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Direct synthesis of cinnamaldehyde derivatives by reaction of aryl bromides with 3,3-diacetoxypropene catalyzed by a palladium–tetraphosphine complex

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The tetraphosphine all-*cis*-1,2,3,4-*tetrakis*(diphenylphosphinomethyl)cyclopentane in combination with $[Pd(C_3H_5)Cl]_2$ affords an efficient catalyst for the synthesis of cinnamaldehyde derivatives by reaction of aryl bromides with 3,3-diacetoxypropene. The reaction gave directly the cinnamaldehyde derivatives very selectively. The coupling reaction of heteroaryl bromides or sterically congested aryl bromides such as 2,4,6-trimethylbromobenzene also proceeds.

KEY WORDS: palladium; tetraphosphine; catalysis; Heck reaction; aryl bromide.

Cinnamaldehyde derivatives bearing various substituents on the aromatic ring are useful precursors for synthetic organic chemist. Palladium-catalyzed Heck reaction is one of the most powerful method for the formation of C–C bonds [1–7]. However, the synthesis of cinnamaldehyde derivatives by coupling of aryl bromides and acrolein is difficult due to the low stability and the low boiling point of acrolein. Most of the reaction described with acrolein were performed using reactive but expensive aryl iodides [8–12]. Few results have been described with less reactive aryl bromides [13]. Some examples of synthesis of cinnamaldehyde derivatives using the *protected* acrolein: acrolein diethylacetal have also been described [14]. With this substrate the reactions proceed in good yields with a variety of aryl bromides and iodides. These reactions were performed using $Pd(OAc)_2$ (3%), K_2CO_3 (1.5 equiv.), KCl (1 equiv.), $^nBu_4NOAc$ (2 equiv.) as reaction mixture. However, the reactions performed with acrolein diethylacetal in the presence of a *palladium/phosphine ligand* catalyst led to mixtures of cinnamaldehyde derivatives and 3-arylpropionic esters. Palladium catalysts bearing ligands are often more efficient than "ligand free" palladium catalysts for Heck reaction using aryl bromides [15–23]. In order to obtain selectively cinnamaldehyde derivatives with catalysts bearing phosphine ligands we have studied this reaction in the presence of 3,3-diacetoxypropene. To our knowledge, the selectivity of Heck reaction with 3,3-diacetoxypropene has never been described. We studied this reaction using the thermally stable all-*cis*-1,2,3,4-*tetrakis* (diphenylphosphinomethyl)cyclopentane or tedicyp [24]/palladium catalyst (figure 1). We have already reported some results obtained in allylic substitution [24], for Suzuki cross-coupling [25] and for Sonogashira reaction [26] using this tedicyp/palladium catalyst. We have also reported several results obtained for Heck reaction [27–35]. We herein report on the reaction of aryl and heteroaryl bromides with 3,3-diacetoxypropene.

For this study, based on our previous results [27], DMF was chosen as the solvent. The reactions were performed at 130 °C, under argon, in the presence of a ratio 1/2 of $[Pd(C_3H_5)Cl]_2$/tedicyp as catalyst. 3,3-Diacetoxypropene was prepared on a large scale by addition of 3 mol% of $FeCl_3.6H_2O$ to a mixture of acrolein (1 equiv.) and acetic anhydride (3 equiv.) at 0 °C [36].

First, we studied the reaction of 4-*t*butylbromobenzene with 3,3-diacetoxypropene using K_2CO_3 as base. The formation of 3-(4-*tert*-butylphenyl)propenal was observed selectively in the presence of 1% catalyst (scheme 1, table 1, entry 10). 1-Aryl-3,3-diacetoxypropene was not detected. This observation indicates that the deprotection of the aldehyde function occurs before or during the catalytic cycle. This coupling reaction might proceed by reaction of aryl bromides with palladium followed by coordination of 3,3-diacetoxypropene. Then, the deprotection of the aldehyde would occur during one of the next steps of the catalytic cycle. However, 3,3-diacetoxypropene is not very stable under basic conditions [36], and the addition of acrolein coming from a slow base-deprotection of 3,3-diacetoxypropene to the palladium complex is also possible. Several bases have been tested such as Na_2CO_3, $NaHCO_3$, Cs_2CO_3, K_2CO_3 or KF for the coupling with 4-*t*butylbromobenzene. The best results were obtained

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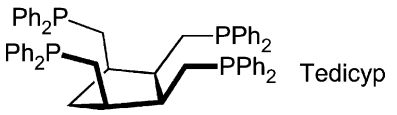
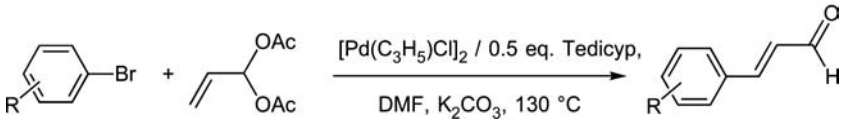


Figure 1. Tedicyp ligand.



