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A Catalytic Application of Co/Zr Heterobimetallic Complexes: Kumada Coupling of Unactivated Alkyl Halides with Alkyl Grignard Reagents

Wen Zhou,[a] Jonathan Wesley Napoline,[a] and Christine M. Thomas*[a]

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Tris(phosphanylamide) early/late heterobimetallic Zr/Co complexes, $ClZr(R'NPR_2)_3CoI$ [R′ = *i*Pr, R = Ph (**1**), R′ = 2,4,6-trimethylphenyl, R = *i*Pr (**2**), R′ = R = *i*Pr (**3**)], have been utilized as catalysts for the cross-coupling of alkyl halides with *n*-octylmagnesium bromide. While yields are consistently higher for alkyl bromide substrates, it is found that these unusual heterobimetallic complexes are also active towards more challenging alkyl chloride substrates. This is particularly interesting in light of the fact that monometallic cobalt complexes are inert towards these substrates, suggesting that Zr also plays a role in catalysis. Radical trapping studies suggest that a one-electron transfer radical oxidative addition pathway is operative.

Introduction

Cross-coupling reactions to form carbon–carbon bonds have become one of the most common catalytic processes in organic synthesis.[1] Many such reactions have found large scale applications,[2–4] and transition metal-catalyzed cross couplings have also been used for key steps in the total synthesis of a number of natural products.[5] While the palladium catalyzed cross-coupling reactions of aryl and vinyl halides have become ubiquitous methods, this chemistry has only recently been extended to *alkyl* halides and transformations of this type are far from becoming widely applicable.[6] Recently, researchers have begun focusing on first row transition metal catalysts to access cross-coupling reactions with alkyl halide substrates.[7–12] The resistance of first row transition metal complexes to β-hydride elimination, combined with their availability and low cost, renders these complexes sustainable targets for cross-coupling applications. Researchers have recently demonstrated that, with the appropriate reaction conditions, cobalt complexes can be utilized as catalysts for the formation of C–C bonds from organic halides and Grignard reagents – a reaction known as Kumada–Corriu–Tamao, or simply Kumada coupling.[13–17] While cobalt catalysts, including those as simple as $CoCl_2$ + LiI + TMEDA, that function adequately for the coupling of alkyl bromides or iodides with Grignard reagents have been reported, the widespread utility of this reaction has not been extended to more readily available alkyl chlorides.

We previously reported the synthesis and characterization of a family of Zr/Co heterobimetallic complexes linked by three phosphanylamide ligands, $ClZr(R'NPR_2)_3CoI$ (**1**: R′ = *i*Pr, R = Ph; **2**: R′ = 2,4,6-trimethylphenyl, R = *i*Pr; **3**: R′ = R = *i*Pr), as shown in Scheme 1.[18] It was found that the dative Co→Zr interactions in these complexes facilitated two electron reduction at potentials ca. 1 V more positive than observed for an analogous monometallic cobalt complex, $ICo(Ph_2PNH\textit{i}Pr)_3$ (**4**).[18] Upon chemical reduction, highly reduced Zr/Co species, such as $(THF)Zr(MesNP\textit{i}Pr_2)_3Co\text{-}N_2$ (**5**), featuring metal-metal multiple bonds and weakly coordinating apical ligands are generated.[19] These species are highly reactive towards oxidative addition of small molecule substrates, including alkyl halides such as methyl iodide, cyclohexyl chloride, and 2-iodopropane to generate species such as $(\eta^2\text{-}MesNP\textit{i}Pr_2)Zr(MesNP\textit{i}Pr_2)_2(\mu\text{-}CH_3)CoI$ (**6**) and $\{\eta^2\text{-}P\textit{i}Pr_2N[C_6(CH_3)_2H_2(CH_2)]\}Zr(MesNP\textit{i}Pr_2)_2CoI$ (**7**).[20] Since alkyl halide activation is an important step in carbon-carbon bond-forming reactions, we have chosen to examine the catalytic performance of Zr/Co early/late heterobimetallic complexes in the cross-coupling reactions of alkyl halides with alkyl Grignard reagents (Kumada coupling). Herein we discuss the remarkable catalytic activity of these Zr/Co complexes compared to monometallic Co species, including activity towards alkyl chlorides.

