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A General Organocatalyzed Michael−Michael Cascade Reaction Generates Functionalized Cyclohexenes

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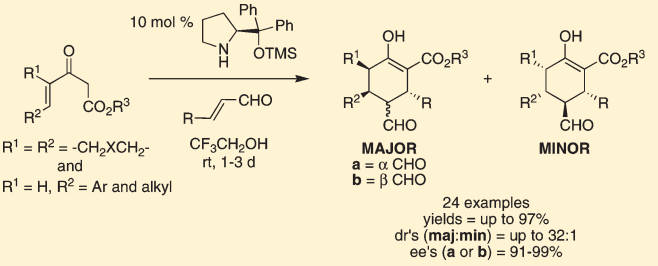
Supporting Information

ABSTRACT: Although β-dicarbonyl compounds are regularly employed as Michael donors, intermediates arising from the Michael addition of unsaturated β-ketoesters to α,β-unsaturated aldehydes are susceptible to multiple subsequent reaction pathways. We designed cyclic unsaturated β-ketoester substrates that enabled the development of the first diphenyl prolinol silyl ether catalyzed Michael−Michael cascade reaction initiated by a β-dicarbonyl Michael donor to form cyclohexene products. The reaction conditions we developed for this Michael−Michael cascade reaction were also amenable to a variety of linear unsaturated β-ketoester substrates, including some of the same linear unsaturated β-ketoester substrates that were previously ineffective in Michael−Michael cascade reactions. These studies thus revealed that a change in simple reaction conditions, such as solvent and additives, enables the same substrate to undergo different cascade reactions, thereby accessing different molecular scaffolds. These studies also culminated in the development of a general organocatalyzed Michael−Michael cascade reaction that generates highly functionalized cyclohexenes with up to four stereocenters, in up to 97% yield, 32:1 dr, and 99% ee, in a single step from a variety of unsaturated β-ketoesters.



INTRODUCTION

Organocatalytic cascade reactions are an efficient, green chemical method for rapidly building molecular complexity from simple starting materials.[1] Particularly useful for this purpose are diphenyl prolinol silyl ether catalysts (i.e., **1a**, Scheme 1). These catalysts have been used to generate carbocyclic products via cascade reactions in which multiple C−C single bonds are formed by a combination of iminium and/or enamine catalyzed reactions.[2−12] Although the use of β-dicarbonyl compounds as Michael donors in organocatalytic conjugate additions is widespread,[13−20] they had previously initiated only one **1a**-catalyzed Michael−Michael cascade reaction (Reaction 1).[21]

Michael reactions initiated by related β-dicarbonyl compounds resulted in other cascade reactions. Unsaturated β-dicarbonyl compounds without substitution at the 2-position (**5**) underwent a Michael−Morita−Baylis−Hillman cascade reaction instead (Reaction 2).[22] These unhindered substrates facilitate conjugate addition of the amine catalyst to the 2-position (*vida infra*) and contain a removable proton at the 1-position, both prerequisites for the Morita−Baylis−Hillman reaction. Alternatively, β-dicarbonyl compounds with aryl substituents at the 2-position (**7**) underwent a Michael-acetalization cascade reaction in the presence of catalytic *p*-$NO_2C_6H_4CO_2H$ in CH_2Cl_2 (Reaction 3).[23] These substrates are thermodynamically predisposed to undergo the acetalization pathway, which generates products (**8**) in which the extended conjugation is preserved.

We recently reported a Michael−Michael cascade reaction, catalyzed by **1a**, that formed highly functionalized, fused carbocycles (**10**).[24] This was the first example of the formation of cyclohexene products via a **1a**-catalyzed Michael−Michael cascade reaction initiated by a β-dicarbonyl Michael donor. These findings prompted further questions, primarily: are these reaction conditions limited to cyclic unsaturated β-dicarbonyl compounds of type **9**? We set out to answer this question and report the full substrate scope of this transformation herein.

RESULTS AND DISCUSSION

A. Reactions with Cyclic Unsaturated β-Dicarbonyl Substrates. Cyclic unsaturated β-dicarbonyl compounds, **9**, were designed to preclude the Morita−Baylis−Hillman pathway (through substitution at the 1-position) and to disfavor the acetalization pathway (by being void of aryl substituents at the 2-position). When studies began, substrate **9a** generated only 13% of the Michael−Michael product after 10 days (entry 1, Table 1). Use of benzoic acid, an additive known to accelerate the turnover of catalyst **1a**, nearly doubled the yield of the Michael−Michael product (entry 2). In 1,2-dichloroethane (DCE) and other solvents (toluene, Et_2O, THF, MeCN), the initial Michael addition went to completion overnight, whereas the subsequent

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Scheme 1. Cascade Reactions Catalyzed by 1a

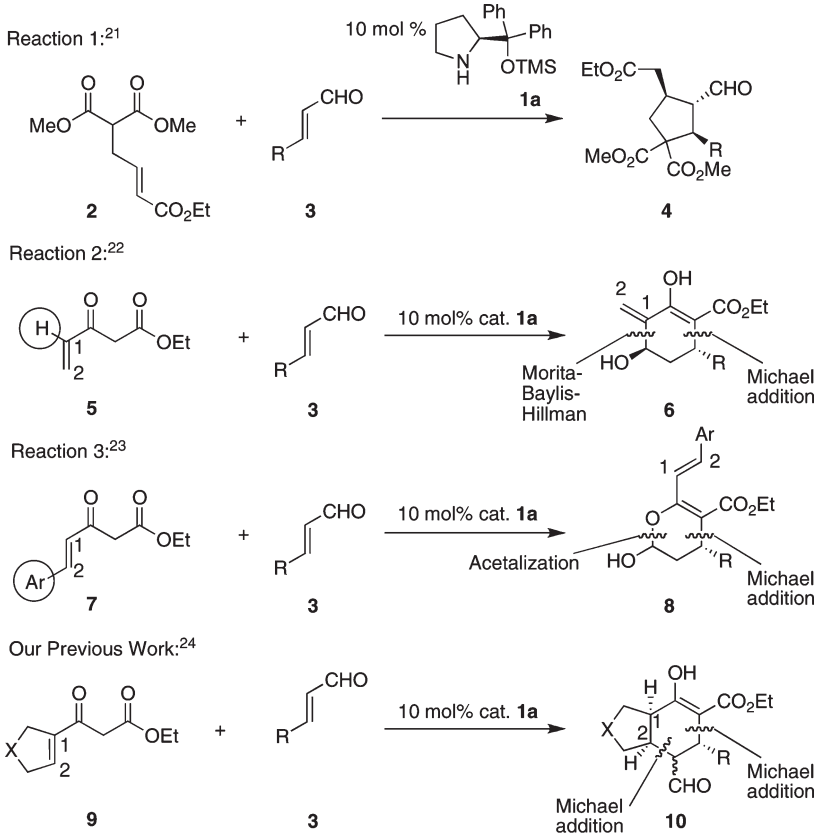
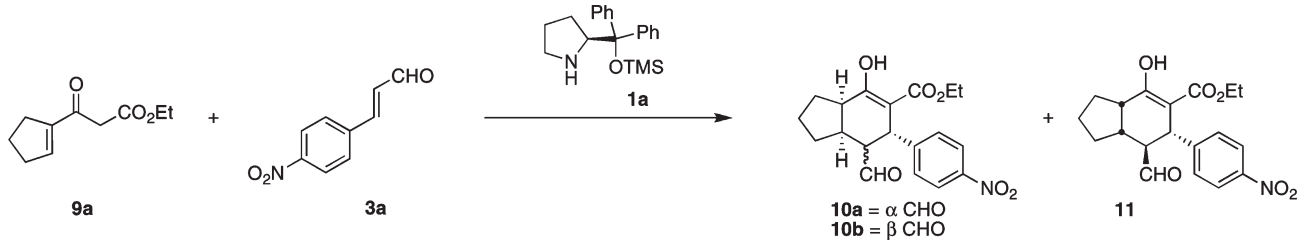


Table 1. Summary of Key Optimizations[a]



entry	additive	solvent	time (h)	conversion[b] (%)	ratio[b] (**10a**:**10b**)	dr[b] (**10**:**11**)	% ee[c] (**10a**)	% ee[c] (**10b**)
1		DCE	240	13	1:1.1	4:1	nd	nd
2	$PhCO_2H$	DCE	168	25	1.5:1	5:1	99	99
3	$PhCO_2H$	EtOH	168	61	1:1.1	4:1	99	99
4	$PhCO_2H$	CF_3CH_2OH	2	12	1:29	8:1	nd	nd
5	$PhCO_2H$	CF_3CH_2OH	41	17	1:5	10:1	99	99
6		CF_3CH_2OH	17	85	1:1.1	9:1	99	99
7[d]		CF_3CH_2OH	17	87	1:1.1	10:1	99	99

[a] Reaction conditions: **3a** (1 equiv), **9a** (1 equiv), **1a** (20 mol %), additive (20 mol %), solvent (0.3 M), rt. [b] Determined by ^{1}H NMR. [c] Determined by chiral phase HPLC. [d] 10 mol % **1a** used.

Michael addition required prolonged reaction times. Additionally, in all solvents, the ratio of **10a**:**10b** was approximately 1:1. Ethanol as solvent further doubled the yield of the Michael−Michael product, presumably by activating the second Michael addition through hydrogen bonding interactions with the ketoester moiety (entry 3). Use of a stronger hydrogen bonding solvent, trifluoroethanol, ultimately proved optimal after consideration of the results for this solvent in the context of the catalytic cycle (Scheme 2).

