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Redox-Neutral Atom-Economic Rhodium-Catalyzed Coupling of Terminal Alkynes with Carboxylic Acids Toward Branched Allylic Esters

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Supporting Information

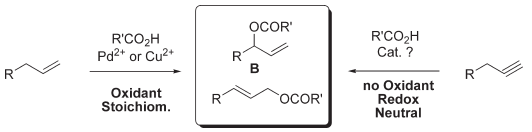
ABSTRACT: A new method for the preparation of a wide range of branched allylic esters from terminal alkynes that proceeds via a redox-neutral propargylic CH activation employing a rhodium(I)/DPEphos catalyst is reported.

Branched allylic alcohols and their ester derivatives are important building blocks in organic synthesis. Numerous approaches for their preparation are known, including asymmetric versions.[1−6] More recently, formation of allylic esters via CH bond oxidation has attracted considerable interest and is emerging as a new tool in the synthesis of complex molecules (Scheme 1).[7−9] A drawback of these reactions with regard to atom economy is the requirement of stoichiometric amounts of an oxidant. Furthermore, while palladium catalysts usually allow for regioselective formation of the linear allylic esters, only one method for regioselective generation of the branched product **B** is known (Scheme 1).[8b,8d] We wondered whether replacing the alkene starting material with the corresponding terminal alkyne could lead to an internal redox-neutral formal propargylic CH oxidation with concomitant hydride shift.[10,11] Thus, the alkyne would serve as an internal oxidant to be reduced simultaneously toward the alkene, thus avoiding the need for an external oxidant. The overall process would be a highly attractive atom- and redox-economic one-pot reaction toward allylic esters from readily available terminal alkynes and carboxylic acids.[12,13]

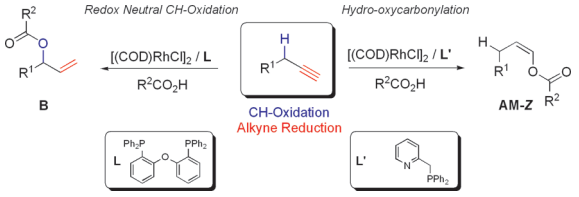
We recently reported on the rhodium-catalyzed addition of carboxylic acids to alkynes to furnish (*Z*)-enol esters (**AM-Z**) employing the P,N ligand 2-(diphenylphosphinomethyl)-pyridine (**L′**; Scheme 2).[14] In this work, we have found that when this P,N ligand is replaced with the diphosphine ligand DPEphos (**L**), which has a wider bite angle, a complete chemoselectivity switch occurs, leading to the formation of the branched allylic esters **B** (Scheme 2).

The best results in terms of yield and selectivity for the branched product **B** over the *gem*-enol ester **M** (the Markovnikov product; see Table 1) were obtained by employing $[(COD)RhCl]_2$ (2.5 mol %) and DPEphos (5 mol %) in 1,2-dichloroethane at 70 °C for 16 h (for optimization of the reaction conditions, see the Supporting Information).[15,16] The reaction is rather general, and Table 1 depicts an overview of the reaction scope. Reasonable yields and chemoselectivities (**B** vs **M**) ranging from 84 to 65% and 98/2 to 87/13, respectively, were

Scheme 1. Oxidative Allylic versus Redox-Neutral Propargylic CH Activation for Formation of Allylic Esters



Scheme 2. Rhodium-Catalyzed Addition of Carboxylic Acids to Alkynes in the Presence of Either DPEphos (L) or 2-(Diphenylphosphinomethyl)pyridine (L′)



obtained for the addition of benzoic acids bearing either electron-withdrawing or -donating substituents to 1-octyne to give products **1a**−**f**. Notably, the reaction between *p*-toluic acid and 1-octyne (**1b**, Table 1) was run on a 5 mmol scale and gave an even better yield (84%) and the same selectivity (**B**/**M** = 97/3). Also, an aryl bromide function was compatible with this catalyst system (**1g**). Furthermore, benzoic acid could be coupled to either 1-hexyne (**2**) or 3-cyclohexyl-1-propyne (**3**). Unsaturated acids (**4**−**7**), aliphatic carboxylic acids (**8** and **9**), heteroarylcarboxylic acids (**10**−**12**), and even N-protected α-amino acids were excellent reaction partners. Finally, the compatibility of this new methodology with a series of oxygen- and nitrogen-functionalized alkynes, including standard protecting groups, was demonstrated (**14**−**20**).

