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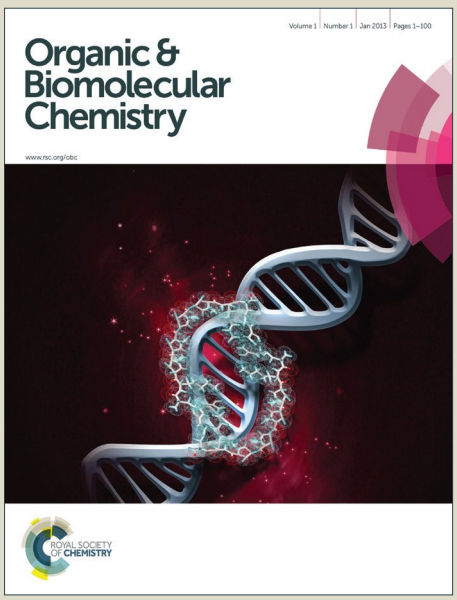

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DBU-mediated metal-free oxidative cyanation of α-amino carbonyl compounds: using molecular oxygen as the oxidant

Lei Li,[a] Qian Wang,[a] Pei Liu,[a] Hua Meng,[b] Xing-Lan Kan,[a] Qun Liu,[a] and Yu-Long Zhao,*[a]

[a] Department of Chemistry, Northeast Normal University, Changchun, 130024, P. R. China

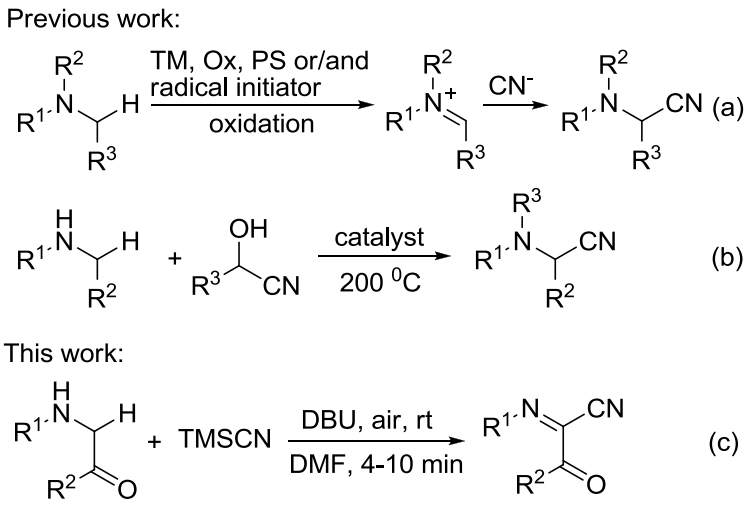
[b] Zhejiang Sucon Silicone Co.,Ltd., Shaoxing, 312088, P. R. China

A novel DBU-mediated oxidative cyanation of α-amino carbonyl compounds by using air as the sole oxidant was developed under mild metal-free conditions for the first time. The reaction involves a tandem oxidation/Strecker reaction/oxidation process and provides a new and efficient method for the construction of α-iminonitriles in good to high yields in a single step.

Introduction

α-Aminonitriles are an important class of versatile intermediates for a wide range of natural products, pharmaceuticals, functional materials, and agricultural chemicals.[1] In addition, nucleophilic additions to the nitrile group can provide access to valuable α-amino aldehydes, ketones, and alcohols, as well as 1,2-diamines.[2] Accordingly, the development of novel and efficient synthetic methods for α-aminonitriles has been a major topic in synthetic organic chemistry. Among the different methods available for the preparation of these compounds,[3-7] the oxidative cyanation of sp^3 C–H bonds adjacent to nitrogen atom represents one of the most straightforward and convenient methods for the synthesis of α-aminonitriles.[4-7] However, in all these reactions reported except the electrochemical methods,[5] transition metal (TM) catalysts/mediators, chemical oxidants (Ox), photosensitizers (PS, in light induced reaction) and/or radical initiators are generally required (Scheme 1, a).[6] Recently, Seidel and co-workers developed a conceptually new strategy for the direct α-cyanation of amines in redox-neutral fashion, but the reaction was carried out under microwave conditions at rather high temperature (200 ^{o}C, Scheme 1, b).[7] *Obviously, the development of oxidative cyanation of sp^3 C–H bonds adjacent to nitrogen atom in the absence of transition metals, chemical oxidants, photosensitizers and radical initiators under very mild reactions remains a formidable challenge. Herein, we report the first DBU-mediated oxidative cyanation of sp^3*

C–H bonds adjacent to nitrogen atom without using any redox-active catalysts, chemical oxidants, photosensitizers and radical initiators (Scheme 1, c). *Moreover, the reaction takes place under rather mild conditions with molecular oxygen as a green oxidant and provides a new and efficient method for the construction of functionalized α-iminonitriles in a single step.*



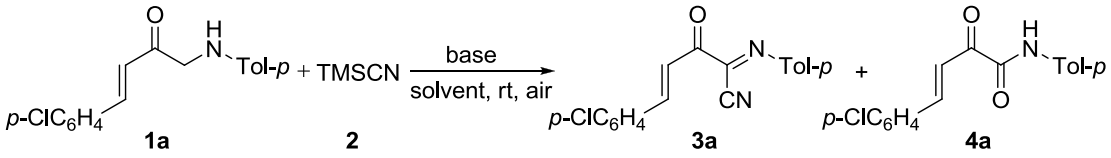
Scheme 1 Oxidative cyanation of sp^3 C-H bonds adjacent to nitrogen atom