Although trifluoroethanol as solvent led to a rapid Michael−Michael cascade reaction (entry 4 vs entry 1), longer reaction times led only to a nominal improvement in conversion

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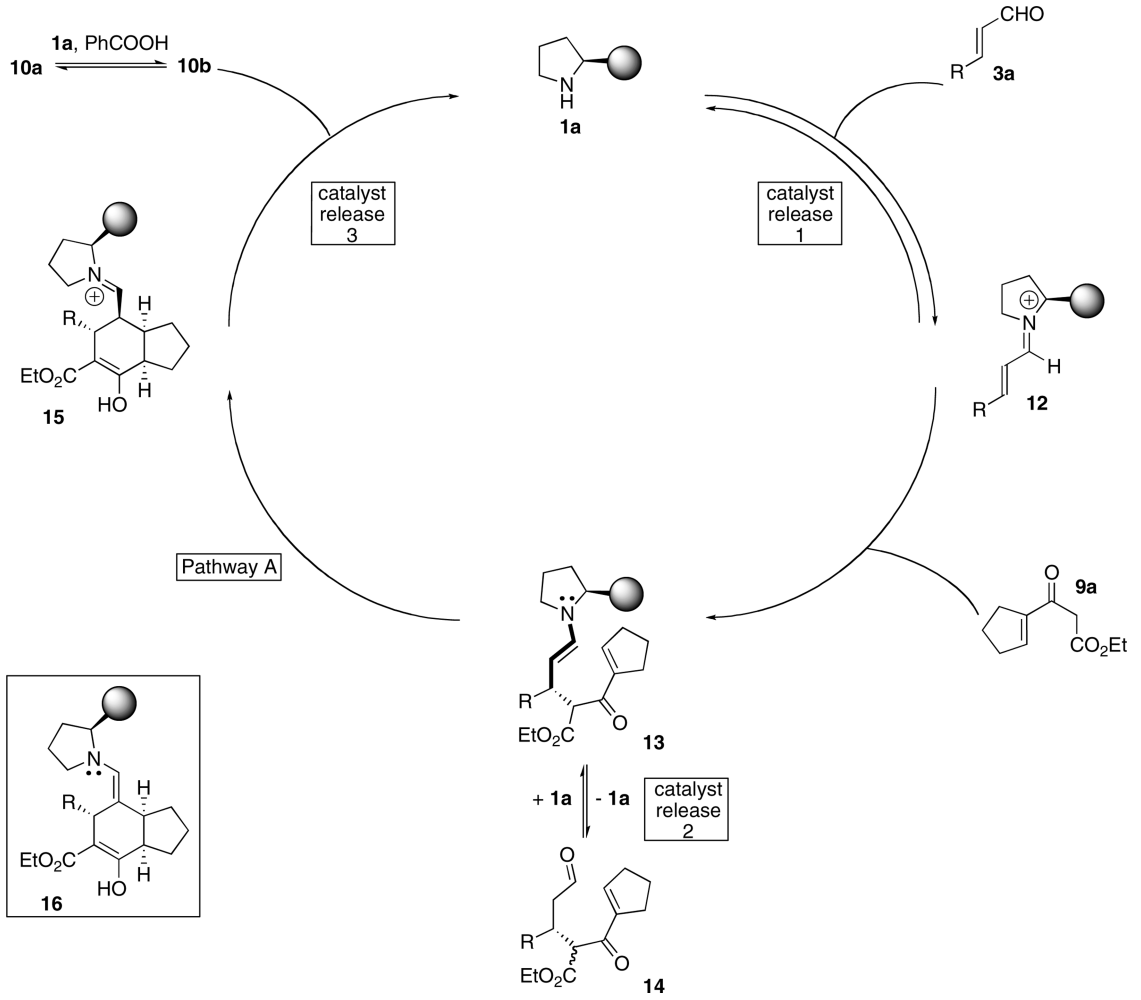
Scheme 2. Catalytic Cycle



(entry 5 vs entry 4). This was partly because the initial Michael addition had still not gone to completion, which was indicative of either a preference for the "catalyst release 1" pathway (**12** → **3a**) over the productive Michael addition pathway (**12** → **14**) or of a reversible Michael addition (**14** → **3a**). Resubjecting single Michael adduct **14** to reaction conditions resulted in rapid conversion to **10** only. This revealed that the formation of **14** was effectively irreversible and confirmed that the "catalyst release 1" pathway was predominating under these conditions. It also revealed that the second Michael addition (pathway A) was rapid in trifluoroethanol. This was substantiated by the formation of cascade product in this solvent after just 2 h (entry 4). The plateau in conversion can be explained by the predominance of the "catalyst release 2" pathway over the productive pathway (pathway A) using benzoic acid in trifluoroethanol. Additionally, under these conditions, **3a** is present in sufficient quantities (as explained above) to compete with intermediate **14** for the catalyst, thereby inhibiting **14** from re-entering the catalytic cycle and proceeding to product.

Finally, while the conversion to **10a** and **10b** did not change dramatically over the course of 39 h in trifluoroethanol, the ratio of **10a** to **10b** did (entries 4 and 5). This suggested that **10b** formed first and was slowly epimerizing to and equilibrating with **10a**. This epimerization is believed to occur via an enamine intermediate (**16**) and not via an enol intermediate, since catalyst **1a** was required for epimerization, which did not occur in the presence of benzoic acid alone. The dramatically reduced rate of epimerization in these conditions versus in other solvents can be explained by the predominance of "catalyst release 3" over formation of enamine **16** either from **15** prior to catalyst release or from **10b** (via **15**) after its ejection from the catalytic cycle.

Thus, whereas in all other solvents an exceedingly sluggish second Michael addition was the primary culprit in the low yields, in trifluoroethanol, multiple predominant "catalyst release" (i.e., turnover) pathways were detrimental to this transformation. Running this reaction in the absence of benzoic acid, an additive known to accelerate the turnover of catalyst **1a**, resulted in nearly complete conversion to cascade products overnight and restored the 1:1 ratio of **10a**:**10b** (entry 6). Reducing the catalyst loading to 10 mol % provided the optimal reaction conditions (entry 7), although the catalyst loading could be reduced to 1 mol % before the conversion and diastereoselectivity were impacted.

The reaction was run with a variety of substrates, the results of which are summarized in Table 2. In all cases, the ratio of **a**:**b** was approximately 1:1. Also, α,β-unsaturated aldehydes with an *o*-nitro-phenyl or an alkyl R group were unreactive.

B. Reactions with Linear Alkyl-Substituted Unsaturated β-Dicarbonyl Substrates. We next sought to determine whether

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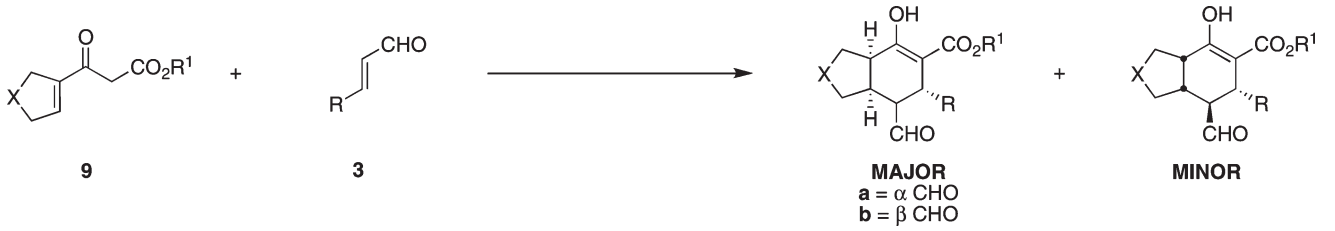
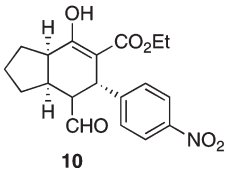
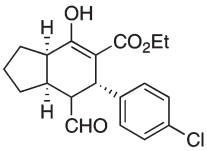
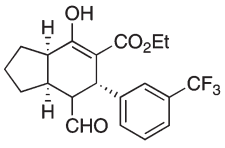
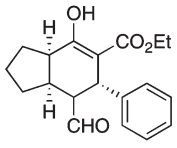
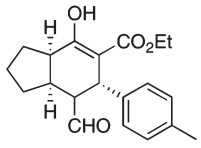
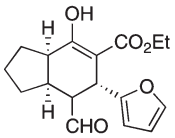
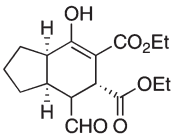
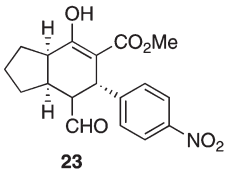
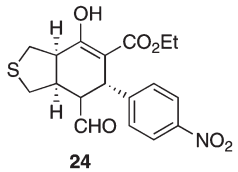
Table 2. Cyclic Unsaturated β-Dicarbonyl Substrates[a]



1		2		3	
	10		**17**		**18**
	87% yield, 17 h 10:1 dr 99% ee (**a**) 99% ee (**b**)		82% yield, 20 h 12:1 dr 99% ee (**a**) 98% ee (**b**)		79% yield, 17 h 13:1 dr 99% ee (**a**) 99% ee (**b**)
4		5			
	19		**20**		
	87% yield, 40 h 12:1 dr 99% ee (**a**) 98% ee (**b**)		79% yield, 168 h 13:1 dr 99% ee (**a**) 99% ee (**b**)		
6		7		8	
	21		**22**		**23**
	61% yield, 142 h 32:1 dr 98% ee (**a**) 98% ee (**b**)		67% yield, 22 h 32:1 dr 98% ee (**a**) 98% ee (**b**)		76% yield, 21 h 10:1 dr 97% ee (**a**) 98% ee (**b**)
9					
	24				
	80% yield, 28 h 13:1 dr 98% ee (**a**) 96% ee (**b**)				

[a] Reaction conditions: **3** (1 equiv), **9** (1 equiv), **1a** (10 mol %), CF_3CH_2OH (0.3 M), rt. Yield = isolated yield. dr determined by ^1H NMR. ee determined by chiral phase HPLC. dr = ratio of MAJOR:MINOR.

linear alkyl-substituted unsaturated β-dicarbonyl substrates of type **25a** (Table 3) would furnish Michael−Michael adducts under these conditions. Compound **25a** lacks an aromatic substituent at the 2-position and therefore, for reasons explained earlier, may not be prone to a Michael-acetalization reaction pathway. It does, however, contain a proton at the 1-position and may be susceptible to the Michael−Morita−Baylis−Hillman reaction pathway. Pleasingly, using the optimal reaction conditions for β-ketoesters of type **9**, β-ketoester **25a** generated the desired Michael−Michael cascade product in high conversion and good diastereoselectivity (entry 1). There was also non-insignificant conversion (13%) to the corresponding Michael−Morita−Baylis−Hillman product. However, the ee of both epimers of the major Michael−Michael adduct (**26a** and **26b**) was excellent, and notably, the ee of the minor diastereomer (**27**) was also high. Additionally, epimers **26a** and **26b** were present in a 1:8 ratio, which is in contrast to what was observed with products arising from cyclic unsaturated β-dicarbonyl substrates. In light of the high selectivity of Michael−Michael reactions using **25a**, efforts were directed toward minimizing the formation of the Michael−Morita−Baylis−Hillman byproduct.

