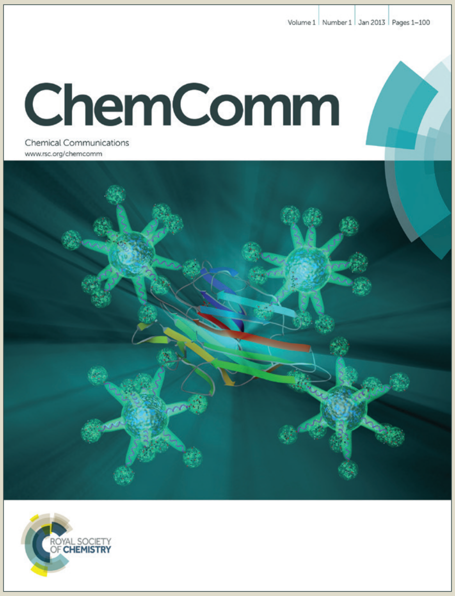
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Palladium-Catalyzed Intermolecular Heck Reaction of Alkyl Halides

Yinjun Zou and Jianrong (Steve) Zhou*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

Intermolecular Heck reaction of common alkyl halides, a longstanding problem in palladium catalysis, is realized with a simple Pd/dppf catalyst. Both primary and secondary alkyl halides are suitable in coupling with aromatic olefins. Single electron transfer from (dppf)Pd^0 to alkyl halide initiated the catalytic cycle and gave alkyl radicals.

Heck reaction of aryl and vinyl halides is well developed and has been widely used in organic synthesis.[1] However, Heck reaction of common alkyl halides is difficult owing to premature β-hydride elimination.[2] For alkyl halides that lack eliminable β-hydrogens, Heck products can indeed be obtained, e.g., from benzyl halides, allyl halides and α-bromoesters.[3] For alkyl halides that carry eliminable β-hydrogens, intramolecular cyclization with pedant olefins also proceeded efficiently to form five- or six-membered rings (Fig 1a-b).[4] However, Pd-catalyzed intermolecular Heck reaction of common alkyl halides remained a great challenge. For example, Alexanian *et al.* reported Pd(PPh$_3$)$_4$-catalyzed Heck reaction of cyclohexyl iodide and styrene that gave around 50% yield. The scope of the reaction was very limited.[5] In 2002, Oshima *et al.* reported cobalt-catalyzed intermolecular coupling between both primary and secondary alkyl halides with styrene, but very basic Grignard reagents must be used to form the active catalyst (Fig 1c).[6] A similar Heck-type process of styrene was disclosed by Kambe *et al.* using a titanocene catalyst and a Grignard reagent.[7]

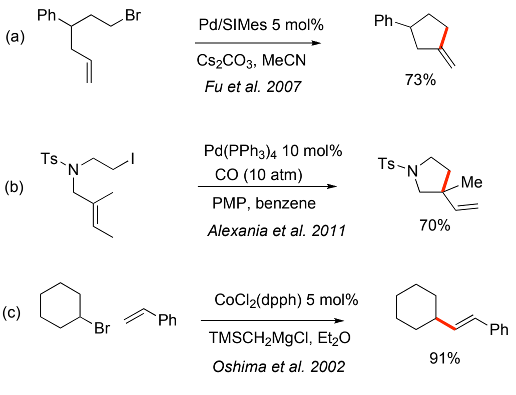


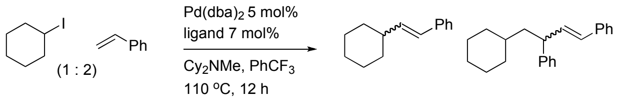
Fig. 1 Examples of Heck reaction of alkyl halides.

