Organocatalysis Hot Paper

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Thiophosphoramide-Based Cooperative Catalysts for Brønsted Acid Promoted Ionic Diels–Alder Reactions**

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Over the past several decades, chemists have gathered significant evidence that enzymes could drastically accelerate nucleophilic addition reactions by establishing mutually reinforcing or cooperative hydrogen bonds within a receptor. These observations have inspired the development of various catalytic transformations in which substrate activation is achieved by the formation of multiple hydrogen bonds with a synthetic hydrogen-bond donor (HBD).[1]

The majority of such transformations rely on HBD activation of neutral substrates by enhancing their electrophilicity. Recent studies, however, demonstrate that various ionic reactions proceeding through polar intermediates could also be catalyzed by HBDs.[1b] In this case, HBD association with the counter anion of an in situ generated ion pair results in enhanced reactivity of the cation (Figure 1). Pioneered by

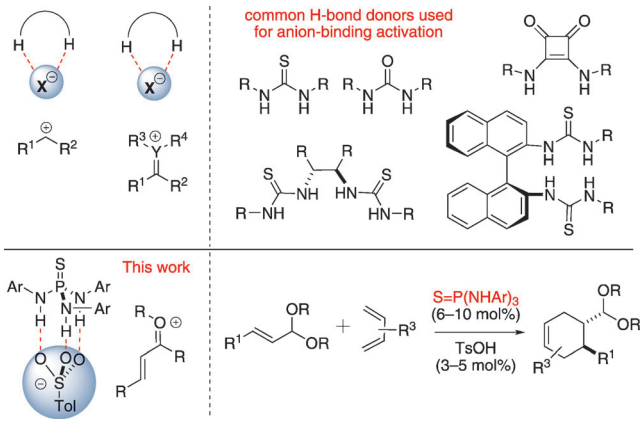

Figure 1. Hydrogen-bond donor/anion acceptor organocatalysis. Ts = 4-toluenesulfonyl.

the Jacobsen group,[2] counterion activation has been utilized to enhance the reactivity of various iminium ions as well as certain reactions proceeding through stabilized oxocarbenium- and carbenium-based ion pairs.[3]

Our group is interested in developing organocatalytic transformations involving unsaturated oxocarbenium ions.[4] Among the best known transformations of this type is the ionic [2+4] cycloaddition reaction (Gassman cycloaddition) exemplified by the transformation depicted in Figure 2.[5,6]

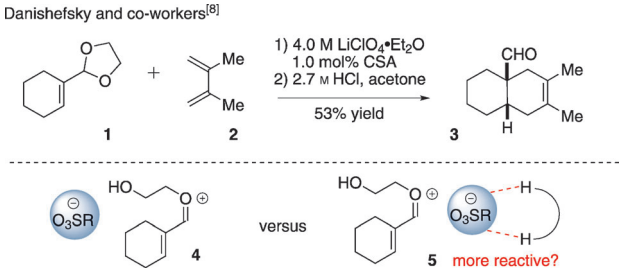

Figure 2. Proposed activation of oxocarbenium ions in ionic [2+4] cycloadditions. CSA = camphorsulfonic acid.

One of the most popular protocols for such cycloadditions has been developed by the Grieco group and relies on the use of a concentrated lithium(I) perchlorate solution (4.0 M in diethyl ether) and catalytic amounts of sulfonic acids.[7a] Remarkably, challenging cycloaddition reactions could be achieved under these reaction conditions. Thus, by employing the Grieco protocol, Danishefsky and co-workers accomplished the formation of the cycloadduct **3** (Figure 2),[8] which is notoriously difficult to obtain by Lewis-acid activation of the carbonyl-containing dienophiles equivalent to **1**. Both the presence of lithium(I) perchlorate and catalytic sulfonic acid are essential for the progression of this reaction, and no reaction occurs if one of these components is omitted. It has been proposed that a highly ionic medium is essential for the separation of the counterions and the generation of a more reactive separated ion pair (**4**).[7] At the same time, a highly polar medium is important for the tighter association of **4** and diene **2**, and results in a decreased transition-state volume.

