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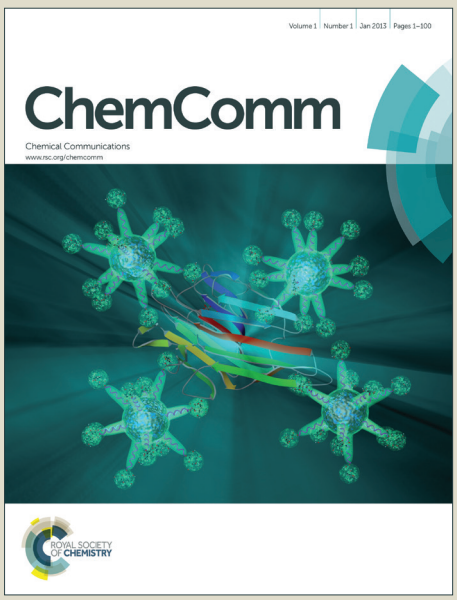

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A Rapid and Divergent Entry to Chiral Azacyclic Nucleoside Analogues via Highly Enantioselective 1,3-Dipolar Cycloaddition of β-Nucleobase Substituted Acrylates†

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Qi-Liang Yang, Ming-Sheng Xie, Chao Xia, Huan-Li Sun, Dan-Jie Zhang, Ke-Xin Huang, Zhen Guo, Gui-Rong Qu* and Hai-Ming Guo*

A rapid and divergent entry to chiral azacyclic nucleoside analogues has been established via highly *exo*-selective and enantioselective 1,3-dipolar cycloaddition of azomethine ylides with β-nucleobase substituted acrylates. Under 1 mol% of a chiral copper complex, various chiral azacyclic nucleoside analogues were afforded in high yields, excellent *exo*-selectivities and enantioselectivities (98–>99% ee). Moreover, other β-heteroaryl acrylates including pyrimidine-, benzimidazole-, imidazole-, benzotriazole-, and indole-substituted acrylates also functioned as suitable dipolarophiles.

Nucleoside analogues and their derivatives have displayed significant antivirus and anticancer activities.[1] To date, several clinically useful nucleosides, such as AZT, 3TC, Abacavir, and Entecavir, have been approved by the FDA for the treatment of HIV and HBV infection (Fig. 1).[2] Therefore, there is an intense interest in the synthesis of new nucleoside analogues with potential antiviral activity. The synthesis of nucleoside analogues was focused on the modification of the heterocyclic base or sugar or both moieties.[3] Due to the substantial similarity to the furan and cyclopentyl structures, the pyrrolidine ring might be a possible functional moiety that could be incorporated in nucleosides, leading to a new family of biologically significant substances. However, most of synthetic methods available to build up the skeletons are based on a linear approach involving the synthesis of a sugar ring analogue followed by introduction of the nucleobase by formation of the C-N bond using a substitution reaction (Scheme 1a).[4] Thus, we anticipated a straightforward preparation of azacyclic nucleoside analogues by 1,3-dipolar cycloaddition of

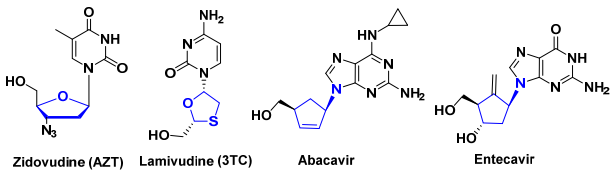
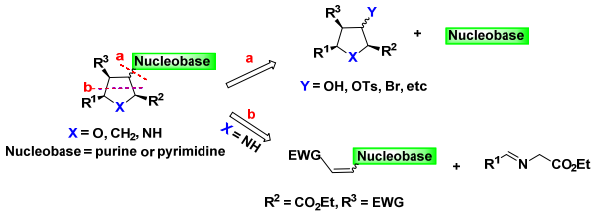


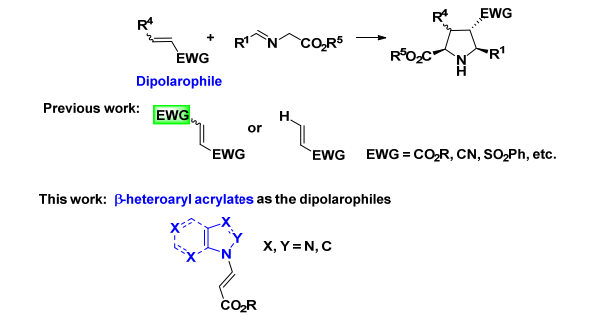
Fig. 1 Selected nucleosides with biological activities.



