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Direct Diastereo- and Enantioselective Vinylogous Michael Additions of Linear Enones

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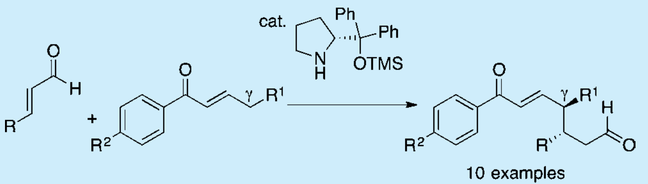
Supporting Information

ABSTRACT: A direct vinylogous Michael addition using linear vinylogous Michael donors has been developed. Notably, even γ-substituted Michael donors cleanly afforded γ-alkylated products in high yield and ee by this method. Moreover, control experiments revealed that, for these and related linear vinylogous Michael donors, the size of the Michael acceptor strongly influences whether α- or γ-alkylation occurs, not simply blocking effects of cocatalysts as suggested previously.



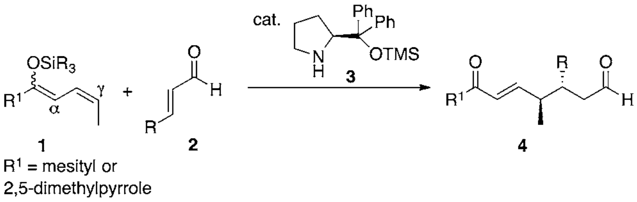
10 examples
55-83% yield
87-98% ee

While Michael additions using enamine or enol(ate) Michael donors are a well-established method for C−C bond construction, the corresponding vinylogous Michael additions using dienamine or dienol(ate) Michael donors remain a synthetic challenge.[1] The principal challenge associated with the latter is that both the α- and γ-carbons of vinylogous Michael donors are nucleophilic; thus, controlling the regioselectivity of reactions is not straightforward. To circumvent this issue, nearly all vinylogous Michael additions employ cyclic vinylogous Michael donors.[1−8] The combination of at least one endocyclic, electron-rich double bond and steric and/or electronic biases renders these cyclic vinylogous Michael donors highly reactive toward γ-substitution. The relative dearth of examples of vinylogous Michael additions using linear vinylogous Michael donors means that the factors that influence regioselectivity in these reactions are comparatively poorly understood.

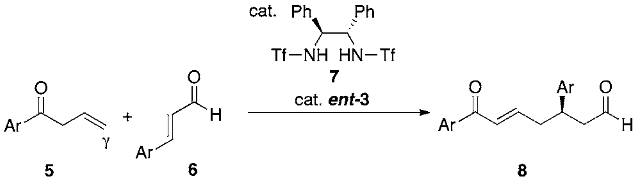
In 2012, the first report of use of a linear vinylogous Michael donor in an indirect vinylogous Michael addition emerged (Scheme 1).[9] The Mukaiyama−Michael donors (**1**) contained bulky R^1 groups to block reactivity at the α-position. Around this time, as part of our broader interest in γ-functionalizations of α,β-unsaturated carbonyl compounds,[10] we set out to develop the first direct vinylogous Michael addition using linear vinylogous Michael donors. While our investigations were underway, the first such reaction was reported.[11] Deconjugated ketones without substitution at the γ-position (i.e., **5**)[11] were used in conjunction with enals (**6**) with aromatic substituents at the β-position.[11a] While the γ-position of **5** remains unhindered by the lack of substitution at this position, the authors propose that the α-position is sterically shielded as a result of hydrogen-bonding interactions of the adjacent carbonyl oxygen with the cocatalyst, **7**.[11a] Our investigations focused, instead, on enones (**9**) both with and without γ-substitution, and our findings provide new information about the factors that influence α- vs γ-alkylation in direct vinylogous Michal additions using linear vinylogous Michael donors.

