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Lewis base mediated halogenation/semipinacol rearrangement of diazo compounds: new access to α-halo-quaternary ketones†

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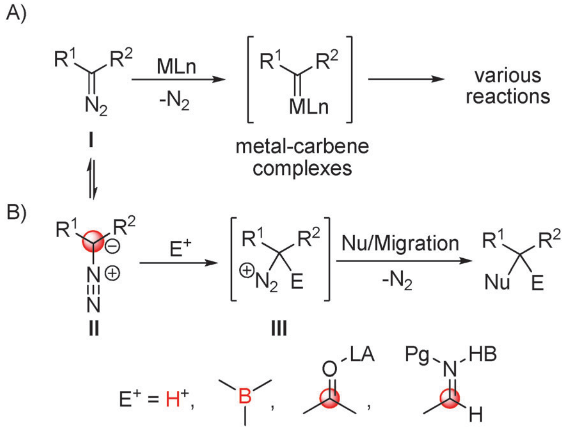
A novel halogenation/semipinacol rearrangement of α-diazo alcohol catalyzed by Lewis base has been developed through a carbene-free mechanism. This semipinacol transposition, initiated by an electrophilic halogenation (X = Cl^+, Br^+, and I^+) of diazo carbon event, furnished a convenient synthetic route for the efficient synthesis of α-halo-quaternary ketones under mild conditions.

As metal carbene precursors, diazo compounds have been widely applied in organic synthesis which participate in metal-catalyzed rearrangements, cycloadditions, X–H (X = C, N, O, Si, S, *etc.*) bond insertions, and ylide-forming reactions (Scheme 1A).[1] On the other hand, diazo group transformations can also be realized through the carbene-free mechanism since diazo carbon is electron-rich in nature,[2] as evident from the resonance structure **II** (Scheme 1B). Diazo carbon can react with the electron-deficient species (E^+ = H^+,[3] organoboron,[4] carbonyl activated by Lewis acids,[5] imine activated by Brønsted acids,[6] *etc.*) to form a procarbonium ion intermediate **III**, which is quenched by the electron-rich species with concomitant expulsion of N_2 (Scheme 1B). It is observed that the long-standing interest in the diazo chemistry was based on the reactions of carbene, particularly in transition-metal catalysis. While in consideration of environmental friendliness, convenient operation and diversity of diazo transformation, the development of efficient and elegant functionalization of diazo compounds by the carbene-free mechanism is really of great significance for further application of diazo compounds in organic synthesis.

Very recently, chiral Lewis bases (LB) were used to catalyze the asymmetric halogenation of alkenes.[7,9] Especially, Tu developed a novel asymmetric halogenation/semipinacol rearrangement[8] reaction of allylic alcohols catalyzed by chiral Lewis bases for the synthesis of chiral α-quaternary β-haloketones (Scheme 2A).[9] Furthermore, Murphy realized the *gem*-dihalogenation of diazoacetate derivatives using Lewis bases as catalysts.[10] Inspired by this previous work, and also in conjunction with our ongoing interest in the synthesis and applications of diazo compounds without a metal catalyst,[11] we describe herein our results on the Lewis base catalyzed halogenation/semipinacol rearrangement of diazo compounds (Scheme 2B). This strategy provides new access to α-halo-quaternary ketones *via* the carbon-chain extension or ring expansion of ketones. These organohalo compounds are a very important class of synthetic intermediates that are useful for the construction of α-quaternary ketones.[12] Moreover, we also make a preliminary effort to develop the catalytic, asymmetric version of this reaction, which led to moderate enantioselectivity.



Scheme 1 Activation patterns of the diazo carbon.

