α-Hydroxy Ketones as Masked Ester Donors in Brønsted Base-Catalyzed Conjugate Additions to Nitroalkenes

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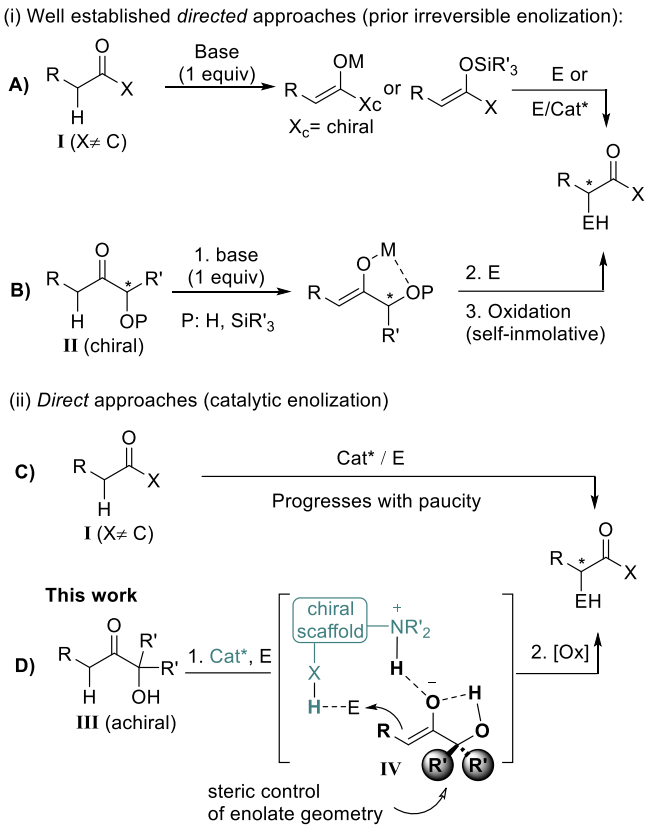
Abstract: Catalyst-controlled enantioselective direct addition reaction of enolizable esters and related carboxylic acid derivatives to π-electrophiles remains a difficult synthetic transformation. Here α-hydroxy ketones are presented for the first time as donor ester equivalents capable of being activated by bifunctional Brønsted base catalysts in this endeavour. Thus, α-hydroxy ketones react efficiently with nitroalkenes in the presence of chiral tertiary amine/H-bond donor catalysts to give the Michael addition adducts with very high stereoselectivity (dr ≥95:5, up to 99% ee).

One of the most general entries to new carbon-carbon bonds relies on the nucleophilic addition of an enolizable carbonyl compound to a π-electrophile which results in synthetically useful carbonyl compounds modified at Cα. Stereoselective variants of such a process involving an enolizable carbonyl substrate in the carboxylic acid oxidation state have been established by using chiral stoichiometric reagents and auxiliaries and commonly require a previous, irreversible enolization step (Scheme 1A).[1] However, direct type versions involving an enolizable ester, amide or the like, in which a chiral catalyst controls the stereoinduction (Scheme 1C), are less developed. Catalytic activation of these types of substrates is challenging owing to their diminished carbon acidity. Some progress in the area has been made by using as enolizable substrates thioamides/lactams,[2] amides,[3] nitriles,[4] imides,[5] and free carboxylic acids[6] and a chiral metallic catalyst in combination with a base in sub-[2-4] or superstoichiometric[5-6] amount. Among organocatalytic approaches, covalent activation of carboxylic acids and esters by chiral NHC and isothiourea catalysts has been reported to (mainly) afford lactone- and lactam-type cyclic products,[7] while seldom examples of non covalent activation of reactive ester equivalents (acyl silanes, thioesters, pyrazoleamides, cyclic anhydrides, β,γ-unsaturated esters) by Brønsted base catalysts have also been explored.[8] Despite these advances, methods that combined both reasonably broad scope —many require an additional activating α-substituent—[9] and high stereocontrol in terms of reaction diastereo- and enantioselectivity are rare. While all these studies deal with enolizable substrates of the type **I** (acyl–heteroatom systems), a conceptually different, but in practice equivalent, strategy would involve α-hydroxy ketones **II** as a carboxylic acid surrogate (Scheme 1B). Early work by the groups of Heathcock[10] and Masamune,[11] independently, established a route to α-modified carboxylic acids upon an enolization/α'-functionalization/ketol scission sequence starting from **II**. This approach was further advanced in such a way that the chiral information source was



