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# Organocatalytic Enantioselective Vinylogous Aldol Reaction of Allyl Aryl Ketones to Activated Acyclic Ketones

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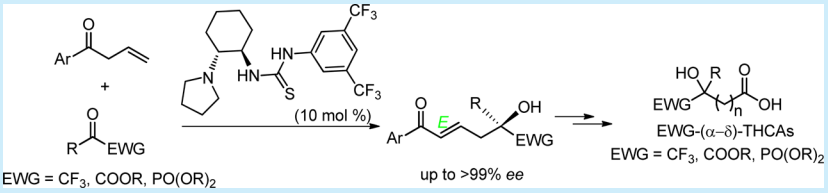
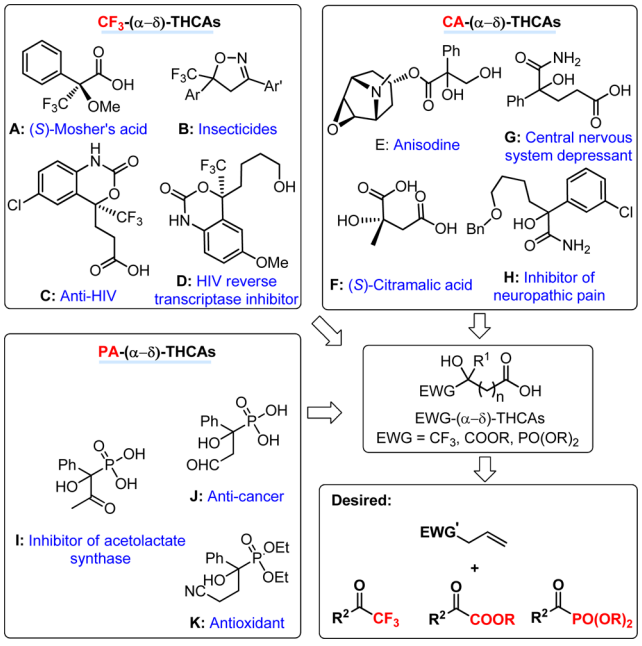
Supporting Information




**ABSTRACT:** The first catalytic asymmetric vinylogous aldol reaction of activated allyls to activated acyclic ketones is disclosed. A variety of activated acyclic ketones, such as trifluoromethyl ketones, $\alpha$-ketoesters, and $\alpha$-keto phosphonates, were found to be involved forming diverse $\gamma$-selective aldol adducts with high enantioselectivities (up to >99% ee). The method provides an effective, general strategy to access valuable chiral electron-withdrawing group-substituted tertiary hydroxyl-based carboxylic acids.

Chiral electron-withdrawing-group-functionalized tertiary hydroxy-based carboxylic acids (EWG-THCAs) constitute a wide range of key structural motifs in molecules with important biological activities (Scheme 1). Over 2800 compounds with potential bioactivities feature $CF_3$-$\alpha$-THCA as the structural unit,[1,2] especially Mosher's acid[1a,2] **A**, which is widely used in asymmetric synthesis. The trifluoromethyl-substituted 2-isoxazolines (**B**) as $CF_3$-$\beta$-THCAs[3] found in almost 27000 molecules have synthetic applications in veterinary medicine and agrochemicals. Notably, $CF_3$-$\gamma$-THCAs (e.g., molecule **C**) and $CF_3$-$\delta$-THCAs (e.g., molecule **D**) often exhibit anti-HIV activities.[4] THCAs featuring other electron-withdrawing groups, such as carboxylic acid derivatives (CA-THCAs, e.g., molecules **E**–**H**) and phosphonates (PA-THCAs, e.g., molecules **I**–**K**), on the $\alpha$–$\delta$ positions of carboxylic acids are also important frameworks of many bioactive compounds.[5] Despite the existence of key catalytic asymmetric strategies to diverse enantiomerically enriched EWG-THCAs,[6−8] a divergent strategy to simultaneously furnish chiral $CF_3$-($\alpha$–$\delta$)-THCAs, CA-($\alpha$–$\delta$)-THCAs, and PA-($\alpha$–$\delta$)-THCAs is lacking. It is thus highly desirable to devise a practical and efficient method to realize this important task.

