JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Enantioselective Conjugate Addition of Donor–Acceptor Hydrazones to α,β-Unsaturated Aldehydes through Formal Diaza–Ene Reaction: Access to 1,4-Dicarbonyl Compounds

Maitane Fernández, Uxue Uria, Jose L. Vicario,* Efraím Reyes, and Luisa Carrillo

Departamento de Química Orgánica II, Facultad de Ciencia y Tecnología, Universidad del País Vasco/Euskal Herriko Unibertsitatea (UPV/EHU), P.O. Box 644, E-48080 Bilbao, Spain

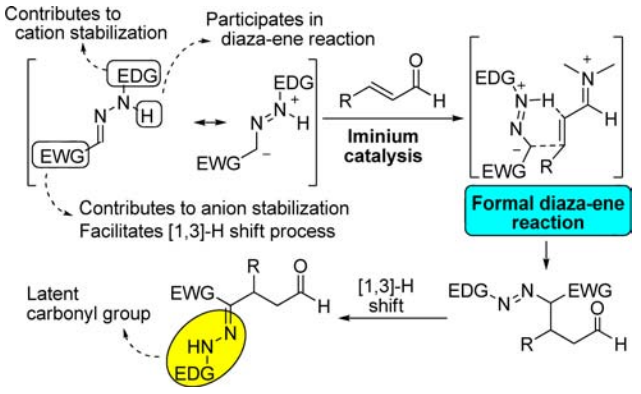
Supporting Information

ABSTRACT: Donor–acceptor monosubstituted hydrazones participate as suitable reagents able to undergo an enantioselective formal diaza–ene reaction with α,β-unsaturated aldehydes under chiral secondary amine catalysis. This constitutes a new approach for the enantioselective conjugate addition of hydrazones to enals under metal-free conditions and leads to the formation of γ-hydrazono carboxylic acids after oxidation/[1,3]-H shift. The methodology is also useful for the synthesis of enantioenriched β-substituted α-keto-1,5-diesters by using the hydrazone moiety as a masked carbonyl group.

The discovery of new umpolung transformations in which inversion of the natural reactivity pattern of a given chemical reagent takes place during the overall process has been an important field of research since Corey and Seebach introduced the concept.[1] In particular, conjugate addition of acyl anion equivalents, the archetypical example of umpolung reactivity, enables the preparation of 1,4-dicarbonyl compounds, a molecular architecture that is difficult to access by conventional methods. In this context, several approaches have been devised using conveniently designed nucleophilic reagents that, after the conjugate addition process takes place, are able to deliver the final 1,4-dicarbonyl compound by unmasking the γ-carbonyl group through a simple and high-yielding transformation.[2] In addition, if an enantiomerically enriched product is desired, several catalytic enantioselective approaches have been reported in the past few years, focused on the use of either metal catalysis[3] or organocatalysis.[4] Alternatively, the enantioselective Stetter reaction using N-heterocyclic carbenes as catalysts can be extremely efficient for the direct conjugate addition of acyl anions,[5] directly affording the final 1,4-dicarbonyl adduct without the need for additional synthetic steps to reveal the latent carbonyl functionality. However, this reaction normally demands a highly electrophilic Michael acceptor, such as a nitroalkene or an alkylidene malonate, in order to proceed with high yield for the intermolecular version.[6]

With these precedents in mind and in connection with our ongoing efforts to develop new organocatalytic reactions, we decided to survey the possibility of carrying out the conjugate addition of a suitable acyl anion equivalent to α,β-unsaturated aldehydes by applying the iminium activation concept,[7] therefore opening the way to achieve enantiocontrol by using a chiral secondary amine as the catalyst. In particular, we thought of donor–acceptor hydrazones such as those shown in Scheme 1 as potential acyl anion equivalents. The principles behind the reaction design rely on the ability of an N-monosubstituted hydrazone to undergo a diaza–ene reaction with a chiral α,β-unsaturated iminium ion intermediate that operates as an activated Michael acceptor. This initial step would deliver a γ-azoaldehyde adduct that, after a [1,3]-hydride shift, would render a γ-hydrazono aldehyde product where the hydrazone moiety could be considered as a latent carbonyl functionality. Under this design, we anticipated that a donor–acceptor hydrazone reagent would presumably fulfill the requisites for becoming an active Michael donor in the projected reaction under the typical neutral or slightly basic conditions associated with iminium catalysis. In particular, it was envisaged that the concurrent incorporation of an electron-donating group (EDG) as the nitrogen substituent and an electron-withdrawing group (EWG) as the substituent at the azomethine carbon would enhance the reactivity of the azomethine carbon atom toward its interaction with the electrophilic β-carbon of the iminium ion, therefore resulting in a highly productive situation.

