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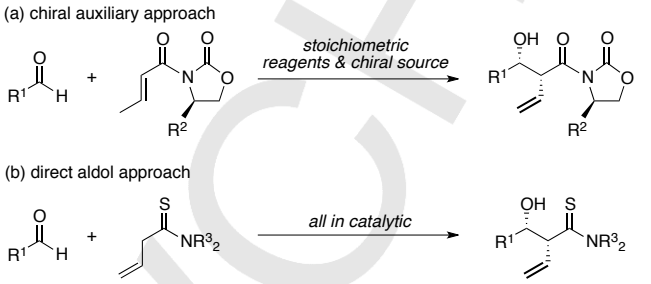
Direct Catalytic Asymmetric Aldol Reaction of Thioamide with an α-Vinyl Appendage

Jin Cui, Akimichi Ohtsuki, Takumi Watanabe,* Naoya Kumagai,* and Masakatsu Shibasaki*

Abstract: The direct catalytic asymmetric aldol reaction is an emerging catalytic methodology that provides atom-economical access to functionalized chiral building blocks. Thioamides are useful aldol donors due to their high-fidelity chemoselective enolization and divergent post-aldol transformations. Herein we describe the incorporation of an α-vinyl appendage on a thioamide, which expands the utility of aldol adducts for natural product synthesis. This vinylated thioamide was not accommodated under the previously identified catalyst settings, but the newly developed catalytic conditions furnished aldol products containing the pendant vinyl group.

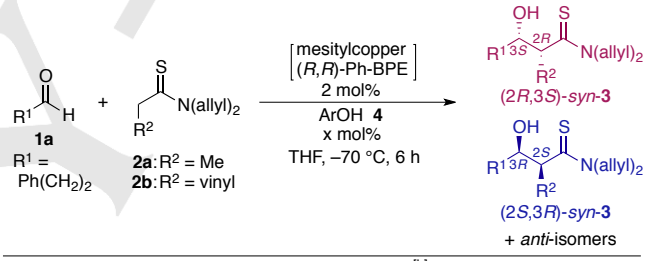
Optically active acyclic chiral molecules comprise a class of building blocks that is in high demand for the synthesis of natural products and therapeutics. The aldol reaction offers a robust method for obtaining synthetically useful β-hydroxy carbonyl compounds with consecutive stereogenic centers, and has long attracted attention.[1] Because stereochemical purity is critically important for the synthesis of chiral building blocks, the chiral auxiliary approach using *N*-acyloxazolidin-2-ones developed by Evans et al. is widely applied to access this class of compounds with excellent stereocontrol.[2],[3] Recent efforts in this field have advanced the direct-type option to access these enantioenriched aldol products, in which in situ-generated enolates engage in a stereoselective aldol addition driven by designed chiral catalysts, eliminating the stoichiometric use of chiral auxiliaries.[1, 4],[5] Despite the increasing number of catalytic systems amenable for promoting direct aldol reactions, a diastereo- and enantioselective reaction to furnish β-hydroxy α-vinyl aldol adducts in a direct-type reaction manifold has remained elusive (Scheme 1). A pendant vinyl group on aldol adducts can leverage the flexible transformation to widen the opportunity for synthesis; therefore, the Evans-aldol method is extensively used in the synthesis of complex natural products.[6] The Mukaiyama-type aldol reaction, another arena of reliable aldol reactions using preformed silylated enolates as reactive aldol donors,[7],[8] generally exhibits vinylogous reactivity in which the C–C bond-forming event takes place at the γ-carbon to afford nonbranched products.[9] Herein we report our exploration of the direct aldol reaction of thioamides possessing an α-vinyl appendage, allowing for truly catalytic access to these useful chiral building blocks (Scheme 1b).[10] Unexpected difficulties arose from this vinyl group, which were addressed by a newly identified catalytic system.

