Letter

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Ruthenium(0)-Catalyzed Cross-Coupling of Anilines with Organoboranes by Selective Carbon–Nitrogen Cleavage

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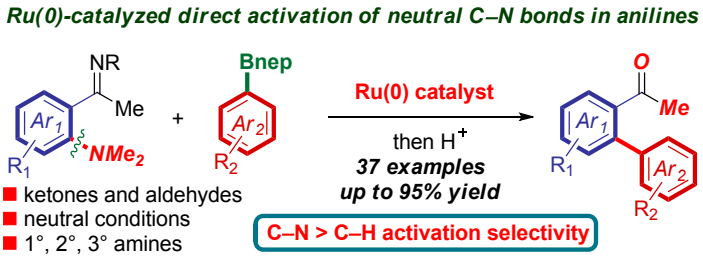
Supporting Information



ABSTRACT: Selective activation of neutral carbon–nitrogen bonds is of great synthetic importance because amines are among the most prevalent motifs across organic and bioactive molecules. Herein, we report the Ru(0)-catalyzed selective cleavage of neutral C(aryl)–N bonds in generic aniline derivatives enabled by a combination of $Ru_3(CO)_{12}$ and an imino auxiliary. These mild conditions provide a direct route to high-value biaryl ketones and biaryl aldehydes after facile in situ hydrolysis. A broad range of organoboranes and anilines can be coupled with high C–N cleavage selectivity. Most crucially, the reaction achieves exquisite selectivity for activation of C(aryl)–N bonds in the presence of typically more kinetically favorable C(aryl)–H bonds. The method provides a strategy for the construction of functionalized terphenyls by exploiting orthogonal properties of the Ru(0)-catalyst system and traceless nucleophilic properties of anilines.

KEYWORDS: *C–N activation, ruthenium, anilines, carbon–nitrogen cleavage, cross-coupling*

The direct activation of neutral carbon–nitrogen bonds may have a tremendous impact on organic synthesis because amines are among the most commonly encountered motifs in synthetic and bioactive molecules.[1,2] Because neutral C–N bonds are typically inert, the catalytic and stoichiometric cleavage of neutral C–N has been extremely rare.[3] Typical activation of C–N bonds involves converting the nitrogen into highly reactive intermediates, such as diazonium salts,[4] ammonium salts,[5] pyridinium salts,[6] or amides,[7] including conformationally-enforced C–N scission in twisted amides.[8] To date, only two examples of directed catalytic functionalization of neutral C(aryl)–N bonds in anilines have been achieved. Kakiuchi reported $RuH_2(CO)(PPh_3)_3$ for scission of C–N bonds in sterically-hindered ketones (Figure 1A).[9] Zeng developed an efficient platform for Kumada cross-coupling of C(aryl)–N bonds using low-valent chromium catalysis (Figure 1A).[10] Herein, we report the Ru(0)-catalyzed selective cleavage of neutral C(aryl)–N bonds (Figure 1B-C) in generic aniline derivatives enabled by a combination of $Ru_3(CO)_{12}$ and an imino auxiliary as a highly effective regioselectivity control principle for C(aryl)–N activation (Figure 1D).

Our laboratory has been interested in activation of C–N bonds as a versatile platform for catalysis.[11] In contrast to the continuing evolution of activation of C–H bonds,[12] the direct activation of neutral C–N bonds remains an unsolved synthetic task. The broad interest in activation of neutral C(aryl)–N bonds is twofold: (1) unprecedented potential to establish orthogonal strategies for functionalization of inherently and naturally-occurring amine motifs; (2) the use of electron-donating, nucleophilic NR_2 group as a traceless functional handle to selectively install functional groups impossible with inert C–H bonds.

