A Journal of the Gesellschaft Deutscher Chemiker
Angewandte Chemie
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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201708800
Angew. Chem. 10.1002/ange.201708800

Link to VoR: http://dx.doi.org/10.1002/anie.201708800
http://dx.doi.org/10.1002/ange.201708800

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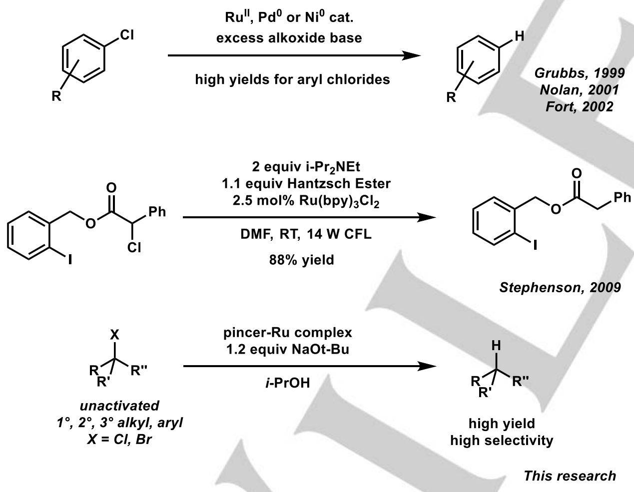
10.1002/anie.201708800

Catalytic Reduction of Alkyl and Aryl Bromides Using Isopropanol

Michael C. Haibach[a], Brian M. Stoltz,[a] and Robert H. Grubbs*[a]

Abstract: Milstein's complex (PNN)RuHCl(CO) catalyzes the efficient reduction of aryl and alkyl halides under relatively mild conditions, using isopropanol and a base. Sterically hindered tertiary and neopentyl substrates are reduced efficiently, as well as more functionalized aryl and alkyl bromides. The reduction process is proposed to occur via radical abstraction/hydrodehalogenation steps at ruthenium. Our research represents a safer and more sustainable alternative to typical silane, lithium aluminium hydride, and tin-based conditions for these reductions.

The reduction of carbonyl and carboxyl groups to the corresponding alkyl groups is an important process in the construction of saturated hydrocarbon frameworks, particularly those bearing all-carbon quaternary centers.[1] The final step in this sequence often requires the reduction of an alkyl halide or alkyl sulfonate ester. Alkyl halides are traditionally reduced with reactive metal hydrides such as $LiAlH_4$ or under ionic and radical conditions using silanes, hydroiodic acid/phosphorus (HI-P), or Bu_3SnH/AIBN.[2a-b] Each of these reagents presents a significant challenge: $LiAlH_4$ is pyrophoric and challenging to handle on a large scale, some silanes can generate explosive SiH_4 via disproportionation, HI-P is strictly controlled due to its use in illicit methamphetamine synthesis, and Bu_3SnH is both toxic and difficult to remove from lipophilic products.[2c-d] Recent developments in transfer hydrogenation catalysis have led to safer conditions for the reduction of esters[3] and ketones[4], and we wondered whether the same advance could be achieved for alkyl halides.



Scheme 1. Recent approaches to transfer dehalogenation.

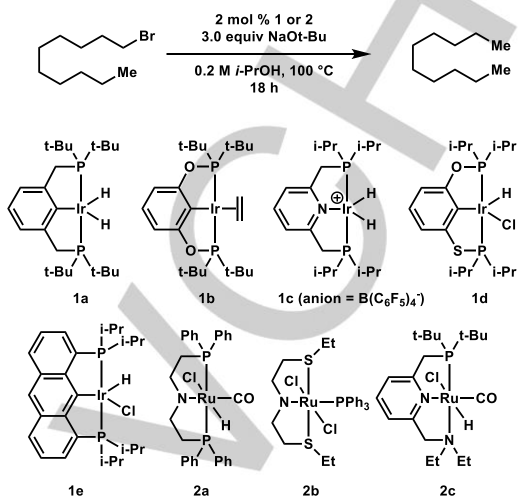


Table 1. Optimization of the reduction of 1-bromodecane

Entry[a]	Catalyst	% conv. to n-decane[b]	Temp.
1	none	0%[c]	100°C
2	1a	49	100°C
3	1b	61	100°C
4	1c	18	100°C
5	1d	51	100°C
6	1e	27	100°C
7	2a	44	100°C
8	2b	33	100°C
9[d,e]	2c	97 (93)	100°C
10[d,f]	2c	87	100°C
11[g]	2c	91	50°C
12	2c	91	50°C

