J|A|C|S
ARTICLES
Published on Web 05/30/2002

Formation of Vinyl Halides via a Ruthenium-Catalyzed Three-Component Coupling

Barry M. Trost* and Anthony B. Pinkerton

Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305

Received June 11, 2001

Abstract: The ruthenium-catalyzed three-component coupling of an alkyne, an enone, and halide ion to form *E*- or *Z*-vinyl halides has been investigated. Through systematic optimization experiments, the conditions effecting the olefin selectivity were examined. In general, more polar solvents such as DMF favored the formation of the *E*-isomer, and less polar solvents such as acetone favored formation of the *Z*-isomer. The optimized conditions for the formation of *E*-vinyl chlorides were found to be the use of cyclopentadienyl ruthenium (II) cyclooctadiene chloride, stannic chloride pentahydrate as a cocatalyst, and for a chloride source, either ammonium chloride in DMF/water mixtures or tetramethylammonium chloride in DMF. A range of several other ruthenium (II) catalysts was also shown to be effective. A wide variety of vinyl chlorides could be formed under these conditions. Substrates with tethered alcohols or ketones either five or six carbons from the alkyne portion gave instead diketone or cyclohexenone products. For formation of vinyl bromides, a catalyst system involving the use of cyclopentadienylruthenium (II) tris(acetonitrile) hexafluorophosphate with stannic bromide as a cocatalyst was found to be most effective. The use of ammonium bromide in DMF/acetone mixtures was optimal for the synthesis of *E*-vinyl bromides, and the use of lithium bromide in acetone was optimal for formation of the corresponding *Z*-isomer. Under either set of conditions, a wide range of vinyl bromides could be formed. When alkynes with propargylic substituents are used, enhanced selectivity for formation of the *Z*-isomer is observed. When aryl acetylenes are used as the coupling partners, complete selectivity for the *Z*-isomer is obtained. A mechanism involving a *cis* or *trans* halometalation is invoked to explain formation of the observed products. The vinyl halides have been shown to be precursors to α-hydroxy ketones and cyclopentenones, and as coupling partners in Suzuki-type reactions.

Introduction

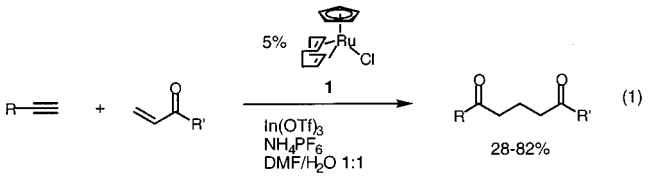
The efficient formation of functionalized alkenes, especially vinyl halides, in a stereoselective fashion is an important goal in organic synthesis. Olefination reactions represent the main method for formation of such compounds,[1] although stoichiometric halogenation of carbon−metal bonds is also frequently utilized.[2] The use of transition-metal catalysts wherein vinyl halides are formed by additions to alkynes is an area of growing interest.[3] Addition reactions to alkynes catalyzed by transition metals generally lead to either a *cis* or *trans* addition. A catalytic system wherein either isomer can be formed selectively enhances the utility of that method. In this paper, we describe the development of a ruthenium-catalyzed three-component coupling to form either *Z*- or *E*-vinyl halides. The development of this reaction was part of our program to further explore atom-economical reactions catalyzed by ruthenium complexes.[4]

* To whom correspondence should be addressed. E-mail: bmtrost@stanford.edu.

(1) Pine, S. H. *Org. React.* **1994**, *43*, 1. Ager, D. J. *Org. React.* **1990**, *38*, 1. Maryanoff, B. E. *Chem. Rev.* **1989**, *89*, 863.
(2) Matteson, D. S. *Tetrahedron* **1989**, *45*, 1859. Takada, E.; Hara, S.; Suzuki, A. *Tetrahedron Lett.* **1993**, *34*, 7067.
(3) See, for example: Li, J.; Jiang, H.; Feng, A.; Jia, L. *J. Org. Chem.* **1999**, *64*, 5984. Hua, R.; Shimada, S.; Tanaka, M. *J. Am. Chem. Soc.* **1998**, *120*, 12365.
(4) Trost, B. M. *Science* **1991**, *254*, 1471. Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.

Background

During the course of our development of new ruthenium-catalyzed reactions, it was discovered that terminal alkynes and enones could be reacted under ruthenium catalysis in DMF/water mixtures to form 1,5-diketones, as depicted in eq 1.[5] The



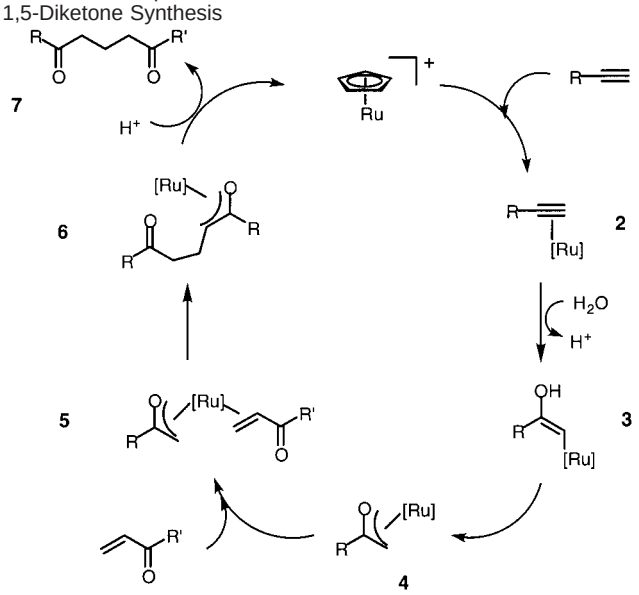
(1)

mechanism that was originally postulated for this reaction is shown in Scheme 1. When CpRu(COD)Cl (**1**) was used as a precatalyst, the initial catalyst generation involves reaction of the COD ligand in a [2 + 2 + 2] cycloaddition[6] with the alkyne and dissociation of chloride to provide the catalytically active species, a cationic cyclopentadienyl ruthenium fragment. This species catalyzes addition of water to the alkyne to form a ruthenium enolate (**3**), that can also exist as its *O*-bound form

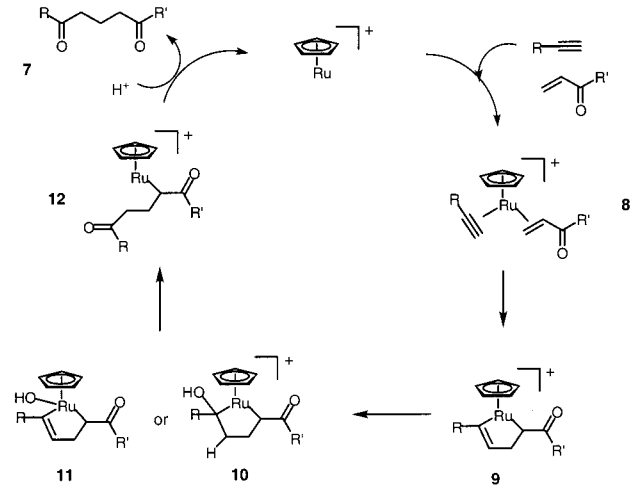
(5) Trost, B. M.; Portnoy, M.; Kurihara, H. *J. Am. Chem. Soc.* **1997**, *119*, 836.
(6) Trost, B. M.; Imi, K.; Indolese, A. F. *J. Am. Chem. Soc.* **1993**, *115*, 8831.

10.1021/ja011426w CCC: $22.00

Scheme 1. Proposed Ruthenium Enolate Mechanism for the 1,5-Diketone Synthesis



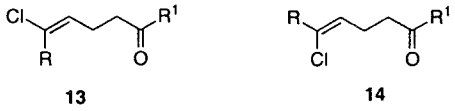
Scheme 2. Proposed Ruthenacycle Mechanism for 1,5-Diketone Formation



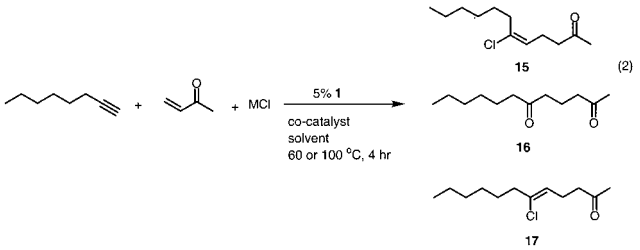
4. The enone is then coordinated to the ruthenium, giving **5**. Insertion into the enone leads to another ruthenium enolate **6**, which is then protonated to release product.

Another potential mechanism for this reaction involves ruthenacycle formation and hydrolysis. Some evidence for this ruthenacycle mechanism is found in two related examples, one involving the use of alkynes with propargylic alcohols[7] and the other an intramolecular version of the reaction depicted in eq 1, wherein either 1,5-diketones or pyrans could be formed.[8] As shown in Scheme 2, and in analogy to the ruthenium-catalyzed Alder-ene reaction, the mechanism involves initial coordination to the coordinatively unsaturated ruthenium to form **8**. Metallacycle formation then gives **9**. At this point, there are several possibilities for addition of water. Two will be outlined here. First, coordination of water to the ruthenium can lead to **11**. Alternatively, addition of water across the double bond could lead to **10**. Reductive elimination of the hydroxy group can occur from **11**. A β-hydrogen elimination (from the hydroxyl proton) could occur from **10**. Both lead to ruthenium enolate **12**, which is then protonated to release the product and regenerate the active catalyst.

Differentiation between the ruthenacycle mechanism and the ruthenium enolate mechanism might be achieved if we could define the stereochemistry of the addition of water across the alkyne. A potential approach was revealed in the presence of a byproduct of the reaction- the formation of a vinyl chloride, for example, **13** or **14**. Scheme 1 requires a *trans* addition which would lead to **13**, whereas Scheme 2 suggests the *cis* addition to be more likely and would lead to **14**. We therefore initially turned to the examination of a three-component coupling involving a chloride source in lieu of water and its stereochemistry.[9]



Optimization of the Reaction: Vinyl Chloride Formation. We initially examined the use of various metal halide cocatalysts. The reaction chosen for optimization is depicted in eq 2,



with 1-octyne and methyl vinyl ketone (MVK) as the coupling partner. Two products were formed in this reaction, *E*-vinyl chloride **15** and diketone **16**. A wide range of initial optimization experiments (full details of which can be found in the Supporting Information) was performed. A range of Lewis acid cocatalysts ($InCl_3$, $AlCl_3 \cdot 6H_2O$, $CeCl_3 \cdot 7H_2O$, $PbCl_2$, $NiCl_2.6H_2O$, $ZnCl_2$ and $SnCl_4 \cdot 5H_2O$), chloride sources (LiCl, NH_4Cl, $N(CH_3)_4Cl$), additives (NH_4PF_6, PPh_3), and solvents (DMF, DMF/water mixtures, MeOH, acetone) were examined. Screening determined that 15 mol % hydrated stannic chloride was the best cocatalyst, with 3.3 equiv of ammonium chloride in DMF/water, 20/1, at 100 °C. In all cases, except when acetone was used as a solvent, approximately a 6:1 *E*/*Z* mixture of vinyl chlorides was formed.

