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Ruthenium-Catalyzed Reductive Coupling of 1,3-Enynes and Aldehydes by Transfer Hydrogenation: *anti*-Diastereoselective Carbonyl Propargylation

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Abstract: Under the conditions of ruthenium-catalyzed transfer hydrogenation employing isopropanol as a source of hydrogen, isopropoxy-substituted enyne **1b** and aldehydes **3a–3l** engage in reductive coupling to provide products of propargylation **4a–4l** with good to complete levels of *anti*-diastereoselectivity. The unprotected tertiary hydroxy moiety of isopropoxy enyne **1b** is required to enforce diastereoselectivity. Deuterium-labeling studies corroborate reversible enyne hydrometalation in advance of carbonyl addition. As demonstrated in the conversion of **4f–h** and **4k** to **5f–h** and **5k**, the isopropoxy group of the product is readily cleaved upon exposure to aqueous sodium hydroxide to reveal the terminal alkyne.

Keywords: homogeneous catalysis · diastereoselectivity · propargylation · ruthenium · transfer hydrogenation

Introduction

The propargylation of carbonyl compounds represents a subset of C–C bond-forming reactions that have found broad use in the construction of polyketide natural products.[1,2] Most methods for enantioselective carbonyl propargylation promote formation of the parent α-unsubstituted homopropargylic alcohols. In this capacity, allenylboron,[3] indium,[4] and tin[5] reagents that possess chiral modifiers at the metal center have proven effective. Beyond stoichiometric chiral reagents, catalytic enantioselective additions of achiral allenyltin[6] and allenylsilicon[7] reagents promoted by either chiral Lewis acidic or chiral Lewis basic catalysts have been developed. Similarly, chiral copper catalysts promote enantioselective aldehyde propargylation employing allenylboron and propargylboron reagents.[8] More recently, chiral hydrogen-bond donors and Brønsted acids have been found to catalyze the asymmetric addition of allenylboron reagents to aldehydes to form homopropargyl alcohols.[9] Finally, catalytic enantioselective Nozaki–Hiyama propargylations have been described (Figure 1).[10]

Less attention has been devoted to the development of diastereo- and enantioselective propargylation protocols that generate (α-methyl)homopropargyl alcohols, despite their importance vis-á-vis polypropionate construction (Figure 1).[11] Typically, allenylstannanes,[12] allenylsilanes,[13] and allenylboronates[14] reagents are used as propargyl donors to form (α-methyl)homopropargylic alcohols. Although such reagents promote diastereo- and enantioselective propargylation, their syntheses are lengthy and require successive use of multiple stoichiometric organometallic reagents. The research group of Marshall has developed a more desirable protocol wherein enantiomerically enriched propargyl mesylates are reductively coupled to aldehydes through generation of either transient allenylzinc[15] or transient allenylindium[16] species. Although their protocol circumvents the need for isolation of discrete allenylmetal species, the reactions employ superstoichiometric quantities of a pyrophoric metallic reagent ($ZnEt_2$), the propargyl mesy-

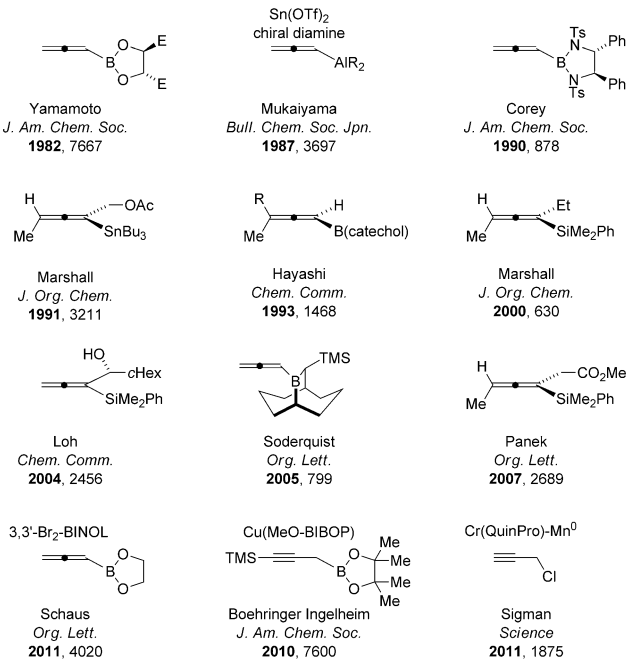

Figure 1. Selected protocols for enantioselective carbonyl propargylation.

