Letter

A Base and Solvent-Free Ruthenium-Catalyzed Alkylation of Amines

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A Base and Solvent-Free Ruthenium-Catalyzed Alkylation of Amines

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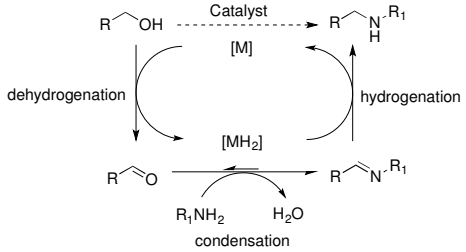
ABSTRACT:A (pyridyl)phosphine-ligated ruthenium(II) catalyst is reported for the chemoselective benzylic *N*-alkylation of amines, via a hydrogen borrowing mechanism. The catalyst operates under mild conditions, neat, and without a base or other additive. These conditions offer remarkable functional group compatibility for applications in organic synthesis, including reactions involving phenols and anilines, which are very difficult to achieve. Mechanistic studies suggest that,unlike other catalysts for this reaction, the redox steps are fast and reversible while imine formation is slow. We perceive that this is the origin of the selectivity realized with these reaction conditions.

KEYWORDS Amination, hydrogen borrowing, catalysis, imine, dehydrogenation

Amine alkylation is a quintessential synthetic transformation.[1]Recently, classical methodslike alkylation with alkyl halides[2]and reductive amination[3]are being replaced with catalytic reactions like coupling of amines with aryl halides,[4] hydroamination,[5]and direct coupling of amines and alcohols.[6,7] Unlike classical methods, this latter approach does not require the use of an alkyl halide or a borohydride co-reagent, so it presents a very cost-competitive, sustainable approach for decoration of amines. The most common catalysts for this method are ruthenium[8] and iridium[9] complexes, but many other noble (Au,[10] Ag,[11] Pd,[12] Rh,[13] Os[14]) and non-noble (Cu,[15] Ni,[16] Co,[17] Fe,[18,17a]Mn,[19]Re[20]) transition metals will work. Scheme 1 shows a general mechanism for these reactions, the hydrogen borrowingstrategy, which involves the following steps: 1) dehydrogenation of the alcohol to a carbonyl group, 2) condensation with the amine to form an imine, and 3) hydrogenation of the imine to form the alkylated amine product.

Scheme 1. Amination byHydrogen Borrowing.



Given the utility of these reactions, a great amount of work has been reported on developing substrate scope, although need remains for conditions that tolerate fragile functionality, particularly protic, nucleophilic, and base-sensitive groups. Further, although there is consensus about the organic transformations in the mechanism (Scheme 1), there are few studies on the organometallic redox events in this process, which are those that govern rate and selectivity.[21,22] In this study, we report base-free conditions for amine-alcohol coupling and show that these are advantageous in enabling functional group tolerance that cannot be realized with other conditions. We also show that this is possible by enabling a relatively rapid C—H oxidation step—a situation unseen in the amine-alcohol coupling literature—and demonstrate that under these conditions both alcohol and amine oxidation are rapid, thus enabling product chemoselectivity that is otherwise difficult to achieve.

We entered this area, because we have a long-standing interest in devising dual site catalysts for C—H hydride abstraction.[23] We further observed that althoughbisphosphines have been widely used as ligands for ruthenium-catalyzed coupling of amines with alcohols,[24,8s,8u,8x] the utility of phosphinopyridine(P—N)ligands—which have succeeded in our hands in other dehydrogenation applications[25]—haverarely been studied in these reactions.[26]We wereinterested in studying a (pyridylphosphine)ruthenium complex,because we thought it could act asa bidentate analog to Milstein's PNP and PNN pincer ligands, which are remarkably useful and versatile catalysts for many acceptorless dehydrogenationapplications.[27,8c]Here we report the synthesis, characterization, and reactivity of a novel precatalyst(**1**) possessing a simple (P—N) ligand,and we find it to be a very convenient pre-catalyst for coupling of amines with benzylic alcohols, requiring no solvent, inorganic base, or other additive.[28]A variety of functional groups that are traditionally incompatible with these coupling reactions,including unprotected phenols and anilines,[29] are tolerated in our conditions.

