Mn-Catalyzed Three-Component Reactions of Imines/Nitriles, Grignard Reagents, and Tetrahydrofuran: An Expedient Access to 1,5-Amino/Keto Alcohols

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Ⓢ *Supporting Information*

ABSTRACT: An expedient Mn-catalyzed three-component synthesis of 1,5-amino/keto alcohols from Grignard reagents, imines/nitriles, and tetrahydrofuran (THF) is described, which deviates from the classic Grignard addition to imines/nitriles in THF solvent. THF is split and "sewn" in an unprecedented manner in the reaction, leading to the formation of two geminal C–C bonds via C–H and C–O cleavage. Mechanistic experiments and DFT calculations reveal radical and organo-Mn intermediates in the catalytic cycle and the α-arylative ring-opening of THF as the key reaction step.

Since the pioneering discovery of organomagnesium compounds by V. Grignard, the use of Grignard reagents has been an indispensable tool for C–C bond formation in organic synthesis.[1] Among various reactions of Grignard reagents, their addition to unsaturated C–N bonds of imines and nitriles has evolved as a textbook approach to a plethora of amines and ketones, respectively (Scheme 1).[1,2] Generally,

Scheme 1. Classic and Interrupted Grignard Additions to Imines/Nitriles in THF
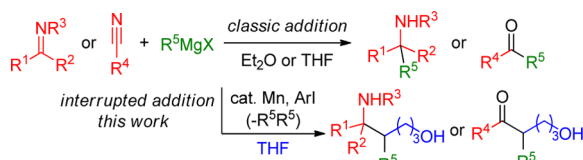
ethereal solvents like diethyl ether and tetrahydrofuran (THF) are the most reliable reaction media for these transformations because Grignard reagents are highly soluble and reactive in them. In a broader sense, THF has long been employed as solvent in preparations and reactions of various organometallics. In general, THF is inert to organometallics at low temperature, but deprotonation at α-C of THF was observed when strong organo-Li bases were used.[3] Recently, Mulvey et al. elegantly demonstrated the "synergetic sedation" of hypersensitive α-metalated THF by adopting a bimetallic reagent, sodium zincate.[4a] Notably, this mixed-metal strategy allows low-electropositive metals (Zn, Mg, Mn, etc.) to metalate THF, which was previously achieved only with highly electropositive metals like Li. Remarkably, the same group further showed that the more
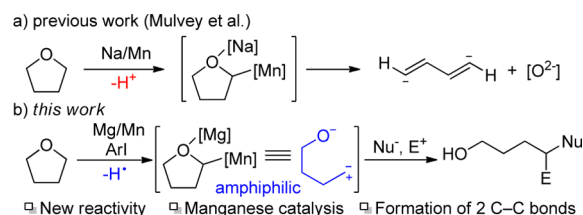

Figure 1. Approaches toward α-manganated THF and its reactivities. Na/Mn = (TMEDA)Na(TMP)(CH$_2$SiMe$_3$)Mn(TMP). Mg/Mn = RMgX and Mn(TMHD)$_3$ or RMgX and MnCl$_2$.

reactive bimetallic base Na/Mn (or Na/Mg) could α-deprotonatively metalate and further dismember THF into a butadienyl dianion and an oxide anion, which were both captured by metal ions to form the final products (Figure 1a).[4b,c] In marked contrast to these reactions of THF, here we disclose an unprecedented radical approach to α-manganated THF, which reacts as a formal 1-butoxide 4-carbenoid equivalent, using a bimetallic combination of Mn and Mg compounds in the presence of an aryl iodide (Figure 1b). Thus, THF was induced to react with both a nucleophilic Grignard reagent and an electrophilic imine/nitrile at its C-2 position to generate two geminal C–C bonds (Scheme 1).[5] A wide range of 1,5-amino and -keto alcohols is efficiently accessed by this three-component reaction, which deviates from the classic addition of Grignard reagents to imines and nitriles.