**Scheme 1. Representative Bioactive Compounds**




In recent years, asymmetric vinylogous aldol (AVA) reaction has been demonstrated to be expedient in generating multifunctional chiral alcohols with an easily modified unsaturated long carbon skeleton, thereby allowing structurally complex chiral molecules with divergent synthetic targets.[9] Retrosynthetic analyses (Scheme 1) of a general AVA reaction of activated allyls to activated acyclic ketones, including trifluoromethyl ketones, $\gamma$-ketoesters, and $\alpha$-keto phosphonates, reveal the possibility of achieving the divergent synthesis of these desired chiral EWG-($\alpha$–$\delta$)-THCAs.

In 2009, Shibasaki and co-workers described a highly enantio- and $\gamma$-selective aldol reaction of allyl cyanide to simple acyclic ketones, to pioneer the work of activated allyls in the

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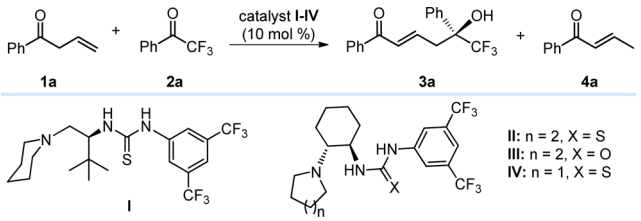
asymmetric vinylogous reaction.[10] Reports of vinylogous reactions involving activated allyls as nucleophiles have been described since then.[11] Nonetheless, the AVA reaction of activated allyls to activated acyclic ketones is still unmet, and two formidable challenges remain. The first is $\gamma$-selectivity. Lower electron density on the $\gamma$ position of activated allyl-generating dienolates than the $\alpha$ position often leads to the poor $\gamma$-selectivity.[12] For example, asymmetric allylic alkylation of Morita–Baylis–Hillman carbonates with allyl ketones is highly $\alpha$-selective.[12c] For more sterically hindered cyclic ketimines, good $\alpha$-selectivity is found in the asymmetric Mannich reaction of allyl ketones.[12d] To discriminate the reactive enolate site, shielding the $\alpha$ position by introducing a bulky modifier at the $\alpha$-position[13] or using an additional catalyst[14c] is necessary.

Another issue is enantioselectivity and universality. No example to date has been reported of an asymmetric vinylogous reaction of activated allyls to trifluoromethyl ketones and $\alpha$-keto phosphonates, and only modest enantioselectivity was obtained for the asymmetric reaction of allyl cyanide with $\alpha$-ketoesters.[10] Universality-wise, no asymmetric protocol has been able to be effectively performed on trifluoromethyl ketones, $\alpha$-ketoesters, and $\alpha$-keto phosphonates electrophiles. Herein, we report the first catalytic asymmetric VA reaction of activated allyls to activated acyclic ketones. The strategy is general in that it is applicable to diverse activated acyclic ketones, including trifluoromethyl ketones, $\alpha$-ketoesters, and $\alpha$-keto phosphonates, thus furnishing the desired divergent synthesis of chiral EWG-($\alpha$–$\delta$)-THCAs.

Allyl ketones[11b,12c,d,14] are easily prepared and most commonly used as activated allyls for asymmetric direct vinylogous reactions.[14] To probe the feasibility of the desired reaction on its reactivity, regioselectivity, and stereoselectivity, our study was thus initiated with the model reaction between allyl phenyl ketone **1a** and trifluoromethyl acetophenone **2a**. The reaction was first performed in toluene at 25 °C, using 10 mol % of L-leucine-derived tertiary amine–thiourea **I** as the catalyst[15] (Table 1, entry 1). It was observed that most of **1a** was transformed to the $\alpha,\beta$-alkene **4a** via proton transfer, and the desired AVA adduct **3a** was obtained in only 12% yield. Although the reactivity was poor, moderate enantioselectivity and excellent *E*-selectivity were observed, indicating the effectiveness of the bifunctional catalyst. Takemoto's chiral 1,2-cyclohexanediamine-based tertiary amine–thiourea **II**[16] was then examined, providing **3a** in 17% yield with 91% ee and modest *E*-selectivity (entry 2). We replaced the thiourea of **II** by the urea, but the corresponding catalyst **III** promoted **1a** to completely generate **4a** (entry 3). Next, the reaction was performed in different solvents using 10 mol % of **II** as the catalyst (entries 4–7). The results revealed that *tert*-butylbenzene was the most suitable solvent, affording **3a** in 28% yield with 92% ee and an 8:1 *E*/*Z* ratio (entry 7). A variation of the reaction temperature showed that the *E*/*Z* ratio of **3a** could be raised to >20:1 at a lower temperature (entries 8–10) and −10 °C was optimal (entry 9). When the amount of **1a** was increased to 3.0 equiv, 65% yield of **3a** was achieved (entry 11). The adduct **3a** could be obtained in 87% yield and 94% ee by utilizing catalyst **IV**,[16c] an analogue of catalyst **II** with a pyrrolidine as the tertiary amine moiety (entry 12). The basic $Na_3PO_4$ additive was found to further positively influence both yield and enantioselectivity (entry 13).

