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Enantioselective Mannich Reaction of β-Keto Esters with Aromatic and Aliphatic Imines Using a Cooperatively Assisted Bifunctional Catalyst

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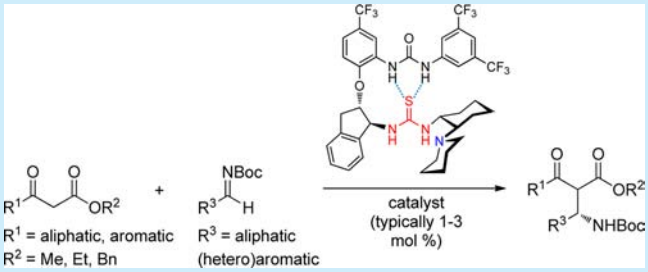
Supporting Information

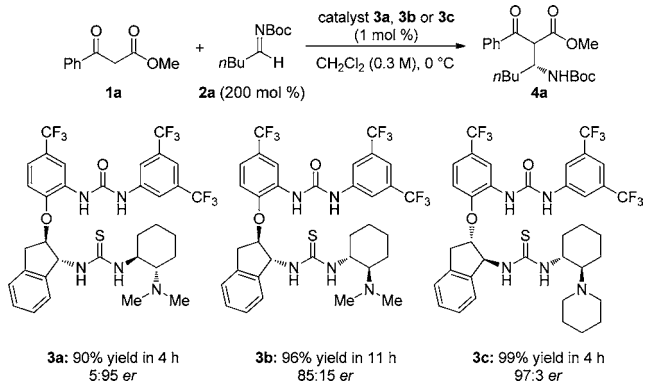
ABSTRACT: An efficient urea-enhanced thiourea catalyst enables the enantioselective Mannich reaction between β-keto esters and *N*-Boc-protected imines under mild conditions and minimal catalyst loading (1−3 mol %). Aliphatic and aromatic substituents are tolerated on both reaction partners, affording the products in good enantiomeric purity. The corresponding β-amino ketones can readily be accessed via decarboxylation without loss of enantiomeric purity.



β-Amino ketones are highly valuable functionalities that can be found, typically in a protected form, in a large number of natural products and biologically active compounds.[1] A typical synthesis of the β-amino ketone subunit involves a classical Mannich-type reaction between enolates or enamines and imines.[1,2] With enamine catalysis, the reaction appears to be restricted to *N*-arylimines or aromatic *N*-Boc-protected imines.[3] With alternative enol equivalents such as enol silanes or β-dicarbonyl compounds, several enantioselective Mannich reactions with imines have been discovered,[4,5] especially with malonate esters. However, enantioselective reactions involving ketone and β-keto ester enolates are less common. Typically, Mannich reactions with β-keto esters and *N*-carbamoylimines are restricted to imines derived from aromatic aldehydes[6] or glyoxalates.[7] A third alternative to the β-amino ketone subunit involves Michael addition of nitrogen nucleophiles to enones.[8] Although the Michael addition strategy offers excellent enantioselectivities and wide substrate scope including aliphatic side chains, the methods still have practical limitations, such as the potentially hazardous use of azides under acidic conditions[8c] or high catalyst loadings (20 mol %).[8d] Herein, we report a practical protocol for a catalytic enantioselective Mannich reaction of both β-keto esters **1** with imines **2** using a highly efficient catalyst **3c**. Aliphatic and aromatic side chains are tolerated on both components, and the products can be readily converted to chiral β-amino ketones.

In our previous study,[9] we established the use of bifunctional, conformationally restricted urea−thiourea catalysts **3a** and **3b** (Scheme 1) for the organocatalytic Mannich reaction between malonates and both aliphatic and aromatic *N*-Boc imines.[9,10] Catalysts **3a** and **3b** were found to be profoundly more active in the Mannich reaction with aliphatic imines, which failed to react at all under catalytic conditions with the Takemoto[11] or the Chen−Dixon−Soós[12] catalysts lacking the extra urea group of **3a** or **3b**.

Scheme 1. Cooperatively Assisted Bifunctional Organocatalysts



The β-keto ester derived enolates are less basic and, therefore, less reactive than the malonate enolates as substrates for reactions with less activated imines such as Boc-protected imines.[13] As such, we expected that the reaction might require even more active catalysts. Indeed, a preliminary screen with diastereomeric catalysts **3a** and **3b** revealed that the Mannich reaction with β-keto ester **1a** and imine **2a** afforded good enantioselectivity only with catalyst **3a**. Further optimization by replacing the dimethylamino group of catalyst **3a** with a slightly more basic and bulky piperidine unit afforded a more active and selective catalyst **3c** (Scheme 1). This catalyst was thus selected for further reaction optimization.

