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3,3′-Bimorpholine Derivatives as a New Class of Organocatalysts for Asymmetric Michael Addition

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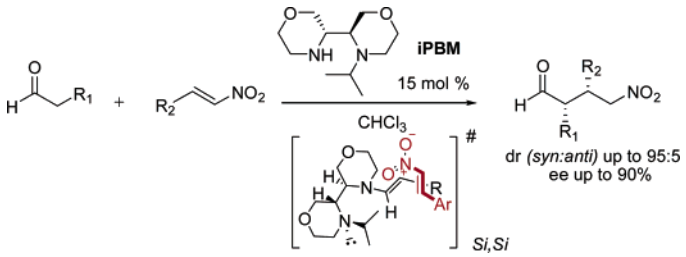
ABSTRACT



New *N*-alkyl-3,3′-bimorpholine derivatives (*i*PBM) were revealed to be efficient organocatalysts for the asymmetric direct Michael addition of aldehydes to nitroolefins and a vinyl sulfone. In these transformations using *i*PBM, 1,4-adducts were afforded in high yields, with good to high levels of diastereo- and enantioselectivity. The stereochemical outcome of the reaction could be explained by an acyclic synclinal model.

Interest in the field of organocatalysis has increased intensively in the past few years.[1,2] Many asymmetric reactions can be promoted by organic amino compounds. 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,[3] Hajos, and Parrish[4] for the intramolecular aldol reaction catalyzed by L-proline. Only recently, a great number of examples have been reported opening new areas for enamine catalysis. Among all these organocatalyzed reactions, conjugate addition has been less extensively explored,[5−9] although it represents one of the most important C−C bond

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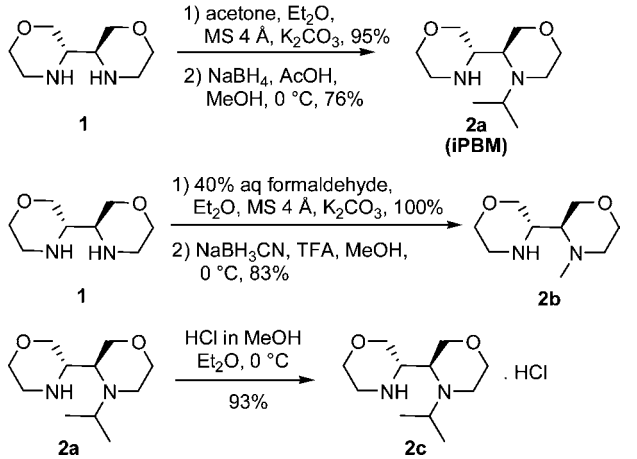
forming reactions in organic chemistry.[10] In this area, we have recently synthesized new chiral pyrrolidine-type amine organocatalysts derived from 2,2′-bipyrrolidine, and we have applied them to the enantioselective conjugate addition of aldehydes and ketones to nitroolefins via an enamine intermediate in high yields and selectivities.[11] We have furthermore developed the first asymmetric Michael addition of aldehydes to vinyl sulfones catalyzed by our diamines in enantioselectivities up to 80% ee.[12]

In our investigations to design new organocatalysts, we have described the first asymmetric synthesis of heterocyclic C_2-symmetric 3,3′-bimorpholine,[13] and we were interested in introducing *N*-alkyl moiety to perform asymmetric conjugate additions of carbonyl donors to Michael acceptors. Other than the results reported by Seebach on diastereoselective conjugate addition of preformed enamine derived from morpholine to nitroolefins,[14] only Dixon has performed an enantioselective variant.[15] Typically, pyrrolidine-based catalysts are much more effective than six-membered cyclic amines as organocatalysts. Although some organocatalysts contain a morpholine moiety or morpholine sometimes acts as organocatalyst,[16] to the best of our knowledge, there is no example of efficient bicyclic six-membered ring organocatalysts, such as 3,3′-bimorpholine derivatives.

Herein, we present the synthesis of new *N*-alkyl-3*S*,3′*S*-bimorpholine derivatives and their applications in asymmetric direct Michael addition of aldehydes to nitroolefins and a preliminary result concerning conjugate addition of isovaleraldehyde to 1,1-bis(benzenesulfonyl)ethylene.

