Organocatalysis

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A Catalytic Asymmetric Ugi-type Reaction With Acyclic Azomethine Imines**

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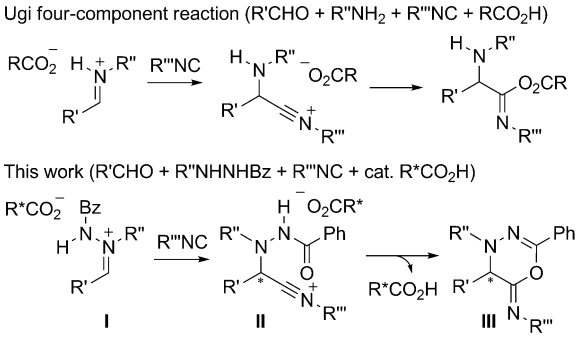
More than half a century ago, Ugi reported a four-component reaction consisting of an aldehyde, a primary amine, an isocyanide and a carboxylic acid.[1] Whereas the ease of assembling a variety of complex structures in one step has prompted its widespread application in a range of organic syntheses,[2] the realization of a catalytic asymmetric Ugi reaction still remains a largely unsolved issue, owing to its logical limitation. Namely, whereas the crucial C–C bond formation between the isocyanide and the imine is thought to be a carboxylic acid catalyzed process (Scheme 1), the carboxylic acid is then taken up in the product, thus ruling out the possibility of using a catalytic amount of chiral carboxylic acid. The only solution reported to date is the use of isocyanoacetamides in the presence of chiral phosphoric acid,[3,4] a strategy that is more successful in the related Passerini reaction.[5,6]

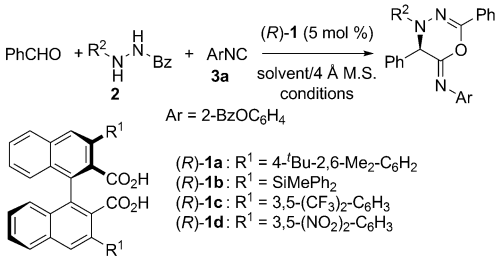


Scheme 1. Ugi-type reaction of imines and acyclic azomethine imines.

To provide a completely new solution to this long-standing problem, we came up with an idea to use acyclic azomethine imines **I**, which was recently revealed by us as a novel prochiral electrophile generated with a catalytic amount of axially chiral dicarboxylic acid.[7,8] By applying this reaction system in the Ugi reaction, we envisaged that the intermediary nitrilium ion **II** would be trapped internally by the oxygen of the hydrazide to give heterocyclic compound **III**, and the carboxylic acid could be regenerated to enter the next catalytic cycle.[9]

As a source of the isocyanide, we opted to use 2-benzoyloxyphenyl isocyanide **3a** developed by Pirrung and co-workers,[10] because of its odorless nature, and more importantly, its equivalency to a pharmaceutically valuable benzoxazole unit (see below).[11] Preliminary experiments using benzaldehyde and *N*′-benzylbenzohydrazide (**2a**) in the presence of the representative chiral dicarboxylic acids (*R*)-**1a** and (*R*)-**1b** were rather disappointing in terms of both the reactivity and selectivity (Table 1, entries 1 and 2).[7,12] A considerable improvement in reactivity was observed by using catalyst (*R*)-**1c**, which bears 3,5-bis(trifluoromethyl)phenyl groups, although the selectivity remained very low (entry 3). As a next step, we introduced catalyst (*R*)-**1d**, which bears 3,5-dinitrophenyl groups. Through the use of this catalyst, the enantioselectivity could be dramatically increased to 55% *ee* (entry 4). To further improve the enantioselectivity of the process, we then screened a variety of hydrazides bearing

Table 1: Optimization of reaction conditions.[a]



Entry	R^2	Cat.	Solvent	Temp. [°C], time [h]	Yield [%][b]	*ee* [%][c]
1	Bn (**2a**)	**1a**	toluene	0, 24	12	−7
2		**1b**	toluene	0, 24	10	−6
3		**1c**	toluene	0, 24	73	15
4		**1d**	toluene	0, 24	85	55
5	2-MeOBn (**2b**)	**1d**	toluene	0, 24	94	82
6		**1d**	toluene	−20, 24	70	85
7		**1d**	mesitylene	−20, 24	70	89
8		**1d**	*m*-xylene	−20, 24	88	90
9[d]		**1d**	*m*-xylene	−30, 40	93	93

