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Cross-Coupling Reactions |*Hot Paper*|

Cross-Coupling of Organolithium with Ethers or Aryl Ammonium Salts by C–O or C–N Bond Cleavage

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Abstract: Various aryl-, alkenyl-, and/or alkyllithium species reacted smoothly with aryl and/or benzyl ethers with cleavage of the inert C–O bond to afford cross-coupled products, catalyzed by commercially available [Ni(cod)$_2$] (cod = 1,5-cyclooctadiene) catalysts with N-heterocyclic carbene (NHC) ligands. Furthermore, the coupling reaction between the aryllithium compounds and aryl ammonium salts proceeded under mild conditions with C–N bond cleavage in the presence of a [Pd(PPh$_3$)$_2$Cl$_2$] catalyst. These methods enable selective sequential functionalizations of arenes having both C–N and C–O bonds in one pot.

Introduction

The study of organolithium compounds has a long and rich history, and the chemistry is employed in many areas of science.[1] The use of organolithium as a nucleophilic partner in the transition metal (TM)-catalyzed cross-coupling can be traced back to 1975, when Murahashi et al. reported the first reaction between organolithium and an organic halide catalyzed by Pd.[2] However, since then, the utilization of organolithium in modern TM-catalyzed cross-coupling chemistry has been largely neglected, in favor of organoboron (Suzuki–Miyaura reaction), organozinc (Negishi reaction), organomagnesium (Kumada–Tamao reaction), and organotin (Stille reaction) reagents,[3] despite many advantages of organolithium compounds including low cost, commercial availability, and facile accessibility. The major problem that restricts the applicability of a cross-coupling with organolithium is the competing lithium–halogen exchange (dehalogenation), which is usually quite fast and, thus, lowers the selectivity. In recent years, new approaches for the Murahashi reaction have been reported, such as the usage of a flow microreactor for the biaryl coupling,[4] roundabout routes with stoichiometric silicon or boron-based transfer agents,[5] or a protocol that uses an in situ deprotonation.[6] A remarkable improvement in the applicability of organolithium for cross-coupling reactions was achieved in 2013, when Feringa et al. re-examined the Murahashi coupling and optimized both the selectivity (versus the lithium–halogen exchange) and efficiency.[7] Since then, several new protocols for Murahashi couplings have been reported, enabling reactions between various types of organolithium compounds and halides.[8,9] Herein, we describe our recent studies on the TM-catalyzed cross-coupling of organolithium with ethers and ammonium salts by a C–O or C–N bond cleavage with simultaneous C–C bond formation, and without lithium–halogen-exchange side reactions.

Results and Discussion

Ni-catalyzed cross-coupling between organolithium and ethers/silyl ethers

Many phenol/alcohol derivatives such as sulfonates, phosphates, and carboxylates are currently available as C–O electrophiles in place of halides for TM-catalyzed cross-coupling reactions.[10] Among them aryl alkyl ethers (ArOR) appear particularly attractive,[11] featuring easy accessibility, structural diversity, low cost, and a high atom efficiency. In 1979, Wenkert et al. reported the first cross-coupling reaction of an ether with a Grignard reagent in the presence of a Ni catalyst.[12] In recent decades, several groups, including ours, have developed various types of etheric cross-coupling reactions, including Kumada–Tamao–Corriu,[13] Suzuki–Miyaura,[14] Negishi,[15] and other reactions.[16] In 2014 and 2015, Rueping et al. reported a Ni-catalyzed alkylation of aryl or alkenyl ethers with TMS-CH$_2$Li (TMS = trimethylsilyl), in which the C(sp^2)–O bond cleavage occurred in the absence of a ligand.[17] Around the same time, we independently explored the potential of a cross-coupling between organolithium and ethers.[18] We selected phe-

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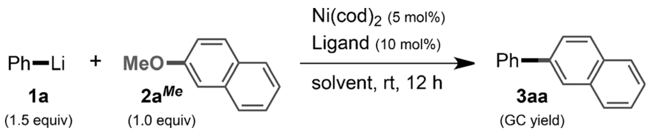
nyllithium (**1a**, prepared by a Li/I exchange between iodobenzene and *t*BuLi) and 2-methoxynaphthalene ($\mathbf{2a}^{Me}$) as model reactants for the optimization of the reaction conditions (Table 1).

