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Enhanced Olefin Cross Metathesis Reactions: The Copper Iodide Effect

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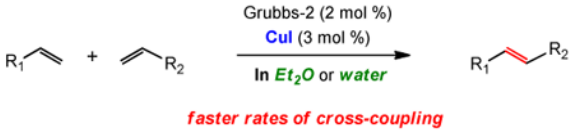
Abstract



Copper iodide has been shown to be an effective co-catalyst for the olefin cross metathesis reaction. In particular, it has both a catalyst stabilizing effect due to iodide ion, as well as copper(I)-based phosphine-scavenging properties that apply to use of the Grubbs-2 catalyst. A variety of Michael acceptors and olefinic partners can be cross-coupled under mild conditions in refluxing diethyl ether that avoid chlorinated solvents. This effect has also been applied to chemistry in water at room temperature using the new surfactant TPGS-750-M.

The formation of carbon-carbon double bonds by olefin metathesis is among the most powerful and broadly applicable synthetic tools of modern organic chemistry.[1] In particular, cross metathesis (CM) reactions promoted by ruthenium-based catalysts have been widely utilized by synthetic organic as well as polymer chemists in the construction of higher olefins from simple alkene precursors.[2] *N*-Heterocyclic carbene (NHC) ligand-containing catalysts,[3] such as the second-generation Grubbs catalyst **1**[4] (Figure 1), have emerged as especially promising in selective CM.[5] For some conjugated olefins, however, reactions can be rather challenging, most notably with vinyl ketones,[6] acrylic acid,[7] and acrylonitrile,[8] oftentimes requiring higher loadings of catalyst and heat. Although CuCl serves as phosphine scavenger to assist with formation of Grubbs-Hoveyda-1[9] or Grubbs-Hoveyda-2[10] ruthenium carbene complexes, use of copper salts to enhance rates of metathesis reactions themselves is rare.[8,11] In this note we describe a new procedure for carrying out CM reactions under the beneficial impact of a copper(I) salt, CuI, which not only leads to faster rates of cross-couplings but avoids chlorinated solvents as well.

Several conditions and copper salts were screened utilizing a TBS-protected allylphenol **4** as a representative substrate (Table 1). Moving from CuCN (entry 1) to counter ions with increased solubility in organic solvents (entries 2-8) showed little effect on turnover enhancement. An increase from 4% to 6 mol % of CuI showed no effect (entry 13), while an increase in the Grubbs-2 catalyst loading showed only modest improvement (entry 14). Changing the solvent to toluene (entry 15) had no impact, while an improvement was noted in both THF (entry 16) and in diethyl ether (entry 17). Better results were obtained by diluting the latter ethereal mixture from 0.5 M to 0.1 M (entry 19). Ultimately, running the

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Supporting Information **Available**. Copies of ^{1}H and ^{13}C NMR spectra of all new compounds and copies of ^{1}H NMR spectra of all known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

reaction at 35 °C in refluxing Et_2O for three hours gave a nearly quantitative yield (entry 21), while in the absence of CuI, the yield was only 57%. The corresponding control reactions, each run in CH_2Cl_2 and Et_2O in the absence of CuI, clearly show an effect on the rate and extent of reaction (entries 12, 20).

Figure 2 illustrates graphically the effect of CuI. The data suggests that iodide ion may be serving an important role as a stabilizing ligand on ruthenium, thereby extending the lifetime of the original Grubbs-2 catalyst.[11] To test this, an identical coupling with MVK was performed with NaI, which in fact led to the same result as that seen with CuI (Scheme 1). Replacing MVK with methyl acrylate to afford product **6** in the presence of NaI alone led to the same positive outcome. However, the NaI effect was not operative in the corresponding metathesis reactions involving acrylic acid en route to product **7** (or acrylonitrile; vide infra). Thus, while CuI gave complete conversion after three hours, NaI afforded only 64% consumption of educt **4**. Curiously, switching solvents from ether to DME in which NaI is especially soluble, the level of conversion for MVK dropped to 70% (from 79%) and that for methyl acrylate to 67% (from 100%). Hence, unlike previously studied additives and solvents, it appears that CuI in ether provides both the ligand stabilizing effect of iodide on ruthenium,[12] as well as presumably a phosphine sequestering effect by copper(I) from ruthenium.[8]

Other olefin metathesis catalysts bearing phosphines were also tested for reactivity in the presence of catalytic amounts of CuI (Table 2). As noted previously, the Grubbs-2 catalyst showed a remarkable near doubling in turnover when tested with CuI at room temperature for fifteen hours (entry 1; see also Table 1, entries 19 vs. 20). The less sterically encumbered, more reactive Grubbs catalyst **2**[13] (entry 2), as well as the Neolyst M2 catalyst[14] (**3**, entry 3), showed similar increases in reactivity, but were not pursued further due to the lower levels of conversions seen relative to those noted using catalyst **1**.

