Organocatalysis

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Rationally Designed Amide Donors for Organocatalytic Asymmetric Michael Reactions**

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Michael reactions are among the most powerful and efficient methods for carbon–carbon bond formation,[1] and a great deal of effort has been devoted to the development of organocatalytic asymmetric Michael reactions of carbonyl compounds with nitroalkenes.[2,3] The carbonyl substrates for these reactions are limited to aldehydes,[4] ketones,[5] 1,3-dicarbonyl compounds,[6] and 3-substituted oxindoles[7] that have a relatively low pK_a value associated with the α hydrogen atoms. To date, there have been no reports concerning the use of amides as donors in these reactions. Recently, the use of ester equivalents as pronucleophiles in direct transformations has been demonstrated.[8] The use of ester equivalents is challenging, however, because their pK_a values (the values being approximately 19) are much higher than those of ketones, aldehydes, and 1,3-dicarbonyl substrates. In addition, challenges still remain regarding substrate scope and reaction selectivity, including diastereo- and enantioselectivity. We have reported strategies based on the use of trifluoroethyl thioesters as pronucleophiles in organocatalytic Michael reactions.[8c] The drawbacks of this approach include the cost of trifluoroethanethiol and the fact that the diastereoselectivity of these reactions is modest. Therefore, mild reaction conditions for the direct organocatalytic asymmetric carbon–carbon bond formation involving ester equivalents have yet to be fully established. Furthermore, the use of amides as pronucleophiles in such transformations has not been reported.

Recently, Sibi and Itoh have described the use of the 3,5-dimethyl pyrazole template as a hydrogen bond acceptor to facilitate activation of the electrophilic substrate in an organocatalytic Michael reaction.[9] We recently reported a novel organocatalytic asymmetric [3+2] cycloaddition reaction between pyrazoleamide[10] and methyleneindolinones that allows extraordinary levels of stereocontrol in the construction of spirocyclic oxindole derivatives. In these studies the pyrazoleamide serves as a directing group for enhancing stereocontrol, and as a good leaving group for subsequent transformations. We hypothesized that the aromatic properties of the pyrazoleamide should engender an amide of relatively low pK_a value that would facilitate enolization with weak amine bases, thus allowing the use of amide pronucleophiles in organocatalysis to be explored. From a synthetic point of view, it is noteworthy that these pyrazoleamide derivatives are also stable and are readily synthesized from carboxylic acids in a single step and in quantitative yields. We assume that simple pyrazoleamides, (Figure 1) should act as general amide substrates for a variety of transformations.

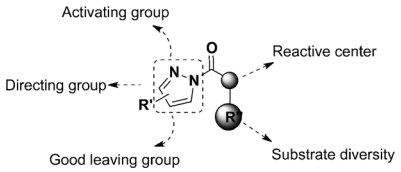

Figure 1. Features of pyrazoleamide substrates.

We initiated our studies by evaluating the reaction between pyrazoleamide **1a** and nitrostyrene **2a** in dichloromethane at room temperature, in the presence of the bifunctional Takemoto catalyst **I** (Scheme 1). The reaction proceeded smoothly and afforded the desired product in high yield, albeit with moderate diastereoselectivity (3:1 d.r.) and enantioselectivity (52% *ee*). Given the pioneering studies of the group of Deng[11] and other groups on cinchona alkaloid catalysis[12] and our own findings that this class of catalyst efficiently promotes pyrazole-based cycloaddition reactions, we decided to test the use of catalyst **II** in the reaction under investigation. With catalyst **II**, we obtained slightly better yields and selectivities than those that were observed when catalyst **I** was used (Scheme 1). However, the use of the 6′-hydroxy cinchona catalysts (**III** and **IV**), described by Deng and co-workers, and the use of other thiourea-based catalysts (**V** and **VI**) gave poor results (Scheme 1).

