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Amide-Directed Ru-Catalyzed Hydrodemethoxylation of *o*-Methoxybenzamides and -naphthamides: A DoM Reaction Counterpart

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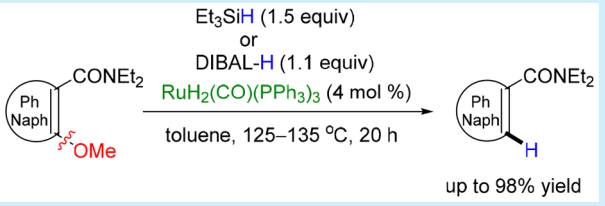
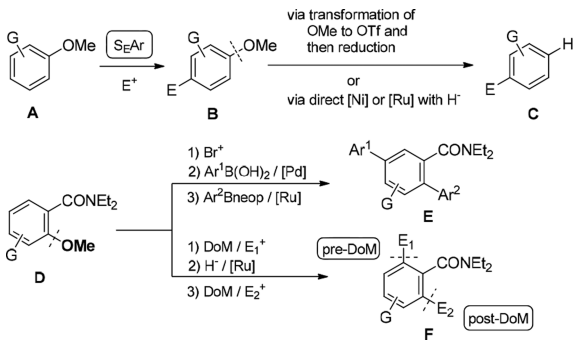
Supporting Information

ABSTRACT: A new ruthenium-catalyzed hydrodemethoxylation of *o*-methoxybenzamides and -naphthamides involving amide-directed C−OMe bond activation and hydride reduction is disclosed. The reaction is general, proceeding under $RuH_2(CO)(PPh_3)_3$ catalysis using either triethylsilane (Et_3SiH) or diisobutylaluminum hydride (DIBAL-H) as the reductant. The corresponding C−N hydrodeamination reaction is also briefly reported.



Aryl methyl ethers are present in numerous classes of natural products[1] and play a vital role as starting materials and synthetic intermediates as a consequence of their S_EAr,[2] S_NAr,[3] and directed *ortho* metalation (DoM)[4] reactivity patterns. Alkoxy aromatics provide the opportunity for enhanced S_EAr reactivity, which by subsequent reductive removal of an alkoxy group may serve to generate new aromatics as a function of present (G) and introduced (E) groups (**A** → **B** → **C**, Scheme 1). The most reliable and popular method for such reductive dealkoxylation has been via conversion into an aryl OTf derivative followed by Pd-catalyzed hydrodetriflation.[5] The requirement of OTf as a leaving group involves the use of an expensive reagent, thereby representing a major limitation of this procedure. The direct catalytic reductive cleavage of the C−O bond in O-functionalized aromatics would be of advantage in advancing the above strategy. This was already evident in the early seminal studies of Wenkert, who reported on the Kumada−Corriu cross-coupling reaction of aryl and naphthyl ethers with aryl Grignard reagents under Ni(0) catalysis to form biaryls,[6] and subsequently in our demonstration of the Ni(0)-catalyzed Kumada−Corriu cross-coupling reaction of $ArOCONEt_2$ with the *β*-hydride donor Grignard reagent *i*-PrMgCl to afford decarbamoylated products.[7] The challenge of uncovering the catalytic reductive cleavage of the strong aryl−OMe bond[8] was successfully surmounted in 2004 by the Kakiuchi group, who reported Ar−OMe bond activation by coordination assistance of an *o*-ketone carbonyl directing group (DG) in a organoboronate cross-coupling reaction under Ru catalysis.[9] Subsequently, Chatani demonstrated the direct Ni-catalyzed Ar−OMe activation/boronate coupling reaction.[10] These results provided substantial momentum to this area, and shortly thereafter, the first hydrodemethoxylation of unactivated Ar−OMe bonds (**B** → **C**, Scheme 1) using tetramethyldisiloxane as a hydride source under Ni catalysis was described by Martin[11] and then by Chatani and other groups.[12] We recently reported the Ru-catalyzed, amide-directed C−O activation/aryl boronate cross-coupling reaction, which provides a general and efficient new methodology for the synthesis of functionalized biaryls and heterobiaryls and, in addition, creates synthetically valuable links to S_EAr and DoM strategies (**D** → **E** and **F**, Scheme 1).[13] On the basis of this work, we envisaged that a hydrodemethoxylation reaction of *o*-methoxybenzamides may be achieved via C−O activation/reduction by an appropriate hydride source under Ru catalysis.

