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Water-Promoted Dehydrative Tsuji-Trost reaction of Non-Derivatized Allylic Alcohols with Sulfinic Acids

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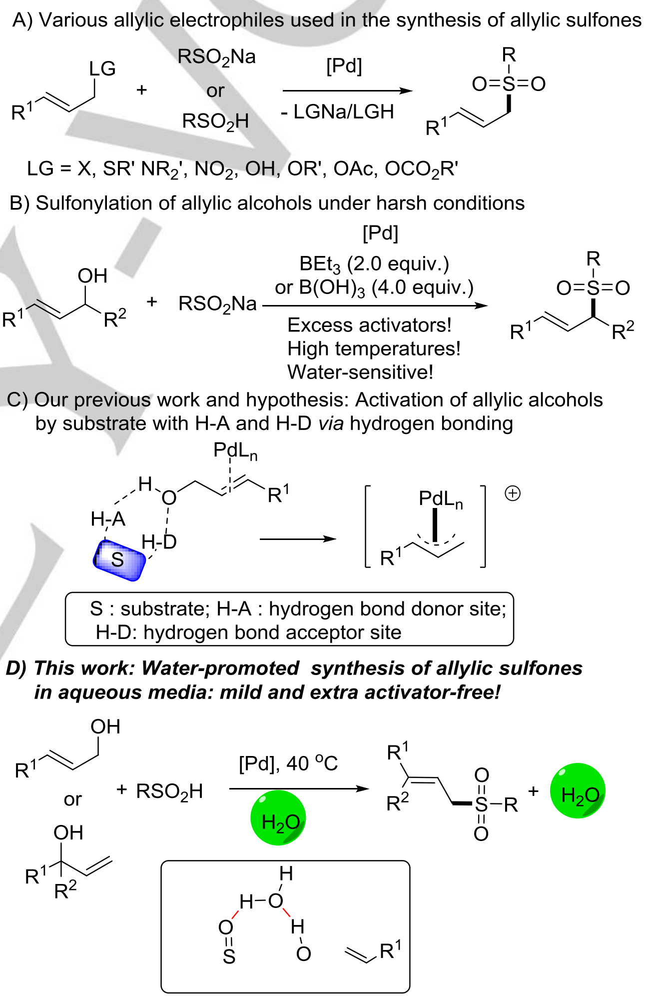
Abstract: A mild, green and extra activator-free synthesis of allylic sulfones from non-derivatized allylic alcohols and sulfinic acids was developed and only the easily-available Pd(PPh_3)$_4$ was used as the catalyst. This new method could be easily scaled up in gram scale, affording the target allylic sulfones in a nearly quantitative yield with water as the sole byproduct. Mechanism studies both by various NMR techniques and by theoretical calculations suggested two reaction pathways may be involved in the reaction which is dependent on the reaction media, that is, an eight-membered ring binding species may be formed in aqueous media between allylic alcohol, sulfinic acid and water, while a six- membered ring binding species may be formed in common aprotic organic solvent between allylic alcohol and sulfinic acid. Both two binding species may be account for the efficient activation of allylic alcohols *via* hydrogen bonding.

Allylic sulfones are important motifs in biologically and pharmaceutically active molecules showing unique anticancer, antibacterial and anti-inflammatory activities.[1] Besides, they can also serve as versatile building blocks in organic reactions, such as Julia olefination.[2] Therefore, numerous methods have been developed for the synthesis of allylic sulfones, which can be mainly classified into transition metal (TM)-free cross-couplings of the reactive allylic reagents with sulfonyl surrogates,[3] the selective addition of sulfonyl surrogates to unsaturated compounds[4] and Pd-catalyzed Tsuji-Trost reaction.[5] Owing to the advantages of the simple reaction conditions, broad substrate scopes and high selectivity, various allylic electrophiles such as allylic halides,[6] carboxylates,[7] carbonates,[8] alcohols[9] and amines[10] were employed in Tsuji-Trost reactions for the synthesis of allylic sulfones (Scheme 1A). In terms of atom- and step economy, Tsuji-Trost reactions of allylic alcohols are much more attractive.[11] However, owing to the poor leaving character of the hydroxy group, a stoichiometric amount of an acid activator such as BEt_3 or $B(OH)_3$, and harsh reaction conditions (such as high temperatures and strict water-free conditions) were generally required to promote the direct activation of non-derivatized allylic alcohols (Scheme 1B).[9] Therefore, a mild, green and extra activator-free synthesis of allylic sulfones from non-derivatized allylic alcohols is still urgently desired.