Effects of concentration and temperature were then examined (Table 1). Entry 1 shows the previously optimized conditions (*vide supra*). Increasing the concentration of the alkyne to 0.5 M (entry 2) gave an increased yield. A further increase in concentration to 1 M (entry 4) was detrimental, however. Unfortunately, even at a higher concentration, the catalyst could not be lowered to 5 from 10% without a much lower yield (entry 3). Although it was originally believed that high temperatures were necessary for generation of the active catalyst, we were delighted to discover that lower temperatures were in fact beneficial for the reaction, giving now a good yield of the vinyl

(7) Trost, B. M.; Krause, L.; Portnoy, M. *J. Am. Chem. Soc.* **1997**, *119*, 11319.
(8) Trost, B. M.; Brown, R. E.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 5877.
(9) For preliminary reports, see: Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 1988; Trost, B. M.; Pinkerton, A. B. *Angew. Chem., Int. Ed.* **2000**, *39*, 360; Trost, B. M.; Pinkerton, A. B., *Tetrahedron Lett.* **2000,** *41*, 9627.

Table 1. Concentration and Temperature Effects[a]

entry	alkyne concentration (M)	temperature (°C)	16 (%)	15 (%)
1	0.25	100	2	48
2	0.5	100	4	56
3[b]	0.5	100	6	20
4	1.0	100	17	45
5	0.5	60	5	72

[a] In all cases, approximately a 6/1 *E*/*Z* mixture was obtained for the vinyl chloride. [b] Run with 5% **1**.

Table 2. Use of Tetramethylammonium Chloride in DMF at 60 °C

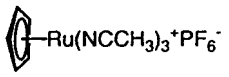
entry	chloride source (equiv)	solvent (%)	16 (%)	15 (%)
1	NH_4Cl (3)	DMF	0	63[a]
2	$N(CH_3)_4Cl$ (1)	DMF	0	57[b]
3	$N(CH_3)_4Cl$ (2)	DMF	0	61[b]
4	$N(CH_3)_4Cl$ (3)	DMF	0	72[b]
5[c]	$N(CH_3)_4Cl$ (3)	DMF	0	68[b]

[a] *E*/*Z* ratio of 6.2/1. [b] *E*/*Z* ratio of >15/1. [c] Complex **18** employed as catalyst.

chloride (entry 5). Indeed, decomposition of the vinyl chloride product was observed at 100 °C under the reaction conditions.[12] Control experiments showed that the product was stable at the lower temperature.

Finally, with the milder conditions in hand, we reexamined the chloride source as well as the solvent (Table 2). It was initially presumed that some water was necessary for a polar medium for the active catalyst. Also, we assumed that some water was necessary for solubility of the ammonium chloride and stannic chloride. Indeed, the use of straight DMF instead of DMF/water, 20/1, gave a decreased yield (63% vs 72%), but no diketone was formed (entry 1). Switching to a more soluble chloride source, tetramethylammonium chloride, gave some very nice results (entries 2−4). As shown, 3 equiv of tetramethylammonium chloride gave a comparable yield of the vinyl chloride with no diketone (entry 4). Furthermore, the product was formed as exclusively the *E*-isomer as determined by proton NMR spectroscopy (see Supporting Information). The conditions in entry 4 were therefore used as one of the general methods for the formation of vinyl chlorides.

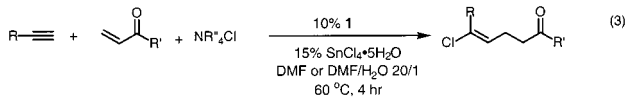
Due to the interesting results obtained with the use of acetone as a solvent in terms of olefin selectivity (vide supra), we further examined this effect. For example, the use of acetone in place of DMF as the solvent using our optimized conditions (see eq 2) gave the *Z*-isomer **17** (*Z*/*E* > 15:1, 24% yield). Unfortunately, diketone formation dominated in this case.[13] Other ruthenium catalysts were also successful in giving the desired vinyl chloride. However, both a methyallyl ruthenium[14,15] catalyst ($CpRu(C_4H_7)PPh_3$) and a bis-phosphine ruthenium[16] ($CpRu(PPh_3)_2Cl$) gave inferior results (see Supporting Information). Last, the tris(acetonitrile) catalyst **18**[17] was found to be equally



18

active compared to the COD catalyst **1**. With this catalyst, reaction of 1-octyne with MVK provides the vinyl chloride **15** in 68% with an *E*/*Z* ratio of >15/1. This compares to 72% and >15/1 for the COD catalyst **1**. Therefore, it appears that the same active species is generated with either **1** or **18** and similar reactivity profiles are seen.

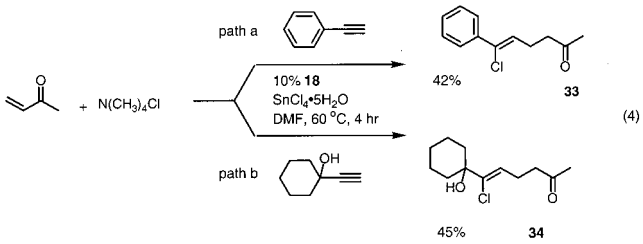
Substrate Range: Vinyl Chlorides. With optimized conditions in hand, a range of substrates was examined according to eq 3, with the results summarized in Table 3. Two general



methods were used. The first, method A, consisted of the use of ammonium chloride in DMF/water, 20/1, and method B consisted of the use of tetramethylammonium chloride in DMF. In general, the use of method B was preferred due to the generally higher yields and selectivities that were obtained.

As we see from Table 3, a broad range of functionality is tolerated. Excellent chemoselectvity is observed with nitrile (entries 4−7), ester (entries 8 and 9), phthalimido (entry 16), and keto (entry 17) groups. Significantly, isolated, nonconjugated olefins (entries 18 and 19) are tolerated, with only bond formation to the enone observed (although in this case some unidentified byproducts were isolated). Also, a range of primary (entries 10, 13, and 20), secondary (entries 11, 12, 14, and 15) and tertiary alcohols (entries 18 and 19) are compatible with the reaction conditions. Interestingly, even propargylic alcohols are tolerated (entry 14). Finally, a range of enones can serve as partners, with cyclohexylvinyl ketone reacting equally well (entries 3, 6, and 7). However, acyl oxazolidinone **32** fails to react under the standard conditions (entry 21). Other partners such as ethyl acrylate and acrylonitrile also give no products in this reaction.

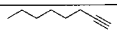
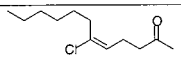
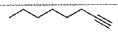
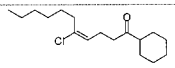
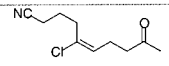
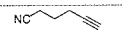
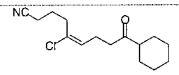
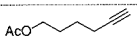
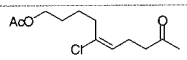
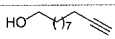
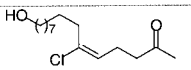
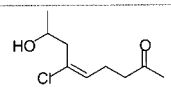
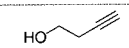
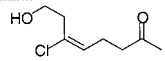
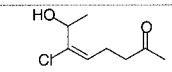
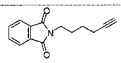
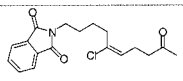
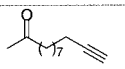
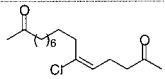
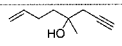
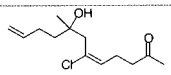
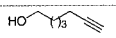
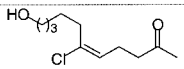
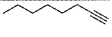
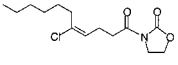
Interestingly, when the standard conditions that were used to form *E*-vinyl chlorides were tested with phenylacetylene (eq 4, path a) and 1-ethynylcyclohexanol (eq 4, path b), only the *Z*



products **33** and **34**, respectively, were obtained.[18] Thus, it appears that such large steric factors override the intrinsic geometrical preference. It should be noted that in both of these cases, lower yields were obtained, perhaps reflective of the competing selectivities.

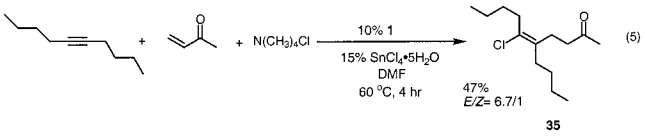
(10) See, for example: Trost, B. M.; Indolese, A. F.; Müller, T. J. J.; Treptow, B. *J. Am. Chem. Soc.* **1995**, *117*, 615. Trost, B. M.; Müller, T. J. J.; Martinez, J. *J. Am. Chem. Soc.* **1995**, *117*, 1888.
(11) Either MeOH or DMF/water mixtures appear to be the best solvent for most applications of this catalyst. See the ref 10.
(12) Approximately 20% of the material was lost when resubmitted to the reaction conditions.
(13) Thoroughly dried acetone was not examined in this reaction, but later results showed the necessity of some water for catalytic turnover.
(14) Trost, B. M.; Pinkerton, A. B.; Toste, F. D.; Sperrle, M. *J. Am. Chem. Soc.* **2001**, *123*, 12504.
(15) Albers, M. O.; Robinson, D. J.; Shaver, A.; Singleton, E. *Organometallics* **1986**, *5*, 2199.
(16) Joslin, F. L.; Mague, J. T.; Roundhill, D. M. *Organometallics* **1991**, *10*, 521.
(17) Gill, T. B.; Mann, K. R. *Organometallics* **1982**, *1*, 485.
(18) The olefin geometry was determined by nOe difference experiments. See Supporting Information.

Table 3. Examples of Ruthenium-Catalyzed *E*-Vinyl Chloride Formation[a]

Entry	Alkyne	R'	Product	Meth.[b]	Yield (%)	*E*/*Z*
1		-CH_3	 **15**	A	72	6.0/1
2				B	72	>15/1
3			 **19**	A	74	6.1/1
4		-CH_3	 **20**	A	83	8.8/1
5				B	80	12/1
6			 **21**	A	78	7.7/1
7				B	80	8.2/1
8		-CH_3	 **22**	A	75	7.0/1
9				B	77	>15/1
10		-CH_3	 **23**	A	67	5.5/1
11		-CH_3	 **24**	A	74	7.2/1
12				B	80	8.5/1
13		-CH_3	 **25**	A	68	6.7/1
14		-CH_3	 **26**	A	72	4.1/1
15				B	78	5.3/1
16		-CH_3	 **27**	A	62	5.7/1
17		-CH_3	 **28**	A	60	6.2/1
18		-CH_3	 **29**	A	54	5.9/1
19				B	58	6.3/1
20		-CH_3	 **30**	A	61	6.4/1
21		 **32**	 **31**	A	traces	--

[a] All reactions run according to eq 3 with a 1/2 ratio of alkyne to enone, at 0.5 M in alkyne. [b] Method A: 20/1 DMF/water and NH_4Cl; Method B: DMF and NMe_4Cl.

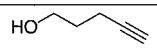
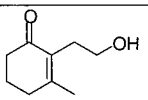
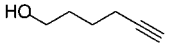
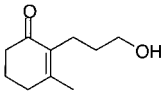
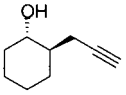
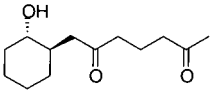
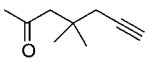
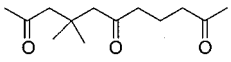
Disubstituted alkynes also act as coupling partners in this reaction, as shown in eq 5. In this example, 5-decyne reacts



with MVK to form vinyl chloride **35** in reasonable yield. Extension to nonsymmetrically disubstituted alkynes raises the question of regioselectivity- a question that has not been addressed. This method offers a nice access to stereodefined tetrasubstituted olefins.