Results and discussion

In addition, α-amino carbonyl compounds are ubiquitous subunits in biologically active natural products, biomolecules and therapeutic agents.[8] Thus, it is reasonable that considerable efforts have been devoted to the development of novel methods for their assembly. In this field, α-C–H functionalization of the preexisting α-amino carbonyl structures has attracted considerable attention due to its direction and site-specificity.[9-11] Among these reactions, the generation of electrophilic iminium intermediates through oxidation of sp^3 C−H bonds adjacent to nitrogen atom of α-amino carbonyl compounds, followed by attack of various nucleophiles, has recently been recognized as a powerful mean for preparation of α-amino carbonyl compounds.[11] To the best of our knowledge, however, the direct oxidative α-cyanation of α-amino carbonyl compounds has not been exploited. As part of our continuing research on the formation of carbon–carbon and carbon–nitrogen bonds based on oxidative coupling reactions,[12] we recently developed an efficient method for C–C formation via a base-promoted intramolecular CDC of α-amino carbonyl compounds under

very mild metal-free conditions.[13] These results and our continuous interest in the carbocyanation reaction[14] prompted us to investigate the α-cyanation of *N*-aryl *α*-amino ketones under basic conditions using molecular oxygen as the oxidant under metal-free conditions. As a result, it was found that the oxidative Strecker reaction of *N*-aryl *α*′-amino-*α*,*β*-unsaturated ketone **1a** (0.2 mmol) with trimethylsilyl cyanide (TMSCN) **2a** (0.3 mmol) could proceed rapidly to give (1*E*,3*E*)-4-(4-chlorophenyl)-2-oxo-N-*p*-tolylbut-3-enimidoyl cyanide **3a** in 72% yield in the presence of DBU (0.3 mmol, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene) in DMF (1.5 mL) at room temperature in open air for only 4 min along with the oxidation product **4a** in 5% yield (entry 3). This reaction is highly chemoselective leaving the cinnamoyl moiety of **1a** intact. Further increasing the amounts of DBU leads to lower yield of **3a** (entry 4). Other bases such as DBN (1,5-diazabicyclo[4.3.0]non-5-ene), NaOH, DABCO (1,4-diazabicyclo[2.2.2]octane), Et_3N and Cs_2CO_3, were less (entries 5 and 6) or not effective (entries 7-9). The solvent, DMF, was a much better choice than other solvents examined, including CH_3CN, THF, CH_2Cl_2 and toluene (entries 10-13). The structure of **3a** was determined based on its spectroscopic and analytical data and confirmed by X-ray crystal structure analysis (Fig. 1).[15]

Table 1 Optimization of Reaction Conditions[a]



Entry	Base (equiv)	Solvent	Time (min)	**3a** Yield[b] (%)	**4a** Yield[b] (%)
1	DBU (0.5)	DMF	5	38	14
2	DBU (1.0)	DMF	4	65	10
3[c]	DBU (1.5)	DMF	4	72	5
4[c]	DBU (2.0)	DMF	4	66	5
5	DBN (2.0)	DMF	4	35	10
6	NaOH (1.5)	DMF	8	41	7
7[d]	DABCO (1.5)	DMF	30	---	---
8[d]	Et_3N (1.5)	DMF	30	---	---
9[d]	Cs_2CO_3 (1.5)	DMF	30	---	---
10	DBU (1.5)	MeCN	5	64	12
11	DBU (1.5)	THF	8	61	15
12	DBU (1.5)	CH_2Cl_2	8	35	18
13	DBU (1.5)	Toluene	6	61	17

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), base (0.1-0.4 mmol), solvent (1.5 mL), at room temperature for 4-30 min. [b] Estimated by ^1H NMR spectroscopy using dimethyl phthalate as an internal standard. [c] Isolated yield. [d] Complex mixture was obtained.

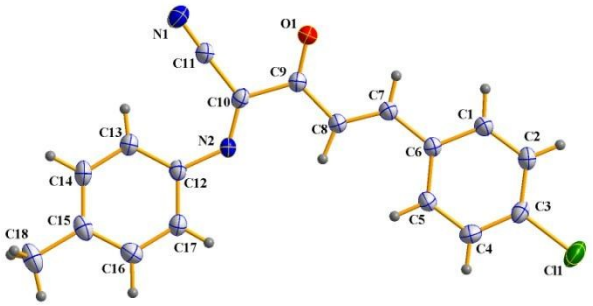
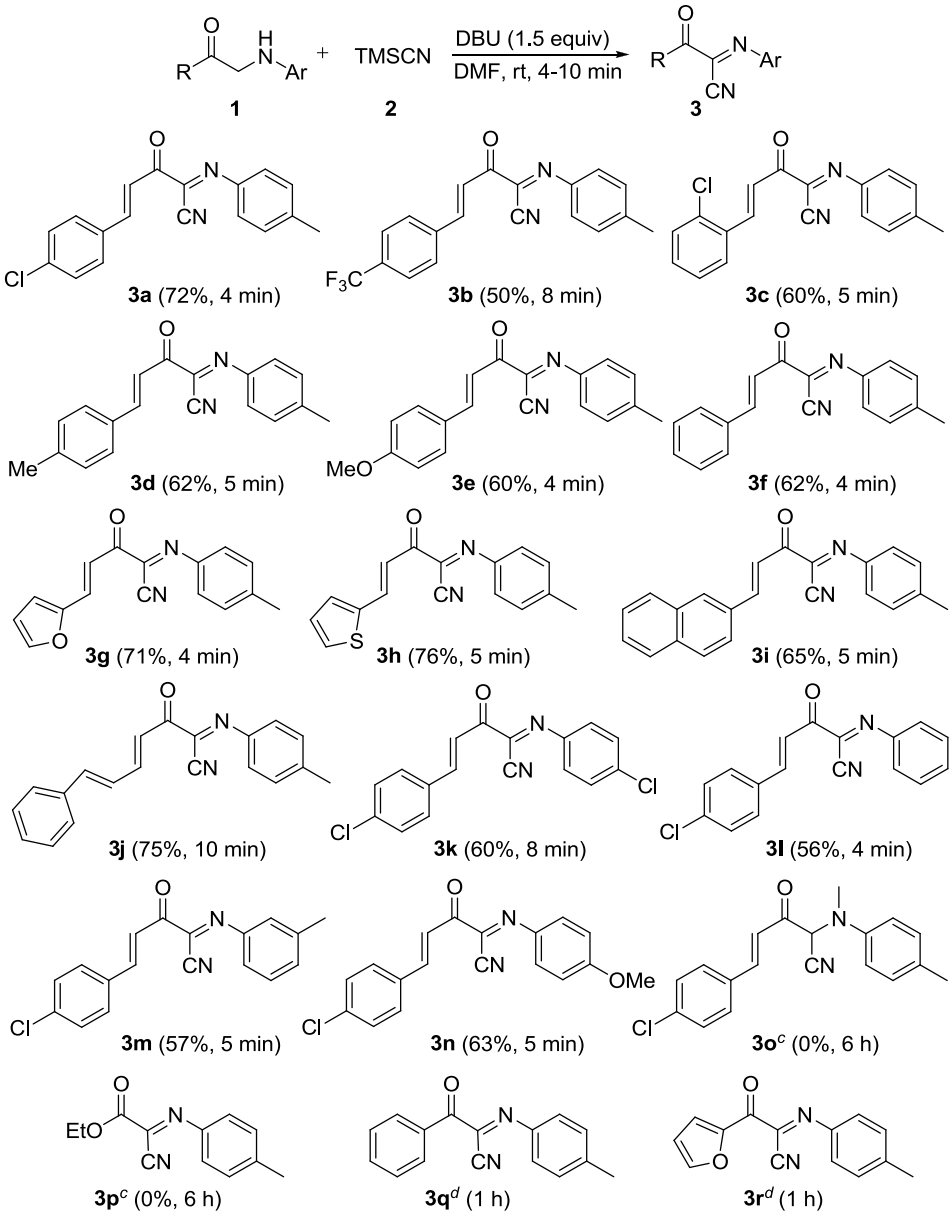