Scheme 1. Donor–acceptor Monosubstituted Hydrazones as Acyl Anion Equivalents in Enantioselective Conjugate Addition under Iminium Activation



Received: April 28, 2012
Published: July 9, 2012

   dx.doi.org/10.1021/ja3041042 | J. Am. Chem. Soc. 2012, 134, 11872–11875

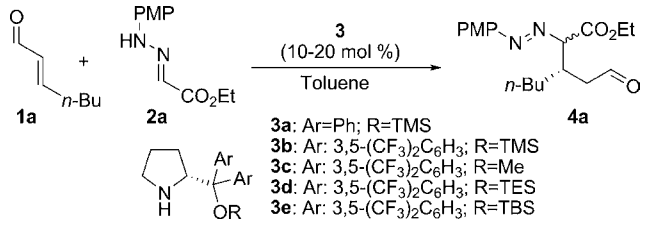
It should be mentioned that there is one precedent in the literature describing the use of disubstituted *N*,*N*-dialkylhydrazones derived from formaldehyde as Michael donors in the conjugate addition to β,γ-unsaturated α-keto esters under chiral Brønsted acid catalysis, furnishing moderate levels of enantioselectivity.[8] Monosubstituted hydrazones have also been used by Scheidt under cooperative Mg(II)/NHC catalysis,[9] but in that case, they act as *electrophiles*, which is the natural reactivity pattern expected for these azomethine compounds. Thus, even though formaldehyde pyrrolidinyl hydrazones have been employed as nucleophiles in several transformations,[10] there are no precedents showing their behavior toward α,β-unsaturated aldehydes or ketones under iminium activation. This is probably due to their predictable tendency to undergo intramolecular condensation after conjugate addition, rendering the corresponding aromatic *N*-aminopyrrole derivatives.[11] In addition, and to the best of our knowledge, the application of this type of donor−acceptor hydrazone in catalytic enantioselective diaza−ene-type reactions is still unprecedented in the chemical literature,[12] and even the possibility of carrying out this reaction in an asymmetric fashion under metal-free conditions is still undocumented.

On the basis of these postulates, we started our work by surveying the viability of the projected transformation using the reaction between enal **1a** and hydrazone **2a** as a representative model system (Table 1). We first tested the performance of *O*-trimethylsilyl (*O*-TMS)-substituted diphenylprolinol derivative **3a** as a chiral secondary amine catalyst in toluene at 4 °C, which are standard reaction conditions employed in other examples of conjugate addition reactions under iminium activation.[7,13] This demonstrated the ability of the hydrazone reagent **2a** to behave as we anticipated in Scheme 1, leading to the formation of the desired γ-azoaldehyde **4a** in moderate yield as a 70:30 mixture of diastereoisomers (entry 1) in a rather fast reaction (3 h reaction time). However, even though the enantioselectivity offered by this catalyst for the main diastereoisomer was remarkably high (98% ee), the minor diastereoisomer was isolated in only 10% ee. In this sense, and taking into consideration that both diastereoisomers of **4a** would converge into a single product after the projected [1,3]-hydride shift process, we next focused on searching for the best conditions to obtain a highly enantioenriched material regardless the diastereomeric proportion. We therefore tested the use of catalyst **3b** containing larger aryl groups, which delivered **4a** in a similar yield but with a significant improvement in the enantioselectivity of the minor diastereoisomer (entry 2). We next evaluated a family of related diarylprolinol catalysts incorporating substituents of different sizes at the oxygen atom (entries 3−5), observing that the use of *O*-methyl-containing catalyst **3c** provided poorer results in terms of both yield and stereoselectivity (entry 3), whereas results similar to those for the **3b**-catalyzed reaction were obtained when the steric bulk was slightly increased to triethylsilyl in **3d** (entry 4 vs 2). Interestingly, the introduction of an even larger *O*-trialkylsilyl group (catalyst **3e**; entry 5) increased the enantioselectivity for the minor diastereoisomer up to a satisfactory 86% ee while maintaining a 98% ee for the major diastereoisomer.

