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Ruthenium(0)-Catalyzed C–C Coupling of Alkynes and 3-Hydroxy-2-oxindoles: Direct C–H Vinylation of Alcohols

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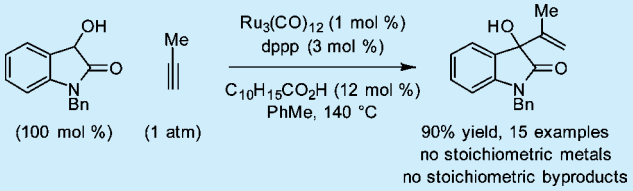
Supporting Information

ABSTRACT: Upon exposure to a ruthenium(0) catalyst, *N*-benzyl-3-hydroxy-2-oxindoles react with diverse alkynes to form products of C–H vinylation with complete control of regioselectivity and olefin geometry. This method contributes to a growing body of catalytic processes that enable direct conversion of lower alcohols to higher alcohols in the absence of stoichiometric organometallic reagents.



We have developed a broad, new class of catalytic C–C bond formations that merge the characteristics of carbonyl addition and transfer hydrogenation.[1] The majority of these processes enable direct conversion of primary to secondary alcohols through mechanisms wherein alcohol oxidation is balanced by (a) reductive C–X bond cleavage[2] or (b) π-bond hydrometalation[3] to form transient aldehyde–organometal pairs that engage in carbonyl addition. Recently, we found that ruthenium(0) catalysts promote the conversion of activated secondary alcohols to tertiary alcohols.[4] These processes proceed through a distinctly different mechanism wherein C═O/C═C oxidative coupling forms oxaruthenacycles,[4,5] which undergo transfer hydrogenolysis mediated by the secondary alcohol reactant to release product and regenerate the ketone required for oxidative coupling.

In the course of exploring ruthenium(0)-catalyzed C–C couplings of secondary alcohols, it was found that 1,2-diols and other vicinally dioxygenated hydrocarbons (α-ketols, 1,2-diones) will react with alkynes to form products of carbinol C–H vinylation, that is, tertiary allylic alcohols in the form of α-hydroxy-β,γ-unsaturated ketones (Scheme 1).[4e] Although a variety of different diol partners could be employed, preparatively useful isolated yields were only achieved using aryl-substituted alkynes. In view of the highly electrophilic nature of isatins, it was postulated that 3-hydroxy-2-oxindoles might serve as efficient partners for ruthenium(0)-catalyzed C–C couplings with alkynes, potentially enabling broader scope with respect to the alkyne partner. Our interest was further motivated by the ubiquity of 3-substituted 3-hydroxy-2-oxindoles in naturally occurring compounds and as scaffolds in human medicine.[6]

In a series of initial experiments (Table 1), *N*-benzyl-3-hydroxy-2-oxindole (**1a**) (100 mol %) was exposed to 1-phenyl-1-butyne (**2a**) (300 mol %) in the presence of $Ru_3(CO)_{12}$ (2 mol %) in toluene (2.0 M) at 140 °C. While in the absence of ligand no reaction occurred (Table 1, entry 1), in the presence of 1,3-bis(diphenylphosphino)propane (dppp), the C–C coupling product **3a** was formed in 54% yield as a single regioisomer (Table 1, entry 2). Carboxylic acid additives have been shown to enhance yields dramatically by cocatalyzing the transfer hydrogenolysis of oxaruthenacycles.[7] Upon evaluation of a series of carboxylic acids (Table 1, entries 3–6), adamantanecarboxylic acid was most effective, allowing adduct **3a** to be obtained in 90% yield (Table 1, entry 6). Further variation of the ligand (Table 1, entries 7–13) and temperature (Table 1, entries 14–16) did not enhance the isolated yield of **3a**. Finally, an attempt was made to decrease the loadings of the catalyst, ligand, and alkyne **2a** (Table 1, entries 17–20). Although reduced loadings of alkyne **2a** were not possible, a 90% yield of **3a** could be obtained using only 1 mol % $Ru_3(CO)_{12}$ and 3 mol % dppp (Table 1, entry 19).

