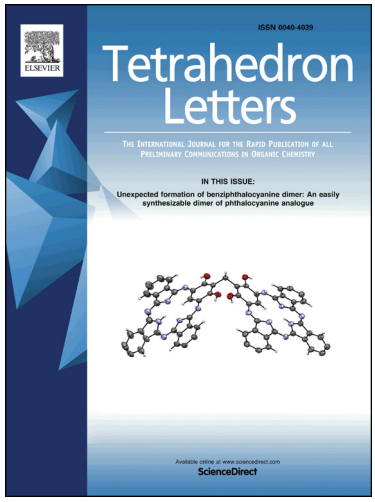

Highly stereoselective synthesis of 1-cyanocyclopropane-carboxamides from 3-substituted-2-cyanoacrylamides with N-tosylhydrazones under metal-free conditions

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Graphical Abstract

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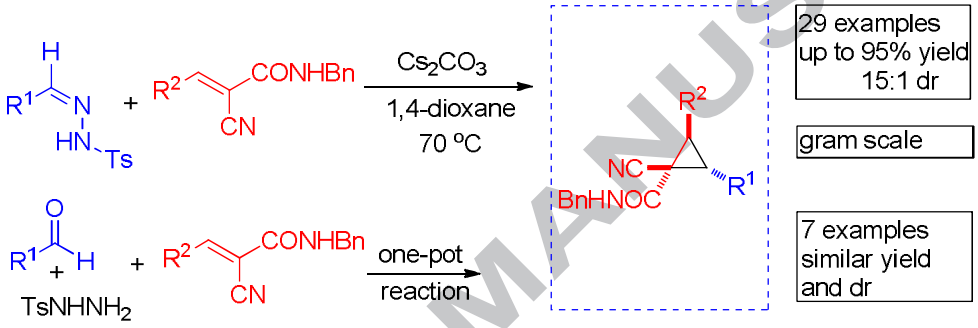
Xufeng Nie[a], Yachuan Wang [a], Lijun Yang [a], Zaijun Yang[a], and Tairan Kang[a,b]*

A metal-free cyclopropanation of electron-deficient olefins 3-substituted-2-cyanoacrylamides with N-tosylhydrazones has been successfully developed. This strategy provide a simple route to the synthesis of very valuable 1-cyanocyclopropanecarboxamides with a quaternary stereogenic center in good yields and with high diastereoselectivities (up to 90% yield with 19:1 dr). The reaction could be performed in one-pot fashion and in a gram-scale from aryl aldehydes.



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ABSTRACT

A metal-free cyclopropanation of electron-deficient olefins 3-substituted-2-cyanoacrylamides with N-tosylhydrazones has been successfully developed. This strategy provide a simple route to the synthesis of very valuable 1-cyanocyclopropanecarboxamides with a quaternary stereogenic center in good yields and with high diastereoselectivities (up to 90% yield with 19:1 dr). The reaction could be performed in one-pot fashion and in a gram-scale from aryl aldehydes.

