New Reagent for Reductive Coupling of Carbonyl and Imine Compounds: Highly Reactive Manganese-Mediated Pinacol Coupling of Aryl Aldehydes, Aryl Ketones, and Aldimines

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Introduction

One of the most powerful methods for constructing carbon−carbon bond is the reductive coupling of carbonyl compounds giving olefins and/or 1,2-diols.[1] Of these methods, the pinacol coupling,[2] which was described in 1859, is still a useful tool for the synthesis of vicinal diols. The corresponding products of this reaction can be used as intermediates for the preparation of ketones and alkenes.[3] More importantly, this methodology has been applied to the synthesis of biologically active natural compounds.[4]

Generally, the reaction is effected by treatment of carbonyl compounds with an appropriate metal reagent and/or metal complex to give rise to the corresponding coupled product. A number of different types of metal reagents have been used to carry out the pinacol reaction. For instance, the reaction with various low-valent metal complexes of Al,[5] Ce,[6] Fe,[7] Mg,[8] Nb,[9] Sm,[10] Si,[11] Ti,[12] V,[13] Yb,[14] Zr,[15] and main group organometallic hydrides (Bu_3SnH, Ph_3SnH, Bu_3GeH, and $(TMS)_3SiH$)[16] afforded inter- or intramolecular coupling products of carbonyls.

The coupling products can have two newly formed stereocenters. As a consequence, efficient reaction conditions have been required to control the stereochemistry of the 1,2-diols. Recent efforts have focused on the development of new reagents and reaction systems to improve the reactivity of the reagents and diasteroselectivity of the products. In addition, functional group tolerance has been a challenge for reductive coupling of carbonyl compounds using the reaction systems mentioned above, and many successful results have been reported.

In 1984, Lukehart[17] reported a formal reductive coupling of mangana-β-diketonato complexes to give carbon−carbon bond formation. Manganese complexes also have been used as a good single-electron source in oxidative free-radical cyclizations.[18] On the basis of these findings, we postulated that our active manganese might be a good single-electron donor and, therefore, be utilized for pinacol coupling.

During the course of our investigation on active metals, we have found that treatment of aryl aldehydes and aryl ketones with active manganese (Mn*) prepared via the Rieke method gave the corresponding pinacolic coupling product (Tables 1 and 2). As shown in Scheme 1, the reaction of aldimines with this active manganese also afforded the corresponding coupling products, vicinal diamines. Due to the potential utility of vicinal diamines

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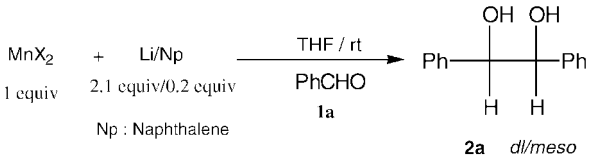
Table 1. Study of Reactivity Depending on Halides



MnX_2	condns (T (°C)/time)	yield[a] (%)	dl/meso[b]
$MnCl_2$	rt/30 min	86	63:37
$MnBr_2$	rt/overnight	89	68:32
MnI_2	rt/24 h	80	54:46

[a] Isolated yields (based on aldehyde). [b] Purified from recrystallization (2% ethyl ether/hexanes).

in organic synthesis, especially in natural products and medicinal reagents,[19] synthetic methodologies of vicinal diamines have attracted considerable attention. To date, several methods have been described to perform the reductive dimerization of imines into vicinal diamines.[20] The most widely used method is metal-mediated pinacolic coupling of imines. Several metals have been utilized, including samarium,[21] sodium,[20c,22] ziroconium,[23] aluminum, bismuth,[24] zinc,[25] titanium,[26] indium,[27] niobium,[28] and ytterbium.[29]

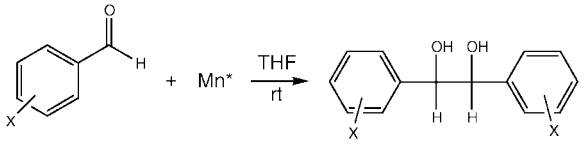
To date, no report has appeared using manganese metal. In this paper, we wish to report a mild method for reductive coupling reactions of aryl aldehydes, aryl ketones, and aldimines.

