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Article

Stereo- and Regiospecific S_N2' Reaction of MBH Adducts with Isocyanoacetates: *en* Route to Transition-Metal-Free α-Allylation of Isocyanoacetates

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Cite This: *ACS Omega* 2023, 8, 6854−6859

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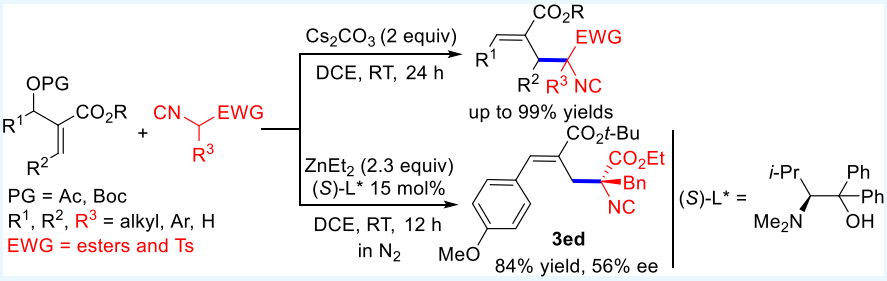


ABSTRACT: Herein, we report that under mild and transition-metal-free conditions an unprecedented and practical S_N2' reaction of Morita−Baylis−Hillman adducts with isocyanoacetates takes place in a stereo- and regiospecific manner. This reaction which tolerates a wide variety of functionalities delivers transformable α-allylated isocyanoacetates in high efficiencies. Preliminary studies on the asymmetric version of this reaction indicate that $ZnEt_2$/chiral amino alcohol combinations are an asymmetric catalytic system for this transformation, giving an enantioenriched α-allylated isocyanoacetate with a chiral quaternary carbon in a high yield.

INTRODUCTION

Isocyanoacetates have proven to be synthetically very useful building blocks for the assembly of a large array of functional organic molecules.[1] They have been widely used in the synthesis of many biologically active natural products,[2] pharmaceuticals,[3] organometallics,[4] and so on. Thereafter, there has been long-standing interests in the innovation of new reactivity and accordingly developing novel transformations involving them.

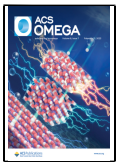
Being a type of activated methylene compounds, isocyanoacetates have been widely employed as α-nucleophiles to attack electrophiles leading to a variety of nucleophilic addition and cycloaddition. Typical electrophilic acceptors include alkyl (pseudo)halides,[2a] electron-deficient alkenes[2c,5] and heterocycles,[6] alkynes,[7] cumulated double bonds,[8] imines,[9] carbonyls,[2d,10] aziridines,[11] nitrones,[12] 1,3-dipoles,[13] aryl diazonium salts[14] and so forth. Morita−Baylis−Hillman (MBH) adducts, which have proven to be a type of versatile electrophiles,[15] however, have never been reported to react with isocyanoacetates to the best of our knowledge. Thereafter, the exploration on the interaction between isocyanoacetates and MBH adducts is of much significance and deserves investigation.

As a type of structures containing multiple transformable functionalities, α-allylic isocyanoacetates are assumed to be synthetically useful manifolds which can be used to construct diverse products. Nevertheless, existing methods for the synthesis of α-allylic isocyanoacetates have proven to be very scarce. Known methods that utilize allylic alcohol esters as allylation components under palladium catalysis conditions[16] suffer from expensive and contaminative palladium metal, uncontrollable regioselectivity, and/or limited reaction scope (Scheme 1a). Hence, the development of novel, regiospecific, and especially transition-metal free allylation of isocyanoacetates is of much significance and worth investigation. In this work, we report that under transition-metal-free conditions isocyanoacetates can be regio- and stereospecifically allylated by employing MBH adducts as allylating components, giving α-allylic isocyanoacetates in high efficiency (Scheme 1b).

