Exploring $SmBr_2$-, SmI_2-, and YbI_2-Mediated Reactions Assisted by Microwave Irradiation

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Abstract: The use of microwave heating in lanthanide(II) halide (LnX_2 = $SmBr_2$, SmI_2, and YbI_2) mediated reduction and coupling reactions has been investigated for a variety of functional groups including α,β-unsaturated esters, aldehydes, ketones, imines, and alkyl halides. Good to quantitative transformations were obtained within a few minutes without the addition of any co-solvents, such as hexamethyl phosphoramide (HMPA). The redox potential of YbI_2 in tetrahydrofuran (THF) has been determined as -1.02 ± 0.05 V (versus $Ag/AgNO_3$) by cyclic voltammetry. A large selectivity difference in various reactions was observed depending on the redox potential of the LnX_2 reagent. The more powerful reductant, $SmBr_2$, afforded mainly pinacol-coupling products of ketones whereas the weaker reductant YbI_2 afforded mainly reduction products. The results indicate that the reducing power of LnX_2 has a large impact on not only the pinacol coupling/reduction product ratio of ketones but also on other substrates in which there are competing coupling and reduction reactions. The use of in situ generated LnX_2 has also been explored and proven useful in many of these reactions.

Keywords: cyclic voltammetry · lanthanides · microwave irradiation · reduction · reductive coupling

Introduction

Divalent lanthanides have been widely explored during recent years and have become much appreciated as single-electron-transfer reagents in various organic transformations.[1] The chemistry developed around the divalent lanthanides has been focused predominantly on SmI_2 as a result of its ease of preparation, commercial availability, and broad utility in organic synthesis. The more reactive $SmBr_2$ and the less reactive YbI_2 have so far been considerably less utilized.

The development of rapid and reliable SmI_2-mediated syntheses has been largely dependent on the addition of co-solvents, for example, hexamethyl phosphoramide (HMPA).[2] Numerous coupling reactions, as well as the reduction of ketones, alkyl halides, and α,β-unsaturated esters, have been effectively accelerated with the addition of co-solvents. This is due to the co-solvent causing a large increase in the oxidation potential.[3] Recently, there have also been reports on the use of $SmBr_2$, DyI_2, NdI_2, and TmI_2, which have a higher oxidation potential than SmI_2 in tetrahydrofuran (THF). With these more potent reducing agents the use of HMPA is less important.[4] The replacement of the carcinogenic additive HMPA with amine/water has also been successful in some SmI_2-mediated reactions, particularly in the reduction of alkyl halides and conjugated alkenes, and pinacol-coupling reactions of aromatic aldehydes, ketones, and imines.[5]

The reagent mixtures of SmI_2/H_2O/amine often favor reduction over intermolecular coupling reactions, such as pinacol and Barbier-coupling reactions. Due to the importance of SmI_2-mediated intermolecular coupling reactions in organic synthesis, it is most desirable to find alternative conditions that limit the use of HMPA. Recently, we reported that microwave heating is a simple and fast method for the preparation of SmI_2, YbI_2, $SmBr_2$, and EuI_2.[6] Several single-electron-transfer processes using SmI_2 alone are slow at room temperature. Recently, microwave-accelerated synthesis has proven superior to conventional heating in many reactions,[7] including homogeneous palladium-catalyzed reactions such as Heck,[8] Sonogashira,[9] and cross-coupling reactions (Suzuki[10] and Stille[11]), and allylic substitution reactions.[12] As a result of the success of these reactions, it

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seemed reasonable to study some of the fundamental chemistry mediated by divalent lanthanides under microwave heating for use as a viable alternative to the addition of co-solvents.

Herein we report the use of microwave irradiation in selected lanthanide(II) halide (LnX_2) mediated reactions, in which $SmBr_2$, SmI_2, and YbI_2 have been compared in various reductive coupling and reduction reactions. The reduction potentials of $SmBr_2$ and SmI_2 in THF are −2.07 and −1.55 V (versus $Ag/AgNO_3$), respectively. We have now also measured the reduction potential of YbI_2 in THF. The reducing power of the divalent lanthanide reagent is found to have a strong influence on the course of the reaction, for example, reduction versus coupling.