Table 1. Screening of ligands for the Ni-catalyzed cross-coupling between phenyllithium (**1a**) and 2-methoxynaphthalene ($\mathbf{2a}^{Me}$). Internal standard for GC analysis: *n*-dodecane (similarly hereafter).



Entry	Ligand	Solvent	GC yield **3aa**
1	–	toluene	73
2	PCy_3	toluene	62
3	DCYPE	toluene	–
4	I*t*Bu·HBF_4	toluene	76
5	ICy·HCl	toluene	66
6	IPr·HCl	toluene	72
7	IMes·HCl	toluene	72
8	SIPr·HCl	toluene	71
9	SIMes·HCl	toluene	86
10	SIMes·HCl	Et_2O	70
11	SIMes·HCl	THF	6

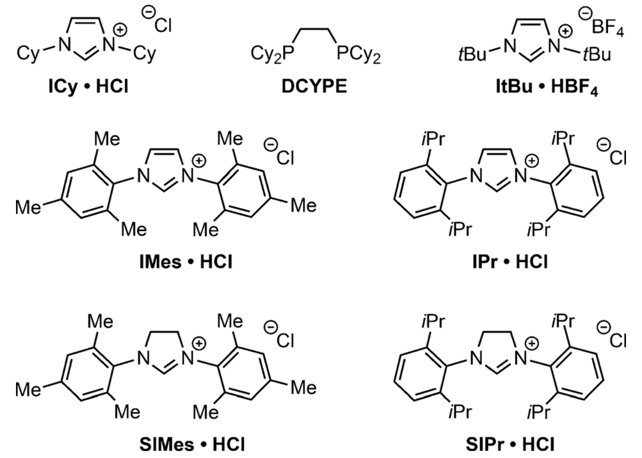
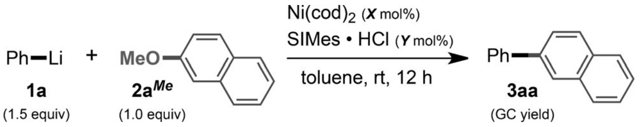


Table 2. Tuning of the catalyst/ligand loadings.



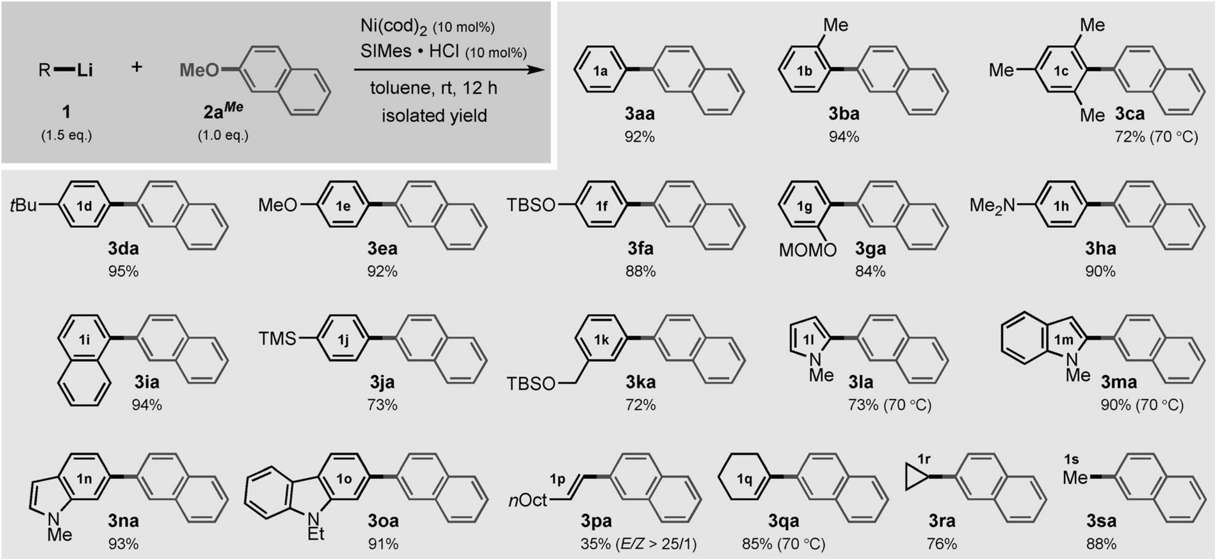
Entry	$[Ni(cod)_2]$ [mol %]	SIMes·HCl [mol %]	GC yield **3aa** [%]
1	2	4	69
2	5	10	86
3	5	15	83
4	7.5	15	86
5	10	20	93
6	10	10	92

