Multi-Catalytic Approach to One-Pot Stereoselective Synthesis of Secondary Benzylic Alcohols

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ABSTRACT: One-pot multi-step procedures bear the potential to rapidly build up molecular complexity while avoiding the wasteful and costly isolations and purifications of consecutive intermediates. Here we report multi-catalytic protocols that convert alkenes, unsaturated aliphatic alcohols, and aryl boronic acids into secondary benzylic alcohols with high stereoselectivities under sequential catalysis that integrates alkene cross-metathesis, isomerization, and nucleophilic addition. Because each transformation of the sequence is executed by an independent catalyst, without any catalytic cross-reactivity, allylic alcohols bearing a prochiral double bond can be converted to any stereoisomer of the product with high stereoselectivity (>98:2 er and >20:1 dr). Overall, with the aid of up to four catalysts operating in a single vessel, the protocols directly convert simple starting materials into a range of value-added products with high stereocontrol and excellent material efficiency, demonstrating both the efficacy and the advantages of the one-pot synthesis employing multiple transition-metal catalysts.

Despite substantial progress, the preparation of fine-chemicals and pharmaceuticals remains resource-intensive, raising serious sustainability and environmental concerns.[1,2] According to the analysis of organic processes performed by GlaxoSmithKline,[3] organic solvents account for 80% of all material consumption, except of water, and 75% of the energy use as well as 50% of the greenhouse gas emissions. Because the bulk of organic solvents is used for isolation and purification of synthetic intermediates, rather than as the medium of the actual chemical reactions, procedures that execute multiple synthetic steps in a one-pot fashion are advantageous from the efficiency standpoint.[4–20] The economy of one-pot synthesis[21] that connects stoichiometric and catalytic reactions, with or without limited intermediary work-up, proved highly beneficial for the synthesis of complex molecules,[22] including natural products and pharmaceuticals.[23–25] However, the development of one-pot protocols with multiple transition-metal catalyzed reactions operating in one vessel remains a challenge.[26–33] The prospective cross-reactivity of the catalysts, including the exchange of ligands and formation of a mixture of complexes, is likely to hinder the required activity.[15] The issues are further enhanced in asymmetric catalysis, where any cross-reactivity is likely to deteriorate the stereoselectivity of the intended transformations.[34–39]

Stereoselective synthesis has been facilitated by the development of transition metal-catalyzed asymmetric hydrogenation.[40–42] For instance, secondary benzylic alcohols, a prevalent moiety in biologically active molecules and valuable building blocks in synthesis,[43–47] are readily prepared by enantioselective hydrogenation of aryl ketones in the presence of chiral Ru-complexes developed by Noyori.[40] However, the preparation of ketones often requires a series of wasteful stochiometric oxidation and addition reactions, impeding the process efficiency (Figure 1a).

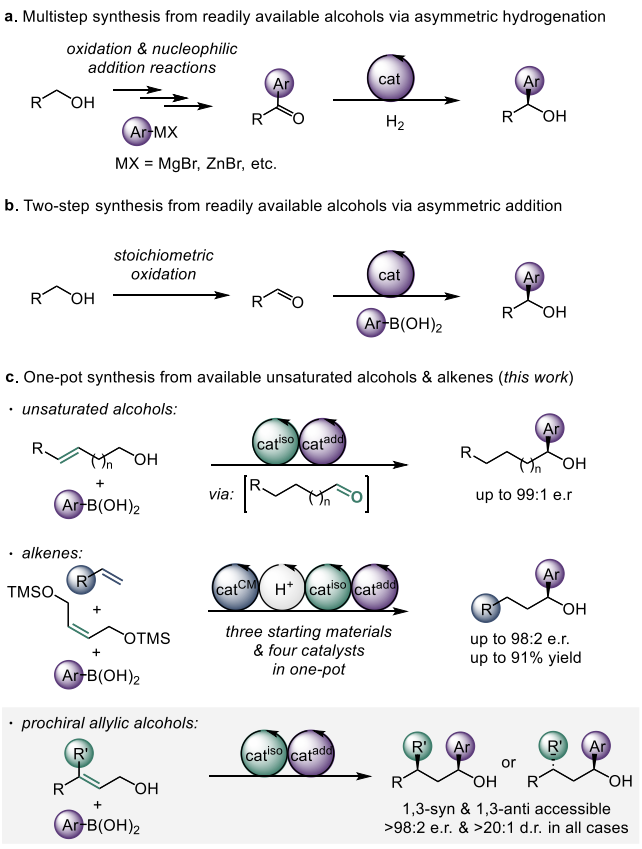

Figure 1. Context and the current study: stereoselective synthesis of secondary benzylic alcohols from readily available starting materials.

