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N,*N*-Diethyl *O*-Carbamate: Directed Metalation Group and Orthogonal Suzuki−Miyaura Cross-Coupling Partner

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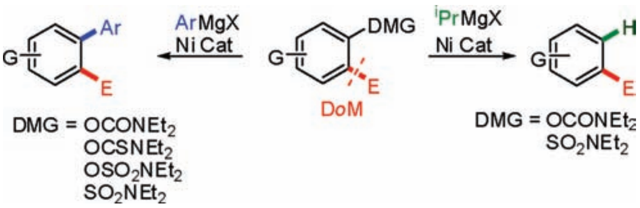
For C−C bond formation in general, and for the aryl−aryl conjunction in particular, transition metal-catalyzed cross-coupling reactions[1] have superseded all previous classical methodologies.[2] The Pd-catalyzed Suzuki−Miyaura reaction[1c,3] has proven particularly robust, while Ni-catalyzed cross-coupling of organoboranes has been successfully achieved with a variety of leaving groups (LG = halo,[4] OTs,[5] OMs[6]). With the background of original results of Wenkert[7] and Dankwardt,[8] organoborane couplings with LG = OMe has been reinforced by the seminal contributions of Chatani[9] and Kakiuchi.[10] Recently, more manipulable groups (LG = OAc,[11] OPiv[12]) have been introduced as cross-coupling partners.[13]

With aims to enhance and extend the scope of directed ortho metalation (D*o*M)−cross-coupling strategies,[14] we have established aryl *O*-carbamate,[15,16] *S*-thiocarbamate,[17] sulfonamide,[18] and *O*-sulfamate[19] Ni-catalyzed Grignard (Kumada−Corriu) cross-coupling reactions (Scheme 1). In addition, we have demonstrated reductive cleavage of some of these functionalities,[15a,18] which allows their use as latent directed metalation groups (DMGs) for the synthesis of less common, e.g. *meta*-substituted, aromatics.

Scheme 1. Cross-Coupling and Reductive Latency of DMGs



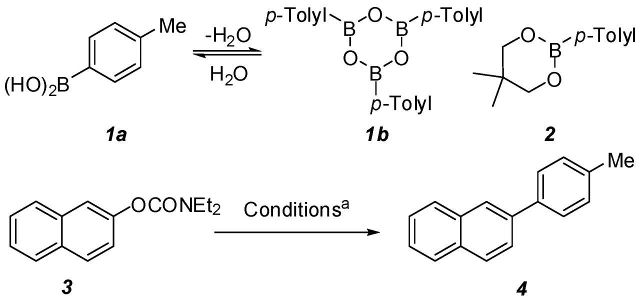
The positional apex in the D*o*M hierarchy of the *O*-carbamate DMG and its considerable utility in synthetic aromatic chemistry[19−22] have motivated our continuing efforts to increase its cross-coupling potential. Herein we report on the Suzuki−Miyaura cross-coupling of Ar-OCONEt$_2$ systems as a general methodology for the synthesis of biaryls and heterobiaryls.[23] Furthermore, we demonstrate the inherent D*o*M−cross-coupling link that allows the regioselective preparation of polysubstituted aromatics as well as selective and sequential orthogonal coupling to establish 1,2-diarylbenzene substitution. The combined results offer a functional group compatibility advantage over the previous Kumada−Corriu reactions,[15,18,19] thereby providing a new general process for the conversion of phenolic derivatives to biaryls starting from large selections of commercial materials as well as those derived from D*o*M tactics.

Based in part on conditions reported by Garg,[12] scouting coupling experiments on 2-naphthyl *O*-carbamate **3** with *p*-tolylboronic acid (PTBA, **1a**) were carried out, selected results of which are shown in Table 1. Initial attempts were not promising, resulting in irreproducible reaction rates and yields. The more stable NiCl$_2$(PCy$_3$)$_2$ was used rather than Ni(cod)$_2$ because inconsistent results were observed with the latter catalyst.[24] The hygroscopic nature of K$_3$PO$_4$ necessitated the use of scrupulously dried material (compare entries 5 and 8). Other potentially critical factors investigated were the presence of NiO[25] (derived from Ni(cod)$_2$ oxidation) (entry 2) and traces of Pd[26] (entry 4).

