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PAPER

C–H functionalization of tertiary amines by cross dehydrogenative coupling reactions: solvent-free synthesis of α-aminonitriles and β-nitroamines under aerobic condition†

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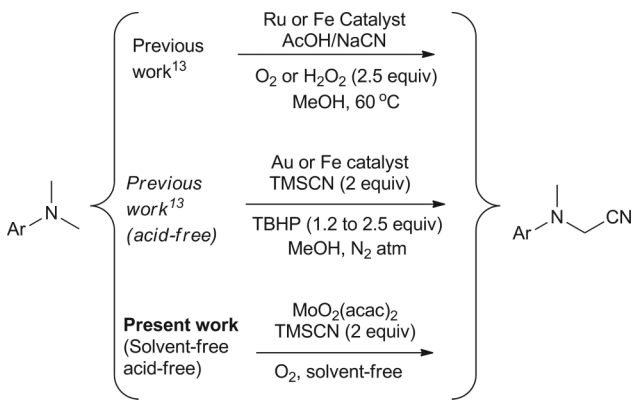
A solvent-free synthesis of α-aminonitriles and β-nitroamines by oxidative cross-dehydrogenative coupling under aerobic condition is reported. A catalytic amount of molybdenum(VI) acetylacetonoate was found to catalyze cyanation of tertiary amines to form α-aminonitriles, whereas vanadium pentoxide was found to promote aza-Henry reaction to furnish β-nitroamines. Both of these environmentally benign reactions are performed in the absence of solvents using molecular oxygen as an oxidant.

Introduction

The functionalization of C–H bonds by oxidative cross dehydrogenative coupling (CDC) methods is a fast emerging area with wide applications.[1] Generally, CDC reactions are accomplished by a variety of conditions using transition metal catalysts.[2–5] The prospect of using unfunctionalized precursors to construct C–C bonds is one of the greatest advantages of CDC methods over traditional methods.[6] Further, the selectivity and simplicity shown by these methods started showing promises in their application in synthesizing complex natural products.[1a,7] Hence, user-friendly protocols by adopting environmentally benign strategies, particularly solvent-free reaction,[8] play an important role in developing economically viable methods. Additionally, synthesis of bifunctional molecules such as α-aminonitriles[9] and β-nitroamines[10] is beneficial as these molecules can be easily transformed to a variety of functional groups.[9–10]

The occurrence of nitrogen functionalities in biological systems, which are commercially important molecules, is one of the major motifs for the development of a variety of methods to synthesize such molecules.[11] In this context, direct incorporation of nitrogen functionalities in near proximity, for example at either α- or β-position to an amino functionality, requires a multi-step operation.[9] Functionalization of tertiary amines to synthesize bifunctional molecules such as α- or β-amino derivatives is an useful strategy as it provide access to valuable products,[9–10] which can be easily transformed to a variety of intermediates such as amino acids, α-amino carbonyl compounds, α-amino alcohols or vicinal diamines which find applications in catalysis and asymmetric synthesis.[12,13b] Hence, there is a surge in the literature to develop methods to accomplish α- or β-amino derivatives of tertiary amines.[13–14] In continuation of our efforts to design methodologies under environmentally benign conditions,[15] we undertook an investigation of C–H functionalization of tertiary amines by oxidative CDC reactions under aerobic conditions. For this purpose, we employed TMSCN (trimethylsilyl cyanide) and nitroalkanes as nucleophiles to functionalize tertiary amines to accomplish bifunctional molecules such as α-aminonitriles and β-nitroamines as presented in this paper (Scheme1).



Scheme 1 Cyanation of tertiary amines.

The application of CDC methods to synthesize α-aminonitriles was first demonstrated by Murahashi and co-workers by reacting tertiary amines with ruthenium catalyst along with NaCN, H_2O_2 and large excess of AcOH at 60 °C, [13a–c] whereas Han and Ofial[13d] reported synthesis of α-aminonitriles by employing Cu or Fe catalyst along with TBHP (*tert*-butyl hydroperoxide) as oxidant[13d,e] and TMSCN as the cyanide source under inert atmosphere. Additional examples of synthesizing α-aminonitrile by CDC methods employed a variety of catalysts such as vanadium,[13f]

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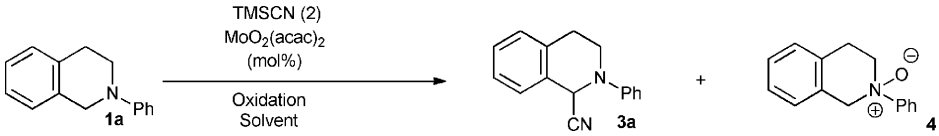
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and NMR spectra for all products. See DOI: 10.1039/c1ob06466e

Table 1 Optimization of reaction conditions



Entry	Catalyst (mol%)	**2** (equiv)	Oxidant (equiv)	Solvent	T/°C	t/h	Yield **3a**[a] (%)	Yield **4**[a] (%)
1	5	2	H_2O_2 (2)	MeOH	rt	28	—	99
2	5	2	H_2O_2 (2)	MeOH	50	12	—	99
3	10	2	TBHP (2)	none	rt	15	34	66
4	10	2	TBHP (2)	none	50	15	12	88
5	10	2	TBHP (2)	MeOH	rt	15	50	50
6	10	2	TBHP (2)	MeOH	50	15	40	60
7	10	2	O_2	MeOH	60	12	77	23
8	10	3	O_2	MeOH	60	14	79	21
9	10	2	O_2	EtOAc	75	24	24	—
10	10	2	O_2	THF	60	24	32	—
11	10	2	O_2	$CHCl_3$	60	24	12	—
12	10	2	O_2	CH_3CN	80	24	83	—
13	10	2	O_2	Toluene	100	22	93	—
14	**10**	**2**	**O_2**	**none**	**80**	**17**	**96**	**—**
15	10	2.5	O_2	none	80	17	93	—
16	10	1.2	O_2	none	80	24	66	—
17	none	2	O_2	none	80	24	trace	—