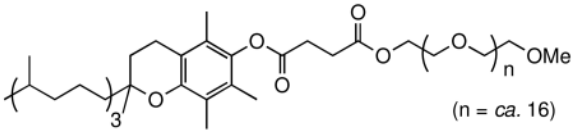
A series of olefins were screened under these newly developed conditions (Table 3). As these examples indicate, a variety of olefinic partners can be successfully cross-coupled in refluxing ether at 0.1 M concentration within three hours. Challenging cases, such as acrylic acid and methyl vinyl ketone readily participated and led to high isolated yields, as did both methyl and *t*-butyl acrylate derivatives. An olefinic tetrazole[15] and *p*-methoxy-substituted allylbenzene each coupled smoothly with high *E*/*Z* selectivities. Prospects for enyne cross-metathesis[16] also look encouraging, with improved stereoselectivity due to the reduced temperatures involved, as well as a reduced catalyst loading all being used in a more attractive, non-chlorinated solvent (**8**, Scheme 2).[17] Substituted furans **9** are also accessible via sequential CM/acid-catalyzed cyclization, with lower levels of Grubbs-2 catalyst loadings (Scheme 3).[18]

Selective and high-yielding CM using acrylonitrile remains a challenge in olefin metathesis chemistry, presumably due to competitive complexation of Ru by the nitrile group.[19] Blechert has studied this coupling reaction and finds that CuCl in the presence of a Grubbs-2 precatalyst in refluxing CH_2Cl_2 leads to somewhat improved results.[8d] Heating reaction mixture, especially under microwave conditions, can also be very effective in such reactions.[20] An initial attempt using, typically, an excess of the nitrile under optimized conditions in refluxing ether led to a discouraging 35% conversion to **10**, even after extended reaction times (Table 4, entry 1). Reducing the nitrile concentration led to an increase in homocoupling with the type I olefinic partner, as well as a slight increase in the nitrile CM products (*E* + *Z*; entry 2). To maximize the production of the desired unsaturated nitrile and minimize any decomposition of the highly reactive, phosphine-free Ru complex, the catalyst was added over time. Best results were obtained under these conditions (entries 4 and 5). As before, increasing the amount of copper did not improve the conversion to

product (entry 6); leaving copper out of the reaction entirely cut the conversion in half (entry 7). Using NaI alone gave poor levels of conversion using three, or even six, mole percent of this additive (Scheme 4).

Opportunities to apply the CuI effect to cross metathesis reactions involving trisubstituted olefins of the isopropylidene variety also exist, and while uncommon in general, could prove especially useful.[21] A challenging reaction between this Type III olefin and a Type II acrylate was attempted on the natural product osthole, **11**, an antiplatelet agent that inhibits phosphoinositide breakdown.[22] As shown in Scheme 5, the desired *t*-butyl acrylate **12** (all *E*) was formed in good yield (81%, quant. brsm) under standard conditions in refluxing ether over 24 hours.

Lastly, we have recently reported that the amphiphile "TPGS-750-M" (**13**),[23] present only to the extent of ca. 2.5% (by weight), allows for cross-metathesis to take place within nanometer micelles in water as the gross reaction medium.[24] As illustrated by several examples in Table 5, the benefits ascribed to the presence of CuI can be realized as well under conditions of micellar catalysis[25] using this new nonionic surfactant.



13 (TPGS-750-M)

In summary, the positive impact of catalytic quantities of CuI in cross-metathesis reactions mediated by the Grubbs-2 catalyst has been demonstrated, in particular where more challenging Type II and Type III olefinic reaction partners are involved (e.g., MVK, acrylic acid, acrylonitrile, and isopropylidene derivatives). These couplings are done in ethereal solvent, rather than chlorinated media, as the former is preferred both insofar as the chemistry is concerned, and from the environmental perspective.[26] It has also been shown that equally effective couplings can be achieved using micellar catalysis conditions, where CM within nanoparticles takes place in water at room temperature.

Experimental Section

General Procedure for Cross Metathesis Reactions in Et_2O

A flame dried pear shaped flask with a rubber septum containing a stir bar was charged with alkene (0.50 mmol), acrylate/ketone (1.50 mmol), Grubbs-2 catalyst (8.5 mg, 10.0 μmol), and CuI (2.9 mg, 15.0 μmol) under an Ar atmosphere. Freshly distilled ethyl ether (5.0 mL) was added, and the rubber septum was then replaced with a reflux condenser. The solution was heated at 40 °C (oil bath temperature) for 3 hours. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography, under the conditions noted, to afford the corresponding metathesis adduct.

(*E*)-4-(2-(*tert*-Butyldimethylsilyloxy)phenyl)but-2-enoic acid (Table 3, entry 1)

The general procedure was above followed using *tert*-butyl(2-allylphenoxy)dimethylsilane (124 mg, 0.50 mmol), acrylic acid (72.1 mg, 1.0 mmol), Grubbs-2 catalyst (8.5 mg, 10.0 μmol), and CuI (2.9 mg, 15.0 μmol). Column chromatography on silica gel (eluting with 30% EtOAc/hexanes) afforded the product as a white solid (133 mg, 82%). mp 81-83 °C; IR (thin-film): 3022, 2955, 2930, 2859, 1697, 1649, 1492, 1263, 926 $cm^{-1;}$ ^1H NMR (400 MHz, $CDCl_3$): δ 7.23 (dt, *J* = 15.6, 6.4 Hz, 1H), 7.14 (dt, *J* = 7.5, 1.8 Hz, 1H), 7.10 (dd, *J* = 7.5, 1.8 Hz, 1H), 6.91 (dt, *J* = 7.5, 1.1 Hz, 1H), 6.83 (dd, *J* = 8.1, 1.1 Hz, 1H), 5.76, (dt, *J* = 15.6,

1.8 Hz, 1H), 3.54, (dd, *J* = 6.4, 1.6 Hz, 2H), 1.01 (s, 9H), 0.26 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 153.7, 150.5, 130.7, 128.2, 128.1, 121.5, 121.4, 118.6, 33.4, 26.0, 18.4, -3.9; ESI-MS *m/z*: 315 (M + Na); HRMS (ESI) calcd for $C_{16}H_{24}O_3SiNa$ $[M + Na]^+$ 315.1392, found 315.1395.