Asymmetric transformations that form a new stereogenic center and build up the molecular scaffold by connecting two building blocks are attractive. For instance, the

enantioselective addition of an aryl nucleophile to an aldehyde to form a secondary benzylic alcohol[48] represents an appealing alternative to the stepwise synthesis involving the enantioselective hydrogenation (Figure 1b). However, in this case, the aldehyde starting material typically also needs to be prepared from an accessible alcohol or carboxylic acid, burdening the process efficiency.

Within the framework of our program to target the inefficiency issues of organic synthesis with the aid of multi-catalytic systems,[49] we propose a strategy to access enantioenriched secondary benzylic alcohols directly from aliphatic alcohols bearing an unsaturated bond. Such starting materials are both common motifs in bio-derived materials (e.g., terpenols) and readily accessible from abundant alkenes and simple alkenols by olefin cross-metathesis.[50,51] In this context, we also consider alkenes and unsaturated alcohols as attractive redox-neutral surrogates of aliphatic aldehydes,[52–55] given the alkene cross-metathesis, double bond isomerization,[56] and the subsequent enantioselective addition reaction[48] might be executed in situ with the aid of compatible catalysts.

Here we report broadly applicable multi-catalytic transition-metal protocols that execute redox-neutral transformations for a series of alkenes, unsaturated alcohols, and aryl boronic acids to furnish varied secondary benzylic alcohols in high stereoselectivity, with up to 99:1 er, dr >20:1, and 91% yield (Figure 1c). The protocols exploit a relay of up to 4 catalysts – 3 transition metal-complexes and a Brønsted acid – operating sequentially in the same reaction mixture. We showed that not only the one-pot protocol is operationally simpler and ~3-fold less resource-intensive than the stepwise synthesis, but also that the overall yield of the product is increased (77% versus 43%) thanks to preventing cumulative losses of the materials during subsequent isolations and purifications of the intermediates.

We initiated the study by validating the possibility to conduct in situ both the isomerization of unsaturated alcohols and the addition of aryl boronic acids to aldehyde intermediates. In exploratory experiments, we found that model substrates, *trans*-2-hexenol **1a** and phenylboronic acid **2a**, reacted to furnish racemic secondary benzylic alcohol **3aa**, 1-phenyl-1-hexanol in 84% yield in the presence of $[Ir(cod)Cl]_2$ (**Ir^{iso1}**) and $[Rh(cod)(CH_3CN)_2](BF_4)_2$ (**Rh^{iso1}**) (Figure 2a).[48,56] The control experiments confirmed the active role of both complexes. The reactivity was completely suppressed or substantially diminished when either the rhodium or the iridium complex was not present (<2% or 31% yield, respectively).

Subsequent experimentation toward an enantioselective variant of the transformation indicated the requirement to exchange the Rh-catalyst for the Ru-complex bearing chiral Me-BIPAM, (**Ru^{add}**, Figure 2b); the latter being a privileged ligand developed by Yamamoto and Miyaura for enantioselective Rh- or Ru-catalyzed reactions, including 1,2-addition reactions.[18,57–62] We found that although a Rh-catalyst bearing chiral diene ligand **Rh^{add2}/cod***, broadly investigated by Hayashi, Carreira, and others,[48,63–65] proved active in the model reaction of **1a** and **2a**, product **3aa** was formed in modest enantioselectivity, with up to 70:30 er, independently of the reaction conditions. The evaluation of other Rh-complexes bearing N-sulfinyl chiral sulfur-

