Guanidine-Catalyzed γ-Selective Morita–Baylis–Hillman Reactions on α,γ-Dialkyl-Allenoates: Access to Densely Substituted Heterocycles

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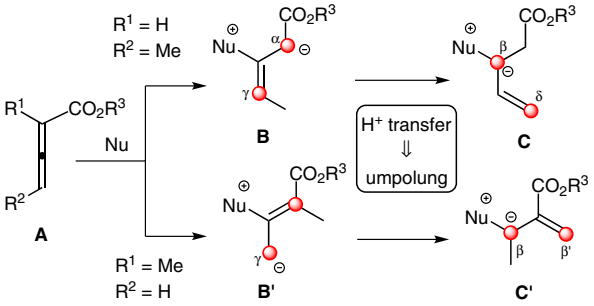
Abstract: *N*-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) was discovered as an excellent catalyst for the Morita–Baylis–Hillman reaction for previously hard-to-activate α,γ-dialkyl allenoate substrates. The obtained densely substituted allenic alcohols, which are generally inaccessible with other Lewis base catalysts, could be further converted into 2,5-dihydrofuran and 2*H*-pyran-2-one heterocyclic structures with challenging substitution patterns.

Key words: allenes, catalysis, nucleophiles, guanidines, cyclization

In organic chemistry, 'superbases' are most commonly defined by their Brønsted basic properties.[1] While more thorough definitions do in fact exist,[2] a superbase is often simply regarded as any species of which the corresponding acid can no longer be easily deprotonated by the hydroxide ion OH^-. Considering only the organic, that is, nonmetal superbases, guanidines have emerged as especially versatile reagents and organocatalysts for synthetic organic chemistry.[3] While the employment of the Brønsted basic properties of guanidines is thus quite firmly established nowadays, applications of their pronounced Lewis basic properties are still in their infancy.[4] Especially bicyclic guanidines,[5] however, have recently been recognized as not only strongly Brønsted basic, but also remarkably Lewis basic and highly nucleophilic reagents.[6] We herein report a further application of these 'super' Lewis basic properties of guanidines for the nucleophilic activation of densely substituted allenoates.

Lewis basic allenoate activations and their applications in organic synthesis have undergone a staggering development since their initial discovery in 1995.[7,8] Most commonly, tertiary phosphines are employed as the nucleophilic catalysts due to their high nucleophilicity and Lewis basicity.[9] In general, the initial attack of a nucleophilic catalyst on an allenoate ester **A** generates zwitterionic dienolate intermediates **B**/**B′**, which behave as nucleophiles at the α- and/or γ-positions (Scheme 1). While this dienolate reactivity is readily exploited in the case of buta-2,3-dienoates, that is, allenoates without any further alkyl substituents, the situation becomes much more complex in the case of α- and/or γ-substituted allenoates. γ-Methyl-derived dienolates **B** can thus undergo an umpolung reaction by a proton shift to form vinyl ylides **C** with nucleophilic properties at the β- and δ-positions.



Scheme 1 Potentially undesirable umpolung reactions after nucleophilic activation of α- or γ-methyl allenoates by phosphine catalysts. Nucleophilic positions are shown in red.

Similarly, an α-methyl allenoate derived dienolate **B′** could be transformed into a methylene ylide **C′**, which is nucleophilic at the β- and β′-positions. While both umpolung reactions have been exploited synthetically,[10,11] they also represent a major limitation on the use of dienolate reactivity for substituted allenoate substrates. The use of nitrogen Lewis bases (e.g. DABCO) could theoretically prevent unwanted umpolung reactions and allow for dienolate reactivity even in alkyl-substituted cases. Unfortunately, however, tertiary amines generally proved insufficiently reactive for the activation of sterically demanding substrates and accordingly, many dienolate-based transformations, like the prototypical reaction between allenoates and aromatic aldehydes, could be realized for simple buta-2,3-dienoates only.[12] The introduction of further alkyl groups either effectively shut down the reaction for N-nucleophiles, or opened competing reaction pathways by umpolung for P-nucleophiles.