Fig. 1 ORTEP drawing if **3a**.

Scheme 2 DBU-Promoted oxidative cyanation of **1** with **2**[a,b]

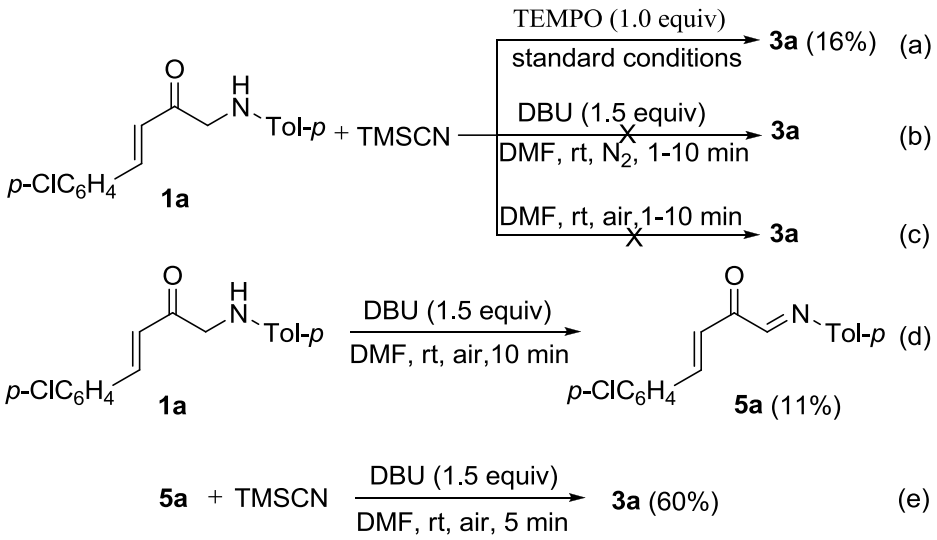


[a] Reaction conditions: **1** (0.2 mmol), **2** (0.30 mmol), DBU (0.30 mmol), DMF (1.5 mL), rt, 4-10 min. [b] Isolated yield. [c] **1o** and **1p** were recovered in 95% and 94% yields, respectively. [d] A complex mixture was produced.

Under the optimal conditions (Table 1, entry 3), the scope and generality of the reaction was next examined. As described in Scheme 2, all of selected *N*-aryl α'-amino-α,β-unsaturated ketone substrates **1a**-**i**, bearing phenyl, electron-deficient and electron-rich aryl, heteroaryl and 2-naphthyl groups at the β-position of the enone moiety, reacted smoothly with trimethylsilyl cyanide **2** to give the corresponding (1*E*,3*E*)-2-oxo-*N*,4-diarylbut-3-enimidoyl cyanides **3a-i** in good to high yields at room temperature in open air for 4-10 min. In addition, the reaction of substrate **1j** bearing a (*E*)-phenylvinyl group (R) gave the desired product **3j** in 75% yield (Scheme 2). On the other hand, various *N*-aryl groups of **1** were also well-tolerated and the corresponding (1*E*,3*E*)-2-oxo-*N*,4-diarylbut-3-enimidoyl cyanides **3k-n** were prepared in good to high yields (Scheme 2). No reaction was observed when α-amino carbonyl compounds **1o** and **1p** were used as substrates (Scheme 2). In addition, the reaction of α-amino carbonyl compound **1q** or **1r** with trimethylsilyl cyanide **2** led to a complex mixture under the identical conditions as above (Scheme 2), which may be due to the lower pKa value of the hydrogen at the nitrogen.

