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Highly Enantioselective Direct Vinylogous Michael Addition of γ-Butenolide to Enals

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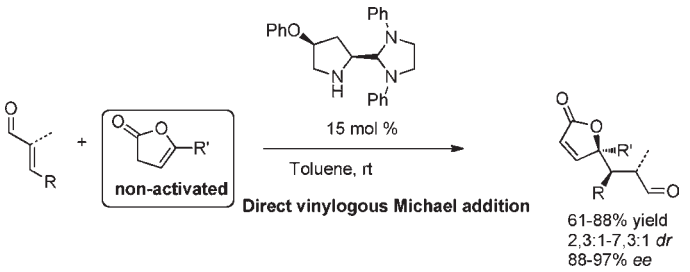
ABSTRACT



An unprecedented and simple direct vinylogous addition of deconjugated butenolide to enals has been developed in excellent stereoselectivities (>95% ee), with Aminal-PYrrolidine (APY) catalyst. This methodology allows for the efficient preparation of complex γ-butenolide from readily available renewable resources. Furthermore, preliminary mechanistic investigations have allowed for the better understanding of the origin of both stereoselectivities and of the observed high reactivities.

Constructing enantiopure molecules in a minimum of operations and from renewable resources is one of the key challenges for modern chemistry.[1] In this view, derivatizing plant biomass resources to high added value chemicals by simple, cheap, and efficient methods should be one of the ultimate goals for new methodology development.[2] Levulinic acid and its cyclized butenolide derivative Angelica lactone are cheap materials readily prepared on an industrial scale from carbohydrate.[3] Given the great number of natural products containing the γ-butenolide motif, the application of Angelica lactone as a direct vinylogous nucleophile is highly promising.[4]

Aminocatalysis and particularly iminium catalysis have appeared as essential activation modes for the asymmetric β-functionalization of conjugated carbonyl compounds.[5] In 2003, MacMillan and co-workers disclosed the organocatalyzed Mukaiyama−Michael addition of silyloxyfuran to enals (Scheme 1).[6] This reaction gave rise to highly versatile compounds but in terms of atom and step economy, the use of silyloxyfuran is detrimental for the efficiency of the sequence.[7] Thus, the development of the direct vinylogous addition of butenolide avoiding these

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(2) For reviews on the production of fine chemicals from biomass, see: (a) Chheda, J. N.; Huber, G. W.; Dumesic, J. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7164. (b) Corma, A.; Iborra, S.; Velty, A. *Chem. Rev.* **2007**, *107*, 2411. (c) Christensen, C. H.; Rass-Hansen, J.; Mardsen, C. C.; Taarning, E.; Eglebad, K. *ChemSusChem* **2008**, *1*, 283.

(3) For a review see: Bozell, J. J.; Moens, L.; Elliot, D. C.; Wang, Y.; Neuenscwander, G. G.; Fitzpatrick, S. W.; Bilski, R. J.; Jarnefeld, J. L. *Resour., Conserv. Recycl.* **2000**, *28*, 227.

(4) For reviews on butenolide, see: (a) Rao, Y. S. *Chem. Rev.* **1964**, *64*, 353. (b) Bruckner, R. *Curr. Org. Chem.* **2001**, *5*, 679. (c) Ugurchieva, T. M.; Veselovsky, V. V. *Russ. Chem. Rev.* **2009**, *78*, 337.

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(6) For the initial report see: (a) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192. For applications of this methodology, see; (b) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (c) Simmons, B.; Walji, A. M.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 4349. (d) Robichaud, J.; Tremblay, F. *Org. Lett.* **2006**, *8*, 597.

(7) For a review on atom and step economy, see: (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695. (c) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40. (d) Young, I. S.; Baran, P. S. *Nat. Chem.* **2009**, *1*, 193. (e) Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657. (f) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854. (g) Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, 1477.

