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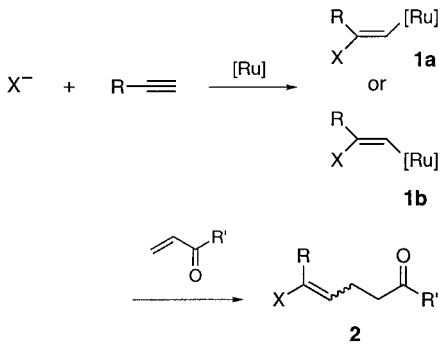
A Mechanistic Dichotomy Leading to a Ruthenium-Catalyzed *cis*-Addition for Stereoselective Formation of (*Z*)-Vinyl Bromides**

Barry M. Trost* and Anthony B. Pinkerton

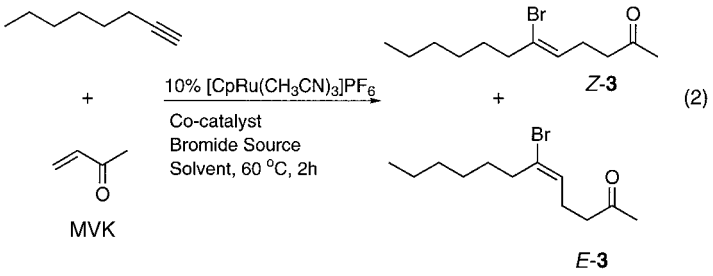
Addition reactions of alkenes and alkynes catalyzed by transition metals normally lead either to a *cis* or to a *trans* product (excluding stereorandom processes). A situation wherein both mechanistic pathways are energetically accessible with the same catalyst system has not been described. In our exploration of ruthenium-catalyzed three-component couplings, we have discovered such a mechanistic duality, which has led to the *cis*-bromoalkylation of alkynes. Vinyl bromides are extremely useful as cross-coupling partners in a variety of transition metal catalyzed processes[1] and as precursors to organolithium and related organometallic compounds. However, there are difficulties of selectivity during their preparation. Poor steroselectivity in the addition of HBr to alkynes or in the bromination–dehydrobromination processes in the case of alkenes limits the utility of these classic protocols. Olefination reactions[2] and stoichiometric bromination of carbon–metal bonds[3, 4] are the main pathways for the more selective preparation of vinyl bromides. More efficient methods, notably wherein such entities are created by simple additions,[5] become an important objective. Our earlier work demonstrated the viability of (*E*)-vinyl chloride formation via a three-component coupling,[6] presumably through a *trans*-chlororuthenation followed by olefin insertion into the metal–halide bond. The availability of a nonhalogen-bearing ruthenium complex as a useful catalyst induced us to consider the development of a stereoselective synthesis of vinyl bromides. This led to a geometrically complementary process compared to our earlier study with chloride wherein tri- and tetra-substituted (*Z*)-vinyl bromides are available by a three-component coupling.

Initial experiments using $[CpRu(cod)Cl]$[7] (Cp = cyclopentadienyl, cod = cycloocta-1,4-diene) gave competitive vinyl chloride formation (the chloride source is the catalyst) even at high concentration of bromide salts [Eq. (1)]. The



(1)

development of a bromo-alkylation reaction led us to turn to a halide-free ruthenium complex, $[CpRu(CH_3CN)_3]PF_6$,[8] as a potential catalyst [Eq. (2), MVK = methyl vinyl ketone].



(2)

Table 1 summarizes the initial studies for optimizing cocatalyst concentration, bromide source, and solvent for these reactions. Improved yields were achieved upon switching from dimethylformamide (DMF) to an acetone/DMF mixture as solvent (entry 3 versus 2). In this mixture a more soluble bromide source, such as tetramethylammonium bromide instead of ammonium bromide, gave more of the (*Z*)-product, but in lower yields (entry 4 versus 3). In acetone alone the (*Z*)-product was formed with very high selectivity, albeit in even lower yields (entries 5 and 6). Adding DMF to acetone increased the yield but lowered the geometrical selectivity drastically (entries 7 and 8). Switching to a bromide source fully soluble in acetone, lithium bromide, gave high yields as well as high selectivities (entry 9); further, only 1.5 equivalents of the salt were necessary (entry 10). Entries 1, 11, and 12 show the vital nature of the co-catalyst for high yields as well as higher selectivities, an effect that has been observed previously.[6]

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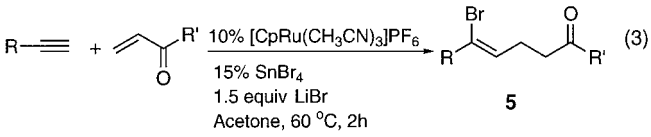
Table 1. Selected optimization experiments for (*Z*)-vinyl bromide formation [Eq. (2)].[a]