Results and Discussion

Cyclic voltammetry investigation: Cyclic voltammetry was used to estimate the redox potential of YbI_2 in THF for comparison with the potentials known for SmI_2 and $SmBr_2$. The potential for YbI_2 was estimated to be -1.02 ± 0.05 V (versus $Ag/AgNO_3$; Figure 1). Thus, the reducing agent YbI_2 has a reducing power approximately 0.5 V smaller than that of SmI_2 (-1.55 ± 0.05 V). In addition, $SmBr_2$ (-2.07 ± 0.05 V) is a more powerful reducing agent than SmI_2 by about 0.5 V.

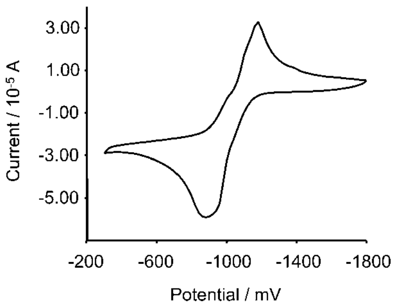
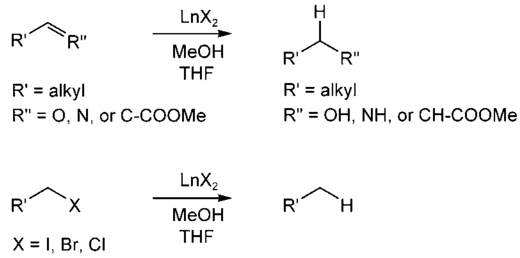


Figure 1. Cyclic voltammogram for YbI_2 in THF.

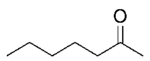
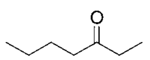
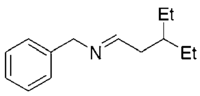
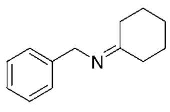
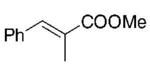
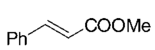
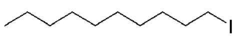
Microwave-assisted reduction mediated by $SmBr_2$, SmI_2, and YbI_2: Reduction of ketones with SmI_2 is very slow at normal pressure and room temperature yielding only 10% alcohol after several days with methanol as the proton source.[13] In contrast to this, a quantitative yield was obtained in less than 5 min at 180 °C with microwave heating mediated by either of $SmBr_2$, SmI_2, or YbI_2 in the presence of methanol (Scheme 1). This corresponds to a rate enhancement of approximately 2000-fold compared with the rate of reduction at room temperature. This rate enhancement is roughly similar to that expected for the same reaction carried out at a temperature 160 °C higher, and it does not appear to be any microwave effect.[7c] Imines were reduced in the same way (Table 1).

The double bond in α,β-unsaturated esters was easily reduced by the LnX_2/alcohol mixture. Conversely, reduction of conjugated carbon–carbon double bonds was not observed either in the presence, or in the absence of methanol. Another recalcitrant case is the reduction of alkyl halides. 1-Iododecane was easily reduced within five minutes with SmI_2/MeOH, while 1-chlorodecane, which is hard to reduce using SmI_2/MeOH at room temperature, was difficult to reduce even under microwave irradiation. Nevertheless, with the addition of Et_3N/H_2O instead of methanol the reduction was completed within five minutes under microwave irradiation. On the contrary, chlorobenzene was not under any circumstances reduced by using microwave irradiation even though the SmI_2/H_2O/amine mixture readily reduces



Scheme 1. Reduction of ketones, imines, α,β-unsaturated esters, and halides with LnX_2 under microwave irradiation.

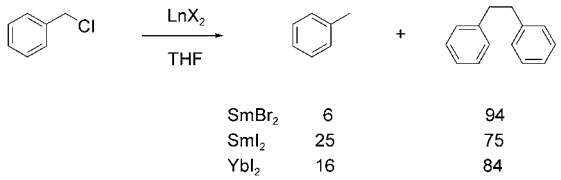
Table 1. Microwave-assisted reduction reactions at 180 °C in the presence of MeOH in THF.[a]

Substrate	Reagent (LnX_2)	Reduction [%]
	$SmBr_2$ SmI_2 YbI_2	>99 >99 >99[b]
	$SmBr_2$ SmI_2 YbI_2	>99 >99 >99[b]
	$SmBr_2$ SmI_2 YbI_2	>99 >99 >99[b]
	$SmBr_2$ SmI_2 YbI_2	>99 >99 >99[b]
	$SmBr_2$ SmI_2 YbI_2	>99 >99 >99[b]
	$SmBr_2$ SmI_2 YbI_2	>99 >99 >99[b]
	$SmBr_2$ SmI_2 YbI_2	>99 >99 >99[b]