Consideration of the competing reaction pathways for the direct product of the initial Michael addition (**28**, Scheme 3) identified variables for optimization. If **28** undergoes an intramolecular Michael addition, intermediate **29** will be generated and will ultimately furnish the desired Michael−Michael product, **26a**. However, if **28** undergoes a catalyst turnover, both the catalyst and aldehyde **30** will be liberated. Subsequent intermolecular conjugate addition of the catalyst to **30** would initiate the Morita−Baylis−Hillman reaction, leading to byproducts of type **6a**. Thus, conditions that would impact intermolecular reactions between catalyst and substrate, as well as catalyst turnover, were varied.

Dilute reaction concentration, lower catalyst loading, and electronically or sterically less nucleophilic catalysts were examined in an effort to hamper the intermolecular conjugate addition of the catalyst to **30** (entries 2−7). Additionally, additives that affect catalyst turnover were also examined (entries 8 and 9). In all cases, either the amount of **6a** formed did not decrease, or it decreased at the expense of decreased conversion to or ee of the desired product. The original conditions (i.e., those reported for cyclic unsaturated β-ketoesters; entry 1) were therefore chosen as optimal for linear alkyl-substituted unsaturated β-ketoesters.

Using these conditions, several linear alkyl-substituted unsaturated β-ketoesters were examined (Table 4). In all cases, the Michael−Michael adduct was obtained in high conversion and dr, and the β-epimer of the major diastereomer was formed in greater proportion and in excellent ee (entries 1−4). Notably, this cascade reaction is amenable to β-ketoesters with sterically demanding R substituents, such as *i*-Pr, which gave the best results (entry 4). β-Ketoesters of type **25** where R = H (i.e., **5**, Scheme 1) were not compatible with these conditions.

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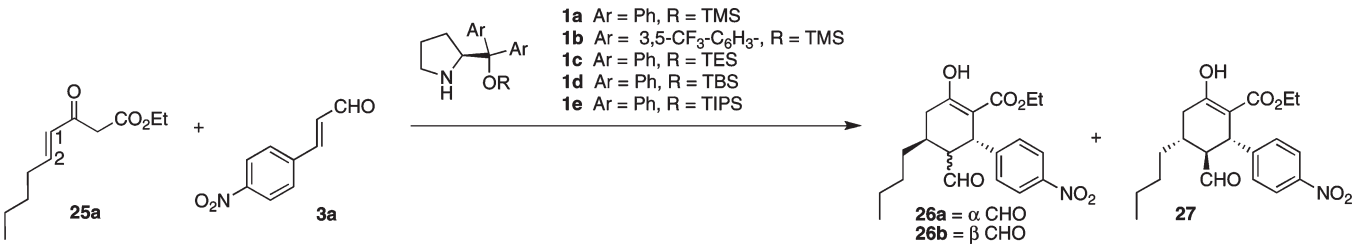
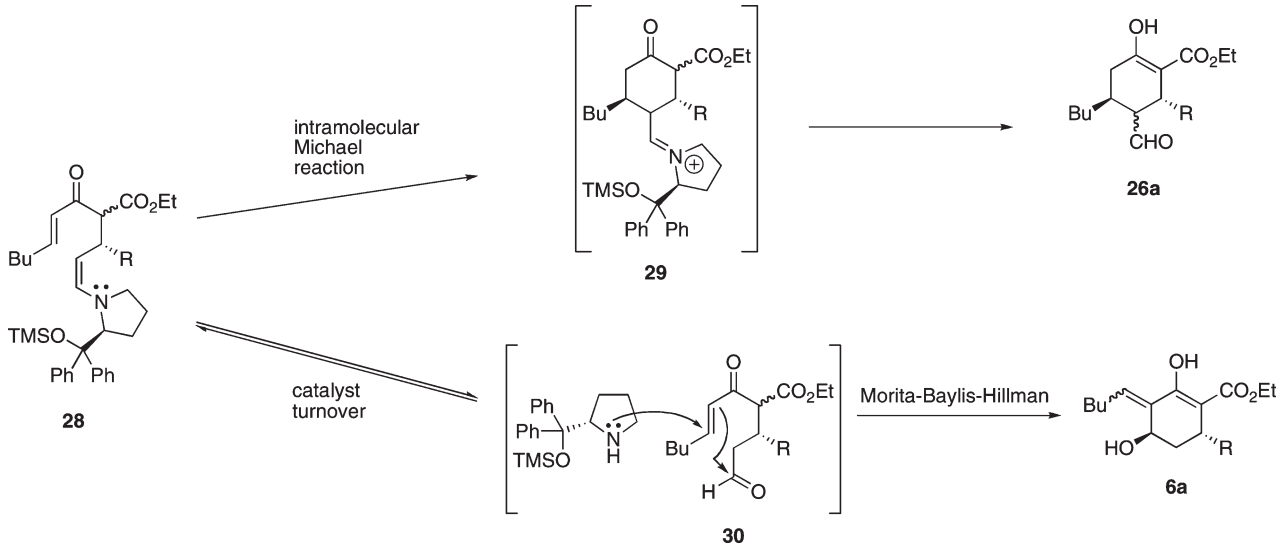
Table 3. Optimizations To Minimize Byproduct Formation[a]



entry	catalyst	additive	concn (M)	conversion[b,c] (%)	dr[b] (26:27)	% ee[d] (26a)	% ee[d,e] (26b)
1	**1a**		0.30	87 (13)	4:1[f]	93	94 (82)
2	**1a**		0.15	79 (21)[g]	4:1	nd	nd
3	**1a**[h]		0.30	84 (16)	4:1	nd	nd
4	**1b**		0.30	trace	nd	nd	nd
5	**1c**		0.30	89 (11)	5:1	90	91
6	**1d**		0.30	89 (8)	5:1	84	84
7	**1e**		0.30	91 (7)	7:1	85	88
8	**1a**	4 Å MS	0.30	77 (9)	4:1	nd	nd
9	**1a**	$PhCO_2H$[i]	0.30	78 (22)	4:1	nd	nd

[a] Reaction conditions: **25a** (1 equiv), **3a** (1 equiv), catalyst (10 mol %), CF_3CH_2OH, rt, 2 days. [b] Determined by ^1H NMR. [c] Number in parentheses is conversion to products of type **6**. [d] Determined by chiral phase HPLC. [e] Number in parentheses is ee of **27**. [f] Ratio of **26a**:**26b** = 1:8. [g] Reaction time = 1 day. [h] 5 mol % **1a** used. [i] 10 mol % $PhCO_2H$ used.

Scheme 3. Competing Pathways for the Single Michael Adduct



C. Reactions with Linear Aryl-Substituted *β*-Dicarbonyl Substrates. To our delight, *β*-ketoesters of type **7**, the exact same substrates that form Michael-acetalization products, generated the Michael−Michael cascade product in high conversion and selectivity using our reaction conditions (Table 5)! These *β*-ketoesters furnished the desired product with α,*β*-unsaturated aldehydes with electron-deficient, -neutral, and -rich aromatic R groups (entries 1−3). Additionally, an α,*β*-unsaturated aldehyde with an *ortho*-substituted phenyl R group was tolerated, without detriment to the yield or selectivity of this reaction (entry 4). This is in contrast to what was observed with cyclic unsaturated *β*-dicarbonyl compounds; as mentioned previously, no reaction occurred with an α,*β*-unsaturated aldehyde with an *o*-nitro phenyl R group. α,*β*-Unsaturated aldehydes with heteroaromatic and nonaromatic R groups also furnished the desired products in high yield and dr and in excellent ee (entries 5 and 6). Even α,*β*-unsaturated aldehydes with aliphatic R groups were amenable to this reaction (entry 7), whereas no reaction occurred when used in conjunction with cyclic unsaturated *β*-dicarbonyl compounds. This may be because linear compounds of type **7** have a proton at the 1-position, proximal to the nucleophilic *β*-ketoester moiety, whereas cyclic compounds of type **9** have alkyl substitution at the 1-position. Compounds of type **7**, being less hindered, may be more reactive nucleophiles, and thus capable of reacting with less reactive α,*β*-unsaturated aldehydes, such as those with *ortho*-substituted phenyl and alkyl R groups.