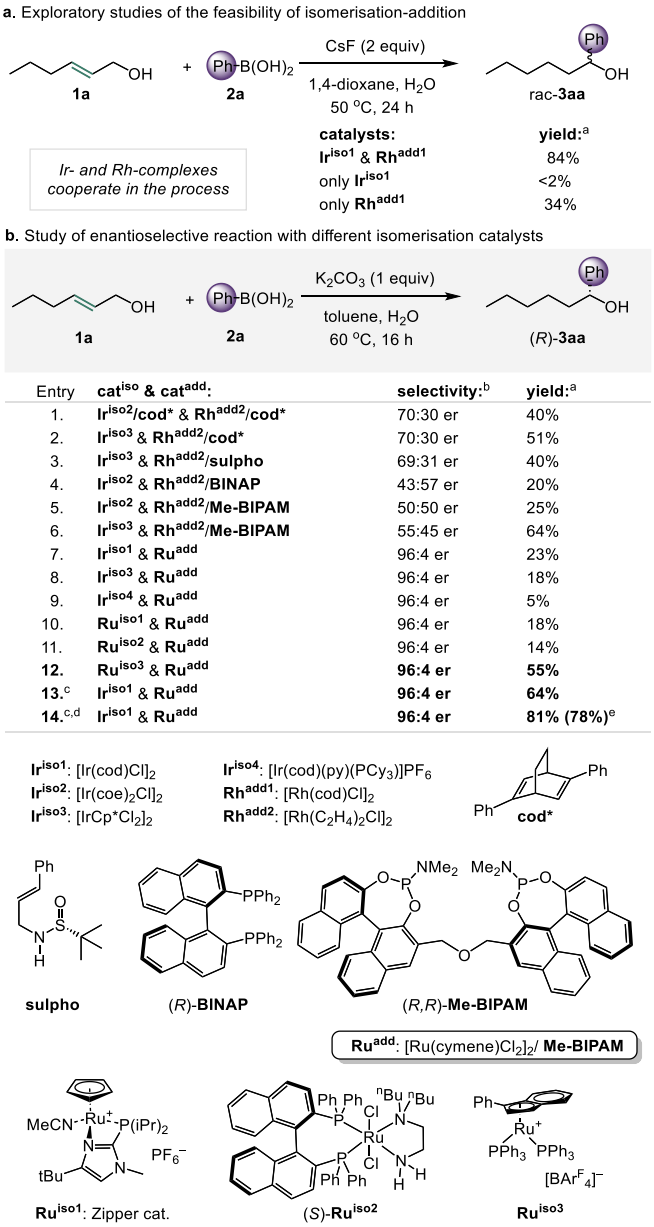

Figure 2. Studies toward dual-catalytic enantioselective conversion of linear allylic alcohols to secondary benzylic alcohols. [a] Yields determined by ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as an internal standard. [b] Enantiomeric ratios determined by GC or SFC analysis on a chiral stationary phase. For further details, see the SI. [c] A mixture of **1a**, $[Ir(cod)Cl]_2$, and K_2CO_3 in toluene (1 mL) and water (0.15 mL) was first kept at 30 °C for 2 h, followed by the addition of **2a** (3 equiv), and (*R,R*)-**Ru^{add}** (6.0 mol%) in toluene (1 mL), and kept at 60 °C for 6 h. [d] 0.125 mol% Ir. [e] Yield of isolated material.

olefin[66,67] **Rh^{add2}/sulpho** or phosphine[63] **Rh^{add2}/BINAP** ligands, known for their activity in Rh-catalyzed 1,4-addition, did not secure any highly enantioselective protocol. In sharp contrast, the reaction of **1a** and **2a** in the presence of **Ir^{iso1}** and (*R,R*)-**Ru^{add}**,[58] furnished product (*R*)-**3aa** in high er of 96:4, albeit in a low yield of 23%. The use of other isomerization catalysts[56,68–74] in place of **Ir^{iso1}** enabled the formation of (*R*)-**3aa** in higher yields. The reaction in the presence of **Ru^{iso3}** and (*R,R*)-**Ru^{add}** furnished the product in 55% yield and 96:4 er, executing the envisioned system of

merging isomerization and enantioselective 1,2-addition reactions. Further experiments revealed that the presence of **Ru^{add}** complex partially inhibits the isomerization activity of **Ir^{iso1}**. Fortunately, when **1a** was shortly incubated in the presence of just 0.125 mol% **Ir^{iso1}**, prior to the addition of **2a** and (*R,R*)-**Ru^{add}**, the target product (*R*)-**3aa** was formed in 81% yield and 96:4 er.