With the optimal reaction conditions in hand, we investigated direct AVA reaction of distinct allyl aryl ketones

**Table 1. Optimization of the Reaction Conditions**[a]

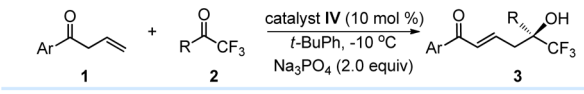



| entry | catalyst | solvent | temp (°C) | $t$ (h) | yield (%)[b] | ee (%)[c] | $E/Z$[d] |
|---|---|---|---|---|---|---|---|
| 1 | **I** | toluene | 25 | 45 | 12 | 77 | >20:1 |
| 2 | **II** | toluene | 25 | 45 | 17 | 91 | 4:1 |
| 3 | **III** | toluene | 25 | 45 | trace | N.A. | N.A. |
| 4 | **II** | THF | 25 | 45 | N.R. | N.A. | N.A. |
| 5 | **II** | DCM | 25 | 45 | 10 | 80 | 3:1 |
| 6 | **II** | $Et_2O$ | 25 | 45 | 14 | 88 | >20:1 |
| 7 | **II** | *t*-BuPh | 25 | 45 | 28 | 92 | 8:1 |
| 8 | **II** | *t*-BuPh | 0 | 45 | 43 | 95 | >20:1 |
| 9 | **II** | *t*-BuPh | −10 | 45 | 42 | 96 | >20:1 |
| 10 | **II** | *t*-BuPh | −20 | 45 | 44 | 96 | >20:1 |
| 11[e] | **II** | *t*-BuPh | −10 | 62 | 65 | 96 | >20:1 |
| 12[e] | **IV** | *t*-BuPh | −10 | 38 | 87 | 94 | >20:1 |
| 13[e,f] | **IV** | *t*-BuPh | −10 | 38 | 91 | 95 | >20:1 |

[a]Reaction conditions: **1a** (0.075 mmol), **2a** (0.05 mmol), catalyst (0.005 mmol), 0.5 mL of solvent. [b]Yield of isolated product. [c]Determined by HPLC analysis on a chiral stationary phase. [d]Determined by crude $^1H$ NMR spectra. [e]**1a**:**2a** = 3:1. [f]2.0 equiv of $Na_3PO_4$ were used as an additive.

**1** to various trifluoromethyl ketones **2** (Scheme 2). The reactions were often complete within 24–72 h, providing

**Scheme 2. Direct AVA Reaction between 1 and 2**[a]




**3a:** R = Ph, 30 h, 93% yield, 95% ee[b]
**3b:** R = 4-$CF_3$Ph, 40 h, 90% yield, 92% ee
**3c:** R = 4-FPh, 39 h, 89% yield, 95% ee
**3d:** R = 4-ClPh, 39 h, 94% yield, 95% ee
**3e:** R = 4-BrPh, 34 h, 90% yield, 94% ee
**3f:** R = 3-FPh, 64 h, 89% yield, 91% ee
**3g:** R = 3-ClPh, 47 h, 94% yield, 90% ee
**3h:** R = 2-FPh, 40 h, 73% yield, 98% ee[c]
**3i:** R = 4-MePh, 46 h, 75% yield, 94% ee
**3j:** R = 3-MePh, 60 h, 76% yield, 94% ee
**3k:** R = 2-naphtyl, 61 h, 81% yield, 94% ee
**3l:** R = 2-thienyl, 48 h, 93% yield, 92% ee
**3m:** R = Et, 61 h, 72% yield, 93% ee