Scheme 1. Vinylogous Michael Additions Using Linear Vinylogous Michael Donors[a]

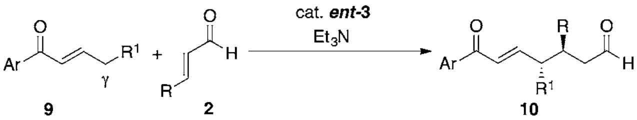
a) First vinylogous Michael additions with linear substrates[9]



b) First direct vinylogous Michael additions with linear substrates[11a]



c) This work



[a](a) First vinylogous Michael additions with linear substrates.[9] (b) First direct vinylogous Michael additions with linear substrates.[11a]

We expected the nucleophilic dienol tautomer of **9a**, which possesses an extended system of conjugation, to be formed rather easily and favored in hydrogen bonding solvents such as MeOH. Indeed, the reaction did proceed in this solvent in good ee, albeit low yield (entry 1, Table 1). Use of Et_3N or cinnamic acid additives to facilitate the formation of the reactive

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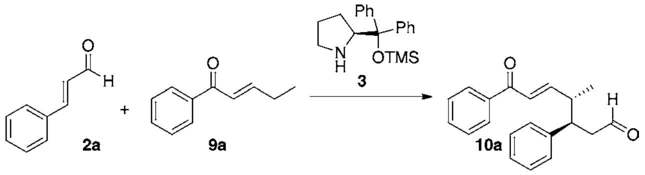
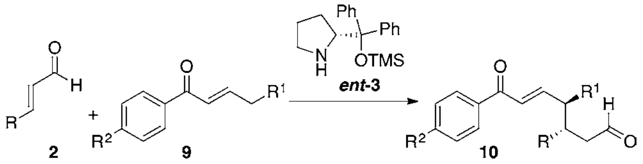
Table 1. Reaction Optimization[a]



entry	ratio (2a:9a)	additive	yield[b] (%)	ee[c] (%)
1	3:1		20	88
2	3:1	Et_3N (1 equiv)	trace	nd
3	3:1	$PhCHCHCO_2H$ (20%)	trace	nd
4	3:1	Et_3N (1 equiv), $PhCHCHCO_2H$ (20%)	43	88
5	1:1	Et_3N (1 equiv), $PhCHCHCO_2H$ (20%)	14	nd
6	1:3	Et_3N (1 equiv), $PhCHCHCO_2H$ (20%)	trace	88
7[d]	3:1	Et_3N (1 equiv), $PhCHCHCO_2H$ (20%)	46	88
8[e]	3:1	Et_3N (1 equiv), $PhCHCHCO_2H$ (20%)	65	88
9[e,f]	3:1	Et_3N (1 equiv), $PhCHCHCO_2H$ (20%)	65	−92

[a]Reaction conditions: **9a** (0.2 mmol), **2a**, **3** (0.04 mmol), additive, MeOH (0.5 mL), rt, 3 d. [b]Isolated yield of **10a**. [c]ee determined by chiral-phase HPLC. [d]0.1 mL of MeOH was used. [e]0.1 mL of THF was used. [f]***ent*-3** was used. nd = not determined.

Table 2. Substrate Scope[a]



entry	R	R^1	R^2	10	yield[b] (%)	ee[c] (%)
1	Ph	Me	H	**10a**	65	92
2	Ph	Et	H	**10b**	80	91
3	Ph	H	H	**10c**	75	98
4	Ph	*i*Pr	H		nr	
5	Ph	Me	Cl	**10d**	83	94
6	2-FC_6H_4	Me	H	**10e**	81	97[d]
7	4-ClC_6H_4	Me	H	**10f**	80	91
8	4-$OMeC_6H_4$	Me	H	**10g**	75	93
9	4-$NO_2C_6H_4$	Me	H	**10h**	82	96
10	2-furyl	Me	H	**10i**	79	96
11	1-naphthyl	Me	H	**10j**	55	87
12	Et	Me	H		nr	

[a]Reaction conditions: **9** (0.2 mmol), **2** (0.6 mmol), ***ent*-3** (0.04 mmol), Et_3N (0.2 mmol), $PhCHCHCO_2H$ (0.04 mmol), THF (0.1 mL), rt, 3 d. [b]Isolated yield of **10**. [c]ee determined by chiral-phase HPLC. [d]ee of derivative arising from Wittig homologation with $Ph_3P{=}CHCO_2Et$. nr = no reaction.

