Palladium−Tetraphosphine as Catalyst Precursor for High-Turnover-Number Negishi Cross-Coupling of Alkyl- or Phenylzinc Derivatives with Aryl Bromides

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Summary: The system combining the tetraphosphine cis,cis,cis-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane (Tedicyp) and [Pd(C_3H_5)Cl]$_2$ has been found to be a very active catalyst for the cross-coupling of aryl bromides with alkyl- or arylzinc derivatives (Negishi reaction). A variety of aryl bromides react in good yields and high turnover numbers (TONs) (up to 800 000) with diethylzinc, n-butylzinc bromide, or n-hexylzinc bromide in the presence of 0.1−0.0001 mol % catalyst in most cases.

Among the palladium-catalyzed reactions, the synthesis of biaryl or aryl−alklyl compounds via carbon−carbon bond formation using organozinc reagents with aryl halides has been one of the less intensively studied in terms of substrate/catalyst ratio.[1] Several results were described using arylzinc derivatives with reactive, but expensive aryl iodides;[2−8] however, in most cases the substrate/catalyst ratio was not optimized. Theses couplings were generally performed using PPh_3[2] or P(2-furyl)$_3$[3] as ligands. For the coupling with aryl iodides the highest turnover numbers (TONs) have probably been reported by Knochel et al. using $P(C_6H_4\text{-}nC_6F_{13})_3$[4] and by Negishi et al. using 1,1′-bis(diphenylphosphino)ferrocene.[8] The arylation of aryl bromides with arylzinc halides has also been described.[9−11] Again, these reactions were performed with PPh_3,[9] dppf,[10] or P(2-furyl)$_3$[11] as ligands, but generally with 1−5 mol % catalyst. The synthesis of biaryl via coupling of arylzinc halides with aryl chlorides has also been studied.[12−15] The most promising results with these substrates have been reported by Fu et al. using P(*t*Bu)$_3$[13] and by Buchwald et al. using a biphenyl-based monophosphine ligand.[15a] With theses hindered monophosphine ligands the coupling of 2-chlorobenzonitrile with arylzinc chlorides can be performed with as little as 0.03 and 0.01 mol % catalyst. The Negishi coupling of alkylzinc derivatives with aryl halides has attracted less attention.[13,16,21] Several results have been described using the monophosphine ligand PPh_3[16] or P(*o*Tol)$_3$[17] with 3−5 mol % catalyst or using P(2-furyl)$_3$[18] with 1 mol % complex. The diphosphine 1,1′-bis(diphenylphosphino)ferrocene has also been used successfully for the alkylation of aryl halides using 1−10 mol % catalyst.[19] The butylation of aryl chlorides with butylzinc chloride has been reported using the hindered strongly σ-electron-donating ligand P(*t*Bu)$_3$ in the presence of 1−2 mol % palladium complex.[20,21] Finally, alkylzinc chlorides have been reacted with alkyl halides using $Pd_2(dba)_3$ associated with PCy_3 as catalyst.[22]

Considering these stimulating results, we found it of particular interest to study the catalytic activity of *cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane (Tedicyp)[23] combined with palladium in the Negishi cross-coupling. We have already reported the results obtained in allylic substitution,[23] for Suzuki cross-coupling,[24] for Heck vinylation,[25] and for

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[1] Negishi, E., Ed. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, 2002; Part III, p 213.

[2] (a) Rieke, R. D.; Wu, X. *J. Org. Chem.* **1995**, *60*, 6658. (b) Okano, M.; Amano, M.; Takagi, K. *Tetrahedron Lett.* **1998**, *39*, 3001. (c) Krascsenicsova, K.; Walla, P.; Kasak, P.; Uray, G.; Kappe, C. O.; Putala, M. *Chem. Commun.* **2004**, 2606.

[3] (a) Rottländer, M.; Palmer, N.; Knochel, P. *Synlett* **1996**, 573. (b) Prasad, A. S. B.; Stevenson, T. M.; Citineni, J. R.; Nyzam, V.; Knochel, P. *Tetrahedron* **1997**, *53*, 7237. (c) Dohle, W.; Staubitz, A.; Knochel, P. *Chem. Eur. J.* **2003**, 5323.

[4] Betzemeier, B.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1997**, 2623.

[5] Sirieix, J.; Ossberger, M.; Betzemeier, B.; Knochel, P. *Synlett* **2000**, 1613.

