A Versatile Catalyst for Heck Reactions of Aryl Chlorides and Aryl Bromides under Mild Conditions

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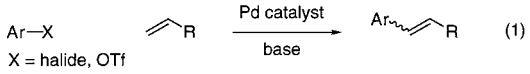
Abstract: In the presence of Cy_2NMe, Pd/P(*t*-Bu)$_3$ serves as an exceptionally mild and versatile catalyst for Heck reactions of aryl chlorides and bromides. A sterically and electronically diverse array of aryl bromides, as well as activated aryl chlorides, couple with a range of mono- and disubstituted olefins *at room temperature*, furnishing the arylated product with high *E*/*Z* stereoselection. The corresponding reactions of a broad spectrum of electron-neutral and electron-rich aryl chlorides proceed at elevated temperature, also with high selectivity. In terms of scope and mildness, Pd/P(*t*-Bu)$_3$/Cy_2NMe represents an advance over previously reported catalysts for these Heck coupling processes.

Introduction

Since its discovery in the early 1970s, the palladium-catalyzed arylation of olefins (Heck reaction, eq 1)[1,2] has been applied to a diverse array of fields, ranging from natural products synthesis[3,4] to materials science[5] to bioorganic chemistry.[6] This powerful carbon−carbon bond-forming process has been practiced on an industrial scale for the production of compounds such as naproxen[7] and octyl methoxycinnamate.[8]



Functional group tolerance and the ready availability and low cost of simple olefins, compared to the vinylmetal compounds that are employed in the corresponding Suzuki, Stille, Kumada, and other cross-coupling reactions, contribute to the exceptional utility of the Heck arylation. In contrast to many coupling processes,[9] for the Heck reaction, nickel-based catalysts are generally ineffective.[10]

Aryl Chlorides as Substrates. Among aryl halides, aryl chlorides are arguably the most attractive class of substrates for coupling reactions, due to their lower price and higher availability. However, until very recently, palladium-catalyzed couplings of aryl chlorides were very uncommon.[11] This low reactivity has usually been attributed to the reluctance of the aryl−chloride bond to oxidatively add to Pd(0) (Figure 1).

By 1999, however, several investigators, most notably Milstein (bulky, electron-rich chelating bisphosphines),[12] Herrmann (palladacycles, *N*-heterocyclic carbenes),[13] Reetz (tetraphenylphosphonium salts),[14] and Beller (phosphites),[15] had established the viability of Heck couplings of aryl chlorides using homo-

(1) (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (b) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320−2322.

(2) For reviews of the Heck reaction, see: (a) Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley: New York, 1998; Chapter 3. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066. (c) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 4, Chapter 4.3. (d) Heck R. F. *Org. React.* **1982**, *27*, 345−390. (e) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427−436. (f) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379−2411. (g) Jeffery, T. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: London, 1996; Vol. 5, pp 153−260. (h) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2−7.

(3) For example, see the following. (a) Taxol: Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843−2859. (b) Scopadulcic acid: Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1993**, *115*, 2042−2044.

(4) For overviews of applications of the Heck reaction in natural products synthesis, see: (a) Link, J. T.; Overman, L. E. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 6. (b) Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley: New York, 1998; Chapter 3.6. (c) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: New York, 1996; Chapter 31. These authors refer to the Heck reaction as "one of the true 'power tools' of contemporary organic synthesis" (p 566).

(5) For example, see: (a) *Step-Growth Polymers for High-Performance Materials*; Hedrick, J. L., Labadie, J. W., Eds.; ACS Symposium Series 624; American Chemical Society: Washington, DC, 1996; Chapters 1, 2, and 4. (b) DeVries, R. A.; Vosejpka, P. C.; Ash, M. L. *Catalysis of Organic Reactions*; Herkes, F. E., Ed.; Marcel Dekker: New York, 1998; Chapter 37. (c) Tietze, L. F.; Kettschau, G.; Heuschert, U.; Nordmann, G. *Chem. Eur. J.* **2001**, *7*, 368−373.

(6) For some recent examples, see: (a) Haberli, A.; Leumann, C. J. *Org. Lett.* **2001**, *3*, 489−492. (b) Burke, T. R., Jr.; Liu, D.-G.; Gao, Y. *J. Org. Chem.* **2000**, *65*, 6288−6292.

(7) Stinson, S. C. *Chem. Eng. News* **1999**, January 18, 81.

(8) Octyl methoxycinnamate (OMC) is the most common UV-B sunscreen that is on the market: Eisenstadt, A. In *Catalysis of Organic Reactions*; Herkes, F. E., Ed.; Marcel Dekker: New York, 1998; Chapter 33.

(9) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley: New York, 1998.

(10) (a) Geissler, H. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: New York, 1998; p 166. (b) Beller, M.; Riermeier, T. H.; Stark, G. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: New York, 1998; p 214. (c) Herrmann, W. A. In *Applied Homogeneous Catalysis with Organometallic Compounds. A Comprehensive Handbook*; Cornils, B., Herrmann, W. A., Eds.; VCH: New York, 1996; p 713. (d) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 4, p 834.

(11) (a) Grushin, V. V.; Alper, H. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer-Verlag: Berlin, 1999; pp 193−226. (b) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047−1062.

(12) (a) Ben-David, Y.; Portnoy, M.; Gozin, M.; Milstein, D. *Organometallics* **1992**, *11*, 1995−1996. (b) Portnoy, M.; Ben-David, Y.; Milstein, D. *Organometallics* **1993**, *12*, 4734−4735. (c) Portnoy, M.; Ben-David, Y.; Rousso, I.; Milstein, D. *Organometallics* **1994**, *13*, 3465−3479.

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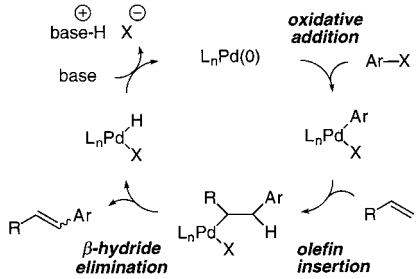
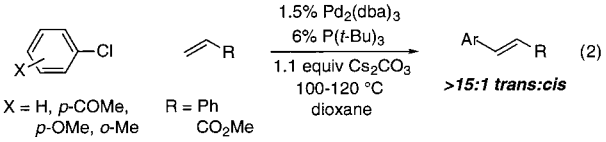


Figure 1. Outline of the catalytic cycle for the Heck coupling reaction.

geneous catalysts.[16,17] Unfortunately, the reaction temperatures were somewhat high (120−160 °C), and the reaction scope was somewhat narrow. With respect to the aryl chloride, just one coupling of a sterically demanding substrate had been reported,[18] and only two reactions of highly electron-rich aryl chlorides (⇒less reactive) had been described;[19] with respect to the olefin, only reactive substrates (styrene and acrylic acid derivatives) had been examined.

In 1999, we reported that $Pd_2(dba)_3$/P(*t*-Bu)$_3$ catalyzes Heck couplings of an array of aryl chlorides, including sterically demanding and electron-rich aryl chlorides, at 100−120 °C (eq 2; Cs_2CO_3 as the base).[20−22] Although we demonstrated that $Pd_2(dba)_3$/P(*t*-Bu)$_3$ provides broader scope than previous catalysts with respect to the aryl chloride (under milder conditions), we did not establish increased generality with respect to the olefin.



It is important to note that, around the time of our initial publication, two other groups also reported that Pd/P(*t*-Bu)$_3$ serves as an active catalyst for Heck reactions. Thus, DeVries described a coupling of an aryl bromide with a vinylsilane (95 °C),[23] and Hartwig discovered that Pd/P(*t*-Bu)$_3$ effects Heck reactions of para-substituted aryl chlorides with *n*-butyl acrylate (110 °C).[24−27]

While Pd/P(*t*-Bu)$_3$/Cs_2CO_3 provided a comparatively mild and general method for accomplishing Heck reactions of aryl chlorides (eq 2), we felt that important challenges remained, including demonstrating broader scope (particularly with respect to the olefin component) and developing even milder conditions.

Aryl Bromides as Substrates. In contrast to the situation with aryl chlorides, there are numerous examples of aryl bromides with wide-ranging steric and electronic properties undergoing Heck reactions with a variety of olefins.[2] Despite this more advanced state-of-the-art, there is still significant room for improvement with regard to the same general issues of versatility and mildness of conditions that were raised for aryl chlorides.

With respect to versatility, although current catalyst systems can, collectively, effect Heck reactions of a broad spectrum of coupling partners, particular catalysts have not proved to be widely applicable. Comments from recent reviews of the Heck reaction have noted this shortcoming. For example, Overman has observed that, "It is apparent in the examples highlighted in this summary that no single catalyst recipe has emerged as optimal. We have found it useful when conducting a Heck cyclization for the first time to screen catalysts on the extreme of reactivity and stability." [28] In addition, de Meijere has referred to "the diverse and sometimes mysterious compositions of applicable catalyst 'cocktails' " for the Heck reaction.[29] Clearly, the development of a versatile catalyst would greatly facilitate applications of the Heck coupling reaction, particularly in areas such as automated parallel synthesis.

The development of milder conditions (e.g., room temperature) for Heck couplings of aryl bromides would also be a significant advance. From the standpoints of functional group tolerance, substrate stability, and regio-/stereoselectivity issues, the elevated temperatures that are required for most Heck reactions are not ideal. Furthermore, as chemistry moves from basic research laboratories into the industrial process/development arena, the practical advantage of room-temperature reactions can become increasingly important.

(13) (a) Herrmann, W. A.; Brossmer, C.; Ofele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844−1848. (b) Herrmann, W. A.; Brossmer, C.; Reisinger, C.-P.; Reirmeier, T. H.; Ofele, K.; Beller, M. *Chem. Eur. J.* **1997**, *3*, 1357−1364. (c) Herrmann, W. A.; Elison, M.; Fischer, J.; Köcher, C.; Artus, G. R. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2371−2374. (d) See also: Herrmann, W. A.; Brossmer, C.; Ofele, K.; Beller, M.; Fischer, H. *J. Mol. Catal. A* **1995**, *103*, 133−146.

(14) Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 481−483.

(15) Beller, M.; Zapf, A. *Synlett* **1998**, 792−793.

(16) See also: Kaufmann, D. E.; Nouroozian, M.; Henze, H. *Synlett* **1996**, 1091−1092.

(17) For very early work on Heck reactions of aryl chlorides, see: (a) Davison, J. B.; Simon, N. M.; Sojka, S. A. *J. Mol. Catal.* **1984**, *22*, 349−352. (b) Spencer, A. *J. Organomet. Chem.* **1984**, *270*, 115−120.

(18) Coupling of 2-chloro-5-nitrotoluene and *n*-butyl acrylate: Beller, M.; Zapf, A. *Synlett* **1998**, 792−793.

(19) (a) Coupling of 4-chloroanisole and styrene (49% yield; 3:1 cis:trans): Portnoy, M.; Ben-David, Y.; Milstein, D. *Organometallics* **1993**, *12*, 4734−4735. (b) Coupling of 4-chloroanisole and *n*-butyl acrylate (48% yield): Herrmann, W. A.; Brossmer, C.; Ofele, K.; Beller, M.; Fischer, H. *J. Mol. Catal. A* **1995**, *103*, 133−146.

(20) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10−11.

(21) For our other studies of Pd/P(*t*-Bu)$_3$-catalyzed coupling reactions, see the following. (a) Suzuki cross-couplings: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387−3388. Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028. (b) Stille cross-couplings: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2411−2413. (c) Sonogashira cross-couplings: Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729−1731. (d) Negishi cross-couplings: Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719−2724.

(22) For pioneering studies of the use of P(*t*-Bu)$_3$ in a palladium-catalyzed process (amination), see: (a) Nishiyama, M.; Yamamoto, T.; Koie, Y.; *Tetrahedron Lett.* **1998**, *39*, 617−620. (b) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367−2370.

(23) DeVries, R. A.; Vosejpka, P. C.; Ash, M. L. In *Catalysis of Organic Reactions*; Herkes, F. E., Ed.; Marcel Dekker: New York, 1998; Chapter 37.

(24) Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 2123−2132.

(25) Since our initial report, Herrmann has determined that $Pd_2(dba)_3$/P(*t*-Bu)$_3$ was the most effective catalyst, among those surveyed, for Heck couplings of aryl chlorides in nonaqueous ionic liquids: Bohm, V. P. W.; Herrmann, W. A. *Chem. Eur. J.* **2000**, *6*, 1017−1025.

(26) For recent examples of Heck couplings of activated aryl chlorides, see: (a) McGuinness, D. S.; Cavell, K. J. *Organometallics* **2000**, *19*, 741−748. (b) Iyer, S.; Ramesh, C. *Tetrahedron Lett.* **2000**, *41*, 8981−8984. (c) Peris, E.; Loch, J. A.; Mata, J.; Crabtree, R. H. *Chem. Commun.* **2000**, 201−202. (d) Calo, V.; Nacci, A.; Lopez, L.; Mannarini, N. *Tetrahedron Lett.* **2000**, *41*, 8973−8976. (e) Gruber, A. S.; Zim, D.; Ebeling, G.; Monteiro, A. L.; Dupont, J. *Org. Lett.* **2000**, *2*, 1287−1290.

(27) For recent examples of Heck couplings of unactivated aryl chlorides, see: (a) Herrmann, W. A.; Bohm, V. P. W. *J. Organomet. Chem.* **1999**, *572*, 141−145. Herrmann, W. A.; Reisinger, C.-P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557*, 93−96. Bohm, V. P. W.; Herrmann, W. A. *Chem. Eur. J.* **2000**, *6*, 1017−1025. (b) Morales-Morales, D.; Redon, R.; Yung, C.; Jensen, C. M. *Chem. Commun.* **2000**, 1619−1620. (c) Ehrentraut, A.; Zapf, A.; Beller, M. *Synlett* **2000**, *11*, 1589−1592.

