

A Multifaceted Directing Group Switching Ynones as Michael Donors in Chemo-, Enantio-, and γ -Selective 1,4-Conjugate Additions with Nitroolefins

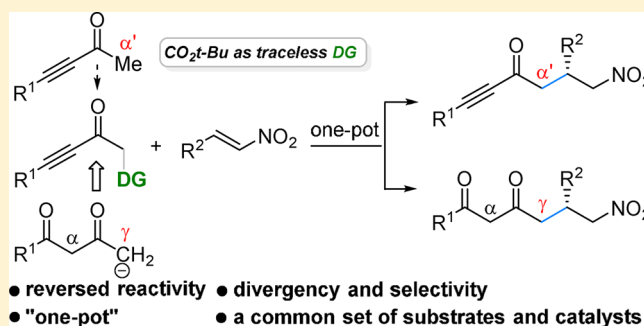
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Supporting Information

ABSTRACT: α,β -Unsaturated ynones have historically been used as Michael acceptors in conjugate addition reactions. Herein, we have demonstrated for the first time that ynones can be harnessed as Michael donors for use in catalytic asymmetric conjugate addition reactions by strategically introducing a $\text{CO}_2t\text{-Bu}$ group as a multitasking directing group. Furthermore, this concept has enabled designer ynones as versatile synthetic equivalents of both α' anions of ynones and γ monoanions of 1,3-diketones, which are synthetically valued but difficult to generate. The first catalytic enantioselective conjugate addition of ynones as Michael donors has been realized in good yields with high enantioselectivities. A unified approach to regiospecifically and chemo- and enantioselectively access hitherto elusive γ -Michael adducts of 1,3-diketones has been achieved in a divergent manner. The strategy described here by exploring new reactivity and creating new reagents holds great potential applications in other still unsolved transformations.

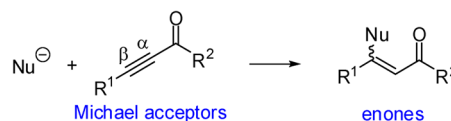


INTRODUCTION

The design of enabling strategies to explore new reactivity and create new reagents is an important but challenging task in modern synthesis and catalysis. The 1,4-conjugate addition is one of the most fundamental and broadly utilized transformations for the construction of C–C bonds. In this context, the conjugate addition reactions of carbonyl compounds have received remarkable attention given their dominance in organic synthesis and catalysis. Significant progress in this area, including diverse Michael acceptors and well-explored catalyst systems, has made available a wide variety of asymmetric conjugate additions of carbonyl compounds.¹ However, the overwhelming majority of reports to date with respect to Michael donors are limited to simple carbonyl compounds. Strategies that allow for the use of functionalized substrates are highly desirable in high demanding complex synthesis.

Ynones are valuable yet underexplored nucleophiles in this research area. Their propensity to act as Michael acceptors renders them challenging substrates² and, in particular, has precluded the development of general conjugate addition methods with ynones as Michael donors (Figure 1). Nonetheless, ynones are versatile compounds for structural proliferation into various synthetic targets. For example, they are attractive precursors to chiral propargylic alcohols,³ and various heterocycles, such as pyrroles,⁴ furans,⁵ furanones,⁶ pyrazoles,⁷

a. Normal reactivity of ynones as Michael acceptors (well known)



b. Reactivity of ynones as Michael donors (unprecedented)

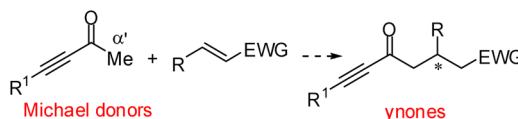


Figure 1. Reactivity of ynone substrates in Michael addition reactions.

isoxazoles,⁸ pyrimidines,⁹ flavones,¹⁰ quinolones,¹¹ and so forth. Ynones also serve as key intermediates for the synthesis of many complex natural products.¹² Thus, if a strategy could enable altering their normal reactivity (from Michael acceptors) to Michael donors, it would represent a significant advance in this field. However, this has proven very challenging.

To date, no general catalytic enantioselective 1,4-conjugate addition reactions of ynones as Michael donors have been

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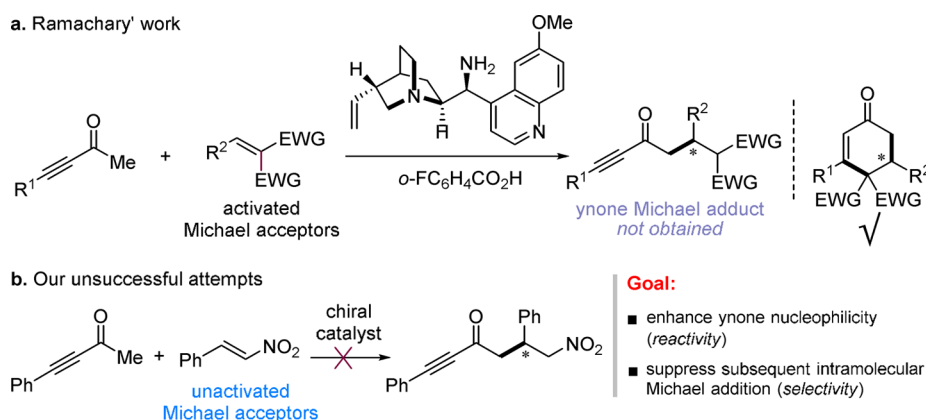


Figure 2. Challenges in the 1,4-addition of ynones as Michael donors.

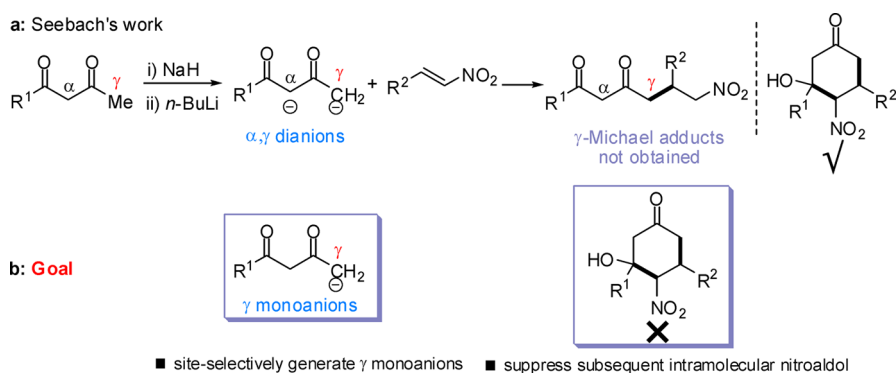


Figure 3. Difficulties in both generating γ -monoanions of 1,3-diketones and accessing γ -Michael adducts.

reported. Recently, the Ramachary group has investigated the catalytic asymmetric conjugate addition reactions of methyl ynones with highly activated Michael acceptors by engineering two strong electron-withdrawing groups (EWGs) (Figure 2a).¹³ Although the utilization of highly active Michael acceptors facilitated the conjugate addition reaction to occur, this Michael acceptor activation strategy did not lead to the ynone Michael adducts; instead, the cyclized products were obtained in good yields with high enantioselectivities as the subsequent intramolecular Michael addition could not be avoided.^{13,14} The ynone in Ramachary's processes definitely acts as a Michael donor/acceptor. Furthermore, the use of highly active electro-deficient olefins bearing two EWGs also significantly limits the reaction scope. The difficulty of using unactivated Michael acceptors was shown by our control studies between 4-phenyl-3-buten-2-one and *trans*- β -nitrostyrene (Figure 2b). Despite extensive attempts, the process failed to deliver the desired ynone Michael adduct. Thus, a new paradigm capable of enhancing the nucleophilicity of ynones for the conjugate addition to unactivated Michael acceptors while concurrently suppressing the subsequent undesired intramolecular Michael addition is highly needed.

On the other hand, because the α -position of 1,3-diketones contains the most acidic proton, 1,3-diketones¹⁵ generally behave as α -anionic nucleophiles in the presence of a base, and such reactivity has been extensively utilized in organic chemistry.¹⁶ In contrast, the site-selective generation of γ monoanions of 1,3-diketones is extremely difficult despite their high potential synthetic utility. Traditionally, α,γ dianions rather than γ monoanions of 1,3-diketones are formed in the presence of a base, which is strong enough to doubly deprotonate the

1,3-dicarbonyl compounds. Furthermore, the use of stoichiometric amounts of strong base compromises practicality. The Seebach group has investigated the γ -selective racemic Michael addition of α,γ dianions of 1,3-diketones with nitroolefins. However, as shown in Figure 3, the corresponding γ -Michael addition products were not obtained; instead, the tandem Michael addition/intramolecular nitroaldol products were formed.¹⁷ Hence, a new protocol that enables inverting the inherent α -selectivity of 1,3-diketones to γ -selectivity, thus allowing efficient access to hitherto inaccessible chiral γ -Michael adducts, is highly desirable.

As part of our continuing effort toward developing new reactivities of the alkyne chemistry for organic transformations,¹⁸ herein we wish to report a simple yet practically useful strategy capable of reversing the reactivity of ynones from Michael acceptors to donors and overcoming the issue of double Michael addition by the incorporation of a traceless directing group (DG).¹⁹ Moreover, this strategy has also enabled designer ynones as versatile synthetic equivalents of both α' anions of ynones and γ monoanions of 1,3-diketones. As demonstrated, the first catalytic enantioselective conjugate addition reaction with ynones as donors has been achieved in good yields with high enantioselectivities. Moreover, an unprecedented unified approach for the regioselective and enantioselective access to hitherto elusive γ -Michael adducts of 1,3-diketones possessing additional, enolizable positions and acidic protons, has been accomplished. Importantly, two different conjugate addition transformations are efficiently carried out in a one-pot manner²⁰ by the use of a common set of substrates and catalysts in a divergent fashion.

