ChemPubSoc Europe

DOI: 10.1002/chem.201402192

CHEMISTRY
A European Journal
Full Paper

Organocatalysis

Organocatalytic Enantio- and Diastereoselective Conjugate Addition to Nitroolefins: When β-Ketoamides Surpass β-Ketoesters

Haiying Du, Jean Rodriguez, Xavier Bugaut,* and Thierry Constantieux*[a]

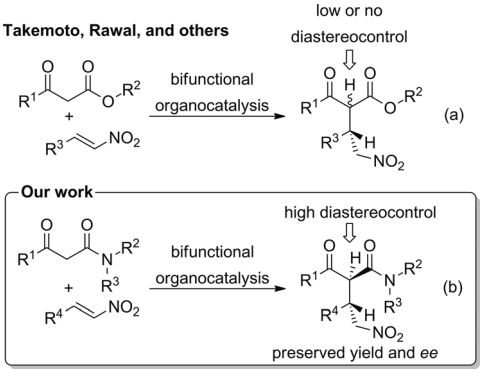
Dedicated to Professor Max Malacria on the occasion of his 65th birthday

Abstract: Our findings on the bifunctional squaramide-catalyzed enantioselective conjugate addition of β-ketoamides to nitroolefins are disclosed. It appears that simple acyclic methylene β-ketoamides, unlike the extensively studied β-ketoesters, afford the products in excellent diastereoselectivities, and maintain high yields and enantioselectivities. Moreover, competition and kinetic studies were conducted to rationalize the observed reactivity and selectivity. The high level of diastereocontrol, along with the amenability of the amide group to postfunctionalization, dramatically increase the synthetic usefulness of the transformation.

Introduction

The ideal enantioselective catalytic reaction consists of mixing stoichiometric amounts of starting materials in the presence of a low loading of a chiral non-racemic catalyst able to efficiently control all the bond- and stereogenic center-forming events of the process; that is, to deliver a highly functionalized product in high yield and enantio- and diastereoselectivity. Easy access to the substrates and catalyst, atom economy, high functional-group tolerance, operationally simple reaction conditions, and scalability are also important criteria.

The conjugate addition of readily available β-dicarbonyl compounds to nitroolefins is a fully atom-economic transformation with high synthetic potential because it delivers products with different functionalities that can be selectively reacted in subsequent steps.[1] In 2003, Takemoto and co-workers identified bifunctional thiourea–tertiary amine catalysts as efficient tools to control the enantioselectivity of this reaction.[2] Follow-up studies exemplified and broadened the scope of this transformation,[3] and include a milestone report by the group of Rawal, which showed that replacement of the thiourea function by a squaramide as the hydrogen-bond donor unit allows a dramatic decrease in the catalyst loading.[4] A significant limitation of this transformation for acyclic methylene β-ketoesters (Scheme 1 a) is that despite good yields and enantioselectivities, the products are obtained with low or no diastereoselectivity (generally the diastereomeric ratio (d.r.) is 1:1 to 2:1),[2b,4,5] which damages the synthetic usefulness of the process. Contrary to the abundant literature available for β-diketones or β-ketoesters, only specific examples of amide-containing β-dicarbonyl compounds have been studied in these transformations.[6] Based on our interest in the use of α- and β-ketoamides as pronucleophiles in organocatalysis,[6g,7,8] we hypothesized that acyclic methylene β-ketoamides might be interesting candidates to achieve highly diastereo- and enantioselective additions to nitroolefins (Scheme 1 b).



Scheme 1. Challenges for the conjugate addition of β-dicarbonyls to nitroolefins (*ee* = enantiomeric excess).

Our working hypothesis relied on the fundamental structural differences between β-ketoamides and β-ketoesters (Figure 1):

1) The α position of acyclic methylene β-ketoamides is 10000 times less acidic relative to their ester counterparts.[9] Activation of β-ketoamides will therefore be more difficult. However, this phenomenon could also prevent the epimeri-

[a] H. Du, Prof. Dr. J. Rodriguez, Dr. X. Bugaut, Prof. Dr. T. Constantieux
Aix Marseille Université
Centrale Marseille, CNRS
iSm2 UMR 7313, 13397, Marseille (France)
Fax: (+33) 491-289-187
E-mail: xavier.bugaut@univ-amu.fr
thierry.constantieux@univ-amu.fr

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201402192.

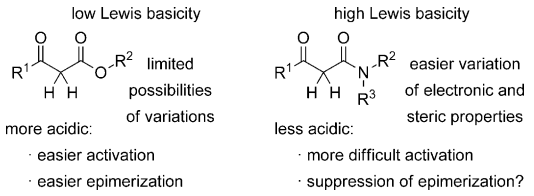


Figure 1. Comparison of the properties of β-ketoesters and β-ketoamides.

zation probably responsible for the low diastereoselectivity observed with β-ketoesters.

2) Amides are generally better Lewis bases than esters and ketones.[10] This larger difference between the Lewis basicity of the two carbonyl units of the substrate might assist more differentiated interactions with the catalyst and result in better facial selectivity of the approach in the stereochemistry-determining step.
3) Because the nitrogen atom can hold two additional substituents, whereas the oxygen atom can accommodate only one, more diversified amides can be prepared, which permits easier variation of the electronic and steric properties of the substrate.

Herein, we wish to discuss our results on the use of bifunctional organocatalysts to efficiently control the diastereo- and enantioselectivity of the conjugate addition of acyclic methylene β-ketoamides to nitroolefins. Gratifyingly, we found general conditions to afford the expected Michael adducts with excellent yields and stereoselectivities. This transformation, which involves equimolar ratios of the reactants with a low loading of the bifunctional organocatalyst, can be easily performed on a synthetically useful scale. The adducts can be further processed to afford highly valuable chiral scaffolds that contain up to three adjacent stereogenic centers with full retention of the stereoselectivity. Additionally, we conducted competition and kinetic experiments to determine the factors that influence the reactivity of β-ketoamides and the stereoselectivity of their reaction with nitroolefins.

Results and Discussion

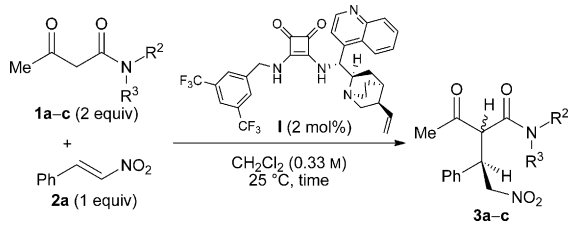
Organocatalytic addition of acyclic β-ketoamides to nitroolefins

Choice of β-ketoamide substrates

The first challenge of our study was to identify acyclic methylene β-ketoamide substrates that could combine both good reactivity and selectivity. Our former studies of the organocatalytic Michael addition of cyclic α-substituted β-ketoamides to α,β-unsaturated carbonyl compounds[7d,8a,d–e] or nitroolefins[6g] highlighted the importance of the presence of a proton on the nitrogen atom. Its absence generally resulted in no reactivity and the acidity of the secondary amide could be correlated with the observed enantioselectivities.

