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1,3-Dicyclohexylimidazol-2-ylidene as a Superior Ligand for the Nickel-Catalyzed Cross-Couplings of Aryl and Benzyl Methyl Ethers with Organoboron Reagents

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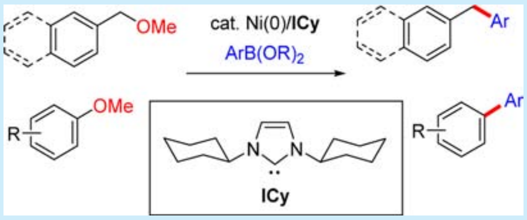
Supporting Information

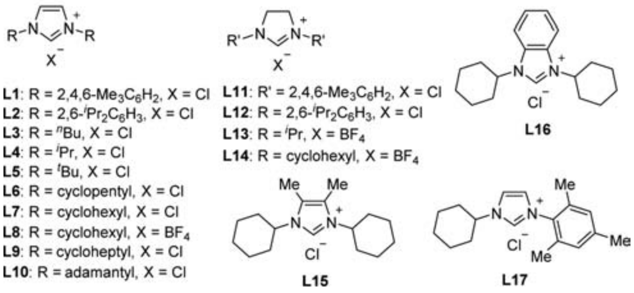
ABSTRACT: A new catalytic system has been developed involving the use of Ni(cod)$_2$ in conjunction with 1,3-dicyclohexylimidazol-2-ylidene for the cross-coupling of aryl and benzyl methyl ethers with organoboron reagents. This method not only allows for the use of readily available methyl ethers as halide surrogates but also provides a functional group tolerant method for the late-stage derivatization of complex molecules.



The replacement of organic halides with alcoholic derivatives as electrophiles for use in cross-coupling reactions allows for the utilization of a naturally abundant feedstock.[1] Traditionally, this process has been accomplished by converting hydroxyl groups into better leaving groups, such as triflates. Recent efforts, however, have focused instead on the use of relatively inert yet readily available alcohol derivatives, including carboxylates and carbamates, which provide several advantages over activated sulfonates in terms of their general stability, cost, and atom efficiency.[2] In this context, methyl ethers represent particularly good candidates as prospective electrophiles.[3] The C−OMe bonds of methyl ethers, however, are very electron-rich, which renders their activation by oxidative addition challenging, and this factor has limited their widespread application in cross-coupling reactions.[4−11] Particularly nascent is their cross-coupling with organoboron reagents; applicable substrates have been limited to aryl ethers containing a fused aromatic ring (e.g., naphthalenes)[10a] or an *ortho*-directing group[11] as well as alkenyl ethers.[10b] Herein, we report the use of 1,3-dicyclohexylimidazol-2-ylidene (ICy) as a ligand to enable the nickel-catalyzed[12] Suzuki−Miyaura cross-coupling of methyl ethers with a substantially broadened scope, including an unprecedented C(sp^3)-OMe/organoboron coupling.[13]

Table 1. Ni-Catalyzed Cross-Coupling of 1 with 2a: The Effect of the Ligand[a]

entry	ligand	GC yield of **3a** (%)	entry	ligand	GC yield of **3a** (%)
1[b]	PCy$_3$	0	10	**L9**	0
2	**L1**	0	11	**L10**	0
3	**L2**	0	12	**L11**	0
4	**L3**	0	13	**L12**	0
5	**L4**	29	14	**L13**	9
6	**L5**	0	15	**L14**	10
7	**L6**	0	16	**L15**	11
8	**L7**	70 (67)[c]	17	**L16**	0
9	**L8**	63	18	**L17**	0



L1: R = 2,4,6-$Me_3C_6H_2$, X = Cl
L2: R = 2,6-^{i}$Pr_2C_6H_3$, X = Cl
L3: R = ^{n}Bu, X = Cl
L4: R = ^{i}Pr, X = Cl
L5: R = ^{t}Bu, X = Cl
L6: R = cyclopentyl, X = Cl
L7: R = cyclohexyl, X = Cl
L8: R = cyclohexyl, X = BF_4
L9: R = cycloheptyl, X = Cl
L10: R = adamantyl, X = Cl
L11: R' = 2,4,6-$Me_3C_6H_2$, X = Cl
L12: R = 2,6-^{i}$Pr_2C_6H_3$, X = Cl
L13: R = ^{i}Pr, X = BF_4
L14: R = cyclohexyl, X = BF_4

[a]Reaction conditions: **1** (0.30 mmol), **2a** (0.45 mmol), Ni(cod)$_2$ (0.030 mmol), ligand (0.060 mmol), NaO^{t}Bu (0.075 mmol), and CsF (0.60 mmol) in toluene (1.0 mL) at 120 °C for 12 h. [b]NaO^{t}Bu was not added. [c]Isolated yield.