The present method significantly advances nucleophilic ruthenium-catalysis[13–20] for activation of neutral C(aryl)–N bonds. An important example reported by Shi[20] describes a non-directed, Ni-catalyzed, Mg mediated cross-coupling of C–N bonds that is limited to conjugated arenes. Notable features of our findings include: (1) in contrast to

the previous state-of-the-art, the reaction does not require

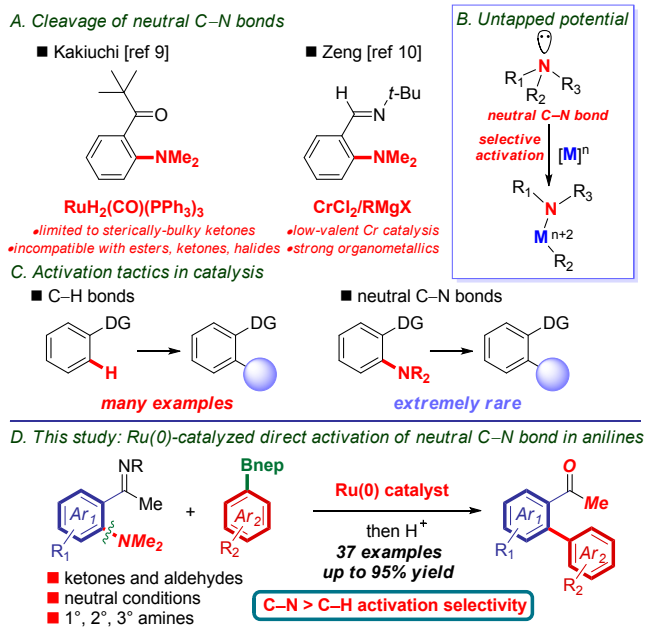
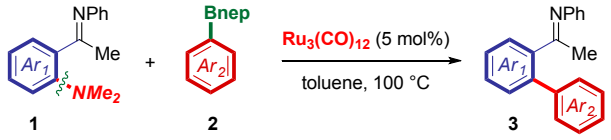


Figure 1. Context of the present work: A) Examples of N–C activation; B) Untapped potential of neutral N–C activation; C) Tactics in catalysis; D) Present study: the first Ru(0)-catalyzed mono-selective activation of neutral N–C bonds.

bulky pivaloyl groups to afford regioselective C–N (vs. C–H) activation;[21] (2) the product acetophenones are essential compounds in organic synthesis and can be readily functionalized through classical enolate activation;[22] (3) the method can be applied for the synthesis of biaryl aldehydes by C(aryl)–N activation after mild in situ hydrolysis first time in Ru(0)-catalysis;[23] (4) the method exploits unprecedented functional group tolerance of $Ru_3(CO)_{12}$ (halides, esters, ketones) that is unattainable with $RuH_2(CO)(PPh_3)_3$[13–15] and thus establishes a unique strategy for the construction of functionalized and broadly useful terphenyls; (5) *most remarkably, the method is highly selective for C(aryl)–N activation in the presence of multiple C–H bonds (8:1 C–N selectivity vs. 3 possible C–H activation sites).*[24]

Unlike pivaloyl groups, simple ketones and aldehydes are readily amenable for synthetic manipulations. Synthetically-useful mono-arylation requires the catalyst to de-coordinate from the directing group.[16j,k] This has been the major issue with ketone-directed $RuH_2(CO)(PPh_3)_3$ neutral C(aryl)–N activation, requiring the presence of a bulky pivaloyl group. We hypothesized that a strategy using imine auxiliary[25] and much more selective $Ru_3(CO)_{12}$ would provide a milder and more attractive approach to neutral C(aryl)–N activation. In this scenario the competing C–H activation is kinetically inaccessible, making the C–N bond the preferred activation site. Reaction of acetophenone ketimine (**1**) was investigated as a model system (Table 1). After extensive optimization, best results were obtained using N-Ph imine (**1**) as C–N functionalization substrate and neopentyl aryl boronate[26] (**2**) as nucleophile in toluene at 100 °C providing the desired product in 83% yield (Table 1, entry). It is noteworthy that the reaction

Table 1. Optimization of Reaction Conditions[a]



