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Transition-Metal-Free Cyclopropanation of 2-Aminoacrylates with *N*-Tosylhydrazones: A General Route to Cyclopropane α-Amino Acid with Contiguous Quaternary Carbon Centers

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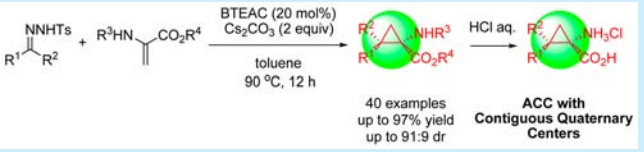
Supporting Information

ABSTRACT: Cyclopropanation of 2-aminoacrylates with *N*-tosylhydrazones could proceed smoothly under transition-metal-free conditions via a [3 + 2] cycloaddition process. This robust protocol exhibits excellent generality, delivering a wide spectrum of cyclopropane α-amino acid esters bearing contiguous quaternary carbon centers in high yields and diastereoselectivities. With these readily available products, the steric convergence of cyclopropane α-amino acids could be readily obtained.



Since Vähätalo and Virtanen first isolated it from cowberries in 1955, α-aminocyclopropanecarboxylic acid (ACC) has attracted considerable attention.[1] ACC motifs not only exist in many natural products, bioactive compounds, and pharmaceuticals[2] but also serve as valuable tools for mechanistic studies and characterization of enzymes.[3] As a result of the impressive usefulness of ACC derivatives, the efficient construction of ACC frameworks, especially those with tertiary−quaternary carbon centers, has become the subject of intensive investigation in the area of synthetic and medicinal chemistry.[4] In contrast, recent medicinal research revealed that steric convergence of ACC (**II**),[5] which possessed contiguous quaternary carbon centers, was much better in selectivity and pharmacokinetic profiles than ACC (**I**),[6] which had tertiary−quaternary carbon centers (Figure 1). However, a multiple-step synthesis was necessary to construct

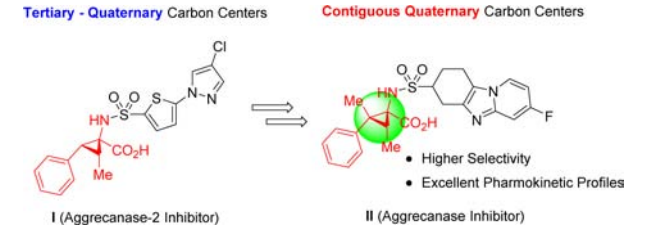
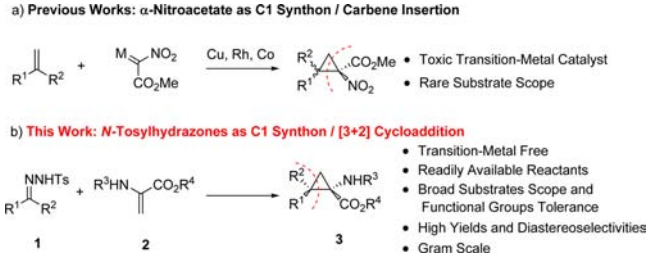


Figure 1. Steric convergence of ACC for medicinal applications.

two contiguous quaternary carbon centers.[5] Therefore, the development of more efficient and general methods for the synthesis of ACC derivatives containing contiguous quaternary centers is highly desirable.

One of the most straightforward and convenient routes for the diastereoselective construction of ACC subunits, which have contiguous quaternary carbon centers, was degradation of diazo compounds in the presence of disubstituted alkenes, in which a formal [2 + 1] cyclocondensation reaction proceeded smoothly with high selectivity. Early studies focused on the insertion reaction of transition-metal-mediated α-nitroacetate carbene with disubstituted alkenes (Scheme 1a).[7] However, these

Scheme 1. Diastereoselective Synthesis of Contiguous Quaternary Carbon Centers Containing ACC



methods suffered two severe limitations: (i) the utilization of toxic transition-metal catalysts, which were unfriendly to the products; and (ii) sparse substrate scope, due to the steric hindrance of disubstituted alkenes. In this context, the development of a general and practical method to construct ACC derivatives, bearing contiguous quaternary carbon centers, is a challenging but demanding target. Outwardly, the cyclopropanation of 2-aminoacrylates with a C_1 synthon would be a competitive strategy (Scheme 1b). In 2012, we reported the cyclopropanation reaction of electron-deficient alkenes with C_1 synthons initiated from *N*-tosylhydrazones.[8,9] Encouraged by these results and our continuous effort on exploring the utilities of *N*-tosylhydrazones,[10] we disclose our recent progress on the synthesis of contiguous quaternary carbon centers containing ACC derivatives. It should be noted that this cyclopropanation reaction of 2-aminoacrylates with *N*-tosylhydrazones is transition-metal-free. This robust approach adapts to broad

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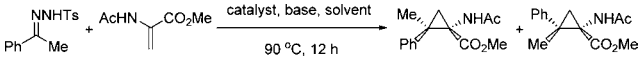
substrates and tolerates diverse functional groups, delivering the corresponding ACC derivatives with high yields and diastereoselectivities. Significantly, this reaction can be carried out easily on a gram scale.

