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# N-Heterocyclic Carbene/Lewis Acid Catalyzed Enantioselective Aerobic Annulation of α,β-Unsaturated Aldehydes with 1,3-Dicarbonyl Compounds

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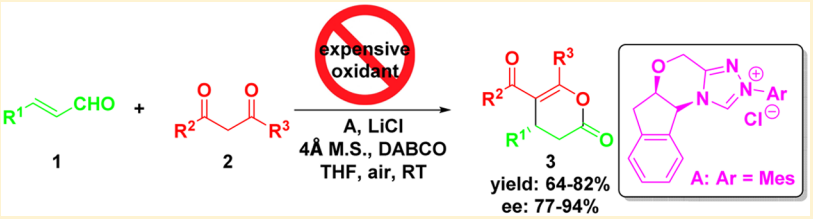
Supporting Information

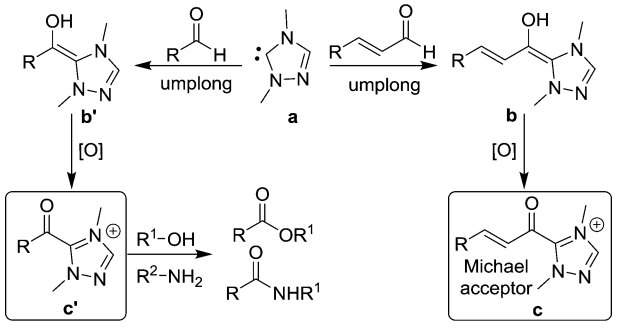



**ABSTRACT:** A novel and efficient aerobic asymmetric cyclization reaction of cinnamaldehydes and 1,3-dicarbonyl compounds through oxidative NHC-catalysis has been developed, and it allows the synthesis of a wide range of enantiomeric enriched dihydropyranone derivatives in good yields with good to excellent enantioselectivities. Various α,β-unsaturated aldehydes with aliphatic and aromatic substitution groups and 1,3-dicarbonyl compounds were well tolerated. The air was directly used as the oxidant, which made this asymmetric cyclization reaction in a highly efficient, cheap, and green manner.

Over the past two decades, N-heterocyclic carbene (NHC) catalysis has emerged as a powerful and useful methodology in organic synthesis by providing an assortment of new scaffolds as well as enantiomerically enriched compounds.[1] In this synthetic strategy, aldehydes and their derivatives are activated by NHCs (**a**) through the formation of acyl anion equivalent (**b** and **b′**, so-called Breslow intermediate[2]), which can react as enolate or homoenolate with various electrophiles to undergo the nucleophilic addition process (Scheme 1). With this unique chemistry termed umpolung, dozens of reactivity manifolds have been developed across a range of reaction subtypes for the formation of C−C, C−N, and C−O bonds and corresponding compounds with significant importance.

While the activation modes of NHC catalysis have been well established, chemists realized that the Breslow intermediate could be readily oxidized by mild inorganic and organic oxidants to acylazolium ion species **c** and **c′**, which could undergo subsequent esterification reaction through O acylation with different O nucleophiles.[3] Moreover, the oxidative generated α,β-unsaturated acylazolium intermediate **c**, could serve as a unique and efficient Michael acceptor, which has been succefully employed in the 1,4-addition by reacting with soft carbon nucleophiles. In this strategy the intermediate **c** is typically generated from the nucleophilic addition of NHC with α,β-unsaturated acyl fluoride,[4] esters,[5] acids,[6] or anhydrides,[7] the internal redox reaction generated ynals,[8] or enals in the presence of the high cost 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone[9] (DPQ, $125/50 mg) as external oxidant, which greatly limited the large scale synthesis.

**Scheme 1. Activation of Carbonyl Compounds Through Enolate/Homoenolate and Oxidative Acylazolium Salt Intermediates in NHC Catalysis**




The incorporation of atmosphere molecular oxygen ($O_2$) into an organic oxidation reaction offers one of the most ideal processes in organic synthesis.[10] The activation of $O_2$ by NHC catalysts was succeeded by several research groups in NHC-catalyzed oxidation of aldehydes, the corresponding carboxylic acids[11] and esters[12] could be obtained in moderate to good yields. In these approaches, the Breslow intermediates generated from aldehydes and NHC catalyst could be oxidized to acylazolium ions by $O_2$, which can undergo the next *O*-acylation reactions. We therefore envisioned that this chemistry could be more attractive if $O_2$ could be directly used as oxidant in NHC-catalyzed enantioselective reactions. However, to the best of our knowledge, there is no successful example concerning an NHC-catalyzed asymmetric reaction with $O_2$

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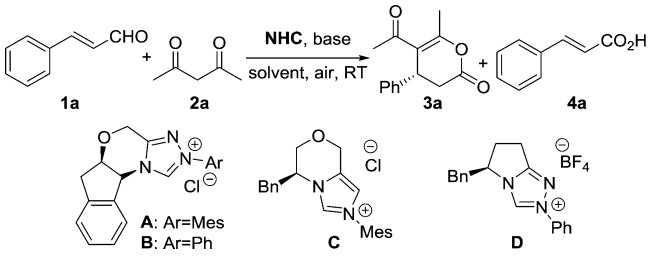
as oxidant. Given the fact that, 3,4-dihydro-$\alpha$-pyranones are important intermediates for the construction of pyridones, $\gamma$-lactones, benzenoid derivatives, etc.,[13] some successful examples in the synthesis of 3,4-dihydro-$\alpha$-pyranones were reported by several groups.[14] To make the synthesis of this kind of compound in a more efficient and green manner, we decided to contribute a catalytically asymmetric synthesis of 3,4-dihydro-$\alpha$-pyranones through a chiral NHC-catalyzed reaction of cinnamaldehyde with 1,3-dicarbonyl compounds by using air as the oxidant.