The optimization of conditions was started from toluene as the solvent at 0 °C (Table 1, entry 1) since these conditions were found to be optimal for the related Mannich reaction

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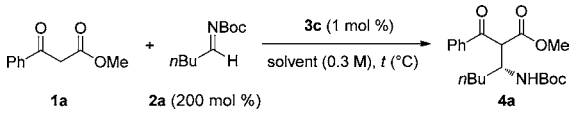
Table 1. Optimization of Reaction Conditions[a]



entry	t (°C)	solvent	additive	time (h)	yield[b] (%)	er[c]
1	0	toluene		1	98	89:11
2	0	mesitylene		1	95	93:7
3	−30	mesitylene		3	97	95:5
4	−30	mesitylene/ hexane (1:1)		3	95	96:4
5	28	CH_2Cl_2		3	98	81:19
6[d]	0	CH_2Cl_2		3	94 −99	91:9 −96:4
7	−30	CH_2Cl_2		3	98	97:3
8	0	CH_2Cl_2	granular 4 Å MS	3	97	88:12
9	0	CH_2Cl_2	Na_2SO_4	4	99	97:3
10	0	CH_2Cl_2	H_2O	4	99	97:3

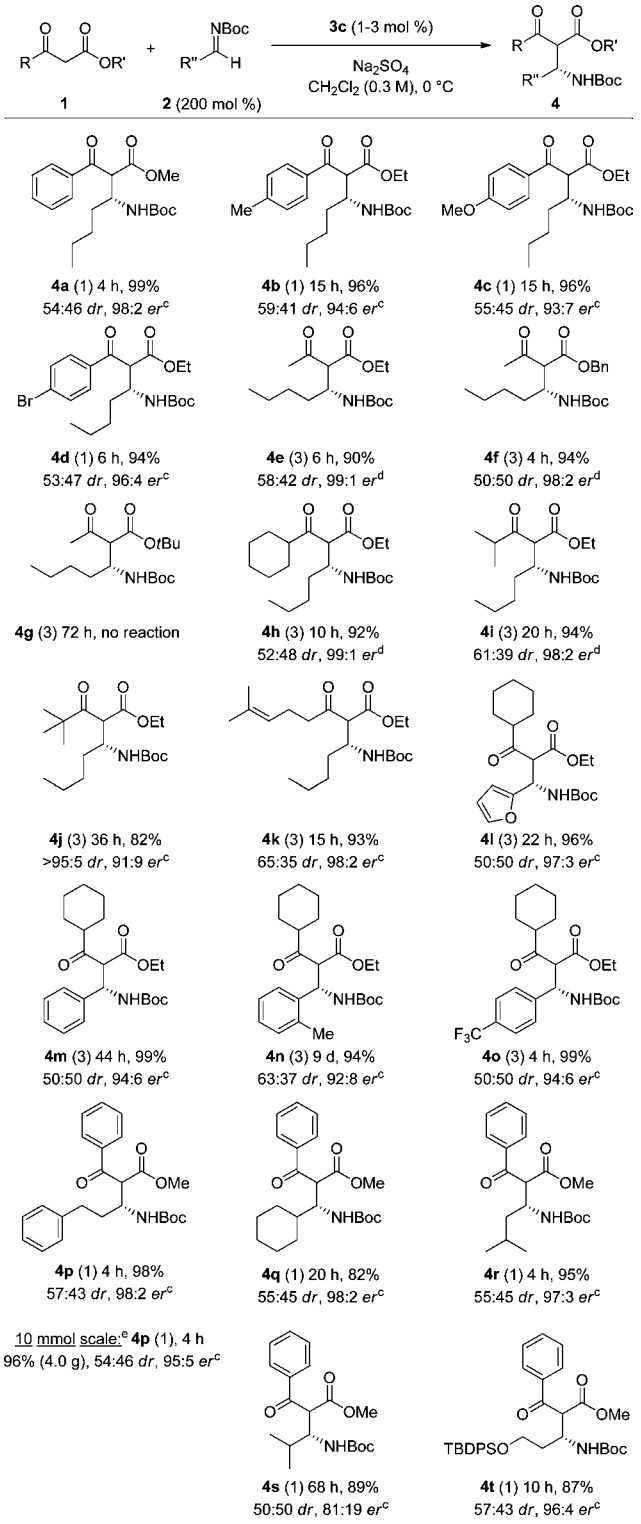
[a]Reactions were conducted with 0.2 mmol of **1a**, 0.4 mmol of **2a**, and 0.002 mmol of **3c** in 0.66 mL of indicated solvent. [b]Yields of isolated product. [c]Determined by chiral HPLC as a sum of diastereomers. [d]Results of three independent reactions.

