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Alkyne–Aldehyde Reductive C–C Coupling through Ruthenium-Catalyzed Transfer Hydrogenation: Direct Regio- and Stereoselective Carbonyl Vinylation to Form Trisubstituted Allylic Alcohols in the Absence of Premetallated Reagents

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Abstract

Nonsymmetric 1,2-disubstituted alkynes engage in reductive coupling to a variety of aldehydes under the conditions of ruthenium-catalyzed transfer hydrogenation by employing formic acid as the terminal reductant and delivering the products of carbonyl vinylation with good to excellent levels of regioselectivity and with complete control of olefin stereochemistry. As revealed in an assessment of the ruthenium counterion, iodide plays an essential role in directing the regioselectivity of C–C bond formation. Isotopic labeling studies corroborate reversible catalytic propargyl C–H oxidative addition in advance of the C–C coupling, and demonstrate that the C–C coupling products do not experience reversible dehydrogenation by way of enone intermediates. This transfer hydrogenation protocol enables carbonyl vinylation in the absence of stoichiometric metallic reagents.

Keywords

green chemistry; homogeneous catalysis; hydrogenation; ruthenium; transfer hydrogenation; vinylation

Introduction

Under hydrogenation and transfer-hydrogenation conditions, π-unsaturated reactants may serve as functional equivalents to organometallic reagents in diverse C–C bond-forming processes.[1] In the specific case of C=X (X=O, NR) vinylation,[1b] rhodium- or iridium-catalyzed hydrogenation of alkynes in the presence of carbonyl compounds or imines delivers allylic alcohols or allylic amines, respectively.[2,3] Notably, these transformations do not generate stoichiometric metallic by-products as they circumvent the use of discrete vinylmetal reagents.[4–6] This atom economy differentiates hydrogen-mediated C=X vinylation from the related rhodium-,[7] titanium-,[8] and nickel-catalyzed[9–11] alkyne-carbonyl reductive couplings, which employ reductants that are more mass-intensive, such as silanes, or even pyrophoric, such as borane and organozinc reagents.[7–11]

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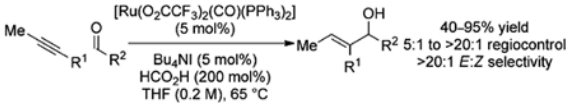
In recent studies from our laboratory, it was found that direct alkyne–carbonyl reductive coupling is possible under the conditions of ruthenium-catalyzed transfer hydrogenation, employing formic acid as the terminal reductant.[12–14] Notably, beyond alkyne–aldehyde reductive coupling mediated by formic acid, primary alcohol dehydrogenation was found to trigger alkyne hydrometallation to generate aldehyde–vinylruthenium pairs en route to products of carbonyl vinylation. In this way, carbonyl vinylation is achieved from the alcohol or aldehyde oxidation level. The ability to engage alcohols directly in C–C coupling bypasses discrete alcohol oxidation and, hence, is reminiscent of related "hydrogen auto-transfer" or "borrowing hydrogen" processes.[15]

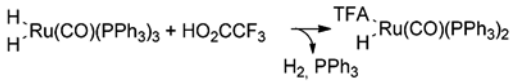
Whereas previous studies focused primarily on the reductive coupling of 2-butyne, a symmetrical alkyne,[12a,b] it was found that the catalyst prepared from [Ru(TFA)$_2$(CO)-(PPh$_3$)$_2$] (TFA = O$_2$CCF$_3$) and Bu$_4$NI enables the regioselective reductive coupling of nonsymmetric alkynes and paraformaldehyde.[12c] Based on this result, a survey of higher aldehydes was undertaken. Herein, we report that ruthenium catalyzed transfer hydrogenation of nonsymmetric 1,2-disubstituted alkynes **1a**–**1f** in the presence of aldehydes **2a**–**2d** results in reductive coupling to furnish trisubstituted allylic alcohols **3a**–**3f, 4a**–**4f, 5a**–**5f**, and **6a**–**6f** with good to excellent levels of regioselectivity and with complete control of olefin geometry.



