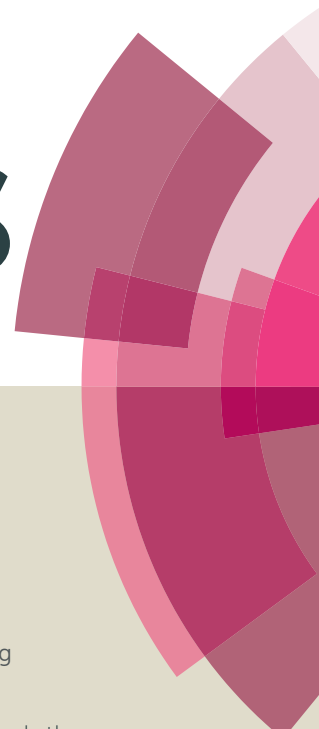


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ARTICLE TYPE

Diaryliodonium Salts as Efficient Lewis Acid Catalysts for Direct Three Component Mannich Reactions

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Diaryliodonium(III) salts, as highly active and versatile Lewis acid catalysts for the direct three component Mannich reaction under solvent free conditions have been investigated. The Mannich products were isolated in good to excellent yields in a very clean manner. Additionally, the catalyst could be recycled without significant loss of its catalytic activity.

In the vital part of green chemistry, catalysis has been identified to be one of the most valuable contributors to improve the synthetic efficiency while minimizing the chemical wastes.¹ As a result, the recent decades witnessed an explosive growth in this field with the development of various novel catalysts.² Lewis acids are considered to be the most popular catalytic species in a broad variety of transformations.³ Apart from a numbers of metal-based Lewis acid catalysts, many organic ionic salts bearing cationic center as electron pair acceptor have shown highly catalytic activity in the name of ionic liquids and ion-pair catalysts.⁴ So far, several major classes of cations including ammonium, imidazolium, pyridinium, phosphonium, sulfonium, silylium and carbeniums were well documented (1-7, Figure 1).⁵ However, the hypervalent halogen cations received much less attention for exploring their Lewis acid catalytic activity although oxidations of various alcohols and phenols, α -functionalizations of carbonyl compounds, cyclizations, and rearrangements catalyzed by hypervalent iodines were well documented.⁶ In 2012, we reported a cationic bromonium, which generated from N-halosuccinimide with triphenylphosphine oxide, as an efficient Lewis acid catalyst for Nazarov cycization of dihydropyran derivatives.⁷

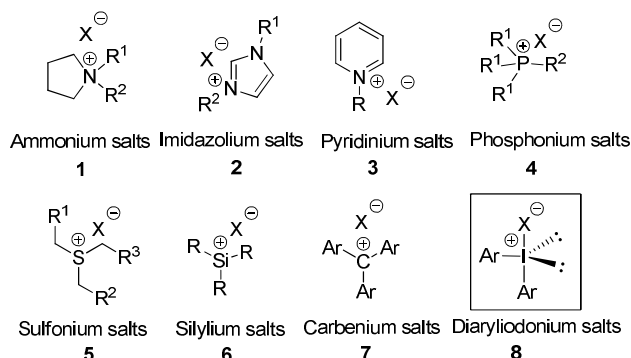


Figure 1. Major ionic salts with various cations as Lewis acid catalysts in organic reactions.

