

HETEROCYCLES, Vol. 68, No. 3, 2006, pp. 459 - 463. © The Japan Institute of Heterocyclic Chemistry
Received, 6th February, 2006, Accepted, 7th February, 2006, Published online, 14th February, 2006. COM-06-10689

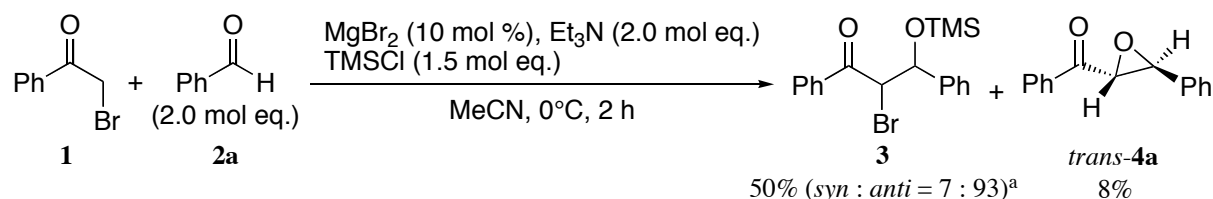
A NOVEL AND EFFICIENT DARZENS REACTION CATALYZED BY MAGNESIUM BROMIDE

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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.

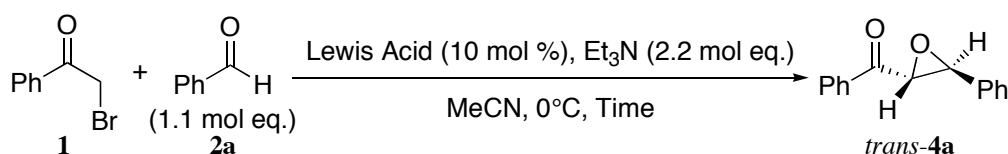


^a Determined by $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) analysis.

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 phenacyl 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, Entry 1). The structure of *trans*-**4a** was confirmed by a comparison of its spectroscopic data with the reported values.^{2c} 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.



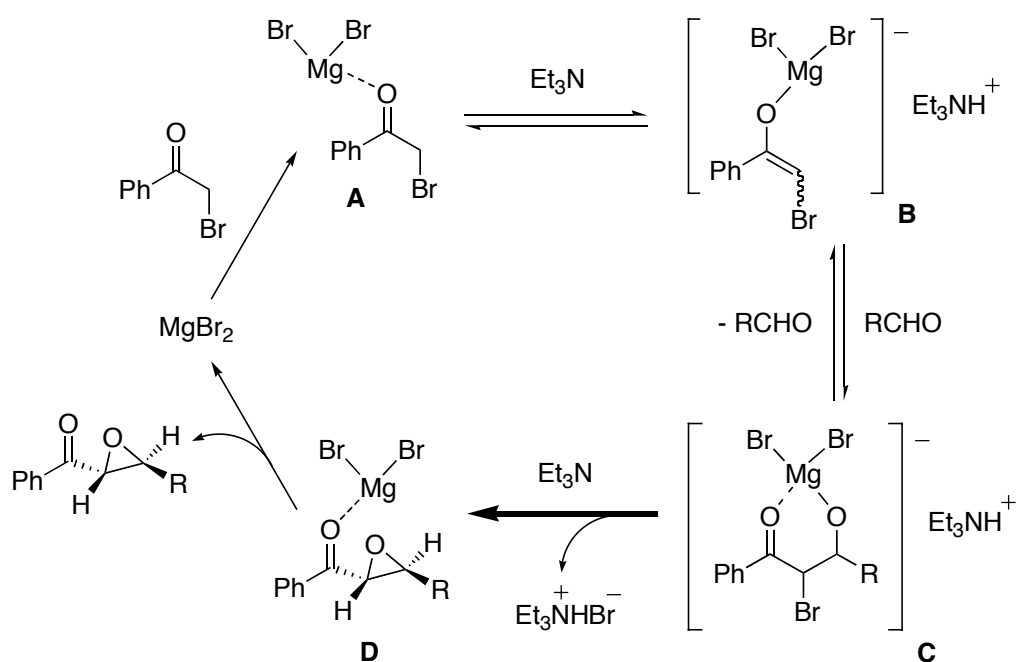
Entry	Lewis Acid	Time/h	Yield/%
1	MgBr_2	1	85
2	$\text{MgBr}_2 \cdot \text{OEt}_2$	1	77
3	MgCl_2	1	73
4	MgI_2	1	78
5	$\text{Mg}(\text{OTf})_2$	4	37
6	$\text{Mg}(\text{NTf}_2)_2$	2	73
7	$\text{Mg}(\text{ClO}_4)_2$	1.5	88

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, respectively (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. MgBr₂-Promoted Catalytic Darzens Reaction Employing Various Aldehydes (**2a-h**).

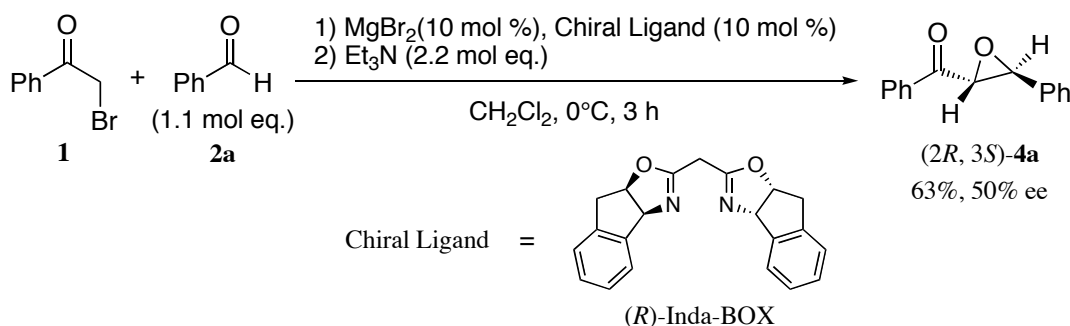
Entry	R	Time/h	Yield/%
1	Ph (2a)	1	87 (4a)
2	<i>p</i> -ClC ₆ H ₄ (2b)	1	85 (4b)
3	<i>p</i> -NO ₂ C ₆ H ₄ (2c)	2	quant. (4c)
4	<i>p</i> -MeOC ₆ H ₄ (2d)	2	39 (4d)
5	<i>p</i> -MeC ₆ H ₄ (2e)	2	76 (4e)
6	<i>p</i> -PhC ₆ H ₄ (2f)	1	75 (4f)
7	2-Naphthyl (2g)	1	81 (4g)
8	Ph(CH ₂) ₂ (2h)	2	trace (4h)

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 MgBr₂ and (*R*)-Inda-BOX in the presence of 2.2 mol eq. of TEA in CH₂Cl₂ 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 MgBr₂ 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

This work was financially supported in part by a Grant-in-Aid for Exploratory Research (16659030) from the Japan Society for the Promotion of Science.

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