[a] NMR conversion based on tertiary amine; TBHP (5–6 M solution in decane), H_2O_2 (50% aqueous solution).

iron phthalocyanine,[13g] *etc.*, as the catalyst. Recently, Hari and Konig[13h] reported cyanation of tertiary amines catalyzed by eosin Y under visible light. Further, most of these methods employ metal cyanides along with excess of peroxides[13b,d,e,g] and acid additives[13a–c,f,g] and use organic solvents as the reaction media[13] or utilize TMSCN with excess of TBHP (in decane) under anhydrous conditions[13d,e] (Scheme 1). Utility of acid additives limit the use of these methods in the presence of acid sensitive groups. Additionally, the main focus of most of these methods is functionalization of *N*,*N*-dimethylaniline, whereas functionalization of *N*-aryltetrahydroisoquinolines are not addressed in greater detail.[13] Therefore, there is great scope to address functionalization of tertiary amines, particularly *N*-aryl tetrahydroisoquinolines, under environmentally benign conditions.

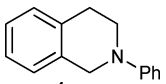
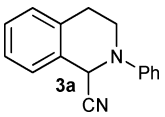
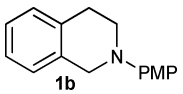
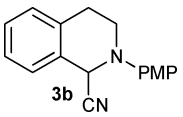
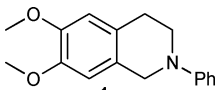
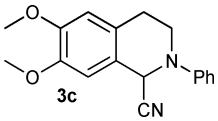
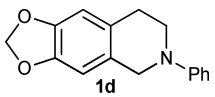
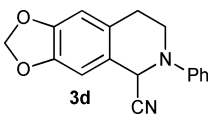
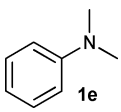
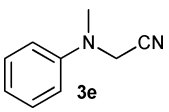
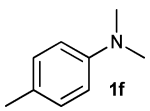
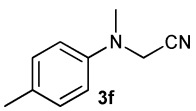
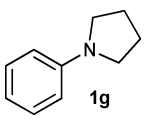
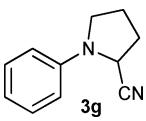
Results and discussions

Cyanation of tertiary amines

The optimization studies for C–H functionalization were initiated by using *N*-phenyl tetrahydroisoquinoline (**1a**) as tertiary amine and TMSCN (**2**) as cyanide source along with $MoO_2(acac)_2$ in MeOH. As depicted in Table 1, reaction of **1a**, and **2** (2 equiv) with $MoO_2(acac)_2$ (5 mol%) using H_2O_2 (2 equiv, 50% aqueous solution) as oxidant was performed in MeOH. This reaction did not furnish the desired product either at room temperature or at 50 °C, but produced quantitative yield of corresponding *N*-oxide **4** as the sole product (Table 1, entries 1 and 2). Varying the oxidant to TBHP and performing the reaction either at room temperature or at 50 °C, with or without solvent, furnished the mixture of products **3a** and **4**, with **4** in major amount (Table 1, entries 3–6). Using molecular oxygen as the oxidant and performing the reaction in MeOH resulted in the formation of desired product **3a** as the major product along with a minor amount of *N*-oxide **4** (Table 1, entries 7 and 8). Although, the reaction in solvents such as EtOAc, THF or $CHCl_3$ resulted in the formation of **3a** as the sole product, the yields were poor (Table 1, entries 9–11). Interestingly, varying solvent of the reaction to CH_3CN or toluene brought a remarkable change, and furnished **3a** as the sole product in good yields (Table 1, entries 12 and 13). Ultimately, the optimal reaction condition was reached by heating the reaction mixture of **1a**, $MoO_2(acac)_2$ (10 mol%), TMSCN (2 equiv), at 80 °C in molecular oxygen (1 atm) under solvent-free condition to yield the desired product **3a** in excellent yield (96%, Table 1, entry 14). However, varying the amount of TMSCN and performing the coupling reaction did not result in improving the yields (Table 1, entries 15–16). Notably, there was no reaction in the absence of catalyst (Table 1, entry 17).

To generalize the reaction, a variety of tertiary amines were reacted with TMSCN (**2**) using the optimal reaction conditions, and the results are presented in Table 2. *N*-Phenyltetrahydroisoquinoline (**1a**) underwent a smooth reaction with **2** and $MoO_2(acac)_2$ (10 mol%), in oxygen atmosphere to furnish the product **3a** in excellent yield (96%, Table 2, entry 1). *p*-Methoxyphenyl (PMP)-protected tetrahydroisoquinoline (**1b**) underwent a smooth reaction with **2** to afford the product **3b** in quantitative yield (Table 2, entry 2). Further, *N*-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**1c**) and heliotropin derived *N*-phenyltetrahydroisoquinoline (**1d**) was found to react well under the optimized condition to produce **3c** and **3d** in almost quantitative yields (Table 2, entries 3 and 4). Acyclic tertiary amines are also good precursor for this reaction, as *N*, *N*-dimethyl aniline (**1e**) and 4-methyl-*N*,*N*-dimethyl aniline (**1f**) with **2** afforded **3e** and **3f** in good to moderate yields, respectively (Table 2,

Table 2 CDC reaction of tertiary amine and TMSCN catalyzed by $MoO_2(acac)_2$–O_2[a]

Entry	Amine	Product	Yield (%)[b,c]
1	 1a	 3a	96 (80)
2	 1b	 3b	99 (82)
3	 1c	 3c	98 (82)
4	 1d	 3d	98 (86)
5	 1e	 3e	82 (70)[d]
6	 1f	 3f	52 (48)[d]
7	 1g	 3g	(50)[d]

[a] Reaction conditions: **1a** (0.5 mmol), **2** (1 mmol), $MoO_2(acac)_2$, (10 mol%), O_2 (1 atm), 80 °C, 17 h. [b] NMR conversion based on tertiary amine. [c] Isolated yields. [d] Reaction at 100 °C.

entries 5 and 6). Further, *N*-phenylpyrrolidine (**1g**) underwent coupling with **2** to furnish **3g** in moderate yield (50%, Table 2, entry 7).

