Asymmetric Catalysis

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Organocatalytic Enantioselective [3+2] Cycloaddition of Azomethine Ylides and α,β-Unsaturated Aldehydes**

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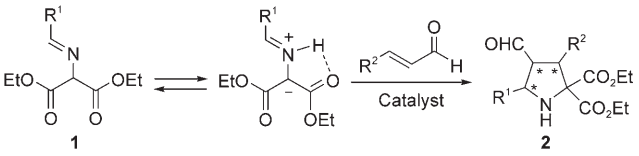
Asymmetric organocatalysis is a very rapidly growing field of research as a result of both the novelty of the concept and the high efficiency and selectivity of many organocatalytic transformations.[1] The operational and economic advantages associated with this methodology, together with the fact that organocatalysts are environmentally friendly, robust, and very often commercially available, have led many research groups to engage in the development of organocatalytic procedures for transformations which are typically carried out with transition-metal catalysts. In this context, proline and other chiral secondary amines proved to be extremely useful catalysts for many reactions. Recently, McMillan and coworkers showed that cycloaddition reactions can take place in a very efficient manner under organocatalytic conditions owing to the formation of an iminium ion intermediate and a consequent decrease in the energy of the lowest unoccupied molecular orbital (LUMO) of the dienophile.[2]

The catalytic asymmetric [3+2] cycloaddition reaction can be considered as one of the most powerful and reliable tools for the enantioselective synthesis of five-membered heterocyclic systems.[3] The asymmetric [3+2] cycloaddition of azomethine ylides and alkenes is of particular interest because it allows the preparation of enantiomerically enriched pyrrolidine structures,[4] which are constituents of many natural products and pharmaceuticals. However, despite intensive efforts in recent years by several research groups, who have developed a number of very efficient protocols for performing this reaction with chiral metal complexes as catalysts,[5] an organocatalytic asymmetric version of this important transformation remains elusive.[6]

We designed the transformation depicted in Scheme 1. It is known that α-amino acid imines can undergo thermal 1,2-prototropy to produce azomethine ylides in a kinetically controlled process;[7] the acidity of the α hydrogen atom is a key parameter in terms of whether or not this process occurs.[8] We envisaged that imines **1** would undergo this 1,2-prototropy process very readily to afford a stabilized azomethine ylide, which would react with an α,β-unsaturated aldehyde under organocatalytic conditions upon the activation of the aldehyde as an iminium ion. Differentiation of the enantiotopic faces of the dienophile as a result of the chirality of the secondary amine catalyst would lead to the formation of an enantiomerically enriched pyrrolidine **2**.



Scheme 1. Proposed enantioselective organocatalytic [3+2] cycloaddition of azomethyne ylides and α,β-unsaturated aldehydes.

We started our investigation with a set of experiments directed at the identification of the most efficient amine catalyst for the cycloaddition of imine **1a** and crotonaldehyde as a model reaction (Table 1).[9] We found that proline (**3**) catalyzed the reaction very efficiently to afford **2a** in good yield as a single *endo* isomer but with moderate enantioselectivity (Table 1, entry 1), while the use of modified proline compounds, such as **4** and **5**, did not lead to a significant improvement (Table 1, entries 2 and 3). The pyrrolidine catalyst **6** furnished **2a** in excellent yield but with almost no stereoselectivity (Table 1, entry 4), and imidazolidinone **7**, which performs well in the [3+2] cycloaddition of α,β-unsaturated aldehydes with nitrones,[6a] was inactive in this transformation (entry 5). However, when we carried out the reaction with commercially available α,α-diphenylprolinol (**8**) as the catalyst, the cycloaddition product was obtained as a single *endo* isomer and with excellent enantioselectivity (Table 1, entry 6). The necessity of the free OH group in the catalyst structure was verified by the lack of catalytic activity of the protected derivative **9** (Table 1, entry 7). The use of the modified diaryl prolinol **10** led to a similar yield and similar stereoselectivity to those observed with **8** (Table 1, entry 8).

