the selection of a leaving group is a key for achieving the reaction with high enantioselectivity, we first searched for functional groups that could act as a leaving group in the presence of a Brønsted acid (Scheme 1). Free alcohol **1a** was treated with a catalytic amount of diphenyl phosphate in toluene at room temperature in the presence of powdered molecular sieves but was unreactive. Next, a 3-nitro-2-pyridyl group was tested,[13] but **1b** was also left unchanged. When *N*-phenyltrifluoroacetimidate **1c** was used,[14] however, a small amount of the desired pyrrolidine **2a** was observed. To our delight, when trichloroacetimidate



Scheme 1. Screening of leaving groups. The reactions were performed with **1** (0.1 mmol), $(PhO)_2PO_2H$ (0.01 mmol), and MS 4 Å (50 mg) in toluene (0.4 mL). Yields of isolated compound **2a** are shown.

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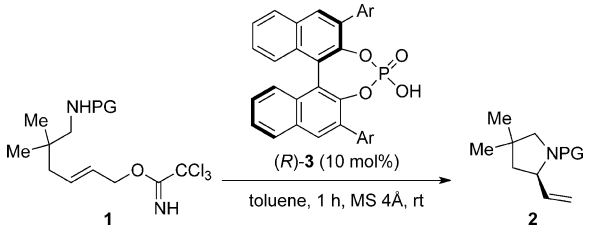
1da was used,[15] the substitution occurred efficiently with marked improvement in the yield of **2a**. Trichloroacetate **1e**, an oxygen analogue of **1da**, was totally unreactive. This result indicates that protonation at the basic imino group was operative in the reaction of **1da**.

With the appropriate leaving group in hand, we screened chiral phosphoric acids[16] in toluene at room temperature in the presence of powdered molecular sieves.[17] Using catalyst **3a** substituted with 9-anthracenyl provided us with a promising start point (Table 1, entries 1–3). Subsequently, we turned our attention to the substituent of the nitrogen nucleophile. We reasoned that a substrate with a more acidic NH group could interact more tightly with the Brønsted-basic phosphoryl oxygen of **3** to enhance the enantioselectivity of the reaction. Consistent with this expectation, changing the substituent of the amino group to a 4-nitrobenzensulfonyl (4-Ns) group remarkably increased the enantioselectivity (entry 4). The position of the nitro substituent was important, as the enantioselectivity was increased when 2-nitrosulfonyl amino substrate **1dc** was used (entry 5). Further improvement was realized with 2,4-dinitrobenzensulfonyl (DNs)[18] amino substrate **1dd**, which provided pyrrolidine **2d** in 69% yield and 86% *ee* (entry 6).

With the best substituent of the amino group, the catalyst was further optimized by extending the 3,3′-substituents of the BINOL backbone. We postulated that addition of a bulky substituent at the 10-position of the anthracene moiety could enhance the discrimination between the enantiotopic faces of the C=C bond far away from the chiral scaffold. As expected, catalyst **3d**, bearing 10-phenylanthracene,[19] remarkably enhanced the enantioselectivity, furnishing **2d** in 86% yield and 91% *ee* (entry 7). Further investigation revealed that catalyst **3e**, bearing 10-mesitylanthracene, was the optimal catalyst, giving the desired product in 93% yield and 96% *ee* (entry 8). Finally, the use of fluorobenzene as solvent at 0°C enabled us to reduce the catalyst loading to 5 mol% with the same level of catalyst activity (entry 9).[20]

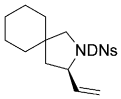
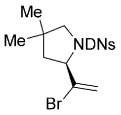
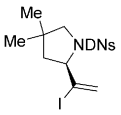
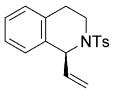
Table 1: Optimization of the phosphoric-acid-catalyzed S_N2' reaction of sulfonamide **1**.[a]