RESULTS AND DISCUSSION

We commenced our investigation by selecting readily available MBH adduct **1a**[17] and ethyl isocyanoacetate **2a** as starting materials. Under an inert atmosphere, this reaction in the presence of Cs_2CO_3 in DCM (dichloromethane) at room temperature for 24 h produced α-allylic isocyanoacetate **3aa** in a 73% yield (Table 1, entry 1). In the case that Cs_2CO_3 was

Received: November 27, 2022
Accepted: January 30, 2023
Published: February 9, 2023



Scheme 1. α-Allylation of Isocyanoacetates

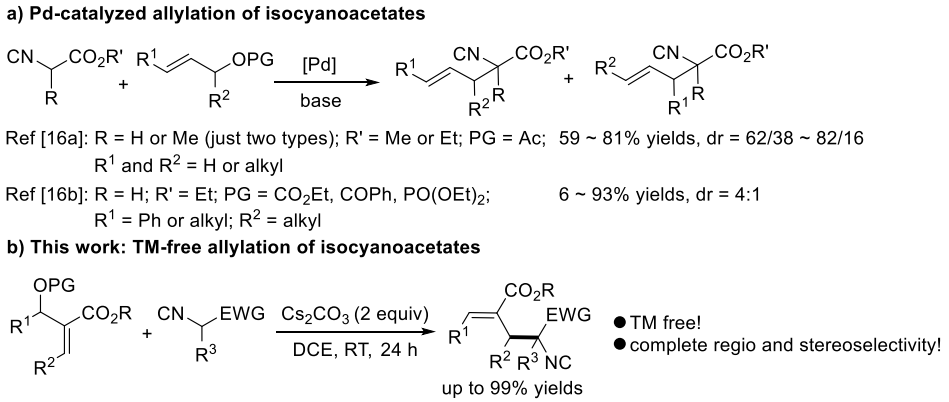
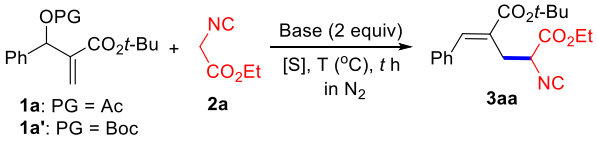


Table 1. Optimization Work[a]



entry	base	[S]	T (°C)	t h	yield[b] (%)
1	Cs_2CO_3	DCM	RT	24	73
2	K_2CO_3	DCM	RT	24	0
3	Na_2CO_3	DCM	RT	24	0
4	K_3PO_4	DCM	RT	24	37
5	Et_3N	DCM	RT	24	0
6	DBU	DCM	45	24	0
7	no	DCM	RT	24	0
8[c]	Cs_2CO_3	DCM	RT	24	5
9[d]	Cs_2CO_3	DCM	RT	24	58
10[e]	Cs_2CO_3	DCM	RT	24	66
11	Cs_2CO_3	MeCN	RT	24	15
12	Cs_2CO_3	toluene	RT	24	71
13	Cs_2CO_3	THF	RT	24	69
14	Cs_2CO_3	DMF	RT	24	75
15	Cs_2CO_3	DCE	RT	24	76
16	Cs_2CO_3	DCE	0	24	25
17	Cs_2CO_3	DCE	45	24	73
18	Cs_2CO_3	DCE	RT	12	68
19	Cs_2CO_3	DCE	RT	48	59
20[f]	Cs_2CO_3	DCE	RT	24	80
21[g]	Cs_2CO_3	DCE	RT	24	87
22[h]	Cs_2CO_3	DCE	RT	24	83
23[g,i]	NaOH	DCE	RT	24	0
24[g,i]	t-BuOK	DCE	RT	24	70
25[c,g,i]	t-BuOK	DCE	RT	24	14

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), base (0.4 mmol), [S] (1 mL). [b]Isolated yields. [c]Base (0.04 mmol). [d]Base (0.2 mmol). [e]Base (0.6 mmol). [f]**2a** (0.4 mmol). [g]**2a** (0.6 mmol). [h]**2a** (0.8 mmol). [i]1a′ was used instead of **1a**.