(*E*)-5-(2-(*tert*-Butyldimethylsilyloxy)phenyl)pent-3-en-2-one (Table 3, entry 2)

The general procedure above was followed using *tert*-butyl(2-allylphenoxy)dimethylsilane (124 mg, 0.50 mmol), methyl vinyl ketone (106 mg, 1.50 mmol), Grubbs-2 catalyst (8.5 mg, 10.0 μmol), and CuI (2.9 mg, 15.0 μmol). Column chromatography on silica gel (eluting with 3% EtOAc/hexanes) afforded the product as a colorless oil (142 mg, 98%). IR (neat): 3062, 3034, 2932, 2894, 2859, 1699, 1676, 1626, 1599, 1582, 1492, 1472, 1452, 1422, 1390, 1361, 1254, 1182, 1108, 1043, 982, 929 $cm^{-1;}$ ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (td, *J* = 7.6, 1.6 Hz, 1H), 7.11 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.95 (dt, *J* = 16.0, 6.4 Hz, 1H), 6.92 (td, *J* = 7.6, 1.2 Hz, 1H), 6.84 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.03 (dt, *J* = 16.0, 1.6 Hz, 1H), 3.54 (dd, *J* = 6.4, 1.6 Hz, 2H), 2.24 (s, 3H), 1.01 (s, 9H), 0.26 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.8, 153.7, 146.8, 132.0, 130.7, 128.4, 128.1, 121.4, 118.6, 33.7, 26.9, 25.9, 18.4, -4.0; EI-MS *m/z* (%): 275 ($M - CH_3^+$, 2), 233 ($M - C_4H_9^+$, 100), 215 (20), 151 (8), 75 (42); HRMS (EI) calcd for $C_{13}H_{17}O_2Si$ $[M - C_4H_9]^+$ 233.0998, found 233.1006.

(*E*)-*tert*-Butyl 4-(2-(*tert*-butyldimethylsilyloxy)phenyl)-2-butenoate (Table 3, entry 3)

The general procedure above was followed using *tert*-butyl(2-allylphenoxy)dimethylsilane (124 mg, 0.50 mmol), *tert*-butyl acrylate (192 mg, 1.50 mmol), Grubbs-2 catalyst (8.5 mg, 10.0 μmol), and CuI (2.9 mg, 15.0 μmol). Column chromatography on silica gel (eluting with 3% EtOAc/hexanes) afforded the product as a pale yellow oil (162 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15-7.10 (m, 2H), 7.00 (dt, *J* = 15.6, 6.4 Hz, 1H), 6.91 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.82 (dd, *J* = 8.0, 0.8 Hz, 1H), 5.68 (dt, *J* = 15.6, 1.6 Hz, 1H), 3.48 (dd, *J* = 6.4, 1.6 Hz, 2H), 1.46 (s, 9H), 1.01 (s, 9H), 0.25 (s, 6H).[8a]

(*E*)-Methyl 4-(2-(*tert*-butyldimethylsilyloxy)phenyl)but-2-enoate (Table 3, entry 4)

The general procedure above was followed using *tert*-butyl(2-allylphenoxy)dimethylsilane (124 mg, 0.50 mmol), methyl acrylate (129 mg, 1.50 mmol), Grubbs-2 catalyst (8.5 mg, 10.0 μmol), and CuI (2.9 mg, 15.0 μmol). Column chromatography on silica gel (eluting with 3% EtOAc/hexanes) afforded the product as a pale yellow oil (143 mg, 93%). IR (neat): 3063, 3023, 2953, 2931, 2859, 1726, 1656, 1492, 1265, 1161, 930; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16-7.08 (m, 3H), 6.90 (dt, *J* = 7.2, 1.1 Hz, 1H), 6.82 (dd, *J* = 8.2, 1.1 Hz, 1H), 5.77 (dt, *J* = 15.6, 1.8 Hz, 1H), 3.72 (s, 3H), 3.51 (dd, *J* = 6.3, 1.5 Hz, 2H), 1.01 (s, 9H), 0.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 153.6, 147.8, 130.6, 128.5, 128.0, 122.0, 121.4, 119.0, 51.5, 33.2, 25.9, 18.4, -4.0; FI-MS *m/z*: 306 $[M]^+$, 249 $[M - C_4H_9]^+$; HRFIMS calcd for $C_{17}H_{26}O_3Si$ $[M]^+$ 306.1651, found 306.1645.