[6] Fruit, C.; Turck, A.; Plé, N.; Mojovic, L.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 9429.

[7] Yang, Y.-C.; Luh, T.-Y. *J. Org. Chem.* **2003**, *68*, 9870.

[8] Huang, Z.; Qian, M.; Babinski, D. J.; Negishi, E.-I. *Organometallics* **2005**, *24*, 475.

[9] (a) Amatore, C.; Jutand, A.; Negri, S.; Fauvarque, J.-C. *J. Organomet. Chem.* **1990**, *390*, 389. (b) Borner, R. C.; Jackson, R. F. W. *J. Chem. Soc., Chem. Commun.* **1994**, 845. (c) Kuroboshi, M.; Mizuno, K.; Kanie, K.; Hiyama, T. *Tetrahedron Lett.* **1995**, *36*, 563. (d) Hoye, T. R.; Chen, M. *J. Org. Chem.* **1996**, *61*, 7940. (e) Oehberg, L.; Westman, J. *Synlett* **2001**, 1893.

[10] (a) Marquais, S.; Arlt, M. *Tetrahedron Lett.* **1996**, *37*, 5491. (b) Arlt, M.; Boettcher, H.; Riethmueller, A.; Schneider, G.; Bartoszyk, G. D.; Greiner, H.; Seyfried, C. A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2033. (c) Corley, E. G.; Conrad, K.; Murry, J. A.; Savarin, C.; Holko, J.; Boice, G. *J. Org. Chem.* **2004**, *69*, 5120.

[11] Rottländer, M.; Knochel, P. *Synlett* **1997**, 1084.

[12] Miller, J. A.; Farrell, R. P. *Tetrahedron Lett.* **1998**, *39*, 6441.

[13] Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719.

[14] Li, G. Y. *J. Org. Chem.* **2002**, *67*, 3643.

[15] (a) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028. (b) Hamilton, C. W.; Laitar, D. S.; Sadighi, J. P. *Chem. Commun.* **2004**, 1628.

[16] (a) Negishi, E.-I.; Luo, F.-T.; Frisbee, R.; Matsushita, H. *Heterocycles* **1982**, *18*, 117. (b) Kalinin, A. V.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 4999. (c) Dinsmore, A.; Garner, C. D.; Joule, J. A. *Tetrahedron* **1998**, *54*, 3291. (d) Toudic, F.; Plé, N.; Turck, A.; Quéguiner, G. *Tetrahedron* **2002**, *58*, 283.

[17] Kurono, N.; Sugita, K.; Takasugi, S.; Tokuda, M. *Tetrahedron* **1999**, *55*, 6097.

[18] Rottländer, M.; Knochel, P. *Tetrahedron Lett.* **1997**, *38*, 1749.

[19] (a) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158. (b) Bumagin, N. A.; Nikitina, A. F.; Beletskaya, I. P. *Russ. J. Org. Chem.* **1996**, *32*, 1803. (c) Bach, T.; Bartels, M. *Synlett* **2001**, 1284.

[20] Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

[21] Walla, P.; Kappe, C. O. *Chem. Commun.* **2004**, 564.

[22] Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527.

[23] Laurenti, D.; Feuerstein, M.; Pèpe, G.; Doucet, H.; Santelli, M. *J. Org. Chem.* **2001**, *66*, 1633.

[24] (a) Feuerstein, M.; Laurenti, D.; Bougeant, C.; Doucet, H.; Santelli, M. *Chem. Commun.* **2001**, 325. (b) Kondolff, I.; Doucet, H.; Santelli, M. *Synlett* **2005**, 2057.

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Scheme 1

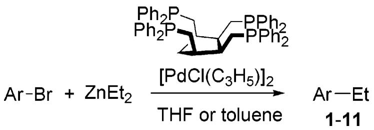


Table 1. Negishi Coupling of Diethylzinc with 1-Bromonaphthalene: Influence of the Reaction Conditions (Scheme 1)[a]