It was only after observing a significant difference in reactivity using various samples of both commercial and prepared PTBA under identical experimental conditions that the culprit parameters of the reaction were revealed.

Extensive ^{1}H NMR studies established that (a) under strictly anhydrous conditions, the boroxine **1b** is a sluggish coupling partner (entry 7); (b) in organic solvents, PTBA liberates excessive water which is detrimental to the reaction (entry 6); and (c) a ratio of **1b**:**1a** = 10:1 is most effective.[27] Resolution of the reproducibility problem, as delineated below, and further optimization led to full conversion within 5 h using only 5 mol % of catalyst (entry 11).

Table 1. Optimization Studies for the Conversion **3** → **4**



entry	solvent	*T* (°C)	cat. (5 mol %)	L (mol %)[b]	K$_3$PO$_4$ (equiv)	ArB(OR)$_2$ (equiv)[c]	yield (%)[d]
1	dioxane	120	Ni(cod)$_2$	10	3	**1b**:**a** (2.0)	0
2	PhMe	120	NiO	10	3	**1b**:**a** (2.0)	0
3	PhMe	120	Ni(cod)$_2$	10	3	**2** (2.5)	0
4	PhMe	120	Ni(cod)$_2$[e]	10	5	**1b**:**a** (2.5)	11
5[f]	PhMe	120	NiCl$_2$(PCy$_3$)$_2$	10	3[g]	**1b**:**a** (2.0)	37
6	*o*-xylene	150	NiCl$_2$(PCy$_3$)$_2$	10	5	**1b**:**a**[h] (2.5)	26
7[f]	*o*-xylene	150	NiCl$_2$(PCy$_3$)$_2$	10	5	**1b** (2.5)	61
8	PhMe	120	NiCl$_2$(PCy$_3$)$_2$[i]	–	7.2	**1b**:**a** (2.5)	62
9	PhMe	120	Ni(cod)$_2$	10	5	**1b**:**a** (4.0)	69
10	PhMe	120	NiCl$_2$(PCy$_3$)$_2$[i]	–	7.2	**1b**:**a** (2.5)	69
11[f]	*o*-xylene	150	NiCl$_2$(PCy$_3$)$_2$	10	5	**1b**:**a** (2.0)	100 (84)[j]

[a] All reactions run for 20 h. [b] Ligand = PCy$_3$HBF$_4$. [c] Based on [ArB(OR)$_2$], ratio of **1b**:**1a** = 10:1. [d] Yield based on GC/MS analysis. [e] With added 1 mol % of PdCl$_2$. [f] Reaction run for 5 h. [g] Hydrate was used. [h] Ratio of **1b**:**1a** = 1:1. [i] 10 mol % used. [j] Yield of isolated product.

