## Asymmetric Organocatalytic 1,6-Conjugate Addition of Aldehydes to Dienic Sulfones\*\*

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Building enantiopure complex molecules simply, in a minimum number of operations, and in an environmentally friendly approach is one of the greatest challenges for synthetic chemistry, and particularly, for chemical industry.<sup>[1]</sup> Taking into account the requirements for the industrial application of an laboratory-scale reaction (functional group/H<sub>2</sub>O tolerance, simple procedures, no extreme temperatures), enamine catalysis has recently appeared as a method of choice to fulfil this ideal goal of reaction efficiency.<sup>[2,3]</sup>

In this field, the asymmetric conjugate addition to activated alkenes has been extensively studied, as evidenced by the large number of publications on the subject.<sup>[4]</sup> In contrast, the analogous asymmetric 1,6-addition to extended conjugated systems remains underdeveloped.<sup>[5,6]</sup> Several groups reported the 1,4-addition to activated dienes in enamine catalysis without any traces of vinylogous 1,6addition.<sup>[7]</sup> This higher reactivity of the  $\beta$  position compared to the  $\delta$  position seems to be a general trend difficult to overcome (Scheme 1). It probably arises from the poor propagation of the electronic effect through the conjugated system. This problem of charge delocalization is in contrast to the principle of vinylogy where the reactivity is in theory extended through the  $\pi$ - $\pi$  system.<sup>[8]</sup> In our continuing efforts toward the development of new approaches for the stereoselective construction of enantiopure synthetically useful buildings blocks, we thought about expanding the scope of enamine Michael reactions to 1,6-addition.

We hypothesized that a suitably designed Michael acceptor would be able to promote exclusively the 1,6-addition. To this purpose, we have focused our attention on unsaturated sulfones. The sulfonyl group is known for its

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[**]	We thank the Irish Research Council for Science, Engineering & Technology (IRCSET) and NUI Maynooth for funding. We also thank

Technology (IRCSET) and NUI Maynooth for funding. We also thank Dr. Padraig McLoughlin of Teagasc and the Ashtown Food Research Centre, Dublin for some NMR analysis.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201100804.



non-activated Nu<sup>-</sup> exclusive nositior 1.6-addition (En) SO<sub>2</sub>Ph SO<sub>2</sub>Ph R<sup>2</sup> 1 ŚO₂Ph ŚO₂Ph  $-H_2O$ cooperative-charge delocalisation spontaneous PhO<sub>2</sub>S R 'R<sup>2</sup> ŚO₂Ph versatile dienes

**Scheme 1.** Proposal for the organocatalytic vinylogous 1,6-addition reaction. En = enamine catalysis.

electron-withdrawing ability together with high synthetic versatility.<sup>[9]</sup> It has been shown that a vinyl sulfone with a single activating sulfone group was not sufficiently reactive to promote intermolecular enamine attack and generate a 1,4conjugate addition. Instead a second sulfone was required to generate the Michael-type addition.<sup>[10]</sup> As a result, 1,3-bis-(sulfonyl) butadiene (Scheme 1), should be able to promote exclusively the 1,6-addition by the insertion of an appropriately placed second electron-withdrawing group.<sup>[11]</sup> This butadiene should serve as an exciting application of the exceptional potential of charge delocalization in vinylogous reactions. The sulfone in the  $\alpha$  position would not sufficiently activate the  $\beta$ -carbon atom toward enamine addition but would be expected to sufficiently delocalize the charge of the  $\delta$ -carbon atom thanks to the cooperative effect of the second sulfonyl group, thus promoting the single 1,6-addition (Scheme 1). Herein, we present our results on this unprecedented asymmetric 1,6-addition that leads, in operationally simple conditions, to exceptional levels of diastereo- and enantioselectivities for the formation of highly attractive chiral dienes.