(*E*)-*tert*-Butyl 6-(1-phenyl-1*H*-tetrazol-5-ylthio)-2-hexenoate (Table 3, entry 5)

The general procedure above was followed using 5-(pent-4-en-1-ylthio)-1-phenyl-1*H*-tetrazole5-(pent-4-en-1-ylthio)-1-phenyl-1*H*-tetrazole[8a] (123 mg, 0.50 mmol), *tert*-butyl acrylate (192 mg, 1.50 mmol), Grubbs-2 catalyst (8.5 mg, 10.0 μmol), and CuI (2.9 mg, 15.0 μmol). Column chromatography on silica gel (eluting with 10% EtOAc/hexanes) afforded the product as a colorless oil (145 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.53 (m, 5H), 6.80 (dt, *J* = 15.6, 7.2 Hz, 1H), 5.77 (dt, *J* = 15.6, 1.6 Hz, 1H), 3.39 (t, *J* = 7.2 Hz, 2H), 2.33 (qd, *J* = 6.8, 1.6 Hz, 2H), 2.01 (quintet, *J* = 7.6 Hz, 2H), 1.46 (s, 9H).[8a]

(*E*)-Methyl 4-(4-methoxyphenyl)-2-butenoate (Table 3, entry 6)

The general procedure above was followed using 4-allylanisole (74 mg, 0.50 mmol), methyl acrylate (129 mg, 1.50 mmol), Grubbs-2 catalyst (8.5 mg, 10.0 μmol), and CuI (2.9 mg, 15.0 μmol). Column chromatography on silica gel (eluting with 2.5% EtOAc/hexanes) afforded the product as a colorless oil (97 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13-7.06 (m, 3H), 6.86 (d, J = 8.8 Hz, 2H), 5.80 (dt, J = 15.6, 1.6 Hz, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 3.47 (d, J = 6.8 Hz, 2H).[8a]

(*E*)-4-Methylene-6-(triisopropylsilyloxy)hex-2-en-1-ol (8)

The general procedure above was followed using (but-3-yn-1-yloxy)triisopropylsilane (106.2 mg, 0.50 mmol), prop-2-en-1-ol (174.2 mg, 3.00 mmol), Grubbs-2 catalyst (8.5 mg, 10.0 μmol), and CuI (2.9 mg, 15.0 μmol). Column chromatography on silica gel (eluting with 20% EtOAc/hexanes) afforded the product as a pale yellow oil (106 mg, 80%, E/Z = 6:1). IR (neat): 3337, 3083, 2943, 2867, 1684, 1607, 1464, 1384, 1104, 883 cm$^{-1;}$ ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.27 (d, J = 16.1 Hz, 1H), 5.89 (dt, J = 15.8, 5.8 Hz, 1H), 5.07 (s, 1H), 5.03 (s, 1H), 4.22 (br t, J = 4.0 Hz, 2H), 3.81 (t, J = 7.0 Hz, 2H), 2.49 (dt, J = 7.4, 0.9 Hz, 2H) 1.07-1.05 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.5, 133.5, 128.1, 117.4, 63.7, 62.8, 35.9, 18.2, 12.2; FI-MS *m/z*: 284 $[M]^+$, 241 $[M - C_3H_7]^+$; HRFIMS calcd for $C_{16}H_{32}O_2Si$ $[M]^+$ 284.2172, found 284.2179.

2-Ethyl-5-phenethylfuran (9)

A flame dried pear shaped flask with a rubber septum containing a stir bar was charged with 5-phenylpent-1-en-3-ol (41 mg, 0.25 mmol), ethyl vinyl ketone (53 mg, 0.63 mmol), Grubbs-2 catalyst (4.2 mg, 5.0 μmol), and CuI (1.4 mg, 7.5 μmol) in Et_2O (2.5 mL) under an argon atmosphere. The rubber septum was then replaced with a reflux condenser and the solution was heated at 40 °C (oil bath temperature) for 3 hours. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. PPTS (1.6 mg, 6.3 μmol) and CH_2Cl_2 (1 mL) were added and the reaction was allowed to stir for an additional 12 hours at 40 °C. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. Column chromatography on silica gel (eluting with 2% EtOAc/hexanes) afforded the product as a colorless oil (34 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.27 (m, 2H), 7.23-7.18 (m, 3H), 5.88-5.85 (m, 2H), 2.98-2.93 (m, 2H), 2.92-2.86 (m, 2H), 2.63 (q, J = 7.5 Hz, 2H), 1.23 (t, J = 7.5 Hz, 3H).[17]

(*Z*)-4-(2-(*tert*-Butyldimethylsilyloxy)phenyl)but-2-enenitrile (10)

The general procedure above was followed using *tert*-butyl(2-allylphenoxy)dimethylsilane (124 mg, 0.50 mmol), acrylonitrile (39.8 mg, 0.75 mmol), Grubbs-2 catalyst (8.5 mg, 10.0 μmol), and CuI (2.9 mg, 15.0 μmol). Column chromatography on silica gel (eluting with 3% EtOAc/hexanes) afforded the product as a colorless oil (70 mg, 51%, Z/E = 3.3:1.0). IR (neat): 3067, 3035, 2956, 2931, 2896, 2859, 2222, 1683, 1620, 1599, 1583, 1492, 1472, 1454, 1390, 1362, 1258, 1184, 1109, 1045, 1108, 928, 838 cm$^{-1;}$ ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17-7.14 (m, 2H), 6.93 (t, J = 7.6 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.65 (dt, J = 11.2, 7.2 Hz, 1H), 5.38 (d, J = 11.2 Hz, 1H), 3.74 (d, J = 7.2 Hz, 2H), 1.03 (s, 9H), 0.27 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3, 130.8, 130.4, 128.6, 128.4, 121.6, 118.7, 116.3, 99.7, 34.4, 33.2, 26.0, -3.9; FI-MS *m/z*: 273 $[M]^+$, 216 $[M - C_4H_9]^+$; HRFIMS calcd for $C_{16}H_{23}NOSi$ $[M]^+$ 273.1549, found 273.1557.

