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Palladium-Catalyzed Cross-Coupling Reactions in One-Pot Multicatalytic Processes

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Abstract: Palladium-catalyzed cross-coupling reactions have been investigated in multicatalytic processes to synthesize disubstituted alkenes and alkanes from carbonyl derivatives. The use of copper-catalyzed methylenation reactions is the key starting reaction to produce terminal alkenes which are not isolated, but submitted to further structure elongation. Not only is the isolation of the alkene intermediate unnecessary, but also the copper catalyst is a beneficial cocatalyst in the palladium-catalyzed cross-coupling reactions. The desired products are thus typically obtained in higher yields using this one-pot approach. We have used these processes to synthesize hydroxylated (*E*)-stilbenoids, which are known chemopreventive and chemotherapeutic agents, odorant-substituted indanes, and non-natural amino acids, such as homophenylalanine.

Introduction

One-pot strategies are well-known in organic synthesis as efficient processes to access complex molecules without isolating intermediates.[1] More recently, the use of transition-metal-catalyzed reactions has further improved these processes.[2,3] For instance, one metal complex can be used to catalyze more than one reaction, or various metal complexes could be added concomitantly or sequentially to achieve various transformations, without isolation of intermediate species. These types of processes have been called tandem catalysis,[2e] pseudodomino strategies,[2f] or multicatalytic cascades.[4] In any case, all of these processes eliminate intermediate recovery steps, thereby considerably decreasing the amount of generated waste.[5] Moreover, it has been shown in many cases that the overall yields for one-pot procedures are higher than those obtained with step-by-step procedures. Among the one-pot processes, the ones that allow the formation of multiple C−C bonds are of great importance, because of the predominance of these bonds in organic molecules.

Recently, our group has disclosed novel one-pot procedures based on the transition-metal-catalyzed methylenation of carbonyl compounds. Both rhodium(I) and copper(I) complexes catalyzed the formation of methylenetriphenylphosphorane in the presence of (trimethylsilyl)diazomethane, 2-propanol, and triphenylphosphine.[6] This reagent performed the methylenation of aldehyde and ketone substrates to produce the corresponding terminal alkenes in high yields and chemoselectivity. We have

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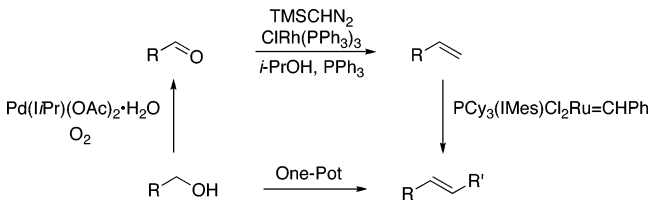
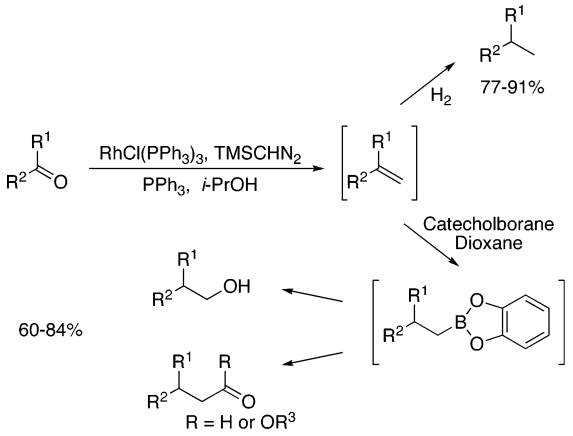
Scheme 1



Scheme 2

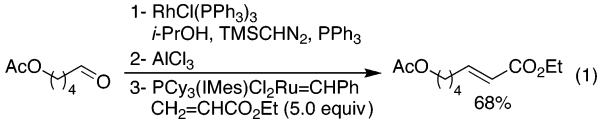


also reported multicatalytic processes for the synthesis of alkenes, using an oxidation−methylenation procedure and a methylenation−metathesis procedure with the sequential addition of various palladium, rhodium, and ruthenium complexes (Scheme 1).[7] Furthermore, we have shown that we could take advantage of the dual activity of Wilkinson's catalyst with both carbonyl derivatives and alkene derivatives. Indeed, one-pot procedures involving rhodium-catalyzed methylenation−hydroboration reactions[8] and rhodium-catalyzed methylenation−hydrogenation[9] reactions have been described (Scheme 2).

