Cobalt-Catalyzed Diastereo- and Enantioselective Allyl Addition to Aldehydes and α-Ketoesters through Allylic C–H Functionalization

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Abstract

Catalytic reactions that can generate nucleophilic allyl–metal intermediates directly from simple alkenes without prefunctionalization, and ones that produce various homoallylic alcohols diastereo- and enantioselectively are of great importance in organic synthesis. Transformations that accomplish these two tasks simultaneously are in high demand, particularly if the catalysts, substrates and reagents are inexpensive and easy to access. Here we report a catalytic process that chemoselective formation of nucleophilic allyl–cobalt complexes through oxidative allylic C–H cleavage of alkenes followed by site-, diastereo- and enantioselective addition to aldehydes and α-ketoesters. The enantioenriched products that are otherwise difficult to access are obtained in up to 96% yield, with >95:5 dr and 98:2 er. The cobalt-based catalyst is derived from a commercially available chiral phosphine ligand. The utility of the method is demonstrated through enantioselective formal synthesis of lithospermic acid and total synthesis of dihydrodehydrodiconiferylalcohol.

Introduction

Transition-metal-catalyzed carbon–hydrogen (C–H) bond functionalization has long been central to researchers in organic chemistry, as it enables direct installation of functional groups without the need of multistep manipulations to introduce functionalities, allowing significant shortening synthetic routes and improving the overall efficiency of organic synthesis.[1–5] Although activation of C(sp^2)–H bonds promoted by transition-metal complexes have been well-studied, catalytic functionalization of C(sp^3)–H bonds has been much less developed due to their inherent inertness to metal complexes insertion and low reactivity and instability of the resulting C(sp^3)–metal bonds.[6,7] The greatest challenge for such process is the control of selectivity.[8] Although significant advances have been made in regioselective C–H activation through directing effects or electronic biases, enantioselective C(sp^3)–H functionalization has been received less attention (see Supplementary Information for more references).[9] Allyls are versatile groups that can be easily transformed to various functional groups and widely used in organic synthesis.[10–12] Enantioselective functionalization of allylic C–H bonds constitutes an ideal approach to introduce allyl groups to chiral molecules and attracts researchers' interests.[13] Several catalytic enantioselective protocols of allylic C–H functionalization via an electrophilic allyl–metal intermediate promoted by a Pd[14–27] or Rh[28,29] complex have been developed (Figure 1a). More recently, enantioselective allylic C–H functionalization via allyl radicals through metal-catalyzed or photocatalyzed C–H bond cleavage has been revealed (Figure 1a).[30–36] However, enantioselective transformations of nucleophilic allyl–metal intermediates directly produced from oxidative allylic C–H bond cleavage promoted by a single catalyst remained undeveloped. Herein, we report an unprecedented protocol for catalytic generation of nucleophilic allyl–Co complexes followed by diastereo- and enantioselective addition to aldehydes and a-ketoesters to furnish a variety of homoallylic alcohols that are otherwise difficult to access.

Enantioenriched homoallylic alcohols are important building blocks in complex molecule synthesis.[10] The most attractive approach to access such class of molecules is direct formation of nucleophilic allyl–metal complexes from readily available alkenes followed by enantioselective addition to carbonyls. Although generation of allyl–Cu intermediates from Cu–H[37–41] or Cu–B[42,43] addition to polyunsaturated hydrocarbons or deprotonation[44–46] followed by enantioselective addition to carbonyl compounds has been studied, access to nucleophilic allyl–metal complex from direct oxidative cleavage of the inert allylic C–H bond of simple alkenes and subsequent enantioselective addition to carbonyls promoted by a single multi-tasking catalyst remained unknown. Inspired by Sato's works (Figure 1b),[47–50] we envisioned that Co(I)–Me complex **I** in situ produced from $AlMe_3$ and Co(II) salt coordinates with the alkene moiety chemoselectively (vs. aldehyde) and facilitates the oxidative insertion to the allylic C–H bond to provide the h^3-Co(III)–allyl complex **III**. Complex **III** has to undergo reductive elimination chemoselectively to afford Co(I)–allyl complexes **IV** and **V** instead of generation of **VII** and **VIII** or Me, H-addition to the aldehyde (**IX**, **X**). One of the two possible h^1-Co(I)–allyl complexes have to react with the aldehyde **2** selectively to deliver the homoallylic alcohol **VI** and regenerate the catalyst. Successful implementation of the aforementioned plan demands that the single catalyst has to not only efficiently promote the C–H bond cleavage and subsequent aldehyde addition, but also accurately control the chemo-, site- and stereoselectivity of each step.

Results

To identify conditions that would deliver homoallylic alcohol **3** in favor of 1,2-disubstiuted alkenes (**VII**, **VIII**, Figure 1c) or alcohols (**IX**, **X**, Figure 1c), we chose the reaction involving allylbenzene **1a** and benzaldehyde **2a** (Figure 2). We soon found that unlike reactions with CO_2 and ketones,[47–49] branched homoallylic alcohol **3a** was furnished exclusively, indicating that h^1-Co(I)–allyl complex **V** reacts preferentially and the rate of isomerization of **IV** to **V** is more rapid than that of aldehyde addition of h^1-Co(I)–allyl complex **IV** to afford **4a** (Figure 1c). Further investigation of a variety of chiral phosphine ligands led us to find that few chiral Co complexes could promote the reaction. Reaction of allylbenzene **1a** with benzaldehyde **2a** in the presence of Co complex derived from **6b** furnished homoallylic alcohol **3a** in trace amount (16% yield). Co complex formed from **6f** provided significant higher efficiency (52% yield) albeit low enantioselectivity (56:44 er). Follow-up studies revealed that reaction involving phosphine **6j** produced homoallylic alcohol **3a** in 69% yield, 90:10 dr and 93.5:6.5 er. Control experiment showed that in the absence of the allylbenzene **1a**, the Me-addition product **5a** was generated in 21% yield, whereas **5a** was not detected in the reaction of allylbenzene **1a** and benzaldehyde **2a**. It is worth mentioning that although most ligands did not deliver the homoallylic alcohol **3a**, b-methyl-styrene and b-ethyl-styrene (trace amount) formed from reductive elimination of the allyl and Me/H (complex **III**, Figure 1c) was observed in most cases, illustrating that most ligands promoted the C–H bond cleavage but not the aldehyde addition.