A standard catalytic system comprising (*R*,*R*)-Ph-BPE/mesitylcopper/2,2,5,7,8-pentamethylchromanol **4a** was

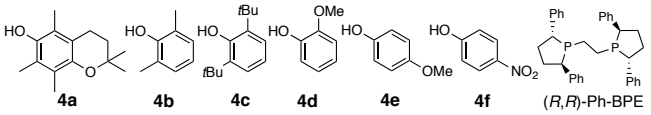


Scheme 1. Synthetic routes to access enantioenriched β-hydroxy-α-vinyl aldol adducts.

Table 1. Significant phenol effect on stereoselectivity of the aldol reactions of α-vinyl thioacetamide **2b**[a]



Entry	Thioamide 2		ArOH 4	x	pdt	Yield[b] (%)	*syn*/*anti*	ee	major enantiomer
1	Me	**2a**	**4a**	2	**3aa**	95	>20/1	98	2*R*,3*S*
2	vinyl	**2b**	**4a**	2	**3ab**	90	1.6/1	38	2*S*,3*R*
3	vinyl	**2b**	**4b**	2	**3ab**	89	1.7/1	24	2*S*,3*R*
4	vinyl	**2b**	**4c**	2	**3ab**	89	1.6/1	56	2*S*,3*R*
5	vinyl	**2b**	**4d**	2	**3ab**	88	2.5/1	18	2*R*,3*S*
6	vinyl	**2b**	**4e**	2	**3ab**	90	2.7/1	30	2*R*,3*S*
7	vinyl	**2b**	**4e**	4	**3ab**	90	4/1	70	2*R*,3*S*
8	vinyl	**2b**	**4e**	16	**3ab**	91	17/1	88	2*R*,3*S*
9	Me	**2a**	**4e**	16	**3aa**	trace	—	—	—
10	vinyl	**2b**	**4f**	16	**3ab**	0	—	—	—



[a] **1a**: 0.2 mmol, **2**: 0.24 mmol. [b] Determined by ^{1}H NMR analysis of the crude mixture using 3,4,5-trichloropyridine as an internal standard.

previously identified for *N*,*N*-diallylthiopropionamide **2a**,[11] promoting a direct aldol reaction with hydrocinnamaldehyde **1a** to afford the (2*R*,3*S*)-*syn* product **3aa** with high stereoselectivity (Table 1, entry 1). At the outset, α-vinyl thioacetamide **2b**, bearing the identical substituents on the nitrogen, was submitted to the identical conditions. Strikingly, this resulted in a substantially different reaction output (entries 1 vs 2); in contrast to the reasonable stereoselectivity observed for **2a**, **2b** exhibited significantly worse stereoselectivity and the antipodal (2*S*,3*R*)-*syn*-**3ab** was preferentially obtained. This stereochemical profile suggested that the retro-reaction or epimerization of the product was not likely involved. Indeed, product **3ab** was sufficiently stable under catalytic conditions,[12],[13] suggesting that the irregular stereochemistry of product **3ab** was kinetically

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determined. Given that amides generally prefer the formation of a *Z*-enolate irrespective of the α-substituents due to steric issues, this stereochemical anomaly likely originated from the distinct prochiral face-selection of the thioamide enolate and/or aldehyde **1a**. Electron-rich phenol derivative **4a** is best for the relatively high basicity of the conjugate base to ensure the efficient deprotonation of α-alkylthioamides.[14] α-Vinyl thioacetamide **2b** is likely more prone to deprotonation, leading us to screen several phenol derivatives instead of **4a**. Intriguingly, catalysts prepared with phenol derivatives with distinct structural and electronic features produced divergent reaction outcomes with a conceivable trend (entries 3–6). Generally, phenols bearing non-coordinative alkyl groups at the *ortho*-position favored the formation of irregular product (2*S*,3*R*)-*syn*-**3ab** as observed with **4a**, and enantioselectivity was proportional to the apparent steric bias of the phenols (in the order of 2,6-dimethylphenol **4b**, chromanol derivative **4a**, and 2,6-di-*tert*-butylphenol **4c** (entries 2–4)). On the other hand, guaiacol **4d**, having a coordinative MeO group at the *ortho* position, preferred the formation of normal (2*R*,3*S*)-*syn*-**3ab**, and this tendency became more obvious with the use of electronically similar, less sterically hindered isomeric *p*-MeO-substituted phenol **4e** (entries 5,6). This effect was significantly enhanced in an amount-dependent manner; both the *syn*-selectivity and fraction of normal (2*R*,3*S*)-*syn*-**3ab** were