[a] Reactions carried out in a sealed vial under N_2 on a 0.1 mmol scale. [b] Conversions into *n*-decane measured using GC/authentic samples/internal standards after 18 h reaction time. Isolated yield in parentheses. [c] 9% conversion to a mixture of decenes. [d] 1.0 mmol scale [e] 1 mol % 2c, 1.2 equiv NaO*t*-Bu [f] 0.4 mol % 2c, 1.2 equiv NaO*t*-Bu [g] 1.2 equiv Cs_2CO_3

Grubbs, Nolan, and Fort have independently reported transition-metal catalyzed reduction of aryl halides using metal alkoxides/alcohols as bases and hydrogen donors.[5] (Scheme 1) Alternatively, Stephenson and coworkers have reported an efficient photoredox approach to alkyl halide reduction, using *i*-Pr_2NEt/HCOOH or *i*-Pr_2NEt/Hantzsch ester as the co-reductant.[6] Their system is highly functional-group tolerant and applies to "activated" alkyl halides (benzylic or α-carbonyl). To the best of our knowledge, there is no general catalytic transfer

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reduction of alkyl halides, especially for unactivated or hindered substrates.[7] In this paper we report an efficient catalyst system for the reduction of both aryl and unactivated alkyl halides using *i*-PrOH as the hydrogen source.[8-9]

Pincer complexes of Ir and Ru are among the most effective catalysts for alcohol dehydrogenation.[10] Iridium pincers, such as those of the type (PCP)Ir and (PNP)Ir, undergo net oxidative addition of various aryl and alkyl halides.[11] We thus envisioned combining these steps into a catalytic cycle for transfer halide reduction using *i*-PrOH and a base. We began by examining the reaction of 1-bromodecane (**3a**) with 3.0 equivalents of NaO*t*-Bu in *i*-PrOH in the presence of a catalytic amount of various readily available pincer-Ir and Ru complexes shown in Table 1. Milstein's catalyst precursor **2c**[12a] generated *n*-decane in near quantitative yield. Iridium pincers **1a-e** and ruthenium pincers **2a-b** afforded low to moderate conversion after 18 hours at 100 °C. No obvious relationship between conversion and reported catalyst activity for dehydrogenation or steric hindrance existed.[13]

Using **2c**, we were also able to decrease the amount of NaO*t*-Bu to 1.2 equivalents and the catalyst loading to 1 mol % without affecting the yield.[14] Notably, we detected no decene or *n*-decyl isopropyl ether in the reactions using **1** or **2**. As a control experiment, only limited conversion into decenes was observed in the absence of a pincer catalyst, suggesting that these alternative reaction pathways are slow under our conditions (Entry 1). In all catalytic reactions, the formation of acetone and *t*-BuOH was observed.[15]

The standard conditions were applied to a several unactivated alkyl bromides and chlorides, using 1 mol % of **2c** as shown in Figure 1. High conversions and good to excellent yields were obtained after 18 hours. Chlorodecane **3b** exhibited decreased reactivity, and conversion stalled at <50%. Addition of excess LiBr allowed the reaction to proceed to full conversion. The phenethyl chloride **3c** reacted efficiently to afford the reduced product in excellent yield without modification. The tertiary bromide **3d** and neopentyl bromide **3h**, challenging substrates for C–X bond reduction, both afforded the corresponding reduction products in high yield. Significantly, no rearrangement of the neopentyl bromide was detected. Hindered neophyl bromide **3f** also reacted readily, and we observed the formation of both *tert*- and *iso*-butylbenzene by GC. The phenyl group of **3f** is well-known to migrate under both radical conditions.[16] Decyl tosylate **3k** afforded no *n*-decane when subjected to the reaction conditions. The high reactivity of hindered alkyl bromides, the rearrangement of **3f**, and the divergent reactivity of tosylate **3k** are all consistent with a C–X bond activation via a radical mechanism.[17]