At the outset of this transformation, we investigated the cyclopropanation reaction of *N*-tosylhydrazone **1a** with methyl 2-acetamidoacrylate **2a** in the presence of $Pd(OAc)_2$ as the catalyst. Desired products **3a** and **4a** were obtained in 75% isolated yield (**3a** = 41%, **4a** = 34%; dr = 55:45) (Table 1, entry 1). Unfortunately, either poor diastereoselectivities or low yields were observed under transition-metal catalysis (for details, see Supporting Information). In this sense, the avoidance of transition-metal catalyst utilization became the logical follow-up consideration. The diastereoselectivity was greatly improved to dr = 83:17 with BTEAC (benzyltriethylammonium chloride) as the catalyst (Table 1, entry 2). Further investigation of the bases enhanced the total yield to 94% (Table 1, entries 3−5). Next, we evaluated other reaction solvents, DMF, MeCN, THF, and DCE, but we found that toluene was optimum for this cyclopropanation (Table 1, entries 6−9). Finally, different types of phase-transfer catalysts were screened, and BTEAC was found to be optimal (Table 1, entries 10−13).

Table 1. Optimization of Reaction Conditions[a]



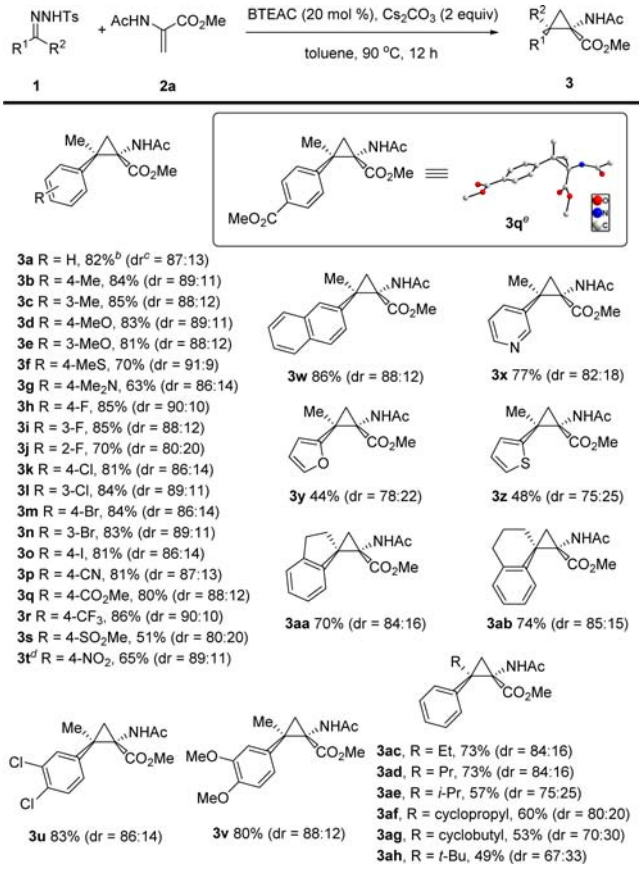
1a 2a 3a 4a

entry	catalyst	base	solvent	yield[b] (%)	dr[b] (3a/4a)
1	$Pd(OAc)_2$	*t*-BuOK	toluene	76 (75)	55:45
2	BTEAC	*t*-BuOK	toluene	77	87:13
3	BTEAC	Na_2CO_3	toluene	66	83:17
4	BTEAC	K_2CO_3	toluene	70	84:16
5	BTEAC	Cs_2CO_3	toluene	94	87:13
6	BTEAC	Cs_2CO_3	DMF	27	67:33
7	BTEAC	Cs_2CO_3	MeCN	48	68:22
8	BTEAC	Cs_2CO_3	THF	39	65:35
9	BTEAC	Cs_2CO_3	DCE	65	80:20
10	$(n\text{-Bu})_4N^+Br^-$	Cs_2CO_3	toluene	81	85:15
11	$(n\text{-Bu})_4N^+HSO_4^-$	Cs_2CO_3	toluene	90	86:14
12	$(n\text{-Bu})_4N^+I^-$	Cs_2CO_3	toluene	87	86:14
13	$(n\text{-Bu})_4P^+Br^-$	Cs_2CO_3	toluene	80	85:15

[a]A mixture of **1a** (0.2 mmol, 2 equiv), **2a** (0.1 mmol, 1 equiv), base (0.2 mmol, 2 equiv), catalyst (20 mol %), and solvent (2 mL) was sealed in a 25 mL Schlenk tube at 90 °C for 12 h. [b]Yield and diastereomeric ratio (dr) were determined by ^1H NMR spectroscopy of the product with CH_2ClBr as an internal standard. The number in parentheses was isolated yield.