Results and Discussion

Heterobimetallic complexes **1**–**3** were screened as catalysts for the Kumada coupling of alkyl halides with *n*-octylmagnesium bromide. Optimization of reaction conditions (see Supporting Information) suggested that catalytic performance was better in THF than in Et_2O and the optimal

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[a] Department of Chemistry, Brandeis University,
415 South Street, Waltham, MA 02451, USA
Fax: +1-781-736-2516
E-mail: thomasc@brandeis.edu

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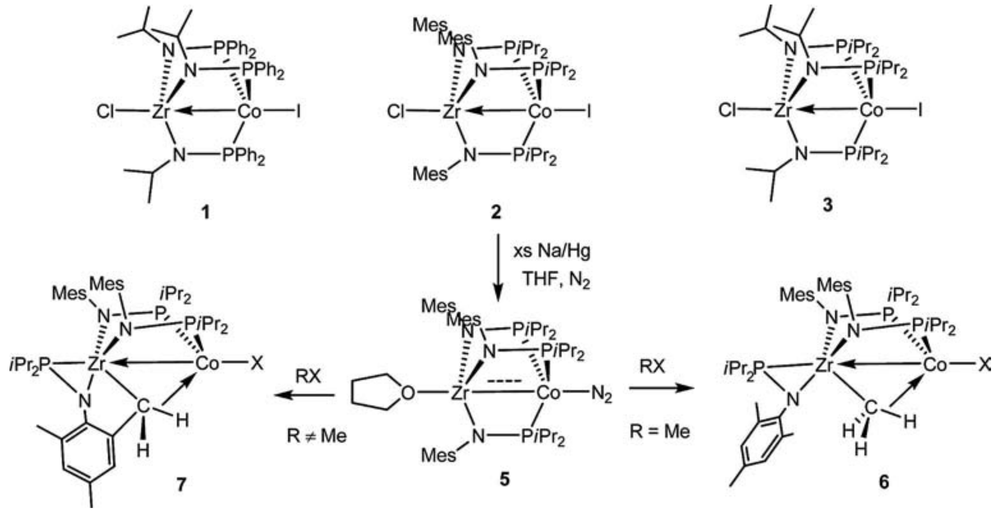


Scheme 1. Heterobimetallic Zr/Co complexes **1**–**3** and **5**–**7** (Mes = 2,4,6-trimethylphenyl).

catalyst loading was 5 mol-%. Reactions were carried out at room temperature, as low temperature conditions did not serve to improve yields. It is important to note that the addition of 30 mol-% TMEDA was necessary to obtain high yields of coupled product and we suspect this is an effect of TMEDA chelation to the Grignard reagent, particularly since neither **2** nor **5** reacted with TMEDA in control experiments. Kumada coupling processes catalyzed by first row transition metal salts have also been found to require excess TMEDA, however in these cases TMEDA is likely coordinating to the transition metal salt.[17,21,22] Both primary and secondary alkyl halide substrates, including iodides, bromides, and chlorides were investigated. Yields of coupled product were obtained using GC–MS and the results for precatalysts **1**–**3** are shown in Table 1. No cross-coupling products were observed in the absence of Zr/Co precatalyst. Notably, the Ph_2P-substituted precatalyst **1** showed significantly diminished activity from that of precatalysts **2** and **3**. This is likely a result of both the less electron-rich nature of **1** as well as the difference in the nature and reactivity of the two-electron reduction products of **2** and **3**.[20]