We also evaluated more functionalized substrates to probe the chemoselectivity of our process. The reaction tolerated the presence of ether, CF_3, pyridyl and ester groups in the aryl substrates **3l**-**p**. The methyl ester in **3p** was not reduced[18], though it did undergo full transesterification. These examples demonstrate improved chemoselectivity compared to $LiAlH_4$ and other reactive metal hydride reagents. The sterically hindered mesityl bromide **3j** could also be reduced in high yield using 2 mol % **2c** after 48 h.

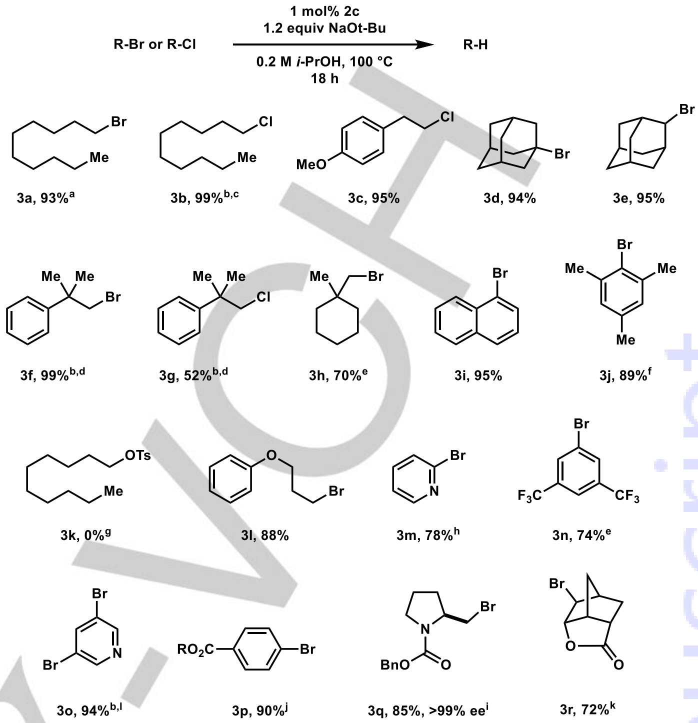
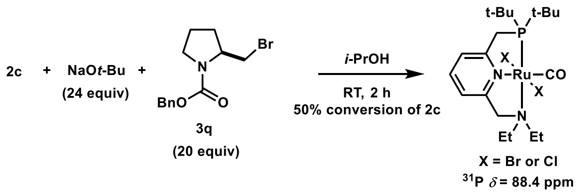


Figure 1. Scope of the reduction using isopropanol

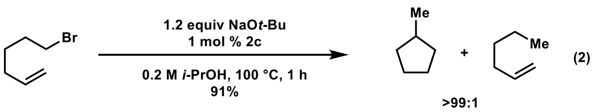
a) All reactions were carried out on a 1.00 mmol scale in a sealed vial under N_2, and reached >95% conversion according to GC. Percentages are isolated yields of reduction product unless otherwise noted. b) Yield determined using GC c) with 10 equiv LiBr d) 1.8:1 ratio of *t*-BuPh:*i*-BuPh observed by GC e) Reduced isolated yield due to volatile product f) 2 mol % **2c**, 48 h reaction time g) Formation of *i*-PrO-*n*-Dec observed by GC h) 1 h reaction time i) Reaction carried out at 23 °C for 24 h j) Reduction of **3p** (R = Me) afforded PhO*i*-Pr k) 1.0 equiv NaO*t*-Bu, 23 °C, 24 h l) 2.4 equiv NaO*t*-Bu, pyridine observed as the exclusive product.

