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Cationic bromonium complex: NBS/P(OPh)$_3$ as an efficient catalyst for Nazarov cyclization

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ABSTRACT

A general, catalytic method for Nazarov cyclization of dihydropyran derivatives has been developed. Cationic bromonium complex: NBS/P(OPh)$_3$ was identified as an efficient catalyst for the synthesis of a number of different cyclopentenones in high yields with an excellent level of diastereocontrol.

1. Introduction

Lewis acids are considered to be the most popular species for the development of catalytic processes in the broad variety of transformations.[1] Due to a large potential in this research field, we have disclosed some new rare earth salts as Lewis acid catalysts in organic synthesis.[2] Apart from a number of metal complexes, compounds containing carbenium, silyl or phosphonium cations can also act as metal free Lewis acids, which incorporate a Lewis acidic cation or a hypervalent center.[3] It is well known that the use of *N*-bromosuccinimide (NBS) and triphenyl phosphine as a halide source yielded alkyl bromides from alcohols (Type I, Fig. 1).[4] Recently, Ishihara group and others reported that the nucleophilic promoters can activate NBS to form cationic bromonium ('Br+') as the reagent in electrophilic halocyclization reaction.[5] Very recently, a new concept of Lewis base catalysis by thiourea: NBS mediated oxidation of alcohols was presented (Type II, Fig. 1).[6] Therefore, from the point of mechanism view, the cationic halonium is generated from *N*-halosuccinimide with nucleophilic promoters, which can display a Lewis acid catalytic activity. We became interested in the chemistry of cationic bromonium as Lewis acid catalyst in the organic synthesis.

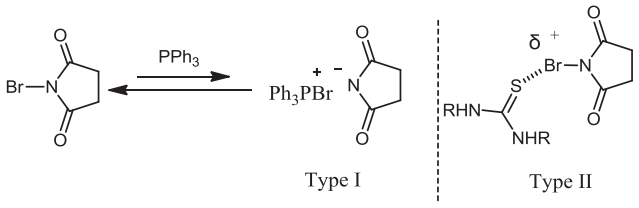

Fig. 1. The formation of cationic bromonium.

The Nazarov cyclization reaction,[7] a highly effective method for the generation of five-membered rings, has been successfully utilized in the synthesis of many complex molecules, including many biologically-active natural products. As a result, the Nazarov cyclization has received tremendous attention in the past decades, and the viability of the substoichiometric catalytic process promoted by strong Lewis or Brønsted acids has been revealed.[8] However, as far as we know, cationic bromonium as Lewis acid catalyst induced Nazarov cyclization has not been reported.

2. Results and discussion

Herein, we describe a successful catalytic Nazarov cyclization of dihydropyran substrates catalyzed by a combination of NBS and P(OPh)$_3$, in which, bromonium ion was activated by Lewis base.

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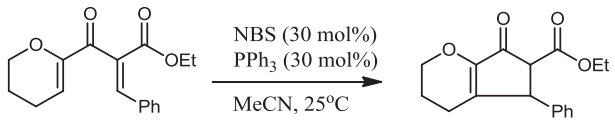
Our investigations began with the optimization of the reaction conditions for the model reaction shown in Scheme 1. A catalyst



1a 2a

Scheme 1. Nazarov cyclization catalyzed by bromonium ion–Lewis base.

loading of 30 mol % *N*-bromosuccinimide (NBS) in the presence of different phosphorus species was studied. To our delight, the triphenyl phosphine as Lewis base afforded the desired product **2a** in 99% yield within 4.5 h at room temperature (Table 1 entry 1). Only a trace amount of product was observed in the absence of triphenylphospine (Table 1, entry 2). When the PPh_3 was switched to $P(OPh)_3$, reaction went into completion in less than 1 min, thus suggesting that more nucleophilic the triphenyl phosphite is better for the reaction to proceed efficiently (Table 1, entry 3). Different substituted phosphines could promote this reaction with moderate to excellent yield except tricyclohexyl phosphine (Table 1, entries 4–7) under this condition. The NBS combined with triphenyl phosphate or triphenyl phosphorus oxide displayed non-catalytic activity. As expected, no cyclized product was observed under this catalytic system when the base additives, such as DABCO or DMAP was employed, this finding possibly points toward the inactivation cationic bromonium Lewis acid species by *N*-Lewis bases.

