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Beyond Directed *Ortho* Metalation: Ruthenium-Catalyzed Amide-Directed C_{Ar}–N Activation/C–C Coupling Reaction of Anthranilamides with Organoboronates

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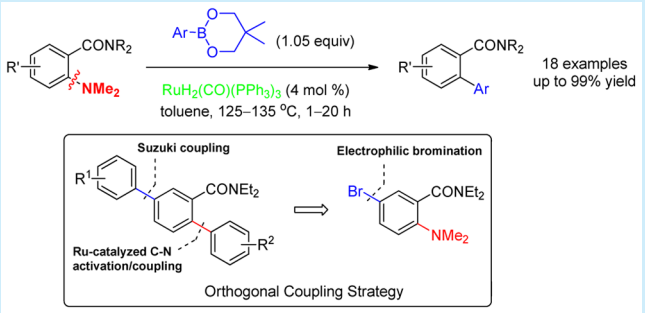
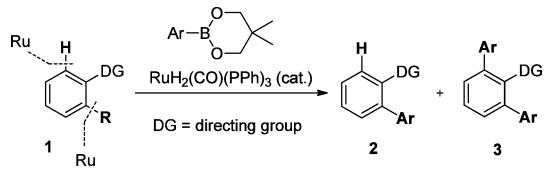
Supporting Information

ABSTRACT: A new, catalytic, and general methodology for the synthesis of biaryls and heterobiaryls by the cross coupling of anthranilamide derivatives (*o*-NMe_2 benzamides) with aryl boroneopentylates is described. The reaction proceeds under catalytic $RuH_2(CO)(PPh_3)_3$ conditions driven by the activation of the unreactive C–N bond by amide directing group (DG)-Ru catalyst chelation. High regioselectivity, orthogonality with the Suzuki–Miyaura reaction, operational simplicity, and convenient scale-up are features of these reactions which may lend themselves to industrial applications.



Although still in nascent development, the area of activation of unreactive C–H, C–O, and C–N bonds mediated by transition-metal catalysis promises to greatly enrich the toolbox of synthetic organic chemists.[1] Amines constitute one of the most prevalent and unreactive classes of organic compounds, among which the arylamines have particularly high C–N bond dissociation energy[2] whose cleavage usually invokes conversion to more reactive leaving groups[3] such as diazonium salts,[3a−c] ammonium salts,[3d−h] triazenes,[3i] azoles,[3j] and arylhydrazines.[3k] Although scattered observations of aniline C–N bond cleavage had been reported,[3d−h,k,4] it was the discovery of Kakiuchi in 2007 which provided the first, catalytic C–N coupling reaction of *o*-NMe_2 substituted pivalophenones with organoboronates under $RuH_2(CO)(PPh_3)_3$-catalyzed conditions[1g] (Table 1), parallel to their equally important original findings of the aryl C–OMe bond activation–cleavage process in the corresponding *o*-OMe substituted aryl ketones.[5] In the Kakiuchi C–NMe_2 activation reaction, consistent also with the requirements for C–H and C–OMe activation processes,[5,6] chelation assistance from an anchoring ketone directing group (DG)[7] was established as the significant initial event of the highly efficient C–NMe_2 activation/organoboronate cross coupling reactions (Table 1, DG = C(O)Me and C(O)-*t*-Bu).

Table 1. Selectivity of Ketone- and Amide-Directed C–NMe_2 and C–H Activation/Coupling Reactions



DG	R	activation/coupling via C-H	activation/coupling via C-N	product	ref
C(O)Me	NMe_2	✓	✓	3	1g
C(O)*t*-Bu	NMe_2, NHMe, NH_2, N(Me)Ac	X	✓	2	1g
$CONEt_2$	NMe_2	X	✓	2	this work

Motivated by these findings, we proposed that the tertiary amide $CONEt_2$, a powerful directed metalation group (DMG), widely exploited in directed *ortho* metalation (DoM) synthetic strategies,[8] may offer a chelating DG consequence for C–H, C–O, and C–N bond activation/cross-coupling reactions based on the following rationale: the $CONEt_2$ group should exhibit greater coordinating ability than esters and ketones,[9] DGs whose activation of these bonds has been established; although two different reaction types are compared, the well-known steric bulk of $CONEt_2$ in DoM chemistry in resisting nucleophilic attack by organolithium reagents suggested that it would exhibit properties similar to those of the *tert*-butyl group in *o*-NMe_2/OMe-pivalophenones in preventing nonregioselective C–H, C–O, and C–N activation and, therefore, diarylation.[1g,5]

