JOC The Journal of Organic Chemistry

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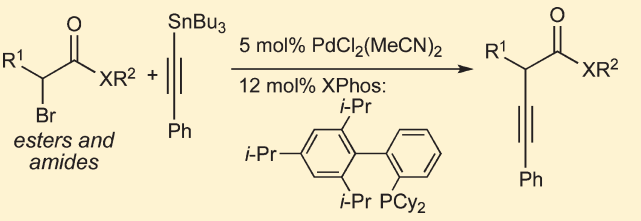
Palladium-Catalyzed Alkynylation of Secondary α-Bromo Carbonyl Compounds via Stille Coupling

Jun Yong Kang and Brian T. Connell*

Department of Chemistry, Texas A&M University, P.O. Box 30012, College Station, Texas 77842-3012, United States

Supporting Information

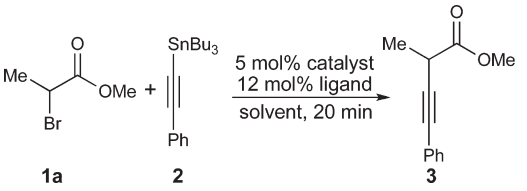
ABSTRACT: A catalytic intermolecular cross-coupling reaction that couples secondary α-bromo carbonyl compounds with alkynylstannanes to form secondary alkynyl carbonyl compounds via palladium catalysis employing the XPhos ligand is described.



Although numerous transition-metal-catalyzed cross-coupling reactions of α-halo carbonyl compounds with arylmetals,[1,2] alkenylmetals,[3,4] and alkylmetals[5,6] have recently been reported, few cases of cross-coupling reactions of alkynylmetals have been reported.[7,8] This is likely due to the sensitivity of the product β,γ-alkynyl carbonyls toward isomerization to conjugated species, processes which have been exploited in their own right.[9−17] Fu has developed a robust method for the synthesis of achiral 3-alkynoates not involving cross-coupling,[18] while Lei and coworkers[7] demonstrated a coupling reaction between primary α-halo carbonyl compounds and an alkynylstannane. However, secondary α-halo carbonyl compounds have remained elusive as starting materials. The chiral, tertiary alkynyl carbonyl compounds which would arise from such a coupling have demonstrated versatile utility in organic synthesis, including natural product synthesis.[9−17] Therefore, we desired a mild, efficient cross-coupling reaction that could directly produce secondary α-alkynyl carbonyl compounds. Herein, we report a palladium-catalyzed cross-coupling reaction between secondary α-bromo carbonyl compounds and alkynylstannanes to provide secondary α-alkynyl carbonyl compounds. The key to success is the use of the bulky XPhos ligand.

Palladium catalysts with bound phosphine ligands have been extensively utilized in cross-coupling reactions generating carbon−carbon bonds.[19−22] Results from our initial cross-coupling reaction studies are summarized in Table 1. We examined several bulky ligands due to their demonstrated superiority in other coupling reactions.[23,24] When methyl 2-bromopropanoate (**1a**) (1 equiv) and an excess of tributyl(phenylethynyl)stannane[25] (**2**) (2 equiv) were treated with $PdCl_2(MeCN)_2$ and the bulky ligand[26] Xantphos[27] under standard coupling conditions (110 °C, 20 min, PhMe), the desired cross-coupling product **3** was generated in 31% yield (Table 1, entry 1). Other phosphine ligands[23,24] were examined, including JohnPhos, DavePhos, TangPhos,[28] and BINAP,[29] affording cross-coupling products in 55%, 43%, 42%, and 51% yield, respectively (entries 2, 3, 4, and 6). The highest yield of **3** was obtained employing the XPhos[30] ligand, providing a 60% yield (entry 7). A benzonitrile-containing Pd catalyst did not substantially change the outcome

Table 1. Initial Screening Results of Cross-Coupling Reactions[a]



