Copper−Carbene Complexes as Catalysts in the Synthesis of Functionalized Styrenes and Aliphatic Alkenes

Hélène Lebel,*[†] Michaël Davi,[†] Silvia Díez-González,[‡,§] and Steven P. Nolan[‡,§]

Département de Chimie, Université de Montréal, P.O. Box 6128, Station Downtown, Montréal, Québec, Canada, H3C 3J7, Department of Chemistry, University of New Orleans, New Orleans, Louisiana 70148, and Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007 Tarragona, Spain

helene.lebel@umontreal.ca

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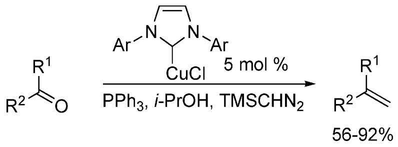

(NHC)−Cu (NHC = *N*-heterocyclic carbene) complexes efficiently catalyzed the methylenation of a variety of aliphatic and aromatic aldehydes and ketones in the presence of trimethylsilyldiazomethane, triphenylphosphine, and 2-propanol. The copper catalysts are not only inexpensive compared to rhodium complexes, but they also exhibit better functional group compatibility with aromatic aldehydes and ketones. Indeed very high yields were obtained for the formation of styrenes containing nitro, trifluoromethyl, amino, and ester groups, as well as for pyridine-, pyrrole-, and indole-substituted alkenes.

Introduction

A number of late transition metal complexes derived from Mo,[1] Re,[2] Fe,[3] Ru,[4] and Co[5] are known to catalyze the olefination reaction of carbonyl substrates in the presence of diazo carbonyl reagents.[6] The synthesis of methylenetriphenylphosphorane from trimethylsilyldiazomethane, triphenylphosphine, and 2-propanol in the presence of Wilkinson's catalyst ($RhCl(PPh_3)_3$) has been recently reported.[7] Under these reaction conditions, the methylenation of aldehydes and ketones leading to the formation of terminal alkenes was achieved in high yields. Although a low catalyst loading (0.25 mol % on a 10 mmol scale)[8] can be used in this reaction, Wilkinson's catalyst and rhodium complexes are in general relatively expensive. The method would greatly benefit from the use of less expensive metal complexes. The use of copper catalysts in the methylenation of carbonyl compounds with trimethylsilyldiazomethane was investigated to achieve such a goal. Only two reports describe the use of copper(I) salts (CuX) as catalysts for the olefination of carbonyl compounds with diazo carbonyl compounds via the formation of stabilized antimony,

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[†] Université de Montréal.

[‡] University of New Orleans.

[§] Institute of Chemical Research of Catalonia (ICIQ).

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arsenic, and tellurium ylides.[9] Although in these cases the formation of stabilized phosphonium ylides was shown to be inefficient, we believed that optimization of reaction conditions using trimethylsilyldiazomethane could lead to the formation of methylenetriphenylphosphorane. In addition to the cost of rhodium complexes, the rhodium-catalyzed methylenation reaction proved problematic with aromatic nitro-containing substrates, leading to degradation reactions.[7e] As the nitro group appeared to react with the metal center, we hypothesized that the replacement of phosphine ligands with stronger σ-donor ligands, such as *N*-heterocyclic carbenes (NHC),[10] would overcome this functional group compatibility problem. Furthermore, (NHC)−copper complexes have been reported to catalyze a number of reactions,[11,12] including cyclopropanation reactions with diazo carbonyl compounds.[13] Here, we disclose the use of copper salts and (NHC)−copper complexes as catalysts for the methylenation of aldehydes and ketones with trimethylsilyldiazomethane, triphenylphosphine, and 2-propanol. The transformation of substrates containing nitro, trifluoromethyl, amino, ester, pyridine, pyrrole, and indole groups with aromatic (NHC)−copper complexes (IPr and IMes, see Figure 1) is also presented.