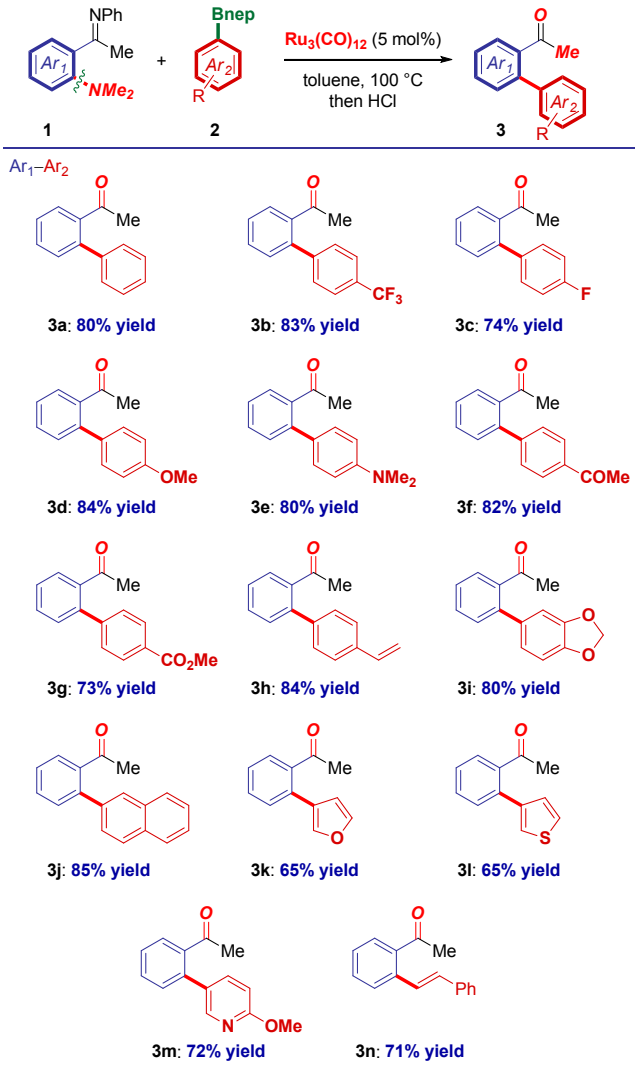
entry	variation from the standard conditions	conversion[b] (%)	yield[b] (%)
1	no change	>98	83
2	$RuH_2(CO)(PPh_3)_3$	10	<5
3	$RuH_2(PPh_3)_4$	5	<5
4	$RhCl(PPh_3)_3$	14	<5
5	$[Rh(COD)Cl]_2$	>98	<5
6[c]	$[RuCl_2(p\text{-cym})]_2$	>98	<5
7[d]	$[RuCl_2(p\text{-cym})]_2$	>98	<5
8	Ph-Bpin instead of Ph-Bnep	>98	73
9	Ph-BF_3K instead of Ph-Bnep	11	<5
10	Ph-$B(OH)_2$ instead of Ph-Bnep	41	<5
11[e]	Ph-$Si(OMe)_4$ instead of Ph-Bnep	16	<5
12	125 °C instead of 100 °C	>98	80
13	Ph-Bnep 1.5 equiv instead of 1.1 equiv	>98	76

[a]Conditions: imine (1.0 equiv), PhBnep (1.1 equiv), catalyst (5 mol%), toluene (1.0 M), 100 °C. [b]Determined by ^{1}H NMR and GC. [c]Ph–$B(OH)_2$ (3 equiv), $AgSbF_6$ (12 mol%), $Cu(OAc)_2H_2O$ (1.0 equiv). [d]Ph–$B(OH)_2$ (2 equiv), Ag_2O (1.0 equiv), $Cu(OTf)_2$ (1.0 equiv). [e]KF (1.0 equiv). Bnep = 5,5-dimethyl-1,3,2-dioxaborolane. See SI for details.

proceeded with unprecedented mono-arylation selectivity (C–N vs. combined C–N and C–H selectivity >10:1), and it did not require the presence of hydride acceptor or inorganic base additives. Selected optimization results are outlined in Table 1. Various catalysts were tested, and $Ru_3(CO)_{12}$ proved the most effective, in agreement with our design (entries 1-7). Neopentyl aryl boronate is the preferred nucleophile (entries 8-11). Specifically, the use of pinacol aryl boronate is feasible but less efficient due to material decomposition (entry 8). At the present stage, other nucleophiles are ineffective (entries 9-11). The effect of temperature and stoichiometry is critical for the efficient C–N activation, with higher temperatures or higher loading of nucleophile leading to competing di-arylation (entries 12-13). Finally, N-Ph imine is the preferred imine auxiliary for ketone arylation, with N-alkyl imines leading to low conversions due to imine decomposition (not shown), while bulky N-Ar imines are vastly preferred for aldehyde arylation to control mono-selective activation of C(aryl)–N bond (see SI).