To assess the reaction scope, the optimal conditions determined for the coupling of oxindole **1a** with alkyne **2a** were applied to alkynes **2b–i** (Table 2). Aryl-substituted alkynes **2a–c** delivered adducts **3a–c** in excellent yield. Heteroatoms are not tolerated at the propargylic position of

Scheme 1. Ruthenium(0)-Catalyzed Couplings of Activated Secondary Alcohols with Alkynes

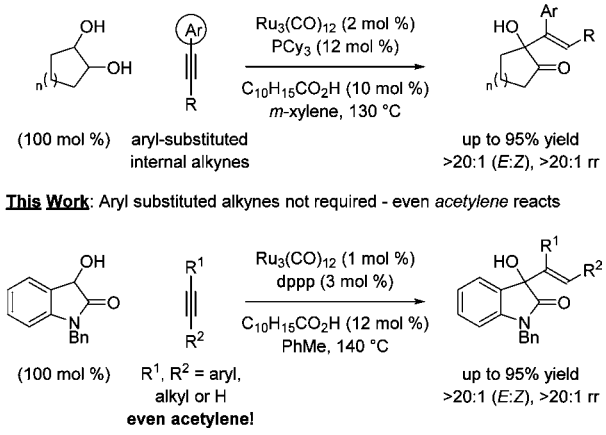


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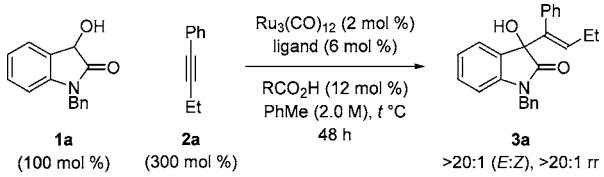
Table 1. Selected Optimization Experiments in the Ruthenium(0)-Catalyzed Coupling of 3-Hydroxy-2-oxindole 1a with Alkyne 2a To Form Adduct 3a[a]



1a (100 mol %) **2a** (300 mol %) **3a** >20:1 (*E*:*Z*), >20:1 rr

entry	ligand	t (°C)	RCO_2H	yield of **3a** (%)
1	–	140	–	trace
2	dppp	140	–	54
3	dppp	140	$PhCO_2H$	60
4	dppp	140	p-$NO_2C_6H_4CO_2H$	26
5	dppp	140	$C_6F_5CO_2H$	71
6	dppp	140	$C_{10}H_{15}CO_2H$	90
7	dppe	140	$C_{10}H_{15}CO_2H$	63
8	dCype	140	$C_{10}H_{15}CO_2H$	39
9	dppb	140	$C_{10}H_{15}CO_2H$	59
10	dppf	140	$C_{10}H_{15}CO_2H$	45
11	*rac*-BINAP	140	$C_{10}H_{15}CO_2H$	49
12	BIPHEP	140	$C_{10}H_{15}CO_2H$	59
13	PCy_3	140	$C_{10}H_{15}CO_2H$	53
14	dppp	120	$C_{10}H_{15}CO_2H$	34
15	dppp	130	$C_{10}H_{15}CO_2H$	54
16	dppp	150	$C_{10}H_{15}CO_2H$	60
17[b]	dppp	140	$C_{10}H_{15}CO_2H$	47
18[c]	dppp	140	$C_{10}H_{15}CO_2H$	56
19[d]	**dppp**	**140**	**$C_{10}H_{15}CO_2H$**	**90**
20[d,e]	dppp	140	$C_{10}H_{15}CO_2H$	65

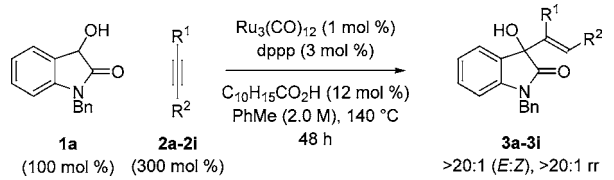
[a]Cited yields are of material isolated by silica gel chromatography. $C_{10}H_{15}CO_2H$ refers to adamantanecarboxylic acid. See the Supporting Information for further experimental details. [b]**2a** (150 mol %). [c]$Ru_3(CO)_{12}$ (1 mol %), dppp (3 mol %), $C_{10}H_{15}CO_2H$ (6 mol %). [d]$Ru_3(CO)_{12}$ (1 mol %), dppp (3 mol %), $C_{10}H_{15}CO_2H$ (12 mol %). [e]**2a** (200 mol %).

the alkyne. However, as demonstrated by the formation of adduct **2d**, the presence of heteroatoms at the homopropargylic position is not problematic. Encouraged by these results, we explored the coupling of oxindole **1a** with terminal alkynes **2e** and **2f**. Adducts **3e** and **3f** were obtained in good yield as single regioisomers. The coupling of oxindole **1a** with acetylene **2i** (1 atm) also was attempted. Remarkably, the carbinol C–H vinylation product **3i** was obtained in 69% yield.

