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Graphical Abstract

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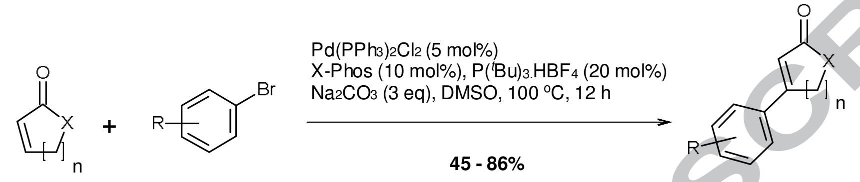

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Selective Heck reaction of electron-rich aryl bromides with cyclic alkenones

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ABSTRACT

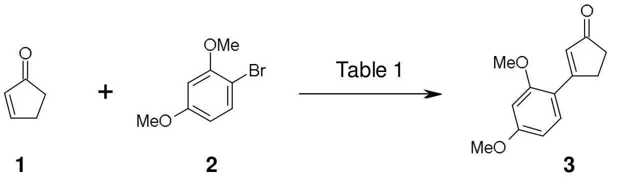
A simple and efficient protocol for the Heck reaction of cyclic alkenones with electron-rich aryl bromides has been developed. A ligand combination of X-Phos and tri-tert-butylphosphonium hydrogen tetrafluoroborate in the presence of $Pd(PPh_3)_2Cl_2$ and Na_2CO_3 in DMSO was found to be efficient and selective for electron-rich aryl bromides with high substrate scope for cyclic alkenones.

The Heck reaction is one of the most efficient palladium catalyzed carbon-carbon bond forming reactions.[1] Though Heck reaction with diverse range of olefins is very popular in organic synthesis, *α,β*-unsaturated ketones like cyclic alkenones are challenging substrates due to the unfavorable stereo-chemical orientation required for *syn β*-hydride elimination in the final step of traditional Heck reaction pathway.[2-5] There are a few literature reports describing protocols for the Heck reaction of cyclic alkenones with aryl iodides,[2,3,5-7] aryl boronic acids under oxidative conditions[8] and other not readily available substrates.[6,9] Heck reaction of cycloalkenones with readily available substrated like aryl bromides[10-13] is also not very well explored.

Electron-rich aryl halides are known to be poor substrates in the Heck reactions.[1e,6] Development of efficient reaction conditions for the Heck reaction with difficult substrates like cyclic alkenones and electron-rich aryl halides is of interest. To our best knowledge, a generic and efficient protocol for the Heck reaction of electron-rich aryl halides with cyclic alkenones is not known in literature. We report in this paper a simple and efficient protocol for the Heck reaction of cyclic alkenones selective for electron-rich aryl bromides.

We started with the catalyst screening by choosing the substrates as cyclopentenone (cyclic alkenone) **1** and 2,4-dimethoxybromobenzene (electron-rich aryl bromide) **2** (Scheme 1). K_2CO_3 and N,N-dimethylacetamide were chosen as base and solvent, respectively. Trials with a few palladium catalysts with different ligand combinations (Table 1) suggested that $Pd(PPh_3)_2Cl_2$ together with X-Phos (2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl) ligand forms a good catalyst system for such Heck reactions providing coupling product **3** in a moderate yield of 40% (entry 2, Table 1).

Scheme 1



Considering that addition of ammonium or phosphonium salts sometimes improves yields of Heck reactions,[1a,3,11,14] we then explored the Heck reaction of cyclopentenone **1** with 2,4-dimethoxybromobenzene together with ammonium and phosphine additives (Table 1). Heck coupling product yield was improved moderately (by about 25%) with tri-tert-butylphosphonium hydrogen tetrafluoroborate (entry 9, Table 1) while other ammonium salts did not improve the yield significantly (entries 10-11, Table 1). Other protocols postulated to involve Pd-colloids[15] for efficient Heck coupling like Jeffrey's conditions[16] (entry 13, Table 1) and de Vries protocol[17] (entry 14, Table 1) were also found to be unsuccessful.

Table 1: Catalyst screening with K_2CO_3 in N,N-dimethylacetamide at 135 °C for 15 h under nitrogen atmosphere.

