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Carbonyl *anti*-(α-Amino)allylation *via* Ruthenium Catalyzed Hydrogen Auto-Transfer: Use of an Acetylenic Pyrrole as an Allylmetal Pronucleophile

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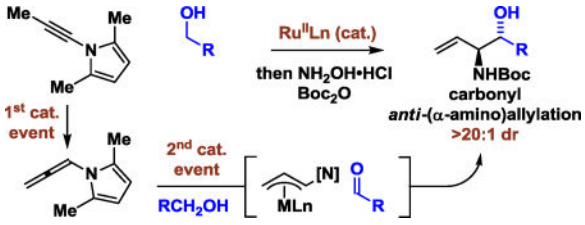
Abstract

A single ruthenium complex catalyzes two discrete transformations resulting in the net conversion of an acetylenic pyrrole and alcohols to products of carbonyl *anti*-(α-amino)allylation. An initial catalytic process enables isomerization of an alkyne to a kinetically more reactive allene. A second catalytic process promotes alcohol-to-allene hydrogen transfer to form an aldehyde-allylruthenium pair that engages in regio- and diastereoselective carbonyl addition. A related reductive coupling conducted of aldehydes mediated by 2-propanol also is described. The present catalytic processes represent rare examples of the use of alkynes as nucleophilic allylmetal precursors.

Graphical abstract



Classical methods for carbonyl and imine addition rely on the use of preformed organometallic reagents.[1] Merging the characteristics of transfer hydrogenation and carbonyl addition, we have developed a broad, new family of catalytic C-C couplings that directly convert lower alcohols to higher alcohols in the absence of stoichiometric metals.[2] In these processes, π-unsaturated reactants serve as equivalents to non-stabilized carbanions. For example, while molar quantities of allylmetal reagents are typically exploited in carbonyl additions to form homoallylic alcohols,[3] we find that such products are accessible through the catalytic coupling of primary alcohols (or methanol[4f,j]) with allenes.[4] In these processes, alcohol dehydrogenation triggers allene hydrometalation to generate aldehyde-allylmetal

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Supporting Information **Available**. Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS). Single crystal X-ray diffraction data for compound **4b**. This material is available free of charge *via* the internet at http://pubs.acs.org.

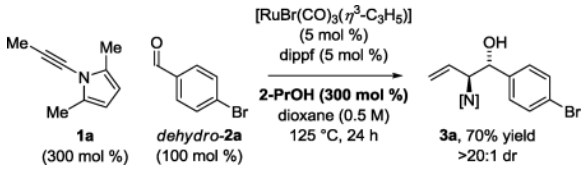
pairs, which upon carbonyl addition and subsequent protonolysis of the resulting ruthenium alkoxide delivers the homoallylic alcohols. The net transformation – a formal insertion of the more substituted allene π-bond into the carbinol C-H bond – is byproduct-free.

Based on this concept, an alternative to classical asymmetric carbonyl (α-amino)allylations mediated by (aminoallyl)diisopinocampheylboranes was sought (Figure 1).[5] Using *N*-substituted-allenes as allyl donors, carbonyl *anti*-(α-amino)allylation could be achieved under the conditions of ruthenium catalysis *via* 2-propanol mediated reductive coupling[6a] or through redox-neutral coupling to primary alcohols.[6b] Good yields and *anti*-diastereoselectivities were observed, but the allenamide required both *p*-nitrobenzenesulfonyl and 2,4-dimethoxybenzyl protecting groups at nitrogen, which impeded elaboration of the coupling products. A potentially more desirable allyl donor is found in *N*-allenyl-2,5-dimethylpyrrole *iso*-**1**, as the pyrrole moiety is readily converted to the primary amine upon treatment with hydroxylamine hydrochloride.[7] However, *N*-allenyl-2,5-dimethylpyrrole *iso*-**1** did not engage in efficient transfer hydrogenative carbonyl addition due to its thermal instability and high kinetic reactivity under the conditions of ruthenium catalysis.