To probe the reaction scope further, a set of substituted *N*-benzyl-3-hydroxy-2-oxindoles **1a–f** (100 mol %) were exposed to 1-phenylpropyne (**2b**) (300 mol %) under the optimal conditions determined for the coupling of oxindole **1a** with alkyne **2a** (Table 3). Uniformly high isolated yields of the respective coupling products **3b** and **3j–n** were obtained, and in each case, a single geometrical isomer of the trisubstituted olefin was observed by ^1H NMR spectroscopy. Finally, reductive coupling of *N*-benzylisatin (*dehydro*-**1a**) (100 mol %) with 1-phenyl-1-butyne (**2a**) (300 mol %) mediated by 2-propanol (200 mol %) was attempted under otherwise standard conditions (eq 1). The adduct **3a** was obtained in 65% yield as a single regioisomer with complete control of the olefin geometry.

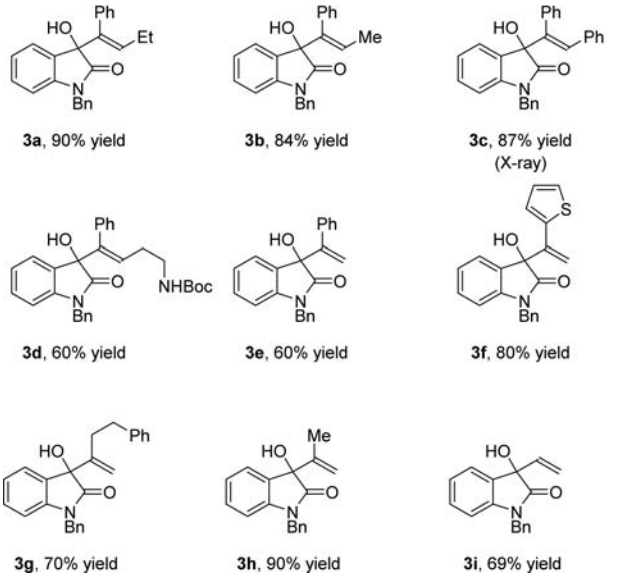
To illustrate how the coupling products may be used as building blocks in chemical synthesis, adduct **3i** was converted to the corresponding acrylic ester, which was subjected to

Table 2. Ruthenium(0)-Catalyzed Coupling of 3-Hydroxy-2-oxindole 1a with Alkynes 2a–i To Form Adducts 3a–i[a]

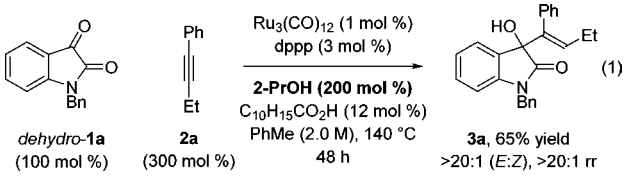


1a (100 mol %) **2a-2i** (300 mol %) **3a-3i** >20:1 (*E*:*Z*), >20:1 rr

2a, R^1 = Ph, R^2 = Et; **2b**, R^1 = Ph, R^2 = Me; **2c**, R^1 = R^2 = Ph
2d, R^1 = Ph, R^2 = $(CH_2)_2NHBoc$; **2e**, R^1 = Ph, R^2 = H; **2f**, R^1 = 2-thienyl, R^2 = H
2g, R^1 = $(CH_2)_2Ph$, R^2 = H; **2h**, R^1 = Me, R^2 = H; **2i**, R^1 = R^2 = H

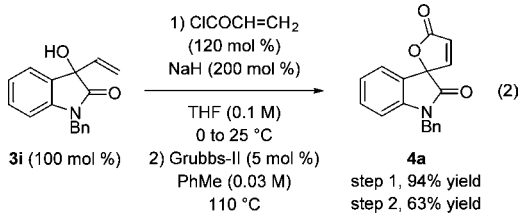


[a]Cited yields are of material isolated by silica gel chromatography. $C_{10}H_{15}CO_2H$ refers to adamantanecarboxylic acid. See the Supporting Information for further experimental details.

