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Synthesis and characterization of bisoxazolines- and pybox-copper(II) complexes and their application in the coupling of α-carbonyls with functionalized amines†

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Binuclear complexes [{(DMOX)CuCl}$_2$(μ-Cl)$_2$] (**1**), mononuclear complexes [(DMOX)CuBr$_2$] (**2**) (DMOX = 4,5-dihydro-2-(4,5-dihydro-4,4-dimethyloxazol-2-yl)-4,4-dimethyloxazole) and the pybox Cu(II) complex [(Dm-Pybox)CuBr$_2$] (**3**) (Dm-Pybox = 2,6-bis[4′,4′-dimethyloxazolin-2′-yl]pyridine) were obtained by reactions of CuX$_2$ (X = Cl, Br) with DMOX and Dm-Pybox ligands, respectively. The molecular structures of **1**, **2** and **3** have been determined by single-crystal X-ray diffraction analyses. The complexes **2** and **3** are efficient in catalyzing α-amination of ketones and esters through α-bromo carbonyl intermediate. The procedures are environmentally benign methods using molecular oxygen as an oxidant with water as the only byproduct.

Introduction

Bisoxazolines[1] and tridentate *NNN* pybox pincer ligands[2] are important ligands in organometallic chemistry with broad application in homogeneous catalysis and asymmetric synthesis. Typically, these ligands are good σ-donors and weak π-acceptors and can be easily modified to achieve the desired steric, bulkiness- or electronic properties. Furthermore chirality can be endowed using an appropriate commercially available amino alcohol precursor. Over the past two decades, reports about bisoxazolines and pybox transition metal complexes' exceptional catalytic abilities have been published.[3] Owing to our continued interest in Cu complexes due to their superior catalytic activities,[4] we seek to discover new Cu complexes to exploit their chemistry in a variety of potential catalytic applications.[5]

The aromatic unit attached at the α-position of a ketone, ester or amide represents an important structural motif in natural products, pharmaceuticals and organic synthetic intermediates.[6] Thus efforts have not been spared to construct tailored amine substrates at the carbonyl α-position. Recently, Loh and coworkers first discovered a useful α-amination of carbonyl compound reactions;[7] Miura and coworkers described the synthesis of α-amino acid derivatives and ester using copper catalysts;[8] MacMillan and co-workers published a procedure for the preparation of α-amination of ketones, esters, and aldehydes *via* copper catalysis and bidentate nitrogen ligands have shown excellent results.[9] More importantly, these procedures are environmentally benign methods due to the advantages of catalyst regeneration and using molecular oxygen as an oxidant with water as the byproduct.

In this work, we report the synthesis and characterization of three novel Cu(II) complexes with bisoxazolines and tridentate pybox pincer ligands: [{(DMOX)CuCl}(μ-Cl)$_2$] (**1**), [(DMOX)-CuBr$_2$] (**2**) and [(Dm-Pybox)CuBr$_2$] (**3**), and further examine their catalytic ability in direct α-amination of ketones and esters. Our preliminary results suggest that Cu complexes **3** show promising catalytic activity in direct α-amination of ketones and esters with a broad substrate scope. Solid state structures of the Cu complexes **1**, **2** and **3** were also revealed with single crystal X-ray diffraction studies.

Results and discussion

Binuclear [{(DMOX)CuCl}$_2$(μ-Cl)$_2$] (**1**), mononuclear [(DMOX)-CuBr$_2$] (**2**) and pybox Cu complexes [(Dm-Pybox)CuBr$_2$] (**3**)

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Table 1 Crystallographic data and structure refinement parameters for complexes **1**, **2**, **3** and **3a**

	1	2	3	3a
Empirical formula	$C_{20}H_{32}Cl_4Cu_2N_4O_4$	$C_{10}H_{16}Br_2CuN_2O_2$	$C_{15}H_{19}Br_2CuN_3O_2$	$C_{14}H_{19}NO_2$
Formula weight	661.38	419.61	496.69	233.30
Crystal syst., space group	Orthorhombic, *Pbca*	Monoclinic, *P*2(1)/*n*	Monoclinic, *P*2(1)/*n*	Monoclinic, *P*2(1)/*n*
a (Å)	11.6403(9)	10.506(5)	10.5479(7)	14.4443(15)
b (Å)	14.5767(11)	12.627(6)	15.7383(11)	6.1524(6)
c (Å)	16.4463(12)	12.057(5)	11.3501(8)	14.5492(15)
α (°)	90	90	90	90
β (°)	90	115.714(5)	99.8020(10)	98.2260(10)
γ (°)	90	90	90	90
Volume (Å^3), *Z*	2790.6(4), 4	1441.1(11), 4	1856.7(2), 4	1279.6(2), 4
D_c (mg m^{-3})	1.574	1.934	1.777	1.211
μ (Mo-Kα) (mm^{-1})	1.939	7.053	5.491	0.080
F(000)	1352	820	980	504
θ range (°)	2.48–27.69	2.15–27.57	2.23–27.32	2.83–27.43
Limiting indices	−15, 14, −19, 17, −21, 21	−12, 13, −15, 16, −15, 15	−13, 13, −20, 20, −13, 14	−18, 18, −7, 7, −18, 18
Reflections/unique[*R*(int)]	22 830/3261[0.0299]	11 871/3309[0.1099]	15 784/4219 [0.0363]	10 565/2904 [0.0512]
Completeness to *θ* (°)	27.69 (99.8%)	27.57 (98.9%)	27.41 (99.6%)	27.43 (99.5%)
Data/restraints/parameters	3261/0/158	3309/0/154	4219/0/212	2904/0/154
Goodness-of-fit on F^2	1.042	0.933	1.028	0.998
R_1, wR_2 [$I > 2\sigma(I)$][a]	0.0264, 0.0676	0.0581, 0.1252	0.0282, 0.0639	0.0483, 0.1086
R_1, wR_2 (all data)	0.0354, 0.0722	0.1637, 0.1699	0.0446, 0.0702	0.1085, 0.1341
Larg. diff. peak/hole(e Å^{-3})	0.510/−0.301	0.156/−1.037	0.436/−0.421	0.200/−0.151