**3n:** Ar = 4-FPh, 45 h, 93% yield, 94% ee
**3o:** Ar = 4-ClPh, 60 h, 92% yield, 94% ee
**3p:** Ar = 3-FPh, 44 h, 94% yield, 95% ee
**3q:** Ar = 3-ClPh, 60 h, 93% yield, 94% ee
**3r:** Ar = 2-FPh, 72 h, 87% yield, 83% ee
**3s:** Ar = 4-MePh, 36 h, 82% yield, 94% ee
**3t:** Ar = 3-MePh, 46 h, 80% yield, 93% ee
**3u:** Ar = 4-MeOPh, 36 h, 89% yield, 94% ee
**3v:** Ar = 3-MeOPh, 45 h, 91% yield, 94% ee
**3w:** Ar = 2-MeOPh, 44 h, 60% yield, 70% ee
**3x:** Ar = 2-naphtyl, 24 h, 97% yield, 94% ee
**3y:** Ar = 2-thienyl, 61 h, 98% yield, 99% ee

[a]Reaction conditions: **1** (0.3 mmol), **2** (0.1 mmol), catalyst (0.01 mmol), $Na_3PO_4$ (0.2 mmol), 1.0 mL of *t*BuPh. [b]After a single recrystallization, ee > 99%. [c]The ee value and yield were obtained after a single recrystallization. Initial data: 80% yield, 85% ee.

adducts **3a–y** with yields of 60–98%, enantioselectivites of 70–99% ee, and *E*/*Z* ratios of more than 20:1. It should be noted that allyl ketones **1** with the ortho-substituents on phenyl rings (**3r** and **3w**) gave depressed enantiomeric excesses, whereas allyl 2-thienyl ketone gave **3y** with excellent enantioselectivity.



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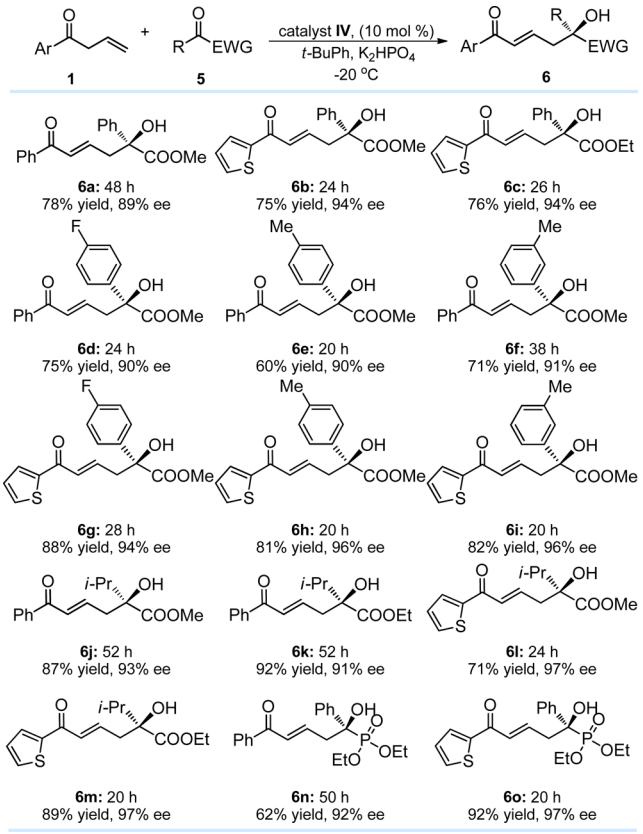
We then selected two classes of acylic activated ketones **5**, i.e. $\alpha$-ketoesters and $\alpha$-ketophosphonates for further examination (Scheme 3). Under slightly modified reaction conditions (10 mol % of catalyst **IV**, 2.0 equiv of $K_2HPO_4$, −20 °C), a range of $\alpha$-ketoesters were first explored, including aromatic substrates with diverse substitution patterns and methyl/ethyl $\alpha$-ketoisovalerate as the representative of aliphatic substrates. The corresponding AVA adducts (**6a**−**m**) were obtained in 60−92% yields with 89−97% ee and >20:1 *E*-selectivity within 20−52 h. The different ester groups of $\alpha$-ketoesters resulted in similar reactivity and enantioselectivity. $\alpha$-Ketophosphonate also proved to be a viable substrate, giving $\alpha$-hydroxyphosphonates **6n**−**o** in excellent enantioselectivity.

