

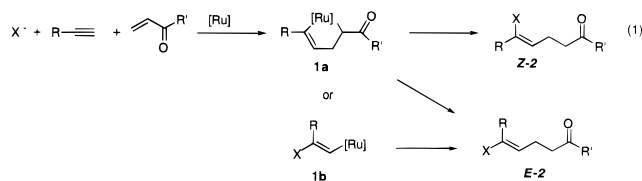
A Ruthenium-Catalyzed Three-Component Coupling to Form *E*-Vinyl Chlorides

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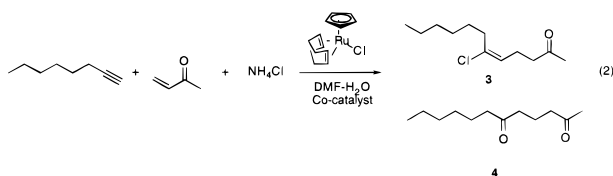
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The efficient formation of functionalized alkenes in a stereo-selective fashion is an important continuing goal in organic synthesis. Olefination reactions form the core of most of the methods wherein such functional groups are created simultaneously with C–C bond formation.¹ A rarer strategy involves hydrometalation of functionalized alkynes followed by cross-coupling.² We have been pursuing the invention of more atom economical³ strategies whereby such functional groups are produced by simpler additions using transition-metal catalysis.⁴ Equation 1 illustrates the concept. While our previous studies of



the ruthenium-catalyzed Alder ene reaction suggested a ruthenacycle intermediate,⁵ ruthenium-promoted additions of carboxylic acids to alkynes have been suggested to proceed via a *trans* addition to form species such as **1b**.⁶ In the former case, capture by X⁻ could lead to either *Z*-2 or *E*-2; whereas, in the latter case, *E*-2 is the expected product. In this paper, we report the realization of this reaction where X⁻ is chloride anion.⁷

We chose to examine the formation of vinyl chlorides since, during the course of an ancillary study,⁸ we detected small amounts of such products. Using the reaction of eq 2 as our test



(1) For some illustrations, see: Pine, S. H. *Org. React.* **1994**, *43*, 1; Ager, D. J. *Org. React.* **1990**, *38*, 1; Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

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(6) For a *trans* chloroalkylation of activated alkynes using palladium catalysis, see: Wang, Z.; Lu, X. *Chem. Commun.* **1996**, 535; *J. Org. Chem.* **1996**, *61*, 2254. On the other hand, a *cis* chloropalladation has been claimed, see: Dietl, H.; Reinheimer, H.; Moffatt, J.; Maitlis, P. M. *J. Am. Chem. Soc.* **1970**, *92*, 2276. Also, see: Kaneda, K.; Uchiyama, T.; Fujiwara, Y.; Imanaka, T.; Teranishi, S. *J. Org. Chem.* **1979**, *44*, 55. After submission of our paper, a Rh-catalyzed *cis* chloroalkoxy-carbonylation of alkynes has been reported, see Hua, R.; Shimada, S.; Tanaka, M. *J. Am. Chem. Soc.* **1998**, *120*, 12365.

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case, the results are summarized in Table 1. A polar medium, such as DMF–water, normally is required to generate an active catalyst; thus, this solvent system was adopted. The chloride source, a metal chloride versus ammonium chloride, had no effect; therefore, we adopted ammonium chloride. An examination of Table 1 reveals, not surprisingly, that reduction of the amount of water decreased the amount of diketone **4** (entries 1–5 versus 6–10). The reaction was too sluggish in the absence of water using ammonium chloride because of solubility problems. Increasing the amount of chloride suppressed diketone formation (entries 4–6). Significantly, the choice of cocatalyst also influenced the ratio of **3**:**4** (entry 6 versus 7). Increasing substrate concentration and lowering the temperature from 100 to 60 °C led to our initial general conditions shown in entry 10 (method A). Replacing ammonium chloride by tetramethylammonium chloride and using just DMF (method B) led to a further improvement such that only **3** was observed. In the absence of a cocatalyst, very low yields were obtained (entry 12).

Spectral data confirm the structure of the vinyl chloride as depicted.⁹ GC and ¹H NMR spectroscopy indicate an *E*:*Z* ratio of 6.0–6.5, depending upon reaction conditions for method A, which increased to >15:1 for method B. NOE experiments establish the geometry of the major isomer as *E*. Control experiments indicate that equilibration of alkene geometry does not occur under the reaction conditions.