We found that an increase in the temperature to 4 °C had a positive influence on the yield of the product. At this temperature, the high stereoselectivity of the reaction with catalyst **8** was maintained (Table 1, entry 9). Furthermore, we were able to carry out the reaction in THF with no loss of efficiency (Table 1, entry 10) and, remarkably, observed that the inclusion of water as an additive resulted in a significant acceleration of the reaction to furnish the cycloadduct **2a** in better yield in the same reaction time (entry 11). The incorporation of acid additives to assist the formation of the activated iminium intermediate was also surveyed, but upon all attempts the yield of **2a** was found to be significantly lower

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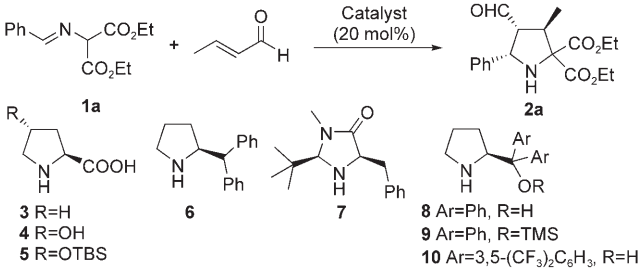
Table 1: [3+2] cycloaddition reaction of **1a** and crotonaldehyde.[a]



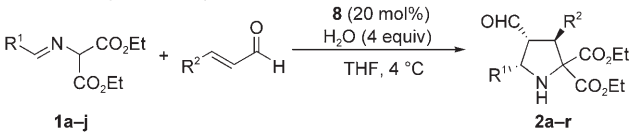
Entry	Catalyst	Solvent	*T* [°C]	Yield [%][b]	*endo*/*exo*[c]	*ee* [%][d]
1	**3**	DMF	−30	77	>95:5	72
2	**4**	DMF	−30	60	>95:5	82
3	**5**	DMF	−30	44	90:10	84
4	**6**	DMF	−30	86	60:40	5
5	**7**	DMF	−30	<5	n.d.	n.d.
6	**8**	DMF	−30	58	>95:5	>99
7	**9**	DMF	−30	<5	n.d.	n.d.
8	**10**	DMF	−30	56	>95:5	>99
9	**8**	DMF	4	67	>95:5	98
10	**8**	THF	4	65	>95:5	98
11	**8**	THF[e]	4	89	>95:5	98
12	**8**	THF[e,f]	4	55	>95:5	97
13	**8**	THF[e,g]	4	79	>95:5	98

[a] Reactions were carried out with **1a** (0.75 mmol), crotonaldehyde (0.70 mmol), and the catalyst (0.14 mmol) in the indicated solvent (6 mL). The reaction mixture was stirred for 72 h at the temperature indicated. [b] Yield of the isolated product. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [d] Determined by HPLC analysis of the corresponding alcohol on a chiral phase. [e] H_2O (4.0 equiv) was used as an additive. [f] $PhCO_2H$ (0.14 mmol) was used as an additive. [g] Catalyst: 10 mol%. DMF = *N*,*N*-dimethylformamide, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl, n.d. = not determined.

after the same reaction time (Table 1, entry 12).[10] Finally, we also tried to reduce the amount of the catalyst; however, a slight decrease in the yield of the product was observed after the same reaction time (Table 1, entry 13). In all experiments, the cycloaddition product **2a** was obtained as a single regioisomer.