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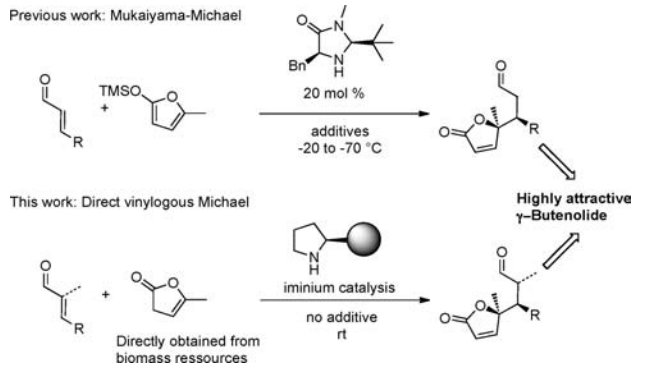
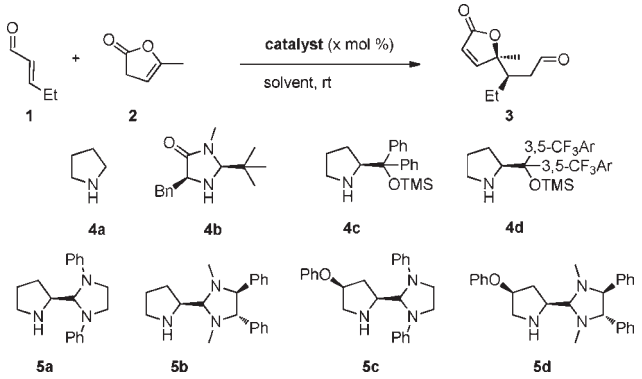
Scheme 1. Proposed Approach to Enantioenriched γ-Butenolides



costly transformations would represent an interesting improvement in view of potential industrial applications.[8] Given the fact that Angelica lactone possesses an acidic hydrogen α to a double bond we postulated that it would be possible to add to a sufficiently activated iminium ion without any required additive. Herein, we disclose the development of an operationally simple, additive-free, and highly efficient direct vinylogous addition of furanone to enals, constructing multiple stereocenters in high stereocontrol. Furthermore, preliminary mechanistic investigations have allowed for a better understanding of the process.

The application of our proposed direct vinylogous-Michael addition was first evaluated with pentenal **1** in toluene using a large range of different catalysts (Table 1). As expected in our proposal, achiral pyrrolidine did catalyze the given reaction furnishing the expected compound with the tetrasubstituted carbon center in a 4,5:1 dr, indicating that the diastereoselectivity is mainly under substrate control (entry 1). Surprisingly, MacMillan imidazolidinone **4b**, the catalyst used in the addition of silyloxyfuran, did not lead to any reaction (entry 2). Using 5 mol % of diphenylprolinol silyl ether **4c**, a promising 43% conversion together with a good 90% ee was observed, while only traces of the adduct were obtained with the fluorinated catalyst **4d** (entry 4).[9] We recently

Table 1. Optimization of the Vinylogous Michael Addition



entry	catalyst	solvent	time (h)	conv[a] (%)	dr[b]	ee[c] (%)
1	**4a** (30 mol %)	toluene	1	>95	4,5:1	
2	**4b** (5 mol %)	toluene	18	0		
2	**4c** (5 mol %)	toluene	17	43	9,0:1	90
3	**4d** (5 mol %)	toluene	14	traces		
4	**5a** (5 mol %)	toluene	17	51	6,6:1	70
5	**5b** (5 mol %)	toluene	14	28	6,1:1	70
6	**5c** (5 mol %)	toluene	14	48	9,2:1	93
7	**5d** (5 mol %)	toluene	17	23	7,3:1	81
10	**5c** (5 mol %)	MeOH	18	>95	5,5:1	88
11	**5c** (15 mol %)	toluene	13	>95 (88)	7,6:1	94
12	**4c** (15 mol %)	toluene	18	>95	7,6:1	94

[a] Conversion determined by ^{1}H NMR on the reaction mixture. Yield of isolated product in parentheses. [b] Determined by ^{1}H NMR analysis. [c] Determined by chiral GC for the major diasteroisomer.

