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The Use of N-*i*Pr-2,2'-bipyrrolidine Derivatives as Organocatalysts for Asymmetric Michael Additions

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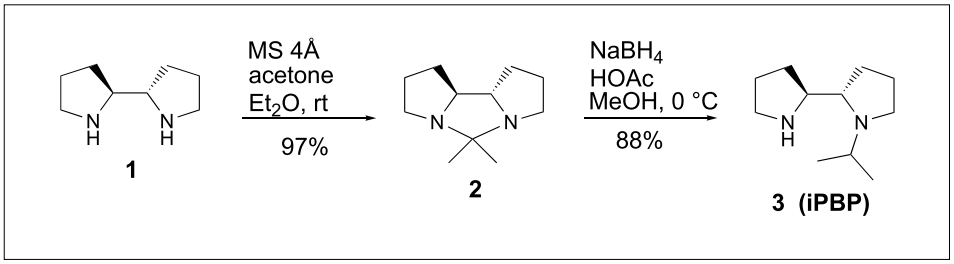
Abstract: The recent rapid growth of organocatalysis has shown a new approach in organic chemistry and presents the obvious advantage in the avoidance of expensive and often toxic metals. Moreover, the organocatalysts are generally easier to make than standard catalytic reagents. Therefore, our laboratory has synthesized N-alkyl-2,2'bipyrrolidine derivatives as a new class of organocatalysts and applied them to the asymmetric Michael addition of ketones and aldehydes to nitroolefins *via* an enamine intermediate. We have furthermore developed the first asymmetric Michael addition of aldehydes to vinyl sulfones catalyzed with our diamines. The 1,4 adducts are obtained in good yields with enantioselectivities up to 80% ee. The determination of absolute configuration allowed us to postulate a *Si*,*Si* transition state model, as described previously for nitroolefins.

Keywords: Asymmetric catalysis · Conjugate addition · Diamine · Organocatalysis · Vinyl sulfones

Introduction

The interest in the field of organocatalysis has increased intensively in the last few years [1–5]. Many asymmetric reactions can be promoted by organic aminocompounds. These aminocatalysts operate through diverse mechanisms by converting the substrates either into activated nucleophiles or electrophiles. Among these mechanisms, enamine catalysis involves a nucleophilic enamine intermediate catalytically generated *via* deprotonation of an iminium ion. The first asymmetric enamine catalysis was developed by Wiechert and coworkers [6], and Hajos and Parrish [7] for the intramolecular aldol reaction catalyzed by l-proline. Only recently, a great number of examples have been reported opening up new areas for enamine catalysis. Among all these organocatalyzed reactions, conjugate addition has been less extensively explored [8–20] although it represents one of the most important C–C bond forming reactions in organic chemistry [21].



Scheme 1. Synthesis of organocatalyst N-*i*Pr-2,2'-bipyrrolidine **3** (**iPBP**)

Our laboratory recently reported a new asymmetric synthesis of optically pure 2,2'-bipyrrolidine [22] which can also be obtained easily by photodimerization of the pyrrolidine followed by a resolution with tartaric acid [23]. We then decided to study this new chiral pyrrolidine-type amine as an organocatalyst for Michael reactions. Here, we will give a short overview on our research aimed at the synthesis of 2,2'-bipyrrolidine derivatives and their applications in the enantioselective Michael addition of aldehydes to nitrostyrene [24] and vinyl sulfones [25].