Herein, we disclosed Pd-catalyzed intermolecular Heck reaction of alkyl halides and styrenes. The products, *trans*-β-alkylstyrenes are commonly prepared from metal-catalyzed cross-couplings using *trans*-alkenylmetal reagents or *trans*-alkenyl electrophiles, but these reagents usually need additional steps to prepare.[8] Wittig reaction of aryl-substituted triphenylphosphine ylides typically gave a mixture of *trans*- and *cis*-isomers.[9] To form selectively *trans*-olefins, modified *P*-ylides reagents, arylaldimine or Schlosser modification was needed.[10] The *trans*-β-alkylstyrenes can also be accessed from olefin Ru-catalyzed metathesis.[11]

Initially, we used a model reaction between cyclohexyl iodide and styrene to find an active Pd catalyst. After many experiments, we found that ferrocene bisphosphine dppf was a quite active ligand (entry 1, Table 1). The desired *trans*-isomer was obtained in 70% yield and in good *E*/*Z* ratio (14:1). Other phosphines were much worse, for example, dppp and BINAP furnished 0% and 40% yield, respectively (entries 6-7).

Other reaction parameters were also critical to the realization of this difficult transformation. When the Pd source was switched from Pd(dba)$_2$ to Pd(PPh$_3$)$_4$, the yield of Heck product was further improved to about 80% (entry 16). Pd(dppf)$_2$ itself was a highly active catalyst (entry 17). Under these conditions, some byproduct derived from insertion of two molecules of styrene was detected (mostly <10%). PhCF$_3$ was the solvent of choice. In other aromatic solvents (toluene and xylenes) and ethereal solvents (1,4-dioxane, monoglyme and triglyme), the yield was slightly lower. Cy$_2$NMe was the most suitable base for this reaction. The product yield decreased significantly if *i*Pr$_2$NEt or Et$_3$N was used instead. In the dark, the catalysis also proceeded with the same efficiency, so the model reaction was not catalyzed by light.

Table 1 Effect of phosphorus ligands on Heck reaction (GC yield)



Entry	Ligand	Conv. (%)	(*E*)-isomer (%)	*E*/*Z* ratio	Double insertion (%)
1	dppf	100	70	14	9
2	dnpf	57	12	38	5
3	dippf	18	2	7	2
4	dppp	15	0	--	0
5	dppe	14	0	--	0
6	dppb	23	0	--	0
7	(*R*)-BINAP	96	40	4	10
8	(*R*)-Segphos	59	10	3	4
9	XantPhos	14	3	--	0

10	DPE-Phos	96	56	9	11
11	PPF-Xyl	20	0	--	0
12	P(*o*-tolyl)$_3$	5	0	--	0
13	P(2-furyl)$_3$	14	4	9	4
14	P(cyclohexyl)$_3$	26	1	--	0
15	P*t*Bu$_3$	28	1	--	5
16	dppf + Pd(PPh$_3$)$_4$	100	79	19	11
17	Pd(dppf)$_2$	100	81	62	7

Under optimized conditions using 1:2 stoichiometry of RX and styrene and 5% Pd catalyst, most secondary alkyl halides can couple in good yield (Fig. 2). In most cases, only two isomers were produced, the *trans* and *cis* olefins with the ratio shown in parentheses. The use of an additive, LiI can improve the yields from alkyl bromides (about 10%). The presence of oxygen and nitrogen atoms into the rings did not affect the coupling process. In cases such as cyclopentyl and cyclohexyl bromides, the yields were only around 50%, which can be improved by using an alternative procedure (3:1 ratio of RX and styrene; 10 mol% Pd/dppf). Notably, *exo*-2-norbornyl bromide gave exclusively the *exo*-Heck product, while *trans*-1-iodo-2-methoxycyclopentane afforded the *trans*-olefinic isomer selectively with a trans configuration on cyclopentane. Both examples indicated that most likely alkyl radicals are involved so that subsequent styrene insertion occurred at the less hindered face. The reaction of CyI and styrene was scaled up to gram scale synthesis (75% yield).