Following our previous work with the bicyclic guanidine 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as highly active Lewis base catalyst for the umpolung-free nucleophilic activation of allenoates,[13] we set out to investigate the reaction of very challenging α,γ-dialkyl-substituted substrates with aromatic aldehydes. To our delight, a test reaction employing ethyl 2-methylpenta-2,3-dienoate (**1a**), 4-chlorobenzaldehyde (**2a**), TBD as the catalyst, and

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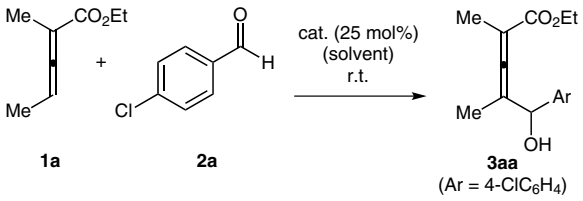
MeCN as the solvent smoothly provided the desired allenic alcohol **3aa** as the only discernible product (Table 1, entry 1).

Table 1 γ-Selective Morita–Baylis–Hillman Reaction of Ethyl 2-Methylpenta-2,3-dienoate (**1a**) and 4-Chlorobenzaldehyde (**2a**)[a]



1a **2a** **3aa** (Ar = 4-ClC$_6$H$_4$)

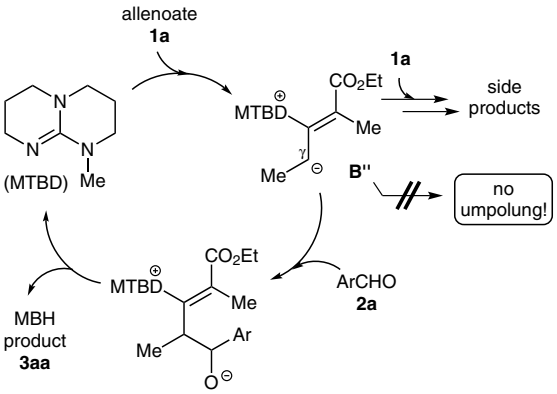
Entry	Catalyst	Solvent	**1a** (equiv)	Time	Yield of **3aa** (%)[b]
1	TBD	MeCN	1.0	30 min	52
2	TBD	DMF	1.0	20 min	60
3	TBD	DMF	1.5	45 min	65
4	TBD	DMF	2.0	30 min	76
5	TBD	DMF	3.0	1.5 h	75
6	TBD	CH_2Cl_2	2.0	5.25 h	38
7	TBD	THF	2.0	6 h	n.r.[c]
8	DBU	DMF	1.0	1.5 h	62
9	DBU	DMF	1.5	1.5 h	78
10	DBU	DMF	2.0	1.5 h	80
11	MTBD	DMF	2.0	1.5 h	88
12[d]	MTBD	DMF	2.0	15 h	81
13[e]	MTBD	DMF	2.0	1.5 h	84
14	DABCO	DMF	2.0	1.5 h	n.r.[c]
15	DMAP	DMF	2.0	1.5 h	traces

[a] Reactions were run at a 0.3–0.4 mmol scale with *c* (**2a**) = 0.1 M,
[b] Yield of isolated product (dr = ca. 1:1).
[c] No reaction.
[d] Reaction run at –20 °C.
[e] Reaction run with 15 mol% of catalyst.

Alcohol **3aa**, which can be described as the product of a γ-selective Morita–Baylis–Hillman (MBH) reaction,[14] was formed as a mixture of diastereoisomers within very short reaction times. To the best of our knowledge, this represents the first example of a MBH reaction on α,γ-disubstituted allenoates.[15] Moreover, even the corresponding transformation of γ-unsubstituted allenic substrates under DMAP catalysis could previously only be realized for highly reactive allenic ketones, but not for the synthetically more versatile allenic esters.[16] Yields could be slightly improved by conducting the reaction in DMF (Table 1, entry 2). As some undesired TBD-induced polymerization reactions of the allenoate substrate were still encountered as side reactions at room temperature, a further improvement of yields to 76% was achieved by increasing the amount of allenoate to 2.0 equivalents relative to the aldehyde. Even bigger excesses of 3.0 equivalents of allenoate led to no further improvement (Table 1, entries 3–5). The reaction was most efficient in highly polar DMF, but yields decreased dramatically in CH_2Cl_2, and in THF no reaction was observable at all (Table 1, entries 6 and 7). In order to further suppress unwanted side reactions, we also investigated slightly less reactive Lewis base catalysts. Indeed, yields of **3aa** could be further improved up to 80% when using the amidine base DBU (Table 1, entries 8–10), and finally, *N*-methyl TBD (MTBD) was identified as the optimal catalyst, which gave the product **3aa** in an excellent and reproducible yield of 88% (Table 1, entry 11).