We began by testing the halogenation/semipinacol rearrangement of α-diazo alcohols **2a**, which could be easily prepared from the commercially available benzophenone and ethyl diazoacetate.[13] We observed that a combination of **2a** and 1,3-dichloro-5,5-dimethylhydantoin (DCDMH, **3a**) in THF at room temperature

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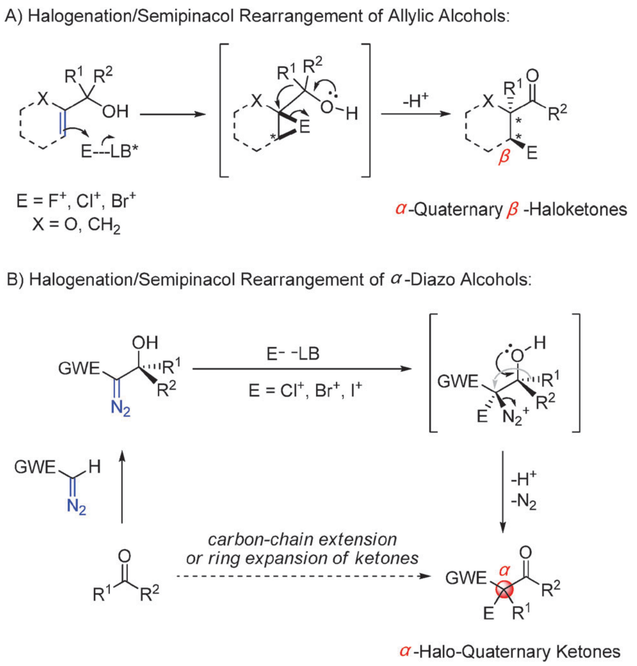
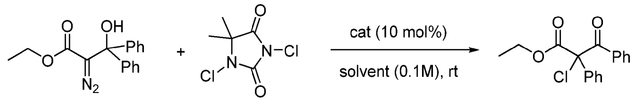


Scheme 2 Semipinacol rearrangement initiated by electrophilic halogenation.

afforded the corresponding product in 72% yield (Table 1, entry 1). To further improve reaction efficiency, we examined a number of Lewis bases (Table 1, entries 2–5). The addition of 10 mol% triethylamine prolonged the reaction time obviously compared with the background reaction (Table 1, entry 3). Surprisingly, when 10 mol% of DABCO was used, the desired α-chloro-quaternary ketone **4a** was obtained in 78% isolated yield in 20 min (Table 1, entry 4). Next, a variety of common organic solvents were screened (Table 1, entries 4, 6–9). The experimental results revealed that increased solvent polarity led to the increase of reaction efficiency. However, this was associated with some by-products, resulting in significantly reduced yields.

With the optimal reaction conditions in hand, we investigated the substrate scope of this halogenation/semipinacol rearrangement (Table 2). Various α-diazo alcohols **2** derived from symmetrical benzophenone derivatives with halogen or electron-donating substituents were suitable substrates for the chlorination (Table 2, entries 1–5) or bromination reaction (Table 2, entries 11–14), leading to the desired products in excellent yields (up to 93%). Generally, chlorination reaction gave lower yields and lower reaction efficiency, while bromination reaction gave higher yields and higher reaction efficiency. Besides the carbon-chain extension, this method could effectively achieve the ring expansion of cyclic ketones (Table 2, entries 6 and 15). Interestingly, the chlorination reaction proceeded well over substrates derived from dissymmetrical alkyl aryl ketones, giving the products chemoselectively in good yields. When employing the chain alkyl aryl ketones as substrates, electron-rich phenyl ring migration had priority in the selective formal C–C insertion process (Table 2, entries 7–9). While when the diazo compound **2j** derived from α-tetralone was used, alkyl migration is dominant

Table 1 Optimization of the reaction conditions[a]

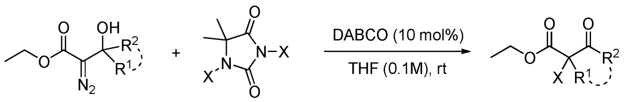


2a **3a** **4a**

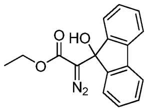
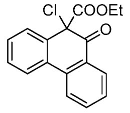
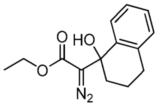
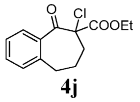
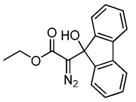
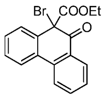
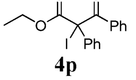
Entry	Cat.	Solvent	*t*	Yield[b] (%)
1	None	THF	2 h	72
2	Py	THF	40 min	72
3	Et_3N	THF	12 h	71
4	**DABCO**	**THF**	**20 min**	**78**
5	DBU	THF	1 h	68
6	DABCO	Toluene	1 h	76
7	DABCO	DCM	10 min	72
8	DABCO	EA	10 min	68
9	DABCO	MeCN	1 min	67

[a] Unless otherwise noted, the reaction was carried out using 0.20 mmol of **2a**, 0.25 mmol of **3a**, and 10 mol% of the catalyst (0.02 mmol). [b] Yield of the isolated product.

