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Enhanced geometrical control in a Ru-catalyzed three component coupling†

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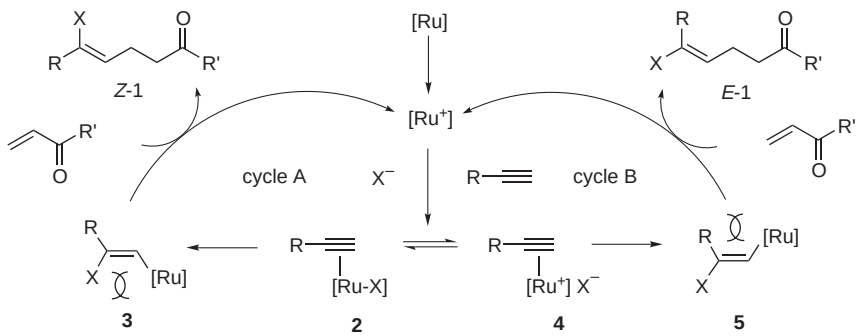
Abstract

Exclusive *Z*-selectivity in the Ru-catalyzed bromoalkylation of alkynes with vinyl ketones is observed with aryl and other tertiary substituted acetylenic substrates, a feature that has led to an efficient synthesis of a COX-2 inhibitor. © 2000 Elsevier Science Ltd. All rights reserved.

In previous papers, we reported the ruthenium-catalyzed haloalkylation of acetylenes could occur with either a *cis*[1] or *trans*[2] geometry to form ***Z*-1** or ***E*-1**, respectively, as outlined in Scheme 1.[3] The competition of the conversion of **2** to **3** compared to the conversion of **4** to **5** determines the geometric selectivity. Our interest in employing the *Z*-bromoalkenes (***Z*-1**, X = Br) in a cyclopentenone synthesis[4] stimulated the need to enhance the *Z*-selectivity of the bromoalkylation process. Examination of **3** and **5** suggests that the steric interactions between



Scheme 1. Proposed mechanism of Ru-catalyzed haloalkylation

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† Dedicated with great admiration to Professor Harry H. Wasserman in honor of his 80th birthday and with best wishes for many more to come.

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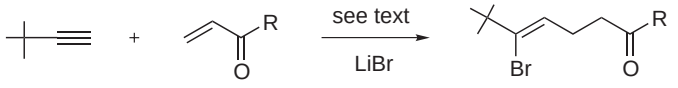
the alkyne substituent R and the metal may affect their ease of formation. In this paper, we report the results of our investigation of this effect. The success of these studies led to a very successful synthesis of 2-arylcyclopentenones as demonstrated by the completion of a short synthesis of a COX-2 inhibitor.

Using a classical *t*-butyl group as the acetylenic substituent to maximize steric interactions, *t*-butylacetylene (**6**) and methyl vinyl ketone (**7b**, PVK) were subjected to 10 mol% $[CpRu(CH_3CN)_3]^+PF_6^-$ (**8**), 15 mol% stannic bromide and 1.5 equiv. of lithium bromide in acetone at 60°C (Eq. (1)). Delightfully only a single geometric isomer **9**[5] is observed as product. Changing the acceptor to phenyl vinyl ketone **7b** gave virtually identical results. Replacing the *t*-butyl group with trimethylsilyl (e.g. **10**) shows no deterioration in the *Z*-selectivity to produce exclusively bromide **11**[5] as shown in Eq. (2). The more modest yields may reflect the volatility of the products upon isolation since the reactions are quite clean.

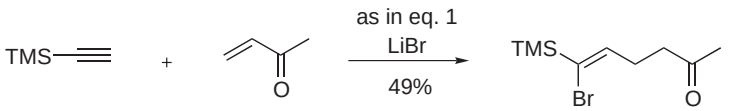


6 **7** **9**

a) R = CH_3 54% a) R = CH_3

b) R = Ph 56% b) R = Ph

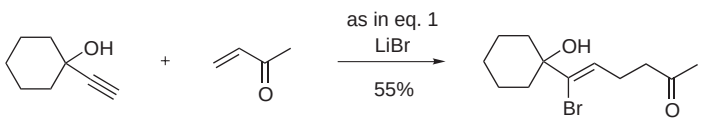
(1)



