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Copper-catalyzed radical oxidative C(sp^3)–H/C(sp^3)–H cross-coupling between arylacetonitriles and benzylic compounds

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ABSTRACT

For the first time, a novel copper-catalyzed direct C(sp^3)–H/C(sp^3)–H cross-coupling of arylacetonitriles with unactivated benzylic compounds was described, allowing various a-benzylated arylacetonitriles to be readily accessible under base-free conditions. Mechanistic investigations suggested that the reaction proceeds through radical process and the C(sp^3)–H cleavage of arylacetonitriles probably is the rate-determining step.

1. Introduction

Nitriles are one of the most fundamental structural motifs in many drugs and natural products [1]. They also serve as versatile building blocks in many chemical transformations [2]. The α-alkylation of nitrile is one of the most simple and popular approach for synthesis of substituted nitriles [3]. Traditional methods for preparation of substituted nitriles are nucleophilic substitution reactions between nitriles and alkyl halides in the presence of a stoichiometric amount of strong base (Scheme 1a) [4]. Over the last decades, the transition-metal catalyzed cross-coupling of nitriles with alcohols through hydrogen-borrowing strategy has also been used to synthesis of substituted nitriles. However, it usually requires precious metals such as Ru [5], Os [6], Rh [7], Ir [8] and Pd [9] etc. What's more, secondary nitriles do not applicable to these catalytic systems (Scheme 1b). In 2016, we reported an efficient nickel catalyzed direct cross-couplings of benzylic alcohol derivatives with arylacetonitriles via C-O activation [3a]. Various α-benzylated arylacetonitriles can be prepared (Scheme 1c). However, the requirement of not readily available starting materials, expensive catalyst and phosphine ligand was limited its application.

Recently, direct C(sp^3)–H functionalization has attracted much attention due to its atom economy and sustainable development [10]. However, direct C(sp^3)–H alkylation of arylacetonitriles with inert alkylation reagents to form substituted nitriles is still a great challenge and remains unexplored. Herein, we report a copper-catalyzed radical oxidative C(sp^3)–H/C(sp^3)–H cross-coupling between, arylacetonitriles and unactivated benzylic compounds (Scheme 1d). For the first time, readily available benzylic compounds were used as alkylation reagents instead of halides and alcohols to afford various substituted nitriles.

2. Results and discussion

We started to investigate this α-benzylation reactions between toluene **1a** and 1-naphthylacetonitrile **2a** (Table 1). Initially, in the presence of different metal catalysts, a mixture of **1a** (3.0 mL), **2a** (0.2 mmol), 2, 2′-dipyridyl (bpy) and di-*tert*-butyl peroxide (DTBP) was stirred at 130 °C for 13 h under N_2. The obtained results

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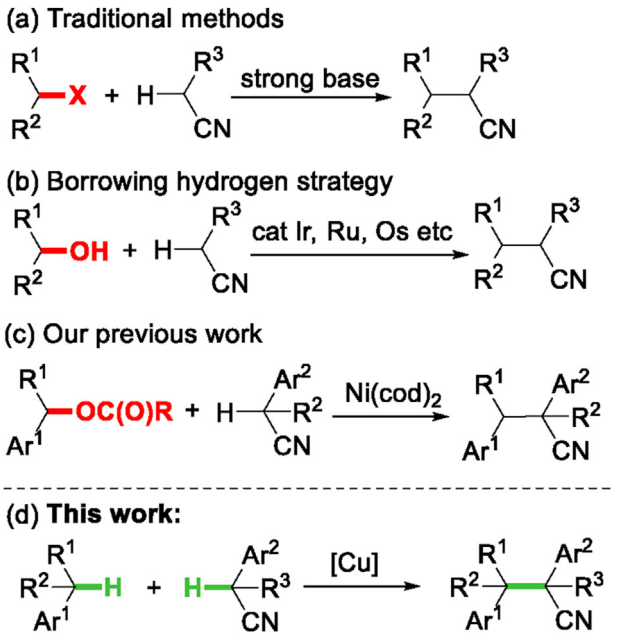
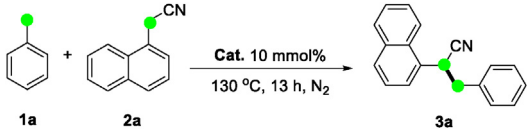


Scheme 1. α-Alkylation of nitriles.

Table 1
Optimization of the reaction conditions.[a]



Run	1a (mL)	Cat.	Ligand (mmol%)	Co-solvent (mL)	Yield[b]
1	3.0	CuO	Bpy (20)	–	36%
2	3.0	Cu_2O	Bpy (20)	–	42%
3	3.0	CuBr	Bpy (20)	–	34%
4	3.0	CuI	Bpy (20)	–	21%
5	3.0	$FeCl_3$	Bpy (20)	–	41%
6	3.0	Cu_2O	Bpy (20)	PhCl (1.0)	59%
7	3.0	Cu_2O	Bpy (20)	PhCl (3.0)	44%
8	3.0	Cu_2O	Bpy (20)	PhCl (2.0)	39%
9	3.0	Cu_2O	Bpy (0)	PhCl (1.0)	38%
10	3.0	Cu_2O	Bpy (10)	PhCl (1.0)	51%
11	**2.0**	**Cu_2O**	Bpy (20)	**PhCl (1.0)**	**61%**
12	2.0	Cu_2O	Bpy (20)	PhCl (0.5)	5e%
13	2.0	Cu_2O	Bpy (20)	PhCl (1.0)	58%[c]
14	2.0	Cu_2O	Bpy ()20	PhCl (1.0)	56%[d]
15	2.0	Cu_2O	1,10-Phen (20)	PhCl (1.0)	35%
16	2.0	Cu_2O	Bpy (20)	PhCl (1.0)	Trace[e]
17	2.0	None	None	PhCl (1.0)	28%

[a] Reaction conditions: Reaction conditions: a mixture of **1a**, **2a** (0.2 mmol), Cat. (10 mmol%), ligand and DTBP (3.0 equiv.) in solvent was stirred at 130 °C for 13 h. Bpy: 2, 2′-dipyridyl.
[b] GC yield using dodecane as internal standard.
[c] DTBP (4.0 equiv.) was used.
[d] DTBP (2.0 equiv.) was used.
[e] TBHP (3.0 equiv.) was used.