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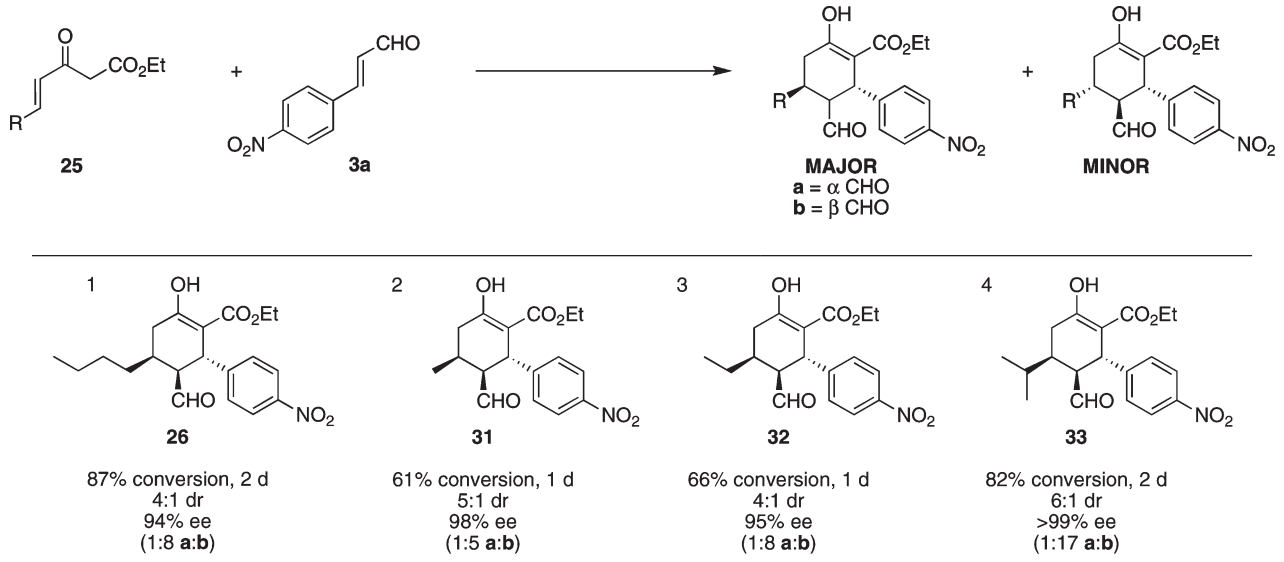
Table 4. Linear Alkyl-Substituted Unsaturated β-Dicarbonyl Substrates[a]



[a] Reaction conditions: **3a** (1 equiv), **25** (1 equiv), **1a** (10 mol %), CF_3CH_2OH (0.3 M), rt. Conversion, dr, and ratio of **a**:**b** determined by ^1H NMR. ee determined by chiral phase HPLC. dr = ratio of MAJOR:MINOR.

β-Ketoesters of type **7** with electron-rich, electron-deficient, or *ortho*-substituted phenyl Ar groups all produced the desired Michael−Michael products in high yield and excellent ee, and in moderate to high dr (entries 8−10). Finally, β-ketoesters of type **7** with a heteroaromatic Ar group also gave the desired product in excellent ee, albeit in reduced yield and dr (entry 11).

As with linear alkyl-substituted unsaturated β-ketoesters, linear aryl-substituted unsaturated β-ketoesters formed the β-epimer of the major diastereomer in greater proportion in all but three cases (entries 5, 8, and 10). The absolute stereochemistry of **42** was established by X-ray crystallography.[25] Additionally, as with **10a** and **10b**, we established that **26a** and **26b** were epimers by resubjecting pure **26a** to **1a** in CF_3CH_2OH, which produced a mixture of **26a** and **26b**. All other stereochemical assignments were made by analogy.

For all β-ketoesters of type **7**, no Michael−Morita−Baylis−Hillman product *and* no Michael-acetalization product was observed. The direct product of the initial Michael addition of β-ketoester **7** to enal **3**, activated by catalyst **1a** through iminium ion formation, is **45** (Scheme 4). In a nonpolar aprotic solvent such as CH_2Cl_2, the keto−enol equilibrium of the β-ketoester moiety may favor the enol form, as in **46**, due to stabilization by extended conjugation and by an intramolecular hydrogen bond. Moreover, in the presence of catalytic acid, the enamine moiety in **45** can be protonated to from an iminium species, as in **46**. Alternatively, the catalytic acid can facilitate catalyst turnover, liberating the corresponding free aldehyde. Intermediate **46** (or its corresponding free aldehyde) undergoes an intramolecular acetalization to form dihydropyrans (**8**) in moderate to good yields and in good to excellent enantioselectivities.[23] On the other hand, a polar protic solvent such as CF_3CH_2OH disrupts the intramolecular hydrogen bond in **46**, biasing the keto−enol equilibrium of the β-ketoester moiety toward the keto form. Moreover, CF_3CH_2OH presumably activates the Michael acceptor moiety toward the intramolecular conjugate addition through hydrogen bonding. Intermediate **45** undergoes a subsequent Michael addition to form cyclohexenes (**34**−**44**) in moderate to excellent yields and in excellent enantioselectivities.

This is illustrative of a powerful concept: the same substrates, using the same organocatalyst and identical catalyst loadings, can produce completely different molecular scaffolds in high yields and selectivities by simply changing the solvent and additives used. Since, as mentioned, β-dicarbonyl compounds are widely employed as Michael donors in organocatalytic conjugate addition reactions, it is anticipated that this idea can be exploited in many other organocatalytic cascade reactions.

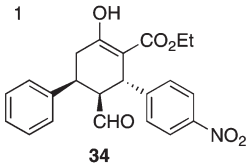
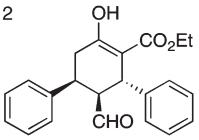
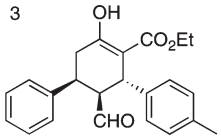
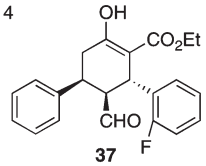
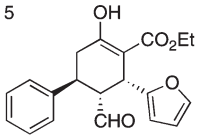
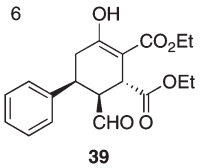
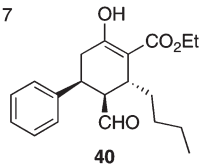
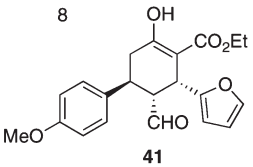
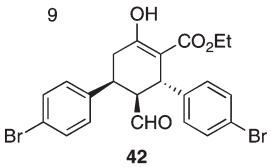
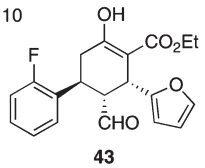
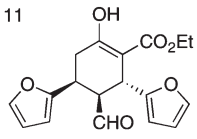
CONCLUSION

In conclusion, despite the fact that unsaturated β-dicarbonyl compounds are susceptible to multiple reaction pathways, we have developed general conditions for a **1a**-catalyzed Michael−Michael cascade reaction that are compatible with cyclic unsaturated β-dicarbonyl compounds as well as linear unsaturated β-dicarbonyl compounds with both alkyl and aryl substituents. This cascade reaction generates highly functionalized cyclohexene rings with up to four chiral centers in up to 97% yield, 32:1 dr, and 99% ee in a single step from achiral starting materials. Moreover, this cascade reaction demonstrates that the same starting materials and catalyst enable efficient access to diverse molecular scaffolds through modification of simple reaction conditions, a principle that should be applicable to many other organocascade reactions.

EXPERIMENTAL SECTION

General Information. ^1H and ^{13}C NMR spectra were collected using a 400 MHz spectrometer. The NMR data herein uses the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublets of doublets, td = triplet of doublets, dt = doublet of triplets, qd = quartet of doublets. Enantiomeric excesses were determined using chiral phase HPLC with Chiralpak AD-H (0.46 × 25 cm) and Chiralpak AS-H (0.46 × 25 cm) columns. Optical rotations were determined using a polarimeter. IR spectra were collected using a FT-IR. High-resolution mass spectra were collected using a MS spectrometer. Flash chromatography

Table 5. Linear Aryl-Substituted β-Dicarbonyl Substrates[a]

1  **34**	2  **35**	3  **36**	4  **37**	5  **38**
93% yield, 1 d 5:1 dr 97% ee (1:3 **a**:**b**)	91% yield, 1 d 7:1 dr 99% ee (1:11 **a**:**b**)	96% yield, 1 d 9:1 dr 99% ee (1:2 **a**:**b**)	97% yield, 2 d 10:1 dr 98% ee (1:5 **a**:**b**)	95% yield, 2 d 5:1 dr 98% ee (2:1 **a**:**b**)
6  **39**	7  **40**	8  **41**	9  **42**	10  **43**
71% yield, 1 d 7:1 dr 91% ee (no **a** detected)	89% conversion, 1 d 2:1 dr 98% ee (no **a** detected)	78% yield, 3 d 4:1 dr 97% ee (2:1 **a**:**b**)	73% yield, 1 d 6:1 dr 99% ee (1:20 **a**:**b**)	87% yield, 2 d 3:1 dr 93% ee (2:1 **a**:**b**)
11  **44**				
39% yield, 2 d 2:1 dr 95% ee (1:2 **a**:**b**)				

[a] Reaction conditions: **3** (1 equiv), **7** (1 equiv), **1a** (10 mol %), CF_3CH_2OH (0.3 M), rt. Yield = isolated yield. Conversion, dr, and ratio of **a**:**b** determined by ^{1}H NMR. ee determined by chiral phase HPLC. dr = ratio of MAJOR:MINOR.

was carried out with F60, 40−63 μm 60 Å silica gel and with EMD silica 60 F_{254} glass TLC plates. Solvents were dried and kept air-free in a solvent purification unit or stored under an argon atmosphere. Solvents were evaporated using a standard rotovapor and a high vacuum. All reactions were carried out in oven-dried glassware and conducted under an argon atmosphere.

Characterization and Supporting Information for 10a−b, 11, and 17−24. Full characterization of **10a**−**b**, **11**, and **17**−**24** as well as copies of ^{1}H NMR spectra, ^{13}C NMR spectra, HPLC chromatograms, and X-ray crystal data for compound **10a** are contained in the Supporting Information for ref 24.

Preparation of Catalysts (1a−e), Enals (3c−3d), and β-Ketoesters (7 and 25). Catalysts **1a**−**e**[26] were prepared from the corresponding diarylprolinols[27] using known procedures. Characterization of **1a**−**e** via ^{1}H NMR was in agreement with that in the literature. (*E*)-3-(*p*-Tolyl)acrylaldehyde (**3c**) and (*E*)-3-(2-fluorophenyl)acrylaldehyde (**3d**) were prepared using a known procedure.[28] Characterization of **3c** and **3d** via ^{1}H NMR was in agreement with that in the literature. β-Ketoesters of type **25** and type **7** (except **7a**, **7b**, and **7c** whose preparation and characterization are described below) were prepared according to a known literature procedure.[29] Characterization of β-ketoesters of type **25** and type **7** via ^{1}H NMR was in agreement with that in the literature.

