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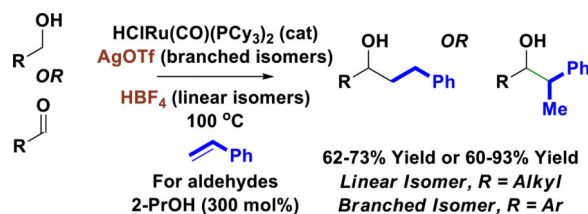
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Regioselective Hydrohydroxyalkylation of Styrene with Primary Alcohols or Aldehydes *via* Ruthenium Catalyzed C-C Bond Forming Transfer Hydrogenation

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Graphical abstract



Feedstocks to Building Blocks. Transfer hydrogenative coupling of styrene with primary alcohols delivers branched or linear adducts from benzylic or aliphatic alcohols when modified by AgOTf or HBF₄, respectively. Related 2-propanol mediated reductive couplings also are described.

Keywords

Homogenous Catalysis; Cross-Coupling; C-C Bond Formation; Ruthenium; Hydrogenation

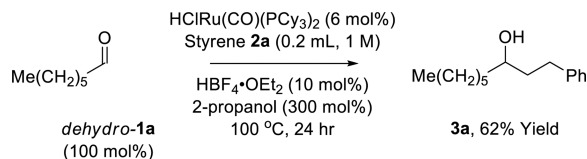
Beginning with the work of Butlerov and Grignard, the use of premetalated *C*-nucleophiles in carbonyl addition has opened vast volumes of chemical space and is now a longstanding cornerstone of chemical synthesis.^[1,2] The catalytic reductive coupling of π -unsaturated reactants with carbonyl compounds represents an alternative to classical carbonyl addition that potentially avoids stoichiometric organometallic reagents and the issues of safety, selectivity and waste that attend their use.^[3,5c] Hydroformylation,^[4] the largest volume application of homogenous catalysis, is a powerful example of metal catalyzed reductive coupling that illustrates several important characteristics of a scalable process: the ability to transform abundant chemical feedstocks in a byproduct-free manner and, less obviously, the importance of utilizing terminal reductants that are less costly than the coupling partners themselves. Accordingly, the discovery and development of transfer hydrogenative carbonyl additions wherein alcohols serve dually as reductants and carbonyl precursors represent a major focus of research in our laboratory (Figure 1).^[5]

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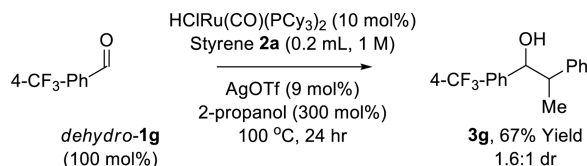
[†]These authors contributed equally to this work.

While the transfer hydrogenative coupling of primary alcohols with diverse olefin pronucleophiles have been developed (1,3-dienes^[5,7] and 1,3-enynes^[5,8]), related reactions of styrene, an abundant petrochemical feedstock ($>25 \times 10^6$ tons/2010)^[6] have proven challenging and are restricted to the use of α -hydroxy-carbonyl compounds,^[9] that is, precursors to highly activated vicinal dicarbonyl compounds. We were inspired by Yi's observation^[10] that the addition of $\text{HBF}_4 \cdot \text{OEt}_2$ to the ruthenium-hydride complex $\text{HClRu}(\text{CO})(\text{PCy}_3)_2$ dramatically enhances catalytic activity in alkene hydrogenation^[10a] and hydrovinylation.^[10b] As corroborated by Yi's mechanistic studies, HBF_4 opens a coordination site at ruthenium by protonating a tricyclohexylphosphine ligand.^[10] In the hope that such coordinative unsaturation would unlock the transfer hydrogenative coupling of styrene with primary alcohols,^[11,12] a series of experiments were conducted using the $\text{HClRu}(\text{CO})(\text{PCy}_3)_2/\text{HBF}_4 \cdot \text{OEt}_2$ catalyst system (Scheme 1, eq. 1). Whereas exposure of heptanol **1a** to styrene **2a** in the presence of commercially available $\text{HClRu}(\text{CO})(\text{PPh}_3)_3$ did not lead to products of C-C coupling in the absence or presence of $\text{HBF}_4 \cdot \text{OEt}_2$, $\text{HClRu}(\text{CO})(\text{PCy}_3)_2/\text{HBF}_4 \cdot \text{OEt}_2$ delivered the product of C-C bond formation **3a** in 73% yield as a linear single regioisomer. In the absence of $\text{HBF}_4 \cdot \text{OEt}_2$, adduct **3a** was not formed. Other Brønsted acids were assayed, but were uniformly less effective. It was reasoned that cationic ruthenium(II) complexes derived from $\text{HClRu}(\text{CO})(\text{PCy}_3)_2$ and AgOTf might also display enhanced catalytic activity due to coordinative unsaturation.^[13] Hence, the coupling of **1a** and **2a** was attempted using $\text{HClRu}(\text{CO})(\text{PCy}_3)_2$ in the presence of AgOTf . Here, the linear regioisomer **3a** was not formed, yet a small quantity of the corresponding branched regioisomer was detected. This result supported the feasibility of optimizing a catalytic pathway to branched adducts. While aliphatic alcohols were recalcitrant partners for branch-selective coupling, the coupling of benzylic alcohol **1g** with styrene **2a** to form the branched adduct **3g** was amenable to optimization (Scheme 1, eq. 2).