Further optimization of reaction temperature indicated that transformation performed at 65 °C furnished the desired product **3a** with improved diastereo- and enantioselectivity (92:8 dr and 95:5 er) without significant erosion of yield (68%). The approach can be utilized to prepare a wide range of enantioenriched homoallylic alcohols (Figure 3). The requisite Co complex is derived from commercially available Co salt and chiral phosphine ligand **4j**. Aldehydes bearing halogens are tolerant in the reaction conditions (**3b**–**d**, 3**h**–**j**), although it is known that phosphine–Co(I) complex can undergo oxidative addition to carbon–halogen bond.[51] Aldehydes that contain electron-donating (**3e**–**g**), electron-withdrawing (**3k**–**m**) and sterically demanding (**3n**–**o**) aryl groups are suitable substrates. Reactions of heteroaryl aldehydes afforded the homoallylic alcohols (**3p**–**q**, **3s**–**v**) in 51–67% yield, 83:17–>95:5 dr and 95:5–98:2 er. Furyl, thienyl and 3-indoyl are not tolerate in the elevated temperature, but the reactions proceeded smoothly at room temperature (**3s**–**v**). Aliphatic aldehydes were transformed to the desired products as a single diastereomer albeit with diminished enantioselectivity (**3r**, **3w**). Allylbenzenes substituted with electron-donating groups were transformed to the homoallylic alcohols (**7a**–**c**, **7m**–**n**) in 49–67% yield, 88:12–91:9 dr and 90:10–95:5 er at 65 °C. We found that reactions with allylbenzenes bearing electron-withdrawing groups can proceed in high efficiency even at room temperature with high diastereo- and enantioselectivity (**7d**–**l**, **7o**–**r**). Particularly, the aldehyde moiety in the substrates that contain ketone (**7i**–**j**, **7q**) or cyano groups (**7g**, **7p**) reacted chemoselectively. Allylbenzenes that contain sterically congested aryl (**7s**–**v**) and various heteroaryl groups (**7w**–**aa**) are suitable substrates.

1,4-Dienes, upon undergoing the enantioselective allylic C–H functionalization, will produce homoallylic alcohols bearing a 1,4-diene unit, which widely exist in natural products[52] and are intermediates that are commonly used in the synthesis of biological active molecule[53] and small molecule probe[54] (see Supplementary Information for more references). It is more challenging to control the chemo- and site selectivity compared with allybenzenes, as two different olefins are present in the substrate. However, very few enantioselective methods have been developed for addition of a 1,4-diene unit to carbonyls and the diversity of 1,4-diene groups that can be introduced is very limited.[55,56] We next applied the reaction conditions to the transformations of 1,4-dienes (Figure 4). Unexpectedly, we found that a trisubstituted alkene moiety is required for high efficiency and stereoselectivity. 1,4-Dienes containing a (*E*)- or (*Z*)-trisubstituted alkene moiety can be transformed to the desired homoallylic alcohols in 41–67% yield, 91:9 dr and 94:6–95:5 er (**8a**–**b**) at room temperature. Further studies suggested that 1,4-dienes bearing a range of aryl (**8c**–**m**) and heteroaryl (**8n**–**q**) alkenes are suitable substrates. The reactions proceeded in high efficiency and stereoselectivity without the need of elevated temperature, whereas transformations of 1,4-dienes that contain trisubstituted alkenes of other substitution patterns (**8s**–**t**) or without an aryl group (**8r**, **8t**) furnished the homoallylic alcohols in 38–42% yield, 87:13–>95:5 dr and 90:10–91:9 er. The limitation of this method for the allyl precursors is that 1,4-enynes and simple alkyl-substituted alkenes are not reactive.

Enantioenriched a-hydroxyl acids and their derivatives are important motifs in biologically active molecules. However, only two examples of enantioselective allyl addition to a-ketoesters have been disclosed so far and only simple allyl group can be introduced,[57,58] as it is more difficult for the catalyst

to provide good efficiency and differentiate the two substituents on the carbonyl effectively. We further expanded the scope of electrophile to a-ketoesters (Figure 5). Compared with aldehydes, a-ketoesters are less reactive and require higher reaction temperatures. Both allylbenzene **1a** and 1,4-diene **11a** can react with a variety of a-ketoesters (**10a**–**h**, **12a**–**h**) to afford tertiary homoallylic alcohols in 38–60% yield, 75:25–>95:5 dr and 90:10–98:2 er. a-Ketoesters derived from various alcohols are suitable substrates (**10f**–**h**, **12f**–**h**). Reactions of the a-ketoester bearing an ester group delivered g-lactones (**10e**, **12e**), which are key intermediates to access spirocycles that are common structures in biologically active molecules.[59] Surprisingly, aryl-substituted a-ketoester provided low diastereo- and enantioselectivity. It might be because that the ester group serves as a larger substituent in the six-membered transition state of the carbonyl addition.

