Homogeneous Catalysis

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Divergent Regioselectivity in the Synthesis of Trisubstituted Allylic Alcohols by Nickel- and Ruthenium-Catalyzed Alkyne Hydrohydroxymethylation with Formaldehyde**

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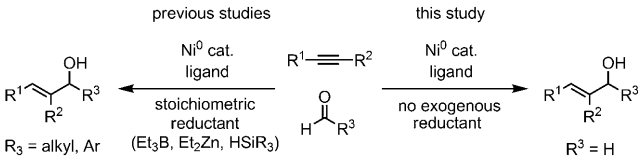
Dedicated to Professor Barry M. Trost on the occasion of his 70th birthday.

Trisubstituted allylic alcohols[1,2] are ubiquitous in natural products and are readily converted into diverse chiral building blocks by enantioselective epoxidation,[2a,b] cyclopropanation,[2a,c] hydrogenation,[2a,d] and allylic substitution.[2a,e] Among methods for the regio- and stereoselective synthesis of trisubstituted primary allylic alcohols, alkyne hydrometalation or carbometalation mediated by stoichiometric organometallic reagents has found broad use.[3–7] For example, in seminal studies by Corey et al. (1967),[4c] the regio- and stereoselective hydroalumination of propargyl alcohols was used to construct vinyl iodides, which were converted into trisubstituted allylic alcohols upon exposure to lithium dialkyl cuprates. Similarly, alkyne hydromagnesiation and carbomagnesiation with Grignard reagents delivered trisubstituted allylic alcohols regio- and stereoselectively.[6,7]

Although alkyne functionalization through hydrometalation and carbometalation remains at the forefront of research,[3–7] the development of equivalent transformations that avoid stoichiometric metal reagents is clearly desirable. Conversely, whereas related nickel-catalyzed alkyne–carbonyl reductive couplings can be highly regioselective, such processes require terminal reductants that are metallic, pyrophoric, or highly mass intensive (e.g. ZnR_2, BEt_3, $HSiR_3$; Scheme 1),[8–10] although nickel-catalyzed alcohol-mediated alkyne–enone couplings were recently disclosed.[11]



Scheme 1. Previously developed approaches requiring a stoichiometric amount of a reducing agent, and the approach investigated in the current study without exogenous reductants.

Hence, the discovery of alkyne–carbonyl (or alkyne–imine) reductive couplings under hydrogenation conditions is significant.[12,13] More recently, an alkyne–carbonyl reductive coupling by ruthenium-catalyzed transfer hydrogenation was developed; however, regioselectivity in such processes remains largely unexplored.[14,15] Herein, we report the regio- and stereoselective synthesis of trisubstituted primary allylic alcohols from alkynes in the absence of stoichiometric metallic reagents. In this reaction, paraformaldehyde is used as a C_1 feedstock and, more remarkably, as a reductant under conditions of transfer hydrogenation with nickel and ruthenium catalysts, which exhibit complementary regioselectivity (Scheme 2).

In response to the lack of efficient methods for diene hydroformylation,[16] we recently developed a process for diene hydrohydroxymethylation under the conditions of ruthenium-catalyzed transfer hydrogenation using paraformaldehyde as a C1 feedstock;[17] paraformaldehyde was itself prepared from synthesis gas (via methanol). As the development of efficient catalysts for alkyne hydroformylation remains an unmet challenge,[18] we undertook the current investigation into alkyne–paraformaldehyde reductive coupling. Initial studies focused on the reductive coupling of 1-phenylpropyne (**1a**) with paraformaldehyde. We explored the nickel-catalyzed reductive coupling of **1a** with paraformaldehyde in the absence of a reducing agent.[8–10] Remarkably, conditions were identified under which the nickel catalyst produced adduct **3a** as a single regio- and stereoisomer, as determined by ^{1}H NMR spectroscopic analysis. Previously determined conditions for ruthenium-catalyzed alkyne–carbonyl coupling with higher aldehydes[14] were further evaluated and meticulously adapted for the use of paraformaldehyde to enable formation of the isomeric primary trisubstituted allylic alcohol **2a** in 85% yield as a single regio- and

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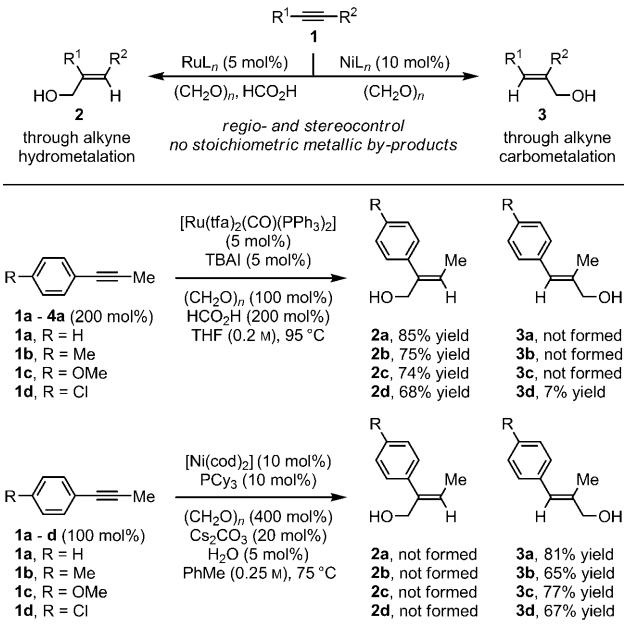
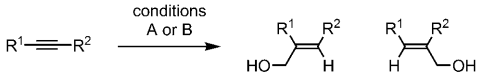