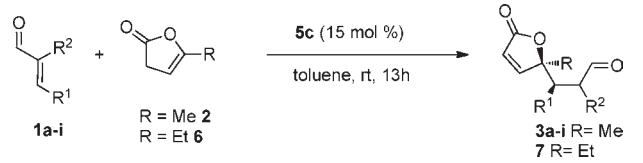
introduced Aminal-PYrrolidine (APY) catalysts as powerful tools for enamine-catalyzed reactions.[10] In addition to finding better conditions for the vinylogous Michael addition, we were highly interested to check the behavior of this catalyst backbone in this iminium process. Gratifyingly, our first generation catalyst **5a** and **5b** derived from proline did catalyze the reaction in a promising 70% ee (entries 4 and 5). As already observed for enamine catalysis, phenoxy derivatives of hydroxyproline **5c** and **5d** gave a dramatic improvement in the enantioselectivity (entries 6 and 7). The best catalyst **5c** gave an excellent 93% ee for the phenoxy derivative compared to the 70% ee for the proline analogue **5a**. This result is crucial in terms of mode of action of aminal-pyrrolidine. Indeed, given the distance of the phenoxy group from the active site, it is probable that this phenoxy group is not only encumbering the upper face (*Re* face) of the iminium but also that it has a crucial role in slightly distorting the

(8) For pioneering direct vinylogous use of furanone in asymmetric catalysis, see: (a) Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 2319. (b) Trost, B. M.; Hitce, J. *J. Am. Chem. Soc.* **2009**, *131*, 4572. (c) Shepherd, N. E.; Tanabe, H.; Xu, Y.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 3666. For recent examples of asymmetric organocatalytic vinylogous application of furanone for the creation of enantioenriched γ-butenolide, see: (d) Cui, H.-L.; Huang, J.-R.; Lei, J.; Wang, Z.-F.; Chen, S.; Wu, L.; Chen, Y.-C. *Org. Lett.* **2010**, *12*, 720. (e) Feng, X.; Cui, H.-L.; Xu, S.; Wu, L.; Chen, Y.-C. *Chem.—Eur. J.* **2010**, *16*, 10309. (f) Pansare, S.; Paul, E. K. *Chem. Commun.* 2010, *47*, 1027. (g) Ube, H.; Shimada, N.; Terada, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1858. (h) Zhang, Y.; Yu, C.; Ji, Y.; Wang, W. *Chem. Asian J.* **2010**, *5*, 1303. (i) Wang, J.; Qi, C.; Ge, Z.; Cheng, T.; Li, R. *Chem. Commun.* **2010**, *46*, 2124. (j) Yang, Y.; Zheng, K.; Zhao, J.; Shi, J.; Lin, L.; Liu, X.; Feng, X. *J. Org. Chem.* **2010**, *75*, 5382.

(9) For leading references on the application of **4c** and **4d** as organocatalysts, see: (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. For reviews, see:(c) Mielgo, A.; Palomo, C. *Chem. Asian J.* **2008**, *3*, 922. (d) Xu, L. W.; Li, L.; Shi, Z.-H. *Adv. Synth. Catal.* **2010**, *352*, 243.

(10) For the development and applications of Aminal-PYrrolidine catalysts, see: (a) Quintard, A.; Bournaud, C.; Alexakis, A. *Chem.—Eur. J.* **2008**, *14*, 7504. (b) Quintard, A.; Alexakis, A. *Chem.—Eur. J.* **2009**, *15*, 11109. (c) Belot, S.; Quintard, A.; Krause, N.; Alexakis, A. *Adv. Synth. Catal.* **2010**, *352*, 667. (d) Quintard, A.; Alexakis, A. *Adv. Synth. Catal.* **2010**, *352*, 1856. (e) Quintard, A.; Belot, S.; Marchal, E.; Alexakis, A. *Eur. J. Org. Chem.* **2010**, 927. (f) Quintard, A.; Alexakis, A. *Chem. Commun.* **2010**, *46*, 4085. (g) Quintard, A.; Alexakis, A. *Org. Biomol. Chem.* DOI: 10.1039/C0OB00818D. Published Online: Jan 7, 2011. (h) Quintard, A.; Alexakis, A.; Mazet, C. *Angew. Chem., Int. Ed.* DOI: 10.1002/anie.201007001. Published Online: Feb 3, 2011.

Table 2. Scope of the Vinylogous Michael Addition



entry	R^1	R^2	yield[a] (%)	dr[b]	ee[c] (%)
1	Me	H	**3b**: 79	4,7:1	97
2	Et	H	**3a**: 88	7,6:1	94
3	*n*Pr	H	**3c**: 83	6,6:1	94
4	nC_7H_{15}	H	**3d**: 63	6,9:1	95
5	*i*Pr	H	**3e**: 82[d]	7,3:1	91
6	Ph	H	**3f**: 61	2,6:1	96
7	(*E*)-CH=CH-*n*(C_4H_9)	H	**3g**: 63	3,3:1	96
8	Me	Me	**3h**: 74	17:1:1:1	93
9[e]	H	Me	**3i**: 95	1,1:1	36/43
10[e,f]	H	Me	**3i**: 84	1,2:1	−7/−8
11	Me	H	**7**: 60	5,6:1	88

[a] Yield of isolated product. [b] Determined by ^{1}H NMR analysis and chiral GC. [c] Determined by chiral GC for the major diasteroisomer. [d] Conversion determined by ^{1}H NMR. [e] Methanol used as solvent and 20 mol % of **5c**. [f] Use of catalyst **4c**.

