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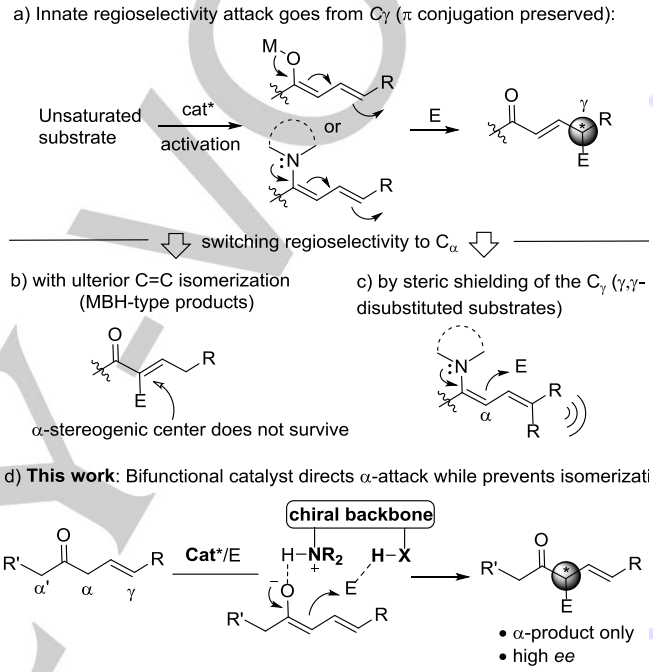
Controlling α- vs γ-Reactivity of Vinylogous Ketone Enolates in Organocatalytic Enantioselective Michael Reactions

Igor Iriarte, Olatz Olaizola, Silvia Vera, Iñaki Gamboa, Mikel Oiarbide* and Claudio Palomo*

Abstract: The fully regio-, diastereo- and enantiocontrolled direct Michael reaction of allyl ketones with nitroolefins is reported for the first time under enabling Brønsted base/H-bond bifunctional catalysis. It is shown that squaramide-tertiary amine catalysts induce the reaction of a survey of allyl ketones to proceed at the α-site exclusively giving rise adducts with two consecutive tertiary carbon stereocenters in diastereomeric ratios up to >20:1 and enantioselectivities generally in the 90%-98% *ee* range.

Catalyst-controlled reactions of in situ generated vinylogous nucleophiles are of great synthetic value.[1] The overwhelming majority of catalytic reactions involving vinylogous enolate equivalents proceed from the γ-carbon of the unsaturated carbonyl substrate, a process that preserves π-conjugation along the reaction coordinate (Scheme 1a). This reactivity pattern is well illustrated in the literature for a broad range of enolizable substrate families using either metallic catalysis[2] or different aminocatalytic approaches.[3,4,5]

In contrast, the alternative α-reaction pathway implies disruption of the π-conjugation at some point of the reaction coordinate. Not surprisingly, switching the reactivity from the most usual γ- to α-carbon has resulted troublesome, with only few direct enantioselective approaches reported. Shibasaki's group described a barium alkoxide-catalyzed Mannich reaction of β,γ-unsaturated benzyl esters that upon C=C isomerisation provides the corresponding Morita-Baylis-Hilmann type adducts[6] (Scheme1b). On the other hand, γ,γ-disubstituted enals have been found to react through Cα of the dienamine intermediate[7] because of the steric shielding of the disubstituted γ-carbon (Scheme 1c).[8] A few Brønsted base-catalyzed α-site functionalizations of vinylogous enolic intermediates have also appeared,[9] but the reported examples lead to moderate enantioselectivity[9a] or apply to very restricted substrate categories.[9b-d] Notably, the readily available allyl alkyl ketones, with three potentially reactive sites (α, γ, and α') remain undeveloped pronucleophiles in this context.[10] Here, we report the first Brønsted base-catalyzed direct Michael reactions of allyl alkyl ketones with nitroolefins that proceed through the ketone α-carbon exclusively and with high diastereo- and enantioselectivity. During the preparation of this manuscript an α-selective functionalization of preformed silyl dienol ethers with nitroolefins to give Rauhut-Currier type products under bifunctional catalysis appeared.[11]



Scheme 1. Site-selectivity in catalyst-driven functionalization of ambivalent vinylogous enolates.

While the Cα vs Cγ selectivity problem appears to be multivariable,[12] we hypothesized that a bifunctional Brønsted base/H-bond catalyst,[13] might anchor both the dienolate and the electrophilic reagent in a way favouring α-reaction trajectory (Scheme 1d). However, additional issues, namely (i) the α- vs. α'-selectivity; (ii) the reaction diastereo- and enantioselectivity; and (iii) the potential loss of α-stereogenicity through C=C bond isomerization, also needed to be addressed.