dienol(ate) or iminium ion species, respectively, hampered the reaction instead (entries 2 and 3). Curiously, however, the combination of these two additives resulted in a 2-fold rate increase (entry 4). Also interesting was the observation that the combination of Et_3N with a related carboxylic acid (i.e., benzoic acid) did not produce any rate enhancement effect.[12] Use of the two reactants in other ratios was not beneficial to the reaction yield (entries 5 and 6). Increasing the solvent concentration did slightly improve the reaction yield (entry 7). An investigation into reaction solvents, including neat conditions, revealed that in the presence of Et_3N and cinnamic acid additives, aprotic solvents were optimal for this transformation.[12] With THF as reaction solvent, **10a** was isolated in 65% yield (entry 8), with only a trace quantity of the *syn* diastereomer being observed (97:3 dr). Use of the *R* enantiomer of the catalyst, ***ent*-3**, provided the enantiomer of **10a** in identical yield and in slightly improved ee (entry 9).

Using the conditions in entry 9, which were established after extensive optimizations,[12] an investigation into substrate scope was undertaken. The enone substrate was amenable to variation. Unbranched alkyl chains were well tolerated, with the substrate with the least hindered γ-position generating **10** in the highest ee (entries 1−3, Table 2). Sterically congested R^1 groups such as a branched alkyl group, however, hampered the reaction (entry 4). The phenyl group was also amenable to substitution (entry 5).

With regard to the enal substrate, electron-withdrawing or -releasing substituents on cinnamaldehydes, either proximal to (*ortho*) or remote from (*para*) the reactive center, had minimal impact on product yield or ee (entries 6−9). Heteroaromatic and polyaromatic R groups were also tolerated, including the very sterically demanding 1-naphthyl group, although the corresponding product in this case was obtained in moderate yield and slightly reduced ee (entries 10 and 11).

The absolute configuration of the δ-stereocenter of enone **10a** was assigned by analogy with other ***ent*-3**-catalyzed conjugate addition reactions. The configuration of the γ-stereocenter was assigned through conversion of **10a** to a known lactone,[12] the *syn* and *anti* diastereomers of which have distinct ^1H NMR chemical shifts.

After observing no reaction with an aliphatic enal (entry 12), we were curious whether an aromatic R group was a requirement for desired enal reactivity or simply an sp^2-hybridized γ-carbon. Thus, substrate **2b** was examined (eq 1, Scheme 2). Interestingly, using this substrate, only α-alkylated product **12** was isolated from the reaction mixture, albeit in moderate yield and low ee, presumably due to the increased steric hindrance of the α-center of the enone relative to the γ-center. Furthermore, as evidenced by the reaction with maleimide (**11**), under these conditions, alkylation at the α-center of the enone appeared to be the inherent reactivity preference with Michael acceptors other than enals (**2**) with R = Ar.

Moreover, this inherent reactivity preference was not specific to our reaction conditions. After reproducing the original reaction from ref 11a (b, Scheme 1, with Ar = Ph for both **5** and **6**), we found that, even under these conditions, enal **2b** also alkylated **5** exclusively at the α-position (eq 2, Scheme 2).

The α- and γ-products could be distinguished by ^1H NMR based on the chemical shift and multiplicity of characteristic protons. For example, in **12**, the terminal Me group is allylic and appears as a doublet at 1.7 ppm, whereas the terminal Me group in **10a** is homoallylic and appears as a doublet more upfield, at 1.1 ppm. Similarly, the olefin in **10a** is in conjugation with the carbonyl. Its α-olefinic proton appears as a doublet at 6.7 ppm and the β-olefinic proton appears as a doublet of doublets at 6.8 ppm. By contrast, the olefin in **12** is not in conjugation with the carbonyl group, and thus the olefinic protons appear more upfield, as a multiplet at 5.7 ppm and as a triplet at 5.2 ppm.