(*E*)-*tert*-Butyl 4-(7-methoxy-2-oxo-2*H*-chromen-8-yl)but-2-enoate (12)

The general procedure above was followed using osthole **11**) (40 mg, 0.16 mmol), *tert*-butyl acrylate (63 mg, 0.49 mmol), Grubbs-2 catalyst (4.2 mg, 4.91 μmol), and CuI (1.4 mg, 7.37 μmol). The catalyst and acrylate were added over time and the solution was allowed to stir

for 24 hours at 40 °C (oil bath temperature). Column chromatography on silica gel (eluting with 10% EtOAc/hexanes) afforded the product as a white solid (42 mg, 81%). mp 137-140 °C; IR (thin-film): 3071, 2979, 2931, 2843, 1734, 1713, 1605, 1287, 1253, 1119, 1103 $cm^{-1;}$ ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 9.2 Hz, 1H), 7.36 (d, *J* = 8.6 Hz, 1H), 6.94 (dt, *J* = 15.4, 6.6 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 1H), 6.22 (d, *J* = 9.3 Hz, 1H), 5.67 (dt *J* = 15.6, 1.7 Hz, 1H), 3.91 (s, 3H), 3.71 (d, *J* = 1.7 Hz, 2H) 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 161.3, 160.5, 153.1, 144.3, 143.9, 127.5, 123.7, 114.1, 113.3, 113.1, 107.5, 80.3, 56.3, 28.3, 25.3; ESI-MS *m/z*: 355 (M + K), 339 (M + Na); HRMS (ESI) calcd for $C_{18}H_{20}O_5Na$ $[M + Na]^+$ 339.1208, found 339.1195.

General Procedure for Cross Metathesis Reactions in Water

Alkene (0.50 mmol), acrylate (1.00 mmol)/ketone (1.50 mmol), CuI (2.9 mg, 15.0 μmol) and Grubbs-2 catalyst (8.5 mg, 10.0 μmol) were sequentially added into a Teflon-coated-stir-bar-containing Biotage 2-5 mL microwave reactor vial at rt, and then sealed with a septum. An aliquot of TPGS-750-M/H_2O (1.0 mL; 2.5% TPGS-750-M by weight; all cross-coupling reactions were conducted at 0.5 M unless stated otherwise) was added, via syringe, and the resulting solution was allowed to stir at rt for 12-20 h. The homogeneous reaction mixture was then diluted with EtOAc (2 mL), filtered through a bed of silica gel, and the bed further washed (3 × 3 mL) with EtOAc to collect all of the cross-coupled material. The volatiles were removed *in vacuo* to afford the crude product that was subsequently purified by flash chromatography on silica gel.

(*E*)-5-(2-(*tert*-Butyldimethylsilyloxy)phenyl)pent-3-en-2-one (Table 5, entry 1)

The general procedure above was followed using *tert*-butyl(2-allylphenoxy)dimethylsilane (124 mg, 0.50 mmol), methyl vinyl ketone (106 mg, 1.50 mmol), CuI (2.9 mg, 15.0 μmol) and Grubbs-2 catalyst (8.5 mg, 10.0 μmol). Column chromatography on silica gel (eluting with 3% EtOAc/hexanes) afforded the product as a colorless oil (135 mg, 93%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.15 (td, *J* = 7.6, 1.6 Hz, 1H), 7.11 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.95 (dt, *J* = 16.0, 6.4 Hz, 1H), 6.92 (td, *J* = 7.6, 1.2 Hz, 1H), 6.84 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.03 (dt, *J* = 16.0, 1.6 Hz, 1H), 3.54 (dd, *J* = 6.4, 1.6 Hz, 2H), 2.24 (s, 3H), 1.01 (s, 9H), 0.26 (s, 6H).

(*E*)-*tert*-Butyl 3-(2,4-dimethylphenyl)acrylate (Table 5, entry 2)

The general procedure above was followed using 2,4-dimethyl-1-vinylbenzene (66 mg, 0.50 mmol), *tert*-butyl acrylate (128 mg, 1.00 mmol), CuI (2.9 mg, 15.0 μmol) and Grubbs-2 catalyst (8.5 mg, 10.0 μmol). Column chromatography on silica gel (eluting with 2% EtOAc/hexanes) afforded the product as a colorless oil (97 mg, 84%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 15.6 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.03-7.01 (m, 2H), 6.29 (d, *J* = 15.6 Hz, 1H), 2.42 (s, 3H), 2.34 (s, 3H), 1.55 (s, 9H).[8a]

(*E*)-13-(*tert*-Butyldimethylsilyloxy)tridec-3-en-2-one (Table 5, entry 3)