Table 1
Survey of Lewis bases[a]

Entry	Lewis base	Time	Yield (%)[b]
1[c]	PPh_3	4.5 h	99
2	—	10 h	Trace
3	$P(OPh)_3$	<1 min	99
4	Tri(2-furyl)phosphine	13 min	99
5	Tri(4-fluorophenyl) phsophine	5 h	99
6	Tris(4-methoxyphenyl) phosphine	6 h	60
7	Tricyclohexyl phosphine	20 h	Trace
8	$POPh_3$	20 h	n.r.
9	$PO(PhO)_3$	20 h	n.r.
10	HMPA	20 h	n.r.
11	DMAP	20 h	n.r.
12	DABCO	20 h	n.r.

[a] Reaction conditions: **1a** (0.1 mmol), NBS (10 mol %), Lewis base (10 mol %), MeCN (0.5 mL), rt.
[b] Isolated yield by silica gel column chromatography; dr value was not determined.
[c] 30 mol % PPh_3, 25 °C.

In order to indicate the exact reaction time, the reaction temperature was decreased to 10 °C, the reaction catalyzed by NBS and $P(OPh)_3$ proceeds smoothly to give the desired product in high yields after 10 min (Table 2, entry 1). Additional studies showed that solvents have dramatic effects on the reaction yield, and acetonitrile was found as an optimal solvent for this reaction (Table 2, entries 2–5). With 5 mol % catalyst , the reaction were finished after 40 min indicated by TLC to give 99% yield of the desired product (Table 2, entry 6), however, with 1 mol % catalyst loading, only 10% **2a** was isolated after 6 h (Table 2, entry 7).

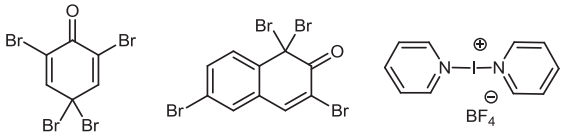
As shown in Table 3, alternative bromonium sources, such as **3**, **4**, or Br_2 showed excellent catalytic activity in the presence of triphenyl phosphite (Table 3, entries 1–3). Once again, by using 30 mol % of either **3** or **4** (Table 3, entries 4, 5), no reaction occurred even after 17 h. In contrast, 80% conversion of **1a** to **2a** were achieved in the presence of Br_2, or I_2, which demonstrated that iodine is emerged as an effective Lewis acid catalyst for Nazarov cyclization. As far as we know, this reaction has never been reported by employing any of halogen catalyst systems. No cyclization product was observed in the presence of triphenyl phosphite without halide source (Table 3, entry 8). To prove that an oxidation state of I^+ is the source of catalytic species, **5** was further investigated with $P(OPh)_3$, the cyclization was conducted, but with a significant loss in the catalytic efficiency (Table 3, entry 9).

Table 2
Survey of reaction conditions[a]

Entry	Solvent	Temp./Time	Yield(%)[b]
1	MeCN	10 °C/10 min	99
2	EtOH	10 °C/12 h	Trace
3	THF	10 °C/24 h	Trace
4	Toluene	10 °C/12 h	18
5	DCM	10 °C/12 h	33
6[c]	MeCN	10 °C/40 min	99
7[d]	MeCN	10 °C/6 h	10

[a] Reaction conditions: **1a** (0.1 mmol), NBS (10 mol %), $P(OPh)_3$ (10 mol %).
[b] Isolated yield by silica gel column chromatography; dr value was not determined.
[c] 5 mol % NBS, 5 mol % $P(OPh)_3$.
[d] 1 mol % NBS, 1 mol % $P(OPh)_3$.

Table 3
Survey of bromonium sources[a]



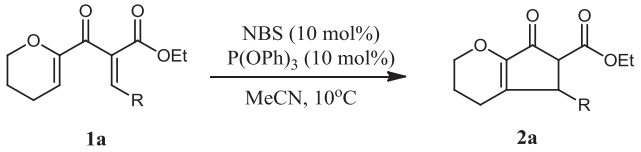
3 4 5

Entry	Bromonium source	Lewis base	Time	Yield (%)[b]
1	**3**	$P(OPh)_3$	25 min	99
2	**4**	$P(OPh)_3$	11 min	99
3	Br_2	$P(OPh)_3$	2 h	99
4	**3**	—	17 h	n.r.
5	**4**	—	17 h	n.r.
6	Br_2	—	8 h	80
7[c]	I_2	—	18 h	90
8[d]	—	$P(OPh)_3$	17 h	n.r.
9	**5**	$P(OPh)_3$	12 h	36

[a] Reaction conditions: **1a** (0.1 mmol), bromonium source (10 mol %) or and Lewis base (10 mol %), MeCN (0.5 mL), 10 °C.
[b] Isolated yield by silica gel column chromatography; dr value was not determined.
[c] 30 mol % Br_2 or I_2, 25 °C.
[d] 30 mol % $P(OPh)_3$, 50 °C.

