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Synthesis of Homoallylic Alcohols with Acyclic Quaternary Centers via Co^{III}-Catalyzed Three-Component C–H Bond Addition to Internally Substituted Dienes and Carbonyls

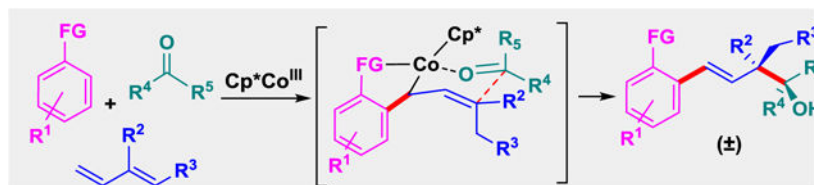
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Abstract

An efficient Co^{III}-catalyzed three-component strategy to prepare homoallylic alcohols containing acyclic quaternary centers is disclosed. This transformation enables introduction of two C–C σ bonds *via* C–H bond activation and sequential addition to internally substituted dienes and a wide range of aldehydes and activated ketones. Isoprene and other internally monosubstituted dienes are effective inputs, with the reaction proceeding with high diastereoselectivity for those substrate combinations that result in more than one stereogenic center. Moreover, the opposite relative stereochemistry can be achieved by employing 1,2-disubstituted dienes. A mechanism for the transformation is proposed based upon the relative stereochemistry of the products and studies with isotopically labeled starting materials.

Graphical Abstract



An efficient Co^{III}-catalyzed three-component synthesis of homoallylic alcohols containing acyclic quaternary centers is disclosed. This highly diastereoselective approach introduces two C–C σ bonds *via* C–H bond activation and sequential addition to internally substituted dienes and a wide range of aldehydes or activated ketones.

Keywords

C–H activation; homogeneous catalysis; multicomponent reactions; cobalt; diastereoselectivity

Transition metal-catalyzed C–H bond functionalization has become an effective strategy to access synthetically useful structural motifs.^[1] While remarkable progress has been made for two-component C–H bond additions to diverse coupling partners, the sequential addition

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of C–H bonds across two different coupling partners to access complex motifs has only recently begun to be developed.^[2,3] Recently, our lab reported the Co^{III}-catalyzed C–H bond addition to dienes and aldehydes [Figure 1, Eq. (1)].^[2c,4] In this approach, two new C–C σ bonds are formed in a regio- and stereoselective manner as dictated by a Co^{III}-allyl chair-like transition state. To expand upon this work, we have focused on internally substituted dienes to introduce acyclic quaternary centers, which are synthetically challenging motifs to access due to their congested nature.^[5,6] Recently Zhao *et al.* reported the first Rh^{III}-catalyzed three-component C–H bond addition to a range of monosubstituted dienes and aldehydes [Eq. (1)].^[2a] Although two examples of additions of internally substituted dienes were included, these reactions proceeded in modest yields and were demonstrated only for the highly activated aldehyde ethyl glyoxylate.

Herein, we describe a three-component strategy to access homoallylic alcohols containing acyclic quaternary centers *via* Co^{III}-catalyzed C–H bond activation and sequential addition to internally substituted dienes and aldehydes or activated ketones [Figure 1, Eq. (2–4)]. For isoprene, secondary alcohol products are obtained by reactions of a variety of C–H bond substrates with both activated and unactivated alkyl and aryl aldehydes [Eq. (2)]. In addition, the first examples of three-component coupling with activated ketones^[7] provide tertiary alcohols that incorporate contiguous tetrasubstituted carbons [Eq. (2)]. Upon extending the three-component reaction to internally monosubstituted dienes other than isoprene, two stereogenic centers are introduced with high diastereoselectivity [Eq. (3)].^[5] Moreover, the opposite relative stereochemistry of the methyl and hydroxyl groups on the two vicinal stereogenic carbon centers can be obtained by employing previously unexplored 1,2-disubstituted dienes [Eq. (4)]. The catalytic cycle, which is supported by studies with isotope labeled starting materials, provides a rationale for the disparate stereochemical outcomes for the two different diene substitution patterns [Eqs (3) and (4)].