Ruthenium complexes **1** and **1a** were prepared from the reaction of 2-((di-*tert*-butylphosphino)methyl)pyridine[30] with $[RuCl_2(Cym)]_2$ and $[IrCl_2Cp^*]_2$, respectively, in the presence of excess sodium triflate (Figure 1). Complexes **1** and **1a** were characterized by X-ray crystallography.

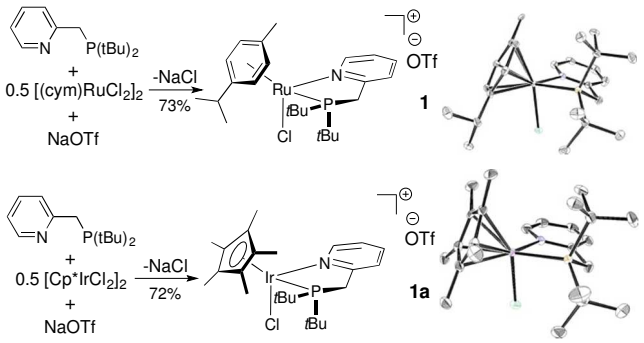
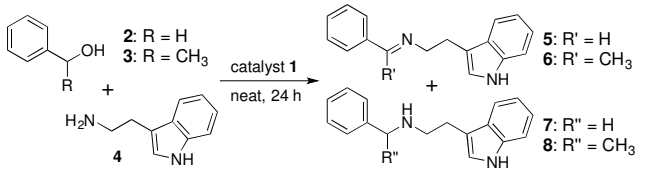


Figure 1. Syntheses andORTEP diagrams of **1** and **1a**. Ellipsoids are drawn at the 50% probability level,triflate counterions are omitted for clarity.Co-crystalized dichloromethane in **1** (0.5 equiv.) is also omitted. Cp* =pentamethylcyclopentadienyl anion.

We firstdemonstrated the 1-catalyzed coupling of tryptamine with benzyl alcohol and 1-phenylethanol under a nitrogen stream.This gave the corresponding imines**5**and **6**, with little or no *N*-benzylated amine product (Table 1, entries 1 and 3). By contrast, when benzyl alcohol and tryptamine are heated with 1 mol% **1** in a sealed flask, complete conversion to the desired benzylated amine is observed after 24 h. 1-Phenylethanol can also be coupled at 5 mol% catalyst loading.Thus, ruthenium **1** is an effective catalyst for coupling of both primary and secondary benzyl alcohols to amines. It functions under mild, neutral conditions and does not require solvents or additives.[28]Surprisingly, iridium congeners **1a** and [(cod)Ir(P—N)]$^{+}$TfO^{-}(**1b**) did not afford useful reactivity.[25]

Table 1. Coupling of Benzylic Alcohols with Tryptamine.

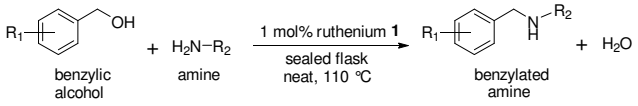


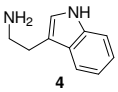
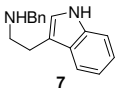
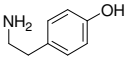
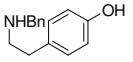
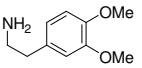
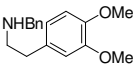
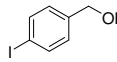
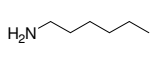
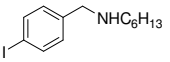
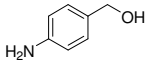
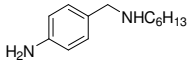
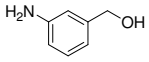
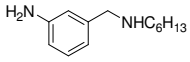
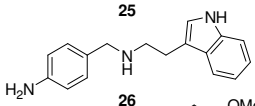
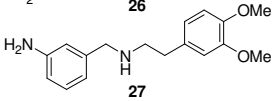
Entry	ROH (equiv)	conditions	1 (mol %)	Temp (ºC)	conv (%)	product(s) imine	amine
1	**2**(2.2)	open flask	1	110	75	**5**75%	**7**25%
2	**2** (2.2)	sealed flask	1	110	100		**7**
3	**3** (1.5)	open flask	1	110	33	**6**	
4	**3** (1.5)	sealed flask	1	130	25		**8**
5	**3** (7.5)	sealed flask	5	130	100		**8**

