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Iridium-Catalyzed Hydrohydroxyalkylation of Butadiene: Carbonyl Crotylation

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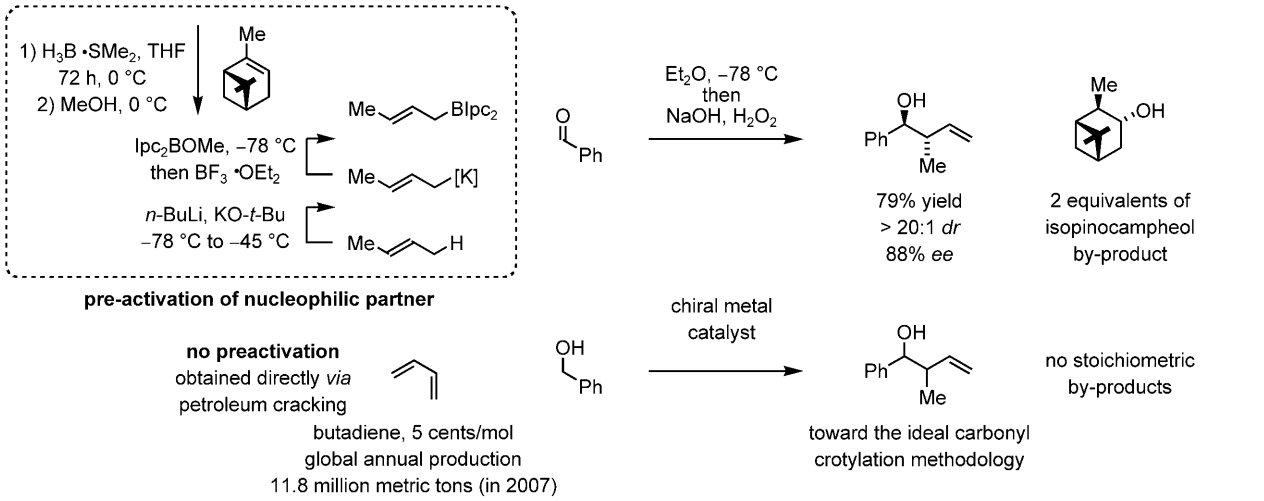
Abstract: Exposure of alcohols **1a**–**1i** to butadiene in the presence of a cyclometallated iridium catalyst derived from allyl acetate, 4-methoxy-3-nitrobenzoic acid and 2,2′-bis(diphenylphosphino)biphenyl (BIPHEP) results in hydrogen transfer to generate aldehyde-allyliridium pairs, which engage in C–C coupling to form products of carbonyl crotylation. Under related conditions using 1,4-butanediol as hydrogen donor, butadiene reductively couples to aldehydes **2e**–**2g** and **2i** to furnish carbonyl crotylation products **3e**–**3g** and **3i**. Thus, butadiene-mediated carbonyl crotylation occurs with equal facility from the alcohol or aldehyde oxidation level with complete levels of branched regioselectivity.

Keywords: butadiene; by-product-free process; crotylation; green chemistry; iridium

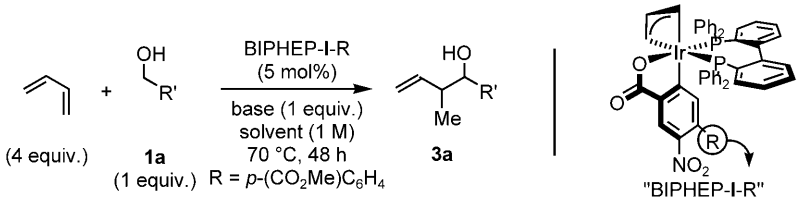
We have found that hydrogen exchange between alcohols and π-unsaturated reactants triggers generation of electrophile-nucleophile pairs *en route* to products of C–C coupling.[1,2] Using ruthenium catalysts, the "*transfer hydrogenative coupling*" of alcohols to dienes,[3] enynes,[4] alkynes,[5] and allenes[6] delivers products of carbinol C–H functionalization or "*hydrohydroxyalkylation*". Recently, related alcohol-enal couplings catalyzed by ruthenium were reported where C–C bond formation is followed by redox isomerization.[7] Using ruthenium-based catalysts, diastereoselective hydrohydroxyalkylation only has been achieved in one isolated case[6c] and, to date, enantioselective variants have proven elusive. In contrast, excellent levels of relative and absolute stereocontrol have been achieved in the iridium catalyzed C–C coupling of alcohols to π-unsaturated reactants, including allylic acetates,[8,9] dimethylallene[8e,g,10] and 1,3-cyclohexadiene.[11] This fact prompted us to explore alcohol-butadiene C–C coupling under the conditions of iridium-catalyzed transfer hydrogenation. Our efforts were further motivated by the fact that the most broadly utilized protocol for stereoselective carbonyl crotylation, the method reported by Brown,[12] is attended by significant preactivation and the superstoichiometric generation of the secondary alcohol by-product, isopinocampheol, has proven problematic.[13] In contrast, butadiene is an abundant petrochemical feedstock that could potentially deliver products of carbonyl crotylation in the absence of stoichiometric by-products, while bypassing discrete steps devoted to alcohol oxidation (Scheme 1).[14]

