Inorganic Chemistry
Article
Cite This: Inorg. Chem. XXXX, XXX, XXX-XXX
pubs.acs.org/IC

Highly Efficient Rh(I) Homo- and Heterogeneous Catalysts for C−N Couplings via Hydrogen Borrowing

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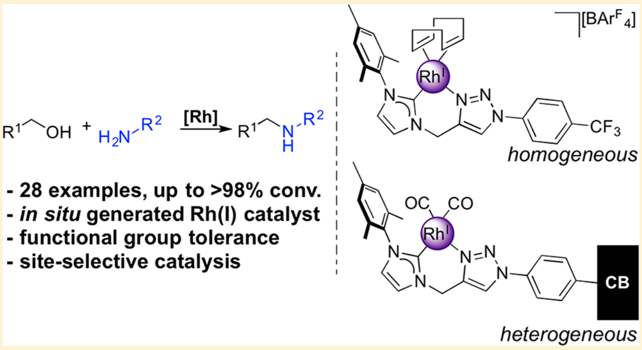
Supporting Information

ABSTRACT: Rhodium(I) complexes were explored as catalysts for the hydrogen borrowing reactions of amines and alcohols. Bidentate carbene-triazole ligands were readily synthesized via “click” reactions which allowed a diversity of ligand backbones to be accessed. The catalytic transformations are highly efficient, able to reach completion in under 6 h, and promote C−N bond formation across a range of primary alcohol and amine substrates. Moreover, site-selective catalysis can be achieved using substrates with more than one reactive site. A rhodium(I) complex covalently attached to a carbon black surface was also deployed in the hydrogen borrowing coupling reaction of aniline with benzyl alcohol. This represents the first report of a heterogeneous rhodium catalyst used for hydrogen borrowing.



INTRODUCTION

Alkylated amines are an important structural motif found in many bulk and fine chemicals.[1] Traditional synthetic routes to alkylated amines typically involve the use of potentially expensive and/or toxic reagents, the formation of stoichiometric amounts of waste, unwanted side reactions, and tedious workup procedures.[2] “Hydrogen borrowing” provides an alternate, sustainable synthetic pathway for directly reacting alcohols with amines to form new C−N bonds.[1,3] Homogeneously catalyzed bond formations via hydrogen borrowing have largely been achieved using ruthenium,[4] iridium,[5] and more recently manganese,[6] cobalt,[7] iron,[7b] and nickel[8] complexes. Despite $RhH(PPh_3)_4$ being first used over 35 years ago to catalyze a hydrogen borrowing C−N bond formation reaction,[9] rhodium has since received very little attention. The only other reports featuring rhodium salts as catalysts for hydrogen borrowing relied on either high temperature (200 °C)[10] or high catalyst loadings (5 mol %) in order to achieve short reaction times (8 h).[11]

Current progress in this field has delivered some iridium based catalyst systems that show high reactivity at low catalyst loadings (<0.5 mol %) or comparatively mild temperatures (≤70 °C), though these examples do require longer reaction times.[12] Hence, catalysts possessing greater catalytic activity, which work at lower temperatures and have shorter reaction times, are highly desirable. Furthermore, coupling excellent homogeneous catalytic activity with the ease of separation and recyclability offered by heterogeneous catalysis, “hybrid catalysis”,[13] has the potential to increase their industrial applicability.

Encouraged by the results using iridium complexes as hydrogen borrowing catalysts and the relatively scarce use of rhodium, we were curious to probe the catalytic ability of Rh(I) complexes as catalysts for the hydrogen borrowing reaction. To obtain a direct comparison, the rhodium complexes chosen are analogous to the iridium complexes recently investigated in our group.[14] Herein, we report a series of readily synthesized Rh(I)-carbene-triazole complexes (Scheme 1) that act as homogeneous catalysts with excellent activity and efficiency for C−N bond formation reactions.