Scheme 1 Different strategies to construct cyclic nucleoside analogues.

azomethine ylides with nucleobase substituted acrylates (Scheme 1b).[5-6]

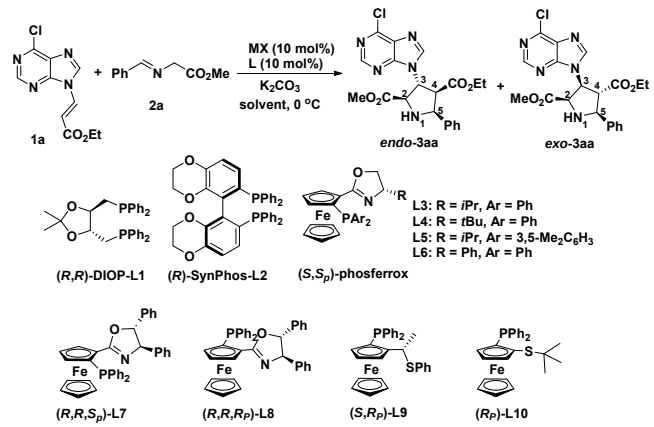
Since the pioneering reports of Grigg and co-workers,[7] a large number of asymmetric variants of activated dipolarophiles with azomethine ylides have been discovered, enabling the efficient synthesis of highly functionalized pyrrolidines.[8] However, the dipolarophiles in most of the cases are limited to electron-deficient alkenes, in which one terminal is an electron-withdrawing group (EWG), the other terminal is usually a EWG or a hydrogen atom (Scheme 2). Until now, β-heteroaryl acrylates, either racemic or asymmetric, have never been used as dipolarophiles in the 1,3-dipolar cycloaddition to azomethine ylides.[9] Furthermore, β-heteroaryl acrylates may competitively coordinate to the catalyst, presumably leading to deactivation or inhibition of the catalyst due to containing multi-nitrogen atoms to render the 1,3-dipolar cycloaddition even more challenging.



Scheme 2 Dipolarophiles in the 1,3-dipolar cycloaddition to azomethine ylides.

Herein, we will describe the first synthesis of chiral azacyclic nucleoside analogues via asymmetric 1,3-dipolar cycloaddition with β- nucleobase acrylates as dipolarophiles.

Table 1 Optimization of the reaction conditions[a]

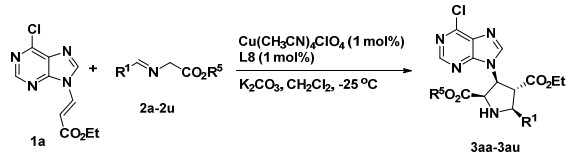


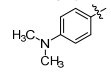
Entry	MXn	L	Solvent	Yield[b] (%)	*endo*/*exo*[c]	ee[d] (%) (*endo*/*exo*)
1	AgOAc	**L1**	CH_2Cl_2	47	66:34	53/19
2	AgOAc	**L2**	CH_2Cl_2	95	60:40	11/14
3	AgOAc	**L3**	CH_2Cl_2	95	60:40	67/89
4	AgOAc	**L4**	CH_2Cl_2	81	65:35	55/38
5	AgOAc	**L5**	CH_2Cl_2	77	54:46	71/85
6	AgOAc	**L6**	CH_2Cl_2	85	35:65	36/75
7	AgOAc	**L7**	CH_2Cl_2	86	20:80	5/9
8	AgOAc	**L8**	CH_2Cl_2	83	20:80	78/91
9	AgOAc	**L8**	$HC(OCH_3)_3$	>99	30:70	72/93
10	$AgSbF_6$	**L8**	$HC(OCH_3)_3$	56	30:70	56/72
11	CuI	**L8**	$HC(OCH_3)_3$	86	18:82	-/>99
12	$Cu(CH_3CN)_4ClO_4$	**L8**	$HC(OCH_3)_3$	>99	17:83	85/>99
13	$Cu(CH_3CN)_4ClO_4$	**L8**	THF	>99	25:75	87/>99
14	$Cu(CH_3CN)_4ClO_4$	**L8**	1,4-dioxane	>99	20:80	-/>99
15	$Cu(CH_3CN)_4ClO_4$	**L8**	CH_2Cl_2	>99	10:90	-/>99
16[e]	$Cu(CH_3CN)_4ClO_4$	**L8**	CH_2Cl_2	>99	7:93	-/>99
17	$Cu(CH_3CN)_4ClO_4$	**L9**	CH_2Cl_2	85	80:20	71/95
18	$Cu(CH_3CN)_4ClO_4$	**L10**	CH_2Cl_2	>99	50:50	97/98
19[e,f]	$Cu(CH_3CN)_4ClO_4$	**L8**	CH_2Cl_2	>99	7:93	-/>99
20[e,g]	$Cu(CH_3CN)_4ClO_4$	**L8**	CH_2Cl_2	61	7:93	-/>99