In pursuit of demonstration of these objectives, we have recently achieved the Ru-catalyzed *N,N*-diethyl *o*-OMe benzamide (*o*-anisamide)/aryl boronate cross-coupling reaction.[10] Coincident with these studies, we initiated work on the corresponding *o*-NMe_2 benzamide/aryl boronate coupling (Table 1, DG = $CONEt_2$) and herein report our preliminary results. We demonstrate that the DG = $CONEt_2$ serves effectively for C–NMe_2 activation in the Ru-catalyzed cross coupling with aryl boroneopentylates (ArBneop), thus

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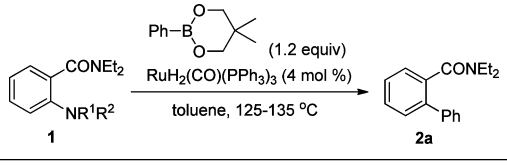
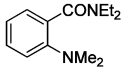
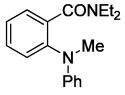
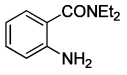
providing a new general methodology which (a) displays all the advantageous attributes of the regioselective DoM strategy in pre- and postcoupling modes; (b) offers complementarity to the DoM reaction in a process that avoids cryogenic temperatures and strong base conditions; (c) is amenable to orthogonal cross coupling variation;[11] and (d) provides opportunity for ready amide to other functional group conversions.[12] Combined, these features offer new promising opportunities for synthetic aromatic chemistry.

In the prototype experiment, treatment of *N,N*-diethyl *o*-NMe_2 benzamide (anthranilamide) with PhBneop under conditions similar to those applied in the *o*-anisamide reaction[10] afforded the diphenyl amide **2a** (Table 2) in quantitative yield

Table 2. Screening Amino Groups for the Cross-Coupling Reaction of *o*-Amino Benzamides with PhBneop



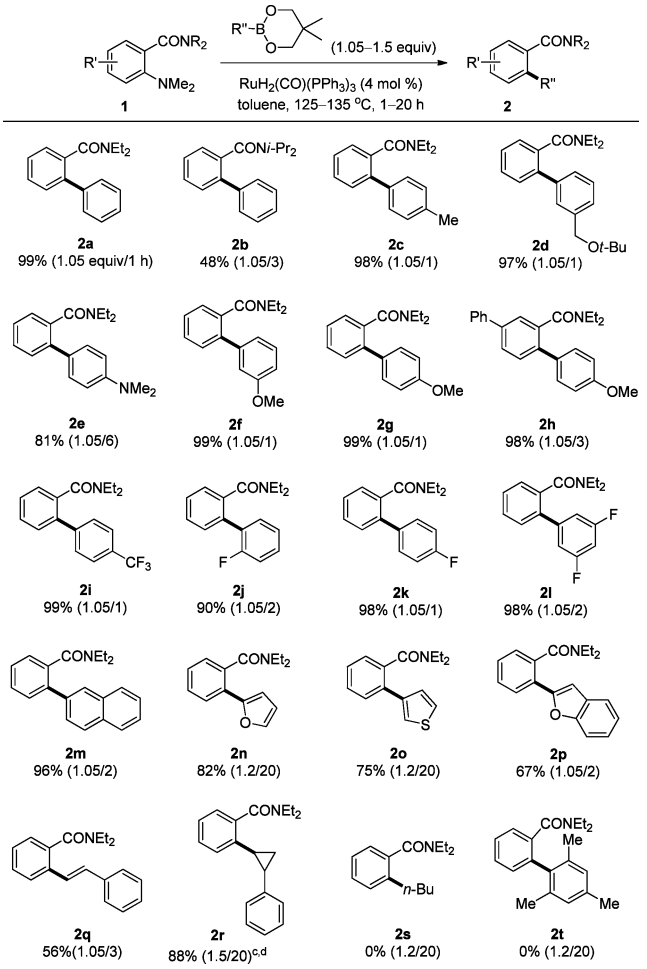
entry	amide	time (h)	product	yield (%)
1		1	**2a**	99[a]
2		20	**2a**	(44)[b]
3		20	---	--[c]

[a]Yields are of isolated and purified products. [b]Yield determined by GC–MS analysis; PhNHMe was also formed in 11% yield (GC). [c]Starting material recovery (95%).