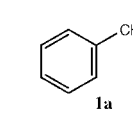
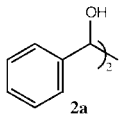
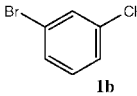
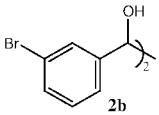
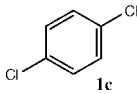
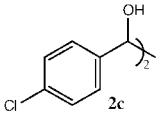
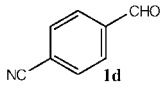
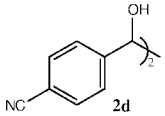
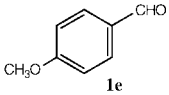
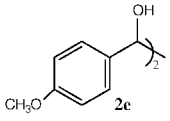
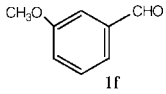
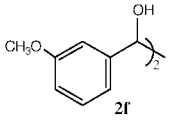
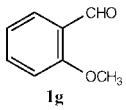
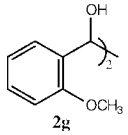
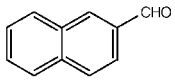
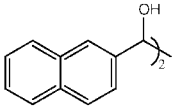
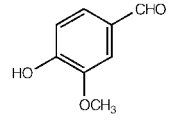
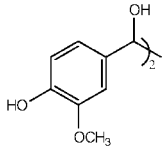
Results and Discussion

Reduction of manganese halides (MnI_2, $MnBr_2$, and $MnCl_2$) by Li using naphthalene as an electron carrier in THF affords a slurry of Mn* at room temperature. The resulting Mn*, however, appears to be partially soluble in THF. Due to this, no washing was performed to remove naphthalene and other salts, and the Mn* was used as a slurry. The preparation of the active metals and the subsequent reaction of the organometallic reagents are conducted under an argon atmosphere.

Reductive Coupling Reactions of Aryl Aldehydes. As described above, three different types of manganese halides can be used to prepare active manganese. Therefore, reactivity depending on metal halide was studied first. The results are summarized in Table 1, and it was found that there are no significant differences in both yield and stereochemistry of the product (**2a**). Good isolated yields (80−89%) and an almost 1:1 mixture of dl/meso isomers were obtained from three different attempts described in Table 1. Longer reaction times were required to complete the coupling reaction in the

Table 2. Coupling Reaction of Aldehydes with Active Manganese



Entry	Carbonyls	Aldehyde:Mn*	Product[a]	Yield (%)[b,c]	dl/meso[d]
1	 **1a**	0.8 : 1 0.8 : 1 0.5 : 1	 **2a**	64 (62)[c] 86	63 : 37 73 : 27
2	 **1b**	0.5 : 1	 **2b**	60	93 : 7
3	 **1c**	0.8 : 1 0.5 : 1	 **2c**	51[f] 81	58 : 42 83 : 17
4	 **1d**	0.5 : 1	 **2d**	94	63 : 37
5	 **1e**	0.5 : 1	 **2e**	83	66 : 34
6	 **1f**	0.5 : 1	 **2f**	90[f]	64 : 36
7	 **1g**	0.5 : 1	 **2g**	90	66 : 34
8	 **1h**	0.7 : 1	 **2h**	72	51 : 49
9	 **1i**	0.5 : 1	 **2i**	0[g]	

[a] All products have been fully characterized by ^1H NMR, ^{13}C NMR, and HRFAB-MS. [b] Isolated yields (based on aldehydes). [c] Obtained from recrystallization (1−2% ethyl ether/hexanes) unless mentioned. [d] Determined by ^1H NMR (300 MHz) analysis of the isolated product. [e] Reaction was carried out at 0 °C. [f] Obtained from flash chromatography. [g] According to TLC analysis, starting material (aldehyde) was recovered after hydrolysis of the reaction mixture.