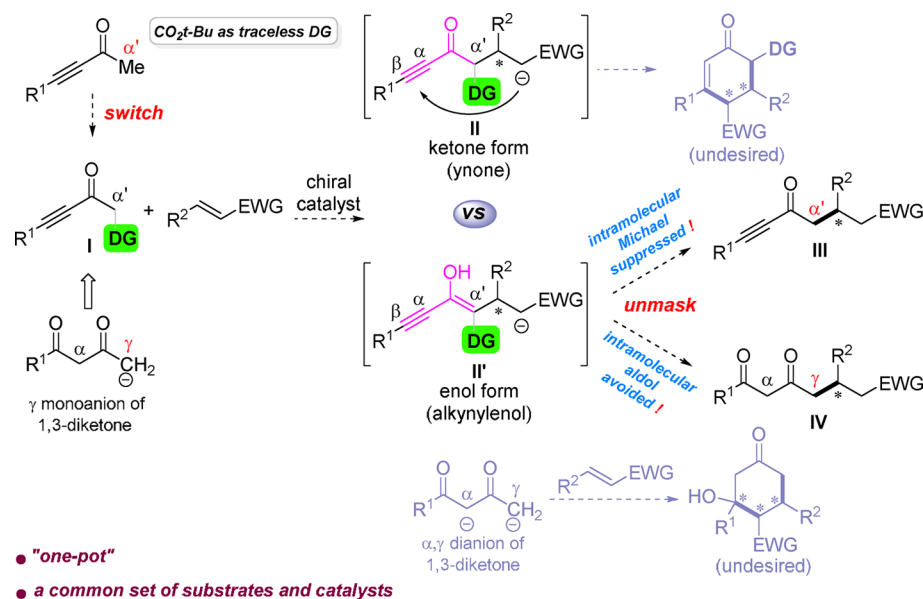


Figure 4. Our design strategy.

RESULTS AND DISCUSSION

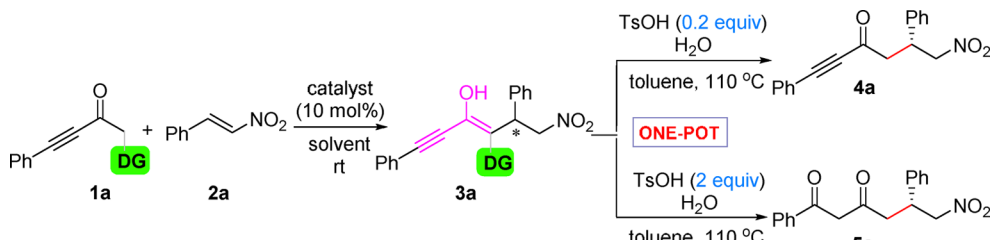
Our design strategy is depicted in Figure 4. We hoped to obtain two different classes of addition products from a common intermediate by using a common and simple catalyst in a controlled fashion. This unified strategy was to incorporate a $\text{CO}_2t\text{-Bu}$ group as the traceless directing group on ynones. The $\text{CO}_2t\text{-Bu}$ group can efficiently activate the α' -position of ynones and significantly enhance the nucleophilicity, thus facilitating the conjugate addition to unactivated Michael acceptors. At the same time, it provides an additional binding site for potential interaction with a catalyst. The resulting bidentate coordination mode of I may facilitate much finer stereocontrol. However, unlike conventional β -keto esters, I bears additional reactive Michael acceptor ynone functionality, the resulting Michael adducts II might undergo an intramolecular Michael addition reaction to form the undesired cyclized products. However, we reasoned that if the resulting Michael adducts could exist in an enol form, such as II', the subsequent undesired intramolecular Michael addition would be strategically suppressed as the result of reduced electrophilicity of the β -position of alkynlenols. The $\text{CO}_2t\text{-Bu}$ group could easily be removed afterward under the catalysis of a Brønsted acid through mild hydrolytic decarboxylation and deliver the ynone products of type III equivalent to conjugate addition of methyl ynones to electron-deficient olefins, which has not been realized to date. It is noteworthy that by carefully controlling the hydrolytic decarboxylation reaction conditions, it might also enable removal of the directing group and simultaneous alkyne hydration to unmask 1,3-diketone functionality, thus revealing hitherto elusive 1,3-diketone γ -conjugate addition adducts IV. Therefore, it would provide a unified solution to two challenging conjugate addition transformations in an efficient and divergent manner. It is worth noting that the employment of I as synthetic equivalents of α' anions of ynones and γ monoanions of 1,3-diketones is unprecedented, and the use of I in a catalytic asymmetric reaction has also not been reported.

To test our hypothesis, and in light of the unmet challenge of γ -selective Michael addition to nitroolefins shown by Seebach,¹⁷ nitroolefins were selected as Michael acceptors²¹ for the reaction with I, which can be easily prepared.²² To our

delight, unlike the Michael addition reaction shown in Figure 2b, the present Michael addition reaction took place smoothly to provide the desired single Michael addition product 3a (Table 1). Notably, the double Michael addition product was not observed. As expected, compound 3a existed in a stable alkynlenol form. Among chiral catalysts examined, bifunctional tertiary amine catalysts were effective.²³ Catalysts 6a–g^{16c,d,f,g} gave low to moderate enantioselectivities (entries 1–7), whereas catalysts 6h^{16b} and 6i^{16e} furnished 80 and 85% ee (entries 8 and 9), respectively. To further improve the enantioselectivity of the product, solvents and additives were screened. Among solvents probed, CH_2Cl_2 was identified to be the choice. The addition of 4 Å molecular sieves resulted in a significant enhancement of the enantioselectivity to an excellent level (96% ee, entry 17). Although the exact role of molecular sieves was not clear, it was proposed that it could absorb the trace water in the reaction system.

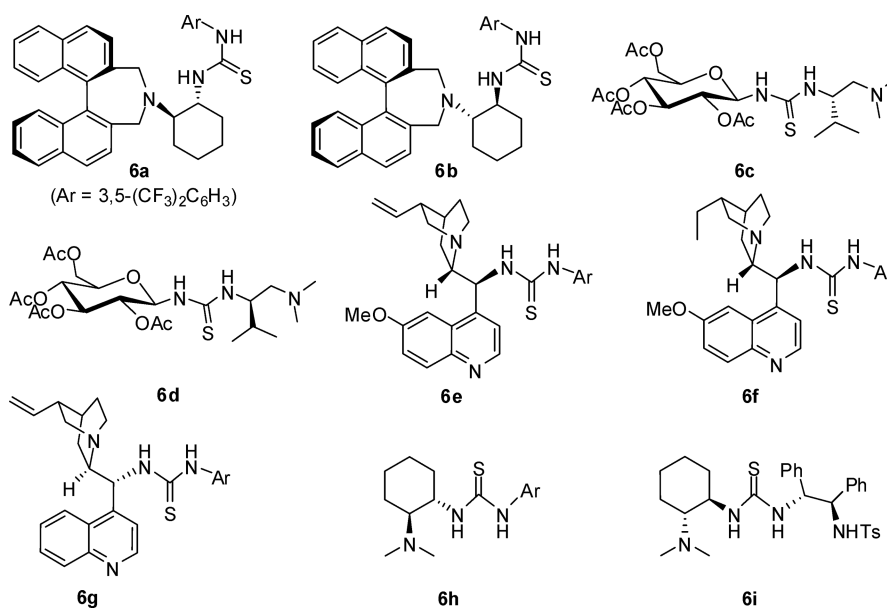
Next, selective removal of the $\text{CO}_2t\text{-Bu}$ directing group was explored. Although acid-mediated hydrolytic decarboxylative removal of the $\text{CO}_2t\text{-Bu}$ group is well-known, selective decarboxylative removal of the $\text{CO}_2t\text{-Bu}$ group of 3a bearing an acid sensitive ynone functionality has not been reported. After an extensive search of the reaction conditions, to our delight, either hydrolytic decarboxylation or decarboxylation/hydration could be highly selectively achieved with the use of a single Brønsted acid TsOH by simply controlling the amount of TsOH without the loss of enantiomeric purity. Notably, the protocol could be performed in a one-pot operation (entry 17). It is noted that Seebach's dianion protocol could not afford γ -Michael product 5a (please see Figure 3),¹⁷ thus highlighting the important merit of I as γ monoanion equivalents of 1,3-ketones.