(28) Link, J. T.; Overman, L. E. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; p 262.

(29) Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley: New York, 1998; p 99, see also Tables 3−5.

The only reasonably general room-temperature protocol for the Heck reaction that has been reported is the Jeffery system ($Pd(OAc)_2$, HCO_3^-, R_4NX), which can be applied to couplings of aryl and vinyl iodides;[30] in a recent review, this development has been characterized as "a major achievement".[31] Jeffery has documented how the mildness of this procedure provides significant advantages over other catalyst systems with regard to selectivity issues and reactions of thermally labile compounds.[2g] To the best of our knowledge, however, until this year no catalysts that effect room-temperature Heck couplings of aryl bromides[32] (or chlorides) had been described.

In summary, in view of the importance of the Heck reaction, we felt that the development of a more versatile and milder catalyst system would be a worthwhile achievement. In this article we present our progress toward accomplishing this objective.

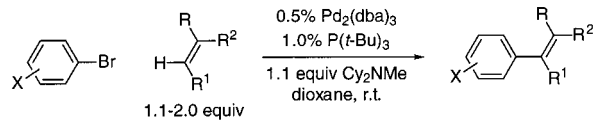
Results and Discussion

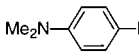
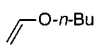
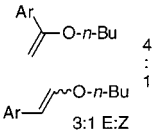
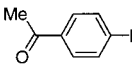
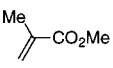
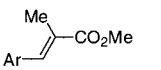
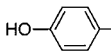
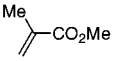
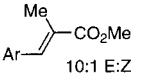
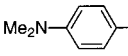
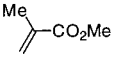
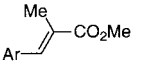
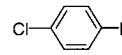
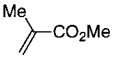
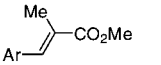
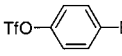
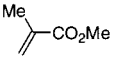
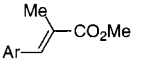
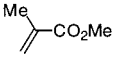
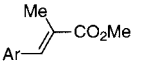
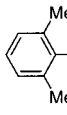
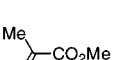
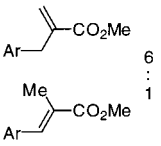
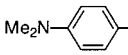
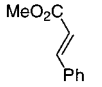
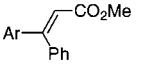
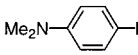
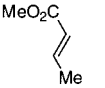
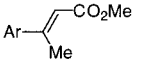
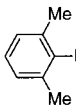
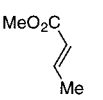
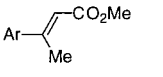
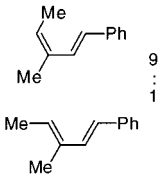
Room-Temperature Heck Couplings of Aryl Bromides. In our 1999 communication, we reported that $Pd_2(dba)_3$/P(*t*-Bu)$_3$/Cs_2CO_3 catalyzes the Heck coupling of a variety of aryl chlorides with styrene and methyl acrylate (eq 2).[20] We employed this system as a starting point in our development of a catalyst for room-temperature Heck reactions of aryl bromides. In an initial study, we established that, although $Pd_2(dba)_3$/P(*t*-Bu)$_3$/Cs_2CO_3 does effect the room-temperature coupling of a wide array of aryl bromides with styrene and methyl acrylate, we observe little or no reaction with more challenging olefins such as 1-hexene and methyl methacrylate. Since our objective was an extremely versatile catalyst for room-temperature Heck couplings of aryl bromides, we were forced to conclude that our first-generation system was inadequate.

The choice of base can have a crucial effect on the rate and the product distribution of Heck reactions.[33] Prompted by a recent report from the Buchwald laboratory that described the unusual effectiveness of a bulky tertiary amine, Cy_2NMe, in Heck couplings of disubstituted olefins at 85−100 °C,[34] we investigated the replacement of Cs_2CO_3 with Cy_2NMe. We were pleased to observe that use of Cy_2NMe leads to a significantly more active catalyst, permitting the room-temperature coupling of a wide array of aryl bromides with a broad spectrum of olefins (Table 1).[35,36]

A 1:1 Pd:P(*t*-Bu)$_3$ ratio appears to provide the most active catalyst for these room-temperature Heck reactions, consistent with our observations regarding room-temperature Suzuki cross-couplings.[21a] As illustrated in entry 1 of Table 1, the usual regioselectivity for Heck arylations of alkyl vinyl ethers is observed; i.e., electron-rich aromatic rings preferentially add

Table 1. Heck Couplings of Aryl and Vinyl Bromides at Room Temperature



Entry	Aryl Bromide	Olefin	Product	Yield[a,b]
1			 4 : 1, 3:1 E:Z	97%
2				74%
3			 10:1 E:Z	77%
4				96%
5				70%[c]
6				64%[c]
7				86%[d]
8			 6 : 1	97%
9[e]				80%
10[e]				68%
11[f]				83%
12[f]			 9 : 1	89%

[a] Isolated yield, average of two runs. [b] Unless otherwise indicated, the *E*:*Z* ratio is >20:1, as determined by ^{1}H NMR. [c] 16:1 ratio of internal:terminal olefin. [d] 20:1 ratio of internal:terminal olefin. [e] 1.0% $Pd_2(dba)_3$, 2.0% P(*t*-Bu)$_3$ were used. [f] 1.5% $Pd_2(dba)_3$, 3.0% P(*t*-Bu)$_3$ were used.

(30) Jeffery, T. In *Advances in Metal−Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: London, 1996; Vol. 5, pp 153−260.

(31) Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley: New York, 1998; p 106.

(32) Very recently, Hartwig has reported that room-temperature Heck arylation of reactive olefins (styrene and methyl acrylate) by a variety of aryl bromides can be accomplished by using 1-adamantyl-di-*tert*-butyl phosphine and a ferrocenyl-di-*tert*-butyl phosphine as ligands: Stambuli, J. P.; Stauffer, S. R.; Shaughnessy, K. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 2677−2678.

(33) For some recent examples, see: (a) Morales-Morales, D.; Grause, C.; Kasaoka, K.; Redon, R.; Cramer, R. E.; Jensen, C. M. *Inorg. Chim. Acta* **2000**, *300*−*302*, 958−963. (b) Hartung, C. G.; Köhler, K.; Beller, M. *Org. Lett.* **1999**, *1*, 709−711. (c) Beller, M.; Riermeier, T. H. *Eur. J. Inorg. Chem.* **1998**, 29−35. (d) Beller, M.; Riermeier, T. H. *Tetrahedron Lett.* **1996**, *37*, 6535−6538.

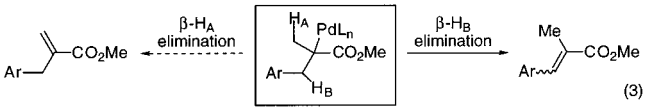
(34) Gürtler, C.; Buchwald, S. L. *Chem. Eur. J.* **1999**, *5*, 3107−3112.

(35) Notes: (a) A variety of other amines (tertiary, secondary, cyclic, and aromatic) were surveyed, but all were inferior to Cy_2NMe. (b) Toluene and THF are also suitable solvents for these couplings. (c) $Pd_2(dba)_3$ is superior to $Pd(OAc)_2$ and $Pd(MeCN)_2Cl_2$. (d) No reaction is observed in the absence of P(*t*-Bu)$_3$.

(36) For all of the Heck reactions that are reported in this article, no regio- or stereoisomers, except those that are described, are detected by ^{1}H or ^{13}C NMR.

to the α carbon of the enol ether.[37] Although the regioselection is moderate (4:1), it compares favorably with that of other catalysts[38,39] and may be due to the lower reaction temperature.

Heck reactions of aryl halides with methyl methacrylate, a 1,1-disubstituted olefin, can furnish α-methylcinnamic acid derivatives, an important family of compounds that both possess biological activity (e.g., hypolipidemic[40] and antiobiotic[41]) and serve as intermediates in the synthesis of pharmaceuticals (e.g., Sulindac, a non-steroidal anti-inflammatory drug[42]). In Heck reactions of methacrylates, there are two possible pathways for β-hydride elimination, one leading to a 1,1-disubstituted olefin, which is susceptible to further Heck arylation,[43] and the other leading to the desired trisubstituted olefin, for which there is an *E*/*Z* stereochemical issue (eq 3).[44]



(3)

Entries 2−7 of Table 1 establish that $Pd_2(dba)_3$/P(*t*-Bu)$_3$/Cy_2NMe effects the Heck coupling of methyl methacrylate with electronically and sterically diverse aryl bromides, at room temperature, to produce α-methylcinnamates with very good selectivity (>15:1 trisubstituted:disubstituted olefin; >20:1 *E*:*Z*, except for entry 3). Methyl ketones (entry 2) and phenols (entry 3)[45] are compatible with the reaction conditions. Even the Heck coupling of deactivated, highly electron-rich 4-bromo-*N*,*N*-dimethylaniline proceeds smoothly at room temperature, furnishing the desired product in excellent yield (96%; entry 4). An aryl bromide reacts selectively in the presence of either a chloride (entry 5) or a triflate (entry 6).

Most catalysts for the Heck reaction do not effectively couple hindered substrate pairs,[2] but $Pd_2(dba)_3$/P(*t*-Bu)$_3$/Cy_2NMe arylates methyl methacrylate with 2-bromotoluene in good yield at room temperature (entry 7). Interestingly, reaction of very bulky 2-bromo-*m*-xylene leads to preferential formation of the 1,1-disubstituted olefin (entry 8); this coupling is the only example that we have encountered in which this isomer is the major product. Presumably, the steric demand of the two ortho methyl groups disfavors β-hydride elimination to generate the trisubstituted olefin.[46]

As noted in a recent review, intermolecular Heck reactions of 1,2-disubstituted olefins are relatively uncommon, due to their low reactivity toward typical catalysts.[47] $Pd_2(dba)_3$/P(*t*-Bu)$_3$/Cy_2NMe couples 1,2-disubstituted olefins with aryl bromides at room temperature (entries 9−11). The stereoselective generation of β,β-diarylacrylates, which are useful intermediates in the synthesis of a variety of medicinally interesting compounds, including angiotension II antagonists,[48] can be difficult, as a result of isomerization of the olefin at the elevated temperatures typically employed for Heck reactions.[49] Under our conditions, we can couple 4-bromo-*N*,*N*-dimethylaniline with methyl *trans*-cinnamate to furnish the desired β,β-diarylacrylate with >20:1 *E*:*Z* selectivity (entry 9).

$Pd_2(dba)_3$/P(*t*-Bu)$_3$/Cy_2NMe can also be applied to the stereoselective construction of synthetically useful β-arylcrotonic esters, which can be converted, for example, into biologically important 2(5*H*)-furanones.[50] Not only electronically deactivated (entry 10) but also extremely sterically demanding (entry 11) aryl bromides can be coupled with methyl crotonate at room temperature (>20:1 *E*:*Z*). Significantly, we have established that this catalyst system is not limited to Heck reactions of aryl bromides—vinyl bromides are also efficiently coupled at room temperature (entry 12).

In summary, both in terms of reaction scope and temperature, $Pd_2(dba)_3$/P(*t*-Bu)$_3$/Cy_2NMe represents an unusually effective catalyst for Heck reactions of bromides.

Room-Temperature Heck Couplings of Activated Aryl Chlorides. We next turned our attention to reactions of chlorides, and we were pleased to discover that $Pd_2(dba)_3$/P(*t*-Bu)$_3$/Cy_2NMe also catalyzes the room-temperature Heck coupling of a variety of activated aryl chlorides with an array of olefins (Table 2). These results are particularly interesting in view of the fact that Heck reactions of aryl chlorides using other homogeneous catalysts require temperatures ≥100 °C, even for couplings with highly reactive olefins.

As illustrated in Table 2, Heck coupling of 4′-chloroacetophenone with styrene proceeds smoothly at room temperature, affording the stilbene derivative with good *E*:*Z* stereoselection (>20:1; entry 1). Heck reactions of unactivated, alkyl-substituted terminal olefins can be plagued by modest regioselectivity and by olefin isomerization;[51] under our conditions, 4′-chloroacetophenone couples with 1-hexene to provide the 1,2-disubstituted olefin exclusively with *E*:*Z* selectivity that compares favorably with that of other catalyst systems (6:1; entry 2).[52] *n*-Butyl vinyl

(37) (a) Andersson, C.-M.; Hallberg, A.; Daves, G. D., Jr. *J. Org. Chem.* **1987**, *52*, 3529−3536. (b) Daves, G. D., Jr.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433−1445.

(38) For example, see: (a) Reference 13b. (b) Bohm, V. P. W.; Herrmann, W. A. *Chem. Eur. J.* **2000**, *6*, 1017−1025.

(39) The use of additives such as AgOTf or TlOAc (Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S.; Santi, R. *J. Org. Chem.* **1992**, *57*, 1481−1486) or of an ionic-liquid solvent (Xu, L.; Chen, W.; Ross, J.; Xiao, J. *Org. Lett.* **2001**, *3*, 295−297) is generally required to obtain high α:β selectivity in Heck reactions of aryl halides.

(40) For example, see: Watanabe, T.; Hayashi, K.; Yoshimatsu, S.; Sakai, K.; Takeyama, S.; Takashima, K. *J. Med. Chem.* **1980**, *23*, 50−59.

(41) For example, see: Buchanan, J. G.; Hill, D. G.; Wightman, R. H.; Boddy, I. K.; Hewitt, B. D. *Tetrahedron* **1995**, *51*, 6033−6050.