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We began our study by synthesizing 1,3-bis(sulfonyl) butadiene substrates **1** by a high-yielding, four-step reaction sequence.<sup>[12]</sup> To evaluate the feasibility of the asymmetric 1,6-addition, we subjected the sulfonyl diene **1** to the addition of butanal **2a** using 30 mol% of the organocatalyst (*R*)-diphenylprolinol silyl ether **3**. Chloroform was chosen as it easily solubilized the 1,3-bis(sulfonyl) butadiene. As we expected from our proposal (Scheme 1), only the 1,6-addition product was obtained in an excellent yield of 91% using only 2 equivalents of aldehyde (Table 1, entry 1). The observed



[a] Yield of isolated product. [b] Determined by <sup>1</sup>H NMR spectroscopy and HPLC analysis. [c] Determined by HPLC on a chiral stationary phase for the *anti* products. [d] Opposite *S*,*S* enantiomer of the product formed. [e] Isolated as a single diastereoisomer as determined by <sup>1</sup>H NMR spectroscopy. TMS = trimethylsilyl.

high reactivity and regioselectivity is in total agreement with our preliminary hypothesis of charge delocalization. The intermediate linear product was not observed and spontaneously cyclized to form the conjugated diene 4. It must be pointed out here that the cyclized product could be isolated from the crude reaction mixture by a very simple procedure. After evaporation of the solvent, the solid was only triturated with ice-cold methanol to directly obtain the pure compound. More remarkably, an exceptional diastereo- and enantiocontrol was observed in this reaction to furnish the 1,6-adduct in an astonishingly high 99% ee and 99:1 d.r. while performing the reaction at room temperature. Decreasing the catalyst loading to 10 mol% led to the same excellent stereoselectivities (99% ee, 99:1 d.r.) but as expected, a prolonged reaction time was needed to obtain 100% conversion (120 h vs. 24 h, result not shown).

We explored the scope and limitations of this reaction by testing 1,3-bis(phenylsulfonyl)butadiene **1a** with a variety of different sterically demanding aldehydes **2a–f** (Table 1). Gratifyingly, all reactions gave the 1,6-addition product exclusively with no trace of the 1,4-adduct. Furthermore, the products were all isolated as virtually pure stereoisomers. The unbranched aldehydes **2a–c** underwent a fast 1,6-addition in excellent yields, diastereoselectivities, and enantioselectivities (Table 1, entries 1–3). Perhaps most notable,

branched aldehydes isovaleraldehyde 2d and citronellal 2e reacted efficiently even though longer reaction times where required to reach completion (40 h and 144 h respectively; Table 1, entries 5 and 6). This lower reactivity is consistent with the higher steric hindrance of the substrates. Again we were happy to see that the expected compounds were still formed with perfect stereocontrol even though they required a longer reaction time (compound 4d and 4e were isolated as single stereoisomers). Furthermore, this protocol could also be applied for unsaturated phenylacetaldehyde 2f, that underwent a high-yielding reaction with excellent diastereoselectivity and enantioselectivity (Table 1, entry 7). This attractive synthon should lead to an enantiomerically pure  $C_2$  symmetric diene by sulfone removal.

To fully explore this remarkable transformation, we then continued to investigate the scope of the reaction by testing the 1,6-conjugate addition of valeraldehyde 2b to a family of 1,3-bis(phenylsulfonyl)butadienes 1a-e in the presence of 30 mol% of organocatalyst in chloroform (Table 2). A variety

Table 2: Scope of the bis(arylsulfonyl) butadienes.



<sup>[</sup>a] Yield of isolated product. [b] Determined by <sup>1</sup>H NMR spectroscopy and HPLC analysis. [c] Determined by HPLC on a chiral stationary phase for the *anti* products.

of different aryl substituents with a range of electronic properties could be used without affecting the overall selectivity of the reaction. All reactions gave greater than 99% conversion by <sup>1</sup>H NMR spectroscopy. The yields of the isolated 1,6-addition products were slightly lower in all cases (71 to 81% yield vs. 98% for the phenyl). This outcome probably arises from an increase in the solubility of the final compounds and results in product loss during workup. When the electron-withdrawing properties of the substituents were increased from F, Cl, to Br the reactions were slightly accelerated. The lower electron density of the acceptor 5f containing a nitro substituent resulted in an impressive increase in reactivity (4 h vs. 24 h to obtain a full conversion; Table 2, entry 6 vs. entry 2). This result is in agreement with a Michael 1,6-addition mechanism and should indicate that the C-C bond formation and not the cyclization is the ratedetermining step. This finding is consistent with the fact that no traces of the noncyclized product could be observed when monitoring the reaction by <sup>1</sup>H NMR spectroscopy.

In addition, the absolute and relative configuration of both the R,R adduct and S,S adduct of **4b** could be determined by X-ray crystallography (Figure 1 and the Supporting Information).<sup>[13]</sup>



*Figure 1.* ORTEP drawing of (R,R)-4b with ellipsoids at 20% probability.

