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A Cooperative Participation of the Amido Group in the Organocatalytic Construction of All-Carbon Quaternary Stereocenters by Michael Addition with β-Ketoamides

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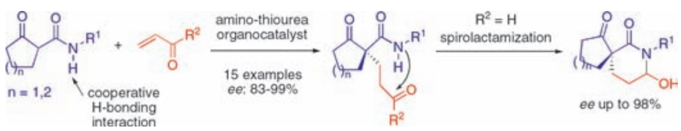
ABSTRACT



The secondary amido group of α-substituted β-ketoamides plays a crucial role in the control of the reactivity and spatial arrangement (selectivity) in the organocatalyzed Michael addition to unsaturated carbonyls. This results in an unprecedented activation mode of substrates through H-bonding interactions allowing the construction of enantiomerically enriched functionalized all-carbon quaternary centers and spiroaminals of high synthetic potential.

The enantioselective construction of quaternary centers is one of the most demanding key steps in the stereocontrolled synthesis of complex natural and/or pharmaceuticals products.[1] In this context, the asymmetric conjugate addition represents a powerful tool for the elaboration of these particular stereocenters. Despite well-established transition-metal-based catalytic methods,[2] the generation of all-carbon quaternary stereocenters via Michael addition still constitutes a formidable challenge owing to additional steric hindrance considerations.[3] In the past decade, extensive studies have been devoted to the development of organocatalytic systems performing with excellent enantioselectivities,[4] employing simple substrates. In this way, a wide variety of α-substituted-1,3-dicarbonyls or synthetic equivalents such as β-diketones, β-ketoesters[5] or α-cyanoesters and ketones[6] have been extensively and successfully used. On the other hand, asymmetric conjugate addition with simple β-ketoamides, of broad

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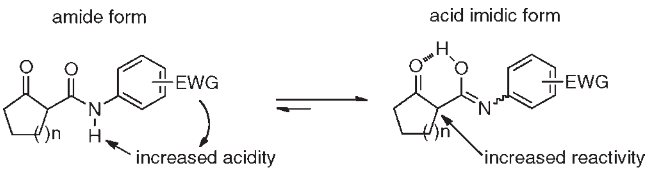
synthetic value by post-transformations involving the amido functionality,[7,8] remained unsolved. This limitation is due to the lack of efficient activation modes of these peculiar substrates. According to mechanistic studies on proton exchange in amides and related compounds,[9] β-ketoamides are better represented under their imidic acid form that could constitute a new activation mode of these unexplored potential pronucleophiles in Michael addition (Scheme 1).

Scheme 1. Equilibrium between Amide and Acid Imidic Forms



Moreover, based on the seminal works from Miller's group,[10] the presence of the amido moiety will result in a favorable cooperative effect in the organization of the transition state for efficient enantiocontrol of the reaction. Based on our precedent developments in ketoamide reactivity[11] and organocatalytic conjugate additions,[12] we present these unprecedented achievements under thiourea-based bifunctional catalysis,[13] for the enantioselective construction of functionalized all-carbon quaternary stereocenters from α-substituted β-ketoamides as pronucleophiles.[14] Also, the synthetic advantage of the additional amide function is illustrated through an efficient enantioselective domino Michael/spirolactamization sequence leading to chiral scaffolds of high synthetic interest.

To initiate our study, we selected the conjugate addition of β-ketoamide **1a** to methylvinylketone (**2a**) in the presence of 10 mol % of various organocatalysts **3a**–**h**, as a test experiment (Table 1).

(7) Pilling, A. W.; Boehmer, J.; Dixon, D. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 5428. Yang, T.; Campbell, L.; Dixon, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 12070. Pilling, A. W.; Böhmer, J.; Dixon, D. J. *Chem. Commun.* **2008**, 832.

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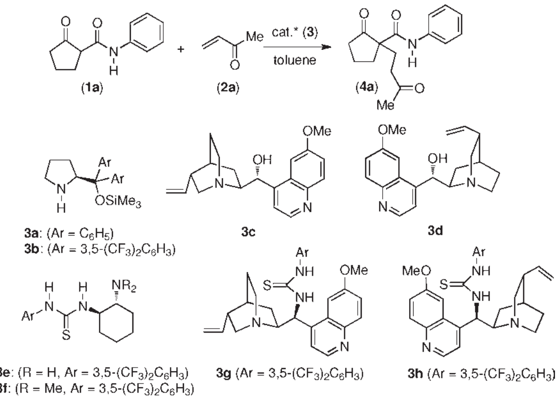
(14) For isolated examples of enantioselective addition of an α-substituted-β-amidoester to a nitroolefin, see: Jakubec, P.; Helliwell, M.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 4267. Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632.