(42) Eisenstadt, A. In *Catalysis of Organic Reactions*; Herkes, F. E., Ed.; Marcel Dekker: New York, 1998; Chapter 33.

(43) For some recent examples, see: (a) Morales-Morales, D.; Grause, C.; Kasaoka, K.; Redon, R.; Cramer, R. E.; Jensen, C. M. *Inorg. Chim. Acta* **2000**, *300*−*302*, 958−963. (b) Beller, M.; Riermeier, T. H. *Eur. J. Inorg. Chem.* **1998**, 29−35. (c) Beller, M.; Riermeier, T. H. *Tetrahedron Lett.* **1996**, *37*, 6535−6538.

(44) We do not intend to imply that product formation in these Heck couplings must be under kinetic control. In fact, for one reaction we have evidence that an appreciable quantity of disubstituted olefin is generated initially, and that it is converted to the trisubstituted olefin under the coupling conditions.

(45) Heck couplings of halophenols can be problematic. For example, see: (a) Bates, R. W.; Gabel, C. J. *Tetrahedron Lett.* **1993**, *34*, 3547−3550. (b) Ziegler, C. B., Jr.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2941−2946.

(46) We believe that the disubstituted olefin may be the kinetic product. When we conduct this coupling at 120 °C with 0.5% $Pd_2(dba)_3$/2.0% P(*t*-Bu)$_3$, we obtain an 87% yield (by NMR, vs an internal standard) of the *E* trisubstituted olefin, with no evidence of other isomers. Thus, by appropriate choice of conditions, we can preferentially generate either a di- or a trisubstituted olefin.

(47) Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley: New York, 1998; p 102.

(48) For example, see: Almansa, C.; Gomez, L. A.; Cavalcanti, F. L.; de Arriba, A. F.; Rodriguez, R.; Carcellar, E.; Garcia-Rafanell, J.; Forn, J. *J. Med. Chem.* **1996**, *39*, 2197−2206.

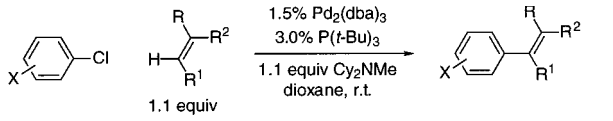
(49) For example, see: (a) Moreno-Manas, M.; Perez, M.; Pleixats, R. *Tetrahedron Lett.* **1996**, *37*, 7449−7452. (b) Reference 34.

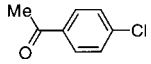
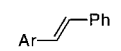
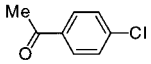
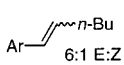
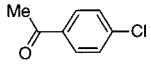
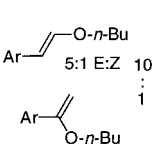
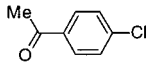
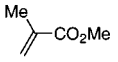
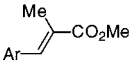
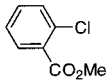
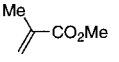
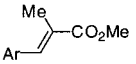
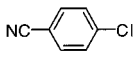
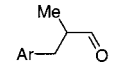
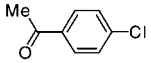
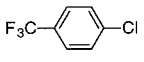
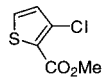
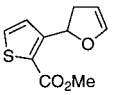
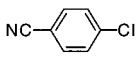
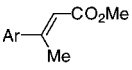
(50) For example, see: Kagabu, S.; Shimizu, Y.; Ito, C.; Moriya, K. *Synthesis* **1992**, 830−832.

(51) (a) References 2d and 2h. (b) For recent examples, see: Mabic, S.; Vaysse, L.; Benezra, C.; Lepoittevin, J.-P. *Synthesis* **1999**, *7*, 1127−1134. Bräse, S.; Schroen, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1071−1073.

(52) With other catalysts, lower *E*:*Z* stereoselectivity is often observed. For example, see: Brunner, H.; de Courcy, N. L. C.; Genet, J.-P. *Tetrahedron Lett.* **1999**, *40*, 4815−4818.

Table 2. Heck Couplings of Activated Aryl Chlorides at Room Temperature



Entry	Aryl Chloride	Olefin	Product	Yield[a,b]
1				78%
2			 6:1 E:Z	70%
3			 5:1 E:Z 10 : 1	87%[c]
4				79%
5				90%
6				79%
7[d,e]				72%[f]
8[e]				76%[g]
9[e]				87%
10[h]				57%[i]

[a] Isolated yield, average of two runs. [b] Unless otherwise indicated, the *E*:*Z* ratio is >20:1, as determined by ^{1}H NMR. [c] Product includes 5% 4′-chloroacetophenone. [d] 0.5% $Pd_2(dba)_3$, 1.0% P(*t*-Bu)$_3$ were used. [e] 3 equiv of olefin was used. [f] A small amount of the diarylated product was also generated, and it was removed by chromatography. [g] Product includes 6% diarylated product. [h] 2 equiv of olefin was used. [i] Product includes 2% P(*t*-Bu)$_3$/OP(*t*-Bu)$_3$.

ether reacts with 4′-chloroacetophenone to yield primarily the β-arylated product (10:1; entry 3).[53]

$Pd_2(dba)_3$/P(*t*-Bu)$_3$/Cy_2NMe also effects Heck couplings of 1,1-disubstituted olefins at room temperature (entries 4−6). Thus, methyl methacrylate reacts smoothly with activated aryl chlorides, including ortho-substituted ones, to generate trisubstituted olefins (no 1,1-disubstituted olefin) in good yield and with excellent *E*:*Z* stereoselectivity (>20:1; entries 4 and 5).[54] The Heck reaction of *p*-chlorobenzonitrile with a primary allylic alcohol furnishes the aldehyde exclusively, due to regioselective β-hydride elimination (entry 6).[55,56]

Even 1,2-disubstituted olefins are suitable substrates for room-temperature arylation by this catalyst (entries 7−10). For Heck reactions of 2,3-dihydrofuran, we obtain the 2-aryl-2,3-dihydrofuran, resulting from arylation of the olefin followed by isomerization (entries 7−9);[57] the only other product that we observe is the diarylated furan, the formation of which we discourage through the use of excess olefin (3 equiv). Acyclic 1,2-disubstituted olefins can also undergo Heck coupling at room temperature, although in somewhat modest yield (entry 10).

Until now, only styrene and acrylic acid derivatives, as well as cyclopentene (which furnished an undetermined mixture of isomeric arylated products),[27c] have participated in Heck reactions with aryl chlorides; all of these couplings have required an elevated reaction temperature (≥100 °C). The results provided in Table 2 represent the first examples of room-temperature Heck reactions of aryl chlorides, as well as the first examples of couplings of aryl chlorides to form trisubstituted olefins. The high levels of regio- and stereoselection, as well as the functional group tolerance (nitriles, ketones, esters, thiophenes, alcohols, etc.) of $Pd_2(dba)_3$/P(*t*-Bu)$_3$/Cy_2NMe, are worthy of note.

Heck Couplings of Aryl Chlorides at Elevated Temperature. Methyl *trans*-cinnamate is the only olefin that we have examined that does not undergo Heck coupling at room temperature with activated aryl chlorides in the presence of $Pd_2(dba)_3$/P(*t*-Bu)$_3$/Cy_2NMe. However, the arylation does proceed at 70 °C, furnishing the *E*-β,β-diarylacrylate with excellent stereoselection (>20:1 *E*:*Z*; Table 3, entry 1).[58,59]

$Pd_2(dba)_3$/P(*t*-Bu)$_3$/Cy_2NMe effectively catalyzes the Heck reactions of deactivated, electron-rich 4-chloroanisole with styrene (entry 2) and of chlorobenzene and 4-chloroanisole with methyl methacrylate (entries 3 and 4), providing excellent stereoselection (>20:1). Even hindered aryl chlorides can be coupled in good yield (entries 5 and 6), including a di-ortho-substituted substrate, the most hindered aryl chloride that has undergone a Heck coupling. 3-Chloropyridine is also a suitable substrate (entry 7).

However, this catalyst system does have some limitations. For example, although 3-chloropyridine can be coupled, 2-chloropyridine is unreactive under identical conditions.[60] In addition, Heck arylation of methyl methacrylate with extremely electron-rich 4-chloroaniline furnishes only a moderate yield of the desired product (47%), albeit with excellent stereoselectivity (>20:1); simple dehalogenation to generate aniline is the major side reaction. Finally, Heck couplings of 1,2-disubstituted

(53) Heck reactions of 4′-bromoacetophenone typically generate this regioisomer preferentially, although the selectivity is often modest. For example, see: (a) Herrmann, W. A.; Brossmer, C.; Reisinger, C.-P.; Reirmeier, T. H.; Ofele, K.; Beller, M. *Chem. Eur. J.* **1997**, *3*, 1357−1364. (b) Bohm, V. P. W.; Herrmann, W. A. *Chem. Eur. J.* **2000**, *6*, 1017−1025.

(54) In contrast to reactions of aryl bromides with methyl methacrylate, for which diarylation had to be discouraged through the use of excess olefin (up to 2 equivalents; Table 1), diarylation is not a problem in the analogous couplings of aryl chlorides, and 1.1 equiv of olefin may be employed (Tables 2−3).

(55) For precedent, see: (a) Melpolder, J. B.; Heck, R. F. *J. Org. Chem.* **1976**, *41*, 265−272. (b) Chalk, A. J.; Magennis, S. A. *J. Org. Chem.* **1976**, *41*, 1206−1209.

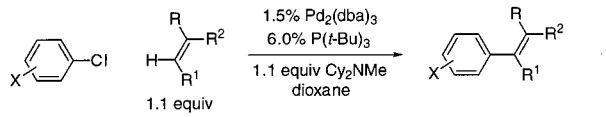
(56) When we arylate a secondary allylic alcohol, 2-methyl-1-penten-3-ol, with *p*-chlorobenzonitrile, we obtain 57% of the ketone and 37% of the allylic alcohol, due to poor regioselectivity in the β-hydride elimination. Others have also reported mixtures of products from Heck reactions of secondary allylic alcohols. For example, see: Kang, S.-K.; Jung, K.-Y.; Park, C.-H.; Namkoong, E.-Y.; Kim, T.-H. *Tetrahedron Lett.* **1995**, *36*, 6287−6290.

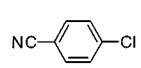
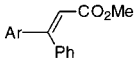
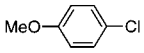
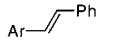
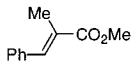
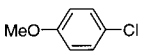
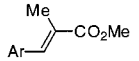
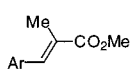
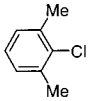
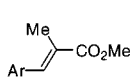
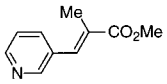
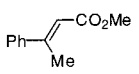
(57) For leading references to isomerization reactions during Heck couplings of 2,3-dihydrofuran, see: Jeffery, T.; David, M. *Tetrahedron Lett.* **1998**, *39*, 5751−5754.

(58) The major side product in this reaction is 4,4′-dicyanobiphenyl, arising from reductive homocoupling of the aryl chloride. This undesired pathway has been observed by others in Heck arylations of cinnamic acid esters with electron-deficient aryl iodides. For example, see: Moreno-Manas, M.; Perez, M.; Pleixats, R. *Tetrahedron Lett.* **1996**, *37*, 7449−7452.

(59) Heck couplings of electron-deficient aryl bromides and iodides with cinnamic acid esters generally require unusually vigorous reaction conditions and often afford modest yield and stereoselectivity. For example, see ref 49.

Table 3. Heck Couplings of Unactivated Aryl Chlorides

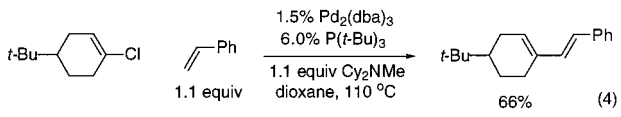


Entry	Aryl Chloride	Olefin	Temperature	Product	Yield[a,b]
1[c]			70 °C		67%[d]
2			120 °C		72%
3			100 °C		84%
4			120 °C		72%
5			110 °C		89%
6			120 °C		80%
7			100 °C		76%
8[e]			120 °C		52%

[a] Isolated yield, average of two runs. [b] *E*:*Z* ratio is >20:1, as determined by ^{1}H NMR. [c] 3.6% P(*t*-Bu)$_3$ was used. [d] Product includes 2.5% P(*t*-Bu)$_3$/OP(*t*-Bu)$_3$. [e] 2 equiv of olefin was used.

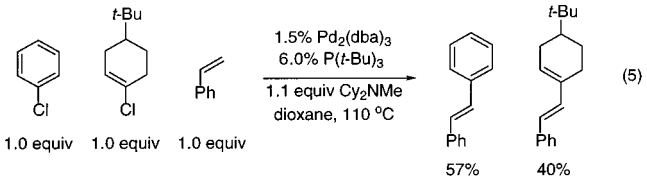
olefins have thus far provided either modest stereoselection or modest yield (e.g., Table 3, entry 8). Despite these limitations, the examples illustrated in Table 3 significantly expand the scope of the Heck reaction of unactivated aryl chlorides.

Heck Coupling of an Unactivated Vinyl Chloride. To the best of our knowledge, there are no examples of Heck couplings of unactivated vinyl chlorides.[61] We have determined that Pd$_2$(dba)$_3$/P(*t*-Bu)$_3$/Cy$_2$NMe can accomplish this transformation (eq 4).



(4)

In virtually all palladium-catalyzed coupling processes, vinyl chlorides are markedly more reactive than aryl chlorides, with the Pd$_2$(dba)$_3$/P(*t*-Bu)$_3$-catalyzed Suzuki reaction being the lone exception of which we are aware.[21a,62] We have established that this unusual reactivity profile applies not only to Pd$_2$(dba)$_3$/P(*t*-Bu)$_3$-catalyzed Suzuki couplings, but also to Heck reactions. Thus, in a competition experiment between chlorobenzene and 1-chloro-4-*tert*-butyl-cyclohexene for styrene, the aryl chloride couples preferentially (eq 5).