Despite its abundance in the Earth's crust, Mn has been only sporadically exploited for C–C bond formation via catalytic cleavage of inert C–H bonds, unlike noble transition metals.[6,7] As part of our ongoing interest in Mn-catalyzed C–H transformations,[6c,7b] we initially attempted to realize Mn-catalyzed hydroarylation of diphenylacetylene with N-4-bromobenzylidene aniline **1a** using phenylmagnesium bromide (PhMgBr) as an activating reagent for Mn (eq 1). Surprisingly, instead of the desired C–H alkenylation product **4**, 1,5-amino alcohol **3aa** was obtained in 23% isolated yield, which might derive from the three-component reaction of imine **1a**, PhMgBr, and THF. Intriguingly, N-benzylidene aniline **1b**, an analogue of **1a**, did not afford the corresponding product **3ba** under otherwise identical conditions, suggesting a crucial role of the C$_{aryl}$–Br bond of **1a**. Inspired by Nakamura's work on organo-Fe-triggered C$_{aryl}$–I cleavage,[8] we assumed that an organo-Mn-

eq 1

1a: R = Br
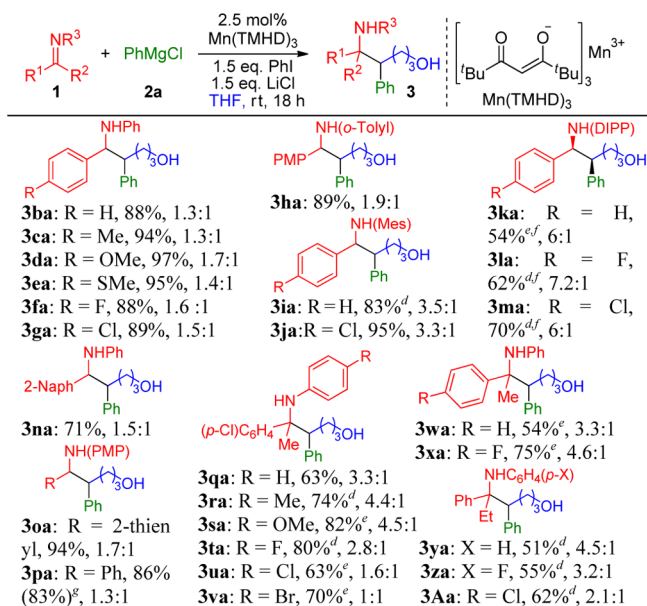**1b:** R = H

3aa 23%
3ba 0% (27% with PhI)