Diaryliodonium(III) salts (8, Figure 1) have been extensively used in organic synthesis. As one of the most versatile hypervalent iodine compounds, diaryliodonium(III) salts were employed as electrophilic arylating agents in a wide range of reactions and the interest in iodine(III)-mediated reaction has recently increased considerably due to their structural properties.⁸ Iodine(III) compounds are electrophilic at iodine, because of the lone pair in the non-bonding orbital of the hypervalent bond. With this consideration, cationic iodine, which has a low-lying LUMO that can accept an electron pair, was able to form adducts with electro-negative atoms in the substrate, such as oxygen, nitrogen, sulfur and halogens. This interaction has partial charge transfer character thus activating the substrates towards nucleophilic attack for catalysis. Moreover, diaryliodonium salts are air- and moisture-stable compounds, whose chemical properties are similar to transition metals derivatives of Hg, Pb and Pd complexes, but without the toxicity and environmental problems associated with these heavy metals.⁸ Herein, we would like to describe our results on the evaluation of diaryliodonium(III) salts as catalysts in three component Mannich reactions. To the best of our knowledge, there is no report concerning diaryliodonium salts as Lewis acid catalysts in organic synthesis.

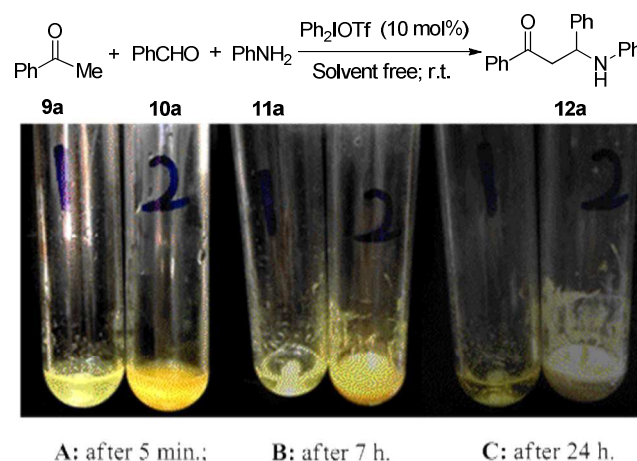


Figure 2. The photographs for comparison of Mannich reaction with/without iodonium catalysis. Tube 1: without catalyst; Tube 2: 10 mol% diphenyliodonium triflate as the catalyst.

Although a number of Mannich-type reactions have been reported,⁹ the reaction of acetophenone (9a), benzaldehyde (10a)

and aniline (**11a**) still remains as a good model to evaluate newly developed Lewis acid catalysts due to the easy availability of starting materials.¹⁰ Initially, we explored the diphenyliodonium triflate as a catalyst in this reaction for probing the potential catalytic activity. To our delight, the desired product of **12a** was isolated in 83% yield with a 10 mol% catalyst loading by using chloroform as solvent at ambient temperature. To establish the optimal reaction conditions, various solvents were screened (see Supporting Information), it was found that solvent free conditions give the best yield of 86%. The model reaction could be monitored by phase transition phenomena as shown in **Figure 2**, the reaction mixture was totally solidified after 24 hours in the presence of 10 mol% diphenyliodonium triflate as catalyst. As a comparison, the reaction did not occur checked by thin layer chromatography (TLC) if no catalyst was employed. In order to compare the activity with common acid catalysts, several Brønsted acids such as trifluoromethanesulfonic acid (TfOH), hydrochloric acid (conc. HCl), camphorsulfonic acid (CSA) and Lewis acid of calcium chloride were tried in Mannich reaction under the standard solvent free conditions, noteworthy is that the acids as promoters were used in one equivalent for improving efficiency. TfOH and HCl can also provide an excellent yield of 91% and 92% while the rest of acids gave the moderate to good yields of 57-85% (entries 2-5, Table 1).

Table 1 Optimization of catalysts for Mannich reaction under solvent free conditions^a