For Heck reaction of most primary alkyl halides, Pd(dba)$_2$ and dppf formed the most active catalysis (Fig. 3). The main side reaction was Pd-assisted premature elimination of alkyl halides to olefins.[12] In a control experiment without the Pd catalyst, *N*-alkylation of Cy$_2$NMe to form quaternary salts became the major side reaction at 110 ^{o}C. Thus, 3:1 ratio of primary RX and styrene was used to furnish good yields (>70%) in most cases. The procedure using 1:2 ratio generally gave about 50% yield. Hindered neopentyl iodide also coupled well. Polar groups such as esters, nitriles and phthalimides were tolerated. 6-Iodo-1-hexene afforded the ring-closed Heck product in 52% yield and in 3:1 selectivity versus other isomers. Primary alkyl chlorides can also couple. Alkyl iodides that were in situ generated from RCl and LiI may be the actual coupling reagents. Cyclopropylmethyl bromide failed to give any Heck product (judged by GC and GCMS). Benzylic and allylic halides gave little Heck products, either.

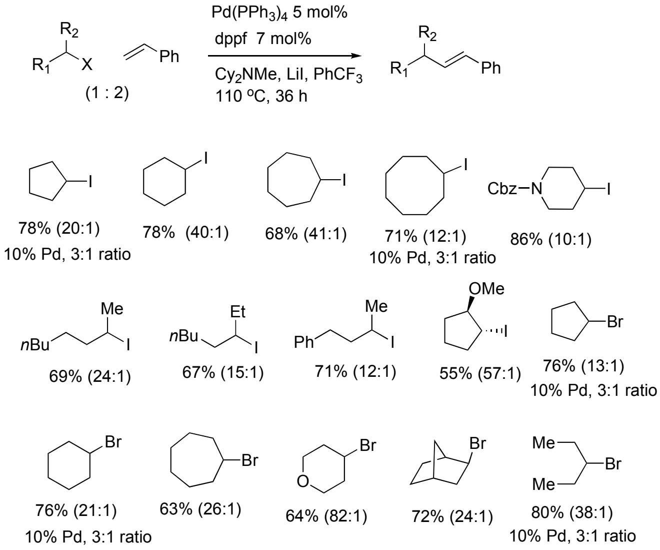


Fig. 2 Heck reaction of secondary alkyl halides.

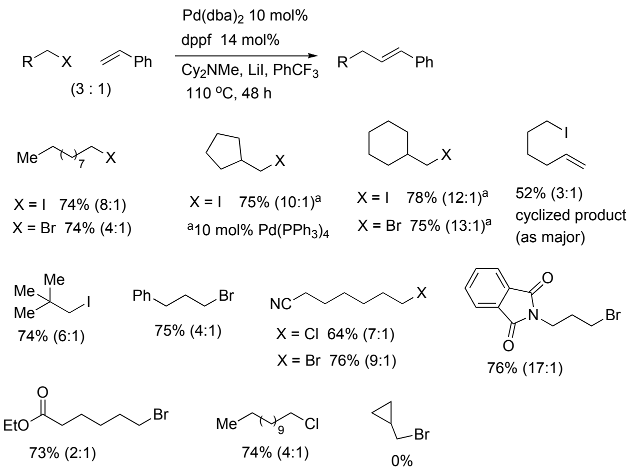


Fig. 3 Heck reaction of primary alkyl halides.

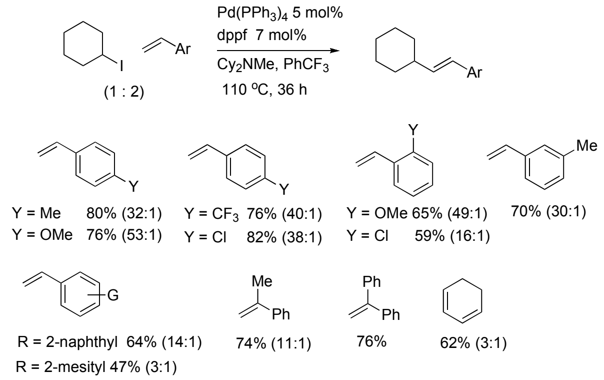


Fig. 4 Examples of aromatic olefins and a conjugated diene.