showed that Cu_2O gave the highest yield (runs 1–5). Fortunately, when a co-solvent PhCl (1.0 mL) was added, the yield of reaction was improved from 42% to 59% (run 6). Further reducing or increasing the amount of PhCl failed to improve the reaction efficiency (runs 7 and 8). Attempts to decrease the ligand loading were unfavourable to the reaction (runs 9 and 10). Pleasingly, 61% yield of the product was obtained when 2.0 mL toluene was used in the reaction (run 11). Changing the amount of PhCl decreased the reaction efficiency (run 12). Additionally, the amount of DTBP was screened, both decreasing or increasing the amount of DTBP did not lead to good results (runs 13 and 14). 1,10-Phenanthroline and TBHP were also examined in this reaction, poor yields were obtained (runs 15 and 16). However, in the absence of Cu_2O and pyridine, only 28% yield of product was obtained (run 17). This reaction is sensitive to the concentration of substrates and no self-coupling by-products were detected by GC-MS. The main reasons for the relatively low yields are arylacetonitriles were remined after reaction and a little of double-benzylated compounds were generated.

With the optimized reaction conditions in hand, we next examined the generality of this reaction by exploring the scope of benzylic compounds (Table 2). To our delight, when mesitylene or 4-methylanisole were used as solvent, corresponding benzylated nitriles were obtained in 67% and 34%, respectively (**3b** and **3c**). Substrates bearing halogen (F, Cl, Br) on the *para* position of benzene ring were also work well under this system (**3d**-**3f**). Benzylic compounds bearing electron-deficient group such as acetyl and C(O)OMe were coupled with **2a** in moderate yileds with a small amount of **2a** remaining (**3g** and **3h**). Notably, some secondary or tertiary benzylic substrates were found to be compatible with this catalytic system as well (**3i**-**3k**). Direct oxidative cross-coupling of 1-methylnaphthalene with **2a** was also achieved in 36% yield (**3l**). As for the above examples with poor yields, we also analyzed reaction mixtures by GC-MS and found that the by-products in these reactions were double-benzylated compounds and small amount of **2a** was still remained.

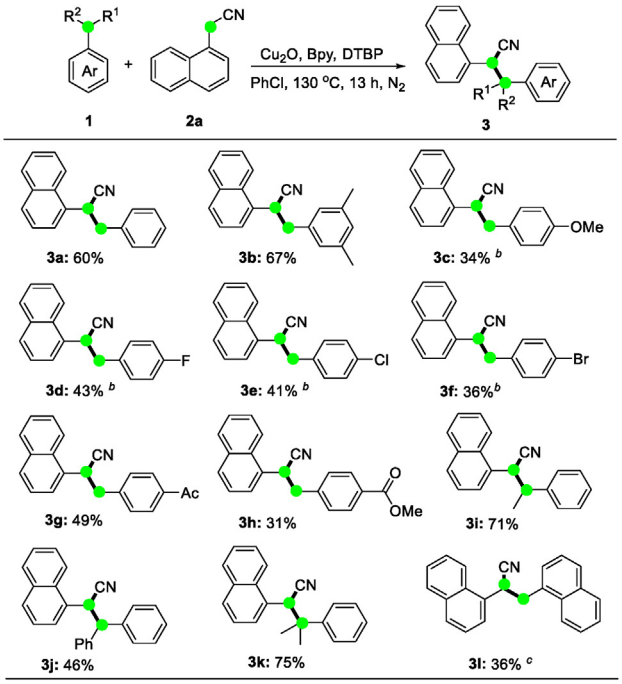
This catalytic system was also applicable to other simple nitriles and benzylic compounds. As shown in Table 3, phenylacetonitrile and substrates whether bearing electron-rich or electron-deficient groups such as Me, OMe, F, and CF_3 all coupled with toluene smoothly, producing the corresponding substituted nitriles in moderate yields (**3m**-**3q**). Secondary nitrile **2r** was also tolerated in this system and a prochiral carbon center was generated in the product (**3r**). It was worth noting that a bioactive compound **3t** was synthesized easily by direct C(sp^3)–H/C(sp^3)–H cross-coupling of 4-methoxybenzyl cyanide with 1,2,3-trimethoxy-5-methylbenzene [11]. Subsequently, various unactivated benzylic compounds were applied as substrates to couple with phenylacetonitrile. The obtained results indicating that the reaction efficiency was not sensitive to the electronic property of the groups on the benzene ring of phenylacetonitrile, and a low to moderate yields of products was given (**3u**-**3w**). Importantly, Tertiary or secondary benzylic compounds such as isopropylbenzene and ethylbenzene were found to be compatible with this catalytic system (**3x**-**3z**).

To gain some insight about the mechanism of this α-benzylation reactions, radical trapping experiments were conducted (Scheme 2). Thus 3.0 equiv. of (2, 2, 6, 6-tetramethylpiperidin-1-yl)oxy (TEMPO) and butylated hydroxytoluene (BHT) were added additionally in the model reaction independently. A significant reduction in the yield of **3a** was observed. Moreover, species **4** and **5** which were generated by the reaction of nitrile and benzyl radical with radical scavengers were detected by HRMS. These results suggest that this reaction may proceeds through a radical process.

Next, kinetic isotope effect (KIE) experiments were carried out to gain insights into the rate-determining step for this C(sp^3)–H/C(sp^3)–H cross-coupling reaction. As shown in Scheme 3, no obvious kinetic isotope effect (k_H/k_D = 1.67) was observed for C(sp^3)–H cleavage of **1a** while a primary kinetic isotope effect (k_H/k_D = 2.88) was observed for C(sp^3)–H cleavage of **2a**, indicating that the C(sp^3)–H cleavage of **2a** perhaps was the rate-determining step in this transformation.

On the basis of the above results and known reports [12], a

Table 2
Copper-catalyzed α-benzylation of 1-naphthylacetonitrile 2a with various benzylic compounds.[a].