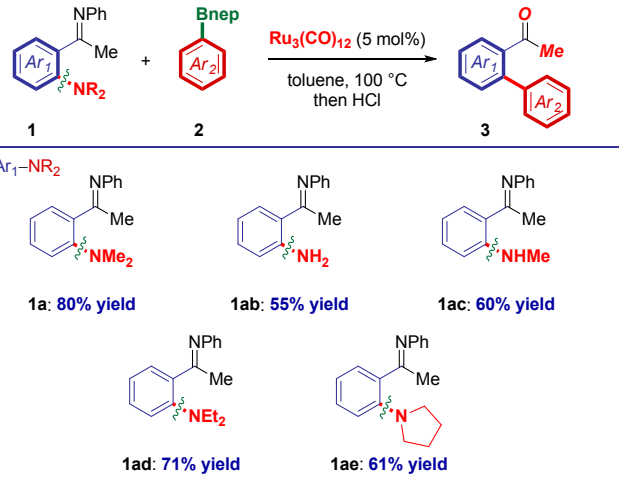
Having identified optimal conditions, the scope of this novel neutral C(aryl)–N activation was next investigated (Scheme 1). We were delighted to find that a wide range of organoboranes readily participates in this cross-

Scheme 1. Ru(0)-Catalyzed C(Aryl)–N Activation: Ketimines[a,b]



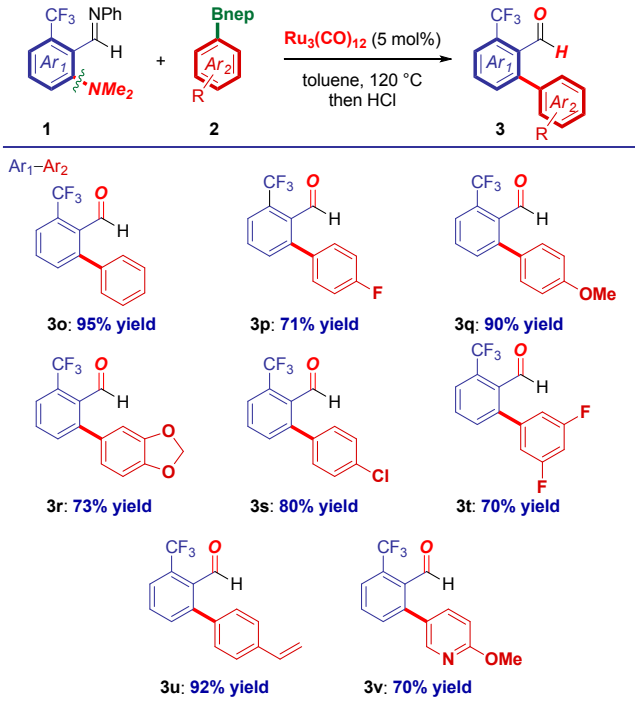
[a]Imine (1.0 equiv), PhBnep (1.1 equiv), catalyst (5 mol%), PhMe (1.0 M), 100 °C, 15 h. [b]Isolated after hydrolysis. See SI for details.

Scheme 2. Ru(0)-Catalyzed C(Aryl)–N Activation: Amine Scope[a,b]



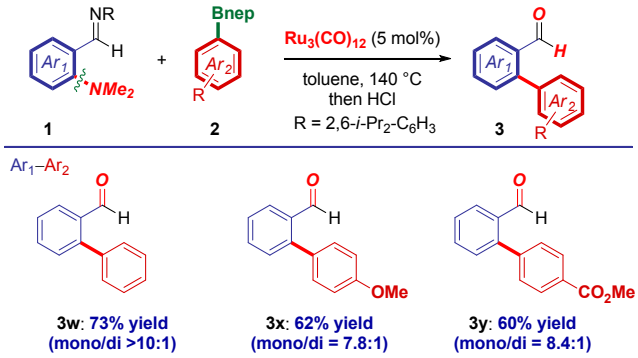
[a,b]See Scheme 1.