With the optimized reaction conditions in hand, the generality of this methodology was investigated (Table 2). The two established protocols both show a broad scope. A variety of 1 and 2 can participate in these processes. It appears that the substitution pattern and the electronic property of the substituents on aromatic rings of nitroolefins are well-tolerated. Electron-donating (entries 2–6), or -withdrawing (entries 7–9) groups performed well to give ynones 4b–i and α -

Table 1. Reaction Optimization^b


The reaction scheme illustrates the synthesis of ynone 3a from 1a and 2a using a catalyst (10 mol%) in a solvent at room temperature. Ynone 3a is then converted to 4a and 5a via a one-pot process using TsOH (0.2 equiv) and H₂O in toluene at 110 °C.

entry	catalyst ^a	solvent	yield (%) ^c /ee (%) ^d (3a)	yield (%) ^c /ee (%) ^d (4a)	yield (%) ^c /ee (%) ^d (5a)
1	6a	DCM	71/66		
2	6b	DCM	70/-67		
3	6c	DCM	63/-51		
4	6d	DCM	65/50		
5	6e	DCM	55/-37		
6	6f	DCM	60/-27		
7	6g	DCM	52/39		
8	6h	DCM	73/-80		
9	6i	DCM	84/85		
10	6i	DCE	72/68		
11	6i	CHCl ₃	76/71		
12	6i	THF	80/67		
13	6i	Et ₂ O	46/15		
14	6i	PhCH ₃	60/17		
15 ^e	6i	DCM	57/27		
16 ^f	6i	DCM	65/35		
17 ^g	6i	DCM	85/96	81/96	84/96

^a

^bReaction was performed with **1a** (0.2 mmol) and **2a** (0.24 mmol). ^cYield of isolated product. ^dee was determined by chiral HPLC. ^ePhCO₂H (10 mol %) was added. ^fEt₃N (10 mol %) was added. ^gMS (4 Å, 12 mg) was added.

unsubstituted 1,3-diketones **5b–i** in good yields with high enantioselectivities, respectively. Heteroaryl nitroolefins are also suitable substrates (entries 10 and 11). Moreover, the procedures are also applicable for aliphatic nitroolefin to afford 97% ee value (entry 12). Structural variations on ynones are probed next. It is found that various aryl- and alkyl-ynones reacted well with aryl nitroolefins (entries 1 and 13–16). Thus, structurally diverse adducts, ynones **4**, and α -unsubstituted 1,3-diketones **5** were attended from the same set of substrates and

catalysts in good yields with high enantioselectivities. It is noted that given the versatility of ynones in organic synthesis, various methods have been developed for their synthesis.²⁴ The present protocol provides a conceptually distinct and powerful manifold for the preparation of highly enantiomerically enriched ynones. The resulting α -unsubstituted 1,3-diketones obtained are important structural motifs widely distributed in a number of natural products, pharmaceuticals, and biologically active

Table 2. Substrate Scope

entry	R ¹	R ²	yield (%) ^a /ee (%) ^b (4)	yield (%) ^a /ee (%) ^b (5)
1	C ₆ H ₅	C ₆ H ₅	81/96 (4a)	84/96 (5a)
2	C ₆ H ₅	4-Me-C ₆ H ₄	80/99 (4b)	83/99 (5b)
3	C ₆ H ₅	3-Me-C ₆ H ₄	81/97 (4c)	82/97 (5c)
4	C ₆ H ₅	4-MeO-C ₆ H ₄	80/99 (4d)	84/99 (5d)
5	C ₆ H ₅	2-MeO-C ₆ H ₄	80/97 (4e)	84/97 (5e)
6	C ₆ H ₅	1,3-benzodioxole	81/98 (4f)	84/98 (5f)
7	C ₆ H ₅	4-Br-C ₆ H ₄	84/95 (4g)	85/95 (5g)
8	C ₆ H ₅	2-Br-C ₆ H ₄	81/95 (4h)	83/96 (5h)
9	C ₆ H ₅	4-CF ₃ -C ₆ H ₄	81/93 (4i)	84/92 (5i)
10	C ₆ H ₅	2-furyl	81/98 (4j)	85/97 (5j)
11	C ₆ H ₅	2-thienyl	81/97 (4k)	85/97 (5k)
12	C ₆ H ₅	<i>i</i> -Bu	81/97 (4l)	85/97 (5l)
13	4-Me-C ₆ H ₄	C ₆ H ₅	81/98 (4m)	84/99 (5m)
14	4-F-C ₆ H ₄	C ₆ H ₅	82/94 (4n)	84/94 (5n)
15	<i>n</i> -Bu	C ₆ H ₅	80/96 (4o)	81/96 (5o)
16	<i>n</i> -Hex	C ₆ H ₅	82/93 (4p)	84/94 (5p)
17	<i>n</i> -Hex	<i>i</i> -Bu	N.R.	N.R.

^aYield of isolated product. ^bee was determined by chiral HPLC.

compounds or are key intermediates en route to such species.^{15,25}

The absolute configuration of product 4a could be determined by a three-step procedure (Figure 5). The

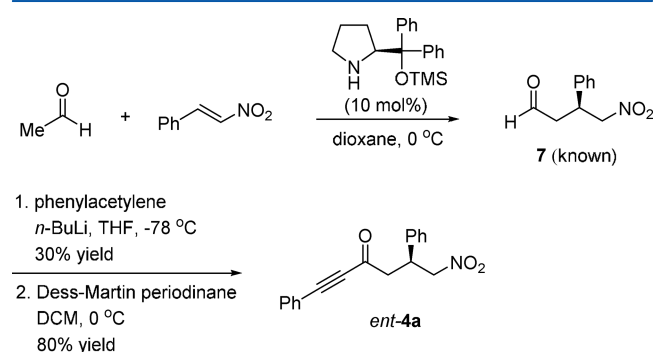


Figure 5. Determination of the absolute configuration of 4a.

enantioselective organocatalyzed conjugate addition of acetaldehyde to *trans*- β -nitrostyrene afforded aldehyde 7 whose absolute configuration is known.²⁶ Aldehyde 7 reacted with PhC \equiv CLi at -78 °C followed by Dess–Martin oxidation to provide *ent*-4a.

The enantioselectivity of the conjugate addition step could be explained via the transition state model shown in Figure 6.

The synthetic utility of the Michael products for generating new useful chiral building blocks has been demonstrated in several selective transformations (Figure 7). Chiral catalyst-controlled chemo- and diastereoselective reductions of ynone 4a by (*S*)- and (*R*)-CBS were implemented to give *syn*- and *anti*-propargylic alcohols 9 and 10, respectively, which are useful building blocks in organic synthesis.²⁷ Pd/C-catalyzed selective hydrogenation of C \equiv C triple bond of 4a afforded

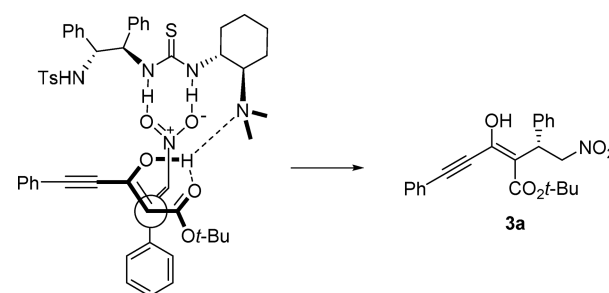


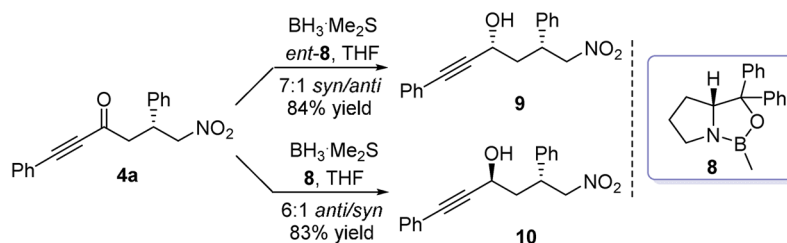
Figure 6. Proposed stereochemical model.

compound 11, a formal conjugate addition product of the ketone bearing two enolizable positions. The conjugate addition of a dithiol to ynone 4a offered β -keto 1,3-dithianes 12, which are versatile building blocks in organic synthesis.²⁸ In these transformations, no erosion of optical purity was observed.

CONCLUSIONS

In summary, we have developed a general and practically useful strategy for switching the inherent reactivity of ynones, generally used as Michael acceptors, to Michael donors, by the efficient incorporation a traceless directing group. Incorporation of a simple CO₂*t*-Bu group into the α '-position of ynones not only enables the catalytic enantioselective Michael addition of ynones to unactivated Michael acceptors but also significantly retards the subsequent undesired intramolecular Michael addition reaction. Furthermore, the CO₂*t*-Bu group provides an additional interaction site with the catalyst to achieve excellent enantioselectivity. Notably, this strategy has also enabled convenient synthetic equivalents of γ monoanions of 1,3-diketones, allowing regiospecific and enantioselective access to γ -Michael adducts of 1,3-diketones,

a. Diastereoselective, catalyst-controlled synthesis of propargylic alcohols



b. Chemoselective reduction of unsaturated bonds

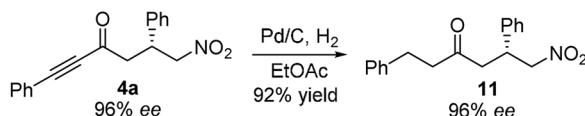
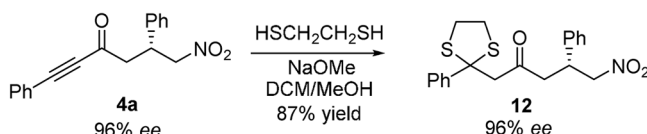
c. Generation of β -keto 1,3-dithianes

Figure 7. Diverse transformations of Michael adducts.

which could not be achieved by the traditional dianion method. Impressively, two different conjugate addition transformations are efficiently carried out in a one-pot manner by the use of a common set of substrates and catalysts. We believe that the powerful strategy and versatile synthetic equivalents of both α' anions of ynones and γ monoanions of 1,3-diketones described in this work will find more applications in other challenging transformations.

EXPERIMENTAL SECTION

^1H and ^{13}C NMR spectra were recorded at 300 and 400 MHz on a spectrophotometer. Chemical shifts (δ) are expressed in ppm, and J values are given in Hz. The enantiomeric excess was determined by chiral HPLC with *n*-hexane and 2-propanol as eluents. High resolution mass spectrometry (HRMS) was recorded on a spectrometer using a time-of-flight (TOF) analyzer. Optical rotations were measured on a polarimeter. All chemicals and solvents were used as received without further purification unless otherwise stated. Flash column chromatography was performed on silica gel (230–400 mesh).