4 *not observed*
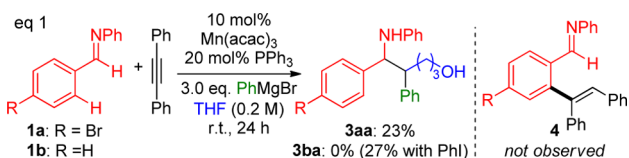
initiated split of the C_{aryl}–Br bond of **1a** to give an aryl radical might operate in our reaction. We also envisioned that addition of iodobenzene (PhI) as an external radical provider would make the reaction applicable to simple imine **1b**. To our delight, **3ba** was indeed isolated in 27% yield when the reaction of **1b** was conducted in the presence of PhI.
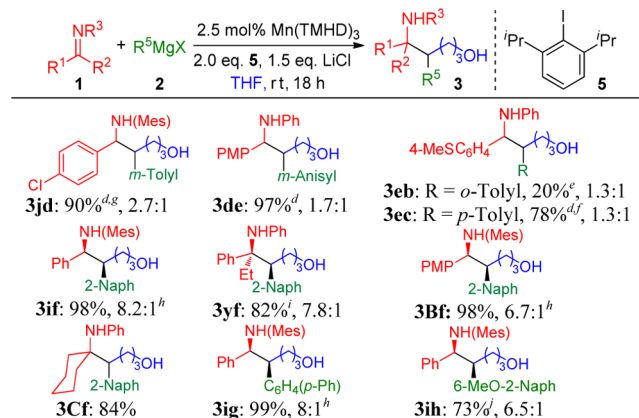
After extensive screening of reaction conditions,[9] we were gratified to find that, with 2.5 mol% of $Mn(TMHD)_3$, 1.5 equiv of LiCl, and 1.5 equiv of PhI, the three-component reaction delivered product **3ba** in 88% isolated yield at room temperature (Scheme 2). It is worth noting that **3ba** was also obtained in reasonable yields with inexpensive $MnCl_2$ and $Mn(acac)_2$, among other Mn catalysts. Moderate yields of **3ba** were achieved with iron catalysts like $Fe(acac)_3$, while cobalt catalysts showed no effect in this reaction.[9] With the optimal conditions secured, we set out to explore the scope of imines (Scheme 2). Imines derived from benzaldehydes bearing both electron-donating and -withdrawing groups reacted smoothly with **2a** and THF, affording 1,5-amino alcohols **3ba–ga** in excellent yields. Benzylic and (thio)etheric α-C–H bonds were well tolerated (**3ca–ea**). The *p*-fluoro and -chloro substituents remained intact after reaction (**3fa–ga**).[10] The diastereomeric ratio (dr) of the products increased to 7.2:1 in the case of imines bearing N-aryl groups with enhanced steric hindrance (**3ha–ma**). Imines originating from 2-naphthaldehyde and 2-thienaldehyde were

Scheme 2. Scope of Imines[a,b,c]

3ba: R = H, 88%, 1.3:1
3ca: R = Me, 94%, 1.3:1
3da: R = OMe, 97%, 1.7:1
3ea: R = SMe, 95%, 1.4:1
3fa: R = F, 88%, 1.6:1
3ga: R = Cl, 89%, 1.5:1

3ha: 89%, 1.9:1

3ka: R = H, 54%[e,f], 6:1
3la: R = F, 62%[d,f], 7.2:1
3ma: R = Cl, 70%[d,f], 6:1

3ia: R = H, 83%[d], 3.5:1
3ja: R = Cl, 95%, 3.3:1

3na: 71%, 1.5:1

3oa: R = 2-thienyl, 94%, 1.7:1
3pa: R = Ph, 86% (83%)[g], 1.3:1

3qa: R = H, 63%, 3.3:1
3ra: R = Me, 74%[d], 4.4:1
3sa: R = OMe, 82%[e], 4.5:1
3ta: R = F, 80%[d], 2.8:1
3ua: R = Cl, 63%[e], 1.6:1
3va: R = Br, 70%[e], 1:1

3wa: R = H, 54%[e], 3.3:1
3xa: R = F, 75%[e], 4.6:1

3ya: X = H, 51%[d], 4.5:1
3za: X = F, 55%[d], 3.2:1
3Aa: R = Cl, 62%[d], 2.1:1

[a]Reaction condtions: **1** (2.0 mmol), **2a** (8.0 mmol), $Mn(TMHD)_3$ (0.05 mmol), PhI (3.0 mmol), LiCl (3.0 mmol), THF (15 mL), rt, 18 h. [b]Combined isolated yields and dr values of **3** are shown. [c]dr values were determined by ^{1}H NMR analysis of the reaction mixture. [d]$Mn(TMHD)_3$ (0.1 mmol). [e]$Mn(TMHD)_3$ (0.1 mmol), PhMgCl (10 mmol), PhI (4.0 mmol). [f]Yield of *syn* isomer. [g]10 mmol scale. PMP = *p*-methoxyphenyl, Mes = 2,4,6-trimethylphenyl, DIPP = 2,6-diisopropylphenyl.