Despite their synthetic utility, current ionic [2+4] cycloaddition protocols have significant limitations since the use of Lewis acids in combination with low reaction temperatures or explosive additives such as lithium(I) perchlorate are necessary. Herein we describe a mild organocatalytic protocol that is based on the cooperative catalysis of Brønsted acids and HBD co-catalysts.[9] Driven by the hypothesis that complexation to a hydrogen-bond donor could significantly enhance the reactivity of **4** by the formation of a more separated ion pair (**5**, Figure 2), we evaluated various HBDs and discovered that catalytic quantities of the thiophosphoramide **7e** (see Table 1) significantly accelerate the rates of ionic Diels–Alder

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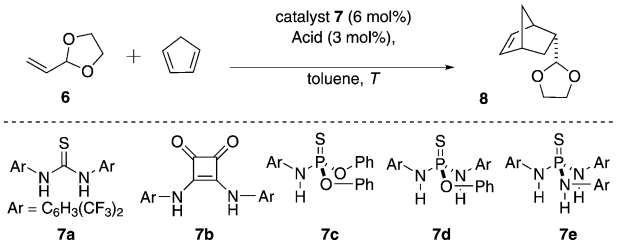
reactions catalyzed by the Brønsted acids. We are not aware of the prior use of three-hydrogen-bond donors such as **7e** for anion-binding activation, and demonstrate that **7e** is an excellent activator of sulfonate anions associated with vinyl oxocarbenium ions.

Our studies commenced with the evaluation of various HBD cocatalysts in the *p*-TSA-catalyzed reaction of commercially available acrolein acetal (**6**) and cyclopentadiene (Table 1) in toluene at −10 °C. When exposed to *p*-TSA (3 mol%) without a co-catalyst or in combination with the thiourea **7a** (6 mol%), no formation of the cycloadduct **8** was detected after one hour under the aforementioned reaction conditions (entries 1 and 2). The NH hydrogen atoms of the squaramide **7b** are further apart than those in **7a**, and consequently **7b** is better geometrically suited for binding the oxygen atoms of the sulfate anion.[10] Indeed, when used as a cocatalyst under identical reaction conditions, **7b** promoted the formation of **8** (entry 3), albeit in 15% conversion. In our search for alternative HBDs, we turned our attention to the thiophosphoramides **7c–e**.[11,12] We surmised that **7e** is geometrically more suited for binding a sulfate anion and could potentially form up to three hydrogen bonds with the negatively charged oxygen atoms of sulfate (see Figure 1 for an example of such complex).[13] Gratifyingly, when used as a cocatalyst, **7e** significantly accelerated the reaction of **6** and cyclopentadiene, and the quantitative formation of **8** was detected within one hour (entry 6). To test if all three NH bonds are essential for the anion activation, **7c** and **7d** were evaluated next (entries 4 and 5). Both catalysts were inferior to **7e** in promoting the formation of **8** and only minor amounts of the product were observed in each case. A control experiment in the absence of *p*-TSA was conducted (entry 7), and formation of the product was not detected.

Table 1: Evaluation of HBD-based cocatalysts of the ionic [2+4] cycloaddition.[a]



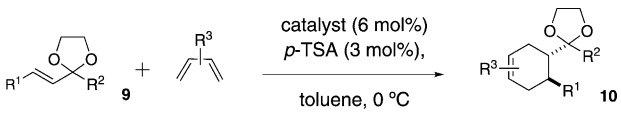
Entry	Acid	Catalyst	*t* [h]	*T* [°C]	*endo*/*exo*	Conv. [%][b]
1	*p*-TSA	none	1	−10	n.a.	0
2	*p*-TSA	**7a**	1	−10	n.a.	0
3	*p*-TSA	**7b**	1	−10	1.5:1	15
4	*p*-TSA	**7c**	1	−10	n.a.	2
5	*p*-TSA	**7d**	1	−10	2.5:1	7
6	*p*-TSA	**7e**	1	−10	3:1	98
7	none	**7e**	1	−10	n.a.	0
8	HCl	none	24	−10	n.a.	0
9	HCl	**7a**	24	−10	3:1	22
10	HCl	**7e**	24	−10	2.9:1	33
11	HBr	none	10	−10	n.a.	37
12	HBr	**7a**	10	−10	3:1	46
13	HBr	**7e**	10	−10	3:1	97
14	TfOH	none	1.5	−35	n.a.	20
15	TfOH	**7a**	1.5	−35	n.a.	0
16	TfOH	**7e**	1.5	−35	3:1	78