Having established that NBS/$P(OPh)_3$ in MeCN was the optimal system to promote the reaction, a number of dialkenyl ketones of **1** was subjected to cyclization and the results are showed in Table 4. It is apparent that the electron-donating group of the substituent gave the corresponding products in excellent isolated yield with moderate to high levels of diastereocontrol (Table 4, entries 2, 3). The desired products were also obtained in excellent yields with better stereoinduction for substrates **1d**-**1j**, which have an electron-withdrawing group, such as a halogen, nitro, cyano or trifluoromethyl group on the phenyl ring (Table 4, entries 4–10). The reaction of **1f** proceeded at a considerably slower rate than **1e** (Table 4, entry 5 vs 6). On the other hand, reactions using substrates **1k**, **1l** gave decreased yields with excellent diastereocontrol (Table 4, entries 11, 12). When the R group of **1** was 9-anthracenyl, styryl or 2-furyl, the cyclization proceeded efficiently as well as the model reaction (Table 4, entries 13–15).

Table 4
Scope of the Nazarov cyclization catalyzed by NBS–P(OPh)$_3$[a]



1a 2a

Entry		Substrate (R)	Time	Yield(%)[b]	trans:cis[c]
1	**1a**	Ph	10 min	99	17:1
2	**1b**	4-MeO–C_6H_4	<1 min	99	12:1
3	**1c**	4-Me–C_6H_4	9 min	99	15:1
4	**1d**	4-Cl–C_6H_4	2 h	99	15:1
5	**1e**	4-Br–C_6H_4	2 h	92	17:1
6	**1f**	2-Br–C_6H_4	2 h	60	20:1
7	**1g**	4–NO_2–C_6H_4	3 h	82	20:1
8	**1h**	3–NO_2–C_6H_4	3 h	88	17:1
9	**1i**	4–CN–C_6H_4	2 h	99	15:1
10	**1j**	4–CF_3–C_6H_4	4 h	89	17:1
11	**1k**	*c*-Hexyl	22 h	60	>99:1
12	**1l**	*i*-Pr	22 h	50	>99:1
13	**1m**	9-Anthracenyl	3 h	90	>99:1
14	**1n**	Styryl	5 min	99	10:1
15	**1o**	2-Furyl	<5 min	99	20:1

[a] Reaction conditions: **1** (0.1 mmol), NBS (10 mol %), P(OPh)$_3$ (10 mol %), MeCN (0.5 mL), 10 °C.
[b] Isolated yield by silica gel column chromatography.
[c] The ratio was determined by 400 MHz ^{1}H NMR.

Although the mechanism of the reaction is not clear, on the basis of the reports concerning the reaction of NBS with good electron donors, such as triphenyl phosphine, it is assumed that charge-transfer complexes of the type $[Ph_3P–Br]^+X^-$ is formed. Therefore, a ^{31}P NMR study was performed with PPh_3 and PPh_3–NBS complex, respectively. The parent signal (−7.02 ppm) of PPh_3 was replaced by a new signal (25.57 ppm) of PPh_3–NBS adduct (the spectrogram was provided in Supplementary data). This evidence revealed that there was a coordination between NBS and PPh_3. However, there are two possible ways to form the complexes as shown in Fig. 2. (Route I or Route II), thus, based on Denmark's pioneer work,[9]