Several substrates did not form vinyl chlorides under the standard conditions (see Table 4). Using method A, primary

Table 4. Formation of 1,5-Diketones or Cyclohexenones

Entry	Alkyne	Product	Yield (%)
1		 **36**	58
2		 **37**	68
3		 **38**	63
4		 **39**	47

alcohol substrates bearing a hydroxy function four or five carbons removed from the alkyne gave cyclohexenones **36** and **37** as the sole products (entries 1 and 2). These products were characterized by the proton NMR spectra, which showed singlets at δ 1.98, indicating an allylic methyl group, and matched the previously obtained spectra for these compounds.[5] They were also clearly differentiated from the vinyl chlorides by the lack of vinylic triplets in the proton NMR spectra. It should be noted that this cyclization reaction is specific to these alcohol substrates. Clearly, longer or shorter chain alcohols are well tolerated in the reaction, as evidenced by the results in Table 3. Ketone substrates with the keto functionality 6 carbons from the alkyne (entry 4) gave 1,5-diketone such as **39** products, as did secondary alcohols (entry 3). These products have been previously described, and the proton and carbon NMR data correlated. The mechanistic implications of these interesting and useful reactions will be discussed subsequently (vide infra).

Optimization of the Reaction: Vinyl Bromides. With the successful formation of vinyl chlorides, we obviously wished to examine the corresponding formation of vinyl bromides, due to their greater synthetic utility as partners in cross-coupling reactions. Although the catalyst **1** employed for the vinyl chloride reaction possesses a chloride, it was anticipated that excess bromide would swamp out its competition. Interestingly, that proved not to be the case; mixtures of vinyl chlorides and vinyl bromides formed, even at high bromide concentration. Presumably the chloride came from the catalyst and was very

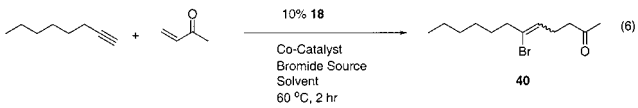
Table 5. Initial Screening Experiments for Vinyl Bromide Formation

entry	cocatalyst (%)	bromide source (equiv)	solvent	40 (%)	*E*/*Z*
1	$SnBr_2$ (15)	NH_4Br (3.0)	DMF	13	3.3/1
2[b]	$SnBr_2$ (15)	NH_4Br (3.0)	DMF	14	3.2/1
3	$SnBr_4$ (15)	NH_4Br (3.0)	DMF	54	2.1/1
4	$SnBr_4$ (15)	$N(CH_3)_4Br$ (5.0)	DMF	61	1.2/1
5	$SnBr_4$ (15)	NH_4Br (3.0)	DMF/CH_3CN	11	5.1/1
6	$SnBr_4$ (15)	NH_4Br (3.0)	DMSO	-	-
7	$SnBr_4$ (15)	NH_4Br (3.0)	acetone	40	1/10
8	$SnBr_4$ (15)	NH_4Br (3.0)	acetone/DMF, 1/1	48	5.1/1
9	$SnBr_4$ (15)	NH_4Br (3.0)	acetone/DMF, 4/1	56	1/1.4
10	$SnBr_4$ (15)	NH_4Br (3.0)	acetone/DMF, 2/1	62	2.2/1
11	$SnBr_4$ (15)	NH_4Br (3.0)	acetone/DMF, 1/2	70	2.4/1
12	$SnBr_4$ (15)	NH_4Br (3.0)	acetone/DMF, 1/4	48	2.6/1
13	$SnBr_4$ (15)	NH_4Br (3.0)	MeOH	40	1/3.0
14	$SnBr_4$ (15)	$N(CH_3)_4Br$ (3.0)	acetone	35	>1/15
15[a]	$SnBr_4$ (15)	$N(CH_3)_4Br$ (1.5)	acetone	33	1/8.0
16	$SnBr_4$ (15)	$N(CH_3)_4Br$ (3.0)	acetone/DMF, 1/1	54	1/4.0
17[a]	$SnBr_4$ (15)	LiBr (1.5)	acetone	88	1/6.6
18[a,c]	$SnBr_4$ (15)	LiBr (1.5)	acetone	56	1.3/1
19[a]	$SnBr_4$ (5)	LiBr (1.5)	acetone	54	1/6.7
20[a]	$SnBr_4$ (15)	LiBr (3.0)	acetone	87	1/4.0
21	$SnBr_4$ (15)	NaBr (1.5)	acetone/DMF, 1/1	59	1/6.9
22[a]	None	LiBr (1.5)	acetone	22	1/4.2
23[d]	$SnBr_4$ (15)	NH_4Br (3.0)	acetone/DMF, 1/1	0	–

[a] Run with 1.5 equiv of MVK. [b] Run at room temperature for 4 h. [c] Run with 5% catalyst. [d] Run with no catalyst.

effective in competing against the bromide. We therefore turned to alternative catalysts lacking chloride. Indeed, complex **18**, which is postulated to give the same active intermediate, proved effective and avoided this problem.

The reaction of eq 6 was examined for optimization and the



initial results shown in Table 5. The success of tin salts as cocatalysts focused our efforts on tin bromide. Initial efforts used stannous bromide (entries 1 and 2), but only low yields were obtained. We then turned to stannic bromide as the cocatalyst for our subsequent experiments. Using ammonium bromide in DMF, a moderate yield of vinyl bromide was obtained, also predominately as the *E*-isomer (entry 3). However, the *E*/*Z* ratio was much lower than for the corresponding vinyl chloride formation. Use of tetramethylammonium bromide in DMF (entry 4) did not dramatically improve the yield and actually lowered the selectivity. Other solvents, such as DMF/acetonitrile (entry 5) and DMSO (entry 6) gave poor results. Interestingly, the use of acetone as a solvent (entry 7) with ammonium bromide gave a moderate yield, but with good *Z* selectivity, also an effect that was observed in the vinyl chloride formation.

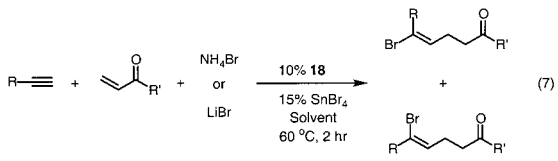
We next examined mixtures of DMF and acetone as solvent in the attempt to have high selectivity as well as an increased yield. As shown in entries 8−12, when more DMF is present relative to acetone, more of the *E*-isomer is formed. Conversely, when more acetone is present, more of the *Z*-isomer is formed. However, in general only moderate yields are obtained in these cases. The use of methanol as a solvent (entry 13) was only moderately effective. Interestingly, with tetramethylammonium bromide in acetone (entries 14 and 15) or acetone/DMF (entry 16), good *Z* selectivity could be obtained, but only in moderate yields.

Concerned that solubility of the ammonium salts was an issue, we investigated the use of other bromides. Indeed, lithium bromide is fully soluble in acetone and gave an excellent yield of the vinyl bromide with good *Z* selectivity (entry 17). Curiously, increasing the amount of lithium bromide to 3 equiv leads to a decrease in *Z* selectivity (entry 20). Although neither catalyst (entry 18) nor cocatalyst loading (entry 19) could be lowered, we nevertheless adopted these conditions as our optimal conditions for *Z*-vinyl bromide formation. Entry 22 shows the vital nature of the cocatalyst once again, with only low yields of vinyl bromide obtained in its absence. Finally, a control experiment with no catalyst gives no product (entry 23).

The results of Table 5 indicate that the *E*/*Z* selectivities can range from 5:1 to >1:15. Ideally, obtaining either geometric isomer at will is desirable. Therefore, we attempted optimization of formation of *E*-vinyl bromides as well. Performing the reaction of eq 6 using 15 mol % stannic bromide and 3 equiv of ammonium bromide in 1/1 acetone/DMF at 0.5 M alkyne with 1.5 equiv of MVK gave a 71% yield of a 2.1:1 *E*/*Z* ratio. Increasing the MVK to 2 equiv increased the *E*/*Z* ratio to 3.4:1. Decreasing the amount of MVK or concentration of alkyne had no effect. The results suggest that the solvent might be serving as ligand in competition with the acetonitrile ligands originally present. Thus, the effects of nitrile concentration and type of nitrile was examined. Adding 30 mol % excess acetonitrile had no effect on the reaction in DMF nor in 1/1 acetone/DMF. Use of acetonitrile as solvent shuts down the reaction. Employing 15 mol % of adiponitrile or glutaronitrile in 1/1 acetone/DMF increases the *E*/*Z* ratio to 3.4 ± 0.2, a modest increase over the control. At this stage, selectivity for forming the *E*-isomer in good yields stands at 2−4:1.

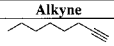
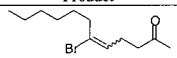
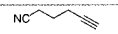
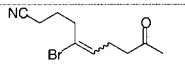
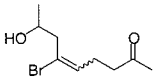
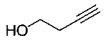
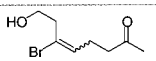
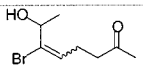
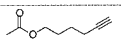
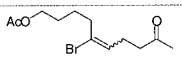
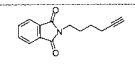
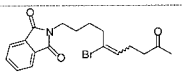
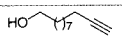
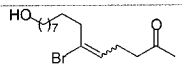
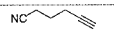
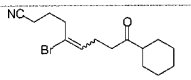
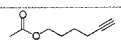
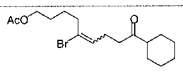
Table 5 indicates that the use of tetramethylammonium bromide significantly increased the *Z* selectivity but only in moderate yield. Therefore, an attempt was made to increase the yield while maintaining the geometrical selectivity using tetraalkylammonium salts. Unfortunately, variation of the amounts of tetramethylammonium bromide, solvent, and the nature of the alkyl group of ammonium salt did not improve the overall results. While higher yields were obtained with tetraethylammonium bromide in DMF (63%), the *E*/*Z* selectivity dropped to 1:2. Curiously, the best yields were obtained with a spirotetraalkylammonium salt **(41)**. Although the *E*/*Z* ratio is 1/4.l to 1/3.l, the yields in both acetone (73%) and DMF (73%) are good. Nevertheless, these best results using ammonium salts are inferior to those obtained with using lithium bromide as the bromide source (Table 5, entry 17).

Substrate Range: Vinyl Bromides. With several different sets of conditions in hand, the effect of substrate variation was examined (see eq 7 and Table 6). The initial set of experiments



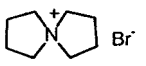
focused on the use of ammonium bromide as the bromide source, and the formation of either *Z*- or *E*-vinyl bromides depending on the solvent used. In general, a 1/1 mixture of acetone/DMF (solvent A) was used for *E*-vinyl bromide formation and solely acetone (solvent B) or 2-butanone (solvent

Table 6. Examples of Ruthenium-Catalyzed *E*- or *Z*-Vinyl Bromide Formation Using Ammonium Bromide[a]

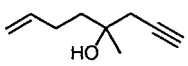
Entry	Alkyne	R'	Product	Solv[b]	Yield (%)	*E*/*Z*
1		-CH_3	 **40**	A	67	3.4/1
2				B	38	1/10
3		-CH_3	 **42**	A	92	2.3/1
4				B	64	1/2.4
5				C	64	1/3.4
6		-CH_3	 **43**	A	82	1.7/1
7				B	61	1/8.2
8		-CH_3	 **44**	A	84	1.3/1
9				B	55	1/3.8
10				C	48	1/1.5
11		-CH_3	 **45**	A	57	1/1.7
12				B	21	1/7.3
13		-CH_3	 **46**	A	91	2.9/1
14				B	35	1/7.8
15		-CH_3	 **47**	A	68	1.7/1
16				B	39	1/5.4
17		-CH_3	 **48**	A	75	2.7/1
18				B	36	1/4.9
19			 **49**	A	68	1.1/1
20				B	54	1/2.5
21			 **50**	A	70	1.3/1
22				B	41	1/7.0

[a] All reactions run according to eq 7 with a 1/1.5 ratio of alkyne to enone, at 0.5 M in alkyne with 10% catalyst and 15% stannic bromide in acetone at 60°C for 2 h unless indicated otherwise. [b] Solvents: A = DMF/Acetone 1/1, B = Acetone, C = 2-Butanone

C) for *Z*-vinyl bromide formation. The yields in the acetone/DMF mixture were higher, indicative of the increased solubility of the ammonium bromide in the more polar solvent. In general, this was the most appropriate method for forming *E*-vinyl bromides selectively and in good yields.