The identified protocol proved applicable to a substantial range of aryl boronic acids and alkenylic alcohols (Figure 3). The reactions of **1a** with phenylboronic acid derivatives containing an electron-donating or an electron-withdrawing group in the para- or meta-position of the phenyl ring (**2b**-**2i**, **2k**-**2n**), as well as those with a sizeable aryl moiety (**2o**-**2r**) formed the product with 92:8 to 99:1 er and up to 93% yield. The reactions for aryl boronic acids bearing either a strongly electron-withdrawing group or steric hindrance in the ortho-position, such as **2j** and **2s**-**2u**, respectively, furnished the products in modest yields (up to 35%) and moderate enantioselectivity (<79:21 er), indicating the limitations of the protocol. Noteworthy are the transformations involving heteroaryl derivatives, including dibenzothiophene **2o** and 1,3-benzodioxole **2p**, which delivered secondary benzylic alcohols in 95:5 er and 44-66% yields. Alcohols containing a more remote double bond, such as homoallylic 3-hexenol **1b** and 5-hexenol **1c**, are also suitable substrates for this sequential transformation; however, when the Zipper catalyst (**Ru^{iso2}**, cf. Figure 2b) was used in place of **Ir^{iso1}** the products were formed in higher yields (93% and 90%, respectively), maintaining high enantioselectivity (96:4 er). It is worth noting that the presence of **Ru^{iso2}** bearing an achiral phosphine ligand does not erode the enantioselectivity of the step executed by chiral **Ru^{add}** catalyst, demonstrating the key compatibility between the catalysts.

Because cross-metathesis represents a convenient approach to install an alkenylic alcohol moiety on olefins,[50,51] we next sought a protocol that would enable the direct assembly of a secondary benzylic alcohol from an alkene, a simple alkenylic alcohol, and an aryl boronic acid in a one-pot fashion. Such a method would be attractive due to the increase in the structural diversity of the products, by using combinations of readily accessible building blocks. However, the requirement of the compatibility of 3 transition-metal catalysts in the series of 3 subsequent processes represents a major challenge.[15] Cross-inhibition issues aside, any ligand exchange processes between a metathesis or an isomerization catalyst and a chiral catalyst that operates in the final 1,2-addition step are likely to deteriorate the overall stereoselectivity of the process.[28]

Initial experiments indicated that a cross-metathesis reaction of alkene **4a** and cis-2-butene-1,4-diol (**5**) in the presence of the o-tolyl Hoveyda-Grubbs Catalyst® M721(**Ru^{CM}**, often referred to as the Stewart-Grubbs catalyst)[75,76] followed in situ by the isomerization-addition sequence with **2a**, **Ru^{iso1}**, and (*R,R*)-**Ru^{add}** furnished the target benzylic alcohol (*R*)-**6aa** in 98:2 er (Figure 4). High stereoselectivity of the overall reaction confirmed the critical compatibility of chiral **Ru^{add}** with the other catalysts in the sequence. However, because of the limited conversion of alkene **4a** to allylic alcohol intermediate **7**, even in the presence of a large excess **5**, product (*R*)-**6aa** was formed in only

