

Vanadium-Catalyzed Cross-Coupling Reactions of Alkyl Halides with Aryl Grignard Reagents

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Vanadium(III) chloride catalyzed cross-coupling reactions of alkyl halides with arylmagnesium bromides. Various arylmagnesium bromides, except for an *ortho*-substituted arylmagnesium reagent, could be used for the reaction. Among alkyl halides tested, cyclohexyl halides and primary alkyl halides were good substrates. The reactions likely proceed via carbon-centered radical intermediates.

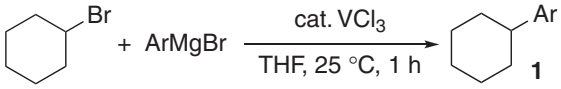
Transition-metal-catalyzed cross-coupling reactions are useful in organic synthesis, and recently, cross-coupling reactions of alkyl halides with organometallic reagents have attracted increasing attention.[1,2] To achieve this rather difficult transformation, copper, palladium, nickel, manganese, iron, and cobalt have been used as the catalysts. Herein, we report the catalytic activity of vanadium for the cross-coupling reactions of alkyl halides with aryl Grignard reagents.

Results and Discussion

Treatment of bromocyclohexane with phenylmagnesium bromide in the presence of a catalytic amount of vanadium(III) chloride in THF afforded cyclohexylbenzene (**1a**) in high yield (Table 1, Entry 1). *p*-Methoxy- and *p*-*tert*-butylphenylmagnesium bromides also reacted with bromocyclohexane smoothly (Entries 2 and 3). The reaction with *p*-fluorophenylmagnesium bromide gave the corresponding coupling product **1d** in good yield, although the reaction required a higher temperature (Entry 4). An aryl Grignard reagent having a trifluoromethyl group at the meta position reacted less efficiently to yield product **1e** in modest yield (Entry 5). When an aryl Grignard reagent had a substituent at the ortho position, the coupling reaction was completely suppressed (Entry 6). In all cases, except for Entry 6, bromocyclohexane was completely consumed.

Not only bromocyclohexane but also its iodo and chloro analogues reacted with phenylmagnesium bromide in the presence of VCl_3 (Table 2, Entries 1 and 2). Halocyclohexanes are exceptionally good substrates for the vanadium-catalyzed reaction. The reactions of bromocyclopentane and bromocycloheptane afforded the corresponding products in 37% and 8% yields, respectively, in refluxing THF (Entries 3 and 4). The reactions of acyclic secondary alkyl halides were not efficient. Namely, 2-bromododecane and 2-iodobutane were converted to the corresponding phenylated products in low yields (Entries 5 and 6). In contrast, primary alkyl iodide, 1-iododecane, reacted smoothly at room temperature (Entry 7). The reaction of 1-bromodecane was slow and required an elevated temperature (Entry 8). *tert*-Butyl bromide did not undergo

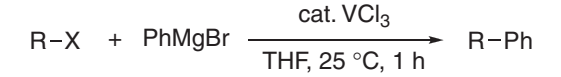
Table 1. Vanadium-Catalyzed Reactions of Bromocyclohexane with Arylmagnesium Bromide[a)]



Entry	Ar	Yield/%
1	Ph	**1a**, 75
2	*p*-MeO–C_6H_4	**1b**, 68
3	*p*-(*t*-Bu)–C_6H_4	**1c**, 67
4	*p*-F–C_6H_4	**1d**, 69[b)]
5	*m*-CF_3–C_6H_4	**1e**, 49[b),c)]
6	*o*-Me–C_6H_4	**1f**, 0[b),c),d)]

a) Conditions: bromocyclohexane (0.50 mmol), ArMgBr (1.0 mmol, 1 M THF solution), VCl_3 (0.050 mmol, 0.050 M THF solution). b) Performed at reflux. c) Performed for 3 h. d) Bromocyclohexane (15%) was recovered.

Table 2. Vanadium-Catalyzed Reactions of Various Alkyl Halides with Phenylmagnesium Bromide[a)]



Entry	R–X	Yield/%
1	Iodocyclohexane	**1a**, 75
2	Chlorocyclohexane	**1a**, 62[b),c)]
3	Bromocyclopentane	**2a**, 37[b)]
4	Bromocycloheptane	**2b**, 8[b),c)]
5	2-Bromododecane	**2c**, 34[d)]
6	2-Iodobutane	**2d**, 21
7	1-Iododecane	**2e**, 74
8	1-Bromodecane	**2e**, 66[b)]

a) Conditions: haloalkane (0.50 mmol), PhMgBr (1.0 mmol, 1 M THF solution), VCl_3 (0.050 mmol, 0.050 M THF solution). b) Performed at reflux. c) Performed for 5 h. d) 1-Dodecene (39%), 2-dodecene (14%), and dodecane (10%) were formed.

