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Organocatalytic Diastereo- and Enantioselective Michael Addition of α-Aryl Isocyanoacetates to Aurone-Derived Azadienes

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A highly diastereo- and enantioselective organocatalytic Michael addition of α-aryl isocyanoacetates to aurone-derived azadienes under mild conditions has been developed. This efficient methodology enables access to chiral α,α-disubstituted α-amino ester derivatives with two adjacent stereocenters, one of them quaternary, bearing a benzofuran scaffold in their structure in high yields and stereocontrol. Furthermore, the reaction product can be readily converted into an α,α-disubstituted α-amino acid in high yield *via* hydrolysis of the isocyano group without compromising enantioselectivity.

Introduction

Benzofurans are important compounds due to their ubiquitous presence in nature and their diverse pharmacological properties. Their unique structure makes them attractive targets and key scaffolds for the synthesis of numerous biologically active molecules and they are also valuable in medicinal chemistry and drug discovery.[1] The related aurone-derived azadienes hold substantial importance in organic chemistry, primarily due to their application in the asymmetric synthesis of chiral benzofuran derivatives. These versatile molecules, characterized by their α,β-unsaturated imine structure, serve as key intermediates in the construction of nitrogen-containing compounds.[2] Asymmetric catalytic Michael reactions to 1-azadienes enable the incorporation of diverse nucleophiles, leading to the formation of chiral benzofuran derivatives with high stereochemical control. In this context, nucleophiles such as phosphites,[3] γ-substituted β,γ-unsaturated γ-lactones,[4] rhodanines,[5] 3-homoacyl coumarins,[6] naphthols,[7a,b] indoles,[7b,c,d] *5H*-thiazol-4-ones,[8] or 3-methylbenzofuran-2(3*H*)-ones[9] have been successfully explored. Notwithstanding the demonstrated efficacy in these, it remains imperative to develop novel asymmetric Michael addition reaction of aurone-derived azadienes with suitable reactants to obtain a diverse array of chiral benzofuran derivatives, thereby enriching structural diversity and expanding synthetic pathways.

Isocyanoacetate esters are highly valued substrates in organic synthesis on account of their unique reactivity, allowing access to diverse chemical structures.[10] Their divalent nature and the presence of an acidic proton at the α-position make α-isocyanoacetates interesting building blocks. Of particular significance is their capacity to mediate the formation of both carbon-carbon and carbon-heteroatom bonds through formal [3 + 2] cycloadditions. This enables the asymmetric synthesis of diverse five-membered nitrogen heterocycles.[11]

An additional intriguing application involves the application of isocyanoacetates as glycine derivatives, enabling the synthesis of chiral α,α-disubstituted α-amino acid derivatives. The significance of these derivatives lies in their versatility as valuable substrates, ligands, or catalysts in asymmetric synthesis.[12] Moreover, they represent essential building blocks in peptide synthesis, a process integral to drug design and development.[13] The synthesis of these important substrate can be achieved, for example, through enantioselective Michael addition of α-aryl isocyanoacetates to C–C double bonds. Recently, our research group disclosed the arylation of α-aryl isocyanoacetates through conjugate addition to *o*-quinone diimides, resulting in the formation of α,α-diarylisocyano esters. Subsequent acid hydrolysis of the isocyano group yielded the corresponding amino esters featuring a diarylated tetrasubstituted carbon atom in high yields.[14] However, methodologies employing chiral Lewis acid or organo/metal cooperatively catalyzed nucleophilic addition of α-isocyanoacetates to double bonds often yield [3 + 2] cycloadducts.[11]

The scope of organocatalyzed enantioselective Michael addition, where the reaction can be stopped at the Michael adduct to synthesize chiral α,α-disubstituted α-amino acid derivatives, remains limited (Scheme 1a).