41



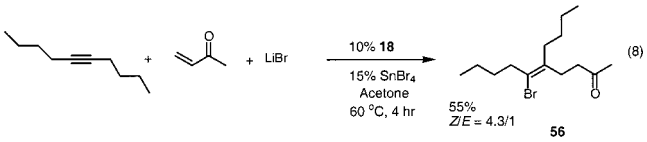
51

A wide range of functionality is tolerated; the reaction is highly chemoselective. Nitriles (entries 3−5, 19−20), primary (entries 8−10, 18−19) and secondary (entries 6−7, 11−12) alcohols, esters (entries 13−14, 21−22) and amides (entries 15−16) are all compatible. Other enones such as cyclohexylvinyl ketone participate (entries 19−22). Interestingly, a substrate with a terminal olefin (**51**) gave no vinyl bromide product. In this case, it is possible that other Alder-ene type reactions are occurring as well, and only decomposition products are observed. However, overall the reactions were quite clean, with the remainder of the alkyne material perhaps oligomerizing.

Although the results in Table 6 are an extremely nice example of how the same catalyst system, including use of the same source of bromide, can give different geometrical selectivities in different solvents, the yields for selective formation of *Z*-vinyl bromides were unacceptably low. We therefore ran a second set of experiments using lithium bromide in acetone as shown in eq 7. The results are summarized in Table 7. In general, this was the best method for forming *Z*-vinyl bromides in good yields and selectivities.

The same wide range of substrates was tolerated. In general, excellent yields were obtained, and for the most part selectivity for the *Z*-isomer was moderate to excellent. For example, using a propargylic alcohol substrate (entry 5), an 1/11.0 *E*/*Z* mixture of vinyl bromide **45** was obtained. The examples also illustrate the excellent chemoselectivity with hydroxyl, cyano, keto, carboxy, and phthalimido all compatible. The example of entry 12 is particularly noteworthy since it shows a *cis*-dialkyl substituted alkene is unaffected. Other enones such as cyclohexylvinyl ketone (entries 9 and 10) and phenylvinyl ketone (entries 13 and 14) were compatible.

Disubstituted alkynes also act as coupling partners in vinyl bromide formation, as shown in eq 8. In this example, 5-decyne



(8)

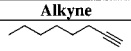
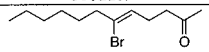
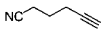
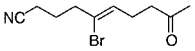
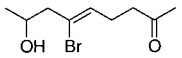
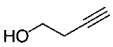
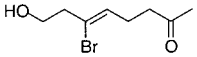
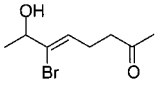
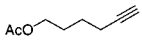
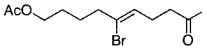
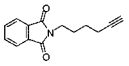
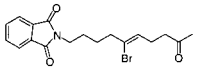
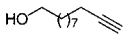
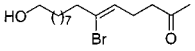
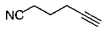
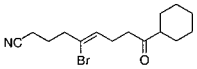
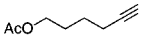
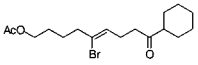
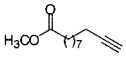
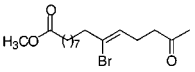
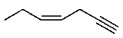
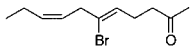
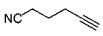
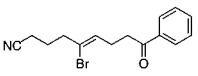
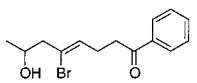
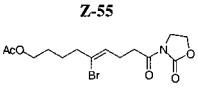
56

reacts with MVK to form vinyl bromide **56** in moderate yield, with the expected geometry of the double bond. The broader general applicability of this reaction will depend on the regioselectivity with nonsymmetrical disubstituted alkynes—an aspect for future study.

The high *Z* selectivity obtained when propargylic substituents were present (as in entry 12, Table 6; entry 5, Table 7) led us to postulate that increasing the steric bulk at the propargylic position should give enhanced selectivity for the *Z*-isomer. We therefore examined a range of substrates with substitution at the propargylic position (see eq 2 and Table 8). When a substituent even as small as methyl is present at the propargylic position (entry 1), a very good *Z*/*E* ratio of 7.9/1 is observed for the vinyl bromide. Increasing the substitution to a quaternary center (entry 2) then produces only the *Z*-isomer. This example is particularly noteworthy due to the high propensity of such compounds to form allenylidene species with ruthenium complexes of the type used here.[19] An all-carbon alkyl group (entry

(19) Trost, B. M.; Flygare, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 5476; Selegue, J. P.; Young, B. A.; Logan, S. L. *Organometallics* **1991**, *10*, 1972; Cadierno, V.; Gamasa, M. P.; Gimeno, J.; Gonzales-Cueva, M.; Lastra, E.; Borge, J.; Garcia-Granda, S.; Pérez-Carreño *Organometallics* **1996**, *15*, 2137. For a recent leading reference, see: Nisbibayashi, Y.; Wakiji, I.; Hidai, M. *J. Am. Chem. Soc.* **2000**, *122*, 11019.

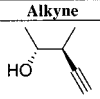
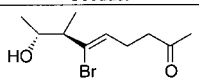
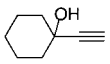
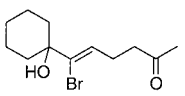
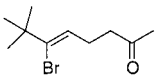
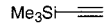
Table 7. Examples of Ruthenium-Catalyzed *Z*-Vinyl Bromide Formation Using Lithium Bromide[a]

Entry	Alkyne	R'	Product	Yield (%)	*E/Z*
1		-CH_3	 **Z-40**	88	1/6.6
2		-CH_3	 **Z-42**	90	1/3.3
3		-CH_3	 **Z-43**	82	1/6.0
4		-CH_3	 **Z-44**	70	1/4.3
5		-CH_3	 **Z-45**	64	1/11.0
6		-CH_3	 **Z-46**	81	1/5.2
7		-CH_3	 **Z-47**	67	1/3.6
8		-CH_3	 **Z-48**	92	1/5.1
9			 **Z-49**	77	1/4.7
10			 **Z-50**	78	1/5.0
11		-CH_3	 **Z-52**	66	1/3.1
12		-CH_3	 **Z-53**	67	1/4.2
13		-Ph	 **Z-54**	84	1/7.3
14		-Ph	 **Z-55**	81	1/5.8
15		 **32**		<5	1/6.0

[a] All reactions run according to eq 7 with a 1/1.5 ratio of alkyne to enone, at 0.5 M in alkyne with 10% catalyst and 15% stannic bromide in acetone at 60 °C for 2 h.

3) and even a trimethylsilyl group (entry 4) also gives only one geometric isomer. Alternatively, an aryl substituent shows the same behavior (entries 5−9). Although the complete selectivity

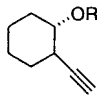
Table 8. Enhanced Selectivity in the Ruthenium-Catalyzed *Z*-Vinyl Bromide Formation Using Lithium Bromide[a]

Entry	Alkyne	R'	Product	Yield (%)	*E/Z*
1		-CH_3	 **57**	69	1/7.9
2		-CH_3	 **58**	55	All *Z*
3		-CH_3	 **59**	54	All *Z*
4		-CH_3	**60**	49	All *Z*
5		-CH_3	**61**	72	All *Z*
6		-Ph	**62**	72	All *Z*
7		-CH_3	**63**	53	All *Z*
8		-CH_3	**64**	53	All *Z*
9		-CH_3	**65**	67	All *Z*
10		-Ph	**66**	56	All *Z*
11		-Ph		55	All Z

[a] All reactions run according to eq 7 with a 1/1.5 ratio of alkyne to enone, at 0.5 M in alkyne with 10% catalyst and 15% stannic bromide in acetone at 60 °C for 2 h.

with aryl acetylenes compared to the result of entry 1 may seem counterintuitive at first, as a phenyl group is generally a sterically less demanding group than an isopropyl group, the effective steric bulk of the aromatic ring may be larger.[20] This effect will be discussed subsequently. Somewhat surprisingly, neither alcohol **68** nor ester **69** gave any vinyl bromide product under the reaction conditions. MVK was replaced with phenylvinyl

(20) Conjugation of the aromatic system with the double bond leads to a more planar geometry and thus increased steric effects.

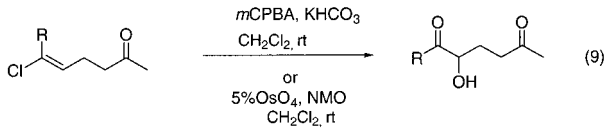


R=H **68**
R=Ac **69**

ketone (entries 6, 10, and 11) to produce the corresponding three-component coupling products with equivalent results. Extension of the reaction to alkenes other than vinyl ketones have, sofar, proved elusive. Low yields of the adduct could be detected in the case of *N*-acryloyloxazolidin-2-one (e.g., see entry 15 of Table 7). On the other hand, three-component coupling products could not be observed with ethyl acrylate, acrylonitrile, *N*,*N*-dimethylacrylamide, ethyl 2-pentenoate, crotonaldehyde, acrolein, nor styrene.

Some Applications

Formation of α-Hydroxyketones *via* Epoxidation or Dihydroxylation. The direct availability of vinyl chlorides by this three-component coupling make them readily available building blocks. To illustrate, we examined the oxidation of the vinyl chlorides to take advantage of the different oxidation levels of the two carbons of the olefin. Initially we examined the epoxidation of the vinyl halides in an attempt to form haloepoxides.[21] It was found, however, that such compounds reacted further to form the α-hydroxyketone either during the reaction or during workup. The products were characterized by the presence of a hydroxy stretching frequency of approximately 3500 cm^{-1} in the infrared spectrum, as well as the presence of two peaks corresponding to carbonyl groups (at approximately 210 ppm) in the carbon NMR spectra. The reactions were performed using an excess of *m*-chloroperbenzoic acid (*m*CPBA) buffered with sodium or potassium bicarbonate (eq 9). In



(9)

general, good to moderate yields were obtained (Table 9). An excellent yield was obtained with vinyl chloride **15** (entry 1), most likely due to the lower polarity of this compound. The more functionalized compounds, especially the alcohol **23** (entry 2), gave very polar products. This led to losses of material during purification (removal of the excess *m*CPBA as well as *m*-chlorobenzoic acid required water washes as well as column chromatography).

An alternative reaction that would lead to the product is a direct dihydroxylation which has the capacity of being performed asymmetrically rather easily. We therefore turned to methods for the dihydroxylation of the vinyl chlorides.[22] This proved to be very successful, and in general the reactions were very clean using quite standard catalytic osmylation conditions with 5% osmium tetraoxide and 4 equivalents of NMO (eq 9). As shown in Table 9 good yields were obtained in all cases, superior to the epoxidation conditions due to ease of workup.

