JOC Article

On the Regiochemistry of Nucleophilic Attack on 2-Halo π-Allyl Complexes. 4. The Effect of Silver Acetate and Nucleophile Concentrations in Competitive Nucleophilic Attack with Malonate and Phenoxide Nucleophiles

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

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

organ@yorku.ca

Received January 29, 2003

2,3-Dibromo-1-propene or its allyl carbonate analogue are ionized under Pd catalysis to generate the 2-bromo Pd-π-allyl complex (triphenylphosphine ligand), which alkylates with malonate nucleophile at the terminal position. The presence of acetate ion in the reaction mixture results in some malonate attack being redirected to the central carbon. The acetate ion can come from the ionization of 1-acetoxy-2-bromo-2-propene or by the addition of silver acetate to the reaction mixture. The addition of phenoxide ion to the reaction also causes the same regiochemical phenomena, although harder anions such as methoxide exert no such effect.

It has been known for some time that nucleophiles can be directed to the central carbon of transition metal π-allyl complexes.[1] In the case where the central carbon is substituted with a hydrogen (Figure 1, X = H), the most common fate is cyclopropane formation (**4**) *via* reductive elimination of the intermediate metallocyclobutane (**3**).[2] However, if the central carbon in **2** is substituted with a suitable leaving group (e.g., X = halide), nucleophilic attack at this position can be followed by ionization of this group from **3** (Figure 1, path a).[3] This re-establishes a π-allyl complex (**5**) that can then undergo a second nucleophilic attack at the terminal position to produce **6**. Terminal attack on π-allyl **2** produces the simple allylic substitution product **7** (X = H or halogen) following path b.

It seems that the choice of path a versus path b may be closely linked to the type of nucleophile and/or ligands on the metal. Bäckvall and co-workers demonstrated that changing the ligands on the metal has a significant effect on the regioselectivity of the attack of malonate-based nucleophiles on the initially formed π-allyl complex (**2**).[3] With the aid of calculations and carbon NMR shift information, this selectivity was attributed to the docking atom of the ligand affecting electron density to the π-allyl complex. Phosphines being moderate σ-donors and good π-acceptors induce a moderate electron deficiency at the C-termini, hence directing malonate attack to these positions leading to **7**. Amine-based ligands are strong σ-donors and weak π-acceptors thus increasing the electron density at the C-termini and directing nucleophilic attack at the central position giving rise to **6**. After the release of these results, we showed that the exact opposite selectivity could be achieved by simply changing the nucleophile from malonate to phenoxide (i.e., in Figure 1 $Nu^1 = Nu^2 = PhO^-$).[4] This demonstrates that regioselectivity is under the integrated control of the nucleophile, the structure of the π-allyl, and the ligands on the metal.

Murai and co-workers proposed that phenoxide itself could form a new intermediate catalytic species by displacing a phosphine from Pd (Figure 2, structure **11**) and it is in fact this entity that is responsible for directing nucleophilic attack to the central carbon of the 2-halo π-allyl complex **2**.[5] In their studies, which involved both malonate and phenoxide co-nucleophiles, the presence of phenoxide promoted attack at the middle carbon, even when phenoxide itself was not incorporated into the product. This seems to be supported by Bäckvall's electronic contentions (vide supra) and by more recent results[6] we have disclosed using bidentate ligands. Of Murai's results, we were particularly intrigued by the reaction of phenyl carbonate **8b** (Figure 2), which pre-

(1) (a) Ephritikhine, M.; Green, M. L. H.; MacKenzie, R. E. *J. Chem. Soc., Chem. Commun.* **1976**, 619−621. (b) Ephritikhine, M.; Francis, B. R.; Green, M. L. H.; MacKenzie, R. E.; Smith, M. J. *J. Chem. Soc., Dalton Trans.* **1977**, 1131−1135. (c) Adam, G. J. A.; Davies, S. G.; Ford, K. A.; Ephritikhine, M.; Todd, P. F.; Green, M. L. H. *J. Mol. Catal.* **1980**, *8*, 15−24.

(2) 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.

(3) (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.

(4) (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.

(5) Kadota, J.; Katsuragi, H.; Fukumoto, Y.; Murai, S. *Organometallics* **2000**, *19*, 979−983.

(6) Organ, M. G.; Arvanitis, E. A.; Hynes, S. J. *Tetrahedron Lett.* **2002**, *43*, 8989−8992.