For initial assessment of these aspects, the model reaction of **1A** with **7a** in the presence of several bifunctional Brønsted base catalysts[14] was investigated (Scheme 2). To our delight, the α-addition adducts were formed exclusively within a few hours of reaction, although product diastereo- and enantioselectivity were strongly catalyst-dependent (Table 1). With cinchona alkaloid-derived thiourea **C1**[15] both the diastereo- and the enantioselectivity were only moderate. The enantioselectivity could be improved by using the squaramide catalysts pioneered by Rawal,[16] such as catalyst **C2**[17] and, especially, the cyclohexylamine-derived catalyst **C4**,[18]

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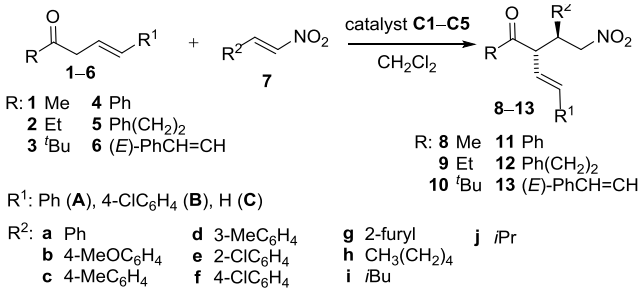
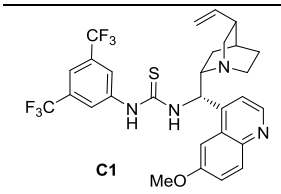


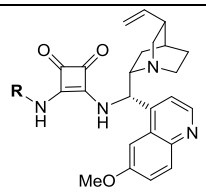
Scheme 2. Catalyst-controlled enantioselective direct reaction of allyl ketones with nitroalkenes.

although diastereoselectivity remained insufficient (dr <2:1). Additional screening showed that the *N*-benzyl squaramide **C5** performed best, affording upon reaction at 0 ºC product **8Aa** in high yield, 6.4:1 diastereomeric ratio and 96% *ee* for both isomers.

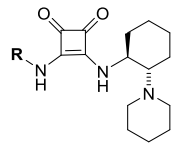
Table 1. Screening of catalysts for the reaction of **1A** with **7a** to give **8Aa**.[a]



T (°C)	t(h)	dr	*ee*
RT	2	1.9:1	66
–20	8	2.4:1	70
–60	64	2.4:1	70 (84% conv)



cat	R	T (°C)	t(h)	dr	*ee*
C2	3,5-$(F_3C)_2C_6H_3$	RT	2	1:1.1	85
		–20	6	1:1.3	93
C3	3,5-$(F_3C)_2C_6H_3CH_2$	RT	2	1.9:1	72
		–20	6	2.3:1	86

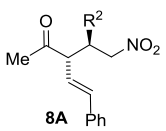


cat	R	T (°C)	t(h)	dr	*ee*
C4	3,5-$(F_3C)_2C_6H_3$	0	16	1.2:1	97
C5	3,5-$(F_3C)_2C_6H_3CH_2$	0	20	6.4:1	96

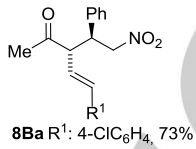
[a] Reactions carried out at 0.2 mmol scale, using 1.5 equiv. of **1A** and 10 mol% catalyst in 0.4 mL CH_2Cl_2. Diastereomeric ratios and *ee* determined by chiral HPLC. *Ee*'s correspond to the major diastereomer.

Once conditions were optimized, the behavior of a survey of allyl ketones and nitroolefins was examined.[19,20] As the results in Table 2 show, the reaction tolerated well a variety of allyl ketones with alkyl- and aryl- sidearm, and nitroolefins with either electron-rich, electron-neutral or electron-poor aryl substituents at C_β. The corresponding adducts **8–11** were produced in diastereomeric ratios of 5:1 or higher and enantioselectivities up to 98% for both the major and minor isomers.[21] For γ-unsubstituted allyl ketones **5C** and **6C**, products **12C** and **13C** were formed in poor diastereomeric ratios whilst the *ee*'s were consistently good. In every case, the alkylation proceeded at Cα of the allyl ketone[22] and no isomerisation of the double bond was observed. Incidentally, the starting ketones **5C** and **6C** underwent partial (about 20%) isomerization to the respective