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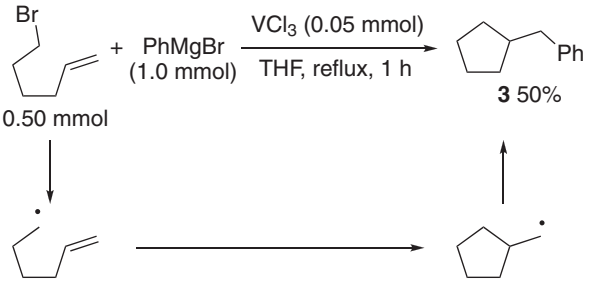
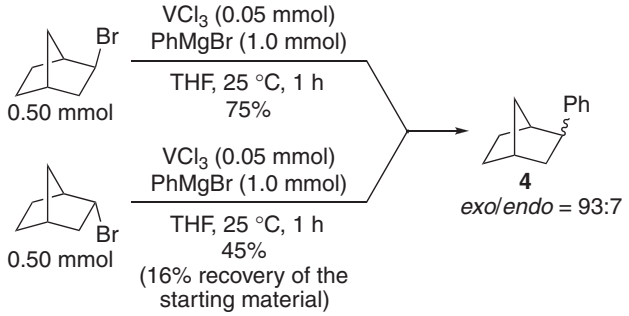


Scheme 1. Reaction of 6-bromo-1-hexene with phenylmagnesium bromide.

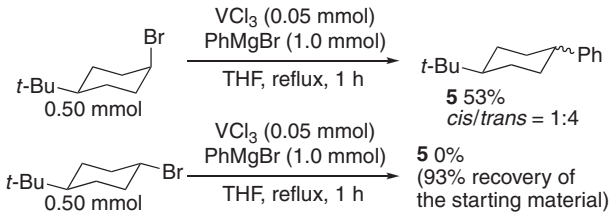


Scheme 2. Reactions of *exo*- and *endo*-2-bromonorbornane with phenylmagnesium bromide.

the coupling reaction, and, instead, 2-methylpropene and isobutane were produced.

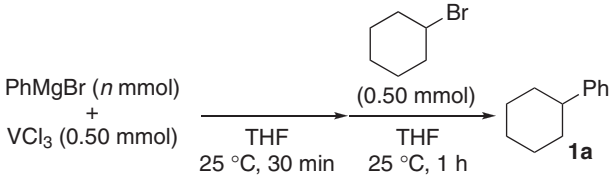
It is worth noting that the reactions in diethyl ether, instead of THF, afforded none of the phenylated products, although the starting material was fully converted. Cyclohexane and cyclohexene were formed instead. Dioxane exhibited virtually no solvent effects. Namely, the reactions in dioxane gave the coupling products in yields similar to those in THF. A variety of additives (0.050 mmol), such as *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, 4-(dimethylamino)pyridine, *N*-methylmorpholine, triphenylphosphine, trimethylphosphine, tricyclohexylphosphine, 1,2-bis(diphenylphosphino)ethane, 1,3-bis(diphenylphosphino)propane, and *N*-heterocyclic carbene ligands, had no effects on the reactions. Addition of 2,2′-bipyridyl suppressed the reaction completely. Other vanadium compounds such as $VO(acac)_2$ and $V(acac)_3$ also exhibited catalytic activity, although their activities were modest (49% and 45% yields, for the reaction of chlorocyclohexane with phenylmagnesium bromide, respectively). Cp_2VCl_2 did not show any catalytic activity.

Treatment of 6-bromo-1-hexene with phenylmagnesium bromide in the presence of a catalytic amount of VCl_3 afforded benzylcyclopentane (**3**) in 50% yield, in addition to a trace amount of 5-hexenylbenzene (<2%) (Scheme 1). It is well-known that 5-hexenyl radical isomerizes into cyclopentylmethyl radical rapidly.[3] The formation of **3** strongly supports the intermediacy of 5-hexenyl radical. The experimental fact that the phenylations of *endo*- and *exo*-2-bromonorbornane yielded the corresponding phenylated product **4** with the same *endo*/*exo* selectivity also suggests a radical pathway (Scheme 2). The stereochemical outcome of the reaction indicates the existence of a planar carbon center with no original stereochemical information,[2j,4] that is, 2-norbornyl radical. These experiments



Scheme 3. Reactions of *cis*- and *trans*-1-bromo-4-*tert*-butylcyclohexane with PhMgBr.

