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A NOVEL AND EFFICIENT DARZENS REACTION CATALYZED BY MAGNESIUM BROMIDE

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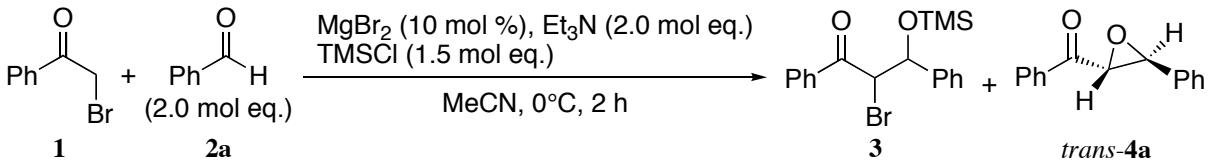
Abstract – The Darzens reaction of phenacyl bromide with aromatic aldehydes catalyzed by $MgBr_2$ in the presence of an excess amount of triethylamine afforded *trans*-α,β–epoxy ketones in good yields.

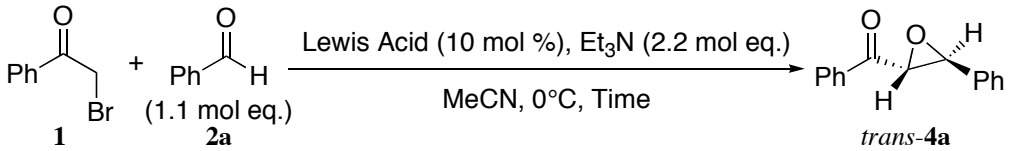
The preparation of α,β–epoxy carbonyl compounds represents an important goal due to their multifunctionality in organic synthesis.[1] The Darzens reaction, which includes an aldol reaction of α–halo carbonyl compound with aldehyde (C-C bond formation) and the following intramolecular cyclization (C-O bond formation) of the resulting halohydrin, is one of the most powerful methodologies for the synthesis of α,β–epoxy carbonyl compounds.[2] Nevertheless, the Darzens reaction suffer from difficulties in establishing a catalytic cycle because of the generation of stable and less reactive inorganic salts derived from metal catalysts and substrates. Therefore, a stoichiometric amount of metal reagents such as sodium, sodium ethoxide, and sodium amide is needed in these procedures. Herein we report a novel and efficient Darzens reactions catalyzed by magnesium bromide in the presence of an excess amount of triethylamine (TEA). An attempt of the asymmetric catalytic Darzens reaction utilizing a chiral ligand is also briefly described.



Scheme 1

We had previously performed a direct imine aldol reaction employing $MgBr_2$ and TEA.[3] Furthermore, in preliminary experiments of direct catalytic aldol reactions of phenacy bromide (**1**) and benzaldehyde (**2a**) under Evans' conditions,[4] *trans*-α,β–epoxy ketone (*trans*-**4a**) was obtained with silylated aldol product (**3**), as shown in Scheme 1. Thus, the compound (**1**) was allowed to react with 1.1 mol eq. of **2a** in the presence of 10 mol % of $MgBr_2$ and 2.2 mol eq. of TEA in MeCN at 0 °C without the use of chlorotrimethylsilane (TMSCl). The Darzens reaction proceeded efficiently and desired *trans*-epoxy ketone (*trans*-**4a**) was obtained in 85% yield (Table 1, Enty 1). The structure of *trans*-**4a** was confirmed by a comparison of its spectroscopic data with the reported values.[2e] Similar treatment of **1** with various Mg(II)-compounds as Lewis acids in MeCN at 0 °C furnished the *trans*-**4a** in 37-88% yields (Entries 2-7), as shown in Table 1. We chose $MgBr_2$ as a suitable Lewis acid for the desirable Darzens reaction based on both of the reaction time and the chemical yield.