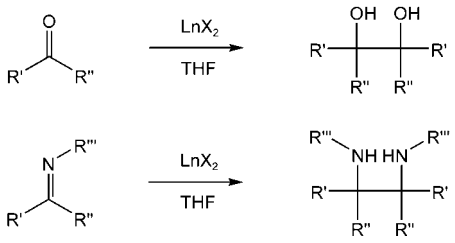
[a] LnX_2 (2.5 equiv) in THF. The substrate (1 equiv) and methanol (9 equiv) were added just before the vessel was placed in the microwave reactor. The reaction mixture was irradiated for 5 min, unless otherwise stated. All reported conversions are based on GC yield. [b] Reduction reactions performed in the presence of YbI_2 were irradiated for 10–20 min to ensure quantitative conversion.

chlorobenzene at room temperature. Further studies showed that the powerful mixture of $SmI_2/H_2O/Et_3N$ could not be employed, as H_2O and Et_3N cause deleterious side reactions with SmI_2 at these elevated temperatures and extended reaction times (i.e., more than 5 min). Methanol was found to be superior to H_2O as a proton donor in the microwave-heated reduction, because it reacts slowly with LnX_2 at any temperature.

Microwave-assisted coupling reactions mediated by $SmBr_2$, SmI_2, and YbI_2: To determine the general utility of microwave-accelerated reactions, the coupling of benzyl chloride with $SmBr_2$, SmI_2, and YbI_2 was tested, as this substrate is easily coupled under ambient conditions. High conversions were obtained for all mixtures, although $SmBr_2$ appears to be the superior coupling reagent (Scheme 2). The addition of methanol to the same mixtures gave almost quantitative reduction of benzyl chloride to toluene.



Scheme 2. Coupling of benzyl chloride with LnX_2 under microwave irradiation. The values represent the yields (%) obtained.

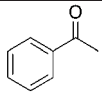
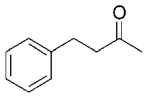
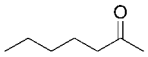
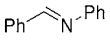
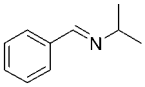


Scheme 3. Pinacol-coupling reactions of aliphatic ketones, aldehydes (top), and imines (bottom) with LnX_2. R, R′, R″, R‴ = alkyl, aryl, or H, see Table 2.

As previously stated, one of the main objectives of this study was to find a replacement for HMPA in pinacol-coupling reactions of aliphatic ketones, aldehydes, and imines (Scheme 3). As reduction is favored for aliphatic ketones when using the water/amine method, this approach cannot be used. Particularly interesting are pinacol-coupling reactions mediated by $SmBr_2$, which were recently reported by Namy et al.[14] The black suspension of $SmBr_2$ in THF is obtained by stirring Sm powder with tetrabromoethane in THF for at least 15 hours at ambient temperature, or alternatively five minutes at 180 °C under microwave irradiation. The ketone or aldehyde was added to $SmBr_2$, SmI_2, or YbI_2 in THF and then irradiated in the microwave reactor. The general trend observed for these coupling reactions was that pinacol coupling was favored over reduction in the order $SmBr_2 > SmI_2 > YbI_2$. A higher reducing power (as determined by the redox potentials) correlates well with the extent of pinacol coupling. With $SmBr_2$, high isolated yields for coupling reactions were obtained (Table 2).

Surprisingly, the diastereoselectivity increased in the opposite order, that is, YbI_2 gave the highest diastereoselectivity. Similar diastereoselectivities

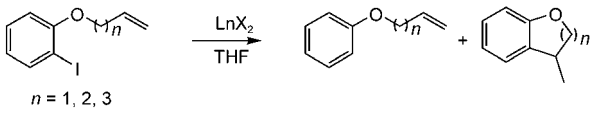
Table 2. Microwave-assisted pinacol-coupling reactions in THF.[a]