Scheme 1. Traditional and DoM-Based Reactions of Methoxyaromatics



Herein we report the Ru-catalyzed hydrodemethoxylation of *N*,*N*-diethyl-*o*-methoxybenzamides and -naphthamides[14] using triethylsilane (Et_3SiH) or diisobutylaluminum hydride (DIBAL-H) as the reductant (Table 1). This general reaction serves to eliminate the methoxy group, a moderate directed-metalation group (DMG)[4d] and strong electron-donating group (EDG),[15] either pre- or post-regioselective DoM and S_EAr reactions, respectively. Furthermore, it exposes the powerful $CONEt_2$ DMG for potential, with or without E group protection, alternative-site metalation chemistry (**D** → **F**, Scheme 1). We

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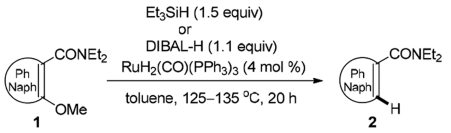
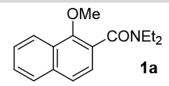
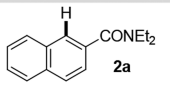
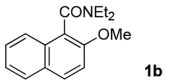
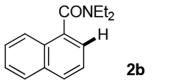
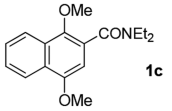
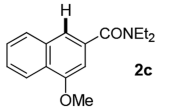
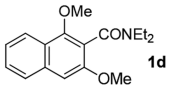
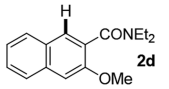
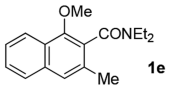
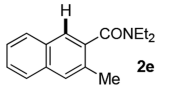
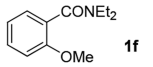
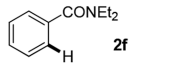
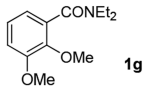
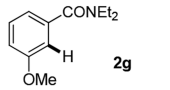
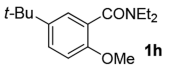
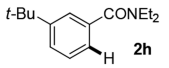
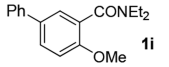
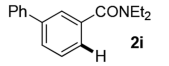
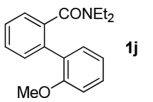
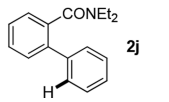
Table 1. Hydrodemethoxylation of *o*-Methoxynaphthamides and -benzamides Using Et_3SiH or DIBAL-H



entry	substrate	product	yield (%)[a] via Et_3SiH	yield (%)[a] via DIBAL-H
1	 **1a**	 **2a**	98	83 0[b]
2	 **1b**	 **2b**	87	70
3	 **1c**	 **2c**	93	–[c]
4	 **1d**	 **2d**	(74)[d]	56 (80)[d]
5	 **1e**	 **2e**	(5)[d]	0
6	 **1f**	 **2f**	(4)[d] 0[b]	51(76)[d]
7	 **1g**	 **2g**	(11)[d]	68 (85)[d]
8	 **1h**	 **2h**	–[c]	55[e]
9	 **1i**	 **2i**	88[e]	–[c]
10	 **1j**	 **2j**	–[c]	0

[a]Yields of isolated and purified products. [b]In the absence of catalyst. [c]Not investigated. [d]Conversion based on GC–MS analysis. [e]10 mol % catalyst loading.