One common application of the Bu_3SnH/AIBN system has been the reduction of nonracemic aminoalkyl halides, affording valuable protected chiral amines from the corresponding amino acids.[19] The reduction of **3q** proceeds in high yield after 24 h at room temperature, with no loss of optical purity. The yield and stereoretention compare well to the literature preparation using Bu_3SnH/AIBN, and a shorter reaction time is required (24 h at 23 °C vs 72 h at 80 °C).[20] The sensitive bicyclic bromolactone **3r** was also reduced selectively at ambient temperature without any ring-opening observed.

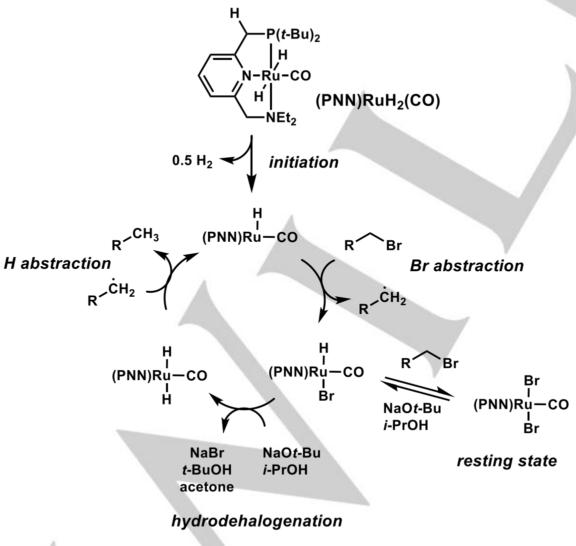


(1)

The phosphorus atom in **2c** provides a convenient spectroscopic handle for determining catalyst speciation during the reaction. The reduction of **3q** was monitored under the conditions shown in Equation 1, using unlocked ^{31}P NMR. After 2 h reaction time, we observed **2c** and a new species with δ = 88.4 ppm in approximately a 1:1 ratio.[21] This new species resonates significantly upfield of the known hydride complexes derived from **2c**.[22] It falls much closer to the reported values of (PNN)$RuCl_2$(CO), δ = 91.4 and [(PNN)$RuCl_2$]$_2$(μ-N_2), δ = 87.8.[23] Thus it seems likely that both complexes of the type (PNN)RuHX(CO) and (PNN)RuX_2(CO) are the catalyst resting state.



As noted earlier, several reactivity trends point to a radical mechanism for the C–X bond reduction step. To probe this hypothesis, we subjected 5-bromohex-1-ene to our optimized conditions (Equation 2). The reaction proceeded efficiently to generate methylcyclopentane with >99:1 selectivity, implying the intermediacy of the 5-hexenyl radical.[24] Alternatively, the reaction could proceed via insertion of the olefin into a Ru–C bond, however this insertion would be expected to be slow.[25] Our proposed radical mechanism[26-27] is shown in Scheme 2. Initiation likely occurs via homolysis of the benzylic C–H bonds in (PNN)RuH_2(CO), ultimately generating H_2 and a putative 15e$^-$ species, (PNN)RuH(CO). This reactive species could abstract a bromine atom from the organic substrate, generating the corresponding alkyl radical and (PNN)RuHBr(CO). (PNN)RuHBr(CO) can undergo facile hydrodehalogenation by *i*-PrO$^-$ to form (PNN)RuH_2(CO), which in turn serves as an H atom donor towards the organic radical. Thus the observed reduced organic product and the active intermediate (PNN)RuH(CO) are regenerated. Entering the same reaction pathway starting from (PNN)RuHBr(CO) would generate (PNN)$RuBr_2$(CO), the observed catalyst resting state. Due to metal-ligand cooperation[23], this intermediate can also re-enter the main cycle via the reaction with *i*-PrO$^-$.



Scheme 2. Proposed mechanism.

In summary, we have developed a catalyst system for the efficient transfer reduction of a range of unactivated and functionalized alkyl and aryl halides, which requires only the relatively inexpensive and safe stoichiometric reagents NaO*t*-Bu and *i*-PrOH. Reaction setup and workup is simple. While many iridium and ruthenium pincer complexes show catalytic activity, Milstein's complex **2c** was key to obtaining high yields. The reaction appears to proceed via a radical mechanism. Our conditions offer a greener alternative for several types of stoichiometric $LiAlH_4$ or Bu_3SnH-mediated reductions. Future studies will be directed the reaction mechanism and catalyst design.