[a] $R_1 = \sum||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\sum w(|F_o^2| - |F_c^2|)^2/\Sigma w|F_o^2|^2]^{1/2}$.

were obtained by reactions of CuX_2 (X = Cl, Br) with DMOX and Dm-Pybox in MeOH–CH_2Cl_2 solvents at room temperature, respectively. All Cu complexes were characterized by IR and elemental analysis, and are stable toward air and moisture in the solid state. The complexes are moderately soluble in most solvents such as CH_2Cl_2, MeOH, MeCN, DMSO and DMF. Crystals of Cu complexes **1**, **2** and **3** suitable for X-ray crystallographic diffraction were obtained by slow diffusion of diethyl ether into a concentrated solution of the complexes in dichloromethane solution. The crystallographic data for complexes **1**, **2** and **3** are summarized in Table 1, and selected bond lengths and angles are shown in Table S1.†

In complexes **1** and **2**, the DMOX acts as a chelating ligand and coordinates the Cu(II) centers through the nitrogen atoms of oxazoline. As shown in Fig. 1, the crystal structure of **1** consists of binuclear units connected by Cl anions, and each Cu atom is coordinated by two N atoms of the DMOX ligand and three Cl atoms. The Cu(II) metal is five-coordinate and exhibits a distorted trigonal-bipyramidal geometry, with $N_1Cu_1Cl_2$ as the principal axis (N(1)–Cu(1)–Cl(2) bond angle is 171.46(5)°), which is different from the distorted square-pyramidal geometry of [{Cu(DPS)Cl}$_2$(μ-Cl)$_2$] (DPS = di(2-pyridyl)sulfide).[10] The equatorial Cu–Cl bonds (2.2299(6) Å and 2.2660(5) Å) are shorter than the axial (2.6241(6) Å), and stronger than those of the complex [{Cu(bipy)Cl}$_2$(μ-Cl)$_2$] (2.291(3) Å, 2.259(3) Å and 2.267(3) Å).[11] As shown in Fig. 2, the copper atom is located in N_2Br_2 distorted tetrahedral arrangement because of the restricted bite angle of DMOX, in which DMOX adopts a normal chelating coordination mode using its two sp^2 N atoms from the oxazoline fragments. The bond length of N–Cu is 2.031(7)Å and 2.116(6) Å, respectively, which is slightly longer than those observed in the [Cu((*S*,*S*)-*tert*-Bu-box)(OH$_2$)$_2$](OTf)$_2$ (1.921(3)Å and 1.955(3)Å) due to the bulky substituent on the oxazoline group.[12] The average bond length of Cu–Br (2.3732 Å) is shorter than that of the complex [Cu(Bipy) Br_2]

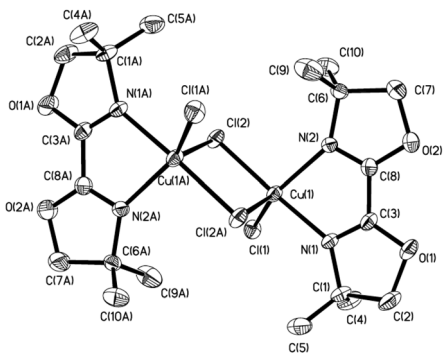


Fig. 1 Molecular structure of **1** with thermal ellipsoids drawn at the 30% level; all hydrogen atoms are omitted for clarity.

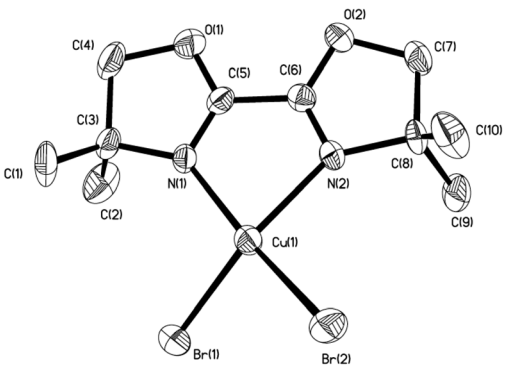


Fig. 2 Molecular structure of **2** with thermal ellipsoids drawn at the 30% level; all hydrogen atoms are omitted for clarity.

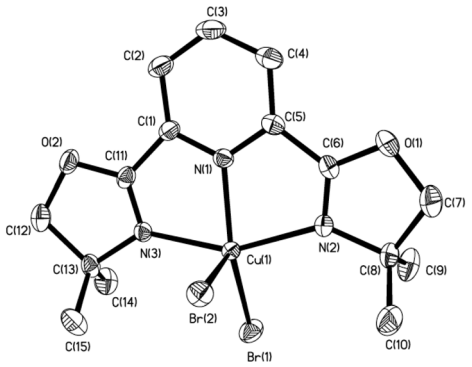


Fig. 3 Molecular structure of **3** with thermal ellipsoids drawn at the 30% level; all hydrogen atoms are omitted for clarity.