As a starting point, we examined the reaction of cinnamaldehyde (**1a**, 2.0 equiv) with acetylacetone (**2a**, 1.0 equiv) in the presence of NHC catalyst **A** (20 mol%) and DABCO (1.5 equiv) in THF under air without any external oxidant. To our delight, the reaction proceeded well and the desired dihydropyranone **3a** was obtained with 80% yield and 60% ee, the cinnamic acid **4a** was found to be the side product. Next, we started to optimize the reaction conditions. It was reported that Lewis acids can be good cooperative catalysts in NHC catalysis due to the complexation of the O atom of the acylazolium ion with the metal cation, which should lower the LUMO and hence activate the Michael acceptor.[15] Therefore, a series of Lewis acids were tested in this reaction, and LiCl was found to be the best, the ee value of **3a** could be improved to 87%. (Table 1, entries 2, 9−11; LiBr, $Mg(OTf)_2$, $MgI_2$ et al. see the Supporting Information) A slight increase of the ee value was achieved when molecular sieves (M.S.) were used, and 4 Å M.S. exhibited most superiority (**3a**: 82% yield and 94% ee) (Table 1, entries 3−5). Catalyst **A** remains the best catalyst among several catalysts that were studied under this condition (Table 1, entries 5−8). After further screening of bases and solvents in the reaction (Table 1, entries 12−16), the best results could be achieved in the presence of catalyst **A** (20 mmol%), LiCl (1.0 equiv), and 4 Å M.S. (20 mg) in THF under air at rt.

**Table 1. Reaction Condition Optimization**[a]

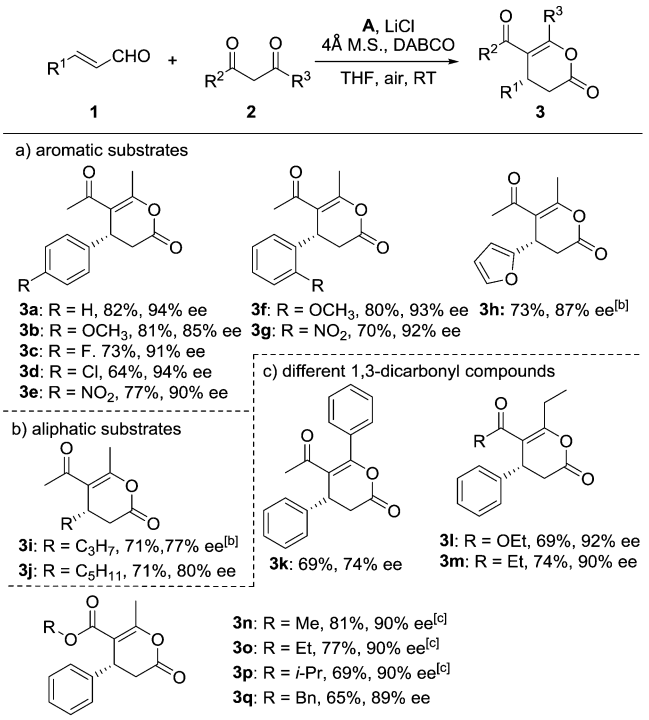



| entry | NHC | base | solvent | additives | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 | **A** | DABCO | THF | | 80 | 60 |
| 2 | **A** | DABCO | THF | LiCl[d] | 79 | 87 |
| 3 | **A** | DABCO | THF | LiCl[e] | 80 | 89 |
| 4 | **A** | DABCO | THF | LiCl[f] | 82 | 94 |
| 5 | **A** | DABCO | THF | LiCl[g] | 81 | 91 |
| 6 | **B** | DABCO | THF | LiCl[f] | 65 | 77 |
| 7 | **C** | DABCO | THF | LiCl[f] | 75 | 85 |
| 8 | **D** | DABCO | THF | LiCl[f] | 82 | 62 |
| 9 | **A** | DABCO | THF | LiOTf | 70 | 80 |
| 10 | **A** | DABCO | THF | $LiBF_3$ | 78 | 85 |
| 11 | **A** | DABCO | THF | $Sc(OTf)_3$ | N.R. | |
| 12 | **A** | $K_2CO_3$ | THF | LiCl[f] | 65 | 83 |
| 13 | **A** | $Cs_2CO_3$ | THF | LiCl[f] | 78 | 89 |
| 14 | **A** | DMAP | THF | LiCl[f] | 65 | 89 |
| 15 | **A** | DABCO | Tol | LiCl[f] | 80 | 92 |
| 16 | **A** | DABCO | DCM | LiCl[f] | 27 | 91 |

[a]General conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), **A** (0.02 mmol), solvent (1 mL), 14 h. [b]Yields of isolated products based on **2a**. [c]Enantiomeric excess of **3a**, determined by HPLC on a chiral stationary phase; absolute configuration of the major enantiomer was assigned based on optical rotation of **3a** (see the Supporting Information). [d]0.1 mmol LiCl. [e]LiCl (0.1 mmol) and 3 Å M.S. powder (20 mg). [f]LiCl (0.1 mmol) and 4 Å M.S. powder (20 mg). [g]LiCl (0.1 mmol) and 5 Å M.S. powder (20 mg).