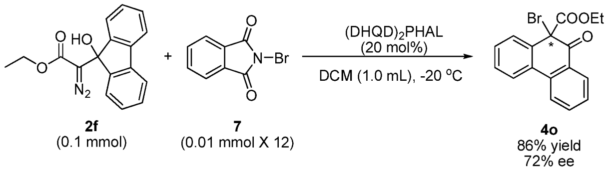
Table 2 Substrate scope studies[a]



2 **3** **4**

Entry	Substrate	X	Product	Yield[b] (%)
1	**2a:** $R^1 = R^2 = Ph$	**3a:**Cl	**4a**	78
2	**2b:** $R^1 = R^2 = 4\text{-F-}C_6H_4$	Cl	**4b**	80
3	**2c:** $R^1 = R^2 = 4\text{-Cl-}C_6H_4$	Cl	**4c**	71
4	**2d:** $R^1 = R^2 = 4\text{-Me-}C_6H_4$	Cl	**4d**	81
5	**2e:** $R^1 = R^2 = 4\text{-OMe-}C_6H_4$	Cl	**4e**	85
6	 **2f**	Cl	 **4f**	91
7	**2g:** $R^1 = Ph, R^2 = Me$	Cl	**4g**	76
8	**2h:** $R^1 = Ph, R^2 = Et$	Cl	**4h**	73
9	**2i:** $R^1 = Ph, R^2 = {}^iPr$	Cl	**4i**	78
10	 **2j**	Cl	 **4j**	61
11	**2a:** $R^1 = R^2 = Ph$	**3b:**Br	**4k**	92
12	**2b:** $R^1 = R^2 = 4\text{-F-}C_6H_4$	Br	**4l**	93
13	**2c:** $R^1 = R^2 = 4\text{-Cl-}C_6H_4$	Br	**4m**	82
14	**2d:** $R^1 = R^2 = 4\text{-Me-}C_6H_4$	Br	**4n**	91
15	 **2f**	Br	 **4o**	95
16[c]	**2a:** $R^1 = R^2 = Ph$	NIS	 **4p**	78

[a] The reaction was carried out using 0.20 mmol of **2**, 0.25 mmol of **3**, and 10 mol% of DABCO (0.02 mmol) in THF (2.0 mL) at room temperature. [b] Yield of the isolated product. [c] The reaction was carried out using 0.20 mmol of **2a** and 0.25 mmol of NIS in THF (0.2 mL) under an argon atmosphere at room temperature for 20 hours.



Scheme 3 Catalytic asymmetric variant of this process.

(Table 2, entry 10; see the ESI† for possible reasons). In addition, under the dry and oxygen-free argon atmosphere, α-iodo-quaternary ketone could be synthesized efficiently by iodination/semipinacol rearrangement (Table 2, entry 16). It is noteworthy that DABCO would drastically reduce the efficiency of iodination reaction.

We also attempted to develop a catalytic asymmetric version of this halogenation/semipinacol rearrangement for gaining access to enantioenriched α-halo-quaternary ketones. After a series of efforts (see the ESI† for further details), we discovered that product **4o** could be obtained in 86% yield with 72% ee when employing 20 mol% cinchona alkaloid (DHQD)$_2$PHAL as a catalyst (Scheme 3).

In conclusion, we have developed a novel halogenation/semipinacol rearrangement of α-diazo alcohol catalyzed by Lewis base. This methodology greatly expands the synthetic applications of diazo compounds through the carbene-free mechanism. The protocol provides a straightforward way to generate the α-halo-quaternary ketones under mild conditions. We believe that the resulting densely functionalized ketones bearing α-halo quaternary carbon could be highly valuable and versatile intermediates for further transformations. To further realize the asymmetric version of this reaction, we examined a number of chiral tertiary amines and various reaction parameters, which led to moderate enantioselectivity. Efforts to realize the highly enantioselective version of this reaction and further exploration of the asymmetric reaction scope are ongoing in our laboratory.

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