An extensive evaluation of different reaction conditions was conducted for the three-component coupling of phenyl pyrazole **1a**, isoprene **2a** and isovaleraldehyde **3a** (Table 1; see Supplementary Table S1). The use of [Cp*Co(C₆H₆)] [B(C₆F₅)₄]₂,^[8] previously developed in our lab, was found to be crucial, with other preformed Co^{III} and Rh^{III} catalysts, such as [Cp*Co(C₆H₆)] [PF₄]₂, [Cp*Rh(MeCN)₂] [SbF₆]₂ and [Cp*Rh(MeCN)₂] [SbF₆]₂, resulting in little to no conversion. A catalytic amount of AcOH was found to be beneficial as opposed to LiOAc^[2f] or PivOH,^[9] which have been used as additives for other Co^{III}-catalyzed C–H bond addition reactions. Concentration was shown to have a critical role in this transformation, with 0.4 M leading to much lower conversion than 1.0 M.^[2c,d,f] Heating at 50 °C was chosen as the standard conditions for isoprene addition, but 70 °C was found to be necessary for some dienes and/or carbonyl compounds bearing bulkier substituents (*vide infra*). In addition, while dioxane was selected for the standard reaction conditions, DCE and toluene were also effective solvents, and toluene was in fact superior to dioxane for some sterically hindered coupling partners (*vide infra*).

Having determined the optimal reaction conditions, we next explored the scope for isoprene addition (Table 1). First, alkyl aldehydes were investigated (**4a–4b**), including those displaying benzyl ether (**4c**), terminal alkene (**4d**), and primary alkyl chloride (**4e**) functionality. The reaction is sensitive to sterics, with α -branched

cyclopropanecarboxaldehyde requiring an elevated 70 °C reaction temperature and toluene as solvent to provide homoallylic alcohol **4f** in 62% yield. Not surprisingly, the more sterically hindered α,α -dibranched pivaldehyde gave only a trace amount of product (data not shown). A series of aryl aldehydes were next examined. Benzaldehyde (**4g**), along with derivatives with electron-deficient groups at the *ortho*, *meta*, or *para*-positions (**4h-4k**) all coupled in high yields. Acidic *m*-hydroxybenzaldehyde (**4l**) and the moderately electron-rich *p*-tolualdehyde (**4m**) coupled in 50% and 62% yields, respectively. The presence of a basic pyridyl nitrogen did not impede the reaction, with homoallylic alcohol **4n** obtained in excellent yield.

Along with alkyl and aromatic aldehydes, the first examples of three-component coupling of more challenging ketones proceeded to give homoallylic tertiary alcohols **4o-4v** that incorporate contiguous tetrasubstituted carbons (Table 1). Electron-deficient isatin and *N*-methylisatin furnished tertiary alcohols **4o** and **4p**, respectively, in moderate yields. Chloro-substituted isatin and *N*-methylisatin also afforded the alcohols **4q** and **4r** in comparable yields, respectively. The highly strained cyclic ketone 3-oxetanone also displayed good reactivity, providing tertiary alcohol **4s** in good yield. Additionally, *N*-carboxybenzyl (Cbz)-protected 3-azetidinone afforded tertiary alcohols **4t** and **4u** in >90% yields. Reaction with the indantrione furnished **4v**, albeit in moderate yield. We also investigated the coupling of unactivated ketones such as acetone and acetophenone, but three-component coupling products were not obtained.

A number of different C–H bond substrates were also investigated. A methyl substituent at either the *ortho* (**4t**) or *meta* (**4u** and **4w**) position prevented bis-functionalization for phenyl pyrazole substrates. Additionally, 2-phenylpyridine served as an excellent C–H bond substrate, furnishing product **4x** in near-quantitative yield. C–H bond substrates with amide directing groups were also effective as demonstrated for secondary *N*-isopropyl (**4y**) and *N*-methyl (**4z**) benzamides as well as for tertiary pyrrolidine benzamide (**4aa-4ac**). Lastly, homoallylic alcohol **4ad** was prepared by C–H functionalization of *N*-methylidihydroisoquinolin-2-one.