Recently, we found that alkynes may serve as a reservoir for allenes, which are kinetically more reactive, under the conditions of ruthenium catalysis, enabling transfer hydrogenative coupling to form homoallylic alcohols.[8,9,10] These processes represent examples of “tandem catalysis,” as a single metal complex mediates two discrete catalytic events: alkyne-to-allene isomerization and allene-carbonyl C-C coupling *via* hydrogen auto-transfer.[11] Consequently, given the instability of allene *iso*-**1** to the conditions of transfer hydrogenative coupling, the possibility of exploiting the corresponding acetylenic compound *N*-propynyl-2,5-dimethylpyrrole **1** as a latent form of allene *iso*-**1** was explored (Figure 1). In fulfillment of this objective, we herewith report the diastereoselective ruthenium catalyzed coupling of acetylenic pyrrole **1** with diverse primary alcohols **2a–2u** to form products of carbonyl *anti*-(α-amino)allylation **3a–3u** and related 2-propanol mediated aldehyde reductive couplings.

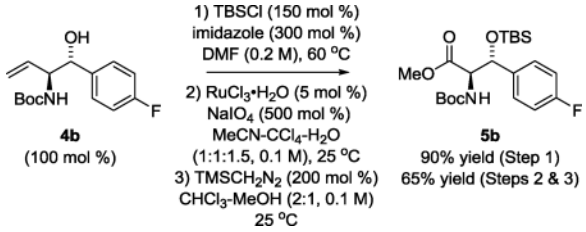
In an initial set of experiments, *para*-bromobenzyl alcohol **2a** (100 mol %) was exposed to acetylenic pyrrole **1** (300 mol %) in the presence of $HClRu(CO)(PPh_3)_3$ (5 mol %) and various chelating bis(phosphine) ligands (5 mol %). As previously observed in certain ruthenium catalyzed allene-alcohol C-C couplings,[4e,6b] the ruthenium complex modified by dippf, bis(diisopropylphosphino)ferrocene, was uniquely effective. By simply exposing acetylenic pyrrole **1** and *para*-bromobenzyl alcohol **2a** to the dippf-modified ruthenium catalyst at 125 °C in dioxane solvent (0.5 M), the desired product of carbonyl (α-amino)allylation **3a** was formed with complete *anti*-diastereoselectivity in 83% yield after isolation by silica gel chromatography. On 1 mmol scale, a 74% yield of **3a** was obtained. These conditions were applied to the coupling of acetylenic pyrrole **1** with diverse primary alcohols **2a–2u** (Scheme 1). Benzylic alcohols **2a–2h** and heterobenzylic alcohols **2i–2m** were converted to the respective products of carbonyl *anti*-(α-amino)allylation **3a–3m**. Allylic alcohols **2n** and **2o** and aliphatic alcohols **2p–2u** also could be transformed to the protected vicinal amino alcohols **3n–3u**, respectively. For adducts **3a–3u**, complete *anti*-diastereoselectivity was observed in each case. The *syn*-diastereomer was not observed upon ^{1}H NMR analysis of the crude reaction product in the formation of **3a** on 1 mmol

scale. The principal side reaction, which was observed in the formation of **3i, 3k** and **3n**, involved alcohol dehydrogenation-olefin isomerization to form the corresponding α,β-unsaturated ketones. However, such over-oxidation could be suppressed upon introduction of 2-propanol. Finally, beyond redox-neutral coupling from the alcohol oxidation level, carbonyl *anti*-(α-amino)allylation also can be achieved through 2-propanol-mediated reductive coupling (eq 1).