Table 3. Reactions of Bromocyclohexane with Various Phenylvanadium Reagents

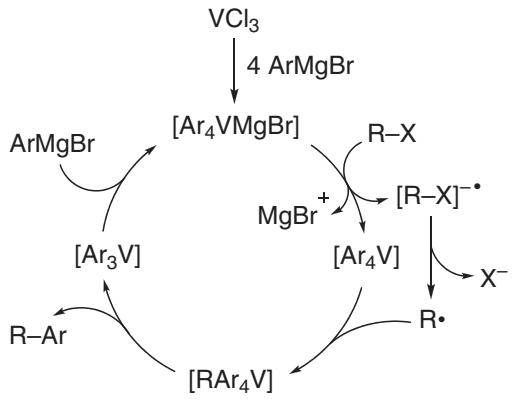


Entry	*n*	Yield/%	*c*-C_6H_{11}–Br recovered/%
1	1.0	<1	52
2	1.5	22	38
3	2.0	58	0
4	2.5	69	0
5	3.0	76	0
6	3.5	76	0

indicate that the vanadium-catalyzed reaction proceeds via carbon-centered radical intermediates. The mechanism should be similar to the cobalt-catalyzed coupling reactions of alkyl halides with aryl Grignard reagents (vide infra).[1e]

The vanadium-catalyzed phenylation exhibited interesting reactivity (Scheme 3). Treatment of *cis*-1-bromo-4-*tert*-butylcyclohexane with phenylmagnesium bromide under the conditions for the vanadium-catalyzed reaction yielded coupling product **5** in moderate yield. On the other hand, no reaction took place when its *trans* isomer was subjected to the reaction. The reason for the marked difference has not been determined.

To gain further information about the reaction mechanism and the actual vanadium species that is responsible for the coupling reaction, the reaction of bromocyclohexane with PhMgBr in the presence of a stoichiometric amount of VCl_3 was examined with different amounts of PhMgBr (Table 3). Treatment of bromocyclohexane (0.50 mmol) with a vanadium complex, prepared from 0.50 mmol of VCl_3 and 1.0 mmol of PhMgBr, gave a trace amount of **1a** (Entry 1). About half of the bromocyclohexane was recovered. Product **1a** formed when three molar amounts of PhMgBr were used (Entry 2), and using larger amounts of PhMgBr increased the yields of the product (Entries 3–5). The yield markedly increased when four molar amounts of PhMgBr were used (Entry 3). However, the yield did not increase when seven molar amounts of PhMgBr were used (Entry 6). It is worth noting that only a small amount of biphenyl was formed in each case, implying that trivalent vanadium species plays a key role in the reaction. It is well known that lithium tetraarylvanadates, $[Ar_4VLi]$, readily form upon treatment of VCl_3 with four molar amounts of ArLi.[5,6] Hence, in the catalytic reaction, vanadate



Scheme 4. Plausible mechanism.

complexes such as [Ar_4VMgBr] should serve as an active species.

We propose the following mechanism for the catalytic reaction as follows (Scheme 4). The reaction of VCl_3 with four molar amounts of ArMgBr gives [Ar_4VMgBr]. The vanadate complex undergoes single electron transfer to the alkyl halide to yield the anion radical of the alkyl halide, [Ar_4V],[5d] and $MgBr^+$. Immediate loss of bromide from the anion radical affords the corresponding alkyl radical intermediate R•, and [Ar_4V] then captures the carbon-centered radical to form [RAr_4V]. The pentavalent organovanadium complex should be so unstable that it should undergo rapid reductive elimination to afford the coupling product and [Ar_3V], which is reconverted into [Ar_4VMgBr] by reacting with the remaining ArMgBr.

In conclusion, we showed the catalytic activity of vanadium(III) chloride in the cross-coupling reactions of alkyl halides with aryl Grignard reagents. Vanadium catalysts are rarely used for carbon–carbon bond-formation reactions.[7] The results herein will open up new possibilities for using vanadium catalysts.

