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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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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.

Graphical abstract

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 cleavage² or (b) π -bond hydrometalation³ 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

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The authors declare no competing financial interest.

Supporting Information Available. Spectral data for all new compounds (¹H NMR, ¹³C NMR, IR, HRMS). Single crystal X-ray diffraction data for compound **3c**. This material is available free of charge *via* the internet at <http://pubs.acs.org>.

variety of different diol partners could be employed, preparatively useful isolated yields were only achieved using aryl-substituted alkynes. Given 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 Ru₃(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 product of C-C coupling **3a** was formed in 54% yield as a single regioisomer (Table 1, entry 2). Carboxylic acid additives have been shown to enhance yield dramatically by co-catalyzing the transfer hydrogenolysis of oxaruthenacycles.⁷ Upon evaluation of a series of carboxylic acids (Table 1, entries 3–6), adamantane carboxylic acid was most effective, allowing adduct **3a** to be obtained in 90% yield (Table 1, entry 6). Further variation of 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 loading 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 Ru₃(CO)₁₂ (1 mol %) and dppp (3 mol %) (Table 1, entry 19).

To assess reaction scope, optimal conditions determined for the coupling of oxindole **1a** with alkyne **2a** were applied to alkynes **2b–2i** (Table 2). Aryl-substituted alkynes **2a–2c** delivered adducts **3a–3c** in excellent yield. Heteroatoms are not tolerated at the propargylic position of 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, the coupling of oxindole **1a** with terminal alkynes **2e–2f** was explored. Adducts **3e–3f** were obtained in good yield as single regioisomers. The coupling of oxindole **1a** with acetylene **2i** (1 atm) also was attempted. Remarkably, the product of carbinol C-H vinylation **3i** was obtained in 69% yield.

To probe reaction scope further, a set of substituted *N*-benzyl 3-hydroxy-2-oxindoles **1a–1f** (100 mol %) were exposed to phenyl-1-propyne **2b** (300 mol %) under optimal conditions determined for the coupling of oxindole **1a** with alkyne **2a** (Table 3). Uniformly high isolated yields of the respective coupling products **3b**, **3j–3n** were obtained, and in each case, a single geometrical isomer of the trisubstituted olefin was observed by ¹H NMR. Finally, reductive coupling of *N*-benzyl isatin *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 olefin geometry.

(1)

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 ring-closing metathesis⁸ to deliver the spirooxindole **4a** (eq 2). Alternatively, conversion of adduct **3i** to the corresponding α -diazo ester using *p*-acetamidobenzenesulfonyl azide (*p*-ABSA)⁹ followed by exposure to rhodium acetate results in diastereoselective intramolecular cyclopropanation to form the spirooxindole **4b** (eq 3).¹⁰ The stereochemistry of **4b** was assigned on the basis of nOe studies, as described in the Supporting Information.

(2)

(3)

In summary, by harnessing the reducing power of alcohols, one may avoid the use of premetallated 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 -olefins¹¹ and related chemical feedstocks

as pronucleophiles in redox-triggered carbonyl addition via alcohol-mediated hydrogen transfer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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This Work: Aryl substituted alkynes not required - even *acetylene* reacts

Scheme 1.

Ruthenium(0) catalyzed couplings of activated secondary alcohols with alkynes.

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

entry	ligand	t °C	RCO_2H	3a yield (%)
1	---	140	---	trace
2	dppp	140	---	54
3	dppp	140	PhCO ₂ H	60
4	dppp	140	<i>p</i> -NO ₂ C ₆ H ₄ CO ₂ H	26
5	dppp	140	C ₆ F ₅ CO ₂ H	71
6	dppp	140	C ₁₀ H ₁₅ CO ₂ H	90
7	dppe	140	C ₁₀ H ₁₅ CO ₂ H	63
8	dCype	140	C ₁₀ H ₁₅ CO ₂ H	39
9	dppb	140	C ₁₀ H ₁₅ CO ₂ H	59
10	dppf	140	C ₁₀ H ₁₅ CO ₂ H	45
11	<i>rac</i> -BINAP	140	C ₁₀ H ₁₅ CO ₂ H	49
12	BIPHEP	140	C ₁₀ H ₁₅ CO ₂ H	59
13	PCy ₃	140	C ₁₀ H ₁₅ CO ₂ H	53
14	dppp	120	C ₁₀ H ₁₅ CO ₂ H	34
15	dppp	130	C ₁₀ H ₁₅ CO ₂ H	54
16	dppp	150	C ₁₀ H ₁₅ CO ₂ H	60
17 ^b	dppp	140	C ₁₀ H ₁₅ CO ₂ H	47
18 ^c	dppp	140	C ₁₀ H ₁₅ CO ₂ H	56
⇒ 19 ^d	dppp	140	C₁₀H₁₅CO₂H	90
20 ^{d,e}	dppp	140	C ₁₀ H ₁₅ CO ₂ H	65

^a Cited yields are of material isolated by silica gel chromatography. C₁₀H₁₅CO₂H refers to adamantane carboxylic acid. See Supporting Information for further experimental details.

^b **2a** (150 mol %).

^c $\text{Ru}_3(\text{CO})_{12}$ (1 mol %), dppp (3 mol %), C₁₀H₁₅CO₂H (6 mol %).

^d $\text{Ru}_3(\text{CO})_{12}$ (1 mol %), dppp (3 mol %), C₁₀H₁₅CO₂H (12 mol %).

^e **2a** (200 mol %).

Table 2

Ruthenium(0) catalyzed coupling of 3-hydroxy-2-oxindole **1a** with alkynes **2a–2i** to form adducts **3a–3i**.^a

^aCited yields are of material isolated by silica gel chromatography. C₁₀H₁₅CO₂H refers to adamantane carboxylic acid. See Supporting Information for further experimental details.

Table 3

Ruthenium(0) catalyzed coupling of 3-hydroxy-2-oxindole **1a–1f** with alkyne **2b** to form adducts **3b, 3j–3n**.^a

^a Cited yields are of material isolated by silica gel chromatography. C₁₀H₁₅CO₂H refers to adamantane carboxylic acid. See Supporting Information for further experimental details.

^b 2-PrOH (200 mol %)