Palladium/Tetraphosphine Catalysed Heck Reaction with *ortho*-Substituted Aryl Bromides

Marie Feuerstein, Henri Doucet,* Maurice Santelli*

Laboratoire de Synthèse Organique associé au CNRS, Faculté des Sciences de St-Jérôme, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France

Fax +33(491)983865; E-mail: henri.doucet@lso.u-3mrs.fr; E-mail: m.santelli@lso.u-3mrs.fr

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Abstract: The tetraphosphine cis, cis, cis, 1, 2, 3, 4-tetrakis(diphenylphosphinomethyl)cyclopentane associated to $[PdCl(C_3H_3)]_2$ catalyses the Heck reaction of butyl acrylate with a wide range of sterically demanding aryl bromides, furnishing the addition product in high yields. Turnover numbers as high as 630–89000 have been obtained using *ortho*-substituted aryl bromides and 43–2600 with di-*ortho*-substituted aryl bromides in the presence of this catalyst.

Key words: catalysis, palladium, tetraphosphine, Heck reaction, aryl bromides

The Heck reaction is one of the most widely used palladium-catalysed methodology in organic synthesis.¹ However this reaction is sensitive to the steric effects of the substituents which are on the aryl halide and on the olefin. Most catalysts do not effectively couple hindered substrates. With hindered aryl bromides low reaction rates are often observed, and with sterically hindered olefins the reaction is even slower. In general, fast decomposition of the catalysts occurs. A few ligands have been employed with sterically hindered aryl bromides. The most popular ones are triphenylphosphine² or tri-*ortho*-tolylphosphine.³ 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 low. In general 1-10% of these catalysts must be used. In recent years a few more robust catalysts have been prepared and tested with these substrates. For example, Herrmann et al. have reported that the palladacycle⁴ [Pd(o-tol)(OAc)]₂ is efficient for the reaction of 2-bromotoluene with *n*-butyl acrylate.⁵ Very recently, Fu et al. described that the ligand $P(t-Bu)_3$ is also an efficient catalyst for sterically hindered substrates even at room temperature.⁶ A few other ligands also led to useful catalysts.⁷ If monophosphines or palladacycles have been successfully used for the reaction with sterically hindered aryl bromides, to the best of our knowledge, the efficiency of tetraphosphines ligands has not yet been demonstrated.

The nature of phosphine ligands has an important effect on the rate of transition-metal catalysed reactions. In order to find more efficient palladium catalysts we have prepared a new tetrapodal⁸ phosphine ligand, *cis,cis,cis*

1,2,3,4-tetrakis(diphenylphosphino-methyl)cyclopentane or tedicyp 1^{9a} (Figure). The presence of 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. A very high efficiency has been observed in allylic substitution,⁹ and for Suzuki crosscoupling using tedicyp as the ligand.¹⁰ We have also reported recently the first results obtained for Heck reactions.¹¹ For example, a TON of 210000000 for the reaction of 3,5-bistrifluoromethylbromobenzene with butyl acrylate acid was observed. While Pd/tedicyp provided an efficient method for accomplishing Heck reaction, we felt that important challenges remained, including demonstrating the broader scope particularly with respect to sterically demanding substrates. In this paper, we wish to report the efficiency of this ligand for the Heck reaction using ortho and di-ortho-substituted aryl bromides.



Tedicyp 1

Figure

First, we studied the influence of the presence of one ortho substituent at the aryl bromide on the rate of the reaction. For this study, based on our previous results,¹¹ DMF was chosen as the solvent and potassium carbonate as the base. The reactions were performed at 130 °C in the presence of a ratio 1/2 of [Pd(C₃H₅)Cl]₂/tedicyp as catalyst. Although this catalyst is quite air-stable,¹¹ the reactions were performed under argon. As illustrated in the Table, using these conditions, we observed that the coupling of 2-methylbromobenzene with *n*-butyl acrylate in the presence of 0.01% catalyst led to the addition adduct in 78% yield (TON 7800) (Scheme). A slightly higher reaction rate was obtained using similar conditions with 1bromonaphthalene (TON 43000). With 2-bromobiphenyl, 2-bromoanisole or 2,4-dimethoxy-bromobenzene lower reaction rates were observed (TONs 630-2100). On the other hand, in the presence of activated aryl bromides such as 2-fluorobromobenzene, 2-trifluoromethylbromobenzene, 2-bromobenzaldehyde, 2-bromobenzonitrile or 2-bromonitrobenzene high reaction rates are observed (2500–89000). Next, we turned our attention to the reaction with 2-bromophenol, and we also observed very high

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reaction rates. However, with this substrate we also observed the formation of an important amount of coumarin, which comes from the cyclisation of *n*-butyl 2-hydroxycinnamate. A longer reaction time led to complete transformation on this hydroxycinnamate into coumarin. This cyclisation is not palladium-catalysed: in absence of palladium, using similar reaction conditions (DMF, K₂CO₃, 130 °C), the cyclisation also proceeds. The Heck reaction was also performed using 2-bromoaniline. With this substrate relatively high reaction rates were also observed, however several side products were formed.