In an initial series of experiments, the coupling of butadiene to alcohol **1a** was explored using the *ortho*-cyclometallated iridium complex derived from $[Ir(COD)Cl]_2$, various 4-substituted 3-nitrobenzoic acids, allyl acetate and the chelating phosphine ligand BIPHEP [2,2′-bis(diphenylphosphino)biphenyl]. Unlike other iridium-catalyzed C–C couplings developed in our laboratory,[8–11] reactions attempted in THF produced only trace quantities of **3a**. Improved conversion to **3a** was observed in non-Lewis basic solvents, and toluene was best among the solvents screened (Table 1, entries 1–5). Additionally, a dramatic electronic effect involving the *C,O*-benzoate was evident: whereas the catalyst derived from 4-cyano-3-nitrobenzoic acid "BIPHEP-**I**-CN" provides only an 8% yield of C–C coupling product **3a**, the catalyst derived from 4-methoxy-3-nitrobenzoic acid "BIPHEP-**I**-OMe" delivers **3a** in 62% yield (Table 1, entries 5–7). Finally, mild basic additives, in particular sodium acetate, were found to enhance conversion (Table 1, entries 5, 8–11). Under optimal conditions employing "BIPHEP-**I**-OMe" as precatalyst in toluene solvent and sodium acetate as base, butadiene and alcohol **1a** are converted to the product of C–C coupling **3a** in 80% isolated yield. Notably, a single regioisomer is formed (Table 1).



Scheme 1. Metal-catalyzed hydrohydroxyalkylation of butadiene circumvents the preactivation and by-product generation that attends "state-of-the-art" carbonyl crotylation methodology.

Table 1. Selected experiments in the optimization of the iridium catalyzed hydrohydroxyalkylation of butadiene.[a]



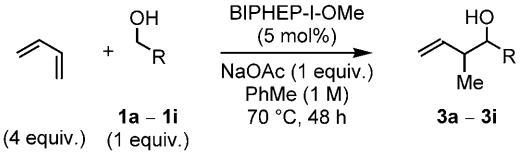
Entry	Solvent	Base	R	Yield of **3a** (*syn*:*anti*)
1	THF	$NaHCO_3$	OMe	trace
2	MeCN	$NaHCO_3$	OMe	trace
3	dioxane	$NaHCO_3$	OMe	32% (1.4:1)
4	DCE	$NaHCO_3$	OMe	49% (1.4:1)
5	PhMe	$NaHCO_3$	OMe	62% (1.4:1)
6	PhMe	$NaHCO_3$	H	57% (1.4:1)
7	PhMe	$NaHCO_3$	CN	8% (1:1)
8	PhMe	No Base	OMe	31% (1.4:1)
9	PhMe	$KHCO_3$	OMe	57% (1.4:1)
10	PhMe	Li_2CO_3	OMe	trace
11	PhMe	NaOAc	OMe	80% (1.4:1)

[a] Reactions were performed in 13×100 mm pressure tubes. The cited yields are of material isolated by silica gel chromatography. See Supporting Information for experimental details.