Once the optimal catalyst had been identified, we directed our efforts to improving the yield of the reaction, which was achieved by working at a higher temperature, without this affecting the enantioselectivity significantly (entry 6). Finally, we also demonstrated that the reaction performed well with a lower catalyst loading (10 mol %; entry 7), which resulted in just a slight decrease in the yield while keeping identical levels of stereoselection. These last conditions were therefore chosen as the optimal ones for our reaction.[14]

Having established a robust experimental protocol for the conjugate addition reaction, and in line with the overall reaction design shown in Scheme 1, we next proceeded to study the most appropriate conditions for inducing a [1,3]-hydride shift process on the conjugate addition adduct **4a** (Scheme 2). Treatment of the aldehyde with different Brønsted acids under a variety of conditions led to the projected [1,3]-hydride shift process smoothly, forming the desired γ-hydrazono aldehyde. However, the isolated compound had a pronounced tendency to undergo intramolecular hemiaminal formation and subsequent dehydration, forming cyclic dihydropyridazine derivative **5a**, albeit with retention of enantiopurity.

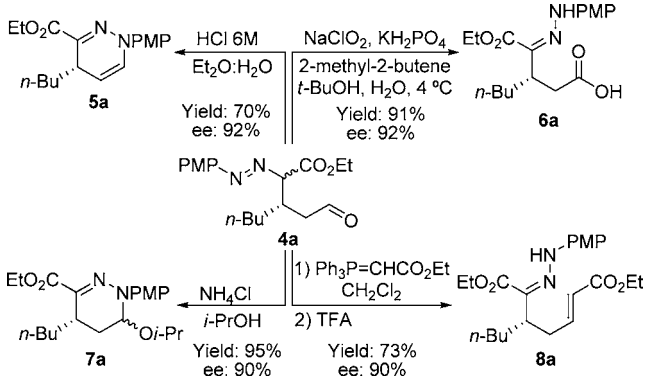
Table 1. Screening for the Best Experimental Conditions Using the Reaction of Enal 1a with Hydrazone 2a as a Model System[a]



entry	catalyst	T (°C)	yield (%)[b]	dr[c]	ee (%)[d]
1	**3a**	4	51	70:30	98/10
2	**3b**	4	63	70:30	95/78
3	**3c**	4	20	70:30	74/12
4	**3d**	4	66	70:30	96/75
5	**3e**	4	64	70:30	98/86
6	**3e**	r.t.	83	70:30	96/84
7[e]	**3e**	r.t.	79	70:30	96/84

[a]Reaction conditions: 2.0 mmol of **1a**, 1.0 mmol of **2a**, and catalyst **3** (20 mol %) were stirred in toluene at the specified temperature for 2−3 h. [b]Yields of pure product as mixtures of diastereoisomers after flash column chromatography. [c]Diastereomeric ratios determined by NMR analysis of the crude reaction mixtures. [d]ee values for the major and minor diastereoisomers respectively, as determined by chiral-stationary-phase HPLC analysis (see the Supporting Information). [e]10 mol % catalyst **3e** was used.