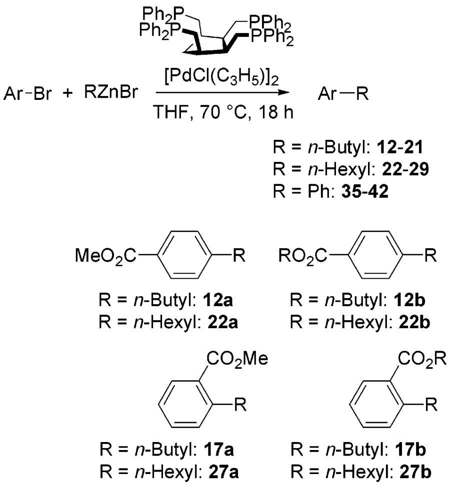
entry	solvent	temp (°C)	base	time (h)	ratio substrate/ catalyst	**1** yield (%)
1	xylene	70	K_2CO_3	2	1000	40
2	xylene	70	K_2CO_3	18	1000	100
3	xylene	70		2	1000	45
4	xylene	70		18	1000	100
5	xylene	25		18	100	20[b]
6	xylene	100		18	1000	100
7	xylene	100		18	10 000	50[b]
8	THF	70		18	1000	100
9	THF	70	K_2CO_3	18	10 000	71[b]
10	THF	70		18	10 000	76[b] (70)[c]

[a] Conditions: catalyst $[Pd(C_3H_5)Cl]_2$/Tedicyp, 1:2, 1-bromonaphthalene (1mmol), diethylzinc (3 mmol), K_2CO_3 (3 mmol), under argon, GC yields; when the GC yield is not 100%, the starting material is generally recovered unreacted. [b] The formation of naphthalene was also observed in low yield. [c] Isolated yield.

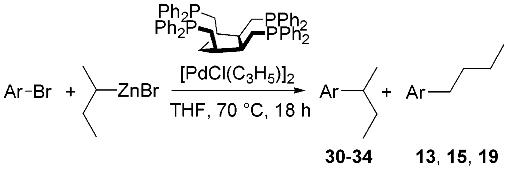
Sonogashira alkynylation[26] using Tedicyp as ligand. We describe here the very high TON Negishi coupling of alkyl- or phenylzinc derivatives with aryl bromides using the palladium/Tedicyp catalyst. We began by exploring the coupling of diethylzinc with 1-bromonaphthalene (Scheme 1, Table 1). The reactions were performed under argon, in the presence of a 1:2 ratio of $[Pd(C_3H_5)Cl]_2$/Tedicyp as catalyst. We found that the coupling proceeds in xylene, but the most suitable solvent appears to be THF. The temperature has an important influence on the yields. At room temperature a low conversion of 20% was obtained using 1 mol % catalyst (Table 1, entry 5). On the other hand, at 70 °C complete conversions were observed using 0.1 mol % catalyst (Table 1, entries 4 and 8) and 76% conversion with 0.01 mol % catalyst using THF as solvent (Table 1, entry 10). Under these conditions, 1-ethylnaphthalene (**1**) was obtained in 70% isolated yield and 7000 TON. The addition of K_2CO_3 to the reaction mixture has almost no influence on the yield (Table 1, entries 1, 2, and 9).

Next, we examined the reactivity of activated and deactivated aryl bromides for the coupling with diethylzinc (Table 2). We have investigated this reaction using two electron-poor aryl bromides, methyl 4-bromobenzoate and 4-bromobenzonitrile (Table 2, entries 1, 2, 7, and 8). With these substrates, products **2** and **3** were obtained with TONs of 75 000 and 53 000, respectively. Using electron-rich aryl bromides, lower TONs were obtained. For example, with 4-bromoanisole or 4-*N*,*N*-dimethylbromoaniline, products **5** and **6** were obtained with 880 and 450 TONs, respectively (Table 2, entries 11−14). This observation indicates that the oxidative addition of the aryl bromide to palladium is probably rate-limiting. With the *ortho*-substituted aryl bromides methyl 2-bromobenzoate or 2-bromotoluene the reactions were also performed with as little as 0.1−0.001 mol % catalyst, indicating that the presence of one *ortho*-substituent on the aryl bromide has a minor effect on the reaction rate (Table 2, entries 18−21). The reaction of the di-*ortho*-substituted aryl bromide 2,4,6-trimethylbromobenzene with diethylzinc proceeds in moderate yield using 2 mol % catalyst (Table 2, entry 25). Finally, we performed a few reactions using heteroaryl bromides. With this catalyst electron-poor heteroaromatics such as 3-bromoquinoline or 4-bromoisoquinoline led to the expected products **10** and **11** in good yields using substrate/catalyst ratios of 10 000 and 100 000 (Table 2, entries 26−29).