Experimental

General. ^{1}H NMR (500 and 300 MHz) and ^{13}C NMR (125.7 and 75.3 MHz) spectra were taken on a Varian UNITY INOVA 500 spectrometer and a Varian GEMINI 300 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were obtained in $CDCl_3$ with tetramethylsilane as an internal standard. Chemical shifts (δ) are in parts per million relative to tetramethylsilane at 0.00 ppm for ^{1}H and relative to $CDCl_3$ at 77.2 ppm for ^{13}C unless otherwise noted. IR spectra were determined on a JASCO IR-810 spectrometer. TLC analyses were performed on commercial glass plates with a 0.25 mm thick layer of Merck Silica gel 60F_{254}. Silica gel (Wakogel 200 mesh) was used for column chromatography. The elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Anhydrous VCl_3·THF was purchased from Aldrich and was diluted to prepare a 0.050 M THF solution.

Typical Procedure for Vanadium-Catalyzed Arylation Reactions of Alkyl Halides. Vanadium(III) chloride (0.050 M THF solution, 1.0 mL, 0.050 mmol) and phenylmagnesium bromide (1.0 M THF solution, 1.0 mL, 1.0 mmol) were sequentially added to a 20-mL reaction flask under argon. The mixture was stirred for about 20 min at room temperature. Bromocyclohexane (0.082 g, 0.50 mmol) was added to the reaction mixture at 25 °C. While the Grignard reagent was being added, the mixture turned dark-brown. After stirring for 1 h at 25 °C, a saturated ammonium chloride solution (0.2 mL) was added to the reaction mixture. The mixture was filtered through a pad of Florisil, and the filtrate was concentrated. Silica-gel column purification (hexane) of the crude product provided cyclohexylbenzene (61 mg, 75% yield).

Characterization Data. The following products are well-known compounds or found in the literature: **1b**,[8] **2b**,[4] **2c**,[9] **3**,[10] **4**,[11] and **5**.[12]

1-*tert*-Butyl-4-cyclohexylbenzene (1c): IR (neat) 2925, 2852, 1521, 1507, 1461, 1448, 1362, 1270, 1109, 825, 570 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.21–1.29 (m, 1H), 1.31 (s, 9H), 1.36–1.45 (m, 4H), 1.72–1.75 (m, 1H), 1.82–1.88 (m, 4H), 2.45–2.49 (m, 1H), 7.13 (d, J = 6.5 Hz, 2H), 7.31 (d, J = 6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 26.49, 27.25 (2C), 31.71 (3C), 34.58, 34.76 (2C), 44.26, 125.37 (2C), 126.67 (2C), 145.27, 148.67; Found: C, 88.58; H, 11.38%. Calcd for $C_{16}H_{24}$: C, 88.82; H, 11.18%.

1-Cyclohexyl-4-fluorobenzene (1d): IR (neat) 2927, 2853, 1605, 1511, 1448, 1159, 827, 807 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19–1.28 (m, 1H), 1.32–1.43 (m, 4H), 1.71–1.76 (m, 1H), 1.80–1.88 (m, 4H), 2.44–2.50 (m, 1H), 6.94–6.98 (m, 2H), 7.13–7.16 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 26.33, 27.09 (2C), 34.88 (2C), 44.07, 115.12 (d, J = 20.6 Hz, 2C), 128.28 (d, J = 7.8 Hz, 2C), 143.94 (d, J = 3.4 Hz,), 161.35 (d, J = 241.5 Hz); Found: C, 80.91; H, 8.49%. Calcd for $C_{12}H_{15}F$: C, 80.86; H, 8.48%.

1-Cyclohexyl-3-trifluoromethylbenzene (1e): IR (neat) 2928, 2855, 1491, 1451, 1437, 1333, 1277, 1232, 1198, 1163, 1125, 1074, 799, 702, 668 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.24–1.31 (m, 1H), 1.35–1.47 (m, 4H), 1.74–1.78 (m, 1H), 1.84–1.90 (m, 4H), 2.53–2.58 (m, 1H), 7.37–7.40 (m, 2H), 7.41–7.44 (m, 1H), 7.44–7.46 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.99, 26.73 (2C), 34.27 (2C), 44.42, 122.62 (q, J = 3.9 Hz), 123.50 (q, J = 3.4 Hz), 124.37 (q, J = 270.6 Hz,), 128.63, 130.26, 130.28, 130.50 (q, J = 31.5 Hz); Found: C, 68.57; H, 6.67%. Calcd for $C_{13}H_{15}F_3$: C, 68.41; H, 6.62%.

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