These rhodium catalysts outperform the current best Rh(I) catalyst reported to date in the literature and are within the same ballpark as the analogous iridium catalyst[14] for coupling of benzyl alcohol with aniline via hydrogen borrowing.[10] A hybrid heterogeneous catalyst was generated by covalently attaching one of these Rh(I) complexes to a carbon black surface,[13,14] and its efficiency was demonstrated in the coupling of benzyl alcohol with aniline.

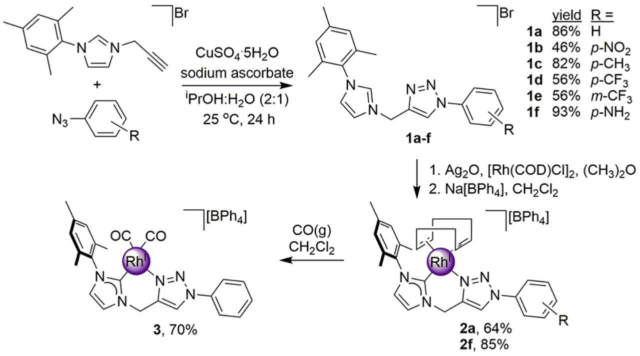
RESULTS AND DISCUSSION

Complex Synthesis. The ligand synthesis took full advantage of the modular nature of triazole formation via a Cu-catalyzed “click” reaction (Scheme 1).[15] Various aryl units were introduced, allowing rapid access to ligands, **1a−f**,

Received: October 9, 2017

DOI: 10.1021/acs.inorgchem.7b02586
Inorg. Chem. XXXX, XXX, XXX−XXX

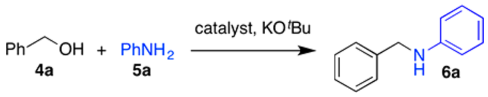
Scheme 1. Synthesis of Homogeneous Rh(I) Catalysts



possessing different electronic characteristics (H, NO_2, CH_3, *para*/*meta*-CF_3) with the triazole moiety used as a ligating site. A carbene unit was chosen as it provides a strong σ-donor, ensuring a strong rhodium–ligand bond which in turn results in a more stable catalyst.[16] The triazole moiety provides a second, weaker ligation site to accommodate the coordination requirements of the metal ion during the catalysis. A silver transmetalation route was used to prepare rhodium(I) catalyst **2a** with COD co-ligands from which **3** with CO co-ligands was prepared.

Initial Catalytic Studies. The catalyzed hydrogen borrowing reaction of benzyl alcohol (**4a**) with aniline (**5a**) to produce *N*-benzylaniline (**6a**) was chosen as a test reaction to allow direct comparison with reported catalysts.[14] Reaction progress using catalysts **2a** and **3** was assessed at 6 h, as was the effect of varying the catalyst loadings (Table 1). Catalysts **2a** and **3** performed well at loadings of 1.0 and 0.5 mol %; however, performance deteriorated at 0.1 mol % loading with just over 50% conversion obtained (TON > 500). Control experiments confirmed the superior performance of our organometallic catalysts to that of the Rh(I) precursors (Table 1, entries 7–9).

Table 1. Effect of Catalyst Loadings[a]



	catalyst	catalyst loading, mol %	% conv.[b]	TON
1	**2a**	1.0	99	99
2	**2a**	0.5	95	190
3	**2a**	0.1	55	550
4	**3**	1.0	99	99
5	**3**	0.5	86	172
6	**3**	0.1	53	530
7	$[Rh(COD)Cl]_2$	0.5	44	88
8	$[Rh(CO)_2Cl]_2$	0.5	50	100
9[c]	$[Rh(COD)Cl]_2$	0.5	47	94

[a] Reagents and conditions: benzyl alcohol **4a** (1.1 equiv), aniline **5a** (1.0 equiv), KO^{t}Bu (1.1 equiv), toluene-d_8, 100 °C, 6 h. [b] % conversions to **6a** were calculated using ^{1}H NMR spectral analysis of crude product mixture. [c] 1 mol % $Na[BAr^F_4]$ added.

