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Mg-promoted mixed pinacol coupling ☆

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Abstract—Mg-promoted reduction of a mixture of aromatic ketones (or imines) and aliphatic carbonyl compounds in *N,N*-dimethylformamide (DMF) brought about unique mixed pinacol type of cross coupling to give unsymmetrical vicinal diols (or amino alcohols) or α-hydroxyketones in good to moderate yields. The reaction may be initiated by electron transfer from magnesium metal to an aromatic carbonyl compound possessing a less negative reduction potential. The difference of reduction potential between aromatic ketones (or imines) and aliphatic carbonyl compounds was found to be one of the important key factors in this selective cross coupling.

Coupling between carbonyl groups such as pinacol coupling, McMurry coupling, and acyloin condensation is one of the most important reactions in organic chemistry, and has been extensively studied from synthetic and mechanistic aspects.[1–5]

Especially, reductive dimerization of aldehydes and ketones by electron transfer process has been well-known as 'pinacol coupling' on which much attention has been focused as useful and important methods for construction of vicinally heteroatom-functionalized compounds such as 1,2- diols.[6–19] Numerous and extensive studies have been accomplished for the homo-coupling of same carbonyl compounds including asymmetric induction. Only a little, however, have been reported for mixed pinacol coupling of different carbonyl compounds as yet[7,8] although their synthetic utility may be relatively limited owing to small applicable range for reduction potential such as Zn, less generality and/or troublesome procedure.

On the other hand, we have found that reductive cross-coupling of aromatic carbonyl compounds with acid chlorides[20] was efficiently promoted by magnesium turnings through electron transfer process to give the corresponding C-acylation products in good yields.

In this study, we wish to report unique and convenient Mg-promoted mixed pinacol coupling of aromatic ketones (or imines) and aliphatic carbonyl compounds to give unsymmetrical vicinal diols (or amino alcohols) in good to moderate yields.

Typical procedure is as follows: To a 100 mL three-necked round flask equipped with a thermometer and a dropping funnel was placed magnesium turnings for Grignard reagent (25 mmol) in dry DMF (25 mL). After cooling the flask in an ice–salt bath, a mixture of aromatic ketone (**1**) (5 mmol), aliphatic carbonyl compound (**2**) (50 mmol), and trimethylchlorosilane (TMSCl: 25 mmol) in DMF (20 mL) was added under magnetic stirring over 30 min. The reaction mixture was allowed to stir at room temperature overnight and was extracted with ether. After evaporation of the solvent under reduced pressure, the crude material was dissolved into 50 mL of methanol with stirring. Aqueous 5% sulfuric acid was carefully added into the methanol solution and the reaction mixture was stirred for 6 h at room temperature. After neutralization, the reaction mixture was treated through usual work-up and the product **3** was purified through column chromatography.

Thus, treatment of a mixture of acetophenone (**1a**) and a large excess of acetone with magnesium turnings in DMF at room temperature followed by acid-catalyzed hydrolysis afforded the cross-coupling product,

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2-phenyl-3-methyl-butan-2,3-diol (**3a**), in 70% yield as the main product. The symmetrical pinacol-coupling product of acetone and aldol condensation product were not observed in this coupling although simply reduced product and pinacol coupling product of acetophenone were detected in gas chromatographic analysis in 1–2% yield, respectively. Stereochemistry of **3i**,**j**, and **3m** were determined through comparison of ^{1}H NMR spectra of the products with those of authentic samples in the literature.[21]

Though commercially easily available magnesium turning for Grignard reaction could be employed without any pre-treatment, some addition of TMSCl was needed for smooth proceedings of the reaction, possibly through continuous activation of magnesium surface.

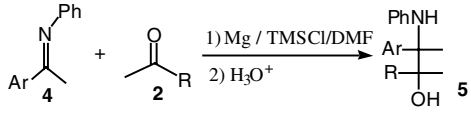
Under the similar conditions, Mg-promoted cross-coupling reactions of various kind of aromatic carbonyl ketones (**1**) with aliphatic ketones and aldehydes (**2**) gave the corresponding vicinal diols (**3**) in moderate to good yields, as shown in Table 1.