Scheme 2



Scheme 3



In order to further demonstrate the enhanced efficiency of the Tedicyp ligand, the reaction of diethylzinc with methyl 4-bromobenzoate, 4-*N*,*N*-dimethylbromoaniline, and 2-bromotoluene was also performed using PPh_3 or dppf as ligand using similar reaction conditions. With PPh_3, no formation of product was observed with 4-*N*,*N*-dimethylbromoaniline or 2-bromotoluene using 1% and 0.4% catalyst (Table 2, entries 15 and 22). As expected, electron-poor methyl 4-bromobenzoate was found to be more reactive with a TON of 280 (Table 2, entry 3). The bidentate ligand dppf gave more satisfactory results than PPh_3 but also led to lower TONs than Tedicyp in all cases (Table 2, entries 5, 6, 16, 17, 23, and 24).

Then, we studied the coupling of *n*-butyl- and *n*-hexylzinc bromides with several aryl bromides (Scheme 2, Table 3). Using *para*-substituted electron-deficient or electron-excessive aryl bromides, we obtained results very similar to those of diethylzinc. 4-Substituted electron-poor aryl bromides gave coupling products with TONs of 10 000−88 000 and electron-rich ones with TONs of 650−8600 (Table 3, entries 1−10 and 20−29). *ortho*-Substituted aryl bromides such as methyl 2-bromobenzoate or 1-bromonaphthalene gave *n*-butyl- or *n*-hexylaryl compounds with TONS of 1000−7400 (Table 3, entries 11−16 and 30−35). With methyl bromobenzoates, the formation of mixtures of methyl benzoate derivatives **12a**, **17a**, **22a**, and **27a** and *n*-butyl or *n*-hexyl benzoate derivatives **12b**, **17b**, **22b**, and **27b** was generally observed (Scheme 2, Table 3, entries 1,

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(25) (a) Feuerstein, M.; Doucet, H.; Santelli, M. *J. Org. Chem.* **2001**, *66*, 5923. (b) Kondolff, I.; Doucet, H.; Santelli, M. *Eur. J. Org. Chem.* **2006**, 765.

(26) (a) Feuerstein, M.; Berthiol, F.; Doucet, H.; Santelli, M. *Org. Biomol. Chem.* **2003**, *1*, 2235. (b) Feuerstein, M.; Chahen, L.; Doucet, H.; Santelli, M. *Tetrahedron* **2006**, *62*, 112.

(27) (a) Kondolff, I.; Doucet, H.; Santelli, M. *Tetrahedron* **2004**, *60*, 3813. (b) Lemhadri, M.; Doucet, H.; Santelli, M. *Synth. Commun.* **2006**, *36*, 121.

Table 2. Negishi Coupling with Diethylzinc: Influence of the Aryl Bromide (Scheme 1)[a]

entry	aryl bromide	ligand	ratio substrate/catalyst	product	yield (%)
1	methyl 4-bromobenzoate	Tedicyp	10 000	**2**	100 (88)
2	methyl 4-bromobenzoate	Tedicyp	100 000	**2**	75
3	methyl 4-bromobenzoate	PPh_3	1000	**2**	28
4	methyl 4-bromobenzoate	PPh_3	10 000		0
5	methyl 4-bromobenzoate	dppf	1000	**2**	56
6	methyl 4-bromobenzoate	dppf	10 000	**2**	5
7	4-bromobenzonitrile	Tedicyp	10 000	**3**	100 (91)
8	4-bromobenzonitrile	Tedicyp	100 000	**3**	53
9	4-*tert*-butylbromobenzene	Tedicyp	250	**4**	97 (87)
10	4-*tert*-butylbromobenzene	Tedicyp	1000	**4**	88
11	4-bromoanisole	Tedicyp	250	**5**	100 (90)
12	4-bromoanisole	Tedicyp	1000	**5**	88
13	4-*N*,*N*-dimethylbromoaniline	Tedicyp	250	**6**	100 (87)
14	4-*N*,*N*-dimethylbromoaniline	Tedicyp	1000	**6**	45
15	4-*N*,*N*-dimethylbromoaniline	PPh_3	100		0
16	4-*N*,*N*-dimethylbromoaniline	dppf	100	**6**	26
17	4-*N*,*N*-dimethylbromoaniline	dppf	250	**6**	0
18	methyl 2-bromobenzoate	Tedicyp	10000	**7**	100 (86)
19	methyl 2-bromobenzoate	Tedicyp	100000	**7**	45
20	2-bromotoluene	Tedicyp	1000	**8**	100 (90)
21	2-bromotoluene	Tedicyp	10000	**8**	15
22	2-bromotoluene	PPh_3	250		0
23	2-bromotoluene	dppf	250	**8**	24
24	2-bromotoluene	dppf	1000	**8**	5
25	2,4,6-trimethylbromobenzene	Tedicyp	50	**9**	35 (30)
26	3-bromoquinoline	Tedicyp	100000	**10**	100 (91)
27	3-bromoquinoline	Tedicyp	1000000	**10**	26
28	4-bromoisoquinoline	Tedicyp	10000	**11**	100 (87)
29	4-bromoisoquinoline	Tedicyp	100000	**11**	77[b]