During the initial catalysis investigation, we found that the $[BAr^F_4]^-$ anion analogue of **2a** could be generated *in situ* using $[Rh(COD)Cl]_2$ (0.5 mol %), ligand **1a** (1.0 mol %), and $Na[BAr^F_4]$ (1.0 mol %). Under the same hydrogen borrowing reaction conditions, *in situ* generated catalyst **7a** promoted 91% conversion of the substrates to **6a**, comparable to the conversion observed using isolated complex **2a**. With this simpler *in situ* protocol established, ligands **1a–e** were used to generate Rh(I) complexes **7a–e** (Figure 1b), and the efficiency of these catalysts was investigated for the same C–N bond formation reaction (Figure 1c). All *in situ* generated Rh(I) complexes gave good to excellent conversions of **4a** and **5a** to **6a**, with the *para*-CF_3 containing catalyst **7d** giving the highest conversion at 94% (93% isolated yield). The complex with the ligand which contains the electron-donating *para*-CH_3 substituent (**7c**) gave the lowest conversion at 80%, implying that an electron-rich environment around the metal center decreases catalytic efficiency.

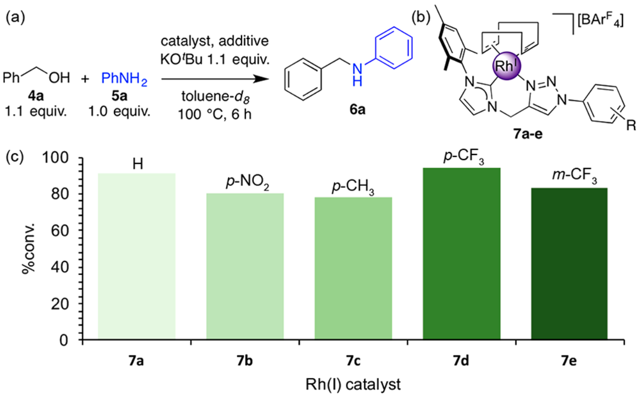
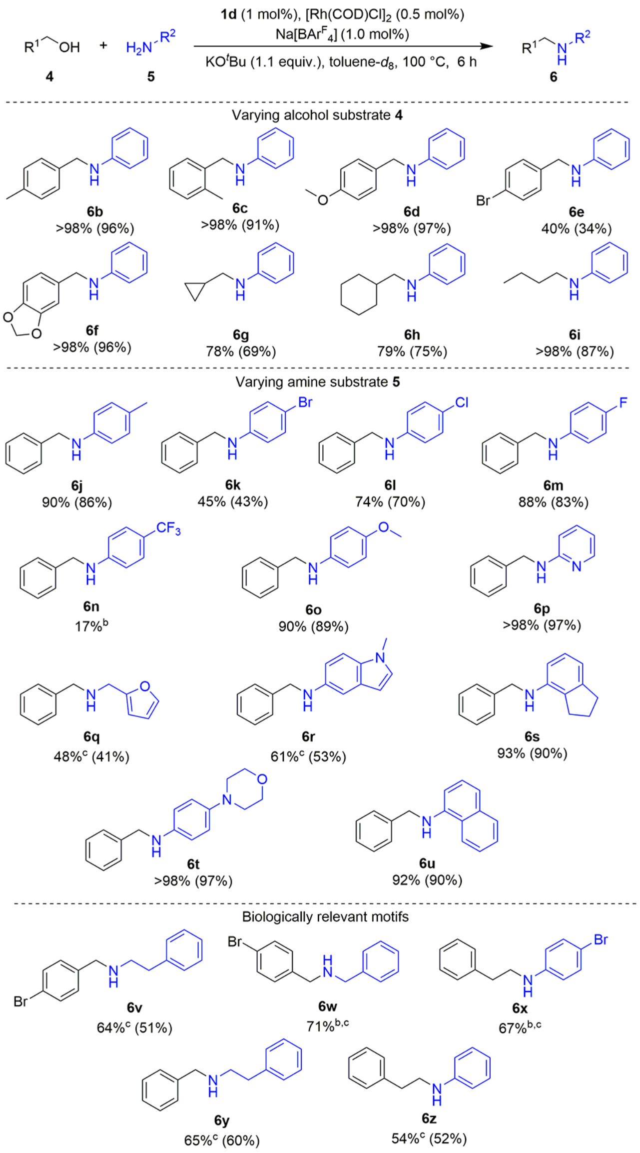