[a] Performed with (*R*)-**1** (0.0025 mmol), benzaldehyde (0.06 mmol), benzohydrazide **2** (0.050 mmol), isocyanide (0.060 mmol), and 4 Å M.S. (50 mg). [b] Yield of isolated product. [c] Determined by chiral-phase HPLC analysis. [d] Performed with (*R*)-**1d** (0.005 mmol), benzaldehyde (0.12 mmol), benzohydrazide **2b** (0.10 mmol), isocyanide (0.12 mmol), and 4 Å M.S. (100 mg). Bn = benzyl, Bz = benzoyl, M.S. = molecular sieves.

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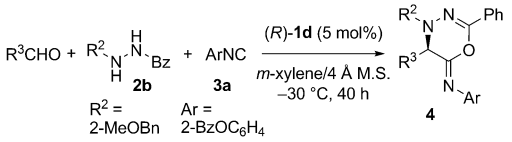
different functionalities. This study revealed a positive effect from the use of *N*′-(2-methoxybenzyl)benzohydrazide (**2b**), with which the corresponding heterocycle was obtained in 82% *ee* (entry 5). In the final optimization, solvents and temperatures were screened (entries 6–8). The optimal conditions were determined to be *m*-xylene at −30 °C, which gave the product in 93% yield with 93% *ee* (entry 9).

With the optimized reaction conditions in hand, we turned our attention to the screening of aldehydes (Table 2). Among

Table 2: Catalytic asymmetric Ugi-type reaction using acyclic azomethine imines.[a]



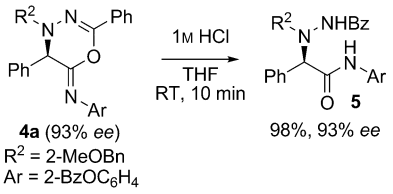
Entry	R^3	Product	Yield [%][b]	*ee* [%][c]
1	Ph	**4a**	93	93
2	4-MeC_6H_4	**4b**	79	90
3	3-MeC_6H_4	**4c**	85	87
4	2-MeC_6H_4	**4d**	55	59
5	4-ClC_6H_4	**4e**	94	92
6	4-BrC_6H_4	**4f**	95	92
7	4-$NO_2C_6H_4$	**4g**	99	90
8	3-BrC_6H_4	**4h**	97	88
9[d]	4-MeOC_6H_4	**4i**	95	90
10	3-MeOC_6H_4	**4j**	98	85
11	2-naphthyl	**4k**	> 99	85
12[e]	cyclohexyl	**4l**	89	68
13[f]	$PhCH_2CH_2$	**4m**	66	42

[a] Performed with (*R*)-**1d** (0.005 mmol), aldehyde (0.12 mmol), benzohydrazide **2b** (0.10 mmol), isocyanide **3a** (0.12 mmol), and 4 Å M.S. (100 mg) in *m*-xylene (1.0 mL). [b] Yield of isolated product. [c] Determined by chiral-phase HPLC analysis. [d] 96 h. [e] −40 °C, 48 h. [f] −40 °C, 20 h. M.S. = molecular sieves.