Substrate	Reagent (LnX_2)	Reduction [%]	Pinacol [%] (*dl*/*meso*)
	$SmBr_2$	3	97 (73:27)
	SmI_2	3	97 (70:30)
	YbI_2	18	82 (77:23)
	$SmBr_2$	2	98 (57:43)
	SmI_2	4	96 (32:68)
	YbI_2	24	76 (66:34)
	$SmBr_2$	<1	>99 (50:50)[b]
	SmI_2	10	90 (50:50)
	YbI_2	84	16 (50:50)[c]
	$SmBr_2$	2	98 (50:50)[b]
	SmI_2	11	89 (49:51)
	YbI_2	83	17 (55:45)[c]
	$SmBr_2$	<1	>99 (96:4)[b]
	SmI_2	5	95 (80:20)
	YbI_2	5	95 (91:9)
	$SmBr_2$	14	86
	SmI_2	23	77
	YbI_2	70	30
	$SmBr_2$	50	50 (100:0)
	SmI_2	27	73 (56:44)
	YbI_2	N.R.[d]	N.R.[d]
	$SmBr_2$	26	74
	SmI_2	8	92
	YbI_2	12	88[c]

[a] LnX_2 (1.1–2.0 equiv) in THF. The substrate (1 equiv) was added before the vessel was placed in the microwave reactor. The reaction mixture was irradiated for 5 min. [b] Selected pinacol-coupled products were isolated yielding 85–95% product after flash chromatography. [c] Reactions performed in the presence of YbI_2 were irradiated for 45–60 min to ensure full conversion. [d] N.R. = no reaction.

were achieved with $SmBr_2$ at room temperature[14] as with microwave irradiation at 180 °C, but the microwave-assisted coupling reactions gave a higher conversion in a much shorter reaction time (5 min compared with 24 h). Moreover, the possibility of pinacolization with several aliphatic and aromatic imines was also explored, and it was found that aromatic imines were efficiently coupled, while aliphatic imines were simply reduced. This was disappointing because we aimed for a general method for pinacolization. Nevertheless, it is still useful for the coupling of aromatic imines, as the reaction time was shortened from 1.5 hours at reflux (65 °C)[15] to five minutes in the microwave environment.

Unfortunately, all attempts to initiate intermolecular coupling between a ketone and an alkyl halide, for example, cyclohexanone and 1-chlorodecane or 1-iododecane, proved unsuccessful and led exclusively to reduction of one or both of the substrates. Ultimately, intramolecular reductive coupling of an aryl iodide to a double bond proved successful (Scheme 4).



Scheme 4. Reduction and cyclization with LnX_2.

Surprisingly, SmI_2 appeared to give the highest degree of coupling versus reduction in these reactions (Table 3). All attempts to obtain seven-membered rings were ineffective and resulted in complete reduction (entries 7–9), which was also previously observed for the SmI_2/H_2O/amine method.[16]

In situ generated $SmBr_2$ and SmI_2 in single-electron-transfer reactions: The scope and limits of reduction and coupling of substrates with in situ generation of $SmBr_2$, SmI_2, and YbI_2 were also studied. The $SmBr_2$- and SmI_2-mediated reduction of 2-heptanone and aliphatic imines (entries 9–12, Table 4) gave complete reduction within 10 minutes in the presence of methanol using microwave heating. Therefore, we employed the in situ conditions on various substrates in the absence of methanol to evaluate the coupling efficiency. $SmBr_2$ mediates pinacol-coupling reactions of ketones in situ effectively, however minor amounts (<10%) of unidentified byproducts were also observed occasionally. The same trend as previously described for prepared SmX_2 is also found for in situ generated $SmBr_2$ and SmI_2, that is, an increasing degree of pinacol coupling is obtained with higher oxidation potential of the lanthanide(II) reagent. Interestingly, irrespective of the addition of methanol, treatment of imines with SmI_2 or $SmBr_2$ results in reduction only.

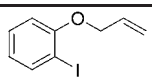
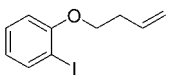
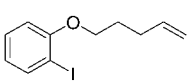
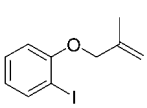
Intramolecular coupling between aryl iodides and alkenes was performed, in which in situ generated SmI_2 was proven to be the superior coupling reagent (Table 5). However, the formation of phenol and other reduction products was also observed.