With the optimized conditions in hand, the generality of *N*-tosylhydrazones was first examined. The results are summarized in Scheme 2. It is worth mentioning that the two diastereoisomers could be easily separated by silica gel chromatography. This cyclopropanation reaction tolerated various substitution patterns and a wide range of substituents on the aromatic ring of *N*-tosylhydrazones. Alkyl-, alkyoxy-, methylthio-, amino-, halo-, cyano-, trifluoromethyl-, ester group, sulfonyl-, and nitro-substituted *N*-tosylhydrazones all could proceed smoothly to give the condensation adducts **3a**−**3v** in good to excellent yields with high diastereoselectivities. Notably, fluorinated products (**3h**, **3i**, **3j**, **3r**) could serve as highly competitive candidates for solid-state ^{19}F NMR spectroscopy technology.[11] Product **3q** was proven to be crystalline, thus allowing the determination of the relative stereochemistry of the contiguous quaternary stereogenic centers by means of X-ray crystallographic analysis.[12] Furthermore, 2-naphthyl-, 3-pyridyl-, 2-furanyl-, and 2-thienyl-bearing *N*-tosylhydrazones were also found to be good substrates, delivering the products (**3w**-**3z**) in 44−86% yields with good diastereoselectivities. Importantly, cyclic *N*-tosylhydrazones were perfectly applicable to this transition-metal-free system and transferred to the corresponding spirocyclopropyl adducts **3aa** and **3ab**. Besides, *N*-tosylhydrazones derived from ethyl-, propyl-, isopropyl-, cyclopropyl-, cyclobutyl-, and *tert*-butyl-(phenyl)methanone all furnished the corresponding products **3ac**−**3ah** efficiently.

Scheme 2. Substrate Scope of *N*-Tosylhydrazones[a]



[a]Unless noted otherwise, the reaction was run at 0.1 mmol scale under standard reaction conditions. [b]Isolated yield of the major diastereoisomer. [c]Diastereoisomer ratio was determined by ^1H NMR of the crude product with CH_2ClBr as an internal standard. [d]Reaction was conducted at 70 °C. [e]ORTEP representation with 50% probability thermal ellipsoids of a crystal structure of **3q**.

To further define the scope of our method, the substrate scope was extended to different types of 2-aminoacrylates (Scheme 3). Ethyl 2-acetoamidoacrylate and benzyl 2-acetoamidoacrylate gave the desired products (**3ai** and **3aj**) in good yields with high diastereoselectivities. Interestingly, amino-protecting groups, such as benzoyl, pivaloyl, *t*-butyloxy carbonyl, and carbobenzyloxy, were all well-tolerated under the standard reaction conditions, and the corresponding adducts were obtained smoothly (**3ak**−**3an**). Remarkably, all of the obtained ACC products are extremely valuable scaffolds in medicinal chemistry.[5]

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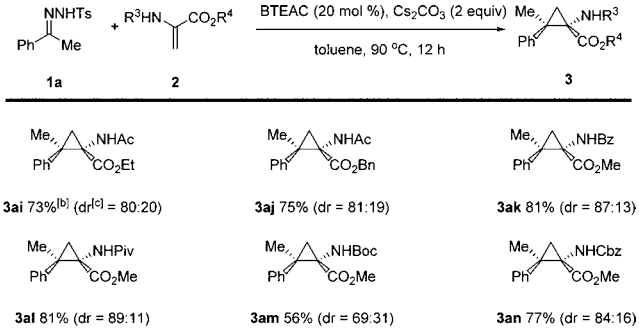
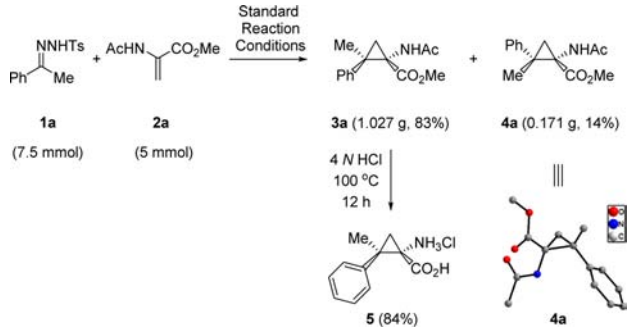
Scheme 3. Substrate Scope of 2-Aminoacrylates[a]



[a]Unless noted otherwise, the reaction was run at 0.1 mmol scale under standard reaction conditions. [b]Isolated yield of the major diastereoisomer. [c]Diastereoisomer ratio was determined by ^{1}H NMR of the crude product with CH_2ClBr as an internal standard.