The scope of this regioselective transfer hydrogenative coupling of aliphatic and benzylic alcohols was briefly surveyed (Tables 1 and 2). The reaction of styrene **2a** with aliphatic alcohols **1a–1f** provided adducts **3a–3f** in good yield with complete levels of linear regioselectivity (Table 1). Even alcohols with branching at the β -position, such as cyclohexyl methanol **1e**, participate in C-C coupling although higher temperatures (120 °C) are required. In contrast, significantly diminished efficiencies were observed using *para*-substituted styrenes bearing either electron donating or electron releasing groups. The coupling of benzylic alcohols **1g–1i** delivered adducts **3g–3i** in good to excellent yields with complete branched regioselectivity (Table 2). Here, electron deficient benzylic alcohols were more efficient partners for coupling, perhaps due to stabilization of the σ -benzylruthenium intermediate (*vide infra*). Finally, beyond the redox-neutral couplings from the alcohol oxidation level, 2-propanol mediated reductive couplings of styrene **2a** with alkyl- and aryl-substituted aldehydes also is possible, as illustrated by the conversion of heptanal (*dehydro-1a*) to the linear secondary alcohol **3a** (eq. 3) and the conversion of *dehydro-1g* to the branched adduct **3g** (eq. 4).



(eq. 3)



(eq. 4)

To gain insight into the catalytic mechanism, in particular the origins of linear *vs* branched regioselectivity, a series of deuterium labelling experiments were performed (Scheme 2). Exposure of *deuterio-1a*, which is deuterated at the carbinol position (97% ^2H), to styrene **2a** under standard conditions results in the formation of *deuterio-3a* (Scheme 2, eq. 5). Complete retention of deuterium at the carbinol methine (96% ^2H) is accompanied by complete transfer of deuterium to the benzylic methylene (>98% ^2H). These data are consistent with a catalytic mechanism involving carbonyl-styrene oxidative coupling to form an oxaruthenacycle, which upon transfer hydrogenolysis mediated by *deuterio-1a* delivers *deuterio-3a*. Here, formation of a benzylic carbon-ruthenium bond defines the regioselectivity of oxaruthenacycle formation and, hence, the linear regioselectivity of C-C coupling. Although the primary alcohol reactant *deuterio-1a* dehydrogenates upon oxaruthenacycle transfer hydrogenolysis, the secondary alcohol product *deuterio-3a* appears kinetically unreactive toward dehydrogenation, presumably due to steric effects. A related deuterium labeling experiment in which alcohol **1a** is reacted with d_8 -styrene **2a** provides a result consistent with this mechanistic interpretation (Scheme 2, eq. 6). Exposure of *deuterio-1h*, to styrene **2a** under standard conditions for the coupling of benzylic alcohols provides *deuterio-3h* (Scheme 2, eq. 7). Significant loss of deuterium is observed at the carbinol methine (61% ^2H) and the transfer of deuterium to the methyl hydrogen is incomplete (11% ^2H). Such loss of deuterium is consistent with a mechanism involving rapid, reversible hydrogen transfer between *deuterio-1h* and styrene **2a** to form aldehyde-benzylruthenium pairs in advance of turn-over limiting carbonyl addition. Here, hydrometalation to form a benzylic carbon-ruthenium bond defines the branched regioselectivity of C-C coupling. The related deuterium labeling experiment wherein the non-deuterated alcohol **1h** is reacted with d_8 -styrene **2a** corroborates reversible transfer of hydrogen between alcohol **1h** and d_8 -styrene **2a** (Scheme 2, eq. 8).