[a] Conversion calculated by ^{1}H NMR integration.

Using these conditions, we studied the substrate scope for this dehydrative coupling reaction. We find excellent scope and functional group tolerance with yields varying among different amines (Table 2). For example, benzyl alcohol is coupled to tryptamine and tyramine (products **7** and **18**) without the need for protection of the indole nitrogen or the phenol hydroxyl group.[29]This has high synthetic value, because amination of **4**, **12**, and **13** presages highly efficient access to building blocks for tryptophan and tyrosine-derived alkaloids, including medicinal agentsdopexamine and dobutamine. Moreover, a free aniline –NH_2 group behaves as an orthogonal functionality as 3- and 4-aminobenzyl alcoholsare smoothly converted to aminoanilines**24 – 27**.[29]For these reactions, it is necessary to utilize the amines in excess: using the aminobenzyl alcohols in excess result in over-alkylation of the free anilines in the products.

Table 2. Substrate Scope for Coupling of Benzylic Alcohols with Amines Using Precatalyst1.[a]



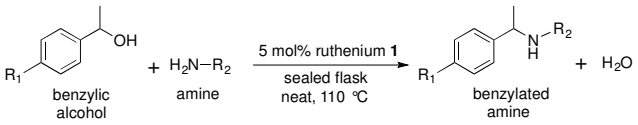
Entry	Alcohol	Amine	Product	Time (h) Conversion (%)[b] Isolated yield (%)
1	BnOH (**2**)	 **4**	 **7**	20 100 74
2	**2**	 **12**	 **18**	5 100 72
3	**2**	 **13**	 **19**	24 100 79
4	**2**	 **14**	 **20**	20 100 90
5	**2**	 **15**	 **21**	24 100 58
6	**2**	 **16**	 **22**	47 100 58
7	 **9**	 **17**	 **23**	20 100 65
8	 **10**	**17**	 **24**	12 100 77
9	 **11**	**17**	 **25**	3 100 74
10	**10**	**4**	 **26**	12 70[c] 57
11	**11**	**13**	 **27**	3 100 72

[a]For entries 1-7, the amineswere the limiting reagents and 1.5 equiv. of the benzylic alcohols were used. For entries 8-11, the benzylic alcohols were the limiting reagents and 1.2 equiv. of the amines were used. [b]Calculated by ^{1}H NMR integration of the crude reaction mixture. [c]An unstirrablemass forms; the reaction was stopped after 12 h (ca. 70% conversion by NMR).

Secondary benzylic alcohols also couple to amines in good yields (Table 3). The coupling of 1-phenylethanol to various amines exhibits a similar functional group compatibility as benzyl alcohol. Free indole and phenol groups are also tolerated. Likewise, 1-phenylethanol derivatives possessing different

substituents from electron rich to electron poor are good coupling partners to tryptamine (products**35 – 37**).

Table 3. Substrate Scope for Coupling of 1-Phenylethanol (and Derivatives) with Amines Using Precatalyst 1.[a]



Entry	Alcohol	Amine	Product	Time (h) Conversion (%)[b] Isolated yield (%)
1	**3**	**4**	**8**	24 100 72
2	**3**	**12**	**31**	20 100 85
3	**3**	**13**	**32**	24 100 67
4	**3**	**14**	**33**	24 100 65
5	**3**	**15**	**34**	19 100 66
6	**28**	**4**	**35**	24 - 77
7	**29**	**4**	**36**	24 - 72
8	**30**	**4**	**37**	24 - 69

[a] The amines were the limiting reagents; 7 – 7.5 equiv. of the benzylic alcohols were used. [b]Calculated by ^{1}H NMR integration of the crude reaction mixture.

