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Heck reaction with heteroaryl halides in the presence of a palladium–tetraphosphine catalyst

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Abstract—*cis,cis,cis*-1,2,3,4-Tetrakis(diphenylphosphinomethyl)cyclopentane/$\frac{1}{2}$[PdCl(C_3H_5)]$_2$ system catalyses efficiently the Heck reaction of heteroaryl halides with *n*-butyl acrylate, styrene, vinylpyridine and vinyl ether derivatives. High turnover numbers can be obtained for the reactions with halo pyridines, quinolines, furans or thiophenes. © 2002 Elsevier Science Ltd. All rights reserved.

Heteroaryl compounds have important biological properties. The palladium-catalysed Heck reaction between heteroaryl halides and alkenes provides a very efficient method for the preparation of several heteroaryl derivatives.[1] A few ligands have been successfully used for the reaction in the presence of these substrates.[2,3] The most popular ones are triphenylphosphine or tri-*ortho*-tolylphosphine. Even if the catalysts formed by association of these ligands with palladium complexes are quite efficient in terms of yield of adduct, the efficiency in terms of ratio substrate/catalyst is quite low. In most cases, fast decomposition of the catalysts occurs, and 1–10% of these catalysts must be used. For a few years, some very efficient catalyst have been described for Heck reaction.[4] For example, Herrmann, Beller et al. have reported that the palladacycle [Pd(*o*-tol)(OAc)]$_2$ is very efficient for the reaction of arylhalides with *n*-butyl acrylate or styrene.[5] The efficiency of such palladacycles for the reaction with several aryl halides has been studied in detail. However, the reaction with heteroaryl halides in the presence of these stable catalysts has attracted less attention, and to the best of our knowledge, the efficiency of tetraphosphine ligands has not been demonstrated.

The nature of phosphine ligands on complexes has an important influence on the rate of catalysed reactions. In order to obtain highly stable palladium catalysts, we have prepared the new tetraphosphine ligand,[6] *cis,cis,cis* - 1,2,3,4 - tetrakis(diphenylphosphinomethyl) - cyclopentane or tedicyp[7a] (Fig. 1) in which four diphenylphosphino groups are stereospecifically bound to the same face of a cyclopentane ring. The presence of these four phosphines close to the metal centre seems to increase the coordination of the ligand to the metal and therefore increases the stability of the catalyst. We have reported recently the first results obtained in allylic substitution,[7] for Suzuki cross-coupling[8] and for Heck reaction[9] using tedicyp as the ligand. Herein, we wish to report on the Heck reaction with heteroaryl halides and acrylate, styrene, vinylpyridine or vinyl ether derivatives in the presence of tedicyp ligand.

For this study, based on our previous results,[9] DMF was chosen as the solvent and potassium carbonate as the base. The reactions were generally performed at 140°C under argon in the presence of a ratio 1/2 of [Pd(C_3H_5)Cl]$_2$/tedicyp as catalyst.

First, we studied the influence of the position of the bromo substituent on pyridines on the rate of the reaction with *n*-butyl acrylate (Scheme 1, Table 1). Due to the electronegativity of the nitrogen atom, the α and γ positions of halo pyridines should be the most susceptible to the oxidative addition to Pd(0).[1] In fact, we observed higher reaction rates for the coupling with the β and γ-substituted bromopyridines. For the reactions

Tedicyp

Figure 1.

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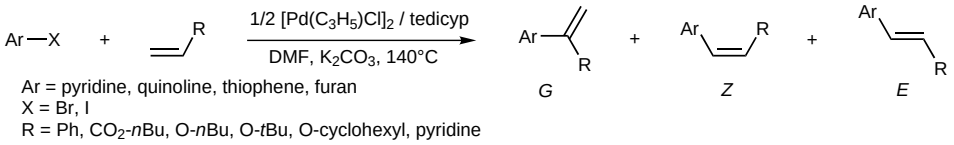

Scheme 1.

with *n*-butyl acrylate, TONs of 96 000 and 42 000 were obtained, respectively (entries 8 and 15). With the α-substituted bromopyridine a low TON of 50 was observed (entry 1). With this substrate, the formation of 2,2′-bipyridine was also observed.[10] The formation of this side product, which can act as a poison for palladium catalysts, might be the reason of the low reactivity of 2-bromopyridine. In the presence of styrene a similar tendency was observed: 3- and 4-bromopyridines are much more reactive than 2-bromopyridine (entries 2, 9, 10, 16 and 17). With styrene and 3-bromopyridine the reaction can be performed with as little as 0.001% catalyst. Then, we studied the influence of halogen on the reaction. In the presence of 3-iodopyridine similar reaction rates to with 3-bromopyridine are observed (entries 3–7). This result seems to indicate that the oxidative addition of these 3-halopyridines to palladium is not the rate-limiting step of the reaction. A double Heck reaction has also been performed successfully with 3,5-dibromopyridine. This substrate with *n*-butyl acrylate or styrene in the presence of 0.1–0.2% catalyst led selectively to the diaddition products (entries 19 and 20).