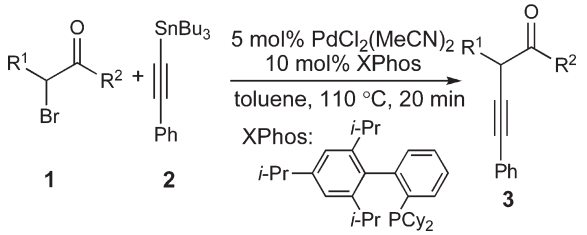
1a **2** **3**

entry	catalyst	ligand[b]	solvent	temp (°C)	yield[c] (%)
1	$PdCl_2(MeCN)_2$	Xantphos	PhMe	110	31
2	$PdCl_2(MeCN)_2$	JohnPhos	PhMe	110	55
3	$PdCl_2(MeCN)_2$	DavePhos	PhMe	110	43
4	$PdCl_2(MeCN)_2$	TangPhos	PhMe	110	42
5	$PdCl_2(MeCN)_2$	PyBox*i*-Pr	PhMe	110	50
6	$PdCl_2(MeCN)_2$	BINAP	PhMe	110	51
7	$PdCl_2(MeCN)_2$	XPhos	PhMe	110	60
8	$PdCl_2(PhCN)_2$	XPhos	PhMe	110	56
9	$Pd(PPh_3)_4$		PhMe	110	50
10	$PdCl_2(MeCN)_2$	XPhos	THF	66	37
11	$PdCl_2(MeCN)_2$	XPhos	MeCN	82	20[d]

[a] Reactions were performed using catalyst (5 mol %, 0.016 mmol), ligand (12 mol %, 0.038 mmol), methyl 2-bromopropanoate (**1a**) (0.32 mmol, 53 mg, 1 equiv), and tributyl(phenylethynyl)stannane (**2**) (0.64 mmol, 250 mg, 2 equiv) in solvent (1.0 mL) at 110 °C for 20 min and then quenched with KF solution (1 M, 1.0 mL). [b] See the Supporting Information for ligand acronyms. [c] Isolated yield after column chromatography. [d] Reaction time of 12 h.

Received: May 11, 2011
Published: July 19, 2011

Table 2. Scope of the Cross-Coupling Reactions[a]

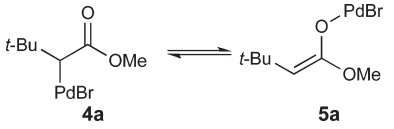


entry	R^1	R^2	reactant	product	yield[b] (%)
1	Me	−OMe	**1a**	**3a**	60
2	Me	−OBn	**1b**	**3b**	60
3	Me	−O-*s*-Bu	**1c**	**3c**	55
4	*i*-Pr	−OMe	**1d**	**3d**	55
5	*i*-Pr	−OBn	**1e**	**3e**	51[c]
6	*t*-Bu	−OMe	**1f**	**3f**	36
7	Me	$-NEt_2$	**1g**	**3g**	42
8	Me	$-N(CH_2)_5$	**1h**	**3h**	35
9	Me	$-N(C_2H_4)_2O$	**1i**	**3i**	55
10	*i*-Pr	$-NEt_2$	**1j**	**3j**	40
11	*i*-Pr	$-N(C_2H_4)_2O$	**1k**	**3k**	50

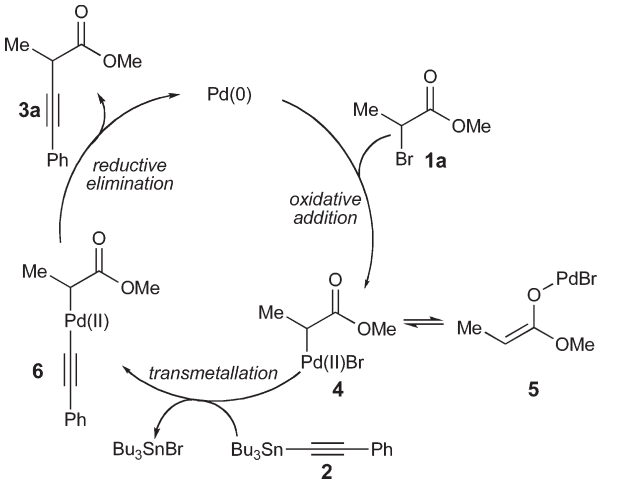
[a] Reactions were performed using $PdCl_2(MeCN)_2$ (5 mol %, 0.016 mmol 4 mg), XPhos (12 mol %, 0.038 mmol, 18 mg), α-bromo carbonyl compound **1** (0.32 mmol, 1 equiv), and tributyl(phenylethynyl)stannane (**2**) (0.64 mmol, 250 mg, 2 equiv) in PhMe (1.0 mL) at 110 °C for 20 min and then quenched with KF solution (1 M, 1.0 mL). [b] Isolated yield after column chromatography. [c] Calculated yield accounting for inseparable impurities.