Results and Discussion

In contrast to results obtained with diamine catalysts, reaction of aldehydes with l-proline and its analogues provided only trace amounts of the Michael adducts in low enantioselectivity [26]. We first synthesized many N-alkyl-2,2'-bipyrrolidine derivatives in order to study their catalytic activity for the organocatalyzed Michael addition of aldehydes (**4a**–**f**) to nitrostyrene (**5**). Thus, a wide range of new diamines were prepared starting from 2,2'-bipyrrolidine and a variety of ketones and aldehydes (Scheme 1). The aminals of aldehydes and not hindered ketones were formed easily whereas bulky ketones such as diisopropylketone or benzophenone did not afford the desired aminals. The aminals

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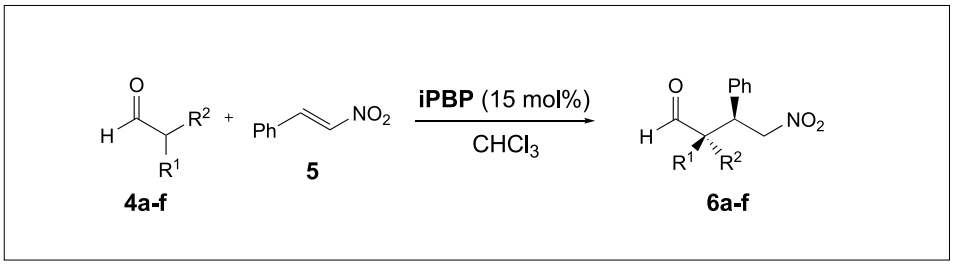
were reduced without previous purification with sodium borohydride in methanol with acetic acid. The mono N-alkylated diamines were obtained in about 85% overall yields after purification by kugelrohr distillation.

In preliminary results, the N-*i*Pr-2,2'-bipyrrolidine **3** (**iPBP**) appeared the most efficient organocatalyst for the conjugate addition of valeraldehyde (**4c**) to nitrostyrene (**5**). Consequently, we focused our attention on the N-iPr derivative and examined several aldehydes (**4a**–**f**) to generalize the scope of the reaction (Scheme 2 and Table 1).

As shown in Table 1, the adducts were obtained in excellent enantioselectivities and with good *syn* diastereoselectivity in all cases. The highest rate of reaction was observed for propionaldehyde (**4a**) (entry 1), even if the reaction was performed at –25 °C (entry 2). Decreasing the temperature improved the enantio- and diastereoselectivity which increased from 77% ee and 75:25 dr (entry 1) to 93% ee and 94:6 dr (entry 2) for (**4a**). Other linear aldehydes such as butyraldehyde (**4b**) and valeraldehyde (**4c**) also reacted at –25°C with high enantioselectivities, 81% ee (entry 3) and 87% ee (entry 4) respectively, nevertheless a longer reaction time is needed. The reactivity becomes slower as the aldehyde becomes bulkier. Indeed, isovaleraldehyde (**4d**) reacted only at room temperature and yielded the adduct (**6d**) with a good enantioselectivity (73% ee) (entry 5). Moreover, the formation of a quaternary carbon center is also satisfying, since in the reaction of isobutyraldehyde (**4f**) with nitrostyrene (**5**) the product (**6f**) was obtained with 80% ee (entry 7). Unfortunately, this method also has its limitations. Phenylacetaldehyde (**4e**) gave the addition product (**6e**) in poor yield (19%) and enantioselectivity (26% ee), probably due to the presence of a too labile proton in the α-position of the carbonyl (entry 6).

We proposed a transition state model based on steric hindrance to explain the selectivity of the 1,4 addition (Scheme 3). The *anti* enamine would be formed selectively and would react with nitrostyrene *via* an acyclic synclinal transition state described by Seebach and Golinski [27] in which there are favorable electrostatic interactions between the nitrogen of the enamine and the nitro group. The bulky isopropyl group would promote the selective formation of the *anti* enamine and selective shielding of the *Re*,*Re* approach.

After having designed a new class of organocatalysts for the enantioselective Michael addition of aldehydes and ketones to nitroolefins [24], we targeted a further use of N-alkyl-2,2'-bipyrrolidine derivatives in the first enantioselective conjugate addition of aldehydes to vinyl sulfones [25].