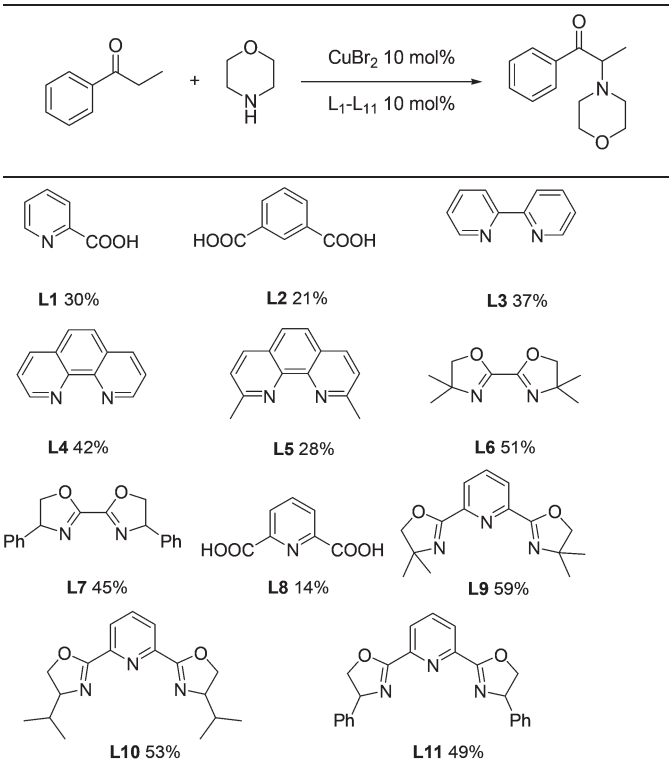
(2.792 Å).[13] The X-ray structure of **3** shows four asymmetric units crystallized in the monoclinic space group $P2_1/n$ (Fig. 3). As expected, the pyridine-based pincer ligand is coordinated to copper in a tridentate fashion by the pyridyl nitrogen and two oxazoline nitrogen atoms. The coordination sphere around the Cu(II) atom is best described as midway between trigonal bipyramidal and square pyramidal in structure.[14] The Cu–N distances (2.001(2), 2.102(2) and 2.071(2) Å) in **3**, which are compatible with a typical single bond length between the copper center and the nitrogen atom reported in the previous literature,[15] can be compared with other Cu complexes containing the 3*N* ligand set.[16]

In order to establish oxazoline and pybox ligand's electronic effect on Cu, the reaction of propiophenone and morpholine was carried out in 10 mol% $CuBr_2$ and screened against a library of ligands **L1–L11** (Table 2). Low yields of 2-morpholino-1-phenylpropan-1-one were observed using bicarboxylic acid and bidentate nitrogen as the ligands (Table 2, **L1–L7**). There is not a big difference in product yields when changing ligand **L1** to **L2** and **L3**. However to our delight, 51% yields of desired products were observed using DMOX as the ligand (Table 2, **L6**). A series of tridentate pincer ligands have been screened on the model reaction (Table 2, **L8–L11**). The best yield amongst all is obtained with the Dm-Pybox (**L9**) (59%) as the ligand. In a control experiment without a ligand, 48% yields of products were obtained.

After ligand screening, we chose Cu complex **3** as the catalyst to test the influence of solvents on reaction yield (Table 3, entries 1–9). To our pleasant surprise, DMSO drastically improved the yield to 95%. However, lower yield was obtained with a lower catalyst loading of 5 mol% **3** and required a longer reaction time of 20 hours (Table 3, entry 7). The yield remains unchanged with 15 mol% of **3** and reaction time shorter than 6 hours (Table 3, entry 8). A control experiment with copper catalyst absent failed to see any reaction (Table 3, entry 11).

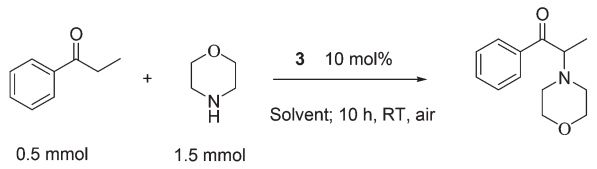
With the best reaction conditions on hand, we started to expand the scope and efficiency of this methodology. A series of α-aminations of carbonyl compounds were obtained in good to excellent yields (Table 4). The morpholines with elec-

Table 2 Ligands tested in the $CuBr_2$-catalyzed α-amination of propiophenone[a,b]



[a] Reaction conditions: $CuBr_2$ (11.2 mg, 0.05 mmol, 0.1 equiv.); **L1–L10** (0.05 mmol, 0.1 equiv.); DMF (0.5 mL); propiophenone (67 μL, 0.5 mmol, 1.0 equiv.); morpholine (130 μL, 1.5 mmol, 3.0 equiv.); 25 °C; 10 hours and under air. [b] Isolated yields.