Scheme 1. α-Functionalization of carboxylic acid equivalents via enolization.

no longer sacrificially destroyed during ketol oxidative scission.[12] Despite its potential and practicality, however, to our knowledge no direct version of this approach has been reported so far. Here the feasibility of achiral α-hydroxy ketones **III** to be used as donor ester equivalents[13] in catalytic, asymmetric conjugate addition reactions, is demonstrated for the first time. The underlying idea is that substrate **III** may get activated by a bifunctional tertiary amine/H-bond donor catalyst as in model **IV** to ultimately attack a

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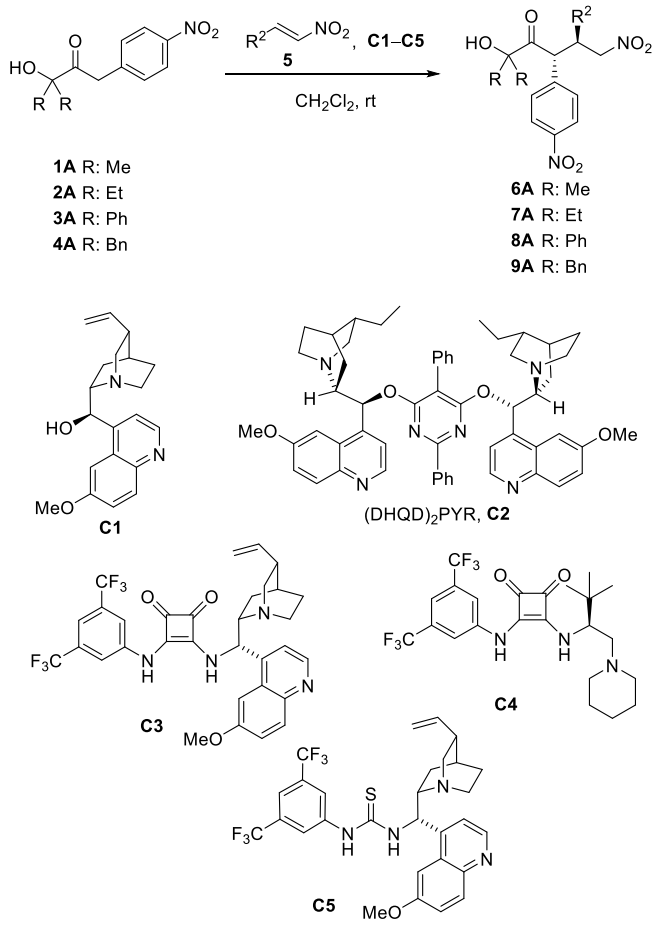
suitable π-electrophilic reaction partner and lead, after final ketol scission, to enantioenriched α-branched carboxylic acids and derivatives.

For initial validation of the idea the reaction of α-hydroxy ketone **1A** with nitroalkenes was selected and several Brønsted bases were screened. As the results in Table 1 show, both catalysts **C1** and **C2** were able to promote the addition reaction, but led to suboptimal enantioselectivity (entries 1 and 2). Among the bifunctional catalysts examined, the squaramide **C3**[14] resulted the most active, providing essentially quantitative yield



Scheme 2. Conjugate addition of α-hydroxy ketones to nitroalkenes catalyzed by Brønsted bases **C1**–**C5**.

of the addition adduct **6** after 5 h, but with yet unsatisfactory levels of selectivity (entry 3). Catalyst **C4**,[15] but specially the thiourea catalyst **C5**,[16] resulted superior in this reaction affording *ee*'s of 70% and 80%, respectively. Then, we decided to study the behavior of the related α-hydroxy ketones **2A**–**4A**, which exhibit different geminal R substituents. These ketones can readily be prepared through the method of Qi employing the corresponding alkyne, simple ketone and CO_2 as starting materials.[17] As the results in the table show, when shifting from **1A**(R=Me) to **2A**(R=Et) and **3A**(R=Ph) there is not much impact on the reaction selectivity (compare entries 3-5, 6-8, and 9). However, an outstanding 99% *ee* was obtained in the reaction with nitrostyrene of **4A**(R=Bn) using either catalyst **C3** or **C5** (entries 10 and 12). Of importance, in all the above experiments essentially one diastereomer was formed with diastereomeric ratios measured by ^{1}H NMR being consistently ≥95:5.