[a] Unless otherwise noted, the reaction conditions are as follows: metal/**L** (1:1), **1a** (0.05 mmol), **2a** (0.2 mmol), and K_2CO_3 (2.0 mg) in solvent (1.0 mL) at 0 °C for 8 h. [b] Isolated yield. [c] Determined by the ^1H NMR spectra of the crude products. [d] Determined by chiral HPLC analysis. [e] Reaction temperature: -25 °C. [f] Catalyst loading: 1 mol%. [g] Catalyst loading: 0.5 mol% and reaction time: 72 h.

Initially, we investigated the 1,3-dipolar reaction of (*E*)-*β*-nucleobase acrylate **1a** with *N*-benzylidene glycine methyl ester **2a** using K_2CO_3 as the base in CH_2Cl_2 catalyzed by a chiral silver catalyst generated in situ from AgOAc and different chiral ligands (Table 1). To our delight, when (*R*,*R*)-DIOP **L1** was used as the ligand, the 1,3-dipolar cycloaddition proceeded and yielded *endo*-**3aa** as the major product, but in a poor yield and stereocontrol (entry 1). After screening different ligands including (*R*)-SynPhos **L2** and (*S*,*Sp*)-phosferrox **L3**, gratifyingly the 1,3-dipolar cycloaddition proceeded well with a chiral phosferrox complex (entries 2 and 3). Encouraged by the results, the steric hindrance and electronic effect of phosferrox ligands were investigated, but no better results were obtained (entries 3–6). For ligand **L3**, one of the best ligands in the previously reported 1,3-dipolar cycloaddition of azomethine ylide was less effective in this reaction (entry 3).[8g] Next, a phenyl group at the 5-position of the oxazoline ring of phosferrox was introduced; however, the enantioselectivity significantly decreased and the *exo*-**3aa** isomer was the major product (entry 7), indicating the mismatched nature of the (*S*)-planar chirality with the (*R*,*R*)-central chirality on the oxazolinyl ring. Thus, (*R*,*R*,*Rp*)-ligand **L8** was examined; the enantioselectivity of *exo*-**3aa** sharply increased to 91% ee (entry 8).[10] By changing the solvent from CH_2Cl_2 to $HC(OCH_3)_3$, the yield was improved from 83% to quantitative yield (entries 8 and 9). After varying the central metal including Ag(I) and Cu(I), $Cu(CH_3CN)_4ClO_4$ afforded the best results, with complete enantiocontrol (>99% ee, entries 9–12). By changing the solvent to CH_2Cl_2 again, the diastereoselectivity increased from 83:17 to 90:10 (entries 12–15). When the reaction temperature was lowered to -25 °C, the diastereoselectivity increased to 93:7 (entry 16). Surprisingly, the diastereoselectivity could be switched when other ligands, **L9** and **L10**, were used (entries 17 and 18). Remarkably, 1 mol% catalyst loading showed satisfactory catalytic efficiency; the product was obtained in a quantitative yield and with excellent *exo*-selectivity and enantioselectivity (>99% ee, entry 19 vs 16). Significantly, even 0.5 mol% of the catalyst still gave excellent *exo*-selectivity and enantioselectivity and moderate yield (entry 20). Meanwhile, the *Z* isomer of *β*-nucleobase acrylate **1a** was also investigated, but the conversion was too low, along with poor enantioselectivity.