Acknowledgements

We acknowledge funding from King Fahd University of Petroleum and Minerals. M.C.H. acknowledges funding from the Resnick Sustainablility Instute in the form of a postdoctral fellowship.

Keywords: halogens • hydrogen transfer • green chemistry • hydrides • hydrocarbons

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[12] a) J. Zhang, G. Leitus, Y. Ben-David, D. Milstein, *J. Am. Chem. Soc.* **2005,** *127*, 10840-10841.; b) Iridium complexes **1a-e** were prepared according to the literature, while Ru complexes **2a-c** were purchased from commercial sources. See the supporting information for details. Milstein has proposed that the NEt_2 group in **2c** is hemilabile, which may be important for our reaction. See ref. 10b for details.

[13] See the supporting information for a comparison of the kinetic profiles of **1b** and **2c**. No induction period was observed.

[14] Other bases were briefly investigated: Na_2HPO_4, $NaHCO_3$, K_2CO_3 and NaOAc all afforded poor conversion or byproducts. Cs_2CO_3, KO*t*-Bu and NaO*t*-Bu were found to be equally effective for the reduction of **3a**. NaO*t*-Bu was chosen due to its lower cost per mole and lower toxicity than Cs_2CO_3. See the supporting information for example reductions using Cs_2CO_3.

[15] Self-condensation of the acetone byproduct does not seem to be an issue. In the reduction of **3a**, <1% mesityl oxide was detected by GC. Isophorone and diacetone alcohol were not detected.

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[17] While single electron chemistry has not been previously observed with complex **2c**, many stoichiometric reductions of alkyl halides with transition metals are known to proceed via radicals. See ref. 2a for details.

[18] **2c** is catalytically active for ester hydrogenation under basic conditions (Ref. 3a), however *i*-PrOH is apparently less effective as a hydrogen source for this transformation. See: A. Dubey, E. Khaskin, *ACS Catal.* **2016**, *6*, 3998-4002.

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[22] For example, δ (PNN)RuH_2(CO) = 124.9 ppm (C_6D_6), (PNN*)RuH(CO) = 94.7 ppm (C_6D_6), see ref. 12. δ (PNN)RuHCl(CO) = 107.1 ppm (*i*-PrOH), our measurement.

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[26] Our reaction may also be represented via electron injection, where e^- takes the place of (PNN)RuH(CO). See A. Studer, D. Curran. *Nature Chemistry*, **2014**, *6*, 765-773.

[27] For a recently proposed radical mechanism for the reduction of aryl halides, see T. Hokamp, A. Dewanji, M. Lübbesmeyer, C. Mück-Lichtenfeld, E.-U. Würthwein, A. Studer. *Angew. Chem. Int. Ed.* **2017**, *56*, 1-5.

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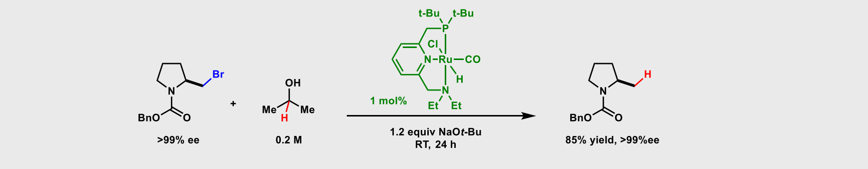

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Catalytic Reduction of Alkyl and Aryl Bromides Using Isopropanol

Milstein's complex (PNN)RuHCl(CO) catalyzes the efficient reduction of alkyl bromides and chlorides under relatively mild conditions, using isopropanol and a base. Sterically hindered tertiary and neopentyl substrates are reduced efficiently, as well as more functionalized aryl and alkyl bromides. The reaction appears to occur via a radical pathway, and provides an alternative to silane, lithium aluminium hydride, and tin-based reductions.