Competing amine coordination is usually not discussed in work on this reaction, which is surprising,because amine decomplexation has been proposed by Crabtree and Eisenstein to be the rate determining step in catalysis involving a d^{6}iridium(III) catalyst.[21e] In the same paper, the coordination of both amine and alcohol substrates were analyzed, and a more facile β-hydride elimination in alcohols was determined to be responsible for the observed selectivity.[21e]Accordingly, we collected evidence to test for redox reversibility and product stability under our reaction conditions.Thus, we performed a ^{13}C NMR time-course study for the coupling of benzyl alcohol-1-d_1 (**2**-1-d_1,ca. 93% D) and*n*-hexylamine in the presence of 1 mol% of precatalyst**1**. The disappearance of the starting materials and formation of thebenzylated amine can be observed clearly. Prior to heating, the deuterated benzylic carbon appears as a three-line ^{13}C-^{2}H coupling pattern centered at 63.5 ppm in the ^{13}C spectrum along with a trace (ca. 7%) of the ^{1}H isotopomerat 63.8 ppm; the α-carbon of the *n*-hexylamine is a singlet at 42.3 ppm (see the Supporting Information). After heating for two hours, the^{1}H isotopomer of benzyl alcoholincreases in integration, indicating equilibration of its α-CH_2 group with *n*-hexylamine through intermediate benzaldehydeand imine species, respectively (Figure 2A).This is corroborated by deuterium incorporation into *n*-hexylamine starting material: this exchange is rapid relative to product formation. The formation of an imine intermediate at 161.0 ppm is observed but no aldehyde is detected (see the Supporting Information). Thus, we show that both the amine and alcohol substrates coordinate to ruthenium and that both can be dehydrogenated. Surprisingly,the alcohol/aldehyde and amine/imine equilibria are both faster than either Tishchenko dimerization of the alcohol or the desired amination. Further, imine formation could enable amine dimerization to form di-*n*-hexylamine, which is observed in the reaction mixture (Figure 2A).[31]Because the major pathway is coupling to the alcohol, product formation seems to be governed by thermodynamics.