between malonate esters and *N*-Boc-imines.[9] Surprisingly, under these conditions, the product (**4a**) was obtained in excellent yield but with only moderate enantioselectivity (89:11 er). We envisioned that reducing the polarity of the solvent and lowering the temperature (entries 2−4) should enhance the enantioselectivity by producing a tighter ion pair between the protonated catalyst and the enolate nucleophile. Although the enantioselectivity was improved significantly, the reaction mixtures became very heterogeneous. This problem was solved by returning to dichloromethane as the solvent (entries 5−7), and excellent yields and good enantioselectivities were obtained without any precipitate formation. Interestingly, the enantioselectivity dropped significantly when the reaction was performed at 28 °C instead of 0 and −30 °C. This type of non-Arrhenius behavior was also observed previously in the Mannich reaction using malonate esters.[9]

Even with dichloromethane as the solvent, we found that the enantioselectivities were not fully reproducible while the yields remained excellent (entry 6). To examine the possibility of residual water affecting the enantioselectivity, we carried out control experiments by excluding the water with solid drying agents and alternatively adding water into the reaction mixture. Molecular sieves decreased the enantioselectivity (entry 8), presumably allowing competing racemic Lewis acid promoted reaction. A less Lewis acidic drying agent, Na_2SO_4, indeed improved both the enantioselectivity and the reproducibility of the reaction (entry 9). However, a control experiment with *added* water also improved the enantioselectivity (entry 10). Presumably, both water and Na_2SO_4 can trap traces of inorganic impurities in the imine that lead to lower selectivities.[14] For maximum reproducibility, Na_2SO_4 was selected as the additive for further screening.

The *β*-keto ester and the imine components were then varied (Scheme 2). Aromatic *β*-keto esters reacted smoothly with only 1 mol % of catalyst to give products **4a−d** and **4p−t**, and with aliphatic *β*-keto esters 3 mol % of catalyst was required to access products **4e−m,o** in a reasonable reaction time. Interestingly, electron-donating substituents in the aromatic

Scheme 2. Substrate Scope[a,b]



[a]Amount of catalyst (mol %) in parentheses. [b]Reaction times, yields of isolated products, diastereomeric ratios, and enantiomeric ratios are reported below each product. [c]Determined by chiral HPLC analysis as a sum of diastereomers. [d]Determined by chiral HPLC analysis after decarboxylation. [e]150 mol % of **2d** (R″ = CH_2CH_2Ph); see the Supporting Information. Boc = *tert*-butyloxycarbonyl, TBDPS = *tert*-butyldiphenylsilyl.

β-keto ester nucleophiles do not increase reactivity but instead result in lower reaction rates (**4a** vs **4c**). The catalytic process is

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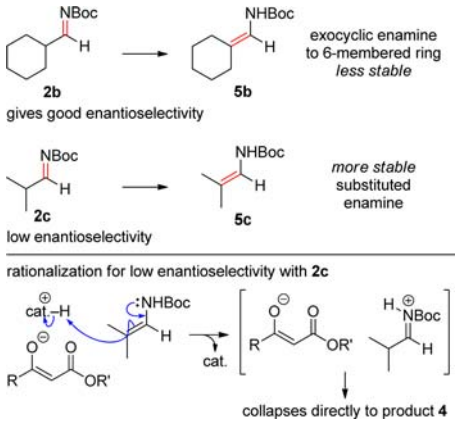
also fairly sensitive to steric properties of the β-keto ester, and while branched alkyl and cycloalkyl substituents are tolerated, *tert*-butyl esters are not (**4e** vs **4g**). Similarly, the quaternary substitution in the γ-position in ethyl pivaloylacetate lowers the rate and affords lower enantioselectivity but nevertheless affords excellent diastereocontrol (**4j**, dr > 95:5).[15] In all of the other cases, the diastereoselectivity was found to be below 2:1, and this ratio is likely to be thermodynamically controlled.

On the side of the imines, aliphatic and electron-poor aromatic imines were found to be highly reactive substrates for the Mannich reaction. In contrast, electron-neutral (**4m**) and electron-rich (**4n**) aromatic imines required longed reaction times. *o*-Methyl substitution in the arylimine was especially challenging for the present catalytic system. With 3 mol % of catalyst, product **4n** was obtained after 9 days in good to moderate yields and slightly lower enantioselectivity (catalyst **3c**, 9 days, 94% yield, 92:8 er; catalyst **3a**: 9 days, 74%, 91:9 er; catalyst **3b**: 9 days 94%, 88:12 er).

Finally, gram-scale synthesis of **4p** using 1 mol % of catalyst and only 1.5 equiv of imine **2d** proceeded smoothly, affording the desired Mannich adduct **4p** in 96% yield and 95:5 enantioselectivity.