Introduction

Amide- or nitrile-substituted cyclopropanes present unique biological activities,[1-5] which include bradykinin β_1 antagonists,[1] hepatitis C virus (HCV) NS3 protease inhibitor,[2] nicotinamide phosphori-bosyl transferase (NAMPT) inhibitor[3] and ketol-acid reducto-isomerase inhibitor[4] (Figure 1). Especially those bearing a cyano group attached to a stereogenic carbon of the cyclopropanecarboxamides not only exist in some bioactive compounds but also serve as valuable tools for medicinal chemistry.[4-7] For example, nitriles can be easily transformed to carboxylic acids, amines, ketones, amides, and aldehydes. Therefore, the synthesis of 1-cyanocyclo-propanecarboxamides motif which can be easily further transformed into densely functionalized cyclopropane molecules, has attracted considerable attention during the past years from synthetic chemists.[6,7] For example, in 2010, Fan and coworkers reported that a tandem reaction of 2-cyanoacetamides with α,β-unsaturated malonates, provided 1-cyanocyclopropanecarbox-amides in good yields and with excellent diastereoselectivities.[6a] In 2014, Liang and Dong's group reported that one-pot synthesis of 1-cyanocyclo-propanecarboxamides derivatives were developed from 2-cyanoacrylamides and dimethyl malonate in the presence of N-bromosuccinimide and triethylamine.[6b] Takemoto also reported that an organocatalyzed asymmetric cyclopropanation of bromonitromethane with 2-cyanoacrylamides providing optically active 1-cyanocyclopropa-ne-carboxamides in excellent enantioselectivities.[6c] Charette developed an enantio- and diastereoselective Rh(II)-catalyzed cyclopropanation of α-cyano diazoacetamides with styrene in the synthesis of chiral 1-cyanocyclopropane-carboxamides in 2009.[6d] In addition, the other examples for synthesis of 1-cyanocyclopropane-1-carboxy derivatives have also been reported.[7] For example, Zhang reported that a Co(II)-catalyzed cyclopropanation of the olefins containing electron-withdrawing groups with diazoacetates affording 2-cyanocyclopropane carboxylates.[7a] In the past three decades, the metal-catalyzed (such as copper, rhodium, and ruthenium) cyclopropanation between styrene or some electron-rich olefins and diazo reagents have been fully developed.[8,9a-f] However, the metal-catalyzed cyclopropanation of electron-deficient olefins containing two electron-withdrawing groups such as α,β-unsaturated carbonyl compounds and nitriles with diazoacetates has proven to be a challenging problem.[6a,7a,8,9]

The metal-free-catalyzed cyclopropanation of olefins with diazo reagents will also be of importance. N-tosylhydrazones are very useful reagents and can be utilized as precursors for the generation of unstable α-aryl or alkyl diazomethanes.[10] Indeed, the metal- or metal-free-catalyzed reaction using the unstable diazo reagents generated from N-tosylhydrazones in situ as substrates have appeared in literatures.[11] The metal-free-catalyzed reaction of various substituted alkenes with N-tosylhydrazones have also been developed in recent years.[10,12] For instance, metal-free-catalyzed cyclopropanation of terminal alkenes with N-tosylhydrazones delivering cyclopropane were reported by Jiang's and other groups (Scheme 1a).[12] However, the reactions of the trisubstituted alkenes bearing one electron withdrawing groups (such as cyano, nitro and ester groups) with N-tosylhydrazones, were described only to afford the sole pyrazole products, in which the expected cyclopropanes were not obtained (Scheme 1b).[13] In 1989, Hirata found that the reaction between 1-phenyldiazoethane and the trisubstituted alkenes 3-substituted-2-cyano-3-phenylacrylates, which bear two electron withdrawing groups, provided to form the mixture of cyclopropane, olefin and pyrazoline products.[14] Therefore, although the metal-catalyzed cyclopropanation of various alkenes with stable diazo reagents have been reported,[9a-i] the metal-free reaction of trisubstituted alkenes bearing one or two electron withdrawing groups with unstable diazo reagents generated from N-tosylhydrazones to form the cyclopropane product has been largely undeveloped so far.[10,12,13]