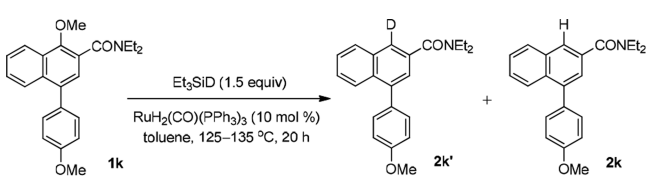
thus demonstrate valuable methodology that serves to erase the strongly S_EAr- and weakly D*o*M-enhancing OMe DMG, leading to the construction of aryl, naphthyl, and biaryl amides that are primed for additional exploitation by D*o*M and other amide group transformations.[16] The method is simple, has broad preparative scope, uses available starting materials, and thereby is in a position to join the useful modern methodologies in synthetic aromatic chemistry.

Brief examination of reductants (see the Supporting Information (SI)) on *N*,*N*-diethyl-1-methoxy-2-naphthamide (**1a**) using the Et_3SiH conditions under $RuH_2(CO)(PPh_3)_3$ catalysis afforded the hydrodemethoxylation product **2a** in almost quantitative yield, while DIBAL-H served as a somewhat less effective but still suitable reagent to give the product in 83% yield (Table 1, entry 1). With these conditions in hand, generalization of the method was pursued. With the Et_3SiH reductant, the hydrodemethoxylation of naphthamides **1b** and **1c** (entries 2 and 3) also proceeded well to give products **2b** and **2c**, while in the two cases **1a** and **1b** studied (entries 1 and 2), DIBAL-H afforded the corresponding products in somewhat lower yields. The formation of **2c** illustrates the significance and necessity of amide chelation assistance for selective hydrodemethoxylation. 1,3-Dimethoxy-2-naphthamide (**1d**) shows highly selective 1-OMe reduction to give **2d**, confirming the greater C-1 over C-3 C–OMe activation reactivity, as previously reported in the amide-directed C_{Ar}–OMe activation/cross-coupling reaction of naphthamides.[13a] The exception, 3-methylnaphthamide **1e**, gave trace amounts or none of product **2e** (entry 5) using both reductants. A similar result was observed in the amide-directed C–O activation/aryl boronate cross-coupling reaction[13] and may be attributable to the inability to achieve Ru catalyst C=O coordination to give the appropriate geometry for C–O activation due to steric effects. On the other hand, the reductive cleavage of the 2-OMe group of **1f** (entry 6) to give **2f** in good yield using DIBAL-H but not Et_3SiH may suggest stronger C=O chelation of the Al reagent versus the Si one.[11a,17] Contrasting results were observed in the comparative Et_3SiH and DIBAL-H reductions of the benzamide series. Thus, while benzamides **1f** and **1g** were found to give very low yields of **2f** and **2g** (entries 6 and 7) using Et_3SiH, they underwent smooth reduction under the DIBAL-H conditions to give these hydrodemethoxylated derivatives in 51–68% yield. Under higher catalyst loading, *tert*-butyl- and phenylanisamides **1h** and **1i** afforded good and excellent yields of the hydrodemethoxylated products **2h** and **2i**, respectively. In general, our empirical observations show that the Et_3SiH conditions work well for naphthamides but less efficiently for benzamides while the DIBAL-H conditions are effective on both substrates. Control experiments showed that in the absence of the catalyst, C–OMe reductions by DIBAL-H or Et_3SiH fail (entries 1 and 6).

Successful carbanionic directed *remote* metalation (D*re*M)/cyclization reactions to give fluorenone derivatives[18] also prompted a study of a remote amide-directed C–OMe activation/hydrodemethoxylation reaction. In the event, *N*,*N*-diethyl-2-(2′-methoxyphenyl)benzamide (**1j**) failed to undergo reaction, which may indicate that because of rotational barriers there is an inability to achieve a preferred conformation and large-ring coordination to attain C–OMe bond activation.