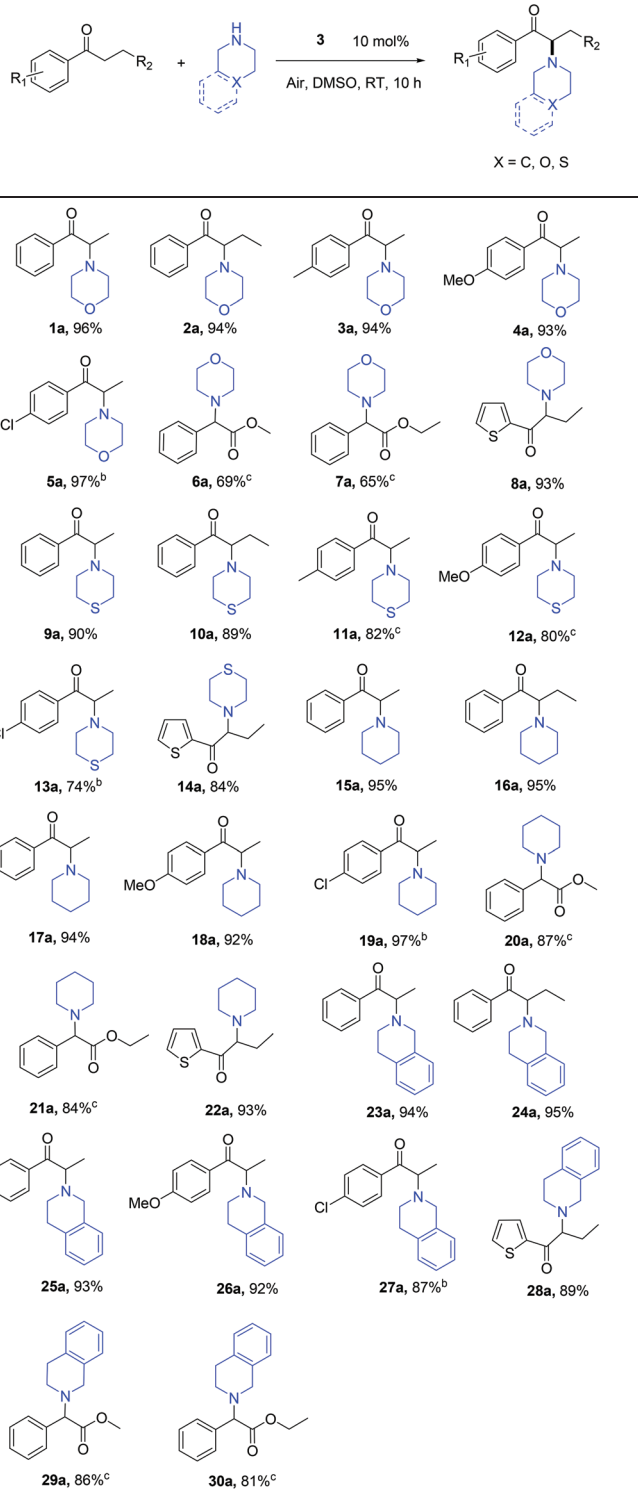
Table 3 Optimized reaction condition screen for the Cu complex catalyzed α-amination of propiophenone[a,b]



Entry	Cu catalyst (10 mol%)	Solvent	Yield[a] (%)
1	**3**	MeCN	31
2	**3**	MeOH	38
3	**3**	THF	40
4	**3**	DMF	59
5	**3**	DMSO	95
6	**3**	DMSO	75[b]
7	**3**	DMSO	81[c]
8	**3**	DMSO	96[d]
9	**1**	DMSO	20
10	**2**	DMSO	94
11		DMSO	NR

[a] Isolated yield. [b] 1 mol% catalyst, reaction time: 40 h. [c] 5 mol% catalyst, reaction time: 20 h. [d] 15 mol% catalyst, reaction time: 6 h.

Table 4 Cu complex catalyzed α-amination of carbonyls[a]



[a] Isolated yield. [b] Reaction was carried out at 10 °C. [c] Reaction was carried out at 50 °C.

tron-withdrawing and electron-donating substituents on the aromatic backbone were investigated to provide the desired products in high yields (Table 4 **3a**, **4a** and **5a**). The configuration of **3a** was determined by X-ray crystallographic analysis (Fig. 4). More specifically, an efficient conversion of electron-deficient ketones was achieved at low temperatures (Table 4 **5a**, **13a**, **19a** and **27a**). Ethyl phenylacetate readily undergoes morpholine, piperidine or 1,2,3,4-tetrahydroisoquinoline incorporation in the presence of catalyst **3** to generate ethyl phenylacetate derivatives (Table 4 **7a**, **21a** and **30a**). The heteroaromatic substrate 2-butyrylthiophene was also transformed well under the standard conditions; for example, 2-morpholino-1-(thiophen-2-yl)butan-1-one (**8a**), 2-thiomorpholino-1-(thiophen-2-yl)butan-1-one (**14a**), 2-(piperidin-1-yl)-1-(thiophen-2-yl)butan-1-one (**22a**) and 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-1-(thiophen-2-yl)butan-1-one (**28a**) were obtained from the corresponding secondary amine in 93%, 84%, 93% and 89% yields, respectively (Table 4).

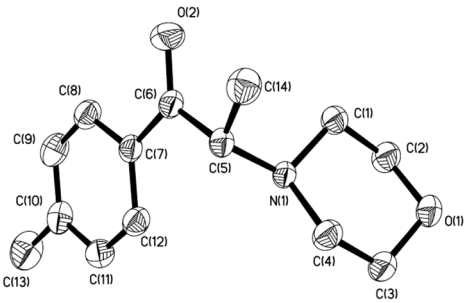


Fig. 4 Molecular structure of **3a** with thermal ellipsoids drawn at the 30% level; all hydrogen atoms are omitted for clarity.