Table 9. Conversion of Vinyl Chlorides to Form α-Hydroxyketones

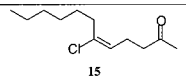
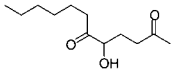
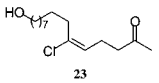
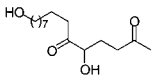
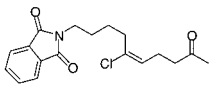
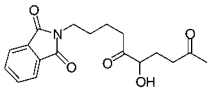
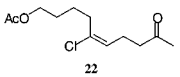
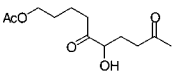
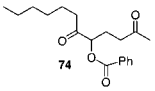
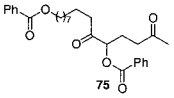
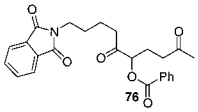
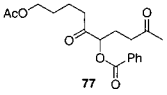
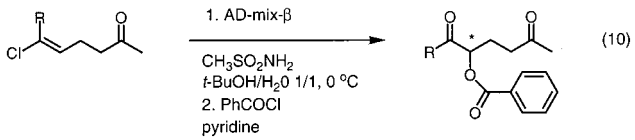
Entry	Substrate	Product	Yield Epoxidation (%)	Yield Dihydroxylation (%)
1	 **15**	 **70**	93	90
2	 **23**	 **71**	40	78
3	 **27**	 **72**	62	86
4	 **22**	 **73**	68	76

Table 10. Asymmetric Dihydroxylation of Vinyl Halides to Form α-Hydroxyketones

Entry	Substrate (*E*/*Z*)	Product	Yield AD (%)	Yield Benzoylation (%)	ee[a]
1	**15** (6.2/1)	 **74**	62	87	80
2	**15** (>15:1)	**74**	60	87	78
3	**40** (1:6.6)	**74**	62	87	86
4	**23** (4.8/1)	 **75**	69	72	76
5	**27** (6.0/1)	 **76**	61	87	60
6	**22** (7.0/1)	 **77**	64	82	86
7	(>15:1)	**77**	58	80	84

[a] Ee's determined by chiral HPLC analysis.

The asymmetric version[23] led to its application with the vinyl chlorides using commercially available AD-mix-β with methanesulfonamide at 0 °C (see eq 10 and Table 10). The ee's were



(10)

determined by chiral HPLC analysis. These reactions were somewhat more sluggish than the typical achiral dihydroxylations using osmium; however, the reactions usually went to completion although longer reaction times were required. For

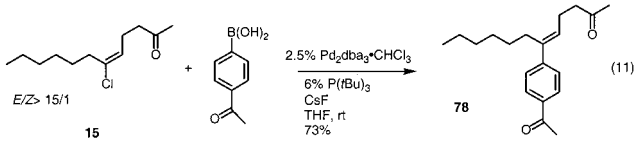
(21) March, J. *Advanced Organic Chemistry*; Wiley: New York, 1992; pp 1087−1088.
(22) Sharpless, K. B.; Teranishi, A. Y.; Bäckvall, J. E. *J. Am. Chem. Soc.* **1977**, *99*, 3120.
(23) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.

easier HPLC analysis, the α-hydroxyketones were converted to their benzoates, as shown in eq 10. As we can see from Table 10, moderate to good ee's may be obtained. It should be noted that no optimization was done for this reaction (i.e., examining different chiral ligands), and therefore it is possible that much better ee's could be obtained.

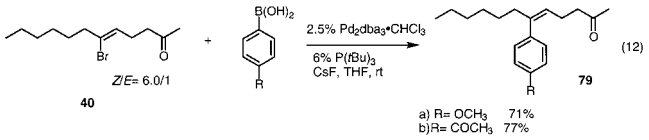
Attempts to increase the ee by lowering the reaction temperature were unsuccessful, as the reaction became too slow. At −20 °C, the reaction of entry 1 of Table 10 occurred only to the extent of 10% after 24 h. To ascertain the role, if any, played by employing *E*−*Z*-alkene mixtures, we examined the reaction of vinyl chlorides **15** and **22**, with *E*/*Z* ratios greater than 15/1. As shown in Table 10 (entries 2 and 7), the results were somewhat surprising; no increase in ee was observed in either case. Thus, the *E*-vinyl chlorides behave like *Z*-1,2-disubstituted alkenes wherein ee's are more modest.[24] Interestingly, the ee's are somewhat higher than would be expected for the *Z*-1,2-disubstituted alkene, indicating that Cl is playing some role. The fact that the ee is independent of alkene geometry precludes the need to use geometrically pure *E*-alkenes for optimum ee.

Application of the dihydroxylation reaction to the vinyl bromides should generate the same products as from the vinyl chlorides. To examine the effect, if any, of the halide on the degree of asymmetric induction, we performed the asymmetric dihydroxylation of **40** as shown in Table 10, entry 3. The initial α-hydroxyketone was directy benzoylated and analyzed as **74** to be 86% ee. This result is a small but significant improvement over the corresponding *E*-vinyl chloride **15** (Table 10, entries 1 and 2). Importantly, the same enantiomer was produced in both cases even though opposite geometric isomers of alkenes were employed—that is, the major peak in the chiral HPLC was the same in both cases. A similar observation has been noted in the AD of the geometric isomers of enol silyl ethers.[25] The enhancement in ee might result from the larger size of Br versus Cl.

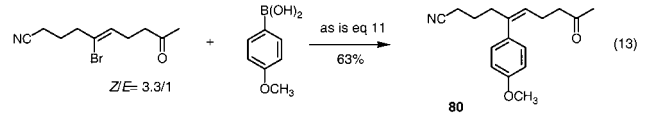
Suzuki-Type Cross-Coupling Reactions. The vinyl chlorides were also examined in Suzuki-type cross-coupling reactions. Using the recently developed coordinatively unsaturated palladium catalyst,[26] Suzuki coupling of chloride **15** with an arylboronic acid proceeds with complete integrity of alkene geometry to give trisubstituted alkene **78** (eq 11), an observation



that validates this approach as an excellent strategy to trisubstituted alkenes of defined geometry. Vinyl bromides also react readily as cross-coupling partners. For example, the *Z*-vinyl bromide **40** underwent Suzuki coupling with both an electron-rich and electron-poor aryl boronic acid (eq 12) to give *Z*-alkenes **79a** and **79b**. The excellent chemoselectivity is highlighted by the example of eq 13 wherein the trisubstituted *Z*-alkene **80** derives in two steps from 5-cyano-1-pentyne, MVK, lithium

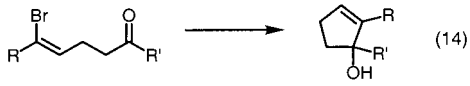


bromide, and an arylboronic acid in sequential ruthenium- and palladium-catalyzed reactions. Since either haloolefin geometric

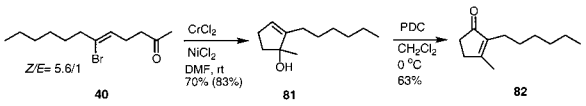


isomer is now available, either trisubstituted alkene is available. For the preparation of the *E*-alkenes, the *E*-vinyl bromides may be used; however, the *E*-vinyl chlorides are the more practical precursors.

Cyclopentenone Formation. Access to *Z*-vinyl bromides opens the opportunity to use the juxtaposition of the C−Br bond to the carbonyl group for cyclization, that is, an intramolecular Barbier reaction. While it is known that metal halogen exchange with organolithiums may be faster than carbonyl addition,[27] attempts to effect cyclization as shown in eq 14 simply by



treating at low temperature with *n*-butyllithium was messy. Nozaki and Kishi described the Barbier reaction of vinylbromides with aldehydes using a chromium−nickel system.[28] While ketones normally did not function well in this reaction, the fact that the reaction of eq 14 was intramolecular encouraged us to examine it.[29] Indeed it works quite well as illustrated in eq 15.



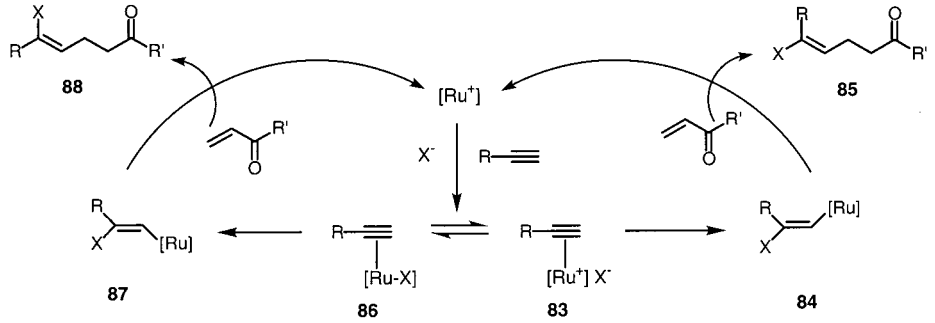
Thus, treating a 5.6/1 *Z*/*E* ratio of vinyl bromide **40** under standard Nozaki−Kishi conditions provided the cyclopentenol **81** in 70% yield. Presumably, the minor *E*-vinyl bromide cannot cyclize, but instead leads to reductive dehalogenation. Thus, the yield should be adjusted to reflect the *Z*/*E* ratio of the starting material to 83%. Such tertiary allylic cyclopentenols can be envisioned to participate in numerous reactions, for example, Claisen and related rearrangements, allyl coupling, and so forth. A simple application is their oxidation concomitant with allylic rearrangement to cyclopentenone **82**.[30]

Discussion

The formation of either vinyl halide isomer conflicts with a metallacycle mechanism of the type proposed in Scheme 2. The

(24) For a review, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(25) Morikawa, K.; Park, J.; Andersson, P. G.; Hashiyama, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 8463.
(26) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.
(27) See: Smith, M. B. *Organic Synthesis*; McGraw-Hill: New York, 1994; pp 719−727.
(28) (a) For a review, see: Cintas, P. *Synthesis* **1992**, 248. (b) For a recent intramolecular example and representative procedure, see: Chen, X.-T.; Bhattacharya, S. K.; Zhou, B.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 6563.
(29) Using a recently disclosed bipyridyl ligand system, ketones have been shown to be reactive. See: Chen, C. *Synlett* **1998**, 1311. See also: Chen, C.; Tagami, K.; Kishi, Y. *J. Org. Chem.* **1995**, *60*, 5386.
(30) Trost, B. M.; Pinkerton, A. B. *Org. Lett.* **2000**, *2*, 1601. Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682. Majetich, G.; Song, J.-S.; Leigh, A. J.; Condon, S. M. *J. Org. Chem.* **1993**, *58*, 1030. Majetich, G.; Condon, S.; Hull, K.; Ahmad, S. *Tetrahedron Lett.* **1989**, *30*, 1033.