Scheme 1.

Table 1
Palladium-catalyzed coupling reaction of aryl halides with 3,3-diacetoxypropene (scheme 1) [37]

Entry	Aryl bromide	Alkene	Product	Ratio substrate/catalyst	Yield[a]
1	Iodobenzene	3,3-Diacetoxypropene	1	1000	100 (89)
2	4-Trifluoromethylbromobenzene	3,3-Diacetoxypropene	2	250	100 (87)
3	4-Trifluoromethylbromobenzene	Acrolein	2	250	0
4	4-Fluorobromobenzene	3,3-Diacetoxypropene	3	100	100 (85)
5	4-Fluorobromobenzene	3,3-Diacetoxypropene	3	250	24
6	4-Fluorobromobenzene	Acrolein	3	100	12
7	Bromobenzene	3,3-Diacetoxypropene	1	250	94 (84)
8	4-Bromotoluene	3,3-Diacetoxypropene	4	100	91 (82)
9	4-Bromotoluene	Acrolein	4	100	0
10	4-*t*Butylbromobenzene	3,3-Diacetoxypropene	5	100	100(91)
11	4-*t*Butylbromobenzene	3,3-Diacetoxypropene	5	250	40
12	4-*t*Butylbromobenzene	3,3-Diacetoxypropene	5	100	57[b]
13	4-*t*Butylbromobenzene	3,3-Diacetoxypropene	5	250	26[c]
14	4-*t*Butylbromobenzene	3,3-Diacetoxypropene	5	250	0[d]
15	4-*t*Butylbromobenzene	3,3-Diacetoxypropene	5	250	0[e]
17	4-*t*Butylbromobenzene	3,3-Diacetoxypropene	5	25	0[f]
18	4-*t*Butylbromobenzene	4-Acrolein	5	50	0
19	3-Trifluoromethylbromobenzene	3,3-Diacetoxypropene	6	250	97 (90)
20	3-Bromotoluene	3,3-Diacetoxypropene	7	100	100 (90)
21	3-Bromotoluene	3,3-Diacetoxypropene	7	250	56
22	2-Bromo-6-methoxynaphthalene	3,3-Diacetoxypropene	8	250	100 (92)
23	2-Bromo-6-methoxynaphthalene	Acrolein	8	250	0
24	2-Trifluoromethylbromobenzene	3,3-Diacetoxypropene	9	100	100 (89)
25	2-Trifluoromethylbromobenzene	3,3-Diacetoxypropene	9	250	67
26	2-Fluorobromobenzene	3,3-Diacetoxypropene	10	100	63 (57)
27	2-Bromotoluene	3,3-Diacetoxypropene	11	100	100 (89)
28	1-Bromonaphthalene	3,3-Diacetoxypropene	12	250	100 (93)
29	1-Bromonaphthalene	3,3-Diacetoxypropene	12	100	2[f]
30	1-Bromonaphthalene	Acrolein	12	100	0
31	2,4,6-Trimethylbromobenzene	3,3-Diacetoxypropene	13	100	46 (42)
32	2,6-Diethyl-4-methylbromobenzene	3,3-Diacetoxypropene	14	50	42 (40)
33	2-Bromopyridine	3,3-Diacetoxypropene	–	100	0[g]
34	3-Bromopyridine	3,3-Diacetoxypropene	15	100	58 (54)
35	3-Bromoquinoline	3,3-Diacetoxypropene	16	250	100 (87)
36	4-Bromoisoquinoline	3,3-Diacetoxypropene	17	100	63 (54)
37	2-Bromothiophene	3,3-Diacetoxypropene	18	100	60 (53)

Conditions: $[ClPd(C_3H_5)]_2$/tedicyp = 1:2, aryl halide: 1 mmol., 3,3-diacetoxypropene or acrolein: 3 mmol., K_2CO_3: 3 mmol., DMF, 130 °C, 20 h, argon, GC and NMR yields.

[a] Yields in parentheses are isolated.

[b] $NaHCO_3$ (3 mmol) was used as base.

[c] Na_2CO_3 (3 mmol) was used as base.

[d] KF (3 mmol) was used as base.

[e] Cs_2CO_3 (3 mmol) was used as base.

[f] Reaction performed with $[ClPd(C_3H_5)]_2$ as catalyst without ligand.