Entry	Catalyst	Ligand	Additive	Yield
1	$Pd(OAc)_2$	X-Phos	-	20

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2	Pd(PPh$_3$)$_2$Cl$_2$	X-Phos	-	40
3	Pd$_3$(dba)$_2$	X-Phos	-	20
4	Pd(dppf)Cl$_2$	X-Phos	-	30
5	Pd(PPh$_3$)$_2$Cl$_2$	XantPhos	-	15
6	Pd(PPh$_3$)$_2$Cl$_2$	S-Phos	-	10
7	Pd(PPh$_3$)$_2$Cl$_2$	DavePhos	-	<10
8	Pd(PPh$_3$)$_2$Cl$_2$	X-Phos	PPh$_3$ (0.5 eq)	50
9	**Pd(PPh$_3$)$_2$Cl$_2$**	**X-Phos**	**PBu$_3$.HBF$_4$ (0.5 eq)**	**65**
10	Pd(PPh$_3$)$_2$Cl$_2$	X-Phos	Bu$_4$NBr (0.5 eq)	52
11	Pd(PPh$_3$)$_2$Cl$_2$	X-Phos	Et$_4$NCl (0.5 eq)	45
12^a	Pd(OAc)$_2$	P(*o*-tol)$_3$	Bu$_4$NBr (1.0 eq)	25
13^b	Pd(OAc)$_2$		Bu$_4$NBr (1.0 eq)	traces
14^c	Pd(OAc)$_2$			<10

Reaction conditions: 2,4-Dimethoxybromobenzene (2.30 mmol), cyclopentenone (2.76 mmol), Catalyst (0.11 mmol), Ligand (0.22 mmol), K$_2$CO$_3$ (6.90 mmol), DMA (5 ml), 135 °C, 15 h. a) Catalyst (0.02 mol%), NaOAc (2.0 eq), Ligand (0.05 mol%) and Bu$_4$NBr (1.0 eq)) in DMA (5 ml) at 130 °C, 12 h. b) Catalyst (0.05 mol%), NaHCO$_3$ (2.5 eq), and Bu$_4$NBr (1.0 eq)) in DMF (5 ml) at 100 °C, 12 h. c) Catalyst (0.05 mol%), and NaOAc (1.2 eq) in NMP (5 ml) at 130 °C, 12 h.

We further optimized the reaction conditions by varying base, solvent and temperature (Table 2). To our delight a combination of Pd(PPh$_3$)$_2$Cl$_2$, X-Phos and tri-tert-butylphosphonium hydrogen tetrafluoroborate in the presence of Na$_2$CO$_3$ in DMSO at 80 °C further enhanced the yield of Heck coupling product to 80%. It is notable that DMSO is the most suitable solvent for this transformation as demonstrated by the consistently high yields with different bases with an additional advantage of lower reaction temperature.

Table 2: Solvent and base screening

Entry	Base	Solvent	Temp	Yield%
1	K$_2$CO$_3$	DMA	135 ^{0}C	65
2	K$_2$CO$_3$	1,4-dioxan	100 ^{0}C	5
3	K$_2$CO$_3$	toluene	110 ^{0}C	5
4	K$_2$CO$_3$	acetonitrile	80 ^{0}C	10
5	K$_2$CO$_3$	1,2-dichloroethane	80 ^{0}C	15
6	K$_2$CO$_3$	DMF	135 ^{0}C	50
7	K$_2$CO$_3$	DMSO	80 ^{0}C	70
8	K$_2$CO$_3$	NMP	80 ^{0}C	30
9	KOAc	DMSO	80 ^{0}C	20
10	**Na$_2$CO$_3$**	**DMSO**	**80 ^{0}C**	**80**
11	Cs$_2$CO$_3$	DMSO	80 ^{0}C	15
12	Ag$_2$CO$_3$	DMSO	80 ^{0}C	15
13	KF	DMSO	80 ^{0}C	70
14	K$_3$PO$_4$	DMSO	80 ^{0}C	10
15	KO^{t}Bu	DMSO	80 ^{0}C	5
16	^{i}Pr$_2$NEt	DMSO	80 ^{0}C	70

Reaction conditions: 2,4-Dimethoxybromobenzene 2 (2.30 mmol), cyclopentenone 1 (2.76 mmol), catalyst (0.11 mmol), ligand (0.22 mmol), ^{t}PBu$_3$.HBF$_4$ (1.15 mmol), Base (6.90 mmol), solvent (5 ml), 12 h, N$_2$ atmosphere.

It is worthwhile to note that the reaction is sensitive to the quantity of phosphine additive improving the yield to 96% (entry 6, Table 3) when the phosphine was used in a stoichiometric ratio. Based on the temperature screening and the best suited additive loading, we fixed 0.2 equivalents of phosphine additive in the presence of Pd(PPh$_3$)$_2$Cl$_2$, X-Phos, and Na$_2$CO$_3$ in DMSO as solvent at 100 ^{0}C (entry 1, Table 3) as our standard reaction conditions for validating Heck reaction between cycloalkenones and aryl bromides.