Scheme 3. Mechanistic Rational for Vinyl Halide Formation



ability to use the ruthenium complexes ($CpRu(C_4H_7)PPh_3$) and ($CpRu(PPh_3)_2Cl$) suggests that perhaps only one open coordination site may be necessary—again inconsistent with the metallacycle mechanism. The results clearly indicate that there is a delicate balance between a *trans*- and a *cis*-haloruthenation to initiate this three-component coupling. While two totally different mechanistic pathways are possible, the most attractive proposal is outlined in Scheme 3. The catalytically active species, a cationic, coordinatively unsaturated ruthenium (which is derived from either **1** or **18**), coordinates with the alkyne and a halide to form two possible species, **83** and **86**. Species **83**, a more ionic species, leads to external halide attack and a *trans* halometalation to give **84**. Upon trapping with the enone, **84** gives *E*-vinyl halide **85**. Conversely, the more covalent species **86** leads to an internal, *cis* halometalation,[31] giving the vinyl ruthenium **87**. This then leads to *Z*-vinyl halide **88** upon trapping with an enone. This mechanism supports the observation that reaction with bromide leads to more of the *cis* halometalation, which is in line with the weaker nucleophilicity of bromide. In contrast, chloride, which is more nucleophilic,[32] gives more of the external attack (i.e., to form **84**) for a net *trans* halometalation.[33,34] Also, the overall effect of solvent strongly supports this mechanism. In both the chloride and bromide cases, the use of a less polar solvent (such as acetone) favors the more covalent species **86**, and thus more *Z*-vinyl halide is produced. Conversely, a more polar solvent (i.e., DMF) supports the more ionic species **83**, and thus more *E*-vinyl halide is formed. However, one interesting aspect is that the Ru−Cl bond is stronger than the Ru−Br bond,[35] and thus one might expect that **86** should be more favored for vinyl chloride formation (which in general it is not). Therefore, it appears that other factors such as the difference in nucleophilicity outweigh this consideration.

Several other observations support this mechanism. First, during the optimization of the vinyl bromide reaction, it was noted that when the amount of lithium bromide was lowered to 1.5 equiv from 3, the *Z*/*E* ratio increased from approximately 4/1 to almost 7/1. This would be explained by the fact that having a higher concentration of bromide should lead to more external attack (i.e., from **83**) and thus more *trans*-halometalation and *E*-vinyl bromide. Generally speaking, the use of more soluble halide sources, such as tetramethylammonium chloride (vs ammonium chloride) not only increases the yield but also increases the selectivity for the *E*-isomer. This is also consistent as above with having a higher concentration of halide ion in solution and thus favoring *trans* attack to form **84**.

Another effect seen that supports this mechanism is the use of alkynes with bulky propargylic substituents. Steric interactions between the R group and ruthenium in **84** disfavor this pathway. Thus, the reaction via **87** becomes more favorable. This is clearly the case when bulky alkynes are used, as exclusively the *Z*-isomer resulting from reaction via **87** is observed. The inability of other coupling partners to be effective in the ruthenium-catalyzed three-component coupling may also disfavor a ruthenacycle mechanism. If a ruthenacycle mechanism were operative, there is no a priori reason that other olefin partners should be unreactive.[36] Conversely, if the mechanism is that outlined in Scheme 3, then it is more understandable that insertion of a vinylmetal species should occur much more readily onto an enone instead of, say, styrene. The failure of acrylates implies more reactive Michael acceptors are required. Another problem with acrylates is their stability under the reaction conditions. The failure of more substituted enones to be reactive can be explained in both mechanisms by steric effects.

The formation of the products of Table 4 provide additional support for the mechanism of Scheme 3 as delineated in Scheme 4. The juxtaposition of a free OH three or four carbons removed from the double bond sets the stage for an intramolecular nucleophilic addition of the OH[37] to compete with the intermolecular addition of chloride, and the former predominates. Complexation with MVK and migratory insertion creates the enol ether **89.** Under these acidic conditions in the presence of

(31) For several examples of *cis* halometalations see: Dietl, H.; Reinheimer, H.; Moffatt, J.; Maitlis, P. M. *J. Am. Chem. Soc.* **1970**, *92*, 2276; Kaneda, K.; Uchiyama, T.; Fujiwara, Y.; Imanaka, T.; Teranishi, S. *J. Org. Chem.* **1979**, *44*, 55; Hua, R.; Shimada, S.; Tanaka, M. *J. Am. Chem. Soc.* **1998**, *120*, 12365. See also: Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731. Hara, S.; Satoh, Y.; Ishiguro, H.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 735.

(32) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry: Part A*, 3rd ed.; Plenum: New York, 1990; p 289.

(33) For a *trans* chloroalkylation see: Wang, Z.; Lu, X. *Chem. Commun.* **1996**, 535.

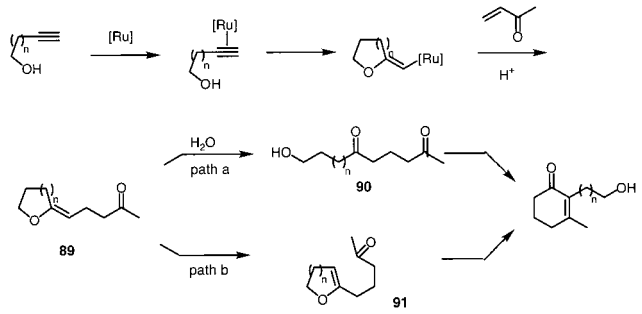
(34) For *trans* addition of carboxylate nucleophiles, see Rothman, E. S.; Hecht, S. S.; Pfeffer, P. E.; Silbert, L. S. *J. Org. Chem.* **1972**, *37*, 3551. Roten, N.; Shvo, Y. *Organometallics* **1983**, *2*, 1689. Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. *J. Org. Chem.* **1987**, *52*, 2230. Bruneau, C.; Neveux, M.; Kabouche, Z.; Ruppin, C.; Dixneuf, P. H. *Synlett* **1991**, 755. Neveux, M.; Seiller, B.; Hagedorn, F.; Bruneau, C.; Dixneuf, P. H. *J. Organomet. Chem.* **1993**, *451*, 133.

(35) Luo, L.; Li, C.; Cucullu, M. E.; Nolan, S. P. *Organometallics* **1995**, *14*, 1333.

(36) Terminal olefins are quite reactive in the Ru-catalyzed Alder-ene reaction. See: Trost, B. M.; Indolese, A. F.; Müller, T. J. J.; Treptow, B. *J. Am. Chem. Soc.* **1995**, *117*, 615. Trost, B. M.; Müller, T. J. J.; Martinez, J. *J. Am. Chem. Soc.* **1995**, *117*, 1888.

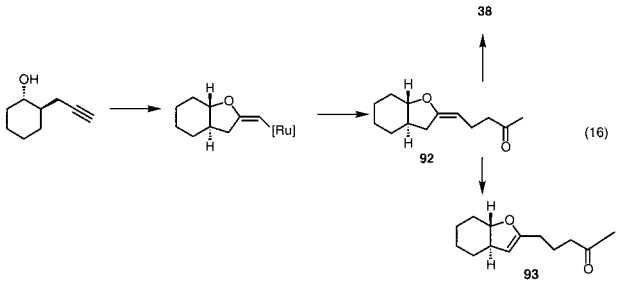
(37) For some examples of −OH addition to alkynes catalyzed by Ru, see: Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **1999**, *121*, 11680. By Pd: Nan, Y.; Miao, H.; Yang, Z. *Org. Lett.* **2000**, *2*, 297. See also: Alper, H.; Despeyroux, B.; Woell, J. B.*Tetrahedron Lett.* **1983**, *24*, 5691. Luo, F.-T.; Schreuder, I.; Wang, R.-T. *J. Org. Chem.* **1992**, *57*, 2213. Marshall, J. A.; Yanik, M. M. *Tetrahedron Lett.* **2000**, *41*, 4717.

Scheme 4. Mechanistic Rationale for Cyclohexenone Formation



water, two paths to product appear reasonable. Conceptually simplest is hydrolysis to diketone **90** which then undergoes standard aldol condensation to the observed products. Alternatively, simple acid-catalyzed isomerization of **89** to the thermodynamically more stable enol ether **91** then would permit direct carbonyl addition to the final product.

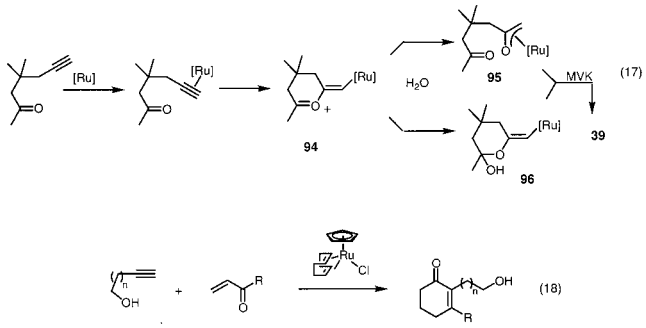
The reaction of entry 3 of Table 4 in which only diketone **38** is observed is interesting in this regard. The strain of the enol ether **92** (eq 16) may disfavor its formation and thereby allow



the competitive hydrolysis of **92** to diketone **38** to dominate. While aldol condensation of **38** might be anticipated to be slower than for diketones **90** ($n = 1$ and 2), it is somewhat surprising that it does not occur at all. Thus, this observation may suggest that the endocyclic enol ethers **91** are the actual precursors of the cyclohexenones rather than the diketones.

Judicious placement of a carbonyl group in the side chain appears to be able to compete effectively with external chloride for the ruthenium-complexed alkyne (eq 17). Hydration of the resultant adduct **94** then forms a ruthenium enolate **95** which then combines with MVK to form triketone **39**. This route is very reminiscent of the three-component coupling of water, alkynes, and vinyl ketones to form diketones.[5] On the other hand, the intermediate **94** may hydrate to **96** and then add MVK faster than collapse of this lactol to generate product. The ability of an oxygen of a carbonyl group to totally divert the course of reaction indicates that the ability of chloride to function as a nucleophile is marginal. These neighboring-group effects have real synthetic value. Thus, a very simple cyclohexenone synthesis emerges as summarized in eq 18.

Another question that must be answered for both the vinyl bromide and the vinyl chloride reaction is where the proton comes from to protonate the proposed ruthenium enolate and release the product. Adventitious water in the solvent or the salts used is the likely source for both reactions. It is clearly the case in the vinyl chloride reaction, where hydrated tin chloride is used. In the case of the vinyl bromides, a series of deuteration experiments were done to determine where the proton came from.



The first experiment involved running the reaction under the standard lithium bromide/acetone conditions, then quenching the reaction with deuterated acetic acid. No deuterium was incorporated (determined by integration of the proton NMR signals, which were assigned above). This indicates that the protonation occurs during the reaction itself and that an enolate is not being stoichiometrically formed. We then investigated whether the proton came from the acetone solvent, that is, a metal (ruthenium?) enolate deprotonating the acetone to release the vinyl halide product. This appears not to be the case either, as when deuteroacetone was used as solvent, no deuterium incorporation was observed. Finally, we investigated the addition of D_2O in place of water, because if water in the reaction mixture was responsible for the protonation of the proposed ruthenium enolate, addition of D_2O should lead to some deuterium incorporation. Expectedly, some deuterium incorporation (~30%) at the methylene position α in the product was observed when the reaction was run in the presence of 1 equiv of D_2O.[38] The modest level of deuterium incorporation derives from the presence of normal water arising from the water of hydration of stannic bromide.

Conclusions

In conclusion, we have developed a system for the formation of stereodefined vinyl halides via a three-component coupling process catalyzed by cationic cyclopentadienyl ruthenium species. The versatility of vinyl halides as cross-coupling partners make this method a useful addition to synthetic methodology.[39] Furthermore, such compounds have been shown to be α-hydroxyketone equivalents as well as precursors to 3-hydroxycyclopentenes, cyclopentenones, and substituted alkenes of defined geometry.