With the optimal reaction conditions in hand, we started to explore the substrate scope through the variation of enals. A range of enals were examined and found to react well with acetylacetone in this study (Table 2, products **3a−j**). The ones

**Table 2. Exploration of Substrate Scope**[a]




[a]General conditions: **1** (0.2 mmol), **2** (0.1 mmol), **A** (0.02 mmol), LiCl (1.0 equiv) and 4 Å M.S. in THF (1 mL) under air at room temperature, 14 h; yields of isolated products based on **2**; enantiomeric excess of **3** were determined by HPLC on a chiral stationary phase. [b]3.0 equiv of aldehyde was used. [c]5.0 equiv of aldehyde was used.

that bear electron-withdrawing and electron-donating groups on the *para*- and *ortho*- positions can provide the corresponding dihydropyraones (**3b−3g**) in good yields (64−81%) and with good to excellent enantioselectivities (85−94% ee). When the (*E*)-3-(furan-2-yl)acrylaldehyde was used, the product **3h** was afforded in 73% yield and with slightly lower enantioselectivity (87% ee). Surprisingly, the $\beta$-alkyl substituted aldehydes in this aerobic annulation reaction also worked well with good yields and relatively lower ee values (**3i**: 71% yield and 77% ee; **3j**: 71% yield and 80% ee), which were usually difficult to succeed in this kind of NHC-catalyzed oxidative asymmetric reaction.

Further investigation of different 1,3-dicarbonyls were also conducted, the heptane-3,5-dione could offer the product **3m** in high yield (74%) and ee (90%); unfortunately, the 1-phenylbutane-1,3-dione only gave **3k** in 69% ee, probably due to the steric reason. We found that $\beta$-keto esters are also good



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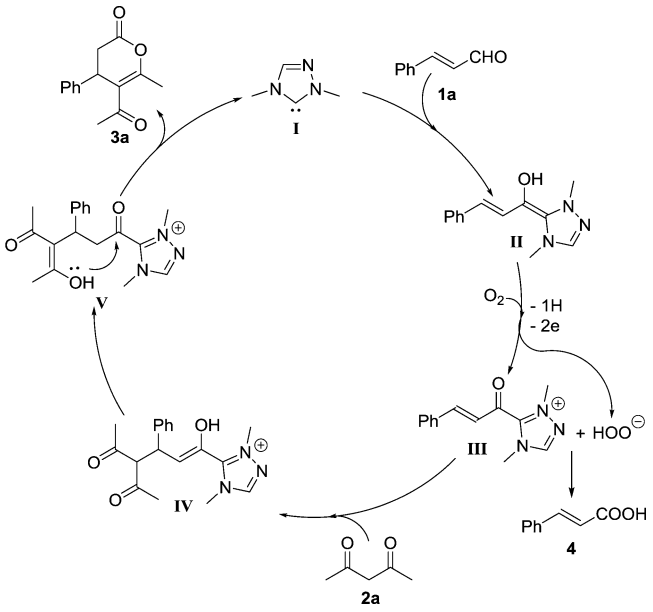
nucleophiles for this NHC-catalyzed aerobic oxidative annulation reaction (**3l** and **3n−q**). All $\beta$-keto esters used can offer the desired products in good yields (65−81%) and excellent enantioselectivities (89−92%); however, a noticeable steric effect of the ester groups on these substrates was not observed in this reaction.

The suggested catalytic cycle is depicted below (Scheme 2). First, the enaminol **II** could be generated through the reaction

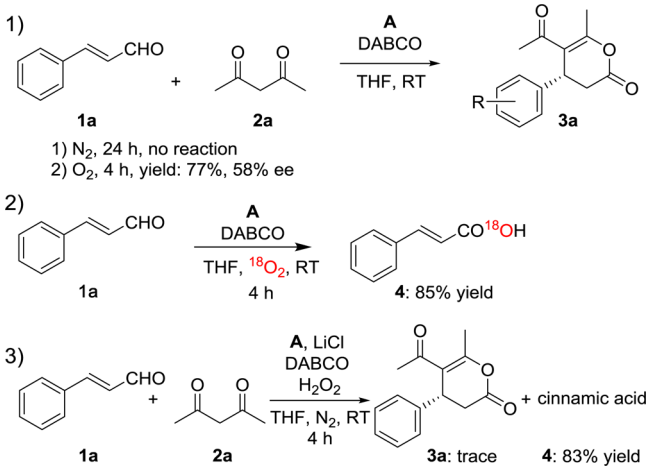
**Scheme 2. Proposed Catalytic Cycle**




of carbene **I** and enal **1a**. Next, in the presence of $O_2$, the enaminol **II** will be oxidized to $\alpha,\beta$-unsaturated acyl triazolium species **III**, which could act as good Michael acceptors; further formation of the product **3a** and liberation of the carbene catalyst **I** are similar to the literature reported by Studer and co-workers. We suppose that, in this aerobic oxidative strategy, a hydroperoxide anion will be generated in the oxidation process, which will greatly facilitate the formation of the side product cinnamic acid **4**. Indeed, we observed the cinnamic acid as main side product in this reaction.