Table 2 Substrate scope of azomethine ylides[a]



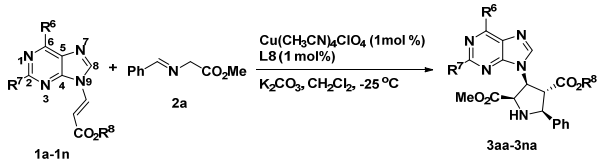
Entry	R^1	R^5	T (h)	Product	Yield[b] (%)	*exo*/*endo*[c]	ee[d] (%) (*exo*)
1	Ph	Me	12	**3aa**	99	93:7	>99
2	Ph	Et	12	**3ab**	98	94:6	>99
3[e]	Ph	Et	32	**3ab**	97	94:6	>99
4	Ph	*i*Pr	16	**3ac**	96	95:5	>99
5	Ph	*t*Bu	16	**3ad**	95	91:9	>99
6	Ph	Bn	16	**3ae**	98	96:4	>99
7	2-$CH_3C_6H_4$	Me	16	**3af**	96	92:8	>99
8	3-$CH_3C_6H_4$	Me	16	**3ag**	95	92:8	>99
9	4-$CH_3C_6H_4$	Me	16	**3ah**	98	93:7	>99
10	2-ClC_6H_4	Me	16	**3ai**	90	90:10	>99
11	3-ClC_6H_4	Me	16	**3aj**	95	89:11	>99
12	4-ClC_6H_4	Me	16	**3ak**	97	93:7	>99
13	4-$CH_3OC_6H_4$	Me	16	**3al**	94	94:6	>99
14	4-FC_6H_4	Me	18	**3am**	97	86:14	>99
15	4-BrC_6H_4	Me	18	**3an**	95	92:8	>99
16	4-$CF_3C_6H_4$	Me	16	**3ao**	93	90:10	>99
17[f]		Me	18	**3ap**	56	96:4	>99
18	2-naphthyl	Me	36	**3aq**	93	94:6	>99
19	2-thienyl	Me	18	**3ar**	95	93:7	>99
20	2-furyl	Me	16	**3as**	96	92:8	>99
21[f]		Me	18	**3at**	90	95:5	99
22	^{t}Bu	Me	18	**3au**	98	98:2	98

[a] Reaction conditions: $Cu(CH_3CN)_4ClO_4$/**L8** (1:1, 1 mol%), **1a** (0.05 mmol), **2a–2u** (0.2 mmol), and K_2CO_3 (2.0 mg) in CH_2Cl_2 (1.0 mL) at -25 °C. [b] Isolated yield. [c] Determined by the ^1H NMR spectra of the crude products. [d] Determined by chiral HPLC analysis. [e] The reaction was carried out on 1.0 mmol scale. [f] The ratio of *endo*/*exo* was determined by chiral HPLC analysis.

Under the optimized reaction conditions, the substrate scope of azomethine ylide precursors, α-iminoesters **2a**–**2u**, was investigated (Table 2). The ester group of α-iminoesters slightly affected the diastereoselectivities, while had no influence on the enantioselectivities (entries 1–6). To further evaluate the synthetic potential of the catalytic system, the reaction was carried out on 1.0 mmol scale, and the desired adduct was obtained without any loss of the yield, diastereo-, or enantioselectivity (entry 3). To our delight, regardless of either the electronic properties or steric hindrance of the substituents

on the aromatic ring of α-iminoesters, the corresponding azacyclic nucleoside analogues **3af**–**3ap** were obtained in high diastereoselectivities (up to 96:4 dr) and enantioselectivities (>99% *ee*) (entries 7–17), but a lower yield was afforded for the α-iminoester **2p** with a strong electron-donating group (entry 17). Moreover, both ring-fused and heteroaromatic α-iminoesters furnished the cycloaddition to afford the corresponding products **3ar**-**3at** in high yields and with >99% *ee* (entries 18–20). In addition, α-iminoester **2t** with an alkenyl substituent and α-iminoester **2u** derived from aliphatic aldehyde were also suitable substrates for the reaction, delivering the targeted nucleoside analogues **3at** and **3au** in excellent diastereo- and enantioselectivities (entries 21 and 22).