Notably, electron-deficient olefins,[15] vinyl ketones,[16] maleimides[17] have been successfully used as substrates for this purpose. However, only one example was described using α,β-unsaturated imines,[18] where the reaction stopped at the Michael adduct yielding the product with low enantiomeric excess (20% ee). In this context, and as a continuation of our interest in asymmetric organocatalysis, we propose the organo-

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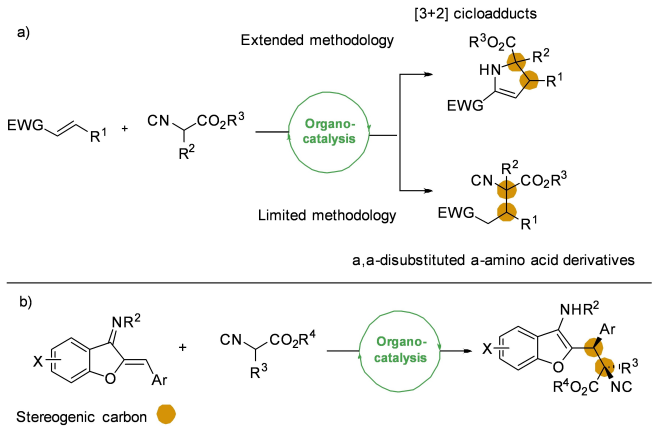


Scheme 1. Stereoselective reactions with α-substituted isocyanoacetate esters and double bonds.

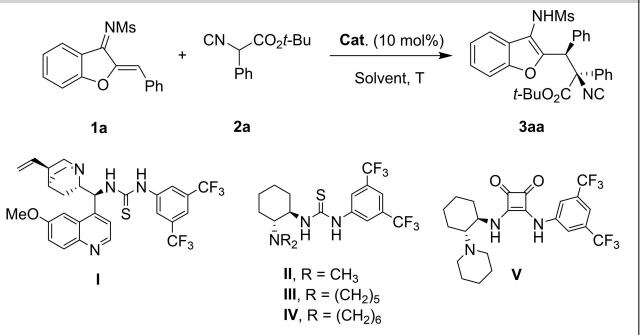
catalyzed enantioselective Michael addition of isocyanoacetate esters to 1-azadienes derived from aurone (Scheme 1b). This methodology enables the highly diastereo- and enantioselective synthesis of α,α-disubstituted α-amino acid derivatives bearing a benzofuran scaffold.

Results and Discussion

We initiated our investigation by testing several organocatalysts for the 1,4-addition reaction of azadiene **1a** and *tert*-butyl 2-isocyano-2-phenylacetate (**2a**) in CH_2Cl_2 at room temperature as a model reaction (Table 1).

It was found that quinine-derived thiourea **I** provided the desired product **3aa** in fair yield and diastereomeric ratio but with low enantiomeric excess (entry 1). To our delight, an increase in yield and enantioselectivity was observed when Takemoto's catalyst **II** was used (entry 2). We also prepared and tested organocatalysts **III**–**IV** bearing a cyclic tertiary amine (entries 3–5). The best result was achieved using thiourea **III** that features a piperidine ring obtaining the desired product in high yield and with a good enantiomeric excess (entry 3). Further increasing the size of the nitrogen-heterocycle of the catalyst **IV** resulted in a decrease in yield while maintaining the stereoselectivity (entry 4). On the other hand, a drastic decrease in both yield and enantioselectivity was observed when using catalyst **V** bearing a squaramide instead of the thiourea moiety (entry 5). Other squaramides, thioureas, and catalysts bearing different H-bond-forming moieties (such as amino-phosphamides), as well as catalysts with basic or acidic characteristics, were tested at room temperature. However, none of these catalysts improved upon the results obtained with thioureas **III** and **IV** (see SI). In order to improve the enantioselectivity, the reaction was performed at −30 °C, resulting in the product being obtained in good yield and improved diastereo- and enantioselectivity (entry 6). However, further lowering the temperature to −50 °C led to an increase in enantiomeric excess but, unfortunately, this was accompanied by a significant decrease in yield and diastereoselectivity (entry 7).

Table 1. Optimization of the reaction conditions.



Entry[a]	Cat	Solvent	T [°C]	Yield [%][b]	dr[c]	ee [%][d]
1	**I**	CH_2Cl_2	rt	60	89:11	−32
2	**II**	CH_2Cl_2	rt	75	78:22	49
3	**III**	CH_2Cl_2	rt	81	85:15	66
4	**IV**	CH_2Cl_2	rt	61	87:13	68
5	**V**	CH_2Cl_2	rt	29	83:17	37
6	**III**	CH_2Cl_2	−30	68	94:6	83
7	**III**	CH_2Cl_2	−50	37	62:38	88
8	**III**	$CHCl_3$	−30	56	94:6	83
9	**III**	$(CH_2Cl)_2$	−30	54	92:8	81
10	**III**	THF	−30	51	83:17	71
11	**III**	Toluene	−30	34	94:6	66
12[e]	**III**	CH_2Cl_2	−30	81	94:6	86
13[e]	**IV**	CH_2Cl_2	−30	63	94:6	87

[a] **1a** (0.10 mmol), **2a** (0.13 mmol), **Cat** (0.01 mmol), solvent (1 mL). [b] Yield of the isolated product. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC. [e] The reaction was carried out in 0.5 mL of CH_2Cl_2 instead of 1 mL.