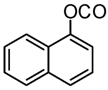
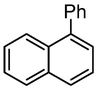
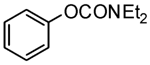
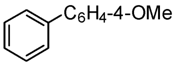
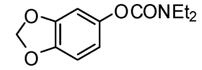
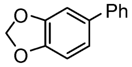
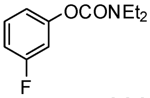
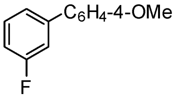
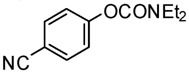
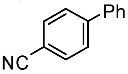
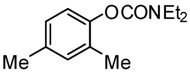
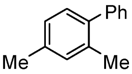
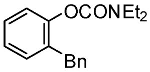
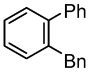
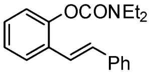
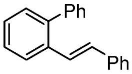
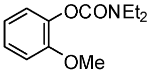
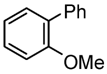
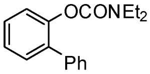
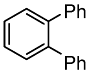
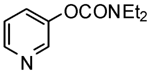
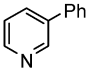
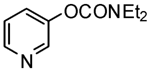
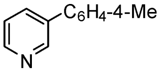
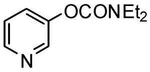
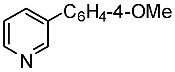
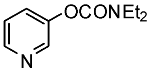
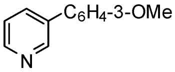
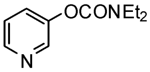
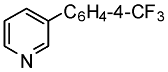
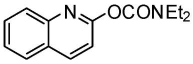
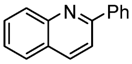
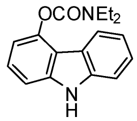
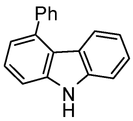
As shown in related couplings of organoboronates, control of the hydrolysis equilibrium of free boronic acid with the less reactive boroxine is important.[28] In this context, Shi[11] reported the crucial role of water content for the Suzuki−Miyaura cross-coupling of aryl acetates, a situation that, however, is inconsequential to *O*-carbamates, which are stable to hydrolysis.[29] The detailed studies by Liu[30] on the coupling of aryl esters suggest oxidative addition

10.1021/ja907700e

Table 2. Ni-Catalyzed Cross-Coupling of Aryl *O*-Carbamates

$$\mathrm{Ar(Het)\text{-}OCONEt_2} + \mathrm{ArB(OR)_2} \xrightarrow[\substack{o\text{-xylene / } 150\ ^\circ\mathrm{C} \\ (5\text{-}20)\ \mathrm{h}}]{\substack{\mathrm{NiCl_2(PCy_3)_2}\ (5\ \mathrm{mol\%}) \\ \mathrm{PCy_3HBF_4}\ (10\ \mathrm{mol\%}) \\ \mathrm{K_3PO_4}\ (5\ \mathrm{equiv})}} \mathrm{Ar(Het)\text{-}Ar}$$

1c, Ar = C_6H_4-4-OMe
1d, Ar = Ph
1e, Ar = p-Tolyl
1f, Ar = C_6H_4-3-OMe
1g, Ar = C_6H_4-4-CF_3

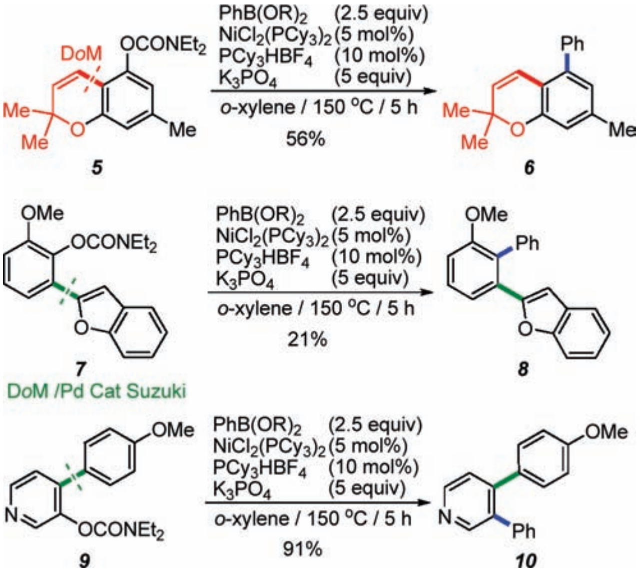
Entry	Ar(Het)-OCONEt$_2$	Ar(BOR)$_2$^{a}	Product	Yield^b
1		***1d***		100% (82)
2		***1c***		64% (58)
3		***1d***		23% (31)
4		***1c***		80% (69)
5		***1d***		36% (28)
6		***1d***		8% (-)
7		***1d***		60% (70)
8		***1d***		99% (93)
9		***1d***		40% (36)
10		***1d***		69% (50)
11		***1d***		100% (85)
12		***1e***		(87)
13		***1c***		(84)
14		***1f***		(65)
15		***1g***		(70)
16		***1d***		100% (51)
17		***1d***		45% (36)