in a 1 h reaction time with no detectable product of alternative C–H activation/cross coupling. As established also in the *o*-anisamide coupling reaction,[10] the significance of DG-chelation assistance was demonstrated by treatment of *N,N*-diethyl 3- and 4-NMe_2 benzamides with PhBneop for an extended time (20 h) which resulted in recovery of starting material with <4% detection of phenylated products (GC–MS analysis, see the SI). Similar to our observations for the C–OMe activation/coupling reactions[13] and as reported by Kakiuchi,[5] aryl boroneopentylates appear to be unique in reactivity as the corresponding boropinacolates and boronic acids failed to give C–N activation/cross coupling products (SI). To obtain appreciation of amide N-substitution steric effects, *N,N*-diisopropyl *o*-NMe_2 benzamide was tested and found, even under 3 h refluxing toluene conditions, to give the corresponding 2-phenyl derivative **2b** in much decreased (48%) yield (Scheme 1). *N,N*-Dimethyl benzamides were not considered in view of their ineffectiveness in DoM chemistry.[14]

Brief examination of *N*-2-amino substitution (Table 2) showed that the bulky 2-N(Me)Ph group inhibited the reaction leading to the corresponding 2-phenyl-coupled product **2a** in only 44% yield after a 20 h reaction time and also to the formation of byproduct PhNHMe (11% yield), as direct evidence of reductive deamination. When *N,N*-diethyl 2-NH_2 benzamide was subjected to the coupling reaction conditions, starting material was recovered in quantitative yield, in contrast

Scheme 1. Ru-Catalyzed Cross Coupling Reaction of *o*-NMe_2 Benzamides with Bneops[a,b]



[a]Yields are of isolated and purified products. [b]Equivalents of boroneopentylates/reaction times in hours are shown in parentheses. [c]10 mol % catalyst loading. [d]*cis* or *trans* stereochemistry not established by ^{1}H NMR due to almost identical J_{cis} and J_{trans} coupling constants[19] and unavailability of crystalline material for X-ray analysis.

to the observations in ketone-directed C–N activation/coupling in which 2-NH_2 (and 2-NHMe) did not prevent efficient aryl coupling.[1g] Thus, it appears that minimal steric hindrance and unavailability of N–H bonds are important requirements to achieve a highly efficient amide-directed C–N activation/cross-coupling result.

To complete our screening experiments, optimum temperatures for short reaction time (130 °C/1 h) and boroneopentylate reactant (1.05 equiv) and $RuH_2(CO)(PPh_3)_3$ catalyst (4 mol %) stoichiometries were determined (SI). With these control and structural parameters in hand, we proceeded to test the generality of the reaction with a variety of aryl boroneopentylates. The results are shown in Scheme 1 and deserve comment. First, the coupling reaction proceeds mostly in excellent yields for EDGs (electron-donating groups) such as Me, CH_2O-*t*-Bu, NMe_2, and OMe (**2c–h**, Scheme 1). However, EWGs (electron-withdrawing groups) showed a range of effects. When F- and CF_3-bearing aryl Bneops were employed, the coupling reaction proceeded in high yields (**2i–l**). However, when CHO-, CN-, and NO_2-substituted ArBneops were used, the arylation was completely inhibited even after a

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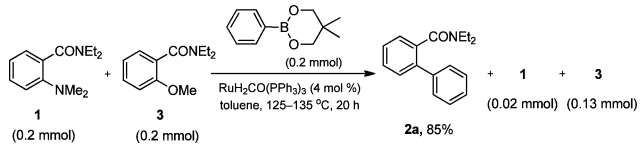
20 h reaction time (SI).[15] While CHO-, CN-, and NO_2-substituted ArBneops were not studied in the *o*-NMe_2 pivalophenones by Kakiuchi, these workers also observed, as part of an insightful mechanistic study, a similar higher reactivity of the corresponding CF_3-arylBneop derivative which was attributed to an accelerating effect of the amido Ru species−arylboronate transmetalation step due to higher Lewis acidity at the boron atom.[7b,16] Similar to our results for the *o*-OMe aryl amide C−O activation/arylation reaction,[13] chloro- and bromo-ArBneop derivatives were found not to undergo this coupling reaction (SI) possibly due to hydrodehalogenation which was not studied in the C−O and C−N pivalophenone series.[1g,5] The naphthalen-2-ylboroneopentylate was found to afford the arylated product **2m** in high yield, and the thiophenenyl, furanyl, and benzofuranyl Bneop derivatives gave good yields of products **2n−p** using a slight excess of boronates and prolonged reaction times (Scheme 1). When a sterically congested boroneopentylate was employed, the expected coupled product **2t** was not detected, and deboronation and reductive de-NMe_2 became the major reactions. The (*E*)-styrylBneop underwent arylation to give the stilbene product **2q** in modest yield. Two alkyl boroneopentylates were tested: while *n*-butyl Bneop failed to undergo the coupling reaction to form product **2s** (isolation of starting material), cyclopropyl Bneop afforded the interesting derivative **2r**. It appears that, in contrast to a single case reported for the 2-amino pivalophenone,[1g] a 2-amino benzamide/C_{sp^3} boroneopentylate coupling reaction fails in both oxidative addition and transmetalation steps as evidenced by quantitative isolation of starting amide. The successful behavior of the cyclopropyl Bneop coupling reaction may be partially attributed to the established C_{sp^2} character of the cyclopropyl C−H bonds[17] but is perhaps surprising in view of the ring-opening reactivity of cyclopropyl derivatives with low-valent transition metals.[18]