Furthermore, an exploration into alternative chlorinated solvents was conducted, which yielded product **3aa** with comparable diastereo- and enantioselectivity albeit in reduced yields (entries 8–9). The use of other solvents such as THF or toluene exhibited an adverse impact on the yield of product **3aa** (entries 10–11). Finally, performing the reaction at a concentration of 0.2 M for substrate **1a**, instead of 0.1 M, led to the desired product **3aa** being obtained in a high yield and enantioselectivity, accompanied by an excellent diastereomeric ratio (entry 12). Catalyst **IV** was also evaluated under these conditions, yielding compound **3aa** with stereoselectivity comparable to that obtained with catalyst **III** but with a significant lower yield (entry 13). Consequently, subsequent experiments were conducted using thiourea **III** as the catalyst.

With the optimized conditions in hand, the scope of the reaction was studied (Scheme 2). Initially, a wide range of aurone-derived azadienes **1** featuring differently substituted aromatic rings attached to the exocyclic double bond were reacted with isocyano ester **2a**. As shown in Scheme 2, both electron-withdrawing and electron-donating substituents could be successfully introduced on the phenyl ring affording the corresponding adducts **3**. Compound **1b**, bearing a *p*-tolyl, yielded compound **3ba** in high yield, and with diastereo- and

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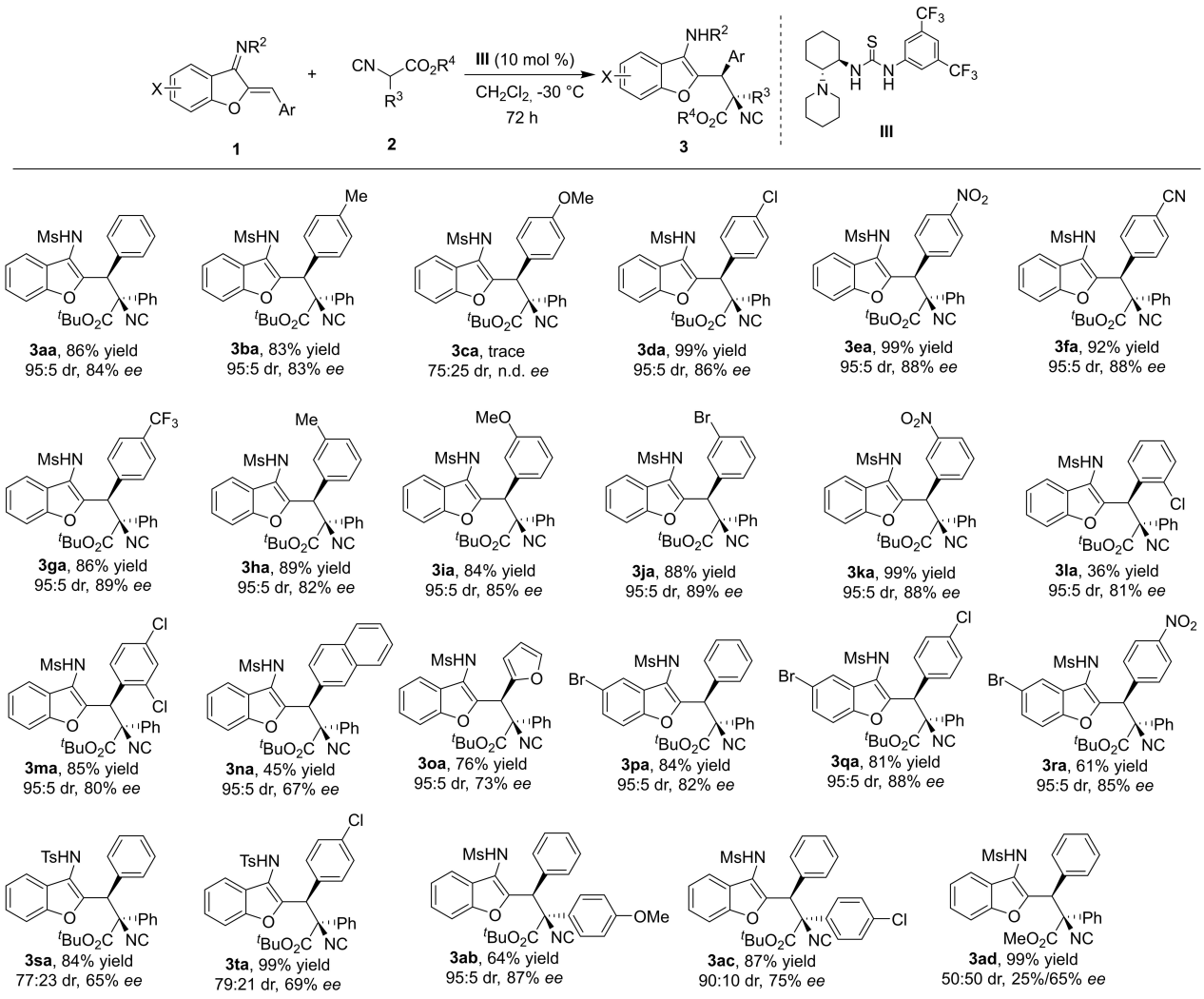