Scheme 2. Transformations Carried out on Aldehyde 4a

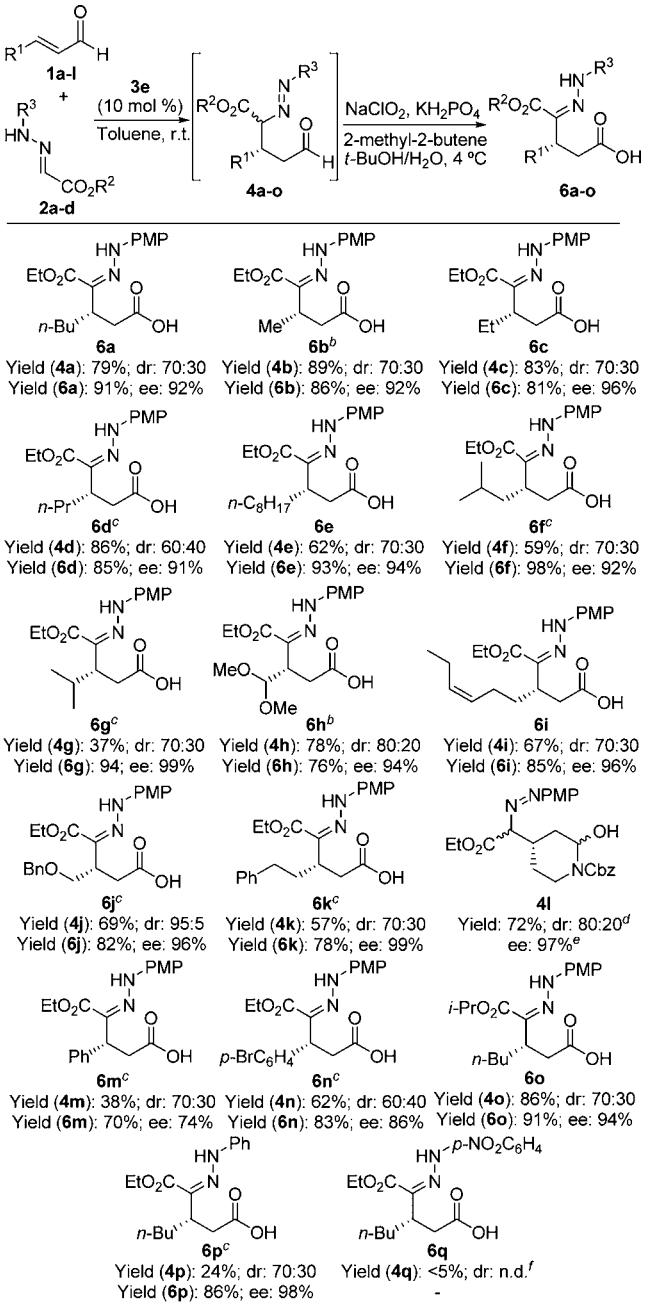


dx.doi.org/10.1021/ja3041042 | J. Am. Chem. Soc. 2012, 134, 11872−11875

To avoid this cyclization process, we decided to carry out the oxidation of the aldehyde moiety. This proceeded simultaneously with the [1,3]-hydride shift process, affording the desired γ-hydrazono carboxylic acid **6a** in excellent yield without erosion of enantiopurity (see Scheme 2). Alternatively, dehydration after the acid-mediated [1,3]-hydride shift could be avoided by using isopropyl alcohol as the solvent, leading to the formation of **7a** in good yield as a mixture of α- and β-anomers, both of which were isolated with high enantiopurity. We also surveyed the possibility of elaborating these adducts by exploiting their aldehyde reactivity. In this sense, Wittig reaction under standard conditions followed by addition of trifluoroacetic acid (TFA) led to the formation of α,β-unsaturated ε-hydrazono ester **8a** in excellent yield and retaining the ee of the starting material.

We next proceeded to extend the reaction, exploring other α,β-unsaturated aldehydes with different substitution patterns in order to determine the scope of the reaction and its performance for the preparation of differently substituted γ-hydrazono carboxylic acids. The results summarized in Scheme 3 show that the reaction proceeded satisfactorily in almost all cases, furnishing adducts **4a**−**o** in good yields, which were further subjected to oxidation leading to γ-hydrazono carboxylic acids **6a**−**o** in excellent overall yields and enantioselectivities. The reaction tolerates well the use of different β-substituted enals containing alkyl chains of different length and size, and we also observed that the yield of the process was only moderately affected when the length of the chain was considerably increased (compounds **6a**−**e**). Aldehydes containing nonlinear alkyl chains also performed well, providing excellent enantioselectivities (compounds **6f** and **6g**), although with an appreciable drop in isolated yield when the size of the substituent was notably increased (i.e., compound **6g**). Furthermore, functionalized α,β-unsaturated aldehydes **1h**−**l** also performed well, furnishing the final adducts in good yields with high enantiopurities. A particular situation appeared with the case of δ-amino aldehyde **1l**, which led to the formation of the final adduct **4l** as the corresponding hemiaminal, resulting from intramolecular reaction between the aldehyde and the pendant protected amine. This adduct showed a different behavior during oxidation (see the Supporting Information for details), leading to the formation of a bicyclic aminal structure after the [1,3]-H shift process, from which suitable crystals for X-ray analysis were obtained, allowing the determination of its absolute stereostructure. This configuration was extended to all the adducts **4a**−**p** and is also in good agreement with the expected stereochemical outcome described for other conjugate addition reactions catalyzed by this type of O-silylated α,α-diarylprolinol derivative.[15] The reactivity of β-aryl-substituted α,β-unsaturated aldehydes proved to be highly dependent on the electronic nature of the aryl group. Aromatic enal **1n** incorporating an electron-withdrawing substituent performed very well in the reaction, leading to **6n** in good yield and enantioselectivity, while cinnamaldehyde (**1m**) reacted very slowly. On the other hand, isopropyl glyoxylate-based hydrazone **2b** could also be utilized, delivering the expected adduct **6o** in high yield and enantioselectivity. An important validation of our strategy was to see the effect of changing the electronic properties of the *N*-aryl group. In this sense, we found out that *N*-phenyl-substituted hydrazone **2c** furnished the conjugate addition product **6p** in 24% yield, although still with excellent stereocontrol, while the related *p*-nitrophenyl-substituted hydrazone **2d** was unable to react with **1a** under the optimized reaction conditions. This is an indication of the appropriateness of the aforementioned strategic design for the hydrazone reagent.

