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First Organocatalyzed Asymmetric Michael Addition of Aldehydes to Vinyl Sulfones

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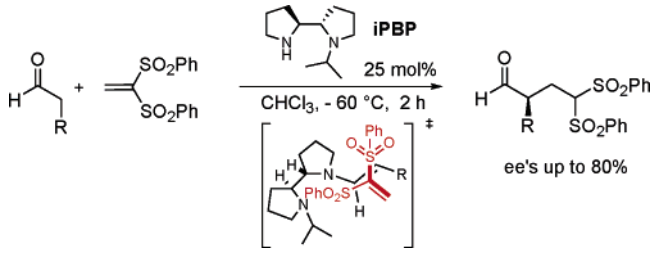
ABSTRACT



The first asymmetric direct Michael addition of aldehydes to vinyl sulfones catalyzed by *N*-*i*Pr-2,2′-bipyrrolidine is described. 1,4-Adducts are obtained in good yields and enantioselectivities. The determination of absolute configuration allowed us to postulate a *Si,Si* transition state model, as shown previously for nitroolefins.

In the past few years, organocatalysis has shown its efficiency in organic synthesis.[1] Following the famous asymmetric annulation developed by Wiechert,[2] Hajos, and Parrish,[3] L-proline brilliantly catalyzed asymmetric 1,2-additions as aldol reactions, Mannich reactions, and α-amination reactions. However, L-proline seems to be less selective in asymmetric 1,4-additions[4] compared to other amines.[4d,5]

Our laboratory has recently reported highly enantioselective Michael addition of aldehydes and ketones to nitroolefins catalyzed by *N*-*i*Pr-2,2′-bipyrrolidine (***i*PBP** 4c).[6] Therefore, we directed our efforts toward applying our catalyst on new Michael acceptors as vinyl sulfones.[7] Although the reaction of preformed enamine with vinyl sulfones has been known for some time,[8] only sporadic examples lead to chiral adducts. Among them, d'Angelo has developed highly diastereoselective Michael additions of chiral imines, derived from

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cyclanones and optically active 1-phenylethylamine to vinyl sulfones. This methodology represents one of the most efficient methods for the stereocontrolled construction of quaternary carbon centers.[9] However, to the best of our knowledge, there is no example of direct enantioselective and/or catalytic conjugate addition of aldehydes to vinyl sulfones.

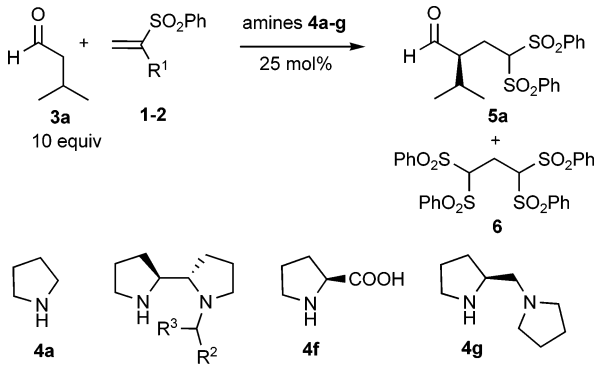
Herein we report the first asymmetric Michael addition of aldehydes to vinyl sulfones catalyzed by 2,2′-bipyrrolidine derivatives. Nowadays, the use of sulfones still remains an important strategy, especially for making C−C bonds.[10] After appropriate transformation, the resulting 1,4-adducts could be involved in reductive alkylation,[11] Julia-type reaction,[12] and remain also powerful nucleophilic reagents.[13]

We first performed the racemic version by using pyrrolidine **4a** as catalyst for the addition of isovaleraldehyde **3a** to phenylvinyl sulfone **1** and 1,1-bis(benzenesulfonyl)-ethylene[14] **2** at room temperature. No conversion was observed with phenylvinyl sulfone **1** after 3 days (Table 1, entry 1), whereas the reaction was completed in 30 min with 1,1-bis(benzenesulfonyl)ethylene **2** (entry 2). The modest yield obtained could be explained by the formation of byproduct **6**, arising from 1,4-addition of bis(phenylsulfonyl)-methane, generated in situ, to 1,1-bis(benzenesulfonyl)-ethylene **2** and the sensitivity of γ-sulfo aldehyde **5a** toward silica gel chromatography.

Therefore, we focused our attention on the vinyl sulfone **2** and carried out the asymmetric version with our previously reported diamines.[6] We ran the experiments at −60 °C to decrease the reaction rate in order to increase stereoselectivity (57% ee, entry 3). The influence of the substituents on the 2,2′-bipyrrolidine was very significant. A small group, such as N-Me **4b** (entry 4), or a too bulky one, such as N-c-Hex **4d** (entry 6) or N-3-pentyl **4e** (entry 7), were revealed to be unselective. Moreover, the smaller the group, the higher was the quantity of byproduct **6**. Finally, the most interesting results were obtained with the secondary group *i*-Pr **4c** (71% yield, 75% ee) (entry 5). This result, with ***i*PBP**, was impressive, as neither L-proline **4f** (entry 8) nor (*S*)-(+)-(1-pyrrolidinylmethyl)pyrrolidine **4g** (entry 9) gave as clean reactions good yields or enantioselectivities.