In this reaction, steric bulkiness of alkyl groups of the substrates (**1**), (**2**) was found to give a noteworthy effect on product yield. Thus, increase in bulkiness of alkyl groups of aromatic ketones (**1**) and those of aliphatic ketones (**2**) brought about some decrease in the yields of **3** (Table 1, **3a**–**c**, **3n**), and similar tendency was also observed in the case of alicyclic ketones (Table 1, **3p**,**q**) while those of aliphatic aldehydes gave less effects on product yield (Table 1, **3i**–**m**), possibly owing to suitable balance between less reactivity toward reduction by Mg and steric hindrance. Presence of an electron-donating group in aromatic ring of acetophenone showed some decrease in the product yield (Table 1, **3d**,**e**,**g**).

Furthermore, aromatic and heteroaromatic imino compounds (**4**) were also found to be usable for the present cross-coupling with acetone followed by hydrolysis to give the corresponding 1,2-amino alcohols (**5**) in moderate to good yields (Table 2).

Similar treatment of diketones (**6**) bearing both of aromatic and aliphatic carbonyl groups in the same molecule, with Mg metal in the presence of TMSCl brought about facile and selective intramolecular reductive cyclization to give the corresponding bis(trimethylsilyl) ethers of 1,2-cycloalkanediols (**7**) in good yields, as shown in Table 3. It is noteworthy that even the 4-membered product (**7a**,**c**) with some ring strain was

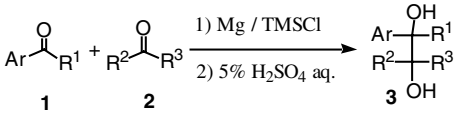
Table 2. Mg-promoted unsymmetrical pinacol coupling between aromatic imine and aliphatic carbonyl compounds



Entry	Ar	R		Yield (%)	RP (**4**)
1	Ph	CH_3	**5a**	85	−2.23
2	Ph	CH_3CH_2	**5b**	41[a]	—
3	2-Pyridyl	CH_3	**5c**	57	−2.04
4	2-Thienyl	CH_3	**5d**	64	−2.18
5	2-Furanyl	CH_3	**5e**	58	−2.24

Reaction conditions: 1%Bu_4NClO_4/DMF, rt, sweep rate 200 mV/s, working electrode: Pt, counter electrode: Pt, reference electrode: Ag/AgCl.
[a] Diastereoisomer ratio (50:50).
[b] Reduction potential (V vs Ag/AgCl).

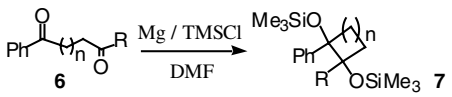
Table 1. Mg-promoted unsymmetrical pinacol coupling



Ar	R^1	R^2	R^3	Yield (%)/**3**	
C_6H_5	CH_3	CH_3	CH_3	**3a**	70
C_6H_5	CH_3CH_2	CH_3	CH_3	**3b**	43
C_6H_5	$CH_3CH_2CH_2$	CH_3	CH_3	**3c**	46
m-$CH_3C_6H_4$	CH_3	CH_3	CH_3	**3d**	53
p-$CH_3C_6H_4$	CH_3	CH_3	CH_3	**3e**	36
m-$CH_3OC_6H_4$	CH_3	CH_3	CH_3	**3f**	60
p-ClC_6H_4	CH_3	CH_3	CH_3	**3g**	40
m-FC_6H_4	CH_3	CH_3	CH_3	**3h**	53
C_6H_5	CH_3	CH_3	H	**3i**	44[a]
C_6H_5	CH_3	CH_3CH_2	H	**3j**	55[a]
C_6H_5	CH_3	$CH_3CH_2CH_2$	H	**3k**	66[a]
C_6H_5	CH_3	$(CH_3)_2CH$	H	**3l**	56[a]
C_6H_5	CH_3	$(CH_3)_3C$	H	**3m**	64[a,b]
C_6H_5	CH_3	CH_3CH_2	CH_3	**3n**	32[a]
C_6H_5	CH_3	$-(CH_2)_4-$		**3p**	44
C_6H_5	CH_3	$-(CH_2)_5-$		**3q**	49

[a] Diastereoisomers ratio (55:45–80:20). The structures of major isomers are not clear.
[b] *erythro*:*threo*=8:2.