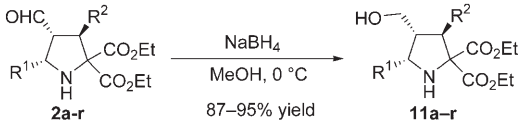
Having established an optimal protocol for the reaction, we examined the scope and limitations of the method with regard to the α,β-unsaturated-aldehyde and imine substrates (Table 2). In all cases, the reaction proceeded smoothly to furnish the desired pyrrolidines **2** in excellent yields and with excellent diastereo- and enantioselectivities. Both linear and branched aliphatic aldehydes, as well as aldehydes with an aryl or heteroaryl group in the β position, were found to be suitable dipolarophiles in the [3+2] cycloaddition reaction with the azomethine ylide derived from **1a** (Table 2, entries 1–9). Good results were also obtained for a variety of imine substrates (Table 2, entries 10–18). We verified the necessity of two electron-withdrawing groups on the imine **1** for the reaction: When we attempted the reaction with the imine derived from glycine methyl ester and benzaldehyde, no cycloaddition product was observed at all.[11] Pyrrolidines **2a–r** were found to be somewhat unstable compounds. Therefore, after isolation, we reduced them to the stable amino alcohols **11a–r** (Scheme 2) that could be characterized and stored for several weeks without decomposition.

Table 2: Scope of the cycloaddition reaction.[a]



Entry	Product	R^1	R^2	Yield [%][b]	*endo*/*exo*[c]	*ee* [%][d]
1	**2a**	Ph	Me	89	>95:5	98
2	**2b**	Ph	Et	91	>95:5	97
3	**2c**	Ph	*n*Pr	87	>95:5	97
4	**2d**	Ph	*i*Pr	85	>95:5	95
5	**2e**	Ph	*n*Bu	88	>95:5	99
6	**2f**	Ph	Ph	82	>95:5	>99
7	**2g**	Ph	*p*-$NO_2C_6H_4$	80	>95:5	94
8	**2h**	Ph	*p*-$MeOC_6H_4$	91	92:8	>99
9	**2i**	Ph	2-furyl	90	>95:5	99
10	**2j**	*p*-$MeOC_6H_4$	Me	88	93:7	85
11	**2k**	(3,4-OCH_2O)C_6H_3	Me	93	>95:5	>99
12	**2l**	3,5-$(MeO)_2C_6H_3$	Me	91	>95:5	94
13	**2m**	*o*-$MeOC_6H_4$	Me	86	91:9	93
14	**2n**	*p*-FC_6H_4	Me	74	>95:5	98
15	**2o**	*o*-FC_6H_4	Me	72	>95:5	93
16	**2p**	*o*-tolyl	Me	91	>95:5	99
17	**2q**	2-furyl	Me	84	>95:5	98
18	**2r**	(*E*)-CH_3CH=CH	Me	57	91:9	97

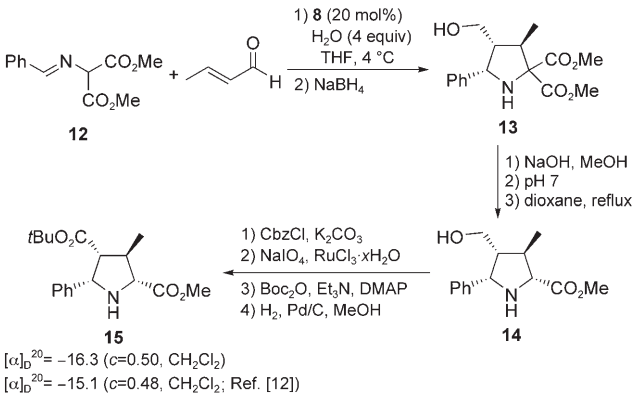
[a] Reactions conditions: **1** (0.75 mmol), α,β-unsaturated aldehyde (0.70 mmol), H_2O (50 μL), **8** (0.14 mmol), THF (6 mL), 4 °C, 72 h. [b] Yield of the isolated product. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [d] Determined by HPLC analysis of the corresponding alcohol on a chiral phase.



