



Cross-coupling of Grignard reagents with alkyl halides or tosylates by the use of nickel or palladium containing perovskite

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ABSTRACT

Nickel and palladium-containing perovskites, LaFe_{0.8}Ni_{0.2}O₃ (LFNO) and LaFe_{0.95}Pd_{0.05}O₃ (LFPO), could be employed as effective catalyst sources for the cross-coupling of nonactivated alkyl halides and tosylates with Grignard reagents in the presence of conjugated dienes. The reaction proceeded efficiently at room temperature or below using only ca. 1 mol % of catalysts with respect to Ni or Pd and the perovskites were reused without considerable loss of activity.

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Perovskites with a general formula of ABO₃ have been widely used in industries, not only as functional inorganic materials having unique electronic, photo, and/or magnetic properties but also as heterogeneous catalysts, especially for oxidation reactions in environmental and related fields.¹ In 2003, Ley and co-workers demonstrated the synthetic utility of perovskites by disclosing that Pd-containing perovskites exhibit high catalytic activity on heating for Suzuki–Miyaura coupling, where they can be used as recoverable and reusable catalysts for cross-coupling of aryl halides with aryl- or vinylboronic acids in alcohol solvents in the presence of base.² They extended the scope of the nucleophiles from organoboranes to terminal acetylenes, phenols, and thiols by using Cu- and Pd-containing perovskites to give the corresponding substituted arenes.³ We have developed alkyl–alkyl cross-couplings between nonactivated alkyl halides and Grignard reagents by the use of Ni, Pd, or Cu catalysts in the presence of hydrocarbon ligands.⁴ Thus we tested the catalytic activities of nickel- and palladium-containing perovskites for these systems and found that the reaction proceeded efficiently at room temperature or below in the presence of a conjugated diene. We also confirmed that the remaining perovskites could be used repeatedly without activation treatment.

Preliminary screening of reaction conditions was performed by using octyl bromide and ⁿBuMgCl in THF. We employed two perovskites, LaFe_{0.8}Ni_{0.2}O₃ (LFNO) and LaFe_{0.95}Pd_{0.05}O₃ (LFPO), and selected results are shown in Table 1.^{5,6} Cross-coupling proceeded efficiently at room temperature for both catalysts by use of either 1,3-butadiene or isoprene as an additive. Phenylpropyne, triethylamine, TMEDA, and HMPA were not effective as a base. Most of the octyl bromide was recovered unchanged in entries 2, 4, 5, and 7.

Table 1
Screening of reaction conditions

Entry	Additive	Temp (°C)	LFNO or LFPO additive		
			Yield ^a (%) ⁿ C ₁₂ H ₂₆	Octene	Octane
1		25	94/81	0/0	<1/<1
2	None	25	3/2	0/0	<1/2
3		25	43/87	0/0	0/1
4	Ph–C≡C–Et	25	2/2	0/0	0/1
5	Et ₃ N	25	3/2	1/0	1/1
6	TMEDA	25	Trace/48	0/0	0/0
7	HMPA	25	4/1	1/0	0/1
8		−30	1/2	0/0	0/0
9		0	21/26	0/0	0/0
10		65	64/37	0/0	0/0

Conditions: ⁿC₈H₁₇Br (1 mmol), ⁿBuMgCl (1.3 equiv, 1 mL), LFNO (10 mg; 0.8 mol %), 0.46 mg Ni, 5 h or LFPO (50 mg; 1 mol %, 1 mg Pd), additive (1.3 equiv), 13 h.

^a Determined by GC.

We performed the cross-coupling of a range of alkyl halides and tosylates with Grignard reagents and summarized the results in Table 2. Alkyl iodide, bromides, and tosylates were all coupled efficiently with ⁿBuMgCl or ⁿOctMgCl in the presence of either perovskite under aforementioned conditions.^{5,6} LFNO and LFPO afforded the products in similar yields but the former tended to give slightly better yields. The reaction using LFNO is clean and GC analysis of the resulting mixtures showed no other large peaks except the desired products and starting materials. Unfortunately, neither octyl chloride nor octyl fluoride reacted with ⁿBuMgCl (Table 2, entries 8 and 9).

