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THE NICKEL AND PALLADIUM CATALYSED STEREOSELECTIVE CROSS COUPLING OF CYCLOPROPYL NUCLEOPHILES WITH ARYL HALIDES

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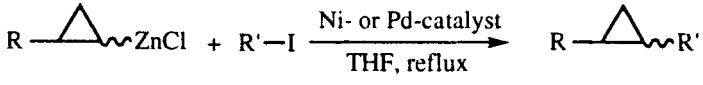
Abstract:
The reaction of 2-phenylcyclopropylzinc chloride with some substituted (het)aryl halides gave the corresponding coupling products with good yields and stereoselectivities under the influence of a catalytic amount of $Pd(PPh_3)_4$. Other Ni- and Pd-catalysts were less efficient. Alkyl-substituted cyclopropyl nucleophiles gave lower yields.

The transition metal-catalysed reactions of organometallics with organic halides have been extensively studied and proven to be a versatile approach to the selective formation of carbon-carbon bonds. Cyclopropanes, however, have rarely been used in transition metal-catalysed cross-coupling reactions.[1-6] In this communication, we report a smooth and efficient procedure for the transition metal-catalysed cross-coupling between cyclopropyl nucleophiles and organic halides (Scheme 1).



Scheme 1

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We started with the cross-coupling between 2-phenylcyclopropylzinc chloride and iodobenzene using various Ni- and Pd-catalysts. The requisite 2-phenylcyclopropylzinc chloride was prepared from 2-phenylcyclopropyl bromide (*E/Z* = 97/3) by a *n*-butyllithium-bromine exchange at low temperatures followed by transmetallation with zinc chloride. The results are listed in Table 1.

Table 1: Cross-coupling between 2-phenylcyclopropylzinc chloride (*E/Z* 97/3) and iodobenzene using various Ni- and Pd-catalysts[a].

entry	Catalyst	Conversion[b]	Selectivity[b]	*E/Z*
1	$Pd(PPh_3)_4$	96	94	99/1
2	$PdCl_2(PPh_3)_2$	72	88	98/2
3	$PdCl_2$DPPF	76	96	99/1
4	$PdCl_2$DPPB	70	95	99/1
5	$PdCl_2$DPPNp[d]	3	37	c
6	$NiCl_2$DPPE	13	99	100/0
7	$NiCl_2$DPPP	73	93	98/2
8	$NiCl_2$DPPF	60	97	98/2
9	$NiCl_2(PPh_3)_2$	58	93	100/0
10	$NiCl_2$DPPNp	1	99	c

[a] Reactions were typically run with 20 mmole of iodobenzene, 1 eq. 2-phenylcyclopropylzinc chloride, 1 mol % catalyst, in THF under reflux. [b] Determined after 1 h by GLC, and compared with previously identified samples. [c] Not determined. [d] DPPNp : 1, 8-*bis*(diphenylphosphino)naphthalene.

As can be seen from Table 1, the most efficient catalyst for the cross-coupling reaction was $Pd(PPh_3)_4$ (entry 1). $PdCl_2$DPPF (entry 3), usually a very effective catalyst in the alkyl-aryl cross-coupling reaction gave no significantly better results than did $PdCl_2(PPh_3)_2$.[7,8] The other Pd-catalysts were all less effective (entries 2, 4 and 5). The Ni-catalysts examined showed lower activities combined with good selectivities (entries 6 to 9). Bidentate ligands were in general not significantly more effective than monodentate ligands. The catalysts prepared with the ligand 1,8-*bis*(diphenylphosphino)naphthalene gave a very low conversion (entries 5 and 10).[9] The reactions with all catalysts gave the expected (2-phenylcyclopropyl)benzene with retention of (*E/Z*)-ratio.

The good results with iodobenzene, 2-phenylcyclopropylzinc chloride and $Pd(PPh_3)_4$ led us to investigate the scope of the reaction. The results are summarised in Table 2.