The one-pot processes that we have reported thus far are based on the rhodium-catalyzed methylenation reaction. Given the recently developed copper-catalyzed methylenation reaction,[6h] and the known ability of copper complexes to serve as cocatalysts in palladium-catalyzed cross-coupling reactions,[10] opportunities to develop new efficient one-pot multicatalytic processes are rich. In this paper, we report the use of copper-catalyzed methylenation reactions in one-pot procedures to access disubstituted alkenes via a palladium-catalyzed Heck reaction and alkanes using a hydroboration−palladium-catalyzed Suzuki reaction.

Results and Discussion

One-Pot Methylenation−Heck Cross-Coupling Reactions: Access to (*E*)-Stilbenoid Derivatives. A number of stilbenes have been isolated from natural sources. Among them, hydroxylated (*E*)-stilbenoids,[11] such as resveratrol (3,4,5-trihydroxystilbene, a phytoalexin found in grapes and other food products), have attracted considerable attention because of their potential therapeutic value as chemopreventive and chemotherapeutic agents.[12,13] Various synthetic routes have been developed, including a number based on Heck technologies.[14] Recently, cross-metathesis reactions have also been successfully used to prepare hydroxylated (*E*)-stilbenoids.[15] However, in all cases, it is required to have a styrene derivative as the substrate. Although some are commercially available, most styrenes need to be prepared from the corresponding benzaldehyde or benzylic alcohol. Using a multicatalytic strategy combining a methylenation reaction with a coupling reaction avoids the need for isolating the styrene intermediate (which can potentially polymerize), thereby decreasing the amount of required reagents and solvents (for workup and purification procedures), while producing less waste. At the outset, we envisioned developing a rhodium-catalyzed methylenation−ruthenium-catalyzed cross-metathesis to address this issue. However, our preliminary results with this multicatalytic process showed limitations, as 5 equiv of the alkene moiety was required (eq 1).[16]



To overcome these problems, we changed the strategy to explore the combination of the rhodium- or copper-catalyzed methylenation reaction with a palladium-catalyzed Heck cross-coupling reaction. The challenge was to find cross-coupling

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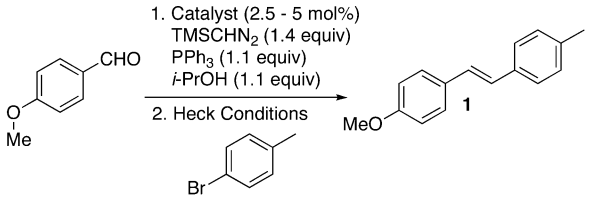
(15) (a) Ferre-Filmon, K.; Delaude, L.; Demonceau, A.; Noels, A. F. *Eur. J. Org. Chem.* **2005**, 3319−3325. (b) Velder, J.; Ritter, S.; Lex, J.; Schmalz, H. G. *Synthesis* **2006**, 273−278.
(16) Lebel, H.; Paquet, V. Unpublished results. Furthermore, the reaction was limited to acrylate derivatives.