Entry	PG	1	Ar	Solvent	2	Yield [%][b]	*ee* [%][c]
1	Ts	**1da**	9-anthracenyl (**3a**)	toluene	**2a**	55	51
2	Ts	**1da**	2,4,6-$(i\text{Pr})_3C_6H_2$ (**3b**)	toluene	**2a**	39	43
3	Ts	**1da**	3,5-$(CF_3)_2C_6H_3$ (**3c**)	toluene	**2a**	96	30
4	4-Ns	**1db**	9-anthracenyl (**3a**)	toluene	**2b**	57	62
5	2-Ns	**1dc**	9-anthracenyl (**3a**)	toluene	**2c**	61	75
6	DNs	**1dd**	9-anthracenyl (**3a**)	toluene	**2d**	69	86
7	DNs	**1dd**	10-phenylanthracen-9-yl (**3d**)	toluene	**2d**	86	91
8	DNs	**1dd**	10-mesitylanthracen-9-yl (**3e**)	toluene	**2d**	93	96
9[d]	DNs	**1dd**	10-mesitylanthracen-9-yl (**3e**)	fluorobenzene	**2d**	93	97

[a] Unless otherwise noted, reactions were performed with sulfonamide **1** (0.1 mmol), catalyst (*R*)-**3** (0.01 mmol) and 4 A molecular sieves (50 mg) in toluene (0.4 mL). [b] Isolated yields. [c] Determined by HPLC on a chiral stationary phase. [d] 5 mol% catalyst at 0°C. PG = protecting group, Ts = *p*-toluenesulfonyl, 4-Ns = 4-nitrobenzenesulfonyl, 2-Ns = 2-nitrobenzenesulfonyl, DNs = 2,4-dinitrobenzenesulfonyl.

Table 2: Substrate scope.[a]

Entry	Product		*t* [h]	Yield [%][b]	*ee* [%][c]
1	(*R*)-**2e**		1	92	96
2[d]	**2f**		1	89	94
3	**2g**		1	94	96
4[d,e]	**2h**		4	93	96
5[d,e]	**2i**		4	92	96
6	**2j**		48	0	–
7[d,f]	**2k**		48	89	6

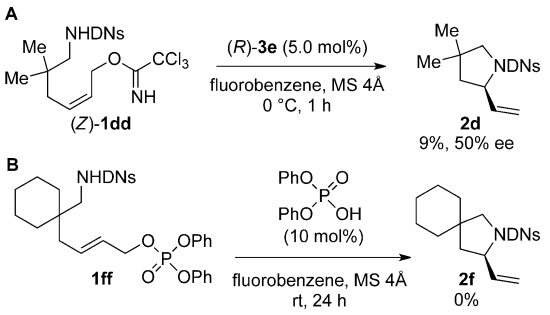
[a] Reactions were performed with sulfonamide (0.1 mmol), (*R*)-**3e** (0.005 mmol), and 4 Å molecular sieves (50 mg) in fluorobenzene (0.4 mL). [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. [d] 7.5 mol% catalyst loading. [e] At 50°C. [f] At room temperature.

The scope of the reaction was then explored (Table 2). The reaction giving (*R*)-**2e** demonstrated that geminal disubstitution is not necessary to achieve high yield and enantioselectivity (entry 1). The reaction giving spiropyrrolidine **2f** also had excellent enantioselectivity, but required higher catalyst loading to achieve a satisfactory yield (entry 2). The reaction was also applied to substrates with trisubstituted alkenes. 2-Propylene-substituted pyrrolidine **2g** was obtained in 94% yield and 96% *ee* (entry 3). Halogen-substituted pyrrolidines such as **2h** and **2i** were produced with excellent enantiomeric excess, although these substrates required a higher temperature (50°C) to achieve complete conversion (entries 4 and 5). The reaction failed to produce piperidine **2j**, probably due to the slower rate of the 6-*exo* cyclization (entry 6).[21] The cyclization proceeded with the substrate bearing an arene tether to give tetrahydro-

isoquinoline **2k** in 89% yield, but with poor selectivity under the present conditions (entry 7).[22]

The absolute configuration of (*R*)-**2e** was determined by comparing the sign of the specific rotation with that of (*S*)-**2e** derived from L-prolinol. For all the other compounds, the absolute configuration was assigned by analogy.