(1)

Having developed efficient conditions for ruthenium catalyzed carbonyl *anti*-(α-amino)allylation of alcohols **2a–2u**, deprotection of the 2,5-dimethylpyrrole moiety[7] was explored for representative adducts **3b, 3n** and **3q** derived from aromatic, allylic and aliphatic alcohols **2b, 2n** and **2q**, respectively (Scheme 2). In the event, exposure of **3b, 3n** and **3q** to hydroxylamine hydrochloride in the aqueous ethanol at 100 °C followed by Boc-protection of the resulting primary amine, delivered the corresponding *N*-Boc-protected *anti*-vicinal amino alcohols **4b, 4n** and **4q** in moderate to good yield after isolation by silica gel chromatography. Finally, to illustrate the utility of these compounds as building blocks in chemical synthesis, Boc-protected amino alcohol **4b** was converted to the nonproteinogenic α-amino-β-hydroxy amino ester **5b** via modified Johnson-Lemieux conditions for alkene oxidative cleavage[12] followed by treatment with TMS-diazomethane (eq 2).



(2)

To gain insight into the catalytic mechanism, the following competition experiment was performed (Scheme 3). Acetylenic pyrrole **1** was exposed to equimolar quantities of alcohol **2a** and aldehyde *dehydro*-**2d** under standard conditions employing the ruthenium catalyst generated *in situ* from $HClRu(CO)(PPh_3)_3$ and dippf at 125 °C in dioxane solvent (0.5 M). The C-C coupling products **3a** and **3d** were produced in a roughly 3:1 ratio. Under the same conditions, but inverting oxidation level by employing equimolar quantities of aldehyde *dehydro*-**2a** and alcohol **2d**, a nearly identical product ratio of coupling products **3a** and **3d** was observed. These data are consistent with rapid, reversible primary alcohol dehydrogenation in advance of turnover-limiting carbonyl addition.[13]