[a]Reaction conditions: a mixture of **1** (4.0 mL), **2a** (0.4 mmol), Cu_2O (10 mmol%), Bpy (20 mmol%) and DTBP (3.0 equiv.) in PhCl (2.0 mL) was stirred at 130 °C for 13 h. Isolated yield. [b]18 hours. [c]DTBP (4.0 equiv.) was used.

possible mechanism of this reaction was proposed (Scheme 4). Firstly, in the presence of $[Cu]^I$, radical **A** and $[Cu]^{II}$ alkoxide were formed from DTBP under heating. Next, benzyl radical **B** and radical **C** were generated by abstracting hydrogen from **1** and **2** with the aid of **A**. Finally, selective radical cross coupling of **B** and **C** afforded the desired product **3**. The excess **B** reacted with $[Cu]^{II}$ alkoxide to give by-product **D** with release of $[Cu]^I$. A large amount of By-product **D** was detected by GC-MS.

3. Conclusion

In summary, a copper-catalyzed direct $C(sp^3)$–H/$C(sp^3)$–H oxidative radical cross-coupling of unactivated benzylic compounds with arylacetonitriles was achieved. This protocol features readily available benzylic compounds as alkylation reagents and good functional group compatibility, providing a new straightforward access to various substituted nitriles. Preliminary mechanism investigations suggested that this transformation proceeds through radical process and the $C(sp^3)$–H cleavage of arylacetonitriles probably is the rate-determining step.

4. Experimental section

4.1. General information

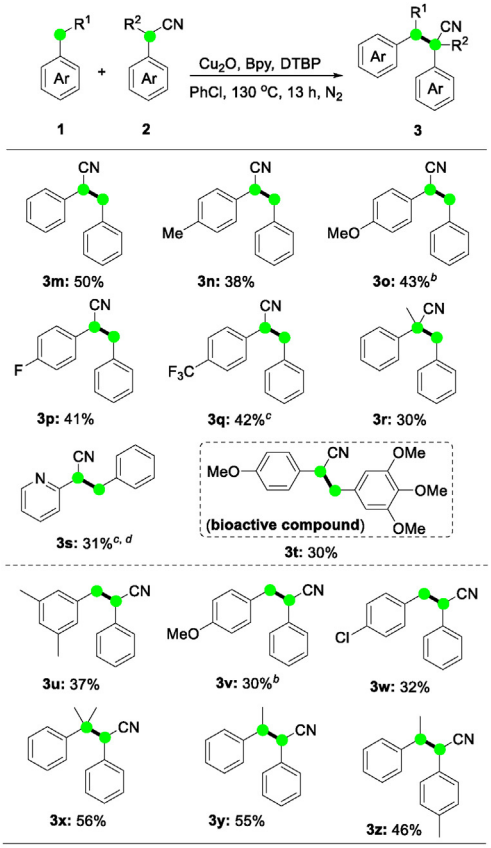
Unless otherwise noted, all reactions were carried out in sealed oven-dried Schlenk tubes under N_2. Reagents and solvents were obtained from commercial suppliers and used without purification. Flash column chromatography was performed using 200–300 mesh silica gel. Visualization on TLC was achieved by the use of UV light (254 nm). FULI GC-9790IIequipped with a FID detector was used to analyze the reaction mixtures. ^1H NMR and ^{13}C NMR spectroscopies were recorded on a Bruker AV-II 500 MHz NMR spectrometer (^1H 500 MHz, ^{13}C 125.76 MHz) in $CDCl_3$. The coupling constants *J* are given in Hz. Chemical shifts for ^1H NMR are referred to internal Me_4Si (0 ppm). GC-MS was conducted on a Shimadzu GCMS-QP2010 plus equipped with an EI ion source. The high-resolution mass spectrum (HRMS) was recorded on a G2-XSQTOF instrument.

4.2. Typical procedure for preparation of targeted molecules

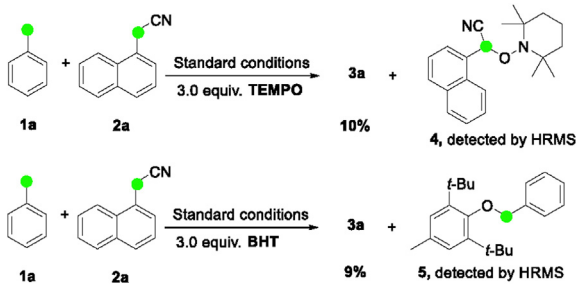
Under N_2, a mixture of arylacetonitrile **2** (0.4 mmol), **1** (4.0 mL), Cu_2O (10 mmol%), Bpy (20 mmol%) and DTBP (3.0 equiv.) in PhCl (2.0 mL) was stirred at 130 °C for indicated time. After the mixture was cooled down to the room temperature, the mixture was passed through a short silica gel column with EtOAc as eluent. The filtrate was concentrated under reduced pressure and the residue was further purified by column chromatography on silica gel to obtain the product **3**.

Procedure for preparation of $[D_2]$-**2a**: $[D_2]$-**2a** was synthesized according to published procedure. A mixture of 1-naphthyl acetonitrile (1.5 mmol), CD_3OD (2.0 mL) and 40% NaOD/D_2O (0.5 mL) was stirred at 40 °C under N_2. After 24 h, the solvent was distilled off and was replaced by D_2O (0.5 mL), CD_3OD (1.5 mL) and 40% NaOD/D_2O (0.5 mL). After 24 h the exchange was repeated a third time. The base was neutralized by dropwise addition of 20% DCl/D_2O and the mixture was extracted with diethyl ether. After remove of the solvent, the product $[D_2]$-**2a** (97% D) was obtained by flash column chromatography on silica gel.

Table 3
The scope of α-benzylation of arylacetonitriles.[a]



[a]Reaction conditions: a mixture of **1** (4.0 mL), **2a** (0.4 mmol), Cu_2O (10 mmol%), Bpy (20 mmol%) and DTBP (3.0 equiv.) in PhCl (2.0 mL) was stirred at 130 °C for 13 h. Isolated yield. [b]DTBP (4.0 equiv.) was used. [c]DTBP (2.0 equiv.) was used. [d]150 °C, 24 h.