To improve stereocontrol, we modified the design of the pyrazoleamide substrate to enhance its potential for hydrogen bonding with catalysts. Specifically, we removed the pyrazole methyl groups to facilitate access of the catalyst to the N–N moiety for hydrogen bonding. This derivative **1b** was tested in the reaction, using **I** as a catalyst, and almost complete diastereocontrol and good enantioselectivity (80% *ee*) was observed (Table 1, entry 1). Attempts to optimize the reaction by conducting it in a different solvent or at different temperatures failed to provide the desired improvements in chemical and optical yield (see the Supporting Information).

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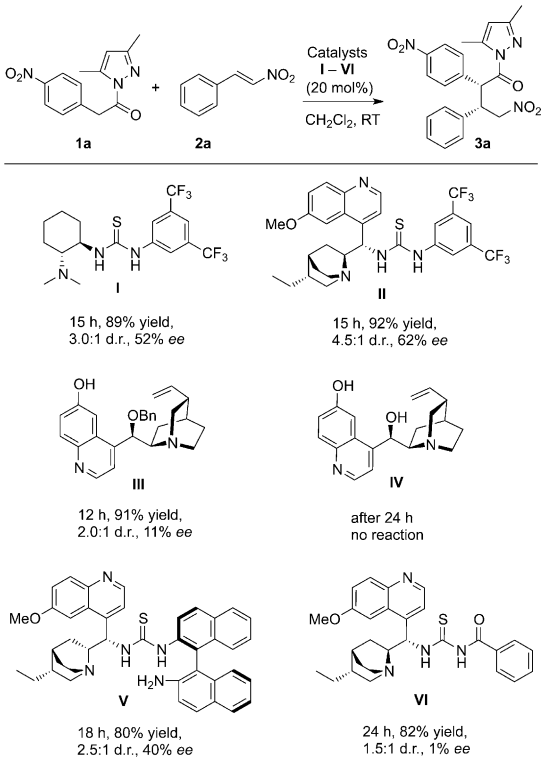
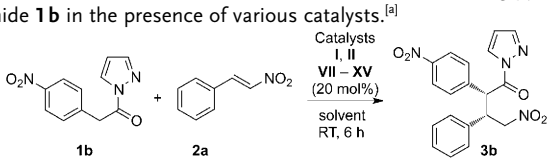


Scheme 1. Initial test reactions involving dimethylpyrazoleamide **1a**. Bn = benzyl.

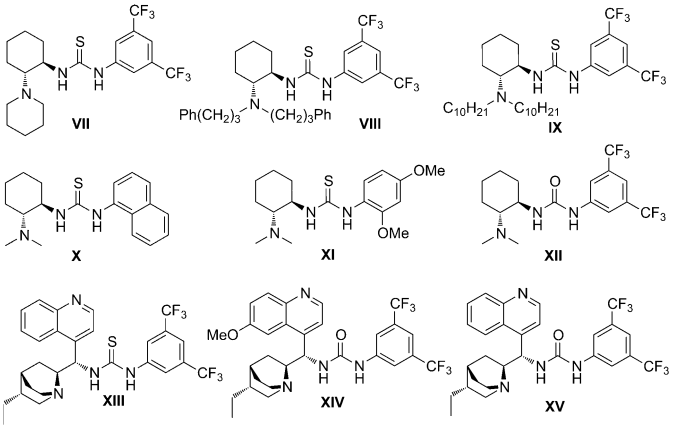
We therefore evaluated the effects that modifications to the structure of catalyst **I** had on the reaction outcome. The use of catalysts representing changes to the structure of the tertiary amine moiety and the thiourea moiety of **I** resulted in poorer enantioselectivity (Table 1, entries 3–8) compared to that obtained when using catalyst **I**, thus suggesting that the electronic properties of the aniline group and the steric environment of the nitrogen center are important for asymmetric induction. Recently, the groups of Wennemers[8a] and Coltart[13] independently reported that the use of enolates derived from thioesters in Michael and Mannich reactions give products with higher enantioselectivity when urea catalysts are used in place of thiourea catalysts. Although thiourea-based catalysts are generally more effective in Michael and Mannich reactions than urea-based analogues because of the former's increased hydrogen bonding capabilities, the latter have been reported to possess superior anion stabilizing properties in some cases.[14] Indeed, the enantioselectivity of the Michael reaction between pyrazoleamide **1b** and nitrostyrene **2a** increased when urea-containing cinchona-based catalysts **XIV** and **XV** (Table 1, entries 9 and 10) were used in place of catalyst **I**. Similarly, the use of the urea analogue of **I** (**XII**) provided enhanced diastereo- and enantioselectivity (Table 1, entry 11). Of the solvents tested for the reaction catalyzed by **XIV**, chloroform proved optimal with respect to the catalytic activity, diastereoselectivity, and enantioselectivity (Table 1, entry 12). Higher diastereoselectivities, enantioselectivities, and yields were observed when the reaction catalyzed by **XIV** was conducted at lower temperatures and in the presence of