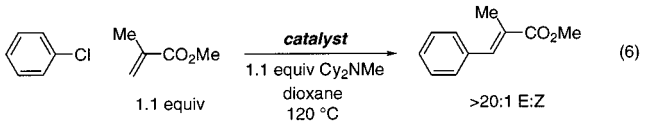


(5)

Heck Couplings with Low Catalyst Loadings. For the Heck reactions described above, we employed moderate catalyst loadings (1−3% Pd). Because our goal is to develop a general, reliable protocol, we did not attempt to individually optimize the catalyst loading for each coupling. However, because for certain applications (e.g., industrial) turnover number can be important, we have briefly examined Heck reactions of both aryl chlorides and aryl bromides using a lower catalyst loading.

In our initial communication, we reported a turnover number (TON) of 400 for the coupling of chlorobenzene with styrene, based on an 80% isolated yield of stilbene and a 0.2% loading of Pd.[20] This is the highest TON that has been described for a Heck reaction of an unactivated aryl chloride using a homogeneous catalyst,[63] although it is worth noting that Buchmeiser has obtained a TON of 23 600 for the coupling of chlorobenzene with styrene by a heterogeneous catalyst.[64]

As noted earlier, prior to this study the only olefins that had been employed in Heck reactions of aryl chlorides (including electron-poor chlorides) were activated monosubstituted olefins (styrene and acrylic acid derivatives), along with cyclopentene, which provided an undefined mixture of isomeric arylation products. We decided to determine if Pd$_2$(dba)$_3$/P(*t*-Bu)$_3$/Cy$_2$NMe can furnish a high TON in the relatively challenging coupling of an unactivated aryl chloride with a disubstituted olefin. We were pleased to find that, for the Heck reaction of chlorobenzene with methyl methacrylate, we obtain a TON ~335 with Pd$_2$(dba)$_3$/P(*t*-Bu)$_3$ as the catalyst (eq 6).[65]



(6)

catalyst: 0.1% Pd$_2$(dba)$_3$/0.4% P(*t*-Bu)$_3$ 67% yield; 0.2% Pd(P(*t*-Bu)$_3$)$_2$ 63% yield } ⟹ TON ~325

When we instead employ Pd(P(*t*-Bu)$_3$)$_2$ as the catalyst, we observe a TON that is comparable to that obtained with Pd$_2$(dba)$_3$/P(*t*-Bu)$_3$ (eq 6). Because Pd(P(*t*-Bu)$_3$)$_2$ is a commercially available,[66] air-stable, crystalline solid,[67] it represents a very user-friendly alternative to Pd$_2$(dba)$_3$/P(*t*-Bu)$_3$ for this process.[68]

(60) 2-Halopyridines can be difficult substrates for Heck couplings, perhaps due to the formation, after oxidative addition, of an unreactive pyridyl-bridged palladium dimer (Nakatsu, K.; Kinoshita, K.; Kanda, H.; Isobe, K.; Nakamura, Y.; Kawaguchi, S. *Chem. Lett.* **1980**, 913−914). For reports of problems effecting Heck reactions of 2-halopyridines, see: (a) Frank, W. C.; Kim, Y. C.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2947−2949. (b) Bozell, J. J.; Vogt, C. E.; Gozum, J. *J. Org. Chem.* **1991**, *56*, 2584−2587. (c) Basu, B.; Frejd, T. *Acta Chem. Scand.* **1996**, *50*, 316−322.

(61) For examples of Heck couplings of activated vinyl chlorides, see: (a) Horino, H.; Inoue, N.; Asao, T. *Tetrahedron Lett.* **1981**, *22*, 741−744. (b) Voigt, K.; Schick, U.; Meyer, F. E.; de Meijere, A. *Synlett* **1994**, 189−190.

(62) (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998. (b) Tsuji, J. *Palladium Reagents and Catalysis*; Wiley: New York, 1995. (c) Farina, V. In *Comprehensive Organometallic Chemistry 2*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: New York, 1995; Vol. 12, Chapter 3.4.

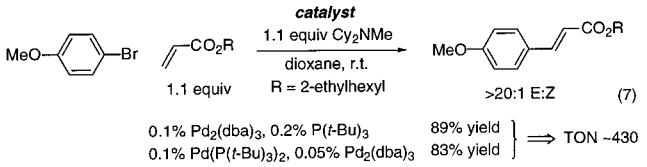
(63) A turnover number of 750 for the Heck coupling of chlorobenzene and *n*-butyl acrylate has been claimed, but this is based on a yield of less than 1.5%: Gruber, A. S.; Zim, D.; Ebeling, G.; Monteiro, A. L.; Dupont, J. *Org. Lett.* **2000**, *2*, 1287−1290.

(64) Buchmeiser, M. R.; Wurst, K. *J. Am. Chem. Soc.* **1999**, *121*, 11101−11107.

(65) An even higher turnover number can be achieved at the expense of lower conversion: with 0.05% Pd$_2$(dba)$_3$/0.2% P(*t*-Bu)$_3$ at 130 °C, we obtain a 53% isolated yield, which corresponds to a TON of 530. In general, it appears that higher reaction temperatures provide higher turnover numbers.

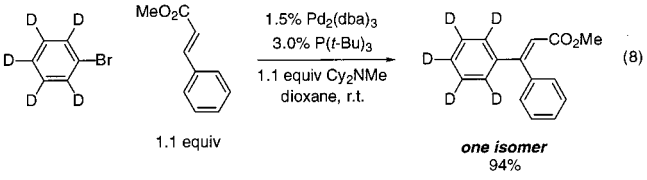
(66) Strem Chemicals (Newburyport, MA), catalog number 46-0252.

We were also interested in determining if a high TON can be achieved in the $Pd_2(dba)_3/P(t\text{-}Bu)_3$-catalyzed Heck reaction of aryl bromides at room temperature. We decided to focus on the coupling of 4-bromoanisole, a deactivated aryl bromide, and 2-ethylhexyl acrylate, which furnishes a cinnamate-derived product that is the most common UV-B sunscreen on the market (eq 7).[8] With 0.1% $Pd_2(dba)_3$ (4.0 mg) and 0.2% $P(t\text{-}Bu)_3$, we obtain an 89% yield (1.1 g) of the desired compound, which corresponds to a turnover number of ~450. For experimental convenience, we have established that a mixture of air-stable $Pd(P(t\text{-}Bu)_3)_2$ and $Pd_2(dba)_3$ provides a catalyst comparable to $Pd_2(dba)_3/P(t\text{-}Bu)_3$ (eq 7; the percentages of Pd and $Pd:P(t\text{-}Bu)_3$ are the same for the two reactions).[68,69]



Kinetic Control of *E*:*Z* Stereoselectivity in Heck Couplings of Methyl *trans*-Cinnamate. Our observation that Heck arylations of methyl *trans*-cinnamate with 4-bromo-*N*,*N*-dimethylaniline (Table 1, entry 9) and 4-chlorobenzonitrile (Table 3, entry 1) exclusively generate the *E*-β,β-diarylacrylate strongly suggests that these processes are under kinetic control, and the data are consistent with a pathway that includes syn olefin insertion and syn β-hydride elimination (Figure 1). By way of contrast, Buchwald has recently shown through a study with C_6D_5Br that the product distribution of Heck reactions using his catalyst, which operates at elevated temperature (85−100 °C), is thermodynamic in origin.[34]

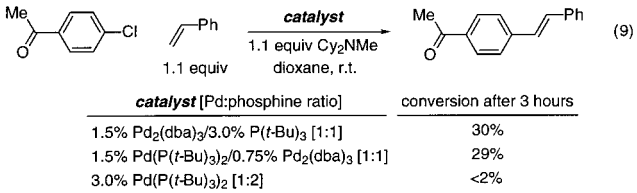
To provide support for our hypothesis that the above arylations catalyzed by $Pd_2(dba)_3/P(t\text{-}Bu)_3/Cy_2NMe$ are under kinetic control, we also coupled C_6D_5Br with methyl *trans*-cinnamate. In contrast to the findings of Buchwald, who obtained a 1:1 mixture of isomeric products, with our room-temperature method the *E* trisubstituted olefin is generated exclusively (eq 8). Interestingly, if we conduct the arylation at 120 °C, we observe a 1:1 mixture of isomers. Thus, through appropriate choice of reaction conditions, we can obtain either the kinetic (room temperature) or the thermodynamic (120 °C) product(s), highlighting an advantage of being able to perform Heck reactions under mild conditions.



Mechanistic Observations on the Heck Coupling of 4′-Chloroacetophenone. An outline of the commonly accepted mechanism for the Heck reaction is illustrated in Figure 1. Although we have not yet had the opportunity to pursue a detailed mechanistic study of couplings catalyzed by $Pd_2(dba)_3/P(t\text{-}Bu)_3/Cy_2NMe$, the preliminary observations that are described below provide some insight into the reaction pathway.

During room-temperature Heck couplings of aryl chlorides, $Pd(P(t\text{-}Bu)_3)_2$ is essentially the only $P(t\text{-}Bu)_3$-containing species that is detected by ^{31}P NMR. Since a 1:1 Pd:phosphine ratio is employed for all room-temperature reactions, half of the palladium is in the form of $Pd(P(t\text{-}Bu)_3)_2$, and the other half is in the form of phosphine-free palladium complexes.

For couplings at room temperature, we have established that changing the Pd:phosphine ratio from 1:1 to 1:2 leads to a marked decrease in the rate of the reaction (eq 9). This suggests that, although $Pd(P(t\text{-}Bu)_3)_2$ is the resting state of the system, it is not the catalytically active species in these Heck couplings. We believe that a palladium monophosphine adduct is the active catalyst and that the presence of phosphine-free palladium complexes leads to a higher concentration of this adduct.[70−74]



To gain insight into which step of the catalytic cycle is turnover-limiting (Figure 1), we undertook a series of reactivity and kinetics studies. For example, we determined the relative rate of arylation of a diverse set of olefins with 4′-chloroacetophenone (Table 4). We discovered that styrene, 1-hexene, *n*-butyl vinyl ether, and methyl methacrylate all react at similar rates, despite their disparate electronic and steric properties (entries 1−4). For most Heck couplings, styrene is considerably more reactive than the other three olefins.[2]

For the arylation of styrene with 4′-chloroacetophenone, a preliminary kinetics study indicates that the reaction rate is first order in aryl chloride and zero order in olefin, which is consistent with oxidative addition being the turnover-limiting step. In the coupling of 4′-chloroacetophenone with methyl crotonate (Table 4, entry 5), it is likely that a step after oxidative addition is turnover-limiting, presumably due to the steric demand of the olefin.

(67) (a) Otsuka, S.; Yoshida, T.; Matsumoto, M.; Nakatsu, K. *J. Am. Chem. Soc.* **1976**, *98*, 5850−5858. (b) Yoshida, T.; Otsuka, S. *J. Am. Chem. Soc.* **1977**, *99*, 2134−2140. (c) Yoshida, T.; Otsuka, S. *Inorg. Synth.* **1990**, *28*, 113−119. This report states that $Pd(P(t\text{-}Bu)_3)_2$ is "stable in air in the solid state". We have observed only slight decomposition after extended (>1 month) exposure to air.

(68) Generally, for $Pd/P(t\text{-}Bu)_3$-catalyzed couplings that proceed at elevated temperature, a 1:2 Pd:phosphine ratio is preferred; for these applications, $Pd(P(t\text{-}Bu)_3)_2$ furnishes a user-friendly, one-component alternative to mixing $Pd_2(dba)_3$ and air-sensitive $P(t\text{-}Bu)_3$. For $Pd/P(t\text{-}Bu)_3$-catalyzed reactions that occur at room temperature, a 1:1 Pd:phosphine ratio is usually preferred; for these processes, a 2:1 mixture of $Pd(P(t\text{-}Bu)_3)_2$:$Pd_2(dba)_3$ (both air-stable) provides the desired Pd:phosphine ratio and avoids the need to handle $P(t\text{-}Bu)_3$.

(69) Even at low catalyst loadings, $Pd/P(t\text{-}Bu)_3$ is not highly sensitive to impurities such as hydroquinone or monomethyl ether hydroquinone, which are present in the 2-ethylhexyl acrylate as inhibitors.

(70) We arrived at the same conclusion as a result of our mechanistic study of the $Pd/P(t\text{-}Bu)_3$-catalyzed Suzuki reaction of aryl chlorides (ref 21a).

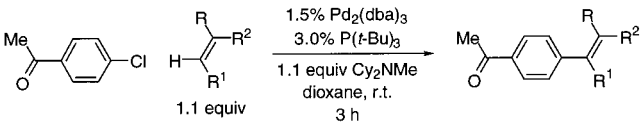
(71) (a) It has been proposed for other Heck catalysts that a palladium monophosphine plays a key role in the catalytic cycle. For example, see: Beller, M.; Riermeier, T. H. *Eur. J. Inorg. Chem.* **1998**, 29−35. van Strijdonck, G. P. F.; Boele, M. D. K.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *Eur. J. Inorg. Chem.* **1999**, 1073−1076. (b) Typically, for Heck reactions of PPh_3-based catalysts, a palladium bisphosphine adduct is invoked (ref 2).

(72) For a study of palladium complexes that contain one $P(t\text{-}Bu)_3$ ligand, see: Krause, J.; Cestaric, G.; Haack, K.-J.; Seevogel, K.; Storm, W.; Pörschke, K.-R. *J. Am. Chem. Soc.* **1999**, *121*, 9807−9823.