In summary, we report diastereoselective ruthenium catalyzed couplings of acetylenic pyrrole **1** with primary alcohols **2a–2u** to form products of carbonyl *anti*-(α-amino)allylation **3a–3u** and related 2-propanol-mediated reductive couplings. These processes occur by way of two discrete catalytic events: alkyne-to-allene isomerization and allene-carbonyl C-C coupling *via* hydrogen auto-transfer. As demonstrated by formation of *N*-Boc-protected amino alcohols **4b, 4n** and **4q**, deprotection of the 2,5-dimethylpyrrole moiety occurs readily upon exposure to hydroxylamine hydrochloride in the aqueous ethanol.[7] These studies along with prior work from our laboratory demonstrate that reactions traditionally employing stoichiometric carbanions may now be conducted catalytically in the absence of stoichiometric metals *via* alcohol-mediated hydrogen transfer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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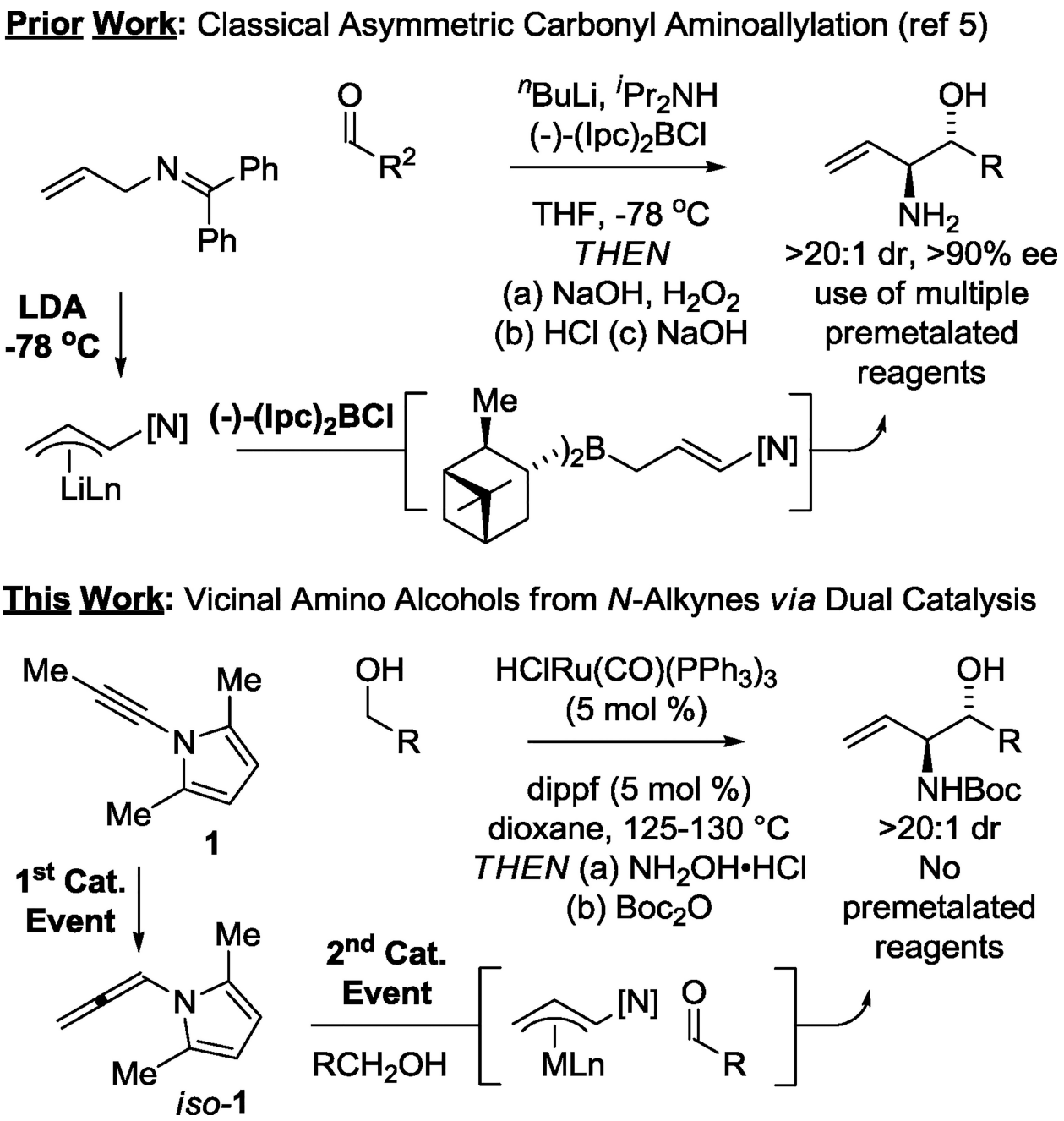
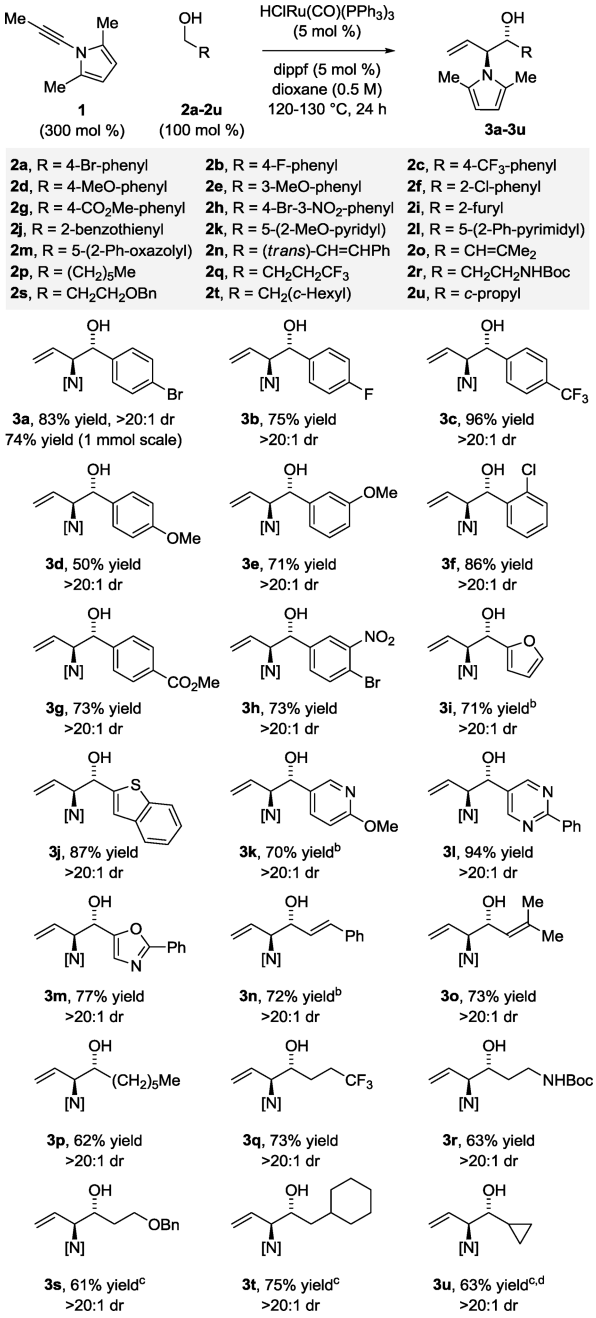