Table 1. Catalyst screening for the reaction of several α-hydroxyketones **1A**–**4A** with **5a** (R^2: Ph).[a]

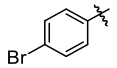
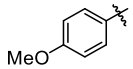
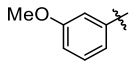
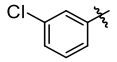
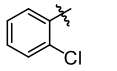
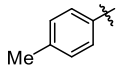
Entry	Ketone, R	Catalyst	Product	Time [h]	Yield [%][b]	*ee* [%][d]
1	**1A**, Me	**C1**	**6Aa**	72	97	10[e]
2	**1A**, Me	**C2**	**6Aa**	72	86	–50[e]
3	**1A**, Me	**C3**	**6Aa**	5	98	60
4	**1A**, Me	**C4**	**6Aa**	72	97	70
5	**1A**, Me	**C5**	**6Aa**	72	98	80[e]
6	**2A**, Et	**C3**	**7Aa**	24	97	76
7	**2A**, Et	**C4**	**7Aa**	48	55[c]	72
8	**2A**, Et	**C5**	**7Aa**	24	97	80
9	**3A**, Ph	**C5**	**8Aa**	24	87	80
10	**4A**, Bn	**C3**	**9Aa**	24	75	99
11	**4A**, Bn	**C4**	**9Aa**	72	70[c]	88
12	**4A**, Bn	**C5**	**9Aa**	24	95	99

[a] Reactions conducted on a 0.1 mmol scale in 0.3 mL CH_2Cl_2 (molar ratio of ketone/**5a**/catalyst 1:2:0.1); dr >95:5 in all entries as determined by ^{1}H NMR (300 MHz) of crude sample. [b] Yields of isolated product after chromatography. [c] Conversion; yield not determined. [d] Determined by HPLC analysis using a chiral stationary phase. [e] Reaction performed at –20 °C.

Based on the above results, α-dibenzyl α-hydroxy ketone **4A** and catalyst **C5** were selected for further exploring the scope of the reaction regarding the nitroalkene component. As data in Table 2 show, several β-aryl substituted nitroalkenes with a range of electron-rich (entries 2,3,6) and electron-poor (entries 1,4,5) arene systems participate in the reaction with **4A** to afford the corresponding products **9A** in good isolated yields and essentially perfect stereocontrol (dr ≥95:5, 99% *ee* in all entries). Importantly, the reaction also tolerates well the more challenging alkyl-substituted nitroalkenes, although considerable longer reaction times were needed. For example, the reactions of nitroalkenes bearing a linear pentyl(**5h**) or propyl(**5i**) substituent afforded the corresponding adduct in 75% and 76% isolated yields, diastereomeric ratios ≥95:5, and *ee*'s of 96% and 99%, respectively. In its turn, the isopropyl-substituted nitroalkene **5j** afforded, after 5 days of reaction, a 45% yield of isolated product with 90:10 dr and 97% *ee* for the major diastereomer.

Next the tolerance of different aromatic substituents at the Cα' position of the ketone was studied. As data in Table 3 show, hydroxyl ketones with electron-deficient arene groups at Cα', such as the *p*-cyanophenyl and *p*-fluorophenyl, were more active than α'-phenyl ketone, the latter necessitating longer times for useful reaction conversions. On the other hand, the influence of the nature of the geminal R substituent on both reactivity and selectivity for the different entries was, once again, clear, and two distinguishable subsets of results were obtained from α-hydroxy ketones **1** (R=Me) and **4** (R=Bn), respectively (Table 3).

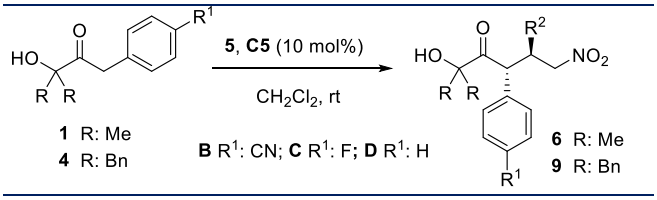
Table 2. Scope of the reaction of **4A** with nitroalkenes **5** catalyzed by **C5**.[a]