(*E*)-3-(4-Bromophenyl)acrylaldehyde, 3b. Enal **3b** was prepared by adapting a known procedure.[30] A solution of 4-bromobenzaldehyde (2.41 g, 13.0 mmol) and triphenylphosphoranylidene acetaldehyde (4.75 g, 15.6 mmol) in toluene (103 mL) was heated at 80 °C for 16 h. To the reaction mixture was added triphenylphosphoranylidene acetaldehyde (250 mg, 0.06 mmol) again, and the reaction mixture was further refluxed for 19 h. After the reaction mixture was concentrated in vacuo, the crude residue was chromatographed on silica gel eluting with Et_2O/petroleum ether (7.5:92.5) to give **3b** (1.82 g, 66%) as a yellow solid. The ^{1}H and ^{13}C NMR spectra for **3b** were in agreement with that in the literature (see Supporting Information for spectra).[31]

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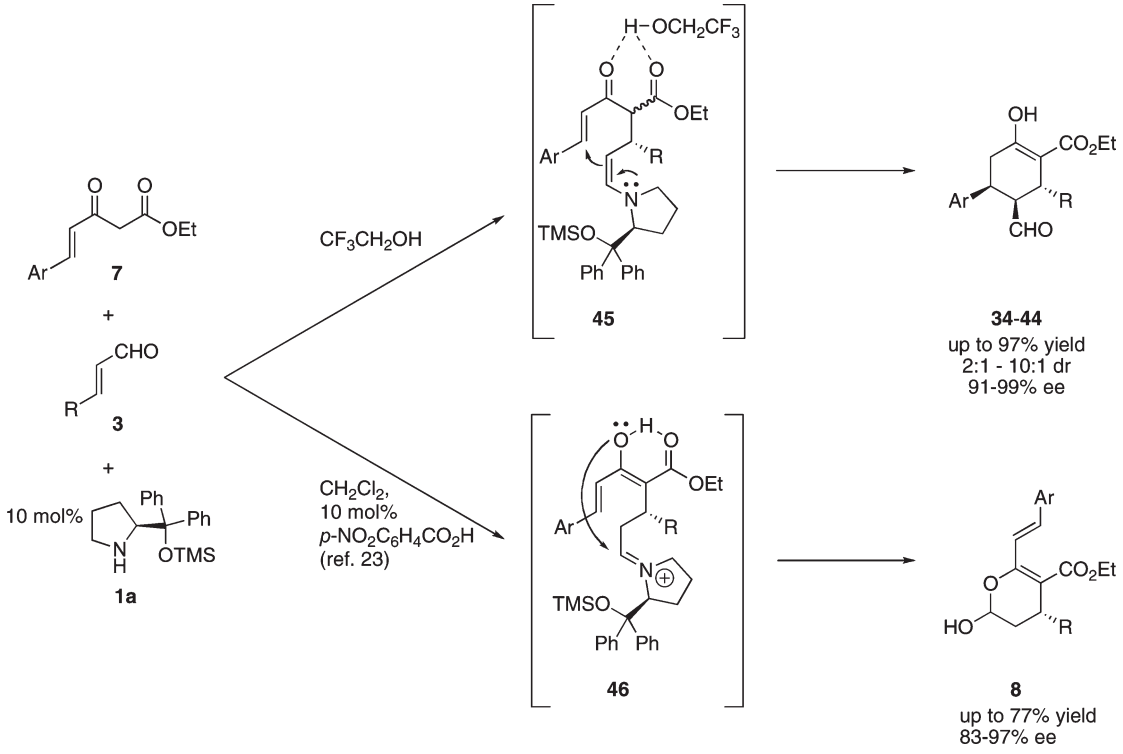
Scheme 4. Solvent and Additives Determine Product Structure



(*E*)-Ethyl 5-(2-Fluorophenyl)-3-oxopent-4-enoate, 7b. To a round-bottom flask were added THF (22 mL) and diisopropylamine (844 μL 6.6 mmol), and the mixture was cooled to −78 °C. *n*-BuLi (2.5 M in hexanes, 6.6 mmol) was added slowly, and the mixture was stirred for 15 min. Ethyl acetate (586 μL, 6.0 mmol) was then added dropwise, and the solution was stirred for 50 min. (*E*)-3-(2-Fluorophenyl)-acrylaldehyde (**3d**) (6.0 mmol) was added dropwise and stirred for 10 min. The reaction was quenched by the addition of sat'd. aq. NH_4Cl (1.7 mL), followed by immediate transfer to a separatory funnel containing diethyl ether (25 mL). The mixture was extracted with diethyl ether (25 mL), washed with brine (2 × 25 mL) and water (2 × 25 mL), and dried over $MgSO_4$. Removal of solvent yielded the corresponding hydroxyester in >99% yield. No further purification was needed before the oxidation with Jones' Reagent. Jones' Reagent was prepared by the addition of concentrated H_2SO_4 (1.8 mL) to CrO_3 (2.0 g) followed by careful dilution with water to give a total volume of 15 mL. Then, Jones' Reagent (9.0 mL, 9.0 mmol) was added dropwise to a stirred solution of the β-hydroxyester (6.0 mmol) in acetone (24 mL) at 0 °C. After complete addition of the oxidizing agent, the reaction was stirred for 10 min, when the absence of starting material was determined by thin-layer chromatography. Methanol (1.5 mL) was added slowly to quench excess Jones' Reagent. The reaction mixture was poured into a separatory funnel and extracted with diethyl ether (30 mL). The organic extracts were washed with water (3 × 20 mL) and then brine (2 × 20 mL). The organic layer was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. Purification of the crude product mixture was achieved by flash chromatography on silica gel eluting with Et_2O/petroleum ether (2.5:97.5), which gave **7b** as a white crystalline solid (338 mg, 24% yield): white solid, mp 57−58 °C; IR (thin film, KBr) 2983, 1741, 1649, 1596, 1486, 1458, 1422, 1235, 1148, 1094, 1039, 969, 799, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (1:2 ratio of keto: enol) δ 11.96 (d, J = 1.3 Hz, 1H, enol), 7.81−6.81 (m, 10H), 6.55 (dd, J = 16.1, 1.5 Hz, 2H), 5.18 (s, 1H, enol), 4.23 (qd, J = 7.1, 4.6 Hz, 4H), 3.71 (s, 2H, keto), 1.36−1.24 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1, 172.8, 168.9, 167.3, 162.9, 162.4, 159.9, 137.0, 136.9, 132.4, 132.3, 130.7, 130.6, 129.5, 129.4, 129.2, 129.1, 128.7, 128.6, 127.4, 127.4, 124.6, 124.6, 124.5, 124.4, 124.4, 124.3, 123.5, 123.4, 116.4, 116.2, 116.2, 116.0, 92.5, 61.5, 60.3, 47.6, 14.3, 14.1 ppm; HRMS (ESI) calcd for $C_{13}H_{13}F\ O_3$ $[M]^+$ 236.0849, found 236.0860.

(*E*)-Ethyl 5-(Furan-2-yl)-3-oxopent-4-enoate, 7c[23]. β-Ketoester **7c** was prepared by a modification of the same procedure used for **7b**. To a round-bottom flask were added THF (22 mL) and diisopropylamine (844 μL 6.6 mmol). The reaction was cooled to −78 °C. *n*-BuLi (2.5 M in hexanes, 6.6 mmol) was added slowly and stirred for 15 min. Ethyl acetate (586 μL, 6.0 mmol) was then added dropwise, and the solution was stirred for 50 min. (*E*)-3-(Furan-2-yl)acrylaldehyde (732.7 mg, 6.0 mmol) was added dropwise and stirred for 10 min. The reaction was quenched by the addition of sat'd. aq. NH_4Cl (1.7 mL), followed by immediate transfer to a separatory funnel containing diethyl ether (25 mL). The mixture was extracted with diethyl ether (25 mL), washed with brine (2 × 25 mL) and water (2 × 25 mL), and then dried over $MgSO_4$. Removal of solvent yielded the hydroxyester. No further purification was needed before the oxidation with DMP. However, purification could be achieved on silica gel with 15−25% Et_2O in petroleum ether. To a solution of the corresponding hydroxyester (420.5 mg, 2.0 mmol) in CH_2Cl_2 (55.5 mL) and MeCN (77.1 mL) at rt was added $NaHCO_3$ (330.6 mg, 3.9 mmol). The mixture was cooled to 0 °C, and Dess−Martin periodinane (848.3 mg, 2.0 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h. TLC (10% EtOAc in petroleum ether) indicated ~10% starting material remaining, so the reaction mixture was warmed to room temperature and stirred for an additional 30 min. TLC at this point indicated all starting material had been consumed. The reaction was quenched with a 1:1 solution (110 mL) of saturated $NaHCO_3$ and saturated $Na_2S_2O_3$ and was stirred vigorously until the organic layer was no longer cloudy. The quenched reaction mixture was then poured into a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography

(silica gel, 5% Et_2O/petroleum ether) provided **7c** as a yellow solid (220.7 mg, 53% yield). The ^1H and ^{13}C NMR spectra for **7c** were in agreement with that in the literature (see Supporting Information for spectra).[23]

(*E*)-Ethyl 5-(4-Methoxyphenyl)-3-oxopent-4-enoate, 7d[32]. β-Ketoester **7d** was prepared according to the same procedure used for the synthesis of **7c** and was collected in 55% yield (273.1 mg). The ^1H NMR spectra for **7d** was in agreement with that in the literature (see Supporting Information for spectra).[32]

General Procedure for Synthesis of Carbocycles (26, 31−44). To an oven-dried flask were added catalyst **1a** (13.0 mg, 0.04 mmol), CF_3CH_2OH (1.33 mL), β-ketoester **7a** (79.3 mg, 0.4 mmol), and enal **3a** (70.8 mg, 0.4 mmol). The reaction was allowed to stir for the indicated time at room temperature. The reaction mixture was concentrated and filtered through a plug of silica, followed by concentration again. The percent conversion of the crude reaction mixture was determined using an internal standard (allyl alcohol). The diastereomeric ratio was determined through comparison of the relative integrations of the aldehyde peaks in this ^1H NMR spectrum. The diastereomeric mixture was then purified via column chromatography (silica gel, 95:5, petroleum ether/Et_2O, unless noted otherwise), and an isolated yield of the diastereomeric mixture was determined. Pure major diastereomer **26a** was obtained by one further chromatography (silica gel, 9:1, petroleum ether/Et_2O). Pure minor diastereomer **26b** was obtained after two additional chromatographies (silica gel, 9:1, petroleum ether/Et_2O). Carbocycles **31**−**44** were prepared and purified using the same procedure. In certain cases (**34**, **35**, **36**), the major epimer of the major diastereomer was inseparable from the minor epimer of the major diastereomer and the epimers were characterized as a mixture. Racemic samples of the Michael−Michael products **26** and **31**−**44** were prepared in a similar manner using racemic catalyst **1a**.