To probe the reaction mechanism, the reaction was conducted using (*Z*)-**1dd**. Under the optimized conditions, only 9% of (*Z*)-**1dd** was converted to **2d** with 50% *ee*, and the rest was quantitatively recovered (Scheme 2A). The striking



Scheme 2. Exclusion of an S_N1 mechanism and nucleophilic catalysis.

difference in reactivity between *E*- and *Z*-isomers suggests that the catalyst should interact with both the leaving group and the sulfonamide moiety by H-bonding, and therefore, the relative position of these functionalities is likely important. This is consistent with the expected S_N2' mechanism rather than the alternative S_N1 pathway.

Phosphonate **1ff** was prepared and subjected to the reaction using diphenylphosphonate as a Brønsted-acidic catalyst (Scheme 2B). Although this catalyst converted imidate **1da** into **2a** (Scheme 1), no reaction occurred with phosphonate **1ff**, which was quantitatively recovered. This result clearly indicates that the developed asymmetric reaction is not a nucleophilic catalysis in which phosphonates are generated as intermediates from allylic imidates **1d** and phosphoric acids **3**.[9]

The geometries of the transition state (TS) model were calculated at the B3LYP/6-31G** level of theory (Figure 2). In the major TS (Figure 2A), the bond lengths of the forming C–N and the breaking C–O were 2.29 and 2.44 Å, respectively. The distances of >N···H···O–P and =N···H···O=P were 1.06 and 1.63, and 1.03 and 1.79 Å, respectively. These atomic distances indicate that this substitution synchronously proceeds with spontaneous activation of the leaving group and the sulfonamide by hydrogen bonding, as expected.

The free energy of the minor TS (Figure 2B) was higher by 1.7 kcal mol^{-1} than that of the major TS. The phenyl substituent of the catalyst was laid over the sulfonyl oxygen with a distance between the oxygen atom and the nearest carbon atom of 3.53 Å. The steric and electronic repulsion between these two electron-rich moieties could be the main factor to elevate the energy of the minor TS. This model accounts for the following results: The catalyst bearing more electron-rich 3,3′-substituents produced higher enantioselectivity (Table 1, entries 1–3). The 2-nitro group of the benze-

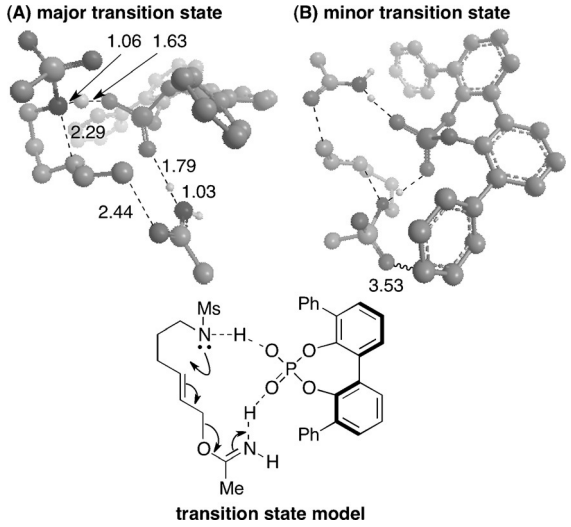


Figure 2. Chem3D perspective view of transition state models. The H atoms of C–H are omitted for clarity.

nesulfonamide moiety and the 10-substituent on the anthracenyl group increased enantioselectivity (Table 1, entries 4 versus 5 and 6 versus 8), probably as a result of the enhanced steric repulsion in the minor TS. The plausibility of the proposed TS is supported by the findings.

In summary, we demonstrated a novel mode of activation for a substitution reaction, wherein a leaving group was activated by a chiral Brønsted acid. The developed intramolecular S_N2' reaction provided a variety of pyrrolidines in good yields with excellent enantioselectivities. The control experiments ruled out the possibility that the nucleophilic catalysis was operative. The reaction tolerated halogen functionality, which is incompatible in a conventional method such as a transition-metal-catalyzed reaction. Further investigations into the mechanism and applications of this methodology are under way.

Keywords: asymmetric catalysis · nucleophilic substitution · organocatalysis · pyrrolidines

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[22] The *N*-Ts substrate was used because of the low solubility of the *N*-DNs substrate.

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