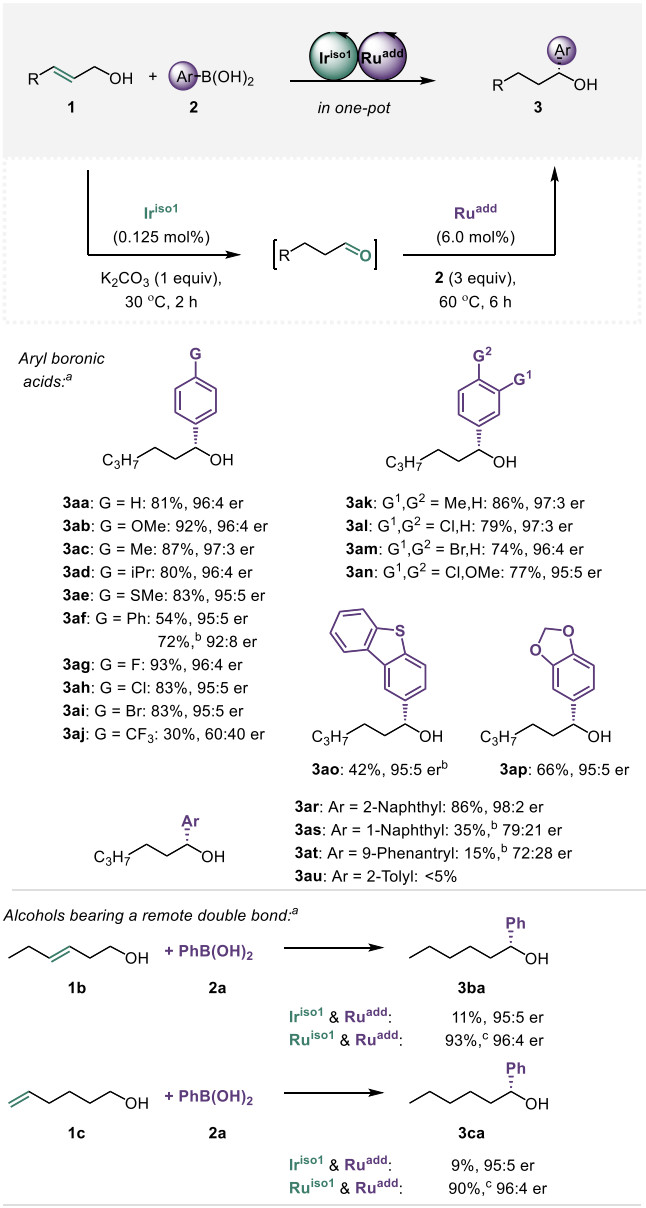

Figure 3. Substrate scope of dual-catalytic enantioselective conversion of linear alkenylic alcohols to secondary benzylic alcohols. [a] Reagents added to the reaction mixture subsequently without any work-up; yields determined by ^{1}H NMR analysis with a standard; yields of isolated material (column chromatography) are ~3-9% lower; er determined by SFC analysis. [b] Upon addition **2** and Ru^{add}, the mixture was kept at 90 °C for 24 h. [c] **Ru^{iso1}** (2 mol%) was used in place of **Ir^{iso1}**.

up to 11% yield (Tables S1-S2 in the SI). Further investigation revealed that alkene **4a** reacts more readily with **5'**, TMS-protected **5**, in the presence of **Ru^{CM}**, forming **7'** in a high yield (>95% by GC analysis).[77] The latter is quickly and quantitatively deprotected to form alkenol **7** in the presence of catalytic trifluoroacetic acid. The acid is simply washed off with an aqueous base solution, and no workup is required for the subsequent isomerization-addition sequence. Such a one-pot protocol involving 4 catalysts, i.e., 3 different Ru-catalysts and a Brønsted acid, converts **4a**, **5'**, and **2a** to furnish the benzylic alcohol (*R*)-**6aa** in 88% overall yield and 98:2 er.