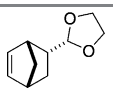
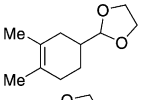
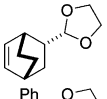
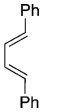
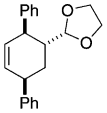
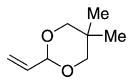
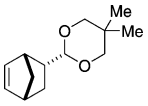
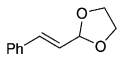
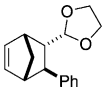
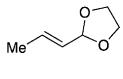
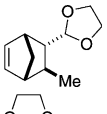
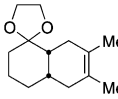
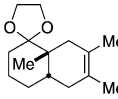
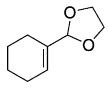
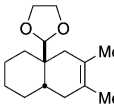
[a] These experiments were performed on 0.5–0.7 mmol scale (0.3 M solution) using 3 equivalents of cyclopentadiene. [b] The reaction yields were determined by ^{1}H NMR analysis of the crude reaction mixtures using an internal standard. *p*-TSA = *para*-toluenesulfonic acid, Tf = trifluoromethanesulfonyl.

The geometry of **7e** is optimal for forming three hydrogen bonds with polyoxygenated tetrahedral anions formed by group III elements (e.g. sulfonates, phosphates, perchlorates, etc.). However, even in the situation when there is no clear geometric preference for anion binding, **7e** outperformed **7a** as the co-catalyst (Table 1, entries 8–13). While the acidity of HCl ($pK_a = 1.8$ in DMSO) is close to the acidity of sulfonic acids (pK_a of MsOH in DMSO is 1.6), a chloride anion could form a tighter ion pair with an oxocarbenium than sulfonate anions, in which the negative charge is distributed across three oxygen atoms. Consistent with this presumption, a significantly longer reaction time (24 h) was required to observe the formation of the product **8**, and the reaction catalyzed by **7e** proceeded to a greater extent (33%, entry 10) than the corresponding reaction promoted by **7a** (22%, entry 9). Similar trends were observed for the HBr-catalyzed formation of **8** (entries 11–13). HBr is stronger than both hydrochloric and *p*-toluenesulfonic acids ($pK_a = 0.9$ in DMSO), and bromide is a weaker coordinating anion than chloride. As expected, HBr alone promoted the reaction to a significantly higher extent than HCl (37% conversion, 10 h, entry 11). Similar to the HCl case, the use of **7e** as a co-catalyst resulted in an accelerated reaction (97% conversion, 10 h, entry 13). Notably, these experiments indicate that the weaker *p*-toluenesulfonic acid is a more effective catalyst than the stronger HBr when combined with **7e** in promoting the formation of cycloadduct **8**. We attribute this effect to the higher affinity of **7e** to the tetrahedral sulfate anion because of its geometric predisposition to form three hydrogen bonds with the sulfonate oxygen atoms. Finally, to demonstrate that hydrogen-bond donors could accelerate reactions promoted by triflic acid, we conducted the experiments described in entries 14–16. Triflic acid alone promoted the formation of **8** at −35 °C. However, this reaction was slow and only 20% of **8** was observed after 1.5 h. The addition of thiourea co-catalyst **7a** did not enhance the cycloaddition, however, 78% conversion was observed when **7e** was employed as the co-catalyst (entry 16).

With the optimal reaction conditions in hand, the scope of the ionic [2+4] cycloadditions was explored next (Table 2). To evaluate synthetic utility of this protocol, the scope of both dienes (entries 1–4) and dienophiles (entries 5–7) as well as the application of this method to the preparation of synthetically useful *cis*-decaline-based building blocks (entries 8–10) has been examined. The reaction of 2-vinyl-1,3-dioxolane with various dienes such as cyclopentadiene (entry 1), 2,3-dimethyl-1,3-butadiene (entry 2), 1,3-cyclohexadiene (entry 3) and 1,4-diphenyl-1,3-butadiene (entry 4) resulted in the formation of the cycloadducts **10** in good to excellent yields (57–92%) upon isolation when *p*-TSA was used in combination with **7e**. However, neither *p*-TSA alone nor the

Table 2: The scope of the organocatalytic ionic [2+4] cycloaddition.[a]



Entry	Dienophile (**9**)	Diene	Product (**10**)	*t* [h]	Catalyst	Yield [%][b]	*endo*/*exo*
1				1	none	18	2.8:1
					7a	<5	–
					7e	92	2.4:1
2				14	none	<5	–
					7a	<5	–
					7e	76	–
3				16	none	<5	–
					7a	<5	–
					7e	85	20:1
4[c,d]				6	none	<5	–
					7a	<5	–
					7e	57	8.3:1
5[c]				0.8	none	7	5.5:1
					7a	17	4.6:1
					7e	91	4.7:1
6				3	none	<5	–
					7a	<5	–
					7e	63	4.8:1
7				2	none	9	2:1
					7a	<5	–
					7e	81	2:1
8[c]				2	none	13	–
					7a	<5	–
					7e	68	–
9[c,d]				24	none	28	–
					7a	13	–
					7e	84	–
10[c]				24	none	<5	–
					7a	<5	–
					7e	59	–