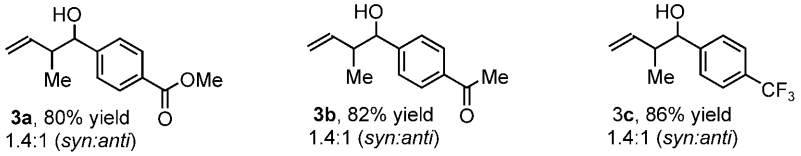
Under these optimized conditions, butadiene was coupled to alcohols **1a**–**1i**. Benzylic alcohols **1a**–**1f** were converted to the products of carbonyl crotylation **3a**–**3f** in good yield. Allylic alcohols **1g** and **1h** also couple to butadiene to provide homoallylic alcohols **3g** and **3h** in moderate yields. Finally, the unactivated aliphatic alcohol **1i** combines with butadiene to provide a 52% yield of the hydrohydroxyalkylation product **3i**. Although products **3a**–**3i** are obtained as mixtures of *syn*- and *anti*-diastereomers, only a single regioisomer is formed in each case (Table 2).

The modest levels of *syn*-diastereoselectivity suggests a kinetic preference for butadiene hydrometallation from the *s-cis* conformer to deliver the *anti*-π-allyl which, in turn, provides the (*Z*)-σ-allyl stereoisomer. It is likely that conversion of the kinetically preferred (*Z*)-σ-allyl stereoisomer to the thermodynamically preferred (*E*)-σ-allyl stereoisomer occurs at a rate comparable to carbonyl addition. Alternatively, a

Table 2. Iridium catalyzed hydro-hydroxyalkylation of butadiene employing alcohols **1a**–**1i**.[a]



1a, R = *p*-$(CO_2Me)C_6H_4$	**1b**, R = *p*-$(COMe)C_6H_4$	**1c**, R = *p*-$CF_3C_6H_4$
1d, R = *p*-$NO_2C_6H_4$	**1e**, R = *p*-BrC_6H_4	**1f**, R = 2-furyl
1g, R = CH=CHPh	**1h**, R = $CH{=}CHCH_2OBn$	**1i**, R = $(CH_2)_7Me$