$\text{Ph-C(=O)-Me} + \text{PhCHO} + \text{PhNH}_2 \xrightarrow[\text{Solv. free; r.t. 24 hours}]{\text{Cat. (10 mol\%)}} \text{Ph-C(=O)-CH(Ph)-CH}_2\text{-NH-Ph}$				
Entry	Cat.	Ar ¹ (Ar ²) of 8	X	% Yield ^b
1	8a	(Ph) ₂	OTf	86
2 ^d	TfOH	--	--	91
3 ^d	TsOH	--	--	85
4 ^e	HCl	--	--	92
5 ^d	CaCl ₂	--	--	57
6	8b	(Ph) ₂	Br	55
7	8c	(Ph) ₂	BF ₄	65
8	8d	(Ph) ₂	OTs	80
9	8e	(Ph) ₂	PF ₆	71
10	8f	(4-FC ₆ H ₄) ₂	OTf	85
11	8g	(4-ClC ₆ H ₄) ₂	OTf	81
12	8h	(4-BrC ₆ H ₄) ₂	OTf	77
13	8i	(4- ^t BuC ₆ H ₄) ₂	OTf	77
14	8j	(4-MeOC ₆ H ₄) ₂	OTf	56
15	8k	(3-NO ₂ C ₆ H ₄) ₂	Br	54
16	8l	4-MeOC ₆ H ₄ (4-NO ₂ C ₆ H ₄)	OTs	89
17	8m	C ₆ H ₄ C≡C(Ph)	OTf	87
18	8n	C ₆ F ₅ (Mesityl)	OTs	93 (83) ^c

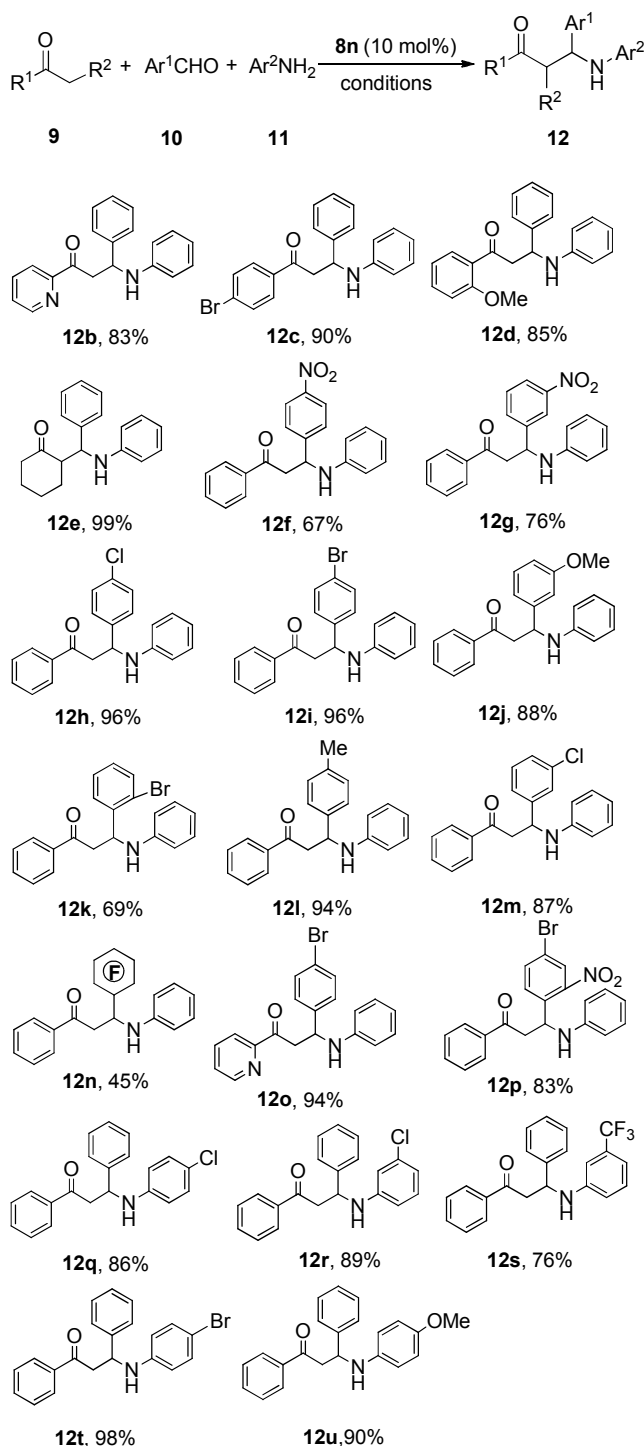
^a Unless otherwise specified, reaction conditions: **9a** (1 mmol), **10a** (1 mmol), **11a** (1 mmol) in the presence of catalyst (0.1 mmol) at room temperature for 24 hours. ^b Isolated yield. ^c Yield in bracket was obtained

