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Palladium-catalyzed coupling of alkynes with alcohols and carboxylic acids

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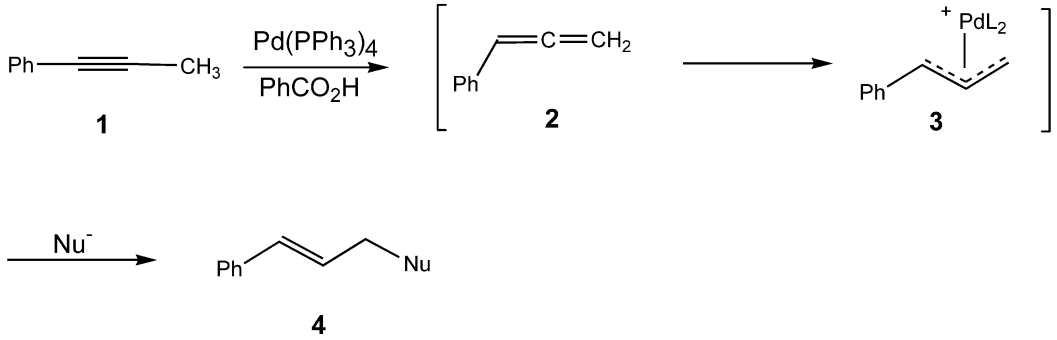
Abstract—The palladium-catalyzed coupling of alkynes with alcohols and carboxylic acids to give allylic ethers and esters has been achieved. With phenols, these conditions furnish the *C*-alkylation products. © 2002 Elsevier Science Ltd. All rights reserved.

Palladium-catalyzed couplings of allenes, allyl esters, and allyl carbonates with nucleophiles such as malonates, amines, and alcohols are widely employed in organic synthesis.[1] These condensations proceed through a common reaction mechanism, via the formation of the π-allyl palladium complex and subsequent nucleophilic attack to complete the allylation process.[2] The isomerization of alkynes to allenes by palladium hydride complexes is also well known in the chemical literature.[3] The coupling of these two transformations offers the opportunity to generate alkene derivatives in tandem from an alkyne and a nucleophile (Scheme 1). It has been previously reported that malononitrile[4] and amines[5] can be allylated using alkynes with palladium catalysis. We wish to report here on the allylation reaction of 1-arylpropynes with oxygen nucleophiles such as alcohols and carboxylic acids.

Excellent yields of the allyl ethers using primary or secondary alcohols were observed (entries 1–3).[6] In the case of *t*-butanol (entry 4), the yield of the corresponding product **6d** was lower.[6] For acids, the yields of allyl esters **6e–h** varied from 75 to 90% (entries 5–8).[6] In these cases, a catalytic amount of triethylamine was found to improve the yield, presumably by deprotonation of the carboxylic acids to enhance the nucleophilicity of the resultant carboxylates. It is worthwhile to note that the *cis*-allyl ether or ester products were not detected under these conditions. In the case of 3-prop-1-ynyl-pyridine, a disappointing 30% yield of **6i** was isolated under the standard conditions (entry 9, Table 1).[6]

To determine the scope of the alkyne substrates, 3-phenylpropyne was subjected to the coupling conditions. Although this system was expected to react similarly to 1-phenylpropyne, only a trace amount of product **6b** was observed (Scheme 2).[6] Aliphatic alkynes such as 3-hexyne and 1-hexyne gave indeterminate mixtures of products.



Scheme 1.

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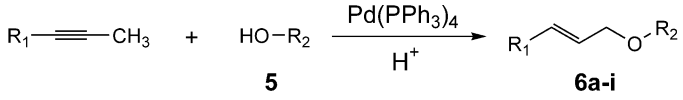
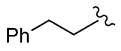
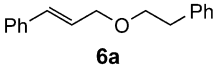
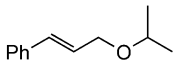
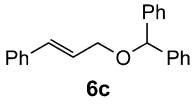
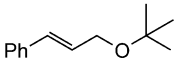
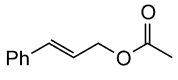
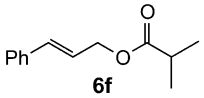
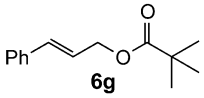
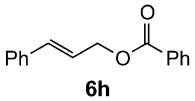
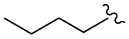
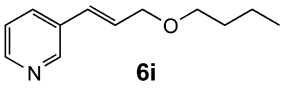
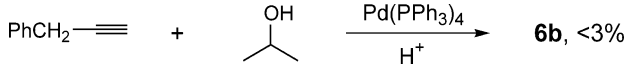
Table 1. Alkylation reactions of 1-arylpropynes to alcohols and acids