Benzyl methyl ether **1** was selected as our initial test substrate, because there have been no reports pertaining to the successful cross-coupling of alkyl ethers with organoboron reagents, even with compounds possessing this class of activated (i.e., benzylic) C(sp^3)−OMe bond.[14,15] The Ni(cod)$_2$/PCy$_3$ system is recognized as the state-of-the-art catalyst for C(sp^2)−OMe/organoboron cross-coupling.[10a] Unfortunately, however, its application to the cross-coupling of **1** with **2a** proved to be a total failure, with none of the desired product **3a** being detected (Table 1, entry 1). We subsequently examined a series of N-heterocyclic carbene (NHC) ligands with the expectation that their pronounced electron-donating abilities[16] would facilitate the difficult oxidative addition of the

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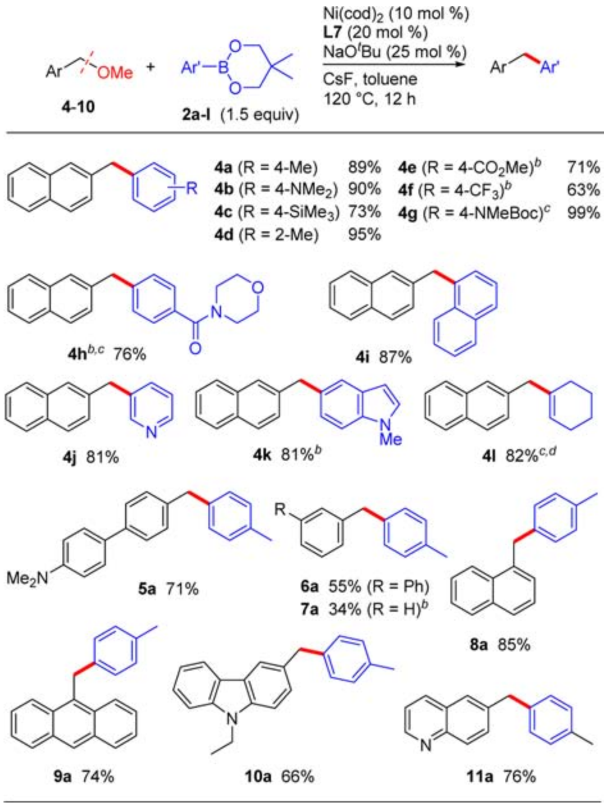
C(sp^3)−OMe bond of **1**. Although the NHC ligands bearing aryl groups on their nitrogen atoms (i.e., **L1**, **L2**, **L11**, **L12**) all failed to promote the cross-coupling reaction, those bearing alkyl groups afforded promising results. Ligand **L4**, for example, bearing ^{i}Pr groups on its nitrogen atoms, provided the desired product **3a** in 29% yield (entry 5), although **L3** and **L5** bearing *n*- and *tert*-butyl groups, respectively, provided much poorer results (entries 4 and 6). Further screening of the secondary alkyl-substituted NHC ligands revealed that cyclohexyl derivatives **L7** and **L8** effectively promoted the cross-coupling of **1** to form **3a** (entries 8 and 9).[17] It is noteworthy that subtle structural changes in **L7**, including the ring size (entries 7 and 10), backbone saturation (entry 15), and substitution (entries 16 and 17), resulted in a marked decrease in activity. The narrow window of opportunity for the development of suitable ligands in this case highlights the difficulties associated with designing suitable catalysts for the cross-coupling of unactivated methyl ethers with relatively unreactive organoboron nucleophiles.

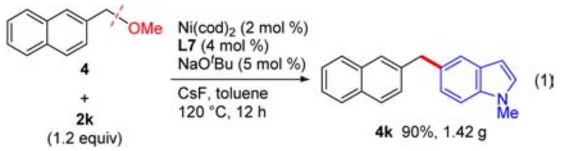
Having identified **L7** as an optimal ligand, we proceeded to explore the scope of this nickel-catalyzed cross-coupling reaction of benzyl methyl ethers with organoboron reagents (Scheme 1). Regarding the organoboron component, several substituted phenylboronic acid derivatives reacted smoothly under the optimized conditions to give the corresponding coupling products **4a−h** in an efficient manner. Esters, amides, and carbamates[18] proved to be compatible (i.e., **4e**, **4g**, and **4h**), which highlights the synthetic advantage of our reaction over Kumada-type reactions.[4e,f,l] Sterically hindered aromatics (i.e., **4d** and **4i**) and heteroaromatics (i.e., **4j** and **4k**) were also successfully incorporated at the benzylic position. Moreover, an alkenylboron reagent was also found to be applicable to form the corresponding cross-coupling product **4l**, which could be converted to an alkylated compound via the hydrogenation of the alkene moiety. With respect to the scope of the benzyl ethers, the methoxy group at the electron-rich benzylic center could also be substituted to form compounds such as **5a** under these nickel-catalyzed conditions. A lower yield was observed with simple benzyl ether **7**, presumably due to a lesser tendency to form the key π-benzylnickel intermediate.[19] Sterically congested methyl ethers, such as **8a** and **9a**, as well as electron-rich and -deficient heteroaromatics, such as **10a** and **11a**, all underwent the cross-coupling in the presence of the Ni/**L7** catalytic system.