In a brief mechanistic study, 4-arylnaphthamide **1k** was subjected to the Ru-catalyzed conditions using Et_3SiD (Scheme 2) and afforded a mixture of the expected reduction products **2k′** and **2k** with a D/H ratio of 1:1.8 in 98% yield (see the SI). The formation of nondeuterated **2k** may occur via D–H exchange between Et_3SiD and PPh_3 under the described conditions[19] to generate additional Et_3SiH reagent for reduction of **1k**. This result is consistent with the observations

Scheme 2. Hydrodemethoxylation of Naphthamide 1k Using Et_3SiD



Ratio D:H = 1:1.8 (HRMS analysis) on mixture of **2k'** and **2k** (98% yield)

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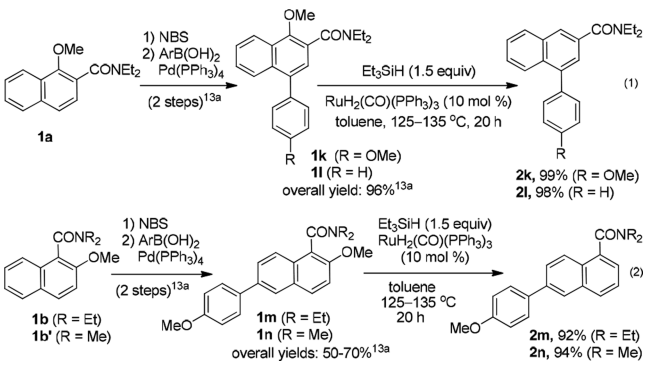
of Martin, which suggest a Ni-catalyzed OMe−hydrosilane σ-bond metathesis as a key step in the mechanism of the reduction process.[11a,20] We note the inertness of the non-*ortho* OMe group in **1k** toward reduction, which supports the necessity of amide chelation assistance for the overall reduction process, as also indicated by the result on **1c** (Table 1, entry 3).

To demonstrate synthetic utility and application, the well-behaved naphthamides **1a**, **1b**, and **1b′** were chosen in parallel hydrodemethoxylation and orthogonal Ru-catalyzed and Suzuki cross-coupling protocols (Scheme 3).[21] By means of the

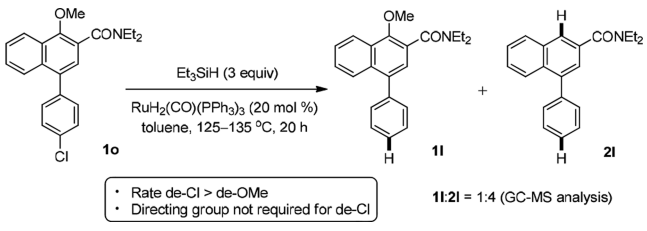
Scheme 3. Synthesis of Naphthyl-Based Biaryls



previously established two-step electrophilic bromination/Suzuki−Miyaura cross-coupling sequence,[13a] compound **1a** was converted to 4-arylnaphthamides **1k** and **1l** in quantitative yields. Treatment under the established Et_3SiH reduction conditions gave 4-aryl-2-naphthamides **2k** and **2l** in quantitative yields. In the second example, the positionally inverted methoxynaphthamide isomers **1b** and **1b′** were subjected to the same two-step sequence to furnish **1m** and **1n**, respectively, which under the same hydrodemethoxylation conditions gave 1-naphthamides **2m** and **2n**, respectively, in excellent yields. Thus, starting from commercially available naphthoic acids, two types of naphthalene-core biaryls and teraryls were synthesized in four steps in 40−90% overall yield.

The availability of 4-chlorophenyl-2-naphthamide **1o** presented an opportunity to test the reactivity of Et_3SiH toward competitive hydrodechlorination (Scheme 4). Subjecting **1o** to