Results and Discussion

The mechanistic studies of the rhodium-catalyzed methylenation reaction with trimethylsilyldiazomethane, triphenylphosphine, and 2-propanol showed the in situ formation of methylenetriphenylphosphorane at room temperature.[7e] Under similar reaction conditions with copper(I) chloride or (IMes)CuCl, we observed the appearance of methylenetriphenylphosphorane by ^1H NMR (C_6D_6). At room temperature, the formation of the phosphorus ylide was slow and did not reach completion, whereas at 60 °C, the conversion was complete after 3 h. When copper(I) chloride was tested in the methylenation of cinnamaldehyde in the presence of trimethylsilyldiazomethane, triphenylphosphine, and 2 propanol, good yields were obtained when the reaction was carried out at 60 °C (Table 1, entry 4).

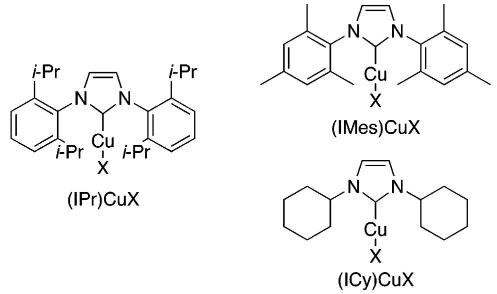
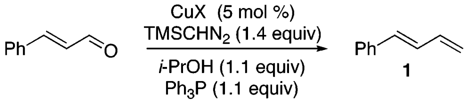


FIGURE 1. (NHC)−copper complexes.

TABLE 1. Copper-Catalyzed Methylenation of Cinnamaldehyde



entry	CuX	conditions	conversion,[a] %
1	CuCl	THF, 25 °C, 16 h	80
2	CuCl	ether, 25 °C, 24 h	≤5
3	CuCl	DCM, 25 °C, 24 h	≤5
4	CuCl	THF, 60 °C, 1 h	≥95 (74)
5	CuCl	DCE, 60 °C, 3 h	70
6	CuCl	dioxane, 60 °C, 24 h	85
7	CuCl	dioxane, 80 °C, 3 h	≥95
8	CuCl	toluene, 80 °C, 3 h	60
9	CuBr	THF, 25 °C, 16 h	90
10	CuBr	THF, 60 °C, 2 h	≥95 (68)
11	CuBr	dioxane, 60 °C, 16 h	≥95
12	CuI	THF, 25 °C, 16 h	70
13	CuI	THF, 60 °C, 3 h	≥95 (67)
14	CuI	dioxane, 60 °C, 16 h	≥95
15	$[Cu(MeCN)_4]PF_6$	THF, 25 °C, 24 h	≤5
16	$CuCl_2$	THF, 25 °C, 16 h	60
17	$CuCl_2$	dioxane, 60 °C, 16 h	75
18	$Cu(OAc)_2$	THF, 25 °C, 24 h	80
19	$Cu(OAc)_2$	dioxane, 60 °C, 24 h	70
20	$Cu(OTf)_2$	THF, 25 °C, 16 h	≤5
21	$Cu(OTf)_2$	dioxane, 60°C , 16 h	50
22	$Cu(BF_4)_2 \cdot 6H_2O$	THF, 25°C , 24 h	≤5

[a] Conversion by GC-MS; isolated yields in parentheses.

Numerous copper(I) complexes were found to be active in this process, including copper(I) salts and (NHC)−copper(I) complexes (Tables 1 and 2). Copper(II) salts also led to the formation of the corresponding alkene, but reaction times proved longer (Table 1, entries 16−22). More dissociative ligands led to less active catalyst, as no conversion was observed at room temperature with $Cu(OTf)_2$ and $Cu(BF_4)_2 \cdot 6H_2O$ compared to

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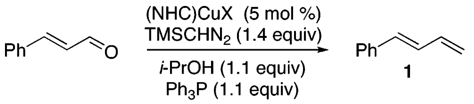
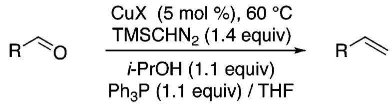
TABLE 2. (NHC)−Copper-Catalyzed Methylenation of Cinnamaldehyde

