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Chiral Brønsted Acid Catalyzed Highly Enantioselective Mannich-type Reaction of α-Diazo Esters with *in Situ* Generated *N*-Acyl Ketimines

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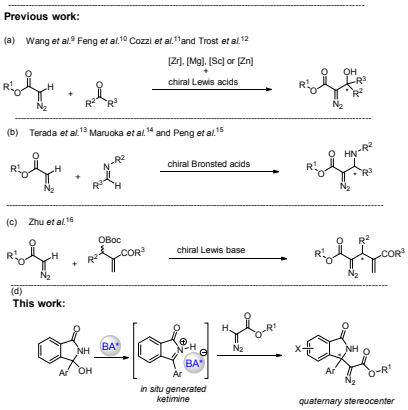
Rajshekhar A. Unhale,[a,‡] Milon M. Sadhu,[a,‡] Sumit K. Ray,[a] Rayhan G. Biswas[a] and Vinod K. Singh*[a,b]

Dedicated to Professor Goverdhan Mehta on the occasion of his 75th birthday

A chiral phosphoric acid catalyzed asymmetric Mannich-type reaction of α-diazo esters with *in situ* generated *N*-acyl ketimines, derived from 3- hydroxyisoindolinones, has been demonstrated in this communication. A variety of isoindolinone based α-amino diazo esters bearing a quaternary stereogenic center were afforded in high yields (up to 99%) with excellent enantioselectivities (up to 99% ee). Furthermore, the synthetic utility of the products has been depicted by hydrogenation of the diazo moiety of adducts.

α-Diazocarbonyl compounds are quite valuable precursors in synthetic organic chemistry due to their versatile reactivity and remarkable synthetic value.[1,2] Consequently, they have been widely used in various organic transformations. For instance, transition-metal-catalyzed decomposition of diazo compounds generates highly reactive metal carbene intermediates which undergo a large variety of reactions including X-H insertions (X= C, N, O, Si, S, etc.),[3] cyclopropanations,[4] 1,2-shift,[5] ylide formations[6] and cycloadditions.[7] Among various diazo compounds, α-diazo esters can serve as important nucleophiles for the construction of enantioselective C-C bond under various conditions with the retention of diazo functionality.[8] Elegant studies have been reported by Wang,[9] Feng,[10] Cozzi,[11] and Trost[12] for the chiral Lewis acid catalyzed enantioselective aldol reaction of carbonyl compound with diazo ester to afford enantioenriched β-hydroxy-α-diazocarbonyl compounds (Scheme 1a). Furthermore, diazo esters as nucleophiles were extensively investigated by the groups of Terada,[13] Maruoka[14] and Peng[15] for the catalytic enantioselective Mannich-type reaction with activated aldimine bearing strong electron withdrawing group at the nitrogen atom (Scheme 1b). Diazo esters have been used as potential nucleophiles in asymmetric allylic substitution reaction of Morita–Baylis–Hillman carbonates under the influence of chiral Lewis base (Scheme 1c).[16] Recently, α-diazo phosphonates have been successfully employed in asymmetric Mannich reaction of isatin-based ketimines.[17] There are few elegant strategies in the literature for the enantioselective decarboxylative Mannich reaction[18] as well as direct Mannich reaction[19] of ketimines with enolate equivalents. However, to the best of our knowledge, there is no report in the literature for the enantioselective nucleophilic addition of diazo esters to functionalized cyclic ketimines.



Scheme 1 Asymmetric reactions using diazo esters as nucleophiles.

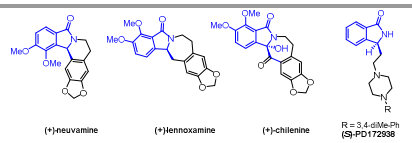


Figure 1 Selected drugs containing isoindolinones

On the other hand, isoindolinone scaffolds are omnipresent in many complex natural products and drug molecules (Figure 1). Their diverse array of pharmaceutical properties are evident from observed antihypertensive,[20] antifungal,[21] antitumor,[22] antileukemic,[23] and antiviral[24] activities. Therefore, development of new synthetic routes for the enantioselective