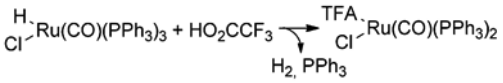
Results and Discussion

In an initial experiment aimed at probing the feasibility of developing a general regioselective process, phenylpropyne (**1a**) was exposed to aldehyde **2b** in the presence of formic acid and substoichiometric quantities of [RuHCl(CO)-(PPh$_3$)$_3$]. However, a complex mixture of isomeric products **4a**, *iso*-**4a**, and allyl-**4a** were isolated in low yield (Table 1, entry 1). In parallel studies on the reductive coupling of paraformaldehyde with nonsymmetric disubstituted alkynes,[12c] it was found that the use of tetrabutylammonium iodide as an additive led to improved regioselectivities. Based on this observation, the discrete ruthenium complexes [RuHX(CO)(PPh$_3$)$_3$] (X=Br and I) were prepared in a manner analogous to the corresponding chloride complex.[16a] These complexes were assessed in the catalytic coupling of phenylpropyne (**1a**) to aldehyde **2b** under otherwise identical conditions to those employed by using [RuHCl(CO)(PPh$_3$)$_3$]. Although no improvement in regioselectivity was observed by using the bromide complex (Table 1, entry 2), the iodide complex provided **4a** and *iso*-**4a** in a ratio of 17:1 but an increased proportion of allyl-**4a** was observed (Table 1, entry 3). Thus, to promote formation of a single isomeric product, use of the iodide complex alone was insufficient, prompting consideration of additional optimization strategies.

It is known that [RuH$_2$(CO)(PPh$_3$)$_3$] reacts with trifluoro-acetic acid (HO$_2$CCF$_3$, TFAA) to form [RuH(TFA)(CO)-(PPh$_3$)$_3$] and elemental hydrogen [Eq. (1)],[16a] as is the reaction of [RuHCl(CO)(PPh$_3$)$_3$] with trifluoroacetic acid to form [RuCl(TFA)(CO)(PPh$_3$)$_3$] [Eq. (2)].[16b] Additionally, stoichiometric and catalytic reactions of [Ru(TFA)$_2$(CO)-(PPh$_3$)$_2$] with alcohols are known to produce [RuH-(TFA)(CO)(PPh$_3$)$_2$] and an aldehyde or ketone [Eq. (3)].[17] Hence, the catalytic coupling of phenylpropyne (**1a**) to aldehyde **2b** was attempted by using the ruthenium complexes [RuHX(CO)(PPh$_3$)$_3$] (X=Cl, Br, and I) in the presence of C$_7$F$_{15}$CO$_2$H. It was hypothesized that counterion exchange would be rapid, and that different counterions might assist different steps in the catalytic cycle.



(1)



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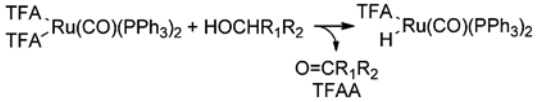


(3)

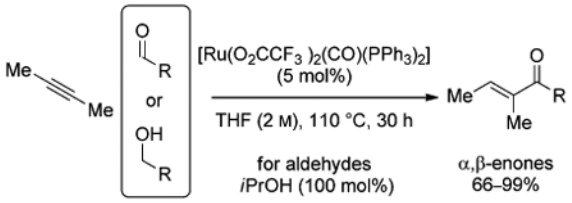
In the event, addition of $C_7F_{15}CO_2H$ promoted no significant enhancement in regioselectivity in combination with the ruthenium-chloride or -bromide complexes, nor was the ratio of **4a**/allyl-**4a** significantly improved (Table 1, entries 4 and 5). In contrast, the use of the ruthenium iodide complex in the presence of $C_7F_{15}CO_2H$ delivered **4a** as a single regioisomer in 71% isolated yield with an enhanced 8:1 ratio of **4a**/allyl-**4a** (Table 1, entry 6). These data suggest that the specific combination of iodide and carboxylate counterions is necessary to promote high levels of regioselectivity and conversion.