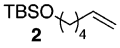
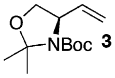
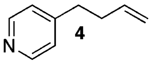
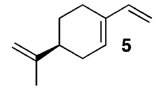
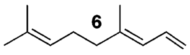
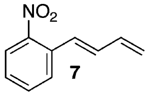
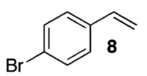
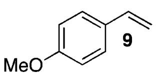
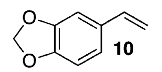
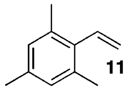
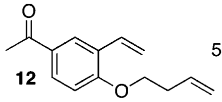
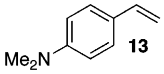
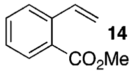
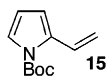
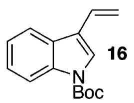


entry	(NHC)CuX	conditions	conversion,[a] %
1	(IPr)CuCl	THF, 25 °C, 16 h	75
2	(IPr)CuCl	dioxane, 25 °C, 24 h	55
3	(IPr)CuCl	THF, 60 °C, 2 h	≥95 (75)
4	(IPr)CuCl	dioxane, 60 °C, 2 h	≥95 (77)
5	(ICy)CuCl	THF, 60 °C, 2 h	≥95 (70)
6	(ICy)CuCl	dioxane, 60 °C, 1 h	≥95
7	(IMes)CuCl	dioxane, 60 °C, 2 h	≥95 (77)

[a] Conversion by GC-MS; isolated yields in parentheses.

TABLE 3. Copper-Catalyzed Methylenation of Aldehydes[a]



entry	product	yield (%)[a]			
		CuCl[b]	CuI[b]	(IPr)CuCl[b]	(IMes)CuCl[c]
1	 **2**	64	70	62	69
2	 **3**	73	63	80	72
3	 **4**	76[d,e]	82[d]	79[d,e]	54[e]
4	 **5**	69	55	70	64
5	 **6**	70	57	49	72
6	 **7**	61	83[e]	27	52[e]
7	 **8**	73	81	50	70
8	 **9**	74	71	57	82
9	 **10**	76	68	78	88
10	 **11**	67	18[f]	54	74
11	 **12**	54	---	66	75
12	 **13**	44	30	70	81
13	 **14**	79	73	58	92[d]
14	 **15**	82	74	83	88
15	 **16**	83	59	87[d]	73

[a] Isolated yields. [b] 0.1 M in THF at 60 °C. [c] 0.1 M in dioxane at 60 °C. [d] 0.05 M in THF. [e] 10 equiv of 2-propanol. [f] ^{1}H NMR conversion with an internal standard.