with recycled catalyst. ^d the loading of acids was used in one equivalent. ^e conc. HCl was used in an excess amounts.

Next, we investigated the influence of the counteranions of the diphenyliodonium salts on the catalytic activity, as shown in Table 1, BF₄⁻, TsO⁻ and PF₆⁻ as anions gave a comparative yield, respectively (entries 6-9, Table 1), however, Br⁻ as anion gave a lower yield of 55% (entry 9, Table 1). Subsequently, we examined the structural diversity of various diaryliodonium salts as Lewis acid catalysts. The functional groups including halogen, *tert*-butyl, and methoxyl on *para*-position of aromatic ring were evaluated in the model reaction. Generally, catalysts of **8f-j** can afford the products in good yields (entries 10-14, Table 1). Electron-donating group of methoxyl gave lower yield of 56% (entry 14, Table 1). Iodonium bromide **8k** of [(3-NO₂C₆H₄)₂I]Br as catalysts was also applied in the reaction, only 54% yield of **12a** were achieved. Unsymmetrical iodonium salts were also employed as the catalysts; it was pleasing to find that **8l-n** can catalyze the reaction more efficiently than **8a**. Alkynyl-mesityliodonium triflate **8m** also afford the desired product in a good yield of 87%. To our surprise, the yield could be improved to 93% with the use of **8n** which bearing a pentafluorobenzene ring in the catalyst structure. Furthermore, in general, the iodonium salts are of excellent solubility in water. The catalyst of **8n** was recycled by water extraction and evaporation. A yield of 83% was achieved by using the recycled iodonium salts under the standard conditions; this result can meet the requirements of green chemistry without obvious loss of activity.

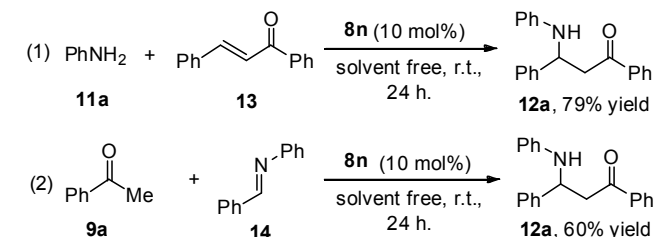
With **8n** as the optimized catalyst in hand, we explored the scope of the three component Mannich reaction with a range of substrates of various aldehydes, ketones and amines. In all cases, the three component Mannich reaction proceeded in the presence of 10 mol% of iodonium salts smoothly to give the corresponding products in good to excellent yields at room temperature (Table 2). It is noted that acetophenones, benzaldehydes and anilines carrying either electron-donating or electron-withdrawing substituents reacted well. Substrates with various substituents on the *ortho*-, *meta*-, and *para*-positions of aromatic ring were well tolerated in this catalytic protocol. However, steric factors affected the reactivity, for example, the products of **12k** were obtained in moderate yield of 69% (Table 2). Interestingly, 4-bromo-2-nitrobenzaldehyde gave **12p** in a good yield of 83%. Pentafluorobenzaldehyde was employed as aldehyde component for checking the fluorine interactions with fluoro-containing catalyst **8n**, however, only 45% yield of **12n** was achieved with standard procedure. For the both aldehyde and aniline derivatives, substrates with electron-donating methoxyl group afford better results. For example, 4-methoxyaniline as reactants furnished product **12u** in an excellent yield of 90%. As expected, cyclohexanone as a more reactive partner gave the desired product **12e** in a quantitative yield. The results of this study on the various substrates were summarized in Table 2. Overall, it can be seen that the scope and generality of the present method has been shown with respect to various aldehydes and anilines.