Scheme 3. Ru(0)-Catalyzed C(Aryl)–N Activation: Trifluoromethyl Ketimines[a,b]



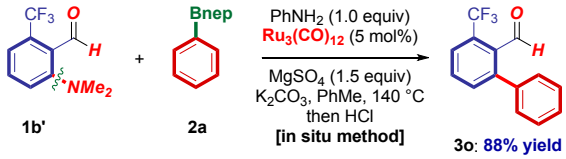
[a]Imine (1.0 equiv), PhBnep (1.1 equiv), catalyst (5 mol%), PhMe (1.0 M), 120 °C, 15 h. [b]Isolated after hydrolysis. See SI for details.

Scheme 4. Ru(0)-Catalyzed C(Aryl)–N Activation: Aldimines[a,b]



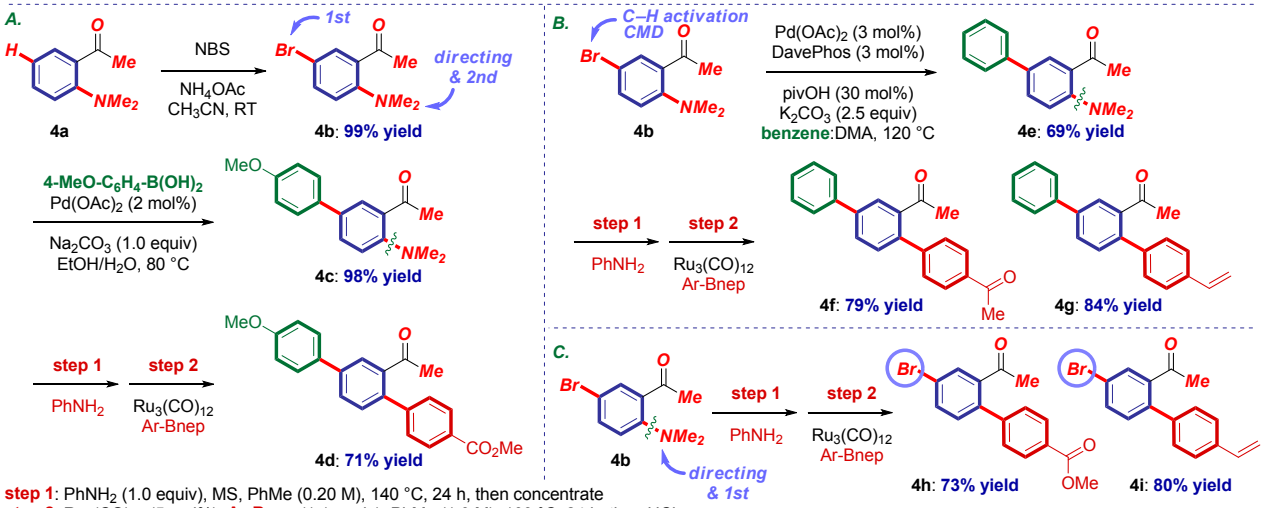
[a]Imine (1.0 equiv), PhBnep (1.1 equiv), catalyst (5 mol%), PhMe (1.0 M), 140 °C, 15 h. [b]Isolated after hydrolysis. See SI for details.

Scheme 5. Ru(0)-Catalyzed in situ C–N Activation



coupling. As shown, electronically-diverse nucleophiles, including electron-neutral (**3a**), electron-deficient (**3b-c**), and electron-rich (**3d-e**) organoboranes coupled with high levels of efficiency. Note that the reaction is fully selective for the cleavage of the electrophilic –NMe_2 adjacent to the imine auxiliary (**3e**). It is notable that the reaction is compatible with electrophilic carbonyl handles,

Scheme 6. Synthetic Transformations and Sequential Catalysis Enabled by C(Aryl)–N Activation



including ketones (**3f**) and esters (**3g**), providing excellent substrates for electrophilic functionalization strategies. Note the facile installation of sterically-differentiated ketones in **3f**, another benefit of using mild imine auxiliary approach. Furthermore, unprotected terminal olefins (**3h**), polyaromatics (**3j**) and heterocycles, such as furan (**3k**), thiophene (**3l**), are well-tolerated, furnishing the C(aryl)–N cleavage products with high C–N scission selectivity. We were pleased to find that functionalized pyridines (**3m**) and styrenyl boronates (**3n**) are also readily tolerated in this protocol, allowing incorporation of various groups. *Note that in all cases examined, we observed exquisite C(aryl)–N vs. C–H activation selectivity (>20:1), with mono- vs. di-arylation selectivity typically >15:1 favoring the thus far unattainable mono-arylation products.* An important feature of the Ru(0)-methodology

