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Cu-Catalyzed [3 + 3] Cycloaddition of Isocyanoacetates with Aziridines and Stereoselective Access to α,γ-Diamino Acids

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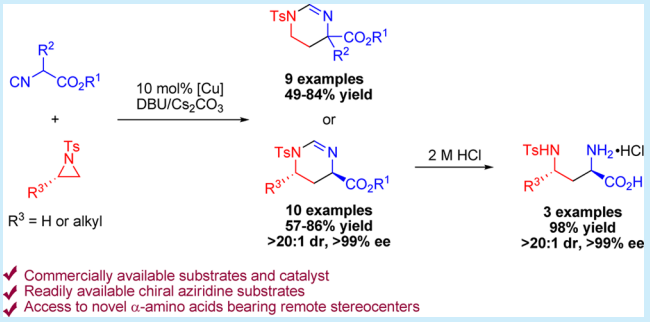
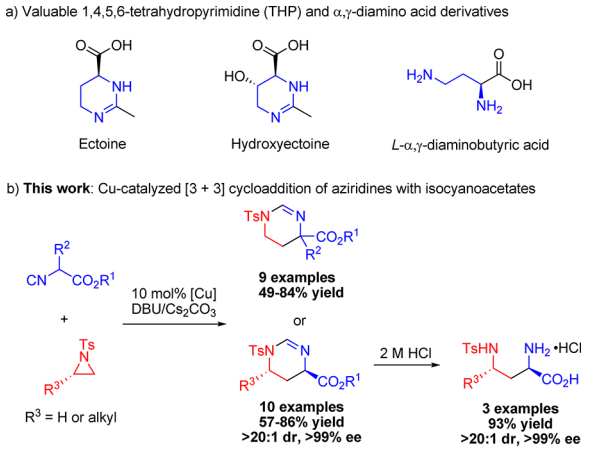
Supporting Information

ABSTRACT: We report herein an efficient Cu-catalyzed formal [3 + 3] cycloaddition of isocyanoacetates with readily available aziridines of different substitution patterns, which provides a practical access to valuable 1,4,5,6-tetrahydropyrimidine derivatives. In particular, the use of enantiopure aziridines delivers disubstituted tetrahydropyrimidines bearing a 1,3-diamino unit in good yields as a single stereoisomer (>20:1 dr, > 99% ee). The heterocyclic products can also be easily converted to synthetically useful amino alcohol derivatives or α,γ-diamino acids.



N-Heterocycles such as 1,4,5,6-tetrahydropyrimidines represent key structural motifs found in natural and synthetic molecules displaying a wide array of biological activities. Ectoine and hydroxyectoine (Scheme 1a), for example, are osmoprotectants produced by bacteria that protects biopolymers from extreme conditions.[1] Despite the great utility of these compounds, their preparation in a diastereo- and enantioselective manner remains a challenging objective in synthetic organic chemistry.[2,3]

Scheme 1. [3 + 3] Cycloaddition of Isocyanoacetates



In addition to tetrahydropyrimidines, the related 1,3-diamino-containing acyclic compounds have also shown great potential in medicinal chemistry. α,γ-Diaminobutyric acid, for instance, is shown to cause inhibition of M1 aminopeptidases that is associated with a wide range of cellular functions.[4] To the best of our knowledge, access to such diamino acid derivatives in a highly diastereo- and enantioselective fashion remains elusive in the literature.[5]

Since the introduction of isocyanoacetates by Ugi in 1961,[6] they have served as efficient building blocks for the synthesis of *N*-heterocycles due to the immense potential of their versatile functionality.[7] A plethora of examples have been reported on the stereoselective cycloaddition reactions of isocyanoacetates with various π-systems including carbonyls,[8] imines,[9] α,β-unsaturated carbonyls,[10] and activated alkenes or alkynes[11] to furnish a wide range of five-membered heterocycles. In contrast, cycloadditions of isocyanoacetates with other synthons bearing three or more atoms to form six-membered or larger heterocycles remains largely unexplored. In 2014, Liu and co-workers reported the first formal [3 + 3] cycloaddition of azomethine ylides or *N*-iminoisoquinolinium ylides with isocyanoacetate using Cu or Ag catalysis to yield di- and tricyclic 1,2,4-triazines in moderate to good yields as a racemate.[12] During the preparation of this manuscript, Ghorai and co-workers also published an elegant domino ring-opening cyclization of aziridines with *p*-toluenesulfonylmethyl isocyanide (TosMIC) to furnish tetrahydropyrimidine derivatives with good yields and excellent diastereoselectivity.[3c]