Despite the high synthetic potential of the disclosed reaction, it is also highly interesting in terms of mechanism. Although further experimentation is needed to have a complete understanding of the reaction mechanism, a plausible stepwise mechanism can be proposed (Scheme 2). The absolute configuration of the products is consistent with previous results obtained in 1,4-addition to other Michael acceptors catalyzed by catalyst **3**.<sup>[14]</sup> The acyclic synclinal transition-state model, as described by Seebach and Goliński, could be applied to the 1,6-conjugate addition of aldehydes to 1,3-bis(sulfonyl) butadienes and explains the observed high levels of stereoselectivities.<sup>[15]</sup> Steric repulsion away from the bulky groups of the pyrrolidine ring promotes the selective attack of the *Re* face of the *E-trans* enamine and the *Re* face



*Scheme 2.* Proposed mechanism and transition state. EWG = electron-withdrawing group.

Angew. Chem. Int. Ed. 2011, 50, 5095-5098

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of the Michael acceptor forming **6**. Previous studies have described a similar model for the 1,4-addition of aldehydes to vinyl sulfones,<sup>[10a,b]</sup> nitroolefins,<sup>[16]</sup> and vinyl phosphonates.<sup>[17]</sup> Even though this classical model can rationalize the observed stereoselectivity, several aspects still need to be addressed. The question on whether the catalyst is involved in the cyclization and in promoting the elimination is still not clear. This is more plausible given the fact that no linear product is observed, which implies that the cyclization/elimination steps are fast with the catalyst still involved. Despite the preliminary evidence for a 1,6-addition, a possible [4+2] cycloaddition cannot be ruled out and further investigations should shed light on these interesting problems.<sup>[11,18]</sup>

The products obtained through the 1,6-conjugate addition/condensation reaction are highly interesting building blocks. To illustrate the synthetic utility of this method the adduct 4a was converted into 8 in excellent 97% yield through another conjugate addition of methyllithium (Scheme 3).



**Scheme 3.** Addition of MeLi to 4b for the creation of four contiguous stereogenic centers. THF = tetrahydrofuran.

Perfect regioselectivity and good levels of diasteroselectivities (4:1 d.r.) were obtained for the subsequent creation of two new stereogenic centers in this final molecule containing four contiguous stereocenters. After a simple recrystallization, compound 8 was isolated as a 12:1 mixture of two diasterosiomers in 99% *ee* among the 16 possible stereosiomers. The addition *anti* to the propyl group on the adjacent carbon atom was confirmed using NOE studies and <sup>1</sup>H, <sup>13</sup>C, DEPT, and HSQC spectra. This result highlights the great potential of the obtained dienes for further transformations by indicating the most electrophilic position in 4b.

In conclusion we have developed an unprecedented enamine 1,6-addition by exploiting the properties of charge delocalization in 1,3-bis-(sulfonyl) butadienes. By appropriately designing a Michael acceptor, unique reactivities were obtained for the formation of highly valuable dienes containing two versatile vinyl sulfones. This remarkable reaction should find its applications in total synthesis thanks to its operational simplicity and to the exceptional levels of stereoselectivities of the final products (typically 99% *ee* and 99:1 d.r.). We are convinced that this activation principle by charge delocalization through the addition of a second electron-withdrawing group should serve as a keystone for the development of new powerful 1,6-

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addition reactions. Full mechanistic studies as well as further investigations employing ketones and additional 1,6-acceptors are currently being pursued in our laboratories and will be published in due course.

## **Experimental Section**

Typical procedure for the organocatalytic 1,6-addition reaction: Diene (0.2 mmol, 1 equiv) was added to a sample vial containing (*R*)-diphenylprolinol silyl ether (19,5 mg, 0.06 mmol, 0.3 equiv) dissolved in chloroform (0.5 mL), followed by direct addition of the aldehyde (0.4 mmol, 2 equiv). The reaction mixture was then stirred at RT until the reaction was complete (as evident by TLC). The reaction mixture was concentrated under reduced pressure and triturated with ice-cold methanol ( $2 \times 3$  mL) to yield the solid pure product.

Received: January 31, 2011 Revised: March 3, 2011 Published online: April 28, 2011

Keywords: asymmetric synthesis  $\cdot$  conjugate addition  $\cdot$  dienes  $\cdot$  organocatalysis  $\cdot$  sulfones

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