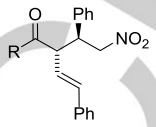
Table 2. Scope of the reaction between ketones **1**-**6** and nitroalkenes **7** .[a]



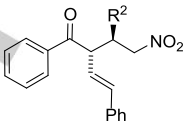
8Ab R^2: 4-$MeOC_6H_4$ 95%, dr 5.2:1, 98%(98%) *ee*
8Ac R^2: 4-MeC_6H_4 90%, dr 6.1:1, 97% (95%) *ee*
8Ad R^2: 3-MeC_6H_4 72%, dr 7.3:1, 96% (94%) *ee*
8Ae R^2: 2-ClC_6H_4 72%, dr 6.7:1, 90% (70%) *ee*
8Ah R^2: $CH_3(CH_2)_4$ (30% conv. after 24h)
8Ai R^2: *i*Bu (40% conv. after 24h)



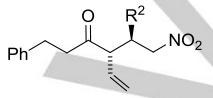
8Ba R^1: 4-ClC_6H_4, 73% dr 9.0:1, 92%(61%) *ee*



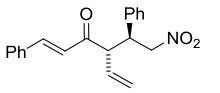
9Aa R: Et, 83% dr 7.3:1, 95%(91%) *ee*
10Aa R: *t*-Bu, 68% dr >20:1, 84% *ee*[b]



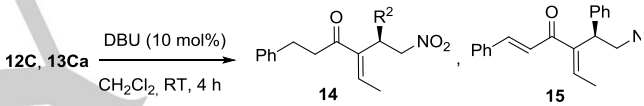
11Aa R^2: Ph, 75% dr 8.5:1, 92%(90%) *ee*
11Ab R^2: 4-$MeOC_6H_4$, 78 dr 8.1:1, 94%(85%) *ee*
11Aj R^2: *i*Pr No reaction



12Ca R^2: Ph 73%, dr 4:1, 94%(99%) *ee*[b]
12Cb R^2: 4-$MeOC_6H_4$ 72%, dr 2.2:1, 91%(97%) *ee*[b]
12Cc R^2: 4-MeC_6H_4 70%, dr 5.7:1, 97%(90%) *ee*[b]
12Cf R^2: 4-ClC_6H_4 75%, dr 5.3:1, 93%(98%) *ee*[b]



13Ca, 81% dr 1.3:1, 84%(90%) *ee*[b]



14a R^2: Ph >98%, 94% *ee*
14b R^2: 4-$MeOC_6H_4$ >98%, 91% *ee*
14c R^2: 4-MeC_6H_4 >98%, 92% *ee*
14f R^2: 4-ClC_6H_4 >98%, 93% *ee*

15 >98%, 88% *ee*[c]

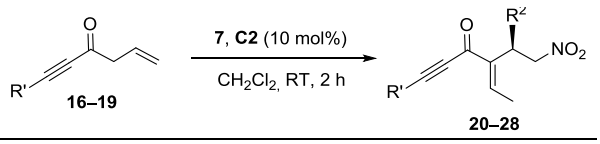
[a] Unless otherwise stated, reactions carried out at 0.2 mmol scale using 1. equiv. of ketone and 10 mol% **C5** at 0 °C in 0.4 mL CH_2Cl_2. Diastereomeri ratios determined by HPLC. Yields of isolated product after chromatography *ee* determined by chiral HPLC. In brackets, *ee*´s of minor diastereomer. [b Reaction conducted at RT using 2 equiv. of ketone. [c] Isomerized b treatment with Et_3N overnight.

α,β-enone during the reaction.[23] However, this circumstance did not affect the reaction outcome provided that two equivalents of the starting **5C** and **6C** were employed. If desired, adducts from the above catalytic reactions, such as **12** and **13**, could be fully isomerized to the corresponding α,β-enone product **14** and **15** almost quantitatively by exposure to 10 mol% DBU at RT in CH_2Cl_2.