Table 1. One-Pot Transition-Metal-Catalyzed Methylenation−Heck Cross-Coupling Process: Optimization of the Reaction Conditions



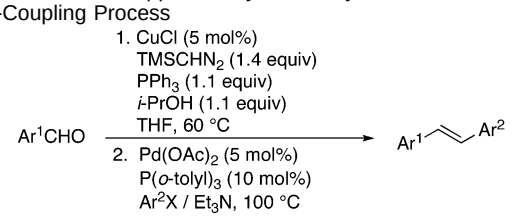
Entry	Heck Conditions	Methylenation Catalyst Yield (%)[a]	
		$RhCl(PPh_3)_3$ 3 mol%	CuCl 5 mol%
1	$Pd(PPh_3)_4$ (2.5 mol%) Cy_2NMe / DMF, 110 °C	24	33
2	$PdCl_2(PPh_3)_2$ (2.5 mol%) Bu_4NBr, Et_3N / DMF, 110 °C	<5	36
3	Pd_2dba_3•$CHCl_3$ (1.5 mol%) $[(t\text{-}Bu)_3PH]BF_4$ (3 mol%) Cy_2NMe / THF, 80 °C	44	55
4	$Pd(OAc)_2$ (5 mol%) P(*o*-tolyl)$_3$ (10 mol%) Et_3N, 100 °C	54	88 (56)[b]

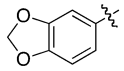
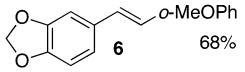
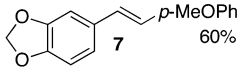
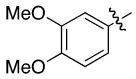
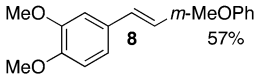
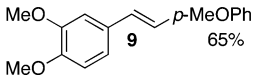
[a] Isolated yields. [b] Step-by-step process.

reaction conditions which would be compatible with residues and the solvent (THF) of the methylenation reaction. We first studied the synthesis of stilbene **1** from *p*-anisaldehyde, testing both methylenation reactions with either Wilkinson's complex or copper(I) chloride and a variety of reaction conditions for the cross-coupling reactions (Table 1). In none of the cases, the corresponding styrene derivative was isolated. Overall, better yields of stilbene **1** were observed when copper(I) chloride was used as the methylenation catalyst rather than Wilkinson's complex. These results suggest that copper(I) chloride serves as a cocatalyst and/or that Wilkinson's catalyst inhibits the Heck cross-coupling reaction. The use of palladium tetrakis(triphenylphosphine)[17] (entry 1) or palladium bis(triphenylphosphine) dichloride under Jeffery reaction conditions[18] (entry 2) led to the desired product in low yield, whereas moderate yields were observed under Fu's reaction conditions[19] (entry 3).

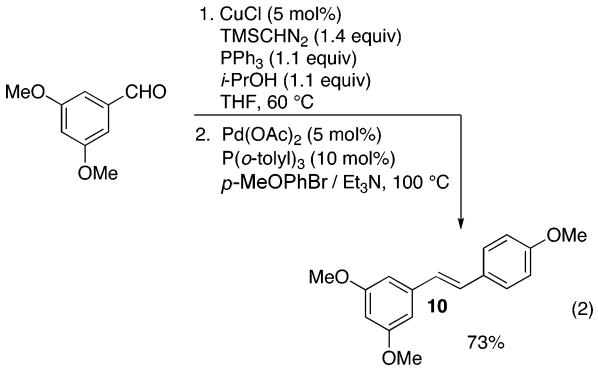
The best yield for the one-pot process was obtained by performing a copper-catalyzed methylenation reaction, followed by a Heck cross-coupling with palladium diacetate and tri-*o*-tolylphosphine in triethylamine (entry 4).[20] The desired (*E*)-stilbene **1** was isolated directly from *p*-anisaldehyde as a single diastereomer in 88% yield, without isolation of the styrene intermediate.[21] In comparison, a 56% yield was obtained for the formation of **1** when the step-by-step process was performed, in which the alkene intermediate was isolated. Table 2 shows the scope of this one-pot process focusing on the synthesis of hydroxylated (*E*)-stilbenoids. The use of electron-rich aryl halides led to moderate yields (Table 2, entry 2 vs entries 1−3), whereas the use of electron-rich aldehydes produced typically the desired stilbene in good yields (Table 2, entries 4 and 6−9).[22]