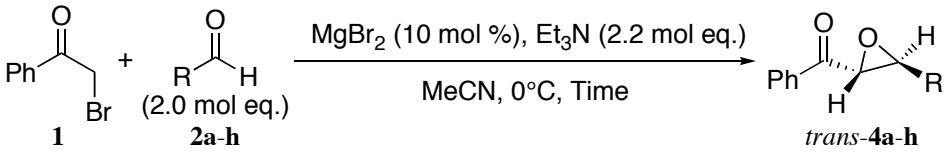
Table 1. Catalytic Darzens Reaction Utilizing Various Mg(II)-Compounds as Lewis Acids.



Entry	Lewis Acid	Time/h	Yield/%
1	$MgBr_2$	1	85
2	$MgBr_2{\cdot}OEt_2$	1	77
3	$MgCl_2$	1	73
4	MgI_2	1	78
5	$Mg(OTf)_2$	4	37
6	$Mg(NTf_2)_2$	2	73
7	$Mg(ClO_4)_2$	1.5	88

Thus, all of the Darzens reactions employing phenacyl bromide (**1**) and 2.0 mol eq. of aldehydes (**2a**-**h**) in the presence of 10 mol % of $MgBr_2$ are summarized in Table 2. Treatment of **1** with aromatic aldehydes (**2b**, **c**) having an electron-withdrawing group such as Cl or NO_2 at the *para* position gave the corresponding Darzens adducts (*trans*-**4b**, **c**) in 85% and quantitative yields, respetively (Entries 2 and 3 in Table 2). The Darzens reaction of **1** with an aromatic aldehyde (**2d**) having an electron-donating *p*-MeO group unfortunately afforded *trans*-**4d** in a poor yield (Entry 4). In the case of an aliphatic aldehyde (**2h**), a trace amount of *trans*-**4h** was obtained probably because of the lability of *trans*-**4h** to the reaction conditions (Entry 8). Other experimental results are shown in Table 2 (Entries 1, 5-7).

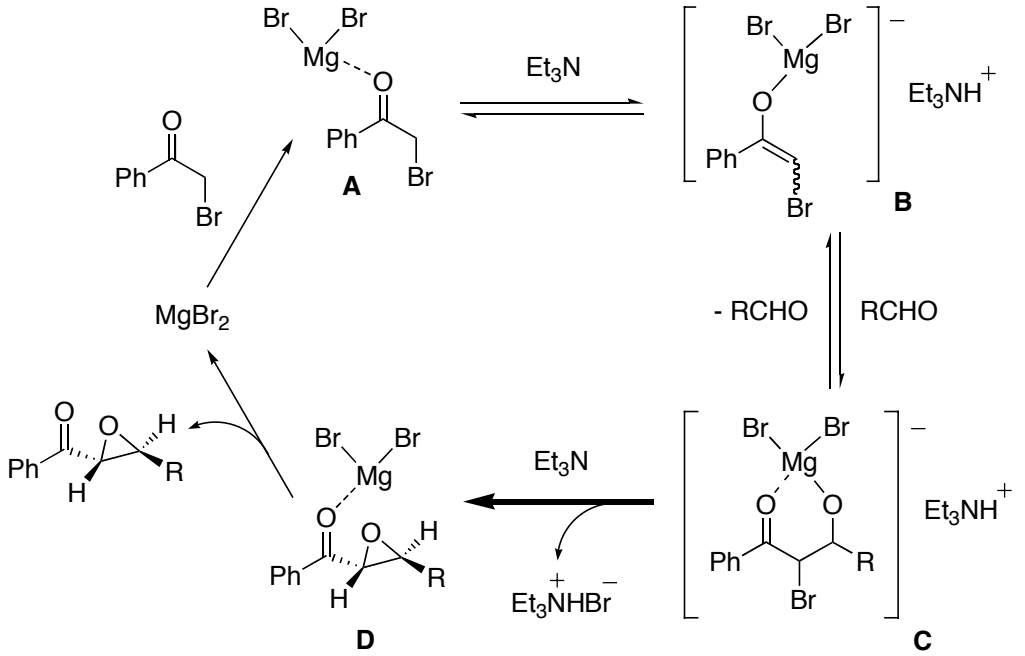
Table 2. $MgBr_2$-Promoted Catalytic Darzens Reaction Employing Various Aldehydes (**2a**-**h**).