Table 2: $Pd(PPh_3)_4$ catalysed cross-coupling of 2-phenylcyclopropylzinc chloride (*E/Z* 97/3) with various sp^2-halides[a].

entry	Substrate	Conversion	Selectivity	E/Z
1	C_6H_5I[b]	96[c] (93)[d]	94	99/1
2	C_6H_5Br	70	94	97/3
3	C_6H_4Cl	0		
4	*p*-MeC_6H_4I	90	99	97/3
5	*p*-$MeOC_6H_4I$	80 (71)	95	e
6	*p*-FC_6H_4I	84 (49)	98	97/3
7	*p*-$I_2C_6H_4$[f]	99 (66)	99	e
8	*p*-FC_6H_4Br	95	88	97/3
9	*p*-MeC_6H_4Br	96 (81)	99	97/3
10	*p*-$NO_2C_6H_4Br$	0		
11	2-I-thiophene	96 (22)	50	100/0
12	1-I-cyclohexene	98 (79)	86	97/3
13	$C_6H_5CH_2Br$	99 (51)	55	99/1

[a] Determined after 24 h by GLC, For details see the experimental section. [b] when no catalyst was added, no product was detected by GLC. [c] after 1 hour. [d] isolated yield in parentheses. [e] not determined. [f] 2 eq. 2-phenylcyclopropylzinc chloride were used.

The cross-coupling of the aromatic iodides with 2-phenylcyclopropylzinc chloride proceeded generally with good yields and selectivities. In all cases the *E/Z*-ratio was preserved. Conversion and selectivity seem to be only marginally influenced by electron-donating (entries 4 and 5) or -withdrawing (entry 6) properties of the substituent, also in the cases of the (substituted) aromatic *bromides* (entries 2, 8 and 9). The observed order of reactivity for the halides is I > Br >> Cl, which is consistent with reactivities of halide leaving groups in other cross-coupling reactions and with the low reactivity of aromatic chlorides in the oxidative addition at the Pd(0)-centre (entries 1, 2 and 3). The reaction of *para*-diiodobenzene with two equivalents of 2-phenylcyclopropylzinc chloride gave the disubstituted product with high yield and with high selectivity (entry 7). The reaction of 2-iodothiophene (entry 11) or benzyl bromide (entry 13) gave the expected cross-coupling product, but accompanied by substantial amounts of homo-coupling products. The high yield and good selectivity in the coupling between 2-phenylcyclopropylzinc chloride and 1-iodocyclohexene

Table 3: Reaction of cyclopropylzinc chlorides with iodobenzene catalysed by $Pd(PPh_3)_4$[a].

entry	R (*E*/*Z*)	Conversion[b]	Selectivity[b]	*E*/*Z*
1	H	98 (90)	96	
2	Ph (97/3)	96 (93)	94	97/3
3	Ph (97/3)[c]	78	98	69/31
4	Ph (33/67)	85	93	25/75
5	Bu (100/0)	45[d]	97	41/59
6	$-(CH_2)_4-$ (100/0)[e]	40	83	70/30[e]

[a] For details see the experimental section. [b] Determined by GLC, isolated yield in parentheses. [c] 2-Phenylcyclopropylmagnesium bromide, prepared by reaction of the cyclopropylbromide with metallic Mg. [d] 2-Butylcyclopropylmagnesium bromide after 48 h. [e] exo/endo.

(entry 12) may lead to the expectation that also other haloolefins can be succesfully coupled.

Table 3 shows the results obtained by the coupling of some cyclopropylzinc chlorides with iodobenzene using $Pd(PPh_3)_4$ as catalyst. The best results were obtained with unsubstituted cyclopropylzinc chloride(entry 1) and 2-phenylcyclopropylzinc chloride (entry 2). The reactivity of 2-butylcyclopropylmagnesiumbromide was lower than that of the 2-phenylcyclopropylzinc derivative.

