Pergamon

Tetrahedron Letters, Vol. 38, No. 47, pp. 8181-8184, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10252-0

New Reactions Involving Palladacyclobutanes: The Attack of Phenoxide Ion at the Central Carbon of Both 1- and 2-Bromo(π–allyl)palladium Complexes

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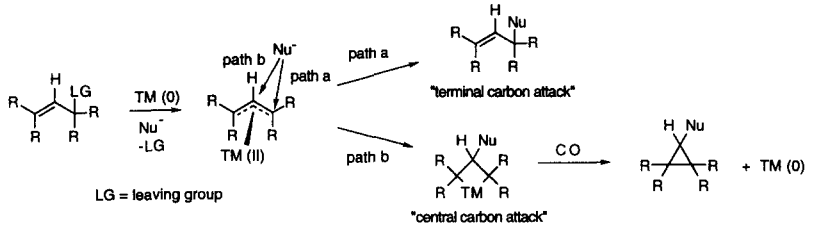
Abstract: Nucleophilic attack of phenoxide ion occurs primarily at the central carbon of halo-substituted (π-allyl)Pd complexes.

The substitution of allylic leaving groups with a variety of nucleophiles using transition metal (TM) catalysis is a very important synthetic transformation.[2] Typically, nucleophilic attack is directed to the terminal carbon of the (π–allyl)TM complex that results in allylic substitution (Scheme 1, path a). It was first demonstrated by Green and co-workers in 1976 that, under the appropriate conditions, nucleophilic attack could be directed to the central carbon of π–allyl complexes of Mo and Wo.[3] Attack at this position generates the metallacyclobutane, the most common fate of which is cyclopropane formation via reductive elimination (Scheme 1, path b). Since this time, an increasing number of examples of this phenomenon have surfaced and thus a greater understanding of the factors that direct nucleophile regioselectivity is emerging.[4,5,6,7,8]



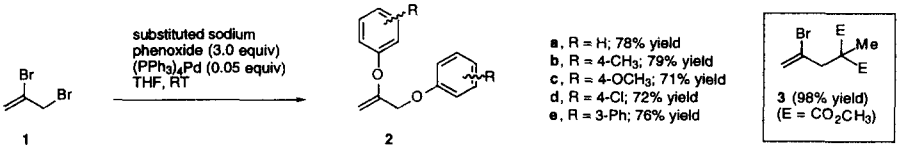
Scheme 1. Regioselectivity in nucleophilic attack on (π–allyl)TM complexes.

Until recently, it was thought that only comparatively non-stabilized nucleophiles underwent attack at the central carbon. Attack at this position with non-stabilized anions such as metal hydride (e.g., lithium aluminum hydride)[3] and alkyl metal (e.g., Grignard)[3,8c] reagents is with precedent. Carbon enolates possess moderate stability (pK_a = 20-30) and they too add to the central carbon under appropriate reaction conditions.[4b,5,6,8d] It has been demonstrated by Murai and co-workers that even stabilized malonate-based anions (pK_a = 14-15) can be directed reliably to the 2-position of the (π–allyl)Pt intermediate generated from 2-chloro-2-propenyl-acetate.[4a] Later it was shown by Bäckvall's group that malonate-based anions can be directed to either the central or terminal carbon of the corresponding (π–allyl)Pd complex by tuning the ligands on the metal.[7] These results support earlier findings of Hegedus et. al. who found that the ligands on Pd play a very important role in controlling regioselectivity of addition with enolate nucleophiles.[5] In both studies, strong σ-donor amine-based ligands promoted central carbon attack while strong π–acceptor phosphine-based ligands directed attack to the terminus.

In this study, the regioselectivity of nucleophilic attack with phenoxide-based anions on the π–allyl(Pd) complex generated from 1,3- and 2,3-dibromo-1-propene was examined. These nucleophiles (pK_a = 10 - 12) have similar anion stability when compared with methyl acetoacetate (pK_a = 10 - 12) or dialkyl malonates (pK_a = 12 -

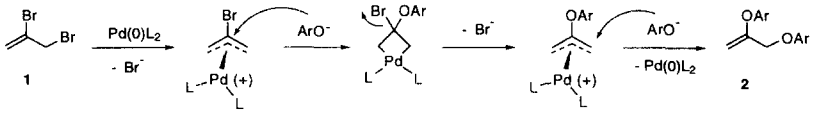
14), but the nature of the oxygen-based anion is significantly different. Altered steric and electronic properties of both the starting dihalide and the phenoxide-based nucleophile were also investigated.