As attempts to prepare the discrete complex [Ru-$(O_2CR)_2$(I)(CO)$(PPh_3)_2$] (R=C_7F_{15}, CF_3) were unsuccessful, experiments conducted from this point onward employed the catalyst generated in situ upon combination of [Ru-$(TFA)_2$(CO)$(PPh_3)_2$] and Bu_4NI. It was found that at lower concentrations, formation of allyl-**4a** was suppressed and good regiocontrol was retained. A minimum of two equivalents of the terminal reductant, formic acid, were necessary to achieve optimal yields of **4a**. At lower loadings of formic acid, the yield of **4a** and the ratio of **4a**/allyl-**4a** deteriorate. Finally, the precise loading of iodide is also crucial in terms of suppressing the formation of both *iso*-**4a** and allyl-**4a**. Thus, by using [Ru$(TFA)_2$(CO)$(PPh_3)_2$] (5 mol%), Bu_4NI (10 mol%), and formic acid (200 mol%) in THF at 65°C, the desired trisubstituted allylic alcohol product **4a** was generated as a single regioisomer in 75% yield with complete stereocontrol and in the absence of allyl-**4a** (Table 2).

To evaluate the generality of these conditions, the catalytic vinylation of aldehydes **2a**–**2d** was conducted by using phenylpropyne (**1a**). The desired trisubstituted allylic alcohols **3a**–**6a** were obtained in good yield with nearly exclusive formation of a single isomeric adduct and with complete stereocontrol. Encouraged by these results, 1,2-disubstituted alkynes **1b**–**1f**, which possess aryl, heteroaryl, or alkyl substituents, were coupled to aldehydes **2a**–**2d**. The corresponding trisubstituted allylic alcohols **4a**–**4f, 5a**–**5f**, and **6a**–**6f** were formed in moderate to good yields, and in most cases a single isomeric adduct predominates (Table 2). The remarkable regioselectivity of this catalytic system is underscored by the ability to differentiate the acetylenic termini of alkyne **1f**, which incorporates CH_2CH_2OBn and CH_3 groups, to form adducts **3f**–**6f** in good yields and as single regioisomers in all cases, notwithstanding adduct **4f**. Finally, whereas the aforementioned transformations were conducted by using 0.3 mmol of the aldehyde, the coupling of phenylpropyne (**1a**) to

aldehyde **2b** on a 3.0 mmol scale provided allylic alcohol **4a** in a slightly higher 79% isolated yield with a comparable level of selectivity.

In previous studies on the coupling of 2-butyne to alcohols and aldehydes under the conditions of ruthenium-catalyzed C–C bond-forming transfer hydrogenation, it was found that dehydrogenation of the initially formed allylic alcohols could be induced to provide products of intermolecular alkyne hydroacylation from the alcohol or aldehyde oxidation level [Eq. (4)].[12b] These products of alkyne hydroacylation are not formed under the conditions used here. As previously observed, dehydrogenation of the initially formed allylic alcohol is suppressed by lower reaction temperatures (65 vs. 110°C) and shorter reaction times (20 vs. 30 h). Also, the presence of iodide and the use of formic acid, rather than isopropanol, as the terminal reductant may be significant, because these species may occupy a coordination site on ruthenium that would be required for β-hydride elimination.



(4)

To gain further insight into the reaction mechanism a series of deuterium labeling experiments were performed. Exposure of phenylpropyne (**1a**) to deuterated aldehyde [D_1]-**2b** under the standard conditions results in the formation of allylic alcohol [D_n]-**4a** with essentially complete retention of deuterium at the carbinol position (>98% D; Table 3, entry 1). This result suggests that **4a** does not experience significant reversible oxidation–reduction by way of enone intermediates, which is important with regard to the potential development of related enantioselective processes. In a kinetic competition experiment, phenylpropyne (**1a**) reacts with [D_1]-**2b** (50% D) under standard conditions to deliver [D_n]-**4a** (48% D), revealing no significant kinetic effect within the error limits of this experiment (Table 3, entry 2).

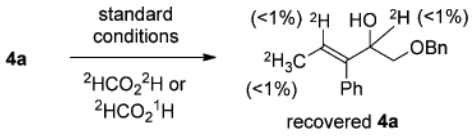
Interestingly, exposure of phenylpropyne (**1a**) to **2b** under standard conditions employing [D_2]-formic acid results in partial deuterium incorporation of [D_n]-**4a** at the vinylic position (21% D) and, remarkably, at the vinylic methyl group (50% D with respect to all three hydrogen atoms; Table 3, entry 3). Given the likelihood that adventitious water compromises the extent of deuterium incorporation, results arising from the use of [D_2]-formic acid and [D_1]-formic acid were compared. Indeed, by using [D_1]-formic acid, substantially less deuterium incorporation is observed at the vinylic position (1% D) and at the vinylic methyl group (8% D; Table 3, entry 4). This result suggests that it is primarily the acidic OD deuterium atom in [D_2]-formic acid that is incorporated at the vinylic position of the product.