One disadvantage of SmI_2-mediated reduction is the low solubility of SmI_2 (0.13 M in THF). In addition, one molecule of SmI_2 can only deliver one electron, therefore each substrate requires two equivalents of the single-electron-transfer reagent. Altogether this makes these reactions less attractive with respect to large-scale syntheses. Previously, we have reported that SmI_2 and particularly $SmBr_2$ can be generated as suspensions in THF,[6] thus requiring a smaller volume of THF. The use of smaller volumes of solvent in reduction reactions is important as it allows reduction reactions to be carried out on a larger scale in smaller reaction vessels.

We generated SmI_2 and $SmBr_2$ from samarium metal and iodine or tetrabromoethane using only 10% of the required volume of THF (i.e., 10% of the volume that gives saturated solutions of SmI_2 in THF). These highly "concentrated" suspensions were then successfully employed in a few of the above-mentioned reduction and cyclization reactions and it was concluded that the results were almost identical in terms of the selectivity using either prepared or in situ generated suspensions of the SmI_2 and $SmBr_2$. Apparently there is no need to use saturated solutions of LnX_2, since the suspensions gave more or less identical results.

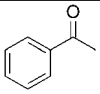
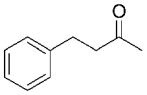
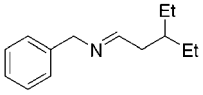
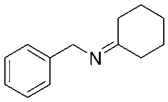
Unfortunately, the use of Yb and I_2 was shown to be less attractive for in situ generation of YbI_2 in the described reactions (Tables 4 and 5). The generation of YbI_2 was too slow even under microwave irradiation, yielding only approximately 43% of the reduced 2-heptanol from heptanone after 60 minutes at 180 °C.

Table 3. Microwave-assisted cyclizations in THF.[a,b,c]

Entry	Substrate	Reagent (LnX_2)	Reduction [%]	Cyclization [%]
1		$SmBr_2$	0	90
2		SmI_2	2	95
3		YbI_2	16	71
4		$SmBr_2$	48	52
5		SmI_2	14	86
6		YbI_2	70	30
7		$SmBr_2$	>99	0
8		SmI_2	>99	0
9		YbI_2	>99	0
10		$SmBr_2$	19	70
11		SmI_2	12	71
12		YbI_2	50	40

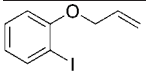
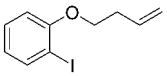
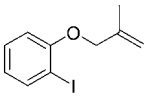
[a] LnX_2 (2.5–3.0 equiv) in THF. The substrate (1 equiv) was added just before the vessel was placed in the microwave reactor. The reaction mixture was irradiated for 10 min. [b] Reactions performed in the presence of YbI_2 were irradiated for 20–30 min. [c] Formation of phenol balances the conversion.

Table 4. In situ generated $SmBr_2$ and SmI_2 reactions in THF.[a]

Entry	Substrate	Reagent (LnX_2)	Reduction [%]	Pinacol [%] (*dl*/*meso*)
1		$SmBr_2$	4	96 (68:32)
2		SmI_2	5	95 (70:30)
3		$SmBr_2$	11	89 (56:44)
4		SmI_2	24	76 (66:34)
5		$SmBr_2$	7	93 (50:50)
6		SmI_2	38	62 (50:50)
7		$SmBr_2$	10	90
8		SmI_2	59	41
9		$SmBr_2$	100	0[b]
10		SmI_2	100	0[b]
11		$SmBr_2$	100	0[b]
12		SmI_2	100	0[b]

[a] Sm (3.0 equiv) and I_2 (2.0 equiv) or tetrabromoethane (1.0 equiv), diluted with THF. The substrate (1 equiv) was added just before the vessel was placed in the microwave reactor. The reaction mixture was irradiated for 10 min. [b] Methanol (9.0 equiv) was added prior to putting the vessel in the microwave chamber to enhance the rate. No coupling was observed either in the presence or in the absence of MeOH.

Table 5. In situ generated $SmBr_2$ and SmI_2 reactions.[a,b]

Substrate	Reagent (LnX_2)	Reduction [%]	Cyclization [%]
	$SmBr_2$	5	84
	SmI_2	2	87
	$SmBr_2$	36	64
	SmI_2	14	86
	$SmBr_2$	19	70
	SmI_2	21	61[c]

[a] Sm (3.0 equiv) and I_2 (2.0 equiv) or tetrabromoethane (1.0 equiv), diluted with THF. The substrate was added just before the vessel was placed in the microwave reactor. The reaction mixture was irradiated for 10 min. [b] Formation of phenol balances the conversion. [c] Formation of decomposition products (up to 10%) was observed.