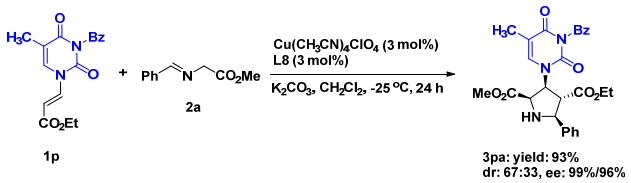
Table 3 Substrate scope of β-nucleobase acrylates[a]



Entry	R^6	R^7/R^8	T (h)	Product	Yield[b] (%)	*exo*/*endo*[c]	ee[d] (%) (*exo*)
1	Cl	H/Et	12	**3aa**	99	93:7	>99
2	Br	H/Et	16	**3ba**	95	92:8	99
3	I	H/Et	16	**3ca**	96	92:8	>99
4[e]	H	H/Et	24	**3da**	92	93:7	>99
5	OMe	H/Et	14	**3ea**	98	95:5	>99
6	OEt	H/Et	14	**3fa**	98	95:5	>99
7		H/Et	16	**3ga**	97	95:5	>99
8		H/Et	16	**3ha**	96	93:7	>99
9		H/Et	18	**3ia**	93	93:7	>99
10		H/Et	16	**3ja**	96	94:6	>99
11	Ph	H/Et	16	**3ka**	95	93:7	>99
12		H/Et	20	**3la**	95	92:8	>99
13	Cl	NH_2/Et	20	**3ma**	91	92:8	99
14	Cl	H/Me	12	**3na**	98	91:9	>99

[a] Reaction conditions: $Cu(CH_3CN)_4ClO_4$/**L8** (1:1, 1 mol%), **1a–1n** (0.05 mmol), **2a** (0.2 mmol), and K_2CO_3 (2.0 mg) in CH_2Cl_2 (1.0 mL) at -25 °C. [b] Isolated yield. [c] Determined by the ^1H NMR spectra of the crude products. [d] Determined by chiral HPLC analysis. [e] The ratio of *exo*/*endo* was determined by chiral HPLC analysis.

Subsequently, the substrate scope of *β*-nucleobase acrylates was investigated (Table 3). Various nucleobase acrylates derived from purines with different substituents at the C6 or C2 position were synthesized. To our delight, in the presence of 1 mol% of Cu(I)-**L8**, these nucleobase acrylates with halogen, hydrogen, alkoxy, amino, and alkyl sulfide substituents at the C6 position of purine participated well in the reaction, generating the corresponding azacyclic nucleoside analogues in excellent yields and with excellent diastereo- and enantioselectivities (99–>99% *ee*) (entries 1–10). In the cases of nucleobase acrylates **1k** and **1l**, with phenyl or 2-naphthyl

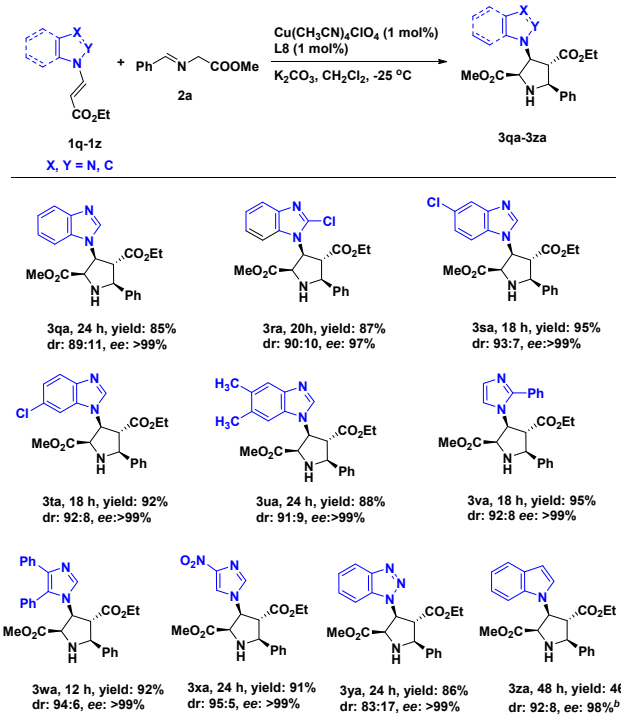


Scheme 3 Synthesis of pyrimidine nucleoside analogue.

groups at the C6 position of purine, the 1,3-dipolar cycloaddition also proceeded well, delivering the desired cycloadducts **3ka**–**3la** in excellent stereocontrol (entries 11 and 12). When an NH_2 group was introduced to the C2 position of the purine part in nucleobase acrylate **1m**, the desired azacyclic nucleoside analogue **3ma**, could be obtained with excellent enantioselectivity (99% *ee*, entry 13). Furthermore, methyl ester-derived nucleobase acrylate **1n** also underwent a clean reaction (entry 14).