Reaction of the deuterated alkyne, [D_3]-**1a**, and aldehyde **2b** under the standard conditions delivers [D_n]-**4a**, which retains approximately half of the isotopic label at the vinylic methyl group (56% D with respect to all three hydrogen atoms) without significant transfer of deuterium to any other position (Table 3, entry 5). As anticipated in view of the initial labeling experiment (Table 3, entry 1), exposure of [D_3]-**1a** to [D_1]-**2b** under the standard conditions does not reduce the loss of deuterium at the vinylic methyl group (53 % D with respect to all three hydrogen atoms) and deuterium is retained at the carbinol position (>99%

D; Table 3, entry 6). Coupling of the deuterated alkyne, [D_3]-**1a**, and aldehyde **2b** by using [D_1]-formic acid does little to mitigate the loss of deuterium at the vinylic methyl group (60% D; Table 3, entry 7). In contrast, the use of [D_2]-formic acid significantly suppresses the loss of deuterium at the vinylic methyl group (83 % D; Table 3, entry 8).

The accumulation of deuterium at the vinylic methyl group in [D_n]-**4a** (Table 3, entries 3 and 4) and the loss of deuterium at the vinylic methyl observed in the conversion of [D_3]-**1a** into [D_n]-**4a** (Table 3, entries 5 and 6) may be accounted for on the basis of the indicated catalytic mechanism for H–D exchange (Scheme 1, right). Therein, a ruthenium(0) complex, generated upon H–I reductive elimination, engages alkyne **1a** in C–H or C–D oxidative addition to the propargylic C–H or C–D bond, which results in the formation of a propargylruthenium hydride. Hydrogen–deuterium exchange then occurs with formic acid through discrete reversible protonation–deprotonation (equivalent to O–H oxidative addition/reductive elimination) or by way of six-centered transition state **A**. Subsequent C–H or C–D reductive elimination of the propargylruthenium hydride or deuteride releases the alkyne, which can enter the catalytic cycle for C–C coupling (see below).

This interpretation suggests that any accumulation or loss of deuterium at the propargylic position of alkyne **1a** occurs prior to C–C coupling. To challenge this hypothesis, coupling product **4a** was resubjected to the standard reaction conditions employing [D_1]-formic acid or [D_2]-formic acid. Analysis of the recovered **4a** by ^{1}H and D NMR spectroscopy revealed no incorporation of deuterium [Eq. (5)]. Additionally, alkyne **1a** was exposed to the standard reaction conditions by using [D_1]-formic acid in the absence of aldehyde **2b**. The product of alkyne reduction, *trans*-β-methyl-styrene, was formed in 70% isolated yield in this reaction [Eq. (6)].



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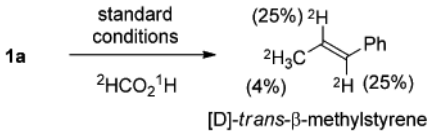

(6)

Although the extent of deuterium incorporation at the vinylic methyl group in *trans*-β-methylstyrene (4% D with respect to all three hydrogen atoms; Table 3, entry 5) is anticipated on the basis of previous observations (Table 3, entry 4), the extent of deuterium incorporation at the vinylic positions (25% D) is higher than that observed in the C–C coupling product [D_n]-**4a** under the same conditions. This is due to the fact that deuterium incorporation at the vinylic positions occurs after the initial reduction of **1a**. Consistent with this interpretation, *cis*-β-methylstyrene is the major reduction product at low conversion. Thus, it would appear that the initially formed *cis*-olefin engages in hydrometallation to generate alkyl ruthenium species, which upon β-hydride elimination delivers *trans*-β-methylstyrene as the sole reduction product. Reversible hydrometallation–β-hydride

elimination accounts for the increase in deuterium incorporation at the vinylic positions [Eq. (5)].