Figure 1.

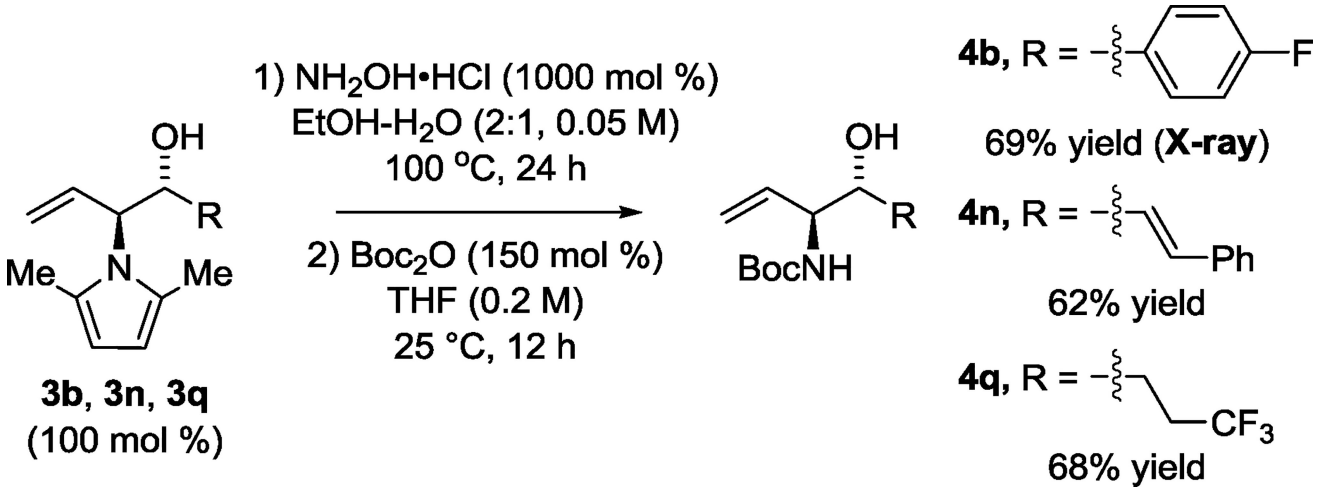
Classical carbonyl (α-amino)allylation and ruthenium tandem-catalysis for carbonyl *anti*-(α-amino)allylation *via* alkyne-alcohol hydrogen auto-transfer.



Scheme 1.