Table 1. Screening of Catalysts for the Organocatalytic Conjugate Addition of β-Ketoamide **1a** to Methylvinylketone (**2a**)[a]



entry	catalyst	time (h)	temp (°C)	conversion[b] (%)	ee (%)[c]
1	**3a**[d]	96	20	20[e]	0
2	**3b**[d]	144	20	No reaction	–
3	**3c**	20	20	100	35
4	**3d**	24	20	100	73
5	**3e**	168	20	100	32
6	**3f**	**48**	**20**	**100**	**87**
7	**3f**	48	0	100	83
8	**3f**	48	−20	100	79
9	**3g**	48	20	100	75
10	**3h**	48	20	100	80

[a] A solution of **1a** (1 equiv), **2a** (2 equiv), and catalyst **3** (10 mol %) in toluene (0.05 M) was stirred until full conversion. [b] Determined by TLC analysis. [c] Determined by HPLC on a chiral stationary phase. [d] Catalyst loading 20 mol %. [e] Determined by ^{1}H NMR.

Efficient in the case of α-unsubstituted β-amidoesters,[8] the (*S*)-proline derivatives **3a** and **3b** either gave a very low conversion with no enantioselection or failed in producing the desired Michael adduct (entries 1 and 2), ruling out a possible mechanism involving enamine or iminium intermediates.[15] On the contrary, H-bonding activation with bifunctional catalysts **3c**–**h** led to complete conversion and moderate to good ee's (entries 3–10). The Takemoto ThioUrea Catalyst[16] (TUC, **3f**) proved to be the most promising, giving the adduct with 87% ee after 48 h at rt (entry 6). It is noteworthy that the presence of a tertiary amine in the structure of the catalyst is crucial, since **3e** with a less basic appended primary amine provided the desired product with decreased efficiency and selectivity (entry 5). Unfortunately, lowering the temperature to 0 or −20 °C did not improve the enantioselectivity of the reaction (entries 7 and 8), and cinchona alkaloids **3c** and **3d** or their more elaborated thiourea derivatives[17] **3g** and **3h** revealed to be less efficient than the TUC **3f** (entries 3, 4, 9, and 10).

(15) Bartoli, G.; Melchiore, P. *Synlett* **2008**, 1759.

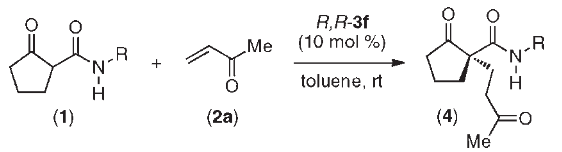
(16) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151.

(17) *Cinchona Alkaloids in Synthesis and Catalysis*; Song, C. E., Ed.; Wiley-VCH: Weinheim, 2009. Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, 1229.

Finally, several solvents have been investigated in combination with **3f**, and toluene was selected as the best one.

We next decided to explore the effect of the amide functionality on reactivity and selectivity and try to identify its role in the activation process. We postulated that simple modification of the secondary amide substituent would impact its H-bonding character and potentially increase the reaction selectivity. Thus, various cyclic aromatic β-ketoamides **1b**–**g** were reacted with methylvinylketone (**2a**) under the optimized conditions to afford the corresponding Michael adducts with good to high yields and high ee values (Table 2).

Table 2. Effect of the Amide Nature on the Enantioselectivity[a]



entry	R	4	time (h)	yield (%)[b]	ee (%)[c]
1	1-naphthyl (**1b**)	(−)-**4b**	48	90	91
2	1-anthracenyl (**1c**)	(−)-**4c**	96	98	90
3	*p*-$NO_2C_6H_4$ (**1d**)	(−)-**4d**	72	62	97
4	*p*-$MeOC_6H_4$ (**1e**)	(−)-**4e**	40	98	83
5	*m*-$MeOC_6H_4$ (**1f**)	(−)-**4f**	48	64	83
6	Tosyl (**1g**)	(−)-**4 g**	72	88	98
7	Tosyl (**1g**)	(+)-**4 g**	72	90	99[d]

[a] A solution of **1** (1 equiv), **2a** (2 equiv), and catalyst (*R,R*)-**3f** (10 mol %) in toluene (0.05 M) was stirred until full conversion. [b] Isolated yield after purification by column chromatography on silica gel. [c] Determined by HPLC on a chiral stationary phase. [d] In this case, catalyst (*S,S*)-**3f** was used, vide infra.

As expected, the modifications that operated on the amide function had a significant impact on the reaction selectivity. Indeed, substrates with polyaromatic substituents **1b** (entry 1) and **1c** (entry 2) or electron-withdrawing group-substituted aniline **1d** (entry 3) led to high ee's, whereas aniline derivatives **1e** (entry 4) and **1f** (entry 5) bearing an electron-donating substituent on the aromatic ring were revealed to be less efficient.