Scheme 3. Scope of the Reaction[a]

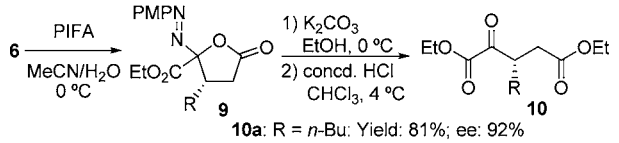


[a]All of the reactions were carried out on a 1.00 mmol scale. Shown are yields of pure products after flash column chromatography, dr values determined by NMR analysis of the crude reaction mixtures, and ee values determined by HPLC analysis (see the Supporting Information). [b]Reaction performed at 4 °C. [c]20 mol % catalyst loading. [d]An 80:20 mixture of diastereoisomers, each one as a 1:1 mixture of anomers, was obtained. [e]Calculated for the bicyclic aminal obtained after the [1,3]-H shift process (see the Supporting Information). [f]n.d. = not determined.

Finally, having succeeded in the development of a general method for the conjugate addition of hydrazones to enals, we proceeded to find the appropriate conditions for transforming the hydrazone into a carbonyl group (Scheme 4). After several

dx.doi.org/10.1021/ja3041042 | J. Am. Chem. Soc. 2012, 134, 11872−11875

Scheme 4. Oxidative Cleavage of the Hydrazone Moiety



10a: R = *n*-Bu: Yield: 81%; ee: 92%
10g: R = *i*-Pr: Yield: 74%; ee: >99%
10i: R = EtCH=CH(CH$_2$)$_2$: Yield: 70%; ee: 94%

unsuccessful attempts under different conditions for hydrolysis or oxidative cleavage through ozonolysis, we found that the hydrazone moiety could be cleanly and easily converted into the corresponding ketone by phenyliodonium bis-(trifluoroacetate) (PIFA)-mediated oxidative hydrolysis.[16] Under the employed conditions, azolactone intermediates **9** were formed first by oxidation of the hydrazone followed by intramolecular reaction with the carboxylic acid moiety. Next, an ethanolysis/acid hydrolysis sequence provided the desired α-keto-1,5-diesters **10**. These conditions were employed for a set of representative compounds **6**, and we observed that in all cases the reaction proceeded cleanly in excellent overall yields without erosion of the enantiopurity of the starting materials.

In summary, we have shown that donor−acceptor hydrazones such as **2** can participate in enantioselective diaza−ene reactions with α,β-unsaturated aldehydes via iminium activation in the presence of a chiral secondary amine as the catalyst. The reaction leads to the formation of γ-azoaldehydes, which are converted into enantiopure γ-hydrazono carboxylic acids through an oxidation/[1,3]-hydride shift sequence,. Moreover, we have also developed a procedure for the conversion of these adducts into 1,4-dicarbonyl compounds, resulting in a very efficient enantioselective methodology for the indirect β-glyoxylation of enals using monosubstituted hydrazones as masked acyl anion equivalents.[17]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Characterization of all new compounds, copies of ^{1}H and ^{13}C NMR spectra and HPLC traces, and crystal structure data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

joseluis.vicario@ehu.es.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the Spanish MICINN (CTQ2011-22790), the Basque Government (IT328-10 and fellowships to M.F. and U.U.), and UPV/EHU (UFI QOSYC 11/22) for financial support. Membership in the COST Action CM0905 is also acknowledged.

■ REFERENCES

(1) (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239. (b) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231. (c) Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1075.

(2) For reviews, see: (a) Brehme, R.; Enders, D.; Fernandez, R.; Lassaletta, J. M. *Eur. J. Org. Chem.* **2007**, 5629. (b) Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326. (c) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359. (d) Marion, N.; Diez-Gonzalez, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988.

(3) Linghu, X.; Potnik, J. R.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 3070.