The use of cyclopropyl Grignard reagents, prepared by the reaction of the organic halide with metallic magnesium, also increased isomerisation (entry 3 and 5). This was ascribed to the radical procedure at the surface of the metal, resulting in loss of stereointegrity. [10,11]

Experimental:

1,1-Dibromo-2-phenylcyclopropane. (Procedure according to Vogel[12] for 7, 7-dichloronorcarane). A 2 L, three-necked, round-bottomed flask, equipped with a mechanical stirrer and a reflux condenser was charged with 52 g (0.5 mole) of styrene, 380 g (1.5 mole, excess) of bromoform and 2 g (8 mmole) of triethylbenzylammonium chloride. The mixture was stirred vigorously and a solution of 80 g (2 mole) of sodium hydroxide in 80 mL of water was added in small portions at such a rate that the temperature of the mixture remained below 50°C. When all the

sodium hydroxide was added and the exothermic reaction had subsided, the reaction mixture was stirred for an additional 2 hours at 60°C after which 300 mL of water was added. After extraction with three 100 mL-portions of chloroform, the combined organic fractions were washed once with 100 mL of water and dried over $MgSO_4$. Distillation resulted in a 68% yield, Bp 130°C/12 mm Hg.[13] ^{1}H-NMR: δ= 7.44-7.26 (m, 5H, $C_{arom.}$(H)), 3.00 (dd, J = 10.4, 8.4, 1H, C_2(H)), 2.16 (dd, J = 10.5, 7.7, 1H, C_3(H)), 2.05 (dd, J = 8.4, 7.7, 1H, C_3(H)). ^{13}C-NMR: δ= 135.6 (C_i), 128.8 (C_o), 128.4 (C_m), 127.5 (C_p), 35.8 (C_2), 28.5 (C_1), 27.1 (C_3).

1,1-Dibromo-2-butylcyclopropane. Prepared following the procedure for 1,1-dibromo-2-phenylcyclopropane., resulting in a 95% yield, b.p. 110-115°C/ 50 mm Hg.[14] ^{1}H-NMR: δ= 1.76-1.70 (m, 2H, C_3(H)), 1.68-1.35 (m, 6H, $C_{(CH2)3}$(H)), 1.19 (t, J = 7.1, 1H, C_2(H)), 0.93 (t, J = 7.1, 3H, C_{CH3}(H)). ^{13}C-NMR: δ= 32.3 (C_1), 31.5 (C_3), 30.5 (C_2), 29.7 ($C_{1'}$), 28.6 ($C_{2'}$), 22.4 ($C_{3'}$), 14.0 ($C_{4'}$).

***E/Z*-1-Bromo-2-phenylcyclopropane, E/Z = 97/3.** A 1L, three-necked, round-bottomed flask was charged with 48 g (0.55 mole) of lithium bromide in 350 mL of dry THF and 350 mL of dry diethyl ether. The air in the flask was replaced by nitrogen and 350 mL (0.56 mole) of 1.6 M *n*-butyllithium in hexane was added with cooling below 0°C. Subsequently a solution of 138.5 g (0.5 mole) of 1,1-dibromo-2-phenylcyclopropane in 150 mL of dry THF was added over a period of 1 h while the temperature of the reaction mixture was kept carefully between -100 and -110°C. The thick white suspension was stirred for 1 hour at -100°C, after which, under continuous cooling, it was cautiously protonated with 100 mL of ethanol. After the exothermic reaction had subsided, 200 mL of water was added and the mixture extracted with 3 portions of 100 mL of hexane. The combined organic fractions were dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude reaction mixture was distilled over a 40 cm Widmer column to afford 87.5 g (0.44 mole, yield 89 %, b.p. 105°C/12 mm Hg) of the desired product. GLC showed that a 97/3 mixture of E/Z-isomers had formed. ^{1}H-NMR: δ= 7.51-7.37 (m, 3H, $C_{arom.}$(H)), 7.22-7.18 (m, 2H, $C_{arom.}$(H)), 3.18 (ddd, J = 7.6, 4.4, 3.5, 1H, C_1(H)), 2.57 (ddd, J = 9.9, 6.5, 3.5, 1H, C_2(H)), 1.72-1.41 (m, 2H, C_3(H)). ^{13}C-NMR: δ= 139.6 (C_i), 128.4 (C_o), 126.4 (C_p), 125.8 (C_m), 26.7 (C_1), 21.5 (C_2), 18.8 (C_3).[2]

***E/Z*-1-Bromo-2-butyl-cyclopropane E/Z= 100/0.** Prepared by using the procedure for *E/Z*-1-bromo-2-phenylcyclopropane, in a 35 % yield (b.p. 65°C/12 mm Hg). ^{1}H-NMR: δ= 2.59 (ddd, J = 7.0, 3.5, 3.0, 1H, C_1(H)), 1.52-0.86 (m, 12H, $C_{1'...4', 2, 3}$(H)). ^{13}C-NMR: δ= 32.5(C_4), 30.9(C_5), 22.9(C_1), 22.5(C_6), 20.0(C_2), 15.9(C_7), 14.0(C_3).