(73) For a study of oxidative addition of an aryl bromide to a palladium monophosphine complex, see: Hartwig, J. F.; Paul, F. *J. Am. Chem. Soc.* **1995**, *117*, 5373−5374.

(74) For a study of reductive elimination of aryl halides from palladium phosphine complexes, including $P(t\text{-}Bu)_3$ adducts, see: Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 1232−1233.

Table 4. Effect of Olefin Structure on the Rate of Heck Coupling of 4′-Chloroacetophenone



Entry	Olefin	% Conversion (GC)
1		30
2		39
3		35
4		37
5		16

Mechanistic Observations on the Heck Coupling of 4-Bromoanisole.[75] In contrast to the Heck reaction of styrene and 4′-chloroacetophenone, during the arylation of styrene by 4-bromoanisole, only a small amount of $Pd(P(t\text{-}Bu)_3)_2$ is evident by ^{31}P NMR. The major phosphorus-containing species resonates at $\delta \sim 64$ (broad), accompanied by a minor compound at δ 92.

When we treat $Pd_2(dba)_3/P(t\text{-}Bu)_3$ with a stoichiometric amount of 4-bromoanisole (1:2:2), we also observe a ^{31}P NMR peak at δ 92, and in the ^1H NMR we can identify a set of resonances for a new compound derived from $P(t\text{-}Bu)_3$ and 4-bromoanisole. On the basis of these results, we speculate that the ^{31}P resonance at δ 92 arises from oxidative addition of the aryl bromide to a palladium monophosphine complex. Our initial attempts to isolate and further characterize this adduct have not been successful.

Conclusions

In summary, we have established that a second-generation $Pd/P(t\text{-}Bu)_3$-based catalyst, using Cy_2NMe rather than Cs_2CO_3 as the base, effects Heck reactions of a wide array of aryl chlorides and bromides under exceptionally mild conditions. This new system provides the following:

(i) a versatile method for Heck reactions of aryl and vinyl bromides at room temperature, including couplings of sterically and electronically demanding partners;

(ii) the first examples of Heck reactions of aryl chlorides that proceed at room temperature (electron-poor aryl chlorides);

(iii) the most general method for Heck couplings of unactivated and deactivated aryl chlorides;

(iv) a highly stereoselective route to trisubstituted olefins through reactions of aryl chlorides and bromides with disubstituted olefins; and

(v) the first Heck coupling of an unactivated vinyl chloride.

In view of the well-documented utility of the Heck reaction in synthesis, we anticipate that this active new catalyst will find wide applicability.

Experimental Section

General. 1,4-Dioxane (anhydrous; Sure-Seal; Aldrich), $Pd_2(dba)_3$ (Aldrich), $Pd(P(t\text{-}Bu)_3)_2$ (Strem), $P(t\text{-}Bu)_3$ (Strem), and $P(t\text{-}Bu)_3$ (10 wt % solution in hexane; Sure-Seal; Strem) were used as received. Cy_2NMe (Aldrich) was degassed prior to use. 4-Bromophenyltrifluoromethanesulfonate[76] was prepared from 4-bromophenol, and 1-chloro-4-*tert*-butyl-cyclohexene was prepared according to a literature procedure;[77] all other chlorides and bromides were purchased (Aldrich, Alfa-Aesar, and Lancaster) and degassed prior to use (if liquids) or used as received (if solids). All olefins were purchased from Aldrich. Methyl methacrylate, methyl crotonate, and *n*-butyl vinyl ether were vacuum transferred. Styrene was distilled. 2,3-Dihydrofuran was distilled from calcium hydride. 1-Hexene was distilled from sodium. 2-Methyl-2-propen-1-ol and 2-ethylhexyl acrylate were degassed. Methyl *trans*-cinnamate was used as received.

All GC yields and conversions have been corrected for response factors. *E* or *Z* olefin geometries were assigned on the basis of NOE studies or by analogy with known compounds.

All reactions were assembled under an inert atmosphere either in a screw-cap vial or a resealable Schlenk tube (oven-dried). Because the yields that are reported in the Results and Discussion section are the average of two runs (one with procedure A and one with procedure B), the yields that are reported below for a specific experiment may differ from those values.

Procedure A. In a glovebox, $Pd_2(dba)_3$, the aryl or vinyl halide, Cy_2NMe, a solution of $P(t\text{-}Bu)_3$ in dioxane, dioxane, and the olefin (olefins that are solids were added prior to the addition of the halide) were added in turn to a reaction vessel equipped with a stir bar. The mixture was stirred at the indicated temperature for the indicated amount of time. At the conclusion of the reaction, the mixture was diluted with Et_2O or EtOAc, filtered through a pad of silica gel with copious washings, concentrated, and purified by column chromatography.

For experiments in which an internal standard was used, the internal standard was added prior to the addition of the aryl or vinyl halide.

Procedure B (No Glovebox). $Pd_2(dba)_3$ was added (along with the aryl or vinyl halide and the olefin, if they are solids) to an oven-dried Schlenk tube equipped with a stir bar. The Schlenk tube was fitted with a rubber septum, evacuated, and then refilled with argon. The halide, Cy_2NMe, a solution of $P(t\text{-}Bu)_3$ in dioxane, the olefin, and then dioxane were added via syringe. The septum was replaced with a Teflon stopcock, and the reaction mixture was stirred at the indicated temperature for the indicated amount of time. At the conclusion of the reaction, the mixture was diluted with Et_2O or EtOAc, filtered through a pad of silica gel with copious washings, concentrated, and purified by column chromatography.

1-Butoxyethenyl-4-dimethylaminobenzene and (*E*)- and (*Z*)-(2-Butoxyethenyl)-4-dimethylaminobenzene (Table 1, Entry 1). Procedure B was employed, using 4-dimethylaminobromobenzene (185 mg, 0.926 mmol), *n*-butyl vinyl ether (0.130 mL, 1.00 mmol), Cy_2NMe (0.220 mL, 1.03 mmol), $Pd_2(dba)_3$ (4.3 mg, 0.0047 mmol), $P(t\text{-}Bu)_3$ (0.10 M solution; 0.096 mL, 0.0096 mmol), and dioxane (0.84 mL). After 48 h at room temperature, workup and column chromatography (4% NEt_3/hexanes) yielded 202 mg (99%) of a slightly pale-yellow liquid, which on the basis of ^1H NMR analysis was determined to consist of the terminal olefin and the *E* and *Z* disubstituted olefins in a 13:3:1 ratio.

^1H NMR (C_6D_6, 300 MHz), terminal olefin: δ 7.83 (d, $J = 9.0$ Hz, 2H), 6.58 (d, $J = 9.0$ Hz, 2H), 4.76 (d, $J = 2.4$ Hz, 1H), 4.16 (d, $J = 2.4$ Hz, 1H), 3.72 (t, $J = 6.3$ Hz, 2H), 2.48 (s, 6H), 1.18−1.81 (m, 4H), 0.86 (t, $J = 7.2$ Hz, 3H). ^1H NMR (C_6D_6, 300 MHz), E olefin: δ 7.23 (d, $J = 8.7$ Hz, 2H), 6.99 (d, $J = 12.9$ Hz, 1H), 6.02 (d, $J = 12.9$ Hz, 1H), 3.54 (t, $J = 6.3$ Hz, 2H), 2.54 (s, 6H); other resonances are obscured by the resonances for the terminal olefin and the *Z* olefin. ^1H NMR (C_6D_6, 300 MHz), *Z* olefin: δ 6.70 (d, $J = 9.0$ Hz, 2H), 5.91 (d, $J = 7.2$ Hz, 1H), 5.35 (d, $J = 7.2$ Hz, 1H), 3.51 (t, $J = 6.3$ Hz, 2H), 2.52 (s, 6H); other resonances are obscured by the resonances for the terminal olefin and the *E* olefin. ^{13}C NMR (C_6D_6, 75 MHz), terminal olefin: δ 161.4, 151.2, 127.1, 126.1, 112.5, 79.5, 67.7, 40.5, 32.1, 20.4, 14.6. IR (neat, cm^{-1}): 2933, 1666, 1600, 1520, 1446, 1367, 1279, 947, 819. HRMS (EI, *m/z*): calcd for $C_{14}H_{21}NO$ (M^+), 219.1623; found, 219.1619.

(75) For a recent mechanistic study of a Heck coupling of an aryl bromide, see: Rosner, T.; Bars, J. L.; Pfaltz, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 1848−1855 and references therein.

(76) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478−5486.

(77) Lambert, J. B.; Wang, G.-T.; Finzel, R. B.; Teramura, D. H. *J. Am. Chem. Soc.* **1987**, *109*, 7838−7845.

(*E*)-3-(4-Acetylphenyl)-2-methyl Acrylic Acid Methyl Ester (Table 1, Entry 2). Procedure B was employed, using 4-bromoacetophenone (185 mg, 0.927 mmol), methyl methacrylate (0.200 mL, 1.87 mmol), Cy_2NMe (0.220 mL, 1.03 mmol), $Pd_2(dba)_3$ (4.3 mg, 0.0047 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.095 mL, 0.0095 mmol), and dioxane (0.84 mL). After 26 h at room temperature, workup and column chromatography (30% Et_2O/hexanes) yielded 155 mg (77%) of the title compound as a pale-yellow solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.98 (d, J = 8.4 Hz, 2H), 7.70 (apparent s, 1H), 7.48 (d, J = 8.4 Hz, 2H), 3.84 (s, 3H), 2.62 (s, 3H), 2.13 (d, J = 1.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.5, 168.7, 140.6, 137.7, 136.4, 130.5, 129.8, 128.4, 52.5, 26.9, 14.5. IR (CH_2Cl_2 solution, cm^{-1}): 2951, 1712, 1684, 1603, 1435, 1260, 1120, 737. HRMS (EI, *m*/*z*): calcd for $C_{13}H_{14}O_3$ (M^+), 218.0943; found, 218.0950.

(*E*)-and (*Z*)-3-(4-Hydroxyphenyl)-2-methyl Acrylic Acid Methyl Ester (Table 1, Entry 3) [153773-39-8] [169237-15-4].[41] Procedure B was employed, using 4-bromophenol (157 mg, 0.910 mmol), methyl methacrylate (0.195 mL, 1.82 mmol), Cy_2NMe (0.21 mL, 0.98 mmol), $Pd_2(dba)_3$ (4.2 mg, 0.0046 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.094 mL, 0.0094 mmol), and dioxane (0.82 mL). After 26 h at room temperature, workup and column chromatography (50% Et_2O/hexanes) yielded two sets of fractions: 114 mg (65%) of a white solid which based on ^{1}H NMR analysis was the *E* isomer and 24 mg (14%) of a yellow solid which based on ^{1}H NMR analysis was a 1.1:1 mixture of the *E* and *Z* isomers. Total yield: 79%. Overall *E*:*Z* ratio = 11:1.

^{1}H NMR ($CDCl_3$, 300 MHz), *E* isomer: δ 7.64 (apparent s, 1H), 7.32 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 5.98 (broad s, 1H), 3.82 (s, 3H), 2.13 (d, J = 1.5 Hz, 3H). ^{1}H NMR ($CDCl_3$, 300 MHz), *Z* isomer: δ 7.12 (d, J = 9.0 Hz, 2H), 6.74 (d, J = 9.0 Hz, 2H), 6.65 (apparent s, 1H), 3.69 (s, 3H), 2.07 (s, J = 1.5 Hz, 3H) (cannot detect phenolic hydrogen). ^{13}C NMR ($CDCl_3$, 75 MHz), *E* isomer: δ 170.0, 156.3, 139.3, 131.8, 128.4, 125.8, 115.6, 52.5, 14.4. ^{13}C NMR ($CDCl_3$, 75 MHz), *Z* isomer: δ 170.9, 155.7, 135.3, 129.9, 128.5, 127.4, 115.3, 52.0, 21.8.

(*E*)-3-(4-Dimethylaminophenyl)-2-methyl Acrylic Acid Methyl Ester (Table 1, Entry 4) [50704-04-6].[78] Procedure B was employed, using 4-dimethylaminobromobenzene (191 mg, 0.956 mmol), methyl methacrylate (0.205 mL, 1.92 mmol), Cy_2NMe (0.230 mL, 1.07 mmol), $Pd_2(dba)_3$ (4.4 mg, 0.0048 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.098 mL, 0.0098 mmol), and dioxane (0.86 mL). After 24 h at room temperature, workup and column chromatography (20% Et_2O/hexanes) yielded 210 mg (100%) of the title compound as a yellow solid.

^{1}H NMR ($CDCl_3$, 300 MHz):δ 7.62 (apparent s, 1H), 7.38 (d, J = 9.0 Hz, 2H), 6.70 (d, J = 9.0 Hz, 2H), 3.79 (s, 3H), 3.00 (s, 6H), 2.16 (d, J = 1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.8, 150.3, 139.5, 131.7, 123.7, 123.1, 111.7, 52.0, 40.4, 14.5.

(*E*)-3-(4-Chlorophenyl)-2-methyl Acrylic Acid Methyl Ester (Table 1, Entry 5) [53059-73-7].[79] Procedure B was employed, using 4-bromochlorobenzene (173 mg, 0.905 mmol), methyl methacrylate (0.195 mL, 1.82 mmol), Cy_2NMe (0.21 mL, 0.98 mmol), $Pd_2(dba)_3$ (4.2 mg, 0.0046 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.094 mL, 0.0094 mmol), and dioxane (0.82 mL). After 10 h at room temperature, workup and column chromatography (5% Et_2O/hexanes) yielded 134 mg (70%) of the title compound as a slightly yellow liquid that contained 8% of the terminal olefin (based on NMR).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.63 (m, 1H), 7.37 (d, J = 9.0 Hz, 2H), 7.32 (d, J = 9.0 Hz, 2H), 3.82 (s, 3H), 2.10 (d, J = 1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.9, 137.7, 134.4, 134.3, 131.0, 129.0, 128.8, 52.4, 14.4.

