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1-(2-Iodophenyl)-1H-tetrazole as a ligand for Pd(II) catalyzed Heck reaction

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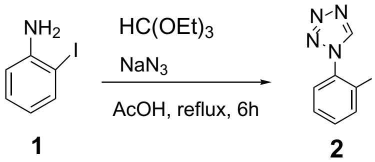
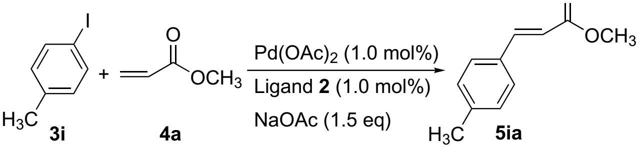
Abstract—1-(2-Iodophenyl)-1H-tetrazole **2** was synthesized by the reaction of 2-iodoaniline, sodium azide and triethyl orthoformate in acetic acid. The newly synthesized ligand **2** was successfully used in Heck reaction to give the cross-coupled products in excellent yields.

For the construction of carbon–carbon single bond, Heck reaction has become one of the standard protocols in the organic synthesis[1] and also it became a bench mark to estimate the efficiency of a catalytic system. In general, phosphine palladium complexes are employed for Heck reactions under inert atmosphere to minimize the deleterious effect of oxygen in the air. Therefore, many research groups have been seriously involved in the development of easy-handling catalysts, which have highly efficient catalytic activity and are stable towards oxidants and moisture variations.[2] Recently new types of nonphosphine ligands such as heterocyclic carbenes, imines, imidazoles and 1,2,3-triazoles have emerged as an alternative for the Heck reaction.[3] Though heterocyclic carbenes show good to excellent catalytic activities with palladium, they easily undergo decomposition pathways at higher temperature.[4] Also nitrogen-based ligands are sensitive towards acidic conditions. There are very few examples that tetrazoles were used as ligands[5] with Ni or Ru. To our knowledge, reports on usage of tetrazole in palladium- or platinum-catalyzed reactions are scarce.[6] Literature reveals that tetrazole functionality survives as one of the important pharmacophore in medicinal chemistry as well as synthon in synthetic organic chemistry.[7] In continuation of our research interest in the development of new and novel synthetic methodologies and catalysts,[8] here we wish to report synthesis of 1-(2-iodo-phenyl)-1H-tetrazole (**2**), a new and novel ligand, which worked efficiently in Heck reaction with good TON and TOF. Ligand **2** was readily prepared in one step from 2-iodo aniline, triethyl orthoformate and sodium azide in acetic acid at 6 h reflux condition (Eq. 1).[9]



(1)

It should be noted that catalyst in this study was neither preformed nor preactivated by any agents. The palladacycle can be easily formed by simply mixing $Pd(OAc)_2$ and base (2 equiv) together under reaction conditions. A characteristic feature of our palladacycle is the thermal stability, which makes it possible to perform the reactions even at temperature above 100 °C, which is necessary for less reactive substrates such as aryl bromides. We assume that ligand **2** can coordinate with palladium either through nitrogen as in the case of 1,2,3-triazole pincer ligand (NCN)[10] or by C–H activation as in the case of 1,2,4-triazole pincer ligand (NHC).[11]



(2)

Keywords: 1H-Tetrazole; Aryl halides; Arylboronic acids; Heck reaction.

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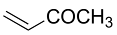
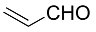
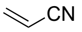
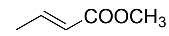
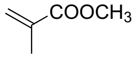
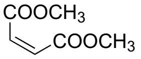
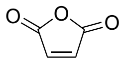
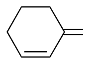
Table 1. Heck arylation of methyl acrylate **4a** with 4-iodotoulene **3i** in various solvents

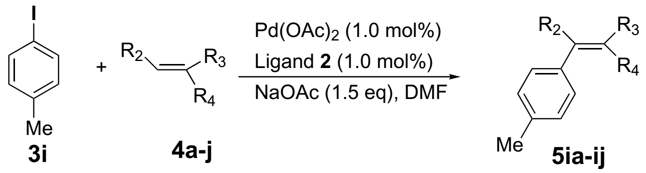
Entry	Solvent	Temp (°C)	Time (h)	% Yield (conversion)
1	THF	60	48	30 (70)
2	Toluene	120	48	45 (50)
3	Chlorofom	60	48	35 (70)
4	DMF	80	6	98 (100)
5	1,4-Dioxane	100	12	75 (80)