Ruthenium catalyzed C-C coupling of alcohols **2a–2u** with acetylenic pyrrole **1** to form products of carbonyl *anti*-(α-amino)allylation **3a–3u**.[a]

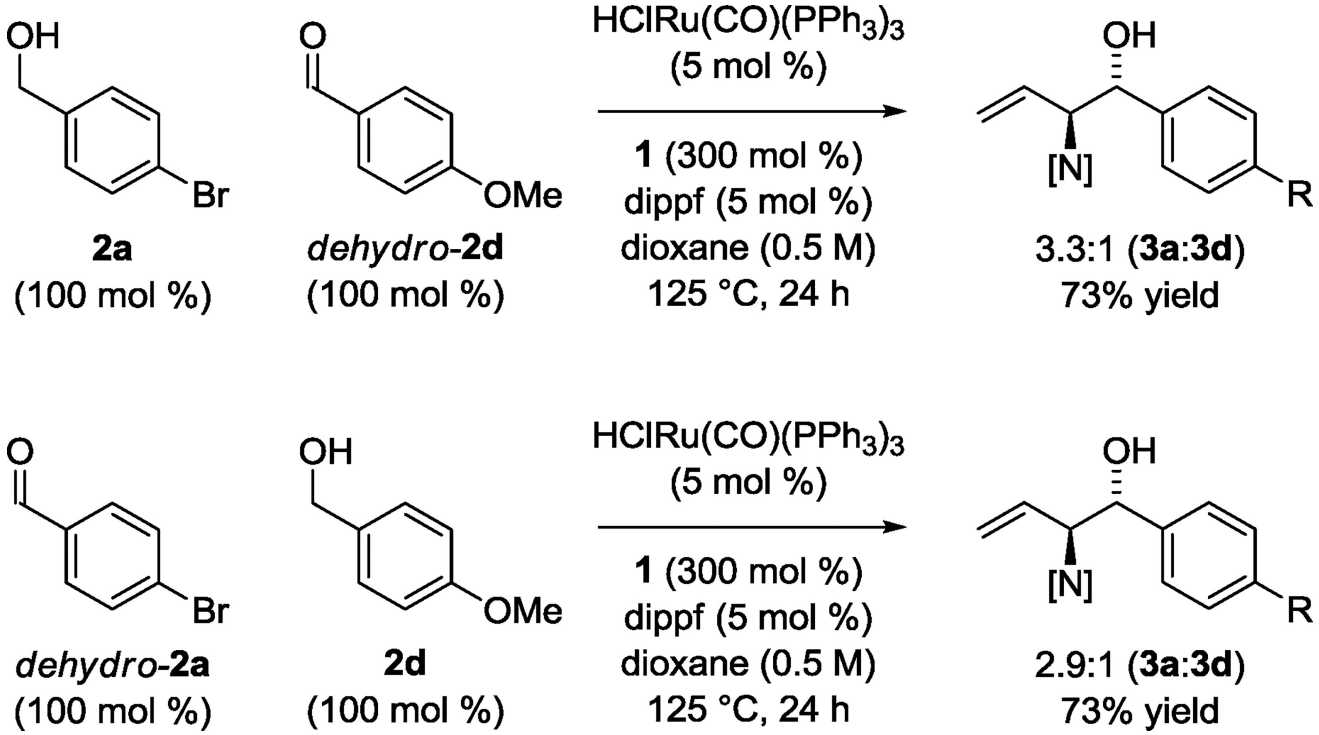
[a]Yields are of material isolated by silica gel chromatography. [b]2-PrOH (200 mol %). [c]48h. [d]dioxane (1 M). See Supporting Information for further experimental details.



Scheme 2.

Deprotection of adducts **3b, 3n**, and **3q** and conversion to corresponding *N*-Boc-protected amino alcohols **4b, 4n**, and **4q**.[a]

[a]Cited yields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details.



Scheme 3.

Competition experiments corroborating rapid, reversible dehydrogenation with respect to C-C coupling.[a]

[a]Cited yields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details.