The general procedure above was followed using *tert*-butyldimethyl(undec-10-enyloxy)silane[10a] (144 mg, 0.50 mmol), methyl vinyl ketone (106 mg, 1.50 mmol), CuI (2.9 mg, 15.0 μmol) and Grubbs-2 catalyst (8.5 mg, 10.0 μmol). Column chromatography on silica gel (eluting with 3% EtOAc/hexanes) afforded the product as a colorless oil (146 mg, 90%). ^1H NMR(400MHz, $CDCl_3$): δ 6.80 (dt, *J* = 16.0, 6.8 Hz, 1H), 6.06 (d, *J* = 16.0 Hz, 1H), 3.59 (t, *J* = 6.8 Hz, 2H), 2.24 (s, 3H), 2.21 (q, *J* = 7.2 Hz, 2H), 1.53–1.42 (m, 4H), 1.28 (br s, 10H), 0.89 (s, 9H), 0.04 (s, 6H).[10a]

(*E*)-*tert*-Butyl 6-(1-phenyl-1*H*-tetrazol-5-ylthio)-2-hexenoate (Table 5, entry 4)

The general procedure above was followed using 5-(pent-4-en-1-ylthio)-1-phenyl-1*H*-tetrazole[8a] (123 mg, 0.50 mmol), *tert*-butyl acrylate (192 mg, 1.50 mmol), CuI (7.2 mg, 38.0

μmol) and Grubbs-2 catalyst (21.2 mg, 25.0 μmol). Column chromatography on silica gel (eluting with 10% EtOAc/hexanes) afforded the product as colorless oil (138 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59-7.55 (m, 5H), 6.82 (dt, *J* = 15.6, 7.2 Hz, 1H), 5.79 (dt, *J* = 15.6, 1.6 Hz, 1H), 3.41 (t, *J* = 7.2 Hz, 2H), 2.36 (qd, *J* = 7.2, 1.6 Hz, 2H), 2.03 (quintet, *J* = 7.2 Hz, 2H), 1.48 (s, 9H).[8a]

(*E*)-2-Adamantyl 4-(4-methoxyphenyl)-2-butenoate (Table 5, entry 5)

The general procedure above was followed using 4-allylanisole (74 mg, 0.50 mmol), 2-adamantyl acrylate (206 mg, 1.00 mmol), CuI (2.9 mg, 15.0 μmol) and Grubbs-2 catalyst (8.5 mg, 10.0 μmol). Column chromatography on silica gel (eluting with 5% EtOAc/hexanes) afforded the product as a colorless oil (145 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16-7.08 (m, 3H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.84 (dt, *J* = 15.2, 1.2 Hz, 1H), 4.99 (br s, 1H), 3.80 (s, 3H), 3.47 (dd, *J* = 6.8, 1.2 Hz, 2H), 2.05-2.01 (m, 4H), 1.90-1.74 (m, 8H), 1.58-1.56 (m, 2H).[8a]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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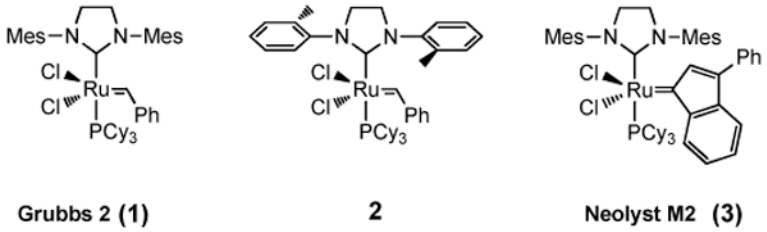


FIGURE 1.
Structures of Ru-based catalysts used for olefin metathesis.

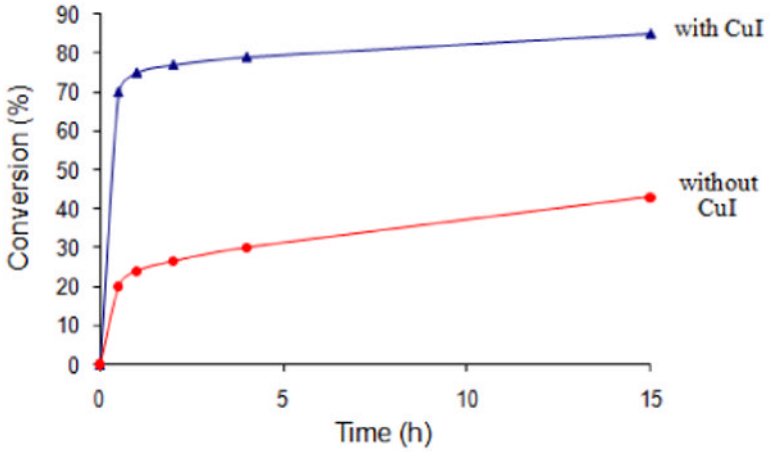
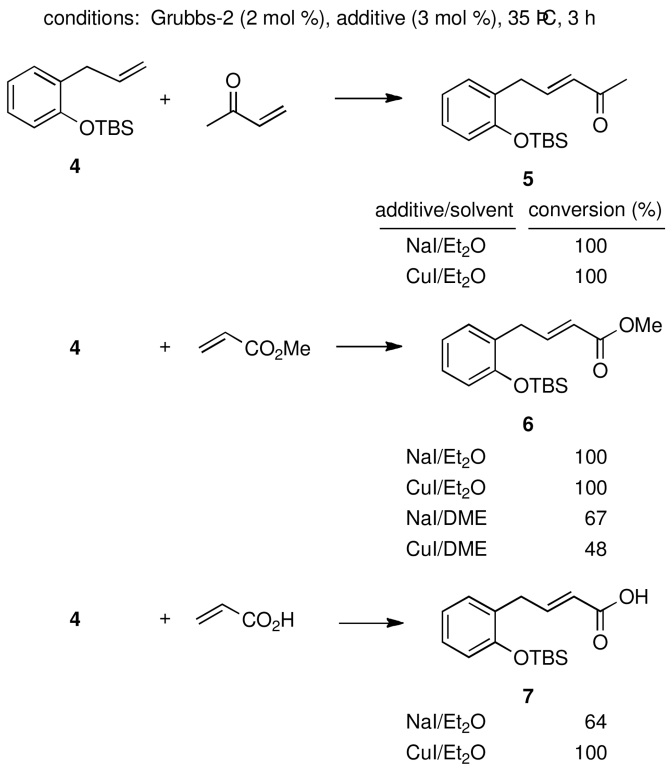
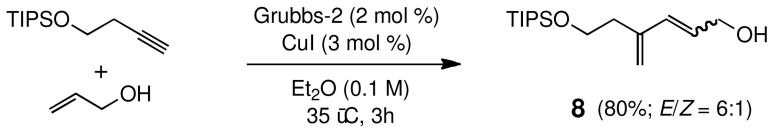