A series of internally substituted dienes **5** were next explored for preparing homoallylic alcohols **6** with stereogenic quaternary carbons (Table 2). Three-component addition to 3-methyleneoctene and acetaldehyde provided alcohol **6a** in 62% yield and with >20:1 *dr*. The relative stereochemistry of **6a** was confirmed by X-ray crystallographic determination of its 3,5-dinitrobenzoylated derivative, confirming a *syn*-relationship between the methyl and hydroxyl groups.^[10] C–H bond substrates with both pyrazole and pyridine directing groups were effective for coupling with benzyloxyacetaldehyde to give alcohols **6b** and **6c** with high diastereoselectivities and 66% and 51% yields, respectively. Benzaldehyde derivatives with electron-withdrawing groups at the *para* position afforded the corresponding products **6d-6f** in moderate yields. *m*-Bromobenzaldehyde was also an effective coupling partner to give alcohol **6g** that incorporates a site for further elaboration. Contiguous tetrasubstituted carbons could also be introduced as demonstrated by coupling the activated ketone 1-Cbz-3-azetidinone to give alcohol **6h** in good yield. More sterically demanding substituents on the diene were investigated as well. The isobutyl substituted diene coupled with 2-

benzyloxyacetaldehyde to give the homoallylic alcohol **6i** with good diastereoselectivity. In contrast, reaction with acetaldehyde provided product **6j** in modest yield and with lower diastereoselectivity. The aryl substituted diene, 2-phenyl-1,3-butadiene, also furnished product **6k**, albeit in low yield and with poor diastereoselectivity.

Next, we extended the scope to 1,2-disubstituted 1,3-dienes **7** (Table 3), which provide the opposite relative stereochemistry for the methyl and hydroxyl groups on the two contiguous stereogenic centers as compared to internally monosubstituted dienes **5** (Table 2). Three-component coupling with 3-methylpentadiene and acetaldehyde gave alcohol **8a** in 49% yield and with high diastereoselectivity (>20:1 *dr*). The relative stereochemistry was confirmed by X-ray crystallographic determination of its 3,5-dinitrobenzoylated derivative,^[10] showing that the methyl and the hydroxyl groups are in an anti-relationship. Three-component coupling for C–H bond substrates with the pyridyl directing group provided moderate to excellent yields and good diastereoselectivity for alkyl, aromatic and heteroaromatic aldehydes (**8b–8f**). Finally, when the diene with R² = Et was employed, both aryl (**8g**) and alkyl (**8h**) aldehydes gave homoallylic products that incorporated a propyl substituent at the quaternary carbon center.

A series of experiments were conducted to obtain mechanistic information using isotopically labeled starting materials. When 2-(phenyl-*D*₅)pyridine was subjected to the standard reaction conditions with isoprene **2** and 4-formylbenzoate as the coupling partners, an 18% conversion to the three-component coupling product was observed after a 30 min reaction time. Under these conditions, 58% of the C–H bond substrate was recovered and showed extensive H/D exchange at the *ortho* positions (Figure 2a). These results establish that the C–H activation step is reversible.

When the terminally dideuterated isoprene **2-d₂** was subjected to the standard reaction conditions, deuterium migration was observed on two different sites in the product **4u-d₂** (Figure 2b). Only one out of the two methyl groups in **4u-d₂** incorporated a significant amount of deuterium. Additionally, the *ortho* position of the aromatic ring incorporated 30% deuterium likely due to reversible C–H activation. The product incorporated 1.65 out of the two deuteriums present in **2-d₂**. Presumably, some deuterium loss occurs from Co^{III}–hydride intermediate **C** (Figure 3) during the catalytic cycle (*vide infra*).

A mechanism is proposed based upon the studies with isotope labeled starting materials, the stereochemistry observed for the products, and prior mechanistic studies for three-component coupling of butadiene^[2c] (Figure 3). In the presence of the Co^{III}-catalyst, a reversible *ortho* C–H bond activation of substrate **1** *via* concerted metalation deprotonation generates 5-membered metallocycle **A**.^[11] Alkene coordination and migratory insertion of the diene affords the η³-Co-allyl species **B**.^[2c] Syn β-hydride elimination provides species **C**, with the syn coplanar hydrogen H_a incorporated as the Co hydride. This intermediate undergoes reversible hydride reinsertion of H_a into the C-4 position of the diene, as evidenced by deuterium incorporation at the C-4 position (Figure 2b). Parallel reactions of **2** and **2-d₂** proceeded at the same rate, establishing that neither the β-hydride elimination nor reinsertion is a rate limiting step (See Supplementary Information VI). Diastereoselective addition of intermediate **D** to aldehyde **3** through the chair-like transition state shown in **E**

provides the observed relative stereochemistry in the final product for both the internally monosubstituted (Table 2) and 1,2-disubstituted (Table 3) dienes. Release of product **F** upon protonolysis regenerates the cobalt catalyst.