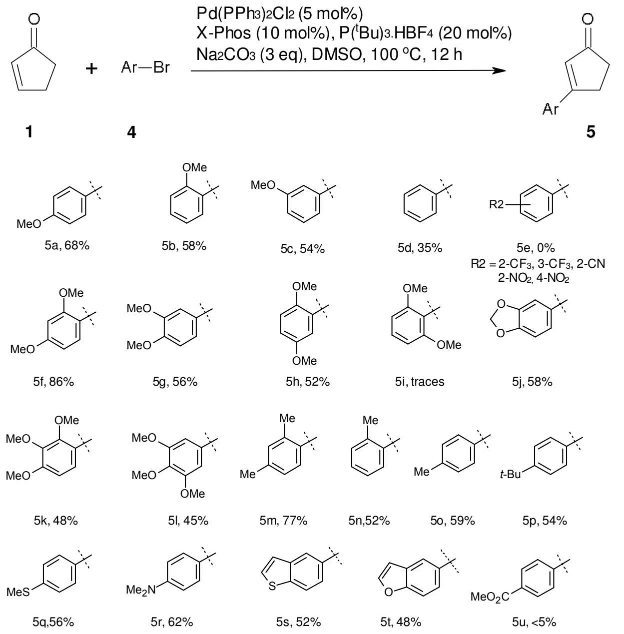
Table 3: Additive screening

Entry	Ligand	Additive	Temp.	Yield (%)
1	**X-Phos**	**P^{t}Bu$_3$.HBF$_4$ (0.2 eq)**	**100 ^{o}C**	**86**
2	X-Phos	P^{t}Bu$_3$.HBF$_4$ (0.2 eq)	120 ^{o}C	66
3	X-Phos	------	100 ^{o}C	62
4	-------	P^{t}Bu$_3$.HBF$_4$ (0.2 eq)	100 ^{o}C	68
5	X-Phos	P^{t}Bu$_3$.HBF$_4$ (0.5 eq)	80 ^{o}C	80
6	X-Phos	P^{t}Bu$_3$.HBF$_4$ (1.0 eq)	80 ^{o}C	96
7	-------	-------	100 ^{o}C	<5

Reaction conditions: 2,4-Dimethoxybromobenzene 2 (2.30 mmol), cyclopentenone 1 (2.76 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (0.11 mmol), X-Phos (0.22 mmol), Additive (shown in table), Na$_2$CO$_3$ (6.90 mmol), DMSO (5 ml), under nitrogen atmosphere, 12 h.

We then investigated the scope of aryl bromide substrates. A range of electron-rich and electron-poor aryl bromides were tested for Heck reaction with cylcopentenone **1** under our standard reaction conditions. Results shown in the Scheme 2 suggest that these reaction conditions generally provide medium to high yield of Heck coupling products with electron-rich aryl bromides (**5a**-**5c**, **5f**-**5r**).

Scheme 2

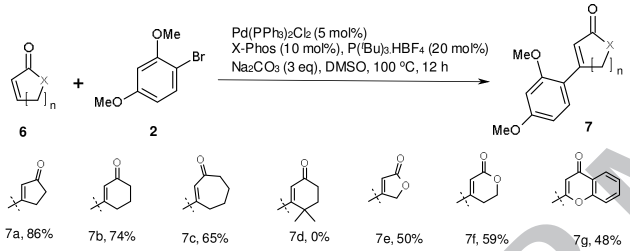


Whereas, electron poor aryl bromides bearing electron withdrawing groups such as CF$_3$, CN, NO$_2$ and CO$_2$Me (**5e**, **5u**) are not suitable substrates under these reaction conditions, in each case we isolated homo coupled products with minor amounts of corresponding debrominated products. Simple bromobenzene without any other substituent resulted in 35% yield of the corresponding coupling product (**5d**).

Steric hindrance seems to be detrimental as demonstrated by the example of arylbromide with two ortho substituents (**5i**) which gave only traces of coupling product. Electron-rich bicyclic heteroaryl bromides (**5s** and **5t**) also reacted under these conditions providing medium yield (~50%) of coupling products.

Heck reaction protocol specific for electron-rich aryl bromides reported here is complementary to the known methods for heck coupling of aryl bromides with cyclic alkenones developed by Santelli and coworkers[12] which in our experience was found to be selective for electron-poor aryl bromides. Our attempts at Heck reaction of electron-rich substrates (**5a, 5b** and **5f**) with cyclopentenone **1** under Santelli and coworker's conditions ($Pd(OAc)_2$, DMF, KF, 130 °C, 20 h) resulted in poor yields. A closely related protocol for heck coupling of aryl bromides with cyclic alkenones described by Wu *et al.*[11] does not seem to differentiate the electron-rich and electron-poor aryl bromides while the catalyst system reported in this work does differentiate between the electron-rich and electron-poor aryl bromides (**5a**, **5p** and **5u**).