Preparation of a stock solution of 2-phenylcyclopropylzinc chloride. A 1 L, three-necked, round-bottomed flask was equipped with a mechanical stirrer, a gas inlet, and a thermometer. The air in the flask was replaced by nitrogen and 98.5 g (0.42 mole) of *E*-1-bromo-2-phenylcyclopropane was homogenised by addition of 265 mL of dry THF and the mixture cooled at -90°C. Subsequently, 263 mL of a solution of 1.6 M *n*-butyllithium in hexane was added while the temperature of the reaction mixture was kept at -90°C. After stirring for 1 hour, an aliquot was taken from the reaction mixture, quenched with water and analysed by GLC. When no starting compound was detected in the reaction mixture, 69 g (0.5 mole) of zinc chloride was added in one portion. The reaction mixture was stirred for one hour, while the temperature was allowed to reach room temperature. The contents of the reaction flask were carefully transferred under an inert atmosphere to a dry storage flask, the reaction flask was rinsed three times with THF which was added to the stock solution. The total volume was brought to 1000 mL by adding dry THF, resulting in a 0.4 M solution of 2-phenylcyclopropylzinc chloride. The bright yellow solution was kept under nitrogen at ambient temperature for further use.

General cross-coupling procedure.

A 100 mL, three-necked round-bottomed reaction flask, equipped with a reflux condenser, gas inlet, thermometer and magnetic stirring bar was flushed with nitrogen and subsequently charged with 25 mmole of the substrate and 0.28 g (1 mole %) of $Pd(PPh_3)_4$. Immediately 63 mL (25 mmole) of a solution of 0.4 M 2-phenylcyclopropylzinc chloride in THF was added at room temperature. The reaction mixture was stirred for 24 h under reflux, and conversion and selectivity were determined by GLC. After the mixture had been cooled to room temperature, it was treated with 10 mL of 2 M HCl. Three extractions with 50 mL portions of diethyl ether were carried out, and the combined organic fractions were dried over $MgSO_4$. The pure product was obtained by removal of the solvent under reduced pressure, subsequent flash chromatography over a 4 cm silica column using pentane as the eluent and finally bulb-to-bulb distillation.

The following products were prepared by this procedure:

Cyclopropylbenzene in a 90 % yield. ^{1}H-NMR: δ= 7.36-7.12 (m, 5H, $C_{arom.}$(H)), 1.94 (m, 1H, C_1(H)), 1.01 (m, 2H, $C_{2,3}$(H)). ^{13}C-NMR: δ= 143.9 (C_i), 128.2 (C_o), 125.6 (C_m), 125.3 (C_p), 15.4 (C_1), 9.1 ($C_{2,3}$).

2'-Phenylcyclopropylbenzene in a 93 % yield. ^{1}H-NMR: δ= 7.63 - 7.38 (m,10H, $C_{arom.}$(H)), 2.49 (t, J = 7.3, 2H, $C_{1'}$, $_{2'}$(H)), 1.75 (t, J = 7.3, 2H, C_3(H)). ^{13}C-NMR:

δ= 142.4 ($C_{1, 1''}$), 128.3 ($C_{2, 2''}$), 125.7 ($C_{3, 3'', 4, 4''}$), 27.9 ($C_{1', 2'}$), 18.1 ($C_{3'}$).

(2'-Phenylcyclopropyl)-4-methoxybenzene in a 71 % yield. ^{1}H-NMR: δ= 7.58 - 6.68 (m, 9H, $C_{arom.}$(H)), 3.80 (s, 3H, C_{CH3}(H)), 2.18 - 2.07 (m, 2H, $C_{1', 2'}$(H)), 1.39 (m, 2H, $C_{3'}$(H)). ^{13}C-NMR: δ= 157.8 (C_4), 142.7 ($C_{1''}$), 134.5 (C_1), 128.4 , 126.9 , 125.7 , 125.6 ($C_{2, 2'', 3, 3''}$), 113.9 ($C_{4''}$), 55.3 (C_{CH3}), 27.5, 27.3 ($C_{1', 2'}$), 17.7 ($C_{3'}$).