Conclusions

In conclusion, we have reported the synthesis of three novel Cu(II) complexes with oxazoline and pybox ligands, respectively. All complexes have been fully characterized and molecular structures were determined by X-ray diffraction analysis. In binuclear $[\{(DMOX)CuCl\}_2(\mu\text{-}Cl)_2]$ (**1**) and mononuclear $[(DMOX)CuBr_2]$ (**2**), the DMOX acts as a chelating ligand and coordinates the Cu(II) centers. Moreover, $[(Dm\text{-}Pybox)CuBr_2]$ (**3**) is efficient in catalyzing α-amination of ketones and esters through a C–N coupling reaction, which readily tolerates a range of functionality on the carbonyl and amine reaction components. We believe that when aldehydes are used as substrates, it will be possible to synthesize α-amination derivatives following this general strategy, and the work is in progress.

Experimental section

General

Commercial reagents were of analytical grade and were used as received from Aladdin and Alfa aesar. All reactions were performed in oven-dried or flame-dried glassware, and were monitored by TLC using 0.25 mm silica gel plates with an UV indicator (60F-254). All solvents were purified and degassed by standard procedures. The starting materials 4,5-dihydro-2-(4,5-

dihydro-4,4-dimethyloxazol-2-yl)-4,4-dimethyloxazole (**L6** DMOX);[17] 2,6-bis[4′,4′-dimethyloxazolin-2′-yl]pyridine (Dm-Pybox **L9**)[18] 2,6-bis(4-isopropyl-4,5-dihydrooxazol-2-yl)pyridine (**L10**)[18] and 2,6-bis(4-phenyl-4,5-dihydrooxazol-2-yl)pyridine (**L11**)[18] were synthesized according to the procedures described in the literature. ^{1}H and ^{13}C NMR were recorded on a 300 MHz or 500 MHz NMR spectrometer at room temperature. Chemical shifts (δ) are given in ppm relative to $CDCl_3$ (7.26 ppm for ^{1}H and 77 ppm for ^{13}C) or internal TMS. High-resolution mass spectra (HRMS) were obtained using APCI-TOF in positive mode. IR spectra were recorded on a Nicolet AVATAR-360IR spectrometer. Elemental analyses were performed on an Elementar III vario EI analyzer.

Preparation of the binuclear complex [{(DMOX)-CuCl}$_2$(μ-Cl)$_2$] (1). A 50 mL round-bottomed flask was filled with DMOX (39 mg, 0.2 mmol), $CuCl_2{\cdot}2H_2O$ (34 mg, 0.2 mmol), 10 mL MeOH and 10 mL CH_2Cl_2 as solvent. The mixture was stirred at room temperature for 5 h and then the solvent was removed with a rotary evaporator; the resulting solid was washed with Et_2O. The product was dried under vacuum to give the corresponding green complex **1** (64 mg, 96%). Anal. Calcd for $C_{20}H_{32}Cl_4Cu_2N_4O_4$: C 36.32, H 4.88, N 8.47; Found: C 36.25, H 4.65, N 8.57. IR (KBr cm^{-1}): 2966(m), 2920(w), 1650(vs), 1487(s), 1458(m), 1401(w), 1365(s), 1332(m), 1274(m), 1217(w), 1160(w), 1045(s), 996(w), 923(s), 824(m), 627(w), 505(s).

Preparation of mononuclear [(DMOX)CuBr$_2$] (2). A 50 mL round-bottomed flask was filled with DMOX (39 mg, 0.2 mmol), $CuBr_2$ (45 mg, 0.2 mmol), 10 mL MeOH and 10 mL CH_2Cl_2 as solvent. The mixture was stirred at room temperature for 5 h and then the solvent was removed with a rotary evaporator; the resulting solid was washed with Et_2O. The product was dried under vacuum to give the corresponding dark purple complex **2** (78 mg, 93%). Anal. Calcd for $C_{10}H_{16}Br_2CuN_2O_2$: C 28.62, H 3.84, N 6.68; Found: C 28.59, H 3.64, N 6.47. IR (KBr cm^{-1}): 2967(m), 2923(w), 1656(s), 1503(s), 1465(s), 1363(s), 1331(s), 1261(m), 1204(m), 1159(w), 999(m), 930(s), 828(w), 618(m).

Preparation of pybox copper complex [(Dm-Pybox)CuBr$_2$] (3). A 50 mL round-bottomed flask was filled with Dm-Pybox (55 mg, 0.2 mmol), $CuBr_2$ (45 mg, 0.2 mmol), 10 mL MeOH and 10 mL CH_2Cl_2 as solvent. The mixture was stirred at room temperature for 5 h and then the solvent was removed with a rotary evaporator; the resulting solid was washed with Et_2O. The product was dried under vacuum to give the corresponding dark green complex [(Dm-Pybox)$CuBr_2$] (**3**) (94 mg, 95%). Anal. Calcd for $C_{15}H_{19}Br_2CuN_3O_2$: C 36.27, H 3.86, N 8.46; Found: C 36.18, H 3.65, N 8.50. IR (KBr cm^{-1}): 3025(m), 2968(w), 2929(w), 1643(m), 1624(s), 1573(s), 1497(m), 1452(w), 1401(s), 1381(m), 1338(m), 1293(m), 1197(s), 1097(m), 1025(m), 980(m), 943(s), 841(m), 764(w), 669(s).