On the other hand, alkynyl allyl ketones also were competent substrates. For example (Table 3), reaction of ketones **16–19** with nitroolefins **7** in the presence of quinine-derivative **C2**, which was the best catalyst for these substrates, proceeded smoothly and with good yields and excellent *ee*. However, unlike in the previous cases, the evolved adducts proved to be quite sensitive towards double bond isomerisation, and products **20–28** were obtained directly. Once again, products from an eventual γ-attack were not observed. It is worth of noting that the otherwise difficult β-alkyl nitroolefins **7h** and **7i** were competent partners for this reaction, affording adducts **23**, **25** and **28** in good yields and excellent selectivity. The absolute configuration

of adducts was primarily established by X-ray analysis of compound **8Aa** and by assuming a uniform reaction mechanism.[24,25]

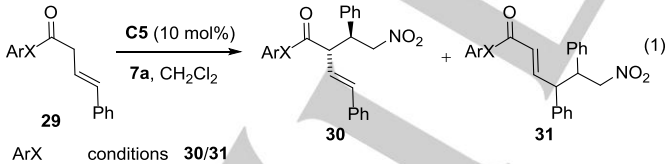
Table 3. Catalytic reactions with allyl ynones **16**–**24**.[a]



entry	R'	R^2	S.M./Product	Yield [%][b]	*ee* [%][c]
1	Ph	Ph	**16** / **20**	68	95
2	Ph	4-MeC_6H_4	**16** / **21**	69	95
3[d]	Ph	4-MeC_6H_4	**16** / **21**	69	73
4	Ph	4-ClC_6H_4	**16** / **22**	71	95
5[d]	Ph	4-ClC_6H_4	**16** / **22**	68	66
6	Ph	$(CH_3)_2CHCH_2$	**16** / **23**	72	97
7	3-MeC_6H_4	Ph	**17** / **24**	77	95
8	4-$MeOC_6H_4$	$CH_3(CH_2)_4$	**18** / **25**	69	95
9	*n*Pr	Ph	**19** / **26**	75	97
10	*n*Pr	4-$MeOC_6H_4$	**19** / **27**	72	94
11	*n*Pr	*i*Bu	**19** / **28**	70	95

[a] Reactions carried out at 0.2 mmol scale, using 2.0 equiv. of ynone. [b] Yields of isolated product after chromatographic purification. [c] *ee* determined by chiral HPLC. [d] Using catalyst **C5**.

Attempts to translate the present conditions to simple allyl esters and equivalents, a substrate category that as far as we know has neither been employed in enantioselective direct conjugate additions,[26] revealed a divergent behavior. As data in equation 1 illustrate, the **C5**-catalyzed reaction of allyl esters/thioesters **29** with nitrostyrene produced a mixture of α- and γ-addition products **30** and **31**, respectively. Thioesters resulted more reactive and selective than the parent esters. However, while the minor γ-adducts were obtained as essentially single isomer in some cases,[27] the respective major α-adduct was obtained with diastereo- and enantioselectivities from low to moderate.

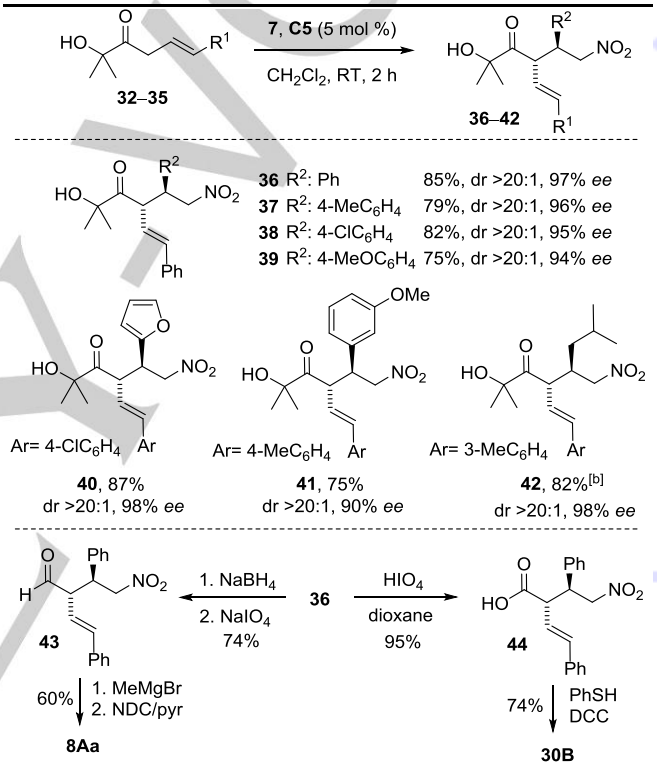


ArX	conditions	**30**/**31**		
PhO (**A**)	RT, 16 h	70:30	*dr*= 2.7:1, 63%/50% *ee*	*dr*= >20:1, 63% *ee*
PhS (**B**)	0 °C, 6 h	80:20	*dr*= 4:1, 89%/80% *ee*	*dr*= >20:1, 91% *ee*

Given the observations noted above, and owing to the easy conversion of the ketol moiety into diverse functionalities,[28] we decided to examine the suitability of allyl ketols as allylester equivalents. As the results in Table 4 show, it was very gratifying to observe that the reaction of the allyl ketols **32**–**35**[29] with nitroolefins **7** in the presence of 5 mol% **C5** led to the corresponding α-addition adduct **36**–**42** in high yield, *essentially complete diastereoselectivity* and *ee*'s typically higher than 95%.