To verify our hypothesis, some control experiments were conducted. When the reaction of cinnamaldehyde **1a** and acetylacetone **2a** in the presence of **A** was carried out under $N_2$ without any external oxidant, nearly no reaction happened; when $O_2$ gas was used instead of $N_2$, the reaction went smoothly and afforded the desired product **3a** in 77% yield, however, the ee value dropped to 58% (Scheme 3, exp. 1). An $^{18}O$ isotope labeling experiment of NHC-catalyzed oxidation of cinnamaldehyde was also conducted by using $^{18}O_2$ as the oxidant, and the product yielded in 85% was found to be cinnamic-$^{18}O$ acid (Scheme 3, exp. 2). This implied that $O_2$ can successfully promote the oxidation of homoenolate **II** to the $\alpha,\beta$-unsaturated acyl triazolium intermediate **III**, which facilitated the consequential Michael addition reaction with 1,3-dicarbonyl compounds. Next, hydrogen peroxide was used as oxidant instead of $O_2$ under $N_2$ atmosphere in the cyclization reaction; we found that only a trace amount of desired **3a** was detected, and the side product cinnamic acid **4** was isolated in 83% yield (Scheme 3, exp. 3), which indicated that the

**Scheme 3. Control Experiments**




hydroperoxide anion generated facilitated the formation of cinnamic acid.

In conclusion, we have developed an aerobic asymmetric annulation reaction of cinnamaldehydes and 1,3-dicarbonyl compounds through oxidative NHC-catalysis, the desired dihydropyranones were obtained in good yields and good to excellent enantioselectivities. The air was directly used as the oxidant, which made this asymmetric annulation reaction in a highly efficient, cheap, and green manner. We expect air to offer alternative, concise, and low cost strategies for oxidative NHC-catalysis.

## EXPERIMENTAL SECTION

Analytical thin layer chromatography (TLC) was performed using precoated silica gel plate (0.2 mm thickness). Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate. Proton nuclear magnetic resonance spectra ($^1H$ NMR) were recorded by using $CDCl_3$ as solvent. Chemical shifts for $^1H$ NMR spectra are reported as $\delta$ in units of parts per million (ppm) downfield from $SiMe_4$ (0.0) and relative to the signal of chloroform-d (7.26, singlet). Multiplicities were given as s (singlet), d (doublet), t (triplet), dd (doublets of doublet), or m (multiplets). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a $J$ value in Hz. Carbon nuclear magnetic resonance spectra ($^{13}C$ NMR) are reported as $\delta$ in units of parts per million (ppm) downfield from $SiMe_4$ (0.0) and relative to the signal of chloroform-d (77.0, triplet). Enantiomeric excesses were determined by high performance liquid chromatography (HPLC) analysis on a chiral stationary phase. Optical rotations were measured in $CHCl_3$ with a 10 cm cell (c given in g/100 mL). Absolute configuration of the products was determined by comparing the optical rotation with the known compounds. High-resolution mass spectrometry (HRMS) was recorded on QTOF perimer for $ESI^+$. The NHC-catalysts were prepared according to the literatures reported.[16] Enals which are not commercially available were prepared following the literatures procedures.[17] The racemic products used to determine the ee values were synthesized by using *cis*-mixture catalyst as racemic catalyst to generate racemic products. It was prepared by mixing the following two catalysts in 1:1 ration.

**General Procedure for the Synthesis of 3.** To an oven-dried 5 mL vial was added aldehyde (**1**, 0.4 mmol, 2.0 equiv), 1,3-dicarbonyl compounds (**2**, 0.2 mmol, 1.0 equiv), and NHC-catalyst **A** (0.04 mmol, 0.2 equiv) in 1 mL solvent, followed by addition of base and additive, the resulting reaction mixture was stirred under air at rt. After the reaction was complete, (monitored by TLC) water was added to the vial, extracted with dichloromethane, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The



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resulting residue was purified by flash chromatography (EtOAc/hexane) to provide **3**.

*(R)-5-Acetyl-6-methyl-4-phenyl-3,4-dihydro-2H-pyran-2-one (**3a**).* Reaction time: 14 h. Colorless oil, yield: 19 mg (82%); $[\alpha]_D^{20}$ = −116.4 (c 0.7, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.34 (t, $J$ = 7.5 Hz, 2H), 7.28 (d, $J$ = 7.4 Hz, 1H), 7.14 (d, $J$ = 7.5 Hz, 2H), 4.14 (d, $J$ = 6.7 Hz, 1H), 2.97 (dd, $J$ = 15.7, 7.2 Hz, 1H), 2.84 (dd, $J$ = 15.7, 2.5 Hz, 1H), 2.43 (s, 3H), 2.12 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 197.9, 165.5, 160.2, 139.8, 129.5, 128.0, 126.7, 117.4, 38.9, 37.2, 29.8, 19.1; HRMS (ESI) calcd for $C_{14}H_{14}O_3$ $(M+H)^+$: 231.1016, Found: 231.1043; 94% ee as determined by HPLC (Chiralcel IB, 80:20 hexanes/*i*-PrOH, 1 mL/min), $t_r$ (major) = 9.5 min, $t_r$ (minor) = 8.2 min.