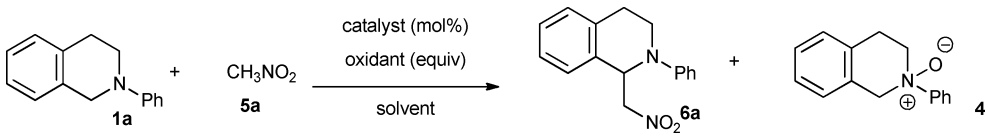
CDC reaction of tertiary amines with nitroalkanes

After successful oxidative cyanation of tertiary amines, we turned our attention to CDC reaction of tertiary amines with nitroalkanes.[14] The direct coupling between nitroalkanes with *N*-aryltetrahydroisoquinolines was first reported by Li and Li by using CuBr/TBHP (in decane) system with large excess of nitroalkanes.[14a] Further, utility of Ru,[14b] Pt,[14c] Ir,[14d] Fe[14e] or DDQ[14f] (stoichiometric amount) catalysts for coupling of nitroalkanes with *N*-aryltetrahydroisoquinolines are documented. Inspired by the work of Li and Li,[14g] and continuation of our observation on the reaction of tertiary amines with TMSCN, we undertook an investigation on CDC reaction of *N*-aryltetrahydroisoquinolines with nitroalkanes to accomplish β-nitroamines.

We started screening the reaction conditions and reagents with the intention of developing an environmentally benign protocol. Hence, we began our studies by employing *N*-phenyltetrahydroisoquinoline (**1a**) and nitromethane (**5a**) as model substrates with catalytic amount of $MoO_2(acac)_2$ using environmentally benign oxidants such as H_2O_2, TBHP or molecular oxygen. Reactions of **1a** and **5a** (2 equiv) with $MoO_2(acac)_2$ (10 mol%) using H_2O_2, or TBHP as terminal oxidants in solvent methanol either at room temperature or at 50 °C resulted in the formation of a mixture of β-nitroamine **6a** (as the major product) with the corresponding *N*-oxide **4** in minor amount (Table 3, entries 1–3). Our attempts to obtain **6a** exclusively by increasing the amount of nitromethane (**5a**) to 5 equiv, either at room temperature or at elevated temperature, also resulted in the formation of mixture of **6a** and **4** (Table 3, entries 4 and 5). Interestingly, $MoO_2(acac)_2$ (10 mol%) catalyzed reaction of **1a** with **5a** in methanol in oxygen (1 atm) resulted in the formation of **6a** exclusively, but in lower yield (Table 3, entry 6). Further exploration revealed that MoO_3/TBHP combination in MeOH is not helpful, as the reaction furnished a mixture of **6a** and **4** (Table 3, entries 7 and 8). However, MoO_3 catalyzed reaction with **1a** in MeOH resulted in the formation of **6a** as the only product in 30% (Table 3, entry 9). Nevertheless, changing the catalyst to V_2O_5 brought a striking change in the outcome of the reactions, which produced the desired product **6a** in excellent yields (90–91%, Table 3, entries 10–12). Hence, reaction of **1a** and **5a** with V_2O_5 (5 mol%) in molecular oxygen (1 atm) proceeded well either in MeOH or in water at 60 °C to furnish **6a** exclusively in excellent yields (24 h, 90%, Table 3, entries 10–11). It is noteworthy that the reaction in water or methanol required only 2 equiv of **5a** (entries 10–11). For our delight, the reaction of **1a** with **5a** in catalytic amount of V_2O_5 (5 mol%) in solvent-free condition furnished **6a** in excellent yield (90%, Table 3, entry 12). On the other hand, it was observed that the reaction of **1a** with **5a** in the absence of catalyst also proceeded in oxygen atmosphere to produce **6a** in low yield (20%, Table 3, entry 13). The aza-Henry reaction of **1a** catalyzed by V_2O_5 (5 mol%) needed only 2 equivalents of **5a** in water to furnish the product **6a** in excellent yield (90%, 24 h, entry 11, Table 3), whereas the same reaction in solvent-free condition required 5 equivalents of **5a** (90%, 24h, entry 12, Table 3). As solvent-free reactions are advantageous, we continued further exploration by employing solvent-free condition. It is important to recognize that most of the CDC reactions of tertiary amines employ a large excess of nitroalkanes,[14a–b,d–f] whereas we used only 5 equivalents of nitroalkanes.