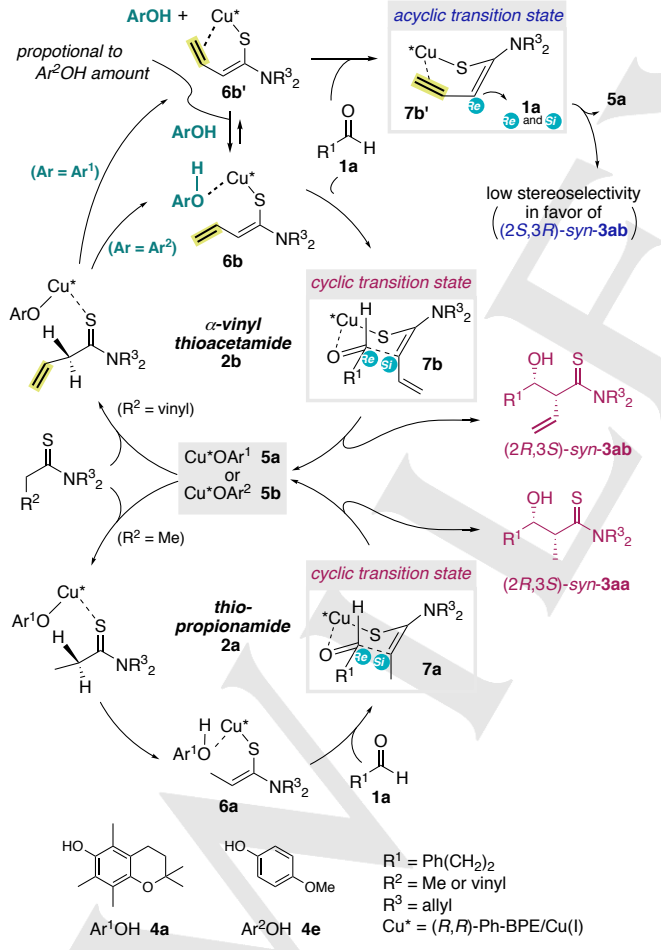

Figure 1. Plausible catalytic cycles for thiopropionamide **2a** and α-vinyl thioacetamide **2b**.

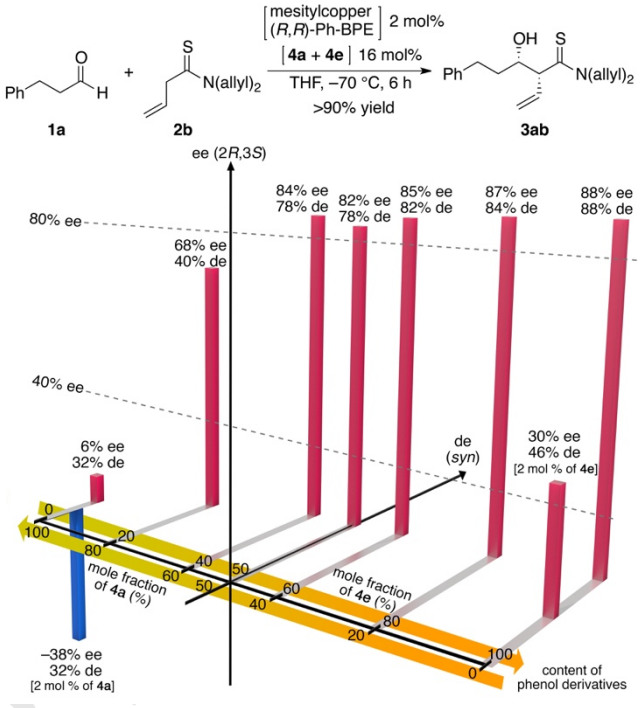

Figure 2. 3-axis diagram showing the reaction outcome using a mixture of phenols **4a** and **4e**.