(*E*)-3-(4-Trifluoromethylsulfonylphenyl)-2-methyl Acrylic Acid Methyl Ester (Table 1, Entry 6). Procedure B was employed, using 4-bromophenyltrifluoromethanesulfonate (311 mg, 1.02 mmol), methyl methacrylate (0.220 mL, 2.06 mmol), Cy_2NMe (0.240 mL, 1.12 mmol), $Pd_2(dba)_3$ (4.7 mg, 0.0051 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.10 mL, 0.010 mmol), and dioxane (0.92 mL). After 19 h at room temperature, workup and column chromatography (20% Et_2O/hexanes) yielded 210 mg (63%) of the title compound as a yellow liquid that contained 7% of the terminal olefin (based on NMR).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.65 (apparent s, 1H), 7.45 (d, J = 9.0 Hz, 2H), 7.30 (d, J = 9.0 Hz, 2H), 3.83 (s, 3H), 2.10 (d, J = 1.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.6, 149.0, 136.7, 136.3, 131.4, 130.2, 121.5, 118.8 (q, J = 318 Hz), 52.5, 14.3. IR (neat, cm^{-1}): 2955, 1718, 1640, 1596, 1426, 1213. 1141, 888. HRMS (EI, *m*/*z*): calcd for $C_{12}H_{11}F_3O_5S$ (M^+), 324.0279; found, 324.0271.

(*E*)-3-(2-Methylphenyl)-2-methyl Acrylic Acid Methyl Ester (Table 1, Entry 7). Procedure B was employed, using 2-bromotoluene (0.150 mL, 1.25 mmol), methyl methacrylate (0.270 mL, 2.52 mmol), Cy_2NMe (0.290 mL, 1.35 mmol), $Pd_2(dba)_3$ (5.7 mg, 0.0062 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.12 mL, 0.012 mmol), and dioxane (1.10 mL). After 69 h at room temperature, workup and column chromatography (5% Et_2O/hexanes) yielded 205 mg (86%) of the title compound as a slightly yellow liquid that contained 5% of the terminal olefin (based on NMR).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.74 (apparent s, 1H), 7.18−7.23 (m, 4H), 3.82 (s, 3H), 2.28 (s, 3H), 1.96 (d, J = 1.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.0, 138.5, 137.0, 135.2, 130.2, 129.1, 128.9, 128.3, 125.6, 52.3, 20.2, 14.3. IR (neat, cm^{-1}): 2950, 1714, 1637, 1435, 1257, 1120, 758, 742. HRMS (EI, *m*/*z*): calcd for $C_{12}H_{14}O_2$ (M^+), 190.0994; found, 190.0991.

2-(2,6-Dimethylphenylbenzyl)acrylic Acid Methyl Ester and (*E*)-3-(2,6-Dimethylphenyl)-2-methyl Acrylic Acid Methyl Ester (Table 1, Entry 8). Procedure B was employed, using 2-bromo-*m*-xylene (0.140 mL, 1.05 mmol), methyl methacrylate (0.125 mL, 1.17 mmol), Cy_2NMe (0.250 mL, 1.17 mmol), $Pd_2(dba)_3$ (4.9 mg, 0.0054 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.11 mL, 0.011 mmol), and dioxane (0.94 mL). After 12 h at room temperature, workup and column chromatography (5% Et_2O/hexanes) yielded 208 mg (97%) of a colorless liquid that was an 8:1 mixture of 2-(2,6-dimethylphenylbenzyl)acrylic acid methyl ester and (*E*)-3-(2,6-dimethylphenyl)-2-methyl acrylic acid methyl ester (based on NMR).

^{1}H NMR ($CDCl_3$, 300 MHz), 2-(2,6-dimethylphenylbenzyl)acrylic acid methyl ester: δ 7.01−7.15 (m, 3H), 6.12 (dt, J = 3.3, 1.5 Hz, 1H), 4.92 (dt, J = 3.6, 1.5 Hz, 1H), 3.83 (s, 3H), 3.62 (apparent triplet, 2H), 2.21 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.8, 137.8, 137.1, 135.0, 128.1, 126.6, 124.4, 52.2, 31.5, 20.0. IR (neat, cm^{-1}): 3067, 3020, 2950, 1720, 1631, 1436, 1279, 1255, 1135, 770. HRMS (EI, *m*/*z*): calcd for $C_{13}H_{16}O_2$, 204.1150 (M^+); found, 204.1154. The ^{1}H and ^{13}C NMR spectra for the minor component, (*E*)-2-methyl-3-(2,6-dimethylphenyl)acrylic acid methyl ester, were the same as those reported in Table 3, entry 6.

(*E*)-3-(4-Dimethyaminophenyl)-3-phenyl Acrylic Acid Methyl Ester (Table 1, Entry 9) [255054-06-9].[34] Procedure B was employed, using 4-dimethylaminobromobenzene (196 mg, 0.978 mmol), methyl *trans*-cinnamate (172 mg, 1.06 mmol), Cy_2NMe (0.230 mL, 1.07 mmol), $Pd_2(dba)_3$ (9.1 mg, 0.010 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.20 mL, 0.020 mmol), and dioxane (0.78 mL). After 72 h at room temperature, workup and column chromatography (70% CH_2Cl_2/hexanes → 85% CH_2Cl_2/hexanes) yielded 200 mg (73%) of the title compound as a yellow solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36−7.41 (m, 3H), 7.18−7.22 (m, 4H), 6.61 (d, J = 9.3 Hz, 2H), 6.30 (s, 1H), 3.58 (s, 3H), 2.98 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.9, 157.7, 151.3, 139.6, 129.6, 129.1, 127.8, 127.7, 111.8, 111.5, 51.2, 40.4.

(*E*)-3-(4-Dimethylaminophenyl)-3-methyl Acrylic Acid Methyl Ester (Table 1, Entry 10). Procedure B was employed, using 4-dimethylaminobromobenzene (186 mg, 0.929 mmol), methyl crotonate (0.200 mL, 1.88 mmol), Cy_2NMe (0.220 mL, 1.03 mmol), $Pd_2(dba)_3$ (8.6 mg, 0.0094 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.19 mL, 0.019 mmol), and dioxane (0.74 mL). After 23 h at room temperature, workup and column chromatography (20% Et_2O/hexanes) yielded 134 mg (66%) of the title compound as a yellow solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.44 (d, J = 9.0 Hz, 2H), 6.67 (d, J = 9.0 Hz, 2H), 6.11 (q, J = 1.5 Hz, 1H), 3.73 (s, 3H), 2.99 (s, 6H), 2.57 (d, J = 1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.9, 155.8, 151.2, 128.9, 127.5, 112.4, 111.8, 51.2, 40.5, 17.5. IR (CH_2Cl_2 solution, cm^{-1}): 3052, 2947, 1707, 1599, 1438, 1349, 1266, 1159, 817. HRMS (EI, *m*/*z*): calcd for $C_{13}H_{17}O_2N$ (M^+), 219.1259; found, 219.1265.

(*E*)-3-(2,6-Dimethylphenyl)-3-methyl Acrylic Acid Methyl Ester (Table 1, Entry 11). Procedure B was employed, using 2-bromo-*m*-

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xylene (0.115 mL, 0.863 mmol), methyl crotonate (0.100 mL, 0.943 mmol), Cy_2NMe (0.200 mL, 0.934 mmol), $Pd_2(dba)_3$ (11.9 mg, 0.013 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.26 mL, 0.026 mmol), and dioxane (0.60 mL). After 49 h at room temperature, workup and column chromatography (5% Et_2O/hexanes) yielded 150 mg (85%) of the title compound as a clear, colorless liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.01−7.12 (m, 3H), 5.70 (q, J = 1.5 Hz, 1H), 3.76 (s, 3H), 2.39 (d, J = 1.5 Hz, 3H), 2.20 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.1, 158.4, 143.2, 133.7, 127.6, 127.2, 119.2, 51.3, 20.3, 19.9. IR (neat, cm^{-1}): 3062, 3017, 2949, 2922, 1719, 1643, 1434, 1265, 1170, 1036, 771. HRMS (EI, *m*/*z*): calcd for $C_{13}H_{16}O_2$ (M^+), 204.1145; found, 204.1144.

(*E*,*Z*)- and (*E*,*E*)-3-Methyl-1-phenylpenta-1,3-diene (Table 1, Entry 12) [104722-44-3] [20414-99-7].[80] Procedure B was employed, using 2-bromo-*trans*-2-butene (0.0800 mL, 0.789 mmol), styrene (0.100 mL, 0.873 mmol), Cy_2NMe (0.190 mL, 0.887 mmol), $Pd_2(dba)_3$ (11.1 mg, 0.012 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.25 mL, 0.025 mmol), and dioxane (0.54 mL). After 77 h at room temperature, workup and column chromatography (pentane) yielded 116 mg (93%) of the title compound as a yellow liquid, which by ^{1}H NMR analysis consisted of an 8:1 mixture of the (*E*,*Z*) and (*E*,*E*) isomers.

^{1}H NMR ($CDCl_3$, 300 MHz), (*E*,*Z*) isomer: δ 7.42−7.47 (m, 2H), 7.28−7.35 (m, 2H), 7.18−7.26 (m, 2H), 6.55 (d, J = 16.2 Hz, 1H), 5.54 (qq, J = 7.2, 1.5 Hz, 1H), 1.93 (apparent quintet, 3H), 1.82−1.87 (m, 3H). ^{1}H NMR ($CDCl_3$, 300 MHz), (*E*,*E*) isomer: δ 6.81 (d, J = 15.9 Hz, 1H), 6.44 (d, J = 15.9 Hz, 1H), 5.67−5.75 (m, 1H), 1.77−1.81 (m, 3H); other resonances are obscured by the major (*E*,*Z*) isomer. ^{13}C NMR ($CDCl_3$, 75 MHz), (*E*,*Z*) isomer: δ 138.1, 132.9, 128.7, 128.1, 127.3, 126.5, 126.2, 125.9, 20.8, 13.6.

***trans*-4-Acetylstilbene (Table 2, Entry 1) [20488-42-0].**[81] Procedure B was employed, using 4′-chloroacetophenone (0.115 mL, 0.887 mmol), styrene (0.110 mL, 0.960 mmol), Cy_2NMe (0.210 mL, 0.980 mmol), $Pd_2(dba)_3$ (12.3 mg, 0.013 mmol), P(*t*-Bu)$_3$ (10 wt % solution in hexane; 0.080 mL, 0.029 mmol), and dioxane (0.80 mL). After 32 h at room temperature, workup and column chromatography (15% Et_2O/hexanes) yielded 149 mg (76%) of the title compound as a pale-yellow solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.94 (d, J = 8.7 Hz, 2H), 7.57 (d, J = 8.7 Hz, 2H), 7.53 (d, J = 7.2 Hz, 2H), 7.24−7.40 (m, 3H), 7.22 (d, J = 16.5 Hz, 1H), 7.11 (d, J = 16.5 Hz, 1H), 2.60 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.5, 142.1, 136.8, 136.0, 131.5, 129.0, 128.9, 128.4, 127.5, 126.9, 126.6, 26.9.

(*E*)- and (*Z*)-1-[4-(Hex-1-enyl)phenyl]ethanone (Table 2, Entry 2) [137365-00-5].[82] Procedure B was employed, using 4′-chloroacetophenone (0.125 mL, 0.964 mmol), 1-hexene (0.135 mL, 1.08 mmol), Cy_2NMe (0.230 mL, 1.07 mmol), $Pd_2(dba)_3$ (13.4 mg, 0.015 mmol), P(*t*-Bu)$_3$ (0.15 M stock solution; 0.20 mL, 0.030 mmol), and dioxane (0.76 mL). After 47 h at room temperature, workup and column chromatography (8% Et_2O/hexanes) yielded 136 mg (70%) of a slightly pale-yellow liquid.

^{1}H NMR ($CDCl_3$, 300 MHz), *E* isomer: δ 7.88 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 6.37−6.45 (m, 2H), 2.58 (s, 3H), 2.19−2.28 (m, 2H), 1.30−1.60 (m, 4H), 0.90−1.00 (m, 3H). ^{1}H NMR ($CDCl_3$, 300 MHz), *Z* isomer: δ 7.45 (d, J = 8.7 Hz, 2H), 5.85−5.98 (m, 2H), 2.59 (s, 3H); other resonances for the *Z* isomer are obscured by the resonances for the *E* isomer. ^{13}C NMR ($CDCl_3$, 75 MHz), *E* isomer: δ 197.6, 142.8, 135.4, 134.6, 129.0, 128.8, 126.0, 33.1, 31.5, 26.8, 22.6, 14.2. IR (neat, cm^{-1}): 2958, 2927, 1682, 1602, 1357, 1267, 1181, 856. HRMS (EI, *m*/*z*): calcd for $C_{14}H_{18}O$ (M^+), 202.1358; found, 202.1361. The *E*:*Z* ratio was determined by GC.

(*E*)- and (*Z*)-(2-Butoxyethenyl)-4-acetylbenzene and 1-Butoxyethenyl-4-acetylbenzene (Table 2, Entry 3) [153390-96-6] [153390-95-5].[83] Procedure B was employed, using 4′-chloroacetophenone (0.110 mL, 0.848 mmol), *n*-butyl vinyl ether (0.120 mL, 0.927 mmol), Cy_2NMe (0.200 mL, 0.934 mmol), $Pd_2(dba)_3$ (11.6 mg, 0.013 mmol), P(*t*-Bu)$_3$ (0.15 M stock solution; 0.17 mL, 0.025 mmol), and dioxane (0.68 mL). After 33 h at room temperature, workup and column chromatography (7% NEt_3/hexanes) yielded 155 mg (84%) of a yellow liquid that was comprised of a mixture of the *E*, *Z*, and terminal olefin isomers in a ratio of 8.2:1.6:1.0 (according to ^{1}H NMR). The olefin mixture was contaminated with 4% of 4′-chloroacetophenone (by ^{1}H NMR).