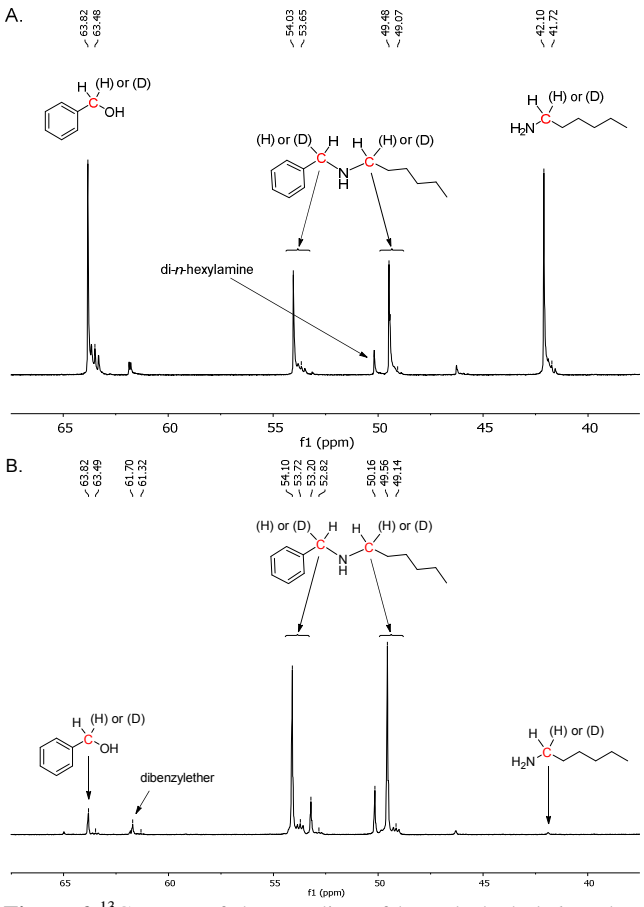


Figure 2.^{13}C NMR of the coupling of benzyl alcohol-d_1 and *n*-hexylamine (1.1:1 mol ratio)after heating to 110 °C for A) 2h and B) 24h under neat reaction conditions. The deuterated carbons appear as 3-line patterns immediately upfield of the corresponding non-deuterated singlets.

Figure 2B shows formation of the *N*-benzylated amine product. The benzylic carbon appears as a three-line pattern at 53.7 ppm (^{13}C-^{2}H) and a singlet at 54.0 ppm (^{13}C-^{1}H). The α-carbon of the hexyl group conversely appears as a three-line

pattern at 49.1 ppm (^{13}C-^{2}H) and a singlet at 49.5 ppm (^{13}C-^{1}H). As the mixture is heated over 24 h, hexylamine is consumed almost completely and the major product is benzylhexylamine. Small amounts of side products—Bn_2O,$(nHex)_2NH$, $Bn_2N(nHex)$, and $BnN(nHex)_2$—also are observed.[31]

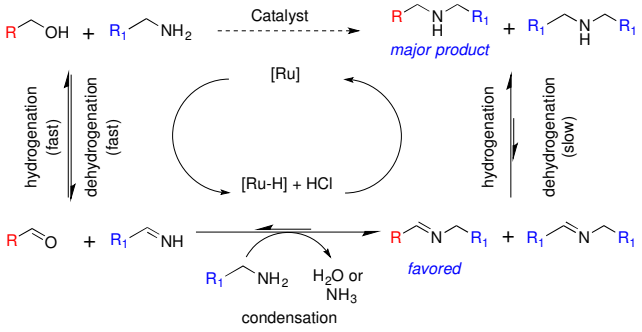
While we do not know the structure of our active redox catalyst, clues from operando NMR spectroscopy enable some understanding. We observe in ^{31}P NMR studies that the bidentate pyridylphosphine ligand remains coordinated to ruthenium during catalysis. After 24 hours of heating the reaction mixture, the^{31}P spectrumshows five peaks: the major species is a broad triplet at 92.1 ppm.Free ligand, which has δ = 36 ppm (singlet), is not observed.We also see that the cymene ligand of **1**dissociatesduring catalysis and is replaced with a transient metal hydride. Operando ^{1}H NMR spectra of the homodimerizationof**2**-1-$d_1$to dibenzyl etherin 1,2-dichlorobenzene-$d_4$in the absence ofhexylamine enables observation of the ligand set on ruthenium through the alcohol/aldehyde interconversion steps of our mechanism (see Supporting Information).Upon heating the reaction mixture, the cymene dissociates from the ruthenium as catalysis initiates andis fully dissociated at median conversion.The predicted benzaldehyde intermediate is observed in low concentrations throughout the reaction, but no Tischenko dimerization (to benzyl benzoate) is observed. We also find a doublet (J_{HP} = 40 Hz) atδ = -8.90 ppm in the ^{1}H NMR spectra, which we assign as a transient ruthenium hydride species.The observedJ_{HP} is consistent with a hydride geometry cis to the phosphine ligand.[32]This group disappears with prolonged heating as conversion continues and this hydride is returned to carbon in the product.Based on these data, we expect that our active catalyst involves a phosphinopyridine-bound, cymene-free ruthenium species that can form a transient ruthenium hydride. We disfavor a $[Ru(P—N)_2]^{2+}$derivative as seen by Langer,[26]because we don't see $^{2}J_{PH}$ coupling appropriate to two ^{31}P centers in our intermediate hydride. This is probably because our more bulky phosphine can't accommodate this coordination mode. None of our active catalytic species have yielded to observation outside of the working catalyst conditions. We do see, however, that metal-ligand cooperation is not operating: our ligand's methylene does not appear to deprotonate under the reaction conditions. We can deprotonate **1**, **1a**, or **1b** with potassium *t*-butoxide, but the neutral species resulting form **1** decompose rapidly.