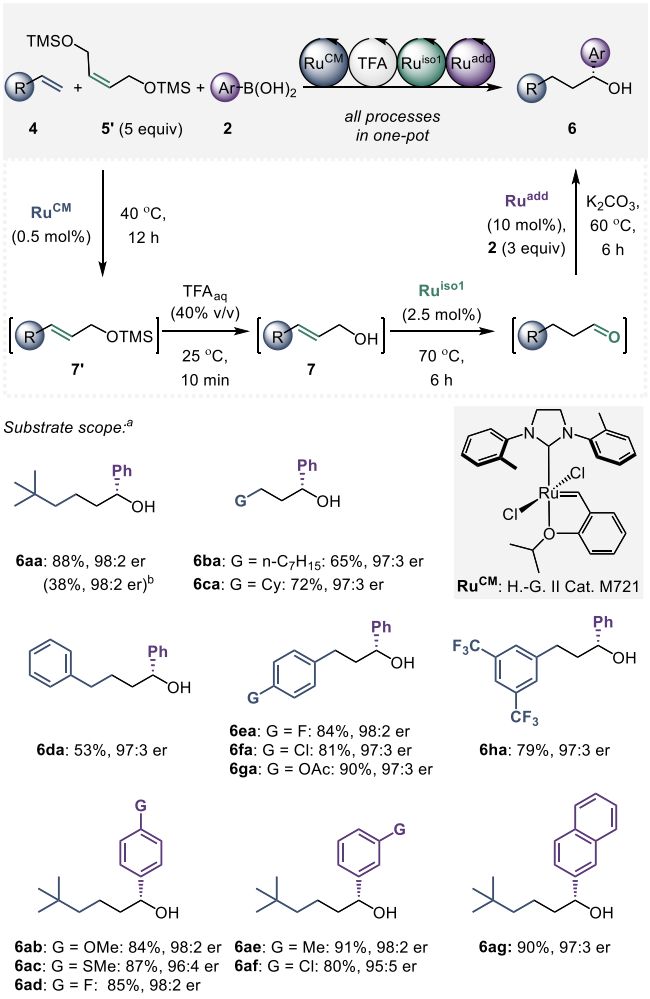

Figure 4. Multi-catalytic enantioselective sequential relay for conversion of alkenes to secondary benzylic alcohols. [a] Reagents added to the reaction mixture subsequently without any work-up (except for washing off TFA with water); yields determined by ^{1}H NMR analysis with a standard; yields of isolated material (column chromatography) are ~3-9% lower; enantioselectivity determined by SFC analysis; see the SI. [b] Cis-2-butene-1,4-diol 5 used in place of 5'; treatment with TFA was omitted.

The side-by-side experiments on a 2.4 mmol scale of **4a** for the synthesis of (*R*)-**6aa** proved that not only is the one-pot protocol faster, more operationally simple, and ~3-fold less resource-intensive than the stepwise approach, but the final yield of the isolated material is also increased, i.e., 77% versus 43%, respectively. Although the consecutive steps of the sequence occurred with similar GC yields in both cases, the one-pot protocol prevented cumulative losses of the material during subsequent isolations and purifications of the intermediates, illustrating an additional advantage of the approach (for details on the yields and amounts of resources used for each approach, see Tables S3-S4 in the SI).

The established protocol integrating alkene cross-metathesis, isomerization, and enantioselective addition is broadly applicable (Figure 4). A series of aliphatic alkenes, electron-rich or electron-deficient vinyl arenes, TMS-protected alkenol, and stereoelectronically varied aryl boronic acids reacted to form a range of secondary benzylic alcohols in high enantioselectivities (er's > 95:5) and 53-91% overall yields.

Lastly, we focused on allylic alcohols bearing a prochiral double bond. The isomerization-addition sequence for 3-substituted allylic alcohols constitutes an attractive strategy to produce the secondary benzylic alcohols bearing two stereocenters with a 1,3-relationship. We surmised that a method utilizing two different chiral catalysts that independently construct each stereogenic center would give access to all 1,3-syn and 1,3-anti stereoisomers of the product. However, the key requirement is the fully independent activity of both chiral catalysts.