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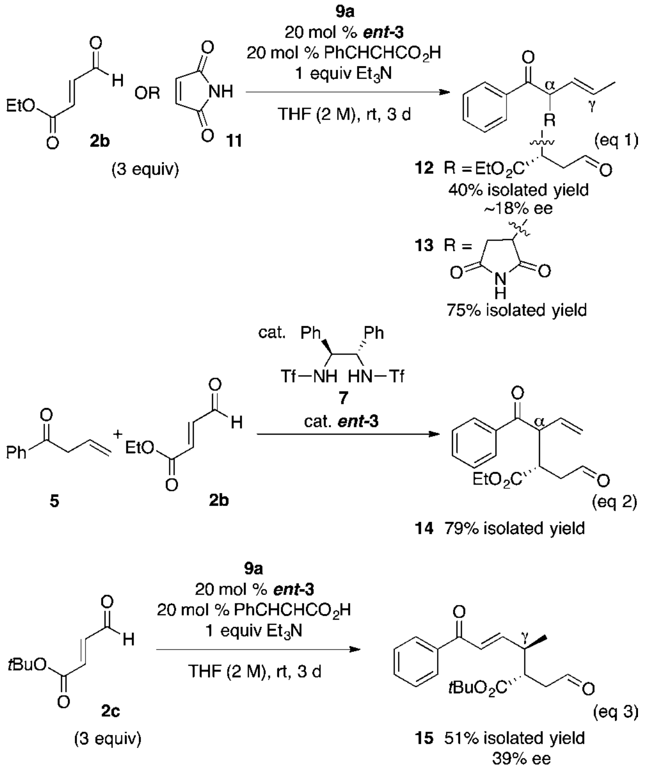
Scheme 2. Control Experiments



We next wondered whether these Michael acceptor-dependent differences in regioselectivity were a result of steric or electronic effects. Perhaps larger electrophiles were simply too sterically encumbered to alkylate the α-position of the enone, whereas smaller electrophiles were not. Alternatively, perhaps some sort of (e.g., π-stacking) interaction between the phenyl ring of the enone and the aromatic ring of enals (**2**) with R = Ar directed the latter to alkylate the γ-position of the enone. To evaluate these possibilities, an enal with a bulky, nonaromatic R group, **2c**, was examined (eq 3, Scheme 2). Indeed, γ-alkylation occurred exclusively, suggesting that sterics of the Michael acceptor, and not electronics, play a role in directing alkylation to the α- vs γ-position of the vinylogous Michael donor, even in spite of any blocking effects of coordinating cocatalysts (i.e., **7**) or conjugate acids (Et_3HN^+).

In conclusion, a direct vinylogous Michael addition using a linear vinylogous Michael donor has been developed. Existing methods employ only γ-unsubstituted linear Michael donors, presumably to facilitate γ-alkylation. By contrast, clean γ-alkylation of Michael donors with alkyl groups at the γ-position using cinnamaldehyde derivatives was observed under these conditions. This method thus offers a direct route to types of products that have previously only been synthesized via multiple steps or with simpler substitution patterns. Further experiments revealed that while enals with larger R groups favored γ-alkylation, enals with smaller R groups favored α-alkylation of these, and related, linear vinylogous Michael donors. These results reveal that the regioselectivity of these reactions is a more complex interplay of steric influences from both the Michael donor *and acceptor* and blocking effects of cocatalysts than previously thought.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01050.

Additional optimizations; complete description of methods and configuration determination; characterization data (PDF)
^{1}H NMR, ^{13}C NMR, and HPLC spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews on catalytic enantioselective vinylogous Michael additions, see: (a) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076–3154. (b) Schneider, C.; Abels, F. *Org. Biomol. Chem.* **2014**, *12*, 3531–3543.

(2) Recent examples using alkylidene malonitriles: (a) Dell'Amico, L.; Rassu, G.; Zambrano, V.; Sartori, A.; Curti, C.; Battistini, L.; Pelosi, G.; Casiraghi, G.; Zanardi, F. *J. Am. Chem. Soc.* **2014**, *136*, 11107–11114. (b) Li, Q.-Z.; Gu, J.; Chen, Y.-C. *RSC Adv.* **2014**, *4*, 37522–37525. (c) Alizadeh, A.; Sedighian, H.; Bayat, F. *Synlett* **2014**, *25*, 389–392. (d) Rout, S.; Ray, S. K.; Unhale, R. A.; Singh, V. K. *Org. Lett.* **2014**, *16*, 5568–5571. (e) Brindani, N.; Rassu, G.; Dell'Amico, L.; Zambrano, V.; Pinna, L.; Curti, C.; Sartori, A.; Battistini, L.; Casiraghi, G.; Pelosi, G.; Greco, D.; Zanardi, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 7386–7390.