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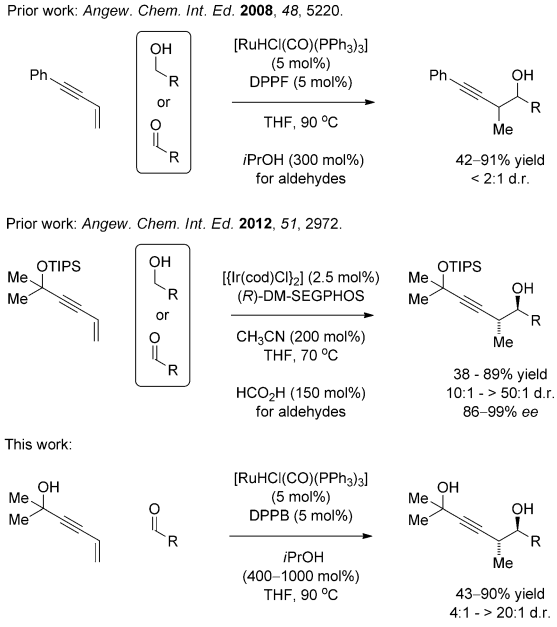
late requires several steps to prepare, and the levels of diastereoselectivity are highly variable.

In the course of developing C–C bond-forming hydrogenations and transfer hydrogenations,[17] we discovered a fundamentally new approach to the synthesis of (α-methyl)homopropargyl alcohols based on the redox-triggered C–C coupling of alcohols and 1,3-enynes by transfer hydrogenation.[18] These results were surprising, as rhodium- and nickel-catalyzed enyne–carbonyl reductive couplings provide products of dienylation.[19–20] In an initial study employing a ruthenium catalyst, the essential reactivity was established, however, the desired (α-methyl)homopropargyl alcohols were not formed stereoselectively.[18a] Later, using an iridium catalyst modified by either (*R*)-SEGPHOS or (*R*)-DM-SEGPHOS, highly *anti*-diastereo- and enantioselective (α-methyl)propargylation was achieved using a sterically demanding enyne substituted by the isopropoxy silyl ether, (TIPSO)Me_2C (TIPS = triisopropylsilyl).[18b] Herein, we report that ruthenium-catalyzed transfer hydrogenation of the unprotected isopropoxy enyne **1b** in the presence of aldehydes **3a–3l** results in reductive coupling to form (α-methyl)homopropargyl alcohols **4a–4l** with good to excellent levels of *anti*-diastereoselectivity, and that the hydroxy moiety of enyne **1b** is itself required to enforce high levels of *anti*-diastereoselectivity (Scheme 1).

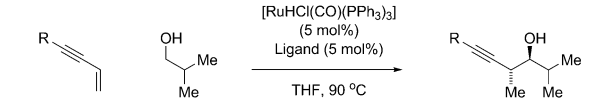


Scheme 1. Ruthenium- and iridium-catalyzed α-(methyl)propargylations based on the redox-triggered C–C coupling of alcohols and 1,3-enynes by transfer hydrogenation. cod = 1,5-cyclooctadiene, DM-SEGPHOS = 5,5′-bis[di(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole, DPPB = 1,4-bis(diphenylphosphino)butane, DPPF = 1,1′-bis(diphenylphosphino)ferrocene.

Results and Discussion

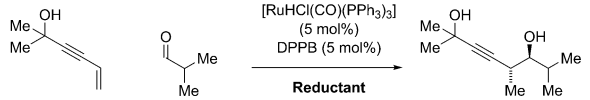
Our initial studies began with the ruthenium-catalyzed C–C coupling of the phenyl-substituted enyne **1a** and isobutyl alcohol **2g** under our previously reported reaction conditions,[18a] which led to the isolation of the homopropargylic alcohol **4g**-Ph in moderate yield and with 7:1 *anti*-diastereoselectivity (Table 1, entry 1). Changing the ligand from DPPF to DPPB led to an increase in the yield of isolated **4g**-Ph with similar levels of *anti*-diastereoselectivity (Table 1, entry 2).