With this input, further experiments of tertiary amines with nitroalkanes (5 equiv) were performed in solvent-free conditions with a catalytic amount of V_2O_5 (5 mol%) in molecular oxygen (1 atm) at 60 °C for 24 h. A variety of *N*-aryltetrahydroisoquinolines were reacted with nitromethane (**5a**) and nitroethane (**5b**). *N*-Phenyltetrahydroisoquinoline (**1a**) reacted well with nitromethane (**5a**) to furnish β-nitroamine **6a** in 90%[16] (Table 4, entry 1). Reaction of *p*-methoxyphenyl (PMP)-protected tetrahydroisoquinoline (**1b**) proceeded well with **5a** to furnish **6b** in quantitative yield (Table 4, entry 2). Nitromethane **5a** reacted well with *N*-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**1c**) and heliotropin derived *N*-phenyltetrahydroisoquinoline (**1d**) to furnish the expected products **6c** and **6d** in good yields (90% and 89% respectively, Table 4, entries 3–4). Further, it was found that *N*-aryl-tetrahydroisoquinoline derivatives **1a–d**, reacted well with nitroethane (**5b**) to furnish the desired product as mixture of

Table 3 Optimization of reaction conditions

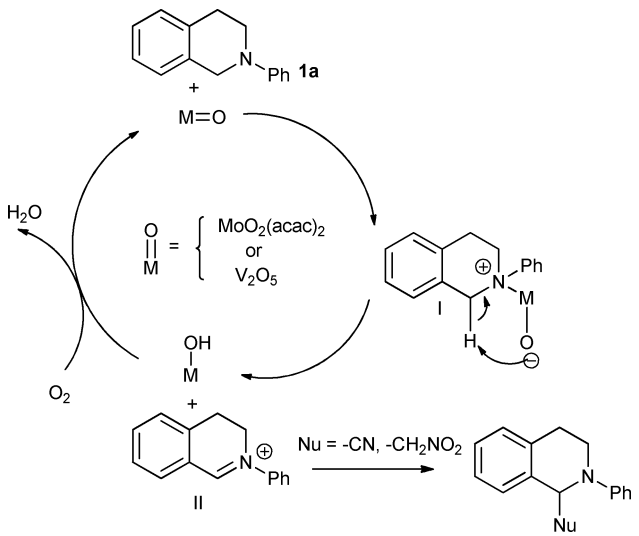


Entry	Catalyst (mol%)	**5a** (equiv)	Oxidant (equiv)	Solvent	T/°C	t/h	Yield (%) **6a**[a] (%)	Yield (%) **4**[a] (%)
1	$MoO_2(acac)_2$ (10)	2	H_2O_2 (2)	MeOH	rt	10	53	47
2	$MnO_2(acac)_2$ (10)	2	TBHP (2)	MeOH	rt	10	75	25
3	$MnO_2(acac)_2$ (10)	2	TBHP (2)	MeOH	50	10	73	27
4	$MnO_2(acac)_2$ (10)	5	TBHP (2)	None	rt	10	69	31
5	$MnO_2(acac)_2$ (10)	5	TBHP (2)	None	50	10	57	43
6	$MnO_2(acac)_2$ (10)	2	O_2	MeOH	60	24	32	—
7	MoO_3(10)	2	TBHP (2)	None	rt	24	40	60
8	MoO_3(10)	2	TBHP (2)	MeOH	rt	24	60	40
9	MoO_3(10)	2	O_2	MeOH	60	24	30	—
10	V_2O_5 (5)	2	O_2	MeOH	60	24	91	—
11	V_2O_5 (5)	2	O_2	H_2O	60	24	90	—
12	**V_2O_5 (5)**	**5**	**O_2**	**None**	**60**	**24**	**90**	**—**
13	None	5	O_2	None	60	24	20	—

[a] NMR conversion based on tertiary amine; TBHP (5–6 M solution in decane); H_2O_2 (50% aqueous solution).

diastereomers (around 2 : 1 ratios) in good to excellent yields (Table 4, entries 5–8). The reaction of 4-methyl-*N*,*N*-dimethylaniline (**1f**) with nitromethane (**5a**) under the standard reaction condition resulted in the formation of desired product **6i** in 30% yield along with inseparable complex mixture (Table 4, entry 9).

The mechanism of these reactions is not clear at this point of time. The catalytic CDC reaction of **1a** with $MoO_2(acac)_2$ or V_2O_5 using TMSCN or CH_3NO_2 as nucleophiles were carried out in the presence of radical scavenger BHT (2,6-bis(1,1-dimethylethyl)-4-methylphenol)[17] to find out that both the reactions proceeded for completion, thereby eliminating the radical pathway. As *N*-oxide is formed in the reactions of **1a** with TMSCN or CH_3NO_2 under standard reaction conditions, we subjected *N*-oxide for CDC reactions under standard reaction conditions with molybdenum or vanadium catalysts. However, these reactions did not produce the desired products even after prolonged reaction time. Based on this information, a tentative mechanism is presented in Scheme 2, which involves coordination of a metal species with tertiary amine **1a** to give I, which forms iminium ion intermediate II. Then II reacts with either TMSCN or nitroalkane to furnish the corresponding products **3a** or **6a**.



Scheme 2 Plausible mechanism for CDC reaction of tertiary amine.

Conclusions

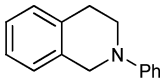
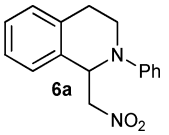
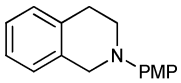
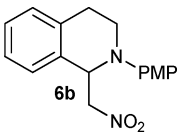
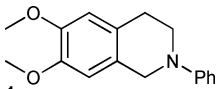
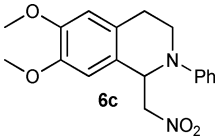
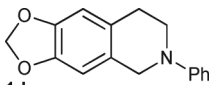
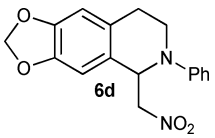
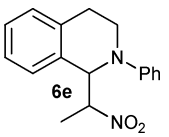
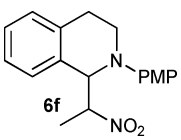
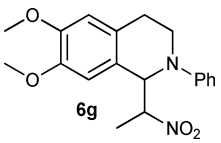
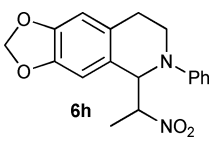
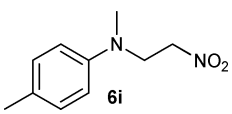
In conclusion, we have demonstrated environmentally benign CDC reactions to accomplish α-aminonitriles and β-nitroamines in user-friendly methods. The present methods employ molecular oxygen as the terminal oxidant, and the reactions are performed under solvent-free conditions. One of the salient features of the present CDC method is that the reaction is performed in acid-free and solvent-free conditions. We believe that the simplicity offered by the present methods to accomplish bifunctional molecule such as α-aminonitriles or β-nitroamines makes the methodology more useful and attractive. Application of this methodology for the synthesis of natural products and mechanistic study are presently pursued in our laboratories.