Figure 1. Catalyst screening results. (a) Hydrogen borrowing reaction of benzyl alcohol **4a** and aniline **5a**. (b) *In situ* formed catalysts **7a–e**. (c) Catalyst screening for hydrogen borrowing C–N bond formation. Reagents and conditions: benzyl alcohol **4a** (1.1 equiv), aniline **5a** (1.0 equiv), ligand **1a–e** (1 mol %), $[Rh(COD)Cl]_2$ (0.5 mol %), KO^{t}Bu (1.1 equiv), $Na[BAr^F_4]$ (1 mol %), toluene-d_8, 100 °C, 6 h.

Rh(I)-Catalyzed Hydrogen Borrowing Reaction Scope. *In situ* generated Rh(I) catalyst **7d** was tested in a series of reactions where either the alcohol (**4**) or the amine substrate (**5**) was varied (Scheme 2). All *in situ* catalyzed reactions of aniline (**5a**) with alcohol functionalized substrates containing electron-donating substituents or an aliphatic chain yielded >98% conversions (products **6b–d**, **6f**, and **6i**) after 6 h at 100 °C. Slightly lower yields were obtained upon using cyclic aliphatic alcohols as substrates (**6g**, **6h**). The catalytic conversion of 4-bromobenzyl alcohol (**4e**) and aniline (**5a**) to form **6e**, led to substantially lower conversion (40%), due to side reactions occurring, including dehalogenation. Significantly, some reactions also proceeded at a lower temperature of 60 °C for 24 h. The reaction of piperonyl alcohol with aniline (**5a**) at 60 °C achieved an identical conversion (>98%) to **6f** as achieved at 100 °C, whereas the reaction of 2-methylbenzyl alcohol and aniline at 60 °C resulted in 73% conversion to product **6c**. Secondary alcohols (such as 1-phenylethane-1-ol) did not react under any of the reaction conditions used in this study.

Various amine substrates were then tested. The reaction proved tolerant of most tested substituents on aniline (*p*-halogen, *p*-OCH_3, *p*-CH_3, 1-naphthyl, 4-morpholino), 5-amino-*N*-methylindole, and furfurylamine with high conversions (>90%) in most cases (Scheme 2). Upon using the highly electron-withdrawing *p*-CF_3 (**6n**), only 17% conversion was seen. Interestingly, when comparing the three *para*-halogenated aniline containing reactions (**6k–m**), the more electron-withdrawing *para*-substituent led to better conversion (*F* >

Scheme 2. Scope of the Reaction Using the *in Situ* Generated Catalyst 7d[a]



[a] Substrate ratio **4**:**5** 1.1:1. % conversions were calculated using ^{1}H NMR spectral analysis of crude product mixture. Isolated yields are given in parentheses. [b] Product isolation was not attempted. [c] 24 h.

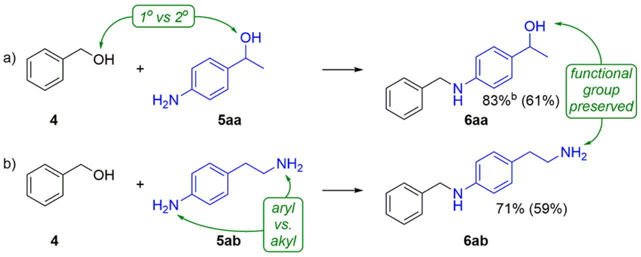
Cl > Br). This is likely due to the weaker C−Cl and C−Br bonds allowing for unwanted side reactions to occur, rather than the electron-withdrawing properties of the *para*-group.[17] Indeed, the ^{1}H NMR spectra of these reactions reveal the formation of dehalogenated species (cf. **6e**). Interestingly, this trend was not observed upon using the analogous iridium(III) catalyst reported by us recently.[14]