As shown above, a wide range of enantioenriched homoallylic alcohols bearing aryl or alkenyl groups at b-position can be prepared through this approach. Such building blocks are still difficult to access in high stereoselectivity with broad scope. We further demonstrated the utility of this method through application to synthesis of biologically active molecules (Figure 6). 2,3-Dihydrobenzofuran moiety is a ubiquitous structural motif in a vast number of natural products and synthetic compounds that display a wide range of biological activity as shown in Figure 6a.[60] We envisioned that enantioselective allylic C–H functionalization involving allylbenzenes bearing an *ortho*-phenol substituent followed by Mitsunobu cyclization would furnish the 2,3-dihydrobenzofuran core of such class of molecules.[61]

Lithospermic acid has been recognized as an active component in *Danshen*, one of the most popular traditional herbs used in the treatment of cardiovascular disorders, cerebrovascular diseases, various types of hepatitis, chronic renal failure, and dysmenorrhea (see Supplementary Information for a complete bibliography).[62] Recent studies revealed that lithospermic acid has potent and non-toxic anti-HIV activity.[63,64] As indicated in Figure 6b, the synthetic route commenced with the enantioselective allylic C–H functionalization process on gram scale.[65] Treatment of the allylbenzene **1b** (2.03 g) prepared in one step and 93% yield from commercially available *o*-eugenol with aldehyde **2b** (1.00 g) derived from vanillin in quantitive yield in the presence of Co complex generated from **6j** at 55 ^{o}C afforded homoallylic alcohol **13** (1.04 g) in 62% yield, >95:5 dr and 93:7 er. The TMS group was removed simultaneously during the work-up. Subsequent Mitsunobu cyclization followed by switching the protecting group delivered 2,3-disubstituted benzofuran moiety in 80% overall yield. Oxidative cleavage of the alkene and Pinnick oxidation of the resulting aldehyde furnished a known fragment that can be converted to lithospermic acid in 71% overall yield. This catalytic enantioselective route is two-step shorter than previously reported with similar efficiency (6 steps vs. 8 steps).[66]

Dihydrodehydrodiconiferylalcohol (also named 3',4-di-*O*-methylcedrusin) was isolated in low yield from the red latex produced by various South American *Croton* species, which has the potential interest as an inhibitor of cell proliferation.[67] Further studies based on this compound indicated that some derivatives inhibit the growth of a variety of cancer cells by interaction with tubulin.[68] The synthesis began with transformation of allylbenzene **1c** (3.19 g) prepared from eugenol in five steps and 78% overall yield with

aldehyde **2b** (1.00 g) promoted by Co complex derived from **6j** afforded the homoallylic alcohol **16** (1.11 g) in 49% yield, >95:5 dr and 93:7 er. Mitsunobu cyclization followed by oxidative cleavage of the alkene and subsequent reduction with simultaneous global deprotection furnished dihydrodehydrodiconiferyalcohol in 60% overall yield, >95:5 dr and 93:7 er, accomplishing a much more efficient and stereoselective synthesis than previously reported (9 steps, 23% overall yield, >95:5 dr, 93:7 er vs. 12 steps, 1.2% overall yield, >95:5 dr, 62:38 er).[69]

To gain some preliminary insight into the reaction mechanism, a series of experiments were conducted (Figure 7). Kinetic experiments revealed that in the transformations of allylbenzenes and 1,4-dienes, allylic C–H bond cleavage might not be the rate-determining step. Allylbenzene **1d** bearing a b-methyl-styrene moiety was transformed chemoselectively to afford **7ab** in 70% yield, 93:7 dr and 93:7 er. To investigate whether the cleavage of the C–H bond is enantioselective, we performed the transformation with allylbenzene **1e**. A roughly 1:1 mixture of **3x** and **3y** associated with trace amount of **3a** was generated, indicating that either the C–H bond cleavage might not be enantioselective, or isomerization of two h^1-allyl–Co complexes might not be stereochemically retaining.

In conclusion, we have developed an unprecedented protocol for catalytic generation of nucleophilic allyl–Co complexes through allylic C–H bond activation followed by site-, diastereo- and enantioselective addition of carbonyls to furnish a wide range of homoallylic alcohols that are otherwise difficult to access. This approach is further applied to enantioselective formal synthesis of lithospermic acid and total synthesis of dihydrodehydrodiconiferylalcohol. The advances outlined here demonstrate that simple unsaturated molecules can be directly converted to functionalized allyl nucleophiles without the need for succumbing to one-at-a-time installation of each functional group, resulting in pathways that are unnecessarily time consuming, costly and waste-generating. A single multifunctional Co-based catalyst assembled from an inexpensive Co salt and commercially available phosphine can accurately control the chemo-, site- and stereoselectivity. The possibility of using other easily available unsaturated hydrocarbons for efficient and stereoselective preparation of high value enantioenriched building blocks through C–H functionalization strategy is under investigation.

Methods

To an oven-dried 8 mL sealed tube were charged with $Co(acac)_2$ (5.1 mg, 0.02mmol, 10 mol %) and **6j** (10.1 mg, 0.02mmol, 10 mol %) followed by addition of DMSO (2.0 mL). The resulting mixture was allowed to stir at room temperature for 1.0 hour. $AlMe_3$ (1.0 M in hexane, 0.30 mL, 0.3 mmol, 1.5 equiv) was added and resulting solution was allowed to stir for 5 minutes, then the substrate **1a** (47.2 mg, 0.4 mmol, 2.0 equiv) and **2a** (21.2 mg, 0.2 mmol, 1.0 equiv) was added. The tube was closed tightly and the mixture was allowed to stir at 65 ºC for 12 h. After cooled to 0 ºC, the sealed tube was carefully opened and the reaction was quenched by 10 mL of 3.0 M HCl aqueous solution and washed with diethyl ether (3 ´20 mL). The combined organic layer was washed with brine (20 mL) and dried over Na_2SO_4. After the solids were filtered off, the solvent was removed under reduced pressure and the residue was purified by

silica-gel column chromatography (eluent: hexane/ethyl acetate, 7:1) to afford the **3a** as colorless oil (30.5 mg, 0.136 mmol, 68%).