Scheme 3. Scope of Grignard Reagents[a,b,c]

3jd: 90%[d,g], 2.7:1
3de: 97%[d], 1.7:1
3eb: R = *o*-Tolyl, 20%[e], 1.3:1
3ec: R = *p*-Tolyl, 78%[d,f], 1.3:1

3if: 98%, 8.2:1[h]
3yf: 82%[i], 7.8:1
3Bf: 98%, 6.7:1[h]

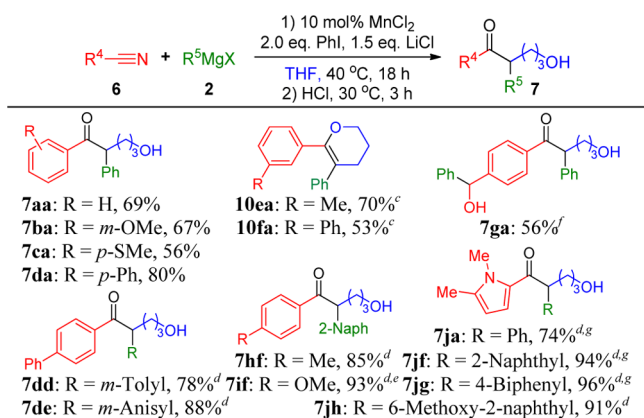**3Cf:** 84%
3ig: 99%, 8:1[h]
3ih: 73%[j], 6.5:1

[a]Reaction conditions: **1** (2.0 mmol), **2** (X = Br, 10 mmol), $Mn(TMHD)_3$ (0.05 mmol), **5** (4.0 mmol), LiCl (3.0 mmol), THF (15 mL), rt, 18 h. [b]Combined isolated yields and dr values of **3** are shown. [c]dr values were determined by ^{1}H NMR analysis of the reaction mixture. [d]RMgCl was used. [e]^{1}H NMR yield on 0.2 mmol scale with 2-methyliodobenzene and *o*-TolylMgCl. [f]$Mn(TMHD)_3$ (0.1 mmol), **5** (3.0 mmol). [g]**2d** (8.0 mmol), **5** (3.0 mmol). [h]Major diastereoisomers are shown. [i]Yield of (*SR*,*SR*) isomer. [j]Yield of *syn* isomer.

also amenable to the reaction, giving **3na–oa** with ease. Notably, the reaction can be easily scaled up to deliver gram quantities of 1,5-amino alcohol **3pa** without a substantial decline in yield. Sterically congested ketimines could also be adopted to furnish the desired products **3qa–3Aa** successfully, with a range of groups on the N-aryl moiety, such as F, Cl, and Br, being well compatible with the reaction.

While varying Grignard reagent R^5MgX, we found that both R^5 and Ph groups were incorporated at the 4-position of the corresponding 1,5-amino alcohols. The latter might be ascribed to Mg/I exchange between R^5MgX and PhI in the reaction.[11] To circumvent this, we screened a series of iodoarenes.[9] To our delight, using 2,6-diisopropyliodobenzene (**5**), we were able to completely inhibit the Mg/I exchange, presumably due to the steric hindrance of **5**. We then examined the scope of Grignard reagents (Scheme 3). *m*-Tolyl, *m*-anisyl, and *p*-tolyl Grignard reagents participated smoothly in the reaction to provide 1,5-amino alcohols **3jd**, **3de**, and **3ec** in good to excellent yields. The reaction of *o*-tolylmagnesium chloride was rather sluggish, presumably due to steric hindrance (**3eb**). 2-Naphthyl and 4-biphenyl Grignard reagents displayed generally superior performance to PhMgCl in terms of both product yields and reaction diastereoselectivities (**3if–h**, **3yf**, **3Bf–Cf**). Of note, the use of aliphatic Grignard reagents gave no desired products under the current reaction conditions.