High yields of >80% could still be achieved even at –20 °C (Table 1, entry 12), or with only 15 mol% of MTBD catalyst (Table 1, entry 13). Most importantly, common N-nucleophiles like DABCO or DMAP were entirely ineffective in catalyzing this reaction (Table 1, entries 14 and 15).

Mechanistically, the reaction most likely follows a classic MBH pathway originating from the zwitterionic intermediate **B″** (Scheme 2). Blocking of the usually more reactive α-position[13a] with the α-Me substituent as well as the suppression of any umpolung reactions forces the nucleophilic attack on the aldehyde to take place at the γ-position. A subsequent proton transfer and elimination finally liberates both the product **3aa** and the catalyst. Side reactions probably originate from zwitterion **B″** as well, as its attack on a second molecule of allenoate would lead to oligo- and later on higher polymeric products.



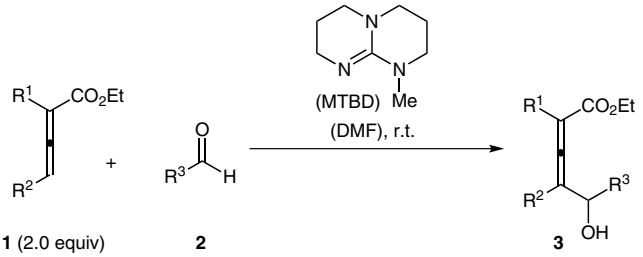
Scheme 2 Mechanistic proposal for the γ-selective MBH reaction

Having established the optimal reaction conditions of the γ-selective MBH reaction (15–30 mol% MTBD, 2.0 equiv allenoate, DMF, r.t.), we investigated the scope of this novel transformation both with regard to different aromatic aldehydes and – more importantly – differently substituted allenoates (Table 2). In reactions with allenoate **3a**, moderate to high yields of γ-MBH products could be isolated with both electron-poor and electron-rich aromatic aldehydes (Table 2, entries 1–6). The *ortho*- and disubstituted aldehydes **2d**,**f** were equally suitable reactants. Employing nonenolizable aliphatic pivaloylaldehyde (**2g**),

the expected product **3ag** could be isolated, but only in low yields (Table 2, entry 7). Excellent yields of >90% were achieved with α-*n*-Pr-γ-Me allenoate **1b** (Table 2, entries 8–10), and even the α-Bn substituted allenoate **1c**, a substrate which is especially prone to undesired umpolung reactions, was successfully employed to give the desired products in satisfactory yields of 61–87% (Table 2, entries 11–13). Introduction of a branched *i*-Pr substituent to the γ-position in substrate **1d** reduced its reactivity significantly and therefore required higher catalyst loadings and longer reaction times. Still, however, the sterically highly encumbered products **3da**, **3db**, **3dc**, and **3df** were obtained in good yields of up to 83% (Table 2, entries 14–17). Interestingly, with aldehyde **2f** the reaction proceeded in a slightly diastereoselective fashion (dr of **3df** = ca. 2:1), while all other reactions were basically unselective (de ≤16%). Scale-up was unproblematic, and in a large-scale experiment, **3aa** could be isolated in 84% yield giving 0.8 gram of product without any further tuning of the reaction conditions.

Having established a straightforward access to both densely and diversely substituted γ-MBH products **3**, we next envisioned the employment of these allenic products for the synthesis of heterocyclic structures. While Bu_3P was entirely unsuitable for the preparation of the γ-MBH products **3**, it retained its activity for the Lewis base induced cyclization of these products to give 3,5-dimethyl-6-aryl-2*H*-pyran-2-ones **4**.[12c] Pyranones **4aa**, **4ac**, and **4ae** were isolated in moderate to good yields after stirring with 1.0 equivalent of Bu_3P in MeCN for 18 hours (Scheme 3).