In summary, we report the first transfer hydrogenative couplings of styrene with primary alcohols. Remarkably, the ruthenium precatalyst $\text{HClRu(CO)(PCy}_3)_2$ delivers branched or linear adducts from benzylic or aliphatic alcohols when modified by AgOTf or HBF_4 ,

respectively. As corroborated by deuterium labelling studies, linear regioselectivity stems from catalytic mechanisms involving carbonyl-styrene oxidative coupling to form oxaruthenacyclic intermediates, whereas branched regioselectivity is a consequence of pathways involving styrene hydrometalation. Ongoing studies are focused on the transfer hydrogenative coupling of alcohols with other abundant π -unsaturated feedstocks, including α -olefins.^[5c]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

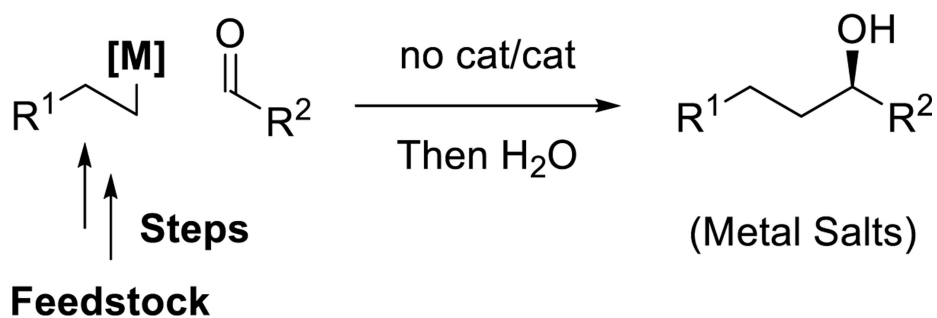
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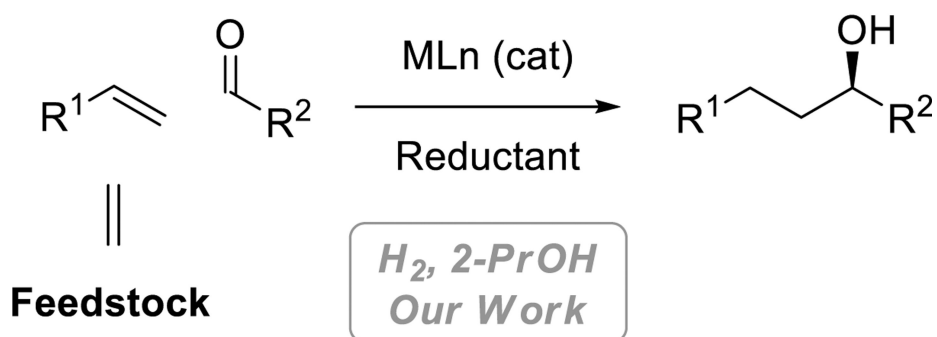
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Classical C=O Addition - Stoichiometric Metals