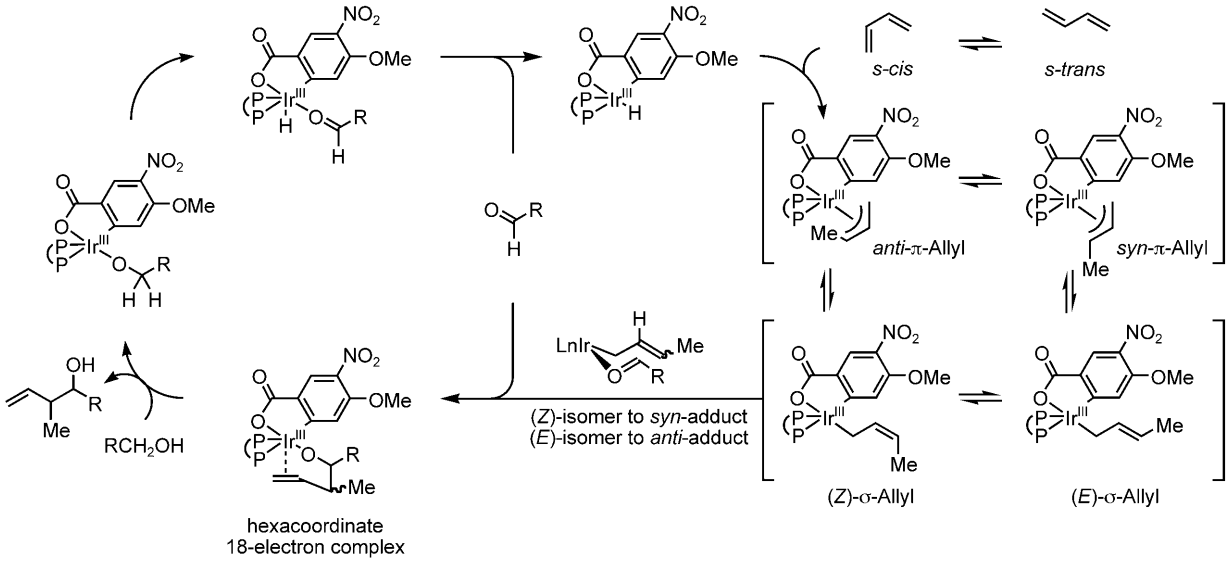


3a, 80% yield, 1.4:1 (*syn:anti*)
3b, 82% yield, 1.4:1 (*syn:anti*)
3c, 86% yield, 1.4:1 (*syn:anti*)
3d, 70% yield, 1:1.3 (*syn:anti*)
3e, 62% yield, 1.7:1 (*syn:anti*)
3f, 73% yield, 1.1:1 (*syn:anti*)[b]
3g, 64% yield, 1.5:1 (*syn:anti*)
3h, 62% yield, 1.4:1 (*syn:anti*)
3i, 52% yield, 1.5:1 (*syn:anti*)[c]

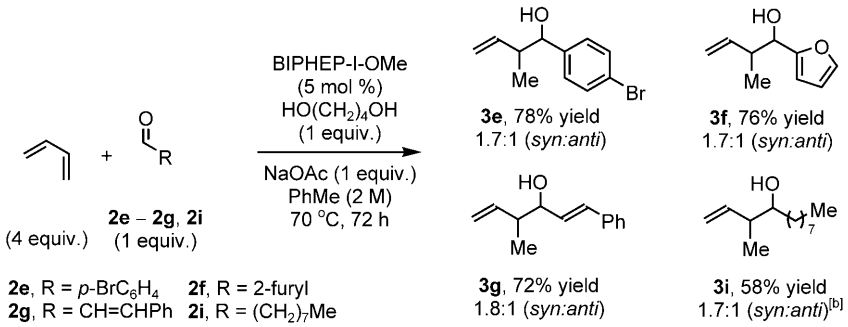
[a] As described in Table 1.
[b] At 95 °C.
[c] For 72 h.

Curtin–Hammett scenario might be operative, wherein full equilibration between the (*Z*) and (*E*)-σ-allyl stereoisomers is achieved, yet there exists a slight kinetic preference for carbonyl addition from the thermodynamically less stable (*Z*)-σ-allyl stereoisomer (Scheme 2).

For nearly all the C–C bond forming transfer hydrogenations we have developed,[3–11] carbonyl addition may be achieved from both the alcohol or alde-



Scheme 2. Proposed catalytic mechanism for iridium-catalyzed hydrohydroxyalkylation of butadiene.

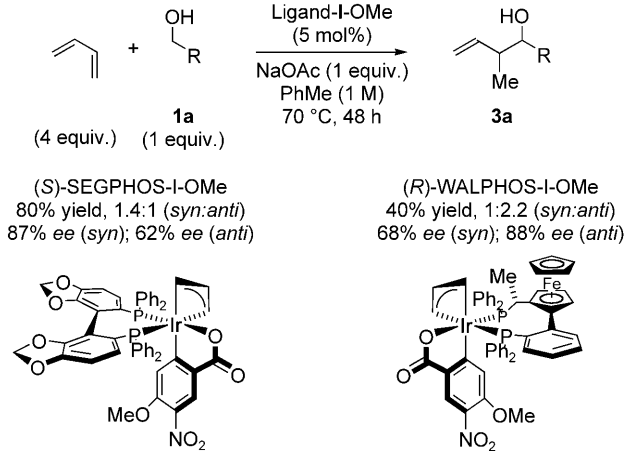


Scheme 3. Iridium-catalyzed reductive coupling of butadiene to aldehydes **2e**–**2g** and **2i**.

hyde oxidation levels. In the latter case, a stoichiometric reductant such as isopropyl alcohol or formic acid is required. Using BIPHEP-**I**-OMe as precatalyst, the reductive coupling of butadiene to aldehydes mediated by 1,4-butanediol[14] occurs smoothly, as demonstrated by the conversion of aldehydes **2e**–**2g** and **2i** to crotylation products **3e**–**3g** and **3i**. Thus, butadiene-mediated carbonyl crotylation occurs with equal facility from the alcohol or aldehyde oxidation level (Scheme 3).