General Procedure for the Asymmetric Catalytic Conjugate Addition of Ynones. To a solution of **1** (0.2 mmol) and **2** (0.24 mmol) in DCM (0.5 mL) were added chiral catalyst **6i** (0.02 mmol, 10 mol %) and a 4 Å molecular sieve (12 mg). After stirring for 72 h at room temperature, the mixture was concentrated at reduced pressure. The residue was purified by flash column chromatography using ethyl acetate/petroleum ether as the eluent to afford **3**.

(S,Z)-tert-Butyl 3-Hydroxy-2-(2-nitro-1-phenylethyl)-5-phenylpent-2-en-4-ynoate (3a). Yellow oil, 66.8 mg, 85% yield. $[\alpha]_{\text{D}}^{20}$ –79.2 (c 1.0 CHCl_3). ^1H NMR (300 MHz, CDCl_3): δ 12.84 (s, 1H), 7.52–7.50 (m, 2H), 7.49–7.23 (m, 2H), 7.21–7.17 (m, 5H), 5.18 (t, J = 7.5 Hz, 1H), 5.11–4.91 (m, 2H), 1.23 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3): δ 171.3, 155.8, 139.1, 132.4, 130.2, 128.6, 128.5, 127.1, 126.7, 120.6, 108.3, 98.8, 84.0, 42.5, 28.1. HPLC (Chiralcel OD-H, *n*-hexane/2-propanol = 98:2, flow rate = 0.8 mL/min, λ = 254 nm): t_{minor} = 10.2 min, t_{major} = 15.4 min. HRMS (EI-TOF): calcd for $\text{C}_{23}\text{H}_{23}\text{NO}_5\text{K}^+$ [$\text{M} + \text{K}$] $^+$, 432.1207; found, 432.1210.

General Procedure for the Catalytic Enantioselective Synthesis of Ynones 4. To a solution of **1** (0.2 mmol) and **2** (0.24 mmol) in DCM (0.5 mL) were added chiral catalyst **6i** (0.02 mmol, 10 mol %) and a 4 Å molecular sieve (12 mg). After stirring for 72 h at room temperature, the mixture was concentrated at reduced pressure. The residue was dissolved in toluene (5 mL). To the resulting solution

was added *p*-toluenesulfonic acid monohydrate (7.6 mg, 0.04 mmol), and the resulting mixture was stirred at 110 °C for 10 h. After removal of solvent by evaporation, the residue was purified by flash column chromatography using ethyl acetate/petroleum ether (1:10) as the eluent to afford **4**.

(R)-6-Nitro-1,5-diphenylhex-1-yn-3-one (4a). White solid, 47.5 mg, 81% yield. $[\alpha]_{\text{D}}^{20}$ +9.4 (c 1.0 CHCl_3). ^1H NMR (300 MHz, CDCl_3): δ 5.79 (dd, J = 5.4 Hz, 8.4 Hz, 2H), 7.37–7.27 (m, 5H), 7.11 (t, J = 8.4 Hz, 2H), 4.79–4.63 (m, 2H), 4.23–4.13 (m, 1H), 3.18 (d, J = 7.2 Hz, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 183.9, 138.1, 135.6, 135.5, 129.2, 128.1, 127.5, 116.5, 116.2, 91.2, 87.4, 79.3, 48.0, 39.5. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 95:5, flow rate = 0.8 mL/min, λ = 254 nm): t_{minor} = 20.1 min, t_{major} = 29.4 min. HRMS (EI-TOF): calcd for $\text{C}_{18}\text{H}_{15}\text{NO}_3\text{Na}^+$ [$\text{M} + \text{Na}$] $^+$, 316.0944; found, 316.0944.

(R)-6-Nitro-1-phenyl-5-*p*-tolylhex-1-yn-3-one (4b). Yellow oil, 49.1 mg, 80% yield. $[\alpha]_{\text{D}}^{20}$ –1.3 (c 1.0 CHCl_3). ^1H NMR (300 MHz, CDCl_3): δ 7.59–7.38 (m, 5H), 7.17 (s, 3H), 4.78–4.61 (m, 2H), 4.21–4.12 (m, 1H), 3.15 (d, J = 6.9 Hz, 2H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 184.1, 137.8, 135.1, 133.2, 131.1, 129.8, 127.3, 119.5, 92.2, 87.5, 79.5, 48.2, 39.1, 21.0. HPLC (Chiralcel OD-H, *n*-hexane/2-propanol = 95:5, flow rate = 0.8 mL/min, λ = 254 nm): t_{minor} = 18.1 min, t_{major} = 25.5 min. HRMS (EI-TOF): calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_3$, 307.1208; found, 307.1201.

(R)-6-Nitro-1-phenyl-5-*m*-tolylhex-1-yn-3-one (4c). Yellow oil, 49.7 mg, 81% yield. $[\alpha]_{\text{D}}^{20}$ +20.5 (c 1.0 CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 7.48–7.28 (m, 5H), 7.13–6.96 (m, 3H), 4.66–4.50 (m, 2H), 4.09–4.02 (m, 1H), 3.06 (d, J = 6.8 Hz, 2H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 184.1, 138.8, 138.1, 133.2, 131.1, 129.0, 128.9, 128.7, 124.4, 119.5, 92.3, 87.5, 79.4, 48.2, 39.4, 21.4. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 95:5, flow rate = 0.8 mL/min, λ = 254 nm): t_{minor} = 21.2 min, t_{major} = 30.2 min. HRMS (EI-TOF): calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_3$, 307.1208; found, 307.1201.

(R)-5-(4-Methoxyphenyl)-6-nitro-1-phenylhex-1-yn-3-one (4d). Yellow oil, 51.7 mg, 80% yield. $[\alpha]_{\text{D}}^{20}$ +13.2 (c 1.0 CHCl_3). ^1H NMR (300 MHz, CDCl_3): δ 7.56 (t, J = 6.9 Hz, 2H), 7.48 (d, J = 7.2 Hz, 1H), 7.40–7.18 (m, 4H), 6.88 (d, J = 8.7 Hz, 2H), 4.76–4.58 (m, 2H), 4.19–4.10 (m, 1H), 3.78 (s, 3H), 3.14 (d, J = 7.2 Hz, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 184.2, 159.3, 133.2, 131.1, 130.0, 128.7, 128.6, 119.5, 114.5, 92.3, 87.5, 79.6, 55.3, 48.3, 38.8. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 95:5, flow rate = 0.8 mL/min, λ = 254 nm): t_{minor} = 16.7 min, t_{major} = 24.1 min. HRMS (EI-TOF): calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_4\text{Na}^+$ [$\text{M} + \text{Na}$] $^+$, 346.1049; found, 346.1050.

(*R*)-5-(2-Methoxyphenyl)-6-nitro-1-phenylhex-1-yn-3-one (**4e**). Yellow oil, 51.7 mg, 80% yield. $[\alpha]_{\text{D}}^{20}$ -15.2 (c 1.0 CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 7.58 (d, *J* = 7.2 Hz, 2H), 7.49–7.38 (m, 3H), 7.28–7.20 (m, 3H), 6.96–6.89 (m, 2H), 4.86–4.74 (m, 2H), 4.57–4.36 (m, 1H), 3.88 (s, 3H), 3.6 (d, *J* = 7.2 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 184.9, 157.2, 133.1, 131.0, 129.5, 129.2, 128.7, 125.8, 121.0, 119.6, 111.1, 91.8, 87.6, 77.7, 55.4, 46.5, 36.0. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 95:5, flow rate = 0.8 mL/min, λ = 254 nm): *t*_{minor} = 20.2 min, *t*_{major} = 25.4 min. HRMS (EI-TOF): calcd for C₁₉H₁₇NO₄Na⁺ [M + Na]⁺, 346.1049; found, 346.1050.

(*R*)-5-(Benzo[d][1,3]dioxol-5-yl)-6-nitro-1-phenylhex-1-yn-3-one (**4f**). Yellow oil, 54.6 mg, 81% yield. $[\alpha]_{\text{D}}^{20}$ -13.4 (c 1.0 CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 7.59–7.28 (m, 5H), 6.76 (d, *J* = 3.6 Hz, 3H), 5.96 (s, 2H), 4.75–4.57 (m, 2H), 4.16–4.07 (m, 1H), 3.12 (d, *J* = 7.2 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 183.9, 148.2, 147.4, 133.2, 131.7, 131.1, 128.7, 120.9, 119.4, 108.8, 107.7, 101.3, 92.4, 87.5, 79.6, 48.3, 39.3. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 95:5, flow rate = 0.8 mL/min, λ = 254 nm): *t*_{minor} = 15.6 min, *t*_{major} = 24.1 min. HRMS (EI-TOF): calcd for C₁₉H₁₅NO₅Na⁺ [M + Na]⁺, 360.0842; found, 360.0843.

(*R*)-5-(4-Bromophenyl)-6-nitro-1-phenylhex-1-yn-3-one (**4g**). Yellow oil, 62.3 mg, 84% yield. $[\alpha]_{\text{D}}^{20}$ +3.3 (c 1.0 CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 7.56 (d, *J* = 7.2 Hz, 2H), 7.49–7.40 (m, 5H), 7.16 (d, *J* = 8.1 Hz, 2H), 4.77–4.59 (m, 2H), 4.15 (t, *J* = 6.9 Hz, 1H), 3.15 (d, *J* = 7.2 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 183.6, 138.8, 137.2, 133.2, 132.3, 131.2, 129.3, 128.8, 122.08, 119.3, 92.6, 87.4, 79.0, 47.9, 38.8. HPLC (Chiralcel OD-H, *n*-hexane/2-propanol = 95:5, flow rate = 0.8 mL/min, λ = 254 nm): *t*_{minor} = 13.2 min, *t*_{major} = 20.8 min. HRMS (EI-TOF): calcd for C₁₈H₁₄NO₃BrNa⁺ [M + Na]⁺, 394.0049; found, 394.0051.