Table 1: Yields and selectivities of Michael reactions involving pyrazoleamide **1b** in the presence of various catalysts.[a]



Entry	Catalyst	Solvent	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**I**	CH_2Cl_2	90	>20:1	80
2	**II**	CH_2Cl_2	76	14:1	72
3	**VII**	CH_2Cl_2	88	>20:1	51
4	**VIII**	CH_2Cl_2	95	>20:1	75
5	**IX**	CH_2Cl_2	90	>20:1	70
6	**X**	CH_2Cl_2	83	9:1	72
7	**XI**	CH_2Cl_2	61	2:1	29
8	**XIII**	CH_2Cl_2	87	17:1	74
9	**XIV**	CH_2Cl_2	88	18:1	84
10	**XV**	CH_2Cl_2	81	**13:1**	**78**
11	**XII**	CH_2Cl_2	77	**7:1**	**75**
12	**XIV**	$CHCl_3$	91	19:1	89
13	**XIV**	*o*-xylene	90	19:1	87
14	**XIV**[e]	$CHCl_3$	90	>20:1	91
15	**XIV**[f]	$CHCl_3$	84	>20:1	93
16	**XIV**[g]	$CHCl_3$	95	>20:1	95

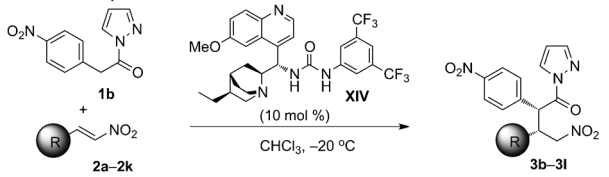
[a] Unless otherwise specified, all reactions were carried out using pyrazoleamide **1b** (0.05 mmol, 1.0 equiv) and nitrostyrene **2a** (0.1 mmol, 2.0 equiv) in specified solvent (0.25 mL) with 20 mol% of catalyst at 22°C for 6 h. [b] Yields of isolated product. [c] Determined by analysis of the ^{1}H NMR spectrum of the crude product. [d] Determined by HPLC using a chiral stationary phase. [e] Reaction was conducted at 0°C. [f] Reaction was conducted at −20°C with 10 mol% of catalyst for 12 h. [g] The reaction was carried out using **1b** (0.11 mmol, 1.1 equiv) and **2a** (0.1 mmol, 1.0 equiv) with 10 mol% of the catalyst at −20°C for 12 h.

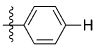
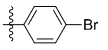
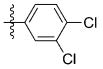
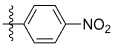
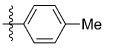
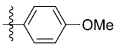
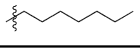


a higher ratio of pyrazoleamide to nitrostyrene (Table 1, compare entry 12 to entries 14–16).