[a] These experiments were performed on 0.5–0.9 mmol scale (0.3 M solution in toluene) using 5 equivalents of cyclopentadiene. [b] The yields of the isolated products are reported for the reactions catalyzed by *p*-TSA/**7e**. The yields for the reactions catalyzed by *p*-TSA or *p*-TSA/**7a** were determined by ^{1}H NMR analysis of the crude reaction mixtures using an internal standard. [c] These experiments were performed on 0.3–0.7 mmol scale (0.6 M solution in dichloromethane) using 5 equivalents of cyclopentadiene, 5 mol% of *p*-TSA and 10 mol% of **7a** or **7e**. [d] The reaction was conducted at room temperature.

combination of *p*-TSA and **7a** could promote the formation of **10** to a significant extent. Similarly, the reactions of 5,5-dimethyl-2-vinyl-1,3-dioxane (entry 5), (*E*)-2-styryl-1,3-dioxolane (entry 6), and (*E*)-2-(prop-1-en-1-yl)-1,3-dioxolane (entry 7) resulted in synthetically useful yields (63–91%) when *p*-TSA/**7e** were employed as the catalysts, but failed to result in significant amounts of **10** when only *p*-TSA or the combination of *p*-TSA and **7a** were used as catalysts.

The ionic [2+4] cycloadditions have found a widespread application in the synthesis of highly functionalized decalins. To demonstrate that our protocol is amenable to the synthesis of these valuable building blocks, the reactions of 2-cyclohexenone and 2-methyl-2-cyclohexenone-derived dioxolanes were tested (Table 2, entries 8 and 9). While the cycloadditions leading to the corresponding products **10** were found to be slow in toluene, the use of dichloromethane as the solvent and an increased catalyst loading (5 mol% of *p*-TSA, 10 mol% of **7e**) led to the formation of the corresponding cycloadducts in good yields (68% and 84% respectively).

Finally, to test whether this method is applicable to the challenging cycloadditions the reaction of 2-(cyclohex-1-en-1-yl)-1,3-dioxolane and 2,3-dimethyl-1,3-butadiene was executed (Table 2, entry 10). The Lewis acid catalyzed reactions of cyclohex-1-enecarbaldehyde or cyclohex-1-enecarboxylates are notoriously difficult to execute with unactivated dienes, while the Grieco protocol could be used to provide the analogous cycloadduct **3** in 53% yield (Figure 2).[8] Remarkably, **7e** in combination with *p*-TSA was sufficient to promote the formation of the corresponding cycloadduct in 59% yield (Table 2, entry 10) without resorting to the use of a highly ionic medium [4 M solution of lithium(I) perchlorate in diethyl ether].

To confirm that **7e** complexes anions and to gain a better understanding of the observed effect, binding and computational studies have been conducted (Figure 3). First, the association of **7e** with sulfonate anions was confirmed by combining **7e** with known methylpyridinium tosylate (**11**) in different proportions. Thus, the addition of **11** to solution of **7e** resulted in a concentration-dependent downfield shift of the phosphoramide NH protons in the ^{1}H NMR spectrum, which is characteristic of hydrogen bonding to anion (Figure 3A).[14] The stoichiometry of the resultant complex between **11** and **7e** was determined by ^{1}H NMR titration and resulted in the Job plot depicted in Figure 3B.[15] The stoichiometry of binding is consistent with the formation of 1:1 complex between **11** and **7e**. WinEQNMR[16] was used to establish the association constant of this complex ($K_a = 7.3 \times 10^4$ M^{-1} in $CDCl_3$). Based on the value of K_a, we conclude that **7e** strongly binds the tosylate anion of **11** in chloroform. However, our further attempts to compare this value with the corresponding K_a values of **7a**/Ts^- or **7e**/Cl^- did not result in conclusive results because of the more complex stoichiometries of the resultant supramolecular complexes.[17]