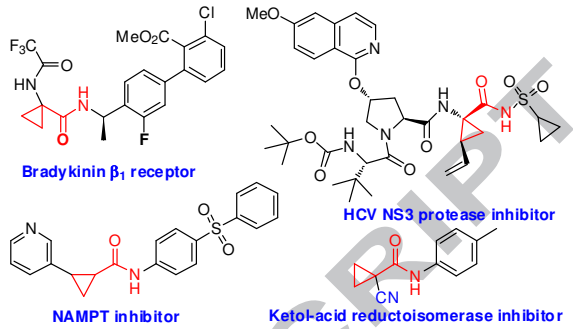
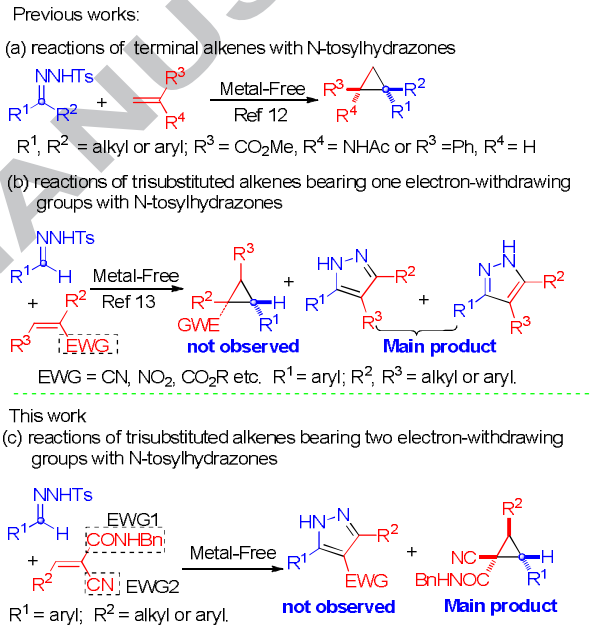


Figure 1. Bioactive cyclopropanecarboxamide containing compounds.



Scheme 1. Reactions of alkenes with N-tosylhydrazones.

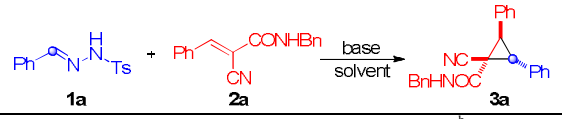
More recently, our group reported that a metal-free ring-expansion reaction of six-membered N-sulfonylimine with N-tosylhydrazone, provided an approach toward seven-membered enesulfonamide.[15f] As a part of our ongoing research on organic synthesis,[15] herein, we report that a metal-free cyclopropanation of the 3-substituted-2-cyano-3-phenyl-acrylamide (2a) with N-tosylhydrazones under metal free conditions, which provides the very valuable 1-cyanocyclo-propanecarboxamides with a quaternary carbon center (Scheme 1c). To the best of our knowledge, there has been few systematic study on this type reaction so far.[12,13]

Results and Discussionthe

At the outset of our studies, the reaction conditions were optimized starting from N-tosylhydrazone (1a) and (E)-N-benzyl-2-cyano-3-phenylacrylamide (2a) in 1,4-dioxane at 70 °C in the presence of a variety of bases, such as DBU, KOtBu, K_2CO_3 and

Cs_2CO_3 (Table 1, entries 1-4). Among these bases, Cs_2CO_3 was the best choice, and the expected cyclopropane product 3a was obtained in 90% yield with >19:1 diastereomeric ratio (dr). The reaction was sensitive to solvent. The other solvents like toluene, DCE, CH_3CN, DMF, DMSO and THF were not suitable (Table 1, entries 5-10). In all these reactions, the cyclopropane 3a was afforded with 19:1 dr. (see Supporting Information for details)

Table 1. Optimization of reaction conditions.[a]



1a **2a** **3a**

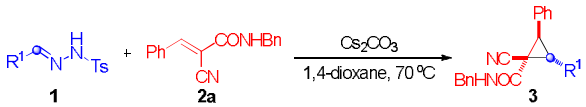
Entry	Base	Solvent	Yield [%][b]	Dr.[c]
1	DBU	Dioxane	58	>19:1
2	KOtBu	Dioxane	82	>19:1
3	K_2CO_3	Dioxane	75	>19:1
4	Cs_2CO_3	Dioxane	90	>19:1
5	Cs_2CO_3	Toluene	44	>19:1
6	Cs_2CO_3	DCE	32	>19:1
7	Cs_2CO_3	CH_3CN	37	>19:1
8	Cs_2CO_3	DMF	60	>19:1
9	Cs_2CO_3	DMSO	69	>19:1
10	Cs_2CO_3	THF	80	>19:1

[a] Reaction conditions: N-Tosylhydrazones 1 (0.11 mmol), 2a (0.1 mmol), base (0.075 mmol) in 0.5 mL of solvent at 70 °C for 5-7 h under N_2 atmosphere.
[b] Isolated yield.
[c] Diastereomeric ratio (dr) were determined by NMR.