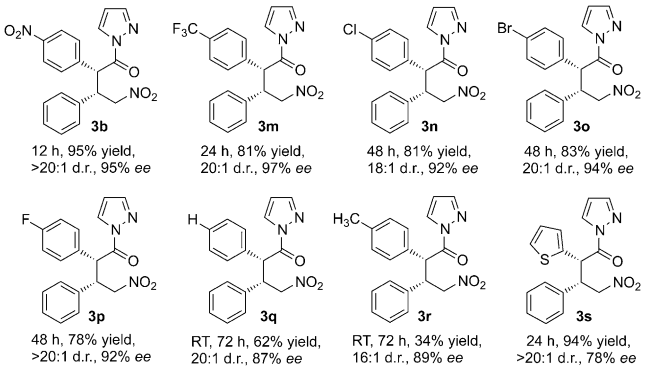
We then evaluated the use of various nitro olefins as reactants (Table 2). Most reactions were complete within 24 hours and gave products in good to excellent yields (85–99%) and with excellent enantioselectivities (88-97% *ee*) and diastereoselectivities (10:1→>20:1 d.r.). For the use of β-aryl nitro olefins, the position and the electronic properties of the substituents on the aromatic ring appeared to have a very limited effect on stereoselectivity. Regardless of the type of substituents on the aromatic rings, be them electron-withdrawing (Table 2, entries 2–6), electron-donating (Table 2,

Table 2: Generality of reaction demonstrated with a variety of nitro olefins electrophiles.[a]



Entry	R	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1		12	**3b**, 95	>20:1	95
2		12	**3c**, 90	18:1	94
3		12	**3d**, 89	>20:1	94
4		12	**3e**, 89	>20:1	94
5		12	**3f**, 98	>20:1	97
6		12	**3g**, 96	>20:1	94
7		18	**3h**, 91	>20:1	92
8		12	**3i**, 93	>20:1	90
9		18	**3j**, 92	>20:1	90
10		12	**3k**, 99	10:1	93
11		24	**3l**, 85	>20:1	88

[a] Unless otherwise specified, all reactions were carried out using pyrazoleamide **1b** (0.11 mmol, 1.1 equiv) and nitrostyrene **2a**–**2k** or **2l** (0.1 mmol, 1.0 equiv) in chloroform (0.5 mL) with 10 mol% of catalyst at −20°C. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC using a chiral stationary phase.

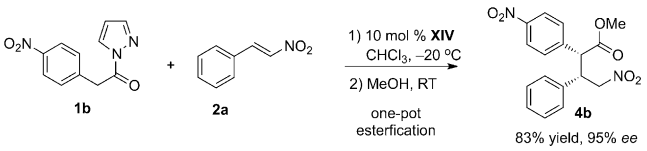


Scheme 2. Generality of the reaction with respect to the pyrazoleamide derivative. For procedures, please see the Supporting Information.

entries 7–8), or neutral (Table 2, entry 1) groups, or the substitution pattern (*para*, *meta*, or *ortho*; Table 2, entries 2–5), the reactions of these nitro olefins gave excellent yields and selectivities. The use of nitro olefins with heteroaromatic groups, such as furyl and thienyl, also afforded the desired product with excellent stereocontrol (Table 2, entries 9 and 10). Although alkyl nitro olefins derived from octanal were not optimal electrophiles, the desired product was obtained under the optimized reaction conditions (Table 2, entry 11).

Next we explored the generality of the reaction with regards to variation of the pyrazoleamide reactant (Scheme 2). The electronic properties of the aromatic ring substituents affected the reactivity of the pyrazoleamide. The presence of electron-withdrawing groups, such as a nitro group, halogens, or a trifluoromethyl group, facilitated the reaction. The presence of chlorine, bromine, or fluorine substituents on an aromatic moiety can also alter the pharmacological activity of a compound class.[15] The use of hetereoaromatic pyrazoleamides gave the desired product in good yield and diastereoselectivity, but in lower enantioselectivity. Derivatives with alkyl, bromine, or trifluoromethyl groups in place of an aromatic ring were virtually unreactive under the reaction conditions, thus suggesting that an aromatic functionality is required to bring the pK_a value into a functional range for these organocatalytic conditions.

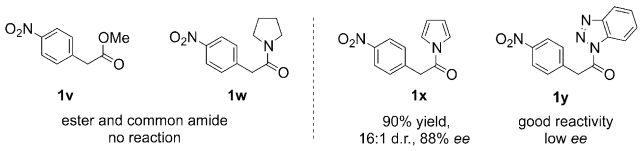
The pyrazoleamide group was introduced because it engenders an acidic α center and provides a handle for stereochemical control through hydrogen bonding with a chiral catalyst. The introduction of the pyrazole group also provides other advantages. Its intrinsic reactivity can be exploited in subsequent reactions to produce a diverse range of products; for example, the pyrazole moiety can be easily displaced by nucleophiles such as alcohols and amines in one-pot or multistep methods (Scheme 3).