is the capacity to tolerate sensitive functional groups on both reaction components.[13,15,18e,f] All starting materials are readily accessible from the corresponding anilines or by established methods.[26b] At the present stage of reaction development alkylboronates are not compatible. Preliminary results suggest that it is possible to prepare arylboronates in situ to improve atom economy. Efforts are currently underway to expand the scope of the C–N cleavage methodology and these studies will be reported in due course.

Importantly, we determined that various neutral anilines, including dimethyl –NMe_2 (**1a**), unprotected –NH_2 (**1ab**), mono-alkyl –NHMe (**1ac**), more sterically-hindered –NEt_2 (**1ad**) and cyclic –pyrrolidine (**1ac**) (Scheme 2) undergo the Ru(0)-catalyzed activation/cross-coupling under the developed conditions with high C(aryl)–N activation selectivity, attesting to the generality of our protocol.

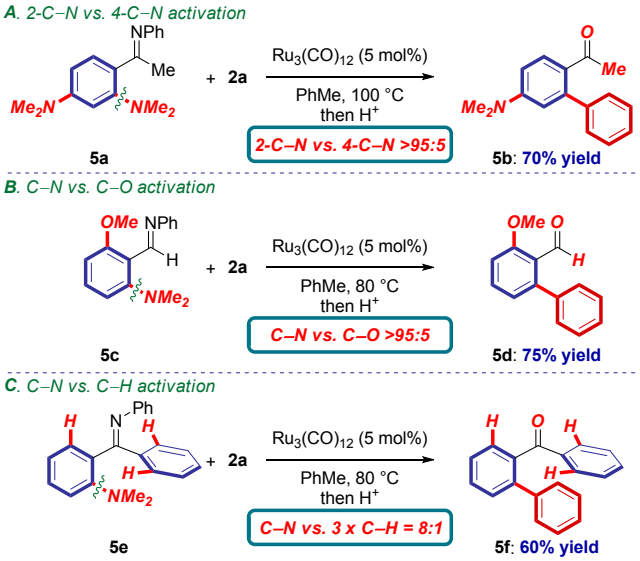
We were further delighted to find that C(aryl)–N activation in aldehyde derivatives is also possible by using imine directing auxiliary (Scheme 3). The ortho-CF_3-aniline was used as a model substrate, and thus provided access to trifluoromethyl-biaryl aldehyde building blocks which prominently feature in pharmaceutical, agrochemical and functional materials applications due to unique properties of fluorine. In general, the yields observed (Scheme 3) matched the C(aryl)–N activation of ketone substrates (Scheme 4). To our knowledge, this reaction represents the first example of generating a versatile biaryl aldehyde linchpin in ruthenium-catalyzed neutral C–N activation.[13–15]

Remarkably, the direct C(aryl)–N activation of unbiased aldehydes is also feasible (Scheme 4). In these cases, we found that the use of a sterically-bulky N-aryl imine is preferred to prevent di-arylation. It is well-established that in benzylideneanilines the aromatic ring is twisted from the imine plane, while the presence of ortho-substituents increases the twist.[27] Thus, representative examples using neutral (**3w**), electron-rich (**3x**) and electron-deficient (**3y**) proceeded with unprecedented >7:1 selectivity for neutral C(aryl)–N arylation.

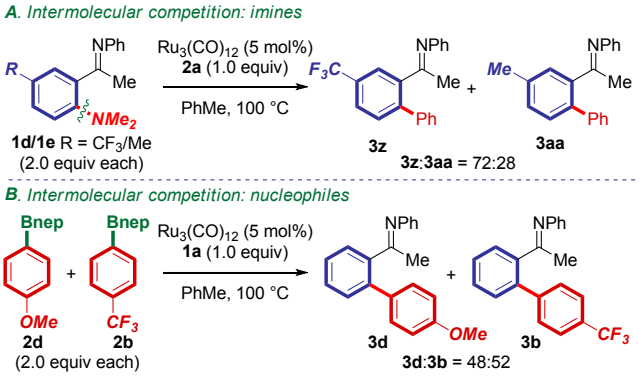
The synthetic advantage of the mild imine auxiliary approach and Ru(0)-catalysis is that the C(aryl)–N activation can be readily performed directly from a carbonyl by an in situ imine synthesis/hydrolysis (Scheme 5).