With the optimized conditions in hand, varieties of N-tosylhydrazones were examined. The results were summarized in Table 2. In general, the electronic effect on the aromatic ring attached on the α-position of N-tosylhydrazone had no apparent effects on the reaction. Aromatic groups bearing electron-withdrawing and electron-donating substituents were tolerated, and the corresponding cyclopropane products **3b-3j** were obtained in 77-90% yield with >14:1 dr (Table 2, entries 2-10). Steric hindrance had slight effect on this transformation, both ortho- and meta-substituted phenyl N-tosylhydrazones led to the formation of 3**k-3p** in 73-85% yields with excellent dr (Table 2, entries 11-16). Notably, 1-naphthyl N-tosylhydrazone also participated in the reaction to give the corresponding product **3q** in 76% yield with >14:1 dr. The heteroaromatic 2-furanyl and 2-thiophenyl N-tosylhydrazone could provide the desired products **3r**, **3s** in 83% and 80% yields, with >14:1 dr respectively (Table 2, entries 18-19). However, the N-tosylhydrazone derived from aliphatic aldehyde (such as butyraldehyde) as substrate failed to give the expected product. (Table 2, entry 20). This might be due to the instability of α-alkyl diazomethane at 70 °C.

Next, we explored the scope of α-cyanoacrylamides (Table 3). It was observed that the electronic effect on the aromatic ring attached on the β-position of α-cyanoacrylamides had little

Table 2. Reactions of various N-Tosylhydrazones 1 with (E)-N-benzyl-2-cyano-3-phenyl-acrylamide 2a.[a]



1 **2a** **3**

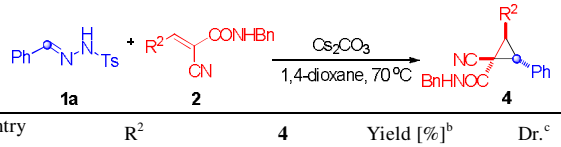
Entry	R^1	**3**	Yield [%][b]	Dr.[c]
1	C_6H_5	**3a**	90	>19:1
2	4-FC_6H_4	**3b**	85	14:1
3	4-ClC_6H_4	**3c**	83	19:1
4	4-Br $_6H_4$	**3d**	84	17:1
5	4-$NO_2C_6H_4$	**3e**	86	19:1
6	4-$CF_3C_6H_4$	**3f**	86	14:1
7	4-CNC_6H_4	**3g**	90	19:1
8	4-MeC_6H_4	**3h**	79	14:1
9	4-$MeOC_6H_4$	**3i**	80	18:1
10	4-$NMe_2C_6H_4$	**3j**	77	19:1
11	3-ClC_6H_4	**3k**	80	19:1
12	3-BrC_6H_4	**3l**	78	19:1
13	3-$NO_2C_6H_4$	**3m**	85	19:1
14	3-MeC_6H_4	**3n**	79	18:1
15	3-$MeOC_6H_4$	**3o**	77	19:1
16	2-BrC_6H_4	**3p**	73	19:1
17	2-naphthyl	**3q**	76	19:1
18	2-thienyl	**3r**	83	14:1
19	2-furyl	**3s**	80	19:1
20	n-Bu	**-**	-	-

[a] Reaction conditions: N-Tosylhydrazones 1 (0.11 mmol), 2a (0.1 mmol), base (0.075 mmol) in 0.5 mL of solvent at 70 °C for 5-7 h under N_2 atmosphere.
[b] Isolated yield.
[c] Diastereomeric ratio (dr) were determined by NMR.