For this reason, we began our screening with *N*-phenyl-substituted secondary β-ketoamide **1a** (Table 1, entry 1). In the presence of cinchonine-derived bifunctional squaramide **I**, under the conditions designed by Rawal for the corresponding reaction with β-ketoesters,[6,11] the addition to (*E*)-β-nitrostyrene (**2a**) afforded the adduct **3a** with good yield and enantioselectivity but a disappointing d.r of 2:1. Results were not improved with the corresponding *N*-benzyl secondary β-ketoamide **1b** (Table 1, entry 2). We then turned our attention towards Weinreb β-ketoamide **1c** (Table 1, entry 3).[12] Although Weinreb β-ketoamides are not yet known as pronucleophiles in such reactions,[13] we hypothesized that they might be interesting candidates to reach our goal because of their increased steric hindrance and Lewis basicity, without too much restriction of their reactivity; indeed, the enolic positions of Weinreb amides usually exhibit higher acidity than other amide derivatives, which ensures easier activation by the organocatalyst. Moreover, the rich reactivity of Weinreb amides would increase the synthetic usefulness of the transformation.[14] Pleasingly, efficiency (97% yield) and enantioselectivity (95% *ee*) were as high as those observed with β-ketoesters and the product **3c** was formed with an unprecedented d.r. of 15:1.

Table 1. Selection of the acyclic β-ketoamide substrate.[a]



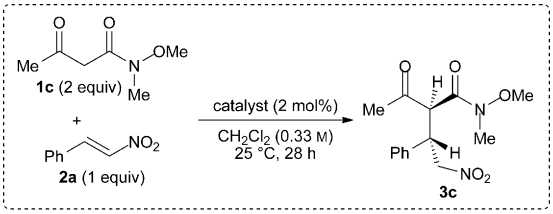
Entry	Ketoamide	R^2, R^3	Time [h]	Yield [%][b]	d.r.[c]	*ee*[d] [%]
1	**1a**	Ph, H	43	73	2:1	95, 69
2	**1b**	CH_2Ph, H	43	78	2:1	69, 58
3	**1c**	OMe, Me	28	97	**15:1**	95

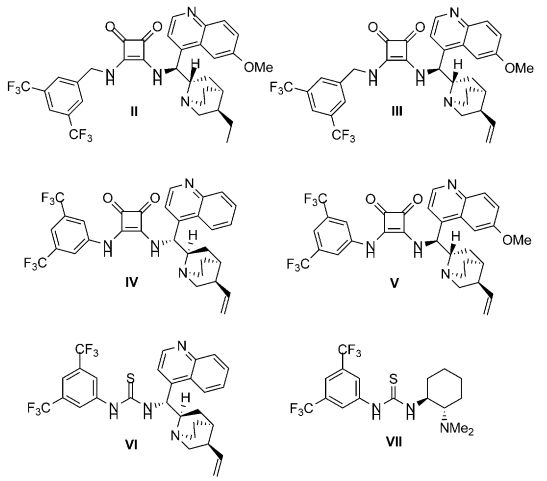
[a] A solution of **1** (2 equiv), **2a** (1 equiv), and catalyst **I** (2 mol%) in CH_2Cl_2 (0.33 M) was stirred at 25 °C until full conversion was achieved. [b] Isolated after silica gel column chromatography. [c] Determined by ^1H NMR spectroscopy of the crude reaction mixture. [d] Determined by HPLC on a chiral stationary phase.

Optimization of the reaction conditions

Having selected Weinreb ketoamide **1c** as the model substrate, the optimization of the reaction conditions was carried out with the standard 2:1 **1c**/**2a** ratio, usually used for reactions with related 1,3-dicarbonyl compounds. First, different bifunctional organocatalysts were evaluated in the present transformation (Table 2). Both catalysts **II** and **III** (Table 2, entries 2 and 3), which were prepared from hydroquinine and quinine, respectively, afforded the target product **3c** with yields and diastereoselectivities similar to those obtained with catalyst **I** (Table 2, entry 1). Pleasingly, a significant increase of the enantiomeric excess from 95 to 98% *ee* was also observed. Conversely, replacement of the 3,5-bis(trifluoromethyl)benzylamine unit in the catalyst structure by its aromatic counterpart (catalysts **IV** and **V**) severely impeded the enantioselectivity and totally annihilated the diastereoselectivity of the reaction

Table 2. Optimization of the reaction conditions with acyclic Weinreb ketoamide **1c**.[a]





Entry	Catalyst	Yield[b] [%]	d.r.[c]	*ee*[d] [%]
1	**I**	97	15:1	95
2	**II**	94	17:1	98
3	**III**	99	16:1	98
4	**IV**	91	1:1	73, 76
5	**V**	89	1:1	83, 81
6	**VI**	95	3:1	83, 67
7	**VII**	97	1:1	60, 66
8[e]	**III**	92	18:1	98

[a] A solution of **1c** (2 equiv), **2a** (1 equiv), and catalyst **I**–**VII** (2 mol%) in CH_2Cl_2 (0.33 M) was stirred at 25 °C until full conversion was achieved. [b] Isolated after silica gel column chromatography. [c] Determined by ^1H NMR spectroscopy of the crude reaction mixture. [d] Absolute value; determined by HPLC on a chiral stationary phase. [e] **1c** (1 equiv), reaction time = 14 h.

(Table 2, entries 4 and 5). In the same way, thiourea-containing catalysts **VI** and **VII** furnished **3c** in high yield with moderate enantioselectivity, but were unable to control the diastereoselectivity of the process (Table 2, entries 6 and 7). Finally, we were pleased to find that by mixing equimolar quantities of both reactants in the presence of selected catalyst **III** (2 mol%), product **3c** was formed with unchanged efficiency (92% yield, d.r. = 18:1, 98% *ee*; Table 2, entry 8).[15] We also realized that the reaction was faster than we had initially assumed and full conversion was reached within 14 h at 25 °C.