Next, we tried to evaluate the difference of reaction rate between mono- and di-*ortho*-substituted aryl bromides and we were pleased to find that the reaction proceeds efficiently even on very hindered aryl bromides, although lower reaction rates were observed than with mono-*ortho*substituted aryl bromides. For example, with 9-bromoanthracene, 1-bromo-2-methylnaphthalene and 1-bromo-2methoxynaphthalene TONs of 450–2600 were obtained. A very significant steric effect was observed in the presence of the extremely sterically demanding aryl bromides 1-bromo-2,6-dimethylbenzene and 1-bromo-2,4,6-triisopropylbenzene. For these substrates TONs of 380 and 43 were obtained, respectively.

Finally, in order to present a simple procedure using a commercially available ligand, we performed a few reactions with dppe. Palladium catalyst prepared with dppe as ligand is less active than with 1 by a factor of ten; however the system $[Pd(C_3H_5)Cl]_2/dppe$ (ratio 1/2) is much more stable and efficient than the popular but unstable catalyst $Pd(PPh_3)_4$. With dppe good yields were obtained with 2-bromobenzaldehyde or 2-bromobenzonitrile in the presence of 0.1% catalyst.





In conclusion, the tedicyp/palladium complex shows high catalytic activity and yields in the Heck reaction of sterically hindered aryl bromides. The system exhibits unprecedented turnovers with such substrates. This catalyst is more efficient than the complexes formed with triphenylphosphine ligand or simple diphosphines such as dppe. This high activity comes from the high stability, even at high temperature, of this catalyst. This stability probably result from the presence of the four diphenylphosphinoalkyl groups stereospecifically bound to the same face of the cyclopentane ring, which seems to increases the coordination of the ligand to the metal and prevents precipitation of the catalyst. The Heck reaction of ortho- and diortho-substituted bromobenzene derivatives can be performed with as little as 0.001% catalyst. Further applications of the tedicyp ligand will be reported in due course.

Table Palladium/tedicyp catalysed Heck Reaction¹²

Aryl bromide	Ligand	Ratio substrate– catalyst	Time (h)	Yield (%)
2-methyl-bro- mobenzene	1 1	1000 10000	20 20	100 ^a 78
	1	100000	48	14 ^a
1-bromo- naphthalene	1	10000	72 20	91 43ª
Implianatorio	-	100000	20	10
2-bromo-	1	1000	20	57ª
biphenyl	1	1000	48	95
	1	10000	20	8"
2-bromo	1	1000	48	72
anisole	1	10000	20	21 ^a
2,4-dimethoxy- bromobenzene	1	1000	20	63
2 fluoro bro	1	10000	20	66a
2-IIu0I0-0I0- mohenzene	1	10000	20 48	94
mobelizene	1	10000	20	7 ^a
	-	100000	20	
2-trifluorometh-	1	1000	20	90
yl-bromobenzene	1	10000	20	62 ^a
	1	10000	48	97 ^a
2-bromo-benzal-	dppe	1000	20	88
dehyde	1	1000	20	98 ^a
5	1	10000	48	72
		1000	•	. .
2-bromo-benzo-	dppe	1000	20	95
nitrile	1	10000	20	100"
	1	100000	20	09 7ª
	1	1000000	20	1
2-bromo-nitro-	dppe	1000	20	48^{a}
benzene	1	1000	20	92
	1	10000	20	25^{a}
2-bromonhenol	1	10000	20	82 ^b
2 bromophenor	1	100000	20	40 ^b
2-bromoaniline	1	1000	20	32°
9-bromo-an-	1	1000	20	62
thracene	1	10000	20	22 ^a
	_		• •	
1-bromo-2-meth-	1	1000	20	92 26
yi-naphthalene	1	10000	20	26"
1-bromo-2-meth- oxynaphthalene	1	1000	20	45
2.6-dimethyl-	1	100	48	95 ^a
bromobenzene	1	500	20	46 ^a
	1	500	48	76
0.4.6.4."	1	50	70	0.6
2,4,6-triiso-	1	50	72	86 40a
propytoromo- benzene	1	100	20	40"

Conditions: catalyst see ref.9a, ArBr (1 equiv), n-butyl acrylate

(2 equiv), K₂CO₃ (2 equiv), DMF, 130 °C, isolated yields.

^a GC yield.

^b The formation of coumarin was also observed.

^c The formation of several side products was observed.

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