An interesting reactivity difference between α-branched aliphatic imines, leading to **4q** and **4s**, was observed. While the cyclohexanecarboxaldehyde-derived imine **2b** provided good enantioselectivity (giving **4q** in 98:2 er), the isobutyraldehyde derived imine **2c** provided only modest enantioselectivity (**4s**, 81:19 er) (Scheme 3). To rationalize these

Scheme 3. Rationalization for Observed Reactivity Difference between Imines 2b and 2c

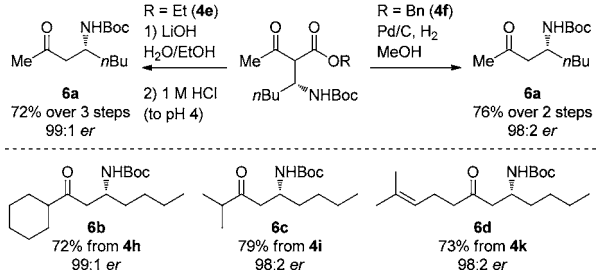


observations, we presume that the reactions proceed through a mechanism where the β-keto ester anion reacts with the imine or iminium ion.[9] In a control experiment in the absence of catalyst **3c**, imine **2c** does not provide product **4s**, suggesting that the catalyst is still involved in the racemic pathway. It should be noted that **2c** readily tautomerizes to the corresponding enecarbamate whereas **2b** does not.[16] Although the enecarbamates do not appear to react directly with β-keto esters, the catalyst β-keto ester salt could protonate the enecarbamate, leading to an enolate–iminium ion pair which should directly collapse to product **4**.[17]

This rationalization is consistent with previously proposed mechanisms for Brønsted[18] and Lewis[19] acid catalyzed enecarbamate to imine tautomerization–nucleophilic addition sequences. Although α-unbranched imines could also tautomerize to the corresponding enecarbamates, these enecarbamates could readily dimerize or oligomerize with the imines and thus would not participate in further reactions. In contrast, **2b** and **2c** are more hindered and less likely to react with the corresponding enecarbamates.

As an application of the Mannich addition protocol, decarboxylation should directly afford enantioenriched β-amino ketones. Since the reaction tolerates both ethyl and benzyl β-keto esters (Scheme 2, **4e** and **4f**), the decarboxylation could be initiated either via saponification or hydrogenation, respectively. These unoptimized decarboxylative transformations (Scheme 4) result in over 70% overall yield of **6a** (form

Scheme 4. Decarboxylation to Chiral β-Amino Ketones[a]



[a]See the Supporting Information for experimental details.

ethyl and benzyl acetoacetate) without compromising the enantiomeric purity. The absolute stereochemistry of **6a** was determined to be *R* by correlation with the corresponding carboxylic acid.[20]

In conclusion, cooperatively assisted urea–thiourea catalyst **3c** catalyzes the Mannich reaction between β-keto esters and *N*-Boc-imines with high yields and enantioselectivities under very mild conditions. Both aliphatic and aromatic substrates are tolerated. A full account on the mechanistic implications of this study is forthcoming.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data, and copies of NMR spectra and chromatograms for synthesized products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(10) For the seminal paper on cooperatively assisted urea−thiourea catalysts, see: Jones, C. R.; Pantoş, G. D.; Morrison, A. J.; Smith, M. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 7391. In contrast to the original design, our catalyst uses a more rigid *trans*-1,2-aminoindanol linker, resulting in a more active catalyst (see ref 9 for details).

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(13) For example, cinchona alkaloid derived bifunctional catalysts typically afford lower yields and enantioselectivities with β-keto esters compared to malonate esters. See ref 6b. The differential reactivity and selectivity of malonate esters and β-keto esters has also been noted with metal enolates; see ref 5c.

(14) Aliphatic imines such as **2a** are prone to decomposition, and they cannot typically be purified by chromatography. See the Supporting Information for a discussion on the effect of additives.

(15) With a cyclic β-keto ester, the Mannich reaction gave the product **4u** in excellent dr but only moderate enantioselectivity. As such, the present catalyst system appears to be optimal for β-keto esters without an α substituent. See the Supporting Information for details.

(16) Presumably, **2b** is less likely to generate an enecarbamate **5b** due to the presence of an exocyclic double bond to a 6-membered ring in **5b**. For a discussion, see: Brown, H. C.; Brewster, J. H.; Shechter, H. *J. Am. Chem. Soc.* **1954**, *76*, 467.

(17) The catalyst−β-keto ester ion pair is expected to be more acidic than the corresponding ion pair with malonate esters, thus rendering this problem more acute with β-keto ester substrates.

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