FIGURE 2.

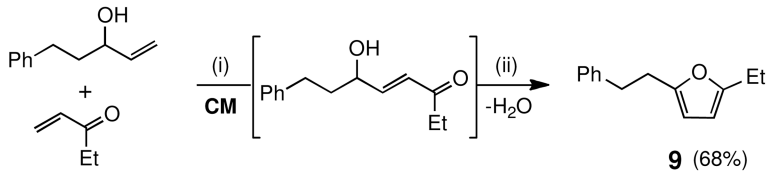
Conversion versus time profile for the CM reaction between olefin **4** and MVK with Grubbs-2 catalyst in refluxing Et_2O, as measured by ^1H NMR. [conditions: 0.1 M, 2 mol% Grubbs-2, with and without 3 mol % CuI at room temperature.]



SCHEME 1. Comparisons of NaI vs. CuI in Olefin Cross-metathesis Reactions

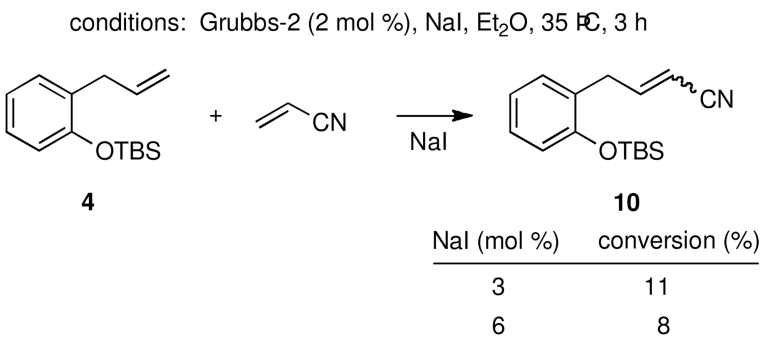


SCHEME 2. Cross Enyne Metathesis with Allyl Alcohol



SCHEME 3. One-pot Synthesis of a Substituted Furan[a]

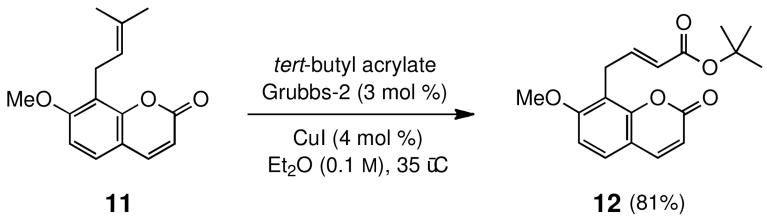
[a] Reagents and conditions: (i) Grubbs-2 (2 mol %), CuI (3 mol %), Et_2O, 35 °C, 3 h. (ii) PPTS (2.5 mol %), CH_2Cl_2, 40 °C, 12 h.



4 **10**

NaI (mol %)	conversion (%)
3	11
6	8

SCHEME 4. Effect of NaI on CM with Acrylonitrile

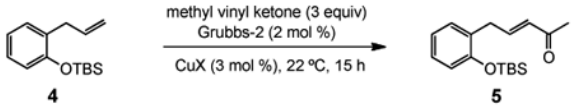


11 **12** (81%)

SCHEME 5. Copper-assisted Cross Metathesis on Osthole

TABLE 1

Optimizing Reaction Conditions



4 5

entry	CuX	solvent[a]	conversion (%)[b]
1	CuCN	CH_2CI_2	24
2	CuOAc	CH_2CI_2	<5
3	$Cu(OTf)_2$	CH_2CI_2	0
4	$Cu(BF_4)_2$	CH_2CI_2	15
5	$Cu(NO_3)_2$	CH_2CI_2	0
6	$Cu(CIO_4)_2$	CH_2CI_2	22
7	$Cu(CF_3COO)_2$	CH_2CI_2	0
8	$Cu(CH_3CN)_4PF_6$	CH_2CI_2	27
9	CuCI	CH_2CI_2	35
10	CuBr	CH_2CI_2	43
11	CuI	CH_2CI_2	64
12	-	CH_2CI_2	45
13[c]	CuI	CH_2CI_2	63
14[d]	CuI	CH_2CI_2	68
15	CuI	Toluene	64
16	CuI	THF	70
17	CuI	Et_2O	71
18[e]	CuI	Et_2O	76
19[f]	CuI	Et_2O	85
20[f]	-	Et_2O	43
21[g]	CuI	Et_2O	>99 (98)[h]

[a] Reaction run in 0.5 M solution.