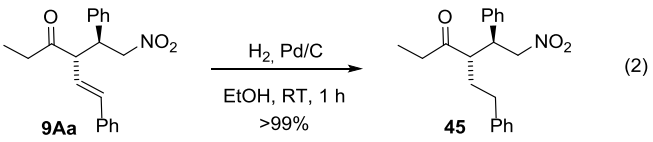
These results, especially the high dr, might be related to the strong preference for *Z*-enolate formation from these bulky ketols, as the corresponding *E*-enolate would present destabilizing 1,3-allylic interactions. Adduct **36** was easily transformed, via reduction and subsequent diol oxidation, into aldehyde **43** which was later converted into ketone **8Aa** thus confirming the stereochemical assignment. Alternatively, **36** was also correlated to thioester **30B** through oxidative cleavage and coupling of the resulting carboxylic acid **44** with thiophenol. In each case, reactions occurred clean and without double bond isomerization nor epimerization.

Table 4. Catalytic reactions with allylic ketols **32**–**35** and further elaboration.[a]



[a] Reactions carried out at 0.2 mmol scale, using 1.1 equiv. of nitroolefin and 5 mol% **C5** at r.t., unless otherwise stated, in 0.4 mL CH_2Cl_2. Diastereomeric ratios determined by ^{1}H NMR analysis of crude sample. Yields of isolated product after chromatographic purification. *ee* determined by chiral HPLC. [b] After 16 h of reaction. NDC: nicotinium dichromate.

In addition to these elaborations, the most obvious is the selective reduction of the double bond that affords products formally derived from the α-alkylation of nonsymmetric aliphatic ketones, which is difficult to achieve regioselectively. For example (eq 2) exposure of **9Aa** to H_2 over Pd on charcoal provided compound **45** almost quantitatively.



In conclusion, we have demonstrated that tertiary amine/squaramide bifunctional catalysts are able to promote the addition reaction of allyl ketones to nitroolefins not only with very good enantio- and diastereocontrol, but also exclusive α-site selectivity. Different subsets of readily available allyl ketones, including those with an alkyl-, aryl-, alkynyl- and hydroxyalkyl sidearm, all participate well, giving access to a variety of α-branched ketone products with generally two vicinal tertiary carbon stereocenters as essentially single isomer. Under similar catalytic conditions, allyl(thio)esters showed inferior α/γ-site as well as stereo-selectivity, but the use of allyl ketols as superb allylester equivalents can remediate this limitation. This study complements previous efforts[9-11] to switch the innate γ-reactivity of most vinylogous enolate equivalents (conjugation preserved) into α-reactivity (conjugation disrupted) and set the basis for further developments.

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Keywords: allyl ketones • organocatalysis • regioselectivity • Brønsted bases • conjugate additions.

[1] Reviews on vinylogous addition reactions: a) G. Casiraghi, L. Battistini, C. Curti, G. Rassu, F. Zanardi, *Chem. Rev*. **2011**, *111*, 3076−3154; b) C. Schneider, F. Abels, *Org. Biomol. Chem*. **2014**, *12*, 3531−3543; c) S E. Denmark, J. R. Heemstra, Jr., G. L. Beutner, *Angew. Chem*. **2005**, *117*, 4760-4777; *Angew. Chem. Int. Ed*. **2005**, *44*, 4682-4698.