With regard to the scope of olefins, electron-donating and –withdrawing groups on aryl rings of styrene were well tolerated (Fig. 4). Hindered 2-vinylmesitylene can also couple. On a position of styrene, alkyl and aryl groups can be present, but β-substitutions were not tolerated. α-Methylstyrene produced α-

(cyclohexylmethyl)styrene as the major isomer with 11:1 selectivity. A conjugated diene, 1,3-cyclohexadiene also coupled in reasonable yield with 3:1 selectivity of 1-alkyl-1,3-cyclohexadiene versus other isomers. Unfortunately, methyl acrylate, 1-octene and *n*-butyl vinyl ether failed to couple.

To confirm the involvement of alkyl radicals in our Heck reaction, we included 1 equiv of TEMPO, a radical trap in the model Heck reaction. No Heck product was detected and *N*-cyclohexyl-TEMPO **a** was formed in 2:1 molar ratio to Pd^0 catalyst (Fig. 5a). Therefore, it is possible that during oxidative addition of $(dppf)Pd^0$, two consecutive single electron transfer events occurred to generate two alkyl radials and $(dppf)PdI_2$.

In another trapping experiment, the alkyl radical from *N*-Cbz-4-iodopiperidine **b** was partially intercepted by 1,4-cyclohexadiene (5 equiv) via hydrogen atom abstraction (Fig. 5b).

In 2012, Jian et al. reported Pd/dppf-catalyzed intramolecular cyclization of alkyl iodides and pedant olefins. Atom transfer radical addition was proposed to account for the formation of alkyl halide products after ring closure.[13] We excluded a possible sequence of atom transfer radical addition to from benzylic halides, followed by base-assisted elimination to form olefin products (Fig. 5c). When a model "intermediate" **c** was added to an active Heck reaction of CyI and styrene, **c** was fully consumed, but the expected elimination product from **c** was only formed in moderate yield (41%). Homocoupling of the benzylic radical derived from **c** was the main side reaction. Furthermore, **c** interfered with the Heck reaction of CyI and the yield of Heck product derived from CyI was reduced from >70% to 13%.

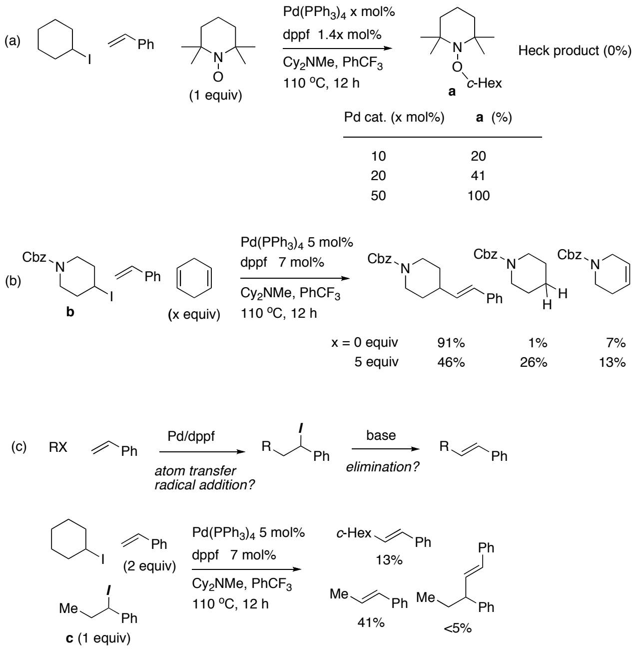


Fig. 5 Mechanistic studies.