Addition of **1** to a THF solution containing 3.0 equiv of sodium phenoxide (prepared in situ) and 0.05 equiv of $(PPh_3)_4Pd$ at RT (hereafter called "standard conditions") provided **2a** as the sole product of the reaction (Scheme 2).[9] The reaction is very rapid and clean producing only one product spot by TLC. To our knowledge,



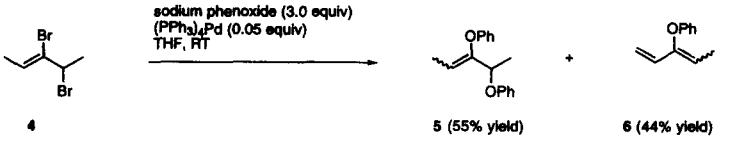
Scheme 2. Addition of phenoxide-based anions to 2,3-dibromo-1-propene.

this is the first such selective nucleophilic attack at the central carbon of a (π–allyl)Pd complex with phosphine-based ligands.[3-8] Presuming the mechanism proposed by Bäckvall[7] is operating here (see mechanism presented for present study in Scheme 3), attack at the central carbon of the initially formed (π–allyl)Pd intermediate initiates the formation of **2a**. Treatment of **1** with 3.0 equiv of sodium dimethyl methylmalonate under otherwise identical reaction conditions gave exclusively the terminal attack product **3**. In uncatalyzed control experiments, both reactions did not proceed at all. Therefore, both processes are Pd catalyzed, but the regioselectivity is completely opposite for attack of the two nucleophiles. With this in mind, we wanted to see if changing the stereo-electronic properties of phenoxide would alter the regioselectivity of nucleophilic attack. A number of substituted phenolates differing in anion stability were reacted with **1** using the standard conditions. The regiochemistry in the products of these reactions was the same observed with the parent phenoxide (see Scheme 2, products **2b-e**). Central carbon attack was even observed with 3-phenylphenoxide which is significantly more hindered than the rest. This indicates that the "fundamental electronic nature" of these phenolate nucleophiles is a strongly dominating effect in directing regioselectivity in these additions. Of course, the other possibility is that the regioselectivity is under substrate control and it is the bromine on the (π–allyl)Pd complex that is controlling selectivity.



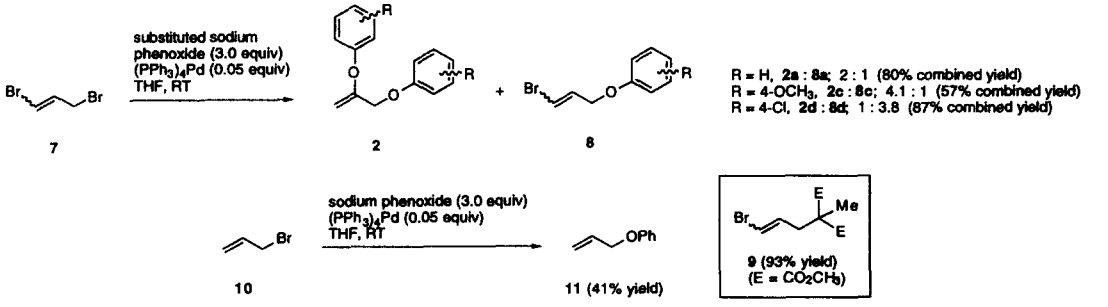
Scheme 3. Proposed mechanism for the formation of compound **2** from 2,3-dibromo-1-propene (**1**).

In order to probe the steric effects imparted by the substrate, **4** was prepared and treated with the standard reaction conditions (Scheme 4). Products **5** and **6** both clearly originate from attack of phenoxide at the central carbon of the now substituted, but still symmetrical, initially formed (π–allyl)Pd intermediate (see Scheme 3). Despite the added steric repulsion caused by the two methyl groups on the substrate, compared with **1**, the reaction is still finished quickly following addition of **4** to the reaction mixture. However, congestion of the second (π–allyl)Pd intermediate formed (see Scheme 3) is apparent because β-hydride elimination providing **6** now is competitive with nucleophilic attack of the second phenoxide molecule that is required to provide **5**. With substrates **1** and **4**, the forces involved that direct phenoxide ion attack to the central carbon are substantial. Electronic or steric changes to the nucleophile do not alter regioselectivity, nor does the added bulk on **4**. The



Scheme 4. Pd-catalyzed reaction of 3,4-dibromo-2-pentene (**4**) with sodium phenoxide.