[2] Selected leading examples: (unsaturated γ-butenolides) a) B. M. Trost, J. Hitce, *J. Am. Chem. Soc*. **2009**, *131*, 4572-4573; b) A. Yamaguchi, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2008**, *10*, 2319-2322; c) L. Yin, H. Takada, N. Kumagai, M: Shibasaki, *Angew. Chem*. **2013**, *125*, 7451-7454; *Angew. Chem. Int. Ed.* **2013**, *52*, 7310-7313. For reviews, see: d) X. Jusseau, L. Chabaud, C. Guillou *Tetrahedron* **2014**, *70*, 2595-2615; e) Q. Zhang, X. Liu, X. Feng, *Curr. Org. Synth.* **2013**, *10*, 764-785. (Unsaturated γ-butyrolactams) f) N. E. Shepherd, H. Tanabe, Y. Xu, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc*. **2010**, *132*, 3666-3667. (Alkylidene oxindoles) g) X. Xiao, H. Mei, Q. Chen, X. Zhao, L. Lin, X. Liu, X. Feng, *Chem. Commun.* **2015**, *51*, 580-583. (Linear enones) h) D. Yang, L. Wang, F. Han, D. Zhao, B. Zhang, R. Wang, *Angew. Chem*. **2013**, *125*, 6871-6874; *Angew. Chem. Int. Ed*. **2013**, *52*, 6739-6742.

[3] Via dienamine intermediates: For reviews, see: a) I. D. Jurberg, I. Chatterjee, R. Tannerta, P. Melchiorre, *Chem. Commun*. **2013**, *49*, 4869-4883; b) V. Marcos, J. Alemán, *Chem. Soc. Rev.* **2016**, *45*, 6812-6832. Selected examples: (cyclic enones) c) G. Bencivenni, P. Galzeranoa, A. Mazzanti, G. Bartoli, P. Melchiorre, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20642-20647 (correction *PNAS* **2013**, *110*, 4852-4853). (Allyl ketones) d) G. Zhan, Q. He, X. Yuan, Y.-C. Chen, *Org. Lett*. **2014**, *16*, 6000-6003; e) M.-L. Shi, G. Zhan, S.-L. Zhou, W. Du, Y.-C. Chen, *Org. Lett*. **2016**, *18*, 6480-6483.

[4] Via iminium activation: (linear enones as donors) a) Q. Guo, A. J. Fraboni, S. E. Brenner-Moyer, *Org. Lett.* **2016**, *18*, 2628-2631; b) Y. Gu, Y. Wang, T.-Y. Yu, Y.-M. Liang, P.-F. Xu, *Angew. Chem*. **2014**, *126*, 14352-14355; *Angew. Chem. Int. Ed*. **2014**, *53*, 14128-14131. (Silyl dienol ethers) c) V. Gupta, S. V. Sudhir, T. Mandal, C. Schneider, *Angew. Chem.* **2012**, *124*, 12778-12781; *Angew. Chem. Int. Ed.* **2012**, *51*, 12609-12612. (γ-Butenolides) d) X. Li, M. Lu, Y. Dong, W. Wu, Q. Qian, J. Ye, D. J. Dixon, *Nat. Commun.* **2014**, *5*, 4479. (Alkylidene malononitriles) e) L. Dell'Amico, G. Rassu, V. Zambrano, A. Sartori, C. Curti, L. Battistini, G. Pelosi, G. Casiraghi, F. Zanardi, *J. Am. Chem. Soc.* **2014**, *136*, 11107-11114.

[5] Brønsted base catalysis: (allyl ketones) a) B. Zhu, W. Zhang, R. Lee, Z. Han, W. Yang, D. Tan, K.-W. Huang, Z. Jiang, *Angew. Chem.* **2013**, *125*, 6798-6802; *Angew. Chem. Int. Ed*. **2013**, *52*, 6666-6670. b) T.-Z. Li, Y. Jiang, Y.-Q. Guan, F. Sha, X.-Y. Wu, *Chem. Commun*. **2014**, *50*, 10790-10792; c) Z. Jing, X. Bai, W. Chen, G. Zhang, B. Zhu, Z. Jiang, *Org. Lett*. **2016**, *18*, 260-263. (Alkylidene malononitriles and oxindoles) d) T. B. Poulsen, M. Bell, K. A. Jørgensen, *Org. Biomol. Chem*., **2006**, *4* 63-70; e) Q. Chen, G. Wang, X. Jiang, Z. Xu, L. Lin, R. Wang, *Org. Lett* **2014**, *16*, 1394-1397; f) C. Curti, G. Rassu, V. Zambrano, L. Pinna, G. Pelosi, A. Sartori, L. Battistini, F. Zanardi, G. Casiraghi, *Angew. Chem.* **2012**, *124*, 6304-6308; *Angew. Chem. Int. Ed*. **2012**, *51*, 6200-6204. (α,β-unsaturated thioesters) g) J. Wang, J. Chen, C. W. Kee, C.-H. Tan, *Angew. Chem.* **2012**, *124*, 2432-2436; *Angew. Chem. Int. Ed*. **2012**, *51*, 2382-2386. (α,β-Enals) h) J.-K. Xie, Y. Wang, J.-B. Lin, X.-R. Ren, P.-F. Xu, *Chem. Eur. J*. **2017**, *23*, 6752-6756.