Scope and limitations of the reaction with acyclic Weinreb β-ketoamides

With these optimized conditions in hand, the generality of the title transformation was explored (Table 3). At first, different nitroolefins were exposed to the reaction conditions in the presence of **1c**. A large variety of electrophilic substrates bearing aromatic rings substituted with both electron-donating and electron-withdrawing groups, including sterically demanding *ortho* functionalization (as in **3f**), reacted successfully; heteroaromatic rings participated equally well in the reaction. Products **3c**–**h** were all obtained in high yields with d.r. values greater than 10:1 and enantioselectivities in the range 90–99% *ee*. Pleasingly, **3f** was crystallized and an analysis by X-ray diffraction allowed the absolute and relative configurations of the product to be identified as (2*S*,3*S*) [Figure 2].[16] A β-alkyl nitroolefin exhibited the same behavior as its aromatic counterparts and adduct **3i** was also formed in a highly stereoselective manner under the standard reaction conditions. As usual in this kind of transformation, more-substituted nitroolefins are more challenging substrates,[17] for example, product **3j** was obtained with somewhat reduced enantioselectivity and lower yield. However, the stereogenic center between the two carbonyl groups was still efficiently controlled and the mixture of diastereomers is due to the presence of an additional stereogenic center α to the nitro group.

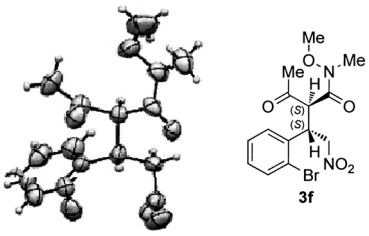


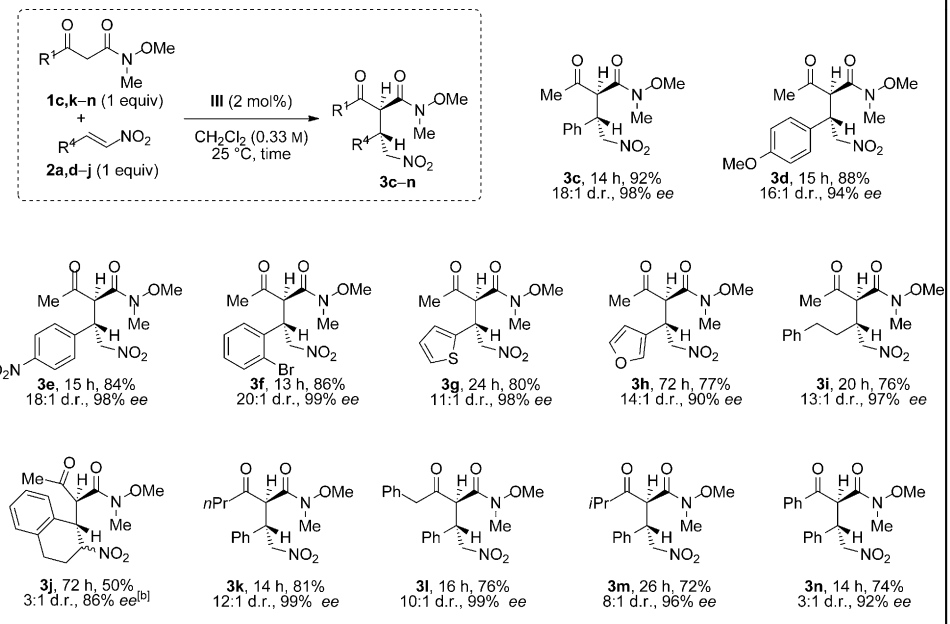
Figure 2. Determination of absolute and relative configurations by X-ray diffraction.

The influence of the ketone substituent of the pronucleophile was also investigated. Starting materials with linear alkyl chains were accommodated and delivered products **3k** and **3l** with a similar efficiency as the model substrate. Both a bulkier ramified alkyl chain or an aromatic R^1 substituent on the ketone somewhat impeded the diastereoselectivity, but the major diastereomers of products **3m** and **3n** were still obtained with high enantioselectivities.

Use of other acyclic β-ketoamides

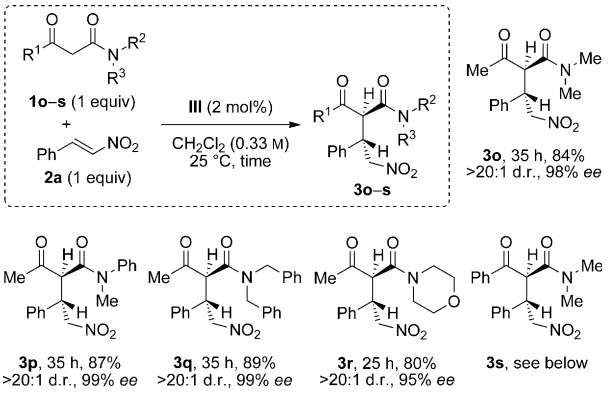
We continued our study by investigation of less-activated acyclic tertiary β-ketoamides (Table 4). We were delighted to see that they generally reacted smoothly with **2a** under the standard reaction conditions. Despite an increase of the reaction time, products **3o**–**r** were obtained with similar yields and enantioselectivitites to their Weinreb amide counterparts. Pleasingly, the diastereoselectivity of the process was even improved and the second diastereomer of the product was generally not observed in the crude reaction mixture. Once again, the substrate with an aromatic ketone R^1 substituent proved to be more challenging. Under the standard reaction conditions, full conversion was not reached even after 6 d and product **3s** was isolated in only 38% yield (Table 4, entry 1). Howev-

Table 3. Scope of the reaction between acyclic Weinreb β-ketoamides and nitroolefins.[a]



[a] A solution of **1** (1 equiv), **2** (1 equiv), and catalyst **III** (2 mol%) in CH_2Cl_2 (0.33 M) was stirred at 25 °C until full conversion was achieved. Yields of isolated product after silica gel column chromatography. Diastereomeric ratio was determined by ^1H NMR spectroscopy of the crude reaction mixture. The *ee* value for the major diastereomer was determined by HPLC on a chiral stationary phase. [b] The presence of diastereomers is due to epimerization α to the nitro group.

Table 4. Scope of the reaction with other acyclic tertiary β-ketoamides.[a]



Entry	Modification of the reaction conditions[b]	Time [d]	Yield [%]	d.r.[c]	*ee*[d] [%]
1	none	6	38[e]	8:1	95, 68
2	**III** (10 mol%), **2a** (1.2 equiv)	6	68	2:1	92, 89
3	**2a** (3 equiv)	5	75	6:1	95, 69

[a] A solution of **1o–s** (1 equiv), **2a** (1 equiv), and catalyst **III** (2 mol%) in CH_2Cl_2 (0.33 M) was stirred at 25 °C until full conversion was achieved. Yields of isolated product after silica gel column chromatography. [b] Re-optimization of the reaction conditions to obtain product **3s**. [c] Determined by ^1H NMR spectroscopy of the crude reaction mixture. [d] The *ee* value of the major diastereomer was determined by HPLC on a chiral stationary phase. [e] Incomplete conversion.

er, the enantioselectivity remained high and the d.r. was improved relative to the reaction with the corresponding Weinreb β-ketoamide **3n** (Table 3). Increasing the amount of catalyst improved the yield but reduced the diastereoselectivity (Table 4, entry 2). Conversely, keeping the catalyst loading at 2 mol% with a three-fold excess of nitroolefin delivered a good yield of product and maintained a 6:1 d.r. (Table 4, entry 3).