In summary, a Co^{III}-catalyzed C–H bond addition to form secondary and tertiary homoallylic alcohols containing quaternary carbons has been developed. The sequential C–H bond addition to internally substituted dienes and carbonyls shows broad scope, including not only alkyl and aryl aldehydes but also the first examples of additions to activated ketones for the formation of tertiary homoallylic alcohols. Additionally, this robust transformation proceeds with high diastereoselectivity for various internally monosubstituted dienes. Notably, with the first application of 1,2-disubstituted dienes, the opposite relative stereochemistry of the two stereogenic centers can be achieved. Both X-ray structural characterization of the products and mechanistic experiments support the proposed mechanism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

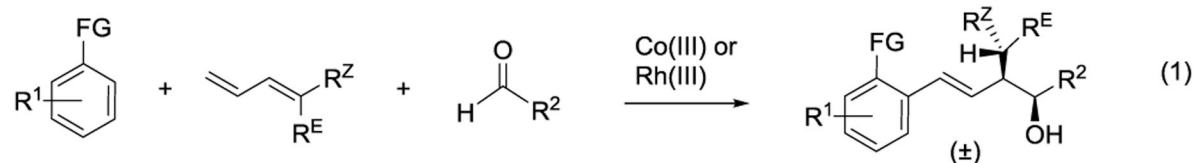
Acknowledgements

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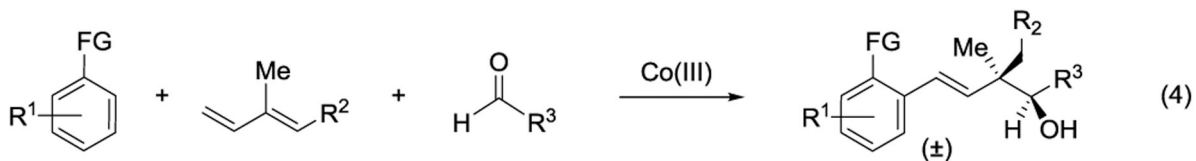
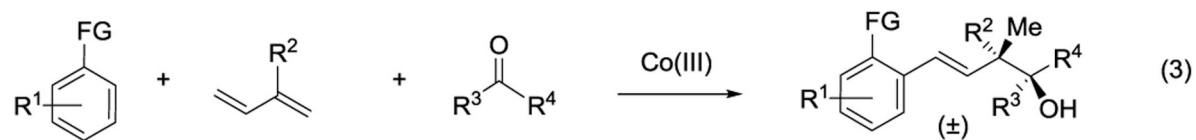
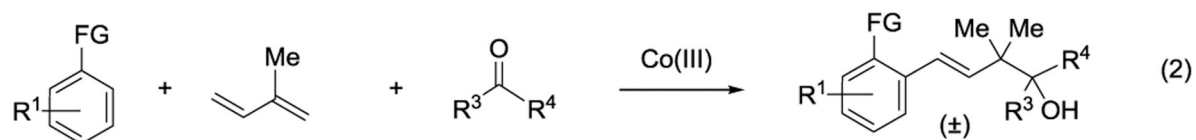
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Previous work:Co^{III}- and Rh^{III}-catalyzed C-H bond addition to terminally substituted dienes and aldehydes^[2a,c]**This work:**

Three component coupling of internally substituted dienes and aldehydes/ketones

**Figure 1.**

Transition metal-catalyzed three-component addition for the synthesis of homoallylic alcohols.