We have first prepared *N*-alkyl-3*S*,3′*S*-bimorpholine derivatives **2a**−**c** using our methodology based on aminal formation, followed by its reduction (Scheme 1).[11d]

Scheme 1. Synthesis of 3,3′-Bimorpholine Derivatives **2a**−**c**



The *N*-*i*Pr-3*S*,3′*S*-bimorpholine **2a** (*i*PBM) was prepared starting from 3*S*,3′*S*-bimorpholine **1** and acetone. The imidazolidine or aminal was formed easily and reduced with sodium borohydride in methanol with acetic acid without previous purification. The mono *N*-*i*Pr-diamine **2a** (*i*PBM) was obtained in 72% overall yields after purification by Kugelrohr distillation. The *N*-Me-3*S*,3′*S*-bimorpholine **2b** was similarly obtained in 83% overall yields. Finally, *i*PBM hydrochloride **2c** was formed nearly quantitatively using a solution of 1.25 M HCl in methanol. A comparative study of their catalytic activity and selectivity has been carried out for the organocatalyzed Michael addition of aldehydes and ketones to nitroolefins.

These new diamines **2a**−**c** were first tested in the asymmetric addition of isovaleraldehyde **3a** to β-nitrostyrene **4** in $CHCl_3$ at room temperature using 15 mol % of catalyst corresponding to the same conditions as described previously[11] (Table 1).

The influence of the substituents on the 3*S*,3′*S*-bimorpholine was very significant. According to the preliminary results, *N*-*i*Pr (entry 1) has been revealed to be more selective than a smaller group, such as *N*-Me (entry 2). The best

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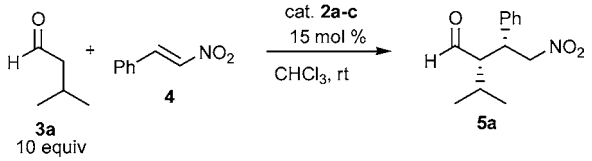
Table 1. Asymmetric Conjugate Addition of Isovaleraldehyde **3a** to β-Nitrostyrene **4** Catalyzed by 3,3′-Bimorpholine Derivatives **2a**−**c**



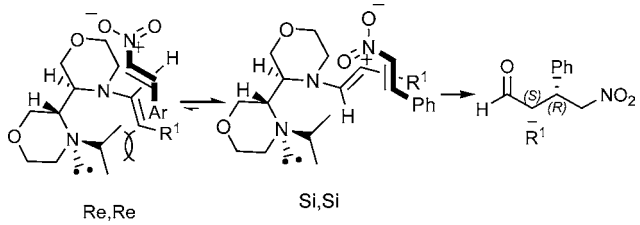
entry	cat.	time (days)	conv[a] (%)	yield[b] (%)	dr[a] *syn*:*anti* (%)	ee[c] (*syn*) (%)
1	**2a**	3	100	85	94:6	88
2	**2b**	8	73	59	93:7	64
3	**2c**	8	100	68	95:5	91

[a] Determined by ^{1}H NMR on the crude material. [b] Isolated yields after purification by column chromatography on silica gel. [c] Enantiomeric excess determined by chiral SFC. Relative (*syn*) and absolute configuration of aldehyde **5a** were determined by comparison with known literature data.[6a,11]

enantioselectivity and diastereoselectivity were observed with *i*PBM hydrochloride **2c** (entry 3) to the detriment of reactivity and yield. Consequently, we have focused our attention on the *N*-*i*Pr derivative *i*PBM **2a** reaching the best compromise in terms of selectivity and reactivity. Moreover, although our 2,2′-bipyrrolidine derivatives have proved themselves to be efficient organocatalysts in conjugate addition, *i*PBM **2a** has displayed better stereoselectivity (entry 3, dr *syn*:*anti* 94:6, 88% ee) than *N*-*i*Pr-2*S*,2′*S*-bipyrrolidine in this case (dr *syn*:*anti* 87:13, 73% ee).[11,17]