Declarations

Author contributions

H.Z. and J. H. performed catalyst studies and method development studies, as well as synthesis of lithospermic acid and dihydrodehydrodiconiferylalcohol. F. M. designed and directed the investigations and composed the manuscript with revisions provided by the other authors.

Conflict of Interest

The authors declare no conflict of interest.

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Figures

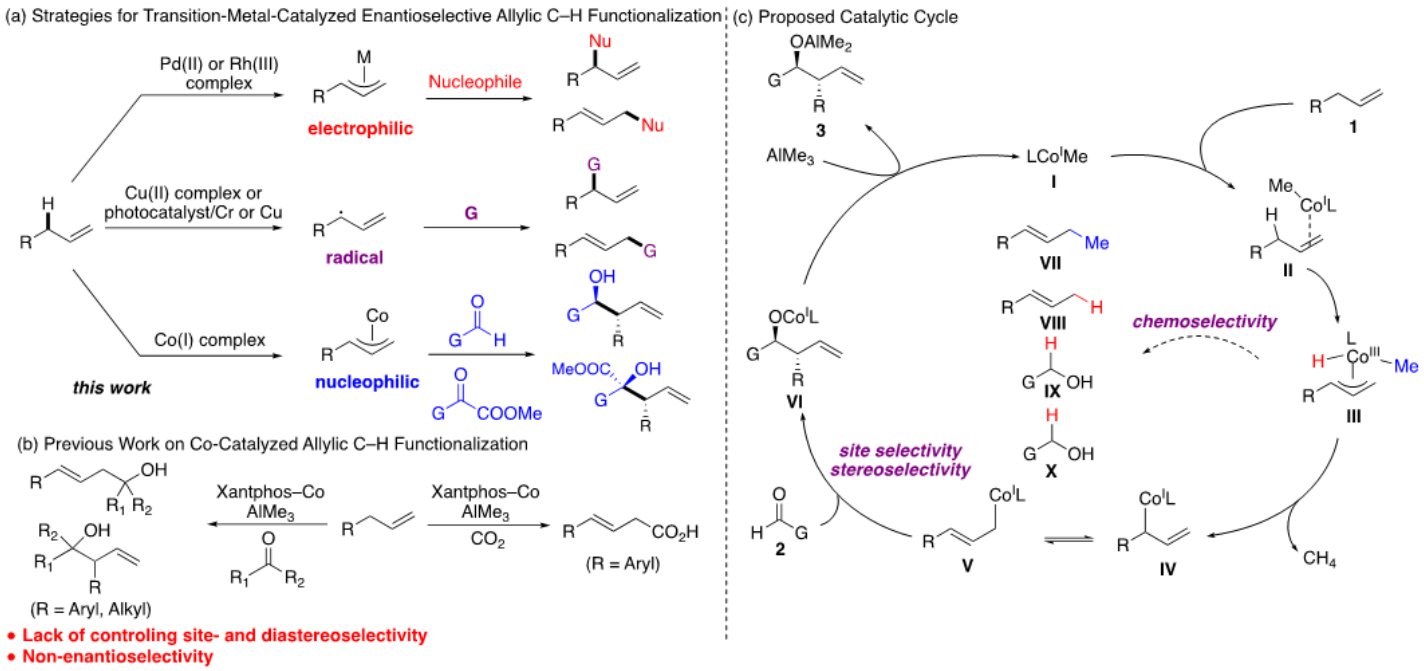
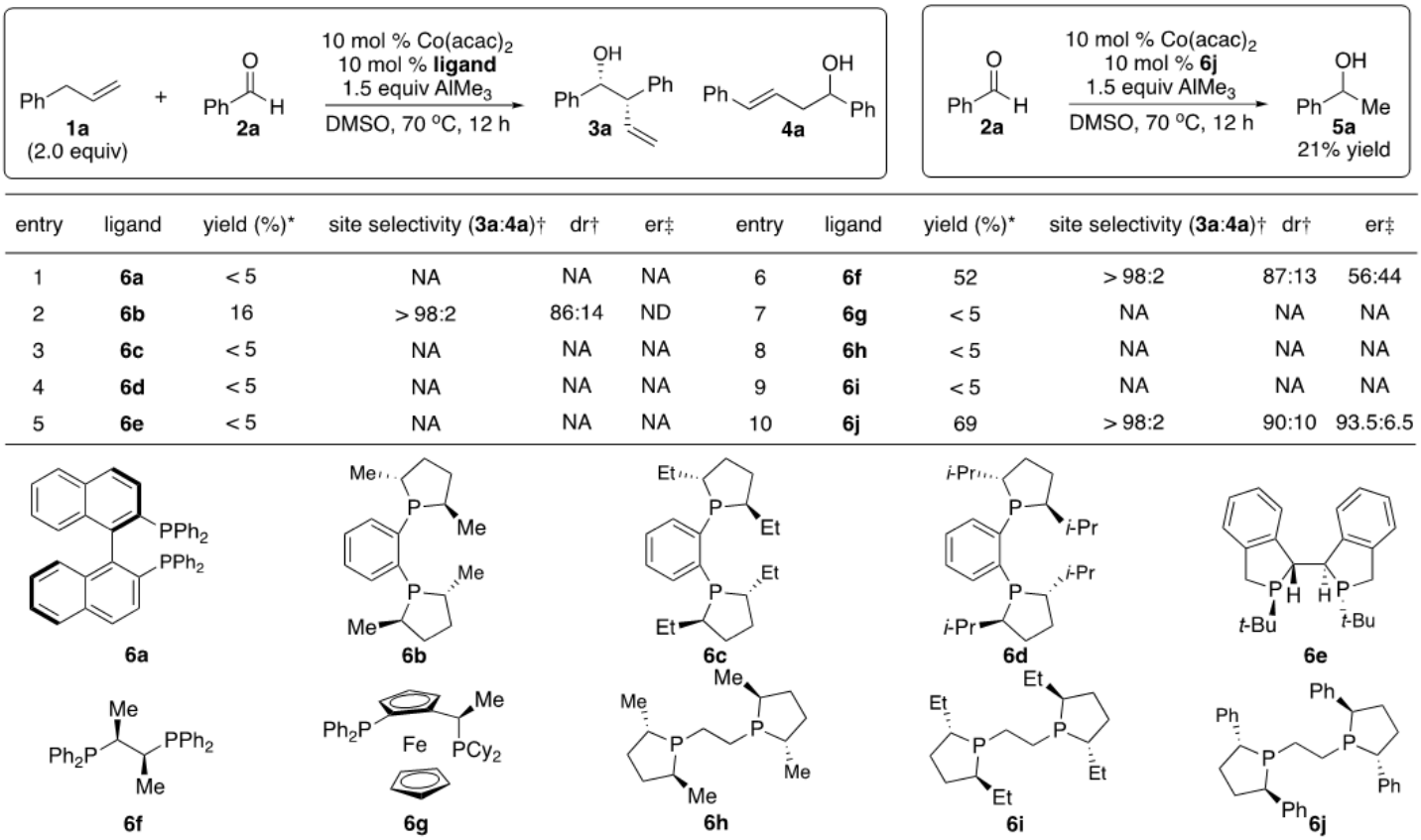