(56% yield, entry 8). The simple triphenylphosphine ligand and PyBox*i*-Pr were both inferior, both providing the desired cross-coupled product in 50% yield (entries 5 and 9). THF and MeCN proved to be inferior to PhMe as solvent for these cross-coupling reactions (entries 7, 10, and 11). Homocoupled diyne byproduct **A**, Ph—C≡C—C≡C—Ph, was typically observed in these reactions.[7,31]

With these optimized reaction conditions in hand, we explored the scope of this reaction with various α-bromo esters and amides. Our results are summarized in Table 2. The reactions of α-bromo benzyl ester **1b** and *sec*-butyl ester **1c** proceed to afford the desired cross-coupling products in 60% and 55% yields, respectively (entries 2 and 3). To test the effect of the *β*-substituents on α-halo carbonyl compounds, the carbonyl compounds with isopropyl and *tert*-butyl groups (entries 4−6) were subjected to our standard reaction conditions and delivered the desired products albeit in reduced yields of 36−55%. A plausible reason for lower product yields with the electrophiles **1e** and **1f** could be a result of adverse competition of steric interaction between *carbo*palladation (**4a**) and *oxo*palladation (**5a**) intermediates.[7] The bulky *tert*-butyl substituent on electrophile **1f** does not favor formation of carbopalladation intermediate **4a** due to steric interaction and instead prefers oxopalladation intermediate **5a**.[32,33]



Scheme 1. Proposed Mechanistic Cycle for Intermolecular Cross-Coupling Reaction



Under these conditions, 2-bromo-*N*,*N*-diethylpropanamide (**1g**) and **2** led to cross-coupling product **3g** in 42% yield. 2-Bromo-1-morpholinopropan-1-one (**1i**) and 2-bromo-3-methyl-1-morpholinobutan-1-one (**1k**) each coupled with **2** to deliver cross-coupled products **3i** and **3k** in 55% and 50% yield, respectively (entries 9 and 11). The structure of compound **3k** has been confirmed by single-crystal X-ray analysis. This reaction still suffers from some limitations that need to be overcome. For example, ketones are not reactive under our reaction conditions. Both 2-bromopropiophenone and α-bromocyclohexenone did not participate in the desired coupling reaction.

A proposed mechanistic cycle for the intermolecular cross-coupling reaction is shown in Scheme 1.[7] Electrophile **1a** undergoes oxidative addition with Pd(0) to form palladation intermediate **4** or **5**, which then is subjected to transmetalation with **2** to form intermediate **6**. Intermediate **6** generates the desired cross-coupling product **3a** via reductive elimination.

In summary, we have reported a catalytic intermolecular cross-coupling reaction that allows transformation of secondary α-bromo esters and amides to secondary alkynyl carbonyl compounds in moderate yields by palladium catalysis employing the bulky XPhos ligand. This reaction sequence allows rapid access to useful, chiral secondary α-alkynyl carbonyl derivatives and is potentially suited to modification for asymmetric catalysis.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under an argon atmosphere in oven-dried glassware with magnetic stirring. Dry THF and toluene were obtained by a solvent purification system under argon. All commercially obtained reagents were used as received. Purification of reaction products was carried out by flash column chromatography using silica gel 60 (230−400 mesh). Analytical thin layer chromatography was performed on 0.25 mm glass-backed silica gel 60-F plates. Visualization was accompanied with UV light and $KMnO_4$ solution. Concentration in vacuo refers to the removal of volatile solvent using a rotary evaporator attached to a dry diaphragm pump (10−15 mmHg) followed by pumping to a constant weight with an oil pump (<300 mTorr). ^1H NMR spectra are recorded at 300 or 500 MHz and are recorded relative to the peak for $CDCl_3$ (δ 7.26) or TMS (δ 0.00). ^1H NMR coupling constants (J) are reported in hertz, and multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet),

dx.doi.org/10.1021/jo200939u |*J. Org. Chem.* 2011, 76, 6856–6859

m (multiplet). Proton-decoupled ^{13}C NMR spectra are recorded at 75 or 125 MHz and are reported relative to the peak for $CDCl_3$ (δ 77).