In order to qualitatively obtain a direct reactivity comparison between the C−N and C−O bond activation/cross-coupling reactions, a competitive experiment was carried out using a 1:1:1 mixture of *N,N*-diethyl *o*-NMe_2 benzamide **1**, *N,N*-diethyl *o*-OMe benzamide **3**, and PhBneop (Scheme 2). The result,

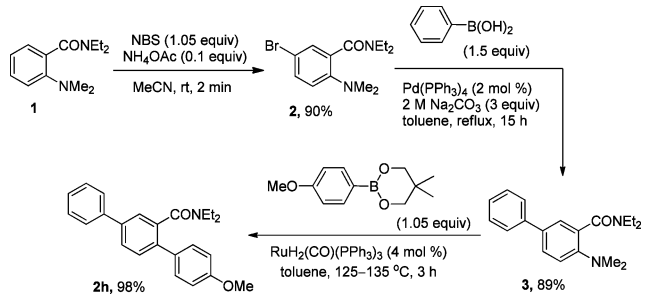
Scheme 2. Competition Experiment for the C−N and C−O Activation/Cross-Coupling Processes



indicating that C−N activation is faster than C−O activation, is consistent with the short reaction times required for the C−N coupling process compared to that of the corresponding C−O reaction.[10]

As demonstrated in the *N,N*-diethyl *o*-anisamide/ArBneop coupling studies,[10] advantage may be taken of the expected high S_EAr reactivity of the *N,N*-diethyl 2-NMe_2-benzamide derivatives for devising orthogonal cross coupling chemistry[11a] (Scheme 3). In this pursuit, treatment of *N,N*-diethyl *o*-NMe_2 benzamide with NBS gave the bromobenzamide **2** which, upon standard Suzuki−Miyaura cross-coupling conditions, afforded the biaryl **3**. Subjection of **3** to the Ru-catalyzed coupling procedure using *p*-anisyl Bneop provided the teraryl **2h** in 80%

Scheme 3. Synthesis of Teraryls via Sequential Bromination, Suzuki−Miyaura Cross-Coupling, and Ru-Catalyzed C−NMe_2 Activation/Coupling Reactions



overall yield in three steps. This may be considered as a prototype sequence for extension to tandem catalysis, tailor-made ligand design and construction,[20] and defined π-conjugated oligomer synthesis.[21]

In summary, the first catalytic amide-directed C−N activation/C−C bond-forming reaction for the synthesis of biaryls and heterobiaryls has been demonstrated. Similar to the Ru-catalyzed *o*-anisamide/aryl boroneopentylate cross-coupling process,[10] the corresponding, readily derived[22] *N,N*-diethyl *o*-NMe_2 benzamide/cross-coupling reaction is general, robust, and proceeds with high efficiency and regioselectivity uncompromised by the competitive C−H activation/cross-coupling reaction as observed for the corresponding *o*-NMe_2 acetophenone derivatives.[1g] Coupled with the standard Suzuki−Miyaura protocol, it has advantages of orthogonal reaction sequences and may be exploited in DoM and DreM (directed *remote* metalation)[8] chemistry prior[23] or post to the C−N cross-coupling event for the construction of more highly substituted and polycondensed aromatic derivatives (Figure 1,

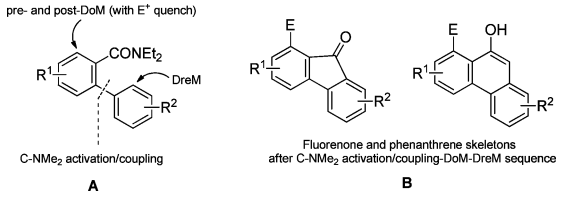


Figure 1. Synthetic potential of combined C−NMe_2 activation/cross coupling−DoM−DreM chemistry.

A and B). Of greatest significance, the *N,N*-diethyl *o*-NMe_2 benzamide/ArBneop cross-coupling reaction presents a new catalytic methodology for the synthesis of biaryl- and polyarylamides which complements the stoichiometric DoM−Suzuki−Miyaura cross-coupling two-step combination[24] but proceeds under noncryogenic temperatures and without use of strong organolithium bases. In view of these features, the application of the coupling reaction for convenient and effective new synthetic methodology may be anticipated.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data for new compounds and 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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