In situ prepared Rh(I) complex **7d** was shown to be efficient for promoting the reaction of benzyl alcohol with 2-aminopyridine, with complete conversion (>98%) to product **6p** (Scheme 2). This is a challenging reaction as both the substrate and the formed product could feasibly coordinate to the metal center and inhibit the catalyst. The formation of **6p** has been reported previously using rhodium-based catalysts, but at lower yields (67−85%) and at longer reaction times (12−20 h) with higher temperatures required (120−150 °C).[11]

We also determined the efficiency of the catalysts for the synthesis of some selected biologically significant molecules containing a 2-phenethylamine core. These motifs (Scheme 2, **6v**−**z**) are often found in pharmaceuticals such as anti-obesity medication.[18] Rh(I) complex **7d** catalyzed the formation of products containing these biologically relevant motifs (**6v**−**z**) in moderate to good conversions (54−71%) after 24 h at 100 °C. The efficiency of the analogous iridium complexes[14] for the synthesis of these same biologically active species was also tested here in order to broaden our understanding of the differences between the rhodium and iridium systems. Interestingly, in all cases, under the same reaction conditions, no conversion was obtained when using the iridium(III) complex as the catalyst (Supporting Information S1.4). Thus, rhodium provides an enhanced catalyst relative to the iridium analogue for hydrogen borrowing using these particular substrates (**6v**−**z**).

Site-Selective Hydrogen Borrowing Catalysis. The significantly different reactivity of the catalyst **7d** toward some substrates (i.e., primary vs secondary alcohols, and the ethyl-linker containing amines/alcohols) allowed us to probe this rhodium catalyst as a site-selective hydrogen borrowing catalyst. This is a useful ability, as it allows for one reactive site to be functionalized while leaving the other one untouched. The substrates chosen were 1-(4-aminophenyl)ethan-1-ol (**5aa**) and 4-(2-aminoethyl)aniline (**5ab**), which were both reacted with benzyl alcohol (**4**) (Scheme 3).

Scheme 3. Selectivity Studies Using Reagents with Different Amine/Alcohol Groups[a]



[a] Conditions: [Rh(COD)Cl]$_2$ (0.5 mol %), **1d** (1.0 mol %), Na[BAr$^{F}_{4}$] (1.0 mol %), KO^{t}Bu (1.1 equiv), toluene-d_8, 100 °C, 6 h. (a) **4a**:**5aa** ratio = 1:1. (b) **4a**:**5ab** ratio = 1:1. % conversions were calculated using ^{1}H NMR spectral analysis of crude product mixture. Isolated yields are given in parentheses. [b] 2.1 equiv of KO^{t}Bu was used.

To gain from the inactivity toward the secondary alcohols, the hydrogen borrowing reaction was conducted using substrates **4a** and **5aa**. As postulated, this allowed for the selective reaction of the amine with benzyl alcohol (83% conversion), while no reactivity toward the secondary alcohol was observed (Scheme 3a). In order to obtain high conversion to **6aa**, an extra equivalent of potassium *tert*-butoxide was used. The standard conditions (1.1 equiv of KO^{t}Bu) resulted in only 34% conversion, indicating that, although no hydrogen borrowing transformation is observed with secondary alcohols, a reaction with the base is still occurring. Another selectivity reaction was designed to allow for discrimination between the aryl and alkyl primary amines. Upon comparing the formation of **6a** and **6y**, it is clear that a longer aliphatic chain between the amine group and the aromatic ring leads to lower yields (96% conversion after 6 h vs 64% conversion after 24 h, respectively). To compare the reactivity with both amine groups simulta-