With a good experimental protocol in hand, a range of substrates was explored according to eq 3 and summarized in

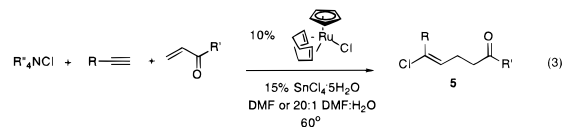


Table 2. It is obvious that excellent chemoselectivity is observed wherein cyano (entries 3, 4, 14, 15), phthalidimido (entry 5), keto (entry 6), hydroxy (entries 9–13), and ester (entry 7) all are tolerated. Cyclohexylvinyl ketone (entries 14–16) also participates equally well. Method B generally gives better yields and *E*/*Z* selectivities. Whereas significant increases in the *E*/*Z* ratio occurred in entries 2 and 4, this effect was attenuated, nevertheless still present, with alkynes bearing hydroxyl groups proximal to the triple bond (entries 11 and 13).

The mechanism of the reaction is not established but does conform to the working hypotheses outlined in eq 1.⁷ The ruthenacycle intermediate would require direct ligand attack by chloride as the major pathway to rationalize product formation. The general unfavorability of S_N2 displacements at vinylic carbon make this suggestion less palatable. A *trans* addition of chloride and ruthenium, followed by capturing the C–Ru bond faster than protonation, then accounts for the major product. This suggestion is consistent with the overall result observed in the ruthenium-catalyzed addition of carboxylic acids to alkynes; however, the C–Ru bond of the proposed intermediate has not been intercepted to form a C–C bond. Consistent with this mechanism is the observation that switching from ammonium chloride to tetramethylammonium chloride led to increased *E*/*Z* ratios. The increased solubility of the latter salt increased the concentration of free chloride ion in solution, thereby favoring external chloride attack. Thus, the use of tetramethylammonium chloride always led to enhanced *E*-selectivity, sometimes dramatically. Similarly, if the alkyne substrate bears a functional group that coordinates to ruthenium, like hydroxyl, this coordination competes with


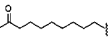



(9) All new compounds have been characterized spectroscopically, and elemental composition has been established by combustion analysis or high resolution mass spectroscopy.

Table 1. Selected Optimization Experiments for Equation 2^a

entry	[Ru]	cocatalyst (mol %)	NR ₄ Cl (eq)	DMF-H ₂ O ratio	[Alkyne] (M)	temp °C	isol. yield 3	isol. yield 4
1	5.0	InCl ₃ (15)	1.1 (R = H)	9:1	0.25	100	14	24
2	5.0	AlCl ₃ ·6H ₂ O(15)	1.1 (R = H)	9:1	0.25	100	34	19
3	10.0	AlCl ₃ ·6H ₂ O(15)	1.1 (R = H)	9:1	0.25	100	25	42
4	10.0	AlCl ₃ ·6H ₂ O(30)	1.1 (R = H)	9:1	0.25	100	39	52
5	10.0	AlCl ₃ ·6H ₂ O(15)	2.2 (R = H)	9:1	0.25	100	44	28
6	10.0	AlCl ₃ ·6H ₂ O(15)	3.3 (R = H)	20:1	0.25	100	45	16
7	10.0	SnCl ₄ ·5H ₂ O(15)	3.3 (R = H)	20:1	0.25	100	48	2
8	10.0	SnCl ₄ ·5H ₂ O(15)	3.3 (R = H)	20:1	0.50	100	56	4
9	10.0	SnCl ₄ ·5H ₂ O(15)	3.3 (R = H)	20:1	1.00	100	45 ^b	17
10	10.0	SnCl ₄ ·5H ₂ O(15)	3.3 (R = H)	20:1	0.50	60	72 ^c	5
11	10.0	SnCl ₄ ·5H ₂ O(15)	3.0 (R = CH ₃)	NA ^d	0.50	60	72	trace
12	10.0	none	3.3 (R = H)	9:1	0.25	100	11	10

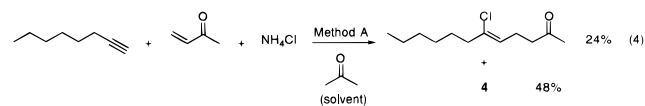
^a All reactions were run according to eq 2 with 1:2 ratio of alkyne to MVK. ^b *E:Z* ratio of 6.2. ^c *E:Z* ratio of 6.0. ^d NA = not applicable since only was DMF employed.