10.1021/jo034119c CCC: $25.00 © 2003 American Chemical Society
Published on Web 04/12/2003

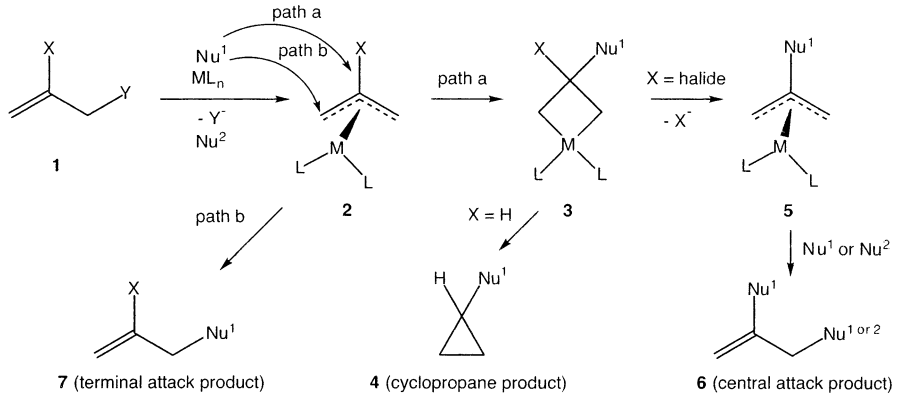


FIGURE 1. Regioselectivity of nucleophilic attack on π-allyl complexes.

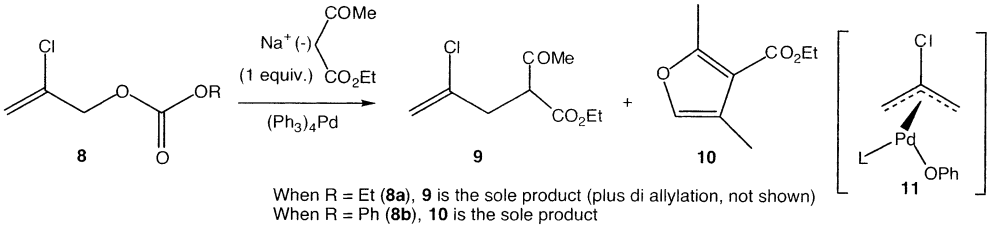
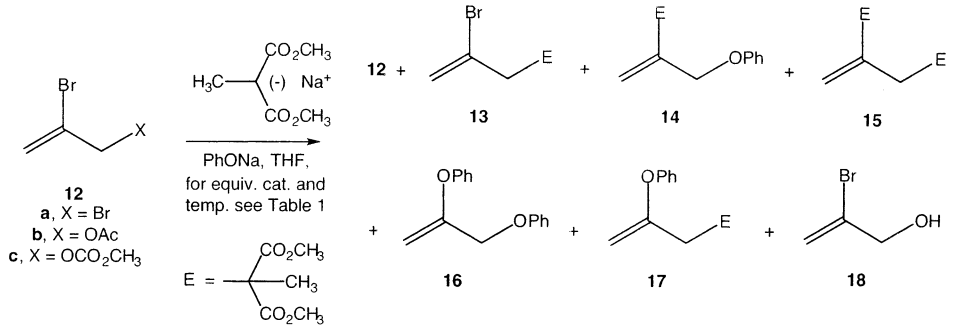


FIGURE 2. Attack of sodium ethyl 3-oxobutanate on a 2-Cl π-allyl Pd complex.

SCHEME 1



sumably liberates phenoxide following ionization. Although phenoxide was not incorporated at all into the product, its in-situ liberation in the reaction medium caused exclusive central carbon attack by the active methylene compound. Once the π-allyl was reestablished, *O*-alkylation took place to provide the furan product **10**. The ethyl carbonate analogue (**8a**) gave the terminal attack product **9** only.

In the reaction of **8b**, only a very small amount of phenoxide was available, especially at the beginning of the reaction. However, phenoxide was being liberated in proximity to Pd, presumably within a solvent cage surrounding the ion pair, and that may have been sufficient to alter the regioselectivity of nucleophilic attack.