Figure 1

Reaction Design. a, Transition-metal catalyzed enantioselective allylic C–H functionalization via allyl–metal complexes of different natures. b, Co-catalyzed allylic C–H functionalization to generate a nucleophilic allyl–Co complex and subsequent reactions with CO2 delivered linear products, whereas transformations of the allyl–Co complexes produced from C–H activation with ketones provided a mixture of linear and branched products without efficient control of diastereoselectivity. c, Proposed catalytic cycle for Co-catalyzed enantioselective allylic C–H functionalization with the issues that need to be addressed.



entry	ligand	yield (%)*	site selectivity (**3a**:**4a**)†	dr†	er‡	entry	ligand	yield (%)*	site selectivity (**3a**:**4a**)†	dr†	er‡
1	**6a**	< 5	NA	NA	NA	6	**6f**	52	> 98:2	87:13	56:44
2	**6b**	16	> 98:2	86:14	ND	7	**6g**	< 5	NA	NA	NA
3	**6c**	< 5	NA	NA	NA	8	**6h**	< 5	NA	NA	NA
4	**6d**	< 5	NA	NA	NA	9	**6i**	< 5	NA	NA	NA
5	**6e**	< 5	NA	NA	NA	10	**6j**	69	> 98:2	90:10	93.5:6.5

Figure 2

Examination of Co catalysts for Enantioselective Allylic C–H Functionalization. Reactions were carried out under N2 atmosphere; see Supplementary Information for details. NA, not applicable; ND, not determined. * Yield of purified products. † Site selectivity and diastereomeric ratios were determined by analysis of 400 MHz 1H NMR spectra. ‡ Enantiomeric ratios were determined by HPLC analysis. See Supplementary Information for details.