bromine on the central carbon could play a role in this selectivity. Bromonium ion formation by resonance (i.e., +R) with the central carbon of the cationic π–allyl(Pd) complex could be operating. This would increase the amount of positive charge that could be housed at the central carbon. It has been postulated that regioselectivity in systems with a large E_{LUMO} - E_{HOMO} gap for the (π–allyl)Pd complex and the nucleophile, respectively, is under charge control.[4b,7b,10,11] If this is the case, there could exist a "charge match" between C2 of **1**, or C3 of **4**, and the low lying E_{HOMO} of these nucleophiles. In other words, the basic electronics of the phenolate derivatives and the charge state at central carbon of the (π–allyl)Pd complexes of **1** or **4** are reinforcing, thus regioselectivity is directed to these sites by both partners. If bromine was involved, moving the bromine to the terminal position of the (π–allyl)Pd complex should promote attack at that site because positive charge would now be better supported there. Such selectivity is with precedent for (π–allyl)Pd complexes substituted with only an alkoxy group at one end of the π–allyl.[12] In that case, attack of malonate-type anions on the π–allyl (THF soln, TPP ligand) was directed exclusively to the position bearing the oxygen-based group, even though the other end was unsubstituted. To explore this possibility, the bromine was moved from C2 to C1 giving rise to compound **7**, that was treated to standard reaction conditions (Scheme 5). Attack of phenoxide occurred preferentially at C2 giving rise to **2a**, *the same product derived from dihalide 1*. The mechanism for the formation of **2** from **7** is clearly more involved than that from **1** although attack at the central carbon of the initially formed (π–allyl)Pd complex is likely involved.



Scheme 5. Effect of Br at the central carbon of the initially-formed (π–allyl)Pd complex.

Moving bromine to C1 altered the regioselectivity somewhat, but not to the extent that charge control might have predicted. Substitution with sodium dimethyl methylmalonate resulted in allylic substitution exclusively at the end distal to bromine (**9**). Therefore, bromine does not impart the pronounced electronic effect that oxygen does at C1 (*vide supra*). This is explained by the ability of oxygen to donate strongly by resonance (+R) which vastly overcomes its large electronegativity leading to a pronounced -I effect. However, the presence of Br at either C1 or C2 is necessary to obtain any product arising from phenoxide attack at C2. When allyl bromide (**10**) was treated to standard reaction conditions, the allylic substitution product **11** was produced exclusively. That **11** was the only product isolated does not rule out the possibility that central carbon attack does take place. Instability of

the resultant 3-phenoxypalladcyclobutane intermediate could promote re-ionization of phenoxide and the allylic substitution product would simply build up over time. Thus far, no unambiguous experiments have been conducted to ascertain if central carbon attack is occurring with **10**. With compound **1**, changing the stability of phenoxide anion had no effect on regioselectivity of nucleophilic attack. However, similar changes in the nucleophile with **7** had a dramatic effect on selectivity. Compared to the parent phenoxide (**2a**:**8a**; 2:1), electron rich 4-methoxyphenoxide gave significantly more product resulting from central carbon attack (**2c**:**8c**; 4.1:1) (Scheme 5). In contrast, less electron rich 4-chlorophenoxide gave inverted selectivity (**2d**:**8d**; 1:3.8). Assuming that there are no significant differences in sterics between these three phenoxides, the basic stabilities, and hence reactivities of these subtly different nucleophiles with the 1-bromo(π–allyl)Pd complex is pronounced.

In this study, we have demonstrated that phenolates are very active nucleophiles in substitution reactions involving (π–allyl)Pd complex formation. With both 1-bromo- and 2-bromo(π–allyl)Pd complexes, phenolates display a strong regioselectivity for nucleophilic attack at the central carbon. This highly selective tendency for attack at this position is the only such published example using Pd metal with phosphine-based ligands. With substrate **1**, terminal attack was never observed over a range of phenolate nucleophiles tested. Terminal attack was observed when **7** was used, although it was only strongly favored when 4-chlorophenolate, a comparatively stable anion, was used. Phenolate nucleophiles provide an extremely valuable tool for studying the reactivity of (π–allyl)Pd complexes because they can be tuned to create very subtle differences in their electronic properties. We are continuing to study the effect of bromine on the electronics of the (π–ally)Pd complex and how the degrees of anion stability of the nucleophile work synergistically or antagonistically with the halogen substituent.

Acknowledgments: This work was supported by research grants from Eli Lilly and Company and the NIH (GM55904-01) (USA).

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9 The structure of all compounds reported in this study has been confirmed using a combination of ^{1}H, ^{13}C, and IR spectroscopy. Acceptable high resolution mass spectroscopy or combustion analysis has been obtained for all compounds.

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(*Received in USA* 4 *September* 1997; *accepted* 25 *September* 1997)