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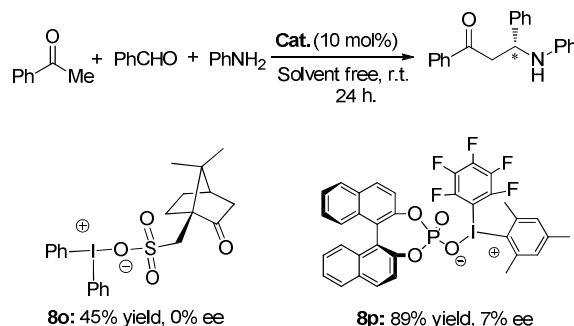
Table 2 Scope of Mannich reactions under solvent free conditions^{a, b}

^a Unless otherwise specified, reaction conditions: **9** (1 mmol), **10** (1 mmol), **11** (1 mmol) in the presence of iodonium salt **8n** (0.1 mmol) at room temperature for 24 hours. ^b Isolated yield.

The mechanism of classic Mannich reaction had been described;¹¹ an enolized carbonyl species was realized from the active hydrogen compounds with the catalysis of an acid, the resulting enol attacked the iminium ion which formed from the amine and aldehyde to yield Mannich base. However, a subject of considerable discussion is the possibility of the formation of chalcones from an enolized carbonyl species with benzaldehydes, chalcone could then react with aniline to afford the desired Mannich bases. In this connection, two control experiments were carried out with this catalytic protocol. The reaction of aniline with chalcone gives Mannich base **12a** in 79% yield [(Scheme 1, Eq. (1))]. Another reaction between acetophenone and imine **14** was attempted; the product **12a** was also obtained in a slight lower yield of 60% [(Scheme 1, Eq. (2))]. Of note, the formation of chalcone in this case was also observed in this procedure [(Scheme 1, Eq. (2))]. Therefore, thus far, no single mechanism which could be accounted for all the experimental facts has been suggested.

**Scheme 1.** Control experiments for reaction pathways in yielding Mannich products.

The asymmetric version of catalytic Mannich reaction is a useful method for the preparation of enantioenriched α -aminocarbonyl molecules which possess favourable pharmacological properties.¹² Diaryliodonium salts with a chiral anion were reported for asymmetric inductions.¹³ Hence, the asymmetric variations of Mannich reaction were investigated as depicted in Scheme 2. D-camphorsulfonate and (*S*)-BINOL-phosphate as chiral anions were employed for the iodonium catalysts in the title reaction. Unfortunately, **8o** afforded the desired product **12a** in 45% yield without enantioselectivity. Enantiomeric excess value of 7% was obtained with **8p** as the catalysts although the yield of **12a** in 89% is satisfactory (Scheme 2).

**Scheme 2.** Attempts on asymmetric Mannich reactions with catalysis by **8o** and **8p**.

In summary, we have firstly demonstrated that diaryliodonium(III) salts are highly active and versatile Lewis acid catalysts for the direct three component Mannich reaction. The products are isolated in good to quantitative yields in a very clean manner. The high yields and recyclable catalyst for this reaction show potential for using hypervalent iodine species as Lewis acid catalysts in the development of novel sustainable processes, both in industry and academia. Furthermore, the catalytic activity could be tuned by the changing the aromatic groups around the iodocation. It is anticipated to discover chiral version of catalysis by using chiral hypervalent iodine(III) compounds or the strategy of asymmetric counteranion-directed catalysis as described above. Therefore, we are continuing to explore the scope and limitation of iodocation catalysis by tuning the Lewis acidity to gain more understanding of reactivity and to further extend the reaction scope. These results will be reported in due course.

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Notes and references

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