Experimental

Typical experimental procedure for the synthesis of α-aminonitrile

To 10 mol% of $MoO_2(acac)_2$ (0.05 mmol) and *N*-phenyltetrahydroisoquinoline (0.5 mmol) was added TMSCN (1.0 mmol). The reaction mixture was stirred at 80 °C under oxygen atmosphere (oxygen balloon) for 17 h. The reaction mixture was cooled to room temperature, added saturated $NaHCO_3$ solution and extracted with DCM (3 × 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on

Table 4 CDC reaction of tertiary amine and nitroalkane catalyzed by V_2O_5–O_2[a]

Entry	Amine	Nitroalkane	Product	Yield (%)[b,c]
1	 **1a**	CH_3NO_2 **5a**	 **6a**	90 (76)
2	 **1b**	**5a**	 **6b**	99 (82)[d]
3	 **1c**	**5a**	 **6c**	90 (78)
4	 **1d**	**5a**	 **6d**	89 (79)[e]
5	**1a**	 **5b**	 **6e**	86 (65)[e]
6	**1b**	**5b**	 **6f**	99 (70)[d,e]
7	**1c**	**5b**	 **6g**	85 (71)[f]
8	**1d**	**5b**	 **6h**	86 (70)[f]
9	**1f**	**5a**	 **6i**	(30)

[a] Reaction conditions: **1a** (0.5 mmol), **5a** or **5b** (2.5 mmol), V_2O_5 (5 mol%), O_2 (1 atm), 60 °C, 24 h. [b] NMR conversion based on tertiary amine. [c] Isolated yields. [d] Reaction has completed in 16 h. [e] 2 : 1 mixture of diastereomers. [f] 1.8 : 1 mixture of diastereomers.

silicagel using hexane/ethyl acetate (95 : 5) and furnished a pale yellow solid (78%, NMR conversion = 96%).

Characterization data for *α*-aminonitriles

Compound (3a)[13a]. Pale yellow solid; yield: 80%; mp: 99–101 °C (lit.[13a] 101–102 °C); R_f (20% EtOAc/hexane) 0.7; prepared as shown in general experimental procedure. IR (KBr, cm^{-1}): 2824, 2222, 1595, 1496, 1452, 1374, 1273, 1205, 1141, 1027, 936, 888, 745; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.32 (2H, m), 7.31– 7.26 (3H, m), 7.23 (1H, d, J = 7.2 Hz), 7.08 (2H, d, J = 7.8 Hz), 7.01 (1H, t, J = 7.3 Hz), 5.50 (1H, s), 3.76 (1H, dddd, J = 12.4, 5.9, 3.0 and 1.0 Hz), 3.48 (1H, ddd, J = 14.8, 10.7 and 4.0 Hz), 3.19–3.11 (1H,

m), 2.96 (1H, dt, J_1 = 3.5 Hz, J_2 = 16.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.3, 134.6, 129.6, 129.5, 129.3, 128.7, 127.0, 126.8, 121.8, 117.7, 117.6, 53.2, 44.2, 28.5; MS (*m/z*): 234 (M^+); elemental analysis: calcd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96%; found C, 81.64; H, 6.50; N, 11.88%.

Compound (3b)[13d]. Pale yellow solid; yield: 82%; mp: 107–108 °C; R_f (20% EtOAc/hexane) 0.5; prepared as shown in general experimental procedure. IR (KBr, cm^{-1}): 2937, 2222, 1615, 1505, 1260, 1206, 1031, 888, 733; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.21 (4H, m), 7.08 (2H, d, J = 8.9 Hz), 6.91 (2H, d, J = 8.9 Hz), 5.36 (1H, s), 3.79 (3H, s), 3.57 (1H, dd, J_1 = 6.0 Hz, J_2 = 12.0 Hz), 3.43 (1H, td, J_1 = 3.9 Hz, J_2 = 11.7 Hz), 3.19–3.11 (1H, m), 2.94–2.90 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 142.5, 134.3, 129.7, 129.4, 128.6, 127.0, 126.6, 120.9, 117.6, 114.7, 55.51, 55.5, 44.9, 28.6; MS (*m/z*): 264 (M^+); elemental analysis: calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60%; found: C, 77.39; H, 5.92; N, 10.87%.

Compound (3c). Pale yellow solid; yield 82%; mp: 111–114 °C; R_f (30% EtOAc/hexane) 0.3; prepared as shown in general experimental procedure. IR (KBr, cm^{-1}): 2933, 2219, 1605, 1506, 1270, 1215, 1025, 856, 761; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (2H, t, J = 8 Hz), 7.09–7.06 (2H, m), 7.03–6.99 (1H, m), 6.75 (1H, s), 6.68 (1H, s), 5.44 (1H, s), 3.88 (6H, s), 3.79–3.74 (1H, m), 3.44 (1H, td, J_1 = 4.0 Hz, J_2 = 11.4 Hz), 3.12–3.03 (1H, m), 2.84 (1H, dt, J_1 = 3.2 Hz, J_2 = 16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.3, 148.4, 148.0, 129.5, 126.8, 121.8, 121.1, 117.8, 117.7, 111.5, 109.3, 56.0, 55.9, 53.0, 44.1, 28.0; MS (*m/z*): 294 (M^+); elemental analysis: calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52%; found C, 73.18; H, 6.46; N, 9.23%.