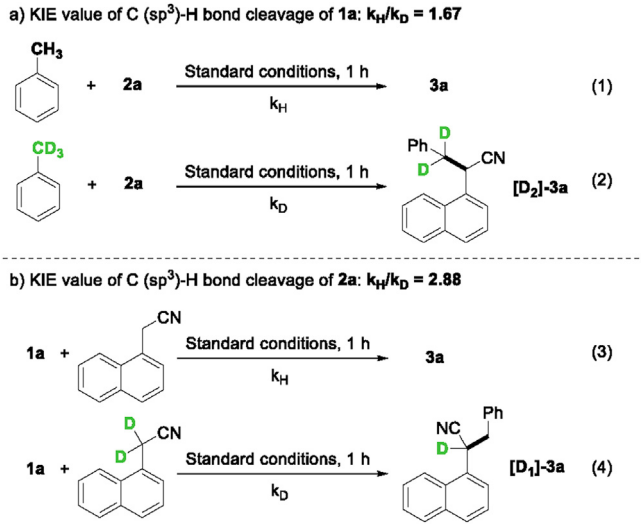


Scheme 2. Radical trapping experiments.

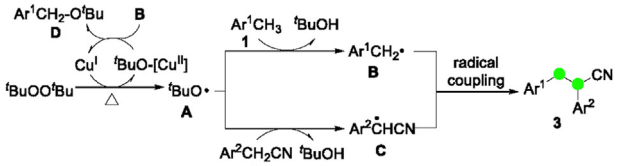
Typical procedure for KIE experiments: Under N_2, a mixture of arylacetonitrile **2a** or [D_2]-**2a** (0.1 mmol), **1a** or [D_3]-**1a** (1.0 mL), Cu_2O (10 mmol%), Bpy (20 mmol%) and DTBP (3.0 equiv.) in PhCl (0.5 mL) was stirred independently at 130 °C for 1 h. After the mixture was cooled down to the room temperature, the mixture was analyzed by GC and GC-MS. The KIE values were obtained based on the average of three parallel reactions.

*4.2.1. 2-(Naphthalen-1-yl)-3-phenylpropanenitrile (**3a**)* [3a]

Light yellow oil, yield 60% (62 mg). Eluent: Petroleum ether/EtOAc = 10/1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88–7.81 (m, 2H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.52–7.43 (m, 3H), 7.37–7.34 (m, 1H), 7.24–7.18 (m, 3H), 7.13–7.11 (m, 2H), 4.67–4.64 (m, 1H), 3.23–3.11 (m, 2H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 136.64, 134.05, 130.90, 129.85, 129.52, 129.25, 129.20, 128.78, 127.57, 127.14, 126.23, 126.00, 125.52, 121.95, 120.72, 40.86, 36.95. GC-MS (EI, 70 eV) *m*/*z* = 257 (M+).



Scheme 3. Kinetic isotope effect experiments.



Scheme 4. Proposed mechanism.

*4.2.2. 3-(3,5-Dimethylphenyl)-2-(naphthalen-1-yl)propanenitrile (**3b**)*

Light yellow oil, yield 67% (77 mg). Eluent: Petroleum ether/EtOAc = 10/1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.5 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.5 Hz, 1H), 7.72–7.67 (m, 2H), 7.63–7.60 (m, 1H), 7.55–7.52 (m, 1H), 6.99 (s, 1H), 6.94 (s, 2H), 4.80–4.77 (m, 1H), 3.31–3.18 (m, 2H), 2.37 (s, 6H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 137.82, 136.16, 133.58, 130.79, 129.40, 128.98, 128.69, 128.63, 126.59, 126.44, 125.70, 125.37, 125.02, 121.51, 120.29, 40.41, 36.55, 20.86. HRMS (ESI^+) Calcd. for $C_{21}H_{19}N$ [M + Na^+]: 308.1410, Found: 308.1349.

*4.2.3. 3-(4-Methoxyphenyl)-2-(naphthalen-1-yl)propanenitrile (**3c**)* [13]

Light yellow oil, yield 34% (39 mg). Eluent: Petroleum ether/EtOAc = 5/1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.56–7.47 (m, 3H), 7.41–7.38 (m, 1H), 7.07–7.04 (m, 2H), 6.79–6.76 (m, 2H), 4.68–4.65 (m, 1H), 2.73 (s, 3H), 3.23–3.10 (m, 2H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 158.98, 134.03, 130.91, 130.27, 129.86, 129.45, 129.07, 128.64, 127.03, 126.13, 126.00, 125.45, 121.92, 120.73, 114.08, 55.29, 40.03, 37.18. GC-MS (EI, 70 eV) *m*/*z* = 287 (M+).

*4.2.4. 3-(4-Fluorophenyl)-2-(naphthalen-1-yl)propanenitrile (**3d**) [14]*

Light yellow oil, yield 43% (48 mg). Eluent: Petroleum ether/EtOAc = 10/1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87–7.84 (m, 2H), 7.77 (d, J = 8.0 Hz, 1H), 7.55–7.45 (m, 3H), 7.38–7.35 (m, 1H), 7.06–7.03 (m, 2H), 6.92–6.88 (m, 2H), 4.68–4.66 (m, 1H), 3.25–3.12 (m, 2H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 162.26 (d, $J_{C\text{-}F}$ = 246.0 Hz), 134.05, 132.2 (d, $J_{C\text{-}F}$ = 3.3 Hz), 130.84 (d, $J_{C\text{-}F}$ = 8.0 Hz), 130.47, 129.80, 129.52, 129.24, 127.13, 126.22, 126.09, 125.43, 121.79, 120.46, 115.56 (d, $J_{C\text{-}F}$ = 21.5 Hz), 39.88, 36.84. GC-MS (EI, 70 eV) m/z = 275 (M+).

*4.2.5. 3-(4-chlorophenyl)-2-(naphthalen-1-yl)propanenitrile (**3e**)*

Colorless oil, yield 41% (48 mg). Eluent: Petroleum ether/EtOAc = 10/1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88–7.86 (m, 2H), 7.79 (d, J = 8.0 Hz, 1H), 7.56–7.53 (m, 1H), 7.51–7.45 (m, 2H), 7.40–7.37 (m, 1H), 7.21–7.18 (m, 2H), 7.03–7.01 (m, 2H), 4.70–4.68 (m, 1H), 3.26–3.13 (m, 2H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 134.83, 134.05, 133.50, 130.61, 130.32, 129.75, 129.54, 129.28, 128.83, 127.16, 126.23, 126.12, 125.43, 121.75, 120.32, 39.97, 36.63. HRMS (ESI$^+$) Calcd. for $C_{19}H_{14}ClN$ [M$^+$]: 291.0815, Found: 291.0891.