Table 2. One-Pot Copper-Catalyzed-Methylenation−Heck Cross-Coupling Process



Entry	Ar^1	Ar^2X	Product Isolated Yield
1	*p*-MePh	*p*-MeOPhBr	*p*-MePh **1** *p*-MeOPh 56%
2	"	*p*-MePhBr	*p*-MePh **2** *p*-MePh 62%
3	"	*m*-MeOPhBr	*p*-MePh **3** *m*-MeOPh 46%
4	*p*-MeOPh	*m*-MeOPhBr	*p*-MeOPh **4** *m*-MeOPh 60%
5	*p*-ClPh	*p*-MePhBr	*p*-ClPh **5** *p*-MePh 50%
6		*o*-MeOPhI	 **6** 68%
7	"	*p*-MeOPhBr	 **7** 60%
8		*m*-MeOPhBr	 **8** 57%
9	"	*p*-MeOPhBr	 **9** 65%

These reaction conditions were used with 3,5-dimethoxybenzaldehyde to give in 73% yield the methylated resveratrol **10**, known to be as biologically active as the resveratrol itself.



(2)

One-Pot Methylenation−Intramolecular Heck Cross-Coupling Reactions: Access to Odorant Indane Precursors. Intramolecular Heck reactions are popular for the synthesis of heterocyclic and carbocyclic moieties.[23] We became interested in the synthesis of substituted indanes, known as odorant products (Figure 1).[24] We envisioned synthesizing these products

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(21) Surprisingly, the use of the more reactive 4-iodotoluene as a coupling agent did not produce the desired product in a better yield. Only 45% was obtained to produce **1** using CuCl and the Heck reaction conditions described in Table 1, entry 4.
(22) The 1,1-disubstituted alkene was also isolated (5−10%) in some cases and accounted for some of the lower yields.
(23) Gibson, S. E.; Middleton, R. J. *Contemp. Org. Synth.* **1996**, *3*, 447−471.

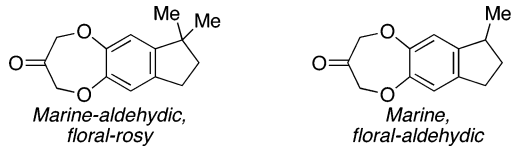
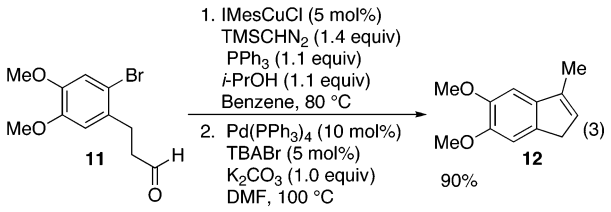
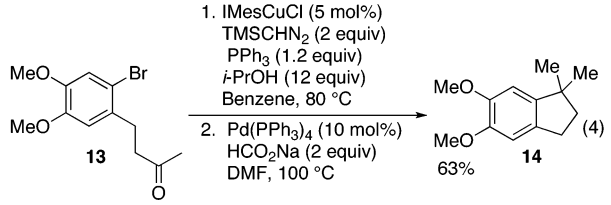


Figure 1. Structure of odorant indanes.

via a one-pot methylenation−intramolecular Heck cross-coupling sequence, starting from aldehyde **11** and ketone **13** (eqs 3 and 4).[25,26]