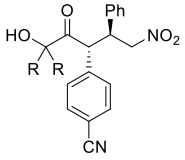
Entry	Nitroalkene	R^2	Product	Time [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**5b**		**9Ab**	16	93	>95:5	99
2	**5c**		**9Ac**	16	92	>95:5	99
3	**5d**		**9Ad**	16	80	>95:5	99
4	**5e**		**9Ae**	16	81	>95:5	99
5	**5f**		**9Af**	16	77	>95:5	99
6	**5g**		**9Ag**	16	85	>95:5	99
7[e]	**5h**	$CH_3(CH_2)_4$	**9Ah**	72	75	>95:5	96
8[e]	**5i**	$CH_3(CH_2)_2$	**9Ai**	44	76	>95:5	99
9[e]	**5j**	$(CH_3)_2CH$	**9Aj**	120	45(75)[f]	90:10	97

[a] Reactions conducted on a 0.1 mmol scale in 0.3 mL CH_2Cl_2 (molar ratio of **4A**/**5**/catalyst, for R^2=aromatic, 1:2:0.1; for R^2=aliphatic, 1:3:0.1) at r.t. unless otherwise stated. [b] Yields of isolated product after chromatography. [c] Determined by ^1H NMR. [d] Determined by HPLC analysis using a chiral stationary phase. [e] Using 20 mol% catalyst. [f] Yield in parentheses based on recovered starting material.

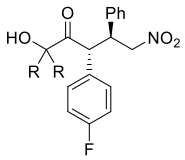
As shown in Table 3, with the sterically more demanding α,α-dibenzyl congeners **4** reactions needed longer times for completion in all entries as compared to the less demanding α,α-dimethyl congeners **1**. However, while both diastereoselectivity (dr≥95:5) and enantioselectivity (96%–99% *ee*) attained with **4B**–**D** was almost perfect, the selectivities were eroded with substrates **1B**–**D**. Importantly, the high stereoselectivity was maintained also with the β-isobutyl-substituted nitroalkene **5k** which upon reaction with **4B** afforded adduct **9Bk** as single diastereomer and 99% *ee*. The absolute configuration of adduct **9Ab** was established by single crystal X-ray structural analysis[18] and that of the remaining adducts was assigned by assuming a uniform reaction mechanism. In this respect, it appears that the free hydroxy group of the template plays a crucial role in the reaction mechanism since the reactivity decreases dramatically when it is blocked as the silyl ether. Thus, we observed that while the reaction of **1B** with nitrostyrene produced adduct **6Ba** in 89% isolated yield in the presence of **C5** (Table 3), the similar reaction of the trimethylsilyl ether derived from **1B** progresses much more slowly, with less than a 25% conversion reached after 20 h at room temperature. Although still premature, in Figure 1 two plausible reaction stereomodels are proposed that would correctly account for the observed stereochemistry.[19]

Table 3. Scope of the reaction regarding the α-hydroxy ketone.[a]

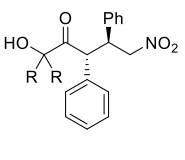




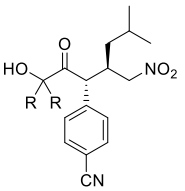
R: Me, **6Ba**; 20 h, 89% *dr* 90:10, 82% *ee*
R: Bn, **9Ba**; 96 h, 70% *dr* >95:5, 99% *ee*



R: Me, **6Ca**; 96 h, 70% *dr* >95:5, 66% *ee*
R: Bn, **9Ca**; 96 h, 49%(96%) *dr* >95:5, 96% *ee*



R: Me, **6Da**; 5 d, 37%(62%) *dr* >95:5, 60% *ee*
R: Bn, **9Da**; 96 h, 46%(92%) *dr* >95:5, 96% *ee*



R: Me, **6Bk**; 64 h, 64% *dr* >95:5, 63% *ee*
R: Bn, **9Bk**; 64 h, 36%(90%) *dr* >95:5, 99% *ee*

[a] Reactions conducted on a 0.1 mmol scale in 0.3 mL CH_2Cl_2 (molar ratio of ketone/**5a**/catalyst 1:3:0.1 or 1:1.2:0.1). Yields in parentheses based on recovered starting material.