Next, we studied the reactivity of bromoquinolines, and we observed that their reactivity is similar to pyridines. 3-Bromoquinoline in the presence of *n*-butyl acrylate or styrene led the addition products in 960 000 and 61 000 TONs, respectively (entries 21 and 22). In the presence of the sterically hindered 4-bromoisoquinoline, lower TONs were obtained: 5000 and 4300 (entries 26–29).

Then, we tried to determine the efficiency of the Pd/tedicyp catalyst in the presence of halo thiophenes. First, we studied the reaction with 2-iodo- and 2-bromothiophenes. The reaction rates with these two substrates in the presence of styrene are quite similar, indicating that the oxidative addition to palladium of these 2-halo thiophenes is probably not the rate-limiting step of the reaction (entries 33 and 38). However, in the presence of *n*-butyl acrylate, we observed higher reaction rates with 2-iodothiophene than with 2-bromothiophene (entries 31, 32, 35 and 36). We also studied the influence of the position of the halogen on thiophenes and we observed that with 3-bromothiophene, slightly lower TONs were obtained: 500–3400 (entries 42–44). The β,β′-disubstituted 3,4-dibromothiophene is not very reactive. The diaddition product using *n*-butyl acrylate can be obtained, however the reaction requires 4% catalyst (entry 46). In the presence of 0.4% catalyst the mono addition product can be obtained quite selectively (entry 47).

A bromofuran: 5-bromo-2-furaldehyde with *n*-butyl acrylate or styrene also led to the addition products. However, these products are not thermally stable and the reactions have to be performed at a lower temperature (entries 48 and 49).

With these heteroaryl halides, several reactions were also performed in the presence of vinyl ethers. Pyridines and quinolines are π-electron deficient heterocycles. The regioselectivity of the addition to π-electron deficient heterocycles should be in favour of the linear isomers *Z* and *E* (Scheme 1). Thiophenes are π-electron excessive.[1] With these heterocycles, the regioselectivity of the reaction should be in favour of the branched isomer *G* (Scheme 1). We observed in all cases the formation of mixtures of linear and branched products. As expected, in the presence of halo pyridines and quinolines the regioselectivity is generally in favour of the linear isomers. They can be obtained in 59–74% selectivity (entries 12, 18, 24, 25 and 30). With thiophenes, the regioselectivity in favour of the branched isomer is very high. This regioisomer is obtained in 89–95% selectivity when 2-halothiophenes are used (entries 34, 39 and 40) and in 95% selectivity with 3-bromothiophene (entry 45).

Finally, a few reactions with the heteroalkenes 2- and 4-vinylpyridines have been performed. The reaction of iodobenzene with 2-vinylpyridine is very slow (entries 50 and 51). Much higher reaction rates are observed in the presence of 4-vinylpyridine (entries 52–54). With this substrate and 3-bromopyridine or 2-bromothiophene, the synthesis of heterobiaryl adducts was also performed in good yields (entries 13 and 41).

In conclusion, the use of the tetradentate ligand tedicyp associated to a palladium complex provides a convenient catalyst for the Heck reaction with several heteroaryl compounds. This catalyst seems to be much more efficient than the complexes formed with triphenylphosphine ligand. This efficiency probably comes from the presence of the four diphenylphosphinoalkyl groups stereospecifically bound to the same face of the cyclopentane ring which prevent precipitation of the catalyst. In the presence of this catalyst, the Heck vinylation of heteroaryl halides such as 3-bromopyridine or 3-bromoquinoline with *n*-butyl acrylate, styrene or vinyl ether derivatives can be performed with as little as 0.1–0.0001% catalyst. These results represent an environmentally friendly procedure. Moreover, due to the high price of palladium, the practical advantage of such low catalyst loading reactions can become increasingly important for industrial processes.

Table 1. Heck reaction catalysed by tedicyp–palladium complex[11]