The catalyst system does not interchange the alcohol's proton (O—H) and hydride (C—H) groups in the course of catalysis. After 48 hours of heating the above reaction, the deuterium content of the starting benzyl alcohol (BnOH-1-d_1) and the product dibenzyl ether were determined to be both ca. 90% (see the Supporting Information).[33]Because no ^{2}H "leaks" into the $^{1}H_2O$ byproduct of this dimerization, we see that proton hydride scrambling cannot be part of the mechanism and that H—D (if formed) cannot be cleaved. This is consistent with a ruthenium monohydride active catalyst,based on Bäckvall's studies of ruthenium-catalyzed transfer hydrogenation reactions.[32] The absence of H/D scramblingfurther indicates that theintermediate ruthenium hydride is derived solely from thealcohol's C–H bond, and not from the O–H. While it is not possible to measure the independent rates of oxidation of benzyl alcohol and *n*-hexylamine in each other's presence without observing coupling, we can measure these separately. We find that dimerization of benzyl alcohol is ca. 3.5-fold faster than dimerization of *n*-hexylamine, with reduction faster than oxidation. Only trace aldehyde or imine is observable in these reactions. These observations, combined with H/D exchange data,are consistent with rapid, reversible alcohol oxidation equilibrium that favors starting material, with imine siphoned off slowly.

To explain the selectivity for coupling of amines in the presence of anilines (Table 2, entries 8 – 11), we examined competitive imine formation to benzaldehyde between aniline and *n*-hexylamine. We observed that the imine formed from *n*-hexylimine (*N*-benzylidenehexylamine) is both the kinetic and thermodynamic imine product. Further, we find the k_{rel} for imine formation is ca. 7-fold faster for*n*-hexylamineversus aniline (see the Supporting Information). Thus, the selectivity for amine coupling is simply explained by selectivity of imine formation. Whereas we observe only a trace amount of the imine intermediate and no aldehyde intermediate in operando ^{13}C NMR studies of the coupling of **2**-1-d_1 and *n*-hexylamine, reduction of the imine to the alkylated amine is kinetically relevant in the catalytic cycle. Moreover, once the amine product is formed, its re-oxidation into an imine is slow: we know this because treatment of **2**-1-d_1 with di-*n*-hexylamine gives H/D exchange with a rate more than 10x slower than the corresponding coupling reaction (see the Supporting Information).

Based on the studies mentioned above, we propose a hydrogen borrowing mechanism wherein the pyridylphosphine ligand remains coordinated to ruthenium, the cymene is uncoordinated, both substrates—alcohol and amine—get easy access to the metal, and the catalytically active ruthenium species include a monohydride. This pathway is consistent with the outline in Scheme 1, except that it features unforeseen rapid reversibility of the hydride transfer events.We show this in a modified mechanism in Scheme 2. We perceive that it is simply selectivity in imine formation and excellent functional group tolerance of the catalyst that enable us to execute selective coupling reactions.

Scheme 2. Proposed Mechanism of Ruthenium 4.1.



In conclusion, the novel ruthenium(II) complex **1**is a good catalyst for dehydrative coupling of benzyl alcohols and amines. Its reactivity is noteworthy, because it is a rare example of a catalyst that works without solvent and additives and becauseit is compatible with unprotected phenols andanilines. It functions via the hydrogen borrowing mechanism. ^{13}C NMR studies under the neat reaction conditions support the proposed mechanism and indicate that product selectivity is governed by imine formation, although some mechanistic details remain uncertain.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/**.

Experimental procedures, graphical and tabular characterization information (PDF)

Crystallographic data for CCDC no. 1510912 (**1**) (CIF)

Crystallographic data for CCDC no. 1510913 (**1a**) (CIF)

Note: CCDC #1510912 (**1**) and #1510913 (**1a**) contain supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Notes

The authors declare no competing financial interests.