Table 1. Defining structure-selectivity relationships in the ruthenium-catalyzed C–C coupling of enynes **1** to isobutyl alcohol **2g** and isobutyraldehyde **3g**.



1a–1d **2g** **4g**, R

Entry	**1**, R	Ligand	Yield [%]	d.r.
1[a]	**1a**, Ph	DPPF	56	7:1
2[a]	**1a**, Ph	DPPB	84	6:1
3[a]	**1b**, $C(Me)_2OH$	DPPB	< 1	–
⇨ **4**[b]	**1b, $C(Me)_2OH$**	**DPPB**	**40**	**> 20:1**
5[a]	**1c**, $C(Me)_2OMe$	DPPB	75	2:1
6[b]	**1d**, CH_2NHTs	DPPB	30	2:1



1b **3g** **4g**

Entry	Reductant [mol%]	Time [h]	Yield [%]	d.r.
7[c]	HCO_2H (120)	16	10	> 20:1
8[c]	HCO_2H (300)	16	18	> 20:1
9[c]	HCO_2H (500)	16	6	> 20:1
10[c]	*i*PrOH (120)	16	8	> 20:1
11[c]	*i*PrOH (300)	16	21	> 20:1
12[c]	*i*PrOH (300)	48	40	> 20:1
13[c]	*i*PrOH (500)	48	46	> 20:1
14[c]	*i*PrOH (1000)	48	63	> 20:1
⇨ **15**[d]	***i*PrOH (500)**	**48**	**73**	**> 20:1**

[a] **1a** or **1c** (200 mol%), **2g** (100 mol%). [b] **1b** or **1d** (100 mol%), **2g** (200 mol%). [c] **1b** (100 mol%), **3g** (300 mol%). [d] **1b** (200 mol%), **3g** (100 mol%), 100 °C

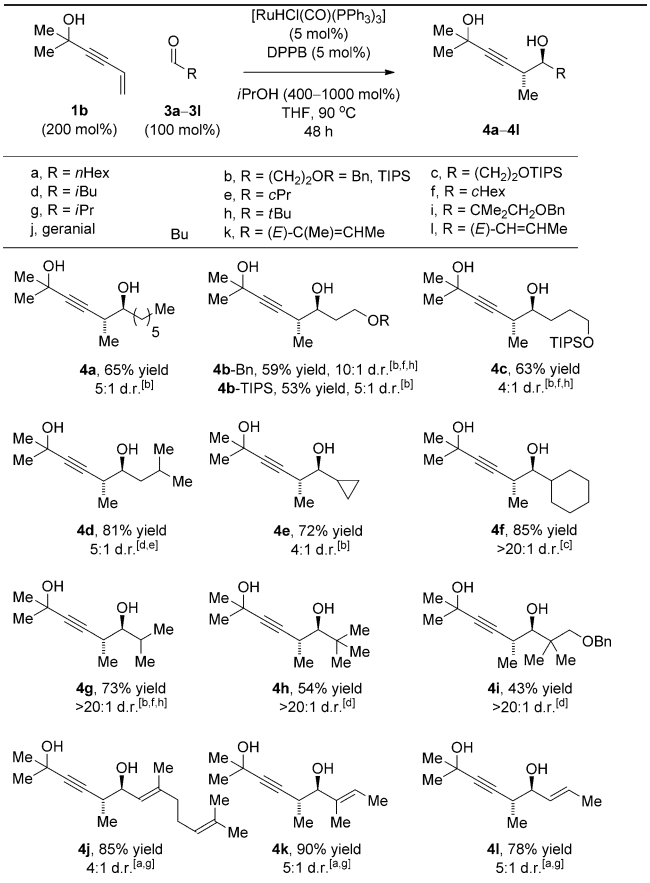
Whereas the phenyl-substituted enyne **1a** displayed good reactivity, enyne **1b** was deemed more desirable, as the isopropoxy group is subject to removal to reveal the terminal alkene, and dimethyl propargyl alcohol is one of the least expensive alkynes commercially available (47 USD/Kg).[21] However, upon use of enyne **1b** under the aforementioned reaction conditions employing isobutyl alcohol **2g** as the limiting reagent, conversion to the desired homopropargylic alcohol **4g**-$C(Me)_2OH$ was not observed (Table 1, entry 3). In contrast, upon use of enyne **1b** as the limiting reagent in the presence of excess isobutyl alcohol **2g** (200 mol%), the homopropargylic alcohol **4g**-$C(Me)_2OH$ was isolated in moderate yield as a single diastereomer (Table 1, entry 4). Notably, although the corresponding methyl ether enyne **1c** displayed excellent reactivity, leading to the isolation of homopropargylic alcohol **4g**-$C(Me)_2OMe$ in 75% yield, diastereoselectivity was poor (Table 1, entry 5).[22] Using the *N*-tosyl substituted enyne **1d**, the homopropargylic alcohol **3g**-CH_2NHTs is formed with poor diastereoselectivity (Table 1,