Encouraged by the above results, we further extended the reaction from imines to nitriles. Specifically, under slightly modified conditions,[9] a wide range of 1,5-keto alcohols were obtained in good to excellent yields by the $MnCl_2$-catalyzed three-component reaction (Scheme 4). In sharp contrast, rather low catalytic activity was observed when an Fe or Co salt was used instead of the Mn catalyst.[9] Of note, 1,5-keto alcohols derived from *m*-methyl- and -phenylbenzonitriles suffered a facile dehydrative cyclization, affording dihydropyrans **10ea–fa** upon treatment with (±)-camphor-10-sulfonic acid (CSA). When *p*-formylbenzonitrile was subjected to the reaction, the expected three-component coupling was accompanied by addition of
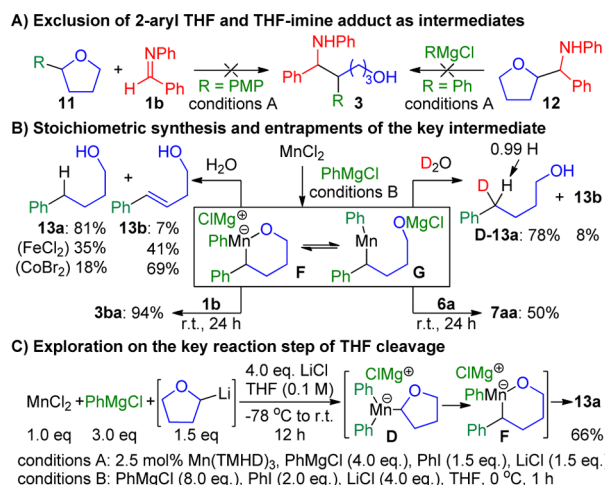
Scheme 4. Three-Component Couplings of Nitriles, Grignard Reagents, and THF[a,b]

R^4—≡N + R^5MgX
6   **2**

1) 10 mol% $MnCl_2$
2.0 eq. PhI, 1.5 eq. LiCl
THF, 40 °C, 18 h
2) HCl, 30 °C, 3 h

R^4 ⟶ $\overset{O}{C}$ — $\overset{R^5}{C}$ — ~~~~OH
7

7aa: R = H, 69%
7ba: R = m-OMe, 67%
7ca: R = p-SMe, 56%
7da: R = p-Ph, 80%

10ea: R = Me, 70%[c]
10fa: R = Ph, 53%[c]

7ga: 56%[f]

7dd: R = m-Tolyl, 78%[d]
7de: R = m-Anisyl, 88%[d]

7hf: R = Me, 85%[d] **7jf:** R = 2-Naphthyl, 94%[d,g]
7if: R = OMe, 93%[d,e] **7jg:** R = 4-Biphenyl, 96%[d,g]

7ja: R = Ph, 74%[d,g]
7jh: R = 6-Methoxy-2-naphthyl, 91%[d]

[a]Reaction conditions: **6** (1.0 mmol), **2** (5.0 mmol), $MnCl_2$ (0.1 mmol), PhI (2.0 mmol), LiCl (1.5 mmol), THF (25 mL), 40°C, 18 h, then HCl (2.5 M, 10 mL), 30°C, 3 h. [b]Isolated yields of **7** are shown. [c]The keto alcohol partially dehydrated to **10** under vacuum after column chromatography and was subjected to the following conditions to obtain a single product: CSA (0.05 mmol), PhH (40 mL), reflux. [d]**5** was used instead of PhI. [e]Hydrolyzed at 50°C. [f]p-Formylbenzonitrile as the substrate, PhMgCl (6.0 mmol). [g]Hydrolyzed for 5 h.

PhMgCl to the formyl group, leading to **7ga** in one pot. Finally, pyrrole-2-carbonitrile, as an example of heterocyclic nitriles, was also amenable to this protocol, giving 1,5-keto alcohols **7ja** and **7jf–h** efficiently.