Our group has been interested in the application of isocyanoacetates to new modes of heterocyclic synthesis.[8f,9e,10c,11e,f,13] In particular, we were attracted to the discovery of suitable partners for the synthesis of heterocycles other than five-membered ones. We hypothesized that the use of epoxides or aziridines would prove fruitful due to the favorable opening of the strained rings. Herein, we report our efforts on the [3 + 3] cycloaddition of simple and substituted *N*-Ts aziridines with isocyanoacetates to deliver tetrahydropyrimidines in excellent stereopurity (Scheme 1b). These products can also be readily

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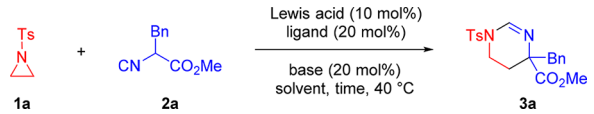
converted to synthetically valuable amino alcohols as well as α,γ-diamino acids in nearly quantitative yield and enantiopurity.

We initiated our investigation using simple aziridine **1a** and α-benzyl-substituted isocyanoacetate **2a** as the model substrate (Table 1). No reaction between **1a** and **2a** was observed simply

Table 1. Optimization of [3 + 3] Cycloaddition[a]



1a 2a 3a

entry	LA	ligand	base	solvent	yield[b] (%)
1	–	–	DBU	THF	<2
2	$Sc(OTf)_3$	–	DBU	THF	<2
3	$BF_3{\cdot}OEt_2$	–	DBU	THF	<2
4	CuI	PPh_3	DBU	THF	65
5	CuI	PPh_3	–	THF	13
6[c]	CuI	PPh_3	DBU	THF	42
7	CuI	Bipyridine	DBU	THF	70
8	CuI	XantPhos	DBU	THF	72
9	CuI	DPPF	DBU	THF	76
10	CuI	DPPF	DBU	toluene	83[d]
11	CuI	DPPF	DBU	MeCN	29
12	CuI	DPPF	KO^{t}Bu	toluene	<2

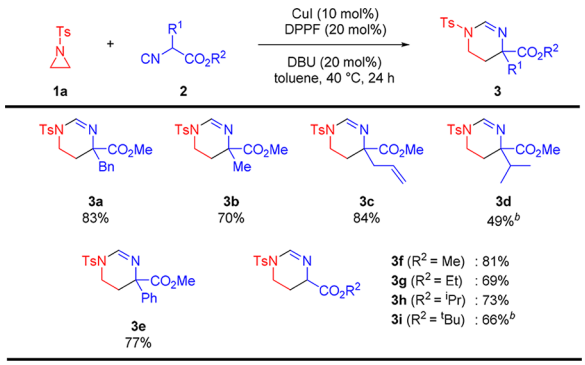
[a]The reaction was conducted using **1a** (1.0 equiv), **2a** (1.5 equiv), LA (10 mol %), ligand (20 mol %), and base (20 mol %) in solvent (0.1 M) at 40 °C, unless stated otherwise. [b]^{1}H NMR yield using 1,3,5-trimethoxybenzene as internal standard. [c]1.0 equiv of **2a** was used. [d]Isolated yield.

in the presence of bases such as DBU (entry 1). The use of Lewis acids such as $Sc(OTf)_3$ and $BF_3{\cdot}OEt_2$ (entries 2 and 3) did not furnish the desired product. However, to our delight, with the use of CuI and PPh_3, we were able to obtain the desired product **3a** in moderate yields (entry 4). The reaction proceeded poorly without the use of base (entry 5). When 1.0 equiv of isocyanoacetate **2a** was used, a drop in the yield was observed (entry 6). This was postulated to be due to the self-dimerization of **2a**, thus reducing the amount of reactant. Next, the screening of ligands (entries 7−9) showed DPPF to be the optimal choice, producing **3a** in 76% yield. Screening of various solvents showed that nonpolar solvents such as toluene proved superior, giving 83% isolated yield (entry 10) as compared to polar solvents such as MeCN, which only gave 29% yield (entry 11). The choice of bases was critical to the reaction as other strong bases such as KO^{t}Bu did not produce **3a** (entry 12).

With the optimal conditions in hand, the scope of substituted isocyanoacetates for the reaction with **1a** was examined (Scheme 2). Alkyl substituents such as benzyl, methyl, and allyl (**3a−c**) were well tolerated, giving good yields of 83%, 79%, and 84%, respectively. Bulky groups such as isopropyl (**3d**) achieved only 49% yield. Aryl substituents such as phenyl (**3e**) were also well tolerated, giving a good yield of 77%. Next, the variation of the ester groups on unsubstituted isocyanoacetates was also examined. Increasing the bulk of the ester groups from methyl to *tert*-butyl (**3f−i**) was well tolerated, with the yields becoming slightly lower as the steric bulk of the ester groups increased.