10 **11**

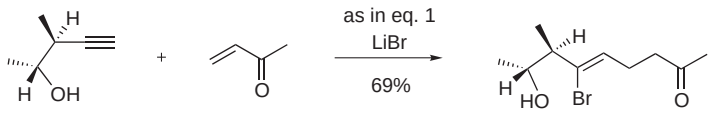
(2)

Replacing an alkyl group with a hydroxy group as shown with the propargyl alcohol substrate **12** also gave only the *Z*-alkene **13**[5] with MVK (Eq. (3)). The compatibility of the tertiary propargylic alcohol is particularly noteworthy because of the well known reactivity of substrates like **12** to form allenylidene ruthenium complexes.[6] Reducing the size of the substituent to an isopropyl like group as in **14** saw a decrease in *Z*-selectivity wherein an 8:1 *Z*:*E* ratio of bromoalkenes **15**[5] was obtained (Eq. (4)).



12 **13**

(3)

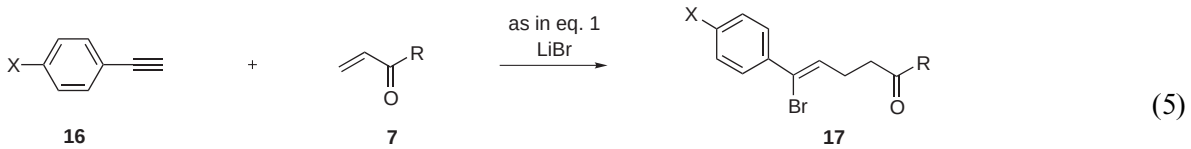


14 **15** *Z*:*E* 8:1

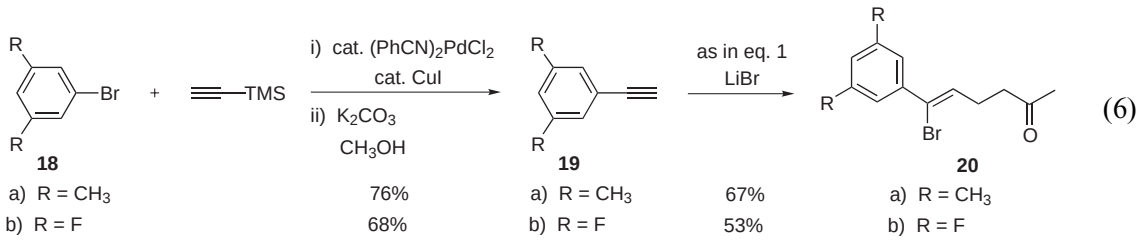
(4)

The steric bulk of an aryl group depends upon its conformation.[7] Thus, we were pleased to observe that phenylacetylene (**16a**) also shows formation of only the *Z*-bromoalkene **17a**[5] (Eq. (5)) with MVK (**7a**). As before, replacing MVK (**7a**) by PVK (**7b**) showed no deterioration in *Z*-alkene selectivity to form **17b**.[5] Using a more electron rich arylacetylene **16b** led to equivalent results and formed only *Z*-alkenes **17c**[5] and **17d**[5]. 3,5-Disubstituted aryl groups are also

tolerated in this reaction as shown in Eq. (6). This equation illustrates the facility of the process since the starting alkynes **19a**,**b** are easily accessible by a Sonogashira type coupling protocol[8] from the bromoarenes **18a**,**b**. Both substrates gave single products **20a** and **20b**, respectively.

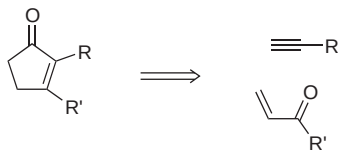


(5)

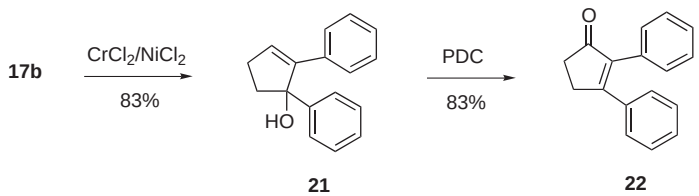


(6)

One particularly useful application of these adducts of three component coupling is their application to a synthesis of cyclopentenones as illustrated in the retrosynthetic analysis of Eq. (7). The sequence is initiated by a Kishi–Nozaki modification[9] of the Barbier reaction which requires the *Z*-bromoalkene. In the case of aryl substituted substrates, the viability of the initial adducts of this reaction such as **21** must be questioned since it entails formation of a highly labile tertiary allylic and benzylic alcohol. Surprisingly, vinylbromide **17b** does form **21** which, upon oxidative rearrangement, provides 2,3-diphenylcyclopentenone **22**[10] in excellent yield (Eq. (8)).