[a] $ArB(OR)_2$ (2.5 equiv), ratio of $Ar_3B_3O_3$:$ArB(OH)_2$ = 10:1. [b] Yield by GC/MS analysis (yield of isolated product).

via a monophosphine-Ni^0 intermediate and transmetalation with K[PhB(OH)$_3$]. Qualitative rate experiments varying the boraxine:water ratio clearly showed the requirement of an optimal balance.[31] Strictly anhydrous conditions resulted in sluggish reaction rates, eventually reaching near completion, while the presence of large amounts of water resulted in poor conversions and almost complete catalyst deactivation after 5 h. On the basis of these observations, we speculate that very little water is necessary to generate the required boronate for entry into the catalytic cycle. However, a large excess of water, generated from trimerization of the free boronic acid, significantly reduces catalytic activity by forming inactive nickel hydroxides/oxides.[32]

After considerable time and effort in the optimization studies,[33] we turned our attention to defining the scope and functional group tolerance of this transformation (Table 2). Prototype naphthyl and phenyl substrates underwent smooth cross-coupling (entries 1, 2). For simple aryl substrates, electron-withdrawing group (EWG)-substituted systems (entry 4) showed higher reactivity, while those with electron-donating groups (EDGs) (entry 3) gave poor yields, including ortho-substituted cases (entries 6, 9). The cyano derivative (entry 5) appeared aberrant, leading to low yields of product as a result of cross-coupling at the cyano group, thus resulting in a mixture of products.[34] The attribution of poor reactivity to steric hindrance is not warranted at present since coupling of *o*-benzyl, -styryl, and -phenyl *O*-carbamates proceeded in good to excellent yields (entries 7, 8, 10).

Scheme 2. Synthetic D*o*M−Cross-Coupling Interconnections of Aryl *O*-Carbamates



The high reactivity of 3-pyridyl *O*-carbamate and ease of purification of derived products led to a more extensive exploration of this substrate with a variety of boroxines (entries 11−15). Aside from phenylboroxine (entry 11), arylboroxines bearing both EDGs (entries 12, 13) and EWGs (entries 14, 15) afforded products in good yields. Extension of coupling to quinolyl and carbazole heterocycles was also achieved, albeit in modest yields (entries 16, 17).

The availability of the new *O*-carbamate cross-coupling manifold in context of the D*o*M−cross-coupling strategy[14] adds new synthetic dimensions, as demonstrated by the construction of three types of heterocycles (Scheme 2). Thus, the 2*H*-chromene *O*-carbamate **5**, prepared previously by a one-pot D*o*M−cyclization sequence[35] and employed in total synthesis,[36] was converted into the uniquely substituted 5-phenyl-2*H*-chromene **6**, representing a heterocyclic framework of bioactivity[37] and natural product[38] interest. Similarly, compounds **7** and **9**, whose origins are rooted in the combined D*o*M/Suzuki−Miyaura methodology, were transformed into heterobiaryls **8**[39] and **10**,[40] respectively.[41] The inertness of the *O*-carbamate to Pd-catalyzed coupling allows it to assume an orthogonal cross-coupling partner role when linked with the Ni coupling strategy. The 1,2,3-substitution pattern of heterobiaryl **8** is unique, while compound **10** represents a class of pyridines with nonidentical diaryl substitution for which only two synthetic methods are available.[42]

In summary, an efficient and general Suzuki−Miyaura cross-coupling reaction of aryl *O*-carbamates has been demonstrated. The transformation was optimized for use with only 5 mol % of the cost-effective, bench-stable catalyst NiCl$_2$(PCy$_3$)$_2$. The critical dependence of water, a point of potential general significance for boronic acid coupling reactions, was delineated. The results, together those of Garg and co-workers,[23] especially on the aryl *O*-sulfamates, are agreeably complementary for synthetic application. A new D*o*M−Ni-catalyzed cross-coupling nexus for the prominent OCONEt$_2$ DMG was established whose orthogonal use with the Pd-catalyzed Suzuki−Miyaura reaction anticipates further utility in aromatic and heteroaromatic synthesis.

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Supporting Information Available: Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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