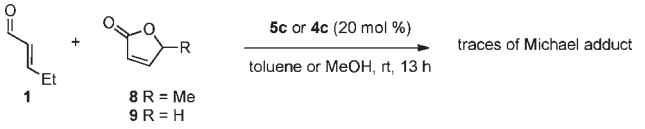
pyrrolidine ring and/or the aminal. Calculations are currently ongoing to confirm this crucial point. With the best catalyst in hand, we then tested different solvent/additives to obtain a better reactivity.[11]

Solvent screening revealed that protic solvents such as methanol impressively increased the turnover of the reaction while slightly decreasing the ee (>95% conversion, 88% ee, entry 10). Keeping in mind this increased reactivity using MeOH as solvent, we decided to pursue the optimization in toluene by increasing the catalyst loading to 15 mol %. As expected, full conversion with perfect regioselectivity control gave a good 88% yield together with an excellent 94% ee and 7,6:1 dr (entry 11). Noteworthy is the fact that these excellent results are obtained at room temperature without any needed extra base/acid additives. Aside from APY catalyst, it is important to notice that diphenylprolinol silyl ether **4c** gave the same result in these optimized conditions (entry 12).

Experiments that probe the scope of the aldehyde component have revealed that a variety of substitution patterns can be tolerated on the enal (Table 2). A linear alkyl chain such as Me, *n*Pr worked perfectly well in this process furnishing the expected adducts in high stereoselectivities (94% to 97% ee, entries 1−4). By increasing the steric hindrance with γ-branched enal **1e**, the reaction rate was disminished, along with a slight lowering in the enantioselectivity (91% ee, entry 5). The unsaturation of the γ-position of the enal in phenylacetaldehyde led to a dramatic drop in diastereoselectivity (2,6:1 dr) while keeping the excellent levels of enantioselectivity (96% ee, entry 7). Most significant, a dienal **1g** could be used giving exclusively the 1,4-addition product in the same excellent 96% ee without any traces of 1,6-addition (entry 7). This regioselectivity control on both nucleophiles and electrophiles demonstrates the powerfulness of the methodology. Finally, the methyl group of Angelica lactone could be changed to an ethyl with a slight decrease in both reactivity and stereoselectivity (entry 11). Perhaps more notable, we have found that using methanol as solvent, α,β-disubstituted enal **1h** did undergo the Michael addition in the same exceptional levels of stereoselectivity for the creation of three contiguous stereocenters. Indeed, compound **3h** was obtained with 85% of the major diasteroisomer in 93% ee. When suppressing the β-substituent in methacrolein **1i**, both diastereoselectivity and enantioselectivity dropped. Compound **3i** was obtained in an equimolar ratio of diasteroisomers and a low 36−43% ee depending on the diasteroisomers. It is important to note that when using diphenylprolinol silyl ether **4c** in the same reaction a near racemate was obtained but with the opposite sense of induction (entry 10).

These last results are particularly interesting in terms of mechanism and for the understanding of the origin of the chiral induction in the Michael addition process. First, it indicates that the origin of the control of the selectivity in the α-position of the aldehyde only comes from the influence of the β-methyl substituent (substrate control). Second, it indicates that APY **5c** is at least partially able to control the face of attack of the entering butenolide on nonsubstituted enals (43% ee, catalyst control). But as soon as a substituent is added in the β-position of the enal, it seems that this substituent becomes the only group controlling the attack on either the *Re* or *Si* face of the butenolide (diastereoselectivity control); the catalyst only controls the face attack of the iminium (enantioselectivity control). This is consistent with the fact that all chiral or even achiral catalysts (pyrrolidine) lead to the same diastereoisomers in approximately equal amount on β-substituted enals.