Scheme 2. Scope of the Michael addition beetwen aurone-derived azadienes **1** with α-aryl isocyanoacetates **2**. Reaction conditions: **1** (0.20 mmol), **2** (0.26 mmol), and **III** (10 mol%) in 1 mL of CH_2Cl_2 at −30 °C for 72 h. Isolated yield after column chromatography. Diastereomeric ration determined by ^{1}H NMR. Enantiomeric excess determined by HPLC using chiral stationary phase.

enantioselectivity similar to those obtained for compound **3aa**. However, when a strong electron-donating group such as MeO was introduced at the *para* position of the phenyl ring (**1c**), the reaction did not proceed. Notably, excellent results were obtained when the group at the *para* position was an electron-withdrawing one (**1d**-**1g**) with enantioselectivities up to 86% ee. Importantly, azadienes with either electron-donating or electron-withdrawing groups at the *meta* position of the phenyl ring (**1h**-**1k**), afforded the corresponding products (**3ha**-**3ka**) with excellent results, even with the 1-azadiene **1i** bearing a MeO group. A steric hindrance effect was observed when *o*-chlorophenyl substituted azadiene **1l** was tested giving compound **3la** product in low yield although with an excellent diastereomeric ratio and good enantioselectivity. Remarkably, excellent results were also obtained when a disubstituted aromatic ring in the azadiene substrate (**1m**) was featured. Moreover, other aromatic substituents such as naphthalene or a heterocyclic furan group were tolerated in the azadiene substrate (**1n**-**1o**), affording the corresponding products with good results.

To further expand the substrate scope azadienes derived of 5-bromobenzofuran (**1p**-**1r**) were prepared. The reaction of these substrates with **2a** proceeded smoothly to furnish the desired products **3pa**-**3ra** in 61–84% yields, 95:5 dr and82–88% ee. The effect of the substituent on the sulfonyl group was next assessed. When the protecting group R^2 of the N atom of the azadiene changed from Ms to Ts, the reaction took place to give products **3sa**-**3ta** with excellent yield but, unfortunately, with lower stereoselectivity.

Finally, the scope regarding the isocyano ester was explored. 1-Azadiene **1a** was reacted with different isocyanoacetates bearing diverse substitutions on the aromatic ring as well as on the ester group.

Regarding *tert*-butyl 2-aryl-isocyanoacetates, substitution of the phenyl ring with a strongly electron-donating group such as in *tert*-butyl 2-isocyano-2-(4-methoxyphenyl)acetate (**2b**) provided product **3ab** with high stereoselectivity. In contrast,