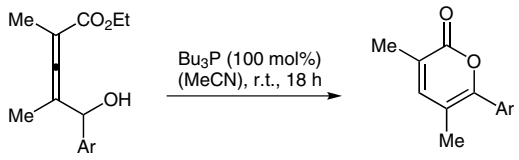
Table 2 Scope of the MTBD-Catalyzed γ-Selective Morita–Baylis–Hillman Reaction[a]



1 (2.0 equiv) **2** **3**

Entry	Allenoate	Aldehyde	Product	R^1	R^2	R^3	MTBD (mol%)	Time (h)	Yield of **3** (%)[b]
1	**1a**	**2a**	**3aa**	Me	Me	4-ClC_6H_4	25	1.5	89
2	**1a**	**2b**	**3ab**	Me	Me	Ph	20	1.5	95
3	**1a**	**2c**	**3ac**	Me	Me	4-$O_2NC_6H_4$	20	1.5	74
4	**1a**	**2d**	**3ad**	Me	Me	2-$O_2NC_6H_4$	20	1.5	81
5	**1a**	**2e**	**3ae**	Me	Me	4-$MeOC_6H_4$	20	1.5	68
6	**1a**	**2f**	**3af**	Me	Me	3,5-$(MeO)_2C_6H_3$	20	1.5	85
7	**1a**	**2g**	**3ag**	Me	Me	*t*-Bu	20	1.5	15
8	**1b**	**2a**	**3ba**	*n*-Pr	Me	4-ClC_6H_4	15	1.5	90
9	**1b**	**2b**	**3bb**	*n*-Pr	Me	Ph	20	1.5	96
10	**1b**	**2f**	**3bf**	*n*-Pr	Me	3,5-$(MeO)_2C_6H_3$	20	1.5	90
11	**1c**	**2a**	**3ca**	Bn	Me	4-ClC_6H_4	20	1.5	61
12	**1c**	**2b**	**3cb**	Bn	Me	Ph	20	1.5	87
13	**1c**	**2f**	**3cf**	Bn	Me	3,5-$(MeO)_2C_6H_3$	20	1.5	73
14	**1d**	**2a**	**3da**	Me	*i*-Pr	4-ClC_6H_4	15	5.0	83
15	**1d**	**2b**	**3db**	Me	*i*-Pr	Ph	30	5.0	54
16	**1d**	**2c**	**3dc**	Me	*i*-Pr	4-$O_2NC_6H_4$	30	5.0	67
17	**1d**	**2f**	**3df**	Me	*i*-Pr	3,5-$(MeO)_2C_6H_3$	30	5.0	76[c]

[a] Reactions were run at a 0.3–0.4 mmol scale with *c* (**2**) = 0.2 M.
[b] Yield of isolated product (dr = ca. 1:1).
[c] dr = ca. 2:1.

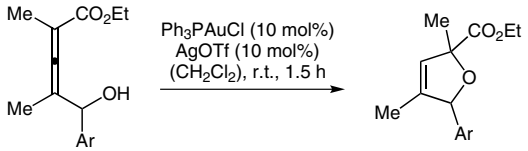


3aa	Ar = 4-ClC_6H_4	**4aa** 67%
3ac	Ar = 4-$O_2NC_6H_4$	**4ac** 83%
3ae	Ar = 4-$MeOC_6H_4$	**4ae** 56%

Scheme 3 Phosphine-catalyzed cyclization of γ-MBH products **3** to 3,5-dimethyl-6-aryl-2*H*-pyran-2-ones **4**

The organocatalytic synthesis of pyranones, which was previously only reported for α,γ-unsubstituted butadienoates,[12c] could thus be successfully expanded to α,γ-dialkyl allenoates. It is also noteworthy that the only two previously reported syntheses of such 3,5-dialkyl-substituted pyranones are both dependent on the use of expensive ruthenium or rhodium catalysts as well as additional silver and copper salts and high reaction temperatures of 100–120 °C.[17] Our MTBD/Bu_3P catalyzed two-step procedure to 2*H*-pyran-2-ones could thus reasonably offer a cheap, simple, and mild organocatalytic alternative.