Scheme 2. Complementary regioselectivity in ruthenium- and nickel-catalyzed hydrohydroxymethylation reactions of alkynes **1a–d** with paraformaldehyde as a C_1 feedstock. Cy = cyclohexyl, TBAI = tetrabutylammonium iodide, tfa = trifluoroacetate.

Table 1: Scope of the regio- and stereoselective ruthenium- and nickel-catalyzed hydrohydroxymethylation of alkynes **1a–n**.



Entry	Cond.[a]	Alkyne	R^1	R^2	Yield [%][b] (**2**/**3**[c])
1	A	**1a**	Ph	Me	85 (≥20:1)
2	A	**1b**	*p*-MeC_6H_4	Me	75 (≥20:1)
3	A	**1c**	*p*-$MeOC_6H_4$	Me	74 (≥20:1)
4	A	**1d**	*p*-ClC_6H_4	Me	75 (10:1)
5	A	**1e**	*o*-MeC_6H_4	Me	63 (≥20:1)
6	A	**1f**	*m*-$MeOC_6H_4$	Me	78 (12:1)
7	A	**1g**	*p*-BrC_6H_4	Me	70 (9:1)
8	A	**1h**	*p*-$MeCOC_6H_4$	Me	70 (8:1)
9	A	**1i**	*p*-$EtCO_2C_6H_4$	Me	69 (9:1)
10	A	**1j**	2-thienyl	Me	76 (11:1)
11	A	**1k**	*N*-Boc-3-indoyl	Me	77 (≥20:1)
12	A	**1l**	$BnOCH_2CH_2$	Me	64 (≥20:1)
13	B	**1a**	Ph	Me	81 (1:≥20)
14	B	**1b**	*p*-MeC_6H_4	Me	65 (1:≥20)
15	B	**1c**	*p*-$MeOC_6H_4$	Me	77 (1:≥20)
16	B	**1d**	*p*-ClC_6H_4	Me	67 (1:≥20)
17	B	**1e**	*o*-MeC_6H_4	Me	52 (1:≥20)
18	B	**1f**	*m*-$MeOC_6H_4$	Me	50 (1:≥20)
19	B	**1j**	2-thienyl	Me	60 (1:≥20)
20	B	**1m**	Ph	Ph	60 (–)
21	B	**1n**	Me	*i*Pr	71 (1:2.3)

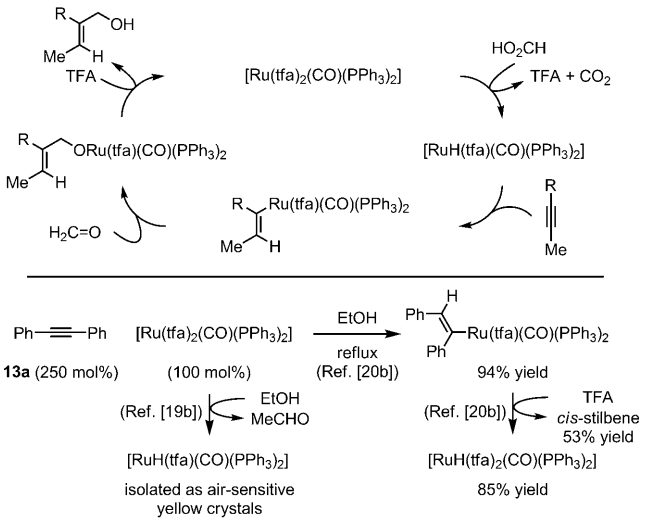
[a] Conditions A: alkyne (200 mol%), $(CH_2O)_n$ (100 mol%), [Ru(tfa)$_2$(CO)(PPh$_3$)$_2$] (5 mol%), Bu_4NI (5 mol%), HCO_2H (100 mol%), THF (0.2 M), 95 °C, 15 h. Conditions B: alkyne (100 mol%), $(CH_2O)_n$ (400 mol%), [Ni(cod)$_2$] (10 mol%), PCy_3 (10 mol%), Cs_2CO_3 (20 mol%), H_2O (5 mol%), toluene (0.25 M), 75 °C, 24 h. See the Supporting Information for further details. [b] Yield of material isolated by silica-gel chromatography. [c] Regio- and diastereoselectivity were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Bn = benzyl, Boc = *tert*-butoxycarbonyl.

stereoisomer, as determined by ^{1}H NMR spectroscopic analysis. In both processes, paraformaldehyde may serve as the electrophilic partner and the reductant. In fact, in the nickel-catalyzed process, no reductant other than paraformaldehyde is required. In the ruthenium-catalyzed process, an exogenous reductant in the form of formic acid is required to enforce complete conversion. These conditions were applicable to aryl propynes **1a–d**, which were converted into adducts **2a–d** and **3a–d** using ruthenium and nickel catalysts, respectively, with excellent partitioning of regioselectivity (Scheme 2).