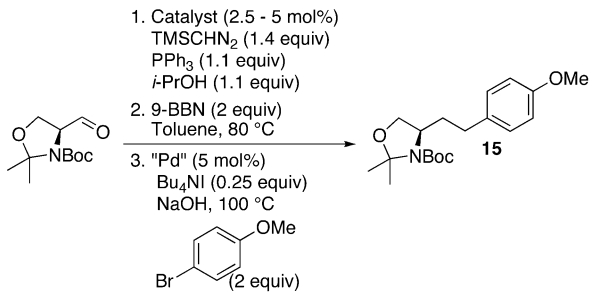




The intramolecular Heck reaction was very efficient, as cyclopentene **12** was isolated in 90% yield starting from aldehyde **11**. The *exo*-alkene was initially formed, but the double bond quickly isomerized to the internal position to produce cyclopentene **12**. The corresponding dimethylindane product **14** was obtained in 63% yield, using palladium tetrakis(triphenylphosphine) and sodium formate in DMF: the organopalladium intermediate (which cannot β-eliminate) was thus reduced in situ, to regenerate the catalyst.[27]

One-Pot Methylenation−Suzuki Cross-Coupling Reactions: Access to Non-Natural Amino Acids. Non-natural amino acids not only display interesting biological properties, but also have been widely used as synthetic building blocks.[28] Homophenylalanine derivatives showed pharmacologic potential, and thus, considerable attention has been devoted to their syntheses.[29] Elongation of unsaturated amino acid derivatives, particularly serine-derived starting material, has been used as a strategy to access homophenylalanine analogues. Indeed, non-natural amino acid derivatives have been produced from the methylenated Garner aldehyde via a hydroboration−Suzuki cross-coupling reaction sequence.[29c,d] As we have previously established that organoboranes could be produced from aldehydes via a one-pot rhodium-catalyzed methylenation−hydroboration process,[8] we envisioned combining this approach with a Suzuki cross-coupling reaction. One of the key points was to find the suitable hydroborating agent to generate the requisite aliphatic organoborane for the Suzuki cross-coupling reaction. Our initial results showed that it was not possible to use an organoborane derived from catecholborane, the hydroborating agent initially used in the rhodium-catalyzed methylenation−hydroboration cascade. Indeed, to perform Suzuki couplings with an aliphatic organoborane, 9-borabicyclo(3.3.1)nonane (9-BBN) was required as the hydroborating reagent. In preliminary studies, both the rhodium- and the copper-catalyzed methylenation reactions of Garner's aldehyde[30] were tested, followed

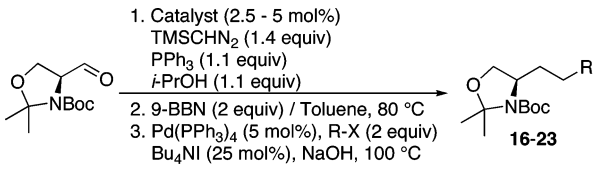
Table 3. One-Pot Transition-Metal-Catalyzed Methylenation−Hydroboration−Suzuki Cross-Coupling Process: Optimization of the Reaction Conditions

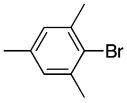
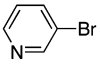


Entry	Suzuki Conditions	Methylenation Catalyst Yield (%)[a,b]	
		$RhCl(PPh_3)_3$ 2.5 mol%	CuCl 5 mol%
1	Pd_2dba_3 (5 mol%) / Toluene	10	10
2	$Pd(PPh_3)_4$ (5 mol%) / THF	35	52
3	**$Pd(PPh_3)_4$ (5 mol%) / Toluene**	77 (73%)	**83** (66%)
4	$PdCl_2$(dppf) (5 mol%) / Toluene	53	63

[a] Isolated yields. [b] In parentheses, isolated yields for the step-by-step process.

Table 4. One-Pot Transition-Metal-Catalyzed Methylenation−Hydroboration−Suzuki Cross-Coupling Process Using Garner's Aldehyde



Entry	R-X	Methylenation Catalyst Yield (%)[a]	
		$RhCl(PPh_3)_3$ 2.5 mol%	CuCl 5 mol%
1	Ph−I	69	76
2	*m*-MeOPh−I	75	81
3	*m*-MeOPh−Br	79	75
4	*p*-Me_2NPh−Br	73	79
5		62	68
6	*p*-MeCOPh	48	59
7	*o*-NO_2Ph−Br	25	78[b]
8		52	62
9	Me−I	65	64

[a] Isolated yields. [b] $PdCl_2$(dppf) as the Suzuki catalyst.