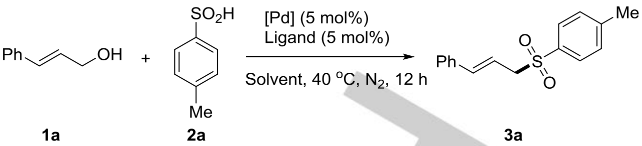
Scheme 1. Pd-catalyzed allylic sulfones synthesis.

However, the development of a mild and activator-free Tsuji-Trost reaction of non-derivatized allylic alcohols is still very challenging because that the activation mechanism of allylic alcohols was investigated only in rare reports and was mainly based on theoretical calculations.[12] We have recently found that allylic alcohols could be activated *via* hydrogen bonding of water or the reaction substrate under mild conditions.[13] The binding species were detailed investigated by various NMR techniques and the results suggested that substrates bearing both a hydrogen bond donor site and an acceptor site may interact with allylic alcohols, thus leading to the activation of C-O bonds in allylic alcohols *via* hydrogen bonding, as a result, the use of an extra activator can be avoided (Scheme 1C).[13b,c] Therefore, sulfinic acid is the very ideal candidate. Meanwhile, in 2018, Xie and Loh reported a water-mediated activation of the reactive MBH (Morita-Baylis-Hillman) alcohols with sulfinic acids under TM-free conditions.[3h] Therefore, it can be hypothesized that hydrogen bond may be formed between non-derivatized allylic alcohols, sulfinic acids and/or water. But whether a synergetic hydrogen bond activation of non-derivatized allylic alcohols in the presence of a Pd catalyst could be achieved is still unknowable and uncertain, especially in an aqueous media, because that it is still challenging to develop TM-catalyzed reactions in aqueous media.[14]

With our continuous interest in Tsuji-Trost reaction and hydrogen bond chemistry,[9b,13,15] herein we wish to report our results on the mild, green and extra activator-free synthesis of allylic sulfones from non-derivatized allylic alcohols and sulfinic acids in aqueous media. This new method allows the synthesis of allylic sulfones under mild conditions and can be easily scaled up in gram scale in a nearly quantitative yield, liberating water as sole byproduct. To the best knowledge, such a mild and activator-free synthesis of allylic sulfones from non-derivatized allylic alcohols has not been reported yet.[16] Interestingly, an obvious promoting effect of water was observed, and rather than the using of precious ligands in activator-free Tsuji-Trost reactions in aqueous media,[17] only the simple and easily-available $Pd(PPh_3)_4$ is used by this new method. Detailed mechanism studies by various NMR techniques and theoretical calculations suggested that the sulfinic acid-assisted activation of allylic alcohol through a six-membered ring species may be not the main path, and a novel water-mediated and substrate self-assisted activation of allylic alcohols through an eight-membered ring species *via* hydrogen bonding may be involved in the aqueous reactions (Scheme 1D).[18] Notably, probably owing to the elusory character of the hydrogen bond, the experimental evidence is still rare so far.[12,13]

A mixture of cinnamyl alcohol (**1a**) and 4-methylbenzenesulfinic acid monohydrate (**2a**) in aqueous media under a nitrogen atmosphere was initially heated at 40 °C for 12 h, however, only trace amount of target allylic sulfone (**3a**) was obtained (Table 1, run 1), suggesting that a common Pd catalyst is required. Inspired by our previous substitution of allylic alcohols in aqueous media,[13a] $[Pd(allyl)Cl]_2$ (2.5 mol%)/dppf (5 mol%) was then employed to catalyze the reaction of cinnamyl alcohol (**1a**) and 4-methylbenzenesulfinic acid monohydrate (**2a**) in aqueous media, to our delight, the target allylic sulfone **3a** was obtained in 92% isolated yield (run 2). Then other palladium catalysts and ligands were screened, the results showed that the reaction using the easily-available $Pd(PPh_3)_4$ as the catalyst gave the target **3a** in the highest yield of 98% (runs 3-6). Moreover, the common organic solvents such as 1,4-dioxane, toluene and EtOH were then screened, but the target **3a** was obtained in inferior yields, revealing the important role of water in the reaction (*vide infra*) (runs 7-9). Moreover, when decreasing the reaction temperature, catalyst loading or using other cheap metal catalysts, the reactions afforded the target product **3a** in low yields.[19] Finally, when 4-methylbenzenesulfinic acid monohydrate (**2a**) was replaced by sodium 4-methyl benzenesulfinate, or cinnamyl alcohol (**1a**) was replaced by cinnamyl ethyl ether, no target **3a** was detected at all, suggesting the indispensable role of both reactive hydrogens of sulfinic acid and allylic alcohol in the reaction (runs 10-11). Therefore, a substrate self-assisted activation of allylic alcohols through the formation of a ring complex *via* hydrogen bonding may be involved in the reaction (*vide infra*).