(*R*)-5-(2-Bromophenyl)-6-nitro-1-phenylhex-1-yn-3-one (**4h**). Pale yellow oil, 60.1 mg, 81% yield. $[\alpha]_{\text{D}}^{20}$ +20.8 (c 1.0 CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 7.64–7.57 (m, 3H), 7.49–7.17 (m, 6H), 4.86–4.67 (m, 3H), 3.26 (d, *J* = 6.9 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 183.8, 136.9, 133.8, 133.2, 131.1, 129.5, 128.7, 128.1, 124.5, 119.4, 92.6, 87.3, 46.7, 38.4. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 95:5, flow rate = 0.8 mL/min, λ = 254 nm): *t*_{minor} = 25.7 min, *t*_{major} = 35.1 min. HRMS (EI-TOF): calcd for C₁₈H₁₄NO₃BrNa⁺ [M + Na]⁺, 394.0049; found, 394.0051.

(*R*)-6-Nitro-1-phenyl-5-(4-(trifluoromethyl)phenyl)hex-1-yn-3-one (**4i**). Pale yellow oil, 60.6 mg, 84% yield. $[\alpha]_{\text{D}}^{20}$ +17.9 (c 1.0 CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 7.36 (d, *J* = 7.8 Hz, 2H), 7.58–7.50 (m, 3H), 7.43 (d, *J* = 7.8 Hz, 4H), 4.83–4.65 (m, 2H), 4.30–4.21 (m, 1H), 3.20 (d, *J* = 6.6 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 183.3, 142.3, 133.2, 131.3, 130.4 (d, ¹*J*_{C-F} = 32.9 Hz), 128.8, 128.0, 126.1, 119.2, 92.8, 87.3, 78.8, 47.8, 39.0. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 95:5, flow rate = 0.8 mL/min, λ = 254 nm): *t*_{minor} = 17.1 min, *t*_{major} = 24.7 min. HRMS (EI-TOF): calcd for C₁₉H₁₄NO₃F₃Na⁺ [M + Na]⁺, 384.0817; found, 384.0816.

(*S*)-5-(Furan-2-yl)-6-nitro-1-phenylhex-1-yn-3-one (**4j**). Brown-yellow oil, 45.8 mg, 81% yield. $[\alpha]_{\text{D}}^{20}$ +4.4 (c 1.0 CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 7.51–7.19 (m, 6H), 6.24 (s, 1H), 6.14 (s, 1H), 4.65 (d, *J* = 5.1 Hz, 2H), 4.21 (t, *J* = 4.5 Hz, 1H), 3.12 (dd, *J* = 4.6 Hz, 9.9 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 183.9, 133.2, 131.7, 131.1, 128.7, 120.9, 119.4, 108.7, 107.7, 101.3, 92.4, 87.5, 79.6, 48.3, 39.3. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 95:5, flow rate = 0.8 mL/min, λ = 220 nm): *t*_{minor} = 20.8 min, *t*_{major} = 30.1 min. HRMS (EI-TOF): calcd for C₁₆H₁₃NO₄Na⁺ [M + Na]⁺, 306.0742; found, 306.0737.

(*S*)-6-Nitro-1-phenyl-5-(thiophen-2-yl)hex-1-yn-3-one (**4k**). Brown oil, 48.4 mg, 81% yield. $[\alpha]_{\text{D}}^{20}$ +22.0 (c 1.0 CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 7.48 (t, *J* = 6.9 Hz, 2H), 7.40–7.29 (m, 3H), 7.16–7.14 (m, 1H), 6.88 (s, 2H), 4.72–4.55 (m, 2H), 4.45–4.36 (m, 1H), 3.14 (d, *J* = 6.9 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 183.5, 140.9, 133.2, 131.1, 128.7, 127.2, 125.8, 125.0, 119.4, 92.6, 87.4, 79.6, 48.8, 34.9. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 95:5, flow rate = 0.8 mL/min, λ = 220 nm): *t*_{minor} = 19.7 min, *t*_{major} = 28.0 min. HRMS (EI-TOF): calcd for C₁₆H₁₃NO₃SN⁺ [M + Na]⁺, 322.0508; found, 322.0504.

(*S*)-7-Methyl-5-(nitromethyl)-1-phenyloct-1-yn-3-one (**4l**). Pale yellow oil, 44.2 mg, 81% yield. $[\alpha]_{\text{D}}^{20}$ +7.8 (c 1.0 CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 7.52–7.32 (m, 5H), 5.71–5.32 (m, 2H), 4.41–4.39 (m, 2H), 2.82–2.73 (m, 2H), 1.60 (d, *J* = 6.6 Hz, 1H), 1.25–1.18 (m, 2H), 0.88–0.82 (m, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 185.3, 133.2, 131.0, 128.7, 118.1, 91.7, 86.0, 78.6, 46.9, 40.5, 31.5, 27.6, 25.1, 22.5. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 95:5, flow rate = 0.8 mL/min, λ = 254 nm): *t*_{minor} = 18.6 min, *t*_{major} = 25.4 min. HRMS (EI-TOF): calcd for C₁₆H₁₉NO₃Na⁺ [M + Na]⁺, 296.1257; found, 296.1256.

(*R*)-6-Nitro-5-phenyl-1-*p*-tolylhex-1-yn-3-one (**4m**). Yellow oil, 49.7 mg, 81% yield. $[\alpha]_{\text{D}}^{20}$ +19.5 (c 1.0 CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 7.48 (d, *J* = 5.7 Hz, 2H), 7.39 (d, *J* = 5.7 Hz, 1H), 7.33 (d, *J* = 5.4 Hz, 2H), 7.16–6.97 (m, 4H), 4.68–4.53 (m, 2H), 4.09–4.03 (m, 1H), 3.10–3.05 (m, 2H), 2.56 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 184.1, 138.9, 138.1, 133.2, 131.1, 129.0, 128.9, 128.7, 128.3, 124.4, 119.5, 92.3, 87.5, 79.4, 5.14, 39.3, 21.5. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 95:5, flow rate = 0.8 mL/min, λ = 254 nm): *t*_{minor} = 20.5 min, *t*_{major} = 25.4 min. HRMS (EI-TOF): calcd for C₁₉H₁₇NO₃ [M]⁺, 307.1208; found, 307.1201.

(*R*)-1-(4-Fluorophenyl)-6-nitro-5-phenylhex-1-yn-3-one (**4n**). Pale yellow oil, 51.0 mg, 82% yield. $[\alpha]_{\text{D}}^{20}$ -0.6 (c 1.0 CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 7.60–7.56 (m, 2H), 7.39–7.27 (m, 5H), 7.12 (t, *J* = 8.8 Hz, 2H), 4.76 (d, *J* = 7.2 Hz, 1H), 4.67 (d, *J* = 7.6 Hz, 1H), 4.22–4.15 (m, 1H), 3.18 (d, *J* = 7.2 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 183.8, 164.2 (d, *J*_{C-F} = 253.3 Hz), 138.1, 135.6, 135.5, 129.2, 128.1, 127.5, 116.4, 116.2, 115.6, 91.2, 87.4, 79.35, 48.1, 39.4. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 95:5, flow rate = 0.8 mL/min, λ = 254 nm): *t*_{minor} = 16.4 min, *t*_{major} = 24.7 min. HRMS (EI-TOF): calcd for C₁₈H₁₄NO₃F Na⁺ [M + Na]⁺, 334.0849; found, 334.0854.

(*R*)-1-Nitro-2-phenyldec-5-yn-4-one (**4o**). Brown oil, 43.7 mg, 80% yield. $[\alpha]_{\text{D}}^{20}$ -5.1 (c 1.0 CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 7.28–7.14 (m, 5H), 4.65–4.49 (m, 2H), 4.02 (t, *J* = 7.2 Hz, 1H), 2.93 (d, *J* = 6.9 Hz, 2H), 2.28 (t, *J* = 7.2 Hz, 2H), 1.52–1.43 (m, 2H), 1.38–1.30 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 184.2, 138.3, 129.1, 128.0, 127.4, 96.2, 80.6, 79.3, 48.1, 39.4, 29.6, 21.9, 18.6, 13.4. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 95:5, flow rate = 0.8 mL/min, λ = 254 nm): *t*_{minor} = 20.2 min, *t*_{major} = 29.5 min. HRMS (EI-TOF): calcd for C₁₆H₁₉NO₃Na⁺ [M + Na]⁺, 296.1257; found, 296.1256.

(*R*)-1-Nitro-2-phenyldodec-5-yn-4-one (**4p**). Colorless oil, 49.4 mg, yield 82%. $[\alpha]_{\text{D}}^{20}$ +5.4 (c 1.0 CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 7.35–7.21 (m, 5H), 4.72–4.58 (m, 2H), 4.13–4.06 (m, 1H), 3.02 (d, 2H, *J* = 7.2 Hz), 2.35 (t, 2H, *J* = 7.2 Hz), 1.58–1.53 (m, 2H), 1.40–1.30 (m, 6H), 0.90 (t, 3H, *J* = 6.4 Hz). ¹³C NMR (400 MHz, CDCl₃): δ 184.2, 138.2, 129.1, 128.0, 127.4, 96.3, 80.6, 79.3, 48.1, 39.4, 31.2, 28.5, 27.6, 22.5, 19.0, 14.0. HPLC (Chiralpak AD-H, *n*-hexane/2-PrOH = 95:5, flow rate = 0.8 mL/min, λ = 254 nm): *t*_{minor} = 11.5 min, *t*_{major} = 12.8 min. HRMS (EI-TOF): calcd for C₁₈H₂₃NO₃ [M]⁺, 301.1678; found, 301.1688.

