Chiral primary amine mediated conjugate addition of branched aldehydes to vinyl sulfone: asymmetric generation of quaternary carbon centers†

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Novel L-threonine-derived bifunctional organic catalysts containing primary amine and sulfonamide groups were utilized to promote asymmetric conjugate addition of α,α-disubstitued aldehydes to 1,1-bis(benzenesulfonyl)ethylene. The adducts with quaternary stereogenic centers adjacent to an aldehyde group were obtained in high yield and with good enantioselectivity.

Asymmetric aminocatalysis represents one of the most powerful activation modes in asymmetric synthesis.[1] The past decade has witnessed remarkable progress in the utilization of proline and its numerous structural analogues as powerful organic catalysts.[2] In this field, the impressive development of enantioselective methods is associated with various effective activation modes of carbonyl functionality, *via* the formation of enamine intermediates,[3] iminium species,[4] or radical cations (SOMO activation).[5] Recently, chiral primary amines have emerged as powerful and versatile organic catalysts in asymmetric synthesis.[6] It is noteworthy that chiral primary amine-promoted reactions are often complementary to those catalyzed by secondary amines. Our group has been actively investigating primary amino acid/primary amine-catalyzed organocatalytic reactions in the past few years. We reported that L-tryptophan and L-threonine-derived organocatalysts were effective enantioselective catalysts for the direct aldol and Mannich reactions in water.[7] By employing a cinchonidine-derived primary amine, we achieved the first highly enantioselective conjugate addition of ketones to a vinyl sulfone.[8] Very recently, we introduced a novel tryptophan-based bifunctional thiourea catalyst that was remarkably effective in promoting enantioselective Mannich reactions of α-fluoro-β-ketoesters.[9] In this report, we show that a novel threonine-derived primary amine with an *N*-sulfonamide group efficiently promotes asymmetric conjugate addition of α,α-disubstituted aldehydes to a vinyl sulfone, generating all-carbon quaternary chiral centers.

Proline and its analogues have been demonstrated to be extremely powerful in activating carbonyl substrates, aldehydes in particular, *via* the enamine intermediates. On the other hand, primary amine-induced enamine formation works best for the ketone donors. This substrate preference could be attributed to the readiness of formation of the enamine intermediates from carbonyl substrates and primary/secondary amines, which is dictated by steric factors in many cases. In an effort to expand the scope of primary amine-catalyzed organocatalytic reactions *via* enamine activation, we became interested in exploring 2-aryl-substituted propanals as potential donors in carbon–carbon bond-forming reactions. Compared with a secondary amine catalyst, a sterically less-hindered primary amine is expected to react readily with an α-branched aldehyde to yield an imine. The presence of the phenyl ring makes the tautomerization to the crucial enamine intermediate favourable due to conjugation, and the subsequent reaction of the enamine intermediate with suitable electrophiles then generates a quaternary center (Fig. 1).

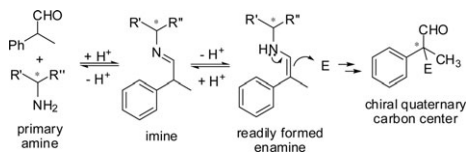

Fig. 1 The enamine formation between 2-phenylpropanal and primary amines.

Construction of quaternary stereogenic centers is one of the most challenging synthetic tasks, and has attracted much attention from organic chemists in the past decade.[10] The all-carbon quaternary chiral center with an adjacent functionality is a useful structural scaffold, existing widely in many biologically and medicinally important molecules[11] (Fig. 2). However, there are only a few methods available which allows their efficient catalytic asymmetric synthesis.[12] To devise a synthetic method to access these structural units, we chose to focus on the potential activation of 2-aryl-substituted propanals *via* primary amine-induced enamine formation.[13] With a properly designed chiral primary amine catalyst, the conjugate addition of 2-aryl-substituted propanals to vinyl sulfones[14] may proceed stereoselectively to create chiral quaternary carbon centers,[15] and the subsequent conversion of the sulfone groups to hydrogen atoms or alkyl groups[16] then generates all-carbon quaternary stereogenic centers with tunable alkyl chains.