proportionally improved as the amount of **4e** increased, resulting in a *syn*/*anti* ratio of 17/1 and 88% ee with the use of 16 mol% of **4e** (entries 6–8). This phenol study also revealed a delicate balance, as the basicity of the phenoxide derivatives was crucial for the deprotonation event. The optimized catalyst with **4e** failed the aldol reaction of thiopropionamide **2a**, presumably due to insufficient basicity of its conjugate base for the alkylthioamide (entry 9). In a similar manner, with the more acidic α-vinyl thioacetamide **2b**, the catalyst prepared from *p*-nitrophenol **4f** instead of **4e** did not promote the reaction due to insufficient basicity of the conjugate base.

Despite the noticeable effects of the phenol derivatives, it is unlikely that they are directly involved in the C–C bond forming event to perturb the stereochemical course. Based on the trend of stereoselectivity dictated by sterics and the amount of phenol derivatives, we reasoned that the flanking vinyl group of **2b** was responsible for the observed divergent stereoselectivity, as delineated in Figure 1. The catalyst components (*R*,*R*)-Ph-BPE/mesitylcopper/**4a** produced the resting state of the catalyst (*R*,*R*)-Ph-BPE/Cu(I)–OAr[1] **5a** with the liberation of mesitylene, which initiated the catalysis by deprotonating the thioamides. For thiopropionamide **2a**, *Z*-enolate **6a** was generated via coordination of **2a** to **5a**, which eventually formed a cyclic transition state with incoming aldehyde **1a** en route to the normal (2*R*,3*S*)-*syn* product. In contrast, the coordination of α-vinyl thioacetamide **2b** to **5a** presumably generated *Z*-enolate **6b'**, in which the juxtaposed vinyl group occupied the remaining coordination site of Cu(I). Coordinatively saturated **6b'** likely reacted with aldehyde **1a** via an acyclic transition state, producing irregular (2*S*,3*R*)-*syn*-**3ab** and other stereoisomers with inferior