This catalytic system shows unusual activity towards alkyl chlorides, although yields from reactions with alkyl iodide and bromide substrates are, in all cases, higher than the corresponding alkyl chlorides. While yields generally decrease in the order R–I, R–Br > R–Cl, these differences in yields are relatively minor in some cases. For example, with catalyst **3**, only slight differences in yield are observed between 2-bromobutane and 2-chlorobutane (entries 1–2) and between 2-iodobutane, 2-bromobutane, and 2-chlorobutane (entries 9–11). These modest differences in alkyl halide reactivity imply a radical mechanism, rather than an oxidative addition mechanism. In addition, yields of coupling products increase in the order cyclohexyl > primary > secondary, which could be attributed to a combination of radical stability and steric factors. It is also important to note that the lowest yields are observed with aryl halide substrates (entries 13–14), consistent with the instability of the phenyl radical. A series of competition experiments were carried out to assess relative reaction rates. In coupling reactions of 1:1 mixtures of alkyl iodide and alkyl bromide with substoichiometric quantities of *n*OctMgBr, iodide derived coupling products were formed preferentially in a ratio of 25:1, while in a competition experiment of R–Br vs. R–Cl, bromide-derived products were formed exclusively. In addition, competition experiments between cyclohexyl, secondary, and primary alkyl halides showed product ratios of 1.25:1.15:1 and 1.20:1.00:1 with R–Br and R–Cl substrates, respectively.

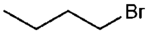
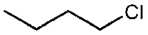
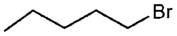
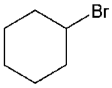
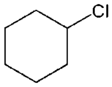
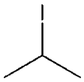
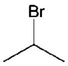
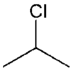
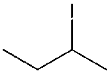
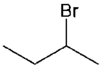
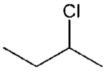
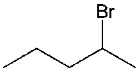
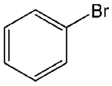
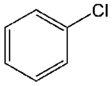
Notably, the monometallic Co analogue of **1**, $ICo(Ph_2PNH\textit{i}Pr)_3$ (**4**), showed diminished catalytic activity towards the Kumada coupling of 1-bromopentane with *n*OctMgBr and comparable activity towards 2-bromopentane (Table 2, entries 1–2). Interestingly, complex **4** was completely unreactive towards 1-chlorobutane and chlorocyclohexane (entries 3–4). Other monometallic Co^I tris(phosphane) complexes including $ICo(PPh_3)_3$ and $ICo(PMe_3)_3$ were equally ineffective (see Supporting Information). In addition, no coupling products between *n*OctMgBr and alkyl bromides or chlorides were obtained with (triphos)CoI {triphos = 1,1,1-tris[(diphenylphosphanyl)methyl]ethane}, indicating that the unusually high yields observed for **1**–**3** are not simply a result of a chelate effect (see Supporting Information). Thus, the unusually efficient catalytic performance of catalysts **1**–**3** must rely, to some extent, on the metal···metal interactions within these complexes.

In contrast to many Pd-catalyzed cross-coupling reactions, the mechanism of monometallic cobalt catalysts for Kumada coupling is generally believed to proceed via single electron transfer from the electron-rich cobalt complex to the alkyl halide.[15–17,23] It is this radical mechanism that allows the activation of alkyl halides, whose oxidative addition is known to be sluggish. For heterobimetallic catalysts **2** and **3**,[24] we propose the radical mechanism illustrated for catalyst **2** in Scheme 2 based on results from stoichiometric reactions as well as our observed trends in yield

Table 1. Results of Kumada–Corriu–Tamao coupling using heterobimetallic Zr/Co catalysts **1**–**3**.

$$n\mathrm{OctMgBr} + \mathrm{R\text{-}X} \xrightarrow[\text{TMEDA (30 mol-\%)}]{\text{cat. (5 mol-\%)}} n\mathrm{Oct\text{-}R}$$

THF, r.t.

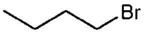
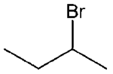
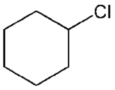
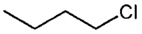
Entry	R–X	% Yield[a]		
		Cat. **1**	Cat. **2**	Cat. **3**
1		62.9	81.9	83.3
2		28.0	45.8	77.2
3		92.6	95.4	99.1
4		63.7	93.2	99.0
5		37.5	55.9	77.9
6		44.4	57.7	55.7
7		42.7	44.2	64.3
8		24.6	46.4	63.0
9		28.8	54.8	41.3
10		10.9	42.7	42.9
11		13.8	33.4	41.7
12		15.2	61.3	49.1
13		11.3	68.1	23.2
14		1.7	2.0	4.0

[a] Average of two values obtained via GC–MS analysis using tetradecane as an internal integration standard.