We also investigated the possibility of employing microwave heating in deallylation reactions, which was recently described with the SmI_2/H_2O/amine method.[17] However, no reaction occurred with any of the three lanthanide(II) reagents. It appears that the microwave irradiation only enhances the reduction rates. However, the powerful SmI_2/water/amine reagent does not appear to be stable under microwave irradiation.

Conclusion

We have shown that it is efficient to perform rapid coupling and reduction reactions by using microwave heating with lanthanide(II) reagents. Pinacol-coupling reactions of ketones are readily obtained within five minutes using $SmBr_2$ as a single-electron donor, while the weaker reducing agent, YbI_2, favors reduction reactions. We have shown that lanthanide(II) reagents generated in situ under microwave irradiation can be a viable alternative for reduction and coupling reactions. Mixing of Sm or Yb metal and iodine in THF, in a vessel approved for use in the microwave reactor, provides an easy method for the execution of LnX_2-mediated reactions.

Experimental Section

General: THF was dried over sodium and distilled before use. All commercially available chemicals were used without further purification. Synthesized substrates were distilled and stored in a glove box.

Cyclic voltammetry of YbI_2: The redox potential of YbI_2 was measured by using cyclic voltammetry, employing a BAS 100/W MF-9063 Electrochemical Workstation. The working electrode was a glassy carbon electrode. The electrode was polished with polishing alumina before use. The auxiliary electrode was a platinum wire, and the reference electrode was a saturated $Ag/AgNO_3$ electrode. The scan rate for the experiment was $100\,mV\,s^{-1}$. The electrolyte used was tetrabutylammonium hexafluorophosphate. The concentrations of YbI_2 and the electrolyte were 5 mM and 0.1 M, respectively. The solution was prepared inside a dry box and transferred to the electrochemical analyzer for analysis.

Microwave-assisted synthesis with prepared LnX_2: In a typical reduction of a ketone, imine, or α,β-unsaturated ester, LnX_2 (2.5 equiv) in THF (5 mL) was added to a vessel approved for use in the microwave reactor, inside a glove box, and sealed with a cap. The substrate (1 equiv) and methanol (9 equiv) were added through the septum just before placing the vessel in the microwave reactor. The reactions were performed utilizing a prototype single-mode applicator equipped with a fluoroptic probe and irradiated in the microwave reactor for five minutes. All reactions were performed at a constant temperature of 180 °C resulting in a pressure of 11–14 bar. The reactions were quenched by air when the caps were removed. Hydrochloric acid (20 mL, 0.1 M) was added to dissolve inorganic salts and the products were then extracted into diethyl ether (3 × 40 mL). The organic layer was washed with sodium thiosulfate and saturated brine, and finally dried over sodium sulfate before filtration. Pinacol-coupling products were separated from the reduced products by flash

chromatography on silica with ethyl acetate/*n*-hexanes (1:10). Isolated products were characterized by ^{1}H and ^{13}C NMR analyses and/or compared to authentic samples by gas chromatography and GC/MS.[18] GC analyses were used to determine the *dl*/*meso* ratio in the pinacol products. The relative amount of pinacol coupling and reduction was established from the crude products, that is, before the purification by flash chromatography.

Microwave-assisted synthesis with in situ generation of LnX_2: In a typical reaction with in situ generation of LnX_2, Sm (3.0 equiv), and I_2 (2.0 equiv) or tetrabromoethane (1.0 equiv) were added to a vessel approved for use in the microwave reactor, inside a glove box. The reagents were diluted with THF (5 mL) and the vessel sealed with a cap. The substrate (1 equiv) was added through the septum just before placing the vessel in the microwave reactor. The reaction mixture was irradiated in the microwave reactor for 10 min. Work-up procedures and isolation of the products were identical to the method described above.

Methanol was added to the reaction vessel when reduction was desired. Absence of a proton source favored pinacol coupling.

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[18] Alcohol products were compared with authentic samples from commercial resources. Pinacol-coupling products and bensofuran derivatives were compared with products obtained from published procedures.[5,14–16]

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