[6] a) A. Yamaguchi, N. Aoyama, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2007**, *9*, 3387-3390. Proline catalyzed Mannich reaction leading to MBH-type aldehydes: b) N. Utsumi, H. Zhang, F. Tanaka, C. F. Barbas, III, *Angew. Chem*. **2007**, *119*, 1910-1912; *Angew. Chem. Int. Ed*. **2007**, *46*, 1878-1880.

[7] For pioneering work on dienamine-mediated asymmetric reactions, see: S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc*. **2006**, *128*, 12973-12980.

[8] a) J. Stiller, E. Marqués-Ló pez, R. P. Herrera, R. Fröhlich, C. Strohmann, M. Christmann, *Org. Lett*. **2011**, *13*, 70-73; b) E. Marqués-López, R. P. Herrera, T. Marks, W. C. Jacobs, D. Könning, R. M. de Figueiredo, M. Christmann, *Org. Lett.* **2009**, *11*, 4116-4119; c) B. Han, Y.-C. Xiao, Z.-Q. He, Y.-C. Chen, *Org. Lett.* **2009**, *11*, 4660-4663; d) D. Enders, X. Yang, C. Wang, G. Raabe, J. Runsik, *Chem. Asian. J.* **2011**, *6*, 2255-2259; e) B. Han, Z.-Q. He, J.-L. Li, R. Li, K. Jiang, T.-Y. Liu, Y.-C. Chen, *Angew. Chem.* **2009**, *121*, 5582-5585; *Angew. Chem. Int. Ed.* **2009**, *48*, 5474-5477. For a review, see: f) V. Marcos, J. Alemán, *Chem Soc. Rev.* **2016**, *45*, 6812-6832.

[9] (Alkylidene cyanoacetates) a) M. Bell, K. Frisch, K. A. Jørgensen, *J. Org. Chem*. **2006**, *71*, 5407-5410; (α-styrylacetates) b) J. Guang, S. Rout, M. Bihani, A. J. Larson, H. D. Arman, J. C.-G. Zhao, *Org. Lett*. **2016**, *18*, 2648-2651; (α-Angelica lactone) c) J. A. Griswold, M. A. Horwitz, L. V. Leiva, J. S. Johnson, *J. Org. Chem.* **2017**, *82*, 2276-2280; (deconjugated butenolides) d) B. Wu, Z. Yu, X. Gao, Y. Lan, Y.-G Zhou, *Angew. Chem.* **2017**, *129*, 4064-4068; *Angew. Chem. Int. Ed.* **2017**, *56*, 4006-4010.

[10] To our knowledge, a sole report deals with allyl ketones and involves the allylic α-alkylation of aryl allyl ketones with Morita-Baylis-Hillman carbonates. See: a) G. Tong, B. Zhu, R. Lee, W. Yang, D. Tan, C. Yang, Z. Han, L. Yan, K.-W. Huang, Z. Jiang, *J. Org. Chem*. **2013**, *78*, 5067-5072. b) Reference 4a includes three examples of (essentially racemic) direct α-functionalization of α,β-unsaturated ketones.

[11] a) M. Frias, R. Mas-Ballesté, S. Arias, C. Alvarado, J. Alemán, *J. Am. Chem. Soc.* **2017**, *139*, 672-679. For catalytic asymmetric reactions involving preformed silyl dienol ethers, see: b) ref 1c; c) S. V. Pansare, E. K. Paul, *Chem. Eur. J*. **2011**, *17*, 8770-8779.

[12] a) R. Gompper, H. U. Wagner, *Angew. Chem*. **1976**, *88*, 389-401; *Angew. Chem., Int. Ed. Engl*. **1976**, *15*, 321-333; b) H. L. van Maanen, H. Kleijn, J. T. B. H. Jastrzebski, M. T. Lakin, A. L. Spek, G. van Koten, *J. Org. Chem*. **1994**, *59*, 7839-7848; c) S. Saito, M. Shiozawa, M. Ito, H. Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 813-814.

[13] Selective reviews on dual or cooperative organocatalysis: a) L. Q. Lu, X.-L. An, J.-R. Chen, W.-J. Xiao, *Synlett* **2012**, *23*, 490-508; b)

Cooperative Catalysis: Designing Efficient Catalysts for Synthesis (Ed.: R. Peters), Wiley-VCH, Weinheim, **2015**.

