Pergamon

Tetrahedron Letters 43 (2002) 8989–8992

TETRAHEDRON LETTERS

On the regiochemistry of nucleophilic attack on 2-halo π-allyl complexes. Part 3: The electronic effect of phenoxide ion and the ligand

Michael G. Organ,* Elena A. Arvanitis and Stephen J. Hynes

The Department of Chemistry, York University, 4700 Keele Street, Toronto, Ontario, Canada, M3J 1P3

Received 1 August 2002; revised 19 August 2002; accepted 23 August 2002

Abstract—2,3-Dibromo-1-propene was subjected to competitive attack by malonate and different phenoxide nucleophiles in the presence of Pd substituted with monodentate or bidentate ligands. The presence of phenoxide promotes central carbon attack on the initially-formed 2-bromo Pd-π-allyl complex by malonate in the presence of mono or bidentate ligands on Pd. However, bidentate ligands on Pd disfavour the attack of phenoxide, either at the central position or the terminal position of either of the two π-ally complexes formed during the course of these di-additions.

We have had interest for some time in studying the reactivity of small, highly functionalized olefin building blocks (olefin templates) for use in the modular synthesis using transition metal catalysts (e.g. allylic substitution and cross coupling reactions).[1] It has been shown that these additional functional groups can alter the reaction pathway of allylic substitution reactions using Pd or Pt catalysts.[2] For example, allyl bromide[3] (Fig. 1, Eq. 1) substitutes cleanly at the terminal position with sodium phenoxide in the presence of $(PPh_3)_4Pd$ catalyst, but this nucleophile attacks the central position of the π-allyl when there is a Br at the 2-position, i.e. with

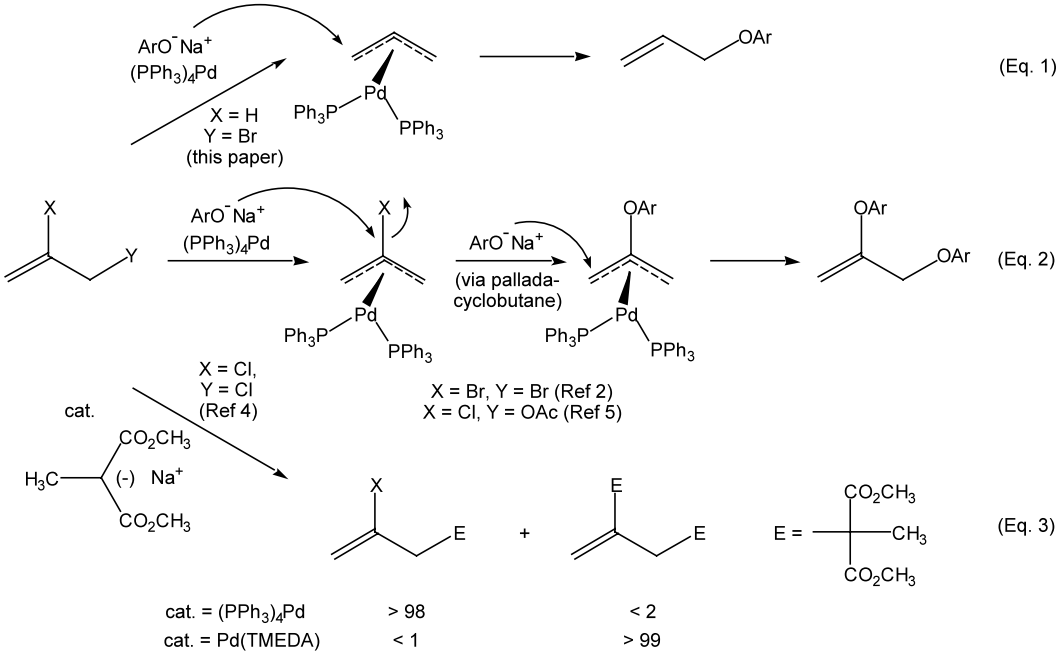


Figure 1. Regioselectivity of nucleophilic attack on various π-allyl complexes.

* Corresponding author.