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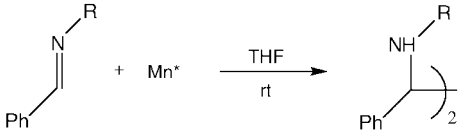
Scheme 1. Reductive Coupling of Aldimines[a]



13 R = Ph

14 R = Ph, 62 %
dl/meso[a] 64 : 36

15 R = CH_2Ph

16 R = CH_2Ph, 56 %
dl/meso 49 : 51

[a] Key: (a) Determined by ^{13}C NMR (75 MNH) analysis.

case of manganese iodide. While we have not conducted a detailed study of the reaction pathway, we believe that this reaction proceeds via one of the mechanisms presented in ref 2b.

Various aromatic aldehydes were reacted with the active manganese prepared from using manganese chloride. Table 2 represents that simple treatment of aryl aldehydes with active manganese gives the corresponding 1,2-diols in moderate to good isolated yields under very mild conditions, room temperature in THF. The results are shown in Table 2.

It is proposed that the reaction proceeds via a single-electron transfer (SET).[2b] With the active manganese supplying the electrons, the ratio of manganese to aldehyde was found to be very important with respect to overall yield. Entry 1 in Table 2 shows that a higher yield is obtained using 2 equiv of Mn* and 1 equiv of aldehyde. This appears to be general for all aldehydes and ketones. All of the reactions with different mole ratios were carried out at room temperature in 30 min. Reaction temperature had little effect on the yield. Reactions at room temperature and 0 °C in 30 min gave 64% and 62% isolated yields, respectively (entry 1 in Table 2).

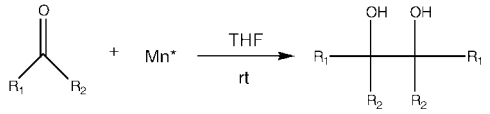
It should be mentioned that this reaction exhibits tolerance of several functional groups on the aromatic ring, including bromine, chlorine, cyano, and methoxy (entries 2−5 in Table 2). According to the high-resolution FAB-MS of **2b**−**g** in Table 2 and **6** in Table 3, the functional groups are still retained in the final products. Unfortunately, according to TLC analysis of the reaction mixture after hydrolysis, the starting material was solely recovered in the coupling reaction of vanillin, which bears a hydroxy group on the aromatic ring (entry 9 in Table 2). Even when 5 equiv of Mn* was used the same result was observed. Probably, the acidic hydrogen of phenolic OH reacts with the Mn* quenching the reaction.

To investigate possible steric effects of substitutents on the coupling reaction, *o*-, *m*-, and *p*-substituted aldehydes were examined. *o*-, *m*-, and *p*-methoxybenzaldehydes were reacted with Mn* under the same conditions (entries 5−7 in Table 2). For these molecules, overnight stirring at room temperature was required to complete the reaction. The results shown in Table 2 indicate that no steric hindrance is observed in terms of yield (83−90%). Table 2 also shows that high diasteroselectivity is not observed in this reaction system except in the case of 3-bromobenzaldehyde. In the reaction of 3-bromobenzaldehyde, the dl-isomer was the major product (dl/meso 93:7), but the reason for this is not clear. To investigate the change of dl/meso ratios depending upon the purification protocols, two different methods, column chromatography and recrystallization, were used to purify the crude reaction mixture obtained from the reaction of 1 equiv of Mn* and 0.5 equiv of benzaldehyde at room temperature. In both cases, the same dl/meso (76:24) was observed. This ratio was essentially the same as that of the crude mixture. The ^1H NMR spectrum of the crude mixture indicated a dl/meso ratio of 74:26. A slightly different dl/meso ratio (79:21) was obtained from the recrystallization (20% ethyl ether/hexanes) of prechromatographically purified product. Interestingly, a significant change in the dl/meso ratio was observed in the coupling product of 4-chlorobenzaldehyde. Recrystallization of the prechromatographically purified product (dl/meso, 63:37) was carried out by using 20% ethyl ether/hexanes. The ^1H NMR spectrum of the recrystallized product showed a higher dl/meso ratio (95:5). This is clearly a result of partial separation upon purification.