Table 3. Intramolecular cyclization of dicarbonyl compounds



Entry	R	*n*		Yield (%)/**3**
a	CH_3	1	**7a**	73 (60:40)[a]
b	CH_3	2	**7b**	88 (60:40)[a]
c	H	1	**7c**	69 (80:20)[a]
d	H	2	**7d**	78 (55:45)[a,b]
e	H	3	**7e**	76 (60:40)[a,c]

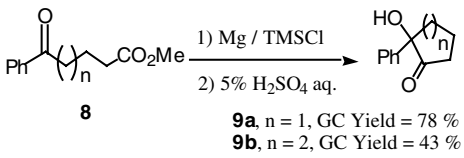
[a] Diastereoisomers ratio.
[b] *trans*:*cis*=8:2.
[c] Product is glycol.

obtained in good yield. The structure of the major isomer of **7c** was determined through ^{1}H NMR spectra since a signal of methin proton of the trans isomer in 4-membered ring showed a high field-shift attributed to ring current of the aromatic ring.

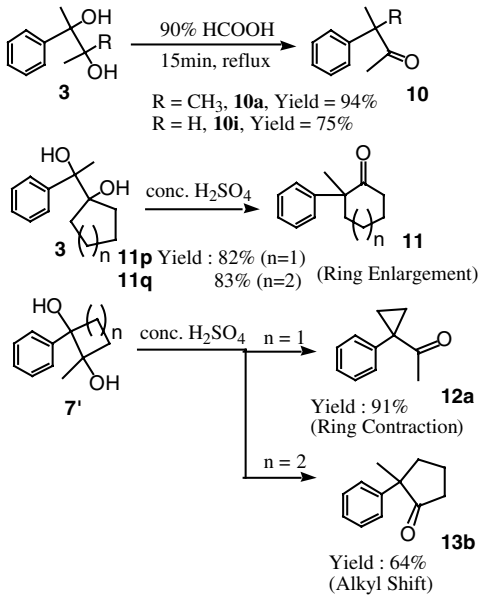
On the other hand, intramolecular cyclization of keto-esters (**8**) could be accomplished to form 5- and 6-membered ring, α-hydroxy-α-phenylcycloalkanones (**9**), as shown in Scheme 1. However, construction of a 4-membered ring product failed to give simply reduced product as a main product in this case.

Acid-catalyzed treatment of the unsymmetrical 1,2-diol derivatives (**3**), (**7**) obtained from the present unique cross coupling provided a various types of rearrangement, such as homologated alkyl shift, ring enlargement, and ring contraction. Thus, pinacol rearrangement of 2-phenyl-2,3-butanediols (**3a**,**i**) obtained by the coupling between acetophenone and acetone led to selective alkyl or hydride-shift, respectively, giving 2-butanones (**10**) in excellent to good yields. Furthermore, ring enlargement was observed on treatment of 1-(1-hydroxy-1-phenylethyl)-cycloalkanols (**3p**,**q**) with concd sulfuric acid at −5–0 °C to afford the corresponding 1-phenyl-1-methylcyclohexanone (**11p**) and cycloheptanone (**11q**) in 82–83% yields, respectively.

It may be quite interesting that the similar acid-catalyzed reaction of 1-phenyl-2-methyl-1,2-cyclobutanol (**7a′**) unexpectedly brought about ring contraction to give 1-phenyl-1-acetylcyclopropane (**12a**) in 91% yield, possibly because of fast rearrangement of a cyclobutyl to a cyclopropylcarbinyl cation stabilized by nonclassical conjugation[1] (Scheme 2).