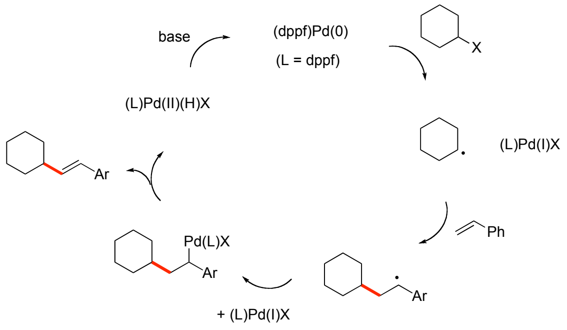


Fig. 6 A possible catalytic cycle for Heck reaction of alkyl halides.

A tentative catalytic cycle is proposed in Fig 6. It starts from single electron transfer from $(dppf)Pd^0$ to alkyl halide, followed by alkyl radical addition to styrene. The rate of alkyl radical addition to styrene in solution was estimated by Minisci *et al.* to be around $10^5\ M^{-1}s^{-1}$.[14] Recombination of the resulting benzylic radical and (dppf)XPd(I) forms (alkyl)PdX which undergoes Pd-assisted β-hydride elimination to afford the Heck product.

In conclusion, we disclose herein an efficient Pd-catalyzed method for intermolecular Heck reaction of alkyl halides, which was an unsolved problem for many years. The simple, easily available Pd/dppf catalyst showed good reactivity. Our mechanistic investigation points to single electron transfer from $(dppf)Pd^0$ to alkyl halides. Compared to Co-catalyzed method reported by Oshima *et al.*,[6] no Grignard reagents were used which allowed base-sensitive functional groups to be present.

Notes and references

Division of Chemistry and Biological Chemistry
School of Physical and Mathematical Sciences
Nanyang Technological University, 21 Nanyang Link, Singapore 637371
Fax: (+65) 67911961; E-mail: jrzhou@ntu.edu.sg

† We thank Singapore National Research Foundation (NRF–RF2008–10) and Nanyang Technological University for financial support. We thank Johnson Matthey for a gift of palladium salts. Electronic Supplementary Information (ESI) available: Experimental procedures and characterization of new compounds. See DOI: 10.1039/b000000x/

1 Reviews: (a) R. F. Heck, *Acc. Chem. Res.*, 1979, **12**, 146; (b) I. P. Beletskaya and A. V. Cheprakov, *Chem. Rev.* 2000, **100**, 3009; (c) K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem., Int. Ed.*, 2005, **44**, 4442; (d) Bräse, S.; de Meijere A. In Metal-Catalyzed Cross-coupling Reactions; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; pp 217-316; (e) G. Zeni and R. C. Larock, *Chem. Rev.*, 2006, **106**, 4644; (f) M. Oestreich, Wiley, New York, **2009**.

2 Examples: (a) R. F. Heck and J. P. Nolley, *J. Org. Chem.*, 1972, **37**, 2320; (b) S. A. Lebedev, V. S. Lopatina, E. S. Petrov and I. P. Beletskaya, *J. Organomet. Chem.*, 1988, **344**, 253; (c) T. Mizoroki, K. Mori and A. Ozaki, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 581.

3 Examples: (a) S. Bräse, B. Waegell and A. de Meijere, *Synthesis*, 1998, 148; (b) Y. Xie, J. Hu, Y. Wang, C. Xia and H. Huang, *J. Am. Chem. Soc.*, 2012, **134**, 20613; (c) Z. Yang and J. Zhou, *J. Am. Chem. Soc.*, 2012, **134**, 11833; (d) G. Z. Wu, F. Lamaty and E. Negishi, *J. Org. Chem.*, 1989, **54**, 2507; (e) K. Higuchi, K. Sawada, H. Nambu, T. Shogaki and Y. Kita, *Org. Lett.*, 2003, **5**, 3703; (f) R. Matsubara, A. C. Gutierrez and T. F. Jamison, *J. Am. Chem. Soc.*, 2011, **133**,