DOI: 10.1021/acs.inorgchem.7b02586
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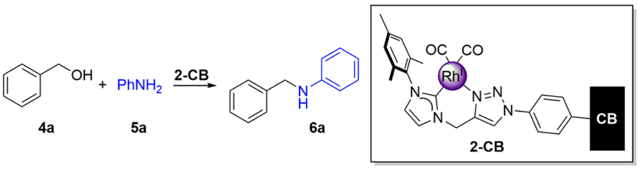
neously, a hydrogen borrowing reaction was carried out using substrates **4a** and **5ab** (Scheme 3b). After 6 h at 100 °C, the reaction led to the selective formation of **6ab** as the main product.

Heterogeneous Catalysis. In recent years, we have seen substantial enhancement in catalyst turnover numbers upon grafting the organometallic complexes to carbon surfaces.[13,14,19] In addition, the use of a solid support allows for the recovery of the catalyst, and in particular, the use of a covalent C−C bond as a connection to the surface results in a stable system that can handle basic conditions and relatively high temperatures. Through an established diazonium route,[13,14] the rhodium complex was covalently attached to carbon black, forming catalyst **2-CB** (Scheme 4, inset). The Rh(I) hybrid complex **2-CB** was tested as a catalyst for the hydrogen borrowing reaction of benzyl alcohol (**4a**) with aniline (**5a**) (Scheme 4). The Rh(I) hybrid catalyst **2-CB** at a loading of 0.05 mol % gave a moderate 53% conversion to *N*-benzylaniline (**6a**) after 24 h at 100 °C, which corresponded to a TON of 977. While homogeneous Rh(I) complex **2a** reached a higher 86% conversion in a shorter reaction time (6 h), the heterogeneous reactions achieved a 5 times larger turnover number due to the lower catalyst loading. Hybrid catalyst **2-CB** was significantly more efficient than the hybrid Ir(III) complex on silica reported by Wang et al. for the reaction of benzyl alcohol (**4a**) and aniline (**5a**), with a turnover number 16 times larger achieved in a shorter reaction time.[20] Our turnover number was lower compared to the 46 000 obtained by Seayad using a hybrid Pd on silica after 72 h.[21] The direct comparison to the analogous iridium complex[14] revealed that, although under homogeneous conditions similar catalytic conversions were obtained for both iridium and rhodium, the use of iridium leads to a more active hybrid catalyst reaching to a TON of >4000. Both of the hybrid catalysis results were obtained using significantly lower catalyst loadings than in the case of **2-CB**.

Scheme 4. Hydrogen Borrowing Catalysis Using the Carbon Surface-Bound Rhodium Catalyst 2-CB[a]



[a]Conditions: **2-CB** (0.05 mol %), KO^{t}Bu (1.1 equiv), toluene-d_8, 100 °C, 24 h. Substrate ratio: **4a**:**5a** 1.1:1.

2-CB has previously been shown to be a highly stable heterogeneous catalyst, with only limited leaching of Rh, attributed to loss of Rh physisorbed on the surface and not from the covalently attached catalyst.[13,14] Upon using **2-CB** as a catalyst for a hydrosilylation reaction, no appreciable loss of reactivity of the catalyst was observed over several reaction cycles.[13] In addition, the iridium analogue of **2-CB** was recently reported as a recyclable hydrogen borrowing catalyst under the same reaction conditions as reported here.[14] On the basis of these data, any leaching of the rhodium complex from **2-CB** is highly unlikely.

■ CONCLUSION

In summary, we have developed a bidentate ligand containing a triazole and carbene coordination motif that, when coordinated to Rh(I), generates catalysts that surpass the best rhodium(I) catalyst reported to-date for the direct coupling of benzyl alcohol with aniline via a hydrogen borrowing reaction. In the case of some of the more demanding substrates, the rhodium catalyst **7d** outperformed its iridium(III) analogue. In addition, high selectivity toward one product was obtained upon using reagents with two reactive sites. Significantly, we demonstrated that the catalysts could be formed *in situ*, greatly simplifying the catalysis reaction. A heterogeneous catalyst composed of a Rh(I) complex covalently attached to carbon black was deployed as a catalyst for the reaction of benzyl alcohol with aniline, achieving a TON of 977.