[14] Reviews on Brønsted base catalysis: a) C. Palomo, M. Oiarbide, R. López, *Chem. Soc. Rev*. **2009**, *38*, 632-653; b) *Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysis, and Additional Topics*: *Science of Synthesis* (Ed.: K. Maruoka), Thieme, Stuttgart, **2012**; c) A. Ting, J. M. Gross, N. T. McDougal, S. E. Schaus, *Top. Curr. Chem.* **2010**, *291*, 145-200.

[15] 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. Sojs, *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.

[16] a) J. P. Malerich, K. Hagihama, V. R. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416-14417; b) Y. Zhu, J. P. Malerich, V. H. Rawal, *Angew. Chem.* **2010**, *122*, 157-160; *Angew. Chem. Int. Ed.* **2010**, *49*, 153-156.

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

[18] W. Yang; D.-M. Du, *Org. Lett*. **2010**, *12*, 5450-5453.

[19] Selected reviews on asymmetric organocatalytic conjugate additions: a) J. L. Vicario, D. Badía, L. Carrillo, E. Reyes, Organocatalytic Enantioselecive Conjugate Addition Reactions: A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules, RSC Publishing, Cambridge, 2010; b) S. B. Tsogoeva, *Eur. J. Org. Chem*. **2007**, 1701-1716; c) D. Almasi, D. A. Alonso, C. Najera, *Tetrahedron: Asymmetry* **2007**, *18*, 299-365.

[20] Selected reviews on conjugate additions to nitroalkenes: a) L. Tedeschi, D. Enders, *Eur. J. Org. Chem*. **2002**, 1877-1894; b) D. Roca-López, D. Sadaba, I. Delso, R. P. Herrera, T. Tejero, P. Merino, *Tetrahedron: Asymmetry* **2010**, *21*, 2561-2601; c) L. S. Aitken, N. R. Arezki, A. Dell Isola, A. J. A. Cobb, *Synthesis* **2013**, 2627-2628.

[21] Separation of diastereomers, while not systematic, was possible by column chromatography in some instances. See the SI for details.

[22] Control experiments in which the bifunctional catalyst was replaced, respectively, with Et_3N, an achiral squaramide, or a combination of both as catalyst, led to no reaction at all or variable amounts of α- and γ-addition adducts. See the SI for details.

[23] Conjugated enones resulted completely unreactive under the present conditions.

[24] CCDC-1542032 (compound **8Aa**) 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.

[25] Although configuration of the minor stereoisomer of compounds **8**-**13** (Table 2) was not determined, they should be epimeric at Cα (stereolabile center) with respect to the major isomer. This assumption would be in agreement with the essentially perfect nitroalkene facial selectivity observed in all examples within Tables 3 and 4 and, most important, the high *ee* of products **14** and **15** formed upon isomerization of the diastereomeric mixtures of **12** and **13**, respectively.

[26] For use on direct γ-site amination and α-Mannich reactions, respectively, see: ref 5g and 9b.

[27] For full screen of allyl(thio)esters, see the Supporting Information.

[28] a) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev*. **2012**, *41*, 4150-4164; b) E. Badiola, B. Fiser, E. Gómez-Bengoa, A. Mielgo, I. Olaizola, I. Urruzuno, J. M. García, J. M. Odriozola, J. Razkin, M. Oiarbide, C. Palomo, *J. Am. Chem. Soc.* **2014**, *136*, 17869-17881.

[29] These allyl ketones are readily prepared from commercial 3-hydroxy-3-methylbutan-2-one in two steps. See the SI for details.

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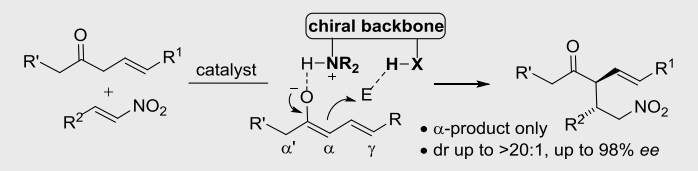

Direct with a switch: Most catalytic reactions involving in situ-generated vinylogous enolate equivalents proceed through γ-carbon (conjugation preserved), being the switch to α-reactivity not obvious. Here a bifunctional tertiary amine/H-bond catalyst-promoted highly diastereo- and enantioselective α-addition of allyl ketones to nitroolefins is presented for the first time.

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Controlling α- vs γ-Reactivity of Vinylogous Ketone Enolates in Organocatalytic Enantioselective Michael Reactions