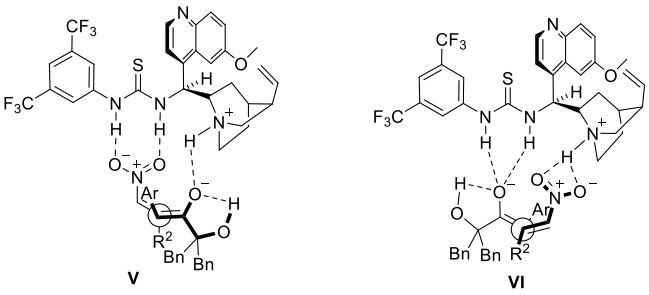
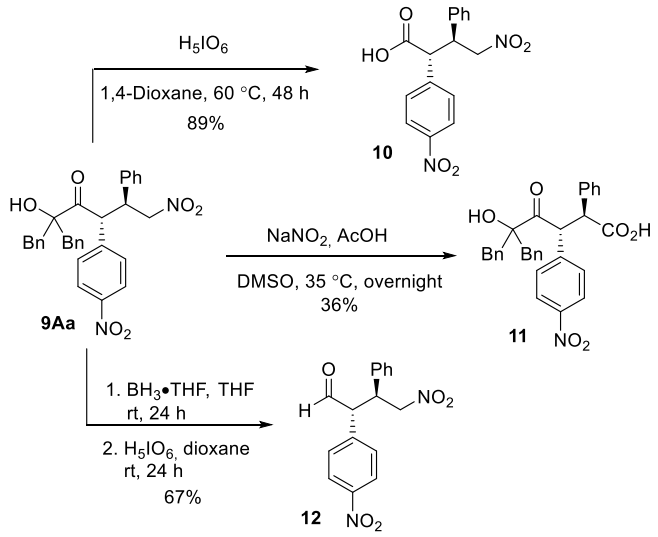


Figure 1. Proposed qualitative stereomodels.

Plausible transformations of adducts obtained through this catalytic conjugate addition are shown in Scheme 3. For instance, direct oxidation of the ketol moiety in **9Aa** using H_5IO_6 afforded carboxylic acid **10**. Conversely, reduction of the ketol carbonyl with borane and subsequent treatment with H_5IO_6 as above gave aldehyde **12**. In each case dibenzyl ketone is also formed as a byproduct that could be recovered and reused. On the other hand, the aliphatic nitro group could be transformed to the carboxylic function without affecting the ketol moiety (**9Aa** → **11**) through Nef oxidation.



Scheme 3. Elaboration of adducts.

In conclusion, enolizable α-hydroxy α,α-disubstituted ketones are presented for the first time as efficient ester donor equivalents in asymmetric catalysis. Specifically, their conjugate addition reaction to nitroalkenes, including the challenging β-alkyl-substituted nitroalkenes, can be triggered by bifunctional Brønsted base catalysts to afford the corresponding adducts with very high diastereo- and enantioselectivity (dr ≥95:5, up to 99% *ee*). The reactivity and the stereodirecting ability of the α-hydroxy ketone template is easily modulated by varying the nature of the geminal α-substituents, with the α,α-dibenzyl-substituted congeners providing the highest enantiocontrol with the selected catalysts. Chemical elaboration of the ketol moiety in the resulting adducts through smooth oxidative protocols gives access to the corresponding enantioenriched α-branched products (either carboxylic acids or aldehydes), *inter alia* aryl acetics, along with dibenzylacetone byproduct which can be separated and recycled. Extension of this catalytic methodology to other π-electrophiles is currently under investigation.

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Keywords: asymmetric organocatalysis • ester equivalents • Brønsted bases • conjugate additions • hydroxy ketones

[1] a) D. A. Evans, G. Helmchen, M. Rüping "*Chiral Auxiliaries in Asymmetric Synthesis*" In *Asymmetric Synthesis — The Essentials* (Eds.: M. Christmann, S. Brase), Wiley-VCH Verlag GmbH & Co., Weinheim, **2007**, pp. 3-9; b) J.-i. Matsuo, M. Murakami *Angew. Chem.* **2013**, *125*, 9280-9289; *Angew. Chem. Int. Ed.* **2013**, *52*, 9109-9118.

[2] a) M. Iwata, R. Yazaki, Y. Suzuki, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 18244-18245; b) Y. Suzuki, R. Yazaki, N. Kumagai, M. Shibasaki, *Angew. Chem.* **2009**, *121*, 5126-5129; *Angew. Chem. Int. Ed.* **2009**, *48*, 5026-5029; c) M. Iwata, R. Yazaki, M. Kumagai, M. Shibasaki, *Tetrahedron: Asymmetry* **2010**, *21*, 1688-1694; d) Y. Kawato, S. Chaudhary, N. Kumagai, M. Shibasaki, *Chem. Eur. J.* **2013**, *19*, 3802-3806. (Cu-diphosphine catalyst) e) D. Sureshkumar, Y. Kawato, M. Iwata, N. Kumagai, M. Shibasaki, *Org. Lett.* **2012**, *14*, 3108-3111; f) K. Alagiri, S. Lin, N. Kumagai, M. Shibasaki, *Org. Lett.* **2014**, *16*, 5301-5303; g) N. Majumdar, N Saito, L. Yin, N. Kumagai, M. Shibasaki, *Org. Lett.* **2015**, *17*, 3362-3365.