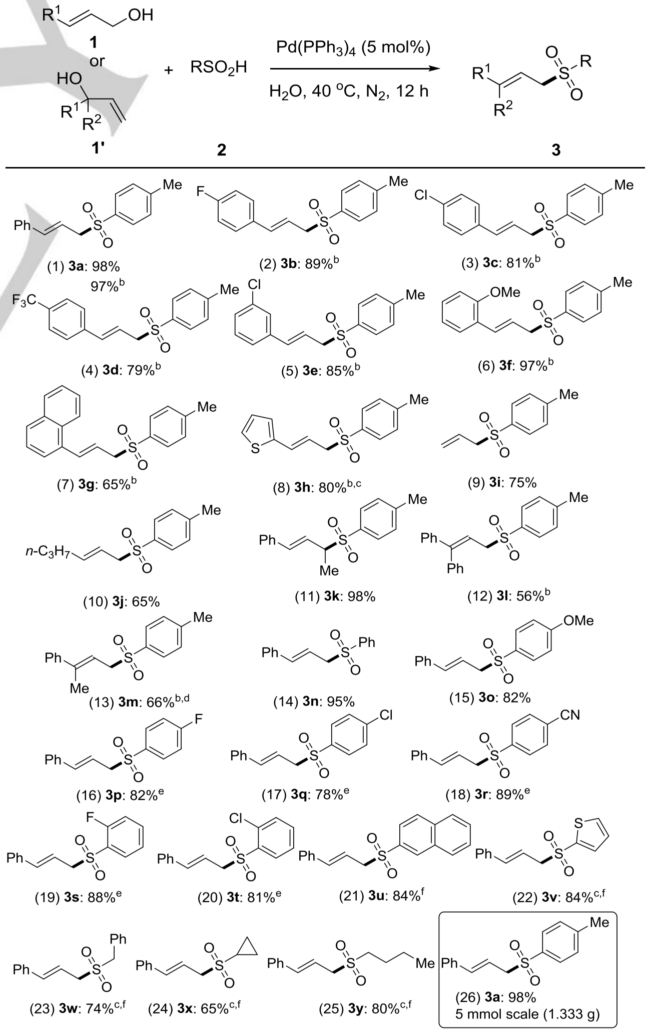
Table 1. Conditions screening for allylic sulfone synthesis.[a]



run	[Pd]	Ligand	Solvent	3a%[b]
1	none	---	H_2O	trace
2[c]	$[Pd(ally)Cl]_2$	dppf	H_2O	92
3	$Pd(OAc)_2$	dppf	H_2O	94
4	$Pd(OAc)_2$	dppb	H_2O	88
5[d]	$Pd(OAc)_2$	PPh_3	H_2O	90
6	*$Pd(PPh_3)_4$*	---	*H_2O*	*98*
7	$Pd(PPh_3)_4$	---	1,4-dioxane	20
8	$Pd(PPh_3)_4$	---	toluene	80
9	$Pd(PPh_3)_4$	---	EtOH	85
10[e]	$Pd(PPh_3)_4$	---	H_2O	0
11[f]	$Pd(PPh_3)_4$	---	H_2O	0

[a] Unlesss otherwise noted, the mixture of cinnamyl alcohol (**1a)** (0.30 mmol), 4-methylbenzenesulfinic acid monohydrate (**2a)** (0.36 mmol), Pd catalyst (5 mol%), ligand (5 mol%) and a solvent (0.50 mL) was heated at 40 °C for 12 h in a 10 mL sealed Schlenk tube under nitrogen, and then monitored by TLC/GC-MS. [b] Isolated yield based on **1a** by column chromatography. [c] 2.5 mol% Pd catalyst. [d] 10 mol% ligand. [e] **2a** was replaced with sodium 4-methyl benzenesulfinate. [f] **1a** was replaced with cinnamyl ethyl ether.