General Procedure for the Asymmetric Catalytic γ -Selective Conjugate Addition of 1,3-Diketones. To a solution of **1** (0.2 mmol) and **2** (0.24 mmol) in DCM (0.5 mL) were added chiral catalyst **6i** (0.02 mmol, 10 mol %) and a 4 Å molecular sieve (12 mg). After stirring for 72 h at room temperature, the mixture was concentrated at reduced pressure. The residue was then dissolved in toluene (5 mL). To the resulting solution was added *p*-toluenesulfonic acid monohydrate (76 mg, 0.4 mmol), and the mixture was stirred at 110 °C for 12 h. After removal of solvent by evaporation, the residue was purified by flash column chromatography using ethyl acetate/petroleum ether (1:15) as the eluent to afford **5**.

(*R,Z*)-1-Hydroxy-6-nitro-1,5-diphenylhex-1-en-3-one (**5a**). Pale yellow oil, 52.2 mg, 84% yield. $[\alpha]_{\text{D}}^{20}$ -6.2 (c 1.0 CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 15.93 (s, 1H), 7.83 (d, *J* = 7.2 Hz, 2H), 7.55–7.46 (m, 3H), 7.42 (t, *J* = 6.9 Hz, 5H), 6.11 (s, 1H), 4.84–4.67 (m, 2H), 4.16–4.06 (m, 1H), 2.90 (m, *J* = 7.5 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 193.4, 182.7, 134.2, 132.6, 129.1, 128.7, 128.0, 127.4, 127.0, 97.0, 79.6, 42.6, 40.6. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 90:10, flow rate = 0.8 mL/min, λ = 254 nm): *t*_{minor} = 30.5

min, $t_{\text{major}} = 35.2$ min. HRMS (EI-TOF): calcd for $\text{C}_{18}\text{H}_{17}\text{NO}_4\text{Na}^+ [\text{M} + \text{Na}]^+$, 334.1056; found, 334.1054.

(R,Z)-1-Hydroxy-6-nitro-1-phenyl-5-p-tolylhex-1-en-3-one (5b). Pale yellow oil, 53.9 mg, 83% yield. $[\alpha]_{\text{D}}^{20} -14.6$ (c 1.0 CHCl_3). ^1H NMR (300 MHz, CDCl_3): δ 15.93 (s, 1H), 7.83 (d, $J = 7.5$ Hz, 2H), 7.48 (t, $J = 7.5$ Hz, 3H), 7.16 (m, 4H), 6.11 (s, 1H), 4.82–4.64 (m, 2H), 4.12–4.02 (m, 1H), 2.88 (d, $J = 7.2$ Hz, 2H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 193.5, 182.7, 137.7, 135.4, 134.3, 132.6, 129.8, 128.7, 127.2, 127.0, 97.0, 79.7, 42.7, 40.2, 21.1. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 90:10, flow rate = 0.8 mL/min, $\lambda = 254$ nm): $t_{\text{minor}} = 30.9$ min, $t_{\text{major}} = 36.1$ min. HRMS (EI-TOF): calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_4\text{Na}^+ [\text{M} + \text{Na}]^+$, 348.1206; found, 348.1202.

(R,Z)-1-Hydroxy-6-nitro-1-phenyl-5-m-tolylhex-1-en-3-one (5c). Yellow oil, 53.3 mg, 82% yield. $[\alpha]_{\text{D}}^{20} -4.9$ (c 1.0 CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 15.82 (s, 1H), 7.73 (d, $J = 5.7$ Hz, 2H), 7.46–7.33 (m, 3H), 7.15 (d, $J = 7.2$ Hz, 1H), 7.12–6.95 (m, 3H), 6.01 (s, 1H), 4.67–4.67 (m, 2H), 4.12–3.90 (m, 1H), 2.78 (d, $J = 5.7$ Hz, 2H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 193.5, 182.6, 138.8, 138.5, 134.3, 132.6, 129.0, 128.8, 128.7, 128.2, 127.0, 124.2, 97.0, 79.6, 42.6, 40.5, 21.4. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 90:10, flow rate = 0.8 mL/min, $\lambda = 254$ nm): $t_{\text{minor}} = 39.2$ min, $t_{\text{major}} = 43.0$ min. HRMS (EI-TOF): calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_4\text{Na}^+ [\text{M} + \text{Na}]^+$, 348.1206; found, 348.1202.

(R,Z)-1-Hydroxy-5-(4-methoxyphenyl)-6-nitro-1-phenylhex-1-en-3-one (5d). Yellow oil, 57.3 mg, 84% yield. $[\alpha]_{\text{D}}^{20} -5.8$ (c 1.0 CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 15.82 (s, 1H), 7.73 (d, $J = 7.2$ Hz, 2H), 7.36 (d, $J = 7.8$ Hz, 3H), 7.09 (d, $J = 8.7$ Hz, 2H), 6.78 (d, $J = 8.7$ Hz, 2H), 6.00 (s, 1H), 4.70–4.52 (m, 2H), 4.00–3.69 (m, 1H), 2.98 (d, $J = 7.2$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 193.4, 182.7, 159.2, 134.3, 132.6, 130.4, 128.7, 128.4, 127.0, 114.5, 97.0, 79.9, 55.2, 42.7, 39.9. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 90:10, flow rate = 0.8 mL/min, $\lambda = 254$ nm): $t_{\text{minor}} = 30.4$ min, $t_{\text{major}} = 35.5$ min. HRMS (EI-TOF): calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_5\text{Na}^+ [\text{M} + \text{Na}]^+$, 364.1155; found, 364.1157.

(R,Z)-1-Hydroxy-5-(2-methoxyphenyl)-6-nitro-1-phenylhex-1-en-3-one (5e). Yellow oil, 57.3 mg, 84% yield. $[\alpha]_{\text{D}}^{20} -2.7$ (c 1.0 CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 15.83 (s, 1H), 7.71 (d, $J = 7.5$ Hz, 2H), 7.41–7.38 (m, 3H), 7.35–7.32 (m, 2H), 7.14–7.05 (dd, $J = 8.7$ Hz, 6.9 Hz, 2H), 6.01 (s, 1H), 4.69 (t, $J = 7.5$ Hz, 4.8 Hz, 2H), 4.22–4.20 (m, 1H), 3.76 (s, 3H), 2.85 (d, $J = 7.2$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 194.3, 182.5, 157.2, 134.5, 132.5, 129.2, 129.1, 128.7, 127.0, 126.2, 121.0, 111.1, 96.9, 78.0, 55.4, 40.8, 36.9. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 90:10, flow rate = 0.8 mL/min, $\lambda = 254$ nm): $t_{\text{minor}} = 30.6$ min, $t_{\text{major}} = 37.2$ min. HRMS (EI-TOF): calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_5\text{Na}^+ [\text{M} + \text{Na}]^+$, 364.1155; found, 364.1157.

(R,Z)-5-(Benzo[d][1,3]dioxol-5-yl)-1-hydroxy-6-nitro-1-phenylhex-1-en-3-one (5f). Brown-yellow oil, 59.6 mg, 84% yield. $[\alpha]_{\text{D}}^{20} -5.0$ (c 1.0 CHCl_3). ^1H NMR (300 MHz, CDCl_3): δ 15.84 (s, 1H), 7.75 (d, $J = 7.5$ Hz, 2H), 7.46–7.36 (m, 3H), 6.70–6.62 (m, 3H), 6.03 (s, 1H), 5.87 (s, 2H), 4.67–4.50 (m, 2H), 3.99–3.91 (m, 1H), 2.75 (d, $J = 7.2$ Hz, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 193.3, 182.7, 148.2, 147.3, 134.2, 132.6, 132.1, 128.7, 127.0, 120.8, 108.7, 107.6, 101.3, 96.9, 79.8, 42.7, 40.3. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 90:10, flow rate = 0.8 mL/min, $\lambda = 254$ nm): $t_{\text{minor}} = 20.7$ min, $t_{\text{major}} = 30.1$ min. HRMS (EI-TOF): calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_6\text{Na}^+ [\text{M} + \text{Na}]^+$, 378.0948; found, 378.0951.

(R,Z)-5-(4-Bromophenyl)-1-hydroxy-6-nitro-1-phenylhex-1-en-3-one (5g). Pale yellow solid, 66.1 mg, 85% yield. $[\alpha]_{\text{D}}^{20} -20.0$ (c 1.0 CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 15.88 (s, 1H), 7.83 (d, $J = 7.2$ Hz, 2H), 7.55–7.44 (m, 5H), 7.15 (d, $J = 8.4$ Hz, 2H), 6.10 (s, 1H), 4.82–4.62 (m, 2H), 4.13–4.06 (m, 1H), 2.87 (d, $J = 7.2$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 193.1, 182.6, 137.6, 134.1, 132.7, 132.2, 128.1, 128.7, 128.5, 127.1, 122.0, 96.9, 79.2, 42.4, 39.9. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 90:10, flow rate = 0.8 mL/min, $\lambda = 254$ nm): $t_{\text{minor}} = 30.2$ min, $t_{\text{major}} = 40.2$ min. HRMS (EI-TOF): calcd for $\text{C}_{18}\text{H}_{16}\text{NO}_4\text{BrNa}^+ [\text{M} + \text{Na}]^+$, 412.0154; found, 412.0154.