Assuming for now that a species resembling **11** forms, we wondered if the central attack regioselectivity was occurring solely because of the proximity of phenoxide to the metal following ionization, or if the affinity of the metal for phenoxide was so high that ligand exchange with a phosphine was kinetically faster than all other chemical events. To address this question, we performed a series of experiments with varying amounts of phenoxide ion (Scheme 1, Table 1). Treatment of **12a** with malonate in the presence of $(PPh_3)_4Pd$ led exclusively to the formation of the terminal attack product **13** (Table 1, Entry 1). However, an equal amount of phenoxide ion and malonate led to primarily central attack products (Entry 2). Even when a catalytic amount of phenoxide was used there was significant central carbon attack (Entry 3).

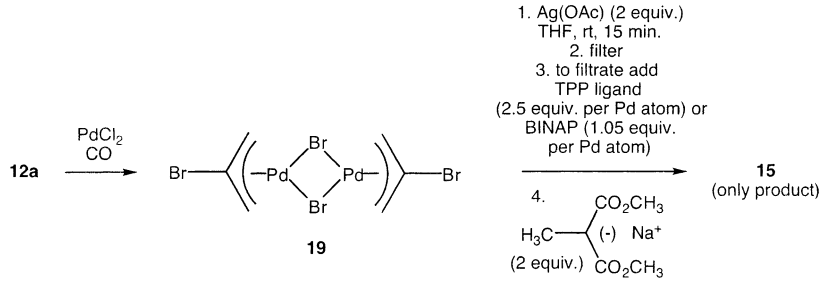
Considering the inherent reactivity of the allylic bromide in **12a**, which could be substituted by malonate ion directly without Pd, the allylic group was changed to either carbonate or acetate to ensure that no noncatalyzed substitutions were taking place. We were surprised to find that simply changing the leaving group to an acetate (without phenoxide) led to noticeable formation of **15** (Entry 4), which was enhanced further by the addition of phenoxide (Entries 5 and 6). Again, the use of a catalytic amount of phenoxide also resulted in a shift toward significant central carbon attack (Entry 7). As of yet, we have not been able to prepare and characterize a catalyst bearing a phenoxide ligand(s) that we could use to provide further evidence for the existence of such a

TABLE 1. Reaction Conditions and Product Percentages[a] for the Reaction of 12 with Sodium Dimethyl Methylmalonate under Pd Catalysis in the Presence or Absence of Various Oxygen-Based Anions

entry	X	phenol (equiv)	malonate (equiv)	catalyst[b]	reaction conditions	**12**	**13**	**14**	**15**	**16**	**17**	**18**
1	Br	0	2.2	$(PPh_3)_4Pd$	18 h, rt		100					
2	Br	2.2	2.2	$(PPh_3)_4Pd$	18 h, rt		23	30	12	12	23	
3	Br	0.10	2.2	$(PPh_3)_4Pd$	4 h, rt		77	-	23			
4	OAc	0	2.2	$(PPh_3)_4Pd$	18 h, rt		67	-	13			20
5	OAc	2.2	2.2	$(PPh_3)_4Pd$	2 min, rt	49	9	19	17			6
6	OAc	2.2	2.2	$(PPh_3)_4Pd$	16 h, rt		9	46	27	trace	18	-
7	OAc	0.15	2.2	$(PPh_3)_4Pd$	16 h, rt		22	9	28			41
8	OAc	0.15	2.2	$(PPh_3)_4Pd$ plus 22% TPP	20 h, rt		53	5	37			5
9	OAc	0	2.2	$Pd(dppp)_2$	5 h, rt	57	36		7			
10	OAc	2.1	2.1	$Pd(dppp)_2$	5 min, rt	13	1	12	59		13	2
11	OAc	2.1	2.1	$Pd(dppp)_2$	5 h, rt		2	17	55		11	15
12	OAc	0.10	2.2	$Pd(dppp)_2$	4 h, rt		12		88			
13	OCO_2Et	0	1.2	$(PPh_3)_4Pd$	7 h, rt		100					
14	OAc	0	2.2	$(PPh_3)_4Pd$ plus 10% NaOH	2.5 h, rt		63		6			31
15	OAc	0	2.2	$(PPh_3)_4Pd$ plus 10% $NaOCH_3$	2.5 h, rt		72		1			28
16	OCO_2Et	0	2.2	$(PPh_3)_4Pd$ plus 4 equiv of NaOAc	2.5 h, rt		72		1			28
17	Br	0	2.2	$(PPh_3)_4Pd$ plus 1 equiv of NH_4OAc	18 h, rt		91		9			-
18	OCO_2Et	0	2.2	$Pd(dppp)_2$ plus 4 equiv of NaOAc	1.5 h, rt		42		46			12
19	OCO_2Et	0	2.2	$(PPh_3)_4Pd$ plus 2 equiv of AgOAc	2 h, rt	81	5		14			
20	OCO_2Et	0	1.2	$Pd_2dba_3{-}CHCl_3$ Ph_3PO (11%)	20 h, rt		77					23

[a] Product percentages were determined by ^1H NMR spectroscopy of the crude reaction mixture. All relevant signals were well resolved to obtain very reliable integrations. The structures of all compounds were determined by IR and ^1H and ^{13}C NMR spectroscopy with either combustion analysis or high-resolution mass spectroscopy. [b] Unless otherwise indicated, 5 mol % catalyst was used in each reaction.