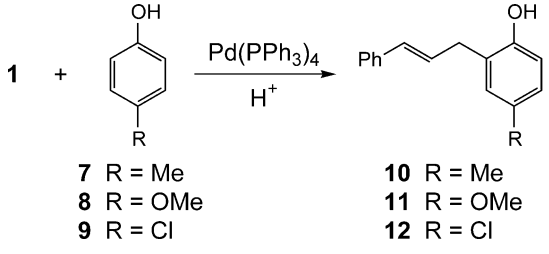
Entry	R_1	R_2	Product	Yield[a]
1	Ph		 **6a**	89%
2	Ph		 **6b**	87%
3	Ph		 **6c**	85%
4	Ph		 **6d**	66%
5	Ph		 **6e**	85%
6	Ph		 **6f**	90%
7	Ph		 **6g**	87%
8	Ph		 **6h**	75%
9			 **6i**	30%

[a] Isolated yield under unoptimized conditions.



Scheme 2.

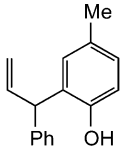
When the allylation reaction with phenolic nucleophiles **7**–**9** was carried out, the *C*-alkylation products, **10**–**12**, were isolated in 76, 65, and 35% yields, respectively (Scheme 3).[6] Further investigation revealed that both the



Scheme 3.

C-alkylated and the *O*-alkylated products formed initially under the reaction conditions, but with prolonged reaction time, the amount of ethers (**13**–**14**)[6] decreased with a concomitant increase in the *C*-alkylation products (**10**–**11**). Presumably, two competitive reaction pathways (*a* and *b* in Scheme 4) furnish the mixture of products. The phenolic ethers, obtained by pathway *b*, can then undergo palladium-catalyzed rearrangement to the more stable *C*-allylated product.[7]

Heating independently prepared **13** to 100°C in 1,4-dioxane for 15 h produced no discernable reaction.[8] However, under the same conditions, in the presence of 5 mol%



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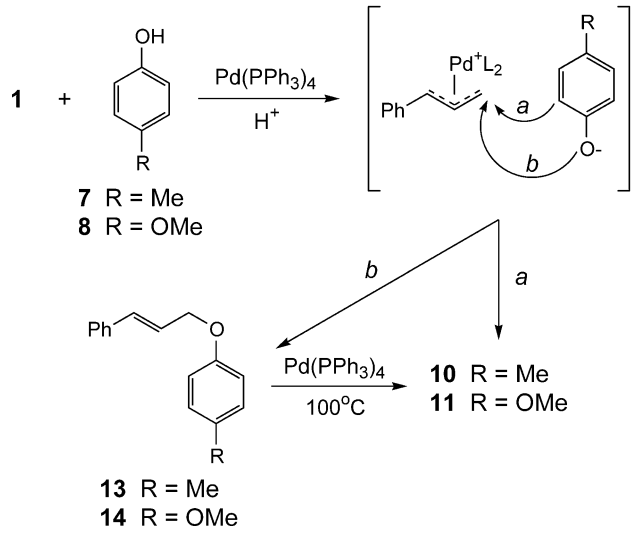

Scheme 4.

$Pd(PPh_3)_4$, phenol **10** was isolated in 55% yield without any detectable trace of the Claisen product **15**.[9] The involvement of the phenoxide in a palladium-catalyzed alkylation can be implied by the failed reactions of anisole and *N*,*N*-dimethylaniline under identical conditions.[10]

In summary, a method for the efficient synthesis of allylic ethers and esters from 1-arylpropynes has been developed. With phenols, the method gives *C*-alkylation products in moderate yields. Due to the readily available nature of alkynes, this chemistry offers another alternative towards the synthesis of allylic ethers and esters.

Representative experimental procedures

For alcohols and phenols: A mixture of 2 mmol 1-phenylpropyne **1**, 4 mmol alcohol, 0.1 mol tetrakis(triphenylphosphine) palladium(0), and 0.2 mmol benzoic acid in 3 ml 1,4-dioxane was heated to 100°C for 16–20 h.