CuCl (entries 20−22 vs entry 1). Solvent optimization revealed that the reaction was more efficient in THF or dioxane (entries 4−8). In diethyl ether, both the copper complex and methylenetriphenylphosphorane were not soluble enough and no reaction was observed at room temperature with CuCl (entries 1 and 2). Variation of the counteranion as well as the *N*-heterocyclic carbene substituent showed little influence on the reaction; thus, Cl, Br, and I as well as IPr, ICy, and IMes could all be used in this reaction (Table 1, entries 4, 10, and 13 and Table 2, entries 3, 5, and 7). However, a strong coordinating ligand, such as acetonitrile, killed the catalysts (Table 1, entry 15). To examine the scope of the copper-catalyzed methylenation reaction with trimethylsilyldiazomethane, triphenylphosphine, and 2-propanol, a variety of aliphatic and aromatic aldehydes were tested by using CuCl, CuI, (IMes)CuCl, and (IPr)CuCl (Table 3). The reaction allowed for the formation of functionalized aliphatic alkenes (entries 1−3), dienes (entries 4−6), styrenes (entries 7−13), and heteroaromatic alkenes (entries 14 and 15) in high yields. Catalyst loading was typically at 5 mol % for 1 mmol scale and could be decreased at 0.5 mol % when the reaction was carried out on 10 mmol scale. Usually, the reaction is faster with CuCl than with CuI, and yields are slightly better with the former. The synthesis of aliphatic alkenes and dienes proceeded equally well with copper(I) salts and (NHC)−copper complexes. In contrast, higher yields are usually achieved by using (IMes)CuCl for the preparation of styrenes (entries 7−13). Even sterically hindered 2-substituted benzaldehydes reacted under these conditions to form the corresponding 2-substituted styrenes (**11** and **14**) in high yields (entries 10 and 13). The functional group tolerance is very good for this reaction, as even strongly coordinating groups, such as pyridine or aromatic ethers and amines, are well tolerated (entries 3, 8, 9, 12, 13). Furthermore, the chemoselectivity of the reaction was preserved, as ketone-containing styrene **12** was obtained in high yields (entry 11). Protected heteroaromatic alkenes were also synthesized in good yields with use of CuCl or (IPr)CuCl (entries 14 and 15). We noticed that with electron-withdrawing groups, such as nitro or ester and even pyridine, a better yield was obtained if the reaction was carried out at higher dilution with an excess of 2-propanol (entries 3, 6, and 13). As 4-nitrobenzaldehyde is a difficult substrate for the methylenation reaction,[14] we decided to investigate more closely these reaction conditions (Table 4). Under the standard reaction conditions for the rhodium-catalyzed methylenation, a complex mixture of products was observed (entry 1).[7e] When adding 10 equiv of 2-propanol the yield improved to 28%, but unfortunately only 17% of styrene **17** was isolated at 0.05 M in THF. Conversely, very good results

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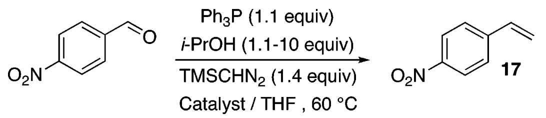
[14] Standard Wittig reaction conditions with NaHMDS or BuLi as a base lead to styrene **17** in low yield. A strong guanidine base must be used to achieve a good yield, see: (a) Simoni, D.; Rossi, M.; Rondanin, R.; Mazzali, A.; Baruchello, R.; Malagutti, C.; Roberti, M.; Invidiata, F. P. *Org. Lett.* **2000**, *2*, 3765−3768. (b) Okuma, K.; Sakai, O.; Shioji, K. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1675−1676.

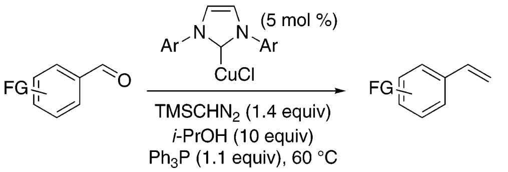
TABLE 4. Transition Metal-Catalyzed Methylenation of 4-Nitrobenzaldehyde

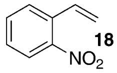
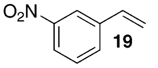
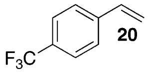
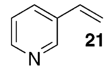


entry	catalyst	*i*-PrOH 1.1 equiv 0.1 M/THF[a]	*i*-PrOH 10 equiv 0.1 M/THF[a]	*i*-PrOH 10 equiv 0.05 M/THF[a]
1	RhCl(PPh$_3$)$_3$ (2.5 mol %)	≤5%[b]	17%	28%
2	(IPr)CuCl 5 mol %)	43%	48%	91%
3	(IMes)CuCl[c] (5 mol %)	29%[c]	41%[c]	77%[c]

[a] Isolated yields. [b] Reaction at 25 °C. [c] Dioxane was used instead of THF.