SCHEME 2



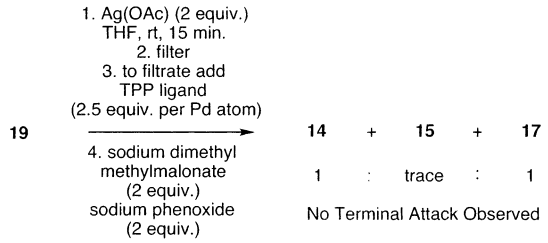
catalytic species. None-the less, when we added additional TPP (4 equiv relative to Pd atom) to the run employing catalytic phenoxide the amount of central carbon attack products dropped significantly (Entry 8). This indirect evidence suggests that phenoxide is indeed involved in coordination to Pd and that this event promotes central carbon attack.

As noted, when compared with all runs involving **12a**, clearly the acetate leaving group in **12b** is also playing some role in promoting central carbon attack. Indeed when the allylic carbonate in **12c** was ionized, only the terminal attack product **13** was isolated (Entry 13). These results initially led us to speculate that the proposed ligand effect of phenoxide might be broadened to other oxygen-based ligands and perhaps acetate was coordinating to Pd in a similar fashion. To probe this, a series of experiments were performed with other oxygen-based anions and triphenylphosphine oxide ligand (Entries 14, 15, and 20), but none led to significant central carbon attack products. There were mixed results when a large excess of sodium acetate was added directly to the reaction mixture. Although there was no central carbon attack product with **12a** (Entry 1), there was 10% of the resultant product formed in Entry 17. With **12c** (Entry 16), only **13** was produced, thus if acetate ion is exerting an effect in these reactions, it does not exert a strong effect when added in the form of sodium or ammonium acetate, which could be a solubility issue. In THF, sodium acetate is quite insoluble, whereas when ionized from **12b** the π-allyl cation maintains it in solution and in proximity to the metal where complexation and possible ligand exchange may be happening.

We observed previously that bidentate ligands on Pd by themselves seem to promote central carbon attack on the π-allyl complex derived from substrates resembling **12** (Entry 9).[6] Further, the presence of phenoxide ion dramatically enhances this regioselectivity (Entries 11 and 12). It is interesting that when sodium acetate was added to the reaction with **12c** (Entry 18, no added phenoxide), over half of the addition products isolated resulted from central carbon attack. This compares to approximately 20% of the addition products without a large excess of acetate ion (i.e., **15** 7% overall, Entry 9). We are not sure why additional sodium acetate seemed to have such a noticeable effect with diphenylphosphinopropane (DPPP) ligand and none with TPP.

Another set of experiments we performed also points strongly toward altered chemical reactivity of the Pd catalyst in the presence of acetate ion (Scheme 2). The dimeric Pd II complex **19** was synthesized following the procedure disclosed by Bäckvall's group for the analogous dichloro compound.[3] They reported that cracking the dimer with $AgBF_4$ followed by the sequential addition of TPP ligand (2 equiv) and malonate nucleophile resulted

SCHEME 3



in terminal attack only. We performed these experiments with **12a** and either TPP or BINAP ligand but with one notable exception, silver acetate was employed to scavenge the halide rather than the tetrafluoroborate salt. Strikingly, this simple change completely reversed the regioselectivity of malonate attack from what Bäckvall observed. When the same sequence was conducted with equal amounts of malonate and phenoxide anions, only central carbon attack products were isolated although this time **15** was formed in trace amounts only (Scheme 3).

The reason for performing the reaction via intermediate **19** was to quantitatively produce the π-allyl intermediate with use of stoichiometric Pd and two ligands of TPP. Presumably, this would ensure that the exact structure of the catalyst was known at the stage in the cycle immediately before the first nucleophilic attack. Alternatively, we treated **12a** and **12d** with a solution containing 1 equiv of $(PPh_3)_4Pd$ and AgOAc followed by a second solution containing malonate and phenoxide nucleophiles (Scheme 4). This should lead to the same catalytic species/intermediate being generated in the reactions outlined in Schemes 2 and 3. Again, primarily central attack products were obtained.