Rationalization of the reactivity and the selectivity

Kinetic studies

Having shown that a variety of acyclic methylene β-ketoamides could efficiently and stereoselectively be coupled with nitroolefins, we aimed to understand the similarities they share with other 1,3-dicarbonyl compounds and also the differences in their behavior that could account for the diastereoselectivity of the reaction. First, the kinetic profiles with four different pronucleophiles under the standard reaction conditions were monitored by ^1H NMR spectroscopy (Figure 3a).[18] For both the secondary β-ketoamide **1a** and ethyl acetoacetate (**4**), 50% conversion was reached in less than 5 min, which highlighted the exceptional reactivity of squaramide catalyst **III**. Substrate **1a** seemed to be more reactive than **4**: full conversion was attained within 15 min. The use of the more-hindered Weinreb ketoamide **1c** and tertiary amide **1p** resulted in significantly slower reactions (45 and 90 min, respectively) to obtain a 50% conversion. However, full conversion was still observed after a few hours of reaction.

Intrigued by the difference in the behaviors of catalysts with either an electron-poor benzylic or aromatic unit, the advancement of the reaction in the presence of these catalysts **III** and **V** was monitored (Figure 3b). It is commonly accepted that both the activity and the selectivity of hydrogen-bonding organocatalysts are correlated to their acidities.[19] In the studied reaction, **III**, which is less acidic than **V**,[19c] was not only far more selective (d.r. = 18:1, 98% *ee* versus d.r. = 1:1, 83 and 81% *ee*; see Table 2, entries 8 and 5, respectively), but also 12 times more active. These observations are in accordance with rare reports that show N-alkyl catalysts perform better than would be expected based on their acidity.[19a,20]

Origin of the diastereoselectivity

Two different hypotheses can be proposed to explain the high diastereoselectivity of the reaction: 1) the kinetic scenario, in which the C–C bond-forming step is intrinsically diastereoselective and the remaining proton in the α position cannot be

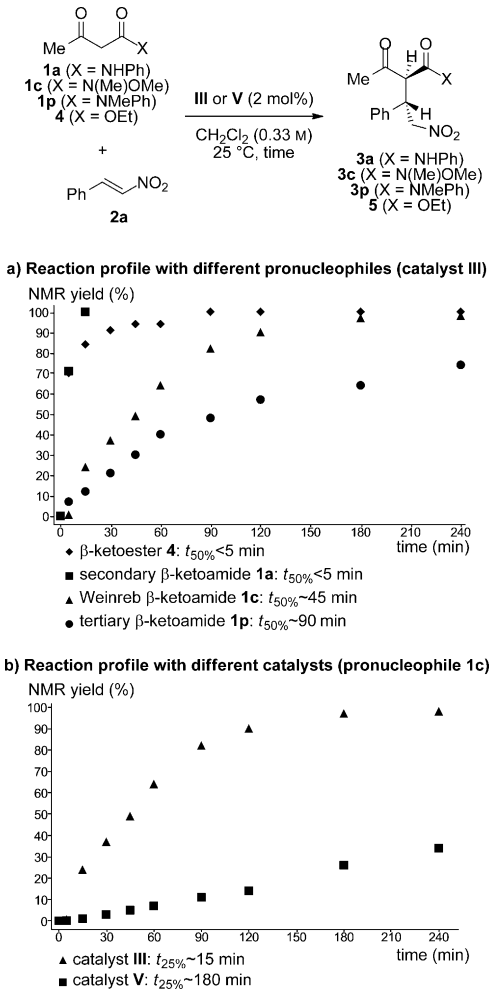


Figure 3. Kinetic study: comparison of the different 1,3-dicarbonyl substrates.

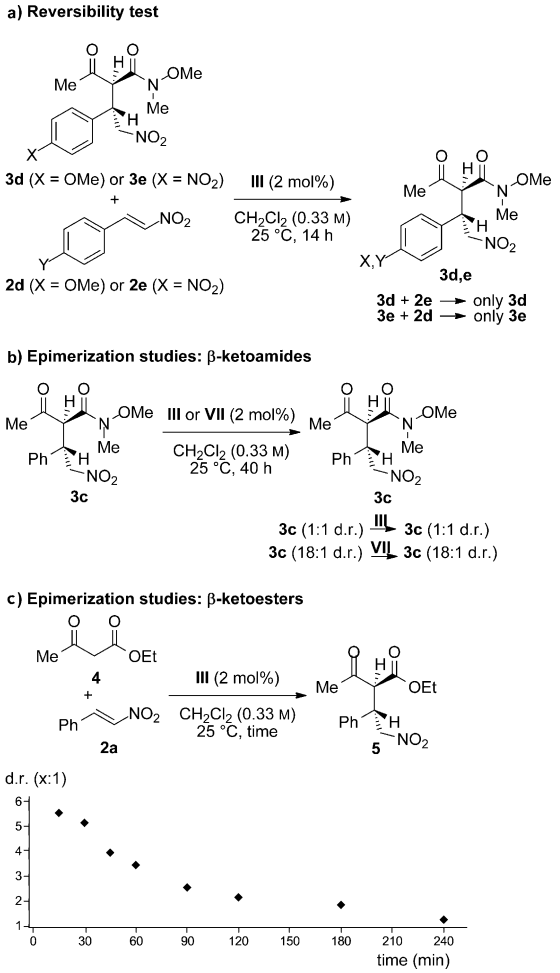


Figure 4. Reversibility and epimerization studies.

abstracted by the catalyst; 2) the thermodynamic scenario, in which the catalyst epimerizes the final product into its more stable diastereomer. Before the epimerization studies were performed, we determined that the reaction was irreversible under the standard reaction conditions based on the results of crossover experiments with **3d/3e** and **2d/2e** (Figure 4a).[18]