*(R)-5-Acetyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydro-2H-pyran-2-one (**3b**).* Reaction time: 14 h. Yellow solid, yield: 21 mg (81%); mp: 92.1−93.5 °C; $[\alpha]_D^{20}$ = −91.0 (c 0.7, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.06 (d, $J$ = 8.6 Hz, 2H), 6.86 (d, $J$ = 8.6 Hz, 2H), 4.09 (d, $J$ = 5.9 Hz, 1H), 3.78 (s, 3H), 2.93 (dd, $J$ = 15.6, 7.1 Hz, 1H), 2.80 (dd, $J$ = 15.6, 1.6 Hz, 1H), 2.41 (s, 3H), 2.12 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 198.0, 165.7, 160.0, 159.2, 131.6, 127.8, 117.6, 114.8, 55.3, 38.1, 37.4, 29.6, 19.0; HRMS(ESI) calcd for $C_{15}H_{16}O_4$ $(M+H)^+$: 261.1121, Found: 261.1130; 85% ee as determined by HPLC (Chiralcel IB, 85:15 hexanes/*i*-PrOH, 1 mL/min), $t_r$ (major) = 12.6 min, $t_r$ (minor) = 11.6 min.

*(R)-5-Acetyl-4-(4-fluorophenyl)-6-methyl-3,4-dihydro-2H-pyran-2-one (**3c**).* Reaction time: 18 h.Yellow solid, yield: 18 mg (73%); mp: 111.8−112.6 °C; $[\alpha]_D^{20}$ = −72.0 (c 0.6, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.12 (dd, $J$ = 8.7, 5.2 Hz, 2H), 7.03 (t, $J$ = 8.6 Hz, 2H), 4.16 (d, $J$ = 6.2 Hz, 1H), 2.95 (dd, $J$ = 15.7, 7.2 Hz, 1H), 2.81 (dd, $J$ = 15.7, 2.5 Hz, 1H), 2.43 (d, $J$ = 0.8 Hz, 3H), 2.14 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 197.6, 165.4, 162.5 (d, 1*JC-F* = 246.8 Hz), 160.4, 135.4, 128.4 (d, 3*JC-F* = 8.7 Hz), 117.5, 116.5 (d, 2*JC-F* = 21.3 Hz), 38.1, 37.2, 29.8, 19.1; HRMS (ESI) calcd for $C_{14}H_{13}$ $FO_3$ $(M+H)^+$: 249.0921, Found: 249.0920; 91% ee as determined by HPLC (Chiralcel IB, 85:15 hexanes/*i*-PrOH, 1 mL/min), $t_r$ (major) = 12.4 min, $t_r$ (minor) = 10.4 min

*(R)-5-Acetyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydro-2H-pyran-2-one (**3d**).* Reaction time: 14 h. Yellow oil, yield: 17 mg (64%); $[\alpha]_D^{20}$ = −21.5 (c 0.5, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.31 (d, $J$ = 8.5 Hz, 2H), 7.09 (d, $J$ = 8.4 Hz, 2H), 4.15 (d, $J$ = 6.6 Hz, 1H), 2.96 (dd, $J$ = 15.7, 7.3 Hz, 1H), 2.80 (dd, $J$ = 15.7, 2.5 Hz, 1H), 2.43 (d, $J$ = 0.8 Hz, 3H), 2.14 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 197.4, 165.3, 160.6, 138.2, 133.8, 129.6, 128.1, 117.2, 38.1, 36.9, 29.8, 19.2; HRMS (ESI) calcd for $C_{14}H_{13}ClO_3$ $(M+H)^+$: 265.0626, Found: 265.0536; 94% ee as determined by HPLC (Chiralcel IB, 95:5 hexanes/*i*-PrOH, 1 mL/min), $t_r$ (major) = 29.9 min, $t_r$ (minor) = 23.5 min.

*(R)-5-Acetyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydro-2H-pyran-2-one (**3e**).* Reaction time: 12 h. Yellow oil, yield: 21 mg (77%); $[\alpha]_D^{20}$ = −74.0 (c 0.5, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.20 (d, $J$ = 8.7 Hz, 2H), 7.34 (d, $J$ = 8.7 Hz, 2H), 4.34 (d, $J$ = 6.7 Hz, 1H), 3.02 (dd, $J$ = 15.9, 7.5 Hz, 1H), 2.85 (dd, $J$ = 15.9, 2.3 Hz, 1H), 2.47 (s, 3H), 2.21 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 196.6, 164.7, 161.2, 147.6, 147.3, 127.8, 124.6, 117.2, 38.3, 36.3, 30.2, 19.5; HRMS (ESI) calcd for $C_{14}H_{13}NO_5$ $(M+H)^+$: 276.0866, Found: 276.0877; 90% ee as determined by HPLC (Chiralcel AD, 90:10 hexanes/*i*-PrOH, 1 mL/min), $t_r$ (major) = 26.9 min, $t_r$ (minor) = 29.2 min.