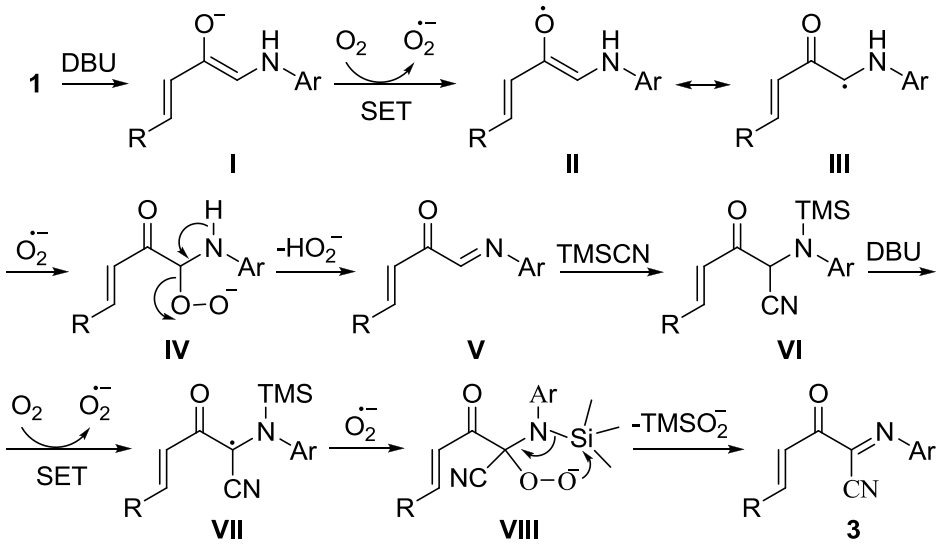
To further probe the mechanisms for formation of **3**, some control experiments were designed and investigated. As a result, it was found that the yield of product **3a** decreased greatly from 72 to 16% under the standard condition when TEMPO (1.0 equiv.; TEMPO = 2,2,6,6-tetramethylpiperidinooxy) was used as a radical inhibitor (Scheme 3, a). No desired product **3a** was produced when the reaction of **1a** with TMSCN **2** was carried out under nitrogen atmosphere (Scheme 3, b). These results indicate that molecular oxygen as oxidant (from air) is necessary for the oxidative cyanation reaction and a radical mechanism may be involved in this oxidative coupling process. No reaction was observed under otherwise identical conditions but in the absence of DBU (Scheme 3, c), which demonstrates that DBU is also crucial for the above oxidative cyanation reaction. In addition, the imine **5a** could be formed in 11% yield (along with a complex mixture) in the absence of TMSCN under otherwise identical conditions as above (Scheme 3, d). According to the results of this transformation, we predicted that the imine **5a** may be a key intermediate in the reaction. Therefore, the reaction of imine **5a** with TMSCN **2** was further investigated.

As expected, under otherwise identical conditions as above, the Strecker reaction of imine **5a** with TMSCN **2** can smoothly proceed to give the product **3a** in 60% yield (Scheme 3, e).



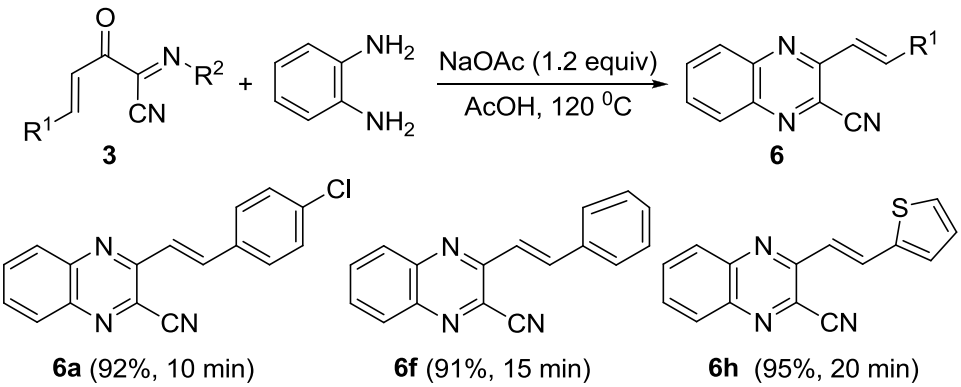
Scheme 3 Control experiments for mechanistic studies.

Based on above experimental results and related report,[4-7,11,13,16] a possible mechanism for the formation of **3** is proposed (Scheme 4). Initially, the deprotonation of **1** into enolate anion **I** followed by a single-electron transfer (SET) process between **I** and triplet oxygen forms the superoxide anion radical and the radical intermediate **II**/**III**. Then, the intermediate **IV**, generated by the reaction of intermediate **III** with superoxide anion radical, undergoes an elimination of hydroperoxide anion to give the imine intermediate **V**, which rapidly reacts with trimethylsilyl cyanide **2** to generate the intermediate **VI**. Finally, (1*E*,3*E*)-2-oxo-*N*,4-diarylbut-3-enimidoyl cyanide **3** was produced via a sequential deprotonation, oxidation and elimination of TMS-peroxide anion process (**VI**→**3**, Scheme 4).



Scheme 4 Proposed mechanism for formation of **3**.

In order to explore the synthetic potential of these functionalized (1*E*,3*E*)-2-oxo-*N*,4-diarylbut-3-enimidoyl cyanides, the cyclization reaction of **3** with benzene-1,2-diamine was examined (Scheme 5). It was found that the cyclization reaction of **3a** (0.2 mmol) with benzene-1,2-diamine (0.24 mmol) could easily proceed to give **2**-cyano quinoxaline **6a** in 92% yield in AcOH (2.0 mL) at 120 ^{0}C for 10 min in the presence of NaOAc (0.24 mmol). Similarly, **2**-cyano quinoxaline derivatives **6f** and **6h** were obtained in 91% and 95% yields from (1*E*,3*E*)-2-oxo-*N*,4-diarylbut-3-enimidoyl cyanides **3f** and **3h**, respectively (Scheme 5).



Scheme 5 Synthesis of 2-cyano quinoxalines **6**.

Conclusions

In conclusion, we have developed a novel DBU-mediated oxidative cyanation of α-amino carbonyl compounds by using air as the sole oxidant under metal-free conditions for the first time. The reaction involves a tandem oxidation/Strecker reaction/oxidation process and provides a new and efficient method for the construction of α-iminonitriles in a single step. The advantages of those methods include: (1) mild reaction conditions and short reaction time; (2) simplicity and safety of operation; (3) any transition metals, synthetic oxidants, photosensitizers and radical initiators are not required and only cheap DBU and air are necessary. These advantages make this protocol very practical. Further studies are in progress.