From these experimental data, we surmised that the observed ee's might be correlated to the acidity of the proton of the amide function. Although this is a simplistic hypothesis,[18] we intended to verify it with substrate **1g** derived from tosylamide.[19] To our delight, the TUC-**3f** catalyst efficiently activated this substrate providing the desired Michael adduct **4g** with the highest ee (Table 2, entry 6). Then, to confirm the importance of the presence of a proton on the amide function, we ran additional experiments with various substrates under the standard conditions.[20] First, we were pleased to note that neither aliphatic **1h** nor aromatic tertiary amides **1i** showed any significant reactivity even after a long reaction time. Also, the sterically crowded and electron-rich aliphatic secondary β-ketoamide **1j** (R = *t*-Bu), with a less acidic amide proton, remained totally unreactive, highlighting the crucial role of the proton in the activation of the substrate.[21]

To lend further credence to the hypothesis of a proposed correlation between ee and the acidity of the N–H proton, we performed theoretical calculations,[20] to determine the N–H pK_a values of ketoamides **1a**, **1d**, **1g**, and **1j**. As depicted in Figure 1, a direct correlation has been evidenced, clearly indicating that the ee increased with the acidity of the amide proton. This theoretical study also revealed that the N–H pK_a value of the amide **1j** bearing a *tert*-butyl substituent is much higher than that of aromatic amides, preventing its participation in activating H-bonding interactions.

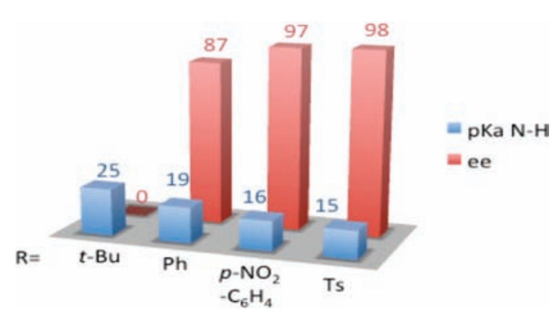


Figure 1. Correlation between *ee* and pK_a (NH).

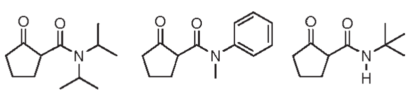
To understand the enantioselective outcome of this transformation, it was of main interest to assess the absolute configuration of the newly created stereogenic center. This was made possible by single crystal X-ray analysis of adduct **4d**.[20,22] In addition, the (+)-(*S*)-enantiomer of **4g** has been also obtained with a very high ee, using catalyst *S,S*-**3f** (Table 1, entry 7). The absolute configurations of the stereogenic centers of both enantiomers of adduct **4g** were determined by comparison of experimental and calculated Vibrational Circular Dichroism (VCD) spectra.[20]

At this early stage of the study, the mode of action of the catalyst is not known with certitude, but the stereochemical data combined with our experimental observations concerning the decisive role of the amide N–H moiety prompted us to propose a transition-state model (Scheme 2). In the presence of the bifunctional catalyst, the activated acid imidic form would favor the base-catalyzed abstraction of the

(18) For a complete study on the pK_a slide rule, see: Gilli, P.; Pretto, L.; Bertolasi, V.; Gilli, G. *Acc. Chem. Res.* **2009**, *42*, 33.

(19) Presset, M.; Coquerel, Y.; Rodriguez, J. *J. Org. Chem.* **2009**, *74*, 415.

(20) See Supporting Information for experimental details. Unreactive substrates **1h**–**j**.

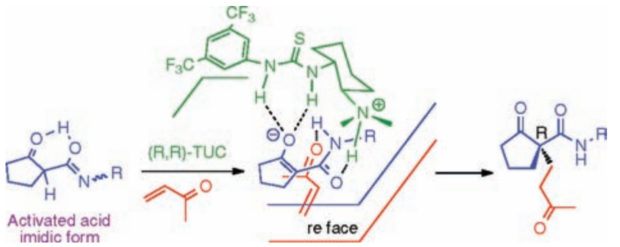


1h 1i 1j

(21) We observed a similar effect with α-ketoamides in organocatalyzed conjugate addition to nitroolefins: Baslé, O.; Raimondi, W.; Sanchez Duque, M. M.; Bonne, D.; Constantieux, T.; Rodriguez, J. *Org. Lett.* **2010**, *12*, 5246.

(22) CCDC 798318 contains the supplementary crystallographic data for this paper which can be obtained free of charge from The Cambridge Crystallographic Data Centre (www.ccdc.cam.uk/data_request/cif).

Scheme 2. Transition-State Model for the Michael Addition of β-Ketoamides



exposed methine proton to generate a reactive enolate intermediate stabilized by the thiourea function. Subsequently, the resulting protonated tertiary amine would coordinate the basic oxygen atom of the tautomeric amide form, resulting in the formation of an ion pair complex in which only the *re* face of the enolate is accessible. As a consequence, the acidic amide N−H would be free to activate the carbonyl of the acceptor, according to Miller's model.[10] This proposed double activation of both the substrate and acceptor by the (*R*,*R*)-TUC catalyst may account for the observed *R* absolute configuration and highlights the crucial cooperative role of the N−H proton in the activation.