General procedure for the synthesis and α-amination of ketones and esters

3 (25 mg, 0.05 mmol, 0.1 equiv.) was dissolved in DMSO (0.1–0.5 mL), and then an appropriate ketone (0.5 mmol, 1.0 equiv.) was added. This mixture was stirred for 10 minutes at room temperature before the addition of the secondary amine (1.5 mmol, 3.0 equiv.). The reaction was stirred for 10 hours after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the desired products.

2-Morpholino-1-phenylpropan-1-one (1a).[9] Yellow liquid, 96% yield (105 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 7.20 Hz, 2H), 7.49 (t, J = 7.20 Hz 1H), 7.40 (t, J = 7.20 Hz, 2H), 4.00 (q, J = 6.75 Hz, 1H), 3.63 (m, 4H), 2.52 (m, 4H), 1.22 (d, J = 6.75 Hz, 3H).

2-Morpholino-1-phenylbutan-1-one (2a).[19] Yellow liquid, 94% yield (110 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 7.20 Hz, 2H), 7.54 (t, J = 7.20 Hz, 1H), 7.43 (t, J = 7.20 Hz 2H), 3.99 (q, J = 4.80 Hz, 1H), 3.63 (m, 4H), 2.59 (m, 4H), 1.88 (m, 1H), 1.74 (m, 1H), 0.84 (t, J = 7.53 Hz, 3H).

1-(1-*p*-Tolyl)-2-morpholinopropan-1-one (3a). Yellow liquid, 94% yield (110 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, J = 7.90 Hz, 2H), 7.19 (d, J = 7.89 Hz, 2H), 3.99 (m, 1H), 3.63 (m, 4H), 2.54 (m, 4H), 2.35 (s, 3H), 1.22 (d, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.19, 144.24, 133.86, 129.44, 129.20, 67.40, 64.92, 50.43, 21.96, 12.36. HRMS (APCI) Calcd for $C_{14}H_{19}NO_2$ $[M + H]^+$ 234.1489, found 234.1483.

1-(4-Methoxyphenyl)-2-morpholinopropan-1-one (4a).[9] Yellow liquid, 93% yield (116 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 8.70 Hz, 2H), 6.99 (d, J = 8.70 Hz, 2H), 3.96 (q, J = 6.90 Hz, 1H), 3.82 (s, 3H), 3.64 (m, 4H), 2.54 (m, 4H), 1.24 (d, J = 6.90 Hz, 3H).

1-(4-Chlorophenyl)-2-morpholinopropan-1-one (5a). Yellow liquid, 97% yield (123 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 8.10 Hz, 2H), 7.41 (d, J = 8.10 Hz, 2H), 4.00 (q, J = 6.90 Hz, 1H), 3.66 (m, 4H), 2.57 (m, 4H), 1.27 (d, J = 6.90 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.29, 139.79, 134.60, 130.70, 129.06, 67.39, 65.36, 50.23, 11.49. HRMS (APCI) Calcd for $C_{13}H_{16}ClNO_2$ $[M + H]^+$ 254.0942, found 254.0940.

Methyl 2-morpholino-2-phenylacetate (6a).[9] Pale yellow liquid, 69% yield (81 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.24 (m, 3H), 3.90 (s, 1H), 3.64 (m, 4H), 3.60 (s, 3H), 2.37 (m, 4H).

Ethyl 2-morpholino-2-phenylacetate (7a). Pale yellow liquid, 65% yield (81 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 2H), 7.24 (m, 3H), 4.07 (m, 2H), 3.88 (s, 1H), 3.65 (m, 4H), 2.38 (m, 4H), 1.12 (t, J = 7.05 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.52, 135.75, 129.18, 128.91, 128.76, 74.83, 67.12, 61.28, 51.91, 14.41. HRMS (APCI) Calcd for $C_{14}H_{19}NO_3$ $[M + H]^+$ 250.1438, found 250.1440.

2-Morpholino-1-(thiophen-2-yl)butan-1-one (8a). Yellow liquid, 93% yield (111 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 3.50 Hz, 1H), 7.57 (d, J = 3.50 Hz, 1H), 7.07 (t, J = 3.5 Hz, 1H), 3.64 (m, 4H), 3.51 (m, 1H), 2.61 (m, 2H), 2.54 (m, 2H), 1.75 (m, 2H), 0.94 (t, J = 4.25 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.30, 142.76, 133.97, 132.85, 127.74, 73.04, 67.03, 50.59, 20.48, 10.90. HRMS (APCI) Calcd for $C_{12}H_{17}NO_2S$ $[M + H]^+$ 240.1053, found 240.1051.

1-Phenyl-2-thiomorpholinopropan-1-one (9a).[9] Yellow liquid, 90% yield (106 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97

(d, J = 7.20 Hz, 2H), 7.47 (t, J = 7.20 Hz, 1H), 7.37 (t, J = 7.20 Hz, 2H), 4.09 (q, J = 6.60 Hz, 1H), 2.80 (m, 4H), 2.52 (m, 4H), 1.19 (d, J = 6.60 Hz, 3H).

Phenyl-2-thiomorpholinobutan-1-one (10a). Yellow liquid, 89% yield (111 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 7.23 Hz, 2H), 7.54 (t, J = 7.25 Hz, 1H), 7.43 (t, J = 7.24 Hz, 2H), 3.93 (m, 1H), 2.88 (m, 4H), 2.56 (m, 4H), 1.87 (m, 1H), 1.69 (m, 1H), 0.86 (t, J = 7.35 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.62, 137.66, 133.23, 128.82, 128.77, 70.94, 52.28, 28.85, 18.91, 11.64. HRMS (APCI) Calcd for $C_{14}H_{19}NOS$ $[M + H]^+$ 250.1260, found 250.1261.