(4) For a review, see: (a) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511. For examples, see: (b) Cabrera, S.; Reyes, E.; Alemán, J.; Milelli, A.; Kobbelgaard, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 12031. (c) Alba, A.-N.; Companyó, X.; Valero, G.; Moyano, A.; Rios, R. *Chem.—Eur. J.* **2010**, *16*, 5354. (d) Jiang, H.; Paixao, M. W.; Monge, D.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 2775. (e) Alonso, B.; Reyes, E.; Carrillo, L.; Vicario, J. L.; Badía, D. *Chem.—Eur. J.* **2011**, *17*, 6048. (f) Uraguchi, D.; Ueki, Y.; Ooi, T. *Science* **2009**, *326*, 20. (g) Uraguchi, D.; Ueki, Y.; Ooi, T. *Chem. Sci.* **2012**, *3*, 842. (h) Enders, D.; Bonten, M. H.; Raabe, G. *Synlett* **2007**, 885.

(5) For leading reviews, see: (a) Vora, H. U.; Rovis, T. *Aldrichimica Acta* **2011**, *44*, 3. (b) Enders, D.; Niemeyer, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606.

(6) (a) Liu, Q.; Perreault, S.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 14066. (b) Enders, D.; Han, J. *Synthesis* **2008**, 3864. (c) Enders, D.; Han, J.; Henseler, A. *Chem. Commun.* **2008**, 3989. (d) DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 10872. (e) DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 10402. (f) Um, J. M.; DiRocco, D. A.; Noey, E. L.; Rovis, T.; Houk, K. N. *J. Am. Chem. Soc.* **2011**, *133*, 11249. Also see: (g) Fang, X.; Chen, X.; Lv, H.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 11782.

(7) For reviews of iminium activation, see: (a) Vicario, J. L.; Reyes, E.; Badía, D.; Carrillo, L. In *Catalytic Asymmetric Conjugate Reactions*; Córdova, A., Ed.; Wiley-VCH: Weinheim, Germany, 2010; pp 219−294. (b) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416. (c) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79. (d) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. For pioneering examples, see: (e) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (f) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1176. (g) Kawara, A.; Taguchi, T. *Tetrahedron Lett.* **1994**, *35*, 8805.

(8) Herrera, R. P.; Monge, D.; Martín-Zamora, E.; Fernandez, R.; Lassaletta, J. M. *Org. Lett.* **2007**, *9*, 3303.

(9) Raup, D. E. R.; Cardinal-David, B.; Holte, D.; Scheidt, K. A. *Nat. Chem.* **2010**, *2*, 766.

(10) For pioneering reports, see: (a) Lassaletta, J. M.; Fernandez, R. *Tetrahedron Lett.* **1992**, *33*, 3691. (b) Lassaletta, J. M.; Fernandez, R.; Martín-Zamora, E.; Diez, E. *J. Am. Chem. Soc.* **1996**, *118*, 7002. For other examples, see: (c) Hashimoto, T.; Hirose, M.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 7556. (d) Dixon, D. J.; Tillman, A. L. *Synlett* **2005**, 2635. (e) Rueping, M.; Sugiono, E.; Theissmann, T.; Kuenkel, A.; Kockritz, A.; Pews-Davtyan, A.; Nemati, N.; Beller, M. *Org. Lett.* **2007**, *9*, 1065. For a review, see ref 2a.

(11) (a) Lerche, H.; Severin, T. *Synthesis* **1978**, 687. (b) Severin, T.; Adam, R.; Lerche, H. *Chem. Ber.* **1975**, *108*, 1756.

(12) There is one precedent regarding the use of metalated *N*-*tert*-butylhydrazones as Michael donors with crotonates. See: Baldwin, J. E.; Adlington, R. M.; Bottaro, J. C.; Kolhe, J. N.; Perry, M. W. D.; Jain, A. U. *Tetrahedron* **1986**, *42*, 4223.

(13) Tests of a set of different solvents showed toluene to be the most efficient one in terms of both conversion and stereoselectivity.

(14) Incorporation of either Brønsted acids (such as PhCO$_2$H) or bases (DABCO, DBU) was also tested while carrying out the reaction screening. However, these did not lead to any improvement.

(15) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun.* **2011**, *47*, 632.

(16) Barton, D. H. R.; Jaszberenyi, J. C.; Liu, W.; Shinada, T. *Tetrahedron* **1996**, *52*, 14673.

(17) For an example of a catalytic enantioselective β-glyoxylation of alkylidene α-ketoamides under NHC catalysis, see: Liu, Q.; Rovis, T. *Org. Lett.* **2009**, *11*, 2856. Also see refs 4h and 6a.