(1*S*,5*S*,6*S*)-Ethyl 5-Butyl-6-formyl-3-hydroxy-4′-nitro-1,4,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxylate, 26b. Clear oil. $[\alpha]^{26}_D$ = +80.4 (*c* 0.60, $CHCl_3$, 93% ee); IR (thin film, KBr) 2957, 2928, 2858, 1721, 1653, 1519, 1347, 1277, 1230, 1094, 1044, 854 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.56 (s, 1H), 9.83 (s, 1H), 8.17 (d, *J* = 8.7 Hz, 2H), 7.36 (d, *J* = 8.7 Hz, 2H), 4.40 (d, *J* = 2.7 Hz, 1H), 4.02 (qd, *J* = 7.1, 1.7 Hz, 2H), 2.50−2.68 (m, 2H), 2.32 (dd, *J* = 18.8, 10.8 Hz, 1H), 1.95 (dd, *J* = 16.3, 6.2 Hz, 1H), 1.42−1.54 (m, 2H), 1.21−1.22 (m, 4H), 0.96 (t, *J* = 7.1 Hz, 3H), 0.83 (dd, *J* = 9.1, 4.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.5, 173.2, 171.4, 152.1, 146.7, 128.6, 123.7, 97.2, 60.7, 56.6, 38.9, 33.0, 31.9, 30.1, 29.4, 22.5, 13.9, 13.8 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane/*i*-PrOH = 99:1), 0.1 mL/min; major enantiomer t_R = 22.9 min, minor enantiomer t_R = 20.3 min; HRMS (ESI) calcd for $C_{20}H_{25}NO_6$ $[M]^+$ 375.1682, found 375.1687.

(1*S*,5*S*,6*R*)-Ethyl 5-Butyl-6-formyl-3-hydroxy-4′-nitro-1,4,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxylate, 26a. Clear oil. $[\alpha]^{23}_D$ = +26.2 (*c* 0.59, $CHCl_3$, 94% ee); IR (thin film, KBr) 2957, 2930, 2860, 1722, 1655, 1621, 1520, 1347, 1278, 1221, 1156, 1109, 854, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.47 (s, 1H), 9.12 (d, *J* = 4.4 Hz, 1H), 8.18 (d, *J* = 8.7 Hz, 2H), 7.31 (d, *J* = 8.7 Hz, 2H), 4.33 (d, *J* = 5.6 Hz, 1H), 4.02 (dd, *J* = 12.5, 7.1 Hz, 2H), 2.82 (dd, *J* = 18.6, 5.7 Hz, 1H), 2.50−2.55 (m, 1H), 2.15−2.35 (m, 2H), 1.14−1.40 (m, 6H), 1.00 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.3, 172.5, 170.9, 148.0, 147.1, 129.9, 123.5, 99.0, 60.7, 54.9, 41.2, 33.9, 33.7, 28.2, 27.9, 22.7, 13.9, 13.8 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane/*i*-PrOH = 90:10), 0.5 mL/min; major enantiomer t_R = 20.2 min, minor enantiomer t_R = 37.8 min. HRMS (ESI) calcd for $C_{20}H_{25}NO_6$ $[M]^+$ 375.1682, found 375.1690.

(1*S*,5*S*,6*S*)-Ethyl 6-Formyl-3-hydroxy-5-methyl-4′-nitro-1,4,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxylate, 31. Clear oil. $[\alpha]^{25}_D$ = +59.8 (*c* 0.45, $CHCl_3$, 98% ee); IR (thin film, KBr) 2962, 2925, 1722, 1651, 1519, 1348, 1277, 1225, 1099, 853, 736, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.56 (s, 1H), 9.81 (d, *J* = 0.6 Hz, 1H), 8.10−8.19 (m, 2H), 7.32−7.40 (m, 2H), 4.40 (d, *J* = 3.8 Hz, 1H), 4.01 (qd, *J* = 7.1, 2.9 Hz, 2H), 2.62 (dd, *J* = 18.5, 5.6 Hz, 1H), 2.53 (t, *J* = 3.4 Hz, 1H), 2.33 (dd, *J* = 18.1, 10.0 Hz, 1H), 2.22 (dd, *J* = 6.8, 3.4 Hz, 1H), 1.13 (d, *J* = 6.9 Hz, 3H), 0.95 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.2, 172.9, 171.4, 152.3, 146.7, 128.6, 123.6, 97.2, 60.7, 57.9, 38.5, 34.9, 24.9, 17.4, 13.8 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane/*i*-PrOH = 99:1), 0.2 mL/min; major enantiomer t_R = 38.4 min, minor enantiomer t_R = 43.8 min. HRMS (ESI) calcd for $C_{17}H_{19}NO_6$ $[M - H]^-$ 332.1139, found 332.1121.

(1*S*,5*S*,6*S*)-Ethyl 5-Ethyl-6-formyl-3-hydroxy-4′-nitro-1,4,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxylate, 32. Clear oil. $[\alpha]^{23}_D$ = +62.9 (*c* 1.67, $CHCl_3$, 95% ee); IR (thin film, KBr) 2965, 2933, 2877, 1721, 1652, 1519, 1348, 1275, 1222, 853, 756, 737, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.57 (s, 1H), 9.83 (s, 1H), 8.17 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.6 Hz, 2H), 4.41 (d, *J* = 2.7 Hz, 1H), 4.02 (qd, *J* = 7.1, 1.7 Hz, 2H), 2.53−2.70 (m, 2H), 2.31 (dd, *J* = 18.8, 10.9 Hz, 1H), 1.79−1.95 (m, 1H), 1.54 (ddd, *J* = 29.7, 14.3, 6.9 Hz, 2H), 0.97 (t, *J* = 7.1 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.5, 173.2, 171.4, 152.1, 146.7, 128.6, 123.7, 97.2, 60.7, 56.5, 38.9, 32.6, 31.8, 25.2, 13.8, 11.8 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane/*i*-PrOH = 97:3), 0.5 mL/min; major enantiomer t_R = 25.8 min, minor enantiomer t_R = 32.7 min. HRMS (ESI) calcd for $C_{18}H_{21}NO_6$ $[M]^+$ 347.1369, found 347.1360.

(1*S*,5*R*,6*S*)-Ethyl 6-Formyl-3-hydroxy-5-isopropyl-4′-nitro-1,4,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxylate, 33. Clear oil. $[\alpha]^{24}_D$ = +71.7 (*c* 1.71, $CHCl_3$, >99% ee); IR (thin film, KBr) 2962, 2927, 2872, 1720, 1655, 1519, 1348, 1301, 1281,1264, 1223, 1096, 1033, 854, 832 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.55 (s, 1H), 9.85 (s, 1H), 8.18 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 4.42 (s, 1H), 4.04 (qd, *J* = 7.1, 0.8 Hz, 2H), 2.76 (s, 1H), 2.66 (dd, *J* = 19.1, 6.1 Hz, 1H), 2.31 (dd, *J* = 19.0, 12.1 Hz, 1H), 1.78−1.94 (m, 1H), 1.35−1.48 (m, 1H), 0.99 (t, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.7, 173.7, 171.3, 151.6, 146.8, 128.4, 123.7, 96.6, 60.8, 54.0, 39.4, 36.9, 31.7, 31.6, 29.7, 21.1, 20.6, 13.9 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane/*i*-PrOH = 99:1), 0.3 mL/min; major enantiomer t_R = 31.6 min, minor enantiomer t_R = 50.4 min. HRMS (ESI) calcd for $C_{19}H_{22}NO_6$ $[M - H]^-$ 360.1447, found 360.1448.