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Experimental

General methods

All reagents were commercial and were used without further purification. Chromatography was carried on flash silica gel (300-400 mesh). All reactions were monitored by TLC, which was performed on precoated aluminum sheets of silica gel 60 (F254). Unless noted, the ^{1}H NMR spectra were recorded at 400 MHz and 500 MHz in $CDCl_3$ and the ^{13}C NMR spectra were recorded at 125 MHz in $CDCl_3$ with TMS as internal standard. All coupling constants (*J* values) were reported in Hertz (Hz). High-resolution mass spectra (HRMS) were obtained using a Bruker microTOF II focus spectrometer (ESI).

General Procedure for the Preparation of 3 (3a as Example).

To a solution of (*E*)-4-(4-chlorophenyl)-1-(*p*-tolylamino)but-3-en-2-one **1a** (0.2 mmol, 57.1 mg) and TMSCN **2** (0.30 mmol, 0.040 mL) in DMF (1.5 mL) was added DBU (0.3 mmol, 0.045 mL). Then the

reaction mixture was stirred at room temperature in open air for 5 min. After **1a** was consumed (monitored by TLC), the reaction mixture was poured into water (50 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to yield the corresponding crude product, which was purified by chromatography (silica gel, petroleum ether/acetone = 10/1, v/v) to give **3a** (44.4 mg, 72%) as a yellow solid.

(1*E*,3*E*)-4-(4-Chlorophenyl)-2-oxo-*N*-(*p*-tolyl)but-3-enimidoyl cyanide (3a). Yellow solid; m.p. 107-109 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.91 (d, *J* = 16.0 Hz, 1H), 7.83 (d, *J* = 16.0 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 2.45 (s, 3H); ^{13}CNMR ($CDCl_3$, 125 MHz) δ: 183.5, 145.4, 143.3, 142.2, 137.4, 135.8, 132.8, 130.3, 130.2, 129.4, 123.0, 118.4, 110.6, 21.6; IR (KBr) *v*: 2921, 2215, 1618, 1600, 1556, 1445, 1319, 1108, 1060 cm^{-1}; HRMS (ESI-TOF)calcd for $C_{18}H_{13}ClN_2ONa^+$ ([M + Na]$^+$): 331.0609, found: 331.0620.

(1*E*,3*E*)-2-Oxo-*N*-(*p*-tolyl)-4-(4-(trifluoromethyl)phenyl)but-3-enimidoyl cyanide (3b). Yellow solid; m.p. 135-137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.94 (d, *J* = 4.0 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.5, 144.7, 143.2, 142.5, 137.6, 135.4, 132.6 (q, $J_{C\text{-}F}$ = 32.7 Hz), 130.3, 129.1, 126.0 (q, $J_{C\text{-}F}$ = 3.6 Hz), 123.7 (q, $J_{C\text{-}F}$ = 270.7 Hz), 123.2, 120.2, 110.6, 21.6; IR (KBr) *v*: 2926, 2211, 1608, 1607, 1550, 1324, 1117, 1066 cm^{-1}; HRMS (ESI-TOF)calcd for $C_{19}H_{14}F_3N_2O^+$([M + H]$^+$): 343.1053, found: 343.1049.

(1*E*,3*E*)-4-(2-Chlorophenyl)-2-oxo-*N*-(*p*-tolyl)but-3-enimidoyl cyanide (3c). Yellow solid; m.p. 118-120 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.39 (d, *J* = 16.0 Hz, 1H), 7.85-7.81 (m, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.46 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H), 7.39-7.32 (m, 4H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.4, 143.2, 142.5, 142.3, 136.2, 135.6, 132.5, 132.0, 130.4, 130.3, 128.0, 127.1, 123.0, 120.3, 110.6, 21.5; IR (KBr) *v*: 3032, 2217, 1663, 1595, 1328, 1272, 1208 cm^{-1}; HRMS (ESI-TOF)calcd for $C_{18}H_{14}ClN_2O^+$([M + H]$^+$): 309.0789, found: 309.0798.

(1*E*,3*E*)-2-Oxo-*N*,4-dip-tolylbut-3-enimidoyl cyanide (3d). Yellow solid; m.p. 133-135 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (d, *J* = 16.0 Hz, 1H), 7.81 (d, *J* = 16.0 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 2.45 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.6, 147.2, 143.5, 142.3, 141.8, 136.2, 131.6, 130.2, 129.8, 129.2,

122.8, 116.8, 110.7, 21.7, 21.5; HRMS (ESI-TOF) calcd for $C_{19}H_{17}N_2O^+$ ([M + H]$^+$): 289.1335, found: 289.1337.

(1*E*,3*E*)-4-(4-Methoxyphenyl)-2-oxo-*N*-p-tolylbut-3-enimidoyl cyanide (3e). Yellow solid; m.p. 112-114 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.94 (d, *J* = 16.0 Hz, 1H), 7.72 (d, *J* = 16.0 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 3.87 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.4, 162.4, 146.9, 143.5, 141.7, 136.4, 131.1, 130.2, 127.1, 122.7, 115.4, 114.5, 110.7, 55.5, 21.5; IR (KBr) *v*: 2960, 2930, 2217, 1730, 1663, 1258, 1170, 1020 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{19}H_{17}N_2O_2^+$ ([M + H]$^+$): 305.1285, found: 305.1286.

(1*E*,3E)-2-Oxo-4-phenyl-*N*-(*p*-tolyl)but-3-enimidoyl cyanide (3f). Yellow solid; m.p. 90-92 ^{o}C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.97 (d, *J* = 16.0 Hz, 1H), 7.85 (d, *J* = 16.0 Hz, 1H), 7.69 (d, *J* = 7.5 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.44-7.46 (m, 3H), 7.34 (d, *J* = 8.0 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 183.6, 146.9, 143.4, 142.0, 135.9, 134.3, 131.4, 130.2, 129.0, 129.0, 122.9, 117.9, 110.6, 21.5; IR (KBr) *v*: 2962, 2938, 2218, 1738, 1670, 1261, 1176, 1032 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{18}H_{15}N_2O^+$ ([M + H]$^+$): 275.1179, found: 275.1179.