(24) Kraft, P.; Eichenberger, W. *Eur. J. Org. Chem.* **2003**, 3735−3743.
(25) Aldehyde **11** is readily available in five steps from commercially available 3,4-dimethoxybenzaldehyde. See the Supporting Information for details.
(26) Ketone **13** is readily available in four steps from known 4-(hydroxymethyl)-2-methoxyphenyl acetate. See the Supporting Information for details.
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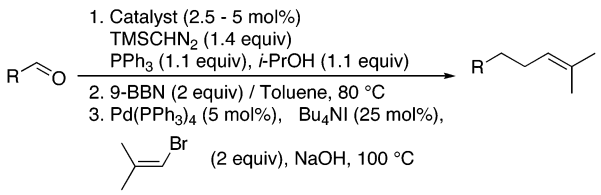
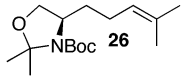
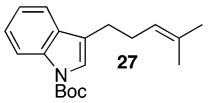
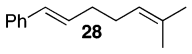
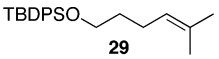
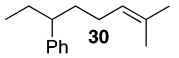
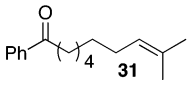
Table 5. One-Pot Transition-Metal-Catalyzed Methylenation−Hydroboration−Suzuki Cross-Coupling Process with Various Aldehydes



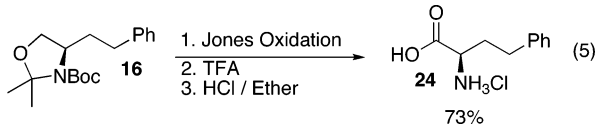
Entry	Methylenation Catalyst	Product	Yield (%)[a]
1	CuCl (5 mol%) THF	 **26**	80
2	CuCl (5 mol%) THF	 **27**	62
3	CuI (5 mol%) Dioxane	 **28**	75
4	IMesCuCl (5 mol%) Dioxane	 **29**	57
5	$RhCl(PPh_3)_3$ (2.5 mol%) THF	 **30**	62
6	$RhCl(PPh_3)_3$ (2.5 mol%) THF	 **31**	49

[a] Isolated yields.

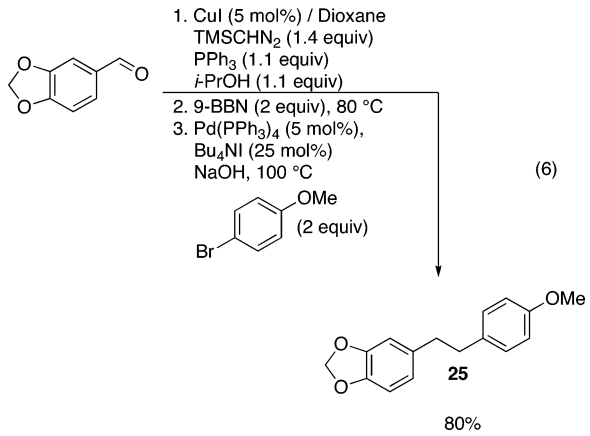
by the addition of 9-BBN and the palladium-catalyzed Suzuki cross-coupling with 4-bromoanisole using various palladium complexes (Table 3). Neither the alkene nor the organoborane intermediates were isolated. The best result was obtained with copper chloride as the methylenation catalyst and tetrakis-(triphenylphosphine) as the Suzuki cross-coupling catalyst, leading to product **15** in 83% isolated yield (entry 3). Higher yields are obtained for the one-pot procedure compared to the step-by-step process, in which the alkene intermediate was isolated.