General Procedure (GP) for Synthesis of Alkynyl Carbonyl Compounds. Methyl 2-Methyl-4-phenylbut-3-ynoate (3a). To a drum vial were added $PdCl_2(MeCN)_2$ (5 mol %, 0.016 mmol, 4 mg), XPhos (12 mol %, 0.038 mmol, 18 mg), and PhMe (1.0 mL). Next α-bromo carbonyl compound **1a** (0.32 mmol, 53 mg, 1 equiv) and tributyl(phenylethynyl)stannane (**2**) (0.64 mmol, 250 mg, 2 equiv) were added. The reaction mixture was heated at 110 °C for 20 min. The reaction mixture was then cooled to rt and quenched with a KF solution (1 M, 1.5 mL). The reaction mixture was passed through a short plug of Celite, and the layers were separated. The aqueous layer was twice extracted with Et_2O, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography to afford a pale yellow oil of **3a** (36 mg, 60%): R_f = 0.3 (hexanes:Et_2O = 20:1); IR (film, cm^{-1}) 1744, 1199, 758; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44−7.42 (m, 2H), 7.31−7.29 (m, 3H), 3.78 (s, 3H), 3.65 (q, J = 7.1 Hz, 1H), 1.54 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 131.7, 128.4, 128.1, 122.9, 86.9, 82.6, 52.6, 32.7, 18.1; HRMS (ESI) m/z calcd for $C_{12}H_{12}O_2$ $[M + H]^+$ 189.0916, found 189.0918.

Benzyl 2-Methyl-4-phenylbut-3-ynoate (3b). α-Bromo carbonyl compound **1b** (0.32 mmol, 78 mg, 1.0 equiv) and **2** (0.64 mmol, 250 mg, 2.0 equiv) were treated to the reaction conditions as described in the GP, affording **3b** as a pale yellow oil (51 mg, 60%): R_f = 0.26 (hexanes:Et_2O = 20:1); IR (film, cm^{-1}) 1744, 1489, 1175, 758, 693; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47−7.29 (m, 10H), 5.26 (s, 2H), 3.73(q, J = 7.4 Hz, 1H), 1.60 (d, J = 7.0, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 135.7, 131.7, 128.6, 128.3, 128.3, 128.2, 128.0, 123.0, 86.9, 82.8, 67.0, 33.0, 18.0; HRMS (ESI) m/z calcd for $C_{18}H_{16}O_2$ $[M + H]^+$ 265.1229, found 265.1222.

***sec*-Butyl 2-Methyl-4-phenylbut-3-ynoate (3c).** α-Bromo carbonyl compound **1c** (0.32 mmol, 67 mg, 1.0 equiv) and **2** (0.64 mmol, 250 mg, 2.0 equiv) were treated to the reaction conditions as described in the GP, affording **3c** as a pale yellow oil (41 mg, 56%): R_f = 0.4 (hexanes:Et_2O = 20:1); IR (film, cm^{-1}) 1735, 1190, 864, 755, 690; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47−7.43 (m, 2H), 7.34−7.29 (m, 3H), 5.00−4.89 (m, 1H), 3.69 (q, J = 7.3 Hz, 1H), 1.72−1.69 (m, 2H), 1.57−1.53 (m, 3H), 1.29 (d, J = 6.5 Hz, 3H), 1.01−0.94 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) (mixture of diastereoisomer) δ 171.1, 171.0, 131.7, 128.2, 128.0, 123.1, 87.4, 87.3, 82.5, 82.4, 73.4, 33.3, 33.1, 28.8, 28.7, 19.4, 19.3, 18.2, 17.9, 9.7, 9.6; HRMS (ESI) m/z calcd for $C_{15}H_{18}O_2$ $[M + H]^+$ 231.1385, found 231.1389.