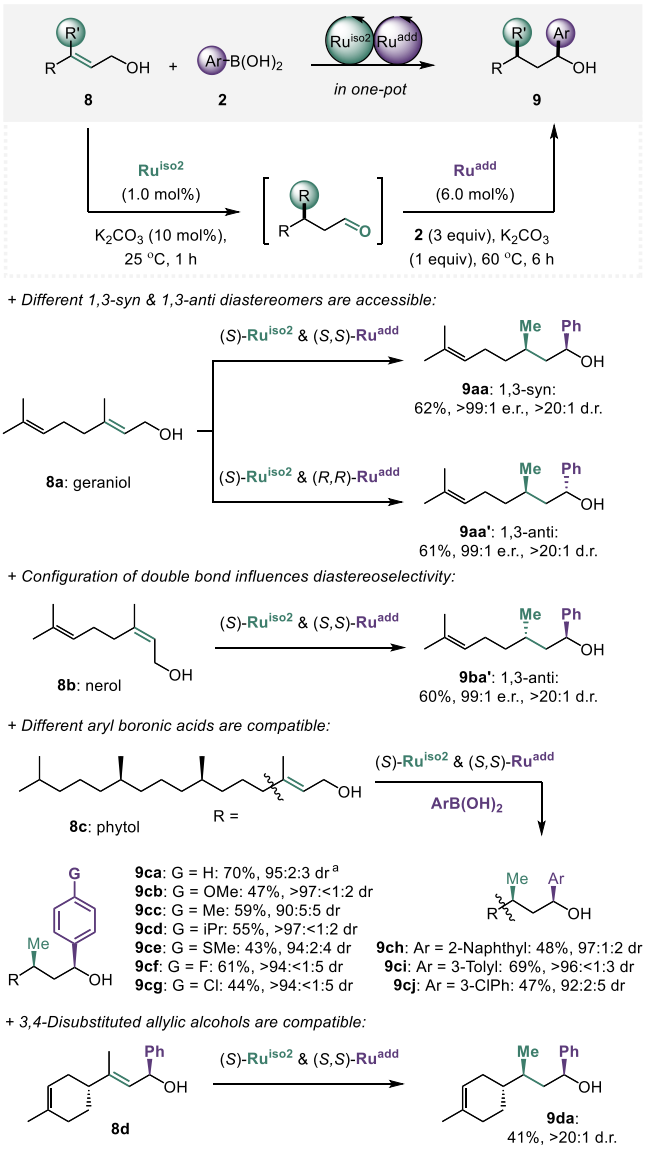

Figure 5. Dual-catalytic enantio- and diastereselective conversion of substitute allylic alcohols to secondary benzylic alcohols. Reagents added to the reaction mixture subsequently without any work-up (except for removal of EtOH under vacuum); stereoselectivity determined by SFC and GC analysis; yields correspond to the amounts of isolated major diastereomer (column chromatography); see the SI. [a] dr of 1,3-syn (major):1,3-syn(minor):sum of 1,3-anti products.

The experimentation identified that pairing enantiomers of **Ru^{iso2}** (cf. Figure 2), the isomerization catalyst reported by Ohkuma,[72] and **Ru^{add}** enables the isomerization-addition sequence to form the products with high stereocontrol in a one-pot fashion (Figure 5). The catalysts proved to require different solvents to operate efficiently (i.e., ethanol and toluene, respectively; for details, see Figures S1-S4, Table S5). Therefore, the medium needs to be exchanged between the steps (evaporation under vacuum); albeit no resource-intensive work-up is needed. Importantly, the stereocontrol for the formation of each stereogenic center is solely determined by the catalyst involved. For instance, while the reaction of geraniol **8a** and **2a** in the presence of (*S*)-**Ru^{iso2}** and (*S,S*)-**Ru^{add}** furnished 1,3-syn benzylic alcohol (*1S,3R*)-**9aa** with >99:1 er, >20:1 dr, in 62% yield, the same reaction but with (*R,R*)-**Ru^{add}** in place of (*S,S*)-**Ru^{add}** furnished 1,3-anti diastereomeric alcohol (*1S,3S*)-**9aa'**, in similarly high 99:1 er, >20:1 dr, and 61% yield. The diastereoselectivity of the transformation depends on the configuration of the double bond in the starting material.[72] Nerol **8b**, the (*Z*)-analogue of geraniol **8a**, reacted to form 1,3-anti **9ba'**, i.e., the other diastereomer, in 99:1 er, >20:1 dr, and 60% yield. Noteworthy, the isolated double bonds of starting materials **8a**-**8b** remained intact in the corresponding products. Chiral phytol **8c**, reacted with varied arylboronic acids to form the products in high stereoselectivity, i.e., 90-97% of the major stereoisomer, and from 44% to 70% yield. The presence of an additional chiral center next to the allylic alcohol moiety in the starting material seems not to disturb the reaction. (+)-Limonene derivative **8d** reacted with **2a** to form **9da** in >20:1 dr, and 41% yield, expanding the scope of the system.

In conclusion, the herein disclosed methods enable the rapid modular stereoselective syntheses of a broad range of secondary benzylic alcohols from simple available starting materials. The strategy relies on the construction of the sequences of multiple catalytic reactions occurring consecutively in a single vessel. A transformation is executed with the aid of up to four catalysts and requires a single isolation and purification of the product. Overall, the approach simplifies the synthesis of target motifs, increases material efficiency, and limits cost, time, and waste associated with the standard stepwise procedures. In a greater perspective, the study highlights the synthetic potential of the multi-catalytic approaches to access increasingly complex architectures from simple starting materials.

ASSOCIATED CONTENT

Supporting Information. Details on experimental procedures for the catalytic reactions, including optimization data, spectroscopic data for the starting materials and the products. This material is available free of charge via the Internet at http://pubs.acs.org

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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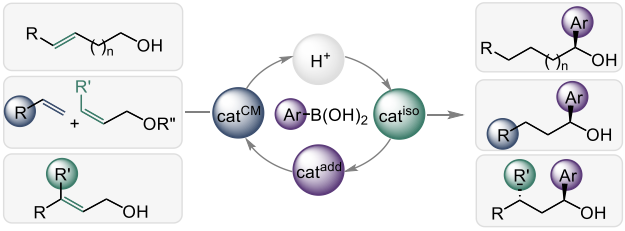
Table of Contents artwork



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