We suppose that selectivity depends on steric hindrance and reaction rate. Thereby, if the reaction rate decreases while keeping enough reactivity, the stereoselectivity can increase. The preferred diastereo- and enantioselectivity could be explained in terms of the potential transition states *Re*,*Re* or *Si*,*Si* for the 1,4-addition using *i*PBM **2a** as organocatalyst (Scheme 2). The *anti* enamine would be formed selectively

Scheme 2. Proposed Transition State Model



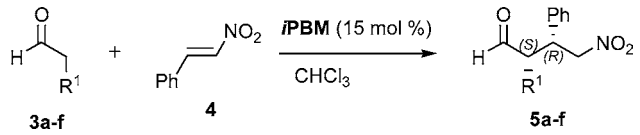
and would react with nitroolefins via an acyclic synclinal transition state described by Seebach,[14] in which there are favorable electrostatic interactions between the nitrogen of the enamine and the nitro group, as shown previously with 2,2′-bipyrrolidine derivatives.[11,12]

(17) This result was obtained for Michael addition of isovaleraldehyde **3a** to β-nitrostyrene **4** catalyzed by *N*-*i*Pr-2*S*,2′*S*-bipyrrolidine (*i*PBP) at room temperature in 2 days for total conversion.

The bulky isopropyl group would promote the selective formation of the *anti* enamine and selective shielding of the *Re*,*Re* approach. Consequently, the less hindered *Si*,*Si* transition state is well favored compared to the *Re*,*Re* and leads to the *syn* (*S*,*R*) adduct.

Then, with the optimal catalyst *i*PBM **2a** in hand, we have examined several aldehydes **3a**−**f** to confirm the efficiency of 3,3′-bimorpholine derivatives in the addition to β-nitrostyrene **4** (Table 2).

Table 2. Asymmetric Conjugate Addition of Aldehydes **3a**−**f** to β-Nitrostyrene **4** Catalyzed by *i*PBM



entry	R^1 (ald./prod.)	reaction conditions	conv[a] (%)	yield[b] (%)	dr[a] *syn*:*anti* (%)	ee[c] (*syn*) (%)
1	*i*Pr (**3a/5a**)	3 days, rt	100	85	94:6	88
2	*t*Bu (**3b/5b**)	8 days, rt	0			
3	Me,Me (**3c/5c**)	8 days, rt	0			
4	*n*Pr (**3d/5d**)	3 days, rt	100	88	87:13	89
5	*c*Hex (**3e/5e**)	13 days, rt	100	88	95:5	90
6	Me (**3f/5f**)	1 day, rt	100	90	82. 18	74
7	Me (**3f/5f**)	3 days, −3 °C	100	86	90:10	80

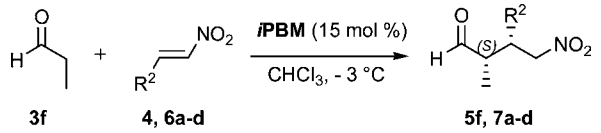
[a] Determined by ^{1}H NMR on the crude material. [b] Isolated yields after purification by column chromatography on silica gel. [c] Enantiomeric excess determined by chiral SFC or chiral GC. Relative (*syn*) and absolute configuration of aldehyde **5a**, **5d**, and **5f** were determined by comparison with known literature data.[6a,11] The stereochemistry of aldehyde **5e** has been assigned by comparison with analogous compounds.

The reactivity differs significantly depending on the type of aldehyde donor. The bulkier 3,3-dimethylbutyraldehyde **3b** (entry 2) and isobutyraldehyde **3e** (entry 3) did not react with nitrostyrene **4**, probably due to a too large steric hindrance. The reaction with moderate hindered aldehydes, such as isovaleraldehyde **3a** (entry 1), valeraldehyde **3d** (entry 4), and 2-cyclohexylacetaldehyde **3e** (entry 5), has proceeded with the formation of the desired products **5a**,**d**,**e** in high yields and with high diastereo- and enantioselectivities. Propionaldehyde **3f** corresponding to the smallest substrate has produced adduct **5f** at room temperature in good yield but with a slightly lower selectivity (entry 6) than that of the others aldehydes. Besides affording good results, linear aldehydes, such as valeraldehyde **3d** and propionaldehyde **3f**, have shown the highest reaction rate at room temperature. Finally, decreasing the temperature has allowed the enantio- and diastereoselectivity to increase from 74% ee and 82:18

dr *syn*:*anti* (entry 6) to 80% ee and 90:10 dr *syn*:*anti* (entry 7) for propionaldehyde **3f**.