2-Thiomorpholino-1-*p*-tolylpropan-1-one (11a). Yellow liquid, 82% yield (102 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 8.10 Hz, 2H), 7.15 (d, J = 8.10 Hz, 2H), 4.03 (m, 1H), 2.77 (m, 4H), 2.50 (m, 4H), 2.32 (s, 3H), 1.15 (d, J = 6.90 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.45, 143.45, 133.45, 128.80, 128.78, 64.76, 51.37, 28.17, 21.45, 9.89. HRMS (APCI) Calcd for $C_{14}H_{19}NOS$ $[M + H]^+$ 250.1260, found 250.1256.

1-(4-Methoxyphenyl)-2-thiomorpholinopropan-1-one (12a). Yellow liquid, 80% yield (106 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 9.00 Hz, 2H), 6.89 (d, J = 9.00 Hz, 2H), 4.05 (q, J = 6.60 Hz, 1H), 3.84 (s, 3H), 2.83 (m, 4H), 2.57 (m, 4H), 1.21 (d, J = 6.60 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.80, 163.54, 131.51, 129.35, 113.67, 65.23, 55.67, 51.83, 28.63, 10.39. HRMS (APCI) Calcd for $C_{14}H_{19}NO_2S$ $[M + H]^+$ 266.1209, found 266.1213.

1-(4-Chlorophenyl)-2-thiomorpholinopropan-1-one (13a). Yellow liquid, 74% yield (99 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 8.40 Hz, 2H), 7.39 (d, J = 8.40 Hz, 2H), 4.05 (q, J = 6.90 Hz, 1H), 2.81 (m, 4H), 2.58 (m, 4H), 1.22 (d, J = 6.90 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.15, 139.58, 134.72, 130.81, 128.94, 65.78, 51.83, 28.68, 9.77. HRMS (APCI) Calcd for $C_{13}H_{16}ClNOS$ $[M + H]^+$ 270.0714, found 270.0712.

2-Thiomorpholino-1-(thiophen-2-yl)butan-1-one (14a). Yellow liquid, 84% yield (107 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 4.00 Hz, 1H), 7.58 (d, J = 4.00 Hz, 1H), 7.08 (t, J = 4.00 Hz, 1H), 3.61 (m, 1H), 2.89 (m, 4H), 2.62 (m, 4H), 1.83 (m, 1H), 1.69 (m, 1H), 0.88 (t, J = 5.00 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.09, 142.19, 133.01, 132.08, 126.93, 72.67, 51.51, 27.54, 18.45, 10.77. HRMS (APCI) Calcd for $C_{12}H_{17}NOS_2$ $[M + H]^+$ 256.0824, found 256.0823.

1-Phenyl-2-(piperidin-1-yl)propan-1-one (15a).[9] Yellow liquid, 95% yield (103 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (m, 2H), 7.51(m, 1H), 7.43 (m, 2H), 4.13 (q, J = 6.90 Hz, 1H), 2.56 (m, 4H), 1.54 (m, 4H), 1.40 (m, 2H), 1.26 (d, J = 6.90 Hz, 3H).

1-Phenyl-2-(piperidin-1-yl)butan-1-one (16a). Yellow liquid, 95% yield (110 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J = 7.00 Hz, 2H), 7.50(d, J = 7.00 Hz, 1H), 7.42 (m, J = 7.00 Hz, 2H), 3.89 (q, J = 7.50 Hz, 1H), 2.57 (m, 2H), 2.49 (m, 2H), 1.87 (m, 1H), 1.70 (m, 1H), 1.49 (m, 4H), 1.36 (m, 2H), 0.83 (t, J = 7.50 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.41, 137.87, 132.78, 128.61, 128.43, 70.58, 51.03, 26.52, 24.57, 19.49, 11.29. HRMS (APCI) Calcd for $C_{15}H_{21}NO$ $[M + H]^+$ 232.1696, found 232.1696.

2-(Piperidin-1-yl)-1-*p*-tolylpropan-1-one (17a). Yellow liquid, 94% yield (109 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, J = 8.10 Hz, 2H), 7.16 (d, J = 8.10 Hz, 2H), 4.06 (q, J = 6.90 Hz, 1H), 2.49 (m, 4H), 2.32 (s, 3H), 1.49 (m, 4H), 1.34 (m, 2H), 1.20 (d, J = 6.90 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.48, 143.75, 133.88, 129.08, 129.05, 64.82, 50.80, 26.16, 24.35, 21.72, 11.84, 11.79. HRMS (APCI) Calcd for $C_{15}H_{21}NO$ $[M + H]^+$ 232.1696, found 232.1696.

1-(4-Methoxyphenyl)-2-(piperidin-1-yl) propan-1-one (18a). Yellow liquid, 92% yield (114 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 8.70 Hz, 2H), 6.90 (d, J = 8.70 Hz, 2H), 4.00 (q, J = 6.90 Hz, 1H), 3.85 (s, 3H), 2.52 (m, 4H), 1.51 (m, 4H), 1.41 (m, 2H), 1.24 (d, J = 6.90 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.98, 163.59, 131.62, 129.82, 113.74, 65.50, 55.76, 51.18, 26.67, 24.78, 11.94. HRMS (APCI) Calcd for $C_{15}H_{21}NO_2$ $[M + H]^+$ 248.1645, found 248.1647.