Metal Catalyzed C=O Reductive Coupling



Metal Catalyzed C=O Reductive Coupling

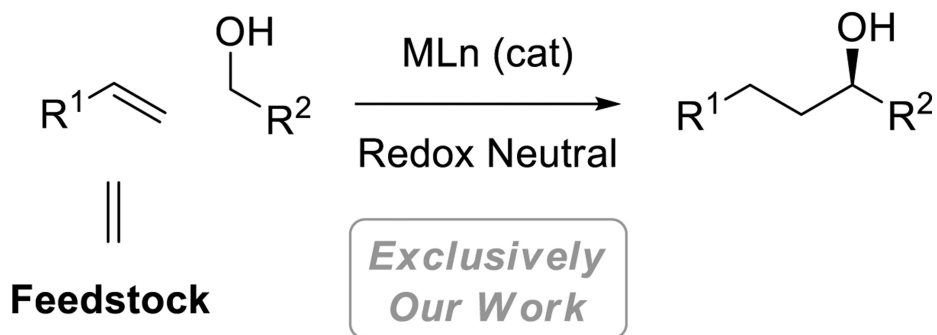
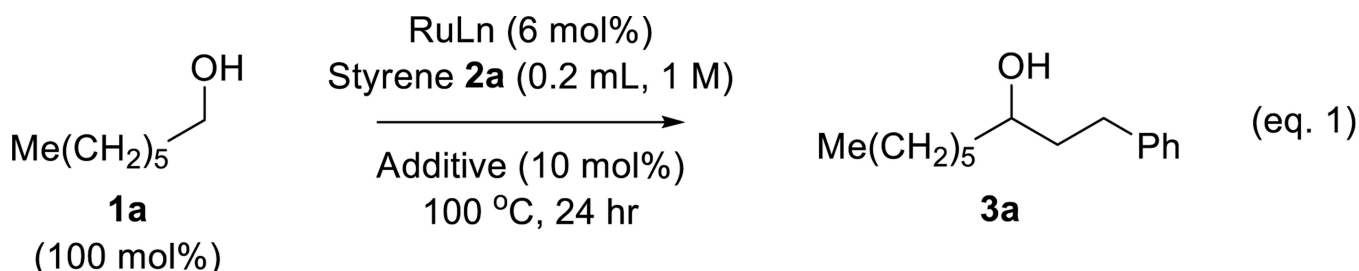
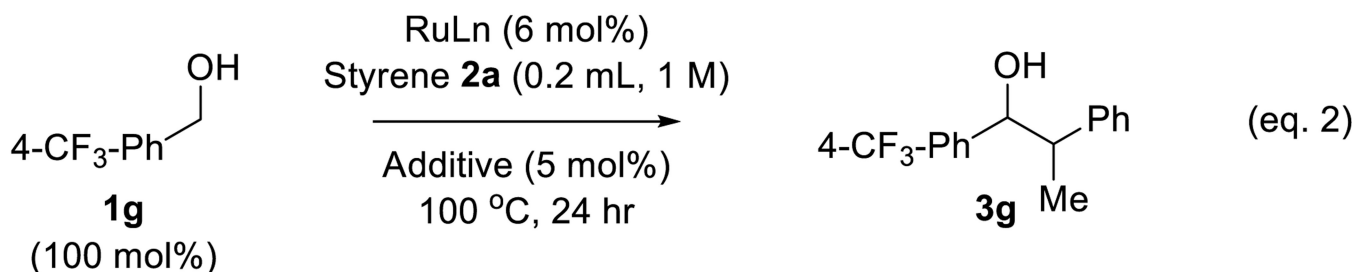


Figure 1.
Carbonyl addition using non-stabilized carbanions and their equivalents.



<u>RuLn/Additive</u>	Isolated Yield 3a
HClRu(CO)(PPh ₃) ₃ / None	---
HClRu(CO)(PPh ₃) ₃ / HBF ₄ •OEt ₂	trace
HClRu(CO)(PCy ₃) ₂ / None	---
➔ HClRu(CO)(PCy ₃) ₂ / HBF ₄ •OEt ₂	73%
HClRu(CO)(PCy ₃) ₂ / F ₃ CSO ₃ H	36%
HClRu(CO)(PCy ₃) ₂ / AgOTf	< 5% (branched)