Interestingly, the coupling reaction proceeded in 73 % yield at room temperature in toluene in the presence of a catalytic amount of $[Ni(cod)_2]$ (cod = 1,5-cyclooctadiene) without any additional ligands (Table 1, Entry 1). No marked improvement of the yields was observed with other ligands (Table 1, Entries 2–8), including PCy_3, which has been widely used in Ni-mediated C–O cleavage reactions. An exceptional reactivity (86 % yield) was obtained when the reaction was performed with SIMes (Table 1, Entry 9). Note that the reaction became rather sluggish in etheric solvents such as Et_2O and THF (Table 1, Entries 10 and 11). Further tuning of the catalyst and ligand loadings indicated that a combination of $[Ni(cod)_2]$ (10 mol %) and SIMes (10 mol %) was optimal (Table 2).

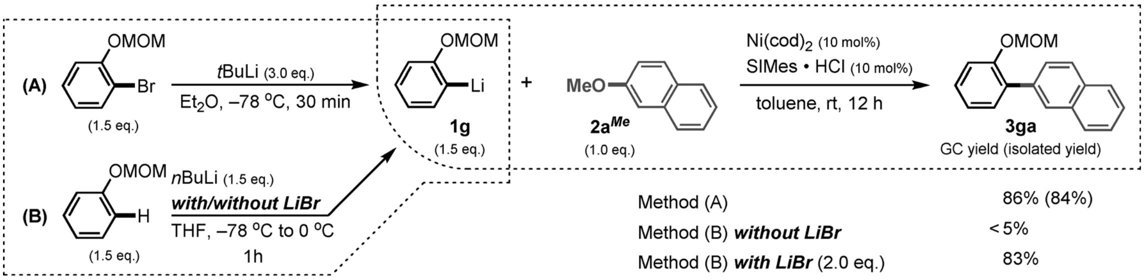
Under the optimal conditions, we evaluated the scope of the present coupling reaction of various organolithium species **1** (prepared by a Li/halogen exchange between ArBr/ArI and *t*BuLi) by taking $\mathbf{2a}^{Me}$ as a representative aryl methyl ether (Scheme 1). It is noteworthy that the OR groups (**1e** OMe, **1f** OTBS, **1g** OMOM) on the phenyl ring remained intact during the reaction, which indicates that cleavage of the ethereal C–O bond is chemoselective. We examined steric effects and found that the very bulky *ortho*-substituted phenyllithium (**1b**) reacted smoothly, although the reaction required heating to 70 °C and the product yield was slightly decreased. As for heterocycles, the reaction of **1** with several π-rich heteroaromatic compounds proceeded in good yields (**3la**–**oa**), whereas thiophenyllithium, furanyllithium, and π-deficient heteroaromatic compounds such as pyridinyllithium showed a rather low reactivity. In addition, alkenyl (**1p**–**q**) and alkyllithium (**1r**–**s**) reacted smoothly, albeit the yield was somewhat decreased (**3pa**–**sa**).