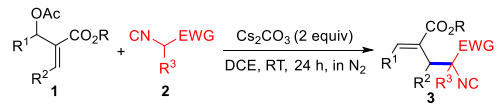
replaced by K_2CO_3 or Na_2CO_3, the reaction did not take place, implying the basicity and/or the solubility of the bases might play critical roles in the reaction (Table 1, entries 2−3). While K_3PO_3 gave the α-allylic isocyanoacetate **3aa** in a 37% yield, organic bases such as Et_3N and DBU were fruitless with the starting materials being recovered in nearly quantitative yields (Table 1, entries 4−6). A control experiment revealed that the reaction did not take place in the absence of any base, showing the critical role of the bases in the reaction (Table 1, entry 7).

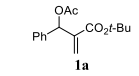
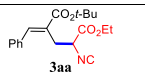
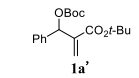
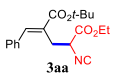
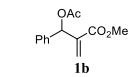
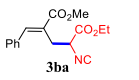
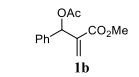
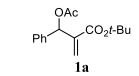
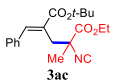
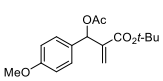
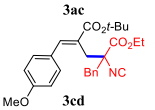
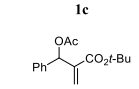
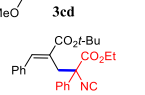
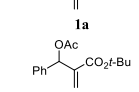
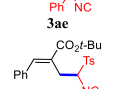
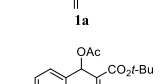
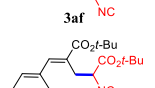
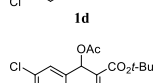
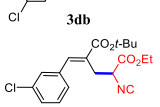
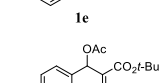
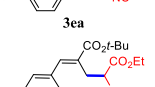
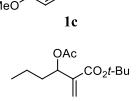
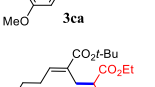
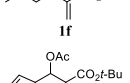
The results that a catalytic amount of Cs_2CO_3 (20 mol %, Table 1, entry 8) just furnished a 5% yield revealed that a stoichiometric amount of the base was necessary for the reaction.[18] Further optimization on the loading of the base revealed that 2 equiv amount was the best, with the highest yield of **3aa** being obtained (Table 1, entries 9−10). The screening on the reaction solvents demonstrated that DCE (dichloroethane) was the best choice, with the highest yield (76%) being afforded (Table 1, entries 11−15). Because neither a lower (0 °C) nor a higher temperature (45 °C) provided a better result, room temperature was proven to be the most suitable temperature for the reaction (Table 1, entries 16−17). As both lengthening and shortening the reaction time led to lower yields, 24 h were proven to be the most proper reaction time (Table 1, entries 18−19). Finally, it was revealed that raising the loading amount of **2a** was beneficial for the reaction (Table 1, entries 20−22). When **2a** was used in three equivalence of **1a**, the highest reaction yield (87%) was obtained (Table 1, entry 21). Moreover, we also tested some strong inorganic bases, such as NaOH and t-BuOK, as the base by employing MBH adduct **1a′** as an allylation component (Table 1, entries 23−25), finding that NaOH was completely incompetent with no desired product **3aa** was obtained (Table 1, entry 23). On the other hand, t-BuOK was proven to be a competent base for the reaction with the desired product **3aa** was produced in a 70% yield (Table 1, entry 24). However, it once again proved that the base must be used in a stoichiometric amount. When the used amount of t-BuOK was reduced to a catalytic amount (20%), only a 14% yield of product **3aa** was furnished (Table 1, entry 25).

With optimal conditions in hand, we next investigated the scope of this reaction, and the results are summarized in Table 2. It was found that besides *tert*-butyl 2-(acetoxy(phenyl)-methyl)acrylate **1a**, *tert*-butyl 2-(((*tert*-butoxycarbonyl)oxy)(phenyl)methyl)acrylate **1a′** was also a reliable substrate in the reaction, giving product **3aa** in a 72% yield in the presence of two equivalence of Cs_2CO_3 (Table 2, entry 2). Methyl 2-(acetoxy(phenyl)methyl)acrylate **1b** could likewise smoothly carry out the reaction, leading to allylic isocyanoacetate **3ba** in a 88% yield (Table 2, entry 3). In addition to ethyl isocyanoacetate **2a**, *tert*-butyl isocyanoacetate **2b** was also able to proceed with this reaction, affording desired product **3bb** in a high yield (91%, Table 2, entry 4). α-Substituted isocyanoacetates such as ethyl 2-isocyanopropanoate **2c**, ethyl 2-isocyano-3-phenylpropanoate **2d**, and ethyl 2-isocyano-2-phenylacetate **2e** were all proven to be competent reactants in the reaction, producing α-allylic isocyanoacetates with