The synthetic utility of this cyclopropanation reaction was then explored. Gram-scale synthesis was conducted at a 5 mmol scale, and as expected, the corresponding products **3a** and **4a** were obtained in a yield of 83 and 14%, respectively. Note that the relative stereochemistry of the minor diastereoisomer **4a** was also determined by X-ray crystallographic analysis.[12] Furthermore, hydrolysis of **3a** by refluxing with 4 *N* HCl provided the amino acid hydrochloride **5** in 84% yield (Scheme 4).

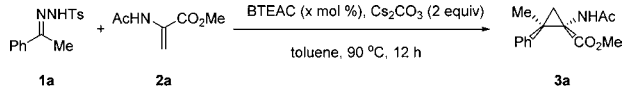
Scheme 4. Gram-Scale Synthesis and Hydrolysis of 3a



It is noteworthy that the amount of BTEAC can significantly interfere with this cyclopropanation reaction. We found that, in the absence of BTEAC, the reaction between *N*-tosylhydrazone **1a** and methyl 2-acetamidoacrylate **2a** proceeded slowly (12 h, <5% yield of **3a**), and **1a** was recovered in 94% yield. In contrast, reactions conducted with various amounts of BTEAC led to respectable yields, while excess BTEAC was found to be detrimental to the yield (Scheme 5). These results indicated that BTEAC played an important role in this transformation.

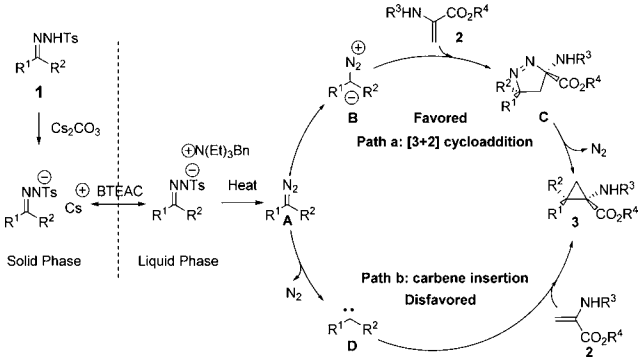
On the basis of these experimental results and previous reports,[8−10,13] we tentatively proposed the reaction mechanisms outlined in Scheme 6. Initially, reactive species **A** was gradually and sustainably formed under the treatment of BTEAC. Isomerization of **A** afforded the zwitterionic intermediate **B**. Subsequent [3 + 2] cycloaddition of intermediate **B** with 2-aminoacrylate gave oxadiazole compound **C**, which finally converted to the desired product **3** by N_2 extrusion (path a).[14] Because of the poor diastereoselectivities, which were observed under metal−carbene conditions (see Supporting Information), the carbene insertion mechanism seemed to be disfavored (path b).

Scheme 5. Control Experiments



The amount of BTEAC	The yields of **3a**	The recovery of **1a**
x = 0	< 5	94%
x = 10	74%	0
x = 20	82%	0
x = 50	77%	0
x = 100	56%	0
x = 200	40%	0

Scheme 6. Possible Mechanism



In summary, we have developed a general, simple, and practical method for the cyclopropanation of readily available 2-aminoacrylates and *N*-tosylhydrazones under transition-metal-free conditions via a [3 + 2] cycloaddition process. This remarkable transformation successfully provides a wide spectrum of contiguous quaternary carbon centers containing ACC derivatives in excellent yields and high diastereoselectivities. Meanwhile, the products are diverse in structure and electronic properties, which are significant motifs in medicinal chemistry. Efforts are currently underway in our laboratory to elucidate the mechanistic details, to investigate the catalytic asymmetric synthesis, and to explore the synthetic applications of the products, and the results of which will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00416.

Experimental procedure and characterization for all products (PDF)
X-ray data for **3q** (CIF)
X-ray data for **4a** (CIF)

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Notes

The authors declare no competing financial interest.

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(12) CCDC 1401714 (**3q**) and 1400910 (**4a**) contain the supplementary crystallographic data. These data can also be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

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