[a] Conditions: catalyst $[Pd(C_3H_5)Cl]_2$/Tedicyp, 1:2, or $[Pd(C_3H_5)Cl]_2/PPh_3$, 1:4, or $[Pd(C_3H_5)Cl]_2$/dppf, 1:2, aryl bromide (1 mmol), diethylzinc (3 mmol), THF, 70 °C, 18 h, under argon, GC yields; when the GC yield is not 100%, the starting material is generally recovered unreacted; yields in parenthesis are isolated. [b] The formation of 10% of 1,4-diethylisoquinoline was also observed.[28]

Table 3. Negishi Coupling with *n*-Butyl- or *n*-Hexylzinc Bromide: Influence of the Aryl Bromide (Scheme 2)[a]

entry	aryl bromide	alkylzinc bromide	ratio substrate/catalyst	product	ratio **a**/**b**	yield (%)
1	methyl 4-bromobenzoate	*n*-butylzinc bromide	1000	**12a** + **12b**	82/18	100 (75)
2	methyl 4-bromobenzoate	*n*-butylzinc bromide	10 000	**12a** + **12b**	61/39	100
3	4-bromobenzonitrile	*n*-butylzinc bromide	10 000	**13**		100 (89)
4	4-bromobenzonitrile	*n*-butylzinc bromide	100 000	**13**		88
5	4-*tert*-butylbromobenzene	*n*-butylzinc bromide	1000	**14**		100 (87)
6	4-*tert*-butylbromobenzene	*n*-butylzinc bromide	10 000	**14**		19
7	4-bromoanisole	*n*-butylzinc bromide	1000	**15**		100 (85)
8	4-bromoanisole	*n*-butylzinc bromide	10 000	**15**		1
9	4-*N*,*N*-dimethylbromoaniline	*n*-butylzinc bromide	250	**16**		100 (88)
10	4-*N*,*N*-dimethylbromoaniline	*n*-butylzinc bromide	1000	**16**		65
11	methyl 2-bromobenzoate	*n*-butylzinc bromide	250	**17a** + **17b**	86/14	100 (80)
12	methyl 2-bromobenzoate	*n*-butylzinc bromide	1000	**17a** + **17b**	70/30	100
13	2-bromotoluene	*n*-butylzinc bromide	1000	**18**		100 (91)
14	2-bromotoluene	*n*-butylzinc bromide	10 000	**18**		8
15	1-bromonaphthalene	*n*-butylzinc bromide	1000	**19**		100 (92)
16	1-bromonaphthalene	*n*-butylzinc bromide	10 000	**19**		38
17	3-bromoquinoline	*n*-butylzinc bromide	10 000	**20**		100 (85)
18	3-bromoquinoline	*n*-butylzinc bromide	100 000	**20**		78
19	4-bromoisoquinoline	*n*-butylzinc bromide	100 000	**21**		100[b] (84)
20	methyl 4-bromobenzoate	*n*-hexylzinc bromide	10 000	**22a** + **22b**	71/29	100 (66)
21	methyl 4-bromobenzoate	*n*-hexylzinc bromide	100 000	**22a** + **22b**	90/10	49
22	4-bromobenzonitrile	*n*-hexylzinc bromide	10 000	**23**		100 (92)
23	4-bromobenzonitrile	*n*-hexylzinc bromide	100 000	**23**		53
24	4-*tert*-butylbromobenzene	*n*-hexylzinc bromide	1000	**24**		100 (90)
25	4-*tert*-butylbromobenzene	*n*-hexylzinc bromide	10 000	**24**		86
26	4-bromoanisole	*n*-hexylzinc bromide	1000	**25**		100 (91)
27	4-bromoanisole	*n*-hexylzinc bromide	10 000	**25**		2
28	4-*N*,*N*-dimethylbromoaniline	*n*-hexylzinc bromide	1000	**26**		100 (88)
29	4-*N*,*N*-dimethylbromoaniline	*n*-hexylzinc bromide	10 000	**26**		2
30	methyl 2-bromobenzoate	*n*-hexylzinc bromide	250	**27a**	100/0	100[c]
31	methyl 2-bromobenzoate	*n*-hexylzinc bromide	250	**27a** + **27b**	82/18	100[d]
32	methyl 2-bromobenzoate	*n*-hexylzinc bromide	1000	**27a** + **27b**	80/20	100 (75)
33	methyl 2-bromobenzoate	*n*-hexylzinc bromide	10 000	**27a** + **27b**	82/18	74
34	1-bromonaphthalene	*n*-hexylzinc bromide	1000	**28**		100 (93)
35	1-bromonaphthalene	*n*-hexylzinc bromide	10 000	**28**		67
36	3-bromoquinoline	*n*-hexylzinc bromide	100 000	**29**		100 (87)
37	3-bromoquinoline	*n*-hexylzinc bromide	1 000 000	**29**		80