Table 2. Results of Kumada–Corriu–Tamao coupling using monometallic cobalt catalysts **4**.

$$n\mathrm{OctMgBr} + \mathrm{R\text{-}X} \xrightarrow[\text{TMEDA (30 mol-\%)}]{\mathrm{ICo(Ph_2PNH}i\mathrm{Pr)_3}\ (\mathbf{4},\ 5\ \text{mol-\%})} n\mathrm{Oct\text{-}R}$$

THF, r.t.

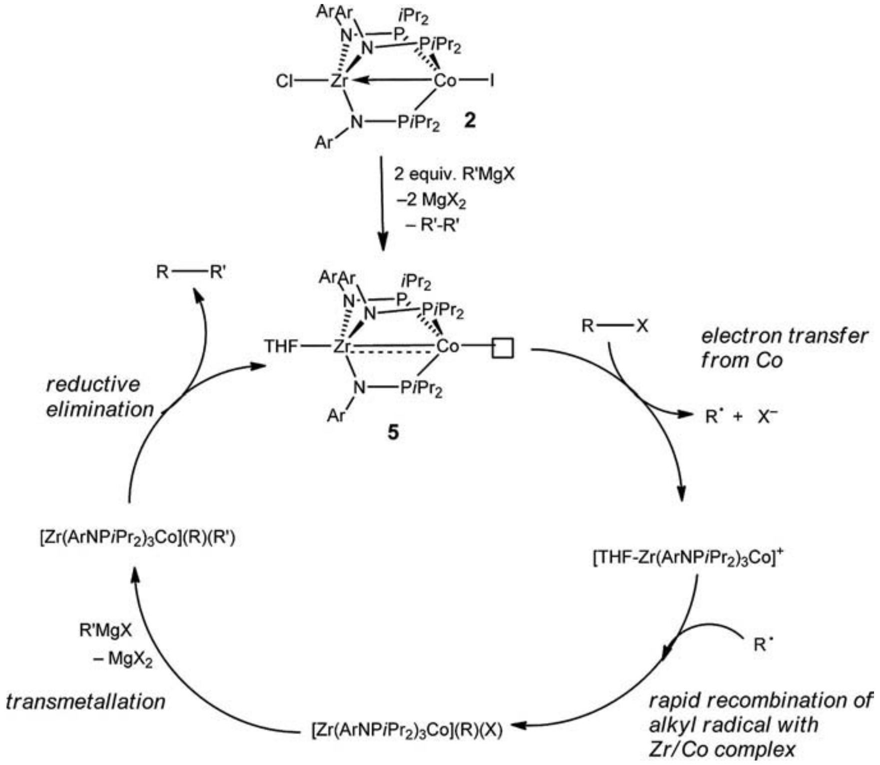
Entry	R–X	% Yield[a]
1		38.0
2		10.2
3		trace
4		trace

[a] Average of two values obtained via GC–MS analysis using tetradecane as an internal integration standard.

as a function of substrate. Entry into the catalytic cycle is achieved via addition of two equivalents of RMgBr to **2** (or **3**), followed by reductive elimination to generate a two-electron reduced species, **5**, analogous to the Zr–Co multiply-bonded species previously reported.[19] In support of this step, addition of two equivalents of phenylmagnesium bromide to **2** resulted in a red/brown product with spectroscopic features identical to that of (THF)Zr(MesNPiPr$_2$)$_3$-Co-N$_2$ (based on ^{1}H NMR and ν_{N2} in IR spectrum, see Supporting Information)[19] with concomitant formation of the homocoupling biphenyl product observed by GC–MS. In addition, alkyl halide substrates do not react with the dihalide precursors **1**–**3**, suggesting that a Co^{I}/Co^{III} mechanism is not operative.