1 **2a**-**h** *trans*-**4a**-**h**

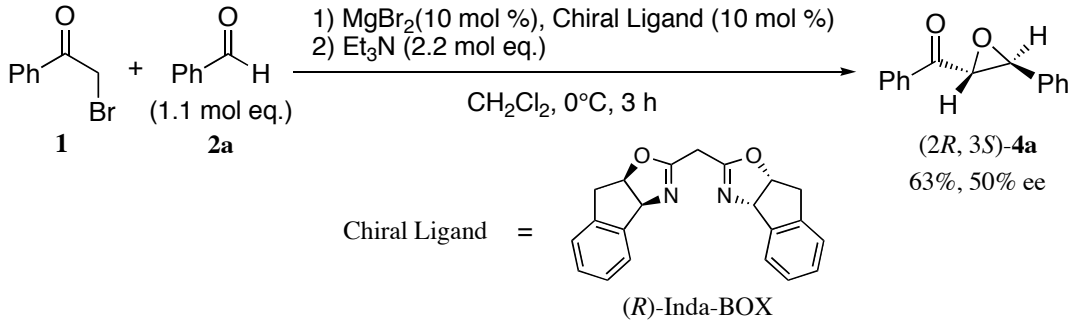
Entry	R	Time/h	Yield/%
1	Ph (**2a**)	1	87 (**4a**)
2	*p*-ClC_6H_4 (**2b**)	1	85 (**4b**)
3	*p*-$NO_2C_6H_4$ (**2c**)	2	quant. (**4c**)
4	*p*-$MeOC_6H_4$ (**2d**)	2	39 (**4d**)
5	*p*-MeC_6H_4 (**2e**)	2	76 (**4e**)
6	*p*-PhC_6H_4 (**2f**)	1	75 (**4f**)
7	2-Naphthyl (**2g**)	1	81 (**4g**)
8	$Ph(CH_2)_2$ (**2h**)	2	trace (**4h**)

On the basis of the experimental results described above, we propose a plausible catalytic reaction pathway involving an equilibrium state with a magnesium enolate **B** and a magnesium aldolate **C**. An excess amount of TEA may irreversibly promote the epoxidation of **C** to **D**.



Scheme 2

Finally, we have attempted a novel catalytic asymmetric Darzens reaction of **1** with **2a** utilizing (-)-2,2'-methylenebis[(3a*S*,8a*R*)-3a,8a-dihydro-8*H*-indeno[1,2-*d*]oxazole [(*R*)-Inda-BOX] as a chiral ligand as follows (Scheme 3). Treatment of **1** with 1.1 mol eq. of **2a** with 10 mol % of $MgBr_2$ and (*R*)-Inda-BOX in the presence of 2.2 mol eq. of TEA in CH_2Cl_2 at 0 °C gave the desired Darzens product [(2*R*,3*S*)-**4a**] in 63% yield (Scheme 3). The ee value of **4a** was determined to be 50% by exploiting chiral-stationary-phase HPLC (Daicel Chiralcel OB-H, hexane/2-propanol). The absolute configuration of the major enantiomer of **4a** was determined to be (2*R*,3*S*) by a comparison of the optical rotation with the reported data.[2e]



Scheme 3

In conclusion, we have demonstrated novel and efficient Darzens reactions catalyzed by $MgBr_2$ as a Lewis acid under the mild conditions. Further investigations of the reaction mechanism in detail and catalytic enantioselective variants of this reaction are underway.

ACKNOWLEDGEMENTS

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