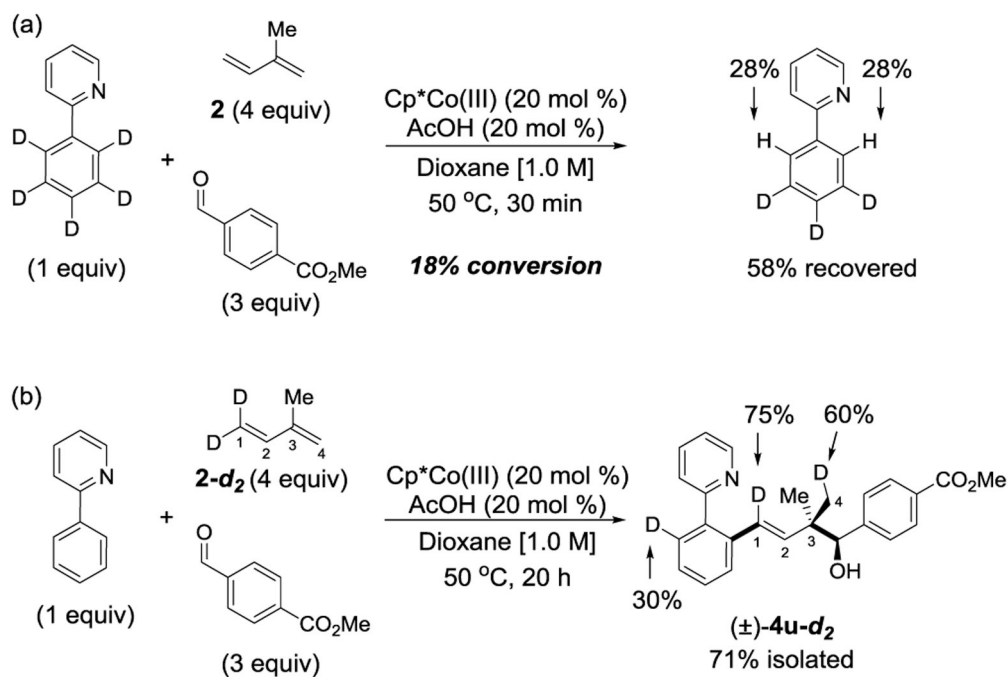
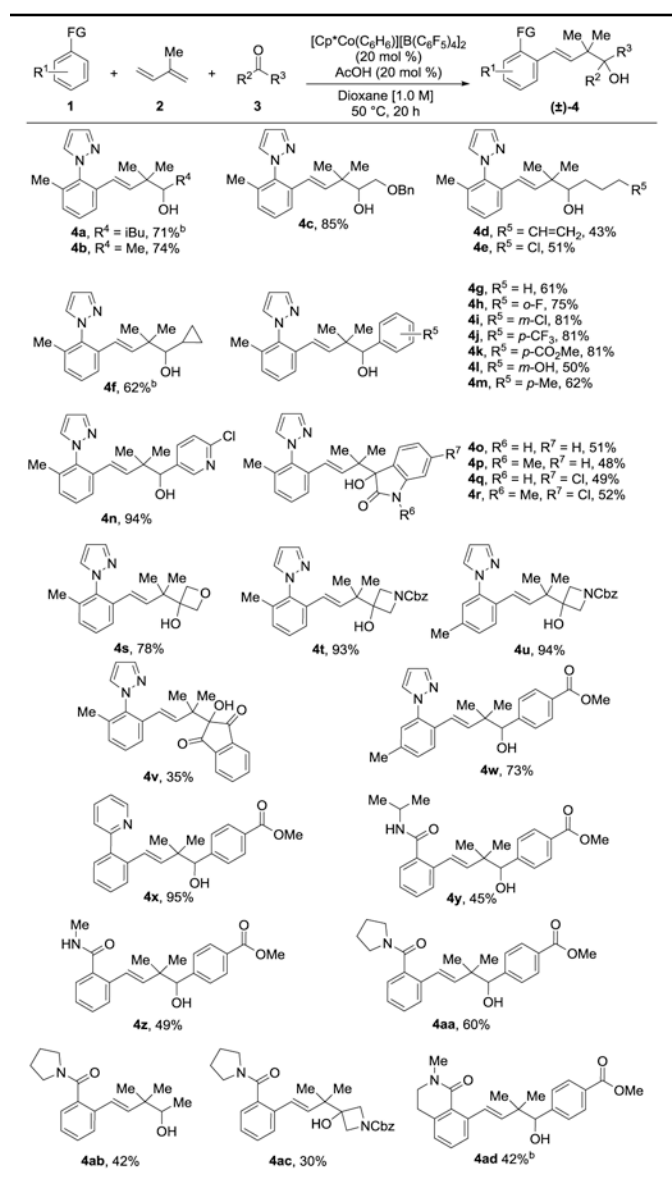


Figure 2.
Mechanistic experiments with deuterium labeled coupling partners.

Table 1.

C–H bond functionalization with isoprene and aldehydes/ketones.