The collective results on isotopic labeling (Table 3, entries 4 and 5) are consistent with the indicated catalytic mechanism for aldehyde vinylation (Scheme 1). Therein, [Ru(TFA)(I)(CO)(PPh_3)$_2$], generated in situ through counterion exchange between [Ru(TFA)$_2$(CO)(PPh_3)$_2$] and Bu_4NI, engages in carboxylate exchange with formic acid to release trifluoroacetic acid and generate a ruthenium formate (not shown), which eliminates carbon dioxide to furnish [RuH(I)(CO)(PPh_3)$_2$]. This species may eliminate HI to generate zero-valent ruthenium, which catalyzes the H–D exchange at the propargylic position, as previously described. Alternatively, regioselective alkyne hydrometallation occurs to deliver a vinylruthenium intermediate that, upon carbonyl addition, provides the indicated ruthenium alkoxide. Trifluoroacetic acid mediated protonolysis of the ruthenium alkoxide releases the product of carbonyl vinylation and regenerates [Ru(TFA)(I)(CO)(PPh_3)$_2$] (Scheme 1).

The proposed hydrometallative mechanism for alkyne–carbonyl reductive coupling is corroborated by the stoichiometric conversion of [Ru(TFA)$_2$(CO)(PPh_3)$_2$] into [Ru-(TFA)(H)(CO)(PPh_3)$_2$] under transfer hydrogenation conditions employing ethanol as the terminal reductant,[17b] and the subsequent reaction of [Ru(TFA)(H)(CO)(PPh_3)$_2$] with PhC≡CPh to provide the corresponding vinylruthenium complex (Scheme 2).[18b] The regioselectivity of hydrometallation, which favors placement of ruthenium adjacent to the aryl substituent in alkynes **1a**–**1e**, may be driven by additional stabilization associated with the π-benzyl character of this intermediate. For alkyne **1f**, the Lewis basic benzyl ether moiety is anticipated to direct the regioselectivity of the hydrometallation.[19] It should be noted that oxidative coupling pathways cannot be excluded on the basis of the available data and may account for contra-steric regiocontrol in the C–C coupling event.

Conclusion

A highly regio- and stereoselective alkyne-aldehyde reductive coupling protocol for the synthesis of trisubstituted allylic alcohols has been developed. Iodide counterions were shown to play an essential role in directing the regioselectivity of the C–C bond formation. Isotopic labeling studies corroborate the reversible catalytic propargyl C–H oxidative addition in advance of C–C coupling, and demonstrate that the C–C coupling products do not experience reversible dehydrogenation by way of enone intermediates. Based on these findings, asymmetric variants of this vinylation process appear feasible.

Experimental Section

See the Supporting Information for full experimental details.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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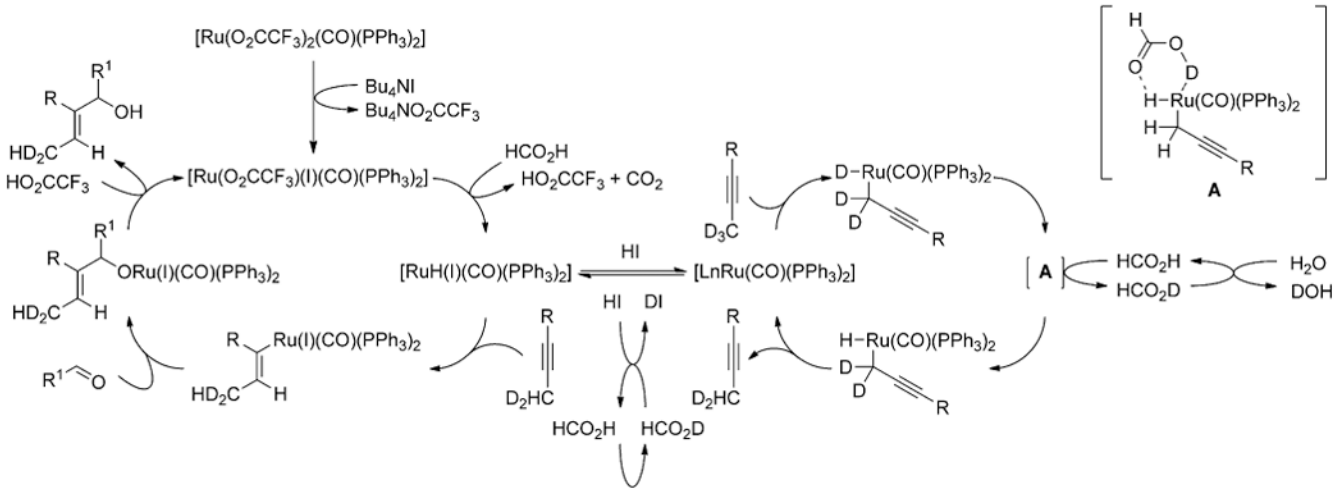
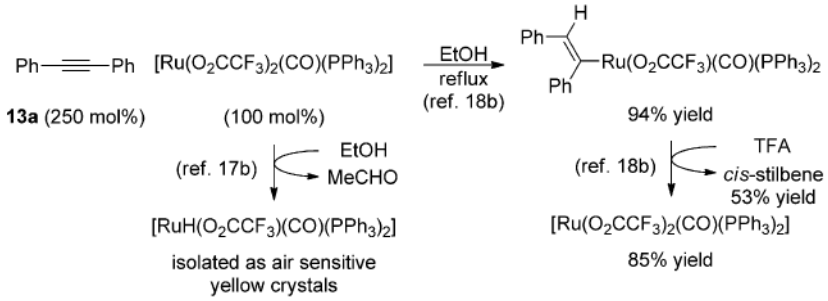