Table 2. Typical Examples of Ruthenium Catalyzed Alkyne Chloroalkylation^a

Entry	R	R'	Method ^b	Yield(%)	<i>E/Z</i>
1	<i>n</i> -C ₆ H ₁₃	CH ₃	A	72 5a	6.0:1
2	<i>n</i> -C ₆ H ₁₃	CH ₃	B	72 5a	>15:1
3	NC(CH ₂) ₃	CH ₃	A	83 5b	8.8:1
4	NC(CH ₂) ₃	CH ₃	B	80 5b	12:1
5		CH ₃	A	62 5c	5.7:1
6		CH ₃	A	60 5d	6.2:1
7	AcO(CH ₂) ₄	CH ₃	A	75 5e	7.0:1
8	AcO(CH ₂) ₄	CH ₃	B	77 5e	>15:1
9	HO(CH ₂) ₅	CH ₃	A	61 5f	6.4:1
10	CH ₃ CH(OH)	CH ₃	A	72 5g	4.1:1
11	CH ₃ CH(OH)	CH ₃	B	78 5g	5.3:1
12	CH ₃ CH(OH)CH ₂	CH ₃	A	74 5h	7.2:1
13	CH ₃ CH(OH)CH ₂	CH ₃	B	80 5h	8.5:1
14	<i>n</i> -C ₆ H ₁₃		A	74 5i	6.1:1
15	NC(CH ₂) ₃		A	78 5j	7.7:1
16	NC(CH ₂) ₃		B	80 5j	8.2:1

^a All reactions were run using 10% CpRu(COD)Cl and 15% SnCl₄·5H₂O with 1:2 ratio of alkyne to vinyl ketone. ^b Method A employs 20:1 DMF:H₂O and NH₄Cl (i.e., R' = H); method B employs DMF and (CH₃)₄NCl (i.e., R' = CH₃). ^c Ratio determined by GC or ¹H NMR spectroscopy.

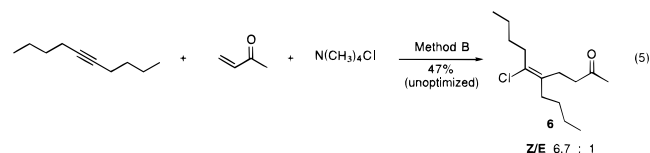
chloride for the ruthenium. The net result is a rather small enhancement in *E*-alkene geometry by switching ammonium salts with such hydroxyl-bearing substrates. The small amount of *Z*-chloroalkene may derive from a *cis* chlororuthenation competing with the more favored *trans* addition. In support of this proposal, using a less polar solvent, acetone, which should favor the less polar *cis* chlororuthenation path but otherwise using the conditions of method A led almost exclusively (> 15:1 *Z:E*) to the *Z*-vinyl chloride, albeit in modest yield since 1,5-diketone formation dominated (eq 4). The role of the cocatalyst is believed to be



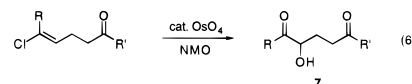
2-fold—(1) to prevent deactivation of the ruthenium catalyst by facilitating chloride dissociation and (2) to activate the vinyl ketone by Lewis acid catalysis.

This reaction serves as a new approach for the synthesis of

geometrically defined trisubstituted alkenes¹⁰ and, after dechlorination, *cis*-disubstituted alkenes. Previous work has shown that substitution on the alkene partner is not tolerated.⁵ While no limits exist for substitution on the alkyne partner, issues of regioselectivity with disubstituted alkynes have usually made such reactions less useful. As shown in eq 5, such reactions do work and are



useful with symmetrical disubstituted alkynes to form a geometrically defined tetrasubstituted alkene **6**. In addition, the vinyl chloride also serves as an enol equivalent. For example, *cis*-hydroxylation un masks an α -hydroxyketone **7** as shown in eq 6.



Further, using asymmetric dihydroxylation will provide such α -hydroxyketones asymmetrically. In addition to mechanistic studies, efforts to utilize groups other than chloride and alkenes other than vinyl ketones in such reactions are underway.

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Supporting Information Available: Typical experimental procedures and characterization data for **5a–j** and **6** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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