(1′*S*,2′*S*,3′*S*)-Ethyl 2′-Formyl-5′-hydroxy-4″-nitro-1′,2′,3′,6′-tetrahydro-[1,1′:3′,1″-terphenyl]-4′-carboxylate, 34. White amorphous solid. $[\alpha]^{23}_D$ = +247.5 (*c* 0.93, $CHCl_3$, 99% ee (**34**), >99% ee (**epi-34**)); IR (thin film, KBr) 2983, 1722, 1653, 1618, 1596, 1518, 1403, 1347, 1259, 1217, 1065, 853, 829, 753, 700 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$) (10:1 mixture of 18 to its C4 epimer) δ 12.69 (s, 1H, **34**), 12.55 (s, 1H, **epi-34**), 9.68 (s, 1H, **34**), 8.88 (d, *J* = 3.8 Hz, 1H, **epi-34**), 8.28−8.17 (m, 4H, **34** + **epi-34**), 7.50−7.04 (m, 14H, **34** + **epi-34**), 4.66−4.49 (m, 2H, **34** + **epi-34**), 4.12−4.07 (m, 4H, **34** + **epi-34**), 3.55−3.26 (m, 2H, **34** + **epi-34**), 3.06−3.19 (m, 1H, **epi-34**), 3.05−2.75 (m, 4H, **34** + **epi-34**), 2.66 (dd, *J* = 19.0, 11.4 Hz, 1H, **epi-34**), 1.06−0.93 (m, 6H, **34** + **epi-34**); ^{13}C NMR (101 MHz, $CDCl_3$) (10:1 mixture of 18 to its C4 epimer) δ 203.4 (**epi-18**), 200.8, 172.5, 172.2 (**epi-18**), 172.1 (**epi-18**), 171.4, 152.1, 146.9, 140.5 (**epi-18**), 139.2, 130.2 (**epi-18**), 129.3 (**epi-18**), 128.9, 128.6, 127.7 (**epi-18**), 127.6 (**epi-18**), 127.4, 127.3, 123.9, 123.6 (**epi-18**), 97.1, 60.8, 58.5, 54.3 (**epi-18**), 41.4 (**epi-18**), 38.8, 37.5 (**epi-18**), 35.3 (**epi-18**), 34.3, 31.0, 30.9 (**epi-18**), 13.8 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane/*i*-PrOH = 95:5), 1.0 mL/min; major diastereomer: major enantiomer t_R = 27.9 min, minor enantiomer t_R = 35.9 min; minor diastereomer: major enantiomer t_R = 48.7 min, minor enantiomer t_R = 56.1 min. HRMS (ESI) calcd for $C_{22}H_{21}NO_6$ $[M - H]^-$ 394.1291, found 394.1271. Purification on silica gel was best achieved using 60/40 CH_2Cl_2/petroleum ether.

(1′*S*,2′*S*,3′*S*)-Ethyl 2′-Formyl-5′-hydroxy-1′,2′,3′,6′-tetrahydro-[1,1′:3′,1″-terphenyl]-4′-carboxylate, 35. Clear oil.

$[\alpha]^{26}_{D}$ = +86.2 (*c* 2.0, $CHCl_3$, 99% ee); IR (thin film, KBr) 3060, 3027, 2907, 2829, 2732, 1722, 1652, 1621, 1495, 1452, 1403, 1370, 1351, 1292, 1259, 1216, 1066, 1032, 831, 756, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (5:1 mixture of **35** to its C4 epimer) δ 12.68 (s, 1H, **35**), 12.53 (s, 1H, **epi-35**), 9.72 (s, 1H, **35**), 8.84 (d, *J* = 4.4 Hz, 1H, **epi-35**), 7.05−7.44 (m, 20H, **35** + **epi-35**), 4.39−4.51 (m, 2H, **35** + **epi-35**), 3.98−4.17 (m, 4H, **35** + **epi-35**), 3.58 (td, *J* = 11.9, 6.2 Hz, 1H, **epi-35**), 3.36−3.48 (m, 1H, **35**), 2.73−3.10 (m, 6H, **35** + **epi-35**), 1.01 (t, *J* = 7.1 Hz, 6H, **35** + **epi-35**); ^{13}C NMR (101 MHz, $CDCl_3$) (5:1 ratio of major **35** to its C4 epimer) δ 204.7 (**epi-19**), 201.9, 171.9, 171.9, 171.4 (**epi-19**), 144.0, 141.2 (**epi-19**), 140.2, 139.5 (**epi-19**), 129.3 (**epi-19**), 129.1 (**epi-19**), 128.7, 128.5, 128.4 (**epi-19**), 127.7 (**epi-19**), 127.6, 127.4 (**epi-19**), 127.4, 127.1 (**epi-19**), 127.0, 126.6, 99.9 (**epi-19**), 97.9, 60.5, 59.0, 54.6 (**epi-19**), 41.7 (**epi-19**), 38.9, 37.5 (**epi-19**), 35.2 (**epi-19**), 34.1, 31.1, 13.8 ppm; the enantiomeric excess of a mixture of **35** and **epi-35** was determined by HPLC with an AS-H column (*n*-hexane/*i*-PrOH = 97:3), 0.5 mL/min; major diastereomer: major enantiomer t_R = 14.8 min, minor enantiomer t_R = 17.8 min; minor diastereomer: major enantiomer t_R = 59.6 min, minor enantiomer t_R = 28.5 min. HRMS (ESI) calcd for $C_{22}H_{22}O_4$ $[M]^+$ 350.1518, found 350.1505.

(1′*S*,2′*S*,3′*S*)-Ethyl 2′-Formyl-5′-hydroxy-4″-methyl-1′,2′,3′,6′-tetrahydro-[1,1′:3′,1″-terphenyl]-4′-carboxylate, 36. Clear oil. $[\alpha]^{23}_{D}$ = +101.3 (*c* 2.0, $CHCl_3$, 99% ee (**36**) 95% ee (**epi-36**)); IR (thin film, KBr) 2979, 2922, 2730, 1723, 1652, 1619, 1510, 1497, 1454, 1403, 1365, 1259, 1215, 1096, 1065, 821, 759, 699; ^1H NMR (400 MHz, $CDCl_3$) (2.5:1 ratio of **36** to its C4 epimer) δ 12.63 (s, 1H, **36**), 12.48 (s, 1H, **epi-36**), 9.69 (d, *J* = 0.6 Hz, 1H, **36**), 8.80 (d, *J* = 4.4 Hz, 1H, **epi-36**), 6.96−7.36 (m, 18H, **36** + **epi-36**), 4.29−4.42 (m, 2H, **36** + **epi-36**), 3.97−4.13 (m, 4H, **36** + **epi-36**), 3.27−3.64 (m, 2H, **36** + **epi-36**), 2.69−3.04 (m, 6H, **36** + **epi-36**), 2.29−2.38 (m, 6H, **36** + **epi-36**), 1.02 (td, *J* = 7.1, 1.1 Hz, 6H, **36** + **epi-36**); ^{13}C NMR (101 MHz, $CDCl_3$) (2.5:1 ratio of **36** to its C4 epimer) δ 204.9 (**epi-20**), 202.1, 172.0, 171.8, 171.5 (**epi-20**), 171.2 (**epi-20**), 141.3 (**epi-20**), 140.9, 140.3, 136.6 (**epi-20**), 136.4 (**epi-20**), 136.0, 129.2, 129.1 (**epi-20**), 129.0 (**epi-20**), 128.7, 127.7 (**epi-20**), 127.5, 127.4, 127.0 (**epi-20**), 100.1 (**epi-20**), 98.1, 60.5, 59.1, 54.6 (**epi-20**), 41.2 (**epi-20**), 38.5, 37.5 (**epi-20**), 35.2 (**epi-20**), 34.1, 31.1, 21.0, 13.8 ppm; the enantiomeric excess of a mixture of **36** and **epi-36** was determined by HPLC with an AS-H column (*n*-hexane/*i*-PrOH = 97:3), 0.5 mL/min; major diastereomer: major enantiomer t_R = 14.3 min, minor enantiomer t_R = 17.9 min; minor diastereomer: major enantiomer t_R = 47.3 min, minor enantiomer t_R = 27.3 min. HRMS (ESI) calcd for $C_{23}H_{24}O_4$ $[M]^+$ 364.1675, found 364.1675.

(1′*S*,2′*S*,3′*R*)-Ethyl 2″-Fluoro-2′-formyl-5′-hydroxy-1′,2′,3′,6′-tetrahydro-[1,1′:3′,1″-terphenyl]-4′-carboxylate, 37. Clear oil. $[\alpha]^{23}_{D}$ = +82.5 (*c* 2.0, $CHCl_3$, 98% ee); IR (thin film, KBr) 2982, 2929, 2734, 1724, 1620, 1654, 1486, 1454, 1404. 1259, 1216, 1094, 1066, 1034, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.68 (s, 1H), 9.71 (s, 1H), 6.99−7.39 (m, 9H), 4.80 (s, 1H), 4.09 (tdd, *J* = 10.8, 7.1, 3.6 Hz, 2H), 3.26−3.40 (m, 1H), 3.02 (dd, *J* = 18.3, 12.4 Hz, 2H), 2.79 (dd, *J* = 18.4, 5.5 Hz, 1H), 1.02 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.6, 172.9, 171.9, 161.8, 159.3, 140.3, 129.5, 129.0, 127.7, 127.4, 124.2, 124.2, 115.9, 115.7, 97.2, 60.9, 56.9, 34.9, 32.3, 32.3, 31.2, 14.1 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane/*i*-PrOH = 97:3), 0.5 mL/min; major enantiomer t_R = 27.1 min, minor enantiomer t_R = 18.8 min. HRMS (ESI) calcd for $C_{22}H_{21}FO_4$ $[M]^+$ 368.1424, found 368.1426.

(1*S*,2*S*,3*R*)-Ethyl 2-Formyl-3-(furan-2-yl)-5-hydroxy-1,2,3,6-tetrahydro-[1,1′-biphenyl]-4-carboxylate, 38. Yellow amorphous solid. $[\alpha]^{23}_{D}$ = +123.4 (*c* 1.7, $CHCl_3$, 98% ee); IR (thin film, KBr) 2926, 2851, 2731, 1724, 1654, 1620, 1498, 1277, 1239, 1218, 1096, 1060, 828, 761, 741, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.49 (s, 1H), 9.07 (d, *J* = 4.0 Hz, 1H), 7.10−7.40 (m, 6H), 6.31 (d, *J* = 1.9 Hz, 1H), 6.08 (d, *J* = 3.0 Hz, 1H), 4.43 (d, *J* = 4.9 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.55 (td, *J* = 11.8, 6.2 Hz, 1H), 2.93 (dt, *J* = 12.4, 4.5 Hz, 1H), 2.81 (dd, *J* = 18.9, 6.2 Hz, 1H), 2.52 (dd, *J* = 18.9, 11.3 Hz, 1H), 1.15 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.1, 171.9, 171.4, 153.9, 141.9, 141.2, 129.1, 127.7, 127.4, 110.3, 108.5, 97.9, 60.7, 54.4, 37.5, 36.4, 35.1, 14.0 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane/*i*-PrOH = 97:3), 0.5 mL/min; major enantiomer t_R = 32.7 min, minor enantiomer t_R = 36.5 min. HRMS (ESI) calcd for $C_{20}H_{20}O_5$ $[M]^+$ 340.1311, found 340.1311.