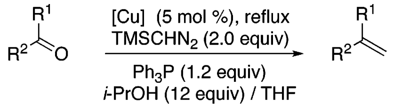
TABLE 5. (NHC)−Copper-Catalyzed Methylenation of Functionalized Aromatic Aldehydes

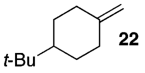
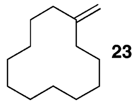
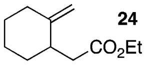
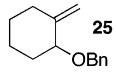
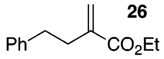
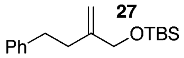
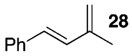
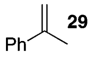
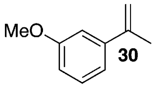
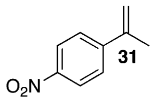
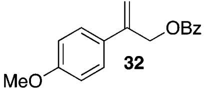


entry	product	yield (%)[a] (IPr)CuCl[b]	yield (%)[a] (IMes)CuCl[c]
1	 **18**	86	dec
2	 **19**	78[d]	74
3	 **20**	43	74[b]
4	 **21**	68	86

[a] Isolated yields. [b] 0.05 M in THF. [c] 0.05 M in dioxane. [d] 0.1 M in THF.

TABLE 6. Copper-Catalyzed Methylenation of Ketones



entry	product	yield (%)[a] CuCl	yield (%)[a] (IPr)CuCl
1	 **22**	82	92
2	 **23**	≤5	68
3	 **24**	75	93
4	 **25**	58	73
5	 **26**	78	86
6	 **27**	69	78
7	 **28**	≤5	75
8	 **29**	50	78
9	 **30**	42	78
10	 **31**	43	73
11	 **32**	73	75

[a] Isolated yields.

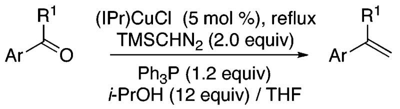
were obtained when the (NHC)−copper complexes were used (entries 2 and 3). In the presence of 10 equiv of 2-propanol, at 0.05 M in THF or dioxane, styrene **17** was isolated in 77% and 91% yields, using (IMes)CuCl and (IPr)CuCl, respectively. In contrast, less than 10% conversion was observed with CuCl.

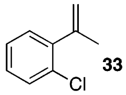
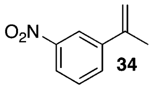
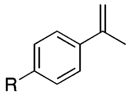
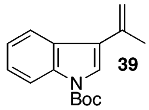
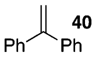
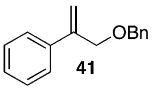
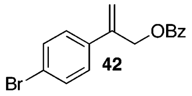
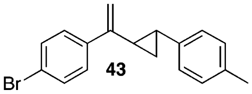
We have used these new reaction conditions with other electron-deficient benzaldehydes as well as with 3-pyridinecarboxaldehyde (Table 5).

For nitro substrates, (IPr)CuCl was the best catalyst leading to styrenes **18** and **19** in 86% and 78% yields, respectively (entries 1 and 2). Surprisingly only decomposition was observed in the methylenation of 2-nitrobenzaldehyde with (IMes)CuCl (entry 1). For the two other substrates, (IMes)CuCl showed the best catalytic activity leading to styrene **20** in 74% yield and 3-vinylpyridine **21** in 86% yield (entries 3 and 4). Here again, it was required to use a NHC-derived copper complex, as low conversion (40−50%) was observed with CuCl.

The copper-catalyzed methylenation reaction was also tested with aliphatic and aromatic ketone substrates by using either copper(I) chloride or (IPr)CuCl (Table 6). The reaction was refluxed in THF with an excess of TMSCHN$_2$ and 2-propanol. The comparison between both catalysts showed the superiority of the (NHC)−copper complex, as typically higher yields are obtained. Furthermore, with copper(I) chloride, ketone substrate leading to product **23** showed no reaction whereas decomposition of diene **28** was observed (entries 2 and 7, presumably due to π-complexation between the copper complex and the diene). In the presence of (IPr)CuCl, both acyclic and cyclic aliphatic disubstituted alkenes were formed in good yields (entries 1−6). Both alkoxy and ester functionality were tolerated under the methylenation reaction conditions (entries 3−6). Aromatic ketones were also tested as substrates and here again, (IPr)-CuCl typically led to higher yields (entries 8−11). Methoxy- and nitro-substituted methyl ketones reacted to produce alkene **29**−**31** in good yields (entries 8−10). In addition, these reaction conditions are compatible with aromatic benzoxymethyl ketones (entry 11). The use of (IPr)CuCl was also tested with other ketone substrates to complete the evaluation of the functional