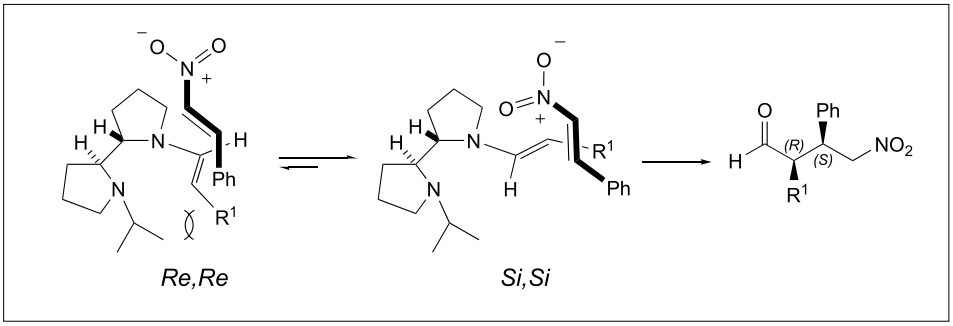


Scheme 2. Asymmetric conjugate addition of aldehydes **4a–f** to nitrostyrene (**5**) catalyzed by diamine **3** (**iPBP**)

Table 1. Asymmetric conjugate addition of aldehydes **4a–f** to nitrostyrene (**5**) catalyzed by diamine **3** (**iPBP**)

entry	Aldehyde/product	R^1	R^2	reaction conditions	yield[a] [%]	dr[b] *syn*:*anti*	ee[c] (*syn*) [%]
1	**4a/6a**	Me	H	rt, 1h 30	99	75:25	77
2	**4a/6a**	Me	H	–25 °C, 2 d	71	94:6	93
3	**4b/6b**	Et	H	–25 °C, 4 d	70	90:10	81
4	**4c/6c**	*n*-Pr	H	–25 °C, 4 d	98	96:4	87
5	**4d/6d**	*i*-Pr	H	rt, 2 d	99	87:13	73
6	**4e/6e**	Ph	H	rt, 2 d	19	72:28	26
7	**4f/6f**	Me	Me	rt, 3 d	72	–	80 (*R*)

[a]Isolated yields after purification by column chromatography on silica gel. [b]Diastereoselectivities were determined by ^{1}H NMR or SFC on the crude material. [c]Enantioselectivities were measured by chiral super fluid chromatography (SFC). Relative (*syn*) and absolute configurations of aldehydes **6a**, **6b** and **6d** were determined by comparison with known literature data [5b]. The stereochemistries of aldehydes **6c**, **6e** and **6f** have been assigned assuming the same stereochemical pathway for all the aldehydes.

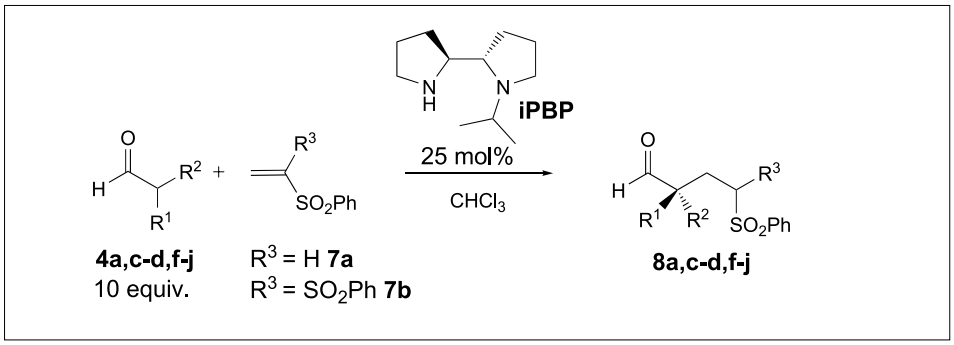


Scheme 3. Proposed transition state model for diamine-catalyzed Michael addition of aldehydes to nitrostyrene

Although significant advancement has been made in the use of chiral auxiliary to develop asymmetric conjugate additions to vinyl sulfones, only sporadic examples constitute an enantioselective pathway. Among them, Deng and coworkers reported the first highly enantioselective organocatalyzed conjugate addition of α-substituted α-cyanoacetate to vinyl sulfones [28].