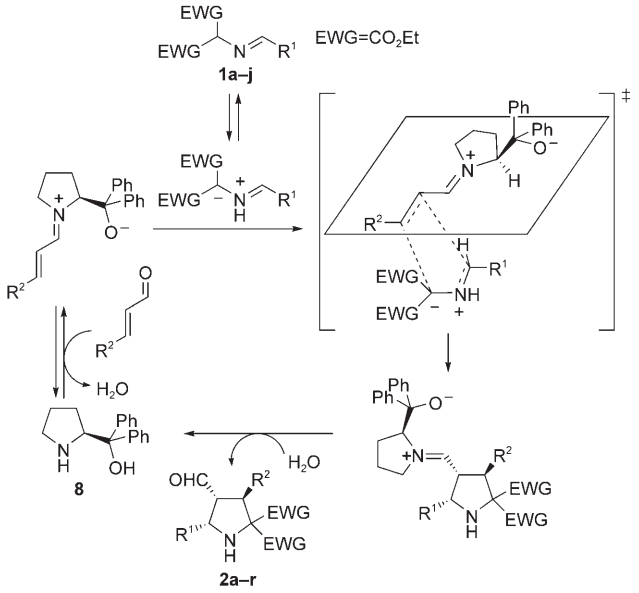
Scheme 2. Reduction of the adducts **2a–r**.

The absolute configuration of the cycloadducts **2** was determined by chemical correlation (Scheme 3). The [3+2] cycloaddition of imine **12** and crotonaldehyde under the optimized conditions, followed by reduction, furnished pyrrolidine **13** as a single *endo* isomer with 98% *ee*. Next, diastereoselective monohydrolysis followed by decarboxylation gave the proline derivative **14** as a single 2,5-*syn* diastereomer. Finally, **14** was converted into the known compound **15**[12] by standard procedures. A new stereocenter was generated with complete selectivity in this sequence, which should facilitate the future preparation of a wide range of proline derivatives.

The absolute configuration assigned to adducts **2a–r** is in agreement with the stereochemical outcome reported for other reactions in which catalyst **8** has been involved through iminium activation.[6c,13] In this context, we propose that efficient shielding of the *Si* face of the chiral iminium intermediate by the bulky aryl groups of **8** leads to a stereoselective *endo*-type approach of the *E* 1,3-dipole to the sterically less hindered *Re* face of the intermediate *E* iminium ion. The proposed reaction pathway is illustrated in Scheme 4.



Scheme 3. Determination of the absolute configuration of the cycloaddition products. Boc = *tert*-butoxycarbonyl, Cbz = benzyloxycarbonyl, DMAP = 4-dimethylaminopyridine.



Scheme 4. A plausible reaction pathway for the enantioselective [3+2] cycloaddition of azomethine ylides and α,β-unsaturated aldehydes with catalyst **8**.

In summary, we have presented the first organocatalytic enantioselective [3+2] cycloaddition reaction between α,β-unsaturated aldehydes and azomethine ylides. The reaction proceeds with complete regioselectivity and with very high diastereo- and enantioselectivity to furnish almost stereoisomerically pure highly functionalized polysubstituted pyrrolidines in excellent yields. The utility of this reaction was exemplified in the synthesis of a proline derivative in which an additional stereogenic center was created with complete stereoselectivity. Further investigations on the application of this method in total synthesis and additional studies focused on the use of related dipoles and dipolarophiles are in progress.

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[9] In a preliminary screening, we found that the reaction proceeded more efficiently in polar solvents, most probably as a result of their ability to stabilize the 1,3-dipole formed upon 1,2-prototropy.

[10] We also tested the following acid cocatalysts: trifluoroacetic acid (13% yield), *para*-toluenesulfonic acid (31% yield), diphenylacetic acid (60% yield), acetic acid (65% yield).

[11] When L-proline (**3**) or (*S*)-α,α-diphenylprolinol (**8**) were used in an attempted reaction between methyl benzylideneaminoacetate and crotonaldehyde in THF or DMF, we did not observe the formation of a cycloaddition product.

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