Compound (3d). Pale yellow solid; yield 86%; mp: 154–156 °C; R_f (20% EtOAc/hexane) 0.6; prepared as shown in general experimental procedure. IR (KBr, cm^{-1}): 2919, 2213, 1598, 1504, 1234, 1190, 1037, 948, 838, 755; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (2H, t, J = 7.9 Hz), 7.07–7.00 (3H, m), 6.72 (1H, s), 6.66 (1H, s), 5.96 (2H, s), 5.38 (1H, s), 3.75–3.70 (1H, m), 3.43 (1H, td, J_1 = 4.0 Hz, J_2 = 11.3 Hz), 3.09–3.01 (1H, m), 2.86–2.82 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2, 148.1, 146.6, 129.5, 128.3, 122.1, 121.9, 117.7, 117.5, 108.8, 106.6, 101.3, 53.2, 44.1, 28.5; MS (*m/z*): 278 (M^+); elemental analysis: calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07%; found C, 73.39; H, 5.29; N, 9.70%.

Compound (3e)[13d]. Pale yellow liquid; yield 70%; R_f (20% EtOAc/hexane) 0.5; prepared as shown in general experimental procedure. IR (Neat, cm^{-1}): 2927, 2237, 1600, 1499, 1343, 1246, 1201, 1118, 1033, 999, 868, 755; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.29 (2H, m), 6.91 (1H, t, J = 7.3 Hz), 6.87 (2H, d, J = 8.3 Hz), 4.16 (2H, s), 3.00 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 129.4, 120.2, 115.4, 114.8, 42.2, 39.2; MS (*m/z*): 146 (M^+).

Compound (3f)[13d]. Pale yellow liquid; yield 48%; R_f (10% EtOAc/hexane) 0.4; prepared as shown in general experimental procedure. IR (Neat, cm^{-1}): 2923, 2236, 1618, 1518, 1341, 1245, 1194, 1115, 1039, 997, 868, 808; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (2H, d, J = 8.2 Hz), 6.78 (2H, d, J = 8.6 Hz), 4.10 (2H, s), 2.94 (3H, s), 2.28 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.6, 129.9, 129.7, 115.4, 115.3, 42.7, 39.4, 20.3; MS (*m/z*): 160 (M^+); elemental analysis: calcd for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55; N, 17.48%; found C, 74.99; H, 7.41; N, 17.04%.

Compound (3g)[13d]. Pale yellow liquid; yield 50%; R_f (10% EtOAc/hexane) 0.3; prepared as shown in general experimental procedure. IR (Neat, cm^{-1}): 2854, 2230, 1600, 1502, 1360, 1255, 1186, 1157, 749, 691; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.28 (2H, m), 6.83 (1H, t, J = 7.3 Hz), 6.69 (2H, d, J = 8.2 Hz), 4.46–4.43 (1H, m), 3.48–3.44 (1H, m), 3.39–3.33 (1H, m), 2.44–2.16 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.1, 129.3, 119.2, 118.0, 112.6, 48.9, 47.3, 31.4, 23.8; MS (*m/z*): 172 (M^+); HRESI-MS (*m/z*): Calculated for $C_{11}H_{12}N_2$ (M + H): 173.1079, found (M + H): 173.1077.

Compound (4). Pale yellow solid; yield 99%; mp: 150–152 °C; R_f (20% EtOAc/hexane) 0.6; prepared as shown in general experimental procedure. IR (KBr, cm^{-1}): 3424, 2925, 1597, 1489, 1352, 1269, 1115, 1055, 968, 753; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99–7.97 (2H, m), 7.48–7.46 (2H, m), 7.44– 7.38 (1H, m), 7.29–7.22 (3H, m), 7.09–7.04 (1H, m), 5.05 (1H, d, J = 15.2 Hz), 4.57 (1H, d, J = 15.2 Hz), 4.17–4.10 (1H, m), 3.81–3.73 (1H, m), 3.68–3.63 (1H, m), 2.84 (1H, dt, J_1 = 4.5 Hz, J_2 = 16.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 131.2, 130.0, 129.1, 128.9, 128.5, 127.4, 126.7, 126.3, 120.5, 65.5, 28.4, 26.2; HRESI-MS (*m/z*): Calculated for $C_{15}H_{15}NO$ (M + Na): 248.1051, found (M + Na): 248.1044.

Typical experimental procedure for the synthesis of β-nitroamines

To the 5 mol% of V_2O_5 (0.025 mmol) and *N*-phenyltetrahydroisoquinoline (0.5 mmol) was added nitromethane (2.5 mmol). The reaction mixture was stirred at 60 °C under oxygen atmosphere (oxygen balloon) for 24 h. The reaction mixture was cooled to room temperature, added saturated $NaHCO_3$ solution and extracted with DCM (3 × 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (95 : 5) and furnished pale yellow solid (76%, NMR conversion = 90%).