Afterwards, **3c** (18:1 d.r.) was exposed to unselective catalyst **VII**, whereas **3c** (1:1 d.r.) was placed in the presence of the best catalyst **III** (Figure 4b). In both cases, no change of the d.r. of the final product was observed, which is clearly in favor of the kinetic scenario with a catalyst-controlled highly diastereoselective C–C bond-forming step. Conversely, the d.r. of **5** was monitored during the course of the reaction with β-ketoester substrate **4**; we observed that the product is first formed with moderate diastereoselectivity and unselectively epimerizes over time (Figure 4c), as already observed by Pedrosa and co-workers in the corresponding thiourea-catalyzed transformation.[5d]

When trying to identify which structural elements influence the diastereoselectivity of the reaction with β-ketoamides, we realized that the diastereoselectivity tended to decrease with more bulky substrates (products **3c** and **3k–n** in Table 3). Plotting the free-energy relationship between log(d.r.) and the Charton steric parameters of the ketone substituents allowed identification of a linear relationship for aliphatic ketones **1c** and **1k–m**, with an acceptable correlation factor (Figure 5).[18,21,22] Accordingly, an increase in the steric differentiation between both carbonyl groups by replacing Weinreb β-ketoamides by bulkier tertiary amides resulted in an improvement of the d.r. (Table 3 versus 4). For aromatic ketones, such

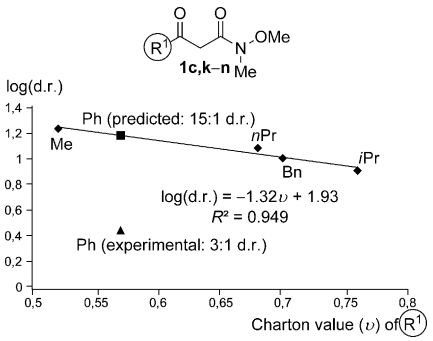


Figure 5. Linear free-energy relationship between d.r. and Charton steric parameters of the ketone substituents.

as **1n**, d.r. = 3:1 was obtained instead of the predicted d.r. = 15:1.[23] Of course, the aromatic group influences not only the steric properties of the substrate but also its electronic properties. The reduced diastereoselectivity can thus be ascribed to an epimerization of the more acidic α position, illustrated by the sensibility of product **3s** to the amount of catalyst (Table 4, entry 2).

Proposed transition state to account for the stereoselectivity

Several transition states can be envisaged to explain how bifunctional organocatalysts are able to activate the substrates. For thioureas, the two main models were proposed by the groups of Takemoto and Pápai.[2,24] Although the models differ significantly in their organization, they predict the same absolute configuration for the stereogenic center created during the reaction. A similar mode of action has been anticipated for squaramides, with the Takemoto-type model being favored.[4,6g,25] In accordance with the observed absolute and relative configurations of products **3**, we propose transition state **A** with like (*lk*) rather than unlike (*ul*) topicity for the stereodetermining step (Figure 6). The nitroolefin is positioned and activated by double hydrogen bonding to the squaramide motif.

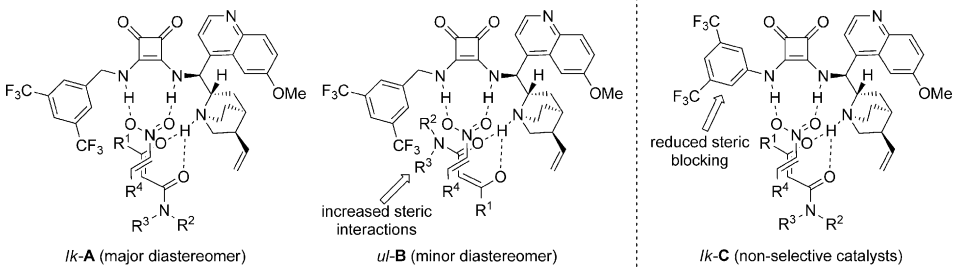


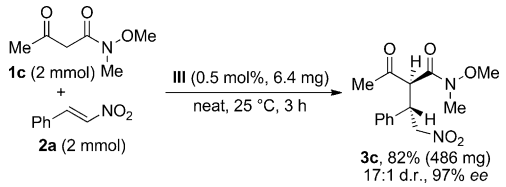
Figure 6. Proposed transition states to explain the stereoselectivity of the reaction.

Because of the absolute configurations of the stereogenic centers of the quinine-derived catalyst **III**, the quinuclidine moiety controls the facial selectivity of the nitroolefin by guiding the approach of the β-dicarbonyl compound to its lower face. The observed diastereoselectivity stems from the addition of the *Si* face of the β-ketoamide to the *Si* face of the nitroolefin. We surmise that the substituent of the ketone is placed on the side of the catalyst, whereas the bulkier tertiary amide points out of the catalytic pocket to minimize steric interactions. Additional hydrogen bonding between the ammonium nitrogen atom and the Lewis basic oxygen atom of the amide might also help to rigidify the transition state and improve the stereoselectivities. In accordance with the linear free energy/Charton steric parameter relationship (Figure 5), with bulkier R^1 groups there is less difference between the size of the two substituents and transition states *lk*-**A** and *ul*-**B** are thus closer in energy, which thereby reduces the diastereoselectivity. Accordingly, switching from Weinreb amides to other bulkier tertiary amides improves the facial selectivity responsible for the higher diastereoselectivity observed. Besides this, the non-selectivity of the N-aryl catalysts **IV**–**VII** could be explained by the lower flexibility of the aryl group in transition state *lk*-**C** relative to its benzyl counterpart, which results in an absence of discrimination between both topicities.

Synthetic usefulness of the transformation

Scale-up of the reaction

Having studied the scope and limitations of the title reaction and rationalized several aspects of the observed reactivity and selectivity, we aimed to study its synthetic potential. First, we needed to show that the reaction could be run on a synthetically useful scale (Scheme 2). Scale-up of the standard reaction conditions proceeded without any difficulty.[18] Moreover,



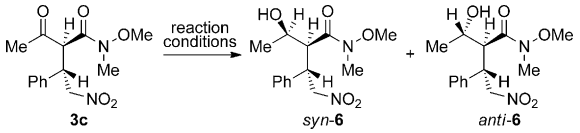
Scheme 2. Scale-up under neat reaction conditions.

2 mmol of each reactant and only 0.5 mol% of catalyst **III**[26] could be mixed without solvent at room temperature for 3 h to afford product **1c** with a slightly lower yield (82%) and virtually unchanged stereoselectivity (d.r. = 17:1, 97% *ee*) to obtain more than 480 mg of highly enantioenriched product with only 6.4 mg of catalyst under these neat reaction conditions.