As a second example to illustrate the synthetic versatility of γ-MBH products **3** we chose the popular transition-metal-catalyzed cycloisomerization of hydroxyallenes into 2,5-dihydrofurans **5** (Scheme 4).[18] While the reaction did not proceed with Ag(I) salts,[19] a cationic gold catalyst formed in situ from Ph_3PAuCl and AgOTf (10 mol% each)[20] enabled the efficient 5-*endo*-trig cyclization of α,γ-dimethyl allenic alcohols under mild conditions and within short reaction times.



3aa	Ar = 4-ClC_6H_4	**5aa** 86%
3ad	Ar = 2-$O_2NC_6H_4$	**5ad** 88%
3af	Ar = 3,5-$(MeO)_2C_6H_3$	**5af** 61%

Scheme 4 Gold-catalyzed cycloisomerization of γ-MBH products **3** to 2,5-dihydrofurans **5**

2,5-Dihydrofurans **5aa**, **5ad**, and **5af** displaying very dense substituent patterns as well as a quaternary center on C-2 were thus easily synthesized in yields of up to 88% from their corresponding alcohol precursors.

In order to facilitate further investigations regarding the stereoselectivity of this and related functionalizations of allenoates, the identification of the product diastereoisomers was also deemed desirable. We therefore obtained the X-ray crystal structure of the tosylcarbamate derivative **6** of product **3aa** which could be crystallized in a diastereomerically pure form (Figure 1).[21]

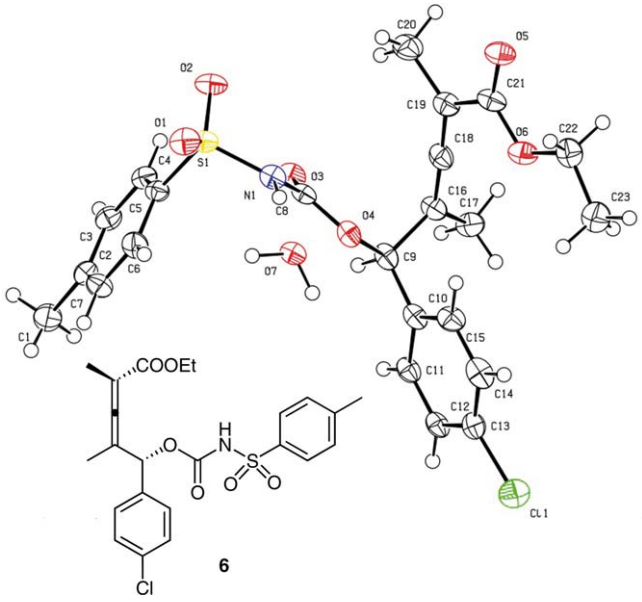


Figure 1 X-ray crystal structure of the tosylcarbamate derivative **6** of product **3aa**[21]

In conclusion, we have developed the first γ-selective MBH reaction of α,γ-dialkyl-substituted allenoate esters **1** and aromatic aldehydes **2**. Using MTBD as a tuned-down variant of the exceedingly active TBD catalyst, a wide variety of allenic alcohols **3** were readily available within short reaction times and under very mild and simple reaction conditions. The reaction is quite general with regard to substitution at the allenoate α- and γ-positions as well as the electronic and steric properties of the aromatic aldehydes. This generality is most likely caused by the absence of any undesired umpolung reactions which typically complicate selective transformations of substituted allenoates under phosphine catalysis. The obtained γ-MBH products **3** were proven to be versatile intermediates for the synthesis of densely substituted and potentially bioactive[22] 2*H*-pyran-2-ones **4** and 2,5-dihydrofurans **5**. Further work is currently directed towards the control of both diastereo- and enantioselectivity as well as the further elaboration of the now easily accessible MBH products into biologically active derivatives.

Representative Procedure for the γ-Selective MBH Reaction of α,γ-Dialkyl Allenoates and Aromatic Aldehydes

Allenoate **1a** (106 mg, 756 μmol, 2.0 equiv) and aldehyde **2a** (51 mg, 366 μmol, 1.0 equiv) were dissolved in DMF (3.8 mL). MTBD (13 μL, 14 mg, 91 μmol, 25 mol%) was added all at once, and the mixture was stirred at r.t. for 1.5 h. The reaction was quenched by the addition of solid NH_4Cl (excess), filtered, and the solids washed with EtOAc (3 × 10 mL). The filtrate was washed with H_2O (30 mL), LiCl (5% aq, 30 mL), dried over $MgSO_4$, filtered, and the solvent evaporated. Flash column chromatography of the residue (SiO_2, 2.0 × 20 cm, pentane–EtOAc = 8:2) gave the γ-MBH product **3aa** (92 mg, 326 mmol, 89%, dr = 48:52) as a slightly yellow oil.