In view of the optimization of the reaction conditions, we have performed the reaction of 4-iodotoulene **3i** with methyl acrylate **4a** in various solvents (Eq. 2). Table 1 showed that DMF was the suitable solvent for our study. These reactions are highly selective and proceed without formatting biphenyl. We found that ligand **2** is more effective than classical Pd(II) salts, because Pd(II)acetate itself catalyzes the Heck reaction a little, when aryl iodides are used. Although we have not attempted to search for lowest possible loads of the precatalyst in the reactions with arylhalides, we have tested the higher limits of activity of the palladacycle (0.01 mol%), in the reaction of 4-iodotoulene **3i** with methyl acrylate **4a** with very low load of ligand and catalyst (Table 2). The use of 1.0 mol% catalyst was turned out to be optimal condition to yield the Heck reaction product **5ia**.

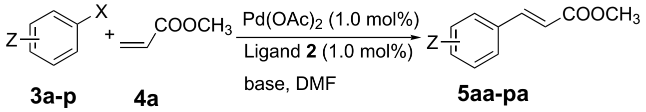
In order to check the activity of ligand **2**, we have performed the reaction with various types of α,β-unsaturated carbonyl compounds **4a-j**, that is highly reactive substances like methyl vinylketone **4b**, acrolien **4c** and acrylonitrile **4d**, substituted α,β-unsaturated carbonyl compounds such as α-methyl methacarylate **4e** and methyl crotonate **4f**, and very less reactive substance such as acryl amide **4g** (Eq. 3). Reactions of all α,β-unsaturated carbonyl compounds **4b–g** gave the corresponding Heck products in good to excellent yields (Table 3). But reactions with diethyl maleate **4h**, maleic anhydride **4i** and cyclohexenone **4j** were ended up to the products in 72%, 65% and 68% yields, respectively. It is surprising that acrylamide **4g**, the least reactive substrate among α,β-unsaturated carbonyl compounds **4a–j**, gave **5id** in almost quantitative yield. To our delight, further data indicated that these Heck reactions catalyzed by the tetrazole–Pd complex afforded to the products **5** stereoselectively in good to excellent yields. Next, we have tested various aryl halides **3a–p** with methyl acrylate (**4a**) (Eq. 4) and the results thus obtained are summarized in Table 4.[12]

Table 3. Reactions of 4-iodotoulene **3i** with various α,β-unsaturated carbonyl compounds (**4a–j**)

Entry	4	Temp (°C)/ Time (h)	Products	% Yield
1	 **4a**	80, 6	**5ia**	99
2	 **4b**	100, 12	**5ib**	93
3	 **4c**	80, 10	**5ic**	96
4	 **4d**	100, 10	**5id**	96
5	 **4e**	120, 15	**5ie**	79
6	 **4f**	120, 12	**5if**	82
7	 **4g**	80, 12	**5ij**	78
8	 **4h**	80, 10	**5ih**	72
9	 **4i**	100, 12	**5ii**	65
10	 **4j**	120, 12	**5ij**	68



(3)



(4)

It is remarkable that our ligand **2** exhibited good catalytic activity in the Heck reaction even for arylbromides

Table 2. Heck reaction of methyl acrylate **4a** with 4-iodotoluene **3i** at various catalyst concentration[a]

Entry	Catalyst (mol%)	Temp (°C)	Time (h)	Yield (%)[b]	TON[c]	TOF[d] (h^{-1})
1	10	80	6	100	100	16.6
2	**1. 0**	**80**	**6**	**99**	**988**	**164**
3	0.1	80	10	87	8793	879
4	0.01	80	24	56	5600	233

[a] Reaction condition: 4-CH_3–PhI (0.01 mol) methyl acrylate (0.02 mol), DMF solvent (25 mL), 80–100 °C, NaOAc (2.0 equiv).

[b] Isolated yield.

[c] TON: turnover number (mol product per mol catalyst).

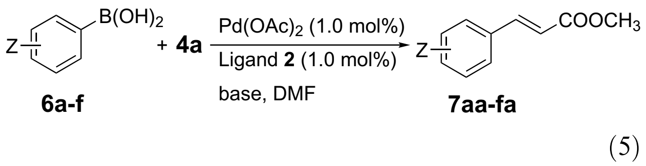
[d] TOF: TON per hour.