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Table 2

Cross-coupling reaction of alkyl halides and tosylates with alkyl Grignard reagents using Ni- and Pd-containing perovskite

Entry	Alkyl-X	R-MgX	Yield ^a (%)	
			Ni-perovskite	Pd-perovskite
1	ⁿ Oct-I	ⁿ Bu-MgCl	78	73
2	 Br	ⁿ Bu-MgCl	82	77
3	ⁿ Non-Br	ⁿ Oct-MgCl	87	80
4	 OTs	ⁿ Bu-MgCl	76	65
5	ⁿ Oct-OTs	Et-MgBr	76	70
6	ⁿ Oct-OTs	ⁿ Bu-MgCl	71	69
7	Et-OTs	ⁿ Oct-MgCl	70	74
8	ⁿ Oct-Cl	ⁿ Bu-MgCl	3	1
9	ⁿ Oct-F	ⁿ Bu-MgCl	2	2

Conditions: alkyl halides or tosylate (1 mmol), catalyst (1 mol % LFPO or 0.8 mol % LFNO), ⁿBuMgCl (1.3 equiv); in case of LFNO, 1,3-butadiene (50 mol %), rt, 5 h, in case of LFPO, isoprene (1.3 equiv), rt, 13 h.

^a Determined by GC.

We then checked the feasibility of recovery and reuse of the catalyst by utilizing the coupling of nonyl bromide and ⁿBuMgCl.⁷ It was found that the recovery of catalysts can be achieved without compromising the operational simplicity of the procedure, and three catalytic runs were performed successively only by repeating removal of the solution phase by syringe, rinsing the remaining solids, and recharging the reagents to the reaction vessel, without observing any appreciable loss of catalytic activity in both LFNO and LFPO cases (Table 3).

In order to shed light on whether this reaction takes place in a heterogeneous or homogeneous fashion, that is, on the surface of the bulk solid catalyst or on a metal complex in the liquid phase of the suspension, we checked the time course of the LFNO catalyzed reactions carried out separately with or without filtration (Fig. 1). Filtration of the dark black suspension (left) with

Table 3

Recycling experiments

Run	Yield (%)	
	Ni-perovskite	Pd-perovskite
1	91	78
2	90	78
3	86	75

Conditions: LFNO (0.8 mol %), 1,3-butadiene (50 mol %), rt, 5 h or LFPO (1 mol %), isoprene (1.3 equiv), rt, 13 h.

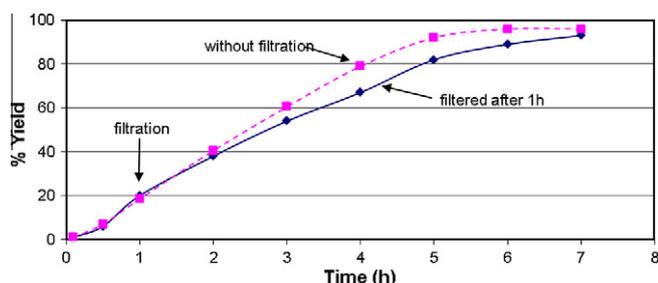


Figure 1. Time course of the LFNO catalyzed cross coupling of ⁿOct-Br with ⁿBuMgCl at rt with (dashed line, average of two separate runs) or without (solid line) removal of solids by filtration.⁸

Table 4

Ni in solution of LFNO catalyzed coupling reactions

Reaction time	0.5 h	1 h	2 h	4 h	5 h
Ni concentration in solution (ppm)	5	7	5	8	8

Conditions: octyl bromide (1 mmol), ⁿBuMgCl (1.3 mmol, 1.94 M in THF, 0.67 mL), LFNO (10 mg; 0.8 mol %, 0.46 mg Ni), rt.

0.45 μ m syringe filter after 1 h of stirring gave a pale yellow transparent solution (right), which was stirred continuously and analyzed by GC. The yields of the coupling product are shown by the solid line along with the results obtained by similar reactions without filtration (dotted line). It is interesting that the transparent filtrate contains the catalytic species and showed similar performance to the original dark suspension, indicating that coupling proceeds in the liquid phase rather than on the bulk solid surface. However, this is not surprising since similar results have been reported by the Ley group.² It is still unclear if the active catalytic species is a single metal complex as proposed in the reaction using Ni salts⁴ or small nano-particles.

In order to determine how much Ni is present in solution we filtered the reaction mixture after stirring a mixture of LFNO, octyl bromide, butyl Grignard reagent, and 1,3-butadiene in THF at rt for 0.5, 1, 2, 4, and 5 h and analyzed the filtrate by ICP-AES after quenching with water. The concentration of Ni in the liquid phase of the resulting mixture after filtration at each stage of the reaction is listed in Table 4, indicating that Ni in solution reached ca. 5 ppm, corresponding to 6×10^{-8} mmol, within 30 min followed by a gradual increase up to 8 ppm (9×10^{-8} mmol) over 5 h.⁹

These results may be explained simply by assuming an equilibrium between Ni in solution and Ni in perovskite, and the cross-coupling is catalyzed in a homogeneous fashion by a complex in solution. If so, TON of Ni in solution is calculated to be in the order of 10^7 . Leaching of Ni is rapid (within 30 min) but stops at low concentrations probably due to the presence of the reverse process. Table 4 shows that only 1/100000 of total Ni in the bulk perovskite (8×10^{-3} mmol) moved into the liquid phase enabling the reuse of the perovskite.