0040-4039/02/$ - see front matter
PII: S0040-4039(02)02183-4

2,3-dibromo-1-propene as the starting material (Fig. 1, Eq. 2).[2] Clearly the nucleophile plays a role in this selectivity as well because sodium dimethyl methylmalonate attacked both substrates at the terminal end of the intermediate Pd π-allyl complex.[2,4,5] That being said, when the ligand on Pd was changed from triphenylphosphine (TPP) to TMEDA, malonate attacked the central position preferentially (Fig. 1, Eq. 3).[4] Conversely, for phenoxide nucleophile, these ligand effects lead to the exactly the opposite regioselectivity.[2] Thus, the regioselectivity shown during these reactions is under the integrated control of the structure of the substrate, the nature of the nucleophile, and the catalyst.

Murai's group has attempted to combine the selectivities demonstrated by malonate- and phenoxide-type nucleophiles to obtain products of mixed nucleophilic attack.[5] That is, using TPP ligand on Pd, they attempted to subject one bifunctional substrate to selective, sequential attack of phenoxide at C2 and malonate at C1 of the resultant Pd π-allyl complexes (Fig. 2). This would coincide with the selectivities demonstrated independently for these nucleophiles with $(PPh_3)_4Pd$ catalyst.[2] While the reaction was not as selective as purposed, they did obtain the products of addition of both nucleophiles on the same substrate. Most interesting in this study were the products that arose from attack of malonate at C2 (i.e. **2** and **3**) which, under otherwise identical reaction conditions without phenoxide, would attack the terminal position. This led them to postulate the existence of a new intermediate species that had phenoxide coordinated to Pd (**6**). Such a species would be more electron rich than the corresponding TPP-coordinated metal and this would be consistent with Bäckvall's contention that such π-allyl intermediates tend to have less positive charge on the terminal carbons which leads to directing nucleophiles to the central carbon.[4]

We conducted similar experiments to Murai to study the effect of the electronics of the phenoxide nucleophile when reacted in the presence of malonate nucleophile (Scheme 1, Table 1). While the structure of **10**, which has no phenoxide incorporation at all, was reported in their paper it was not clear that it was actually observed other than possibly in trace amounts. We observed significant amounts of this compound in most runs and when combined with compound **9** were the major di-addition compounds produced in the presence of phenoxide or electron rich phenoxides. Thus, products originating from central attack by malonate dominate in the presence of phenoxide. These result bring the existence of an intermediate such as **6** into question. First, presuming that phenoxide could readily displace a phosphine on Pd, why would it not reductively eliminate onto the π-allyl such that products of central attack by phenoxide (or even terminal attack) would be formed exclusively? While it has been demonstrated that carboxylate nucleophiles attack Pd π-allyl complexes at carbon,[6] it is not clear whether reductive elimination from Pd to carbon can occur with harder oxygen-based nucleophiles, such as phenoxide. Such a process would be quasi unimolecular and should all take place within the solvent cage, something which would promote it relative to the bimolecular reaction with malonate. Indeed when Murai used the phenyl carbonate derivative of **1**, the amount of **4** and **5** obtained actually decreased. In this case, the only source of phenoxide is from the ionization itself. The

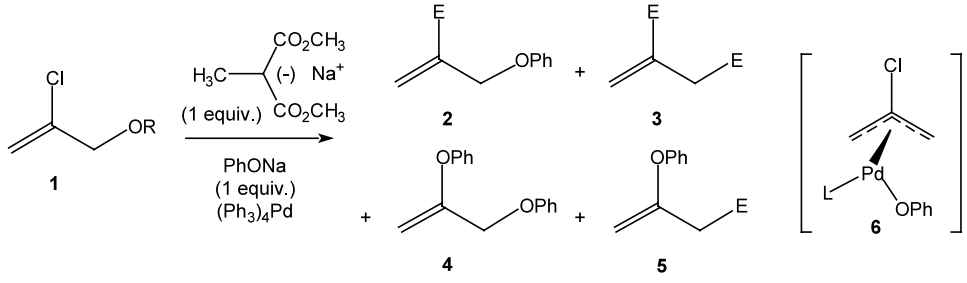
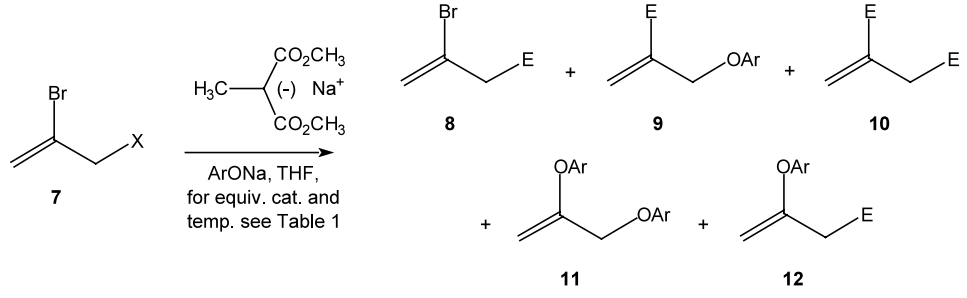


