Beyond Directed *ortho* Metalation: Ru-Catalyzed C_Ar–O Activation/Cross-Coupling Reaction by Amide Chelation

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Ⓢ *Supporting Information*

ABSTRACT: Disclosed is a new, catalytic, and general methodology for the chemical synthesis of biaryl, hetero-biaryl, and polyaryl molecules by the cross-coupling of *o*-methoxybenzamides with aryl boroneopentylates. The reaction is based on the activation of the unreactive C–OMe bond by the proximate amide directing group using catalytic $RuH_2(CO)(PPh_3)_3$ conditions. A one-step, base-free coupling process is thereby established that has the potential to supersede the useful two-step directed *ortho* metalation/cross-coupling reaction involving cryogenic temperature and strong base conditions. High regioselectivity, orthogonality with the Suzuki–Miyaura reaction, operational simplicity, minimum waste, and convenient scale-up make these reactions suitable for industrial applications.

The evolution of transition-metal-catalyzed cross-coupling reactions is undisputedly the most significant advance in organic synthesis of the past 40 years.[1] Of these, the original, fêted, and now Name Reactions for C_{sp^2}–C_{sp^2} (aryl–alkene and aryl–aryl) bond formation between an organometal species (B,[2] Zn,[3] Mg,[4] Sn,[5] Si[6]) and an organo-X (X = halide or pseudohalide) reagent have been broadly explored and exploited, especially for C–C bond construction.[1c,7] In 1993, the seminal report by Murai, concerning transition-metal-catalyzed aryl C–H activation/olefin coupling,[8] heralded a new epoch in synthetic chemistry based on chelation-induced direct activation of unreactive C–H bonds.[8,9] The Murai reaction signaled two immediate advantages: (1) the deficiencies of traditional cross-coupling processes, which generate ecologically undesirable stoichiometric amounts of metal and halide byproducts, were eliminated, and (2) by appendage of a directing group (DG) for coordination and C–H activation, the uncontrollable formation of mixtures of regioisomeric and multi-arylated products in substituted, electronically unbiased arenes was surmounted, leading to regioselective *ortho*-aryl functionalization. Recently, Kakiuchi discovered new types of C–O[10–12] and C–N[13] bond activation reactions that have considerably higher bond dissociation energies[14] than those of carbon–halogen bonds by ketone chelation-assisted Ru catalysis.[12,15] As part of ongoing efforts to develop new synthetic methodologies competitive with and possibly surpassing the widely applied directed *ortho* metalation (DoM) strategy (Scheme 1, **1 → 2 → 3 → 4**),[16] we have discovered an efficient Ru-catalyzed C–O activation/cross-coupling reaction of tertiary *o*-anisamides with aryl boroneo-

Scheme 1. Comparison of Stoichiometric Directed *ortho* Metalation (DoM) and Ru-Catalyzed C–OMe Activation Processes
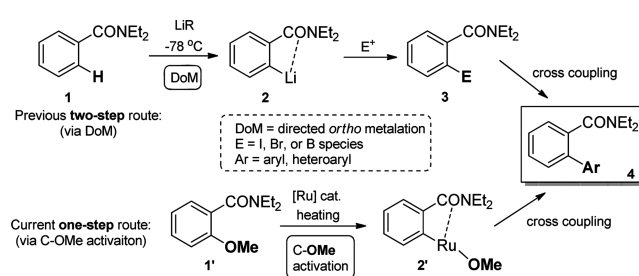
pentylates (ArBneop) by amide chelation (Scheme 1, **1′ → 2′ → 4**).

Herein we report our results, which have the following features: (1) Whereas the *o*-methoxyaryl ketone coupling reaction requires bulky pivaloyl group to overcome simultaneous non-regioselective C–H and C–O activation (Table 1,

Table 1. Selectivity of Ketone- and Amide-Directed (DG) C–OMe and C–H Activation/Coupling Reactions