[a]*Department of Chemistry, Indian Institute of Science Education and Research Bhopal, Bhopal, MP-462 066, India*
[b]*Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur, UP-208016, India*
Email: vinodks@iitk.ac.in; Fax: (+) 91-755-4092392
‡Both authors contributed equally.
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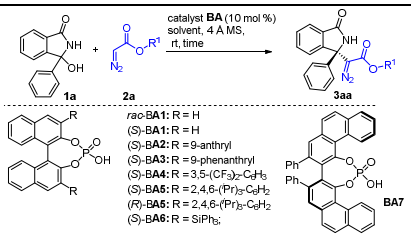
synthesis of this fascinating *N*-heterocyclic scaffold is highly appealing. 3-Aryl-3-hydroxyisoindolinones have been used as excellent substrates for the synthesis of enantioenriched isoindolinone derivatives through various asymmetric strategies, such as Friedel-Craft,[25] arylation,[26] hydrogenolysis,[27] hydrophosponylation,[28] and asymmetric addition of thiols[29] involving organometallic catalysis as well as organocatalysis. Very recently, these substrates have been used for enantioselective three-component reaction *via* trapping of oxonium ylides in presence of Rh(II)/chiral phosphoric acid.[30] Inspired by aforementioned studies, we hypothesized that α-diazo esters can serve as nucleophile to the *in situ* generated *N*-acyl ketimines derived from 3-aryl-3-hydroxyisoindolinones in a Mannich-type fashion. In this communication, we report a enantioselective chiral Brønsted acid catalyzed enantioselective synthesis of isoindolinone based α-amino diazo esters *via* Mannich-type reaction of α-diazo esters with *in situ* generated ketimines of 3-aryl-3-hydroxyisoindolinone (Scheme 1d).

Table 1 Optimization of reaction conditions [a]

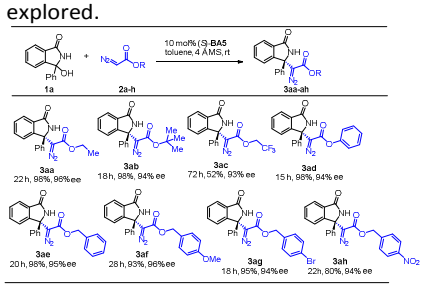


Entry	catalyst	solvent	Time (h)	yield (%)[b]	ee (%)[c]
1	*rac*-**BA1**	CH_2Cl_2	1	81	racemic
2	(*S*)-**BA1**	CH_2Cl_2	2	99	0
3	(*S*)-**BA2**	CH_2Cl_2	20	60	90
4	(*S*)-**BA3**	CH_2Cl_2	20	86	63
5	(*S*)-**BA4**	CH_2Cl_2	5	97	19
6	(*S*)-**BA5**	CH_2Cl_2	5	96	90
7[d]	(*S*)-**BA5**	CH_2Cl_2	72	trace	ND
8[e]	(*R*)-**BA5**	CH_2Cl_2	5	94	90
9	(*S*)-**BA6**	CH_2Cl_2	20	53	86
10	(*S*)-**BA7**	CH_2Cl_2	20	78	5
11	(*S*)-**BA5**	$CHCl_3$	20	98	84
12	(*S*)-**BA5**	DCE	12	99	90
13	(*S*)-**BA5**	Toluene	20	83	95
14	(*S*)-**BA5**	Et_2O	24	32	92
15	(*S*)-**BA5**	EtOAc	36	31	93
16[f]	(*S*)-**BA5**	Toluene	22	98	96
17[g]	(*S*)-**BA5**	Toluene	22	98	96
18[f,h]	(*S*)-**BA5**	Toluene	96	38	95

[a]Reactions conditions: 0.2 mmol of **1a** and 0.24 mmol of **2a** in 1 mL of solvent with 0.02 mmol of Brønsted acid at rt with 4Å MS (50 mg), unless noted otherwise. [b]Isolated yield of **3aa**. [c]Determined by HPLC using chiralpak ID column. [d]Without MS, [e]Product having (*R*) configuration, [f]0.4 mmol of **2a** was used. [g]0.6 mmol of **2a** was used. [h]Reaction was conducted at 0 °C. ND = Not determined