In addition to the coupling of aryl aldehydes, it should be mentioned that a multicompound mixture was obtained from the reactions using aliphatic aldehydes with Mn*. According to Yanada's work, the radical intermediates from the aliphatic aldehydes are unstable and do not have enough time to react with each other to give diols.

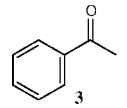
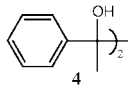
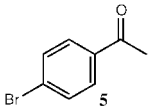
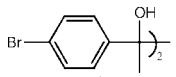
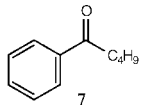
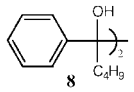
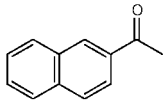
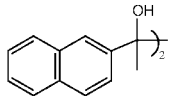
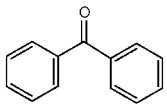
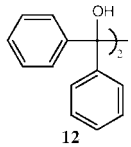
Reductive Coupling Reaction of Aryl Ketones. Table 3 represents the reductive coupling reactions of

Table 3. Coupling Reaction of Ketones with Active Manganese



R_1 = Ph, *p*-BrC_6H_5, Naphthyl

R_2 = CH_3, C_4H_9, Ph

Entry	Ketones	Ketone:Mn*	Product[a]	Yield (%)[b,c]	*dl/meso*[d]
1	 **3**	0.8 : 1 0.5 : 1	 **4**	54[e] 71[e]	>99 : 1 96 : 4
2	 **5**	0.5 : 1	 **6**	91	73 : 27
3	 **7**	0.5 : 1	 **8**	88	76 : 24
4	 **9**	0.5 : 1	 **10**	93	87 : 13
5	 **11**	0.5 : 1	 **12**	91	-

[a] All products have been fully characterized by ^1H NMR, ^{13}C NMR, and HRFAB-MS. [b] Isolated yields (based on ketones). [c] Purified from chromatography unless mentioned. [d] Determined by ^1H NMR (300 MHz) or ^{13}C NMR (75 MHz) analysis of the isolated product. [e] Obtained from recrystallization (1−2% ethyl ether/hexanes).

aryl ketones using active manganese. These reactions were also conducted under almost the same conditions used in aryl aldehyde couplings, and the results are summarized in Table 3. Isolated yields were good to excellent (71−93%), and much higher stereoselectivity was observed. As observed in the aldehyde couplings, the mole ratio of carbonyl to metal reagent greatly effects the yield of the final product as is shown in entry 1 in Table 3. For instance, the reaction of 0.5 equiv of acetophenone (**3**) with 1 equiv of active manganese afforded the 1,2-diol derivative **4** in higher yield (71%) than that (54%) using 0.8 equiv of ketone with 1.0 equiv of Mn*. Interestingly, much higher diasteroselectivity is observed. The reason for this may be steric. The corresponding coupling products (**6**, **8**, and **10**) of alkyl−aryl-substituted ketones (**5**, **7**, and **9**), were obtained in good yields (88−93%) with moderate to good diastereoselectivities under the conditions presented in Table 3. Even for a bulky biaryl ketone, the expected coupling product was obtained in high yield. For example, treatment of benzophenone (**11**) with active manganese gave 1,1,2,2-tetraphenylethanediol (**12**) in 91% isolated yield. Once again, attempts to reductively couple alkyl ketones with Mn* gave a multicompound mixture, which was not identified.