For acids: A mixture of 2 mmol of 1-phenylpropyne **1**, 3 mmol acid, 0.1 mmol tetrakis(triphenylphosphine) palladium(0), and 0.2 mmol triethylamine in 3 ml 1,4-dioxane was heated to 100°C for 10–16 h.

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6. All the compounds prepared by the coupling reaction are literature known. **6a**: Oil; MS *m*/*z* 238 (M^+); ^1H NMR ($CDCl_3$) δ 7.15–7.40 (m, 10H), 6.56 (d, $J=16$ Hz, 1H), 6.27 (dt, $J=16$, 7 Hz, 1H), 4.14 (dd, $J=6.8$, 2 Hz, 2H), 3.69 (t, $J=7.1$ Hz, 2H), 2.93 (t, $J=7.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 138.87, 136.68, 132.16, 128.88, 128.48, 128.33, 127.59, 126.42, 126.18, 126.10, 71.44, 71.21, 36.39. **6b**: Oil; MS *m*/*z* 176 (M^+); ^1H NMR ($CDCl_3$) δ 7.15–7.40 (m, 5H), 6.58 (d, $J=16$ Hz, 1H), 6.28 (dt, $J=16$, 7 Hz, 1H), 4.12 (dd, $J=6.8$, 2 Hz, 2H), 3.66 (hept, $J=6.8$ Hz, 1H), 1.19 (d, $J=6.8$ Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 136.77, 131.60, 128.44, 127.39, 126.76, 126.34, 70.84, 68.61, 22.06. **6c**: Oil; MS *m*/*z* 300 (M^+); ^1H NMR ($CDCl_3$) δ 7.42–7.20 (m, 10H), 6.6 (d, $J=16$ Hz, 1H), 6.34 (dt, $J=16$, 7 Hz, 1H), 5.49 (s, 1H), 4.18 (dd, $J=7$, 2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 142.11, 136.72, 132.26, 128.49, 128.40, 127.59, 127.42, 127.00, 126.44, 126.13, 82.58, 69.33. **6d**: Oil; MS *m*/*z* 190 (M^+); ^1H NMR ($CDCl_3$) δ 7.20–7.40 (m, 5H), 6.60 (d, $J=16$ Hz, 1H), 6.29 (dt, $J=16$, 7 Hz, 1H), 4.18 (dd, $J=7$, 2 Hz, 2H), 1.26 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 137.03, 131.06, 128.38, 127.65, 127.30, 126.37, 73.26, 62.77, 27.61. **6e**: Oil; MS *m*/*z* 176 (M^+); ^1H NMR ($CDCl_3$) δ 7.20–7.42 (m, 5H), 6.66 (d, $J=16$ Hz, 1H), 6.28 (dt, $J=16$, 7 Hz, 1H), 4.72 (dd, $J=7$, 2 Hz, 2H), 2.1 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.78, 136.14, 134.15, 128.56, 128.02, 126.55, 123.11, 65.03, 20.96. **6f**: Oil; MS *m*/*z* 204 (M^+); ^1H NMR ($CDCl_3$) δ 7.22–7.44 (m, 5H), 6.66 (d, $J=16$ Hz, 1H), 6.29 (dt, $J=16$, 7 Hz, 1H), 4.72 (dd, $J=7$, 2 Hz, 2H), 2.59 (hept, $J=7$ Hz, 1H), 1.20 (d, $J=7$ Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 176.82, 136.25, 133.88, 128.57, 127.99, 126.57, 123.41, 64.85, 34.03, 19.01. **6g**: Oil; MS *m*/*z* 218 (M^+); ^1H NMR ($CDCl_3$) δ 7.22–7.43 (m, 5H), 6.64 (d, $J=16$ Hz, 1H), 6.28 (dt, $J=16$, 7 Hz, 1H), 4.73 (dd, $J=7$, 2 Hz, 2H), 1.23 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 178.30, 136.32, 133.57, 128.57, 127.94, 126.55, 123.56, 64.90, 38.80, 27.22. **6h**: Oil; MS *m*/*z* 238 (M^+); ^1H NMR ($CDCl_3$) δ 8.08 (m, 2H), 7.20–7.60 (m, 8H), 6.73 (d, $J=16$ Hz, 1H), 6.39 (dt, $J=16$, 7 Hz, 1H), 4.96 (dd, $J=7$, 2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 166.25, 136.11, 134.15, 132.89, 130.09, 129.56, 128.51, 128.28, 127.99, 126.55, 123.16, 65.44. **6i**: Oil; ^1H NMR ($CDCl_3$) δ 8.59 (d, $J=2$ Hz, 1H), 8.45 (dd, $J=5$, 2 Hz, 1H), 7.69 (ddd, $J=8$, 2, 2 Hz, 1H), 7.23 (dd, $J=8$, 5 Hz, 1H), 6.59 (d, $J=16$ Hz, 1H), 6.36 (ddd, $J=16$, 6, 6 Hz, 1H), 4.14 (dd, $J=6$, 2 Hz, 2H), 3.50 (t, $J=7$ Hz, 2H), 1.62 (m, 2H), 1.42 (m, 2H), 0.94 (t, $J=7$ Hz, 3H). **10**: Oil; MS *m*/*z* 224 (M^+); ^1H NMR ($CDCl_3$) δ 7.14–7.35 (m, 5H), 7.45 (d, $J=2$ Hz, 1H), 6.89 (dd, $J=7$, 2 Hz, 1H), 6.68 (d, $J=7$ Hz, 1H), 6.46 (d, $J=16$ Hz, 1H), 6.35 (dt, $J=16$, 7 Hz, 1H), 4.96 (s, 1H), 3.49 (d, $J=7$ Hz, 2H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 151.52, 137.08, 131.21, 130.90, 130.11, 128.43, 128.14, 128.04, 127.17, 126.11, 125.44, 115.52, 33.93, 20.45. **11**: Oil; MS *m*/*z* 240 (M^+); ^1H NMR ($CDCl_3$) δ 7.15–7.40 (m, 5H), 6.65–6.80 (m, 3H), 6.48 (d, $J=16$ Hz, 1H), 6.35 (dt, $J=16$, 7 Hz, 1H), 4.89 (s, 1H), 3.66 (s, 3H), 3.52 (d, $J=7$ Hz, 2H). **12**: Oil; MS *m*/*z* 244 (M^+); ^1H NMR ($CDCl_3$) δ 7.15–7.37 (m, 5H), 7.15 (d, $J=2$ Hz,