entry 6). These results suggest the free hydroxy moiety of enyne **1b** is essential for achieving high levels of *anti*-diastereoselectivity.

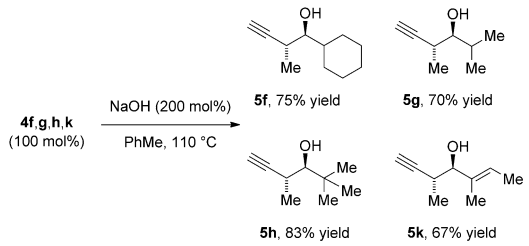
Despite extensive variation of reaction parameters, the yield of the isolated homopropargylic alcohol **4g**-$C(Me)_2OH$ could not be improved. Hence, related reductive couplings of enyne **1b** to isobutyraldehyde **3g** were explored. Although initial attempts at the reductive coupling of enyne **1b** to isobutyraldehyde **3g** mediated by formic acid were disappointing (Table 1, entries 7–9), the use of excess isopropanol as the terminal reductant over longer reaction times ultimately provided the homopropargylic alcohol **4g**-$C(Me)_2OH$ in 63% yield as a single *anti*-diastereomer (Table 1, entries 10–14). Finally, using aldehyde **3g** as the limiting reagent, in combination with an excess of enyne **1b** (200 mol%) and isopropanol (500 mol%) at 100°C, the desired homopropargylic alcohol **4f**-$C(Me)_2OH$ is generated in 73% yield as a single *anti*-diastereomer (Table 1, entry 15).

Withstanding minor variations in isopropanol loading to further optimize the yield of isolated product, the optimal reaction conditions identified for the propargylation of aldehyde **3g** were applied to aldehydes **3a–3l** (Table 2). Linear aliphatic aldehydes **3a–3c**, aldehydes with branching at the β-position, **3d**, and aldehydes with branching at the α-position, **3e–3i**, are converted into homopropargyl alcohols **4a–4i**, which were isolated in modest to good yields. In general, the degree of *anti*-diastereoselectivity increased with increasing steric demand at the position adjacent to the carbonyl moiety of the aldehyde. For example, α-branched aldehydes **3f–3i** provides homopropargyl alcohols **4f–4i** as single diastereomers. α,β-Unsaturated aldehydes **3j–3l** also undergo *anti*-diastereoselective propargylation to deliver adducts **4j–4l**. Under these conditions, the propargylation of aryl aldehydes is unselective albeit high yielding. Propargylation products **4f–h** and **4k** are directly converted into the corresponding terminal alkynes **5f–h** and **5k** upon exposure to NaOH in refluxing toluene (Scheme 2).

Table 2. Ruthenium-catalyzed reductive coupling of enyne **1b** to aldehydes **3a–3l** to form *anti*-propargylation products **4a–4l**.