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28. To the best of our knowledge, there is one report wherein the catalyst for *N*-alkylation of amines with alcohols works without solvent, inorganic base, or additives (reference 8h); other papers report catalysts that function in neat conditions but require either an inorganic base (references 8j) or an additive (reference 8s and 9c).
29. For examples of *N*-alkylation in the presence of unprotected phenol or aniline, see references 8v and 18g. For examples of selective monoamination of 1,2-diols, see: a)Putra, A. E.; Oe, Y.; Ohta, T. *Eur. J. Org. Chem.***2013**, 6146-6151. b) Bähn, S.; Tillack, A.; Imm, S.; Mevius, K.; Michalik, D.; Hollmann, D.; Neubert, L.; Beller, M. *ChemSusChem***2009**, *2*, 551-557. For selective N-alkylation of sulfonamides, see: c) Lu, L.; Ma, J.; Qu, P.; Li, F. *Org. Lett.***2015**, *17*, 2350-2353.
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31. We confirmed the presence of di-*n*-hexylamine by spiking a solution of benzyl alcohol-1-d_1 and *n*-hexylamine with an authentic sample of di-*n*-hexylamine. The presence of the side products (Bn_2O, $(nHex)_2NH$, $Bn_2N(nHex)$,$BnN(nHex)_2$) were observed by GC-MS.
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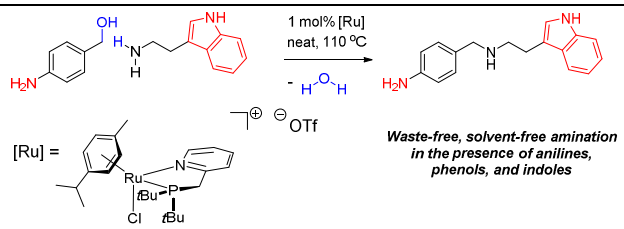
33. We performed the homocoupling of benzyl alcohol **2**-1-d_1 under neat conditions and determined that the deuterium content in the dibenzyl ether product and the remaining starting material were both ca. 90%. This indicates that the experiment in 1,2-dichlorobenzene-$d_4$solvent is a valid comparison to experiments performed neat.



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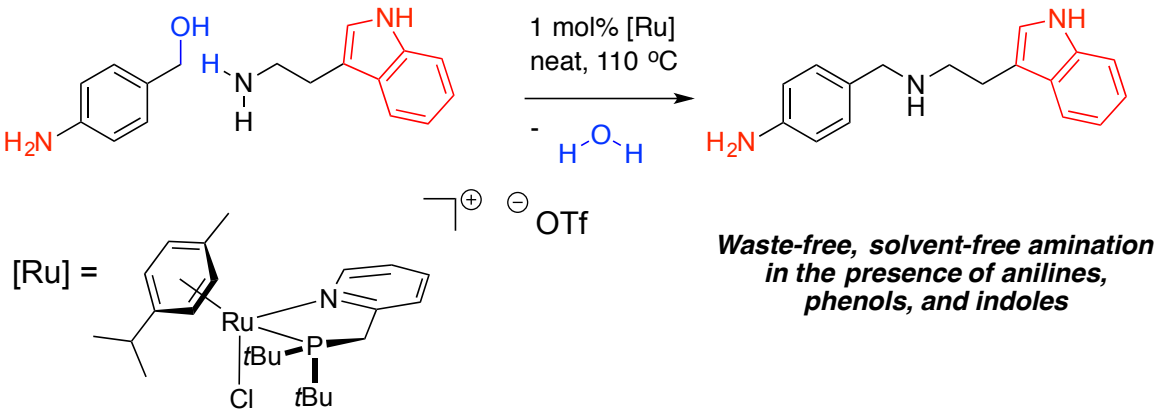

Waste-free, solvent-free amination in the presence of anilines, phenols, and indoles