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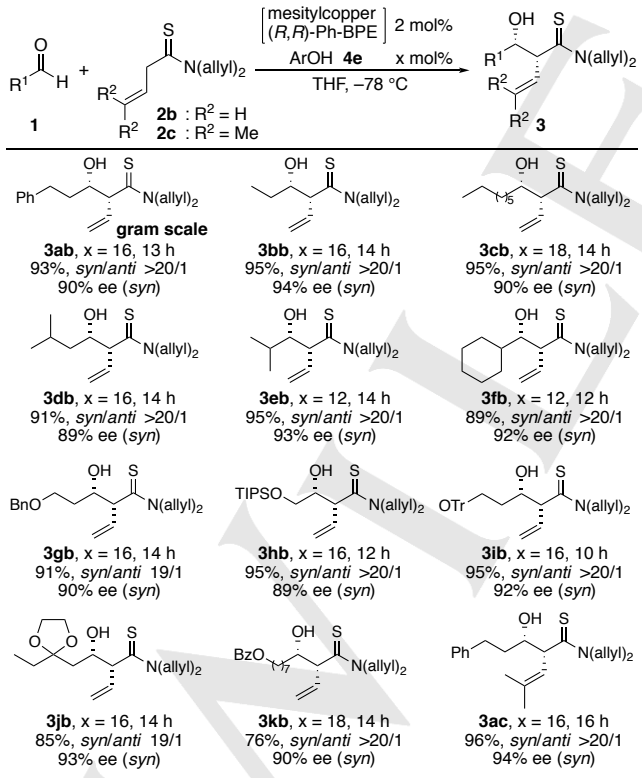
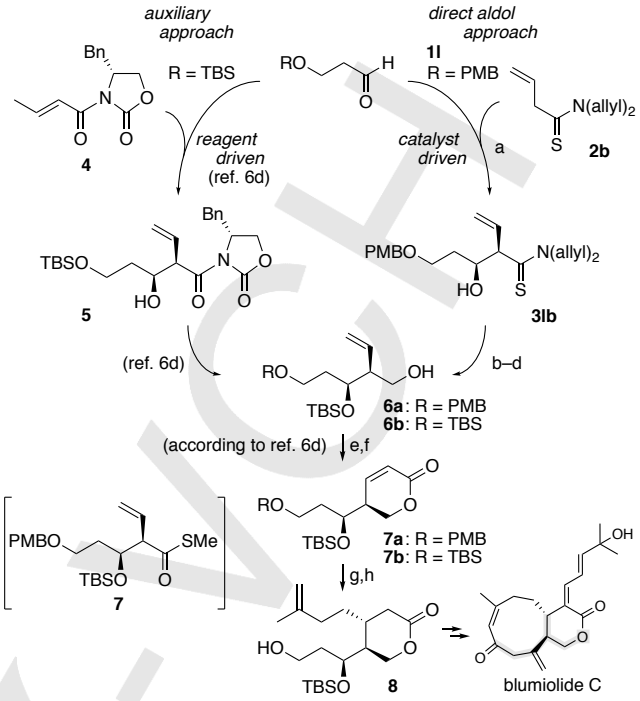
stereoselectivity. **6b'** could be in equilibrium with **6b** having a weakly coordinating phenol derivative as a spectator ligand like in **6a**, which would be more inclined to engage in the cyclic transition state to afford normal (2*R*,3*S*)-*syn*-**3ab** with high stereoselectivity. The observed trend that a more coordinative and larger amount of phenol derivative favored the formation of (2*R*,3*S*)-*syn*-**3ab** through the cyclic transition state is consistent with this assumption. This rationale was further supported by the reaction outcomes of a mixed-phenol system (Figure 2). Reaction of **2b** and **1a** was performed with 2 mol% each of mesitylcopper/(*R*,*R*)-Ph-BPE and 16 mol% of phenols comprising **4a** and **4e**. The mole fraction of **4a** and **4e** was varied, and the stereoselectivity observed in each reaction with the designated ratio of phenols is plotted in a 3-axis diagram (Figure 2). First, this plot explicitly shows that the presence of **4a** is not solely responsible for the irregular stereoselectivity, and the fraction of the normal product, (2*R*,3*S*)-*syn*-**3ab,** rapidly increased in response to the increasing fraction of **4e**. This is ascribed to the fact that the presence of a coordinative phenolic derivative was critically important to manifest the cyclic transition state as the more favorable and thereby faster pathway. Second, amount-dependency was also observed for **4a,** albeit with a much smaller magnitude, suggesting that these phenol effects were involved in a competitive pathway, such as coordination of the neighboring α-vinyl group and intermolecular approach of phenol derivatives.

Substrate generality was evaluated at a commonly used dry ice/acetone temperature (Scheme 2). High diastereoselectivity and enantioselectivity were obtained with 2 mol% catalyst,



Scheme 2. Substrate generality of the direct catalytic asymmetric aldol reaction of α-vinyl thioacetamide **2b** and **2c**. **1**: 0.6 mmol, **2**: 0.72 mmol. Isolated yield is reported.



Scheme 3. Synthesis of the key intermediate of blumiolide via direct aldol reaction of α-vinyl thioacetamide **2b**. (a) (*R*,*R*)-Ph-BPE/mesitylcopper (2 mol%), **4e** (16 mol%), THF, –78 °C, 10 h, 92%, *syn*/*anti* 19/1, 88% ee; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 1 h, 98%; (c) MeOTf, ether, rt, 70 min; then phosphate buffer, THF, –20 °C to rt, 2 h, 73%; (d) $LiBH_4$, MeOH/ether, rt, 4 h, 84%; (e) acryloyl chloride, Et_3N, DMAP, CH_2Cl_2, rt, 1 h, 95%; (f) Grubbs 2nd-Gen catalyst, CH_2Cl_2, reflux, 18 h, 97%; (g) CH_2=$CH(CH_3)CH_2CH_2MgI$, CuI, ether, –78 °C, 1 h, 89%; (h) DDQ, phosphate buffer/CH_2Cl_2 = 1/9, 0 °C, 1 h, 91%.