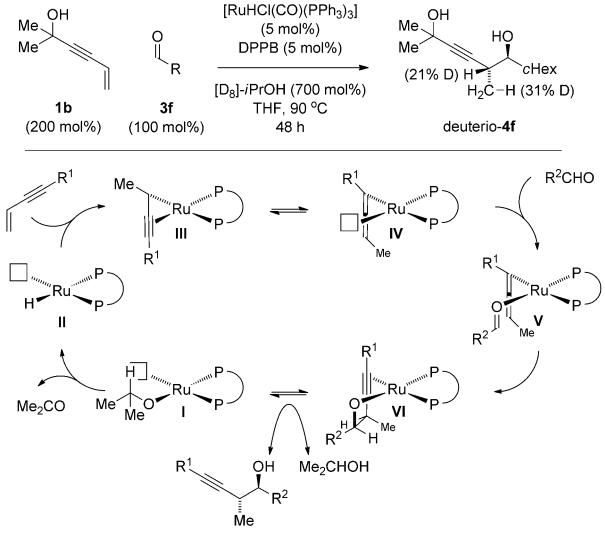


[a] *i*PrOH (400 mol%). [b] *i*PrOH (500 mol%). [c] *i*PrOH (700 mol%). [d] *i*PrOH (1000 mol%). [e] **1b** (100 mol%), **3d** (300 mol%), [f] 100°C. [g] 24 h. [h] $[RuHCl(CO)(PPh_3)_3]$ (7 mol%), DPPB (7 mol%).



Scheme 2. Deprotection of adducts **4f–h** and **4k** to give terminal alkynes **5f–h** and **5k**.

A catalytic mechanism for the propargylation has been formulated and challenged through isotopic labeling (Scheme 3). Specifically, reaction of isopropoxy-substituted enyne **1b** with cyclohexane carboxaldehyde **3f** employing $[D_8]$-isopropanol as the terminal reductant delivers deuterio-**4f**. The distribution of deuterium in deuterio-**4f** suggests



Scheme 3. Deuterium-labeling studies and proposed catalytic mechanism (apical ligands omitted for clarity). See the Supporting Information for images of ^1H and ^2H NMR spectra.

that enyne hydrometalation is reversible and not regioselective, that is, the vinyl moiety of enyne **1b** hydrometallates at both the internal and terminal positions. Reversible hydrometalation in advance of carbonyl addition suggests the latter process is slow, possibly even turnover limiting, and may explain why corresponding reactions performed from the alcohol oxidation level display lower conversions with essentially identical selectivities. The conversion of intermediate **V** to intermediate **VI** serves as a stereochemical model accounting for the observed *anti*-diastereoselectivity. The roughly perpendicular orientation of the allenylruthenium moiety finds precedent in a related η^1-allenylmetal complexes.[23]

Conclusion

In conclusion, ruthenium-catalyzed transfer hydrogenation of isopropoxy-substituted enyne **1b** in the presence of aldehydes **3a**–**3l** promotes reductive C–C coupling to provide products of propargylation **4a**–**4l** with good to complete levels of *anti*-diastereoselectivity. The unprotected hydroxy group of the the enyne isopropoxy substituent is required to enforce high levels of *anti*-diastereoselectivity. However, several limitations in scope remain. Although the present ruthenium-based catalyst system displays good levels of *anti*-diastereoselectivity in propargylations of aliphatic aldehydes and enals, corresponding additions to aryl aldehydes remain unselective. Additionally, poor conversion is observed in reactions conducted from the alcohol oxidation level, although essentially identical levels of selectivity are observed. Studies are currently underway to address these limitations and will be reported in due course.

Experimental Section

General procedure for the ruthenium-catalyzed propargylation: To an oven-dried pressure tube sealed with a septum under an argon atmosphere was added $[RuHCl(CO)(PPh_3)_3]$ (14.3 mg, 0.015 mmol, 5 mol%) and DPPB (6.4 mg, 0.015 mmol, 5 mol%). The pressure tube was purged with argon and THF (0.3 mL, 1.0 M) was added, followed by enyne **1b** (72 μL, 0.6 mmol, 200 mol%), aldehyde (0.3 mmol, 100 mol%), and isopropanol (115 μL, 1.5 mmol, 500 mol%). The septum was replaced with a screw cap and the reaction vessel was placed in 90 °C oil bath. After 48 h, the reaction vessel was removed from the oil bath and was allowed to cool to room temperature. The volatiles were removed and the residue was purified by silica-gel flash chromatography.

Acknowledgements

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