Besides the Li/halogen exchange reaction, the directed *ortho*-lithiation is also commonly used for the preparation of organolithium compounds.[19] While the present coupling reactions of lithium reagents **1** obtained by the Li/halogen exchange proceeded smoothly (Scheme 1 and Scheme 2 A), the reaction became rather sluggish when $\mathbf{1}^{DoM}$ prepared by an *ortho*-lithiation was employed (Scheme 2 B). However, addition of LiBr to the $\mathbf{1}^{DoM}$ solution gave **3ga** in a comparable yield to that obtained with **1** prepared by the Li/halogen exchange. This result demonstrates that lithium salts play an important role in determining the reactivity of organolithium,[20] as well as the yield of this cross-coupling reaction.

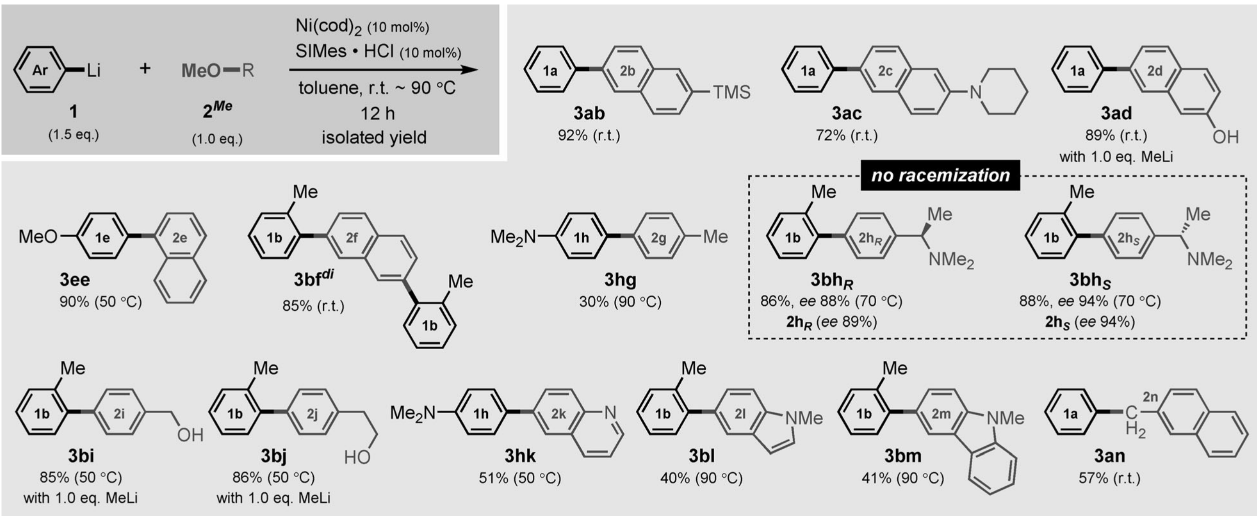
Next, we examined the scope and limitations of the cross-coupling of various methyl ethers ($\mathbf{2}^{Me}$) (Scheme 3). Substituted 2-methoxynaphthalenes (**2b**–**d**), 1-methoxynaphthalene (**2e**), and 2,7-dimethoxynaphthalene ($\mathbf{2f}^{di}$) bearing two C–O moieties, were efficiently converted to the corresponding biaryl products in good to excellent yields. It is known that 1- and 2-methoxynaphthalenes are usually more reactive than anisole derivatives in Ni-catalyzed C–O bond cleavage reactions. In contrast, most anisole derivatives (**2h**–**j**) showed quite high reactivities in the current coupling, with a few exceptions such as **2g**. Strikingly, the C–C bond formation of **2h** was achieved efficiently without racemization at the sensitive benzylic/alpha-amino position. These results demonstrate the potential applicability of this method for late-stage derivatizations of functional molecules. The π-deficient/rich heteroaromatic methyl ethers **2k**–**m** underwent significantly slower reactions, even at high temperatures. The benzyl ether **2n** containing a C(sp^3)–O



Scheme 1. Ni-catalyzed cross-coupling reactions of various organolithium species **1** with 2-methoxynaphthalene ($\mathbf{2a}^{Me}$).