In attempts to realize an enantioselective variant of this transformation, we screened a large number of chiral ligands including bisphosphine, monophosphine, P,N-, as well as diamine-based ones (see the SI for details). However, good enantioselectivity was not achieved. In many other cases, no

Scheme 2. Scope for [3 + 3] Cycloaddition of 1a with Substituted Isocyanoacetates[a]

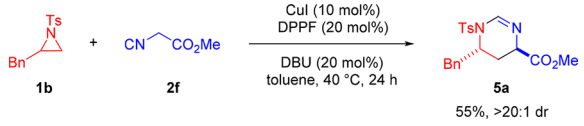


[a]See the SI for the detailed procedure. [b]Reaction carried out at 60 °C.

stereoselectivity was obtained at all. To achieve highly stereoselective access to valuable tetrahydropyrimidines, we then turned our attention to an alternative approach focusing on the cycloaddition of enantiopure monosubstituted aziridines. These compounds are easily accessed from commercially available enantiopure amino alcohols or through catalytic enantioselective aziridination of alkenes.[14] If high diastereoselectivity can be achieved for the formal [3 + 3] cycloaddition, disubstituted tetrahydropyrimidines could be accessed in high stereopurity.

To test our hypothesis, aziridine **1b** was reacted with methyl isocyanoacetate **2f** using CuI and DPPF (Scheme 3). To our

Scheme 3. Diastereoselective [3 + 3] Cycloaddition



delight, the reaction proceeded with excellent regioselectivity and diastereoselectivity (>20:1), albeit with a moderate yield. Further optimization of the reaction conditions (see the SI for details) gave an improved yield of 86% for this process by using $(PPh_3)_3CuCl$ as the catalyst and Cs_2CO_3 as the base (Scheme 4). When enantiopure **1b** (>99% ee) was used, **5a** was obtained as a single stereoisomer with a complete transfer of enantioselectivity.

We then turned our attention to explore the scope of the reaction. Increasing the steric bulk of the ester group on the unsubstituted isocyanoacetate was well tolerated to yield **5a−d** in good yields. The reactions with aziridines bearing alkyl groups such as methyl, isopropyl, 2-isobutyl, and *tert*-butyl afforded desired products **5e−h** with good yields. The relative and absolute configuration of **5f** was unambiguously assigned by single-crystal X-ray analysis, and other compounds were assigned by analogy. Aziridine **1g** bearing a tertiary TMS ether moiety reacted with methyl isocyanoacetate **2f** to afford **5i** in a moderate yield of 57%. The reaction also tolerated a chiral aziridine bearing an indole moiety, and **5j** was obtained with a good yield of 78%. It is noteworthy that we did not observe any corrosion of diastereoselectivity across all examples of compound **5**. Aryl-substituted aziridines were also examined, the use of which unfortunately led to the formation of a mixture (by nonregioselective addition to aziridines) in low efficiency.

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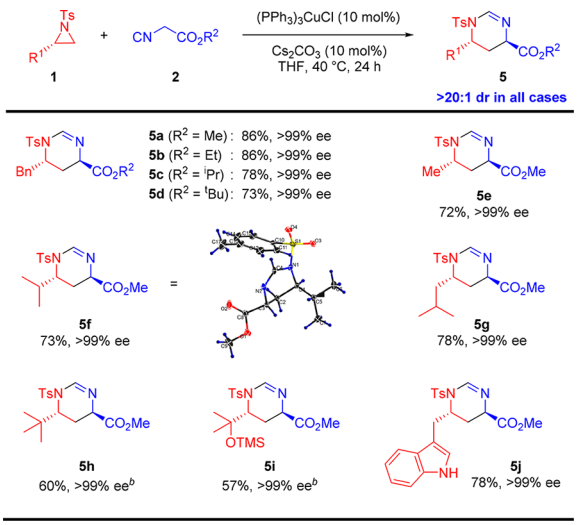
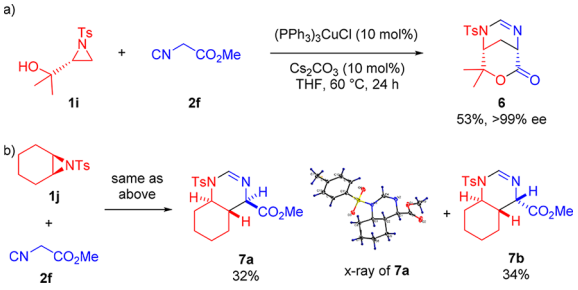
Scheme 4. [3 + 3] Cycloaddition with Enantiopure Aziridines[a]



[a]See the SI for the detailed procedure. [b]The reaction was carried out for 48 h. TMS = trimethylsilyl.