*4.2.6. 3-(4-Bromophenyl)-2-(naphthalen-1-yl)propanenitrile (**3f**)*

Light yellow oil, yield 36% (49 mg). Eluent: Petroleum ether/EtOAc = 10/1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88–7.85 (m, 2H), 7.78 (d, J = 8.5 Hz, 1H), 7.56–7.53 (m, 1H), 7.50–7.45 (m, 2H), 7.39–7.34 (m, 3H), 6.97–6.94 (m, 2H), 4.70–4.67 (m, 1H), 3.24–3.11 (m, 2H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 135.34, 134.05, 131.79, 131.19, 130.97, 130.29, 129.74, 129.55, 129.30, 127.18, 126.24, 126.12, 125.44, 121.74, 120.31, 40.02, 36.55. HRMS (ESI$^+$) Calcd. for $C_{19}H_{14}BrN$ [M$^+$]: 335.0310, Found: 335.0373.

*4.2.7. 3-(4-Acetylphenyl)-2-(naphthalen-1-yl)propanenitrile (**3g**)*

Light yellow oil, yield 49% (59 mg). Eluent: Petroleum ether/EtOAc = 10/1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92–7.86 (m, 4H), 7.79 (d, J = 8.0 Hz, 1H), 7.57–7.54 (m, 1H), 7.51–7.46 (m, 2H), 7.39–7.36 (m, 1H), 7.18–7.16 (m, 2H), 4.75–4.73 (m, 1H), 3.84 (s, 3H), 3.35–3.23 (m, 2H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 166.82, 141.53, 134.05, 130.25, 129.96, 129.73, 129.55, 129.42, 129.33, 129.33, 127.20, 126.25, 126.12, 125.43, 121.73, 120.22, 52.17, 40.52, 36.36. HRMS (ESI$^+$) Calcd. for $C_{21}H_{17}NO$ [M$^+$]: 299.1310, Found: 299.1378.

*4.2.8. Methyl 4-(2-cyano-2-(naphthalen-1-yl)ethyl)benzoate (**3h**)*

Light yellow oil, yield 31% (40 mg). Eluent: Petroleum ether/EtOAc = 5/1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99–7.94 (m, 4H), 7.87 (d, J = 8.0 Hz, 1H), 7.65–7.61 (m, 1H), 7.58–7.53 (m, 2H), 7.46–7.43 (m, 1H), 7.25–7.24 (m, 2H), 4.83–4.80 (m, 1H), 3.92 (s, 3H), 3.42–3.30 (m, 2H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 166.82, 141.53, 134.06, 130.25, 129.97, 129.74, 129.56, 129.43, 129.33, 127.20, 126.26, 126.12, 125.44, 121.73, 120.23, 52.18, 40.53, 36.37. HRMS (ESI$^+$) Calcd. for $C_{21}H_{17}NO_2$ [M$^+$]: 315.1259, Found: 315.0269.

*4.2.9. 2-(Naphthalen-1-yl)-3-phenylbutanenitrile (**3i**)*

Colorless oil, yield 71% (77 mg). Eluent: Petroleum ether/EtOAc = 10/1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97–7.86 (m, 2H), 7.87 (d, J = 8.5 Hz, 1H), 7.73 (d, J = 7.0 Hz, 1H), 7.64–7.61 (m, 1H), 7.58–7.54 (m, 1H), 7.52–7.49 (m, 1H), 7.45–7.37 (m, 4H), 7.33–7.29 (m, 1H), 4.83 (d, J = 4.5 Hz, 1H), 3.45–3.40 (m, 1H), 1.46 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 142.91, 134.13, 130.58, 129.99, 129.49, 129.14, 128.93, 127.57, 127.15, 127.01, 126.71, 126.10, 125.29, 122.15, 119.73, 42.96, 42.66, 16.45. HRMS (ESI$^+$) Calcd. for $C_{20}H_{17}N$ [M$^+$]: 271.1361, Found: 271.1432.

*4.2.10. 2-(Naphthalen-1-yl)-3,3-diphenylpropanenitrile (**3j**)*

Light yellow oil, yield 46% (62 mg). Eluent: Petroleum ether/EtOAc = 10/1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97–7.92 (m, 2H), 7.83 (d, J = 8.4 Hz, 1H), 7.61–7.54 (m, 2H), 7.38–7.22 (m, 10H), 7.13–7.11 (m, 2H), 5.39 (d, J = 6.0 Hz, 1H), 4.69 (d, J = 6.0 Hz, 1H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 140.68, 139.36, 133.99, 130.10, 129.52, 129.31, 129.17, 128.77, 128.40, 127.94, 127.63, 127.46, 127.31, 127.08, 126.07, 125.15, 122.03, 120.17, 54.14, 39.67. HRMS (ESI$^+$) Calcd. for $C_{25}H_{19}N$ [M + Na$^+$]: 356.1410, Found: 356.1379.

*4.2.11. 3-Methyl-2-(naphthalen-1-yl)-3-phenylbutanenitrile (**3k**)*

Light yellow oil, yield 75% (86 mg). Eluent: Petroleum ether/EtOAc = 10/1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86–7.81 (m, 2H), 7.73 (d, J = 8.0 Hz, 1H), 7.46–7.39 (m, 3H), 7.34–7.29 (m, 3H), 7.26–7.22 (m, 3H), 4.85 (s, 1H), 1.61 (m, 3H), 1.50 (s, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 144.23, 133.57, 131.69, 129.34, 129.12, 129.04, 128.59, 128.17, 127.10, 126.80, 126.34, 125.60, 124.77, 122.67, 120.92, 42.66, 27.05, 26.03. HRMS (ESI$^+$) Calcd. for $C_{21}H_{19}N$ [M + Na$^+$]: 308.1410, Found: 308.1503.