To evaluate the scope of the nickel- and ruthenium-catalyzed reductive alkyne coupling with paraformaldehyde, we investigated a range of nonsymmetrical aryl–alkyl-substituted alkynes. The ruthenium catalyst tolerated both electron-donating and electron-withdrawing substituents on the aryl group (Table 1, entries 2–9); the nickel catalyst showed compatibility with methoxy and chloro substituents (Table 1, entries 15–18). Steric hindrance caused by an *ortho* methyl substituent (Table 1, entries 5 and 17) diminished the yield of the isolated product. Heteroaryl substituents, such as a 2-thienyl or an *N*-Boc-protected 3-indolyl group, were tolerated (Table 1, entries 10, 11, and 19). The ruthenium catalyst showed remarkably high regioselectivity (≥20:1) in the hydroxymethylation of a dialkyl-substituted alkyne, with the discrimination of a CH_2CH_2OBn substituent and a methyl group, whereas the nickel-catalyzed process enabled discrimination between a methyl and an isopropyl substituent (Table 1, entries 12 and 21, respectively).

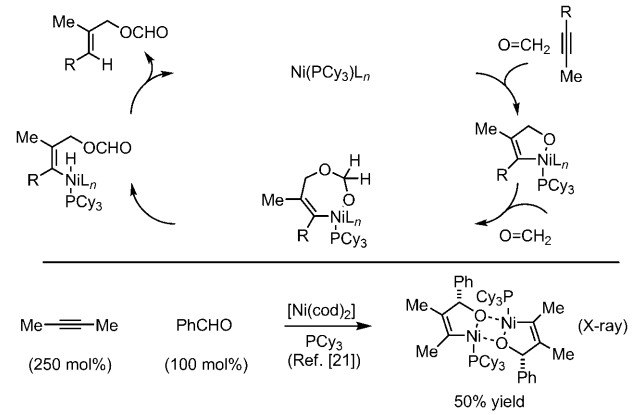
As suggested by established stoichiometric reactions, the mechanistic origins of regiodivergence with regard to the nickel- and ruthenium-catalyzed hydroxymethylation reactions appears to arise through the partitioning of hydrometalative and carbometalative (oxidative coupling) pathways.[19–21] In the case of ruthenium, the stoichiometric reaction of [Ru(tfa)$_2$(CO)(PPh$_3$)$_2$] with alcohols to generate [RuH(tfa)(CO)(PPh$_3$)$_2$] along with an aldehyde or ketone is known.[19] Furthermore, alkyne hydrometalation by [RuH(tfa)(CO)(PPh$_3$)$_2$], generated in situ from [Ru(tfa)$_2$(CO)(PPh$_3$)$_2$] and ethanol, to furnish vinyl ruthenium complexes has been established.[20] Finally, the resulting vinyl ruthenium complexes were subjected to protonolysis by trifluoroacetic acid to regenerate [Ru(tfa)$_2$(CO)(PPh$_3$)$_2$].[20b] These reactions support the feasibility of the proposed hydrometalative mechanism for the ruthenium-catalyzed alkyne hydroxymethylation mediated by formaldehyde (Scheme 3).

Similarly, in the case of nickel, the stoichiometric oxidative coupling of butyne and benzaldehyde in the presence of [Ni(cod)$_2$] and tricyclohexylphosphane delivers isolable nickeladihydrofurans, which have been characterized by single-crystal X-ray diffraction analysis.[21] At room temperature, such metallacycles engage in β-hydride elimination to furnish conjugated enones. These reactions support the feasibility of the proposed carbometalative mechanism for nickel-catalyzed alkyne hydroxymethylation mediated by formaldehyde.



Scheme 3. Proposed mechanism for ruthenium-catalyzed alkyne hydrohydroxymethylation, as supported by established stoichiometric transformations. tfa = trifluoroacetic acid.

An observation consistent with this proposal is that the products of hydroxymethylation are the formate esters, which are cleaved upon isolation (Scheme 4).



Scheme 4. Proposed catalytic mechanism for nickel-catalyzed alkyne hydrohydroxymethylation, as supported by established stoichiometric transformations. (Details on the isolation of the formate ester can be found in the Supporting Information.)

In summary, nonsymmetrical disubstituted alkynes were converted into primary trisubstituted allylic alcohols upon exposure to paraformaldehyde in the presence of ruthenium or nickel catalysts, which exhibit complementary regioselectivity and complete stereoselectivity. These procedures provide an alternative to alkyne hydroformylation, for which efficient regioselective variants do not exist. Furthermore, they serve as alternatives to established methods that rely on the use of stoichiometric amounts of organometallic reagents, and thus pave the way for more environmentally benign organic synthesis. Related reductive carbon–carbon bond-forming reactions are currently under investigation as alternatives to hydroformylation.

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