Scheme 1.

A plausible catalytic mechanism for the C–C coupling and the catalytic mechanism accounting for H–D exchange at the propargylic position of alkyne [D_3]-**1a** in the specific case of deuterium loss.



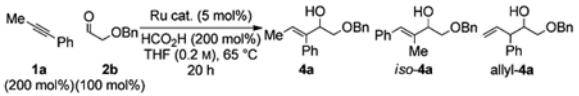
Scheme 2.

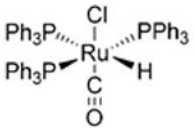
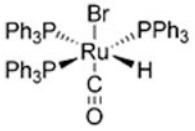
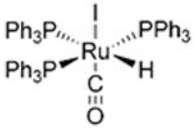
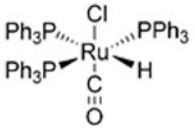
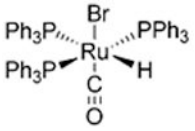
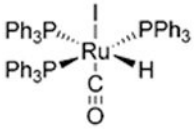
Established stoichiometric transformations that corroborate the proposed hydrometallative mechanism for alkyne-carbonyl reductive coupling.

Chemistry. Author manuscript; available in PMC 2012 October 24.

Table 1

The effect of the counterion on the regio- and stereoselectivity of the catalytic reductive coupling reaction of phenylpropyne (**1a**) to aldehyde **2b** through ruthenium-catalyzed transfer hydrogenation.[a]