19020; (g) R. Matsubara and T. F. Jamison, *J. Am. Chem. Soc.,* 2010, **132**, 6880; (h) C. Liu, S. Tang, D. Liu, J. Yuan, L. Zheng, L. Meng and A. Lei, *Angew. Chem. Int. Ed.,* 2012, **51**, 3638; (i) Q. Liu, H. Yi, J. Liu, Y. Yang, X. Zhang, Z. Zeng and A. Lei, *Chem.-Eur. J.,* 2013, **19**, 5120; (j) Cu-catalyzed radical addition of α-halocarbonyl compounds to styrene: T. Nishikata, Y. Noda, R. Fujimoto and T. Sakashita, *J. Am. Chem. Soc.,* 2013, **135**, 16372.

4 (a) L. Firmansjah and G. C. Fu, *J. Am. Chem. Soc.,* 2007, **129**, 11340; (b) H. Kim and C. Lee, *Org. Lett.,* 2011, **13**, 2050; (c) W. Zhou, G. An, G. Zhang, J. Han and Y. Pan, *Org. Biomol. Chem.,* 2011, **9**, 5833; (d) M. E. Weiss, L. M. Kreis, A. Lauber and E. M. Carreira, *Angew. Chem. Int. Ed.,* 2011, **50**, 11125; (e) B. Giese, P. Erdmann, T. Göbel and R. Springer, *Tetrahedron Lett.,* 1992, **33**, 4545.

5 K. S. Bloome, R. L. McMahen and E. J. Alexanian, *J. Am. Chem. Soc.,* 2011, **133**, 20146.

6 (a) W. Affo, H. Ohmiya, T. Fujioka, Y. Ikeda, T. Nakamura, H. Yorimitsu, K. Oshima, Y. Imamura, T. Mizuta and K. Miyoshi, *J. Am. Chem. Soc.,* 2006, **128**, 8068; (b) Y. Ikeda, T. Nakamura, H. Yorimitsu and K. Oshima, *J. Am. Chem. Soc.,* 2002, **124**, 6514.

7 J. Terao, H. Watabe, M. Miyamoto and N. Kambe, *Bull. Chem. Soc. Jpn.,* 2003, **76**, 2209.

8 (a) T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi and K. Hirotsu, *J. Am. Chem. Soc.,* 1984, **106**, 158; (b) E. Negishi, T. Takahashi, S. Baba, D. E. Van Horn and N. Okukado, *J. Am. Chem. Soc.,* 1987, **109**, 2393; (c) N. Miyaura and A. Suzuki, *J. Chem. Soc., Chem. Commun.,* 1979, 866.

9 A. Maerckar, *Org. React.,* 1965, **14**, 270.

10 (a) Y. Gu and S.-K. Tian, *Top. Curr. Chem.,* 2012, **327**, 197; (b) B. E. Maryanoff and A. B. Reitz, *Chem. Rev.,* 1989, **89**, 863; (c) D.-J. Dong, H.-H. Li and S.-K. Tian, *J. Am. Chem. Soc.,* 2010, **132**, 5018; (d) V. K. Aggarwal, J. R. Fulton, C. G. Sheldon and J. de Vicente, *J. Am. Chem. Soc.,* 2003, **125**, 6034; (e) M. Schlosser and K. F. Christmann, *Angew. Chem., Int. Ed. Engl.,* 1966, **5**, 126.

11 A. K. Chatterjee, T.-L. Choi, D. P. Sanders and R. H. Grubbs, *J. Am. Chem. Soc.,* 2003, **125**, 11360.

12 A. C. Bissember, A. Levina and G. C. Fu, *J. Am. Chem. Soc.,* 2012, **134**, 14232.

13 H. Liu, Z. Qiao and X. Jiang, *Org. Biomol. Chem.,* 2012, **10**, 7274.

14 A. Citterio, A. Arnoldi and F. Minisci, *J. Org. Chem.,* 1979, **44**, 2674.

An efficient Pd-catalyzed method for intermolecular Heck reaction of common alkyl halides is described for the first time.