Scheme 1. Ni/L7-Catalyzed Cross-Coupling of Benzyl Methyl Ethers with Organoboron Reagents[a]

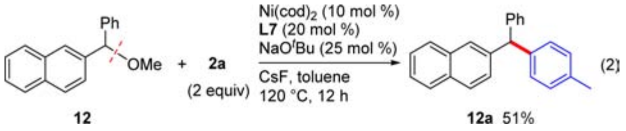


[a]Reaction conditions: benzyl methyl ether (0.30 mmol), boronate **2a−l** (0.45 mmol), Ni(cod)$_2$ (0.030 mmol), **L7** (0.060 mmol), NaO^{t}Bu (0.075 mmol), and CsF (0.60 mmol) in toluene (1.0 mL) at 120 °C for 12 h. Isolated yield is shown. [b] Ni(cod)$_2$ (0.060 mmol), **L7** (0.12 mmol), and NaO^{t}Bu (0.14 mmol) were used. [c] The corresponding Ar′-B(pin) was used. [d] Isolated as a 4.3:1 mixture of **4h** and isomeric 2-(cyclohexylidenemethyl) naphthalene.

It should also be noted that the current protocol was amenable to gram-scale synthesis (eq 1). Although we routinely used 10 mol % catalyst in our exploratory studies, the catalyst loading in this reaction could be reduced to 2 mol % without any discernible decrease in the yield.

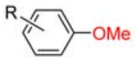
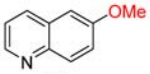
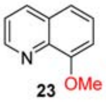
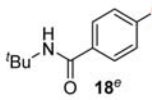
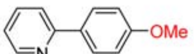
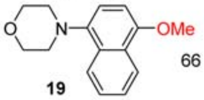
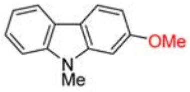
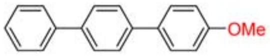
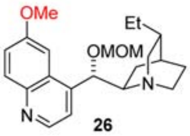
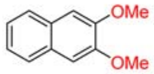


One of the key limitations of the Ni(cod)$_2$/**L7** system, however, was that it could not be applied to secondary benzylic ethers, in that the introduction of a methyl group at the benzylic position completely inhibited the reaction. A notable exception to this observation was provided by the diarylmethyl methyl ether **12**, which afforded the triaryl methane derivative **12a** in 51% yield, along with a reduced product (28%).[20] These results suggested that the oxidative addition of a secondary C(sp^3)−OMe bond in **12** to a nickel center must have proceeded smoothly and that the subsequent transmetalation with **2a** was slow, which would provide an opportunity to form the reduced product.



Pleasingly, the Ni(cod)$_2$/**L7** system was also found to catalyze the cross-coupling of an array of aryl methyl ethers with organoboron reagents (Table 2). In sharp contrast to the Ni(0)/PCy$_3$ system,[10a] anisole derivatives containing no fused aromatic ring (e.g., **13**, **14**, **16**, **17**, **18**, **20**, and **24**) successfully underwent the cross-coupling with **2a** when **L7** was used as the ligand. This reaction also exhibited a high level of tolerance toward substrates bearing a bulky ortho substituent, such as **17**, as well as substrates bearing an acidic NH group, such as **18**. Although electron-rich anisoles (e.g., **15**) performed poorly as substrates for this reaction, electron-rich naphthalene derivatives, such as **19**, behaved as viable substrates when PCy$_3$ was replaced with **L7**. Selective diarylation of 1,2-dimethoxyarene

Table 2. Ni/L7-Catalyzed Cross-Coupling of Aryl Methyl Ethers[a]