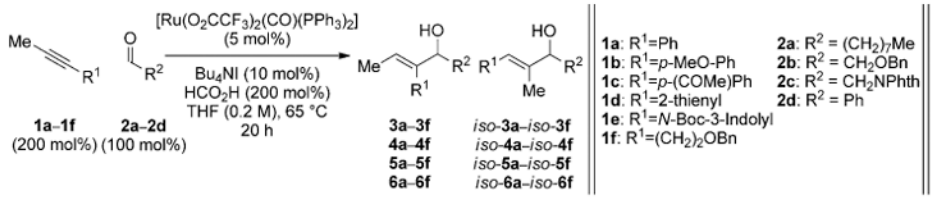


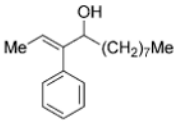
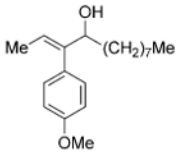
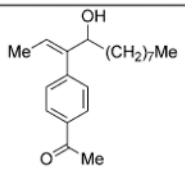
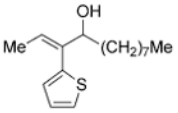
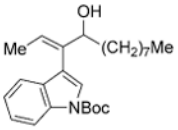
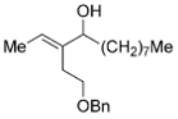
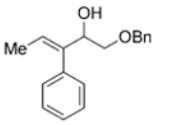
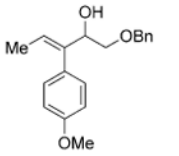
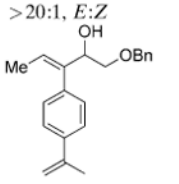
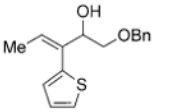
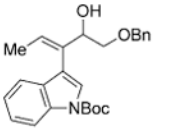
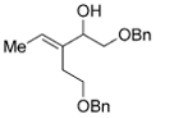
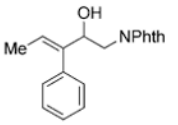
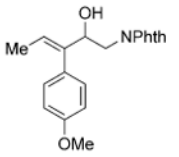
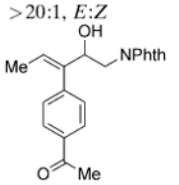
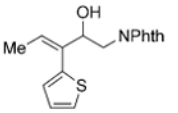
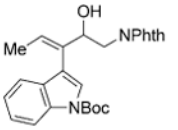
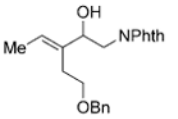
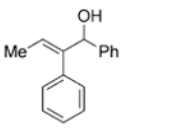
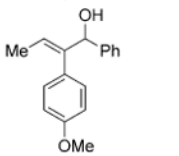
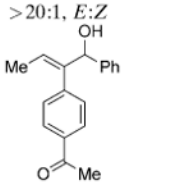
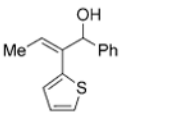
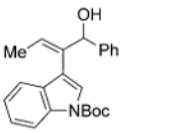
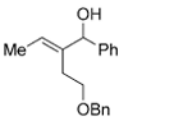
	Ru complex	Additive	Yield [%]	4a/*iso*-4a	4a/allyl-4a
1		–	23	2:1	5:1
2		–	31	2:1	6:1
3		–	40	17:1	2:1
4		$C_7F_{15}CO_2H$	36	1:1	7:1
5		$C_7F_{15}CO_2H$	35	2:1	8:1
6		$C_7F_{15}CO_2H$	71	>20:1	8:1

[a]Yields are of combined isomeric materials. Regio- and stereoselectivity was determined by ^{1}H NMR analysis of the crude reaction mixtures. In general, low yields are due to incomplete conversion.

Table 2

The regio- and stereoselective catalytic reductive coupling reaction of nonsymmetric alkynes **1a**–**1f** to aldehydes **2a**–**2d** through ruthenium-catalyzed transfer hydrogenation.[a]



					
74% yield **3a**[b,c] >20:1, **3a**:*iso*-**3a** >20:1, *E*:*Z*	77% yield **3b**[b,c] 17:1, **3b**:*iso*-**3b** >20:1, *E*:*Z*	80% yield **3c**[b,c] 17:1, **3c**:*iso*-**3c** >20:1, *E*:*Z*	55% yield **3 d**[b,c] 5:1, **3d**:*iso*-**3d** >20:1, *Z*:*E*	76% yield **3e**[b] >20:1, **3e**:*iso*-**3e** >20:1, *E*:*Z*	61% yield **3 f**[b] >20:1, **3f**:*iso*-**3 f** >20:1, *E*:*Z*
					
75% yield **4a** >20:1, **4a**:*iso*-**4a** >20:1, *E*:*Z*	63% yield **4b**[e] 11:1, **4b**:*iso*-**4b** >20:1, *E*:*Z*	80% yield **4 c**[d] 8:1, **4c**:*iso*-**4c** >20:1, *E*:*Z*	67% yield **4d** 11:1, **4d**:*iso*-**4d** >20:1, *Z*:*E*	77% yield **4e** >20:1, **4e**:*iso*-**4e** >20:1, *E*:*Z*	62% yield **4 f**[d] 14:1, **4 f**:*iso*-**4 f** >20:1, *E*:*Z*
					
90% yield **5a**[g] 18:1, **5a**:*iso*-**5a** >20:1, *E*:*Z*	88% yield **5b**[g] 13:1, **5b**:*iso*-**5b** >20:1, *E*:*Z*	86% yield **5c**[g] 8:1, **5c**:*iso*-**5c** >20:1, *E*:*Z*	78% yield **5d**[g] 11:1, **5d**:*iso*-**5d** >20:1, *Z*:*E*	95% yield **5e**[g] >20:1, **5e**:*iso*-**5e** >20:1, *E*:*Z*	52% yield **5 f**[f] >20:1, **5 f**:*iso*-**5 f** >20:1, *E*:*Z*
					