[a] Conditions: catalyst $[Pd(C_3H_5)Cl]_2$/Tedicyp, 1:2, aryl bromide (1 mmol), *n*-butyl- or *n*-hexylzinc bromide (3 mmol), THF, 70 °C, 18 h, under argon, GC yields; when the GC yield is not 100%, the starting material is generally recovered unreacted; yields in parenthesis are isolated. [b] The formation of 7% of 1,4-dibutylisoquinoline was also observed.[28] [c] Reaction time: 30 min. [d] Reaction time: 3 h.

Table 4. Negishi Coupling with *s*-Butylzinc Bromide: Influence of the Aryl Bromide (Scheme 3)[a]

entry	aryl bromide	ratio substrate/catalyst	product	ratio branched/linear isomers	yield (%)
1	4-bromobenzonitrile	25	**30**	100/0	100 (87)
2	4-bromobenzonitrile	50	**30** + **13**	45/55	100[b]
3	4-bromoanisole	50	**31** + **15**	61/39	100[b] (55)[c]
4	4-bromoanisole	100	**31** + **15**	47/53	79[b]
5	4-*N*,*N*-dimethylbromoaniline	100	**32**	100/0	100 (89)
6	1-bromonaphthalene	50	**33**	100/0	100 (85)
7	1-bromonaphthalene	100	**33** + **19**	85/15	100[b]
8	1-bromonaphthalene	250	**33** + **19**	75/25	100[b]
9	3-bromoquinoline	100	**34**	100/0	100 (91)
10	3-bromoquinoline	250	**34**	100/0	47

[a] Conditions: catalyst $[Pd(C_3H_5)Cl]_2$/Tedicyp, 1:2, aryl bromide (1 mmol), *s*-butylzinc bromide (3 mmol), THF, 70 °C, 18 h, under argon, GC yields; when the GC yield is not 100%, the starting material is generally recovered unreacted; yields in parenthesis are isolated. [b] GC yield of the mixture of linear and branched products. [c] Isolated yield in product **31**.

Table 5. Negishi Coupling of Phenylzinc Bromide: Influence of the Aryl Bromide (Scheme 2)[a]

entry	aryl bromide	ratio substrate/catalyst	product	yield (%)
1	methyl 4-bromobenzoate	10 000	**35**	100 (92)
2	methyl 4-bromobenzoate	100 000	**35**	56
3	4-bromobenzonitrile	100 000	**36**	100 (91)
4	4-*t*-butylbromobenzene	1000	**37**	95 (85)
5	4-*t*-butylbromobenzene	10 000	**37**	78
6	4-bromoanisole	1000	**38**	92 (85)
7	4-bromoanisole	10 000	**38**	23
8	4-*n*,*n*-dimethylbromoaniline	1000	**39**	100 (92)
9	4-*n*,*n*-dimethylbromoaniline	10 000	**39**	14
10	methyl 2-bromobenzoate	1000	**40**	100 (90)
11	methyl 2-bromobenzoate	10 000	**40**	50
12	1-bromonaphthalene	1000	**41**	100 (93)
13	1-bromonaphthalene	10 000	**41**	35
14	3-bromoquinoline	100 000	**42**	78 (69)
15	3-bromoquinoline	1 000 000	**42**	68

[a] Conditions: catalyst $[Pd(C_3H_5)Cl]_2$/Tedicyp, 1:2, aryl bromide (1 mmol), phenylzinc bromide (3 mmol), THF, 70 °C, under argon, GC yields; when the GC yield is not 100%, the starting material is generally recovered unreacted; yields in parenthesis are isolated.