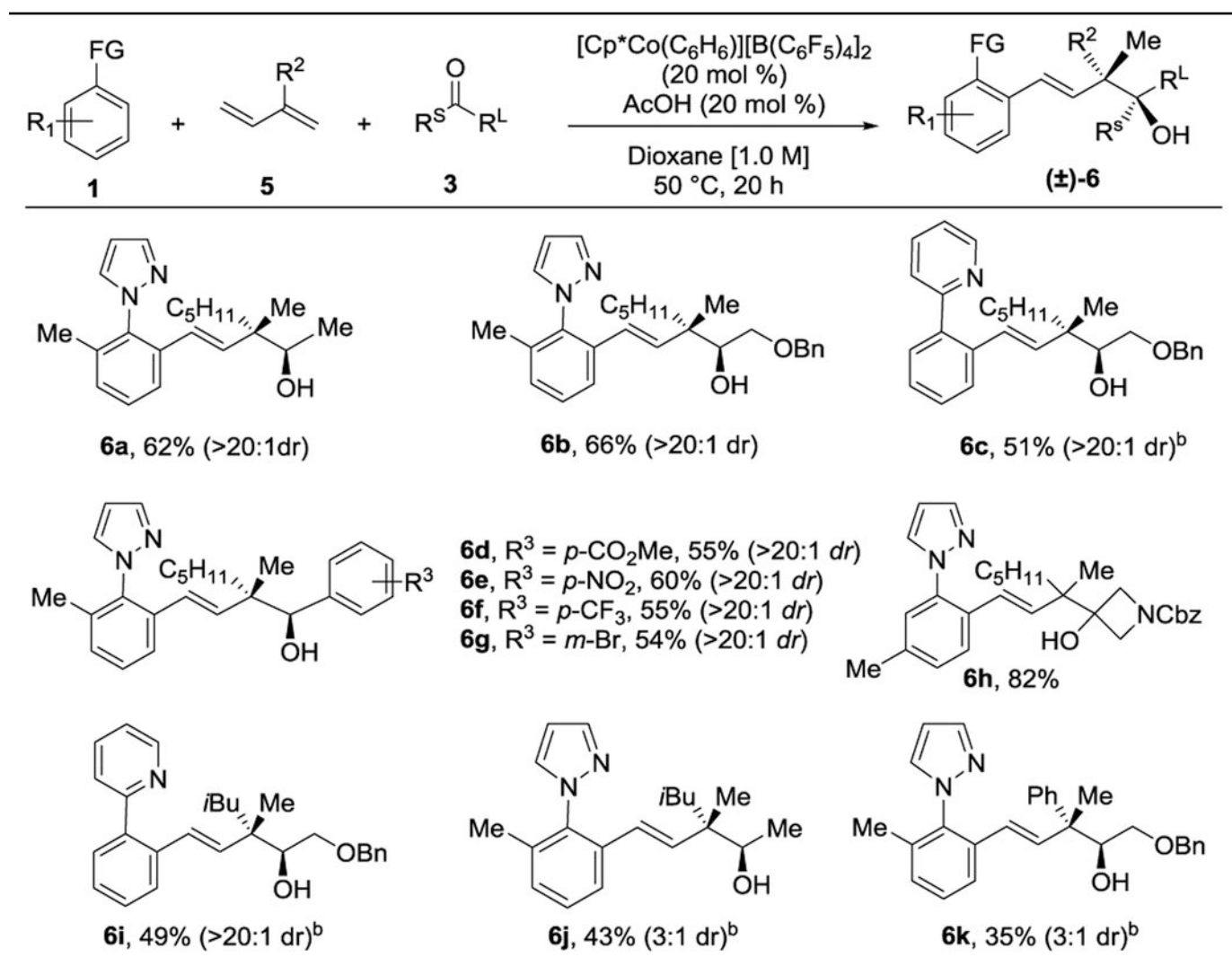


[a] Conditions: 0.2 mmol of 1, 0.8 mmol of 2, 0.6 mmol of 3. Isolated yields of products after purification by chromatography are reported.

[b] Reactions performed in toluene at 70 °C.

Table 2.

C–H bond functionalization with internally monosubstituted dienes and aldehydes/ketones.