Scheme 3

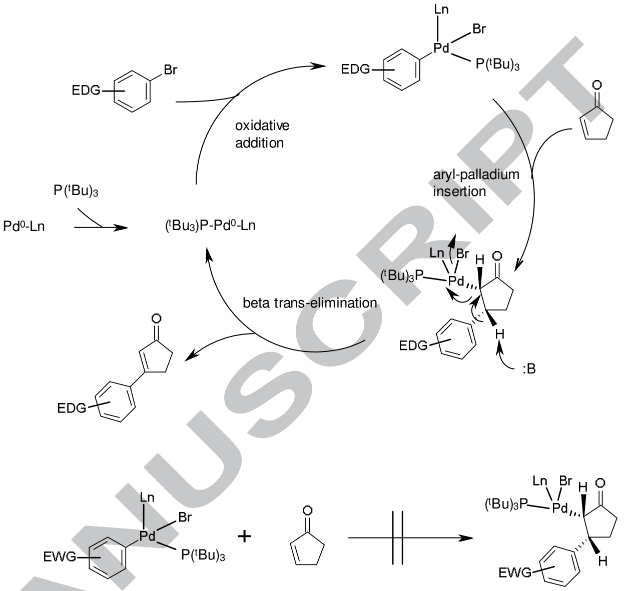


We next examined the substrate scope for cyclic alkenones (Scheme 3). Different ring sizes varying from five to seven membered cyclic alkenones reacted well with aryl bromides (**7a-7c**) to provide Heck coupling products in 65-86% yield with 2,4-dimethoxybromobenzene. Lactone group (**7e** and **7f**) was also tolerated, but resulted in a slight reduction in yield. Cyclohexenone substrate (**7d**) with two methyl substituents next to the double bond did not react with 2,4-dimethoxy-aryl bromide again demonstrating the influence of steric hindrance on the reactivity. Aromatic alkenone like Chromone was also tolerated providing the corresponding coupling product (**7g**) in 48% yield. Overall, the Heck coupling protocol reported here has a large scope of cyclic alkenones.

With regard to the mechanism, we hypothesize that the reaction path way is similar to the standard Heck reaction as shown in Scheme 4 involving oxidative addition, aryl-palladium insertion, and a base induced "formal" beta *trans*-elimination (as postulated for α,β-unsaturated carbonyl compounds).[18] We speculate that oxidative addition occurs rapidly under the described catalytic system without any discrimination of electron-rich and electron-poor aryl bromides. The observed selectivity for the electron-rich aryl bromides may be due to more favorable aryl-palladium insertion onto the cyclic alkenone for electron-rich aryl bromides facilitated by higher nucleophilicity (probably enhanced by the presence of electron rich phosphine ligands tri-tert-butylphosphine and/or X-Phos on palladium) of the aryl group in the oxidative addition product. While, electron-poor aryl halides could not be activated sufficiently under these conditions to undergo aryl-palladium insertion thus resulting in self coupling or reduction products.

Scheme 4

Proposed hypothetical mechanism for the selective heck reaction of electron rich aryl halides with cyclic alkenones



In summary, we developed a simple method for a selective Heck reaction of two difficult coupling partners of electron-rich aryl bromides and cyclic alkenones with diverse scope. A combination of X-Phos with tri-tert butylphosphonium hydrogen tetrafluoroborate as ligands improved the Heck coupling yields. This method could provide access to some of the difficult to obtain building blocks which can be used for further derivatisation with potential applications in medicinal- and agro-chemistry.

Acknowledgments

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References and notes

1. a) Murray, P. M.; Bower , J. F.; Cox, D. K.; Galbraith, E. K.; Parker J. S.; Sweeney, J. B. *Org. Process Res. Dev.* **2013**, 17(3), 397. b) Farina, V. *Adv. Synth. Catal.* **2004**, 346, 1553. c) Overman, L. E.; Dounay, A. B. *Chem. Rev.* **2003**, 103, 2945. d) Littke, A.; Fu, G. *Angew. Chem. Int. Ed.* **2002**, 41, 4176. e) Whitcombe, N. J.; Hii (Mimi), K. K.; Gibson, S. E. *Tetrahedron* **2001**, 57, 7449. f) Beletskaya, I. P.; Cheprakov, A.V. *Chem.Rev.* **2000**, 100, 3009.
2. Gottumukkala, A. L.; de Vries, J. G.; Minnard, A. J. *Chem. Eur. J.* **2011**, 17, 3091.
3. Ikeda, M.; El Bilay, S. A. A.; Yakura, T. *Heterocycles* **1999**, 51(8), 1957.
4. a) Branchaud, B. P.; Friestad, G. K. *Tett. Lett.* **1995**, 36(39), 7047. b) Cacchi, S.; Arcadi, A. *J. Org. Chem.* **1983**, 48(23), 4236.
5. Genet, P. G.; Blart, E.; Savignac, M. *Synlett* **1992**, 715.