Representative Procedure for the Bu_3P-Catalyzed Cyclization of γ-MBH Products to 2*H*-Pyran-2-ones

γ-MBH product **3ac** (64 mg, 220 μmol) was dissolved in MeCN (1.0 mL). Bu_3P (54 μL, 44 mg, 220 μmol, 1.0 equiv) was added, and the mixture was stirred at r.t. for 18 h. After evaporation of all volatile matter, the residue was purified by flash column chromatography (SiO_2, 2.0 × 20 cm, pentane–EtOAc = 75:25 to 70:30) to give the pyrone product **4ac** (45 mg, 183 μmol, 83%) as a yellow solid.

Representative Procedure for the Au-Catalyzed Cycloisomerization of γ-MBH Products to 2,5-Dihydrofurans

γ-MBH product **3aa** (71 mg, 253 μmol, dr = 48:52) was dissolved in CH_2Cl_2 (1.0 mL). Ph_3PAuCl (12.5 mg, 25 μmol, 10 mol%) and AgOTf (6.5 mg, 25 μmol, 10 mol%) were added, and the resulting suspension was stirred at r.t. for 1.5 h. After evaporation of the solvent, the residue was purified by flash column chromatography (SiO_2, 2.0 × 20 cm, pentane–EtOAc = 10:1) to give the dihydrofuran product **5aa** (61 mg, 217 μmol, 86%, dr = 48:52) as a yellow oil.