We performed another reaction with silver acetate, only this time we used catalytic Pd with substrate **12c** (Entry 19). Although the reaction did not go to completion, clearly the amount of central attack product has been enhanced markedly when compared with the same reaction without this additive (Entry 13). It could be that silver is affecting the Pd-π-allyl complex directly, but Bäckvall's results[3] with $AgBF_4$ cast doubt on this. That is, under otherwise identical conditions, his group observed terminal attack exclusively with malonate nucleophile. It is more likely that silver solubilizes acetate better than the other cations used in this report. This would make acetate more available to Pd, and once coordinated produce a new catalytic species with new properties.

In summary, the regioselectivity of nucleophilic attack on the Pd-π-allyl complexes derived from substrates resembling **12** is changed dramatically in the presence of phenoxide-based anions. With TPP-coordinated Pd catalysts, malonate-based nucleophiles on their own tend to attack the terminus of the π-allyl complex. Once phenoxide ion is added to the same reaction, central attack now dominates, both by the phenoxide and malonate nucleophiles. Further, this effect is also seen with acetate ion and the effect is greatest with silver as the counterion. Our studies in this area are ongoing.

Experimental Procedures

All reactions in Table 1 were performed by using the following procedure outlined for Entry 6. All compounds have been reported in the literature previously and sample spectra are included.

To a solution of dimethyl methylmalonate (172 mg, 1.18 mmol) and phenol[11] (111 mg, 1.18 mmol) in THF (2 mL) was added slowly NaH (100 mg, 2.36 mmol of a 60% dispersion in mineral oil). The resulting solution was stirred for 10 min at room temperature. Palladium tetrakistriphenylphosphine (32 mg 0.028 mmol) was added followed immediately by a solution of 1-acetoxy-2-bromo-2-propene (**9b**) (100 mg, 0.56 mmol) in THF (2 mL). The resulting orange solution was stirred at room temperature for 16 h. The orange suspension was diluted with pentane (4 mL). The precipitated solids were removed by filtering through glass wool. Solvents were removed in vacuo to give an oil containing the products **13**, **14**, **15**, and **17** in the ratio 1:5.44:3.2:2.1, according to the proton NMR spectrum. The oil was chromatographed (Silica gel, solvent gradient: 10% ether in pentane to 30% ether in pentane to 50% ether in pentane) to afford compounds **13**[7] (6 mg, 4%) [^{1}H (400 MHz, $CDCl_3$), 5.63 (s, 1H), 5.55 (s, 1H), 3.72 (s, 6H), 3.13 (s,2 H), 1.47 (s, 3H)]; **15**[8] (37 mg, 24%) [^{1}H (400 MHz, $CDCl_3$) δ 5.05 (s, 1H), 4.91 (s, 1H), 3.74 (s, 6H), 3.72 (s, 6H), 2.83 (s, 2H), 1.61 (s, 3H), 1.49 (s, 3H)], and a mixture of **14** and **17**, which was rechromatographed (Silica gel 15% ether in pentane) to give **14**[9] (38 mg, 20%) [^{1}H (400 MHz, $CDCl_3$) δ 7.29−7.25 (m, 2H), 6.96−6.93 (m, 3H), 5.53 (s, 1H), 5.30 (s, 1H), 4.69 (s, 2H), 3.74 (s, 6H), 1.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.1, 158.5, 141.7, 129.3, 129.2, 121.0, 116.4, 114.9, 68.9, 52.8, 48.1, 20.8; IR (thin film) 3056, 2986, 2253, 1732, 1259, 910 cm^{-1}] and **17** (11 mg, 7%) [^{1}H (400 MHz, $CDCl_3$), 7.34−7.31 (m, 2H), 7.13−7.03 (m, 3H), 4.14 (s, 1H), 3.94 (s, 1H), 3.94 (s, 6 H), 2.94 (s, 2H), 1.72 (s, 3H)].