Entry	Aryl halide	Alkene	Ratio substrate/catalyst	Yield (%)[a]
1	2-Bromopyridine	*n*-Butyl acrylate	100	50[b]
2	2-Bromopyridine	Styrene	100	40[b]
3	3-Iodopyridine	*n*-Butyl acrylate	10 000	100[c]
4	3-Iodopyridine	*n*-Butyl acrylate	100 000	55
5	3-Iodopyridine	Styrene	10 000	43
6	3-Iodopyridine	*n*-Butyl vinyl ether	10 000	88 (54/25/21)
7	3-Iodopyridine	Cyclohexyl vinyl ether	1000	68 (60/7/33)
8	3-Bromopyridine	*n*-Butyl acrylate	100 000	96[d]
9	3-Bromopyridine	Styrene	10 000	89
10	3-Bromopyridine	Styrene	100 000	42[c]
11	3-Bromopyridine	*n*-Butyl vinyl ether	10 000	75 (54/24/22)
12	3-Bromopyridine	Cyclohexyl vinyl ether	1000	87 (41/29/30)
13	3-Bromopyridine	4-Vinylpyridine	1000	84
14	4-Bromopyridine[e]	*n*-Butyl acrylate	10 000	82
15	4-Bromopyridine[e]	*n*-Butyl acrylate	100 000	42[c]
16	4-Bromopyridine[e]	Styrene	1000	90
17	4-Bromopyridine[e]	Styrene	10 000	98[c]
18	4-Bromopyridine[e]	*n*-Butyl vinyl ether	1000	61 (26/26/48)
19	3,5-Dibromopyridine	*n*-Butyl acrylate	1000	92[f]
20	3,5-Dibromopyridine	Styrene	500	90[f]
21	3-Bromoquinoline	*n*-Butyl acrylate	1 000 000	96[d]
22	3-Bromoquinoline	Styrene	100 000	61
23	3-Bromoquinoline	*n*-Butyl vinyl ether	10 000	76 (50/21/29)
24	3-Bromoquinoline	Cyclohexyl vinyl ether	1000	89 (41/23/36)
25	3-Bromoquinoline	*t*-Butyl vinyl ether	1000	32 (35/35/30)
26	4-Bromoisoquinoline	*n*-Butyl acrylate	1000	93
27	4-Bromoisoquinoline	*n*-Butyl acrylate	10 000	50[c]
28	4-Bromoisoquinoline	Styrene	1000	94
29	4-Bromoisoquinoline	Styrene	10 000	43[c]
30	4-Bromoisoquinoline	*n*-Butyl vinyl ether	1000	87 (54/20/26)
31	2-Iodothiophene	*n*-Butyl acrylate	10 000	96
32	2-Iodothiophene	*n*-Butyl acrylate	100 000	55[c]
33	2-Iodothiophene	Styrene	10 000	80
34	2-Iodothiophene	*n*-Butyl vinyl ether	1000	86 (95/4/1)
35	2-Bromothiophene	*n*-Butyl acrylate	1000	87
36	2-Bromothiophene	*n*-Butyl acrylate	10 000	56[c]
37	2-Bromothiophene	Styrene	1000	96
38	2-Bromothiophene	Styrene	10 000	74[c]
39	2-Bromothiophene	*n*-Butyl vinyl ether	1000	68 (89/3/8)
40	2-Bromothiophene	Cyclohexyl vinyl ether	100	71 (93/2/5)
41	2-Bromothiophene	4-Vinylpyridine	1000	95
42	3-Bromothiophene	*n*-Butyl acrylate	1000	100[c]
43	3-Bromothiophene	*n*-Butyl acrylate	10 000	34
44	3-Bromothiophene	Styrene	1000	50
45	3-Bromothiophene	*n*-Butyl vinyl ether	250	25 (95/5/0)
46	3,4-Dibromothiophene	*n*-Butyl acrylate	25	95[f]
47	3,4-Dibromothiophene	*n*-Butyl acrylate	250	65[g]
48	5-Bromo-2-furaldehyde	*n*-Butyl acrylate	1000	68[h]
49	5-Bromo-2-furaldehyde	Styrene	1000	61[h]
50	Iodobenzene	2-Vinylpyridine	100	85
51	Iodobenzene	2-Vinylpyridine	1000	24[c]
52	Iodobenzene	4-Vinylpyridine	10 000	98[c]
53	Iodobenzene	4-Vinylpyridine	100 000	40
54	4-Bromobenzophenone	4-Vinylpyridine	10 000	68

Conditions: catalyst $[Pd(C_3H_5)Cl]_2$/tedicyp 1/2 see Ref. 7a, ArX (1 equiv.), alkene (2 equiv.), K_2CO_3 (2 equiv.), DMF, 140°C, 24 h, under argon, isolated yields.

[a] For the reactions with *n*-butyl acrylate, styrene, 2-vinylpyridine, 4-vinylpyridine, *E* isomer was obtained selectively (>95%); for the reactions with vinyl ethers the regio- and stereoselectivities are given in brackets (*G*/*Z*/*E*) (Scheme 1).

[b] The formation of 2,2′-bipyridine was also observed.

[c] GC or NMR yields.

[d] Reaction time: 48 h.

[e] Commercially available 4-bromopyridine hydrochloride was not used directly.

[f] Alkene 4 equiv., K_2CO_3 4 equiv., the diaddition products were obtained selectively.

[g] Alkene 4 equiv., K_2CO_3 4 equiv., the ratio monoaddition/diaddition products was 82/18.

[h] Reaction temp. 80°C.

Acknowledgements

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