Screening of solvents with the best organocatalyst **4c** has shown that chlorinated solvents, $CHCl_3$ (entry 5), and anhydrous CH_2Cl_2 (entry 10) gave the highest yields and enantioselectivities. The other solvents tested were dramatically disappointing. No conversion was obtained with anhydrous CH_3CN. MeOH (entry 11) or anhydrous THF

Table 1. Asymmetric Conjugate Addition of Isovaleraldehyde **3a** to Vinyl Sulfones **1**−**2** Catalyzed by Various Amines **4a**−**g**



entry	R^1	cat.	solvent	reaction conditions	yield[a] **5a**:**6**[b] (%)	ee[c] (%)
1[d]	H	**4a**	$CHCl_3$	rt, 4 days	0:0	
2[d]	SO_2Ph	**4a**	$CHCl_3$	rt, 30 min	75:0 (53)[e]	
3	SO_2Ph	**4c**	$CHCl_3$	rt, 30 min	65	57
4	SO_2Ph	**4b**	$CHCl_3$	−60 °C, 2 h	23:50	54
5	SO_2Ph	**4c**	$CHCl_3$	−60 °C, 2 h	71:13	75
6	SO_2Ph	**4d**	$CHCl_3$	−60 °C, 2 h	43:17	58
7	SO_2Ph	**4e**	$CHCl_3$	−60 °C, 2 h	69:6	47
8[f]	SO_2Ph	**4f**	$CHCl_3$	−60 °C, 2 h	n.d.[g]	n.d.
9[f]	SO_2Ph	**4g**	$CHCl_3$	−60 °C, 2 h	25:4	19
10	SO_2Ph	**4c**	$CHCl_2$	−78 °C, 2 h	50:23	66
11	SO_2Ph	**4c**	MeOH	−60 °C, 2 h	65:18	35
12[f]	SO_2Ph	**4c**	CH_3CN	−45 °C, 2 h	n.d.	n.d.
13[f]	SO_2Ph	**4c**	THF	−78 °C, 2 h	15:19	15

[a] Isolated compounds after purification by column chromatography on Florisil. [b] Proportion of compound **6** determined by ^1H NMR of the crude material. [c] Enantioselectivities were measured by chiral Super Fluid Chromatography (SFC). [d] Reaction performed with 0.5 equiv of pyrrolidine **4a**. [e] Isolated yield after purification by column chromatography on silica gel. [f] The reaction was sluggish and led to many byproducts. [g] Not determined.

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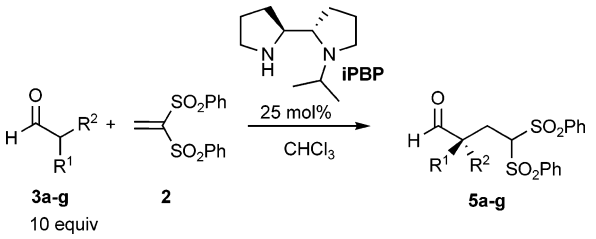
(entry 13) have provided lower yields and enantioselectivities compared to those of $CHCl_3$, which has given the greatest results. Then, with the optimal organocatalyst ***i*PBP 4c** and solvent ($CHCl_3$) in hand, we examined several aldehydes **3a**−**g** to generalize the scope of the reaction.

As revealed in Table 2, the best results were obtained with hindered aldehydes **3a**−**c** (entries 1−3). Isovaleraldehyde **3a**

Table 2. Asymmetric Conjugate Addition of Aldehydes **3a**−**g** to Vinyl Sulfone **2** Catalyzed by Diamine **4c**



entry	aldehyde/ product	R^1	R^2	reaction conditions	yield[a] (%)	ee[b] (%)
1	**3a/5a**	*i*Pr	H	−60 °C, 2 h	71	75
2	**3b/5b**	*t*Bu	H	−60 °C, 2 h	78	80
3	**3c/5c**	*c*Hex	H	−60 °C, 2 h	71	70
4	**3d/5d**	*n*Pr	H	−60 °C, 2 h	76	53
5	**3e/5e**	Me	H	−60 °C, 2 h	72[c]	0[c]
6[d]	**3f/5f**	Me	Me	rt, 1 h	73	
7	**3g/5g**	Et	Me	rt, 4 h	59	12
8	**3h/5h**	Ph	Me	rt, 7 h	14(15)[e]	0