The catalyst system described herein represents the first example where either isomer of a vinyl halide can be accessed in a single catalyst system, depending on the counterion and solvent. Although there are a number of palladium-[40] and rhodium-catalyzed[41] *cis* additions of halides to alkynes, the only examples of *trans* addition involve the addition to alkynes bearing electron-withdrawing groups.[42] The other methods for the formation of vinyl halides involve use of stoichiometric

(38) For capture by an aldehyde as an electrophile leading to four-component coupling, see: Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **2000**, *122*, 8081.
(39) For some recent examples, see: Negishi, E.; Alimardanov, A.; Xu, C. *Org. Lett.* **2000**, *2*, 65. Williams, D. R.; Meyers, B. J.; Mi, L. *Org. Lett.* **2000**, *2*, 945. Maleczka, R. E., Jr.; Gallagher, W. P.; Terstiege, I. *J. Am. Chem. Soc.* **2000**, *122*, 384.
(40) Kaneda, K.; Uchiyama, T.; Fujiwara, Y.; Imanaka, T.; Teranishi, S. *J. Org. Chem.* **1979**, *44*, 55. Li, J.; Jiang, H.; Feng, A.; Jia, L. *J. Org. Chem.* **1999**, *64*, 5984.
(41) Hua, R.; Shimada, S.; Tanaka, M. *J. Am. Chem. Soc.* **1998**, *120*, 12365.
(42) Wang, Z.; Lu, X. *Chem. Commun.* **1996**, 535.

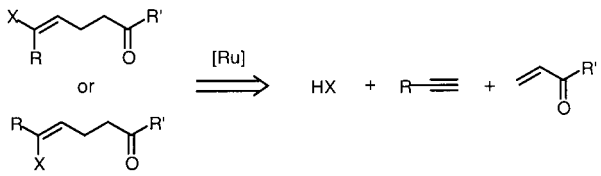


Figure 1. Formation of *E*- or *Z*-Vinyl Halides.

compounds, for example by olefination reactions or stoichiometric halogenation of carbon-metal bonds.[43] The selective formation of *Z*-vinyl bromides (and chlorides) by bromoboration is a useful method and somewhat more selective than the ruthenium-catalyzed reactions.[44] However, it involves the use of multiple equivalents of a very harsh reagent, boron tribromide, which is clearly not compatible with such groups as free alcohols and methyl esters. Both of these groups are tolerated under the much milder ruthenium-catalyzed conditions developed here. Retrosynthetically, *E*- or *Z*-vinyl halides can now be envisioned to come from alkynes and enones as outlined in Figure 1.

Experimental Section

General Procedure for *E*-Vinyl Chloride Formation (Table 3). Method A. The alkyne (0.25 mmol) and enone (0.5 mmol) were added to a solution of CpRu(COD)Cl (7.7 mg, 0.025 mmol), tin (IV) chloride pentahydrate (13.2 mg, 0.0375 mmol), and ammonium chloride (44.1 mg, 0.825 mmol) in DMF/water 20/1 (0.5 mL) in a pressure tube. The tube was capped and then heated to 60 °C for 4 h. It was then cooled to room temperature and poured into saturated sodium bicarbonate (25 mL). The aqueous layer was extracted with ether (2 × 25 mL). The organic layer was dried over magnesium sulfate and the solvent removed by rotary evaporation. The crude mixture was analyzed by proton NMR and then subjected to silica gel chromatography.

Method B. The alkyne (0.25 mmol) and enone (0.5 mmol) were added to a solution of CpRu(COD)Cl (7.7 mg, 0.025 mmol), tin (IV) chloride pentahydrate (13.2 mg, 0.0375 mmol), and tetramethylammonium chloride (82.2 mg, 0.75 mmol) in DMF (0.5 mL) in a pressure tube. The tube was capped and then heated to 60 °C for 4 h. It was then cooled to room temperature and poured into saturated sodium bicarbonate (25 mL). The aqueous layer was extracted with ether (2 × 25 mL). The organic layer was dried over magnesium sulfate and the solvent removed by rotary evaporation. The crude mixture was analyzed by proton NMR and then subjected to silica gel chromatography.

A typical example is given in the following. 3-Butyn-1-ol (17.5 mg, 0.019 mL, 0.25 mmol) and methylvinyl ketone (35.3 mg, 0.042 mL, 0.5 mmol) were added to a solution of CpRu(COD)Cl (7.7 mg, 0.025 mmol), tin (IV) chloride pentahydrate (13.2 mg, 0.0375 mmol), and ammonium chloride (44.1 mg, 0.825 mmol) in DMF/water 20/1 (0.5 mL) in a pressure tube. The tube was capped and then heated to 60 °C for 4 h. It was then cooled to room temperature and poured into saturated sodium bicarbonate (25 mL). The aqueous layer was extracted with ether (2 × 25 mL). The organic layer was dried over magnesium sulfate and the solvent removed by rotary evaporation. The crude mixture was analyzed by proton NMR and then subjected to silica gel chromatography (1/1 petroleum ether/ethyl acetate) to give 30.1 mg of vinyl chloride **25** (68%) as a 6.7/1 *E*/*Z*-mixture as determined by integration of the vinylic triplets.

(43) For some examples, see: Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851. See also: Corey, E. J.; Ulrich, P.; Fitzpatrick, J. M. *J. Am. Chem. Soc.* **1976**, *98*, 222. Ensley, H. E.; Buescher, R. R.; Lee, K. *J. Org. Chem.* **1982**, *47*, 404. Takahashi, T.; Xi, C.; Ura, Y.; Nakajima, K. *J. Am. Chem. Soc.* **2000**, *122*, 3228. See also: Knochel, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 4, pp 865−911.

(44) Satoh, Y.; Serizawa, H.; Hara, S.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 5225.

***E*-6-Chloro-8-hydroxy-oct-5-en-2-one (25):** light yellow oil. R_f = 0.30 (1/1 petroleum ether/ethyl acetate). IR (neat): 3415, 2959, 2926, 1713, 1657, 1410, 1368, 1262, 1233, 1166, 1107, 1050 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.65 (t, J = 7.7 Hz, 1H), 3.81 (t, J = 5.9 Hz, 2H), 2.62 (t, J = 6.0 Hz, 2H), 2.54 (t, J = 6.9 Hz, 2H), 2.33 (q, J = 7.1 Hz, 2H), 2.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.7, 133.1, 130.6, 61.1, 44.1, 38.5, 31.5, 24.1. Anal. Calcd for $C_8H_{13}ClO_2$: C, 54.40; H, 7.42. Found: C, 54.33; H, 7.34.

A larger scale example is given in the following. 4-Pentyn-2-ol (252 mg, 3.0 mmol) and methylvinyl ketone (423 mg, 0.50 mL, 6.0 mmol) were added to a solution of CpRu(COD)Cl (90 mg, 0.3 mmol), tin (IV) chloride pentahydrate (158 mg, 0.45 mmol), and ammonium chloride (529 mg, 9.9 mmol) in DMF/water 20/1 (6 mL) in a pressure tube. The tube was capped and then heated to 60 °C for 4 h. It was then cooled to room temperature and poured into saturated sodium bicarbonate (100 mL). The aqueous layer was extracted with ether (2 × 100 mL). The organic layer was dried over magnesium sulfate and the solvent removed by rotary evaporation. The crude mixture was analyzed by proton NMR and then subjected to silica gel chromatography (1/1 petroleum ether/ethyl acetate) to give 383 mg of vinyl chloride **24** (66%) as a 6.9/1 *E*/*Z*-mixture as determined by integration of the vinylic triplets.

***E*-6-Chloro-8-hydroxy-non-5-en-2-one (24):** light yellow oil. R_f = 0.29 (1/1 petroleum ether/ethyl acetate). IR (neat): 3425, 2969, 2929, 1714, 1655, 1409, 1370, 1264, 1166, 1111, 1075, 940 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.65 (t, J = 7.6 Hz, 1H), 4.13 (m, 1H), 2.65 (dd, J_1 = 14 Hz, J_2 = 8.5 Hz, 1H), 2.54 (t, J = 6.8 Hz, 2H), 2.45−2.24 (m, 4H), 2.13 (s, 3H), 1.24 (d, J = 6.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.5, 133.2, 130.6, 66.9, 44.9, 44.0, 31.4, 24.4, 24.2. Anal. Calcd $C_9H_{15}ClO_2$: C, 56.69; H, 7.93. Found: C, 56.49; H, 7.79.

General Procedure for Ruthenium-Catalyzed *E*- or *Z*-Vinyl Bromide Formation Using Ammonium Bromide (Table 6). The alkyne (0.25 mmol) and enone (0.5 or 0.375 mmol) were dissolved in the appropriate solvent (0.5 mL) (see below) and then added to CpRu$(CH_3CN)_3PF_6$ (10.9 mg, 0.025 mmol), stannic bromide (16.4 mg, 0.0375 mmol), and ammonium bromide (73.4 mg, 0.75 mmol) in a pressure tube. The tube was capped and then heated to 60 °C for 2 h. It was then cooled to room temperature and applied directly to a silica gel column. The eluting solvent for each case is the same solvent used for R_f determination.

A typical example is given in the following. 10-Undecyn-1-ol (42.1 mg, 0.25 mmol) and methylvinyl ketone (26.5 mg, 0.032 mL, 0.375 mmol) were dissolved in the acetone/DMF 1/1 (0.5 mL) and then added to CpRu$(CH_3CN)_3PF_6$ (10.9 mg, 0.025 mmol), stannic bromide (16.4 mg, 0.0375 mmol), and ammonium bromide (73.4 mg, 0.75 mmol) in a pressure tube. The tube was capped and then heated to 60 °C for 2 h. It was then cooled to room temperature and applied directly to a silica gel column (1/1 petroleum ether/ethyl acetate) to give 60 mg (75%) of vinyl bromide **48**, as a 2.7/1 *E*/*Z*-mixture, as determined by integration of the two vinylic triplets at δ 5.80 and 5.67 (for the *E*- and *Z*-isomers respectively) in the proton NMR spectra.

***E*-6-Bromo-15-hydroxy-pentadec-5-en-2-one (*E*-48):** light yellow oil. R_f = 0.38 (1/1 petroleum ether/ethyl acetate). IR (neat): 3412, 2928, 2855, 1717, 1646, 1464, 1427, 1409, 1365, 1198, 1164, 1056 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.80 (t, J = 7.7, 1H), 3.65 (t, J = 6.6, 2H), 2.53 (t, J = 7.3, 2H), 2.44 (t, J = 7.2, 2H), 2.29 (q, J = 7.5, 2H), 2.17 (s, 3H), 1.59−1.51 (m, 5H), 1.36−1.25 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.6, 130.2, 127.3, 63.0, 42.6, 35.4, 32.7, 30.0, 29.4, 29.3, 29.2, 28.5, 27.9, 25.7, 23.6. HRMS: Calcd for $C_{15}H_{27}BrO_2$−H_2OBr: 221.1904. Found: 221.1905.

***Z*-6-Bromo-15-hydroxy-pentadec-5-en-2-one (*Z*-48):** light yellow oil. R_f = 0.38 (1/1 petroleum ether/ethyl acetate). IR (neat): 3412, 2928, 2855, 1717, 1646, 1464, 1427, 1409, 1365, 1198, 1164, 1056 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.67 (t, J = 6.7, 1H), 3.66 (t, J = 6.7, 2H), 2.56 (t, J = 7.2, 2H), 2.44−2.39 (m, 4H), 2.17 (s, 3H), 1.60−1.52 (m, 5H), 1.40−1.25 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$): δ

208.1, 129.8, 126.4, 63.0, 42.2, 41.4, 32.7, 29.8, 29.4, 29.3, 29.2, 28.3, 28.0, 25.7, 25.6. HRMS: Calcd for $C_{15}H_{27}BrO_2-H_2OBr$: 221.1904. Found: 221.1905.