Reductive Coupling of Aldimines. It was also found that the active manganese could be used for the coupling reaction of aldimines with Mn*. As shown in Scheme 1, mild reaction conditions, room temperature in THF, were used to carry out the reaction. The imines (**13** and **15**) and active manganese were allowed to stir overnight at room temperature. After appropriate workup, the corresponding vicinal diamines (**14** and **16**) were afforded in 62% and 56% isolated yields, respectively, with poor diastereoselectivity. ^{1}H NMR and ^{13}C NMR data are consistent with the literature values. Mechanism and optimization studies have not been conducted. However, we believe that this coupling also proceeds via a pinacol-type, single-electron-transfer (SET) mechanism.[2b] We were not able to detect any of the monoamines resulting from the reduction of the starting aldimines.

Conclusion

In conclusion, we have demonstrated that highly reactive manganese can be used for the reductive dimerization of aryl aldehydes, aryl ketones, and aldimines. With this highly reactive manganese, the corresponding coupling products, 1,2-diols and vicinal diamines, were obtained in good isolated yields. The diasteroselectivity is poor except for aryl ketones. It is well-known that pinacol coupling proceeds via a single-electron-transfer mechanism. Accordingly, this work demonstrates that the highly reactive manganese can be used as a good single-electron donor in organic synthesis. Other reactions are under investigation.

Experimental Section

General Methods. ^{1}H NMR (300 MHz) spectra were recorded in $CDCl_3$ or $CDCl_3$/DMSO-d_6 solution. All chemical shifts are reported in parts per million (δ) downfield from internal tetramethylsilane. Fully decoupled ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ or $CDCl_3$/DMSO-d_6 solution. The center peak of $CDCl_3$ (77.0 ppm) was used as the internal reference. Mass spectra were performed by the Nebraska Center for Mass Spectrometry at the University of Nebraska−Lincoln.

All manipulations were carried out under an atmosphere of argon on a dual manifold vacuum/argon system. The Linde prepurified-grade argon was further purified by passage over a BASF R3-11 catalyst column at 150 °C, a phosphorus pentoxide column, and a column of granular potassium hydroxide. Lithium, naphthalene, and metal halides were weighed out and charged into reaction flasks under in a Vacuum Atmospheres Co. drybox. Tetrahydrofuran was distilled immediately before use from Na/K alloy under an atmosphere of argon.

Analytical thin-layer chromatography was performed using Merck 5735 indicating plates precoated with silica gel 60 F254 (layer thickness 0.2 mm). The product spots were visualized with either UV light (254 nm) or a solution of vanillin. Preparative thin-layer chromatographic separations were obtained using Analtech silica gel GF (layer thickness 2 mm) preparative plates. Liquid chromatographic purifications were performed by flash column chromatography using glass columns packed with Merck silica gel 60 (230−400 mesh).

Preparation of Highly Reactive Manganese (Mn*). Highly reactive manganese was prepared by the reduction of anhydrous manganese halides (chloride, bromide, and iodide) with lithium using naphthalene as an electron carrier. In a typical preparation, lithium (9.68 mmol), naphthalene (1.48 mmol), and anhydrous manganese chloride (4.71 mmol) were stirred in freshly distilled THF (15 mL) for 1−3 h at room temperature. A black slurry was obtained and ready for use. (Note: The number of millimoles of Mn* cited in this paper refers to the theoretical amount possible, based on the original amount of anhydrous manganese halide).

A Typical Procedure for the Preparation of 1,2-Diols (2a−2h) from the Reactions of Aryl Aldehydes with Mn*. To a slurry of Mn* was added aryl aldehyde (0.5−0.8 equiv, based on Mn*) via syringe (or cannula) at room temperature. The resulting mixture was allowed to stir for 30 min to overnight. The reaction was monitored by TLC. After being stirred, the reaction was quenched with an aqueous solution of 3 M HCl (20 mL) and then extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated NaCl solution (2 × 30 mL) and dried over anhydrous $MgSO_4$. Evaporation of solvents and flash chromatography (hexanes/ethyl acetate) and/or recrystallization afforded the desired diols in the indicated yield and diastereoselectivity (Table 2).