https://doi.org/10.1021/acsomega.2c07581
ACS Omega 2023, 8, 6854−6859

Table 2. Scope of the Reaction[a]



Entry	1	2	3	Yield %[b]
1	 1a	 2a	 3aa	87
2	 1a'	 2a	 3aa	72
3	 1b	 2a	 3ba	88
4	 1b	 2b	 3bb	91
5	 1a	 2c	 3ac	75[c] (56)[d]
6	 1c	 2d	 3cd	99[c] (81)[d]
7	 1a	 2e	 3ae	99[c] (86)[d] 91[e]
8	 1a	 2f	 3af	84
9	 1d	2b	 3db	63
10	 1e	2a	 3ea	76
11	 1c	2a	 3ca	80
12	 1f	2a	 3fa	54
13	 1g	2a	 3ga	75
14	1h	2a	3ha	51
15	1i	2a	3ia	50

[a]Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), Cs_2CO_3 (0.4 mmol), DCE (1 mL), RT, 24 h. [b]Isolated yields. [c]**2** (0.24 mmol). [d]Cs_2CO_3 (0.2 mmol). [e]**1a'** was used instead of **1a** and DBU was used as the base.

quaternary carbon centers in high yields.[19] For these α-substituted isocyanoacetates **2c**–**2e**, the desired α-quaternary isocyanoacetates **3ac**, **3cd**, and **3ae** were still afforded when one equivalence of Cs_2CO_3 was employed, albeit in slightly lower yields (56–86%) (Table 2, entries 5–7). Additionally, it was found that 1-((isocyanomethyl)sulfonyl)-4-methylbenzene (TosMIC) **2f** was also a good reaction partner with *tert*-butyl 2-(acetoxy(phenyl)methyl)acrylate **1a**, leading to allylation product **3af** in a 84% yield (Table 2, entry 8). With respect to MBH adducts **1** derived from aryl aldehydes, various functionalities on phenyl rings could be tolerated in the reaction. For example, MBH adducts bearing an electron-withdrawing group such as a chlorine atom at their para and meta positions both proved to be reliable substrates in the reaction, furnishing allylic isocyanoacetates **3db** and **3ea** in 63 and 76% yields (Table 2, entries 9–10). MBH adducts having an electron-donating substituent like a methoxy group at their para positions (**1c**) also reacted smoothly with ethyl isocyanoacetate **2a**, providing allylic isocyanoacetate **3ea** in a 80% yield (Table 2, entry 11). Furthermore, it was found that MBH adducts derived from an aliphatic aldehyde, such as *tert*-butyl 3-acetoxy-2-methylenehexanoate **1f**, could be engaged in the reaction, producing allylic isocyanoacetate **3fa** in a 54% yield (Table 2, entry 12). MBH adducts derived from heteroaryl aldehydes such as *tert*-butyl 2-(acetoxy(furan-3-yl)methyl)acrylate **1g** was also a competent substrate in the reaction, giving allylic isocyanoacetate **3ga** in a 75% yield (Table 2, entry 13). Moreover, MBH adducts derived from formaldehyde **1h** could likewise react smoothly with ethyl isocyanoacetate **2a**, furnishing allylic isocyanoacetate **3ha** with a terminal alkene in a 51% yield (Table 2, entry 14). MBH adducts bearing a substituent at their alkene termini such as ethyl (*E*)-2-(acetoxy(phenyl)methyl)-3-phenylacrylate **1i** were also good reaction partners with isocyanoacetate **2a**, giving α-allylic isocyanoacetate **3ia** in a 50% yield (Table 2, entry 15).