reaching completion with 12–18 mol% of *p*-methoxyphenol **4e**. Readily enolizable α-nonbranched aldehydes were accommodated without undesired self-condensation (**3ab**–**3db**), and gram-scale reactions proceeded uneventfully (**3ab**). In contrast to the rapid retro-reaction in the direct aldol reaction of thiopropionamides **2a**,[12] the aldol products of α-vinyl thioacetamides **2b** were sufficiently stable and the retro-aldol reaction was barely observed even when using α-branched aldehydes (**3eb**,**3fb**) in the reaction. An aldehyde with a coordinative Bn ether functionality was compatible and the desired product was obtained with high stereoselectivity (**3gb**). Acid-sensitive functionalities, e.g. a silyl ether, a trityl group, and a ketal, as well as a base-sensitive benzoyl ester group, were tolerated (**3hb**–**3kb**). Similar reactivity and selectivity profiles were observed when using thioamide **2c** bearing two methyl groups at the vinyl terminus, affording an enantioenriched aldol product embedded with a prenyl fragment (**3ac**).

The aldol product decorated with the α-vinyl group is highly advantageous for the synthesis of biologically active natural products, as exemplified in Scheme 3. Blumiolide C is a diterpenoid isolated from soft coral *Xenia blumi*, and characterized by its potent antiproliferative activity.[15] The first total synthesis of blumiolide C was achieved by Altmann et al. with the strategic use of the Evans-aldol method to afford enantioenriched *syn*-β-hydroxy α-vinyl carboxylic acid derivative **5**, leading to a key intermediate **6b**.[6d] With the highly *syn*-

selective and enantioselective direct aldol reaction of α-vinyl thioacetamide in hand, we devised a catalytic alternative to access **6** using the aldol adduct **3lb** obtained from the present catalysis using corresponding aldehyde **1l** and **2b**. After protection of the secondary hydroxyl group as a TBS ether, *S*-methylation by MeOTf followed by hydrolysis with phosphate buffer gave thioester **7**, which was subjected to reduction with $LiBH_4$ to furnish primary alcohol **6a**. According to the original synthesis of blumiolide C,[6d] the **6a** was converted to the corresponding acrylate that engaged in ring-closing metathesis using Grubbs 2nd-Gen catalyst to give unsaturated lactone **7a**.[16] Conjugate addition of the requisite C5 unit followed by removal of the PMB group furnished reported intermediate **8**, whose spectroscopic data were in full accordance to those reported.

In summary, α-vinylated aldol donors were incorporated into a direct aldol arsenal using thioamide chemistry. Enantioenriched *syn*-β-hydroxy α-vinyl carboxylic acid derivatives are accessible in a truly catalytic fashion. Further exploration of the synthetic utility of the present catalysis is ongoing.

Acknowledgements

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Keywords: aldol reaction • asymmetric catalysis • thioamide • cooperative catalysis • formal synthesis

[1] a) R. Mahrwald, *Modern Aldol Reactions*, Wiley-VCH, Weinheim, **2004**; b) R. Mahrwald, Wiley-VCH,, Weinheim, **2013**.

[2] a) D. A. Evans, E. Vogel, J. V. Nelson, *J. Am. Chem. Soc.* **1979**, *101*, 6120; b) D. A. Evans, J. Bartroli, T. L. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 2127.

[3] D. A. Evans, *Aldrichmica Acta* **1982**, *15*, 23.

[4] a) *S. M. Yliniemelå-Sipari and P. M. Pihko, in Science of Synthesis: Stereoselective Synthesis, ed. G. A. Molander, Thieme, Stuttgart, 2010, vol. 2, pp. 621–676*; b) B. Alcaide, P. Almendros, *Eur. J. Org. Chem.* **2002**, 1595; c) W. Notz, F. Tanaka, I. Carlos F. Barbas, *Acc. Chem. Res.* **2004**, *37*, 580; d) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471; e) B. M. Trost, C. S. Brindle, *Chem. Soc. Rev.* **2010**, *39*, 1600.

[5] a) Y. M. A. Yamada, N. Yoshikawa, H. Sasai, M. Shibasaki, *Angew. Chem.* **1997**, *109*, 1942; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871; b) N. Yoshikawa, Y. M. A. Yamada, J. Das, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 4168; c) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395; d) B. M. Trost, H. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 12003.