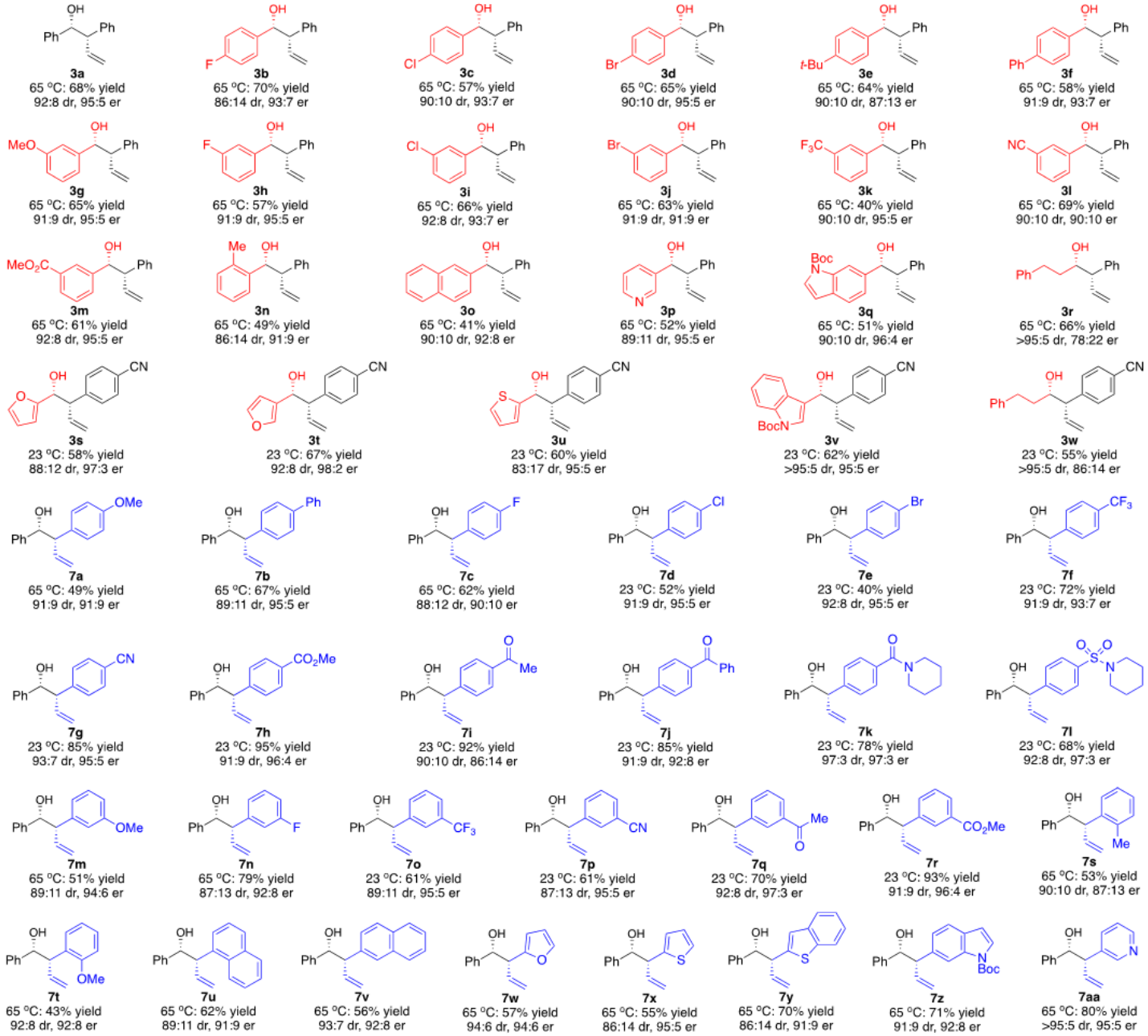


Figure 3

Substrate Scope for Co-Catalyzed Enantioselective Allylic C–H Functionalization of Allylbenzenes with Aldehydes.

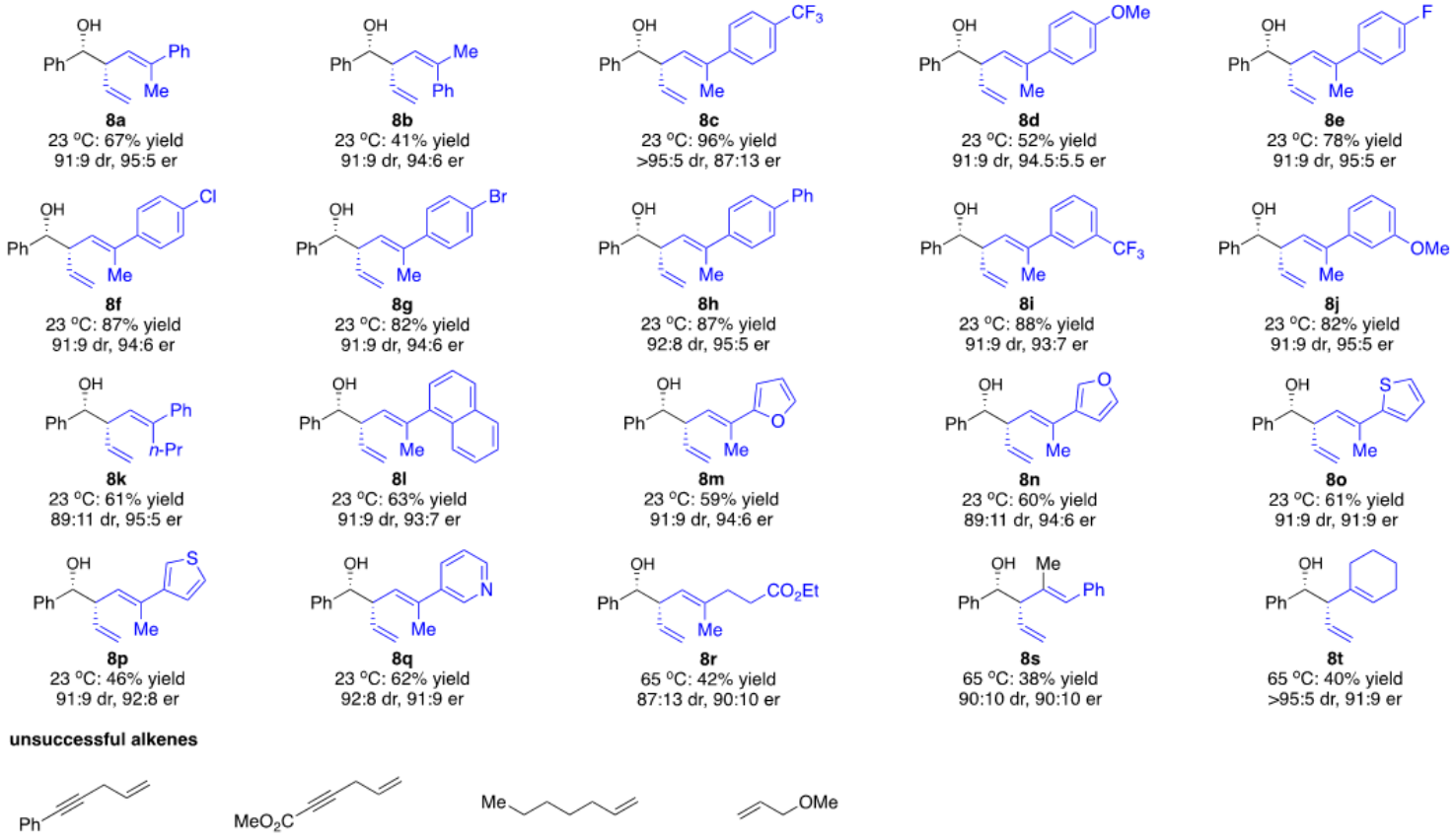


Figure 4

Substrate Scope for Co-Catalyzed Enantioselective Allylic C–H Functionalization of 1,4-Dienes.