We were pleasantly surprised that aziridine **1i** containing a hydroxy group did not furnish **5** but instead underwent a double cyclization to give bicyclic **6** in 53% yield as a single diastereomer (Scheme 5a). It is interesting to note that the diastereoselectivity

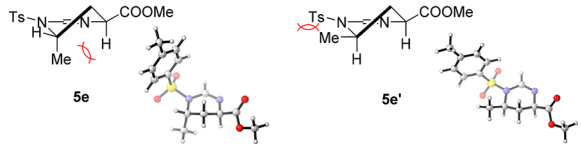
Scheme 5. Reactions of Aziridines 1i and 1j



of **6** is different from that of **5**. To further expand the scope of this methodology, we subjected *meso*-aziridine **1j** to react with isocyanoacetate **2f** (Scheme 5b). From this, we obtained compounds **7a** and **7b** in 32% yield and 34% yield, respectively. The relative configuration of **7a** was assigned by single-crystal X-ray analysis. The relative configuration of **7b** was assigned by 2D COSY and selective 1D NOESY (see the SI for more details).

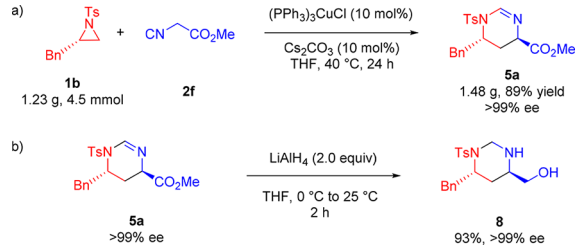
To gain more insight on the various diastereoselectivity of these reactions, DFT calculations at M06-2X/6-311+G(2d, p)//M06-2X/6-31G* level with G16 software suits were carried out. SMD was used as the solvation model with THF as the solvent. The energy difference between **7a** and **7b** was found to be very small (0.14 kcal/mol). In contrast, **5e** was found to be 2.91 kcal/mol lower in free energy than its corresponding diastereomer **5e′**. Conformational studies suggest that the steric hindrance from the neighboring Ts group has a more significant effect than 1,3-axial interaction of two substituents (Scheme 6). These data strongly suggests that the cycloaddition products can epimerize under the basic conditions. While **5e** was formed as a single *trans*-isomer, the intramolecular lactonization in **6** served as a driving force for the formation of the *cis*-isomer.

Scheme 6. Calculated Conformations of 5e and 5e′



To showcase the utility of our methodology, we began by conducting a gram-scale reaction of enantiopure aziridine **1b** and methyl isocyanoacetate **2f**. Under the standard conditions, the reaction proceeded smoothly to produce **5a** with good yield of 89% and excellent diastereoselectivity (>20:1) (Scheme 7a).

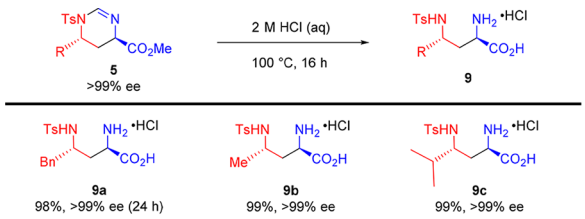
Scheme 7. Gram-Scale Synthesis and Derivatization of Tetrahydropyrimidines



Reduction of **5a** with lithium aluminum hydride in anhydrous THF afforded cyclic amino alcohol **8** with high yields (93%) and complete retention of enantioselectivity (Scheme 7b). Amino alcohols and their derivatives are oftentimes used as ligands, chiral auxiliaries, and chiral organocatalysts.[15] Therefore, compound **8** bearing a six-membered ring structure and multiple stereocenters may find application as a valuable amino alcohol ligand.

Incorporation of nonstandard amino acids is reported to be able to engineer protein−drug conjugates and even to extend the function and properties of biomaterials.[16] We proposed that the hydrolysis of **5** would yield an α,γ-diamino acid. When **5a** was subjected to 2 M aqueous HCl at reflux temperature, the reaction proceeded smoothly to produce α,γ-diamino acid **9a** in nearly quantitative yields in an enantiopure form (Scheme 8).

Scheme 8. Synthesis of α,γ-Diamino Acids 9



Compounds **5b** and **5c** also underwent smooth transition to the desired diamino acids **9b** and **9c**, respectively. This represents a valuable addition to the library of unnatural amino acids that serve as building blocks and molecular scaffolds in combinatorial libraries.

In conclusion, we have developed an efficient and stereoselective [3 + 3] cycloaddition of isocyanoacetates with aziridines to furnish substituted tetrahydropyrimidines. These heterocycles can be readily reduced to form cyclic amino alcohols. Simple hydrolysis of them gave α,γ-diamino acids. The unique structure of the products reported herein, bearing

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multiple functionalities, may offer new opportunities in asymmetric catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01948.

Experimental details and characterization data (PDF)

Accession Codes

CCDC 1850997−1850998 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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