At the outset, the model reaction was conducted using 3-hydroxy-3-phenylisoindolinone **1a** and ethyl diazoacetate (EDA) **2a** in presence of 10 mol % *rac*-BINOL-derived phosphoric acid (*rac*-**BA1**) in dichloromethane at room temperature. To our delight, the reaction worked efficiently, affording the desired racemic product **3aa** in 81% yield (Table 1, entry 1). Encouraged by this preliminary outcome, an array of chiral phosphoric acids **BA1**-**BA7** were screened for the reaction (Table 1, entries 3-10). Among them, **BA5** was found to be the best Brønsted acid catalyst to afford **3aa** in 96% yield and 90% enantioselectivity (Table 1, entry 6). It is noteworthy to mention that the use of 4Å molecular sieves as a water scavenger was essential to promote the reaction (Table 1, entry 7). Interestingly, (*R*)-BINOL-derived phosphoric acid (*R*)-**BA5** afforded the opposite enantiomer of **3aa** (*R*) in the same level of yield and enantioselectivity (Table 1, entry 8). Subsequently, the influence of solvent on enantioselectivity was examined. Among various solvents screened, $CHCl_3$ and 1,2-dichloroethane afforded the product **3aa** in comparable yields and enantioselectivities (Table 1, entries 11-12). Toluene was found to be the choice of solvent as the enantioselectivity of the product **3aa** was improved to 95% albeit with lower yield (Table 1, entry 13). Importantly, the use of two equiv of EDA **2a** was found to be the best way to achieve higher yield (98%) (Table 1, entry 16). To further improve the enantioselectivity of the product, the reaction was conducted at 0 °C. Although the product **3aa** was afforded with similar level of enantioselectivity (95% ee), the chemical yield dropped to 38% (Table 1, entry 18)

Having established optimal reaction condition, the substrate scope was explored.



Scheme 2 Scope of various α-diazo esters in Mannich-type reaction.

First, differently substituted α-diazo esters (**2a-2h**) were subjected to the optimized reaction conditions. To our delight, a variety of chiral diazo compounds (**3aa-3ah**) with delicate functionalities were afforded in synthetically viable yields (up to 98%) and excellent enantioselectivities (up to 96% ee) (Scheme 2). Interestingly, *t*-butyl diazoacetate **2b** having a bulky ester group was equally efficient to this reaction, furnished the product **3ab** with excellent yield (98%) and enantioselectivity (94% ee). In contrast, 2,2,2-trifluroethyl diazoacetate **2c** having a comparable lower *p*Ka value took longer time to complete the reaction, affording the product **3ac** with similar level of enantioselectivity (93% ee) but with lower yield (52%). This probably indicates that electronic factors in the diazo esters play a pivotal role in the reactivity of Mannich-type process. Afterward, differently substituted benzyl diazo acetates (**2e-2h**) were examined affording the chiral diazo compounds (**3ae-3ah**) in synthetically viable yields (up to 98%) and excellent enantioselectivities (up to 96% ee). Noticeable, benzyl diazoacetate having electron donating group took comparable longer time to complete the reaction than benzyl diazoacetate having electron withdrawing group (**3af** *vs* **3ag-ah**).

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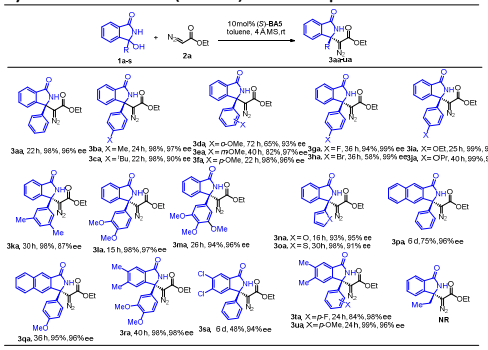
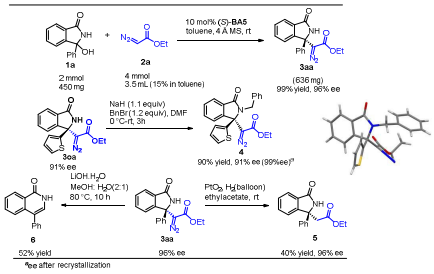
Next, the scope of the reaction was further investigated by the reaction of EDA **2a** with a variety of 3-aryl-3-hydroxyisoindolinones (**3a-3u**) under optimized conditions.



Scheme 3 Scope of various 3-hydroxy-3-arylisoindolinones in Mannich-type reaction