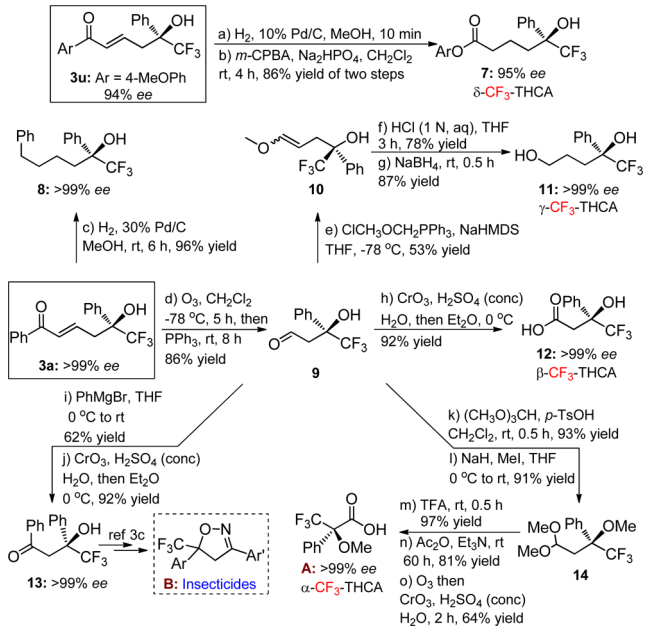
**Scheme 3. Direct AVA Reaction of 1 to 5**[a]




[a]Reaction conditions: **1** (0.3 mmol), **5** (0.1 mmol), catalyst **IV** (0.01 mmol), $K_2HPO_4$ (0.2 mmol), 0.8 mL *t*-BuPh, −20 °C.

To demonstrate the synthetic value of this work, a series of transformations from vinylogous aldol adducts were then performed (Scheme 4). The $\delta$-$CF_3$-THCA derivative **7** was obtained in 86% yield with 95% ee from the reduction of **3u** with $H_2$ on Pd/C, followed by a Baeyer−Villiger rearrangement (BVR) with *m*-CPBA. Reduction of adduct **3a** with $H_2$ on Pd/C for 6 h afforded $CF_3$-based tertiary alcohol **8** featuring a long carbon chain and without compromising the ee value. After ozonolysis, **3a** could be conveniently converted to aldehyde **9**, which herein is demonstrated as a common intermediate to access ($\alpha$−$\gamma$)-$CF_3$-THCAs (Scheme 1). First, through a sequence of Wittig reaction, hydrolysis, and reduction, alcohol **11** as the $\gamma$-$CF_3$-THCA derivative was attainable with >99% ee. Jones oxidation of **9** presented $\beta$-$CF_3$-THCA **12** in 92% yield. By treatment of PhMgBr and then Jones reagents ($CrO_3$, $H_2SO_4$, and $H_2O$), ketone **13** as the precursor of insecticides **B**[3c] was obtained with >99% ee. Since the aldehyde group of **9** inhibited the methylation of the tertiary alcohol, an acetal protecting method by using trimethyl orthoformate was attempted. Unsurprisingly, yields of both protection and the corresponding deprotection by TFA were excellent. Following an efficient acetylation of aldehyde and ozonization, (*R*)-Mosher's acid **A** was obtained with >99% ee. Clearly, these strategies could be readily employed to address the divergent synthesis of chiral CA-($\alpha$−$\delta$)-THCAs and PA-($\alpha$−$\delta$)-THCAs.

**Scheme 4. Synthesis of ($\alpha$−$\delta$)-$CF_3$-THCAs**




In summary, we have developed the first catalytic asymmetric AVA reaction of activated allyls to activated acyclic ketones. A series of activated acyclic ketones, such as trifluoromethyl ketones, $\gamma$-ketoesters, and $\alpha$-keto phosphonates, were suitable in the established strategy, thus generating diverse $\gamma$-selective aldol adducts with high enantioselectivities (up to >99% ee). The reported synthetic method provides an expedient approach to various biologically important chiral EWG-substituted tertiary hydroxy-based $\alpha$-, $\beta$-, $\gamma$-, and $\delta$-carboxylic acids through divergent synthesis with excellent results. Further investigations into the employment of activated allyls in unprecedented AVA reactions, and the resulting divergent synthesis of significant bioactive molecules, are ongoing and will be reported in due course.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03412.

General information, general experimental procedures, procedures of divergent synthesis of THCAs, characterization of adducts including HPLC and NMR spectra of the compounds (PDF)

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## Author Contributions

†Z.J. and X.B. contributed equally to this work.

## Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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