Postfunctionalization of the adducts

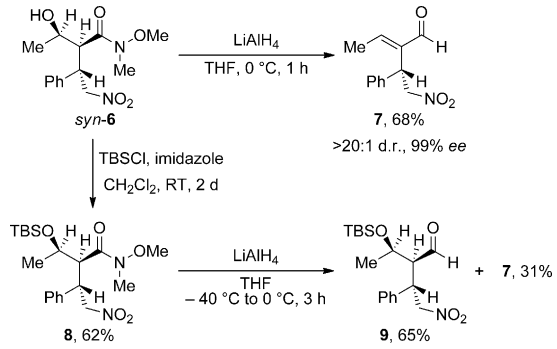
Products **3** possess several functional groups (ketone, Weinreb amide, and nitro group), therefore they are interesting platforms from which various chiral enantioenriched motifs of synthetic interest can be accessed. First, because the main improvement provided by the use of acyclic methylene β-ketoamides is the control of the relative configuration of the stereogenic center between the two carbonyl groups, the diastereoselective reduction of the ketone was investigated to enable efficient access to densely functionalized stereotriads (Table 5). Reduction of α-chiral β-dicarbonyl compounds by $NaBH_4$ in the presence of a Lewis acid is known to proceed with *syn* selectivity.[27] When **3c** was treated with $NaBH_4$ and $MnBr_2$ in MeOH at 0 °C, the reaction proceeded with high diastereoselectivity (13:1) and *syn*-**6** was isolated in 75% yield (Table 5, entry 1). A thorough optimization of the conditions was necessary to favor the formation of its epimer.[18] Non-coordinating Me_4NBH_4[28] in MeOH at −40 °C allowed the d.r. to reach 1:7

Table 5. Diastereoselective reduction of the ketone group of **3c**.



Entry	Reaction conditions	Yield[a] [%]	d.r. (*syn*/*anti*)[b]
1	$NaBH_4$, $MnBr_2$, MeOH, 0 °C, 10 min	75 (*syn*)	13:1
2	Me_4NBH_4, MeOH, −40 °C, 4 h	78 (*anti*)	1:7

[a] Yields of isolated major diastereomer of the product after silica gel column chromatography. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture.



Scheme 3. Postfunctionalization of the Weinreb amide.

(Table 5, entry 2). After purification, *anti*-**6** was isolated in a synthetically useful 78% yield.

Because Weinreb amides can be selectively reduced to aldehydes,[14] the hydroxyl derivatives **6** can be viewed as potential precursors of synthetically challenging α-chiral β-hydroxyaldehydes (Scheme 3). Exposure of *syn*-**6** to $LiAlH_4$ in THF at 0 °C resulted, not only in reduction of the Weinreb amide to the aldehyde, but also in elimination of the alcohol to afford enal **7** in 68% yield as a single diastereomer, without erosion of its *ee* value. Although two stereogenic centers are destroyed in the process, this transformation is interesting because **7** is the product of a formal Rauhut–Currier reaction between crotonaldehyde and β-nitrostyrene and previous attempts to prepare it in enantioenriched form have been unsuccessful.[29] To avoid dehydration of the fragile β-hydroxyaldehyde, the alcohol functionality was protected as the *tert*-butyldimethylsilyl ether **8**. Pleasingly, reduction of **8** with $LiAlH_4$ afforded the versatile protected β-hydroxyaldehyde **9** in synthetically useful yield, even though the formation of **7** could not be completely suppressed.

Conclusion

For the first time, the behavior of simple linear β-ketoamides towards nitroolefins in the presence of bifunctional organocatalysts was evaluated. Similar to other β-dicarbonyl compounds, they deliver the products of conjugate addition with high yields and enantioselectivities. Additionally, interesting unprecedented features were uncovered during this study: 1) with acyclic tertiary methylene β-ketoamides, the second stereogenic center between the two carbonyl groups could be forged with high diastereocontrol; 2) an excess of pronucleophile is not required for the reaction to proceed with high efficiency; 3) quantitative evaluation of the structural elements that influence the selectivity will help to improve the predictability of the results in related transformations; 4) the dramatic differences in terms of reactivity and selectivity between *N*-benzyl- and *N*-aryl-squaramides in the studied reaction could be quantified, which may be helpful in the selection of the ideal catalyst when developing new transformations; 5) original, highly enantioenriched stereotriads and functionalized α-chiral aldehydes could be accessed by postfunctionalization of the Michael adducts. Based on these results, our next efforts will focus on extending the reactivity of hitherto overlooked acyclic methylene β-ketoamides in other organocatalytic transformations.

Experimental Section

General procedure for the enantioselective conjugate addition of acyclic tertiary methylene β-ketoamides to nitroolefins

Substituted nitroolefin **2** (0.200 mmol, 1.0 equiv) was added to a solution of chiral squaramide catalyst **III** (2.6 mg, 4.0 μmol, 2 mol%) and β-ketoamide **1** (0.200 mmol, 1.0 equiv) in dry CH_2Cl_2 (0.6 mL) under argon. The reaction mixture was stirred at 25 °C until complete conversion of the β-ketoamide was detected by TLC. The solution was filtered through a short pad of silica gel, which was thoroughly washed with CH_2Cl_2. The solvent was evaporated under reduced pressure to obtain the crude product, which was analyzed by NMR spectroscopy to determine the diastereomeric ratio. Purification by flash column chromatography on silica gel provided the pure product **3**.

Representative description of product (3c): Reaction time = 14 h; crude product was obtained with 18:1 d.r. Purification by column chromatography (CH_2Cl_2/EtOAc 50:1) afforded **3c** (53.3 mg, 0.184 mmol, 92% yield, 98% *ee*). R_f = 0.57 (CH_2Cl_2/EtOAc 50:1; UV, vanillin); $[\alpha]_D^{20} = -67.4$ (c = 0.23 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.23 (m, 5H), 4.96 (dd, J = 13.1, 9.2 Hz, 1H), 4.87 (dd, J = 13.1, 4.0 Hz, 1H), 4.35 (d, J = 8.4 Hz, 1H), 4.28 (td, J = 8.8, 4.0 Hz, 1H), 3.45 (s, 3H), 3.21 (s, 3H), 1.98 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.3 (C), 168.4 (C), 137.0 (C), 129.3 (2×CH), 128.4 (CH), 128.2 (2×CH), 77.5 (CH_2), 61.3 (CH_3), 58.9 (CH), 42.9 (CH), 32.6 (CH_3), 29.5 ppm (CH_3); HRMS (ESI): m/z calcd for $[C_{14}H_{18}N_2O_5+H]^+$: 295.1288; found: 295.1289; HPLC (Chiralpak AS-H, hexane/EtOH 90:10, 25 °C, 1.0 mL min^{-1}, λ = 220 nm): retention time τ_{major} = 8.10 min, τ_{minor} = 14.56 min.