(3) Recent examples using α,β-unsaturated γ-butyrolactams: (a) Joie, C.; Deckers, K.; Raabe, G.; Enders, D. *Synthesis* **2014**, *46*, 1539–1546. (b) Chen, Y.-R.; Das, U.; Liu, M.-H.; Lin, W. *J. Org. Chem.* **2015**, *80*, 1985–1992. (c) Gu, X.; Guo, T.; Dai, Y.; Franchino, A.; Fei, J.; Zou, C.; Dixon, D. J.; Ye, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 10249–10253.

(4) Recent examples using butenolides: (a) Wang, Z.-H.; Wu, Z.-J.; Huang, X.-Q.; Yue, D.-F.; You, Y.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *Chem. Commun.* **2015**, *51*, 15835–15838. (b) Sekikawa, T.; Kitaguchi, T.; Kitaura, H.; Minami, T.; Hatanaka, Y. *Org. Lett.* **2015**, *17*, 3026–3029.

(5) Recent examples using 3-alkylideneoxindoles: (a) Chen, Q.; Wang, G.; Jiang, X.; Xu, Z.; Lin, L.; Wang, R. *Org. Lett.* **2014**, *16*, 1394–1397. (b) Xiao, X.; Mei, H.; Chen, Q.; Zhao, X.; Lin, L.; Liu, X.; Feng, X. *Chem. Commun.* **2015**, *51*, 580–583. (c) Di Iorio, N.; Righi, P.; Ranieri, S.; Mazzanti, A.; Margutta, R. G.; Bencivenni, G. *J. Org. Chem.* **2015**, *80*, 7158–7171.

(6) Recent example using α-alkylidenepyrazolinones: Rassu, G.; Zambrano, V.; Pinna, L.; Curti, C.; Battistini, L.; Sartori, A.; Pelosi, G.; Casiraghi, G.; Zanardi, F. *Adv. Synth. Catal.* **2014**, *356*, 2330–2336.

(7) Recent example using 4-nitroisoxazoles: Zhang, Y.; Wei, B.; Lin, H.; Cui, W.; Zeng, X.; Fan, X. *Adv. Synth. Catal.* **2015**, *357*, 1299–1304.

(8) Recent examples using siloxyfurans: (a) Steinkamp, A.-D.; Frings, M.; Thomé, I.; Schiffers, I.; Bolm, C. *Chem. - Eur. J.* **2015**, *21*, 7705–7708. (b) Li, J.; Huang, R.; Xing, Y.-K.; Qiu, G.; Tao, H.-Y.; Wang, C.-

J. *J. Am. Chem. Soc.* **2015**, *137*, 10124−10127. (c) Jadhav, A. P.; Bhaskara Rao, V. U. B.; Singh, P.; Gonnade, R. G.; Singh, R. P. *Chem. Commun.* **2015**, *51*, 13941−13944.

(9) (a) Gupta, V.; Sudhir, S.; Mandal, T.; Schneider, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 12609−12612. (b) Basu, S.; Gupta, V.; Nickel, J.; Schneider, C. *Org. Lett.* **2014**, *16*, 274−277.

(10) (a) Appayee, C.; Fraboni, A. J.; Brenner-Moyer, S. E. *J. Org. Chem.* **2012**, *77*, 8828−8834. (b) Fraboni, A. J.; Brenner-Moyer, S. E. *Org. Lett.* **2016**, *18*, 2146−2149.

(11) (a) Gu, Y.; Wang, Y.; Yu, T.-Y.; Liang, Y.-M.; Xu, P.-F. *Angew. Chem., Int. Ed.* **2014**, *53*, 14128−14131. (b) Zhan, G.; He, Q.; Yuan, X.; Chen, Y.-C. *Org. Lett.* **2014**, *16*, 6000−6003.

(12) See the Supporting Information for further details.

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