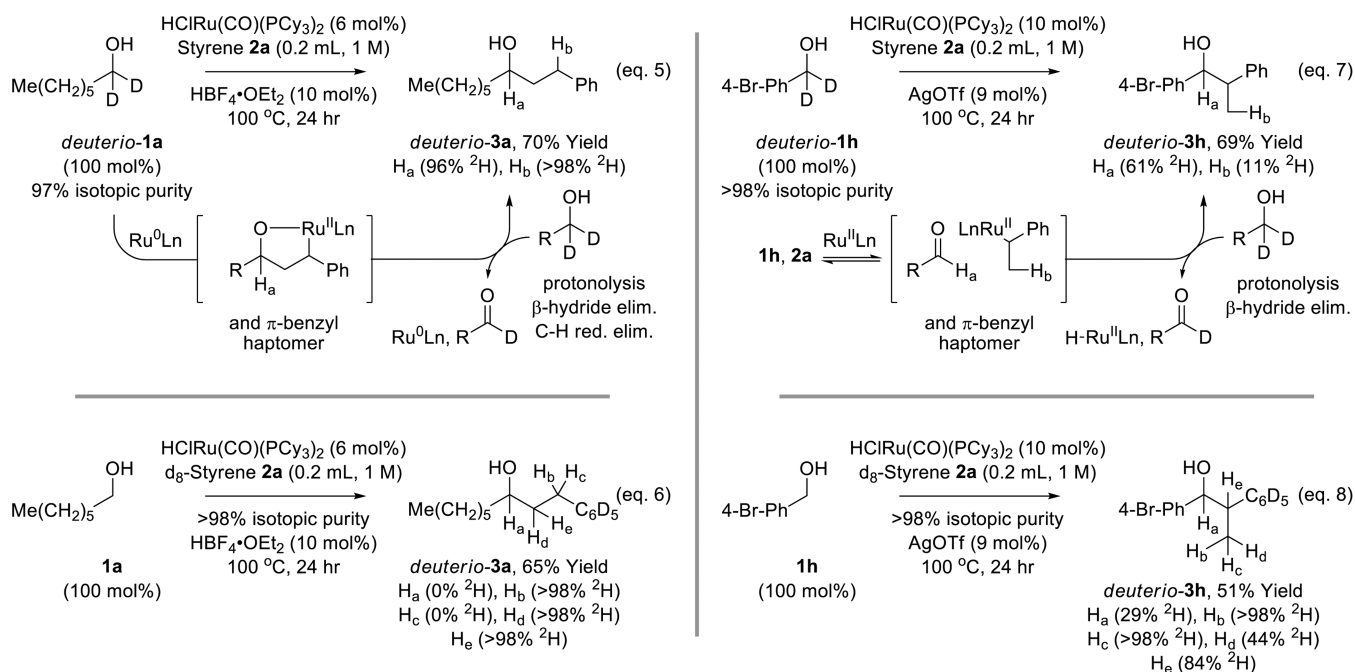


<u>RuLn/Additive</u>	Isolated Yield 3g
HClRu(CO)(PPh ₃) ₃ / None	---
HClRu(CO)(PPh ₃) ₃ / HBF ₄ •OEt ₂	---
HClRu(CO)(PCy ₃) ₂ / None	---
HClRu(CO)(PCy ₃) ₂ / HBF ₄ •OEt ₂	trace
➔ HClRu(CO)(PCy ₃) ₂ / AgOTf	83%
HClRu(CO)(PCy ₃) ₂ / AgBF ₄	32%
HClRu(CO)(PPh ₃) ₃ / AgOTf	trace

Scheme 1.

Selected optimization experiments for the ruthenium catalyzed C-C coupling of 1-heptanol **1a** and benzyl alcohol **1g** with styrene **2a**.^a

^aYields are of material isolated by silica gel chromatography. See Supporting Information for further details.