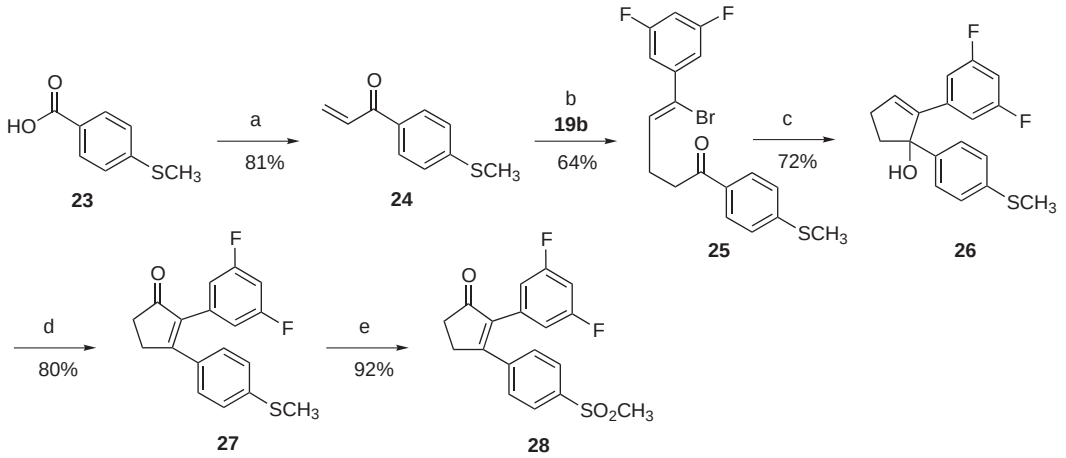
(7)



(8)

The success of this cyclopentenone formation led to our exploration of a synthesis of a potent COX-2 inhibitor **28**[11] as shown in Scheme 2. The requisite vinyl ketone **24** was formed from the commercially available carboxylic acid **23** using a Stille coupling with an in situ formed acid chloride.[12] Ruthenium-catalyzed addition of vinyl ketone **24** with acetylene **19b** generates a single vinyl bromide **25**[5]. The compatibility with divalent sulfur should be noted. In spite of the sensitivity of the tertiary alcohol **26**, it forms in good yield under the standard conditions.

Oxidative rearrangement produces the previously described cyclopentenone **27**[11], which was oxidized as reported using oxone[13] to form the desired target **28** in only five linear steps. Although none of the steps have really been optimized, the overall yield of 28% is quite reasonable.



Scheme 2. A synthesis of a potent cox-2 inhibitor. (a) $(COCl)_2$, cat. DMF, CH_2Cl_2 then $(n\text{-}C_4H_9)_3SnCH{=}CH_2$, 0.01 mol% $(Ph_3P)_2Pd(CH_2Ph)Cl$, $PhCH_3$, 80°C. (b) 10% $[CpRu(NCCH_3)_3]^+PF_6^-$, 15 mol% $SnBr_4$, 1.5 equiv. LiBr, CH_3COCH_3, 60°C. (c) $CrCl_2$, $NiCl_2$, DMF, rt. (d) PDC, CH_2Cl_2, 0°C. (e) Oxone, acetone, H_2O, 45°C

The ability to enhance the *Z*-selectivity by modification of the substrate in the manner indicated supports the mechanistic rationale as outlined in Scheme 1. The synthetic implications stem from the ability to use the geometrically pure products directly for further conversions. The synthesis of the cyclopentenones is but one illustration. Cross-coupling of the vinyl bromides[14] is an obvious additional direction that arises.

Acknowledgements

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