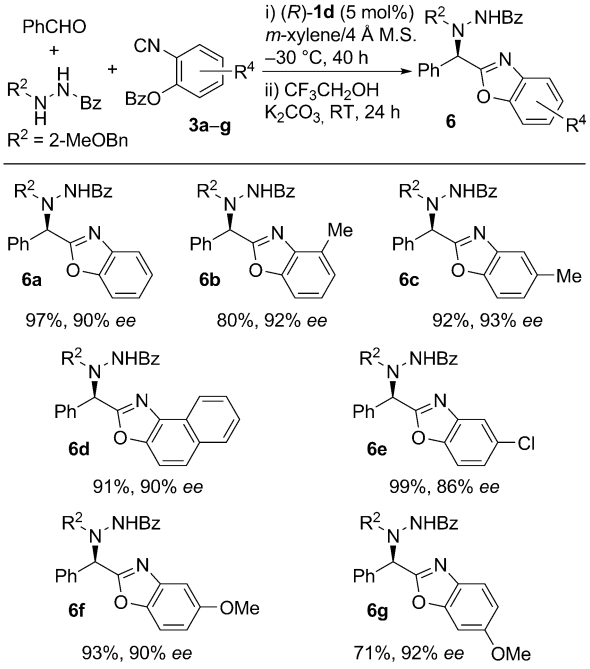
the variety of substituents on the aromatic ring, both 3- and 4-tolualdehydes could be employed without affecting the enantioselectivity (Table 2, entries 2 and 3). The use of 2-tolualdehyde led to a decrease in both the reactivity and selectivity (entry 4). Irrespective of the electronic properties of aldehydes, the reaction proceeded well, producing heterocycles with *ee* values ranging from 85–92% (entries 5–10). 2-Naphthaldehyde could also be employed without difficulty (entry 11). Aliphatic aldehydes like cyclohexanecarbaldehyde and hydrocinnamaldehyde showed fairly good reactivities, but modest selectivities (entries 12 and 13), leaving room for future improvement. The absolute configuration of the product was determined to be *R* by the derivatization of **4a** (see the Supporting Information).

The heterocyclic ring of **4a** could be easily hydrolyzed under acidic conditions to give the corresponding α-hydrazino amide **5** without loss in the enantioselectivity [Eq. (1); Bn = benzyl, Bz = benzoyl].

The successful implementation of this catalytic asymmetric Ugi-type reaction with acyclic azomethine imines generated in situ then prompted us to focus on the isocyanide part (Scheme 2). For this study, we devised a one-pot base-



(1)

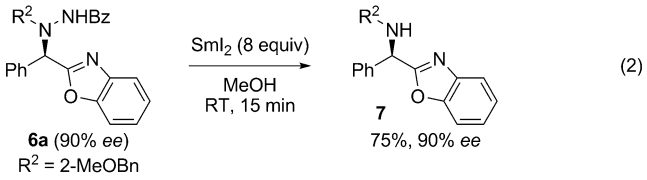


Scheme 2. One-pot catalytic asymmetric Ugi-type reaction/ring reconstruction. i) (*R*)-**1d** (0.005 mmol), benzaldehyde (0.12 mmol), benzohydrazide **2b** (0.10 mmol), isocyanide **3** (0.12 mmol), and 4 Å M.S. (100 mg) in *m*-xylene (1.0 mL). ii) K_2CO_3 (0.30 mmol) and CF_3CH_2OH (1.0 mL). Yields reported are of isolated products. Enantiomeric excesses were determined by chiral-phase HPLC analysis. Bn = benzyl, Bz = benzoyl, M.S. = molecular sieves.

mediated cleavage of the benzoyl moiety derived from the isocyanide after the Ugi-type reaction, as it generates a benzoxazole moiety in the product. Accordingly, 2-benzoyloxyaryl isocyanides can be regarded as masked benzoxazoles with a nucleophilic C2 position.

Our experiment determined that treatment of the Ugi-type reaction solution with K_2CO_3 and CF_3CH_2OH was the method of choice, through which benzoxazole **6a** was obtained in 97% yield and 90% *ee* in the reaction with 2-benzoyloxyphenyl isocyanide **3a**. A mild base was crucial to prevent racemization of the product. A variety of isocyanides could be utilized as well, to give the desired products **6b–g** in consistently high yields and enantioselectivities, irrespective of the electronic properties and the position of the aryl substituent in the isocyanide employed.

The benzamide moiety of the products can be subsequently removed by SmI_2 mediated reductive N–N bond cleavage to give chiral diarylmethylamine **7**, which bears a unique benzoxazole unit, without deterioration in the enantioselectivity [Eq. (2); Bn = benzyl, Bz = benzoyl].



(2)

In summary, we have succeeded in developing a new strategy to implement an Ugi-type reaction in a catalytic asymmetric manner through the use of an axially chiral dicarboxylic acid and acyclic azomethine imines generated in situ. This three-component reaction gave rise to heterocycles with high enantioselectivities, which could be easily transformed into a variety of chiral molecules.[13]

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