We began our investigation by examining conjugate addition of 2-phenylpropanal **1** to vinyl sulfone **2**. A wide range of organic catalysts were screened, and the results are summarized in Table 1. Not surprisingly, L-proline was ineffective, affording the desired product in moderate yield and with poor enantioselectivity (entry 1). Silylated biarylprolinol **5** also led to poor stereoselectivity (entry 2). The sulfonamide derivative

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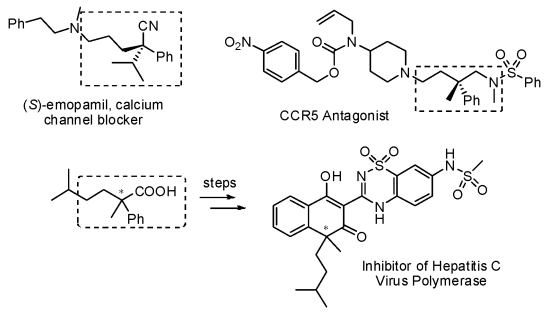


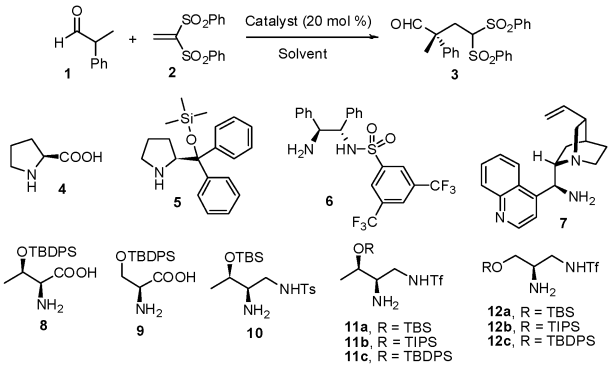
Fig. 2 Examples showing the presence of all-carbon quaternary centers in biologically important compounds.

of (*S*,*S*)-1,2-diphenylethylenediamine (DPEN)[17] **6** afforded the product in very poor yield (entry 3). Cinchonidine-derived primary amine catalyst **7** turned out to be a good catalyst, yielding the desired adduct in high yield and with good enantioselectivity (entry 4). Threonine and serine-based catalysts **8** and **9**, previously disclosed by our group,[7c] afforded the product in high yield, but with low enantioselectivity (entries 5 and 6). Organocatalysts containing *N*-sulfonamide groups have been demonstrated to be very useful in asymmetric catalysis,[18] threonine and serine-derived sulfonamides were thus prepared.[19] Threonine-derived *N*-tosylsulfonamide **10** offered similar stereoselectivity as *O*-silylated threonine (entry 7). For various *N*-trifluoromethanesulfonamide catalysts, threonine (**11a-c**) and serine-based (**12a–c**) structural motifs displayed similar catalytic efficiency (entries 8–13). Threonine-based *O*-TBS-*N*-sulfonamide **11a** was found to be the best catalyst, affording the desired adduct in 94% yield and with 74% ee (entry 8). A solvent screening (entries 14–21) revealed that *p*-fluorotoluene was the best solvent, improving ee value to 79% while maintaining the excellent yield (entry 20). However, lowering the temperature did not give better enantioselectivity for the reaction (entry 22). By performing the reaction with lower substrate concentration, we were able to further improve the enantioselectivity. Under the optimized conditions, the reaction was completed within 12 h in the presence of only 5 mol% of catalyst (entry 23).

Having established the optimized experimental conditions, we next examined the reaction scope (Table 2). Various 2-aryl-substituted propanals could be employed as donors, and the conjugate addition products were generally obtained in excellent yields and with high enantioselectivity (entries 1–8). An electron-withdrawing group on the aromatic ring was found to be detrimental, leading to a lower chemical yield and enantioselectivity (entry 9). When 2-ethylpentanal was utilized as a donor, no desired product was observed. In the absence of an aromatic ring, tautomerization of imine to enamine may not occur readily, resulting in inefficient enamine catalysis.[20]

The conjugate addition product can be readily converted into different building blocks containing a chiral quaternary center and a neighboring functional group. As illustrated in Scheme 1, adduct **3** was subjected to oxidation, followed by removal of the sulfone groups to afford acid **16** with all-carbon quaternary stereogenic center. Alternatively, facile reduction of aldehyde, coupled with sulfone cleavage yielded alcohol **15** containing an all-carbon quaternary chiral center.