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References

(1) *Superbases for Organic Synthesis*; Ishikawa, T., Ed.; John Wiley and Sons: Chichester, **2009**.
(2) Caubere, P. *Chem. Rev.* **1993**, *93*, 2317.
(3) For recent reviews, see: (a) Selig, P. *Synthesis* **2013**, *45*, 703. (b) Terada, M. *J. Synth. Org. Chem. Jpn.* **2010**, *68*, 1159. (c) Ishikawa, T. *Chem. Pharm. Bull.* **2010**, *58*, 1555. (d) Leow, D.; Tan, C.-H. *Chem. Asian J.* **2009**, *4*, 488.
(4) (a) Taylor, J. E.; Bull, S. D.; Williams, J. M. J. *Chem. Soc. Rev.* **2012**, *41*, 2109. (b) Fu, X.; Tan, C.-H. *Chem. Commun.* **2011**, *47*, 8210.
(5) (a) Coles, M. P. *Chem. Commun.* **2009**, 3659. (b) Kiesewetter, M. K.; Scholten, M. D.; Kirn, N.; Weber, R. L.; Hedrick, J. L.; Waymouth, R. M. *J. Org. Chem.* **2009**, *74*, 9490.
(6) Maji, B.; Stephenson, D. S.; Mayr, H. *ChemCatChem* **2012**, *4*, 993.
(7) Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906.
(8) For reviews on allenoate activations, see: (a) Yu, S.; Ma, S. *Angew. Chem. Int. Ed.* **2012**, *51*, 3074; *Angew. Chem.* **2012**, *124*, 3128. (b) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (c) Cowen, B. J.; Miller, S. J. *Chem. Soc. Rev.* **2009**, *38*, 3102.
(9) For selected reviews on phosphine catalysis, see: (a) Fan, Y. C.; Kwon, O. In *Asymmetric Organocatalysis*; List, B., Ed.; Thieme: Stuttgart, **2012**, 723. (b) Marinetti, A.; Voituriez, A. *Synlett* **2010**, 174. (c) Ye, L.-W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140. (d) Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1560; *Angew. Chem.*; **2008**, *120*, 1584. (e) Methot, J. L.; Roush, William. R. *Adv. Synth. Catal.* **2004**, *346*, 1035.
(10) For examples regarding umpolung reactions of γ-alkyl allenoates, see: (a) Xu, S.; Zhou, L.; Zeng, S.; Ma, R.; Wang, Z.; He, Z. *Org. Lett.* **2009**, *11*, 3498. (b) Xu, S.; Zhou, L.; Ma, R.; Song, H.; He, Z. *Chem. Eur. J.* **2009**, *15*, 8698. (c) Ma, R.; Xu, S.; Tang, X.; Wu, G.; He, Z. *Tetrahedron* **2011**, *67*, 1053. (d) Li, E.; Huang, Y.; Liang, L.; Xie, P. *Org. Lett.* **2013**, *15*, 3138.
(11) For examples regarding umpolung reactions of α-alkyl allenoates, see: (a) Xu, S.; Zhou, L.; Ma, R.; Song, H.; He, Z. *Org. Lett.* **2010**, *12*, 544. (b) Xu, S.; Zou, W.; Wu, G.; Song, H.; He, Z. *Org. Lett.* **2010**, *12*, 3556. (c) Wang, T.; Ye, S. *Org. Lett.* **2010**, *12*, 4168. (d) Khong, S. N.; Tran, Y. S.; Kwon, O. *Tetrahedron* **2010**, *66*, 4760. (e) Martin, T. J.; Vakhshori, V. G.; Tran, Y. S.; Kwon, O. *Org. Lett.* **2011**, *13*, 2586.
(12) (a) Tsuboi, S.; Kuroda, H.; Takatsuka, S.; Fukawa, T.; Sakai, T.; Utaka, M. *J. Org. Chem.* **1993**, *58*, 5952. (b) Zhu, X.-F.; Henry, C. E.; Wang, J.; Dudding, T.; Kwon, O. *Org. Lett.* **2005**, *7*, 1387. (c) Zhu, X.-F.; Schaffner, A.-P.; Li, R. C.; Kwon, O. *Org. Lett.* **2005**, *7*, 2977. (d) Creech, G. S.; Kwon, O. *Org. Lett.* **2008**, *10*, 429. (e) Creech, G. S.; Zhu, X.-F.; Fonovic, B.; Dudding, T.; Kwon, O. *Tetrahedron* **2008**, *64*, 6935.
(13) (a) Selig, P.; Turočkin, A.; Raven, W. *Adv. Synth. Catal.* **2013**, *355*, 297. (b) Selig, P.; Turočkin, A.; Raven, W. *Chem. Commun.* **2013**, *49*, 2930.
(14) We intentionally avoid the expression 'vinylogous Morita–Baylis–Hillman reaction', as this term is now generally used to describe the related Rauhut–Currier reaction. For a review, see: Aroyan, C. E.; Dermenci, A.; Miller, S. J. *Tetrahedron* **2009**, *65*, 4069.
(15) For the synthesis of similar products by Brønsted base catalysis, see: Xu, B.; Hammond, G. B. *Angew. Chem. Int. Ed.* **2008**, *47*, 689; *Angew. Chem.* **2008**, *120*, 701.
(16) Zhao, G.-L.; Shi, M. *Org. Biomol. Chem.* **2005**, *3*, 3686.
(17) (a) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 6295. (b) Chinnagolla, R. K.; Jeganmohan, M. *Chem. Commun.* **2012**, *48*, 2030.
(18) For a recent review, see: Krause, N. In *Innovative Catalysis in Organic Chemistry*; Andersson, P. G., Ed.; Wiley-VCH: Weinheim, **2012**, 195.
(19) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966.
(20) Gockel, B.; Krause, N. *Org. Lett.* **2006**, *8*, 4485.
(21) (a) CCDC-945270 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif (b) Spek, A. L. *Acta Crystallogr., Sect. D: Biol. Crystallogr.* **2009**, *65*, 148.
(22) For examples of the diverse bioactivity of 2-pyranones, see: (a) Vara Prasad, J. V. N.; Para, K. S.; Lunney, E. A.; Ortwine, D. F.; Dunbar, J. B. Jr.; Ferguson, D.; Tummino, P. J.; Hupe, D.; Tait, B. D.; Domagala, C. H.; Humblet, C.; Bhat, T. N.; Liu, B.; Guerin, D. M. A.; Baldwin, E. T.; Erickson, J. W.; Sawyer, T. K. *J. Am. Chem. Soc.* **1994**, *116*, 6989. (b) Kanai, A.; Kamino, T.; Kuramochi, K.; Kobayashi, S. *Org. Lett.* **2003**, *5*, 2837.