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

with K_2CO_3. Several reactions using directly acrolein instead of 3,3-diacetoxypropene using similar conditions (DMF, K_2CO_3, 130 °C) were also performed, but in all cases except one the cinnamaldehyde derivative was not detected (table 1, entries 3, 6, 9, 18, 23 and 30). These results seem to indicate that at the elevated temperature required for this reaction (130 °C), acrolein rapidly polymerises. It should also be noted that the two reactions performed with $[Pd(C_3H_5)Cl]_2$ as catalyst in absence of ligand were unsuccessful (Table 1, entries 17 and 29).

Next, we studied the influence of some substituents on the aryl bromide of the reaction-rate and on the selectivity. We observed that in most cases the reactions performed with 3,3-diacetoxypropene proceed very smoothly and the cinnamaldehyde derivative was obtained selectively (scheme 1, table 1). Complete conversions can be achieved with 1–0.4% of this catalyst for activated substrates such as 4-trifluoromethylbromobenzene or 4-fluorobromobenzene (table 1, entries 2, 4 and 5). With the deactivated aryl bromides 4-bromotoluene or 4-tbutylbromobenzene similar reactions rates were observed indicating that the oxidative addition is probably not the rate-limiting step of this reaction (table 1, entries 8, 10 and 11). We also compared the reactivity of iodo- and bromobenzene and, we observed a slower reaction with bromobenzene than with iodobenzene (table 1, entries 1 and 7).

Then, we studied the influence of the presence of *ortho* substituents on the aryl bromides on the reaction rate. We observed that the coupling of 2-trifluoromethylbromobenzene or 2-fluorobromobenzene also proceeds in the presence of 1–0.4% catalyst (table 1, entries 24–26). With the other *ortho*-substituted aryl bromides: 2-bromotoluene or 1-bromonaphthalene similar reaction rates were observed. These results indicate that the presence of one *ortho*-substituent on the aryl bromide has a minor effect on the kinetic of the reaction. Then, we tried to evaluate the difference of reaction rate between mono- and di-*ortho*-substituted aryl bromides, and we observed that even the hindered aryl bromides 2,4,6-trimethylbromobenzene or 2,6-diethyl-4-methylbromobenzene could be coupled with 3,3-diacetoxypropene. However, slower reactions were observed in both cases (table 1, entries 31 and 32). Finally, we have investigated this reaction in the presence of five heteroaryl bromides. With 3-bromopyridine, 3-bromoquinoline, 4-bromoisoquinoline or 2-bromothiophene, the corresponding aldehydes were obtained selectively in the presence of 1–0.4% catalyst (table 1, entries 34–37). On the other hand, 2-bromopyridine gave 2,2′-bipyridine as the only product (table 1, entry 33). We had already observed the formation of this side-product for Heck reaction in the presence of styrene or *n*butylacrylate [30].

In conclusion, the use of 3,3-diacetoxypropene with aryl or heteroaryl bromides and the tetradentate ligand tedicyp associated to a palladium complex provides a convenient method for direct synthesis of cinnamaldehyde derivatives. The formation of 1-aryl-3,3-diacetoxypropene derivatives was not observed. This result indicates that the deprotection of the aldehyde occurs before or during the catalytic cycle. 3,3-Diacetoxypropene appears to be a thermally stable source of acrolein. As expected, the steric hindrance of the aryl bromides has an effect on the reaction rate. The presence of *ortho*-substituents generally led to lower TONs than the reactions performed in the presence of *para*-substituted aryl bromides. For most of the substrates, the reaction can be performed with 1–0.4% catalyst without further optimisation of the reaction conditions. We believe that this procedure compares favourably with the other systems that have been reported for the synthesis of cinnamaldehyde derivatives via Heck reaction.