Characterization data for β-nitroamines

Compound (6a)[14a]. Pale yellow solid; yield 76%; mp: 90–92 °C (lit.[14a] 89–90 °C); R_f (20% EtOAc/hexane) 0.5; prepared as shown in general experimental procedure. IR (KBr, cm^{-1}): 2917, 1598, 1550, 1378, 1217, 1031, 750; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27–7.14 (5H, m), 7.10 (1H, d, J = 7.3 Hz), 6.95 (2H, d, J = 8.5 Hz), 6.82 (1H, t, J = 7.3 Hz), 5.52 (1H, t, J = 7.2 Hz), 4.82 (1H, dd, J_1 = 7.8 Hz, J_2 = 11.8 Hz), 4.51 (1H, dd, J_1 = 6.6 Hz, J_2 = 11.8 Hz), 3.66–3.54 (2H, m), 3.09–3.01 (1H, m), 2.75 (1H, dt, J_1 = 4.9 Hz, J_2 = 16.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4, 135.2, 132.8, 129.4, 129.1, 128.0, 126.9, 126.6, 119.3, 115.0, 78.7, 58.1, 42.0, 26.3; MS (*m/z*): 268 (M^+); elemental analysis: calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44%; found C, 71.57; H, 5.93; N, 10.31%.

Compound (6b)[14a]. Pale yellow solid; yield 82%; mp: 100–102 °C (lit.[13j] 102–105 °C); R_f (20% EtOAc/hexane) 0.5; prepared as shown in general experimental procedure. IR (KBr, cm^{-1}): 2932, 1548, 1512, 1246, 1183, 1035, 948, 826, 753; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25–7.20 (2H, m), 7.17–7.12 (2H, m), 6.91 (2H, d, J = 9.0 Hz), 6.81 (2H, d, J = 9.0 Hz), 5.38 (1H, dd, J_1 = 6.0 Hz, J_2 = 8.4 Hz), 4.82 (1H, dd, J_1 = 8.6 Hz, J_2 = 11.9 Hz), 4.55 (1H, dd, J_1 = 5.8 Hz, J_2 = 11.9 Hz), 3.74 (3H, s), 3.57–3.54 (2H, m), 3.05–2.97 (1H, m), 2.69 (1H, dt, J_1 = 4.0 Hz, J_2 = 16.5 Hz); ^{13}C NMR (100

MHz, $CDCl_3$): δ 154.0, 143.0, 135.4, 132.9, 129.4, 127.9, 126.9, 126.6, 118.9, 114.7, 78.9, 58.9, 55.6, 43.1, 25.8; MS (*m/z*): 298 (M^+); elemental analysis: calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39%; found C, 68.42; H, 6.30; N, 9.19%.

Compound (6c)[14a]. Pale yellow solid; yield 78%; mp: 118–120 °C; R_f (30% EtOAc/hexane) 0.5; prepared as shown in general experimental procedure. IR (KBr, cm^{-1}): 2932, 1599, 1544, 1264, 1247, 1110, 1031, 988, 852, 752; ^1H NMR (400 MHz, $CDCl_3$): δ 7.28–7.24 (2H, m), 6.96 (2H, d, J = 8.3 Hz), 6.84 (1H, t, J = 7.3 Hz), 6.64 (1H, s), 6.60 (1H, s), 5.45 (1H, t, J = 7.0 Hz), 4.84 (1H, dd, J_1 = 8.0 Hz, J_2 = 11.8 Hz), 4.55 (1H, dd, J_1 = 6.4 Hz, J_2 = 11.8 Hz), 3.85 (3H, s), 3.84 (3H, s), 3.70–3.64 (1H, m), 3.60–3.53 (1H, m), 3.03–2.95 (1H, m), 2.67 (1H, dt, J_1 = 4.5 Hz, J_2 = 16.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.8, 148.6, 147.7, 129.4, 127.4, 124.5, 119.5, 115.5, 111.7, 109.6, 78.7, 57.9, 56.0, 55.9, 42.0, 25.8; MS (*m/z*): 328 (M^+); elemental analysis: calcd for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53%; found C, 65.71; H, 6.28; N, 8.71%.

Compound (6d). Pale yellow solid; yield 79%; mp: 121–123 °C; R_f (20% EtOAc/hexane) 0.5; prepared as shown in general experimental procedure. IR (KBr, cm^{-1}): 2901, 1598, 1548, 1487, 1382, 1233, 1040, 942, 756; ^1H NMR (400 MHz, $CDCl_3$): δ 7.28–7.24 (2H, m), 6.94 (2H, d, J = 8.3 Hz), 6.84 (1H, t, J = 7.3 Hz), 6.62 (1H, s), 6.59 (1H, s), 5.91 (2H, s), 5.40 (1H, t, J = 7.2 Hz), 4.81 (1H, dd, J_1 = 7.8 Hz, J_2 = 11.8 Hz), 4.50 (1H, dd, J_1 = 6.6 Hz, J_2 = 11.8 Hz), 3.62–3.51 (2H, m), 2.99–2.91 (1H, m), 2.66 (1H, dt, J_1 = 5.0 Hz, J_2 = 16.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4, 147.4, 146.3, 129.4, 128.8, 125.7, 119.5, 115.2, 108.9, 106.9, 101.1, 78.7, 58.1, 42.1, 26.4; MS (*m/z*): 312 (M^+); elemental analysis: calcd for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97%; found C, 65.36; H, 5.29; N, 9.04%.

Compound (6e)[14a]. Pale yellow liquid; yield 65%; R_f (20% EtOAc/hexane) 0.6; prepared as shown in general experimental procedure. IR (Neat, cm^{-1}): 2921, 1598, 1549, 1503, 1388, 1358, 1233, 1117, 948, 750; ^1H NMR (400 MHz, $CDCl_3$, 2 : 1 mixture of diastereoisomers): δ 7.29–7.08 (6H, m), 7.01–6.97 (2H, m), 6.83–6.79 (1H, m), 5.26–5.21 (1H, m), 5.07–4.84 (1H, m), 3.86–3.50 (2H, m), 3.08–3.00 (1H, m), 2.93–2.83 (1H, m), 1.69 (1H, d, J = 6.8 Hz), 1.53 (2H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 2 : 1 mixture of diastereoisomers): δ 149.1, 148.8, 135.6, 134.7, 133.8, 132.0, 129.4, 129.3, 129.1, 128.7, 128.3, 128.2, 127.2, 126.5, 126.1, 119.3, 118.7, 115.4, 114.4, 88.9, 85.4, 62.7, 61.1, 43.5, 42.6, 26.7, 26.3, 17.4, 16.3; MS (*m/z*): 282 (M^+); elemental analysis: calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92%; found C, 72.08; H, 6.36; N, 10.20%.