We first performed the racemic version by using pyrrolidine as catalyst for the addition of isovaleraldehyde (**4d**) to phenylvinyl sulfone (**7a**) and 1,1-bis(benzenesulfonyl)ethylene (**7b**) at room temperature. No conversion was observed with phenylvinyl sulfone (**7a**) after three days (Scheme 4, Table 2, entry 1), whereas the reaction was completed in 30 min with 1,1-bis(benzenesulfonyl)ethylene (**7b**) (entry 2).

Consequently, we carried on our investigations with vinyl sulfone (**7b**) and performed the asymmetric version with our N-alkyl-2,2'-bipyrrolidine derivatives. Once again, the **iPBP** was revealed to be the best organocatalyst [25]. The enantioselectivity was found to be critically dependent on the temperature. A decrease in the temperature from room temperature to –60 °C resulted

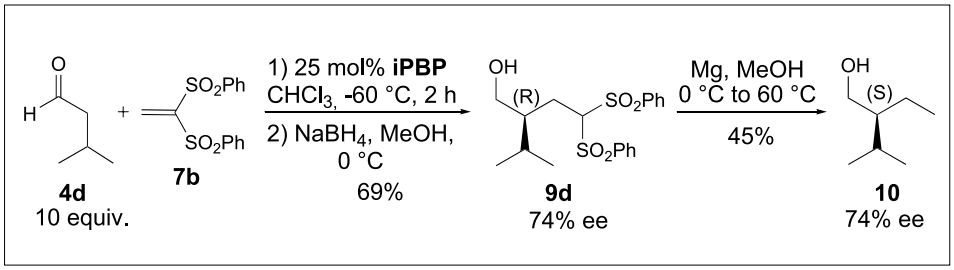


Scheme 4. Asymmetric conjugate addition of aldehydes **4a**,**c**,**d**,**f–h** to vinyl sulfones **7a–b** catalyzed by diamine **3** (**iPBP**)

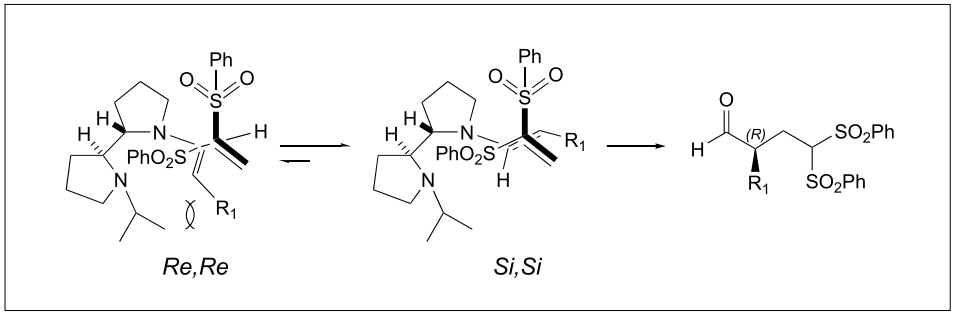
Table 2. Asymmetric conjugate addition of aldehydes **4a,c,d,f–h** to vinyl sulfones **7a–b** catalyzed by diamine **3** (**iPBP**)