A first hint concerning the reaction mechanism was found when cyclohexylallene was employed as a substrate and subjected to our optimized reaction conditions. A clean addition of benzoic acid occurred, furnishing allylic benzoate **3** in 76% yield (Scheme 3).[17] The corresponding 3-cyclohexyl-1-propyne reacted with a slightly lower yield (60%) and chemoselectivity (83/17). Hence, a plausible reaction mechanism might take the formation of an intermediate allene into account (see Scheme 4).

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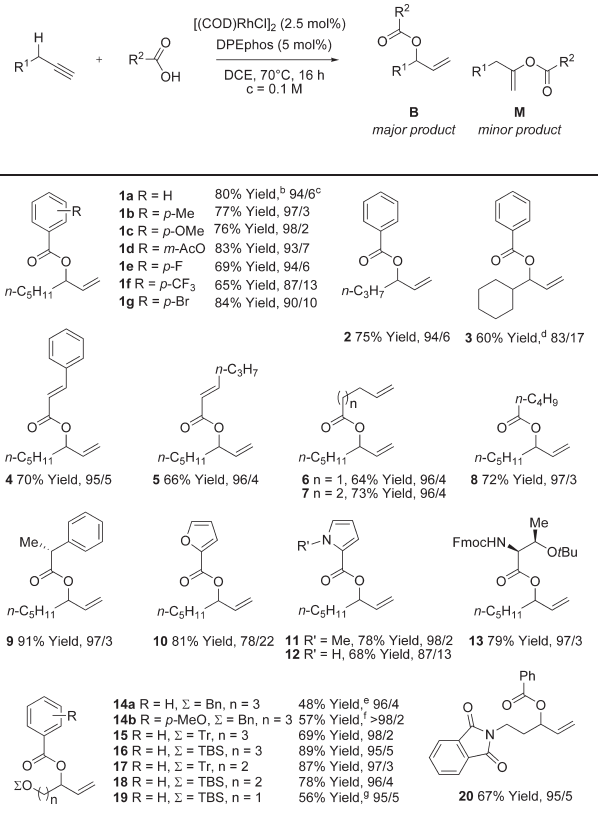
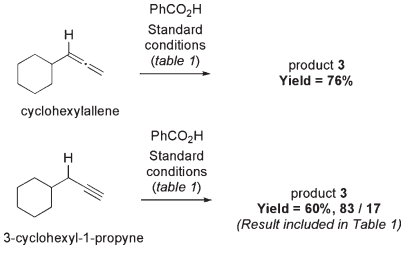
Table 1. Rhodium-Catalyzed Redox-Neutral Coupling of Terminal Alkynes and Carboxylic Acids: Preparation of Branched Allylic Esters B[a]



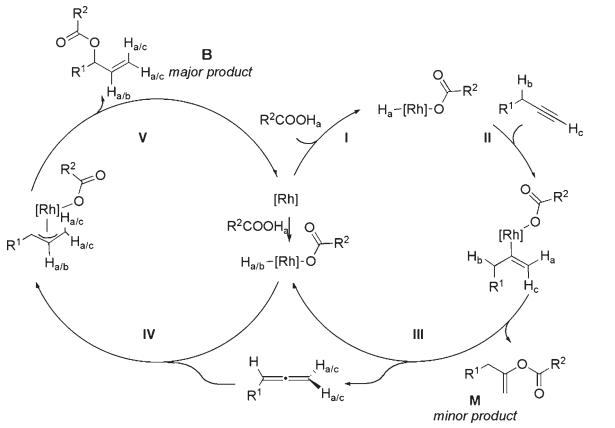
[a] Reaction conditions: 0.011 mmol of $[(COD)RhCl]_2$, 0.022 mmol of DPEphos, 0.44 mmol of acid, and 0.88 mmol of alkyne in 4.4 mL of 1,2-dichloroethane (DCE) were heated in a closed Schlenk flask at 70 °C. [b] Isolated yields. [c] The **B**/**M** ratio was obtained by integration of ethylenic protons in the crude ^{1}H NMR spectrum and/or by GC analysis. [d] 74% conversion. [e] 65% conversion. [f] 75% conversion. [g] 71% conversion.