influence on the reaction. The halogen-substituted (-F, -Cl, -Br) and the electron-donating groups (-CH_3, -OCH_3) at the 4-position of the aryl ring could react smoothly to afford the desired products **4a-4e** in good yield (79-85%) with >14:1 dr (Table 3, entries 1-5). Notably, when meta-Cl, -OCH_3 and ortho-Br on the aromatic ring of the α-cyanoacrylamides were used as the substrates, a moderate to good yields (77-80%) and excellent steroselectivity (>14:1 dr) were afforded (entries 6-8). The reaction also worked with heterocyclic aromatic 2-thienyl substrates, providing product **4i** in 82% yield with 19:1 dr (entry 9). Interestingly, the alkyl group (cyclohexyl ring) attached on the β-position of α- cyanoacrylamide successfully participated in the reaction, giving the product **4j** in 85% yield with 19:1 dr (entry 10).

N-tosylhydrazones can be easily prepared from tosylhydrazide and aldehydes or ketones. Therefore, we investigated that the olefin cyclopropanation reactions were carried out in a one-pot fashion (Table 4). The desired products **3a-3d**, **3i**, **3l** and **3p** were obtained in similar yields and with diastereomeric ratio by heating the corresponding carbonyl compound **5** with tosylhydrazide prior to the addition of the (E)-N-benzyl-2-cyano-3-phenylacrylamide **2a**, without the need to isolate the N-tosylhydrazones (see the Supporting Information for details, selected examples are shown in Table 4). It was

Table 3. Reactions of N-Tosylhydrazone 1a with various α-cyanoacrylamides 2.[a]



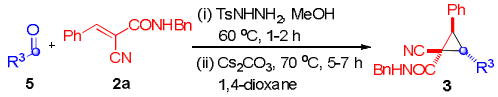
1a **2** **4**

Entry	R^2	**4**	Yield [%][b]	Dr.[c]
1	4-FC_6H_4	**4a**	81	14:1

2	4-ClC_6H_4	**4b**	80	14:1
3	4-BrC_6H_4	**4c**	85	14:1
4	4-MeC_6H_4	**4d**	80	18:1
5	4-$MeOC_6H_4$	**4e**	79	19:1
6	3-ClC_6H_4	**4f**	77	19:1
7	3-$MeOC_6H_4$	**4g**	75	19:1
8	2-BrC_6H_4	**4h**	80	14:1
9	2-thienyl	**4i**	82	19:1
10	cyclohexyl	**4j**	85	19:1

[a] Reaction conditions: N-Tosylhydrazones 1 (0.11 mmol), 2a (0.1 mmol), base (0.075 mmol) in 0.5 mL of solvent at 70 °C for 5-7 h under N_2 atmosphere.
[b] Isolated yield.
[c] Diastereomeric ratio (dr) were determined by NMR.

Table 4. One-pot reaction between aryl aldehydes 5, tosylhydrazide and (E)-N-benzyl-2-cyano-3-phenylacryl-amide 2a.[a]



Entry	R^3	3	Yield [%][b]	Dr.[c]
1	C_6H_5	**3a**	85	19:1
2	4-FC_6H_4	**3b**	82	14:1
3	4-ClC_6H_4	**3c**	80	19:1
4	4-BrC_6H_4	**3d**	78	19:1
5	4-$MeOC_6H_4$	**3i**	77	19:1
6	3-BrC_6H_4	**3l**	75	19:1
7	2-BrC_6H_4	**3p**	70	19:1
8[d]	C_6H_5 (10 mmol)	**3a** (2.817g)	84	19:1

[a] Reaction conditions: **1)** N-Tosylhydrazide (0.11 mmol), aryl aldehydes (0.11 mmol), in 0.5 mL of MeOH, at 60 °C for 1-2 h; **2)** 2a (0.1 mmol), Cs_2CO_3 (0.075 mmol) in 0.5 mL 1,4-dioxane, at 70 °C for 5-7 h.
[b] Isolated yield.
[c] Diastereomeric ratio (dr) were determined by NMR.
[d] 10 mmol scale, reaction conditions: see the Supporting Information for details.

pleasingly found that the one-pot reactions could be carried out on a multigame scale, the product **3a** (2.817 g) was afforded in 80% yield (Table 4, entry 8, see the Supporting Information for details).