Having established favorable reactivity, a preliminary evaluation of chirally modified catalysts was undertaken. Toward this end, the *ortho*-cyclometallated iridium *C,O*-benzoates derived from (*S*)-SEGPHOS and (*R*)-WALPHOS (SL-W002-1) were prepared and assayed in the coupling of butadiene to alcohol **1a**. Using (*S*)-SEGPHOS-**I**-OMe, the crotylation product **3a** was obtained in 80% yield as a 1.4:1 mixture of *syn*- and *anti*-diastereomers, respectively. High levels of enantiomeric enrichment were observed for the *syn*-stereoisomer (87% *ee*). Using (*R*)-WALPHOS-**I**-OMe, the crotylation product **3a** was obtained in 40% yield as a 1:2.2 mixture of *syn*- and *anti*-diastereomers, respectively. High levels of enantiomeric enrichment were observed for the major *anti*-diastereomer (88% *ee*) (Scheme 4).

In summary, we report the iridium-catalyzed hydrohydroxyalkylation of butadiene employing alcohols **1a**–**1i** to furnish products of carbonyl crotylation **3a**–**3i**. Using 1,4-butanediol as hydrogen donor, butadiene couples to aldehydes **2e**–**2g** and **2i** to provide the products of carbonyl crotylation **3e**–**3g** and **3i**. Thus, butadiene-mediated carbonyl crotylation occurs with equal facility from the alcohol or aldehyde oxidation level. Although products **3a**–**3i** are obtained as diastereomeric mixtures, preliminary studies employing chiral iridium catalysts modified by (*S*)- SEGPHOS and (*R*)-WALPHOS (SL-W002-1) reveal promising levels of asymmetric induction and catalyst-directed diastereocontrol. Future studies will focus on the development of second-generation catalysts that promote butadiene-mediated carbonyl crotylation with control of relative and absolute stereochemistry.



Scheme 4. Preliminary evaluation of chirally modified catalysts.

Experimental Section

Procedure for the Synthesis of BIPHEP-I-OMe

To an oven-dried sealed tube under an atmosphere of nitrogen charged with $[Ir(cod)Cl]_2$ (100 mg, 0.15 mmol, 100 mol%), BIPHEP (156 mg, 0.3 mmol, 200 mol%), Cs_2CO_3 (195 mg, 0.6 mmol, 400 mol%) and 4-methoxy-3-nitrobenzoic acid (100 mg, 0.6 mmol, 400 mol%) was added THF (3 mL, 0.05 M). The reaction mixture was heated at 80 °C for 30 min and was then allowed to cool to ambient temperature. Allyl acetate (75 mg, 0.75 mmol, 500 mol%) was added and the reaction mixture was allowed to stir for an additional 90 min at 80 °C, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was filtered and washed with THF (15 mL) until all yellow residue had dissolved. The filtrate was concentrated under vacuum and hexanes (50 mL) was added. The resulting yellow precipitate was collected by filtration and dried under vacuum; yield: 253 mg (80.266 mmol, 90%).

General Procedure for Iridium-Catalyzed Hydrohydroxyalkylation of Butadiene

To an oven-dried sealed tube under an atmosphere of nitrogen charged with alcohol **1a** (50 mg, 0.30 mmol, 100 mol%),

Ir-BIPHEP-1-OMe (14 mg, 0.015 mmol, 5 mol%) and sodium acetate (25 mg, 0.30 mmol, 100 mol%) were added toluene (1.0 m, 0.3 mL) followed by 1,3-butadiene (0.1 mL, 1.2 mmol, 400 mol%, chilled at −78 °C). The reaction mixture was placed in a 70 °C oil bath and was allowed to stir for 48 h, at which point the reaction mixture was concentrated under vacuum. Purification of the product by column chromatography (SiO_2; ethyl acetate:hexanes, 1:10) provides the product of carbonyl crotylation, methyl 4-(-hydroxy-2-methylbut-3-enyl)benzoate (**3a**), as a colorless oil, as a single regioisomer and as a 1.4:1 mixture of *syn/anti* diastereomers; yield: 53 mg (80%).

Supporting Information

Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HR-MS), including scanned images of ^{1}H and ^{13}C NMR spectra. Scanned images of HPLC traces corresponding to racemic and enantiomerically enriched products.

Acknowledgements

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