Diol 2a (Mixture of dl/Meso-Isomers).[30] Recrystallization (hexanes/ethyl ether) of the crude mixture afforded **2a** in 86% yield: ^{1}H NMR ($CDCl_3$) δ 7.35−7.10 (m, 10H), 4.82, 4.69 (ss, 2H), 2.71 (br, 2H); ^{13}C NMR ($CDCl_3$) δ 139.83, 139.71, 128.17, 128.08, 128.04, 127.86, 127.06, 126.92, 79.05, 78.01; HRFAB-MS calcd for $C_{14}H_{14}O_2$ 217.0994, found $(M + Na)^+$ 237.0898.

Typical Procedure for the Preparation of 1,2-Diols from the Reaction of Aryl Ketones with Mn*. The standard procedure used for aryl aldehyde was followed with aryl ketone. Appropriate workup afforded 1,2-diols (**4**, **6**, **8**, **10**, and **12**) in 71−93% isolated yields.

Diol 4 (mixture of dl/meso-isomers) was obtained from recrystallization (hexanes/ethyl ether) of the crude mixture in 71% yield: ^{1}H NMR ($CDCl_3$) δ 7.27−7.18 (m, 10H), 2.58 (br, 2H), 1.60, 1.51 (ss, 6H); ^{13}C NMR ($CDCl_3$) δ 143.41, 127.34, 127.12, 127.03, 78.83, 24.92; HRFAB-MS calcd for $C_{16}H_{18}O_2$ 242.1307, found $(M + Na)^+$ 265.1197.

Reductive Coupling Reaction of Aldimines (13 and 15) into Vicinal Diamines (14 and 16). The standard procedure used for aryl aldehyde was followed using aldimine and Mn* prepared from MnI_2. During the workup step, the combined organic layers were washed with saturated $Na_2S_2O_3$ solution to remove iodine species from the reaction mixture. Flash chromatography (hexanes/ethyl acetate) afforded the corresponding vicinal diamines in 62% and 56% isolated yields, respectively.

Diamine 14 (Mixture of dl/Meso-Isomers). Flash chromatography (hexanes/ethyl acetate) of the crude mixture afforded **14** in 62% yield: ^{1}H NMR ($CDCl_3$) δ 7.25−6.52 (m, 20H), 4.95, 4.57 (ss, 4H); ^{13}C NMR ($CDCl_3$) δ 146.49, 139.90, 138.21, 129.20, 129.08, 128.40, 128.26, 127.56, 127.51, 127.35, 118.10, 117.82, 114.09, 113.74, 63.97, 61.96; HRFAB-MS calcd for $C_{26}H_{24}N_2$ 364.1939, found $(M + H)^+$ 365.2023.

(30) The α-proton to the hydroxyl group in the *dl*-isomer appears ca. 0.1−0.2 ppm higher field than that of the meso-isomer: see ref 12k.

Diamine 16 (Mixture of dl/Meso-Isomers). Flash chromatography (hexanes/ethyl acetate) of the crude mixture afforded **16** in 56% yield: ^{1}H NMR ($CDCl_3$) δ 7.33−7.19 (m, 16H), 6.99−6.98 (m, 4H), 3.77, 3.76 (ss, 2H), 3.44 (center of AB system, J = 17.1 Hz, 4H), 1.72 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 140.80, 140.31, 128.58, 128.34, 128.17, 127.86, 127.63, 126.65, 67.17, 50.91.

Acknowledgment. The financial support provided by the National Science Foundation is gratefully acknowledged.

Supporting Information Available: Characterization data of **2b**−**h**, **6**, **8**, **10**, and **12** and copies of the ^{1}H and ^{13}C NMR spectra for **2a**−**h**, **4**, **6**, **8**, **10**, **14**, and **16** (33 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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