DG	activation/coupling via C–H	activation/coupling via C–OMe	product	ref
C(O)Me	✓	✓	3	21
C(O)*t*-Bu	✗	✓	2	12
CONEt₂	✗	✓	2	this work

compare DG = C(O)Me vs DG = C(O)*t*-Bu), the *o*-anisamide coupling (DG = CONEt₂) is not compromised by C–H activation. (2) Unlike the C(O)Me and C(O)*t*-Bu groups, the amide DG is highly amenable to synthetic manipulations.[17] (3) Most significantly, the methodology overcomes the cryogenic temperature and strong organolithium base conditions of DoM, and, in conjunction with the Suzuki–Miyaura process,[16e–g] establishes orthogonal Ru- and Pd-catalyzed coupling chemistry for teraryl synthesis, thereby providing new, convenient, and
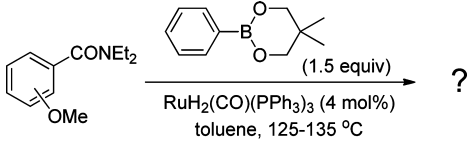
economical processes of interest for synthetic chemists.[18] We anticipated that the powerful directed metalation group (DMG), CONEt$_2$, should provide a greater Ru catalyst chelating ability compared to the ester and ketone DGs,[19] although, comparing two very different reaction types, its well-known steric bulk in DoM chemistry[20] may be similar to or greater than that of the *tert*-butyl ketone group in preventing either non-regioselective C−H or C−O activation and therefore 2,6-disubstitution, as observed in the motivational Kakiuchi studies.[12,21]

In the initial test case, the simple *N,N*-diethyl-2-methoxybenzamide (*o*-anisamide) was subjected to reaction with PhBneop (1.5 equiv) and catalytic RuH$_2$(CO)(PPh$_3$)$_3$ in refluxing toluene solution and afforded, to our delight, the biaryl amide **2a** in 96% yield (Table 2). Notably, no C−H

Table 2. Ru-Catalyzed Cross-Coupling Reaction of Isomeric *N,N*-Diethyl Anisamides with PhBneop
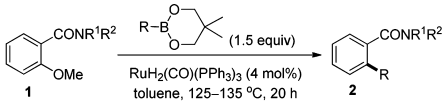
entry	amide	time (h)	product	yield (%)[a]
1	**1a**	20	**2a**	96
2		85	no reaction	--[b]
3		85	**2ag**	7[c]

[a]Yields are of isolated and purified products. [b]Starting amide recovered (98%). [c]Starting amide recovered (88%).

activation product was observed (GC-MS analysis). Control experiments on corresponding 3- and 4-MeO benzamides gave recovery of starting materials, even at prolonged reaction times, and no C−OMe activation/arylation products, demonstrating the amide DG chelation requirement (Table 2).

Using these optimized conditions,[22] the scope and limitation of the reaction were studied first by variation of ArBneop coupling partners (Table 3). Like **1a**, the less hindered *N,N*-dimethyl-*o*-anisamide afforded the expected product **2b** in excellent yield. However, bulky amide substrates led to greatly decreased yields of the coupling products **2c** and **2d**, indicating the operation of steric effects. As expected, the coupling reaction proceeded in good yields with ArBneops bearing Me, CH$_2$O*t*-Bu, and OMe electron-donating groups (EDGs) (**2f**, **2g**, **2i**, **2j**). Furthermore, ArBneops with F and CF$_3$ electron-withdrawing groups (EWGs) also gave high yields of coupled products (**2h**, **2k**−**2m**). Not unexpectedly, steric hindrance from *ortho*-substituted PhBneops was found to decrease the coupling efficiency. Thus, a slightly reduced yield of biaryl product **2e** was obtained in the 2-methylphenyl-Bneop case, and for highly sterically congested boronates, the expected coupled products **2s**, **2t** were not detected. The naphthalen-2-yl-Bneop was found to afford the arylated product **2n** in good yield. In studies of heterocyclic Bneop derivatives, good yields