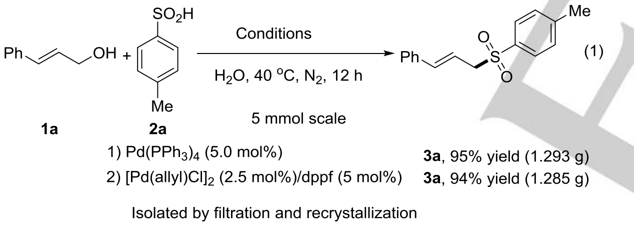
Table 2. Substrate extension of the water-promoted dehydrative synthesis of allylic sulfones.[a]



[a] Unlesss otherwise noted, allylic alcohol **1** was used and see Table 1

run 6 for details, isolated yield based on 1 or 1'. [b] allylic alcohol **1'** was used. [c] $[Pd(allyl)Cl]_2$ (2.5 mol%) and dppf (5 mol%) were used as the catalyst. [d] E/Z>99/1. [e] 60 °C. [f] 1.5 equiv. sulfinic acid was used.

With the optimized conditions in hand (table 1, run 6), various allylic alcohols were then tested to extend the scope of this novel method. As shown in Table 2, like the model reaction, both electron-rich and -deficient aryl allylic alcohols including the sterically more bulky *ortho*-substituted ones reacted effectively with **2a** to afford the desired product in high yields (Table 2, runs 1-8). The method can also be easily extended to heteroaryl, aliphatic allylic alcohols and even the bulky allylic secondary and tertiary alcohols, affording the target products in moderate to high yields (runs 9-14). On the other hands, for sulfinic acids, both electron-rich and electron-deficient aryl sulfinic acids, and heteroaryl sulfinic acids all reacted smoothly with cinnamyl alcohol (**1a**) to give moderate to high yields of the target products under similar conditions (runs 15-23). The method could be readily extended to alkyl sulfinic acids, such as benzyl, cyclopropyl and *n*-butyl sulfinic acids, affording the target products in moderate to high yields (runs 24-26). Finally, the reaction of cinnamyl alcohol (**1a**) and 4-methylbenzenesulfinic acid monohydrate (**2a**) was carried out in gram scale under standard conditions, still affording the target **3a** in 98% yield (1.333 g), showing the practicability of this new method (run 27). Benefiting from the "two-phase" character, column chromatography-free isolation and purification of the gram scale reaction of cinnamyl alcohol (**1a**) and 4-methylbenzenesulfinic acid monohydrate (**2a**) was also attempted.[18] By simple filtration and recrystallization, the target product **3a** could be obtained under different Pd catalysts in 95% or 94% yields, respectively, further showing the practicality of this new method (Eq. 1, runs 1-2).



Then the activation mechanism of allylic alcohols in this mild and extra activator-free synthesis of allylic sulfones was investigated. According to the conditions screening in table 1, both the reactive hydrogens of sulfinic acid (**2a)** and cinnamyl alcohol (**1a)** are indispensable for the reaction (Table 1, runs 10-11), therefore, there may be some interaction between cinnamyl alcohol (**1a)** and sulfinic acid (**2a)**. Various NMR methods such as the Job Plot and ^1H NMR titration techniques were employed to investigate the possible host-guest binding interaction between cinnamyl alcohol (**1a**) and 4-methylbenzenesulfinic acid monohydrate (**2a**).[13,20,21] By continuous variation of the concentration of [**1a**] (Host) and [**2a**] (Guest), our Job Plot experimental results are shown in Figure 1 and the maximum in the curve for cinnamyl alcohol (**1a)** is at X_{1a} = 0.50 (Figure 1), indicating that a 1:1 binding complex of cinnamyl alcohol (**1a**) and 4-methylbenzenesulfinic acid monohydrate (**2a**) was possibly formed.[19] Moreover, the residual distribution analysis of the fitting curve of ^1H NMR titration experiments further suggested that the possible formation of 1:1 binding complex between cinnamyl alcohol (**1a**) and 4-methylbenzenesulfinic acid monohydrate (**2a**) *via* hydrogen bonding (Figure 2).[19,21] Therefore, a 1:1 binding complex between allylic alcohol **1** and sulfinic acid **2** may be formed and it may play a key role in the activation of allylic alcohols.