(1*E*,3*E*)-4-(Furan-2-yl)-2-oxo-*N*-(*p*-tolyl)but-3-enimidoyl cyanide (3g). Yellow solid; m.p. 146-148 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.70 (s, 2H), 7.58 (s, 1H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 3.5 Hz, 1H), 6.56 (dd, *J* = 3.5, 1.6 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.5, 151.4, 146.0, 143.4, 141.9, 135.8, 132.2, 130.2, 122.9, 118.3, 115.5, 113.1, 110.7, 21.5; HRMS (ESI-TOF) calcd for $C_{16}H_{13}N_2O_2^+$ ([M + H]$^+$): 265.0972, found: 265.0977.

(1*E*,3*E*)-2-Oxo-4-(thiophen-2-yl)-*N*-(*p*-tolyl)but-3-enimidoyl cyanide (3h). Yellow solid; m.p. 133-135 ^{o}C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.44 (s, 3H), 7.12 (dd, *J* = 3.5, 5.0 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 2.0 Hz, 1H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 5.0 Hz, 1H), 7.60 (d, *J* = 16.0 Hz, 1H), 8.07 (d, *J* = 15.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ:183.2, 143.4, 141.9, 140.0, 139.1, 135.9, 133.5, 130.5, 130.2, 128.6, 122.9, 116.8, 110.7, 21.5; IR (KBr) *v*: 2926, 2214, 1665, 1582, 1420, 1213, 1001 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{13}N_2OS^+$ ([M + H]$^+$): 281.0743, found: 281.0743.

(1*E*,3*E*)-4-(Naphthalen-2-yl)-2-oxo-*N*-p-tolylbut-3-enimidoyl cyanide (3i). Yellow solid; m.p. 176-178 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.13 (d, *J* = 15.5 Hz, 1H), 8.09 (s, 1H), 7.95 (d, *J* = 16.0 Hz, 1H), 7.92-7.82 (m, 4H), 7.57-7.53 (m, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 2.45

(s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.5, 147.0, 143.4, 141.9, 136.1, 134.7, 133.2, 131.9, 130.2, 128.8, 127.8, 127.7, 126.9, 123.7, 122.9, 118.0, 110.7, 21.5. Two carbon is not visible due to overlapping peaks; IR (KBr) *v*: 2920, 2217, 1666, 1598, 1567, 1363, 1302, 1200, 1002 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{22}H_{17}N_2O^+$ ([M + H]$^+$): 325.1335, found: 325.1336.

(1*E*,3*E*,5*E*)-2-Oxo-6-phenyl-*N*-(*p*-tolyl)hexa-3,5-dienimidoyl cyanide (3j). Yellow solid; m.p. 160-162 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.74 (dd, *J* = 15.5, 11.0 Hz, 1H), 7.52 (d, *J* = 7.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.41-7.35 (m, 4H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 15.5 Hz, 1H), 7.07-7.02 (m, 1H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.6, 146.9, 144.3, 143.4, 141.9, 135.9, 135.7, 130.2, 129.8, 128.9, 127.6, 126.7, 122.9, 121.3, 110.7, 21.5; HRMS (ESI-TOF) calcd for $C_{20}H_{17}N_2O^+$ ([M + H]$^+$): 301.1335, found: 301.1327.

(1*E*,3*E*)-*N*,4-Bis(4-chlorophenyl)-2-oxobut-3-enimidoyl cyanide (3k). Yellow solid; m.p. 148-150 ^{o}C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.42 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 16.0 Hz, 1H), 7.92 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 183.0, 146.0, 144.2, 137.7, 137.6, 136.8, 132.6, 130.2, 129.9, 129.2, 123.7, 118.0, 110.0; IR (KBr) *v*: 2923, 2208, 1668, 1607, 1487, 1335, 1092 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{11}Cl_2N_2O^+$ ([M + H]$^+$): 329.0243, found: 329.0257.

(1*E*,3*E*)-4-(4-Chlorophenyl)-2-oxo-*N*-phenylbut-3-enimidoyl cyanide (3l). Yellow solid; m.p. 165-167 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.93 (d, *J* = 16.0 Hz, 1H), 7.82 (d, *J* = 16.0 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.57-7.54 (m, 2H), 7.50-7.47 (m, 3H), 7.42 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.2, 146.0, 145.8, 137.6, 137.5, 132.6, 130.6, 130.2, 129.6, 129.4, 122.0, 118.1, 110.1; IR (KBr) *v*: 2220, 1728, 1674, 1604, 1564, 1332.67, 1208, 993 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{12}ClN_2O^+$ ([M + H]$^+$): 295.0633, found: 295.0626.

(1*E*,3*E*)-4-(4-Chlorophenyl)-2-oxo-*N*-(*m*-tolyl)but-3-enimidoyl cyanide (3m). Yellow solid; m.p. 132-134 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.92 (d, *J* = 16.0 Hz, 1H), 7.81 (d, *J* = 16.0 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.45-7.40 (m, 3H), 7.29 (d, *J* = 5.5 Hz, 3H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.3, 146.0, 145.7, 139.7, 137.5, 137.2, 132.7, 131.5, 130.2, 129.4, 129.3, 122.8, 118.9, 118.2, 110.2, 21.3; IR (KBr) *v*: 2922, 2217, 1667, 1598, 1563, 1329, 994 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{18}H_{14}ClN_2O^+$ ([M + H]$^+$): 309.0789, found: 309.0791.