Table 3. Ru-Catalyzed Cross-Coupling Reaction of Unsubstituted *o*-Anisamides with Bneops
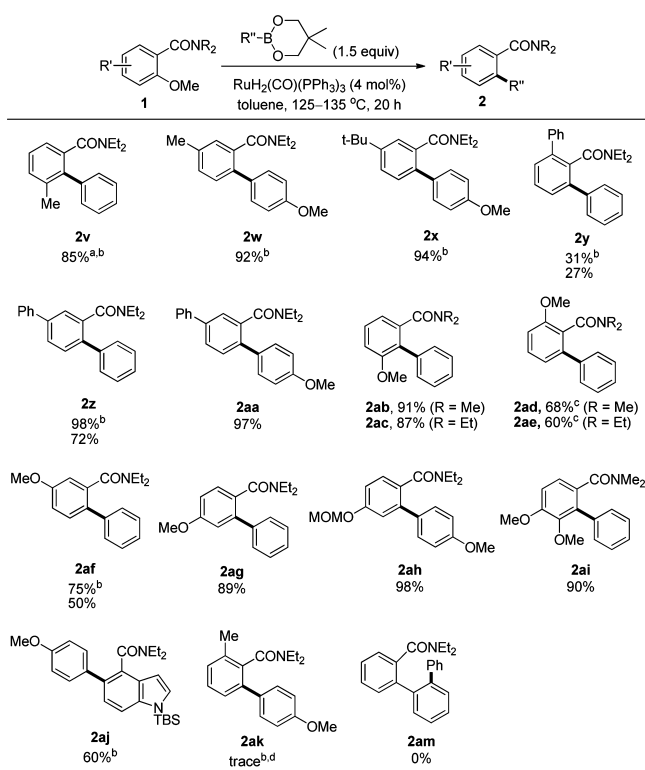
Reaction conditions: *o*-anisamide (1 equiv), boroneopentylate (1.5 equiv), RuH$_2$(CO)(PPh$_3$)$_3$ (4 mol%) in toluene (0.3−1.0 M) was heated at 125−135 °C (oil bath temperature) in a sealed vial for 20 h. [a]All yields are of isolated and purified products. [b]Starting amide recovered (66%). [c]Cumyl = 2-phenylpropan-2-yl; starting amide recovered (43%). [d]10 mol% catalyst loading. [e]Cis or *trans* stereochemistry not established by ^{1}H NMR due to almost identical J_{cis} and J_{trans} coupling constants[23] and unavailability of crystalline material for X-ray analysis.

of heterobiaryls **2o**, **2p** were obtained in the furan and thiophene series; however, the pyridin-3-yl-Bneop failed to give the coupled product **2u**, indicating that electron-deficient heterocycles are inappropriate substrates for the reaction or/and possible coordination of the pyridine N to Ru may impede the further C−O activation. An (*E*)-styryl-Bneop underwent the coupling reaction and afforded a moderate yield of **2q**, thus offering alternatives to Heck and Wittig reaction protocols. Interestingly, cyclopropyl-Bneop provided the coupled product **2r** in good yield.

Next, the scope of substituted *o*-anisamides was investigated, and the results are displayed in Table 4. *o*-Anisamides containing EDGs such as Me, *t*-Bu, OMe, OMOM, and Ph were mostly well tolerated to give products **2v−2z**, **2aa−2ai**. Studies on sterically hindered *o*-anisamides led to some instructive results. Thus, although the reactions of 6-substituted anisamides gave decreased yields of biaryl products **2y**, **2ad**, and **2ae**, minor double C−OMe activation/coupling byproducts were also observed in the **2ad**, **2ae** cases. The 6-methylanisamide led to only a trace of product **2ak** and almost

Table 4. Ru-Catalyzed Cross-Coupling Reaction of Substituted *o*-Anisamides with Bneops

Reaction conditions: substituted *o*-anisamide (1 equiv), boroneopentylate (1.5 equiv), RuH$_2$(CO)(PPh$_3$)$_3$ (4 mol%) in toluene (0.3–1.0 M) was heated at 125–135 °C (oil bath temperature) in a sealed vial for 20 h. [a]All yields are of isolated and purified products. [b]10 mol % catalyst loading. [c]Accompanied by di-C–O activation products: 22% (R = Me); 23% (R = Et). [d]Less than 3% of product determined by GC-MS analysis; starting amide recovered (97%).

complete recovery of starting material, perhaps indicative of the inability of the amide C=O to bring the Ru catalyst into proximity at a proper angle to achieve C–OMe activation. However, this widely used rationale of steric hindrance appears to have limited validity in the coupling reactions of 3-substituted and even 3,4-disubstituted *o*-anisamides, which proceeded well to give products **2v**, **2ab**, **2ac**, and **2ai** in good yields. For an indole case, the coupled product **2aj** was formed in 60% yield. From these results, it can be inferred that free rotation of the amide group is important for a highly efficient C–O bond activation/coupling reaction, viz. cases **2ak/2v**, **2y/2z**, **2ad/2ab**, and **2ae/2ac**. Such comparisons are unavailable from the DG = C(O)Me- and DG = C(O)*t*-Bu-directed C–O activation/coupling study.[12,15] The availability of *N,N*-diethyl-2′-methoxydiphenyl-2-amide from DoM/Suzuki cross-coupling chemistry and the successful carbanionic-directed *remote metalation* (DreM)/cyclization reaction to a fluorenone derivative[16a,b] prompted a risk experiment with the aim of observing a remote amide-directed C–OMe activation/cross-coupling reaction. However, under the optimized conditions, starting material was recovered quantitatively, potentially indicative of the inability to achieve a preferred conformation and large-ring coordination to attain C–OMe bond activation (Table 4, **2am**; details in SI).