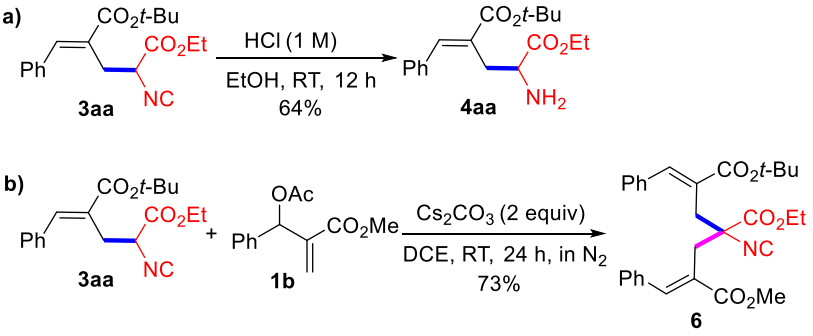
Based on the above results and some literature precedents,[20] a possible reaction pathway is depicted in Scheme 2. Under basic conditions, isocyanoacetates **2** may be converted into nucleophilic anions **I** in which α-carbon anions are stabilized by two election-withdrawing groups[21] (Scheme 2, NC and EWG). Then, an S_N2' process between **I** and electrophilic MBH adducts **1** may regiospecifically take place at the more electrophilic β-postion of the MBH adduct, giving α-allylic isocyanoacetates **3**, and concurrently liberating the conterions PGO^-.

Scheme 2. Proposed Mechanism of the Reaction

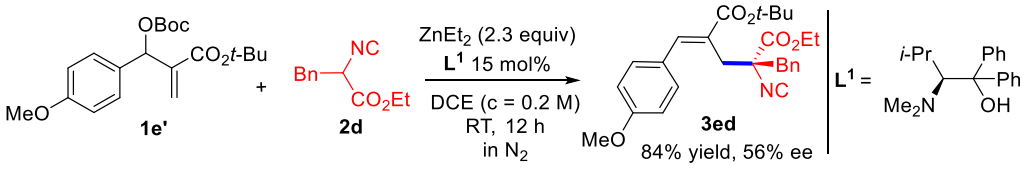
To verify the synthetic value of this reaction, we performed a variety of post-transformations of product **3aa** (Scheme 3). First, the isocyano group in **3aa** could be selectively hydrolyzed by dilute HCl at room temperature, giving unnatural aminoester **4aa** in a 64% yield. Second, regarding the fact that **3aa** itself also belonged to a substituted isocyanoacetate structure, we deduced that it could be engaged into the allylation reaction again under identical conditions. To validate this, we conducted the reaction between **3aa** and MBH adduct **1b** and found that this reaction smoothly took place, furnishing twofold allylation product **6** in a 73% yield. It should be noted that in **6**, the two allyl substituents were different, demonstrating that the α-position of isocyanoacetates could be orthogonally allylated by two different MBH adducts.

https://doi.org/10.1021/acsomega.2c07581
ACS Omega 2023, 8, 6854–6859

Scheme 3. Post-Transformations



Scheme 4. Asymmetric Version of the Transformation



At last, we also tried to develop an asymmetric version of this reaction. After a series of screening and optimization (see the Supporting Information for details), we found that under the promotion of $ZnEt_2$ and a catalytical amount of chiral amino alcohol enantioenriched α-allylated isocyanoacetates **3ed** could be obtained in an 84% yield and 56% ee (Scheme 4). Although the enantioselectivity of this reaction remained at a moderate level and needed to be further improved, this result was of much significance since it supplied a good foundation for the assembly of chiral α-quaternary amino acids, which had proven to be versatile building blocks in a large array of fields,[22] from readily available substrates.