(R,Z)-5-(2-Bromophenyl)-1-hydroxy-6-nitro-1-phenylhex-1-en-3-one (5h). Yellow solid, 64.6 mg, 83% yield. $[\alpha]_{\text{D}}^{20} +43.5$ (c 1.0 CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 15.87 (s, 1H), 7.85 (d, $J = 7.5$ Hz, 2H), 7.65–7.46 (m, 4H), 7.34–7.17 (m, 3H), 6.16 (s, 1H), 4.85 (d, $J = 6.6$ Hz, 2H), 4.61 (d, $J = 10.5$ Hz, 1H), 2.98 (d, $J = 7.2$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 193.3, 182.5, 137.3, 134.2, 133.8, 132.6, 129.4, 128.7, 128.1, 127.1, 124.5, 96.8, 77.7, 41.2, 39.3. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 90:10, flow rate = 0.8 mL/min, $\lambda = 254$ nm): $t_{\text{minor}} = 27.7$ min, $t_{\text{major}} = 38.8$ min. HRMS (EI-TOF): calcd for $\text{C}_{18}\text{H}_{16}\text{NO}_4\text{BrNa}^+ [\text{M} + \text{Na}]^+$, 412.0155; found, 412.0153.

(R,Z)-1-Hydroxy-6-nitro-1-phenyl-5-(4-(trifluoromethyl)phenyl)hex-1-en-3-one (5i). Yellow solid, 63.6 mg, 84% yield. $[\alpha]_{\text{D}}^{20} -5.8$ (c 1.0 CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 15.86 (s, 1H), 7.84 (d, $J = 7.5$ Hz, 2H), 7.49 (m, 7H), 6.12 (s, 1H), 4.87–4.69 (m, 2H), 4.22–4.10 (m, 1H), 2.92 (d, $J = 6.0$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 192.9, 182.6, 139.8, 134.0, 132.7, 130.0, 129.6, 128.7, 127.0, 124.5 (d, $J_{\text{C-F}} = 78.7$ Hz), 96.9, 79.0, 42.4, 40.1. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 90:10, flow rate = 0.8 mL/min, $\lambda = 210$ nm): $t_{\text{minor}} = 20.7$ min, $t_{\text{major}} = 30.7$ min. HRMS (EI-TOF): calcd for $\text{C}_{19}\text{H}_{16}\text{NO}_4\text{F}_3\text{Na}^+ [\text{M} + \text{Na}]^+$, 402.0923; found, 402.0923.

(S,Z)-5-(Furan-2-yl)-1-hydroxy-6-nitro-1-phenylhex-1-en-3-one (5j). Brown-yellow oil, 51.2 mg, 85% yield. $[\alpha]_{\text{D}}^{20} -3.0$ (c 1.0 CHCl_3). ^1H NMR (300 MHz, CDCl_3): δ 15.78 (s, 1H), 7.77 (d, $J = 7.2$ Hz, 2H), 7.46–7.18 (m, 4H), 6.22 (s, 1H), 6.09 (d, $J = 18$ Hz, 2H), 4.66 (d, $J = 6.3$ Hz, 2H), 4.17–4.09 (m, 1H), 2.89–2.78 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 193.4, 182.4, 151.4, 142.4, 134.1, 132.6, 128.7, 127.0, 110.5, 107.4, 97.0, 77.5, 40.2, 34.3. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 90:10, flow rate = 0.8 mL/min, $\lambda = 254$ nm): $t_{\text{minor}} = 31.0$ min, $t_{\text{major}} = 38.0$ min. HRMS (EI-TOF): calcd for $\text{C}_{16}\text{H}_{15}\text{NO}_5\text{Na}^+ [\text{M} + \text{Na}]^+$, 324.0842; found, 324.0843.

(S,Z)-1-Hydroxy-6-nitro-1-phenyl-5-(thiophen-2-yl)hex-1-en-3-one (5k). Brown oil, 53.9 mg, 85% yield. $[\alpha]_{\text{D}}^{20} +9.9$ (c 1.0 CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 15.80 (s, 1H), 7.76 (d, $J = 5.7$ Hz, 2H), 7.51–7.37 (m, 3H), 7.14 (t, $J = 10.7$ Hz, 1H), 6.87 (s, 2H), 6.06 (s, 1H), 4.74–4.34 (m, 2H), 4.36–4.31 (m, 1H), 2.86 (d, $J = 5.8$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 193.1, 182.5, 141.3, 134.1, 132.7, 128.7, 127.1, 125.7, 124.9, 97.0, 80.0, 43.4, 35.9. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 90:10, flow rate = 0.8 mL/min, $\lambda = 254$ nm): $t_{\text{minor}} = 45.2$ min, $t_{\text{major}} = 60.8$ min. HRMS (EI-TOF): calcd for $\text{C}_{16}\text{H}_{15}\text{NO}_4\text{SNa}^+ [\text{M} + \text{Na}]^+$, 340.0614; found, 340.0613.

(S,Z)-1-Hydroxy-7-methyl-5-(nitromethyl)-1-phenylhex-1-en-3-one (5l). Yellow oil, 49.5 mg, 85% yield. $[\alpha]_{\text{D}}^{20} -21.6$ (c 1.0 CHCl_3). ^1H NMR (300 MHz, CDCl_3): δ 16.08 (s, 1H), 7.90 (d, $J = 7.2$ Hz, 2H), 7.59–7.45 (m, 3H), 6.22 (s, 1H), 4.57–4.43 (m, 2H), 2.86–2.77 (m, 1H), 2.57 (d, $J = 8.4$ Hz, 2H), 1.72 (s, 2H), 1.32 (s, 2H), 0.94 (d, $J = 3.3$ Hz, 6H). ^{13}C NMR (75 MHz, CDCl_3): δ 194.2, 183.1, 134.4, 132.6, 128.7, 127.1, 97.2, 78.9, 40.9, 40.6, 32.5, 25.1, 22.5, 22.4. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 90:10, flow rate = 0.8 mL/min, $\lambda = 254$ nm): $t_{\text{minor}} = 20.5$ min, $t_{\text{major}} = 25.5$ min. HRMS (EI-TOF): calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_4\text{Na}^+ [\text{M} + \text{Na}]^+$, 314.1362; found, 314.1366.

(R,Z)-1-Hydroxy-6-nitro-5-phenyl-1-p-tolylhex-1-en-3-one (5m). Pale yellow solid, 54.6 mg, 84% yield. $[\alpha]_{\text{D}}^{20} -0.8$ (c 1.0 CHCl_3). ^1H NMR (300 MHz, CDCl_3): δ 15.86 (s, 1H), 7.58 (d, $J = 6.6$ Hz, 2H), 7.27–7.19 (m, 5H), 7.04 (d, $J = 11.4$ Hz, 2H), 5.95 (s, 1H), 4.73–4.57 (m, 2H), 4.05–3.96 (m, 1H), 2.80 (d, $J = 7.2$ Hz, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 192.6, 182.1, 138.4, 130.6, 129.6, 129.5, 129.1, 128.1, 127.4, 116.1, 115.8, 96.7, 79.6, 42.4, 40.6. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 90:10, flow rate = 0.8 mL/min, $\lambda = 254$ nm): $t_{\text{minor}} = 35.5$ min, $t_{\text{major}} = 39.5$ min. HRMS (EI-TOF): calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_4\text{Na}^+ [\text{M} + \text{Na}]^+$, 348.1206; found, 348.1202.

(R,Z)-1-(4-Fluorophenyl)-1-hydroxy-6-nitro-5-phenylhex-1-en-3-one (5n). Brown oil, 55.3 mg, 84% yield. $[\alpha]_{\text{D}}^{20} -2.3$ (c 1.0 CHCl_3). ^1H NMR (300 MHz, CDCl_3): δ 15.86 (s, 1H), 7.75 (s, 2H), 7.24 (d, $J = 16.8$ Hz, 5H), 7.03 (s, 2H), 5.95 (s, 1H), 4.74–4.57 (m, 2H), 4.05–3.94 (m, 1H), 2.78 (d, $J = 7.2$ Hz, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 192.6, 182.1, 167.2, 165.5 (d, $J_{\text{C-F}} = 252.9$ Hz), 138.4, 130.6, 129.6,

129.5, 129.1, 128.1, 127.4, 116.1, 115.8, 96.7, 79.6, 42.4, 40.6. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 90:10, flow rate = 0.8 mL/min, λ = 254 nm): t_{minor} = 19.5 min, t_{major} = 27.0 min. HRMS (EI-TOF): calcd for $\text{C}_{18}\text{H}_{16}\text{NO}_4\text{Na}^+ [\text{M} + \text{Na}]^+$, 352.0961; found, 352.0963.

(*R,Z*)-6-Hydroxy-1-nitro-2-phenyldec-5-en-4-one (5o). Brown-yellow solid, 47.1 mg, 81% yield. $[\alpha]_{\text{D}}^{20}$ –13.9 (*c* 1.0 CHCl_3). ^1H NMR (300 MHz, CDCl_3): δ 15.20 (s, 1H), 7.26–7.13 (m, 5H), 5.33 (s, 1H), 4.68–4.53 (m, 2H), 3.98–3.88 (m, 1H), 2.64 (d, *J* = 7.5 Hz, 2H), 2.15 (s, 2H), 1.44 (d, *J* = 7.2 Hz, 2H), 1.22 (d, *J* = 7.5 Hz, 2H), 0.82 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 193.5, 191.3, 138.5, 129.0, 128.0, 127.3, 100.1, 79.6, 41.9, 40.5, 37.6, 27.8, 22.3, 13.8. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 90:10, flow rate = 0.8 mL/min, λ = 254 nm): t_{minor} = 25.4 min, t_{major} = 30.5 min. HRMS (EI-TOF): calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_4\text{Na}^+ [\text{M} + \text{Na}]^+$, 314.1362; found, 314.1366.