[3] H. Suzuki, I. Sato, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc*. **2015**, *137*, 4336-4339.

[4] a) Y. Kawato, N. Kumagai, M. Shibasaki, *Chem. Commun.,* **2013**, *49*, 11227-11229; b) T. Deng, W. Wang, C. Cai, *Eur. J. Org. Chem.* **2014**, 7259-7264.

[5] D. A. Evans, C. W. Downey, J. L. Hubbs, *J. Am. Chem. Soc.* **2003**, *125*, 8706-8707.

[6] Y. Morita, T. Yamamoto, H. Nagai, Y. Shimizu, M. Kanai, *J. Am. Chem. Soc.* **2015**, *137*, 7075-7078.

[7] a) L. Hao, Y. Du, H. Lv, X. Chen, H. Jiang, Y. Shao, Y. R. Chi, *Org. Lett.* **2012**, *14*, 2154-2157; b) L. Hao, S. Chen, J. Xu, B. Tiwari, Z. Fu, T. Li, J. Lim, Y. R. Chi, *Org. Lett.* **2013**, *15*, 4956-4959; c) C. Simal, T. Lebl, A. M. Slawin, A. A. D. Smith, *Angew. Chem.* **2012**, *124*, 3713-3717; *Angew. Chem. Int. Ed*. **2012**, *51*, 3653-3657; d) L. C. Morrill, T. Lebl, A. M. Z. Slawin, A. D. Smith, *Chem. Sci*., **2012**, *3*, 2088-2093; e) L. C. Morrill, J. Douglas, T. Lebl, A. M. Z. Slawin, D. J. Fox, A. D. Smith, *Chem. Sci*., **2013**, *4*, 4146-4155; f) D. Belmessieri, L. C. Morrill, C. Simal, A. M. Z. Slawin, A. D. Smith, *J. Am. Chem. Soc*. **2011**, *133*, 2714-2720.

[8] (Acyl silanes) a) L. Wu, G. Li, Q. Fu, L. Yu, Z. Tang, *Org. Biomol. Chem.* **2013**, *11*, 443-447. (Thioesters) b) M. C. Kohler, J. M. Yost, M. R. Garnsey, D. M. Coltart, *Org. Lett.* **2010**, *12*, 3376-3379; c) J. Guang, A. J. Larson, J. C. G. Zhaoa, *Adv. Synth. Catal.* **2015**, *357,* 523-529. (Pyrazoleamides) d) B. Tan, G. Hernández-Torres, C. F. Barbas III, *Angew. Chem.* **2012**, *124*, 5477-5481; *Angew. Chem. Int. Ed.* **2012**, *51*, 5381-5385; e) T.-Z. Li, X.-B. Wang, F. Sha, X.-Y. Wu, *J. Org. Chem.* **2014**, *79*, 4332-4339. (Cyclic anhydrides) f) C. Cornaggia, F. Manoni, E. Torrente, S. Tallon, S. J. Connon, *Org. Lett.* **2012**, *14*, 1850-1853. (β,γ-Unsaturated esters) J. Guang, S. Rout, M. Bihani, A. J. Larson, H. D. Arman, J. C.-G. Zhao, *Org. Lett.* **2016**, *18*, 2648-2651.

[9] In a biomimetic strategy, malonic acid half thioesters can be used as acetate equivalents (decarboxylation-driven enolate formation). For pioneering studies using metal catalysis, see: a) S. Orlandi, M. Benaglia, F. Cozzi, *Tetrahedron Lett.* **2004**, *45*, 1747-1749; b) D. Magdziak, G. Lalic, H. M. Lee, K. C. Fortner, A. D. Aloise, M. D. Shair, *J. Am. Chem. Soc*. **2005**, *127*, 7284-7285. For a review on organocatalytic enantioselective reactions based on this strategy, see: c) S. Nakamura, *Org. Biomol. Chem.* **2014**, *12*, 394-405.