Scheme 2. Aryllithium **1g** prepared by different methods and the coupling reaction with the ether $\mathbf{2a}^{Me}$.



Scheme 3. Ni-catalyzed cross-coupling reactions of various organolithium species **1** with the ether $\mathbf{2a}^{Me}$.

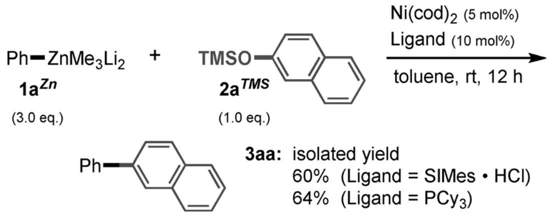
bond also reacted with **1** under the same conditions to afford the desired coupling product **3an** in 57% yield.

The scope of the OR groups in **2a** was then briefly examined using **1a** as the lithium reagent (Scheme 4). Various alkyl ethers $\mathbf{2a}^{Et}$, $\mathbf{2a}^{iPr}$, and silyl ethers $\mathbf{2a}^{TBS}$ could be employed in this coupling, albeit in slightly lower yields than that of $\mathbf{2a}^{Me}$. However, when the trimethylsilyl ether $\mathbf{2a}^{TMS}$ was used, only 2-naphthol was obtained; deprotection of the TMS group pro-

2a^{Me}	92%
2a^{Et}	78%
2a^{iPr}	77%
2a^{TMS}	not detected
2a^{TBS}	71%

Scheme 4. Influence of the alkoxy group (OR) of the aryl alkyl ethers **2** for their reaction with organolithium species **1**.

ceeded preferentially, probably due to the strong nucleophilicity of the organolithium compounds. We have long been investigating the chemistry of zincates[19a] and have previously reported that dianion-type zincates react with ether in the presence of Ni catalysts.[15a] Indeed, the phenyl zincate **1a**^{Zn}, which was prepared easily by an I/Zn exchange of iodobenzene and Li$_2$ZnMe$_4$,[21,22] underwent the cross-coupling reaction with **2a**^{TMS} under the same conditions to afford **3aa** in 64% yield (Scheme 5).

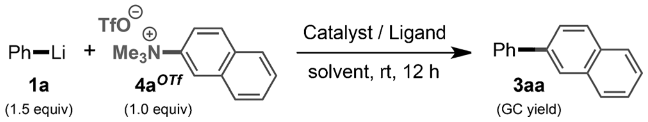


Scheme 5. Ni-catalyzed cross-coupling between the phenyl zincate **1a**^{Zn} and **2a**.

Pd-catalyzed cross-coupling between organolithium and aryl ammonium salts

Like phenols and alcohols, amine groups also widely occur in natural products, pharmaceuticals, dyes, and other functional molecules. Many amines are commercially available, but transformation of NR$_2$ groups is generally difficult, due to the high stability of the C–N bond. This limits the utility of amine derivatives for direct C–N bond conversions.[23] On the other hand, quaternary organo–ammonium salts can be easily prepared from various aryl/alkyl amines, and their C–N bonds exhibit higher reactivities than those of amines. As pioneered by Wenkert et al. in 1988,[24] applications of ammonium salts for cross-coupling and related reactions have been rapidly developed in recent years.[25] In most reported cases, Ni catalysts gave the best outcomes, but the current coupling reaction between the lithium reagents **1** and the ammonium salts **4** was less effective under Ni catalysis in various solvents (THF, toluene, Et$_2$O, 1,4-dioxane, and NMP). The use of Pd catalysts gave better results (Table 3). After extensive experimentation to screen Pd sources and ligands with the lithium reagent **1a** and the ammonium salt **4a**^{OTf} as model reactants, we found that the commonly used [Pd(PPh$_3$)Cl$_2$] gave the highest yield (61%) in THF. In addition, we found that the counter anion of the ammonium salt played a crucial role in determining the yield of this coupling, and I$^-$ was the best, although ammonium triflate has mostly been employed in previous work (Table 4).