^{1}H NMR (C_6D_6, 300 MHz), *E* isomer: δ 7.80 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 12.9 Hz, 1H), 5.75 (d, J = 12.9 Hz, 1H), 3.44 (t, J = 6.3 Hz, 2H), 2.15 (s, 3H), 1.16−1.50 (m, 4H), 0.81 (t, J = 7.2 Hz, 3H). ^{1}H NMR (C_6D_6, 300 MHz), *Z* isomer: δ 7.90 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 5.88 (d, J = 7.2 Hz, 1H), 5.15 (d, J = 7.2 Hz, 1H), 2.12 (s, 3H). Other resonances are obscured by the resonances for the *E* and terminal olefins. Terminal olefin: 4.70 (d, J = 2.7 Hz, 1H), 4.16 (d, J = 2.7 Hz, 1H), 3.56 (t, J = 6.6 Hz, 2H), 2.09 (s, 3H). Other resonances are obscured by the resonances for the *E* and *Z* isomers. ^{13}C NMR (C_6D_6, 75 MHz), *E* isomer: δ 196.0, 150.9, 142.3, 135.3, 129.6, 125.3, 105.7, 70.3, 32.0, 26.6, 19.9, 14.4.

(*E*)-3-(4-Acetylphenyl)-2-methyl Acrylic Acid Methyl Ester (Table 2, Entry 4). Procedure B was employed, using 4′-chloroacetophenone (0.180 mL, 1.39 mmol), methyl methacrylate (0.165 mL, 1.54 mmol), Cy_2NMe (0.330 mL, 1.54 mmol), $Pd_2(dba)_3$ (19.0 mg, 0.021 mmol), P(*t*-Bu)$_3$ (0.15 M stock solution; 0.28 mL, 0.042 mmol), and dioxane (1.10 mL). After 36 h at room temperature, workup and column chromatography (30% Et_2O/hexanes) yielded 240 mg (79%) of the title compound as a slightly yellow solid. Spectral data were the same as those reported in Table 1, entry 2.

(*E*)-3-(2-Carbomethoxyphenyl)-2-methyl Acrylic Acid Methyl Ester (Table 2, Entry 5). Procedure B was employed, using methyl 2-chlorobenzoate (0.125 mL, 0.873 mmol), methyl methacrylate (0.105 mL, 0.982 mmol), Cy_2NMe (0.21 mL, 0.980 mmol), $Pd_2(dba)_3$ (12.0 mg, 0.013 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.26 mL, 0.026 mmol), and dioxane (0.62 mL). After 24 h at room temperature, workup and column chromatography (25% Et_2O/hexanes) yielded 186 mg (91%) of the title compound as a clear yellow liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.11 (apparent s, 1H), 8.04 (dd, J = 7.8, 1.2 Hz, 1H), 7.52−7.57 (m, 1H), 7.37−7.43 (m, 1H), 7.27−7.30 (m, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 1.91 (d, J = 1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.8, 166.9, 139.8, 137.9, 132.1, 130.8, 130.3, 129.1, 128.0, 127.9, 52.4, 52.3, 14.1. IR (neat, cm^{-1}): 3065, 2994, 2951, 1715, 1639, 1598, 1434, 1270, 1203, 1080, 763. HRMS (EI, *m*/*z*): calcd for $C_{13}H_{14}O_4$ (M^+), 234.0887; found, 234.0879.

3-(4-Cyanophenyl)-2-methylpropanal (Table 2, Entry 6) [57918-88-4].[84] Procedure B was employed, using 4-chlorobenzonitrile (142 mg, 1.03 mmol), 2-methyl-2-propen-1-ol (0.0950 mL, 1.13 mmol), Cy_2NMe (0.240 mL, 1.12 mmol), $Pd_2(dba)_3$ (14.3 mg, 0.016 mmol), P(*t*-Bu)$_3$ (10 wt % solution in hexane; 0.090 mL, 0.033 mmol), and dioxane (0.94 mL). After 48 h at room temperature, workup and column chromatography (50% Et_2O/hexanes) yielded 127 mg (71%) of the title compound as a clear, slightly yellow liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.70 (d, J = 1.2 Hz, 1H), 7.58 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 3.10−3.21 (m, 1H), 2.62−2.79 (m, 2H), 1.12 (d, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 203.2, 144.8, 132.4, 129.9, 118.9, 110.4, 47.8, 36.6, 13.6.

2-(4-Acetylphenyl)-2,3-dihydrofuran (Table 2, Entry 7) [131516-06-8].[57] Procedure B was employed, using 4′-chloroacetophenone (0.145 mL, 1.12 mmol), 2,3-dihydrofuran (0.250 mL, 3.31 mmol), Cy_2NMe (0.260 mL, 1.21 mmol), $Pd_2(dba)_3$ (5.1 mg, 0.0060 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.115 mL, 0.012 mmol), and dioxane (1.00 mL). After 24 h at room temperature, workup and column chromatography (20% Et_2O/hexanes) yielded 144 mg (68%) of the title compound as a pale-yellow liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.95 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 6.46 (q, J = 2.4 Hz, 1H), 5.56 (dd, J = 8.4, 11.1 Hz, 1H), 4.96 (q, J = 2.7 Hz, 1H), 3.14 (ddt, J = 15.3, 10.8, 2.4 Hz, 1H), 2.60 (s, 3H), 2.57 (ddt, J = 15.3, 8.1, 2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.7, 148.5, 145.4, 136.5, 128.8, 125.7, 99.2, 81.7, 38.2, 26.9.

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2-(4-Trifluoromethylphenyl)-2,3-dihydrofuran (Table 2, Entry 8). Procedure B was employed, using 4-chlorobenzotrifluoride (0.130 mL, 0.974 mmol), 2,3-dihydrofuran (0.220 mL, 2.91 mmol), Cy_2NMe (0.230 mL, 1.07 mmol), $Pd_2(dba)_3$ (13.3 mg, 0.014 mmol), P(*t*-Bu)$_3$ (0.15 M stock solution; 0.20 mL, 0.030 mmol), and dioxane (0.78 mL). After 26 h at room temperature, workup and column chromatography (2% Et_2O/hexanes) yielded 163 mg (78%) of the title compound as a clear, colorless liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.61 (d, J = 7.8 Hz, 2H), 7.46 (d, J = 7.8 Hz, 2H), 6.46 (q, J = 2.7 Hz, 1H), 5.56 (dd, J = 10.8, 8.1 Hz, 1H), 4.96 (q, J = 2.7 Hz, 1H), 3.14 (ddt, J = 15.6, 10.5, 2.4 Hz, 1H), 2.56 (ddt, J = 15.6, 7.8, 2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 147.2, 145.4, 130.1, 129.7, 125.9, 125.6, 99.2, 81.6, 38.2. IR (neat, cm^{-1}): 3106, 2936, 2864, 1619, 1418, 1326, 1125, 843. HRMS (EI, *m*/*z*): calcd for $C_{11}H_9F_3O$ (M^+), 214.0600; found, 214.0604.

2-(2-Carbomethoxythiophene)-2,3-dihydrofuran (Table 2, Entry 9). Procedure B was employed, using 2-carbomethoxy-3-chlorothiophene (167 mg, 0.946 mmol), 2,3-dihydrofuran (0.215 mL, 2.84 mmol), Cy_2NMe (0.220 mL, 1.03 mmol), $Pd_2(dba)_3$ (13.2 mg, 0.014 mmol), P(*t*-Bu)$_3$ (0.15 M stock solution; 0.20 mL, 0.030 mmol), and dioxane (0.76 mL). After 23 h at room temperature, workup and column chromatography (7% Et_2O/hexanes) yielded 172 mg (86%) of the title compound as a clear, colorless liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.44 (d, J = 5.1 Hz, 1H), 7.18 (d, J = 5.1 Hz, 1H), 6.45 (q, J = 2.7 Hz, 1H), 6.23 (dd, J = 10.8, 7.5 Hz, 1H), 4.94 (q, J = 2.7 Hz, 1H), 3.87 (s, 3H), 3.26 (ddt, J = 15.3, 10.8, 2.7 Hz, 1H), 2.41 (ddt, J = 15.3, 7.5, 2.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.6, 152.8, 145.1, 131.0, 127.4, 125.5, 99.5, 78.2, 52.2, 37.7. IR (cm^{-1}): 3104, 2994, 2950, 1711, 1620, 1532, 1436, 1256, 778. HRMS (EI, *m*/*z*): calcd for $C_{10}H_{10}O_3S$ (M^+), 210.0351; found, 210.0354.

(*E*)-3-(4-Cyanophenyl)-3-methyl Acrylic Acid Methyl Ester (Table 2, Entry 10) [255054-11-6].[34] Procedure B was employed, using 4-chlorobenzonitrile (115 mg, 0.838 mmol), methyl crotonate (0.180 mL, 1.70 mmol), Cy_2NMe (0.200 mL, 0.934 mmol), $Pd_2(dba)_3$ (11.8 mg, 0.013 mmol), P(*t*-Bu)$_3$ (0.15 M stock solution; 0.18 mL, 0.026 mmol), and dioxane (0.66 mL). After 60 h at room temperature, workup and column chromatography (25% Et_2O/hexanes) yielded 88.4 mg (52%) of the title compound as a pale-yellow solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.67 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 6.15 (q, J = 1.2 Hz, 1H), 3.77 (s, 3H), 2.57 (d, J = 1.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.6, 153.5, 146.6, 132.5, 127.1, 119.3, 118.6, 112.6, 51.6, 18.1.

(*E*)-3-(4-Cyanophenyl)-3-phenyl Acrylic Acid Methyl Ester (Table 3, Entry 1). Procedure B was employed, using 4-chlorobenzonitrile (140 mg, 1.01 mmol), methyl *trans*-cinnamate (186 mg, 1.15 mmol), Cy_2NMe (0.240 mL, 1.12 mmol), $Pd_2(dba)_3$ (14.0 mg, 0.015 mmol), P(*t*-Bu)$_3$ (0.15 M stock solution; 0.25 mL, 0.037 mmol), and dioxane (0.76 mL). After 70 h at 70 °C, workup and column chromatography (30% Et_2O/hexanes) yielded 190 mg (71%) of the title compound as a pale-yellow solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.61 (d, J = 8.1 Hz, 2H), 7.36−7.43 (m, 5H), 7.15−7.20 (m, 2H), 6.39 (s, 1H), 3.63 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.9, 154.7, 145.3, 137.6, 132.3, 129.1, 129.0, 128.9, 128.3, 119.6, 118.6, 113.0, 51.8. IR (CH_2Cl_2 solution, cm^{-1}): 3056, 2950, 2229, 1725, 1622, 1434, 1265, 1169, 841, 738. HRMS (EI, *m*/*z*): calcd for $C_{17}H_{13}O_2N$ (M^+), 263.0941; found, 263.0930.

***trans*-4-Methoxystilbene (Table 3, Entry 2).** Procedure B was employed, using 4-chloroanisole (0.145 mL, 1.18 mmol), styrene (0.150 mL, 1.31 mmol), Cy_2NMe (0.280 mL, 1.31 mmol), $Pd_2(dba)_3$ (16.2 mg, 0.018 mmol), P(*t*-Bu)$_3$ (0.15 M stock solution; 0.49 mL, 0.073 mmol), and dioxane (0.70 mL). After 26 h at 120 °C, workup and column chromatography (1% Et_2O/hexanes) yielded 171 mg (69%) of the title compound as a white solid that was identical to authentic material (Alfa-Aesar) by GC, TLC, and ^{1}H NMR.

(*E*)-3-Phenyl-2-methyl Acrylic Acid Methyl Ester (Table 3, Entry 3) [22946-43-6].[85] Procedure B was employed, using chlorobenzene (0.105 mL, 1.03 mmol), methyl methacrylate (0.120 mL, 1.12 mmol), Cy_2NMe (0.245 mL, 1.14 mmol), $Pd_2(dba)_3$ (14.1 mg, 0.015 mmol), P(*t*-Bu)$_3$ (0.14 M stock solution; 0.43 mL, 0.060 mmol), and dioxane (0.60 mL). After 60 h at 100 °C, workup and column chromatography (5% Et_2O/hexanes) yielded 158 mg (87%) of the title compound as a slightly red solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.70 (q, J = 1.5 Hz, 1H), 7.29−7.40 (m, 5H), 3.82 (s, 3H), 2.12 (d, J = 1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.2, 139.0, 135.9, 129.7, 128.4, 128.4, 128.3, 52.3, 14.3.

(*E*)-3-(4-Methoxyphenyl)-2-methyl Acrylic Acid Methyl Ester (Table 3, Entry 4) [126356-04-5].[86] Procedure B was employed, using 4-chloroanisole (0.110 mL, 0.898 mmol), methyl methacrylate (0.105 mL, 0.982 mmol), Cy_2NMe (0.210 mL, 0.980 mmol), $Pd_2(dba)_3$ (12.2 mg, 0.013 mmol), P(*t*-Bu)$_3$ (0.14 M stock solution; 0.37 mL, 0.052 mmol), and dioxane (0.52 mL). After 53 h at 120 °C, workup and column chromatography (20% Et_2O/hexanes) yielded 123 mg (66%) of the title compound as a clear, yellow liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.64 (apparent s, 1H), 7.38 (d, J = 9.0 Hz, 2H), 6.92 (d, J = 9.0 Hz, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 2.13 (d, J = 1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.5, 159.7, 138.8, 131.5, 128.5, 126.1, 114.0, 55.5, 52.2, 14.4.