(2'-Phenylcyclopropyl)-4-fluorobenzene in a 49 % yield. ^{1}H-NMR: δ= 7.58 - 7.19 (m, 9H, $C_{arom.}$(H)), 2.41 - 2.32 (m, 2H, $C_{1', 2'}$(H)), 1.69 - 1.38 (m, 2H, $C_{3'}$(H)). ^{13}C-NMR: δ= 161.2 (d, J_{CF}= 219, C_4), 140.1 (C_1), 138.0 ($C_{1''}$), 128.7, 128.6, 125.7($C_{3, 5, 2''...6''}$), 115.0 (d, J_{CF} = 30, $C_{2, 6}$), 27.6, 27.1 ($C_{1', 2'}$), 17.9 ($C_{3'}$).

(2'-Phenylcyclopropyl)-4-toluene in a 81 % yield. ^{1}H-NMR: δ= 7.64 - 7.38 (m, 9H, $C_{arom.}$(H)), 2.68 (s, 3H, C_{CH3}(H)), 2.50 (m, 2H, $C_{1, 2}$(H)), 1.76 (m, 2H, C_3(H)). ^{13}C-NMR: δ= 142.6, 139.4, 135.1, 129.0, 128.3, 125.6 , 27.8, 27.7, 20.9, 17.9 .

2-(2-Phenylcyclopropyl)thiophene in a 22% yield. ^{1}H-NMR: δ= 7.41 - 7.22 (m, 5H, $C_{arom.}$(H)), 7.16 (d, J = 5.1, 1H, $C_{5\text{-}Th}$(H)), 7.01 (dd, J = 5.1, 3.5, 1H, $C_{4\text{-}Th}$(H)), 6.91 (d, J = 3.5, 1H, $C_{3\text{-}Th}$(H)), 2.46 (m, 1H, C_1(H)), 2.32 (m, 1H, C_2(H)), 1.57 (m, 2H, C_3(H)). ^{13}C-NMR: δ= 146.9, 141.7, 128.4, 126.8, 125.9, 125.8, 122.7, 122.2, 28.6, 23.1, 19.0.

1,4-*Bis*(2'-phenylcyclopropyl)benzene in a 66% yield. ^{1}H-NMR: δ= 7.40 - 6.95 (m, 14H, $C_{arom.}$(H)), 2.23 (dd, J = 7.3, 4H, $C_{1, 2}$(H)), 1.51 (dd, J = 7.4, 4H, C_3(H)). ^{13}C-NMR: δ= 142.6, 140.0, 128.4, 125.9, 125.7, 125.6, 27.9, 27.7 , 18.0.

(2'-Cyclohexenylcyclopropyl)benzene in a 79 % yield. ^{1}H-NMR: δ= 7.33 - 7.12 (m, 5H, $C_{arom.}$(H)), 5.5 (m, 1H, $C_{alkene\text{-}H}$(H)), 2.07 - 1.95 (m, 4H, $C_{3', 6'}$(H)), 1.73 - 1.60 (m, 4H, $C_{4', 5'}$(H)), 1.26 - 1.04 (m, 4H, $C_{1...3}$(H)). ^{13}C-NMR: δ= 143.4 , 137.1, 128.2, 126.0, 125.7, 120.3, 30.1, 27.0, 25.2, 22.9, 22.6, 22.5, 14.2.

(2'-Benzylcyclopropyl)benzene in a 51 % yield. ^{1}H-NMR: δ= 7.47 (m, 10H, $C_{arom.}$(H)), 2.92 (m, 2H, $C_{3'}$(H)), 1.96(m, 1H, $C_{1'}$(H)), 1.51 (m, 1H, $C_{2'}$(H)). ^{13}C-NMR: δ= 143.3, 141.7, 128.4, 128.2, 126.0, 125.7, 125.6, 125.3, 39.9, 25.0, 24.0, 14.5.

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