A variety of other electrophiles (typically aryl bromides) were tested under these reaction conditions (Table 4). Higher yields were obtained when the copper-catalyzed methylenation reaction was used in the one-pot process. Electron-rich aryl bromides were reacted in good yields (entries 2−5), as well as electron-poor aryl bromides (entries 6−8). It is not necessary to protect the ketone (entry 6), and in the presence of $PdCl_2(dppf)_2$, the coupling product with *o*-nitrophenyl bromide was produced in 78% yield (entry 7). It is also possible to use methyl iodide in this one-pot process to obtain the corresponding alkane in 64% yield (entry 9).

The homophenylalanine hydrochloride salt (**24**) was easily synthesized from product **16** via a Jones oxidation, followed by a trifluoroacetic acid cleavage of the Boc protecting group (eq 5).[29e]



It was also possible to transform other aldehydes using this multicatalytic one-pot procedure. Indeed, piperonal was reacted to form product **25** after the Suzuki cross-coupling with 4-bromoanisole (eq 6).



A variety of aldehydes were tested in the one-pot process using 2-methylpropenyl bromide as the coupling partner in the Suzuki reaction (Table 5). Copper catalysts were used with Garner's aldehyde and aromatic and unsaturated aldehydes. After the hydroboration and Suzuki cross-coupling, products **26**−**28** were isolated in 62−80% overall yield (entries 1−3). No workup or purification procedure is required between each step. When other aliphatic aldehydes were reacted, either IMesCuCl[31] or $RhCl(PPh_3)_3$ was used to catalyze the methylenation reaction, as copper chloride or iodide led to lower yields (entries 4−6). The one-pot process tolerated unprotected ketone-containing aldehyde substrate, as both the methylenation and the hydroboration reactions were chemoselective, and compound **31** was isolated in 49% yield (entry 6).

Conclusion

In conclusion, we have developed a series of efficient one-pot procedures to produce substituted alkenes and alkanes in good yields, while minimizing the number of manipulations. Furthermore, these one-pot processes led to products having important biological properties. Finally, synergic effects have been observed, as the copper-catalyzed methylenation reactions proved superior in these one-pot processes, suggesting that copper(I) complexes served as a cocatalyst in cross-coupling reactions.

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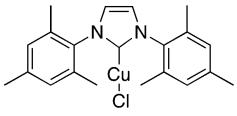
(30) (a) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361−2364. (b) Garner, P.; Park, J. M. *J. Org. Chem.* **1988**, *53*, 2979−2984. (c) Garner, P.; Park, J. M.; Malecki, E. *J. Org. Chem.* **1988**, *53*, 4395−4398.

(31) IMesCuCl:



Experimental Section

Procedure A: Methylenation−Heck Cross-Coupling Process. To a solution of CuCl (50 mg, 0.050 mmol) and triphenylphosphine (263 mg, 1.00 mmol) in dry THF (10 mL) at 25 °C was added 2-propanol (0.0840 mL, 1.10 mmol) followed by the aldehyde (1.00 mmol). The mixture was heated at 60 °C, and then (trimethylsilyl)diazomethane (1.40 mmol) was added. The resulting yellow mixture was stirred at 60 °C. When the methylenation was completed by TLC analysis, THF was concentrated and the mixture was diluted in triethylamine (2.00 mL). To this solution were added the aryl bromide (1.00 mmol), $Pd(OAc)_2$ (0.011 g, 0.050 mmol), and P(*o*-tolyl)$_3$ (0.030 g, 0.10 mmol). The reaction mixture was stirred at 100 °C and was monitored by following the disappearance of the styrene by TLC. After completion, the reaction was quenched by adding water and extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was then purified by flash chromatography, and stilbene was obtained as a white solid.