[b] Based on ^{1}H NMR.

[c] Using 6 mol % CuI.

[d] Using 3 mol % Grubbs-2 and 6 mol % CuI.

[e] Reaction run in 0.2 M solution.

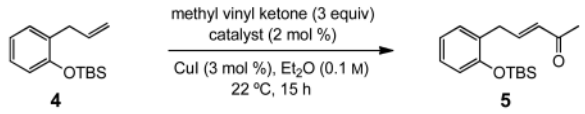
[f] Reaction run in 0.1 M solution.

[g] At 35 °C for 3 h; without CuI; yield = 57%

[h] Isolated yield.

TABLE 2

Screening of Alternative Ruthenium Catalysts



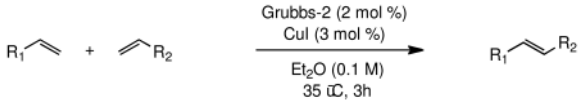
4 **5**

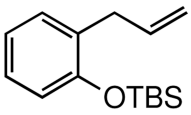
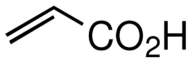
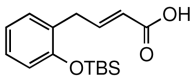
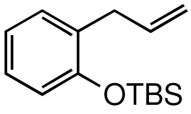
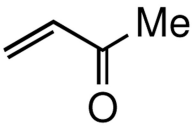
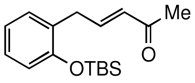
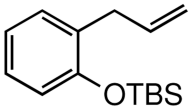
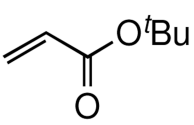
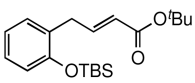
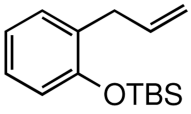
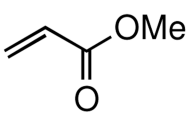
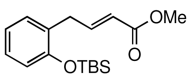
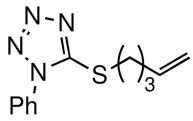
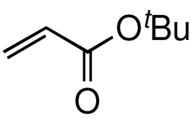
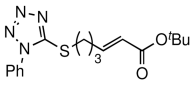
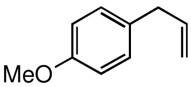
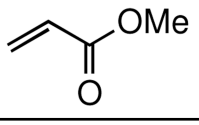
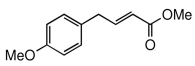
		conversion (%)[a]	
entry	**catalyst**	**with CuI**	**without CuI**
1	**1**	85	43
2	**2**	59	22
3	**3**	71	32

[a]Based on ^{1}H NMR.

TABLE 3

CuI Assisted Olefin Metathesis Reactions[a]



substrate	olefinic partner	product	yield (%)[b,c]
			82 >20:1
			98 >20:1
			93 >20:1
			93 *E* only
			84 >20:1
			94 *E* only

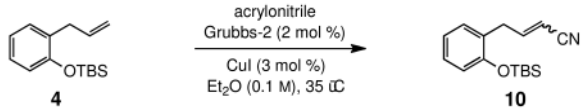
[a]Reactions were conducted at 0.5 mmol scale.

[b]Isolated yields.

[c]*E/Z* ratio was determined by ^{1}H NMR.

TABLE 4

Effect of CuI on CM with Acrylonitrile



4 10

entry	acrylonitrile (equiv)	time (h)	conversion (%)[a]
1	5.0	24	35
2	1.5	3	38[b]
3[c]	1.5	1	53
4[c]	1.5	3	60
5[d]	1.5	3	64 (51)[e]
6[d,f]	1.5	3	61
7[d,g]	1.5	3	30

[a] Based on ^{1}H NMR.

[b] Significant amount of starting material dimer formed.

[c] Grubbs-2 catalyst added as a solution over 30 minutes.

[d] Grubbs-2 catalyst added portionwise as a solid over 2 hours.

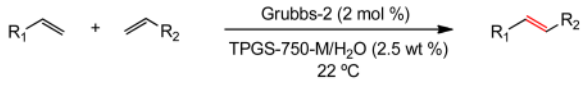
[e] Isolated yield.

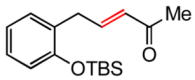
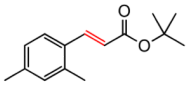
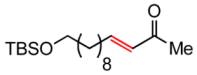
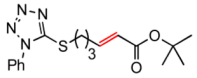
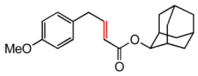
[f] 8 mol % CuI.

[g] No CuI added.

TABLE 5

CuI Assisted Olefin Metathesis Reactions in Water at Room Temperature[a]



			yield (%)[b]	
entry	product	time (h)	without CuI	with CuI[c]
1		12	74	**93**
2		15	74	**84**
3		12	76	**90**
4		20	55	**80**
5		12	82	**89**

[a] Reactions were conducted at 0.5 mmol scale.

[b] Isolated yields.

[c] 3 mol % CuI.