(1*E*,3*E*)-4-(4-Chlorophenyl)-*N*-(4-methoxyphenyl)-2-oxobut-3-enimidoyl cyanide (3n). Yellow solid; m.p. 153-155 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.88 (d, *J* = 16.0 Hz, 1H), 7.84 (d, *J* = 16.0 Hz, 1H), 7.79 (d, *J* = 9.0 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.05 (d, *J* = 9.0 Hz, 2H), 3.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.9, 162.9, 144.8, 138.2, 137.2, 132.9, 132.3, 130.1, 129.3, 126.8, 118.5, 114.9, 111.5, 55.8; IR (KBr) *v*: 2917, 2208, 1667, 1608, 1535, 1312, 1271, 1167, 993 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{18}H_{14}ClN_2O_2^+$ ([M + H]$^+$): 325.0738, found: 325.0733.

General Procedure for the Preparation of 6 (6a as Example).

To a solution of (1*E*,3*E*)-4-(4-chlorophenyl)-2-oxo-*N*-(*p*-tolyl)but-3-enimidoyl cyanide **3a** (0.20 mmol, 61.6 mg) in AcOH (2 mL) was added benzene-1,2-diamine (0.24 mmol, 25.9 mg) and NaOAc (0.24 mmol, 19.7 mg). Then the reaction mixture was stirred at 120 ^{o}C for 10 min. After **3a** was consumed (monitored by TLC), the reaction mixture was poured into water (50 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to yield the corresponding crude product, which was purified by chromatography (silica gel, petroleum ether/acetone = 10/2, v/v) to give **6a** (53.5 mg, 92%) as a yellow solid.

(*E*)-3-(4-Chlorostyryl)quinoxaline-2-carbonitrile (6a). Yellow solid; m.p. 173-175 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.13 (d, *J* = 15.5 Hz, 1H), 8.08 (t, *J* = 8.5 Hz, 2H), 7.89 (t, *J* = 8.0 Hz, 1H), 7.79 (t, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 15.5 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 150.2, 142.7, 140.9, 138.4, 135.8, 133.8, 133.5, 130.9, 129.6, 129.3, 129.2, 129.2, 129.1, 120.8, 115.6; IR (KBr) *v*: 2221, 1615, 1535, 1456, 1355, 1228, 951, 860, 750, 718 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{11}ClN_3^+$ ([M + H]$^+$): 292.0636, found: 292.0636.

(*E*)-3-Styrylquinoxaline-2-carbonitrile (6f). Yellow solid; m.p. 172-174 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.18 (d, *J* = 15.5 Hz, 1H), 8.08 (q, *J* = 8.5 Hz, 2H), 7.88 (t, *J* = 8.0 Hz, 1H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.69 (d, *J* = 7.5 Hz, 2H), 7.64 (d, *J* = 16.0 Hz, 1H), 7.44-7.37 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 150.5, 142.7, 140.8, 139.9, 135.3, 133.4, 130.7, 130.0, 129.5, 129.2, 129.1, 128.9, 128.0, 120.2, 115.6; HRMS (ESI-TOF) calcd for $C_{17}H_{12}N_3^+$ ([M + H]$^+$): 258.1026, found: 258.1031.

(*E*)-3-(2-(Thiophen-2-yl)vinyl)quinoxaline-2-carbonitrile (6h). Yellow solid; m.p. 184-186 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.28 (d, *J* = 15.0 Hz, 1H), 8.04 (d, *J* = 9.0 Hz, 2H), 7.85 (t, *J* = 7.5 Hz, 1H),

7.75 (t, *J* = 7.5 Hz, 1H), 7.39 (d, *J* = 15.0 Hz, 1H), 7.39-7.36 (m, 2H), 7.09 (t, *J* = 4.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 150.4, 142.8, 140.9, 140.7, 133.4, 132.3, 130.6, 130.4, 129.5, 129.1, 128.8, 128.2, 128.1, 119.2, 115.5; IR (KBr) *v*: 2219, 1606, 1510.40, 1355, 1203, 958, 864, 756, 708 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{10}N_3S^+$ ($[M + H]^+$): 264.0590, found: 264.0591.

Notes and references

(1) (a) C. Nájera and J. M. Sansano, *Chem. Rev.*, 2007, **107**, 4584; (b) D. Enders and J. P. Shilvock, *Chem. Soc. Rev.*, 2000, **29**, 359.

(2) (a) Z. Rappoport, *The Chemistry of the Cyano Group*; Interscience Publishers: London, 1970; (b) R. C. Larock, *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*; VCH: New York, 1989.

(3) (a) T. Li, J. Liang, A. Ambrogelly, T. Brennan, G. Gloor, G. Huisman, J. Lalonde, A. Lekhal, B. Mijts, S. Muley, L. Newman, M. Tobin, G. Wong, A. Zaks and X. Zhang, *J. Am. Chem. Soc.*, 2012, **134**, 6467; (b) F. Chen, X. Huang, Y. Cui and N. Jiao, *Chem. Eur. J.*, 2013, **19**, 11199; (c) L. Simón and J. M. Goodman, *J. Am. Chem. Soc.*, 2009, **131**, 4070; (d) T. Sakai, T. Soeta, K. Endo, S. Fujinami and Y. Ukaji, *Org. Lett.*, 2013, **15**, 2422.

(4) For selected recent reviews, see: (a) S. A. Girard, T. Knauber and C.-J. Li, *Angew. Chem. Int. Ed.*, 2014, **53**, 74; (b) C. Zhang, C. Tang and N. Jiao, *Chem. Soc. Rev.*, 2012, **41**, 3464; (c) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (d) C. J. Li, *Acc. Chem. Res.*, 2009, **42**, 335.

(5) Selected articles on electrochemical cyanation reaction of amines: (a) F. Louafi, J.-P. Hurvois, A. Chibani and T. Roisnel, *J. Org. Chem.*, 2010, **75**, 5721; (b) T. Tajima and A. Nakajima, *J. Am. Chem. Soc.*, 2008, **130**, 10496.