5,6-Dimethoxy-1,1-dimethyl-2,3-dihydro-1*H*-indene (14).[24] To a solution of IMesCuCl (20 mg, 0.050 mmol) and triphenylphosphine (315 mg, 1.20 mmol) in dry benzene (10 mL) at 25 °C was added 2-propanol (0.920 mL, 12.0 mmol) followed by 4-(2-bromo-4,5-dimethoxyphenyl)butan-2-one (**13**)[26] (1.00 mmol). The resulting mixture was heated to 80 °C, and (trimethylsilyl)diazomethane (1.00 mmol) was then added. After 4 h, an additional equivalent of (trimethylsilyl)-diazomethane (1.00 mmol) was added. The resulting yellow mixture was stirred at 80 °C for 12 h. Dry DMF (10 mL) was added, followed by $Pd(PPh_3)_4$ (116 mg, 0.100 mmol). The reaction mixture was stirred at 100 °C, and after an hour, sodium formate (2 mmol) was added. After 24 h, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (5% EtOAc/hexanes). The desired product **12** was obtained as a colorless liquid: R_f 0.56 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (s, 1H), 6.67 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.83 (t, $J = 8$ Hz, 2H), 1.93 (t, $J = 8$ Hz, 2H), 1.24 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 148.0, 147.8, 144.2, 134.0, 107.6, 105.4, 56.1, 55.9, 44.0, 41.7, 29.9, 28.7; IR (neat) 2948, 2858, 1765, 1606, 1497, 1464, 1303, 1212, 1067 cm^{-1}.

Procedure B: Rhodium-Catalyzed Methylenation−Suzuki Cross-Coupling Process. To a solution of chlorotris(triphenylphosphine)-rhodium (0.011 g, 0.012 mmol) and triphenylphosphine (0.144 g, 0.550 mmol) in THF (3 mL) was added 2-propanol (0.042 mL, 0.550 mmol) followed by the aldehyde (0.500 mmol). To the resulting red mixture was added (trimethylsilyl)diazomethane (0.700 mmol). Gas evolution was observed, and the resulting mixture was stirred at room temperature. When the methylenation reaction was completed by TLC analysis, toluene (3 mL) was added, followed by 9-BBN (0.122 g, 0.500 mmol). The mixture was then heated to 80 °C, and the disappearance of the alkene was followed by TLC analysis. An aqueous solution of NaOH (1.6 mmol, approximately 0.8 mL) was then added and thus quenched the excess of 9-BBN. After the gas evolution was finished, $Pd(PPh_3)_4$ (0.028 g, 0.025 mmol) was added, followed by the corresponding alkyl or aryl halide (0.750 mmol). Finally, tetrabutylammonium iodide (TBAI) (0.12 mmol) was added, and the resulting mixture was stirred under argon at 90 °C overnight. The reaction mixture was poured into a separatory funnel and washed twice with ethyl acetate (2 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl and then dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography using the indicated solvent.

Procedure C: Copper-Catalyzed Methylenation−Suzuki Cross-Coupling Process. To a solution of copper chloride (2.5 mg, 0.025 mmol) and triphenylphosphine (0.144 g, 0.550 mmol) in THF (3 mL) was added 2-propanol (0.042 mL, 0.550 mmol) followed by the aldehyde (0.500 mmol). To the resulting mixture was added (trimethylsilyl)diazomethane (0.700 mmol), and the reaction mixture was heated to 60 °C. When the methylenation reaction was completed by TLC analysis, toluene (3 mL) was added, followed by 9-BBN (0.122 g, 0.500 mmol). The mixture was then heated at 80 °C, and the disappearance of the alkene was followed by TLC analysis. An aqueous solution of NaOH (1.6 mmol, approximately 0.8 mL) was then added and thus quenched the excess of 9-BBN. After the gas evolution was finished, $Pd(PPh_3)_4$ (0.025 mmol, 0.028 g) was added followed by the corresponding alkyl or aryl halide (0.750 mmol). Finally, TBAI (0.12 mL) was added, and the resulting mixture was stirred under argon at 90 °C overnight. The reaction mixture was poured into a separatory funnel and washed twice with ethyl acetate (2 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl and then dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography using the indicated solvent.

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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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