85% yield **6a**[h] >20:1, **6a**:*iso*-**6a** >20:1, *E*:*Z*	84% yield **6b** 9:1, **6b**:*iso*-**6b** >20:1, *E*:*Z*	79% yield **6c**[i] >20:1, **6c**:*iso*-**6c** >20:1, *E*:*Z*	40% yield **6d** 8:1, **6d**:*iso*-**6d** >20:1, *Z*:*E*	63% yield **6e** >20:1, **6e**:*iso*-**6e** >20:1, *E*:*Z*	62% yield **6 f** >20:1, **6 f**:*iso*-**6 f** >20:1, *E*:*Z*

[a] Yields are of the isolated material. Regio- and stereoselectivity was determined through ^{1}H NMR analysis of the crude reaction mixtures.

[b] The reaction was conducted for 16 h.

[c] Bu_4NI (5 mol%) was employed.

[d] The reaction was conducted at a concentration of 1.0 M.

[e] The reaction was conducted at a concentration of 0.5 M.

[f] The reaction was conducted for 15 h.

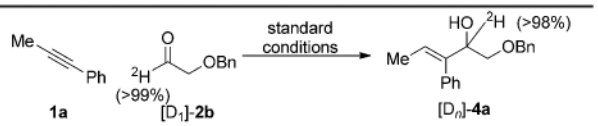
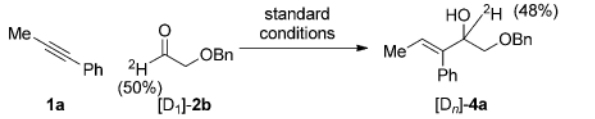
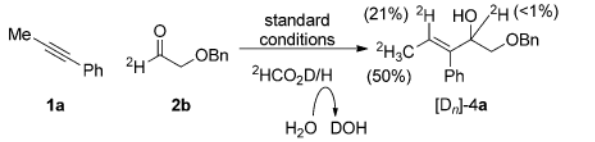
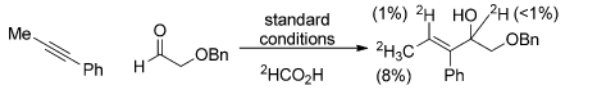
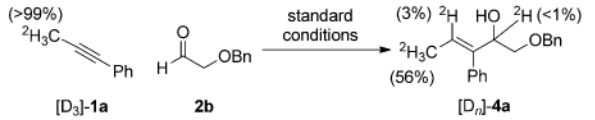
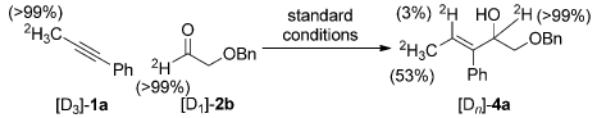
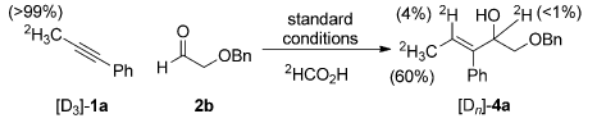
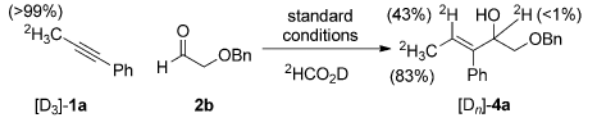
[g] The reaction was conducted at a concentration of 2.0 M for 24 h.

[h] The reaction was conducted at 45°C for 48 h.

[i] HCO_2H (150 mol%) was employed. See the Supporting Information for further experimental details.

Table 3

Deuterium labeling and competition kinetics experiments.[a]

	Reaction
1	
2	
3	
4	
5	
6	
7	
8	

[a]The extent of D incorporation was evaluated by using ^{1}H and D NMR spectroscopy. The indicated values represent the average of two runs. [D$_2$]-formic acid in D$_2$O (95 wt%); [D$_1$]-formic acid in H$_2$O (95 wt%).