(6) (a) E. Boess, C. Schmitz and M. Klussmann, *J. Am. Chem. Soc.*, 2012, **134**, 5317; (b) P. Liu, Y. Liu, E. L.-M. Wong, S. Xiang and C.-M. Che, *Chem. Sci.*, 2011, **2**, 2187; (c) J. M. Allen and T. H. Lambert, *J. Am. Chem. Soc.*, 2011, **133**, 1260; (d) G. Zhang, Y. Ma, G. Cheng, D. Liu and R. Wang, *Org. Lett.*, 2014, **16**, 656; (e) S.-I. Murahashi, N. Komiya and H. Terai, *Angew. Chem. Int. Ed.*, 2005, **44**, 6931; (f) S.-I. Murahashi, N. Komiya, H. Terai and T. Nakae, *J. Am. Chem. Soc.*, 2003, **125**, 15312; (g) Y. Zhang, H. Peng, M. Zhang, Y. Cheng and C. Zhu, *Chem. Commun.*, 2011, **47**, 2354; (h) A. Wagner and A. R. Ofial, *J. Org. Chem.*, 2015, **80**, 2848; (i) C. Yan, Y. Liu and Q. Wang, *RSC Adv.*, 2014, **4**, 60075; (j) M. Rueping, S. Zhu and R. M. Koenigs, *Chem. Commun.*, 2011, **47**, 12709; (k) D. B. Freeman, L. Furst, A. G. Condie and C. R. J. Stephenson, *Org. Lett.*, 2012, **14**, 94; (l) L. Liu, Z. Wang, X. Fu and C. Yan, *Org. Lett.*, 2012, **14**, 5692; (m) S. Kamijo, T. Hoshikawa

and M. Inoue, *Org. Lett.*, 2011, **13**, 5928; (n) K. Alagiri and K. R. Prabhu, *Org. Biomol. Chem.*, 2012, **10**, 835; (o) S. Singhal, S. L. Jain and B. Sain, *Chem. Commun.*, 2009, 2371; (p) D. P. Hari and B. König, *Org. Lett.*, 2011, **13**, 3852; (q) Y. Pan, S. Wang, C. W. Kee, E. Dubuisson, Y. Yang, K. P. Loh and C.-H. Tan, *Green Chem.*, 2011, **13**, 3341.

7 (a) L. Ma, W. Chen and D. Seidel, *J. Am. Chem. Soc.*, 2012, **134**, 15305; (b) D. Das, M. T. Richers, L. Ma and D. Seidel, *Org.Lett.*, 2011, **13**, 6584.

8 (a) J. M. Concellon and H. Rodriguez-Solla, *Curr. Org. Chem.*, 2008, **12**, 524; (b) F. D. Klingler, *Acc. Chem. Res.*, 2007, **40**, 1367; (c) *Chemistry and Biochemistry of the Amino Acids*, (Ed.: G. C. Barrett), Chapman and Hall, London, 1985.

9 For selected reviews and papers on the arylation reaction: (a) F. Bellina and R. Rossi, *Chem. Rev.*, 2010, **110**, 1082; (b) D. A. Culkin and J. F. Hartwig, *Acc. Chem. Res.*, 2003, **36**, 234; (c) M. Miura and M. Nomura, *Top. Curr. Chem.*, 2002, **219**, 211; (d) J.-C. Wu, R.-J. Song, Z.-Q. Wang, X.-C. Huang, Y.-X. Xie and J.-H. Li, *Angew. Chem. Int. Ed.*, 2012, **51**, 3453.

10 For selected reviews on the alkylation reaction using alkyl halides, see: (a) T. Hashimoto and K. Maruoka, *Chem. Rev.*, 2007, **107**, 5656; (b) K. Maruoka and T. Ooi, *Chem. Rev.*, 2003, **103**, 3013.

11 For selected reports, see: (a) L. Zhao and C.-J. Li, *Angew. Chem. Int. Ed.*, 2008, **47**, 7075; (b) K. Li, G. Tan, J. Huang, F. Song and J. You, *Angew. Chem. Int. Ed.*, 2013, **52**, 12942; (c) C. Huo, Y. Yuan, M. Wu, X. Jia, X. Wang, F. Chen and J. Tang, *Angew. Chem. Int. Ed.*, 2014, **53**, 13544; (d) J. Xie and Z.-Z. Huang, *Angew. Chem. Int. Ed.*, 2010, **49**, 10181; (e) B. Yang, T.-T. Yang, X. A. Li, J.-J. Wang and S.-D. Yang, *Org. Lett.*, 2013, **15**, 5024.

12 For selected recent reports, see: (a) Y.-J. Li, X. Li, S.-X. Zhang, Y.-L. Zhao and Q. Liu, *Chem. Commun.*, 2015, **51**, 11564; (b) Y. Dong, B. Liu, P. Chen, Q. Liu and M. Wang, *Angew. Chem. Int. Ed.*, 2014, **53**, 3442; (c) H. Wang, Y.-L. Zhao, L. Li, S.-S. Li and Q. Liu, *Adv. Synth. Catal.*, 2014, **356**, 3157; (d) H. Zhang, W. Pu, T. Xiong, Y. Li, X. Zhou, K. Sun, Q. Liu and Q. Zhang, *Angew. Chem. Int. Ed.*, 2013, **52**, 2529; (e) T. Xiong, Y. Li, X. Bi, Y. Lv and Q. Zhang, *Angew. Chem. Int. Ed.*, 2011, **50**, 7140.

13 L. Li, Y.-L. Zhao, Q. Wang, T. Lin and Q. Liu, *Org. Lett.*, 2015, **17**, 370.

14 J. Meng, Y.-J. Li, Y.-L. Zhao, X.-B. Bu and Q. Liu, *Chem. Commun.*, 2014, **50**, 12490.

15 CCDC 1028181 (**3a)** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ddcd.cam.ac.uk/data_request/cif.

16 H. Kaise, J. Shimokawa and T. Fukuyama, *Org. Lett.*, 2014, **16**, 727.