■ EXPERIMENTAL SECTION

Catalysis Procedure Using Isolated Rh(I) Complexes 2a and 3a. All preparations of catalysis mixtures were performed in air. The Rh(I) complexes **2a**−**3a** (0.0005 mmol, 0.1 mol %, 0.0025 mmol, 0.5 mol %, or 0.005 mmol, 1.0 mol %), aniline (**5a**) (0.5 mmol), benzyl alcohol (**4a**) (0.55 mmol), and KO^{t}Bu (0.55 mmol) were weighed into a 4 mL glass vial fitted with a close-top melamine cap with PTFE liner. Toluene-d_8 (400 mg) was then added to the mixture. The headspace was then purged with nitrogen, and the vial sealed. The reaction mixture was stirred at room temperature for 5 min until a homogeneous mixture is observed. The reaction mixture was then placed in an oil bath at either 100 or 60 °C. After 6 or 24 h, respectively, the reaction mixture was taken out of the oil bath and immediately cooled in the fridge. Subsequently, an NMR sample was prepared by taking an aliquot of the mixture and dissolving it in either toluene-d_8 or chloroform-d_1.

Catalysis Procedure Using *in Situ* Generated Rh(I) Catalysts to Form Products 6a−6u. The *in situ* Rh(I) complexes **7a**−**e** were generated using the ligands (**1a**−**e**) (0.005 mmol, 1.0 mol %), $[Rh(COD)Cl]_2$ (0.0025 mmol, 0.5 mol %), and $Na[BAr^F_4]$ (0.005 mmol, 1.0 mol %). The catalytic reactions using these catalysts were prepared and analyzed following the same procedure as in the case of isolated Rh(I) catalysis (6 h) with amine substrates (**5a**−**u**) (0.5 mmol), alcohol substrate (**4a**−**i**) (0.55 mmol), and KO^{t}Bu (0.55 mmol) in toluene-d_8 (400 mg). The reaction mixture was filtered to remove base, and the conversion calculated by ^{1}H NMR using comparison of substrate and product peaks. Products were isolated by column chromatography using ethyl acetate/*n*-hexane as eluent.

Catalysis Procedure Using *in Situ* Formed Rh(I) Catalysts to Form Products 6v−6z and 6aa−6ab. The *in situ* Rh(I) complexes **7a**−**e** were generated using the ligands (**1a**−**e**) (0.0025 mmol, 5.0 mol %), $[Rh(COD)Cl]_2$ (0.0125 mmol, 2.5 mol %), and $Na[BAr^F_4]$ (0.0025 mmol, 5.0 mol %). The catalytic reactions using these catalysts were prepared and analyzed following the same procedure as in the case of isolated Rh(I) catalysis (24 h) with relevant substrates (amine 0.55 mmol, alcohol 0.55 mmol), and KO^{t}Bu (0.55 mmol) in toluene-d_8 (400 mg). The reaction mixture was filtered to remove base, and the conversion calculated by ^{1}H NMR using comparison of substrate and product peaks. Products were isolated by column chromatography using ethyl acetate/*n*-hexane as eluent.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorgchem.7b02586.

Experimental methods and data, and catalysis procedures (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from Macquarie University, University of New South Wales, and the Australian Research Council is gratefully acknowledged. This research was supported under the Australian Research Council's Discovery Projects funding scheme (project number DP130101838). We are grateful to the NMR facilities at the Mark Wainwright Analytical Centre, UNSW, and Macquarie University. We are grateful to the Cabot Corporation for the donation of the carbon black (Vulcan XC-72R). C.M.W. thanks the Australian Government for the award of an International Postgraduate Research Scholarship (IPRS). M.B.P. thanks the Australian Government for the Australian Government Research Training Program Scholarship (AGRTPS).

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