[6] a) W. R. Roush, D. S. Coffey, D. J. Madar, *J. Am. Chem. Soc.* **1997**, *119*, 11331; b) G. K. Packard, Y. Hu, A. Vescovi, S. D. Rychnovsky, *Angew. Chem.* **2004**, *116*, 2882; *Angew. Chem. Int. Ed.* **2004**, *43*, 2822; c) J. R. Dunetz, L. D. Julian, J. S. Newcom, W. R. Roush, *J. Am. Chem. Soc.* **2008**, *130*, 16407; d) C. Hamel, E. V. Prusov, J. Gertsch, W. B. Schweizer, K. H. Altmann, *Angew. Chem.* **2008**, *120*, 10235; *Angew. Chem. Int. Ed.* **2008**, *47*, 10081; e) C. L. Pereira, Y.-H. Chen, F. E. McDonald, *J. Am. Chem. Soc.* **2009**, *131*, 6066.

[7] T. Mukaiyama, K. Narasaka, K. Banno, *Chem. Lett.* **1973**, 1011.

[8] a) G. L. Beutner, S. E. Denmark, *Angew. Chem.* **2013**, *125*, 9256; *Angew. Chem. Int. Ed.* **2013**, *52*, 9086; b) S. B. Kan, K. K. Ng, I. Paterson, *Angew. Chem.* **2013**, *125*, 9267; *Angew. Chem. Int. Ed.* **2013**, *52*, 9097; c) J. Matsuo, M. Murakami, *Angew. Chem.* **2013**, *125*, 9280; *Angew. Chem. Int. Ed.* **2013**, *52*, 9109.

[9] a) S. E. Denmark, J. R. Heemstra, Jr., G. L. Beutner, *Angew. Chem.* **2005**, *117*, 4760; *Angew. Chem. Int. Ed.* **2005**, *44*, 4682; b) S. E. Denmark, J. John R. Heemstra, *J. Org. Chem.* **2007**, *72*, 5668.

[10] For a direct catalytic asymmetric aldol methodology using β,γ-unsaturated esters to give β-hydroxy α-vinylidene esters after isomerization, see: A. Yamaguchi, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 10842.

[11] a) M. Iwata, R. Yazaki, Y. Suzuki, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 18244; b) M. Iwata, R. Yazaki, I. H. Chen, D. Sureshkumar, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2011**, *133*, 5554.

[12] Y. Bao, N. Kumagai, M. Shibasaki, *Chem. Sci.* **2015**, *6*, 6124.

[13] Retro test

[14] Calculated pK_a of **4a** is 12.3. See 11a for details.

[15] A. A. El-Gamal, C. Y. Chiang, S. H. Huang, S. K. Wang, C. Y. Duh, *J. Nat. Prod.* **2005**, *68*, 1336.

[16] a) K.C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4564; *Angew. Chem. Int. Ed.* **2005**, *44*, 4490; b) G. C. Vougioukalakis, R. H. Grubbs, *Chem. Rev.* **2010**, *110*, 1746.

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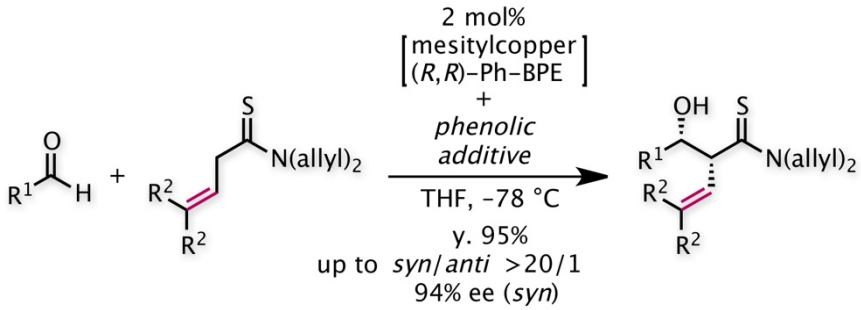

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