In summary, it was demonstrated that the Ni- and Pd-containing perovskites, LaFe_{0.8}Ni_{0.2}O₃ (LFNO) and LaFe_{0.95}Pd_{0.05}O₃ (LFPO), can be used as useful catalyst sources for the cross-coupling of alkyl halides or tosylates with Grignard reagents in the presence of dienes. LFNO showed slightly higher reactivity than LFPO. The present coupling reaction is catalyzed by trace amounts of Ni or Pd in solution leached from perovskites employed with very high TON (ca. 10^7). It was also proved that the remaining bulk perovskites could be reused. According to Ley's report,² coupling of aryl halides with boronic acids catalyzed by palladium containing perovskites is effective only in protic solvents at elevated temperatures in the presence of a base. Our system works efficiently in aprotic solvent and enables alkyl-alkyl cross coupling using Grignard reagents.

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5. *General procedures for Pd-perovskite catalyzed cross-coupling reactions.* A 20 mL tube was charged with the alkyl halides (1 mmol) and alkyl Grignard reagents (1.3 mmol) and cooled to 0 °C. Then isoprene (0.130 mL, 1.3 equiv) was introduced into the reaction vessel. After the addition of LaFe_{0.95}Pd_{0.05}O₃ (LFPO) (50 mg, 1 mol %, 1 mg Pd), the mixture was stirred at room temperature for 13 h. It was then quenched with water (1 mL) and diluted with diethyl ether (5 mL), and the supernatant liquid was removed by syringe and passed through a 0.45 μm syringe filter and washed with diethyl ether (10 mL). The mixture was washed with 1 N HCl (2 mL) followed by water (5 mL) and the aqueous layer was back extracted with diethyl ether (10 mL). The combined organic layers were dried (MgSO₄) and evaporated to give the crude product, which was analyzed by GC using octane as an internal standard.
6. *General procedures for Ni-perovskite catalyzed cross-coupling reactions.* A 20 mL tube was charged with the alkyl halides (1 mmol) and alkyl Grignard reagent (1.3 mmol) and cooled to –78 °C, and then 1,3-butadiene (50 mol %) was added. After addition of LaFe_{0.8}Ni_{0.2}O₃ (LFNO) (10 mg, 0.8 mol %, 0.46 mg Ni), the mixture was stirred at rt for 5 h. It was quenched with water (1 mL) at the same temperature and then diluted with diethyl ether (5 mL), and the supernatant liquid was passed through a 0.45 μm syringe filter and washed with diethyl ether (10 mL). The mixture was washed with 1 N HCl (2 mL) followed by water (5 mL) and the aqueous layer was back extracted with diethyl ether (10 mL). The combined organic layers were dried (MgSO₄) and evaporated to give the crude product, which was analyzed by GC using octane as an internal standard.
7. *Recycling experiments.* The first run was performed according to the procedure in Ref. 5 or 6 presented above. When the reaction was complete (after 5 h or 13 h), stirring was stopped and the mixture was allowed to stand for 30–40 min until the solid catalyst settled down. Then the transparent pale yellow supernatant liquid was carefully filtered using a 0.45 μm syringe filter. Into the solution, 1 N HCl (2 mL) was added to quench the reaction. Products were extracted with diethyl ether and analyzed by GC. The remaining solid catalyst (LFNO or LFPO) in the reaction vessel was washed with water, acetone, and diethyl ether, dried under vacuum, and reused in the subsequent runs by adding the substrates to the reaction vessel.
8. *Filtration experiments.* A 20 mL tube was charged with ⁿoctyl bromide (193 mg, 1 mmol), ⁿBuMgCl (1 mL, 1.3 M in THF, 1.3 mmol) with undecane as an internal standard and cooled to –78 °C then 1,3-butadiene (11.2 mL, at 20 °C under 1 atm, 0.5 mmol) was added. After addition of LaFe_{0.8}Ni_{0.2}O₃ (LFNO) (10 mg, 0.8 mol %, 0.46 mg Ni), the mixture was stirred at room temperature for 1 h and the catalyst was filtered under N₂ using a 0.45 μm syringe filter. The reaction mixture was monitored by GC.
9. In the cross-coupling of ArX with boronic acids catalyzed by Pd-containing perovskites, the concentration of Pd in the reaction mixture filtrates was estimated to be 2 ppm; see Ref. 2.