Procedure for the preparative scale neat reaction

Chiral squaramide catalyst **III** (6.4 mg, 10.0 μmol, 0.5 mol%), **1c** (290 mg, 2.00 mmol, 1.0 equiv), and **2a** (298 mg, 2.00 mmol, 1.0 equiv) were mixed without solvent under argon. After 3 h of stirring at 25 °C, the reaction mixture had solidified and was analyzed by NMR spectroscopy to measure the d.r. (17:1). Purification by column chromatography (CH_2Cl_2) afforded **3c** (486 mg, 1.64 mmol, 82%, 97% *ee*). Analytical data were in accordance with

those obtained when the reaction was run on a 0.2 mmol scale under the standard reaction conditions.

Acknowledgements

We thank Dr. N. Vanthuyne and M. Jean for chiral HPLC analyses, Dr. M. Giorgi for X-ray diffraction analyses, and the whole team at Spectropole (www.spectropole.fr). Dr. Cyril Bressy is acknowledged for helpful discussions and proofreading of the manuscript. Financial support from Aix Marseille Université, Centrale Marseille, the CNRS, the COST action CM0905 ORCA, and the China Scholarship Council (scholarship for H.D.) is acknowledged.

Keywords: diastereoselectivity · enantioselectivity · ketoamides · Michael addition · nitroolefins

[1] E. P. Kohler, H. Engelbrecht, *J. Am. Chem. Soc.* **1919**, *41*, 764 – 770.

[2] a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672 – 12673; b) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119 – 125.

[3] a) For a recent review on organocatalytic enantioselective conjugate additions, see: Y. Zhang, W. Wang, *Catal. Sci. Technol.* **2012**, *2*, 42 – 53; b) for a book chapter on the additions to nitroolefins, see: C. Roux, C. Bressy, in *Comprehensive Enantioselective Organocatalysis* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2013**, pp. 1013 – 1042.

[4] J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416 – 14417.

[5] a) To the best of our knowledge, there is only one example of a methylene β-ketoester delivering the product with a 5:1 d.r. in this transformation: B. Liu, X. Han, Z. Dong, H. Lv, H.-B. Zhou, C. Dong, *Tetrahedron: Asymmetry* **2013**, *24*, 1276 – 1280; for other selected examples of reactions with low or no diastereoselectivity, see: b) X. Jiang, Y. Zhang, X. Liu, G. Zhang, L. Lai, L. Wu, J. Zhang, R. Wang, *J. Org. Chem.* **2009**, *74*, 5562 – 5567; c) D. Almaşi, D. A. Alonso, E. Gómez-Bengoa, C. Nájera, *J. Org. Chem.* **2009**, *74*, 6163 – 6168; d) R. Manzano, J. M. Andrés, R. Pedrosa, *Synlett* **2011**, 2205.

[6] a) Alkyl pyrrolidine-2-one-3-carboxylates: P. Jakubec, M. Helliwell, D. J. Dixon, *Org. Lett.* **2008**, *10*, 4267 – 4270; b) oxazolidinylbutane-1,3-diones: P. Elsner, H. Jiang, J. B. Nielsen, F. Pasi, K. A. Jorgensen, *Chem. Commun.* **2008**, 5827 – 5829; c) a strategic intermediate en route to (−)-nakadomarin A, 1st-generation synthesis: P. Jakubec, D. M. Cockfield, D. J. Dixon, *J. Am. Chem. Soc.* **2009**, *131*, 16632 – 16633; d) 2nd-generation synthesis: A. F. Kyle, P. Jakubec, D. M. Cockfield, E. Cleator, J. Skidmore, D. J. Dixon, *Chem. Commun.* **2011**, *47*, 10037 – 10039; e) succinimidyl esters: P. Jakubec, D. M. Cockfield, P. S. Hynes, E. Cleator, D. J. Dixon, *Tetrahedron: Asymmetry* **2011**, *22*, 1147 – 1155; f) alkyl 2-oxindole-3-carboxylates: X. Chen, W. Zhu, W. Qian, E. Feng, Y. Zhou, J. Wang, H. Jiang, Z.-J. Yao, H. Liu, *Adv. Synth. Catal.* **2012**, *354*, 2151 – 2156; g) β-oxocyclobutanecarboxamides: D. Mailhol, M. M. Sanchez Duque, W. Raimondi, D. Bonne, T. Constantieux, Y. Coquerel, J. Rodriguez, *Adv. Synth. Catal.* **2012**, *354*, 3523 – 3532.

[7] For α-ketoamides, see: a) O. Baslé, W. Raimondi, M. M. Sanchez Duque, D. Bonne, T. Constantieux, J. Rodriguez, *Org. Lett.* **2010**, *12*, 5246 – 5249; b) W. Raimondi, D. Bonne, J. Rodriguez, *Angew. Chem.* **2012**, *124*, 40 – 42; *Angew. Chem. Int. Ed.* **2012**, *51*, 40 – 42; c) W. Raimondi, D. Bonne, J. Rodriguez, *Chem. Commun.* **2012**, *48*, 6763 – 6775; d) W. Raimondi, M. M. Sanchez Duque, S. Goudedranche, A. Quintard, T. Constantieux, X. Bugaut, D. Bonne, J. Rodriguez, *Synthesis* **2013**, *45*, 1659 – 1666.

[8] For β-ketoamides, see: a) M. M. Sanchez Duque, O. Baslé, N. Isambert, A. Gaudel-Siri, Y. Génisson, J.-C. Plaquevent, J. Rodriguez, T. Constantieux, *Org. Lett.* **2011**, *13*, 3296 – 3299; b) K. Mohanan, Y. Coquerel, J. Rodriguez, *Org. Lett.* **2012**, *14*, 4686 – 4689; c) D. Mailhol, J.-C. Castillo, K. Mohanan, R. Abonia, Y. Coquerel, J. Rodriguez, *ChemCatChem* **2013**, *5*, 1192 – 1199; d) M. M. Sanchez Duque, O. Baslé, Y. Génisson, J.-C. Plaquevent, X. Bugaut, T. Constantieux, J. Rodriguez, *Angew. Chem.* **2013**, *125*, 14393 – 14396; *Angew. Chem. Int. Ed.* **2013**, *52*, 14143 – 14146; e) S. Goudedranche, X. Bugaut, T. Constantieux, D. Bonne, J. Rodriguez, *Chem. Eur. J.* **2014**, *20*, 410 – 415; for contributions of other groups, see: f) M. W. Paixão, M. Nielsen, C. B. Jacobsen, K. A. Jørgensen, *Org. Biomol. Chem.* **2008**, *6*, 3467 – 3470; g) T. Yang, A. Ferrali, F. Sladojevich, L. Campbell, D. J. Dixon, *J. Am. Chem. Soc.* **2009**, *131*, 9140 – 9141; h) X. Dai, X. Wu, H. Fang, L. Nie, J. Chen, H. Deng, W. Cao, G. Zhao, *Tetrahedron* **2011**, *67*, 3034 – 3040; i) X. Wu, Q. Liu, H. Fang, J. Chen, W. Cao, G. Zhao, *Chem. Eur. J.* **2012**, *18*, 12196 – 12201; j) C. De Fusco, S. Meninno, C. Tedesco, A. Lattanzi, *Org. Biomol. Chem.* **2013**, *11*, 896 – 899.