*(R)-5-Acetyl-4-(2-methoxyphenyl)-6-methyl-3,4-dihydro-2H-pyran-2-one (**3f**).* Reaction time: 14 h. White solid, yield: 21 mg (80%); mp: 90.5−92.0 °C; $[\alpha]_D^{20}$ = −35.6 (c 0.8, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.26 (td, $J$ = 8.1, 1.7 Hz, 1H), 6.97 (dd, $J$ = 7.4, 1.5 Hz, 1H), 6.89 (dd, $J$ = 11.5, 4.3 Hz, 2H), 4.54−4.46 (m, 1H), 3.86 (s, 3H), 2.91−2.82 (m, 2H), 2.42 (d, $J$ = 0.9 Hz, 3H), 2.08 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 198.3, 166.2, 160.4, 156.5, 129.1, 127.2,127.1, 121.1, 116.4, 110.9, 55.2, 35.0, 32.9, 29.3, 19.0; HRMS (ESI) calcd for $C_{15}H_{16}O_4$ $(M+H)^+$: 261.1120, Found: 261.1109; 93% ee as determined by HPLC (Chiralcel AD, 98:2 hexanes/*i*-PrOH, 1 mL/min), $t_r$ (major) = 18.5 min, $t_r$ (minor) = 21.1 min.

*(R)-5-Acetyl-6-methyl-4-(2-nitrophenyl)-3,4-dihydro-2H-pyran-2-one (**3g**).* Reaction time: 20 h. Yellow oil, yield: 19 mg (70%); $[\alpha]_D^{20}$ = −143.2 (c 0.5, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.99 (dd, $J$ = 8.1, 1.2 Hz, 1H), 7.60−7.56 (m, 1H), 7.48 (td, $J$ = 8.1, 1.3 Hz, 1H), 7.22 (dd, $J$ = 7.8, 1.2 Hz, 1H), 4.86 (d, $J$ = 6.7 Hz, 1H), 3.07 (dd, $J$ = 16.1, 7.7 Hz, 1H), 3.00 (dd, $J$ = 16.1, 2.4 Hz, 1H), 2.48 (d, $J$ = 0.9 Hz, 3H), 2.09 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 196.7, 165.0, 162.0, 148.7, 134.3, 134.1, 129.1, 128.2, 125.7, 116.4, 35.8, 34.2, 29.7, 19.3; HRMS (ESI) calcd for $C_{14}H_{13}NO_5$ $(M+H)^+$: 276.0866, Found: 276.0866; 92% ee as determined by HPLC (Chiralcel AD, 95:5 hexanes/*i*-PrOH, 1 mL/min), $t_r$ (major) = 18.7 min, $t_r$ (minor) = 20.6 min.

*(S)-5-Acetyl-4-(furan-2-yl)-6-methyl-3,4-dihydro-2H-pyran-2-one (**3h**).* Reaction time: 14 h. Yellow oil, yield: 16 mg (73%); $[\alpha]_D^{20}$ = −35.7 (c 0.7, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.34 (d, $J$ = 1.2 Hz, 1H), 6.28 (dd, $J$ = 3.2, 1.9 Hz, 1H), 6.09 (d, $J$ = 3.2 Hz, 1H), 4.26 (d, $J$ = 6.6 Hz, 1H), 3.04 (dd, $J$ = 15.9, 2.1 Hz, 1H), 2.84 (dd, $J$ = 15.9, 6.8 Hz, 1H), 2.37 (s, 3H), 2.31 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 197.1, 165.5, 161.0, 152.5, 142.8, 115.7, 110.4, 106.6, 33.8, 32.3, 29.8, 19.4; HRMS (ESI) calcd for $C_{12}H_{12}O_4$ $(M+H)^+$: 221.0808, Found: 221.0834; 87% ee as determined by HPLC (Chiralcel IB, 90:10 hexanes/*i*-PrOH, 1 mL/min), $t_r$ (major) = 11.0 min, $t_r$ (minor) = 9.4 min.

*(S)-5-Acetyl-6-methyl-4-propyl-3,4-dihydro-2H-pyran-2-one (**3i**).* Reaction time: 14 h. Yellow oil, yield: 14 mg (71%); $[\alpha]_D^{20}$ = −4.3 (c 0.7, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 2.98−2.90 (m, 1H), 2.73 (dd, $J$ = 15.9, 1.9 Hz, 1H), 2.59 (dd, $J$ = 15.9, 6.4 Hz, 1H), 2.35 (s, 3H), 2.27 (s, 3H), 1.53−1.39 (m, 2H), 1.33 (dd, $J$ = 8.1, 4.2 Hz, 2H), 0.91 (t, $J$ = 7.0 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 197.7, 167.0, 158.8, 120.4, 35.6, 33.1, 32.1, 30.2, 19.8, 19.3, 13.8; HRMS (ESI) calcd for $C_{11}H_{16}O_3$ $(M+Na)^+$: 219.0992, Found: 219.0990; 77% ee as determined by HPLC (Chiralcel IB, 90:10 hexanes/*i*-PrOH, 1 mL/min), $t_r$ (major) = 8.0 min, $t_r$ (minor) = 7.5 min.