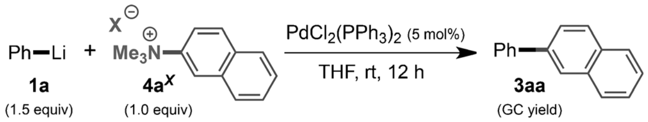
Table 3. Screening of ligands for the Pd-catalyzed cross-coupling between phenyllithium **1a** and ammonium triflate **4a**^{OTf}.



Entry	Ligand[a]	Solvent[b]	GC yield **3aa**
1	[Pd$_2$(dba)$_2$] (5 mol%) P*t*Bu$_3$ (10 mol%)	THF	–
2	[Pd$_2$(dba)$_2$] (5 mol%) tfp (10 mol%)	THF	32
3	PEPPSI-IPr (5 mol%)	THF	16
4	[PdCl$_2$(dppf)] (5 mol%)	THF	43
5	[Pd(PPh$_3$)$_4$] (5 mol%)	THF	42
6	[PdCl$_2$(PPh$_3$)$_2$] (5 mol%)	THF	61
7	[PdCl$_2$(PPh$_3$)$_2$] (5 mol%)	NMP/THF	–
8	[PdCl$_2$(PPh$_3$)$_2$] (5 mol%)	toluene/THF	39
9	[PdCl$_2$(PPh$_3$)$_2$] (5 mol%)	1,4-dioxane	–

[a] dba = Dibenzylideneacetone, dppf = 1,1′-bis(diphenylphosphino)ferrocene, tfp = tris(2-furanyl)phosphine, PEPPSI-IPr = [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride. [b] NMP = *N*-methylpyrrolidone.

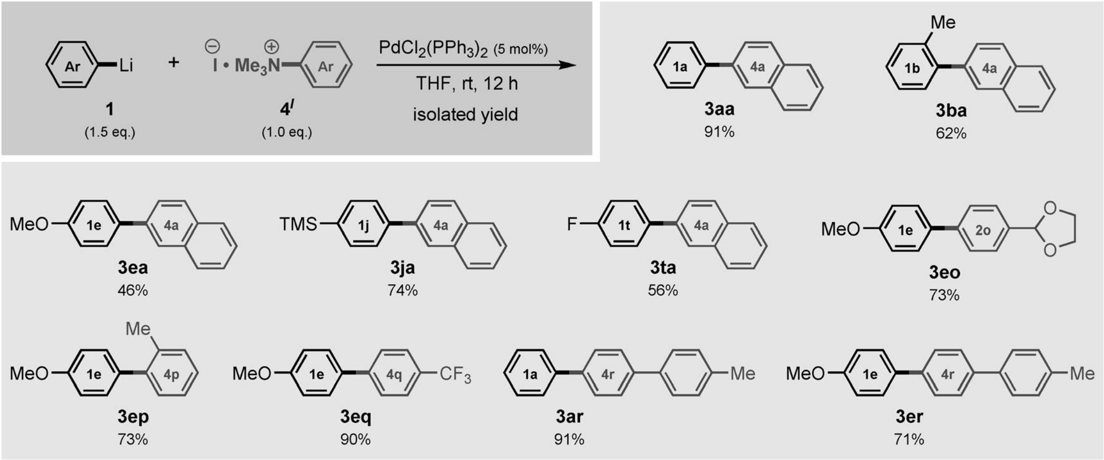
Table 4. Tuning of the catalyst/ligand loadings and the counter anion ***X*** in **4a**^{X}.