Formation of Dimer 19. To a solution of palladium(II) dichloride (5.64 mmol, 1 g) and lithium chloride (18.9 mmol, 0.8 g, 3.3 equiv) in water (1.5 mL) was added a solution of 2,3-dibromopropene (16.9 mmol, 1.75 mL, 3 equiv) and MeOH (30 mL). Carbon monoxide was bubbled through the solution until the mixture turned yellow from the initial red-brown (a yellow precipitate was gradually formed). The reaction mixture was poured into H_2O (500 mL) and extracted into $CHCl_3$ (500 mL in small portions). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo to give an orange-yellow solid. Recrystallization from $CHCl_3$ gave a yellow solid (0.95 g, 11%): mp 145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47 (s, 2H), 3.43 (s, 2H). Anal. Calcd for $C_6H_8Br_4Pd_2$: C, 11.76; H, 1.31. Found: C, 11.42; H, 1.18.

Reaction of Dimer 19 with Sodium Dimethyl Methylmalonate in the Presence of Silver Acetate and TPP Ligand.[10] To a solution of **19** (0.1 mmol, 52.3 mg) in THF (7 mL) under N_2 was added silver acetate (0.2 mmol, 33.4 mg, 2 equiv). The suspension was stirred for 15 min and filtered through filter paper under vacuum; the solid was rinsed with THF (2 mL) and the filtrate was collected in a flask containing TPP (0.5 mmol, 131.1 mg, 5 equiv). To the resultant yellow solution was added a solution of freshly prepared sodium dimethyl methylmalonate anion (0.4 mmol, 4 equiv) in THF (5 mL). The reaction mixture became gradually cloudy and was stirred for 6.5 h before being quenched with H_2O and partitioned between Et_2O and 2 M aqueous NaOH. The organic phase was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed in vacuo to give a black residue (221.0 mg) containing only **15**, as indicated by the ^{1}H NMR spectrum of the crude mixture.

(7) NMR spectral data correspond to literature data: Organ, M. G.; Arvanitis, E. A.; Dixon, C. E.; Cooper, J. T. *J. Am. Chem. Soc.* **2002**, *124*, 1288−1294.

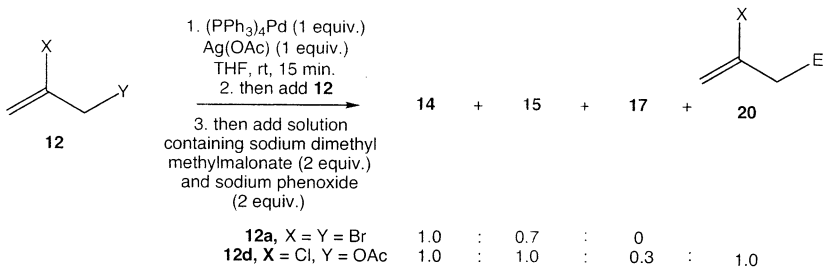
(8) NMR spectral data correspond to literature data, see ref 3b.

(9) NMR spectral data correspond to literature data for analogous ethyl diester, see ref 5.

(10) The same reaction conditions were used for the BINAP ligand.

(11) Note for reactions involving catalytic amounts of sodium phenoxide, the NaOPh was prepared separately and mixed with the Pd catalyst before addition to the reaction flask.

SCHEME 4



Reaction of Dimer 19 with Sodium Dimethyl Methylmalonate and Sodium Phenoxide in the Presence of Silver Acetate and TPP Ligand. To a solution of **19** (0.1 mmol, 52.1 mg) in THF (2 mL) was added silver acetate (0.2 mmol, 33.4 mg, 2 equiv) under N_2. The suspension was stirred for 10 min before being filtered; the precipitate was washed with THF (2 mL) and the filtrate was collected in a flask containing phosphine (0.5 mmol, 131.1 mg, 5 equiv). To the resultant yellow solution was added a solution of freshly prepared sodium phenoxide (0.4 mmol, 4 equiv) and sodium dimethyl methylmalonate (0.4 mmol, 4 equiv) in THF (4.5 mL) dropwise via cannula; the solution became instantly red and turned gradually orange and cloudy over 5 min. The reaction mixture was stirred for 2 h before being quenched with H_2O and partitioned between Et_2O and 2 M aqueous NaOH. The organic phase was dried over anhydrous $MgSO_4$, filtered over Celite, and evaporated under vacuum to give a brown liquid (0.207 g) containing **14** and **17** in a ratio of 1:1, as indicated by the ^1H NMR spectrum of the crude product. The crude mixture was purified by flash chromatography (hexanes:ether, 4:1) to afford 26 mg of both products.

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

JO034119C