(*R,Z*)-6-Hydroxy-1-nitro-2-phenyldec-5-en-4-one (5p). Yellow oil, 53.6 mg, 84% yield. $[\alpha]_{\text{D}}^{20}$ –17.3 (*c* 1.0, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 15.26 (s, 1H), 7.32–7.20 (m, 5H), 5.39 (s, 1H), 4.75–4.60 (m, 2H), 3.99 (t, 1H, *J* = 7.2 Hz), 2.714 (d, 2H, *J* = 7.2 Hz), 2.21 (t, 2H, *J* = 7.6 Hz), 1.53 (s, 2H), 1.27 (s, 6H), 0.870 (d, 3H, *J* = 6.8 Hz). ^{13}C NMR (400 MHz, CDCl_3): δ 193.6, 191.3, 138.5, 129.0, 127.9, 127.3, 100.1, 79.6, 41.9, 40.5, 37.9, 31.5, 28.8, 25.7, 22.5, 14.0. HPLC (Chiralcel OD-H, *n*-hexane/2-PrOH = 98/2, flow rate = 0.5 mL/min, λ = 254 nm), t_{minor} = 89.7 min, t_{major} = 103.1 min. HRMS (EI-TOF): calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_4 [\text{M}]^+$, 319.1784; found, 319.1786.

Synthesis of ent-4a. Phenylacetylene (22.5 mg, 0.22 mmol) was dissolved in 1 mL of THF under a N_2 atmosphere. The flask was cooled to -78°C ; then, *n*-BuLi (1.6 N, 0.22 mmol) was added slowly, and the mixture was stirred at -78°C for 1 h. Compound **7²⁶** (34 mg, 0.2 mmol) was added. The reaction mixture was warmed to room temperature and stirred for another 1 h. The reaction mixture was treated with saturated NH_4Cl and extracted with ethyl acetate. The extracts were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated in vacuo. The residue was purified by column chromatography (petroleum ether/EtOAc = 4:1 to 2:1) to give the alkylation compound (17.0 mg, 30%).

To a solution of this alkylation compound (29.5 mg, 1 mmol) in DCM (0.5 mL) was added Dess–Martin periodinane (63.6 mg, 0.15 mmol). The mixture was stirred at room temperature and monitored by TLC analysis. The reaction mixture was treated with saturated $\text{Na}_2\text{S}_2\text{O}_3$, and the flask was allowed to continue to stir until the solution become clear and was then extracted twice with DCM. The extracts were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated in vacuo. The residue was purified by column chromatography (petroleum ether/EtOAc = 5:1) to give **ent-4a** (23 mg, 80% yield). $[\alpha]_{\text{D}}^{20}$ –9.8 (*c* 1.0 CHCl_3).

Synthesis of syn-Propargylic Alcohol 9. To a solution of compound **4a** (29.3 mg, 0.1 mmol) in 0.5 mL of THF was added 4 Å molecular sieves for 2 h, and subsequently, **ent-8** (0.2 mmol, 1 M) was added in 0.5 mL of THF. The solution was cooled to -30°C . Then, 0.05 mL of $\text{BH}_3\cdot\text{Me}_2\text{S}$ was added. Reaction progress was monitored by TLC. After the reaction appeared to be complete, it was quenched by slow dropwise addition of 1.0 mL of methanol. The solution was diluted with 20 mL of ether and washed with saturated NH_4Cl , 5% NaHCO_3 , and brine. The organic layer was dried over Na_2SO_4 , concentrated under reduced pressure, and purified by column chromatography (ethyl acetate/petroleum ether = 1:3) to give **9** (25 mg, 84%).

Yellow oil, $[\alpha]_{\text{D}}^{20}$ –5.8 (*c* 1.0 CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 7.39–7.26 (m, 10H), 4.71 (q, *J* = 7.2 Hz, 1H), 4.63 (q, *J* = 8.4 Hz, 1H), 4.38–4.33 (m, 1H), 3.95–3.87 (m, 1H), 2.25–2.13 (m, 2H), 1.876 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 138.3, 131.7, 129.2, 128.7, 128.4, 128.0, 127.8, 122.1, 89.1, 85.4, 80.4, 60.0, 41.0, 40.7. HRMS (EI-TOF): calcd for $\text{C}_{18}\text{H}_{17}\text{NO}_3\text{Na}^+ [\text{M} + \text{Na}]^+$, 318.1100; found, 318.1102.

Synthesis of anti-Propargylic Alcohol 10. To a solution of compound **4a** (29.3 mg, 0.1 mmol) in 0.5 mL of THF was added 4 Å molecular sieves for 2 h, and subsequently, **8** (0.2 mmol, 1 M) was added in 0.5 mL of THF. The solution was cooled to -30°C . Then, 0.05 mL of $\text{BH}_3\cdot\text{Me}_2\text{S}$ was added. Reaction progress was monitored by

TLC. After the reaction appeared to be complete, it was quenched by slow dropwise addition of 1.0 mL of methanol. The solution was diluted with 20 mL of ether and washed with saturated NH_4Cl , 5% NaHCO_3 , and brine. The organic layer was dried over Na_2SO_4 , concentrated under reduced pressure, and purified by column chromatography (ethyl acetate/petroleum ether = 1:3) to give **10** (24.7 mg, 83%).

Yellow oil, $[\alpha]_{\text{D}}^{20}$ +25.7 (*c* 1.0 CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 7.47–7.45 (m, 2H), 7.44–7.26 (m, 8H), 4.79–4.77 (m, 1H), 4.68–4.63 (m, 1H), 4.42–4.38 (m, 1H), 3.91–3.81 (m, 1H), 2.29–2.22 (m, 1H), 2.18–2.11 (m, 1H), 1.99 (brs, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 138.6, 131.8, 129.1, 128.8, 128.4, 128.0, 127.5, 122.1, 88.3, 86.6, 80.3, 61.0, 41.3, 40.7. HRMS (EI-TOF): calcd for $\text{C}_{18}\text{H}_{17}\text{NO}_3\text{Na}^+ [\text{M} + \text{Na}]^+$, 318.1100; found, 318.1102.

Synthesis of Compound 11. To a solution of compound **4a** (29.3 mg, 0.10 mmol) in EtOAc (1.0 mL) was added Lindlar's catalyst (10.6 mg, 0.005 mmol). The mixture was allowed to stir under a hydrogen atmosphere at rt for 6 h before being filtered through a plug of Celite and concentrated in vacuo. The crude product was subjected to column chromatography (ethyl acetate/petroleum ether = 1:4) to give **11** (26.9 mg, 92%).

Yellow oil, $[\alpha]_{\text{D}}^{20}$ –7.4 (*c* 1.0 CHCl_3). ^1H NMR (300 MHz, CDCl_3): δ 7.32–7.01 (m, 10H), 4.68–4.52 (m, 2H), 4.05–4.00 (m, 1H), 2.85–2.83 (m, 4H), 2.81–2.60 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3): δ 206.8, 140.6, 138.8, 129.1, 128.6, 128.3, 128.0, 127.4, 126.3, 79.4, 45.7, 44.7, 39.1, 29.6. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 90:10, flow rate = 0.8 mL/min, λ = 210 nm): t_{minor} = 18.7 min, t_{major} = 21.8 min. HRMS (EI-TOF): calcd for $\text{C}_{18}\text{H}_{19}\text{NO}_3\text{Na}^+ [\text{M} + \text{Na}]^+$, 320.1257; found, 320.1256.

Synthesis of β -Keto 1,3-Dithiane 12. To a solution of compound **4a** (44 mg, 0.15 mmol) and 1,2-ethanedithiol (16 mg, 0.17 mmol) in MeOH and CH_2Cl_2 (4:1, 1 mL), stirred at -10°C , was added NaOMe (10.8 mg, 0.20 mmol). The reaction mixture was stirred for 1 h and then allowed to warm to ambient temperature. The reaction mixture was quenched by addition of sat. NH_4Cl solution and extracted with Et_2O . The organic fractions were washed with water and brine, dried (Na_2SO_4), concentrated under reduced pressure, and purified by column chromatography (ethyl acetate/petroleum ether = 1:4) to give **12** (50 mg, 87%).

White solid, $[\alpha]_{\text{D}}^{20}$ –13.9 (*c* 1.0 CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 7.60 (d, *J* = 7.2 Hz, 2H), 7.30–7.18 (m, 6H), 7.08 (d, *J* = 6.4 Hz, 2H), 4.55–4.50 (m, 1H), 4.46–4.40 (m, 1H), 3.90–3.82 (m, 1H), 3.58 (q, *J* = 8.4 Hz, 2H), 3.35–3.22 (m, 4H), 2.73 (d, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 203.7, 143.9, 138.6, 129.0, 128.2, 127.8, 127.3, 127.3, 126.8, 79.0, 68.4, 58.1, 46.0, 39.5, 39.5, 38.8. HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 80:20, flow rate = 0.8 mL/min, λ = 210 nm): t_{minor} = 26.6 min, t_{major} = 38.9 min. HRMS (EI-TOF): calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_3\text{S}_2\text{Na}^+ [\text{M} + \text{Na}]^+$, 410.0855; found, 410.0857.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01425.

NMR spectra and chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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