The 1,5-situated amino/keto and hydroxyl functionalities in the reaction products **3** and **7** provide convenient handles for further synthetic elaborations such as intramolecular cyclizations to give rise to piperidines **8**, **9** (after deprotection) and dihydropyrans **10**,[9] whose skeletons are often found as key structural motifs in natural products and important pharmaceutical compounds.[12]
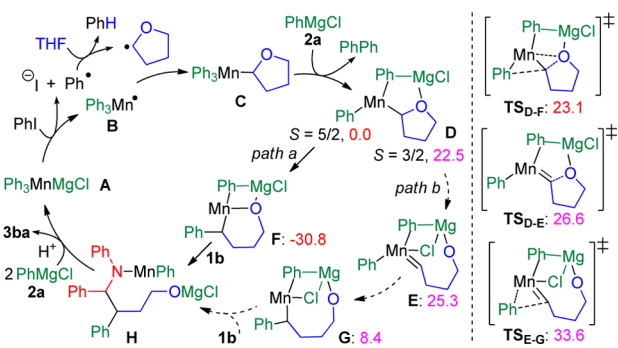
The groups of Oshima[5i] and Nakamura[8] demonstrated that 2-aryl THFs such as **11** could be generated from aryl Grignard reagents and THF by EtMgBr/t-BuCH₂I or under Fe catalysis. Also, Tomioka et. al described the Me_2Zn/air-promoted formation of THF-imine adducts like **12** from imines and THF.[13] To test the possible intermediacy of these two-component products, **11** and **12** were first synthesized and then subjected individually to the catalytic reaction conditions (Scheme 5A). It turned out that no formation of the three-component product **3** was detected after reaction, which excludes the intermediacy of **11** and **12**. Next, we conducted a number of stoichiometric reactions to probe the real reaction intermediates. To our delight, in the presence of PhI and LiCl, treatment of $MnCl_2$ with excessive PhMgCl in THF at 0°C for 1 h did keep the reaction in a two-component stage, at which point various electrophiles were added to trap the reaction intermediate (Scheme 5B). When water was used, phenylbutanol **13a** was obtained as a major product, with formation of a small amount of contaminant phenylbutenol **13b**. Interestingly, the yield of **13a** decreased dramatically and **13b** was formed as the major product when $FeCl_2$ or $CoBr_2$ was employed instead of $MnCl_2$. This result suggested the existence of a C–M (M = Mn, Fe, Co) bond in the reaction intermediate, and the amount of **13b** reflected the varied propensity of these organometallic species for β-H elimination. Quenching the reaction with D_2O resulted in quantitative incorporation of one deuterium atom

Scheme 5. Mechanistic Experiments[a,b]

A) Exclusion of 2-aryl THF and THF-imine adduct as intermediates

11 + **1b** ⟶ **3** ⟵ **12**
R = PMP, conditions A   R = Ph, conditions A

B) Stoichiometric synthesis and entrapments of the key intermediate

13a 81% (FeCl₂) 35% (CoBr₂) 18%
13b 7% (FeCl₂) 41% (CoBr₂) 69%
D-13a: 78%   8%

F ⇌ **G**

3ba 94% ⟵ **1b**, r.t., 24 h   **6a**, r.t., 24 h ⟶ **7aa** 50%

C) Exploration on the key reaction step of THF cleavage

$MnCl_2$ + PhMgCl + THF-Li
1.0 eq   3.0 eq   1.5 eq

4.0 eq. LiCl
THF (0.1 M)
–78 °C to r.t.
12 h

D ⟶ **F** ⟶ **13a** 66%

conditions A: 2.5 mol% Mn(TMHD)₃, PhMgCl (4.0 eq.), PhI (1.5 eq.), LiCl (1.5 eq.).
conditions B: PhMgCl (8.0 eq.), PhI (2.0 eq.), LiCl (4.0 eq.), THF, 0 °C, 1 h

[a]All reactions were carried out on 0.2 mmol scale. [b]Yields and the deuterium ratio were determined by ¹H NMR.

into the benzylic position of the product (**D-13a**), again confirming the presence of the C–M bond. When imine **1b** and benzonitrile **6a** were subjected to the reaction, 1,5-amino alcohol **3ba** and 1,5-keto alcohol **7aa** were obtained, respectively, suggesting that the stoichiometric and catalytic reactions might share a common intermediate. Collectively, we proposed that a six-membered manganacycle **F** and/or an open-chain organo-Mn species **G** were/was formed in the reaction. We also envisioned that **F** might be generated by rearrangement of a phenyl α-THF manganate **D** (Scheme 5C). Accordingly, α-THF lithium was prepared in situ and treated with $MnCl_2$ and PhMgCl in the absence of PhI. As a result, **13a** was indeed obtained in 66% yield, which supported our hypothesis.