Entry	Co-catalyst (mol%)	Bromide source (equiv)	Solvent	Yield of **3** [%]	*Z*/*E*[b]
1	$SnBr_2$ (15)	NH_4Br (3)	DMF	13	1/3.3
2	$SnBr_4$ (15)	NH_4Br (3)	DMF	54	1/2.1
3	$SnBr_4$ (15)	NH_4Br (3)	acetone/DMF 1/1	71	1/2.3
4	$SnBr_4$ (15)	$N(CH_3)_4Br$ (3)	acetone/DMF 1/1	54	4.0/1
5	$SnBr_4$ (15)	$N(CH_3)_4Br$ (3)	acetone	35	15/1
6	$SnBr_4$ (15)	NH_4Br (3)	acetone	40	10/1
7	$SnBr_4$ (15)	NH_4Br (3)	acetone/DMF 2/1	62	1/2.2
8	$SnBr_4$ (15)	NH_4Br (3)	acetone/DMF 4/1	56	1.4/1
9	$SnBr_4$ (15)	LiBr (3)	acetone	81	4.0/1
10	$SnBr_4$ (15)	LiBr (1.5)	acetone	88	6.6/1
11	$SnBr_4$ (5)	LiBr (1.5)	acetone	54	6.7/1
12	none	LiBr (1.5)	acetone	22	4.2/1

[a] All reactions run according to Equation (2) with a 1:1.5 ratio of alkyne to MVK and a concentration of 0.5 M in alkyne. [b] Determined by ^{1}H NMR spectroscopy or GC.

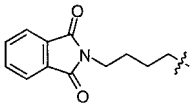
NOE experiments established the geometry of the isomers, and the overall structures were confirmed by spectral data.[9] The products were found not to isomerize under the reaction conditions.

With the optimized set of conditions (Table 1, entry 10) a range of substrates was examined. The reactions were run according to Equation (3) and the results are summarized in Table 2. There is excellent chemoselectivity, and the alkyne can be a nitrile (entries 2 and 6), an alcohol, including propargylic alcohols (entries 3, 4, 8, and 9), a phthalimide (entry 5) and an ester (entry 7). Other enones than MVK are also effective as coupling partners (entries 6–8).



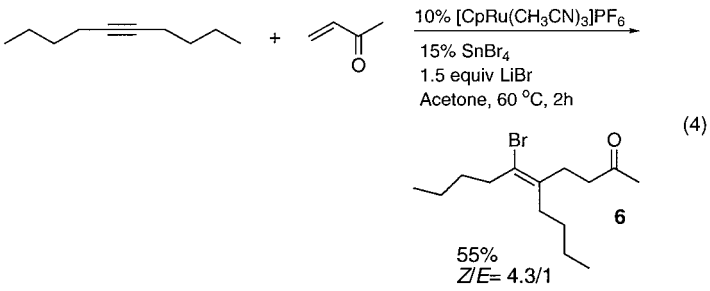
(3)

Table 2. Examples of ruthenium-catalyzed (*Z*)-vinyl bromide formation.[a]

Entry	R–	R′	Yield of **5** [%]	*Z*/*E*[b]
1	$CH_3(CH_2)_5$–	–CH_3	88	6.6/1
2	$NC(CH_2)_3$–	–CH_3	90	3.3/1
3	$CH_3CH(OH)CH_2$–	–CH_3	82	6.0/1
4	$CH_3CH(OH)$–	–CH_3	64	11.0/1
5		–CH_3	67	3.6/1
6	$NC(CH_2)_3$–		77	4.7/1
7	$AcO(CH_2)_4$–		78	5.0/1
8	$CH_3CH(OH)CH_2$–		81	5.8/1
9	$HO(CH_2)_9$–	–CH_3	92	5.1/1

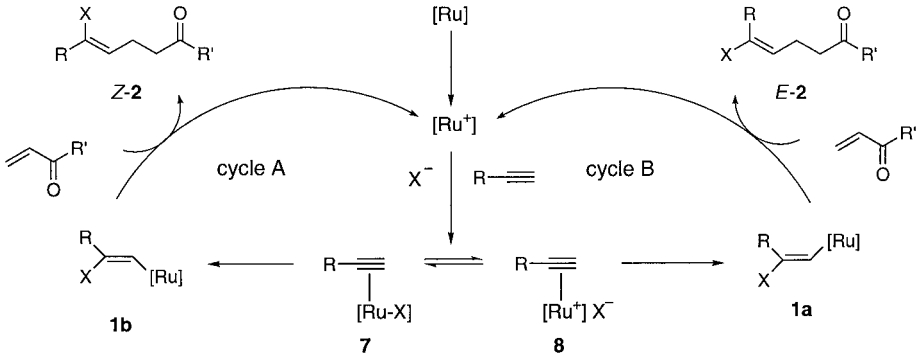
[a] All reactions run according to Equation (3) with a 1:1.5 ratio of alkyne (0.5 M) to the vinyl ketone. [b] Determined by ^{1}H NMR spectroscopy or GC.