*4.2.12. 2,3-Di(naphthalen-1-yl)propanenitrile (**3l**) [4c]*

White solid, yield 36% (45 mg). Eluent: Petroleum ether/EtOAc = 10/1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98–7.86 (m, 5H), 7.82–7.78 (m, 1H), 7.67–7.65 (m, 1H), 7.58–7.47 (m, 5H), 7.43–7.38 (m, 2H), 4.92–4.89 (m, 1H), 3.83–3.77 (m, 2H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 134.05, 133.97, 132.53, 131.54, 131.50, 130.18, 129.38, 129.24, 129.21, 128.33, 127.89, 126.98, 126.48, 126.18, 126.05, 125.82, 125.54, 125.51, 122.70, 122.09, 120.81, 37.93, 35.55. GC-MS (EI, 70 eV) m/z = 307 (M+).

*4.2.13. 2,3-Diphenylpropanenitrile (**3m**) [13]*

Colorless oil, yield 50% (42 mg). Eluent: Petroleum ether = 10/1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.26 (m, 8H), 7.16–7.14 (m, 2H), 4.02–3.99 (m, 1H), 3.23–3.12 (m, 2H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 136.29, 135.23, 129.24, 129.04, 128.65, 128.23, 127.51, 127.41, 120.39, 42.22, 39.83. GC-MS (EI, 70 eV) m/z = 207 (M+).

*4.2.14. 3-Phenyl-2-(p-tolyl)propanenitrile (**3n**) [15]*

White solid, yield 38% (34 mg). Petroleum ether/EtOAc = 10/1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24–7.18 (m, 3H), 7.10–7.06 (m, 6H), 3.90–3.87 (m, 1H), 3.12–3.01 (m, 2H), 2.27 (s, 3H). ^{13}C NMR (125.76 MHz $CDCl_3$): δ 138.04, 136.45, 132.25, 129.69, 129.24, 128.63, 127.36, 120.57, 42.26, 39.47, 21.11. GC-MS (EI, 70 eV) m/z = 221 (M$^+$).

*4.2.15. 2-(4-Methoxyphenyl)-3-phenylpropanenitrile (**3o**) [13]*

White solid, yield 43% (41 mg). Eluent: Petroleum ether/EtOAc = 5/1. ^{1}H NMR (500 MHz $CDCl_3$): δ 7.31–7.37 (m, 3H), 7.18–7.12 (m, 4H), 6.89–6.86 (m, 2H), 3.96–3.93 (m, 1H), 3.81 (s, 3H), 3.19–3.08 (m, 2H). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 159.41, 136.38, 129.25, 128.64, 128.61, 127.33, 127.20, 120.64, 114.35, 55.35, 42.30, 39.00. GC-MS (EI, 70 eV) m/z = 237 (M$^+$).

*4.2.16. 2-(4-Fluorophenyl)-3-phenylpropanenitrile (**3p**) [15]*

White solid, yield 41% (37 mg). Eluent: Petroleum ether/EtOAc = 10/1. ^{1}H NMR (500 MHz $CDCl_3$): δ 7.32–7.27 (m, 3H), 7.22–7.18 (m, 2H), 7.11–7.10 (m, 2H), 7.06–7.01 (m, 2H), 4.01–4.00 (m, 1H), 3.21–3.09 (m, 2H). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 162.46 (d, $J_{C\text{-}F}$ = 247.5 Hz), 135.92, 130.93 (d, $J_{C\text{-}F}$ = 3.4 Hz), 129.26 (d, $J_{C\text{-}F}$ = 8.17 Hz), 129.25, 128.69, 127.50, 120.22, 116.0 (d, $J_{C\text{-}F}$ = 21.9 Hz), 42.19, 39.01. GC-MS (EI, 70 eV) m/z = 225 (M$^+$).

*4.2.17. 3-Phenyl-2-(4-(trifluoromethyl)phenyl)propanenitrile (**3q**) [8c]*

Colorless oil, yield 42% (47 mg). Eluent: Petroleum ether/EtOAc = 10/1. ^{1}H NMR (500 MHz $CDCl_3$): δ 7.63–7.61 (m, 2H), 7.38–7.37 (m, 2H), 7.33–7.27 (m, 3H), 7.13–7.11 (m, 2H), 4.10–4.07 (m, 1H), 3.25–3.13 (m, 2H). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 139.06,

135.56, 130.65 (d, J_{C-F} = 32.7 Hz), 129.21, 128.79, 128.03, 127.68, 126.08–125.99 (m), 123.80(d, J_{C-F} = 272.0 Hz), 119.62, 41.94, 39.57. GC-MS (EI, 70 eV) m/z = 275 (M^+).

*4.2.18. 2-Methyl-2,3-diphenylpropanenitrile (**3r**)* [3a]

Light yellow oil, yield 30% (27 mg). Eluent: Petroleum ether/EtOAc = 10/1. ^{1}H NMR (500 MHz $CDCl_3$): δ 7.31–7.21 (m, 5H), 7.17–7.12 (m, 3H), 6.95–6.94 (m, 2H), 3.09–3.02 (m, 2H), 1.67 (s, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 139.69, 135.11, 130.37, 128.78, 128.15, 127.93, 127.38, 125.93, 123.18, 48.57, 43.54, 26.03. GC-MS (EI, 70 eV) m/z = 221 (M^+).

*4.2.19. 3-Phenyl-2-(pyridin-2-yl)propanenitrile (**3s**)* [15]

White solid, yield 31% (26 mg). Eluent: Petroleum ether/EtOAc = 10/1. ^{1}H NMR (500 MHz $CDCl_3$): δ 8.65–8.63 (m, 1H), 7.69–7.65 (m, 1H), 7.31–7.24 (m, 5H), 7.18–7.15 (m, 2H), 4.23–4.20 (m, 1H), 3.39–3.24 (m, 2H). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 154.48, 149.96, 137.23, 136.26, 129.22, 128.66, 127.39, 123.11, 122.20, 119.62, 42.04, 40.09. GC-MS (EI, 70 eV) m/z = 208 (M^+).