Based on literature clues and the above experimental observations, a plausible mechanism is shown in Scheme 6.

Scheme 6. Proposed Reaction Mechanism with DFT Study[a]

A Ph₃MnMgCl
B Ph₃Mn•
C Ph₃Mn-THF
D S = 5/2, 0.0 ; S = 3/2, 22.5
path a / path b
F: -30.8
E: 25.3
G: 8.4
H
3ba

TS_D-F: 23.1
TS_D-E: 26.6
TS_E-G: 33.6

[a]DFT-computed relative Gibbs free energies ΔG (kcal/mol) are marked, taking **D** (S = 5/2) as zero point.

First, single electron transfer from the triarylmanganate(II) **A** to iodoarene gives rise to species **B** and an aryl radical,[14] which abstracts the α-H of THF afterward. The resulting α-THF radical combines with **B** to form Mn(IV) complex **C**, which undergoes reductive elimination and transmetalation affording α-THF manganate(II) **D**. Two possible pathways might account for the subsequent C–O cleavage of intermediate **D**: (1) ring expansion with concomitant 1,2-aryl migration leading to six-membered manganacycle **F** (path a)[15] and (2) α-O elimination of **D** giving

6560

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manganese carbene complex **E**, followed by a 1,2-aryl shift affording intermediate **G** (path b). To distinguish these two possibilities, we performed the corresponding DFT calculations. Due to the open-shell character of Mn(II) system, all three electronic states were explored.[9] It turned out that only high ($S = 5/2$) and medium ($S = 3/2$) spin states are energetically relevant in the reaction and promote different THF ring-opening modes. In the ground high-spin state, transition state TS_{D-F} is located that directly links **D** and **F** via a rearrangement of four chemical bonds in a concerted but nonsynchronized manner with a reaction barrier of 23.1 kcal/mol. In contrast, in the medium spin state, C–O breakage takes place first through TS_{D-E} to generate **E**, followed by 1,2-aryl migration through TS_{E-G} to form **G**. Because the medium-spin-state reaction profile is always higher in energy than the high-spin one,[9] we conclude that the reactivity in the high-spin state (path a) dominates the reaction. The ensuing insertion of imine **1b** into the C–Mn bond of **F** provides **H**. Final transmetalation regenerates **A** and produces 1,5-amino alcohol **3ba** after quenching with water. In addition, LiCl might contribute to tuning the reactivity and stability of organo-Mn species in the catalytic cycle.[16]

In summary, a first Mn-catalyzed three-component reaction of Grignard reagents, imines/nitriles, and THF has been developed, by which a wide range of 1,5-amino/keto alcohols is expediently synthesized in a convergent manner. Strikingly, THF is formally transformed by the Mn/Mg bimetallic system into a 1-butoxide 4-carbenoid equivalent, which reacts amphiphilically with both electrophilic and nucleophilic reagents. The reaction also features Mn catalysis, low-cost and readily accessible starting materials, reliable scalability, and mild reaction conditions. Simple derivatizations of the 1,5-amino/keto alcohols provide a facile access to piperidines and dihydropyrans. Experimental and computational mechanistic studies disclose the pivotal role of Mn in the radical initiation, C–O bond cleavage, and formation of two geminal C–C bonds. Considering that hundreds of thousands of tonnes of THF is produced annually, exploration of THF as a versatile building block holds great promise in organic synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental and computational details, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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