entry	Aldehyde/product	R^1	R^2	R^3	reaction conditions	yield[a] [%]	ee[b] [%]
1[c]	**4d/8d**	*i*-Pr	H	H	rt, 4 d	0	–
2[c]	**4d/8d**	*i*-Pr	H	SO_2Ph	rt, 30 min	75	–
3	**4d/8d**	*i*-Pr	H	SO_2Ph	rt, 30 min	65	57
4	**4d/8d**	*i*-Pr	H	SO_2Ph	–60 °C, 2 h	71	75
5	**4g/8g**	*t*-Bu	H	SO_2Ph	–60 °C, 2 h	78	80
6	**4h/8h**	*c*-Hex	H	SO_2Ph	–60 °C, 2 h	71	70
7	**4c/8c**	*n*-Pr	H	SO_2Ph	–60 °C, 2 h	76	53
8	**4a/8a**	Me	H	SO_2Ph	–60 °C, 2 h	72[d]	53
9[c]	**4f** / **8f**	Me	Me	SO_2Ph	rt, 1 h	73	–
10[e]	**4d/8d**	*i*-Pr	H	SO_2Ph	–60 °C, 2 h	–	–

[a]Isolated yields after purification by column chromatography on Florisil. [b]Enantioselectivities were measured by chiral super fluid chromatography (SFC). [c]Reaction performed with 0.5 equiv. of pyrrolidine. [d]Determined on the alcohol **9a** coming from the reduction of the aldehyde **8a**.[e]Reaction performed with 0.25 equiv. of L-proline.



Scheme 5. Determination of absolute configuration of 1,4-adduct **8d** with desulfonylation as the key step



Scheme 6. Proposed transition state model for diamine-catalyzed Michael addition of aldehydes to vinyl sulfone

in a significant increase in enantioselectivity to 75% ee (entry 4 *vs.* entry 3). Actually, the hindered aldehydes (**4d**,**g**,**h**) show the best results (entry 4, 5, 6). The adduct (**8h**) coming from 2-cyclohexylacetaldehyde (**4h**) was isolated in good yield (71%) and enantioselectivity (70% ee) (entry 6). Reaction with the more bulky 3,3-dimethylbutyraldehyde gave the highest yield (78%) and enantioselectivity (80% ee) (entry 5). Normally, this aldehyde is too hindered to react as a Michael donor, and there was no conversion with nitroolefins. A linear aldehyde such as valeraldehyde (**4c**) produced adduct (**8c**) in good yield (76%), but in modest enantioselectivity (53% ee, entry 7). The smaller substrate (**4a**) afforded the best enamine with nitroolefins, showed similar reactivity to the other aldehydes with vinyl sulfone (**7b**), but no stereoselectivity was observed (entry 8). Isobutyraldehyde (**4f**) allowed the formation of a quaternary carbon center, but required higher temperature (25 °C) for complete conversion (entry 9). Finally, the results obtained with **iPBP** were impressive since L-proline could not catalyze Michael addition of isovaleraldehyde (**4d**) to vinyl sulfone (**7b**) (entry 10).

The absolute configuration of the adduct (**8d**) was determined by comparison of the optical rotation of alcohol (**10**) with the literature data [29] (Scheme 5). Indeed, the crude aldehyde (**8d**) can be easily converted to the primary alcohol (**9d**) in 69% overall yield and 74% ee.

We then tested several conditions to remove the sulfone group [30] and fortunately, the bis-desulfonylation could be performed using activated magnesium turnings in MeOH [31]. Hence, alcohol (**10**) was obtained in 45% yield without any loss of enantioselectivity (74% ee). We deduced the absolute configuration of product (**8d**) (*R*) by measurement of the optical rotation of the derivative **(10)** (*S*), with an inversion of CIP priority. It may be assumed that the configuration of the other adducts (**8a**,**c**,**d**,**f–h**) is the same.

The determination of absolute configuration allowed us to propose the same transition state model as shown previously for nitroolefins to explain the selectivity of the 1,4-addition. Consequently, the less hindered *Si,Si* transition state is well favored compared to the *Re,Re* and leads to the (*R*)-adduct (Scheme 6).

Conclusion

In summary, we have found new pyrrolidine-type organocatalysts and we have demonstrated their efficiency in enantioselective conjugate addition of aldehydes with two different Michael acceptors: nitroolefins and vinyl sulfones. Further applica-

tions of these 2,2'-bipyrrolidine derivatives and developments of new organo-catalyzed reactions are currently underway in our laboratory.

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