TABLE 7. (NHC)−Copper-Catalyzed Methylenation of Aromatic Ketones



entry	product	yield (%)[a]
1	 **33**	77
2	 **34**	81
3	 R = Me (**35**) MeO (**36**) Br (**37**) —≡—TIPS (**38**)	79 67[b] 84 83
4	 **39**	65
5	 **40**	56
6	 **41**	92
7	 **42**	81
8	 **43**	82

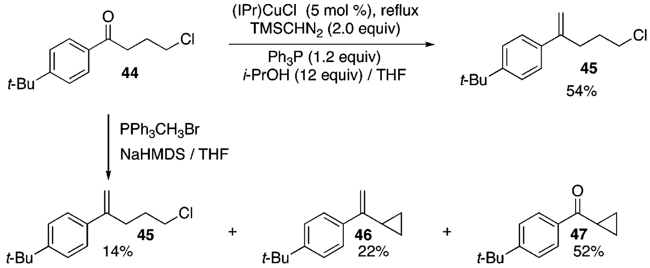
[a] Isolated yields. [b] 5 equiv of $TMSCHN_2$.

group tolerance of this reaction (Table 7). Besides methoxy and nitro groups (entries 2 and 3), we showed that halide-substituted aryl groups were also compatible under these methylenation reaction conditions (entries 1, 3, and 7). Protected alkynes and indoles led also to the desired alkenes in good yields (entries 3 and 4). More substituted and encumbered aromatic ketones were also tested (entries 5 to 7), and even cyclopropyl-substituted alkene was obtained in 82% yield (entry 8).

We have also tested the base-sensitive chloride-substituted ketone **44**, which under the typical Wittig reaction conditions led mostly to the formation of the corresponding cyclopropyl ketone (Scheme 1). In contrast, using (IPr)CuCl-catalyzed methylenation reaction conditions, the desired alkene **45** was isolated in 54%. Even though both reaction conditions led to the formation of methylenetriphenylphosphorane, this example clearly illustrated the deleterious effect of having base and salts in the reaction mixture.

In conclusion, we have disclosed the use of copper catalysts for the methylenation of aldehydes and ketones using trimethylsilyldiazomethane, triphenylphosphine, and 2-propanol. These copper catalysts are not only less expensive than rhodium complexes, but they also displayed an improved functional group tolerance, in particular with substrates containing nitro and pyridine groups. Furthermore, these reaction conditions are compatible with base-sensitive substrates.

SCHEME 1



Experimental Section

Typical Experimental Procedure for the Copper-Catalyzed Methylenation. To a solution of the copper catalyst (0.050 mmol) and triphenylphosphine (288 mg, 1.10 mmol) in THF or dioxane (10 mL (0.1 M) or 20 mL (0.05 M)) at 25 °C was added 2-propanol (84 μL, 1.1 mmol or 770 μL, 10.0 mmol) followed by the carbonyl compound (1.00 mmol) and the trimethylsilyldiazomethane ether solution (1.40−2.00 mmol) under inert atmosphere. The resulting mixture was then heated at 60 °C and the reaction was stirred until the reaction was completed as gauged by GC, ^{1}H NMR, or TLC analysis. Afterward, 3% H_2O_2 (10 mL) was added and the organic layer was extracted with ether (3 × 20 mL). The combined organic layers were washed with brine (2 × 20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude alkene was purified by flash chromatography on silica gel.