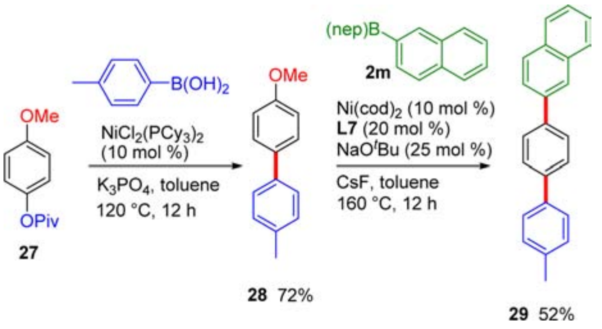
aryl methyl ether	L7	PCy_3[b]	aryl methyl ether	L7	PCy_3[b]
			 **22**	82	0
R = 4-Ph (**13**)	76	0			
R = 4-CF_3 (**14**)	75	0			
R = 4-^{t}Bu (**15**)[c]	32	0	 **23**	80	0
R = 3-Ph (**16**)	74	0			
R = 2-Ph (**17**)[d]	75	0			
 **18**[e]	65	0	 **24**[h]	67	trace
 **19**	66	0	 **25**	74	0
 **20**	69	0	 **26**	51	0
 **21**[f]	96	--[g]			

[a]Reaction conditions: aryl methyl ether (0.30 mmol), **2a** (0.45 mmol), Ni(cod)$_2$ (0.030 mmol), **L7** (0.060 mmol), NaO^{t}Bu (0.075 mmol), and CsF (0.60 mmol) in toluene (1.0 mL) at 120 °C for 12 h. Isolated yield is shown. [b]PCy_3 (0.012 mmol) was used. [c]CsF (1.4 mmol) at 160 °C for 24 h. [d]**2a** (0.60 mmol) and CsF (0.80 mmol). [e]Ni(cod)$_2$ (0.060 mmol), **L7** (0.12 mmol), and NaO^{t}Bu (0.15 mmol) for 36 h. [f]**2a** (1.5 mmol) and CsF (1.6 mmol) in toluene (2.0 mL). [g]The reaction afforded a mixture of **21**, 2-(4-tolyl)naphthalene, and diarylated product. [h]**2a** (0.90 mmol), Ni(cod)$_2$ (0.060 mmol), **L7** (0.12 mmol), NaO^{t}Bu (0.14 mmol), and CsF (1.1 mmol) in toluene (2.0 mL).

21 was also possible, which could serve as a useful method for the extension of the π-system. Another notable benefit of using **L7** instead of PCy_3 was the ability to couple heteroaryl ethers. The catalyst poisoning, which was attributed to the presence of an sp^2-nitrogen atom in the examples involving **22**, **23**, and **24**, was overcome by the use of **L7**, which allowed for the formation of arylated quinoline and pyridine derivatives. Highly deactivated electron-rich heteroaromatics, such as **25**, also reacted smoothly under these newly developed conditions. This arylation protocol could potentially be used to modify natural products containing a methoxyarene moiety, such as **26**.

Interestingly, **L7** was a less effective ligand than PCy_3 for promoting the reaction of 2-naphthyl pivalates and naphthalen-2-yl diethylcarbamate with **2a** (8% and 67% yield, respectively). This specific reactivity of **L7** in the nickel-catalyzed Suzuki–Miyaura-type cross-couplings of different phenolic electrophiles allows for orthogonal cross-couplings of aryl pivalates[21] and methyl ethers (Scheme 2).

Scheme 2. Sequential Cross-Coupling of Aryl Pivalates and Methyl Ether with Organoboron Reagents



In summary, we have developed the first nickel-based catalyst for the cross-coupling of benzyl methyl ethers with organoboron reagents. The success of this reaction has been attributed to the use of the NHC ligand **L7**, which was also used to facilitate a Suzuki–Miyaura-type cross-coupling reaction of a range of aryl methyl ethers that have not previously been successful (i.e., those containing no fused aromatic rings and heteroaryl methyl ethers). Further studies directed toward the application of **L7** to the cross-coupling reactions of methyl ethers with various nucleophiles, as well as the activation of other strong σ-bonds, are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures and details pertaining to the characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(20) Notes: (a) No reaction occurred in the absence of Ni(cod)$_2$. (b) When the reaction was run at 100 °C under otherwise identical conditions, **12a** was not formed, but a reduced product was obtained (13%). (c) The reaction of CD_3-labelled substrate **12-*d*$_3$** resulted in the formation of **12a** (46%) and a reduced product (21%) that contained no deuterium. (d) The reaction of optically pure **12** resulted in the formation of racemic **12a**.

(21) Garg's protocol was used in the first reaction of Scheme 2. Quasdorf, K. W.; Tian, X.; Garg, N. K. *J. Am. Chem. Soc.* **2008**, *130*, 14422.