General Procedure for Ruthenium-Catalyzed *Z*-Vinyl Bromide Formation Using Lithium Bromide (Table 7). The alkyne (0.25 mmol) and enone (0.375 mmol) were dissolved in the acetone (reagent grade, not distilled, 0.5 mL) and then added to $CpRu(CH_3CN)_3PF_6$ (10.9 mg, 0.025 mmol), stannic bromide (16.4 mg, 0.0375 mmol), and lithium bromide (32.6 mg, 0.375 mmol) in a pressure tube. The tube was capped and then heated to 60 °C for 2 h. It was then cooled to room temperature and applied directly to a silica gel column. The eluting solvent for each case is the same solvent used for R_f determination.

A typical example is given in the following. 5-Cyanopentyne (23.4 mg, 0.25 mmol) and methylvinyl ketone (26.5 mg, 0.032 mL, 0.375 mmol) were dissolved in the acetone (reagent grade, not distilled, 0.5 mL) and then added to $CpRu(CH_3CN)_3PF_6$ (10.9 mg, 0.025 mmol), stannic bromide (16.4 mg, 0.0375 mmol), and lithium bromide (32.6 mg, 0.375 mmol) in a pressure tube. The tube was capped and then heated to 60 °C for 2 h. It was then cooled to room temperature and applied directly to a silica gel column (1/1 petroleum ether/ethyl ether) to give 55 mg of vinyl bromide **42** (90%) as a 3.3/1 *Z*/*E* mixture, as determined by integration of the two vinylic triplets at δ 5.89 and 5.80 (for the *E*- and *Z*-isomers respectively) in the proton NMR spectra.

***E*-5-Bromo-9-oxo-dec-5-enenitrile (*E*-42):** light yellow oil. R_f = 0.15 (2/1 petroleum ether/ether). IR (neat): 3529, 2925, 2361, 2247, 1713, 1426, 1363, 1165, 1100, 924, 860, 747 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.89 (t, J = 7.7, 1H), 2.62 (t, J = 7.0, 2H), 2.54 (t, J = 7.1, 2H), 2.39−2.31 (m, 4H), 2.14 (s, 3H), 1.93 (quint, J = 7.0, 2H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.0, 133.0, 123.7, 119.3, 42.2, 33.4, 30.0, 25.5, 23.6, 15.7. Anal. Calcd for $C_{10}H_{14}BrNO$: C, 49.20; H, 5.78; N, 5.74. Found: C, 49.15; H, 6.00; N, 5.50.

***Z*-5-Bromo-9-oxo-dec-5-enenitrile (*Z*-42):** light yellow oil. R_f = 0.15 (2/1 petroleum ether/ether). IR (neat): 3529, 2925, 2361, 2247, 1713, 1426, 1363, 1165, 1100, 924, 860, 747 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.80 (t, J = 6.8, 1H), 2.63−2.52 (m, 4H), 2.41 (q, J = 6.8, 2H), 2.32 (t, J = 7.0, 2H)), 2.16 (s, 3H), 1.91 (quint., J = 7.1, 2H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.6, 129.5, 126.1, 119.2, 41.8, 39.6, 29.8, 25.5, 23.4, 15.5. Anal. Calcd for $C_{10}H_{14}BrNO$: C, 49.20; H, 5.78; N, 5.74. Found: C, 49.15; H, 6.00; N, 5.50.

A larger-scale example is given in the following. Phenylacetylene (510 mg, 5 mmol) and phenylvinyl ketone (990 mg, 7.5 mmol) were dissolved in the acetone (reagent grade, not distilled, 10 mL) and then added to $CpRu(CH_3CN)_3PF_6$ (218 mg, 0.5 mmol), stannic bromide (320 mg, 0.75 mmol), and lithium bromide (652 mg, 7.5 mmol) in a pressure tube. The tube was capped and then heated to 60 °C for 2 h. It was then cooled to room temperature and applied directly to a silica gel column (1/1 petroleum ether/ethyl ether) to give 1.13 g of vinyl bromide **62** (70%). Only the *Z*-isomer was observed by the presence of a single vinylic triplet in the proton NMR spectra.

***Z*-5-Bromo-1,5-diphenyl-pent-4-en-1-one (62):** yellow oil. R_f = 0.35 (12/1 petroleum ether/ethyl acetate). IR (neat): 3059, 1683, 1598, 1489, 1445, 1405, 1361, 1234, 1178, 1074, 993, 754 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.02 (d, J = 8.1, 2H), 7.61−7.59 (m, 1H), 7.56−7.49 (m, 4H), 7.37−7.31 (m, 3H), 6.39 (t, J = 7.1, 2H), 3.24 (t, J = 7.1, 2H), 2.83 (q, J = 7.1, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.0, 136.7, 133.2, 133.0, 130.0, 128.7, 128.6, 128.4, 128.2, 128.1, 127.5, 37.0, 27.0. Anal. Calcd for $C_{17}H_{15}BrO$: C, 64.78; H, 4.80. Found: C, 64.80; H, 4.73.

General Procedure for Asymmetric Dihydroxylation of Vinyl Chlorides To Form α-Hydroxyketones (Table 10). A representative example is given in the following. AD-mix-β (238 mg) and methanesulfonamide (16.2 mg, 0.17 mmol) were mixed in *tert*-butyl alcohol/water, 1/1 (1 mL), at room temperature and stirred for 30 min. The reaction was then cooled to 0 °C, and vinyl chloride **22** (41.9 mg, 0.17 mmol) was added. The mixture was stirred at 0 °C for 24 h. The reaction was stopped by pouring it into ether or ethyl acetate (25 mL) and saturated aqueous sodium chloride (25 mL). The organic layer was separated, washed two times with saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated by rotary evaporation to yield crude product, which was purified with silica gel chromatography (1/2 petroleum ether/ether), giving 25 mg of hydroxyketone **73** (64%). Some of this material (10 mg, 0.04 mmol) was dissolved in pyridine (1 mL), and benzoyl chloride (0.013 mL, 0.11 mml) was added at room temperature. The reaction was stirred for 16 h and then stopped by pouring it into ether (25 mL) and water (25 mL). The organic layer was separated, washed two times with 1 N aqueous hydrochloric acid, dried over magnesium sulfate, and concentrated by rotary evaporation to yield product, which was purified with silica gel chromatography (1/1 petroleum ether/ether) giving 9.2 mg of **77**(82%). The ee was 86.3% determined by chiral HPLC analysis (compared to the racemic material), separated on a Chiralpak AD column, eluting 90/10 heptane/2-propanol, with the major isomer eluting in 15.36 min, and the minor in 20.13 min.

1-Acetoxy-6-hydroxydecan-5,9-dione (73): colorless oil, R_f = 0.15 (1/2 petroleum ether/ether). IR (neat): 3474, 2923, 1714, 1434, 1366, 1241, 1164, 1105, 1039, 804, 737 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.19−4.13 (m, 1H), 4.07 (t, J = 6.0 Hz, 2H), 3.50 (d, J = 4.9 Hz, 1H), 2.73−2.29 (m, 4H), 2.21−2.19 (m, 1H) 2.17 (s, 3H), 2.05 (s, 3H), 1.70−1.60 (m, 5H).^{13}C NMR (75 MHz, $CDCl_3$): δ 211.6, 208.1, 171.1, 75.3, 63.9, 38.5, 37.3, 30.0, 28.1, 27.4, 20.9, 20.0. Full characterization was done for the benzoylated compound.

1-Acetoxy-6-benzoyloxydecan-5,9-dione (77): yellow oil, R_f = 0.18 (1/1 petroleum ether/ether). IR (neat): 3064, 2924, 2853, 1722, 1680, 1602, 1452, 1367, 1316, 1272, 1247, 1112 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.06 (dd, J_1 = 8.2, J_2=1.1, 2H), 7.61 (t, J = 7.3, 1H), 7.47 (t, J = 7.8, 2H), 5.24 (dd, J_1 = 8.1 Hz, J_2 = 4.4 Hz, 1H), 4.06 (t, J = 6.0 Hz, 2H), 2.67−2.59 (m, 4H), 2.30−2.22 (m, 1H) 2.17 (s, 3H), 2.15−2.05 (m, 1H), 2.03 (s, 3H), 1.71−1.61 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.0, 206.5, 171.2, 166.0, 133.6, 129.8, 129.1, 128.6, 77.7, 64.1, 38.6, 38.1, 30.1, 27.9, 24.2, 21.0, 19.6. Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.50; H, 6.94. Found: C, 65.64; H 7.17.

Non-Racemic: separated on Chiralpak AD column (90/10 heptane/2-propanol, 1 mL/min, 254 nm detection); first enantiomer: 15.36 min (major); second enantiomer: 20.13 min.

Experimental Details for Equation 11: Cross-Coupling Reaction of Vinyl Chloride 15. Following the published procedure,[26] vinyl chloride **15** (22 mg, 0.1 mmol) *p*-acetylbenzeneboronic acid (33 mg, 0.2 mmol), potassium fluoride (20 mg, 0.33 mmol), and $Pd_2dba_3{\cdot}CHCl_3$ (2.6 mg, 0.0025 mmol) were added to a test tube. The tube was sealed and placed under argon. THF (0.25 mL) was added to the test tube purged with argon for 5 min. Then, tri-*tert*-butylphosphine (2.6 mg, 0.0015 mL, 0.006 mmol) was added, and the reaction stirred at room temperature for 16 h. The reaction was next poured into ether (25 mL) and extracted three times with water, and then the organic layer was dried over magnesium sulfate. The ether was removed by rotary evaporation to give a crude material that was purified by silica gel chromatography (10/1 petroleum ether/ethyl acetate) to give 22 mg **78** (73%) as the *E*-isomer. The other isomer was not isolated.

6-(4-Acetyl-phenyl)-dodec-5-en-2-one (78): colorless oil. R_f = 0.17 (15/1 petroleum ether/ether). IR (neat): 2957, 2929, 2858, 2358, 1719, 1687, 1456, 1361, 1264, 1162, 1123, 1100 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.99−7.97 (m, 1H), 7.60−7.57 (m, 1H), 7.51−7.47 (m, 2H), 5.55 (t, J = 7.7, 1H), 2.63 (s, 3H), 2.52 (t, J = 7.3, 2H), 2.37−2.29 (m, 4H), 2.17 (s, 3H), 1.58−1.52 (m, 2H), 1.35−1.27 (m, 6H), 0.91 (t, J = 6.9, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.5, 198.2, 137.1, 135.4, 133.1, 128.6, 128.3, 125.9, 42.9, 33.6, 31.6, 30.0, 28.4, 27.2, 26.6, 22.6, 22.5, 14.0. HRMS: Calcd for $C_{20}H_{28}O_2$: 300.2089. Found 300.2095.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs. Mass spectra were

provided by the Mass Spectrometry Regional Center of the University of California-San Francisco, supported by the NIH Division of Research Resources. A.B.P. thanks Abbott Laboratories, Glaxo-Wellcome, the ACS Division of Organic Chemistry (sponsored by Bristol-Myers Squibb), and Eli Lilly for fellowship support.

Supporting Information Available: Experimental details for optimization reactions as well as characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA011426W