[9] Compare the pK_a of ethyl acetoacetate (14.2) with the pK_a of *N*,*N*-dimethylacetoacetamide (18.2): a) F. G. Bordwell, J. A. Harrelson Jr, *Can. J. Chem.* **1990**, *68*, 1714 – 1718; b) F. G. Bordwell, H. E. Fried, *J. Org. Chem.* **1991**, *56*, 4218 – 4223.

[10] C. Laurence, J.-F. Gal, *Lewis Basicity and Affinity Scales: Data and Measurement*, Wiley, Chichester, **2009**.

[11] For reviews on squaramides, see: a) J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890 – 6899; b) R. I. Storer, C. Aciro, L. H. Jones, *Chem. Soc. Rev.* **2011**, *40*, 2330 – 2346.

[12] β-ketoamides were prepared by application and adaptation of known methods: a) Y. Yamamoto, Y. Watanabe, S. Ohnishi, *Chem. Pharm. Bull.* **1987**, *35*, 1860 – 1870; b) Y. Chen, S. M. N. Sieburth, *Synthesis* **2002**, 2191 – 2194; c) B. Miriyala, J. S. Williamson, *Tetrahedron Lett.* **2003**, *44*, 7957 – 7959; d) M. Presset, Y. Coquerel, J. Rodriguez, *J. Org. Chem.* **2009**, *74*, 415 – 418; e) M. Presset, D. Mailhol, Y. Coquerel, J. Rodriguez, *Synthesis* **2011**, 2549 – 2552; see the Supporting Information for more details.

[13] A previous attempt to react these substrates with β-alkyl nitroolefins under bifunctional organocatalysis was unsuccessful, see reference [6b].

[14] a) S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815 – 3818; b) S. Balasubramaniam, I. S. Aidhen, *Synthesis* **2008**, 3707 – 3738.

[15] The possibility to use equimolar quantities of the reactants also holds true for β-ketoesters. Under these reaction conditions, the adduct was obtained with 83% yield, 1.2:1 d.r., and 99% *ee* for both diastereomers versus 89% yield, 1.6:1 d.r., and 97% *ee* under Rawal's conditions.

[16] CCDC-977764 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[17] J. Duschmalé, H. Wennemers, *Chem. Eur. J.* **2012**, *18*, 1111 – 1120, and references therein.

[18] Full details can be found in the Supporting Information.

[19] a) X. Li, H. Deng, B. Zhang, J. Li, L. Zhang, S. Luo, J.-P. Cheng, *Chem. Eur. J.* **2010**, *16*, 450 – 455; b) G. Jakab, C. Tancon, Z. Zhang, K. M. Lippert, P. R. Schreiner, *Org. Lett.* **2012**, *14*, 1724 – 1727; c) X. Ni, X. Li, Z. Wang, J.-P. Cheng, *Org. Lett.* **2014**, *16*, 1786 – 1789.

[20] Alkylamine-derived bifunctional catalysts have exhibited superiority to aniline-derived ones in other transformations. See, for example: H.-P. Deng, Y. Wei, M. Shi, *Eur. J. Org. Chem.* **2011**, 1956 – 1960.

[21] a) R. W. Taft, *J. Am. Chem. Soc.* **1953**, *75*, 4538 – 4539; b) M. Charton, *J. Am. Chem. Soc.* **1975**, *97*, 1552 – 1556; c) M. Charton, *J. Org. Chem.* **1976**, *41*, 2217 – 2220.

[22] For selected recent applications of linear free-energy relationships in enantioselective catalysis, see: a) J. J. Miller, M. S. Sigman, *Angew. Chem.* **2008**, *120*, 783 – 786; *Angew. Chem. Int. Ed.* **2008**, *47*, 771 – 774; b) M. S. Sigman, J. J. Miller, *J. Org. Chem.* **2009**, *74*, 7633 – 7643; c) J. L. Gustafson, M. S. Sigman, S. J. Miller, *Org. Lett.* **2010**, *12*, 2794 – 2797; d) K. H. Jensen, M. S. Sigman, *J. Org. Chem.* **2010**, *75*, 7194 – 7201; e) L. Mantilli, D. Gérard, S. Torche, C. Besnard, C. Mazet, *Chem. Eur. J.* **2010**, *16*, 12736 – 12745; f) A. Quintard, A. Alexakis, *Org. Biomol. Chem.* **2011**, *9*, 1407 – 1418; g) K. C. Harper, M. S. Sigman, *J. Org. Chem.* **2013**, *78*, 2813 – 2818.

[23] Depending on its orientation (coplanar or perpendicular), the phenyl group can also be described by another Charton value of 1.66. This second value was not considered because it would predict the other diastereomer to be the major one, with modest selectivity.

[24] a) A. Hamza, G. Schubert, T. Soós, I. Pápai, *J. Am. Chem. Soc.* **2006**, *128*, 13151 – 13160; b) T. Azuma, Y. Kobayashi, K. Sakata, T. Sasamori, N. Tokitoh, Y. Takemoto, *J. Org. Chem.* **2014**, *79*, 1805 – 1817.

[25] T. Lu, S. E. Wheeler, *Chem. Eur. J.* **2013**, *19*, 15141 – 15147.

[26] For a review on low-loading enantioselective organocatalysis, see: F. Giacalone, M. Gruttadauria, P. Agrigento, R. Noto, *Chem. Soc. Rev.* **2012**, *41*, 2406 – 2447.
[27] H. Fujii, K. Oshima, K. Utimoto, *Tetrahedron Lett.* **1991**, *32*, 6147 – 6150.
[28] D. A. Evans, K. T. Chapman, *Tetrahedron Lett.* **1986**, *27*, 5939 – 5942.
[29] J. Vesely, R. Rios, A. Córdova, *Tetrahedron Lett.* **2008**, *49*, 1137 – 1140, and references therein.

Received: February 14, 2014
Published online on June 4, 2014