The structure of **3e** was confirmed by X-ray crystal structure analysis (Figure 2).[16] Based on the mechanistic study that reported by Barluenga's[11a] group, the formation of **3a** is rationalized as outlined in Scheme 2. The diazo compound **B** is generated in situ by decomposition of N-tosylhydrazone salt **A**. From **B**, there are two possible pathways: a) the pyrazoline **C** or intermediate **D** is formed via an addition reaction of **B** with **2a**, and then, **3a** is generated from pyrazoline **C** or intermediate **D** by

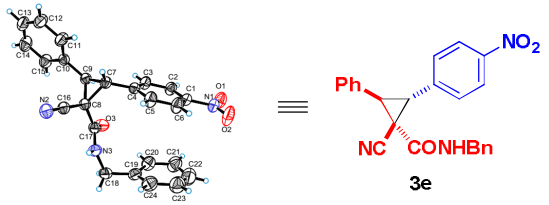
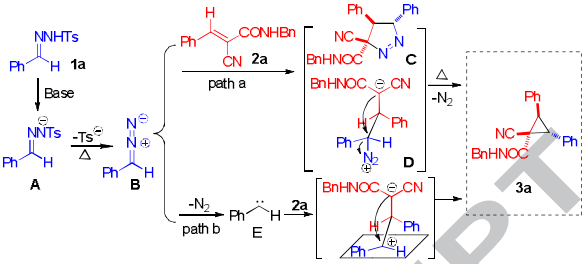


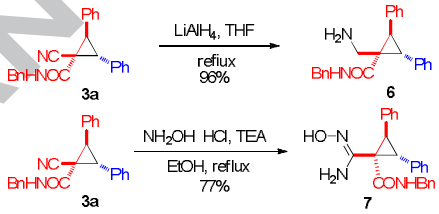
Figure 2. X-ray structure of **3e**; thermal ellipsoids shown at 30% probability.



Scheme 2. Proposed mechanism for this cyclopropanation reaction.

N_2 extrusion. b) The carbene **D**, which is generated from diazo compound **B** in situ react with **2a**, giving the product **3a**.

Synthetic transformations were performed to demonstrate the utility of the valuable cyano group of the cyclopropanes (Scheme 3). Reduction of the cyano group of **3a** by using $LiAlH_4$ gave the corresponding primary amine product **6** in 96% yield. Additionally, the cyano group of **3a** also be easily transformed to the primary amidine **7** in 77% yield by using hydroxylamine hydrochloride and triethylamine in refluxing ethanol.



Scheme 3. Synthetic transformations.

Conclusion

In conclusion, we developed a metal-free cyclopropanation reaction of trisubstituted olefins bearing two electron-withdrawing groups at the same carbon with N-tosylhydrazones. This reaction represents an extremely simple way to afford very valuable 1-cyanocyclopropanecarboxamides containing a quaternary carbon center in good to excellent yield and with excellent diastereomeric ratio. Moreover, the reaction can be performed in one-pot fashion and in a gram-scale from aryl aldehydes and tosylhydrazide. We believe that this reaction producing the 1-cyanocyclopropanecarboxamides motifs would be used in medicinal chemistry.

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/...

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16. CCDC 1506352 (3e) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk /data request/cif.

A metal-free cyclopropanation of olefins with diazomethanes has been developed.
Trisubstituted olefins *bear two electron-withdrawing groups at the same carbon.*
The products contain a quaternary carbon centers.
This reaction can be performed from aldehydes without isolating the tosylhydrazones.
The products were afforded in excellent yields and diastereoselectivities.