Addition of alkyl halide across the highly polar metal-metal multiple bond in intermediate **5** likely proceeds via one electron-transfer to the alkyl halide. To confirm the formation of alkyl radicals during the addition of alkyl halides to **5**, RX was added to **5** in the presence of the radical trapping agent TEMPO (TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl).[25] In the case of RX = benzyl chloride, 2-iodopropane, EtI, and chlorocyclohexane, TEMPO-R was observed by GC–MS. In a more catalytically relevant reaction, a stoichiometric amount of TEMPO was added to the reaction mixture of RX, **3** (5 mol-%) and TMEDA (30 mol-%) and *n*OctMgBr was added slowly following the typical catalysis procedure. In all cases, both cross-coupling products and TEMPO-R were observed by GC–MS, with the ratio of trapped radical to coupling product increasing with alkyl radical stability (iPr > Cy > nBu, see Supporting Information). Organic radicals were not trapped by TEMPO, however, in the absence of Grignard reagent to accomplish the initial reduction of **3**. Additional support for a radical mechanism was obtained via stoichiometric reaction of 6-chloro- and 6-bromo-1-hexene with reduced complex **5**. In the case of both substrates, the radical cyclization product 1-methylcyclopentane was formed exclusively. Under catalytic conditions (5 mol-% **3**, 30 mol-% TMEDA), however, coupling of 6-bromo-1-hexene and 6-chloro-1-hexene with *n*OctMgBr leads to acyclic C–C coupling products in 88.5 and 48.5% yield, respectively. Only a small percentage of cyclized products were formed, implying that the coupling reaction is significantly faster than the cyclization of the 5-hexenylradical intermediate.

We previously reported the products of alkyl halide addition to the reduced complex **5** and found that while MeI



Scheme 2. Proposed mechanism for the coupling of alkyl halides and Grignard reagents by heterobimetallic Zr/Co complexes.

leads to bridging Zr-Me species **6** with one phosphane ligand dissociated from Co, intramolecular C–H activation product **7** is isolated from reactions of **5** with RX substrates where R $\neq$ Me.[20] We suspect that this difference can be attributed to both sterics and to the lesser stability of the methyl radical compared to other alkyl radicals. In support of this, in reactions between MeI and **5** in the presence of TEMPO, TEMPO-Me was not detected by GC–MS and the MeI addition product **6** was formed in high yield.

Once one-electron transfer from **5** to RX occurs to generate an alkyl radical, we propose that it recombines with the one-electron oxidized bimetallic Co/Zr species. Addition of R′MgBr to the resulting complex, followed by subsequent reductive elimination of the cross-coupling product R-R′ would regenerate the catalytically active species **5**. While obvious questions still remain regarding the connectivity of key intermediates in the catalytic cycle and the role of each transition metal center, we have strong evidence for a radical mechanism which is highly dependent on the presence of both Zr and Co. A mechanistic study is currently underway to determine whether Zr's role is to facilitate reductive elimination by withdrawing electron density from Co or if Zr is playing a more active substrate-binding role in this catalytic mechanism.

Conclusions

We have begun to examine the catalytic applications of early/late heterobimetallic Zr/Co complexes and uncovered promising results in the area of Kumada cross-coupling reactions, particularly those involving challenging alkyl chlorides substrates. These catalysts, which feature inexpensive and naturally abundant metals, show activity for both primary and secondary alkyl bromides at room temperature and perform modestly better than comparable monometallic cobalt complexes. More importantly, the Zr/Co heterobimetallic complexes dramatically increase the yield of coupling products with chlorides at room temperature in comparison to monometallic Co complexes, which in most cases are completely inactive towards these substrates. Thus, both Co and Zr are essential for catalytic activity. Future studies will aim at further investigating the potential bimetallic mechanism leading to this remarkable activity and examining additional new catalytic applications of heterobimetallic complexes.

Supporting Information (see footnote on the first page of this article): Experimental procedures and additional tables of data.

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[24] Based on the differences in the structure and reactivity of the chemical reduction product of **1** in comparison to **2** and **3**, we anticipate that the cross-coupling reaction using catalyst **1** proceeds via a different mechanism.
[25] TEMPO does not react with reduced complex **5** in the absence of alkyl halide substrates.

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