Table 1 Screening of organocatalysts for the conjugate addition of 2-phenylpropanal **1** to vinyl sulfone **2**[a]



Entry	Catalyst	Solvent	T/°C	Yield[b] (%)	ee[c] (%)
1	**4**	$CHCl_3$	RT	60	25
2	**5**	$CHCl_3$	RT	82	24
3	**6**	$CHCl_3$	RT	< 30	—[d]
4	**7**	$CHCl_3$	RT	75	70
5	**8**	$CHCl_3$	RT	85	44
6	**9**	$CHCl_3$	RT	90	45
7	**10**	$CHCl_3$	RT	74	44
8	**11a**	$CHCl_3$	RT	94	74
9	**11b**	$CHCl_3$	RT	93	56
10	**11c**	$CHCl_3$	RT	93	55
11	**12a**	$CHCl_3$	RT	91	72
12	**12b**	$CHCl_3$	RT	87	56
13	**12c**	$CHCl_3$	RT	71	61
14	**11a**	CH_2Cl_2	RT	88	62
15	**11a**	CH_3OH	RT	81	40
16	**11a**	THF	RT	94	57
17	**11a**	Et_2O	RT	82	65
18	**11a**	DMF	RT	67	8
19	**11a**	Toluene	RT	93	76
20	**11a**	*p*-F-toluene	RT	92	79
21	**11a**	CF_3-benzene	RT	91	76
22[e]	**11a**	*p*-F-toluene	0	72	72
23[f]	**11a**	***p*-F-toluene**	**RT**	**93**	**83**

[a] The reactions were performed with aldehyde **1** (0.1 mmol), vinyl sulfone (0.05 mmol) and catalyst (0.01 mmol) in the indicated solvent (0.1 mL) at room temperature for 4 h, unless otherwise specified. [b] Isolated yield. [c] The ee value was determined by chiral HPLC analysis. [d] Not determined. [e] The reaction time was 24 h. [f] 0.0025 mmol catalyst was used in *p*-F-toluene (0.8 mL), and the reaction time was 12 h.

In conclusion, novel threonine-based *N*-sulfonamide organocatalysts were introduced for the first time, and such catalysts could efficiently promote enantioselective conjugate addition of 2-aryl-substituted propanals to 1,1-bis(benzenesulfonyl)-ethylene. The described method can be utilized to construct useful chiral building blocks containing all-carbon quaternary stereogenic centers and an adjacent common functional group. We anticipate that our method will find wide applications in the synthesis of medicinally important molecules. Computational studies to understand the observed stereoselectivity, and the full expansion of primary amine-induced enamine activation of α-aryl branched aldehydes are in progress in our laboratory, and will be reported in due course.

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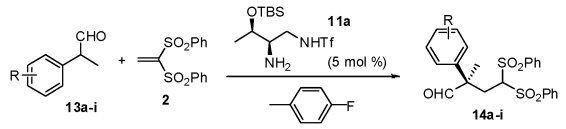
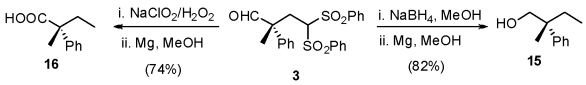
Table 2 Conjugate addition of various 2-aryl-substituted propanals **13** to vinyl sulfone **2** catalyzed by chiral amine **11a**[a]



Entry	Product/R	*t*/h	Yield[b] (%)	ee[c] (%)
1	*p*-Me	12	93	81
2	*p*-F	12	90	75
3	*p*-Br	12	87	80
4	*m*-Br	12	91	80
5	*o*-OMe	10	93	82
6	*m*-OMe	12	95	80
7	2-Naphthyl	10	91	77
8	1-Naphthyl	18	90	86
9	*p*-CN	24	76	68

[a] The reactions were performed with aldehyde (0.1 mmol), vinyl sulfone (0.05 mmol) and catalyst (0.0025 mmol) in *p*-fluoro-toluene (0.8 mL) at room temperature. [b] Isolated yield. [c] The ee value was determined by chiral HPLC analysis.



Scheme 1 Synthesis of different chiral quaternary building blocks.

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