Figure 2. Regioselectivity of attack of malonate and phenoxide co-nucleophiles on 2-Cl π-allyl Pd complex.



Scheme 1.

Table 1. Reaction conditions and product ratios[a] for the reaction of **1** with sodium dimethyl methylmalonate and substituted sodium phenoxides in the presence of a Pd catalyst

Entry	X	Phenol (no. of equiv.)[b]	Catalyst[c]	Reaction conditions	**8**[d]	**9**	**10**	**11**	**12**
1	Br	4-Ome (1.3)	$(PPh_3)_4Pd$	5 h, rt	1.0	1.8	0.5	0.2	0.8
2	Br	4-Ome (2.0)	$Pd(dppp)_2$	15 h, rt	1.0	1.1	0.5	0.1	0.35
3	Br	4-Et (1.1)	$(PPh_3)_4Pd$	5 h, rt or 2 h, reflux	1.0	1.4	0.5	0.3	0.6
4	Br	4-Et (2.0)	$(PPh_3)_4Pd$	5 h, rt	1.0	1.2	0.4	0.5	0.7
5	Br	4-H (2.1)	$Pd(dppp)_2$	16 h, rt	1.0	Trace	0.8	–	–
6	Br	4-H (2.1)	$Pd((S)\text{-}BINAP)_2$	16 h, rt	1.0	Trace	0.11	–	–
7	Br	4-H (1.0)	$(PPh_3)_4Pd$	rt 5 h or 2 h, 50°C	1.0	0.6	0.3	0.2	Trace
8	Br	4-H (2.0)	$(PPh_3)_4Pd$	4 h, rt	1.0	1.3	0.5	0.5	1.0
9	Br	4-H (1.2)	$(PPh_3)_4Pd$ (50 mol%)	4 h, rt	1.0	1.0	Trace	0.2	0.6
10	Br	4-F (1.2)	$(PPh_3)_4Pd$	16 h, rt	1.0	1.2	0.7	0.4	0.7
11	Br	4-CO_2Me (1.2)	$(PPh_3)_4Pd$	2 h, rt	1.0	0.6	0.1	1.0	0.4
12	Br	4-CO_2Me (2.1)	$(PPh_3)_4Pd$	5 h, rt	1.0	0.2	0.07	0.35	0.1
13	Br	3-F (2.0)	$(PPh_3)_4Pd$	3 h, rt	1.0	0.43	0.16	0.45	0.44
14	OAc	4-H (2.1)	$(PPh_3)_4Pd$	16 h, rt	1.0	5.44	3.2	Trace	2.14
15	OAc	4-H (2.1)	$Pd(dppp)_2$	5.5 h, rt	1.0	11.3	36.0	–	7.5

[a] Product ratios were determined by ^1H NMR spectroscopy of the crude reaction mixture—all signals were well resolved to obtain very reliable integrations.

[b] An equal amount of malonate nucleophile was also used.

[c] Unless otherwise indicated, 5 mol% catalyst was used in each reaction.

[d] The simple allylic substitution product by malonate was arbitrarily given an abundance of 1.0 and all other ratios were determined relative to it.

phenoxide released during ionization should be retained within the solvent cage surrounding the Pd π-allyl intermediate thus favouring its re-attack at the central position, relative to malonate. In any case, what is clear is that the presence of phenoxide is altering the regioselectivity of attack of malonate.