[10] a) C. H. Heathcock, M. C. Pirrung, C. T. Buse, J. P. Hagen, S. D. Young, J. E. Sohn, *J. Am. Chem. Soc.* **1979**, *101*, 7077-7079; b) C. H. Heathcock, M. C. Pirrung, J. Lampe, C. T. Buse, S. D. Young, *J. Org. Chem.* **1981**, *46*, 2290-2300; c) N. A. Van Draanen, S. Arseniyadis, M. T. Crimmins, C. H. Heathcock, *J. Org. Chem.* **1991**, *56*, 2499-2506.

[11] a) S. Masamune, Sk. A. Ali, D. L. Snitman, D. S. Garvey, *Angew. Chem.* **1980**, *92*, 573-575; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 557-558; b) S. Masamune, W. Choy, F. A. J. Kerdesky, B. Imperiali, *J. Am. Chem. Soc.* **1981**, *103*, 1566-1568; c) S. Masamune, T. Kaiho, D. S. Garvey, *J. Am. Chem. Soc.* **1982**, *104*, 5521-5523.

[12] (Aldol) a) C. Palomo, A. González, J. M. García, C. Landa, M. Oiarbide, S. Rodríguez, A. Linden, *Angew. Chem.* **1998**, *110*, 190-192; *Angew. Chem. Int. Ed.* **1998**, *37*, 180-182; b) C. Palomo, M. Oiarbide, J. M. Aizpurua, A. González, J. M. García, C. Landa, I. Odriozola and A. Linden, *J. Org. Chem.* **1999**, *64*, 8193-8200. (Mannich) c) C. Palomo, M. Oiarbide, M. C. González-Rego, A. K. Sharma, J. M. García, A. González, C. Landa, A. Linden, *Angew. Chem.* **2000**, *112*, 1105-1107; *Angew.*

Chem. Int. Ed. **2000**, *39*, 1063-1066; d) C. Palomo, M. Oiarbide, A. Landa, M. C. González-Rego, J. M. García, A. González, J. M. Odriozola, M. Martín-Pastor, A. Linden, *J. Am. Chem. Soc.* **2002**, *124*, 8637-8643.

[13] Zhao has reported Brønsted base-catalyzed enantioselective Mannich reactions of enolizable ketones including a single example of a *p*-anisyl ketone acting as an ester donor equivalent. See: Guo, Q.; Zhao, J. C.-G., *Org. Lett.* **2013**, *15*, 508-511.

[14] a) L. Dai, S.-X. Wang, F.-E. Chen, *Adv. Synth. Catal.* **2010**, *352*, 2137-2141; b) W. Yang, D.-M. Du, *Org. Lett.* **2010**, *12*, 5450-5453. For pioneering work on squaramides as catalysts, see: c) J. P. Malerich, K. Hagihara, V. R. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416-14417; d) Y. Zhu, J. P. Malerich, V. H. Rawal, *Angew. Chem.* **2010**, *122*, 157-160; *Angew. Chem. Int. Ed.* **2010**, *49*, 153-156.

[15] K. Hu, A. Lu, Y. Wang, Z. Zhou, C. Tang, *Tetrahedron: Asymmetry* **2013**, *24*, 953-957.

[16] a) S. H. McCooey, S. Connon, *Angew. Chem.* **2005**, *117*, 6525-6528; *Angew. Chem. Int. Ed.* **2005**, *44*, 6367-6370; b) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481-4483; c) B. Vakulya, S. Varga, A. Csampai, T. Soós, *Org. Lett.* **2005**, *7*, 1967-1969; d) B.-J. Li, L. Jiang, M. Liu, Y.-C. Chen, L.-S. Ding, Y. Wu, *Synlett* **2005**, 603-606.

[17] H. He, C. Qi, X. Hu, Y. Guan, H. Jiang, *Green Chem*. **2014**, *16*, 3729-3733.

[18] CCDC-1514777 (compound **9Ab**) contains the supplementary crystallographic data for this paper. These data can be obtained from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information for details.

[19] Both proposed models **V** and **VI** fit well with often invoked models for bifunctional H-bond/Brønsted base catalysts-promoted addition reactions. See, for instance: a) B. Kótai, G. Kardos, A. Hamza, V. Farkas, I. Pápai, T. Soós, *Chem. Eur. J.* **2014**, *20*, 5631-5639; b) M. N. Grayson, K. N. Houk, *J. Am. Chem. Soc*. **2016**, *138*, 9041-9044.