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References and notes

[1] R.F. Heck, in: *Vinyl Substitution with Organopalladium Intermediates, Comprehensive Organic Synthesis*, B.M. Trost and I. Fleming (eds), Vol. 4 (Pergamon, Oxford, 1991).
[2] A. Meijere and F. Meyer, Angew. Chem. Int. Ed. 33 (1994) 2379.
[3] M.T. Reetz, in: *Transition Metal Catalysed Reactions*, S.G. Davies and S.-I. Murahashi (eds) (Blackwell Sci., Oxford, 1999).
[4] I. Beletskaya and A. Cheprakov, Chem. Rev. 100 (2000) 3009.
[5] N. Withcombe, K.K. Hii (Mimi) and S. Gibson, Tetrahedron 57 (2001) 7449.
[6] A. Littke and G. Fu, Angew. Chem. Int. Ed. 41 (2002) 4176.
[7] V. Farina, Adv. Synth. Catal. 346 (2004) 1553.
[8] T. Jeffery, J. Chem. Soc. Chem. Commun. (1984) 1287.
[9] M.R. Unroe and B.A. Reinhardt, Synthesis (1987) 981.
[10] S. Kobayashi, T. Ueda and T. Fukuyama, Synlett (2000) 883.
[11] B.L. Linkelstein, E.A. Benner, M.C. Hendrixson, K.T. Kranis, J.J. Rauh, M.R. Sethuraman and S.F. McCann, Bioorg. Med. Chem. 10 (2002) 599.
[12] A.K. Gupta, C.H. Song and C.H. Oh, Tetrahedron Lett. 45 (2004) 4113.
[13] A. Nejjar, C. Pinel and L. Djakovitch, Adv. Synth. Catal. 345 (2003) 612.
[14] G. Battistuzzi, S. Cacchi and G. Fabrizi, Org. Lett. 5 (2003) 777.
[15] W.A. Herrmann, C. Brossmer, K. Öfele, C. Reisinger, T. Riermeier, M. Beller and H. Fisher, Angew. Chem., Int. Ed. 34 (1995) 1844.
[16] M. Ohff, A. Ohff, M. Boom and D. Milstein, J. Am. Chem. Soc. 119 (1997) 11687.
[17] AlbissonD., R. Bedford and P.N. Scully, Tetrahedron Lett. 39 (1998) 9793.
[18] M. Ohff, A. Ohff and D. Milstein, Chem. Commun. (1999) 357..
[19] F. Miyazaki, K. Yamaguchi and M. Shibasaki, Tetrahedron Lett. 40 (1999) 7379.
[20] D. Bergbreiter, P. Osburn and Y.-S. Liu, J. Am. Chem. Soc. 121 (1999) 9531.
[21] X. Gai, R. Grigg, I. Ramzan, V. Sridharan, S. Collard and J. Muir, Chem. Commun. (2000) 2053.
[22] S. Gibson, D. Foster, D. Eastham, R. Tooze and D. Cole-Hamilton, Chem. Commun. (2001) 779.

[23] J.P. Stambuli, C.D. Incarvito, M. Buehl and J.F. Hartwig, J. Am. Chem. Soc. 126 (2004) 1184.
[24] D. Laurenti, M. Feuerstein, G. Pèpe, H. Doucet and M. Santelli, J. Org. Chem. 66 (2001) 1633.
[25] M. Feuerstein, D. Laurenti, C. Bougeant, H. Doucet and M. Santelli, Chem. Commun. (2001) 325.
[26] M. Feuerstein, F. Berthiol, H. Doucet and M. Santelli, Org. Biomol. Chem. 1 (2003) 2235.
[27] M. Feuerstein, H. Doucet and M. Santelli, J. Org. Chem. 66 (2001) 5923.
[28] M. Feuerstein, H. Doucet and M. Santelli, Synlett (2001) 1980.
[29] M. Feuerstein, H. Doucet and M. Santelli, Tetrahedron Lett. 43 (2002) 2191.
[30] F. Berthiol, M. Feuerstein, H. Doucet and M. Santelli, Tetrahedron Lett. 43 (2002) 5625.
[31] F. Berthiol, H. Doucet and M. Santelli, Tetrahedron Lett. 44 (2003) 1221.
[32] F. Berthiol, H. Doucet and M. Santelli, Synlett (2003) 841.
[33] I. Kondolff, H. Doucet and M. Santelli, Tetrahedron Lett. 44 (2003) 8487.
[34] I. Kondolff, H. Doucet and M. Santelli, Synlett (2004) 1561.
[35] F. Berthiol, H. Doucet and M. Santelli, Tetrahedron Lett. 45 (2004) 5633.
[36] K.S. Kochhar, B.S. Bal, R.P. Deshpande, S.N. Rajadhyaksha and H.W. Pinnick, J. Org. Chem. 48 (1983) 1765.
[37] As a typical experiment, the reaction of aryl halide (1 mmol), 3,3-diacetoxypropene (0.516 g, 3 mmol), K_2CO_3 (0.414 g, 3 mmol) at 130 °C during 20 h in dry DMF (3 mL) in the presence of *cis*,*cis*,*cis*-1,2,3,4-*tetrakis*(diphenylphosphinomethyl)cyclopentane/1/2 $[PdCl(C_3H_5)]_2$ complex under argon affords the corresponding cinnamaldehyde derivative after addition of water, extraction with ether or dichloromethane, separation, drying ($MgSO_4$), evaporation and purification by chromatography on silica gel.