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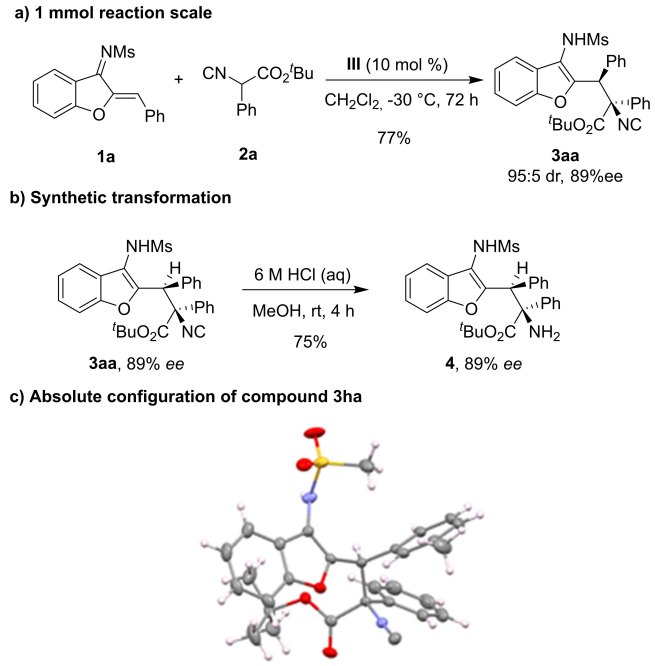
the yield of the reaction decreased from 86% to 64%, which may be due to the lower basicity of **2b** compared with **2a**. On the other hand, substitution of the aromatic ring with an electron-withdrawing chloro group (**2c**) resulted in a good yield of **3ac** but this was obtained with lower diastereomeric ratio and moderate enantiomeric excess. Finally, the methyl ester **2d** was studied, which provided compound **3ad** with lower diastereo- and enantioselectivity than those obtained with the *tert*-butyl ester.

To demonstrate the practicality and robustness of our protocol, we performed the reaction on a 1 mmol scale (Scheme 3a). The product **3aa** was obtained in good yield with a slightly improvement in enantioselectivity while preserving the diastereoselectivity.

In order to showcase the synthetic versatility of these chiral compounds **3**, and recognizing the prevalence of chiral α,α-disubstituted amino esters in various bioactive molecules, we explored the transformation of **3aa** to **4** (Scheme 3b). The acidic hydrolysis of the isocyanide group of compound **3aa** proceeded with good yield and without any degradation of the enantiomeric excess of the product.

Finally, the absolute configurations of the stereogenic centers in compound **3ha** were determined to be (2*S*, 3*S*) on the basis of X-ray crystallographic analysis (Scheme 3c); the configuration of the remaining compounds **3** were assigned as (2*S*,3*S*) on the assumption of a consistent mechanistic pathway.[19]



Scheme 3. a) Reaction at 1 mmol scale, b) acidic hydrolysis of compound **3aa**, c) X-ray structure of the major diastereoisomer **3ha**. Flack parameter 0.02(9).

Conclusions

In conclusion, we have presented a novel organocatalytic diastereo- and enantioselective Michael addition of α-aryl isocyanoacetates to 1-azadienes under mild conditions. A wide variety of 1-azadienes and α-aryl isocyanoacetates were investigated, yielding the corresponding products with two contiguous asymmetric carbon atoms, one of them quaternary, in high yields (up to 99%) and with good to excellent stereoselectivities (up to >95:5 dr, up to 89% ee). Additionally, the straightforward hydrolysis of the isocyanide highlights the versatility of our methodology for the synthesis of biologically relevant chiral α,α-disubstituted amino esters incorporating a benzofuran moiety.

Supporting Information

Additional references cited within the Supporting Information.[20–33]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: organocatalysis · enantioselectivity · azadienes · Michael addition · quaternary stereocenters · α,α-disubstituted amino acids

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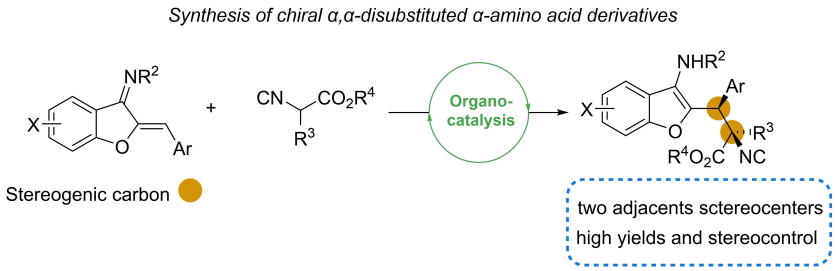

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1 – 6

Organocatalytic Diastereo- and Enantioselective Michael Addition of α-Aryl Isocyanoacetates to Aurone-Derived Azadienes

Efficient synthesis of asymmetric α,α-disubstituted amino acids derivatives through organocatalyzed Michael addition of α-aryl isocyanoacetates and aurone-derived azadienes. The corresponding products bearing a benzofuran scaffold in their structure with two adjacents sctereocenters were obtained in high yields and stereoselectivities.