Scheme 4. Competition of Hydrodemethoxylation and Hydrodechlorination

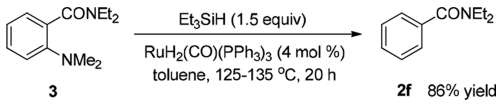


the Ru-catalyzed reduction with Et_3SiH gave products **1l** and **2l** in a ratio of 1:4 (GC−MS analysis), indicating only partial hydrodemethoxylation and full hydrodechlorination. Control experiments with halobenzamides established that reductive dehalogenation does not occur under Et_3SiH/refluxing toluene conditions without the Ru catalyst (see the SI). This result indicates not only that hydrodechlorination is faster than hydrodemethoxylation but also that nonchelative Ru activation of the C−Cl bond and reduction is more favorable than that of the C−O bond.[22] Additional cases of hydrodechlorination but also hydrodebromination and hydrodeiodination (for the full study, see the SI) indicate the generality of this reaction and further establish that under the Ru-catalyzed Et_3SiH/refluxing toluene conditions, successful reductive hydrodehalogenation does not require the amide DG chelation effect for the aromatic amides studied herein.

The distinct failure of amide-directed C−H, C−N, or C−O activation/cross-coupling reactions with previously studied halogenated substrates[13a,23] may be due to the lower bond dissociation energy of the C−halogen bond[8a] and thereby more favorable Ru insertion, which waylays the C−H, C−N, and C−O activation processes.

The above successful results and obvious mechanistic analogy led to the consideration of *o*-(*N*,*N*-dimethylamino)-benzamides as potential substrates for amide-directed C−N hydrodeamination. Treatment of the prototype substrate **3** under the $RuH_2(CO)(PPh_3)_3/Et_3SiH$ conditions resulted in smooth reduction to give *N*,*N*-diethylbenzamide (**2f**) in 86% yield (Scheme 5). This result, juxtaposed to the *o*-anisamide

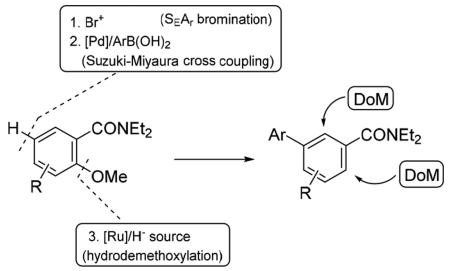
Scheme 5. Amide-Directed Hydrodeamination Using Et_3SiH



study (**1f**; Table 1, entry 6) clearly establishes the higher reactivity of the C−N bond compared with the C−O bond in the Ru-catalyzed reductive process and is a result for potential generalization and utility.

We wish to note that among the various conceivable combinations of reactivity modulation of leaving group and metal partners for orthogonal reactions in biaryl construction, many of which remain unexplored,[21a] our present and previous results constitute short sequences of synthetic value. To this aim, we have demonstrated several-step synthetic sequences of *o*-anisamide S_EAr bromination/Suzuki−Miyaura cross-coupling/Ru-catalyzed aryl C−OMe activation/cross-coupling[13] and hydrodemethoxylation reactions. Further synthetically useful connections (Scheme 6), as also partly realized in the

Scheme 6. Synthetic Links to the *o*-Anisamide Hydrodemethoxylation Reaction



present work, are (a) S_EAr reactivity by other electrophiles, including Friedel−Crafts reagents; (b) the option of D*o*M chemistry at initial (**1a**, **1b**, **1b′**), intermediate (**1k**−**n**), and terminal (**2k**−**n**) C−OMe reduction points and C−OMe cross-coupling stages;[4d,13,24] (c) the conceptual element, evident in most cases of Table 1, that once the OMe function has served in S_EAr chemistry, it may be detached to derive a substance that is again primed for further regioselective D*o*M reaction; (d) the

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additional benefit of DreM/cyclization reactions to more highly condensed aromatics;[18,25] and (e) as insightfully pointed out by Martin,[11a] the use of the hydrodemethoxylation process in late-stage chemoselective C−OMe cleavage of pharmaceutically relevant molecules.[26]

In summary, this work demonstrates new reactions of potential general value based on the conceptual interplay of classical (S_EAr) and modern (DoM, cross-coupling) reactivity whose further utility in the regioselective construction of polysubstituted aromatics and heteroaromatics of natural product and bioactive and materials molecules may be anticipated.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00755.

Experimental procedures and analytical data for new compounds and products (PDF)

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Notes

The authors declare no competing financial interest.

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