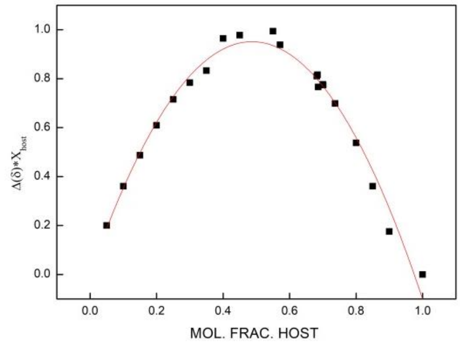


Figure 1. Job plots.

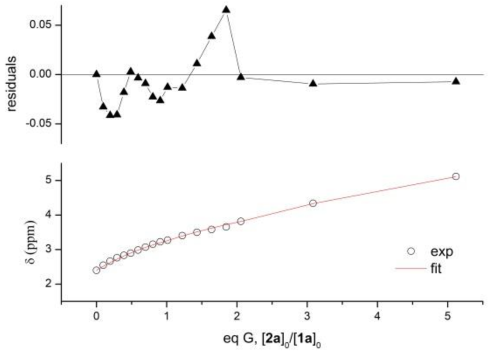
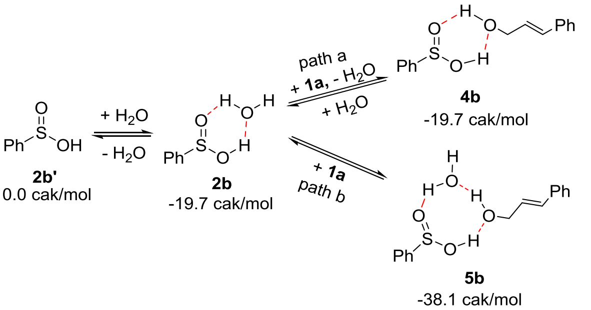


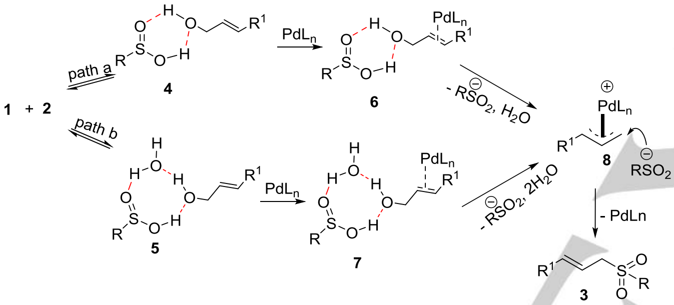
Figure 2. ^1H NMR titration experiments.

Because an obvious promoting effect of water was observed (Table 1, runs 6-9) and sulfinic acids were usually obtained with a molecule of crystal water, it is strongly necessary to make clear that whether water is involved in the abovementioned 1:1 binding complex (Scheme 2). Therefore, density functional theory (DFT) calculations were then conducted to further investigate the role of water.[19] According to the calculation results in Scheme 2, water can dramatically stabilize the benzene sulfinic acid **2b'** by forming a six member ring format **2b**,[3h,19] which is also consistent with the fact that water plays an important role in the reaction (Table 1, runs 6-9). Moreover, a six member ring species **4b** and eight member ring species **5b** may be formed during the reaction (Scheme 2). Interestingly, the eight member ring species is energetically more favored assisted by water, which, to some extent, can account why water could dramatically enhance the overall performance of this reaction.



Scheme 2. B3LYP/6-31G* optimized intermediates and computed energies.

Based on these experimental results and the literature reports,[11,13] a possible reaction mechanism was depicted in scheme 3. A substrate self-assisted activation of the allylic alcohol *via* a six-membered ring complex **4** generated from allylic alcohol **(1)** and sulfinic acid (**2**) may be the main path in common aprotic organic media (such as 1,4-dioxane and toluene) (Scheme 3, Path a). While a water-mediated and substrate self-assisted activation of allylic alcohols *via* the formation of an eight-membered ring complex **5** from allylic alcohols **(1)**, sulfinic acids (**2**) and water may be the main path in aqueous media (Path b). Then assisted by a Pd catalyst, the activation of C-O bonds in complex **6** and **7**, followed by the cleavage of C-O bond affords the crucial π-allyl palladium **8**, meanwhile giving the nucleophilic sulfinate. Finally, a following nucleophilic attack by sulfinate gives the target products **3** and regenerates the palladium catalyst. Possibly owing to that it is energetically more favored, the eight member ring species **5** may be the main binding species, and the reaction mainly follows path b in aqueous media (path b). On the other hand, the six member ring species **4** may be the main species, being in charge of the activation of allylic alcohols in common aprotic organic solvent (path a).[13] These experimental results are also consistent with the facts that the reaction could afford the target product **3a** with the highest yield in aqueous media, while the target **3a** could still be obtained with inferior yields in common organic solvents (Table 1, runs 6-9).[22]