CONCLUSIONS

In summary, we showed that under mild and transition-metal-free conditions S_N2' reactions between readily available MBH adducts and isocyanoacetates could efficiently take place, giving transformable α-allylated isocyanoacetates in high selectivity. Studies on the reaction scope showed that a variety of functional groups could be tolerated in the reaction. Post-transformations demonstrated that as-synthesized α-allylic isocyanoacetate products could be further diversely derived, giving an α-allylic aminoester and α,α-diallylated isocyanoacetate in high efficiencies. Preliminary studies on the asymmetric version of this reaction showed that chiral amino alcohol/$ZnEt_2$ combinations was a potential asymmetric catalytic system for the transformation. Further studies on the improvement of the enantioselectivity of the asymmetric version of this reaction, and the application of this reaction are currently ongoing in our lab.

EXPERIMENTAL SECTION

Representative Procedure of the Racemic Reaction. To an oven-dried flask, Cs_2CO_3 (0.4 mmol), MBH adduct **1a** (0.2 mmol), and isocyanoacetate **2a** (0.6 mmol) were added. The mixture was repeatedly degassed and refilled with N_2 three times. Then, dry DCE (1 mL) was injected by a syringe and the reaction mixture was allowed to stir at room temperature for 24 h. After the completion of the reaction, the mixture was neutralized with 1 N HCl and extracted with DCM three times. After being dried with Na_2SO_4, combined organic layers were filtered through a pad of celite. The filtrate was then concentrated until the solvent was completely removed. The residue was then separated on a silica gel column, and product **3aa** was obtained as pale yellow oil (57 mg, 87%).

Representative Procedure of the Asymmetric Version of This Reaction. Into an oven-dried flask, MBH adduct **1e'** (0.6 mmol), isocyanoacetate **2d** (0.2 mmol), and chiral amino alcohol $\mathbf{L_1}$ (0.03 mmol) were charged. The mixture was repeatedly degassed and refilled with N_2 three times and then cooled to 0 °C and dry DCE (1 mL) and Et_2Zn (0.46 mmol, 1 M in *n*-hexane) were subsequently injected by a syringe. After being stirred at room temperature for 12 h, the system was neutralized with 1 N HCl and extracted with DCM three times. After being dried with Na_2SO_4, the combined organic layers were filtered through a pad of celite. The filtrate was then concentrated until the solvents were completely removed. The residue was then separated on a silica gel column, and product **3ed** was obtained as pale yellow oil (75 mg, 84%).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c07581.

Experimental details; spectral data of ^1H, ^{13}C nuclear magnetic resonance, and high-resolution mass spectrometry of all products; chiral high-performance liquid chromatography for product **3ed**; and optimization details on an asymmetric version of the reaction (PDF)

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https://doi.org/10.1021/acsomega.2c07581
ACS Omega 2023, 8, 6854−6859

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully thank the grant support from Zhejiang Provincial Natural Science Foundation of China (LY17B020007), Hangzhou City Research Project (20191203B12), and Key Laboratory for Preparation and Application of Energy Saving and Emission Reduction New Materials of Jiaxing City.

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(18) A possible reason for the use of stoichiometric amount of the bases may be that the as-produced α-allylic isocyanoacetate product 3aa is an activated methine product. So, after the reaction, they may be deprotonated by and consume an additional mole of the base.

(19) Considering the enhanced α-acidity of the α-phenylisocyanoacetate 2e in comparation with 2a, we also tested the reaction between MBH adduct 1a′ and α-phenylisocyanoacetate 2e by using DBU as the base, and found that the reaction smoothly took placed, giving the α-allylatedisocyanoacetate 3ae in a 91% yield. This result indicated that weaker organic bases could be used in the reaction when more acidic α-aryl isocyanoacetates were used as reaction substrates. We highly thank one of the reviewers for pointing these out.

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(21) A possible reason why DBU cannot promote the reaction between MBH adducts and α-unsubstituted isocyanoacetates such as 2a is that it just partially converts isocyanoacetates into their anions (I, Scheme 2) whose concentration is not high enough to promote the reaction. However, as evidenced by α-phenyl isocyanoacetates 2e (Table 2, entry 7), DBU became an competent base for the α-ary isocyanoacetates possibly due to the strengthening effect of the α-aryl on the α-H acidity of the isocyanoacetates.

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https://doi.org/10.1021/acsomega.2c07581
ACS Omega 2023, 8, 6854−6859