Gratifyingly, the corresponding chiral diazo compounds **3aa-3ua** were afforded in good to excellent yields (up to 99%) and enantioselectivities (up to 99% ee) (Scheme 3). Notable, the electronic nature of substituent on the aromatic ring at the C-3 position of 3-aryl-3-hydroxyisoindolinones had a very little effect on the enantioselectivities of the product formation. However, the rate of the reaction was considerably faster with electron donating substituents at the 3-aryl ring than bearing electron withdrawing groups (**3ba-ca** *vs* **3ga-ha**). Moreover, the position on the substituent on the aromatic ring at the C-3 position of 3-aryl-3-hydroxyisoindolinones had no significant effect in enantioinduction. However, substrate with *ortho* substituent at 3-aryl ring took longer reaction time for completion and afforded albeit lower yield than with the *meta* and *para* substituents at 3-aryl ring (**3da** vs **3ea-fa**). Rewardingly, heteroaromatic substrates **1n-o** having a furan and thiophene moiety furnished corresponding products **3na-oa** with excellent yields and enantioselectivities (up to 95% ee). Additionally, 3,5-dimethyl, 3,4-dimethoxy and 3,4,5-trimethoxy groups on the 3-aryl substituent were well tolerated, affording products **3ak-am** in excellent yields and enantioselectivities (up to 96% ee). Surprisingly, the substrates containing naphthyl ring took six days to complete the reaction, affording the corresponding product **3pa** in 75% yield and 92% ee. Moreover, isoindolinone motifs having different substituent on the phthalimide aromatic ring were tested. A 5,6-dimethyl or 5,6-dichloro substituent on the phthalimide aromatic ring responded well to this protocol, furnished products **3ra-sa** in good yields (up to 98%) and enantioselectivities (up to 98% ee). Unfortunately, the substrate **1v** bearing alkyl side chain at C-3 position and acyclic ketimines such as 1-Phenylethan-1-imine and 4-Methoxy-*N*-(2,2,2-trifluro-1-phenylethylidene)benzamine failed to react with EDA under our optimized reaction conditions.

To illustrate the practical efficacy of our methodology, a higher mmol scale reaction of 3-hydroxy-3-phenylisoindolinone **1a** (2 mmol, 0.45 g) and ethyl diazoacetate (EDA) **2a** (4 mmol) was carried out under optimized reaction conditions, furnishing **3aa** in 99% yield and 96% ee (Scheme 4).



Scheme 4 Higher mmol scale reaction and synthetic transformation of **3aa**

To demonstrate the potential utility of this protocol in organic synthesis, we converted the isoindolinones **3aa** into corresponding benzylated analogue **4** in the presence of benzyl bromide and sodium hydride with the retention of optical purity. Compound **4** was crystallized from the mixture of CH_2Cl_2/hexane solvent. The absolute configuration of compound **4** was unambiguously determined by single crystal X-ray structure analysis. The absolute configuration of the chiral diazo compounds **3** were assigned by analogy. We have also proposed a transition state to rationalize the observed stereochemical outcome of the products (Fig. 3, ESI). The diazo functionality of the adduct **3aa** was subjected to hydrogenation by PtO_2 under hydrogen atmosphere. The hydrogenated product **5** was obtained in 40% yield without compromising the enantiopurity. To our surprise, the treatment of compound **3aa** with $LiOH.H_2O$, afforded the 2-quinolinone derivative **6** in 52% yield *via* a decarboxylative rearrangement reaction. Although during this transformation chiral center was lost, the newly formed 2-quinolinone derivative is a very important skeleton present in many bioactive natural products.[31]

In summary, we have established a process for asymmetric Mannich-type reaction of α-diazo esters with *in situ* generated *N*-acyl ketimines in the presence of chiral Brønsted acid under ambient conditions for the first time, to the best of our knowledge. A variety of diazo esters were utilized to access biologically interesting chiral isoindolinone based α-amino diazo esters with remarkably high enantioselectivities (up to 99% ee). Enantioselective construction of chiral diazo compounds comprising a quaternary stereogenic center is one of the salient features of this exciting chemistry. The utility of this protocol has also been demonstrated by hydrogenation of diazo moiety of the product.

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Conflicts of interest

There are no conflicts to declare.

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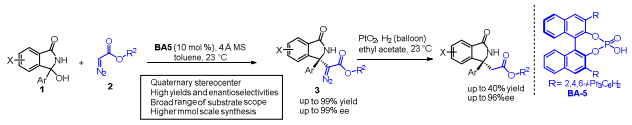
TOC

Chiral Brønsted Acid Catalyzed Highly Enantioselctive Mannich-type Reaction of α-Diazo esters with *in Situ* Generated *N*-Acyl Ketimines

Rajshekhar A. Unhale,[a,‡] Milon M. Sadhu,[a,‡] Sumit K. Ray,[a] Rayhan G. Biswas[a] and Vinod K. Singh*[a,b]



The chiral phosphoric acid catalyzed asymmetric Mannich-type reaction of α-diazo esters with *in situ* generated *N*-acyl ketimines, derived from 3-aryl-3-hydroxyisoindolinones, has been demonstrated. The reaction proceeds smoothly under mild reaction conditions affording a variety of enantioenriched isoindolinone based α-amino diazo esters with a quaternary stereogenic center in high yields (up to 99%) with excellent enantioselectivities (up to 99% ee).