Methyl 2-Isopropyl-4-phenylbut-3-ynoate (3d). α-Bromo carbonyl compound **1d** (0.32 mmol, 62 mg, 1.0 equiv) and **2** (0.64 mmol, 250 mg, 2.0 equiv) were treated to the reaction conditions as described in the GP, affording **3d** as a pale yellow oil (38 mg, 55%): R_f = 0.3 (hexanes:Et_2O = 20:1); IR (film, cm^{-1}) 1744, 1492, 1018, 752, 690; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47−7.41 (m, 2H), 7.31−7.25 (m, 3H), 3.76 (s, 3H), 3.41(d, J = 6.5 Hz, 1H), 2.33−2.26 (m, 1H), 1.09 (dd, J = 5.3, 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 131.7, 128.1, 128.0, 123.1, 84.5, 52.3, 46.0, 31.2, 20.8, 19.2; HRMS (ESI) m/z calcd for $C_{14}H_{16}O_2$ $[M + H]^+$ 217.1229, found 217.1234.

Benzyl 2-Isopropyl-4-phenylbut-3-ynoate (3e). α-Bromo carbonyl compound **1e** (0.32 mmol, 87 mg, 1.0 equiv) and **2** (0.64 mmol, 250 mg, 2.0 equiv) were treated to the reaction conditions as described in the GP, affording **3e** as a pale yellow oil (56 mg, ca. 85% pure by ^1H and ^{13}C NMR): R_f = 0.23 (hexanes:Et_2O = 20:1); IR (film, cm^{-1}) 1741, 1486, 1166, 755, 693; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49−7.29 (m, 10H), 5.14 (s, 2H), 3.48 (d, J = 6.3 Hz, 1H), 2.40−2.30 (m, 1H), 1.11 (t, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 135.7, 131.7, 128.5, 128.2, 128.2, 128.1, 128.0, 123.2, 84.7, 84.6, 66.9, 46.2, 31.3, 20.9, 19.2; HRMS (ESI) m/z calcd for $C_{20}H_{20}O_2$ $[M + H]^+$ 293.1542, found 293.1535.

Methyl 2-(*tert*-Butyl)-4-phenylbut-3-ynoate (3f). α-Bromo carbonyl compound **1f** (0.32 mmol, 67 mg, 1.0 equiv) and **2** (0.64 mmol, 250 mg, 2.0 equiv) were treated to the reaction conditions as described in the GP, affording **3f** as a pale yellow oil (26 mg, 36%): R_f = 0.32 (hexanes:Et_2O = 20:1); IR (film, cm^{-1}) 1735, 1146, 755, 687; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46−7.42 (m, 2H), 7.30−7.28 (m, 3H), 3.75 (s, 3H), 3.37 (s, 1H), 1.14(s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 131.7, 128.1, 128.0, 123.2, 85.2, 84.4, 52.0, 50.1, 35.0, 27.7; MS (EI) m/z calcd for $C_{15}H_{18}O_2$ 230.0, found 230.0.

***N,N*-Diethyl-2-methyl-4-phenylbut-3-ynamide (3g).** α-Bromo carbonyl compound **1g** (0.32 mmol, 67 mg, 1.0 equiv) and **2** (0.64 mmol, 250 mg, 2.0 equiv) were treated to the reaction conditions as described in the GP, affording **3g** as a pale yellow oil (31 mg, 42%): R_f = 0.22 (hexanes:EtOAc = 4:1); IR (film, cm^{-1}) 1646, 1024, 758, 690; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43−7.40 (m, 2H), 7.32−7.29 (m, 3H), 3.72 (q, J = 6.0 Hz, 1H), 3.67−3.38 (m, 4H), 1.52 (d, J = 7.2 Hz, 3H), 1.28 (t, J = 6.6 Hz, 3H), 1.17 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 131.8, 128.3, 128.1, 123.5, 88.5, 82.5, 42.1, 40.6, 30.3, 17.9, 14.4, 12.9; HRMS (ESI) m/z calcd for $C_{15}H_{19}NO$ $[M + H]^+$ 230.1545, found 230.1551.