(*E*)-3-(2-Methylphenyl)-2-methyl Acrylic Acid Methyl Ester (Table 3, Entry 5). Procedure B was employed, using 2-chlorotoluene (0.110 mL, 0.941 mmol), methyl methacrylate (0.110 mL, 1.03 mmol), Cy_2NMe (0.220 mL, 1.03 mmol), $Pd_2(dba)_3$ (12.9 mg, 0.014 mmol), P(*t*-Bu)$_3$ (0.15 M stock solution; 0.38 mL, 0.057 mmol), and dioxane (0.56 mL). After 24 h at 110 °C, workup and column chromatography (5% Et_2O/hexanes) yielded 158 mg (88%) of the title compound as a clear, colorless liquid. Spectral data were the same as those reported in Table 1, entry 7.

(*E*)-3-(2,6-Dimethylphenyl)-2-methyl Acrylic Acid Methyl Ester (Table 3, Entry 6) [124317-09-5].[87] Procedure B was employed, using 2-chloro-*m*-xylene (0.120 mL, 0.905 mmol), methyl methacrylate (0.110 mL, 1.03 mmol), Cy_2NMe (0.210 mL, 0.980 mmol), $Pd_2(dba)_3$ (12.3 mg, 0.013 mmol), P(*t*-Bu)$_3$ (0.15 M stock solution; 0.36 mL, 0.054 mmol), and dioxane (0.54 mL). After 39 h at 120 °C, workup and column chromatography (5% Et_2O/hexanes) yielded 134 mg (72%) of the title compound as a clear, colorless liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.62 (apparent s, 1H), 7.03−7.15 (m, 3H), 3.83 (s, 3H), 2.16 (s, 6H), 1.68 (d, J = 1.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.4, 139.2, 135.5, 135.2, 130.5, 127.5, 127.4, 52.2, 20.4, 14.1.

(*E*)-3-(3-Pyridyl)-2-methyl Acrylic Acid Methyl Ester (Table 3, Entry 7). Procedure B was employed, using 3-chloropyridine (0.0950 mL, 0.999 mmol), methyl methacrylate (0.120 mL, 1.12 mmol), Cy_2NMe (0.240 mL, 1.12 mmol), $Pd_2(dba)_3$ (13.6 mg, 0.015 mmol), P(*t*-Bu)$_3$ (0.15 M stock solution; 0.41 mL, 0.061 mmol), and dioxane (0.58 mL). After 26 h at 100 °C, workup and column chromatography (60% Et_2O/hexanes) yielded 140 mg (79%) of the title compound as a clear, yellow liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.65 (apparent s, 1H), 8.55−8.56 (m, 1H), 7.71 (apparent dt, 1H), 7.64 (s, 1H), 7.32−7.36 (m, 1H), 3.84 (s, 3H), 2.13 (d, J = 1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.5, 150.6, 149.1, 136.5, 135.2, 131.8, 130.7, 123.4, 52.5, 14.4. IR (neat, cm^{-1}): 3027, 2994, 2951, 1709, 1638, 1566, 1435, 1260, 1192, 1118, 1024, 800. HRMS (EI, *m*/*z*): calcd for $C_{10}H_{11}O_2N$ (M^+), 177.0790; found, 177.0787.

(*E*)-3-Phenyl-3-methyl Acrylic Acid Methyl Ester (Table 3, Entry 8) [3461-50-5].[85] Procedure B was employed, using chlorobenzene (0.100 mL, 0.983 mmol), methyl crotonate (0.210 mL, 1.98 mmol), Cy_2NMe (0.230 mL, 1.07 mmol), $Pd_2(dba)_3$ (13.8 mg, 0.015 mmol), P(*t*-Bu)$_3$ (0.14 M stock solution; 0.42 mL, 0.059 mmol), and dioxane (0.56 mL). After 49 h at 120 °C, workup and column chromatography (5% Et_2O/hexanes) yielded 86.7 mg (50%) of the title compound as a slightly pale-yellow liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.44−7.49 (m, 2H), 7.34−7.39 (m, 3H), 6.13 (q, J = 1.5 Hz, 1H), 3.75 (s, 3H), 2.58 (d, J = 1.5 Hz, 3H).

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^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.3, 156.0, 142.2, 129.2, 128.6, 126.4, 116.8, 51.4, 18.3.

2-(4-*tert*-Butyl-1-cyclohexenyl)styrene (Eq 4) [96575-67-6].[88] Procedure B was employed, using 1-chloro-4-*tert*-butyl-cyclohexene (202 mg, 1.17 mmol), styrene (0.145 mL, 1.26 mmol), Cy_2NMe (0.280 mL, 1.31 mmol), $Pd_2(dba)_3$ (16.5 mg, 0.018 mmol), P(*t*-Bu)$_3$ (0.15 M stock solution; 0.50 mL, 0.075 mmol), and dioxane (0.66 mL). After 46 h at 110 °C, workup and column chromatography (hexanes) yielded 188 mg (67%) of the title compound as a white solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.38−7.40 (m, 2H), 7.24−7.31 (m, 2H), 7.14−7.20 (m, 1H), 6.78 (d, J = 16.2 Hz, 1H), 6.41 (d, J = 16.2 Hz, 1H), 5.88−5.90 (m, 1H), 2.43−2.50 (m, 1H), 2.10−2.30 (m, 2H), 1.88−2.04 (m, 2H), 1.14−1.38 (m, 2H), 0.89 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.1, 135.8, 132.2, 131.2, 128.6, 126.9, 126.2, 124.9, 44.5, 32.5, 28.0, 27.5, 26.2, 24.1.

Competition Experiment between an Aryl Chloride and a Vinyl Chloride (Eq 5). Procedure A was employed, using chlorobenzene (0.0750 mL, 0.738 mmol), 1-chloro-4-*tert*-butylcyclohexene (125 mg, 0.723 mmol), styrene (0.0850 mL, 0.742 mmol), Cy_2NMe (0.170 mL, 0.794 mmol), $Pd_2(dba)_3$ (10.0 mg, 0.011 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.43 mL, 0.043 mmol), and dioxane (0.30 mL). After 26 h at 110 °C, workup and column chromatography (hexanes) yielded 76.6 mg (58%) of a white solid that consisted of a 37:1 mixture of stilbene:diene and 68.1 mg (39%) of a white solid that consisted of a 32:1 mixture of diene:stilbene (ratios determined by ^{1}H NMR). The "diene" includes ~10% of an isomer of the expected diene in which both double bonds are part of the six-membered ring.

Heck Coupling of Chlorobenzene with Methyl Methacrylate at Low Catalyst Loading (Eq 6; Typical Procedure). $Pd(P(t\text{-}Bu)_3)_2$ (3.1 mg, 0.0060 mmol) was added to an oven-dried Schlenk tube equipped with a stir bar. A rubber septum was then attached to the reaction vessel, which was evacuated and refilled with argon. Next, chlorobenzene (0.310 mL, 3.05 mmol), Cy_2NMe (0.720 mL, 3.36 mmol), methyl methacrylate (0.360 mL, 3.37 mmol), and dioxane (1.50 mL) were added successively via syringe through the rubber septum. The rubber septum was removed, and the Schlenk tube was sealed with a Teflon stopcock. After the mixture was stirred for 48 h at 120 °C, workup and column chromatography (5% Et_2O/hexanes) yielded 339 mg (63%) of the title compound as a colorless liquid that solidified on standing. Spectral data were the same as those reported in Table 3, entry 3.

Room-Temperature Heck Coupling of 4-Bromoanisole with 2-Ethylhexyl Acrylate Catalyzed at Low Catalyst Loading (Eq 7; Typical Procedure). $Pd(P(t\text{-}Bu)_3)_2$ (3.2 mg, 0.0060 mmol) and $Pd_2(dba)_3$ (3.0 mg, 0.0030 mmol) were added to an oven-dried Schlenk tube equipped with a stir bar. A rubber septum was then attached to the reaction vessel, which was evacuated and refilled with argon. Next, 4-bromoanisole (0.800 mL, 6.39 mmol), Cy_2NMe (1.50 mL, 7.00 mmol), 2-ethylhexyl acrylate (1.45 mL, 6.96 mmol), and dioxane (2.05 mL) were added successively via syringe through the rubber septum. The rubber septum was removed, and the Schlenk tube was sealed with a Teflon stopcock. After the mixture was stirred for 148 h at room temperature, workup and column chromatography (15% Et_2O/hexanes) yielded 1.54 g (83%) of the title compound as a colorless liquid that was identical to authentic material (Aldrich) by GC, TLC, and ^{1}H NMR.

Heck Coupling of Bromobenzene-d_5 with Methyl *trans*-Cinnamate at Room Temperature (Eq 8). Procedure A was employed, using bromobenzene-d_5 (148 mg, 0.914 mmol), methyl *trans*-cinnamate (161 mg, 0.993 mmol), Cy_2NMe (0.220 mL, 1.03 mmol), $Pd_2(dba)_3$ (12.7 mg, 0.014 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.14 mL, 0.028 mmol), and dioxane (0.78 mL). After 14 h at room temperature, workup and column chromatography (5% Et_2O/hexanes) yielded 209 mg (94%) of (*E*)-3-(phenyl-d_5)-3-phenyl acrylic acid methyl ester as a pale-yellow liquid.

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^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35−7.40 (m, 3H), 7.18−7.22 (m, 2H), 6.36 (s, 1H), 3.61 (s, 3H).

^{31}P NMR Study of the Heck Coupling of 4′-Chloroacetophenone with Styrene. Procedure A was employed, using 4′-chloroacetophenone (0.130 mL, 1.00 mmol), styrene (0.125 mL, 1.09 mmol), Cy_2NMe (0.240 mL, 1.12 mmol), $Pd_2(dba)_3$ (14.0 mg, 0.015 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.15 mL, 0.030 mmol), and dioxane (0.84 mL). The reaction was stirred for 10 min at room temperature, and then it was transferred via pipet to an NMR tube equipped with a Teflon screwcap. The tube was sealed and removed from the glovebox, and then the reaction was monitored by ^{31}P NMR. Essentially the only phosphorus-containing species observed during the course of the reaction was $Pd(P(t\text{-}Bu)_3)_2$ at δ 86 (a trace of free P(*t*-Bu)$_3$ was also present).

Heck Coupling of 4′-Chloroacetophenone with Styrene as a Function of Pd:Phosphine Ratio (Eq 9; Typical Procedure). In a glovebox, $Pd_2(dba)_3$ (6.6 mg, 0.0070 mmol), $Pd(P(t\text{-}Bu)_3)_2$ (7.1 mg, 0.014 mmol), *n*-tridecane (internal standard; 38.7 mg, 0.206 mmol), 4′-chloroacetophenone (149 mg, 0.962 mmol), Cy_2NMe (0.230 mL, 1.07 mmol), dioxane (0.96 mL), and styrene (0.120 mL, 1.05 mmol) were added in turn to a 4-mL vial equipped with a stir bar. The reaction mixture was stirred at room temperature; after 3 h, GC revealed 29% conversion.

Rate of Heck Coupling of 4′-Chloroacetophenone as a Function of Olefin (Table 4; Typical Procedure). Procedure A was employed, using 4′-chloroacetophenone (149 mg, 0.964 mmol), styrene (0.120 mL, 1.05 mmol), Cy_2NMe (0.230 mL, 1.07 mmol), $Pd_2(dba)_3$ (13.0 mg, 0.014 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.14 mL, 0.028 mmol), dioxane (0.82 mL), and *n*-tridecane (internal standard; 42.5 mg, 0.230 mmol). After 3 h at room temperature, GC revealed 30% conversion.

^{31}P NMR Study of the Heck Coupling of 4-Bromoanisole with Styrene. Procedure A was employed, using 4-bromoanisole (0.0950 mL, 0.759 mmol), styrene (0.0950 mL, 0.829 mmol), Cy_2NMe (0.180 mL, 0.840 mmol), $Pd_2(dba)_3$ (10.6 mg, 0.012 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.12 mL, 0.024 mmol), and dioxane (0.65 mL). The reaction was stirred for 2−3 min at room temperature, and then it was transferred via pipet to an NMR tube equipped with a Teflon screwcap. The tube was sealed and removed from the glovebox. The reaction was then monitored by ^{31}P NMR, which showed the major phosphorus-containing species to be a broad peak at δ ~64. In addition, resonances at δ 86 ($Pd(P(t\text{-}Bu)_3)_2$) and δ 92 (small) were observed.

^{31}P NMR Study of the Stoichiometric Reaction of 4-Bromoanisole with $Pd_2(dba)_3$/P(*t*-Bu)$_3$. In a glovebox, $Pd_2(dba)_3$ (17.3 mg, 0.019 mmol), 4-bromoanisole (0.0050 mL, 0.040 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.19 mL, 0.038 mmol), and dioxane-d_8 (0.54 mL) were added successively to an NMR tube equipped with a Teflon screwcap. The tube was sealed and removed from the glovebox. The initial ^{31}P NMR spectrum showed an ~1:1 ratio of two species at δ 86 ($Pd(P(t\text{-}Bu)_3)_2$) and δ 93. The initial ^{1}H NMR spectrum revealed a new doublet at δ 1.12 (J = 11.7 Hz; P(*t*-Bu)$_3$ group), a new singlet at δ 3.65 (MeO group), and a new doublet at δ 6.52 (J = 8.4 Hz; aromatic group); in addition, unreacted 4-bromoanisole and $Pd(P(t\text{-}Bu)_3)_2$ were present.

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