Scheme 1.



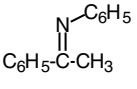
Scheme 2.

From measurement of cyclic voltammetry of some substrates as shown in Tables 2 and 4, the following scheme shown in Scheme 3 may be postulated as one of the most plausible reaction mechanism for the present unsymmetrical pinacol coupling.

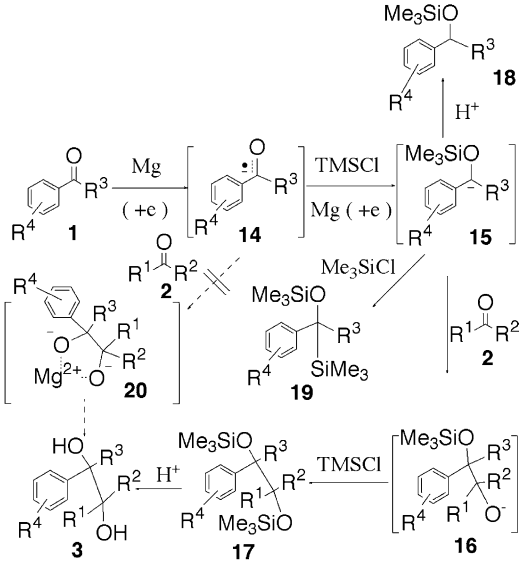
Less negative reduction potentials of aromatic carbonyl compounds ($E_p = -2.05$ to -2.23 V vs Ag/AgCl) in comparison with those of aliphatic carbonyl compounds and TMSCl (E_p =more negative than 3.00 V) indicates that the reaction may be initiated by electron transfer from Mg metal to the carbonyl group of acetophenones (**1**) or the imino group of acetophenone imines (**4**). The generated corresponding anion radicals (**14**) may be subjected to electrophilic attack of TMSCl to the oxygen atom of the carbonyl groups followed by the fast electron transfer, giving α-siloxybenzylic anions (**15**), which may react with aliphatic carbonyl compounds followed by O-silylation to form the mixed coupling products (**17**).

Since it is suggested that standard reduction potential of magnesium metal in aqueous solvent system will be

Table 4. Cyclic voltammetry of aromatic and aliphatic carbonyl compounds and aromatic imine

Reduction potential (V)	
C_6H_5–CO–CH_3	−2.10
C_6H_5–CO–CH_2–CH_2–CO–CH_3	−2.05
	−2.23
CH_3–CO–CH_3	−2.96
$CH_3CH_2CH_2$–CHO	−2.93

Reaction conditions: 1%Bu_4NC1O_4/DMF, rt, sweep rate 200 mV/s, working electrode: Pt, counter electrode: Pt, reference electrode: Ag/AgCl.



Scheme 3.

2.37–2.50 V,[22] this fact may also support that reduction of aliphatic carbonyl group is difficult in this reduction system.

It would be postulated as an another pathway that the second electron transfer prior to electrophilic attack of TMSCl to radical anion followed by second electron transfer might generate the coupled dianion species (**20**) coordinated with Mg^{2+} cation. However, no diastereoselective formation of the coupling products may deny this possibility since the intermediacy of the complex intramolecular magnesium dialkoxide would give high diastereoselectivity in formation of the products.

As a conclusion, Mg-promoted reduction of aromatic ketones and imines in the presence of excess amount of aliphatic ketones or aldehydes gave mixed pinacol products, 1,2-diols or 1,2-aminoethanols in good to moderate yield. The reaction is characterized by unique reaction pattern, simple procedure, mild reaction conditions, use of biologically friendly Mg metal, reasonable yield, and much usefulness of the products.

Supplementary Material. Experimental procedures and characterization for structure of the compounds **3**, **5**,**7**,**9**, **10**, **11**, and **13** are available.

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