2-Methyl-4-phenyl-1-(piperidin-1-yl)but-3-yn-1-one (3h). α-Bromo carbonyl compound **1h** (0.32 mmol, 70 mg, 1.0 equiv) and **2** (0.64 mmol, 250 mg, 2.0 equiv) were treated to the reaction conditions as described in the GP, affording **3h** as a pale yellow oil (27 mg, 35%): R_f = 0.23 (hexanes:EtOAc = 4:1); IR (film, cm^{-1}) 1652, 1436, 1003, 758, 687; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42−7.40 (m, 2H), 7.32−7.30 (m, 3H), 3.81−3.73 (m, 2H), 3.71 (q, J = 6.7, 1H), 3.55−3.31 (m, 2H) 1.73−1.56 (m, 6H), 1.52 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 131.8, 128.5, 128.1, 123.4, 88.3, 82.9, 47.2, 43.7, 30.5, 26.3, 25.8, 25.2, 17.8; MS (EI) m/z calcd for $C_{16}H_{19}NO$ 241.0, found 241.0.

2-Methyl-1-morpholino-4-phenylbut-3-yn-1-one (3i). α-Bromo carbonyl compound **1i** (0.32 mmol, 71 mg, 1.0 equiv) and **2** (0.64 mmol, 250 mg, 2.0 equiv) were treated to the reaction conditions as described in the GP, affording **3i** as a pale yellow oil (43 mg, 55%): R_f = 0.4 (hexanes:EtOAc = 1:1); IR (film, cm^{-1}) 1649, 1027, 758, 690; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41−7.39 (m, 2H), 7.33−7.31 (m, 3H), 3.89−3.50 (m, 8H), 3.67 (q, J = 6.9, 1H), 1.53 (d, J = 7.6, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 131.8, 128.4, 128.3, 122.9, 87.6, 83.3, 66.9, 66.6, 46.6, 42.8, 30.3, 17.3; HRMS (ESI) m/z calcd for $C_{15}H_{17}NO_2$ $[M + H]^+$ 244.1338, found 244.1332.

***N,N*-Diethyl-2-isopropyl-4-phenylbut-3-ynamide (3j).** α-Bromo carbonyl compound **1j** (0.32 mmol, 76 mg, 1.0 equiv) and **2** (0.64 mmol, 250 mg, 2.0 equiv) were treated to the reaction conditions as described in the GP, affording **3j** as a pale yellow oil (33 mg, 40%): R_f = 0.32 (hexanes:EtOAc = 4:1); IR (film, cm^{-1}) 1652, 1030, 755, 690; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−7.42 (m, 2H), 7.32−7.30 (m, 3H), 3.65−3.39 (m, 4H), 3.31 (d, J = 9.0, 1H), 2.43−2.33 (m, 1H), 1.29 (t, J = 7.3 Hz, 3H), 1.18 (t, J = 7.3 Hz, 6H), 1.01 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 131.8, 128.2, 128.0, 123.5, 87.0, 83.7, 43.8, 42.3, 40.8, 31.0, 21.3, 20.6, 14.8, 13.0; HRMS (ESI) m/z calcd for $C_{17}H_{23}NO$ 258.1858, found 258.1863.

2-Isopropyl-1-morpholino-4-phenylbut-3-yn-1-one (3k). α-Bromo carbonyl compound **1k** (0.32 mmol, 80 mg, 1.0 equiv) and **2** (0.64 mmol, 250 mg, 2.0 equiv) were treated to the reaction conditions as described in the GP, affording **3k** as a pale yellow solid (43 mg, 50%): R_f = 0.5 (hexanes:EtOAc = 1:1); IR (film, cm^{-1}) 1649, 1430, 971, 758, 690; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41−7.37 (m, 2H), 7.31−7.26 (m, 3H), 3.85−3.50 (m, 8H), 3.31 (d, J = 8.2 Hz, 1H), 2.37−2.25 (m, 1H), 1.19 (d, J = 7.1 Hz, 3H), 1.03 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 131.7, 128.4, 128.2, 123.1, 86.0, 85.0, 67.2, 66.9, 47.2, 44.2, 43.0, 30.6, 21.7, 20.6; HRMS (ESI) m/z calcd for $C_{17}H_{21}NO_2$ $[M + H]^+$ 272.1651, found 272.1656. The structure assignment was confirmed by X-ray crystallography.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra of new compounds, ligand acronyms, thermal ellipsoid plot for **3k**, and X-ray CIF data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: connell@chem.tamu.edu.

■ ACKNOWLEDGMENT

The Robert A. Welch Foundation (Grant A-1623) is acknowledged for support of this research.

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