Scheme 3. Synthetic transformation involving the pyrazole functional group.

Our findings, together with the dual activation model proposed by the group of Takemoto and co-workers[6a,16] and the theoretical calculations performed by Papai and co-workers,[17] and Zhong and co-workers,[12m] suggest that the nitro olefin and the pyrazoleamide substrates, might be activated simultaneously by the catalyst (see the Supporting Information, Figure S2). Enolization of pyrazoleamide compounds under mild reaction conditions might occur by a productive combination of favourable pyrazoleamide acidity and assistance from the bifunctional catalyst. The urea moiety of the catalyst likely forms hydrogen bonds to both the carbonyl group and a nitrogen atom of the pyrazole moiety, while the tertiary amine moiety most likely functions as a base, thus enabling intracomplex deprotonation. Electrophilic activation of the Michael acceptor through its binding to the protonated amine group of the catalyst is believed to create a steric environment that determines the relative orientation of the approaching substrates for the C–C bond formation, thus inducing stereoselectivity. The absolute configuration of **3o** was determined by X-ray crystallographic analysis (see the Supporting Information, Figure S3) and it is in accordance with the configuration predicted by this model.

The lack of reactivity of methoxy derivative **1v** and pyrrolidinyl **1w** (Scheme 4) indicate that an activating substituent on the carbonyl group is required to bring the



Scheme 4. Control experiments in support of the proposed mechanism.

pK_a value into a functional range. The aromatic functionalities in **1a** and **1b** may stabilize the enolate and thus promote its formation. This hypothesis is supported by the observance of high selectivity in the reaction using the pyrrolyl derivative **1x**. Thus, the reaction of 2-(4-nitrophenyl)-1-(1*H*-pyrrol-1-yl)ethanone (**1x**) and **2a**, under the optimized reaction conditions, afforded the Michael product in 90% yield and 88% *ee*. Furthermore, the presence of another coordinating group in the amide moiety, as in the benzotriazolyl **1y**, compromises the enantioselectivity of the reaction; the reaction of **1y** gave the Michael adduct with only 20% *ee* (Scheme 4).

In summary, we have developed an organocatalytic asymmetric Michael reaction through the rational design of pyrazoleamides as Michael donors, thus providing a rare example of the use of amides as pronucleophiles in organocatalysis. Reactions with pyrazoleamide derivatives gave products in excellent yields and selectivities. Pyrazoleamide functions as an ester equivalent, an activating group, a directing group, as well as a good leaving group for further transformation. The straightforward process described here makes use of simple starting materials and proceeds under mild reaction conditions and will be useful in medicinal chemistry and diversity-oriented syntheses. This class of novel amide substrate as a pronucleophile should facilitate the development of a wide range of asymmetric reactions that can be catalyzed by organic and metal catalysts; a number of these reactions have already been realized in our group and will be reported in the near future.

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Communications

Organocatalysis

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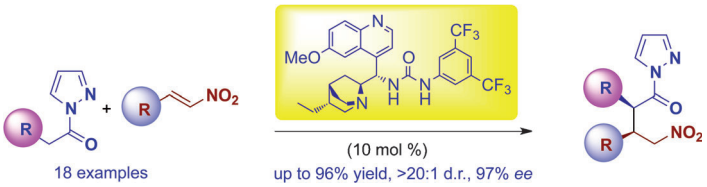
Rationally Designed Amide Donors for Organocatalytic Asymmetric Michael Reactions



Amide nucleophiles on demand: Rationally designed pyrazoleamides function as Michael donors in urea-catalyzed asymmetric Michael reactions with excellent chemical and optical yields (see scheme). The pyrazoleamide group performs as an ester equivalent, a directing group, an activating group, and functions as a good leaving group in further transformations of the product.