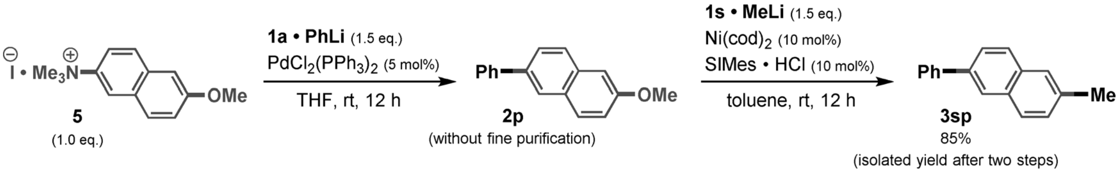
Entry	PhLi (**1a**)[a]	*X*	GC yield **3aa**
1	type A	OTf	–
2	type B	OTf	58
3	type C	BF$_4$	46
4	type C	I	93

[a] Type A: purchased from KANTO (1.06 mol L^{-1} solution in cyclohexane/Et$_2$O, 7:3); type B: type A with LiI (1.5 equiv) as additive; type C: prepared by Li/Br exchange between *t*BuLi and PhI.

With the optimized conditions in hand, we examined the scope and limitations of the present coupling reaction by a C–N bond cleavage (Scheme 6). Aryllithium compounds with electron-donating and -deficient groups on the phenyl ring were found to be generally suitable for this coupling, giving the desired products in moderate to high yields. A sterically demanding aryllithium did not shut down the reaction (**3ba**). Interestingly, this reaction is applicable to phenyl ammonium



Scheme 6. Pd-catalyzed cross-coupling reactions between the organolithium species **1** and the ammonium salts **4**.



Scheme 7. Synthesis of a disubstituted naphthalene by successive cross-coupling reactions.

salts **4m–o** to give the desired biphenyl compounds in high to excellent yields.

Finally, we demonstrated that the two newly developed methods enable selective and sequential functionalizations of arenes that bear both C–N and C–O bonds in one pot (Scheme 7). Substrate **5** firstly reacted with **1a** in the presence of a Pd catalyst to give 2-methoxy-6-phenylnaphthalene (**2p**) by cleavage of the C–N bond, and **2p** could be directly utilized without fine purification for the next coupling reaction with methyllithium (**1s**) in the presence of the Ni/NHC catalyst, leading to the methylated product **3sp** in 85% yield by a C–O bond cleavage. This result opens up a new route for highly regiocontrolled syntheses of multi-substituted arenes by successive C–*X* (*X*=O and N) bond cleavages on poly-functionalized aromatic rings.

Conclusions

In conclusion, we have developed two new cross-coupling reactions of organolithium compounds through C–O and C–N bond cleavages. The use of industrially/naturally abundant ether/amine resources is highly desirable, and these methods provide simple and direct routes for the selective C–C formation from various phenol/aniline precursors. These methodologies also enable late-stage transformations of function-guaranteed versatile multi-substituted phenol/aniline compounds. We believe that this work provides new possibilities for organolithium compounds, as well as new routes for the activation of inert bonds. Further investigations on the reaction scope (e.g., alkyl or alkenyl ethers/ammonium salts, etc.), the reaction mechanism, and synthetic applications of the present method to biologically active substances are in progress.

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Keywords: ammonium salt · cross-coupling · ether · organolithium · transition metal catalyst

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FULL PAPER

Cross-Coupling Reactions

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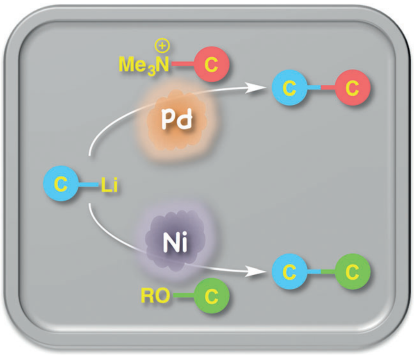
■■ – ■■

Cross-Coupling of Organolithium with Ethers or Aryl Ammonium Salts by C—O or C—N Bond Cleavage



Cut and paste! Various aryl-, alkenyl-, and/or alkyllithium species smoothly reacted with aryl and/or alkyl ethers with cleavage of the inert C—O bond, catalyzed by an Ni catalyst. The coupling reaction between the aryllithium reagents and aryl ammonium salts also proceeded under mild conditions by a C—N bond cleavage in the presence of a Pd catalyst. These methods enable selective and sequential functionalizations of arenes having both C—N and C—O bonds, in one pot.