Encouraged by the excellent results with purine-substituted acrylates, we then investigated the 1,3-dipolar cycloaddition with pyrimidine-substituted acrylates (Scheme 3). When the 5-F-cytosine-substituted acrylate **1o** was examined, the 1,3-dipolar cycloaddition did not occur. Gratifyingly, when the 3-benzoyl-thymine-substituted acrylate **1p** was employed, the adduct **3pa** was formed with high yield and high enantioselectivity, albeit lower diastereoselectivity.

Scheme 4 Substrate scope of other *β*-heteroaryl acrylates.[a]

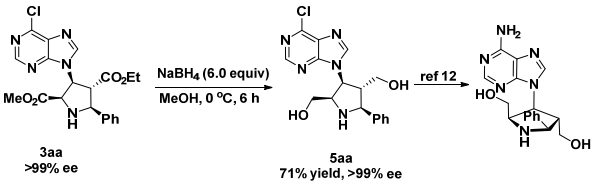


[a] Unless otherwise noted, the reaction conditions are as follows: $Cu(CH_3CN)_4ClO_4$/**L8** (1:1, 1 mol%), **1q–1z** (0.05 mmol), **2a** (0.2 mmol), and K_2CO_3 (2.0 mg) in CH_2Cl_2 (1.0 mL) at -25 °C. Isolated yields are reported. The dr values were determined by the ^1H NMR analysis of the crude products, and the ee values were determined by chiral HPLC analysis. [b] Catalyst loading: 10 mol%.

Then, different types of *β*-heteroaryl acrylates were investigated as the dipolarophiles in the 1,3-dipolar cycloaddition to α-iminoester **2a** (Scheme 4). When a benzimidazole- substituted acrylate **1q** was used, the desired cycloadduct **3qa** was obtained in >99% *ee*. Next, 2-chlorobenzimidazole-, 5-chlorobenzimidazole-, 6-chlorobenzimidazole-, and 5,6-dimethylbenzimidazole-substituted acrylates **1r**–**1u** were investigated, and the corresponding pyrrolidine derivatives **3ra**–**3ua** were identified in high yields and with excellent diastereo- and enantioselectivities. When 2-phenylimidazole-, 4,5-diphenylimidazole-, and 4-nitroimidazole-substituted acrylates **1v**–**1x** were used, the 1,3-dipolar cycloadditions smoothly afforded the corresponding cycloadducts **3va**–**3xa** with

excellent results. Moreover, the benzotriazole-substituted acrylate **1y** was also a suitable substrate for the reaction. In the case of indole- substituted acrylate **1z**, the cycloadduct **3za** was obtained in a low yield but with excellent enantioselectivity.

The absolute configuration of azacyclic nucleoside analogue **3an** was determined to be (2*R*,3*S*,4*R*,5*S*) by the single-crystal X-ray diffraction analysis of the *p*-tosylprotected azacyclic nucleoside analogue **4an**.[11] Then, the azacyclic nucleoside analogue **3aa** was reduced to afford azacyclic nucleoside **5aa**, with two hydroxymethyl groups (Scheme 5), which could be converted to the adenine-derived azacyclic nucleoside.[12]



Scheme 5 Transformations of adduct **3aa**.

In summary, various chiral azacyclic nucleoside analogues were synthesized through asymmetric 1,3-dipolar cycloaddition of *β*-nucleobase acrylates to azomethine ylides for the first time. In the presence of 1 mol% of Cu/N-P complex, the corresponding azacyclic nucleoside analogues were obtained in high yields and with excellent *exo*-selectivities and enantioselectivities (98–>99% *ee*). Moreover, other *β*-heteroaryl acrylates including pyrimidine-, benzimidazole-, imidazole-, benzotriazole-, and indole-substituted acrylates also suitable dipolarophiles for the reaction, affording the desired pyrrolidine derivatives with excellent results. Further study of the reaction mechanism is currently under way.

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Notes and references

Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, Henan 453007, China. E-mail: quguir@sina.com;guohm518@hotmail.com.

† Electronic Supplementary Information (ESI) available: Experimental details, the preparation of the starting β-heteroaryl acrylates, and analytical data of the products (NMR, HPLC, ESI-HRMS, Optical rotations), and crystallographic data in CIF. See DOI: 10.1039/b000000x/

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