Finally, computational studies were initiated to model the interactions of the sulfonate and **7e** (Figure 3C). Thus, DFT-based geometry optimization of **7e** and mesylate (B3LYP, 6-31+G*, toluene) resulted in a complex, in which the three NH hydrogen atoms of **7e** are bound to all three oxygen atoms of the mesylate anion. This complex was found to be more stable by 3.7 kcal mol^{-1} than the corresponding complex of thiourea **7a** (see the Supporting Information). While these results support the proposal that **7e** is the most effective cocatalyst because of its stronger association with anions, and

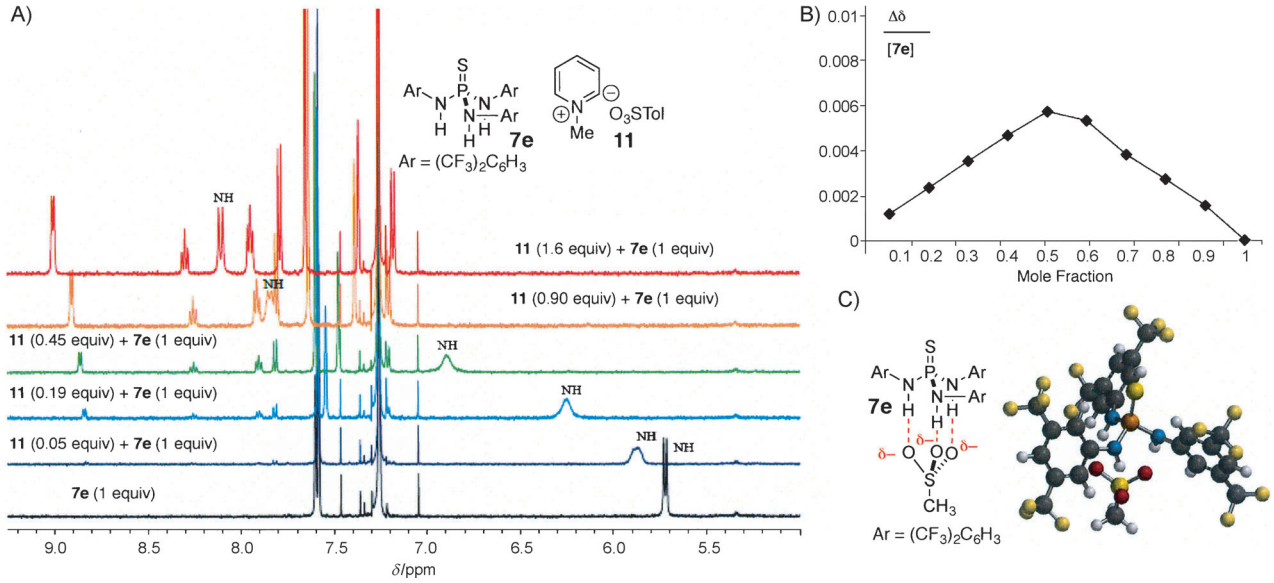


Figure 3. A) ^{1}H NMR spectra for the titration of **7e** (0.5 mM in $CDCl_3$) with **11**. The thiophosphoramide NH downfield shift is observed upon addition of **11**. B) Job plot for the titration of **11** with **7e**. The maximum mole fraction equal to 0.5 is consistent to 1:1 complex between **11** and **7e** with the association constant K_a of 73000 M^{-1} in $CDCl_3$ (determined by WinEQNMR). C) Complex of thiophosphoramide **7e** and mesylate anion (DFT, B3LYP, equilibrium geometry of the ground state in toluene, 6-31 + G*).

consequently results in more activated vinyl oxocarbenium ion, a more complex mechanistic scheme is likely to be operational.

In conclusion, the combination of a Brønsted acid as the catalyst and a hydrogen-bond donor as the co-catalyst can be used to catalyze a variety of ionic [2+4] cycloaddition reactions under mild reaction conditions and does not require the use of a highly ionic medium [e.g. 4 M lithium(I) perchlorate in ether]. Remarkably, the thiophosphoramide **7e**, which has not been previously utilized for the anion binding, was found to be superior to the standard two-hydrogen-bond donors such as **7a** or **7b**. Computational and NMR studies suggest that preference could be attributed to the ability of **7e** to form strong three-hydrogen-bond-containing complexes with the anions. This effect was found to be especially strong for sulfonate anions, the geometry of which favors the formation of three hydrogen bonds with the sulfonate oxygen atoms. Further studies of this and related transformations as well as the development of the asymmetric variants of **7e** are ongoing.

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