2, 11, 12, 20, 32, and 33). This formation of *n*-butyl or *n*-hexyl benzoate derivatives also occurred in the absence of palladium catalyst. Using a higher catalyst loading and a shorter reaction time, the selective formation of **27b** was obtained (Table 3, entries 30 and 31). Again, the heteroaromatics 3-bromoquinoline and 4-bromoisoquinoline gave the *n*-butylation products **20** and **21** in very high TONs of 78 000 and 100 000, respectively, and 3-bromoquinoline with *n*-hexylzinc bromide gave 3-*n*-hexylquinoline (**29**) with a TON of 800 000 (Table 3, entries 17−19, 36, and 37).

A challenging problem in Negishi coupling processes is the ability to combine sterically hindered substrates. As expected, *s*-butylzinc bromide was found to be much less reactive than *n*-butylzinc bromide (Scheme 3, Table 4). We had already observed that with the Tedicyp/Pd catalyst the Suzuki coupling of secondary alkyl boronic acids was difficult. Good results had been obtained for the coupling of cyclopropyl boronic acid or primary alkyl boronic acids with aryl bromides. On the other hand, the reaction of isopropyl boronic acid with aryl halides gave no product.[27] The coupling of *s*-butylzinc chloride with aryl halides had already been described. For example, bromobenzene and *s*-butylzinc chloride using 1 mol % $PdCl_2$(dppf) gave selectively *s*-butylbenzene. With $PdCl_2$(dppp) as catalyst, the reaction gave a mixture of *n*- and *s*-butylbenzene in low yield, and $PdCl_2(PPh_3)_2$ gave an equimolar mixture of *n*- and *s*-butylbenzene.[19a] The coupling of *s*-butylzinc chloride with 2-chlorotoluene has also been reported by Fu et al. using 2 mol % of $Pd[P(tBu)_3]_2$ as catalyst. With this catalyst, the expected 2-*s*-butyltoluene was obtained in 70% yield together with 8% of 2-*n*-butyltoluene as side-product.[13]

With our catalyst we also observed the formation of 2-*n*-butylarene as side-product in some cases (Table 4). Larger amounts of this side-product were observed when higher substrate/catalyst ratios were used. For example, with 1-bromonaphthalene, 1-*s*-butylnaphthalene was selectively obtained using 2 mol % catalyst. With 1 and 0.4 mol % catalyst, 15% and 25% of 1-*n*-butylnaphthalene were formed, respectively (Table 4, entries 6−8). However, the selective formation of *s*-butylaryl derivatives can be obtained with 4-bromobenzonitrile, 4-*N*,*N*-dimethylbromoaniline, or 3-bromoquinoline using 0.4−4 mol % of our catalyst (Table 4, entries 1, 5, 9, and 10).

Finally, we studied the efficiency of the Tedicyp/Pd catalytic system for the Negishi reaction of aryl bromides with phenylzinc bromide (Scheme 2, Table 5). Again, electron-poor aryl bromides were found to be more reactive than the electron-rich ones. For example, methyl 4-bromobenzoate or 4-bromobenzonitrile were converted to the corresponding biphenyl derivatives using 0.01−0.001 mol % catalyst (Table 5, entries 1−3). With 4-*tert*-butylbromobenzene, 4-bromoanisole, or 4-*N*,*N*-dimethylbromoaniline, the presence of 0.1−0.01 mol % catalyst was necessary in order to obtain high yields of biaryles **37**−**39** (Table 5, entries 4−9). Sterically hindered substrates methyl 2-bromobenzoate and 1-bromonaphthalene have also been reacted using 0.1−0.01 mol % catalyst (Table 5, entries 10−13). The highest TON with phenylzinc bromide has been obtained in the presence of the electron-poor heteroaryl bromide 3-bromoquinoline: 680 000 (Table 5, entries 14 and 15).

In summary, we have demonstrated that a tetradentate phosphine ligand associated to palladium gives a very powerful catalyst for Negishi reaction.

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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