*(S)-5-Acetyl-6-methyl-4-pentyl-3,4-dihydro-2H-pyran-2-one (**3j**).* Reaction time: 14 h. Yellow oil, yield: 16 mg (71%); $[\alpha]_D^{20}$ = −2.1 (c 0.7, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 2.95−2.87 (m, 1H), 2.73 (dd, $J$ = 15.9, 1.8 Hz, 1H), 2.58 (dd, $J$ = 15.9, 6.4 Hz, 1H), 2.35 (s, 3H), 2.27 (s, 3H), 1.30 (m, 8H), 0.87 (t, $J$ = 6.9 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 197.8, 167.02, 158.7, 120.4, 33.4, 33.1, 32.3, 31.5, 30.2, 26.2, 22.4, 19.3, 13.9; HRMS (ESI) calcd for $C_{13}H_{20}O_3$ $(M+H)^+$: 225.1485, Found: 225.1480; 80% ee as determined by HPLC (Chiralcel IB, 95:5 hexanes/*i*-PrOH, 1 mL/min), $t_r$ (major) = 8.6 min, $t_r$ (minor) = 8.2 min.

*(R)-5-Acetyl-4,6-diphenyl-3,4-dihydro-2H-pyran-2-one (**3k**).* Reaction time: 14 h. Colorless oil, yield: 20 mg (69%); mp: 76.5−77.6 °C; $[\alpha]_D^{20}$ = −1.8 (c 0.8, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.58−7.53 (m, 2H), 7.46−7.43 (m, 1H), 7.32 (t, $J$ = 7.7 Hz, 2H), 7.19 (t, $J$ = 7.3 Hz, 3H), 7.15−7.11 (m, 1H), 7.08−7.04 (m, 2H), 4.24 (dd, $J$ = 7.1, 3.1 Hz, 1H), 2.99 (dd, $J$ = 16.0, 7.6 Hz, 1H), 2.86 (dd, $J$ = 16.0, 3.6 Hz, 1H), 1.83 (d, $J$ = 1.0 Hz, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 195.8, 166.5, 154.7, 140.0, 138.4, 133.1, 129.1, 128.8, 128.7, 127.6, 126.8, 117.8, 39.5, 36.2, 19.0; HRMS (ESI) calcd for $C_{19}H_{16}O_3$ $(M+H)^+$: 293.1172, Found: 293.1146; 74% ee as determined by HPLC (Chiralcel IB, 90:10 hexanes/*i*-PrOH, 1 mL/min), $t_r$ (major) = 10.4 min, $t_r$ (minor) = 9.6 min.

*Ethyl (R)-6-Ethyl-2-oxo-4-phenyl-3,4-dihydro-2H-pyran-5-carboxylate (**3l**).* Reaction time: 14 h. Yellow oil, yield: 19 mg (69%); $[\alpha]_D^{20}$ = −71.0 (c 0.6, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.29 (t, $J$ = 7.4 Hz, 2H), 7.23 (dd, $J$ = 10.5, 4.2 Hz, 1H), 7.13 (d, $J$ = 7.3 Hz, 2H), 4.27−4.22 (m, 1H), 4.12 (q, $J$ = 7.1 Hz, 2H), 2.92 (ddd, $J$ = 13.7, 12.1, 7.5 Hz, 2H), 2.87−2.77 (m, 2H), 1.27 (t, $J$ = 7.5 Hz, 3H), 1.18 (t, $J$ = 7.1 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 166.3, 165.9, 165.8, 140.6, 129.0, 127.4, 126.5, 109.3, 60.8, 37.8, 36.4, 25.4, 14.0, 11.7; HRMS (ESI) calcd for $C_{16}H_{18}O_4$ $(M+H)^+$: 275.1278, Found: 275.1265; 92% ee as determined by HPLC (Chiralcel IB, 95:5 hexanes/*i*-PrOH, 1 mL/min), $t_r$ (major) = 6.9 min, $t_r$ (minor) = 6.1 min.

*(R)-6-Ethyl-4-phenyl-5-propionyl-3,4-dihydro-2H-pyran-2-one (**3m**).* Reaction time: 14 h. Yellow oil, yield: 19 mg (74%); $[\alpha]_D^{20}$ = −54.2 (c 0.8, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.34 (t, $J$ = 7.4 Hz, 2H), 7.28 (d, $J$ = 7.4 Hz, 1H), 7.14 (d, $J$ = 7.3 Hz, 2H), 4.11 (dd, $J$ = 7.1, 2.8 Hz, 1H), 2.95 (dd, $J$ = 15.7, 7.2 Hz, 1H), 2.81 (dd, $J$ = 15.7,



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3.0 Hz, 1H), 2.73 (qd, $J$ = 13.8, 7.1 Hz, 2H), 2.49 (dq, $J$ = 17.8, 7.2 Hz, 1H), 2.23 (dq, $J$ = 17.8, 7.2 Hz, 1H), 1.28 (t, $J$ = 7.4 Hz, 3H), 0.94 (t, $J$ = 7.2 Hz, 3H).$^{13}$C NMR (126 MHz, $CDCl_3$) $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 201.1, 165.9, 163.7, 139.7, 129.5, 127.9, 126.7, 116.5, 38.7, 37.4, 34.7, 25. 3, 11.9, 7.9; HRMS (ESI) calcd for $C_{16}H_{18}O_3$ $(M+H)^+$: 259.1329, Found: 259.1298; 90% ee as determined by HPLC (Chiralcel IB, 80:20 hexanes/*i*-PrOH, 1 mL/min), $t_r$ (major) = 6.5 min, $t_r$ (minor) = 5.5 min.