4-Phenyl-1,3-butadiene (1). The title compound was prepared from *trans*-cinnamaldehyde (125 μL, 1.00 mmol) according to the general procedure, using CuCl in 0.1 M THF with 1.1 mmol of 2-propanol (reaction time 1 h). The desired alkene (96 mg, 74%) was obtained as a colorless oil after flash chromatography (1% EtOAc/hexanes). R_f 0.54 (1% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.41 (m, 2H), 7.35−7.30 (m, 2H), 7.25−7.22 (m, 1H), 6.80 (dd, J = 16, 10 Hz, 1H), 6.57 (d, J = 16 Hz, 1H), 6.51 (dd, J = 16, 10 Hz, 1H), 5.34 (d, J = 16 Hz, 1H), 5.19 (d, J = 16 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.13, 137.06, 132.8, 129.6, 128.6, 127. 6, 126.4, 117.6.

1-(2-Nitrophenyl)-1,3-butadiene (7). The title compound was prepared from *trans*-2-nitrocinnamaldehyde (177 mg, 1.00 mmol) according to the general procedure, using CuI in 0.1 M THF with 10.0 mmol of 2-propanol (reaction time 16 h). The desired alkene (145 mg, 83%) was obtained as a yellow solid after flash chromatography (2% EtOAc/hexanes). R_f 0.15 (2% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8 Hz, 1H), 7.67 (d, J = 8 Hz, 1H), 7.58−7.54 (m, 1H), 7.39−7.35 (m, 1H), 7.05 (d, J = 15 Hz, 1H), 6.77 (dd, J = 16, 10 Hz, 1H), 6.61−6.51 (m, 1H), 5.43 (d, J = 17 Hz, 1H), 5.32 (d, J = 10 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 136.6, 134.5, 132.9, 132.5, 127.9, 127.8, 127.1, 124.6, 120.3.

1-Nitro-4-vinylbenzene (17). The title compound was prepared from 4-nitrobenzaldehyde (151 mg, 1.00 mmol) according to the general procedure, using (IPr)CuCl in 0.05 M THF with 10.0 mmol of 2-propanol (reaction time 12 h). The desired alkene (136 mg, 91%) was obtained as a yellow oil after flash chromatography (5% ether/hexanes). R_f 0.29 (5% ether/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 9 Hz, 2H), 7.53 (d, J = 9 Hz, 2H), 6.78 (dd, J = 18, 11 Hz, 1H), 5.93 (d, J = 18 Hz, 1H), 5.50 (d, J = 11 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 143.8, 134.9, 126.8, 123.9, 118.6.

3-Vinylpyridine (21). The title compound was prepared from 3-pyridinecarboxaldehyde (94 μL, 1.00 mmol) according to the general procedure, using (IMes)CuCl in 0.05 M dioxane with 10 mmol of 2-propanol (reaction time 16 h). The desired alkene (90 mg, 86%) was obtained as a yellow oil after flash chromatography (50% ether/pentane). R_f 0.45 (50% ether/pentane). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.62 (s, 1H), 8.50−8.48 (m, 1H), 7.75−7.72 (m, 1H), 7.27−7.24 (m, 1H), 6.70 (dd, J = 18, 11 Hz, 1H), 5.83 (d, J = 18 Hz, 1H), 5.38 (d, J = 11 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 148.8, 148.2, 133.4, 133.0, 132.6, 123.4, 116.2.

1-*tert*-Butyl-4-(5-chloropent-1-en-2-yl)benzene (45). The title compound was prepared from 4′-*tert* -butyl-4-chlorobutyrophenone (239 mg, 1.00 mmol) according to the general procedure, using (IPr)CuCl in 0.1 M THF with 12.0 mmol of 2-propanol (reaction time 16 h). The desired alkene (128 mg, 54%) was obtained as a colorless oil. R_f 037 (pentane). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.33 (s(br), 4H), 5.33 (s, 1H), 5.07 (s, 1H), 3.55 (t, J = 7 Hz, 2H), 2.67 (t, J = 10 Hz, 2H), 1.92 (tt, J = 10, 7 Hz, 2H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 150.5, 146.3, 137.4, 125.6, 125.2, 112.5, 44.5, 34.4, 32.2, 31.2, 30.9.

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Supporting Information Available: Characterization data and spectra (^{1}H and ^{13}C NMR) for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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