1H), 7.08 (dd, $J=7$, 2 Hz, 1H), 6.73 (d, $J=7$ Hz, 1H), 6.50 (d, $J=16$ Hz, 1H), 6.32 (dt, $J=16$, 7 Hz, 1H), 4.98 (s, 1H), 3.51 (dd, $J=7$, 1 Hz, 2H), 2.25 (s, 3H). **13**: Colorless crystals, mp: 77–79°C (Heptane); MS m/z 224 (M^+); ^{1}H NMR ($CDCl_3$) δ 7.20–7.45 (m, 5H), 7.09 (d, $J=7$ Hz, 2H), 6.86 (d, $J=7$ Hz, 2H), 6.72 (d, $J=16$ Hz, 1H), 6.41 (dt, $J=16$, 7 Hz, 1H), 4.67 (dd, $J=7$, 2 Hz, 2H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.47, 136.47, 132.79, 130.09, 129.90, 128.54, 127.81, 126.54, 124.69, 114.62, 68.70, 20.48. **14**: Colorless crystals, mp: 107–109°C (Heptane); ^{1}H NMR ($CDCl_3$) δ 7.25–7.45 (m, 5H), 6.91 (d, $J=7$ Hz, 2H), 6.84 (d, $J=7$ Hz, 2H), 6.73 (d, $J=16$ Hz, 1H), 6.41 (dt, $J=16$, 7 Hz, 1H), 4.66 (dd, $J=7$, 2 Hz, 2H), 3.78 (s, 3H). **15**: Oil; ^{1}H NMR ($CDCl_3$) δ 7.20–7.35 (m, 5H), 6.95 (dd, $J=7$, 2 Hz, 1H), 6.88 (d, $J=2$ Hz, 1H), 6.70 (d, $J=7$ Hz, 1H), 6.33 (m, 1H), 5.28 (dt, $J=7$, 1 Hz, 1H), 5.02 (dt, $J=16$, 1 Hz, 1H), 4.91 (d, $J=7$ Hz, 1H), 4.63 (s, 1H), 2.25 (s, 3H).

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