*Methyl (R)-6-Methyl-2-oxo-4-phenyl-3,4-dihydro-2H-pyran-5-carboxylate (**3n**).* Reaction time: 14 h. Yellow oil, yield: 20 mg (81%); $[\alpha]_D^{20}$ = −46.0 (c 0.8, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.30 (t, $J$ = 7.4 Hz, 2H), 7.24 (t, $J$ = 7.4 Hz, 1H), 7.13 (d, $J$ = 7.3 Hz, 2H), 4.26 (d, $J$ = 7.2 Hz, 1H), 3.68 (s, 3H), 2.94 (dd, $J$ = 15.8, 7.5 Hz, 1H), 2.83 (dd, $J$ = 15.8, 2.1 Hz, 1H), 2.48 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 166.4, 166.0, 161.7, 140.4, 129.1, 127.5, 126.6, 109.7, 51.9, 37.8, 36.5, 18.9; HRMS (ESI) calcd for $C_{14}H_{14}O_4$ $(M+H)^+$: 247.0965, Found: 247.0932; 90% ee as determined by HPLC (Chiralcel IB, 80:20 hexanes/*i*-PrOH, 1 mL/min), $t_r$ (major) = 8.8 min, $t_r$ (minor) = 6.3 min.

*Ethyl (R)-6-Methyl-2-oxo-4-phenyl-3,4-dihydro-2H-pyran-5-carboxylate (**3o**).* Reaction time: 14 h. Yellow oil, yield: 20 mg (77%); mp: 78.2−79.5 °C; $[\alpha]_D^{20}$ = −115.0 (c 0.8, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.29 (dd, $J$ = 10.1, 4.6 Hz, 2H), 7.26−7.23 (m, 1H), 7.15−7.12 (m, 2H), 4.25 (d, $J$ = 7.4 Hz, 1H), 4.13 (q, $J$ = 7.1 Hz, 2H), 2.94 (dd, $J$ = 15.9, 7.6 Hz, 1H), 2.82 (dd, $J$ = 15.9, 2.3 Hz, 1H), 2.47 (d, $J$ = 0.8 Hz, 3H), 1.18 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 166.0, 165.9, 161.2, 140.6, 129.0, 127.4, 126.6, 110.0, 60.8, 37.8, 36.3, 18.8, 14.0; HRMS (ESI) calcd for $C_{15}H_{16}O_4$ $(M+H)^+$: 261.1121, Found: 261.1121; 90% ee as determined by HPLC (Chiralcel IB, 80:20 hexanes/*i*-PrOH, 1 mL/min), $t_r$ (major) = 9.1 min, $t_r$ (minor) = 6.5 min.

*Isopropyl (R)-6-Methyl-2-oxo-4-phenyl-3,4-dihydro-2H-pyran-5-carboxylate (**3p**).* Reaction time: 14 h. Yellow oil, yield: 19 mg (69%); $[\alpha]_D^{20}$ = −135.0 (c 0.5, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.31−7.27 (m, 2H), 7.25−7.21 (m, 1H), 7.15−7.11 (m, 2H), 4.98 (dt, $J$ = 12.5, 6.2 Hz, 1H), 4.23 (d, $J$ = 6.7 Hz, 1H), 2.95 (dd, $J$ = 15.9, 7.7 Hz, 1H), 2.82 (dd, $J$ = 15.9, 2.5 Hz, 1H), 2.46 (d, $J$ = 0.9 Hz, 3H), 1.23 (d, $J$ = 6.2 Hz, 3H), 1.06 (d, $J$ = 6.2 Hz, 3H);$^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 166.2, 165.4, 160.9, 140.8, 128.9, 127.4, 126.6, 110.3, 68.4, 37.9, 36.3, 21.9, 21.5, 18.8; HRMS (ESI) calcd for $C_{16}H_{18}O_4$ $(M+H)^+$: 275.1278, Found: 275.1258; 90% ee as determined by HPLC (Chiralcel IB, 95:5 hexanes/*i*-PrOH, 1 mL/min), $t_r$ (major) = 8.2 min, $t_r$ (minor) = 6.4 min.

*Benzyl (R)-6-Methyl-2-oxo-4-phenyl-3,4-dihydro-2H-pyran-5-carboxylate (**3q**).* Reaction time: 14 h. Yellow oil, yield: 22 mg (65%); $[\alpha]_D^{20}$ = −56.4 (c 0.5, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.31 (dd, $J$ = 25.2, 17.2 Hz, 6H), 7.12 (t, $J$ = 7.2 Hz, 4H), 5.11 (q, $J$ = 12.5 Hz, 2H), 4.27 (d, $J$ = 7.4 Hz, 1H), 2.95 (dd, $J$ = 15.9, 7.7 Hz, 1H), 2.82 (d, $J$ = 15.8 Hz, 1H), 2.49 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 165.9, 165.7, 162.0, 140.5, 135.6, 129.1, 128.5, 128.2, 127.9, 127.6, 126.6, 109.6, 66.6, 37.9, 36.4, 18.9; HRMS (ESI) calcd for $C_{20}H_{18}O_4$ $(M+H)^+$: 323.1278, Found: 323.1269; 89% ee as determined by HPLC (Chiralcel IB, 95:5 hexanes/*i*-PrOH, 1 mL/min), $t_r$ (major) = 14.8 min, $t_r$ (minor) = 11.0 min.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01152.

Copies of $^1$H, $^{13}$C NMR and chiral HPLC spectra for compounds **3a−q** and MS spectra of **4** (PDF)

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### Notes

The authors declare no competing financial interest.

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