Scheme 2. Mechanistic Investigations

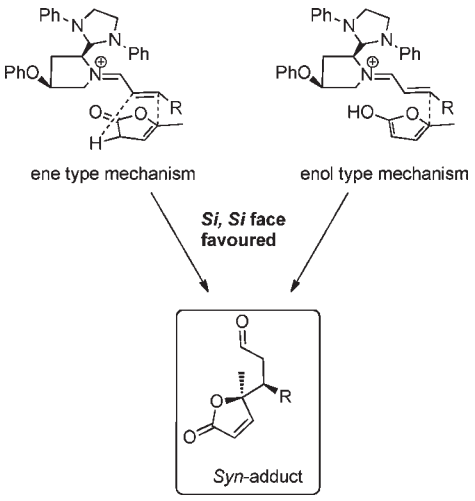


Having solved the origin of the stereoselectivity of this system, we wondered about the origin of the reactivity and of the regioselectivity of the reaction. Indeed, since we start from a nonconjugated furanone and that no additives are necessary for the reaction, the high reactivity and perfect regioselectivity of the system is rather astonishing. To have a better insight into the mechanism of this process, several tests were performed and are summarized in Scheme 2.

Surprisingly addition of conjugated furanone **8** or **9** only gave traces of the adduct (conversion < 5%), even in the presence of triethylamine as additive. This lower reactivity

(11) For full solvent/additives screening see the Supporting Informations.

Scheme 3. Possible Mechanisms for the Conjugate Addition



of the conjugated enones can have several origins. Either the enol equilibrium of the conjugated enone is slower (kinetic difference) and/or the conjugated furanone undergoes a Michael addition trapping the catalyst.[12] NMR experiments of addition of the catalyst on either substrate **2** or **8** did not show any evolution of the substrate in $C_6D_5CD_3$. These experiments, together with the lack of control of the diastereoselectivity by the catalyst, should indicate that the enol equilibrium occurs in Angelica lactone independently from the catalyst.[13] This small amount of enol form could then undergo a fast addition on the highly activated iminium ion. In the case of conjugated enones, the enol equilibrium is slower allowing for a deactivation of the catalyst by other pathways. Another possibility that we are currently investigating is a plausible ene-type mechanim. Indeed, this mechanism where no enol equilibrium is involved was already disclosed by Hayashi in the addition of cyclopentadiene to enals.[14] It would account for the low reactivity of conjugated furanone and for the observation that an excess of butenolide or of a base additive such as Et_3N does not accelerate the reaction.

A transition state can be drawn taking into account all these observations (Scheme 3).[15] The catalyst controls the enantioselectivity by forming the trans iminium, away from the bulky aminal. The *Re* face is shielded by the aminal favoring the single attack from the *Si* face while the interaction between the enal group and the entering butenolide favors the formation of the *Syn* adduct. Further experiments should shed light on the nature of the entering nucleophile.

In conclusion we have developed an unprecedented direct Aminal-PYrrolidine catalyzed vinylogous addition of simple butenolide to enals. This methodology allows for the efficient preparation of complex γ-butenolide from readily available renewable ressources. Excellent stereoselectivities (typical ee $>95\%$) were obtained in this experimentally simple procedure. Furthermore, preliminary mechanistic investigations have allowed for the better understanding of the origin of both stereoselectivities and of the observed high reactivities. We are convinced that this understanding of the mechanism will serve as a keystone for the development of other vinylogous reactions. Furthermore, thanks to its operational simplicity and to the excellent levels of stereoselectivities of the final products, this remarkable reaction should find its applications in total synthesis.

Supporting Information Available. Experimental details and results and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) For an example of the addition of pyrrolidine to butenolide, see: (a) De Lange, B.; Van Bolhuis, F.; Feringa, B. L. *Tetrahedron* **1989**, *45*, 6799. For other pyrrolidine trapping, see: (b) Andrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147.

(13) Changing the enantiomeric excess of catalyst **4c** in the addition of Angelica lactone to pentenal did not show any nonlinear effect in the reaction.

(14) Ene-type organocatalyzed reaction: Gotoh, H.; Masui, R.; Ogino, H.; Shoji, M.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *46*, 6853.

(15) Absolute configuration of the compounds was performed by direct comparison of samples obtained via Mukaiyama−Michael addition as described by MacMillan and co-workers. See the Supporting Information for details.