(1*S*,2*S*,3*R*)-Diethyl 2-Formyl-5-hydroxy-1,2,3,6-tetrahydro-[1,1′-biphenyl]-3,4-dicarboxylate, 39. Clear oil. $[\alpha]^{23}_{D}$ = +18.5 (*c* 1.1, $CHCl_3$, 91% ee); IR (thin film, KBr) 2982, 2936, 2736, 1724, 1660, 1624, 1406, 1371, 1264, 1218, 1183, 1069, 1032, 830, 758, 737, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.44 (s, 1H), 9.54 (s, 1H), 7.34 (dt, *J* = 12.5, 7.8 Hz, 5H), 4.13−4.36 (m, 4H), 4.01 (d, *J* = 1.5 Hz, 1H), 3.43−3.54 (m, 1H), 3.30 (s, 1H), 2.77 (ddd, *J* = 23.4, 18.3, 8.6 Hz, 2H), 1.30 (dd, *J* = 12.9, 7.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.2, 173.6, 171.7, 171.5, 139.3, 128.9, 127.4, 95.5, 61.4, 60.8, 53.5, 39.4, 36.4, 30.7, 14.4, 14.1 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane/*i*-PrOH = 97:3), 0.5 mL/min; major enantiomer t_R = 21.2 min, minor enantiomer t_R = 32.3 min; HRMS (ESI) calcd for $C_{19}H_{22}O_6$ $[M - H]^-$ 345.1338, found 345.1345.

(1*S*,2*S*,3*R*)-Ethyl 3-Butyl-2-formyl-5-hydroxy-1,2,3,6-tetrahydro-[1,1′-biphenyl]-4-carboxylate, 40. Clear oil. $[\alpha]^{23}_{D}$ = −44.5 (*c* 2.23, $CHCl_3$, 98% ee); IR (thin film, KBr) 2956, 2930, 2871, 1722, 1617, 1403, 1261, 1213, 1064, 831, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.45 (s, 1H), 9.60 (s, 1H), 7.32 (ddd, *J* = 17.9, 12.8, 5.6 Hz, 5H), 4.27 (dddd, *J* = 25.1, 10.8, 7.1, 3.7 Hz, 2H), 3.36−3.53 (m, 1H), 2.94−3.08 (m, 2H), 2.89 (d, *J* = 1.7 Hz, 1H), 2.64 (dd, *J* = 18.5, 5.8 Hz, 1H), 1.72−1.84 (m, 1H), 1.29−1.54 (m, 8H), 0.96 (dd, *J* = 9.7, 3.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.8, 172.2, 170.8, 140.9, 128.8, 127.5, 127.0, 100.6, 60.6, 53.2, 34.6, 34.2, 32.8, 31.0, 30.1, 22.4, 14.2, 14.0 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane/*i*-PrOH = 99:1), 0.3 mL/min; major enantiomer t_R = 26.3 min, minor enantiomer t_R = 29.5 min. HRMS (ESI) calcd for $C_{20}H_{26}O_4$ $[M + H]^+$ 331.1904, found 331.1904.

(1*S*,2*S*,3*R*)-Ethyl 2-Formyl-3-(furan-2-yl)-5-hydroxy-4′-methoxy-1,2,3,6-tetrahydro-[1,1′-biphenyl]-4-carboxylate, 41. Clear oil. $[\alpha]^{23}_{D}$ = +106.1 (*c* 0.47, $CHCl_3$, 97% ee); IR (thin film, KBr) 2927, 2837, 1723, 1653, 1513, 1306, 1278, 1250, 1214, 1179, 1062, 1035, 1012, 831, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.47 (s, 1H), 9.04 (d, *J* = 4.2 Hz, 1H), 7.29−7.37 (m, 1H), 7.08 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.30 (dd, *J* = 2.9, 1.9 Hz, 1H), 6.07 (d, *J* = 3.2 Hz, 1H), 4.40 (d, *J* = 5.0 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 3H), 3.50 (td, *J* = 11.7, 6.1 Hz, 1H), 2.69−2.96 (m, 2H), 2.48 (dd, *J* = 18.9, 11.3 Hz, 1H), 1.15 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.4, 172.0, 171.4, 158.8, 153.9, 141.8, 133.1, 128.7, 114.5, 110.3, 108.4, 97.9, 60.7, 55.2, 54.6, 37.7, 35.6, 35.2, 14.0 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane/*i*-PrOH = 90:10), 0.5 mL/min; major enantiomer t_R = 33.7 min, minor enantiomer t_R = 54.0 min. HRMS (ESI) calcd for $C_{21}H_{22}O_6$ $[M + H]^+$ 371.1489, found 371.1481.

(1′*S*,2′*S*,3′*S*)-Ethyl 4,4″-Dibromo-2′-formyl-5′-hydroxy-1′,2′,3′,6′-tetrahydro-[1,1′:3′,1″-terphenyl]-4′-carboxylate, 42. Colorless crystals, mp 118−120 °C; $[\alpha]^{24}_{D}$ = +81.6 (*c* 0.53, $CHCl_3$, 99% ee); IR (thin film, KBr) 2924, 2853, 1723, 1653, 1488, 1406, 1287, 1258, 1215, 1095, 1072, 1009, 821 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.63 (s, 1H), 9.64 (s, 1H), 7.44 (dd, *J* = 22.2, 8.5 Hz, 4H), 7.12 (d, *J* = 8.3 Hz, 2H), 6.99 (d, *J* = 8.3 Hz, 2H), 4.38 (d, *J* = 1.7 Hz, 1H), 4.06 (tt, *J* = 7.1, 3.5 Hz, 2H), 3.22−3.30 (m, 1H), 2.81−3.02 (m, 2H), 2.74 (dd, *J* = 18.4, 5.4 Hz, 1H), 1.02 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9, 171.9, 171.6, 142.9, 138.9, 131.8, 131.7, 129.3, 129.1, 121.1, 120.6, 97.5, 60.8, 58.7, 38.4, 33.7, 30.9, 13.9 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane/*i*-PrOH = 97:3), 0.5 mL/min; major enantiomer t_R = 22.0 min,

minor enantiomer t_R = 31.0 min. HRMS (ESI) calcd for $C_{22}H_{20}Br_2O_4$ $[M - H]^-$ 504.9650, found 504.9665.

(1*S*,2*S*,3*R*)-Ethyl 2′-Fluoro-2-formyl-3-(furan-2-yl)-5-hydroxy-1,2,3,6-tetrahydro-[1,1′-biphenyl]-4-carboxylate, 43. Clear oil. $[\alpha]^{26}_D$ = +120.3 (*c* 0.71, $CHCl_3$, 93% ee); IR (thin film, KBr) 2983, 2930, 2826, 2731, 1725, 1654, 1622, 1491, 1406, 1307, 1232, 1217, 1097, 1061, 1038, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.48 (s, 1H), 9.14 (d, *J* = 3.6 Hz, 1H), 7.33 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.95−7.25 (m, 4H), 6.30 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.09 (d, *J* = 3.2 Hz, 1H), 4.46 (d, *J* = 5.0 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.84 (td, *J* = 11.8, 6.3 Hz, 1H), 2.95−3.13 (m, 1H), 2.81 (dd, *J* = 18.8, 6.3 Hz, 1H), 2.59 (dd, *J* = 18.8, 11.3 Hz, 1H), 1.16 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.5, 171.7, 171.4, 162.0, 159.6, 153.7, 141.9, 129.1, 129.1, 129.0, 128.9, 128.1, 127.9, 124.8, 124.7, 116.1, 115.9, 110.4, 108.5, 97.9, 60.7, 53.6, 53.5, 35.4, 34.8, 30.3, 14.0 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane/*i*-PrOH = 97:3), 0.5 mL/min; major enantiomer t_R = 31.3 min, minor enantiomer t_R = 18.5 min. HRMS (ESI) calcd for $C_{20}H_{19}FO_5$ $[M]^+$ 358.1217, found 358.1218.

(4*S*,5*S*,6*R*)-Ethyl 5-formyl-4,6-di(furan-2-yl)-2-hydroxycyclohex-1-enecarboxylate, 44. Yellow oil. $[\alpha]^{26}_D$ = +65.3 (*c* 0.58, $CHCl_3$, 95% ee); IR (thin film, KBr) 2925, 2853, 1723, 1654, 1407, 1276, 1217, 1094, 1067, 1012, 812, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.57 (s, 1H), 9.69 (s, 1H), 7.32−7.38 (m, 2H), 6.31 (ddd, *J* = 19.6, 3.2, 1.8 Hz, 2H), 6.10−6.16 (m, 1H), 6.00 (dt, *J* = 3.2, 0.8 Hz, 1H), 4.49 (s, 1H), 4.02−4.25 (m, 2H), 3.39−3.56 (m, 1H), 3.22−3.35 (m, 1H), 2.61−2.84 (m, 2H), 1.16 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.2, 171.7, 171.0, 156.1, 154.1, 141.8, 141.7, 110.4, 110.2, 107.0, 106.1, 96.9, 60.7, 52.3, 32.6, 30.1, 30.0, 14.0 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane/*i*-PrOH = 95:5), 1.0 mL/min; major enantiomer t_R = 17.9 min, minor enantiomer t_R = 25.2 min. HRMS (ESI) calcd for $C_{18}H_{18}O_6$ $[M + Na]^+$ 353.1000, found 353.0992.

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^1H, ^{13}C and HPLC spectra for compounds **26a**, **26b**, **31**−**44** and of an X-ray crystal structure of **42** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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