*4.2.20. 2-(4-Methoxyphenyl)-3-(3,4,5-trimethoxyphenyl) propanenitrile (**3t**)* [11]

Light yellow solid, yield 30% (40 mg). Eluent: Petroleum ether/EtOAc = 5/1. ^{1}H NMR (500 MHz $CDCl_3$): δ 7.06 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 6.40 (s, 2H), 3.91–3.79 (m, 13H), 3.16–3.04 (m, 2H). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 157.90, 152.43, 136.69, 129.67, 129.35, 127.21, 119.44, 112.96, 103.60, 59.89, 55.18, 54.26, 40.34, 39.19. GC-MS (EI, 70 eV) m/z = 327 (M^+).

*4.2.21. 3-(3,5-Dimethylphenyl)-2-phenylpropanenitrile (**3u**)*

Light yellow oil, yield 37% (35 mg). Eluent: Petroleum ether/EtOAc = 10/1. ^{1}H NMR (500 MHz $CDCl_3$): δ 7.39–7.28 (m, 5H), 6.91 (s, 1H), 6.78 (s, 2H), 3.99–3.96 (m, 1H), 3.13–3.03 (m, 2H), 2.82 (s, 6H). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 138.16, 136.28, 135.57, 129.00, 128.17, 127.47, 126.96, 120.49, 42.23, 39.95, 21.24. HRMS (ESI^+) Calcd. for $C_{17}H_{17}N$ [M^+]: 235.1361, Found: 235.1362.

*4.2.22. 3-(4-Methoxyphenyl)-2-phenylpropanenitrile (**3v**)* [13]

Colorless oil, yield 30% (29 mg). Eluent: Petroleum ether/EtOAc = 5/1. ^{1}H NMR (500 MHz $CDCl_3$): δ 7.37–7.30 (m, 3H), 7.26–7.24 (m, 2H), 7.05–7.03 (m, 2H), 6.84–6.81 (m, 2H), 3.97–3.94 (m, 1H), 3.79 (s, 3H), 3.16–3.06 (m, 2H). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 158.88, 135.26, 130.31, 129.00, 128.32, 128.16, 127.53, 120.49, 114.00, 55.25, 41.42, 40.09. GC-MS (EI, 70 eV) m/z = 237 (M^+).

*4.2.23. 3-(4-Chlorophenyl)-2-phenylpropanenitrile (**3w**)* [15]

White solid, yield 33% (32 mg). Eluent: Petroleum ether/EtOAc = 10/1. ^{1}H NMR (500 MHz $CDCl_3$): δ 7.38–7.31 (m, 3H), 7.27–7.22 (m, 4H), 7.05–7.03 (m, 2H), 4.00–3.97 (m, 1H), 3.18–3.10 (m, 2H). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 134.75, 134.57, 133.41, 130.63, 129.11, 128.79, 128.37, 127.48, 120.07, 41.43, 39.58. GC-MS (EI, 70 eV) m/z = 241 (M^+).

*4.2.24. 3-Methyl-2,3-diphenylbutanenitrile (**3x**)*

White solid, yield 56% (53 mg). Eluent: Petroleum ether = 10/1. ^{1}H NMR (500 MHz $CDCl_3$): δ7.30–7.25 (m, 3H), 7.24–7.17 (m, 5H), 6.92–6.89 (m, 2H), 3.97 (s, 1H), 1.57 (s, 3H), 1.44 (s, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 144.18, 132.80, 129.40, 128.23, 128.04, 127.96, 127.02, 126.58, 120.11, 50.76, 41.75, 26.82, 25.19. HRMS (ESI^+) Calcd. for $C_{17}H_{17}N$ [M^+]: 249.1154, Found: 235.1391.

*4.2.25. 2,3-Diphenylbutanenitrile (**3y**) [16]*

White solid, yield 55% (49 mg). Eluent: Petroleum ether/EtOAc = 10/1. ^{1}H NMR (500 MHz $CDCl_3$): δ 7.31–7.26 (m, 6H), 7.12–7.10 (m, 4H), 3.95 (d, J = 7.5 Hz, 1H), 3.27–3.21 (m, 1H), 1.38 (d, J = 7.5 Hz, 3H); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 140.99, 134.21, 128.68, 128.44, 128.24, 128.14, 127.81, 127.48, 119.94, 45.54, 44.87, 18.84. GC-MS (EI, 70 eV) m/z = 221 (M^+).

*4.2.26. 3-Phenyl-2-(p-tolyl)butanenitrile (**3z**)*

Colourless oil, yield 46% (44 mg). Eluent: Petroleum ether/EtOAc = 10/1. ^{1}H NMR (500 MHz $CDCl_3$): δ 7.30–7.26 (m, 2H), 7.24–7.22 (m, 1H), 7.18–7.16 (m, 2H), 7.11–7.06 (m, 4H), 3.93 (d, J = 6.5 Hz, 1H), 3.20–7.14 (m, 1H), 2.31 (s, 3H), 1.45 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 142.05, 137.79, 131.69, 129.40, 128.59, 127.82, 127.48, 127.30, 119.84, 45.55, 45.07, 21.06, 17.26. GC-MS (EI, 70 eV) m/z = 235 (M^+).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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References