Table 4. Reactions of aryl halides with methyl acrylate

Substrates			Base	Temp (°C)/Time (h)	% Yield
No	Z	X			
3a	H	Br	K_2CO_3, TBAB	120, 24	65
3b	4-Me	Br	K_2CO_3, TBAB	120, 14	76
3c	2-Me	Br	K_2CO_3, TBAB	120, 32	57
3d	4-CHO	Br	K_2CO_3, TBAB	120, 12	67
3e	4-OMe	Br	K_2CO_3, TBAB	120, 14	76
3f	2-CHO	Br	K_2CO_3, TBAB	120, 12	47
3g	2,6-$(CH_3)_2$	Br	K_2CO_3, TBAB	120, 48	15
3h	H	I	NaOAc	80, 14	86
3i	4-Me	I	NaOAc	80, 6	99
3j	4-OMe	I	NaOAc	80, 12	94
3k	4-NO_2	I	NaOAc	100, 12	95
3l	4-$COCH_3$	I	NaOAc	80, 12	91
3m	4-CHO	I	NaOAc	80, 12	78
3n	3-CHO	I	NaOAc	80, 15	69
3o	4-CN	I	NaOAc	80, 15	79
3p	4-Br	I	NaOAc	80, 6	81
3q	4-Me	Cl	K_2CO_3, TBAB	120, 48	39

3a–g. As Hermann et al. has reported, we have added an additive, tetrabutylammoniumbromide (TBAB), to increase the reactivity (substrates **3a–f**).[13] To check the reactivity of the ligand on sterically hindered aryl halides, we have taken 2,6-dimethylbromobenzene **3g**, but it gave the product **5ga** only in 15% yield even after refluxing conditions. All type of aryl iodides **3h–p** gave the products **4ha–pa** in good to excellent yields with our ligand at 80–100 °C. It is interesting that we have observed a high chemoselectivity when we used 4-bromoiodobenzene **3p**, where only the iodo group was involved in the reaction under these conditions. As expected, the low relativity was observed when we used 4-chlorotoluene **3q**.

Since the report on Heck reactions of arylboronic acids with α,β-unsaturated carbonyl compounds under ligand support is scarce,[14] we extended our work to arylboronic acids. Ligand **2** has showed moderate activity for the reaction of arylboronic acids **6a–f** with methyl acrylate **4a** in the presence of $Mn(OAc)_2$ as an additive (Eq. 5). The results thus obtained were described in Table 5.



(5)

Table 5. Reactions of arylboronic acids with methyl acrylate

Arylboronic acid		Reaction condition		Yield (%)
No	Z	Temp (°C)	Time (h)	
6a	H	110	12	75
6b	4-Me	110	12	62
6c	3,5-$(Me)_2$	110	12	67
6d	4-OMe	110	12	61
6e	2,6-$(OCH_3)_2$	110	12	33
6f	3,5-F_2	100	12	58

In conclusion, we have synthesised the new ligand 1-(2-iodophenyl)-1H-tetrazole **2** and demonstrated that combination of the ligand **2** with $Pd(OAc)_2$ could be an effective catalyst for Heck reactions. Also an excellent chemoselectivity in case of 4-bromoiodobenzene **3p** was observed. The new ligand is air, water and heat stable. Further studies aimed at the improvement of the catalytic activity of our nitrogen catalysts are in progress.

Acknowledgements

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12. Palladium acetate (2.24 mg, 0.01 mmol), ligand **2** (2.72 mg, 0.01 mmol) and base (2 equiv) were taken in DMF (10.0 mL) and the mixture was stirred at room temperature for 1 h. Appropriate aryl halide **3** or aryl boronic acid **6** (1 mmol) and acrylates **4** (2 mmol) were added followed by another additional portion of DMF (1.0 mL). The mixture was then stirred at 80–120 °C. The reaction completion was monitored by TLC. The reaction mixture was cooled, diluted with 50 mL of water and extracted with ether (2 × 50 mL). The combined organic portion was washed with brine solution, dried over anhydrous magnesium sulfate and finally filtered. Evaporatation of the volatiles under reduced pressure to get the corresponding product.
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