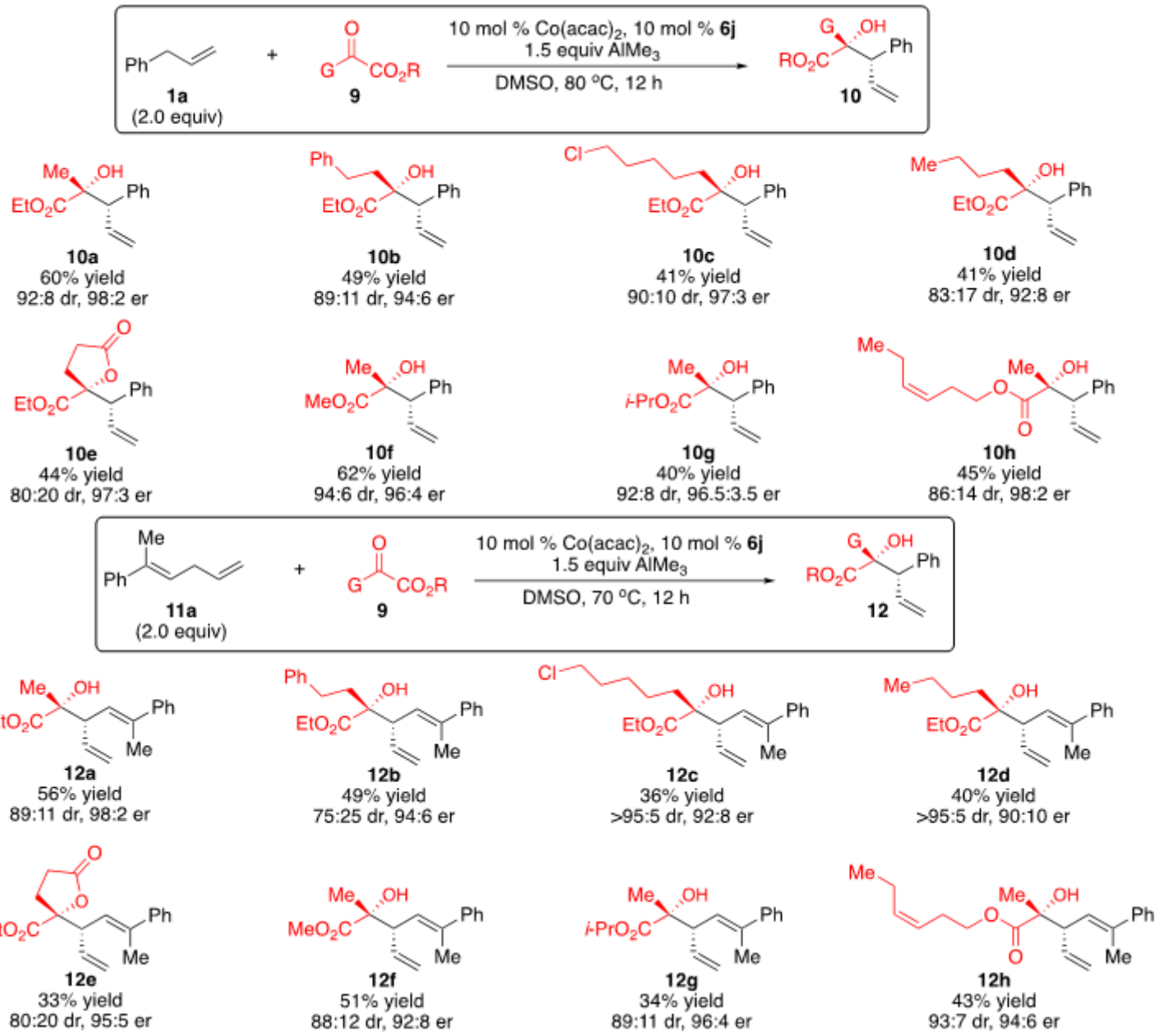


Figure 5

Substrate Scope for Co-Catalyzed Enantioselective Allylic C–H Functionalization of 1,4-Dienes.