[a] Isolated yields after purification by column chromatography on Florisil. [b] Enantioselectivities were measured by Super Fluid Chromatography (SFC). [c] Determined on the reduced aldehyde **5e** to the corresponding primary alcohol **7e**. [d] Reaction performed with 0.5 equiv of pyrrolidine **4a**. [e] Conversion determined by ^{1}H NMR on the crude material.

and 2-cyclohexylacetaldehyde[15] **3c** afforded their respective adducts **5a** and **5c** in good yields (71%) and enantioselectivities (75 and 70%, entries 1 and 3). Reaction with the more bulky 3,3-dimethylbutyraldehyde **3b** gave the highest yield (78%) and enantioselectivity (80%) (entry 2). Valeraldehyde **3d** produced adduct **5d** in good yield (76%), but in modest enantioselectivity (53%, entry 4). Smaller substrate **3e** showed similar reactivity, but no stereoselectivity was observed (entry 5). Consequently, the more hindered the aldehyde, the better was the enantioselectivity.

The formation of quaternary carbon centers with α,α-dialkyl-substituted aldehydes proved to be considerably less easy and required higher temperature (25 °C) for complete conversion (entries 6 and 7). The differentiation between methyl and ethyl in 3-methylbutyraldehyde **3g** was obviously not enough to provide a good stereocontrol (12% ee, entry 7). Finally, 2-phenylpropionaldehyde **3h** reacted very slowly with no selectivity, probably due to the presence of a too labile proton in the α-position of the carbonyl (entry 8).

The absolute configuration of the adduct **5a** was determined by comparison of the optical rotation of alcohol **8**

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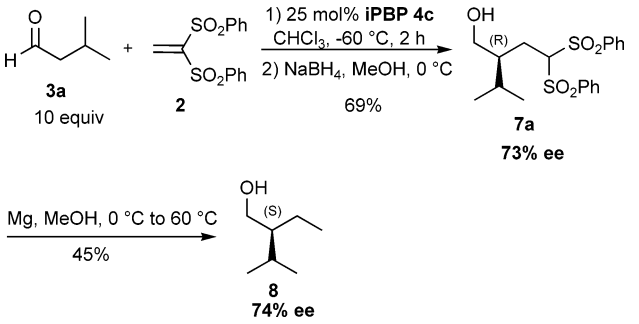
Scheme 1. Determination of Absolute Configuration of 1,4-Adduct **5a** by Synthesis of Alcohol **8**



with the literature data (Scheme 1).[16] Indeed, the crude aldehyde **5a** can be easily converted to the primary alcohol **7a** in 69% overall yield and 73% ee.

We then tested several conditions to transform the sulfone group into hydrogen,[11a] but most of them led either to the recovery of the starting material[17] or to the elimination of only one sulfone,[18] probably due to the presence of nonactivated geminal bis-sulfones. Fortunately, the bis-desulfonylation could be performed using activated magnesium turnings in MeOH.[19] Hence, alcohol **8** was obtained in 45% yield without any loss of enantioselectivity (74% ee). We deduced the absolute configuration of product **5a** (*R*) by measurement of the optical rotation of the derivative **8** (*S*), with an inversion of CIP priority.[20] It may be considered that the configuration of the others adducts **5b**−**h** is the same.

The determination of absolute configuration allowed us to propose a transition state model to explain the selectivity of the 1,4-addition. The acyclic synclinal model described by Seebach,[21] involving a *trans* enamine intermediate, could be applied to the addition of aldehydes to vinyl sulfones, as shown previously for nitroolefins.[6] Actually, α-substituted nitroolefins have displayed better enantioselectivities than geminal bis-sulfone, implying that the selectivity depends on steric hindrance. Consequently, the less hindered *Si*,*Si* transition state is well favored compared to the *Re*,*Re* and leads to the (*R*) adduct (Scheme 2).

Scheme 2. Proposed Transition State Model for Diamine-Catalyzed Michael Addition

In conclusion, we have disclosed the first direct asymmetric conjugate addition of aldehydes to vinyl sulfones

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catalyzed by ***i*PBP** derived from 2,2′-bipyrrolidine. The reaction proceeds with good yields and enantioselectivities. The full scope of this reaction, including addition of ketones, is presently being investigated. Further applications of this methodology and developments of new organo-catalyzed reactions are currently underway in our laboratory.

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Supporting Information Available: Experimental procedures, ^{1}H and ^{13}C spectra, and chiral separations for compounds **5a**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Use of Al−Hg. For the preparation of aluminium amalgam, see: (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345. For examples, see: (b) Du Penhoat, C. H.; Julia, M. *Tetrahedron* **1986**, *42*, 4807. (c) Posner, G. H.; Asirvatham, E. *J. Org. Chem.* **1985**, *50*, 2589.

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