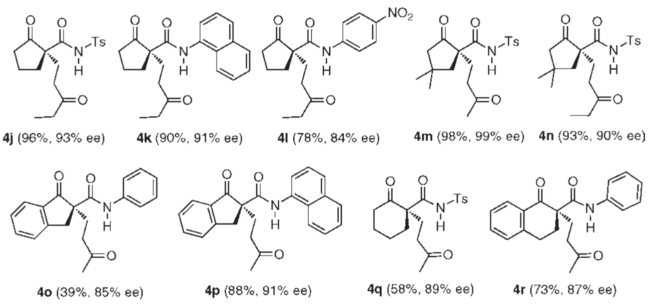
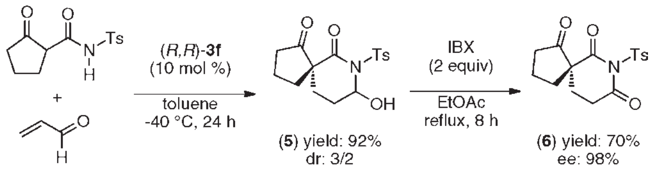


Figure 2. Scope of the enantioselective Michael addition.

The next step was the investigation of the scope of the process compiled in Figure 2. Various cyclic substrates were reacted with either methyl- or ethylvinylketone to afford the corresponding adducts **4j**−**r** in good yields and high ee's up to 99%. This methodology works well with five- and six-membered cyclic compounds, and tosyl and naphthyl derivatives generally give the best results. Substituted indanones and tetralones proved also to be suitable substrates, allowing this methodology to generate complex structure diversity **4o,p,r** without altering the enantioselective potential of the process.

We then investigated the use of enals in place of enones (Scheme 3). To our delight, the (*R*,*R*)-**3f**-catalyzed reaction

Scheme 3. Synthesis and Oxidation of Hemi-aminal **5**



between β-ketoamide **1g** and acrolein, in toluene at −40 °C, produced the spiro-hemiaminal **5** as a 3/2 mixture of two diastereomers according to a domino Michael addition−spiro-hemiacetalization sequence.[23] Oxidation of **5** afforded the corresponding spiroimide **6** isolated with an excellent ee of 98%. This methodology opens the way to a general access to various aza-spiro compounds[24] under an optically active form,[25] which is of prime importance since biological activities are frequently associated with the asymmetric spiro-carbon atom.[26]

In summary, we have developed the first organocatalytic enantioselective conjugate addition of α-substituted β-ketoamides to unsaturated carbonyls by bifunctional catalysts, involving an unprecedented cooperative effect of the amide function in the activation of these pronucleophiles. The corresponding adducts containing a highly functionalized all-carbon quaternary stereocenter are obtained in good yields and high to excellent ee's. The synthetic potential of the products bearing the extra amide function was highlighted using acrolein through a new domino spiroannulation leading to a synthetically valuable intermediate precursor of highly enantioenriched spiro-heterocycles of biological and synthetic interest.

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Supporting Information Available. Experimental procedures, NMR spectra, chiral HPLC chromatograms, and cif file of **4d**. This material is available free of charge via the Internet at http://pubs.acs.org.

(23) The ee of **5** was not determined because of its instability under chiral HPLC analysis conditions.

(24) Zhou, C.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2007**, *129*, 5828. Adam, A. W.; Boehmer, J.; Dixon, D. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 5428. Habib-Zahmani, H.; Viala, J.; Hacini, S.; Rodriguez, J. *Synlett* **2007**, 1037. Boddaert, T.; Coquerel, Y.; Rodriguez, J. *Adv. Synth. Catal.* **2009**, *351*, 1744. Li, M.; Dixon, D. J. *Org. Lett.* **2010**, *12*, 3784. Presset, M.; Coquerel, Y.; Rodriguez, J. *Org. Lett.* **2010**, *12*, 4212.

(25) To our knowledge, there is only one isolated example of an optically pure spirolactam of this type reported in the literature: Hilmey, D. G.; Paquette, L. A. *Org. Lett.* **2005**, *7*, 2067.

(26) Meng, X.; Maggs, J. L.; Pryde, D. C.; Planken, S.; Jenkins, R. E.; Peakman, T. M.; Beaumont, K.; Kohl, C.; Park, B. K.; Stachulski, A. V. *J. Med. Chem.* **2007**, *50*, 6165. Nakagawa, A.; Uno, S.; Makishima, M.; Miyachi, H.; Hashimoto, Y. *Bioorg. Med. Chem.* **2008**, *16*, 7046.