To probe the existence of a species resembling **6**, we incorporated a bidentate phosphine-based ligand on Pd that would discourage the coordination of phenoxide to it, if phenoxide was coordinating to the metal at all under the previous reaction conditions discussed. When the reaction was performed with (*S*)-BINAP or DPPP ligand (Table 1, entries 2, 5, 6 and 15), the products arising from phenoxide attack were reduced significantly, although the di-addition product **10** was still produced in significant amounts with traces of other di-addition products. These results seem counterintuitive. If the bidentate ligands coordinatively saturate the Pd more effectively than TPP, thus preventing anything like **6** from forming, then products such as **10** should not form and yet central attack by malonate is enhanced by the presence of the bidentate ligand. At the same time, the reduction of phenoxide attack products with bidentate ligands on Pd is consistent with a species such as **6** forming with TPP ligands on Pd where it is more feasible for a TPP to be displaced by phenoxide.

We have run competition experiments with phenoxide and malonate (1:1, 1.1 equiv.) with allyl acetate (1.0 equiv.) where no central attack is possible and found that no allylic substitution with phenoxide occurred at all in the presence of $(PPh_3)_4Pd$ (the reaction went to completion with malonate). This indicates that even as malonate is depleted from the reaction mixture, it strongly out competes phenoxide as a nucleophile in a bulk solution situation. This might support the notion that phenoxide is somehow being held within the solvent cage of the 2-halo Pd-π-allyl complex in order to have any products at all arising from attack of phenoxide. When this is precluded from happening with the bidentate ligand, products of phenoxide attack should diminish significantly and this is what is observed.

In summary, we have found that phenoxide ion plays a role in altering the regioselectivity of nucleophilic attack on 2-halo Pd π-allyl complexes. With TPP ligand on Pd, the products of central carbon attack by malonate nucleophile dominate with electron-rich phenoxides and phenoxide itself. The products resulting from central attack by electron-poor phenoxides dominate the product mixture when such nucleophiles are used. The use of bidentate ligands still allow the product of central attack by malonate in the presence of phenoxide, but there is little incorporation of phenoxide into any of the reaction products. The true role of phenoxide ion, in association with Pd, in these reactions still continues to be investigated in our lab.

Acknowledgements

This work was funded by NSERC Canada and the Ontario Research and Development Challenge Fund (ORDCF).

References

1. (a) Organ, M. G.; Bilokin, Y. V.; Bratovanov, S. *J. Org. Chem.* **2002**, *67*, 5176–5183; (b) Organ, M. G.; Mayhew, D.; Cooper, J. T.; Dixon, C. E.; Lavorato, D. J.; Kaldor,

S. W.; Siegel, M. G. *J. Comb. Chem.* **2001**, *3*, 64–67; (c) Organ, M. G.; Cooper, J. T.; Rogers, L. R.; Soleymanzadeh, F.; Paul, T. *J. Org. Chem.* **2000**, *65*, 7959–7970; (d) Organ, M. G.; Bratovanov, S. *Tetrahedron Lett.* **2000**, *41*, 6945–6949.

2. (a) Organ, M. G.; Miller, M.; Konstantinou, Z. *J. Am. Chem. Soc.* **1998**, *120*, 9283–9290; (b) Organ, M. G.; Miller, M. *Tetrahedron Lett.* **1997**, *38*, 8181–8184.
3. Simple allylic substrates have been alkylated at the central carbon leading to cyclopropane formation via reductive elimination of the intermediate metallacyclobutane, see: (a) Hegedus, L. S.; Darlington, W. H.; Russel, C. E. *J. Org. Chem.* **1980**, *45*, 5193–5196; (b) Hoffmann, H. M. R.; Otte, A. R.; Wilde, A. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 234–236; (c) Carfagna, C.; Galarini, R.; Musco, A. *J. Mol. Catal.* **1992**, *72*, 19–27; (d) Tjaden, E. B.; Stryker, J. M. *J. Am. Chem. Soc.* **1990**, *112*, 6420–6422.
4. (a) Castano, A. M.; Aranyos, A.; Szabó, K. J.; Bäckvall, J.-E. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2551–2553; (b) Aranyos, A.; Szabó, K. J.; Castano, A. M.; Bäckvall, J.-E. *Organometallics* **1997**, *16*, 1058–1064.
5. Kadota, J.; Katsuragi, H.; Fukumoto, Y.; Murai, S. *Organometallics* **2000**, *19*, 979–983.
6. Trost, B. M.; Organ, M. G. *J. Am. Chem. Soc.* **1994**, *116*, 10320–10321.