6. a) Tanaka, D.; Myers, A. G. *Org. Lett.* **2004**, 6(3), 433. b) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.***2002**, 124(38), 11250.
7. a) Gupta, A. K.; Song, C. H.; Oh, C. H. *Tett. Lett.* **2004**, 45, 4113. b) Bialy, S. A. A.; Ismail, M. A.; Gad, L. M.; Abdelal, A. M. M. *Med. Chem. Res.* **2002**, 11 (50), 293. c) Ikeda, M.; Bialy, S. A. A.; Hirose, K.; Kotake, M.; Sato, T.; Bayomi, S. M. M.; Shehata, I. A.; Abdelala, A. M.; Gad, L. M.; Yakura, T. *Chem. Pharm. Bull.* **1999**, 47(7), 983. d) Zhang, Y.; O'Connor, B.; Negishi, E. *J. Org. Chem.* **1988**, 53, 5590.
8. a) Khoobi, M.; Alipour, M.; Zarei, S.; Jafarpour, F.; Shafiee, A. *Chem. Commun.* **2012**, 48, 2985. b) O'Neill, J.; Yoo, K. S.; Jung, K. W. *Tett. Lett*. **2008**, 49, 7307.
9. Walker, S. E.; Boehnke, J; Glen, P. E.; Levey, S.; Patrick, L.; Jorrdan-Hore, J. A.; Lee, A. L. *Org. Lett.* **2013**, 15(8), 1886.
10. Verma, A. K.; Jha, R. R.; Chaudhary, R.; Tiwari, R. K.; Danodia, A. K. *Adv. Synth. Catal*. **2013**, 355, 421.
11. Wu, X.; Zhou, J. *Chem. Commun*. **2013**, 49, 4794.
12. Santelli, M.; Doucet, H.; Fall, Y. *Tetrahedron*, **2009**, 65, 489.
13. Xie, Y. X.; Wang, D .P.; Li, J. H. *Synthesis*, **2005**, 13, 2193.
14. a) Jepsen, T. H.; Larsen, M.; Jørgensen, M.; Niesen, M. B.; *Synlett* **2012**, 23, 418. b) Lautens, M.; Fang, Y. Q. *Org. Lett*. **2003**, 5(20), 3679. c) Hartung, C. G.; Kohler, K.; Beller, M.; *Org. Lett.* **1999**, 1, 709.
15. Reetz, M. T.; de Vries, J. G. *Chem. Commun.* **2004**, 1559.
16. Jeffrey, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287.
17. de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M.; Henderickx, H. J. W.; de Vries, J. G. *Org. Lett.* **2003**, 5(18), 3285.
18. Lautens, M.; Fang, Y. –Q.*Org. Lett.* **2013**, 5(20), 3679.
19. *General procedure for Heck coupling*: A solution of aryl halide (2.67 mmol) and cyclic alkenone (3.2 mmol) in DMSO (5 ml) was stirred at ambient temperature for 10 min under nitrogen, and treated with Na_2CO_3 (8.01 mmol) and tri-tert-butylphosphonium tetrafluoroborate (0.53 mmol). The reaction mixture was degassed with nitrogen for 10 min and treated with $Pd(PPh_3)_2Cl_2$ (0.13 mmol) and X-Phos (0.26 mol), and stirred at 100 ^{0}C for 12 h. The reaction mixture was cooled to ambient temperature, diluted with water, and extracted with AcOEt (3 x 50 ml). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated. Flash chromatography on silica gel (AcOEt:Cyclohexane 1:3) provided the Heck coupling product.

Supplementary Material

Experimental procedures and characterization data for all compounds.

Scheme 1: Heck reaction between cyclopent-2-en-1-one and 2,4-dimethoxy-1-bromobenzene.

Scheme 2: Substrate scope of arylbromides for the Heck reaction with cyclopent-2en-1-one.

Scheme 3: Substrate scope of cyclic alkenones for the Heck reaction with 2,4-dimethoxy-1-bromobenzene.

Scheme 4: Proposed hypothetical mechanism for the selective Heck reaction of electron rich aryl bromides with cyclic alkenones.