We next turned our attention to demonstrate the synthetic potential of the neutral C(aryl)–N arylation. As the key advantage the presence of a neutral aniline furnishes a unique strategy for the construction of functionalized molecules by exploiting orthogonal properties of the Ru(0)-catalyst system and traceless nucleophilic properties of anilines. This is demonstrated by facile assembly of functionalized terphenyls via electrophilic bromination/ Suzuki cross-coupling/Ru(0)-catalyzed neutral C(aryl)–N activation (Scheme 6A). Furthermore, C–H activation could be implemented in the sequence by exploiting the Pd-catalyzed CMD (concerted-metallation-deprotonation) pathway (Scheme 6B).[28] Ultimately, this

Scheme 7. Selectivity Studies



Scheme 8. Mechanistic Studies



suggests a great potential of a C(Ar)–Br synthetic handle for post-activation transformations. Indeed, the mild $Ru_3(CO)_{12}$ catalyst permits direct C(aryl)–N activation in the presence of a very sensitive aryl bromide (Scheme 6C). To our knowledge this represents the first example of functional group tolerance for an aryl bromide in the C(aryl)–N bond activation manifold.

Importantly, to have a broad impact, a catalyst system must be selective over other potential activation sites.[12] To determine the inert bond activation selectivity of the present system, we studied the intramolecular competition for C(aryl)–N vs. C(aryl)–N, C(aryl)–N vs. C(aryl)–O and C(aryl)–N vs. C(aryl)–H activation (Scheme 7). To our delight we found that this mild Ru(0)-imine method gives full selectivity for the C(aryl)–N activation at the ortho-position (2-C–N vs. 4-C–N, >20:1) (Scheme 7A), consistent with a directing effect of the imine auxiliary. Furthermore, we observed full selectivity for C(aryl)–N vs. C(aryl)–O activation (>20:1) (Scheme 7B),

despite the well-established potential for metal insertion into –OMe bonds.[29] *Most remarkably, we found an excellent selectivity for C–N activation in the presence of multiple C–H bonds (8:1 C–N selectivity vs. 3 possible C–H activation sites) (Scheme 7C).* These results are unprecedented for neutral C(aryl)–N activation and bode well for the development of general strategies in this inert bond activation pathway.

While conclusions on the mechanism are premature at this stage, Kakiuchi showed that Ru(0)-direct insertion into a C–N bond is feasible.[30] Intermolecular competition studies in the present reaction between differently substituted electrophiles showed that electron-deficient substrates are inherently more reactive (Scheme 8A), consistent with this scenario. Furthermore, competition experiments with electronically-diverse nucleophiles demonstrated that the reaction is not significantly affected by electronic properties of the nucleophile (Scheme 8B), consistent with chelation of the nitrogen to boron in the transmetallation step between Ru–NR_2 and Ar–Bnep. The Bnep moiety is converted into R_2N–Bnep species. The formation of X–$B(OR)_2$ products in Ru(0) catalysis is well-documented.[13,15,29] Studies to elucidate the mechanism are underway.

In summary, we developed a new method for Ru(0)-catalyzed selective cleavage of neutral C(aryl)–N bonds in generic aniline derivatives. We showed that catalyst control in combination with imino auxiliary furnishes an excellent selectivity in neutral C(aryl)–N activation. Despite the significant challenges that are posed by scission of neutral C–N bonds, the present system shows exquisite selectivity for C–N activation, allowing the construction of high-value biaryl ketones and aldehydes via mono-arylation. The method shows excellent functional group tolerance, and provides a unique strategy for the synthesis of biaryls by utilizing orthogonal features of the Ru(0)-catalyst and nucleophilic properties of anilines. The discovery that the reaction achieves full selectivity for activation of C(aryl)–N bonds in the presence of typically more kinetically favorable C(aryl)–H bonds is likely to facilitate the design of future catalyst systems and may also be applicable to the activation of other C(aryl)–X bonds.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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