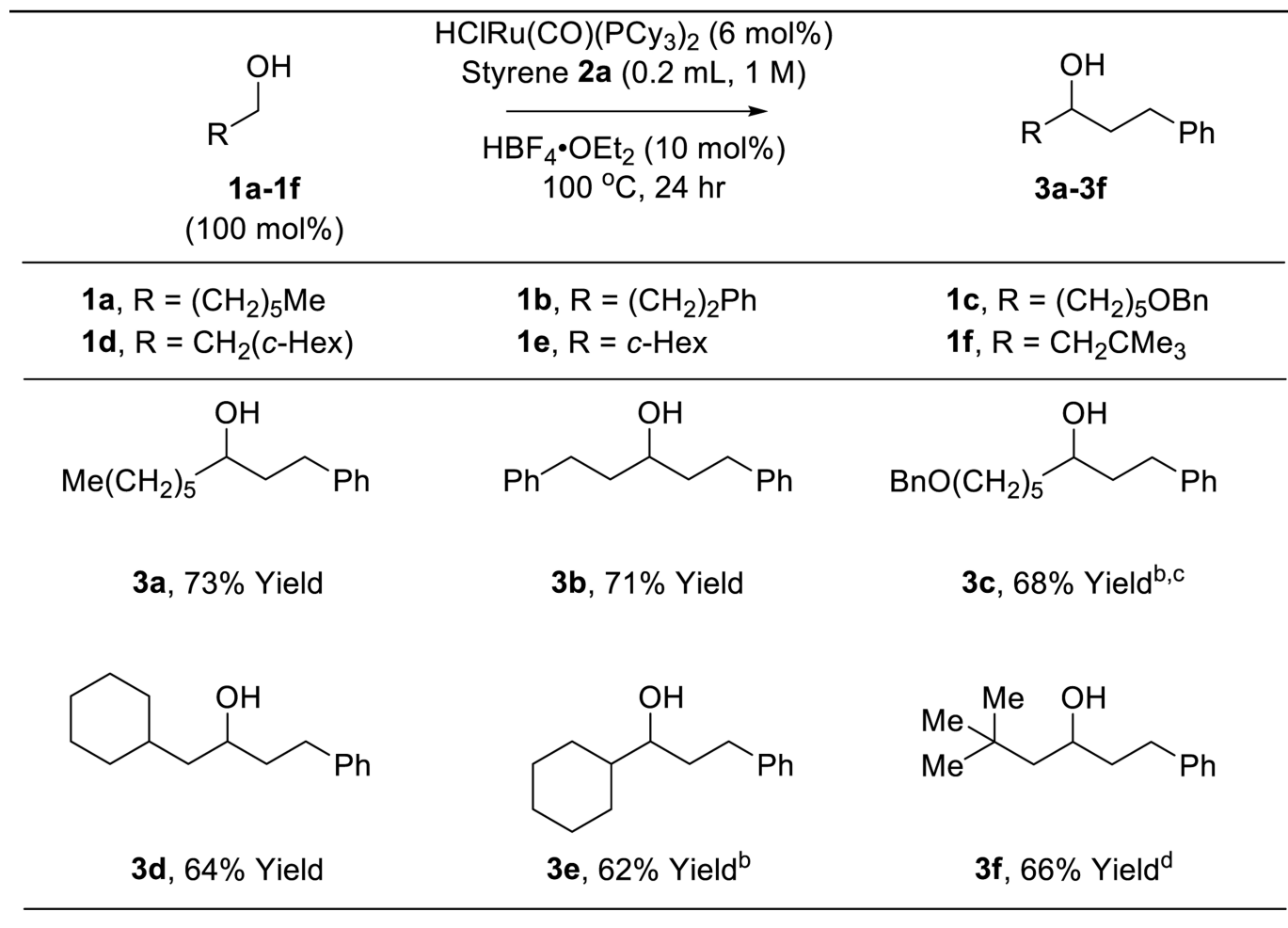
**Scheme 2.**

General catalytic pathways accounting for linear vs branched regioselectivity as corroborated by deuterium labelling studies.^a

^aYields are of material isolated by silica gel chromatography. Isotopic composition determined by HRMS, ^1H and ^2H NMR. See Supporting Information for further details.

Table 1

Ruthenium catalyzed C-C coupling of aliphatic alcohols **1a–1f** with styrene **2a** to form secondary alcohols **3a–3f**.^a



^aYields are of material isolated by silica gel chromatography. See Supporting Information for further details.

^bHClRu(CO)(PCy₃)₂ (10 mol%), HBF₄ (15 mol%).

^cstyrene **2a** (0.4 mL), 120 °C.

^d2-PrOH (100 mol%).

Table 2

Ruthenium catalyzed C-C coupling of benzylic alcohols **1g–1l** with styrene **2a** to form secondary alcohols **3g–3l**.^a

1g-1l (100 mol%)		3g-3l
1g , R = 4-CF ₃ -Ph 1j , R = 3,5-Cl ₂ -Ph	1h , R = 4-Br-Ph 1k , R = 3,5-(CF ₃) ₂ -Ph	1i , R = 4-CO ₂ Me-Ph 1l , R = 2-naphthyl
 3g , 83% Yield 2:1 dr	 3h , 70% Yield ^b 2:1 dr	 3i , 78% Yield 1:1 dr
 3j , 93% Yield 1.5:1 dr	 3k , 72% Yield ^b 2.2:1 dr	 3l , 60% Yield ^b 2.3:1 dr

^aYields are of material isolated by silica gel chromatography. See Supporting Information for further details.

^bHClRu(CO)(PCy₃)₂ (10 mol%), AgOTf (9 mol%).