Scheme 3. Control Experiment with Cyclohexylallene

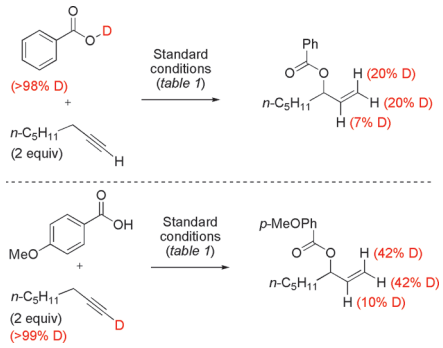


A first reasonable step is the oxidative addition of the carboxylic acid to the Rh(I) center, as the prevalence of O−H oxidative addition over that of C−H from terminal alkynes has previously been demonstrated (step I).[18] Markovnikov-selective hydrometalation furnishes a σ-vinylrhodium complex (step II), which may undergo either reductive elimination to form the *gem*-enol ester byproduct **M** or β-hydride elimination to release an allene (step III). A subsequent second hydrometalation of this allene would form a π-allylrhodium species (step IV), which after intramolecular reductive elimination at the most substituted carbon atom would furnish the desired branched allylic ester (step V).[19] The regiochemistry of this reductive elimination is typical for rhodium[4,20] and iridium[3,21] catalysts and has been noted previously in allylic substitution chemistry.

Scheme 4. Proposed Mechanism for the Rhodium-Catalyzed Redox-Neutral Formal Progargylic CH Oxidation of Terminal Alkynes and Carboxylic Acids To Form Branched Allylic Esters B



Scheme 5. Isotopic Labeling Experiments[a]



[a] The extent of deuterium incorporation was determined using ^{1}H NMR spectroscopy and mass spectrometry (see the Supporting Information for details).

To gain further experimental support for this reaction mechanism, labeling experiments with deuterated benzoic acid on the one hand and 1-octyne-d_1 on the other hand were performed (Scheme 5). Consistent with the proposed mechanism, we found deuterium incorporation at the terminal alkene positions ($H_{a/c}$) to 20% each. We also found 7% incorporation of deuterium in the 2 position ($H_{a/b}$) which is consistent with a (at least partial) dissociation of the allene from the rhodium center in step III followed by intermolecular hydrometalation with a H/D-rhodium-O-acyl species (step IV). Conversely, the reaction with 1-octyne-d_1 (2 equiv) led to the incorporation of deuterium at the terminal alkene positions ($H_{a/c}$) to 42% each. H/D exchange between a terminal alkyne and benzoic acid is well-known[22,23] and may account for the 10% deuterium incorporation at the 2-position in accordance with the proposed reaction mechanism.[24]

We also looked briefly at an asymmetric variant of the redox-neutral atom-economic coupling between carboxylic acids and terminal alkynes. Thus, exchanging DPEphos with (*R*,*R*)-DIOP

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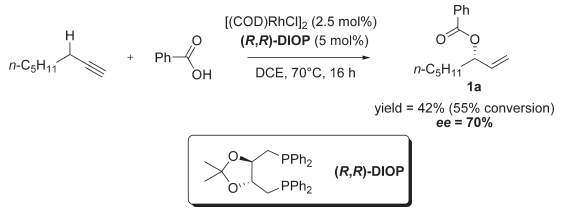
Scheme 6. Enantioselective Coupling Using (*R*,*R*)-DIOP as the Ligand



furnished **1a** in moderate 42% yield with a promising enantioselectivity of 70% ee (Scheme 6), demonstrating the potential for asymmetric catalysis.

In summary, we have developed an efficient method for the first redox-neutral propargylic CH activation of terminal alkynes and their coupling with carboxylic acids under rhodium catalysis to furnish valuable branched allylic esters. This simple atom- and redox-economic procedure is compatible with many functional groups and tolerates substantial structural variation on both the alkyne and the carboxylic acid reaction partner. Future studies will address the extension of this propargylic activation mode to coupling with other nucleophiles and the elaboration of intramolecular and enantioselective variants.

■ ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures and spectral data for new compounds, including scanned images of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For more details on ligand and metal salt screening as well as on optimization of the reaction conditions, see the Supporting Information.

(16) The branched product **B** and the Markovnikov adduct **M** can be separated by chromatography on $AgNO_3$-impregnated silica gel. For example, the products **1b**, **10**, and **19** were purified using this procedure.

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(23) Treatment of $PhCO_2D$ (1 equiv) with 1-octyne (2 equiv) in the presence of $[(COD)RhCl]_2$ (2.5 mol %) and DPEphos (5 mol %) in dry CD_2Cl_2 at room temperature led to complete H/D exchange within 20 min (steady-state concentration ratios: $PhCO_2D/PhCO_2H$ = 0/100; 1-octyne-d_1/1-octyne = 50/50).

(24) Reaction of $PhCO_2D$ with cyclohexylallene gave similar deuterium incorporation as for the corresponding alkyne, in accordance with the proposed reaction mechanism. For details, see the Supporting Information.