We then turned out attention to application of the *o*-anisamide C–OMe activation/coupling chemistry. The glaring

presence of the electron-donating OMe group in this substrate provided the opportunity to establish orthogonal cross-coupling strategies[10c,24] based on our sequential Ru-catalyzed C–OMe activation and the standard Suzuki–Miyaura reactions. Thus, selective electrophilic bromination of *N,N*-diethyl-2-methoxy-benzamide **1** smoothly afforded the expected aryl bromide **2**, which, upon Suzuki cross-coupling with commercially available phenyl- and (4-methoxyphenyl)boronic acids, furnished the biarylamides **3** and **4**, respectively (Scheme 2).

Scheme 2. Synthesis of Teraryls via Sequential Bromination, Suzuki–Miyaura Cross-Coupling, and Ru-Catalyzed C–OMe Activation/Coupling Reactions
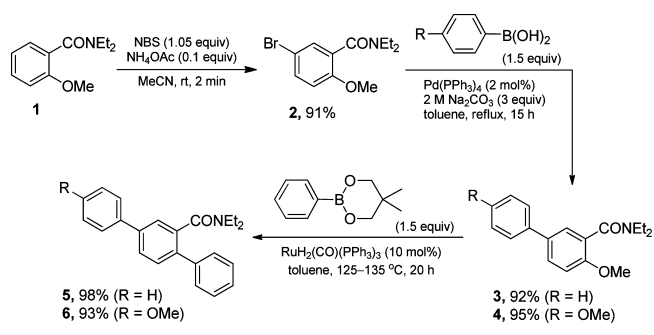
The subsequent Ru-catalyzed amide-directed C–OMe activation/coupling reactions with PhBneop gave compounds **5** and **6**. This efficient and operationally simple synthetic route to teraryl derivatives proceeds in three steps and >80% overall yield, complementing the Ir-catalyzed C–H activation/borylation reaction recently established in our laboratories.[25]

In conclusion, we have demonstrated the first catalytic tertiary amide-directed C–OMe activation/C–C cross-coupling reaction in the *o*-anisamide series for the synthesis of biaryl and heterobiaryl molecules. The Ru-catalyzed method is general, efficient, and of considerable practical potential in organic synthesis. The conditions are simple, requiring no additional ligands or base. The starting *o*-anisamides are readily available from simple and inexpensive commodity chemicals (see SI). Compared to the salient Kakiuchi ketone-directed coupling reaction,[12,21] the amide DG activation is highly C–OMe regioselective without competitive C–H activation process interference. Most significantly, the powerful DMG, CONEt$_2$, sets the stage for amide-to-aldehyde conversion using the *in situ* Schwartz reduction protocol recently developed in our laboratories,[17a,b] for regioselective DoM and DreM,[16a,b] and for combined DoM/Suzuki coupling chemistries[16e−g] to be effected either before or after the C–OMe activation/coupling event. Thus, our method provides arylbenzamides (e.g., **2v–2x**, **2z**, **2aa**, **2af**, Table 4) which are cumbersome or difficult to prepare by the latter methodology. In addition, we illustrate new orthogonal Ru- and Pd-catalyzed cross-coupling sequences for the preparation of teraryls (Scheme 2).

The reported Ru-catalyzed C–O activation/coupling reaction constitutes our initial efforts to invent a replacement for the widely used DoM strategy. It may be viewed as immediately complementing and, in the future, potentially superseding the DoM/cross-coupling methodology with the distinct advantage of not requiring cryogenic temperatures and strong bases. Its broad application in synthesis to provide unusual and unavailable substituted biaryl and polyaryl derivatives may be anticipated.

■ ASSOCIATED CONTENT

⑤ 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.

■ ACKNOWLEDGMENTS

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