Scheme 3. Possible reaction path way

In conclusion, we developed a mild, green and extra activator-free dehydrative synthesis of allylic sulfones *via* Pd-catalyzed allylic substitution of allylic alcohols with sulfinic acids in aqueous media. This new method can tolerate various functional groups such as MeO-, F-, Cl-, CN- etc. and can be easily scaled up in gram scale in a nearly quantitative yield. Mechanism studies suggested the formation of an eight-membered ring complex from allylic alcohols, sulfinic acids and water *via* hydrogen bonding may be crucial to the efficient activation of allylic alcohols.

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Keywords: Allylic sulfones • Tsuji-Trost reaction • Hydrogen bond activation • Dehydrative synthesis • Aqueous media

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[16] During the manuscript was prepared, Xie and Loh reported a mild Pd-catalyzed synthesis of allylic sulfones in DMA facilitated by catalytic amount of the moisture sensitive $Ca(NTf)_2$, see: P. Xie, Z. Sun, S. Li, X. Cai, J. Qiu, W. Fu, C. Gao, S. Wu, X. Yang, T.-P. Loh, *Org. Lett.,* **2020**, *22*, 4893.

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[18] Xie and Loh reported a mild synthesis of allylic sulfones from the reactive MBH allylic alcohols and sulfinic acids under TM-free conditions, and they proposed a water-mediated mechanism mainly based on theoretical calculations, see ref. 3h for details.

[19] See SI for details.

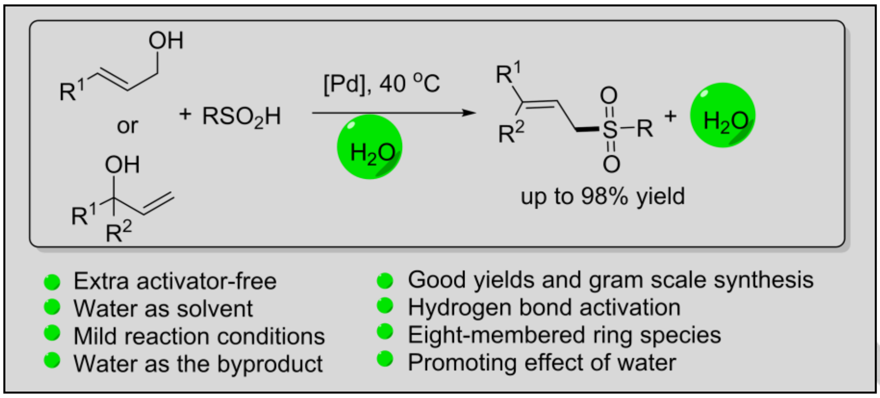
[20] a) L. Du, P. Cao, J. Xing, Y. Lou, L. Jiang, L. Li, J. Liao, *Angew. Chem. Int. Ed.* **2013**, *52*, 4207; b) F. Ulatowski, K. Dąbrowa, T. Bałakier, J. Jurczak, *J. Org. Chem.* **2016**, *81*, 1746.

[21] The data of ^{1}HNMR titration experiments and the residual distribution analysis was dealt with Thordarson's free program at http://supramolecular.org/. For reference, see: P. Thordarson, *Chem. Soc. Rev*. **2011**, *40*, 1305.

[22] Xie and Loh also found that $Ca(NTf)_2$ is not indispensable for the activation of allylic alcohols, but might facilitate the process, see ref. 15 for details. This phenomenon can also be well explained by our mechanism model.

Entry for the Table of Contents

Hydrogen bond activation



A promoting effect of water was observed, leading to the dehydrative synthesis of allylic sulfones byTsuji-Trost reaction of non-derivatized allylic alcohols with sulfinic acids. Mechanism studies suggested the formation of the eight-membered ring complex from allylic alcohols, sulfinic acids and water *via* hydrogen bonding may be crucial to the efficient activation of allylic alcohols.