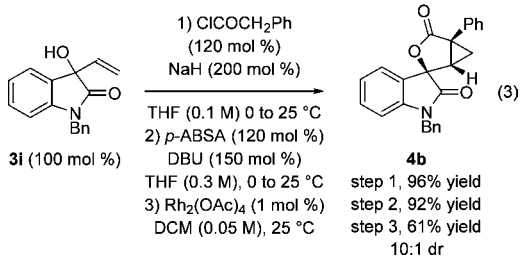


dehydro-**1a** (100 mol %) **2a** (300 mol %) **3a**, 65% yield >20:1 (*E*:*Z*), >20:1 rr

ring-closing metathesis[8] to deliver spirooxindole **4a** (eq 2). Alternatively, conversion of adduct **3i** to the corresponding



3i (100 mol %) **4a** step 1, 94% yield step 2, 63% yield



3i (100 mol %) **4b** step 1, 96% yield step 2, 92% yield step 3, 61% yield 10:1 dr

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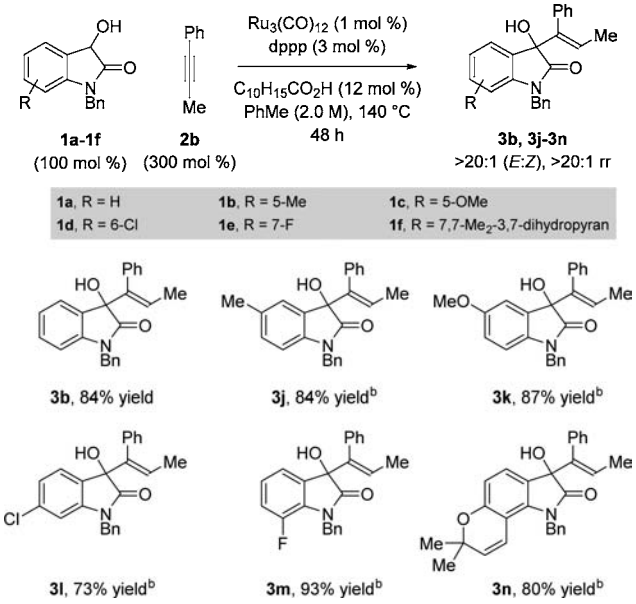
Table 3. Ruthenium(0)-Catalyzed Coupling of 3-Hydroxy-2-oxindoles 1a–f with Alkyne 2b To Form Adducts 3b and 3j–n[a]



[a]Cited yields are of material isolated by silica gel chromatography. $C_{10}H_{15}CO_2H$ refers to adamantanecarboxylic acid. See the Supporting Information for further experimental details. [b]2-PrOH (200 mol %).

α-diazo ester using *p*-acetamidobenzenesulfonyl azide (*p*-ABSA)[9] followed by exposure to rhodium acetate resulted in diastereoselective intramolecular cyclopropanation to form spirooxindole **4b** (eq 3).[10] The stereochemistry of **4b** was assigned on the basis of NOE studies, as described in the Supporting Information.

In summary, by harnessing the reducing power of alcohols, one may avoid the use of premetalated reagents in carbonyl addition.[1] Here, under the conditions of ruthenium(0)-catalyzed C–C bond-forming transfer hydrogenation, *N*-benzyl-3-hydroxy-2-oxindole reacts with internal or terminal alkynes—even acetylene—to form products of hydrohydroxyalkylation. Alternatively, as demonstrated by the coupling of isatin *dehydro*-**1a** with 1-phenyl-1-butyne **2a**, 2-propanol-mediated alkyne–carbonyl reductive coupling also is possible. Future studies will focus on the use of α-olefins[11] and related chemical feedstocks as pronucleophiles in redox-triggered carbonyl addition via alcohol-mediated hydrogen transfer.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00174.

Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS) (PDF)

Single-crystal X-ray diffraction data for compound **3c** (CIF)

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Notes

The authors declare no competing financial interest.

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