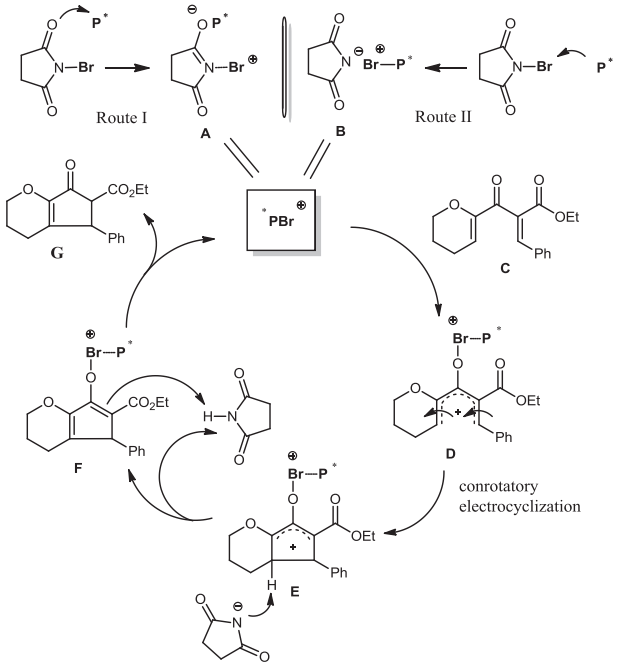


Fig. 2. Proposed catalytic cycle.

a catalytic cycle is proposed, which involves an intermediacy of a highly electrophilic, phosphine-bound bromonium ion **A** or **B** of Lewis base-NBS complex BrP*. The BrP* mediates the pentadienyl cation (**D**). Subsequent a conrotatory closure proceeds to form an oxyallyl cation (**E**), which was deprotonated by the anion of succinimide to give **F**. Protonation of **G** afford the Nazarov product with concomitant ejection of the catalytic complex BrP*.

Asymmetric Nazarov cyclization was also investigated by using NBS with chiral binaphthyl derivative phosphine **6** or phosphites **7** and **8** as promoters. However, as shown in Fig. 3, only racemic products were obtained although in high levels of reaction efficiency, which implied the PPh_3–NBS complex formed though the possible route A in the proposed catalytic cycle.

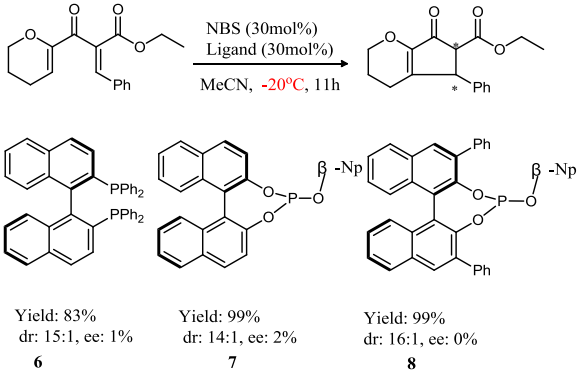


Fig. 3. Asymmetric Nazarov cyclization.

3. Conclusion

In summary, we have developed the first bromonium cation catalyzed Nazarov reaction, in which, bromonium ion could be activated by phosphorus (III) species as a Lewis acid catalyst. The reaction was effectively catalyzed by 10 mol % NBS–P(OPh)$_3$ complex and the desired products were obtained in good to excellent yields with excellent diastereocontrol. Further studies of the reaction mechanism and asymmetric catalysis are ongoing in our lab and will be reported in due course.

4. Experimental section

4.1. General

*4.1.1. Nazarov cyclization of **2a** catalyzed by NBS–P(OPh)$_3$.* To a flask equipped with a stir bar was added the NBS (0.01 mmol, 1.8 mg), then the P(OPh)$_3$ (0.1 mmol, 3.1 mg) in MeCN (0.5 mL) was added. After stirring at 10 °C for 10 min, **1a** (0.1 mmol, 29 mg) was added in one portion. After completion of the reaction, as indicated by TLC, the reaction mixture was concentrated under reduced pressure, and the crude compound was purified by flash chromatography (Ethyl acetate/Petroleum ether: 1/20 to 1/4) to afford the desired Nazarov product **2a** as a yellow solid; yield: 28.7 mg (99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.29 (m, 3H), 7.15 (d, J=7.0 Hz, 2H), 4.31–4.11 (m, 5H), 3.32 (d, J=2.0 Hz, 1H), 2.24 (dt, J=12.2, 5.9 Hz, 1H), 2.11 (dt, J=19.1, 6.1 Hz, 1H), 1.96 (m, 2H), 1.30 (t, J=7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.13, 168.37, 149.87, 147.40, 139.95, 129.18, 127.67, 127.39, 67.09, 61.88, 59.36, 47.72, 22.25, 21.31, 14.18. HRMS-EI (m/z): $[M]^+$calcd for $C_{17}H_{18}O_4$, 286.1205; found, 286.1203.

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Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.06.107.

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