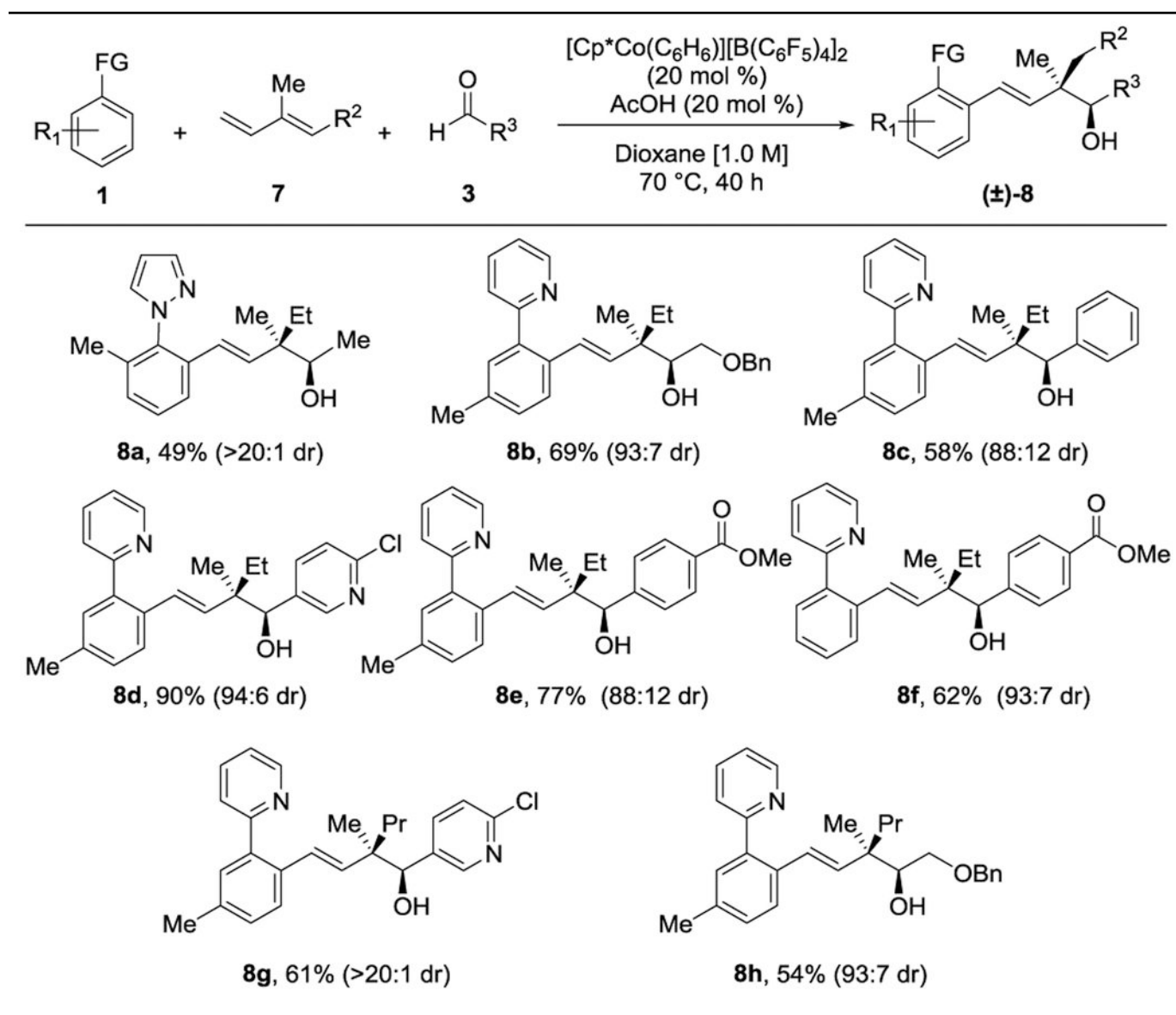


^[a] Conditions: 0.2 mmol of **1**, 0.4 mmol of **5**, 0.6 mmol of **3**. Isolated yields of products after purification by chromatography are reported.

^[b] Reactions performed at 70 °C for 40 h.

Table 3.

C–H bond functionalization with 1,2-disubstituted dienes.



^[a] Conditions: 0.2 mmol of **1**, 0.4 mmol of **7**, 0.6 mmol of **3**. Isolated yields of products after purification by chromatography are reported.