Since the methyl group is one of the most interesting substituents in organic synthesis, we have investigated the addition of propionaldehyde **3f** to various nitroolefins **4** and **6a**−**d** to conclude our study (Table 3).

Table 3. Asymmetric Conjugate Addition of Propionaldehyde **3f** to Nitroolefins **4**, **6a**−**d** Catalyzed by *i*PBM



3f **4, 6a-d** **5f, 7a-d**

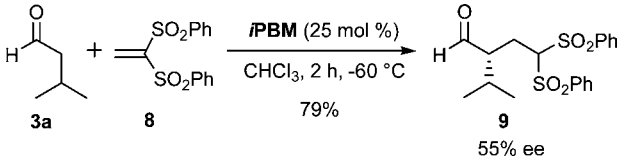
entry	R^2 (nitrool./prod.)	time (days)	conv (%)[a]	yield (%)[b]	dr[a] *syn*:*anti* (%)	ee[c] (*syn*) (%)
1	Ph (**4/5f**)	3	100	86	90:10	80
2	2-thienyl (**6a/7a**)	3	100	89	89:11	79
3	4-ClPh (**6b/7b**)	3	100	84	80:20	75
4	4-MeOPh (**6c/7c**)	3	100	81	84:16	78
5	*c*Hex (**6d/7d**)	13	25	23	85:15	85

[a] Determined by ^{1}H NMR on the crude material. [b] Isolated yields after purification by column chromatography on silica gel. [c] Enantiomeric excess determined by chiral SFC or chiral GC. Relative (*syn*) and absolute configuration of aldehydes **7a**−**d** have been assigned by comparison with aldehyde **5f**.

3*S*,3′*S*-Bimorpholine derivative **2a** (*i*PBM) has given good results in the asymmetric Michael addition, but it was also found to be general with regard to aromatic nitroolefins (entries 1−4). Interestingly, the nature of the aromatic nitroolefins had no influence either on the stereoselectivity or the yield. Neutral nitroolefin **4** (entry 1), heteroaromatic nitroolefin **6a** (entry 2), electron-poor nitroolefin **6b** (entry 3), and electron-rich nitroolefin **6c** (entry 4) have been suitable acceptors. However, the nonaromaticity of the group on the nitroolefin has played a crucial role in terms of reactivity. Although the stereoselectivity was maintained, the reactivity and, consequently, the yield have dramatically decreased in the case of saturated nitroolefin **6d** (entry 5). Finally, irrespective of the substitution pattern, good diastereo- and enantioselectivity were obtained regardless of the nitroolefin (entries 1−5).

Finally, the results of a preliminary study have demonstrated that *i*PBM **2a** has also catalyzed Michael addition of aldehydes to 1,1-bis(benzenesulfonyl)ethylene **8**. Under the reaction conditions described previously,[12] addition of isovaleraldehyde **3a** to vinyl sulfone **8** resulted in the formation of the adduct **9** in 79% yield and 55% ee (Scheme 3).

Scheme 3. Asymmetric Conjugate Addition of Isovaleraldehyde **3a** to Vinyl Sulfone **8** Catalyzed by *i*PBM



3a **8** **9**

55% ee

In conclusion, we have developed new 3,3′-bimorpholine derivatives for the asymmetric conjugate addition of various aldehydes to different nitroolefins. The reaction with *N*-*i*Pr-3,3′-bimorpholine *i*PBM has proceeded in good yields, enantio- and diastereoselectivities. Moreover, we have found that *i*PBM can be interestingly used to promote asymmetric Michael addition of aldehydes to vinyl sulfones. Hence, 3,3′-bimorpholine derivatives have proved to be a new class of efficient bicyclic six-membered ring organocatalysts.

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Supporting Information Available: Experimental procedures, ^{1}H and ^{13}C spectra, and chiral separations for compounds **5a**−**f** and **7a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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