As shown in Equation (4), disubstituted alkynes also participate, giving stereospecifically a tetra-substituted vinyl bromide. However, regiochemical issues arise when such alkynes are not symmetrically substituted.



(4)

A hypothetical mechanism is shown in Scheme 1. Initial formation of a cationic ruthenium species leads to coordination by the alkyne and the halide either covalently attached (**7**) or as an ion pair (**8**). The former would lead to a *cis*-haloruthenation (cycle A),[10] giving rise to intermediate **1b**, while the latter would give a *trans*-haloruthenation[11] (cycle B) to **1a**. Insertion of the enone would then lead to the *Z* or *E* isomer of **2** from **1b** or **1a**, respectively. Three observations support this mechanism. First, use of a less polar solvent, acetone rather than DMF, should favor the neutral **7** over the charged species **8**, and consequently lead to more of the (*Z*)-product stemming from a *cis*-bromoruthenation. Second, increasing bromide ion concentration, by switching to more soluble bromide sources such as tetramethylammonium or lithium bromide, or simply adding more of the bromide source, shifts the equilibrium between **7** and **8** towards **7** and favors cycle A, to give more (*Z*)-product, as observed. Finally, substrates that contain good coordinating groups for ruthenium, such as nitriles (Table 2, entry 2), lead to more of the *E* product—in agreement with the fact that in this case the ruthenium center is more coordinatively saturated and thus disfavors the formation of **7**.



Scheme 1. Proposed mechanism for the ruthenium-catalyzed, stereoselective synthesis of vinyl bromides. Selection of cycle A or B is dependent upon the nature of the solvent and the concentration of halide in solution.

The role of the co-catalyst is thought to be both as a Lewis acid, to activate the enone, as well as a stabilizing entity to prevent deactivation of the ruthenium catalyst. However, the exact nature of its effect is unclear at this point. It should be noted that the ruthenium enolate, formed initially by addition of either **1a** or **1b** to the vinyl ketone, does not undergo β-hydrogen elimination to compete with protonation.

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In conclusion, this method represents a novel, efficient and selective synthesis of (*Z*)-vinyl bromides through a simple addition.[12] The ability to obtain both *trans*- and *cis*-haloalkylation of alkynes is synthetically useful as well as mechanistically intriguing. Current work is focused on further elucidation of the mechanism and expansion of the scope of the reaction.

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Carbocyclic Ring Closure of Unsaturated S-, Se-, and C-Aryl Glycosides

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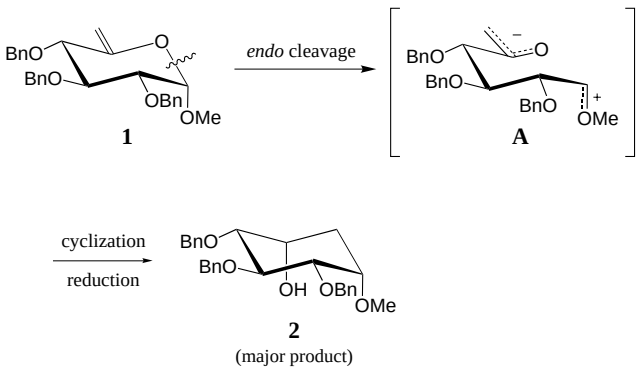
The glycoside-to-carbocycle transformation[1] provides an attractive route for the synthesis of functionalized carbocycle derivatives from readily available sugar precursors. Usually these transformations rely on the cleavage of the glycosidic acetal functionality to liberate the reactive carbonyl group that undergoes carbocyclization.[1b] The disadvantage of these approaches is the loss of the aglycon. Furthermore it is impossible to apply this method to sugars bearing unusual aglycons, particularly C-glycosides, where no acetal functionality is present. Herein, we report the first direct transformation of hex-5-eno S-, Se-, and C-glycosides into carbocycles with retention of the aglycon.

We reported that hex-5-enopyranosides such as **1** undergo reductive rearrangement with triisobutylaluminum (TIBAL) to afford highly substituted cyclohexane derivatives such as **2**,[2] where both the aglycon moiety and anomeric configuration are retained[3] (Scheme 1). The key step in this transformation is the *endo* cleavage of the glycosidic bond to give a stabilized carbocationic intermediate **A**, which then recyclizes and undergoes reduction to afford the observed major product **2**.



Scheme 1. The key step of the TIBAL-promoted rearrangement: *endo*-glycosidic cleavage (the detailed mechanism of this process is not known). Bn = benzyl.

We assumed that it should be possible to replace the methoxy group by other electron-donating groups that would stabilize the analogous carbocationic intermediate **B** and therefore promote *endo* cleavage (Scheme 2). However, when the known C-glucoside **3**[4] was treated with five equivalents of TIBAL at 50 °C, we failed to observe the desired carbocycle

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