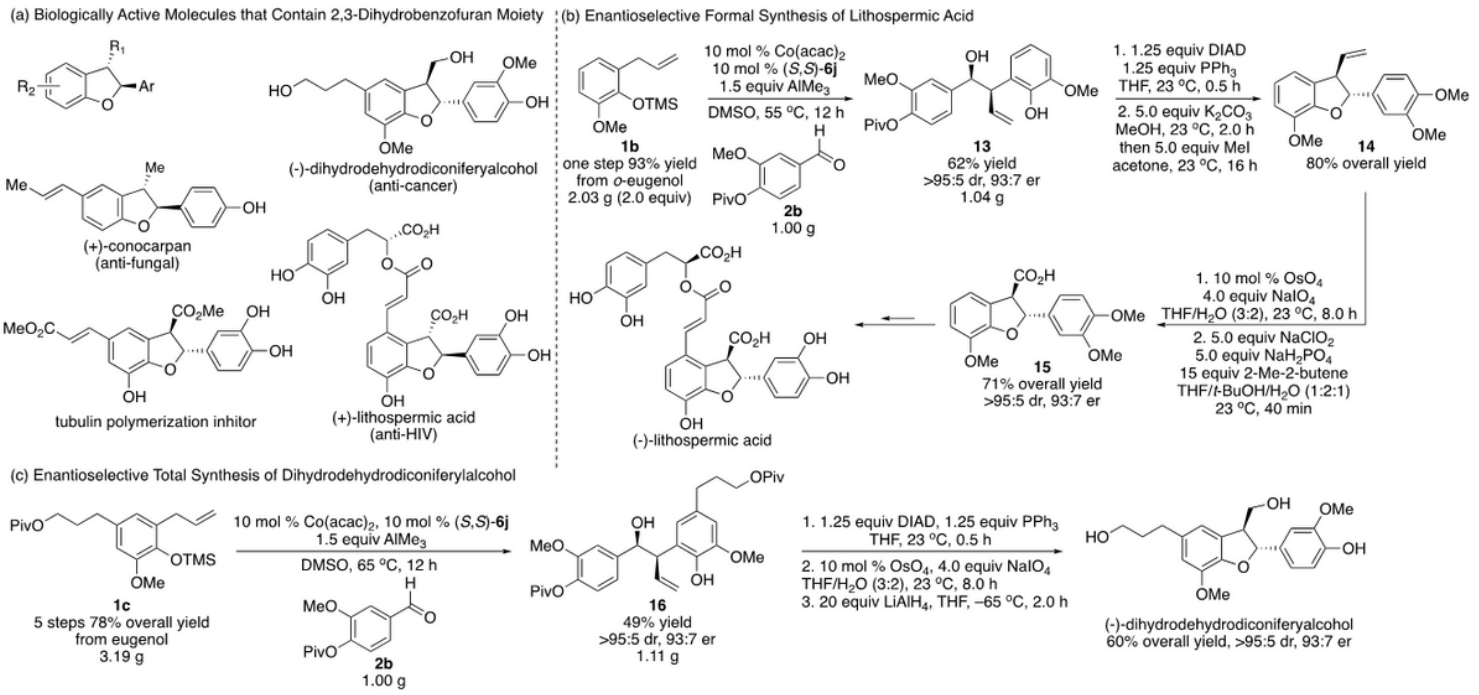


Figure 6

Application of Co-Catalyzed Enantioselective Allylic C–H Functionalization to Biologically Active Natural Product Synthesis. a, Numerous natural products and their derivatives with diversified biologically activities contain a 2,3-disubstituted benzofuran core. b, A known intermediate 15 that can be converted to lithospermic acid was prepared in 6 steps enantioselectively. c, The first catalytic enantioselective total synthesis of dihydrodehydrodiconiferylalcohol was accomplished in 9 steps.

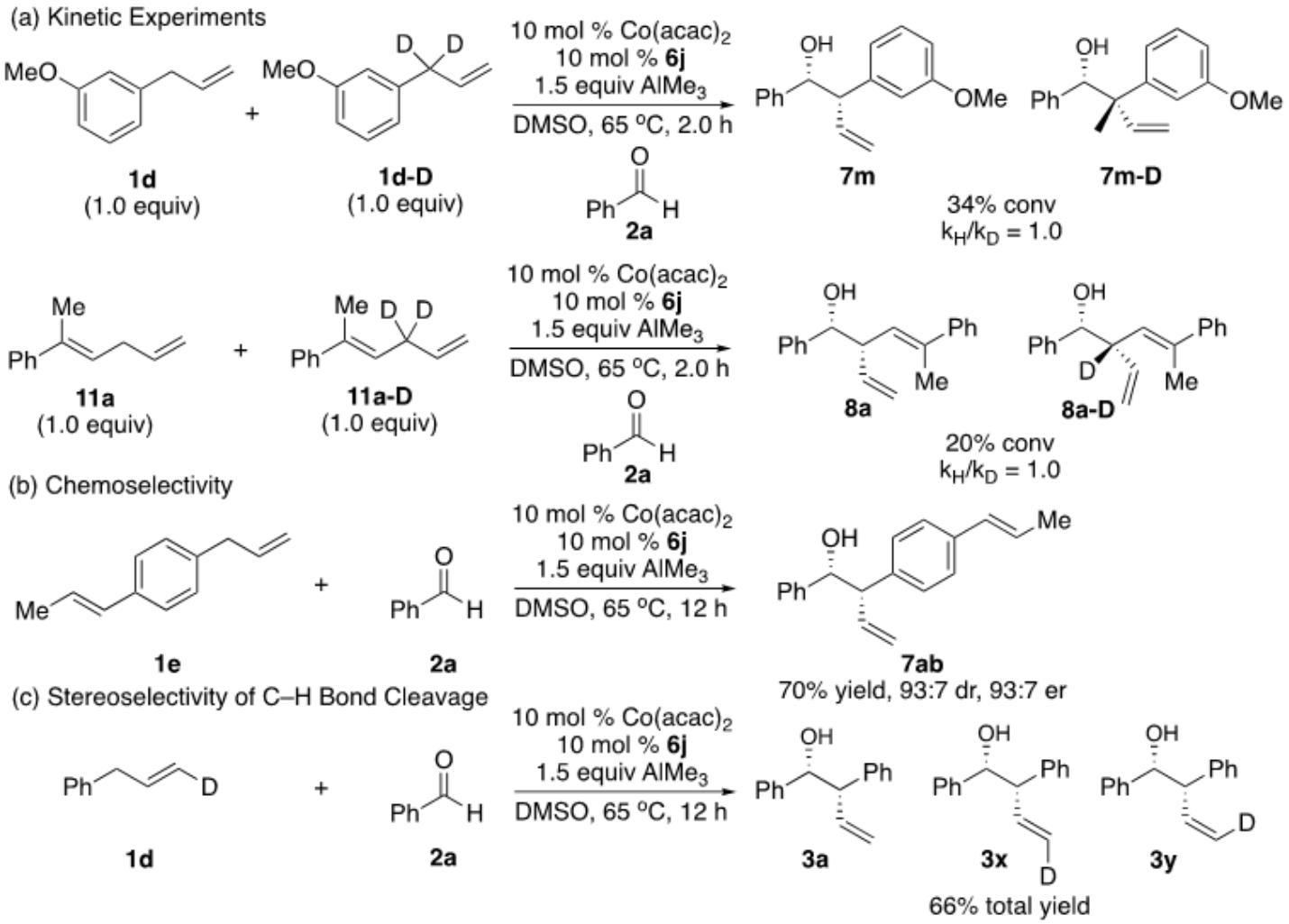


Figure 7

Preliminary Mechanistic Studies. a, Competitive reactions of allylbenzene 1d and 1,4-diene 11a with their deuterated counterparts resulted in similar rates of C–H and C–D bond cleavage.b, Allylic C–H bond is cleaved preferentially compared with that of α-methyl-styrene, and β-methyl-styrenes can react under reaction conditions with lower stereoselectivity than corresponding allylbenzenes. c, Transformation of allylbenzenes substituted with a (E)-deuterium led to isomerization of the stereochemistry of the alkene.

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