[1] (a) F.F. Fleming, L. Yao, P.C. Ravikumar, L. Funk, B.C. Shook, J. Med. Chem. 53 (2010) 7902–7917;
(b) F.F. Fleming, Nat. Prod. Rep. 16 (1999) 597–606;
(c) R.C. Larock, Comprehensive Organic Transformations, VCH, New York, 1989, pp. 819–995;
(d) P. Pollak, G. Romeder, F. Hagedorn, H.-P. Gelbke, Nitriles, in: Ullmannis Encyclopedia of Industrial Chemistry, Wiley-VCH, Weinheim, 2012, pp. 252–265;
(e) J. Xiao, Q. Li, T. Chen, L.-B. Han, Tetrahedron Lett. 56 (2015) 5937–5940.
[2] (a) R. Ljpez, C. Palomo, Angew. Chem. Int. Ed. 54 (2015) 13170–13184;
(b) N. Kurono, T. Ohkuma, ACS Catal. 6 (2016) 989–1023;
(c) J.T. Yu, F. Teng, J. Cheng, Adv. Synth. Catal. 359 (2017) 26–38.
[3] (a) J. Xiao, J. Yang, T. Chen, L.-B. Han, Adv. Synth. Catal. 358 (2016) 816–819;
(b) K. Motokura, D. Nishimura, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, J. Am. Chem. Soc. 126 (2004) 5662–5663.
[4] (a) C. Ivanov, P. Markov, M. Arnaudov, Chem. Ber. 100 (1967) 690–691;
(b) F.F. Fleming, W. Liu, S. Ghosh, O.W. Steward, J. Org. Chem. 73 (2008) 2803–2810;
(c) S. Shoichi, S. Takashi, S. Seiji, S. Yasuyuki, H. Choichiro, Adv. Synth. Catal. 344 (2002) 370–378;
(d) M. Barbasiewicz, K. Marciniak, M. Fedorynski, Tetrahedron Lett. 47 (2006) 3871–3874.
[5] (a) B.C. Roy, S. Debnath, K. Chakrabarti, B. Paul, M. Maji, S. Kundu, Org. Chem. Front. 5 (2018) 1008–1018;
(b) S. Thiyagarajan, C. Gunanathan, ACS Catal. 7 (2017) 5483–5490;
(c) H.W. Cheung, J. Li, W. Zheng, Z. Zhou, Y.H. Chiu, Z. Lin, C.P. Lau, Dalton Trans. 39 (2010) 265–274;
(d) K. Motokura, N. Fujita, K. Mori, T. Mizugaki, K. Ebitani, K.K. Jitsukawa Kaneda, Chem. Eur. J. 12 (2006) 8228–8239;
(e) S. Burling, B.M. Paine, D. Nama, V.S. Brown, M.F. Mahon, T.J. Prior, P.S. Pregosin, M.K. Whittlesey, J.M.J. Williams, J. Am. Chem. Soc. 129 (2007) 1987–1995.
[6] M.L. Buil, M.A. Esteruelas, J. Herrero, S. Izquierdo, I.M. Pastor, M. Yus, ACS Catal. 3 (2013) 2072–2075.
[7] (a) J. Li, Y. Liu, W. Tang, D. Xue, C. Li, J. Xiao, C. Wang, Chem. Eur. J. 23 (2017) 14445–14449;
(b) F. Li, X. Zou, N. Wang, Adv. Synth. Catal. 357 (2015) 1405–1415;
(c) R. Grigg, T.R.B. Mitchell, S. Sutthivaiyakit, N. Tongpenyai, Tetrahedron Lett. 22 (1981) 4107–4110.
[8] (a) B. Anxionnat, D.G. Pardo, G. Ricci, J. Cossy, Org. Lett. 13 (2011) 4084–4087;

(b) S. Takuya, O. Yasushi, Chem. Lett. 40 (2011) 1055–1057;
(c) C. Lçfberg, R. Grigg, M.A. Whittaker, A. Keep, A. Derrick, J. Org. Chem. 71 (2006) 8023–8027;
(d) B. Anxionnat, D. Gomez Pardo, G. Ricci, J. Cossy, Eur. J. Org. Chem. (2012) 4453–4456.
[9] A. Corma, T. Rjdenas, M.J. Sabater, J. Catal. 279 (2011) 319–327.
[10] (a) F.-L. Zhang, K. Hong, T.-J. Li, H. Park, J.-Q. Yu, Science 351 (2016) 252–256;
(b) J. Zhang, Y. Li, F. Zhang, C. Hu, Y. Chen, Angew. Chem. Int. Ed. 55 (2016) 1872–1875;
(c) S. Tang, P. Wang, H. Li, A. Lei, Nat. Commun. 7 (2016) 11676;
(d) D. Liu, C. Liu, H. Li, A. Lei, Angew. Chem. Int. Ed. 52 (2013) 4453–4456;
(e) S.-Y. Zhang, F.-M. Zhang, Y.-Q. Tu, Chem. Soc. Rev. 40 (2011) 1937–1949;
(f) S.A. Girard, T. Knauber, C.-J. Li, Angew. Chem. Int. Ed. 53 (2014) 74–100;
(g) M.C. White, Science 335 (2012) 807–809;
(h) A.P. Antonchick, L. Burgmann, Angew. Chem. Int. Ed. 52 (2013) 3267–3271;
(i) K. Li, Q. Wu, J. Lan, J. You, Nat. Commun. 6 (2015) 8404;
(j) Z. Chen, M.-Y. Rong, J. Nie, X.-F. Zhu, B.-F. Shi, J.-A. Ma, Chem. Soc. Rev. 48 (2019) 4921–4942;
(k) Y.-N. Meng, Q.-Q. Kang, T.-T. Cao, S.-Z. Song, G.-P. Ge, Q. Li, W.-T. Wei, ACS Sustain. Chem. Eng. 7 (2019) 18738–18743;
(l) Z. Chen, M.-Y. Rong, J. Nie, X.-F. Zhu, B.-F. Shi, J.-A. Ma, Chem. Soc. Rev. 48 (2019) 4921–4942;
(m) S. Moghimi, M. Mahdavi, A. Shafiee, A. Foroumadi, Eur. J. Org. Chem. (2016) 3282–3299;
(n) C. Zhang, C. Tang, N. Jiao, Chem. Soc. Rev. 41 (2012) 3464–3484;
(o) C.-J. Li, Acc. Chem. Res. 42 (2009) 335–344.
[11] M. Cushman, D. Nagarathnam, D. Gopal, H.-M. He, C.M. Lin, E. Hamel, J. Med. Chem. 35 (1992) 2293–2306.
[12] (a) H.-T. Zeng, J.-M. Huang, Org. Lett. 17 (2015) 4276–4279;
(b) X.-Q. Chu, X.-P. Xu, H. Meng, S.-J. Ji, RSC Adv. 5 (2015) 67829–67832.
[13] A. Jana, C.B. Reddy, B. Maji, ACS Catal. 8 (2018) 9226–9231.
[14] W. Zhang, F. Wang, S.D. McCann, D. Wang, P. Chen, S.S. Stahl, G. Liu, Science 353 (2016) 1014–1018.
[15] B.C. Roy, I.A. Ansari, S.A. Samim, S. Kundu, Chem. Asian J. 14 (2019) 2215–2219.
[16] W.J. Chambers, W.R. Brasen, C.R. Hauser, J. Am. Chem. Soc. 79 (1957) 879–881.