Compound (6f)[14a]. Pale yellow liquid; yield 70; R_f (20% EtOAc/hexane) 0.6; prepared as shown in general experimental procedure. IR (Neat, cm^{-1}): 2925, 1643, 1549, 1512, 1358, 1246, 1100, 949, 755; ^1H NMR (400 MHz, $CDCl_3$, 2 : 1 mixture of diastereoisomers): δ 7.24–7.09 (4H, m), 6.92–6.90 (2H, m), 6.83–6.77 (2H, m), 5.07–4.82 (2H, m), 3.77–3.71 (4H, m), 3.52–3.47 (1H, m), 3.01–2.93 (1H, m), 2.84–2.75 (1H, m), 1.67 (1H, d, J = 6.8 Hz), 1.52 (2H, d, J = 5.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 2 : 1 mixture of diastereoisomers): δ 153.8, 153.5, 143.5, 135.8, 135.0, 133.6, 132.0, 129.2, 128.9, 128.3, 128.0, 127.9, 127.2, 126.5, 126.0, 118.85, 118.82, 118.2, 114.7, 114.5, 88.8, 85.7, 63.4, 62.1, 55.6, 55.5, 45.0, 45.0, 26.2, 26.0, 17.1, 16.5; MS (*m/z*): 312 (M^+); elemental analysis: calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97%; found C, 69.00; H, 6.11; N, 8.47%.

Compound (6g). Pale yellow liquid; yield 71%; R_f (30% EtOAc/hexane) 0.6; prepared as shown in general experimental procedure. IR (Neat, cm^{-1}): 2927, 1599, 1550, 1518, 1389, 1357, 1259, 1112, 1033, 867, 750; ^1H NMR (400 MHz, $CDCl_3$, 1.8 : 1 mixture of diastereoisomers): δ 7.28–7.21 (2H, m), 6.98 (2H, t, J = 8.7 Hz), 6.81 (1H, t, J = 7.2 Hz), 6.64–6.49 (2H, m), 5.17–5.11 (1H, m), 5.07–4.87 (1H, m), 3.86–3.75 (6H, m), 3.64–3.46 (1H, m), 3.00–2.92 (1H, m), 2.82–2.68 (1H, m), 1.69 (1H, d, J = 6.8 Hz), 1.53 (2H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 2 : 1 mixture of diastereoisomers): δ 149.2, 148.9, 148.8, 148.6, 147.3, 147.1, 129.3, 129.2, 127.8, 126.8, 125.5, 123.5, 119.4, 118.9, 115.6, 115.0, 111.53, 111.5, 111.1, 110.2, 88.9, 85.3, 62.4, 60.9, 56.0, 55.9, 55.79, 55.76, 43.3, 42.6, 25.9, 25.8, 17.5, 16.1; MS (*m/z*): 342 (M^+); elemental analysis: calcd for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18%; found C, 66.68; H, 6.71; N, 8.17%.

Compound (6h). Pale yellow liquid; yield 70%; R_f (20% EtOAc/hexane) 0.6; prepared as shown in general experimental procedure. IR (Neat, cm^{-1}): 2903, 1490, 1381, 1241, 1226, 1038, 941, 749; ^1H NMR (400 MHz, $CDCl_3$, 1.8 : 1 mixture of diastereoisomers): δ 7.29–7.21 (2H, m), 6.96 (2H, d, J = 8.1 Hz), 6.84–6.80 (1H, m), 6.61–6.50 (2H, m), 5.93–5.88 (2H, m), 5.13–4.83 (2H, m), 3.80–3.49 (2H, m), 2.97–2.90 (1H, m), 2.81–2.74 (1H, m), 1.68 (1H, d, J = 6.8 Hz), 1.54 (2H, d, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 2 : 1 mixture of diastereoisomers): δ 149.1, 148.9, 147.5, 147.4, 146.1, 145.9, 129.4, 129.3, 129.2, 128.4, 126.7, 124.8, 119.4, 118.9, 115.6, 114.6, 108.9, 108.7, 108.3, 107.6, 101.1, 101.0, 89.0, 85.5, 62.8, 61.1, 43.6, 42.6, 26.7, 26.4, 17.5, 16.5; MS (*m/z*): 326 (M^+); elemental analysis: calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58%; found C, 66.01; H, 6.10; N, 8.24%.

Compound (6i)[14a]. Pale yellow liquid; yield 30%; R_f (10% EtOAc/hexane) 0.35; prepared as shown in general experimental procedure. IR (Neat, cm^{-1}): 2928, 1654, 1546, 1349, 1122, 1020, 805, 743; ^1H NMR (400 MHz, $CDCl_3$): δ 7.08 (2H, d, J = 8.3 Hz), 6.66 (2H, d, J = 8.4 Hz), 4.55 (2H, t, J = 6.3 Hz), 3.96 (2H, t, J = 6.3 Hz), 2.94 (3H, s), 2.26 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.8, 130.0, 127.5, 113.2, 72.6, 51.0, 39.0, 20.2; MS (*m/z*): 194 (M^+); HRESI-MS (*m/z*): Calculated for $C_{10}H_{14}N_2O_2$ (M + H): 195.1134, found (M + H): 195.1133.

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