1-(4-Chlorophenyl)-2-(piperidin-1-yl) propan-1-one (19a). Yellow liquid, 97% yield (122 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 8.40 Hz, 2H), 7.39 (d, J = 8.40 Hz, 2H), 4.01 (q, J = 6.90 Hz, 1H), 2.51 (m, 4H), 1.51 (m, 4H), 1.39 (m, 2H), 1.23 (d, J = 6.90 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.04, 139.42, 134.98, 130.88, 128.86, 65.85, 50.95, 26.58, 24.63, 10.82. HRMS (APCI) Calcd for $C_{14}H_{18}ClNO$ $[M + H]^+$ 252.1150, found 252.1150.

Methyl 2-phenyl-2-(piperidin-1-yl) acetate (20a).[20] Yellow liquid, 87% yield (101 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.23 (m, 3H), 3.90 (s, 1H), 3.59 (s, 3H), 2.29 (m, 4H), 1.51 (m, 4H), 1.35 (m, 2H).

Ethyl 2-(piperidin-1-yl)-2-phenylacetate (21a). Yellow liquid, 84% yield (104 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.23 (m, 3H), 4.06 (m, 2H), 3.87 (s, 1H), 2.31 (m, 4H), 1.50 (m, 4H), 1.35 (m, 2H), 1.11 (t, J = 7.20 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.06, 136.65, 129.08, 128.65, 128.34, 75.23, 60.94, 52.62, 26.06, 24.64, 14.39. HRMS (APCI) Calcd for $C_{15}H_{21}NO_2$ $[M + H]^+$ 248.1645, found 248.1643.

2-(Piperidin-1-yl)-1-(thiophen-2-yl)butan-1-one (22a). Yellow liquid, 93% yield (110 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 4.00 Hz, 1H), 7.56 (d, J = 4.00 Hz, 1H), 7.09 (t, J = 4.00 Hz, 1H), 3.53 (m, 1H), 2.59 (m, 2H), 2.50 (m, 2H), 1.82 (m, 1H), 1.74 (m, 1H), 1.55 (m, 4H), 1.39 (m, 2H), 0.86 (t, J = 7.50 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.49, 143.32, 133.97, 133.08, 127.82, 73.85, 51.66, 26.52, 24.79, 20.54, 11.71. HRMS (APCI) Calcd for $C_{13}H_{19}NOS$ $[M + H]^+$ 238.1260, found 238.1257.

2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-1-phenylpropan-1-one (23a).[9] Yellow liquid, 94% yield (125 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (m, 2H), 7.46 (m, 1H), 7.35 (m, 2H), 6.99 (m, 4H), 4.24 (q, J = 6.90 Hz, 1H), 3.81 (d, J = 15.0 Hz, 1H), 3.76 (d, J = 15.0 Hz, 1H), 2.77 (m, 4H), 1.31 (d, J = 6.90 Hz, 3H).

2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-1-phenylbutan-1-one (24a). Yellow liquid, 95% yield (133 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.43 (m, 1H), 7.33 (m, 2H), 6.96 (m, 4H), 4.06 (q, J = 4.80 Hz, 1H), 3.80 (d, J = 15.0 Hz, 1H), 3.72 (d, J = 15.0 Hz, 1H), 2.80 (m, 2H), 2.72 (m, 2H), 1.92 (m, 1H), 1.75 (m, 1H), 0.82 (d, J = 7.20 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.59, 137.84, 135.45, 135.00, 133.45, 129.19, 129.07, 128.99, 126.97, 126.44, 125.97, 70.12, 52.76, 47.70, 30.27, 19.89, 11.68. HRMS (APCI) Calcd for $C_{19}H_{21}NO$ $[M + H]^+$ 280.1696, found 280.1695.

2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-1-*p*-tolylpropan-1-one (25a). Yellow liquid, 93% yield (130 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (m, 2H), 7.13 (m, 2H), 6.97 (m, 4H), 4.19 (q, J = 6.90 Hz, 1H), 3.80 (d, J = 14.7 Hz, 1H), 3.70 (d, J = 14.7 Hz, 1H), 2.75 (m, 4H), 2.29 (s, 3H), 1.28 (d, J = 6.90 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.57, 144.09, 135.16, 134.78, 133.99, 129.42, 129.35, 126.87, 126.29, 125.84, 64.39, 52.38, 47.51, 29.91, 21.97, 11.98. HRMS (APCI) Calcd for $C_{19}H_{21}NO$ $[M + H]^+$ 280.1696, found 280.1696.

2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-1-(4-ethoxyphenyl)propan-1-one (26a). Yellow liquid, 92% yield (136 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (m, 2H), 6.98 (m, 4H), 6.90 (m, 2H), 4.15 (q, J = 6.90 Hz, 1H), 3.80 (d, J = 14.7 Hz, 1H), 3.79 (s, 3H), 3.75 (m, 2H), 2.76 (m, 4H), 1.28 (d, J = 6.90 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.46, 163.65, 135.16, 134.76, 131.61, 129.37, 128.97, 126.86, 126.27, 125.82, 113.81, 64.55, 55.67, 52.39, 47.52, 29.90, 11.99. HRMS (APCI) Calcd for $C_{19}H_{21}NO_2$ $[M + H]^+$ 296.1645, found 296.1643.

1-(4-Chlorophenyl)-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)propan-1-one (27a). Yellow liquid, 87% yield (130 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (m, 2H), 7.27 (m, 2H), 6.97 (m, 4H), 4.14 (q, J = 6.90 Hz, 1H), 3.77 (d, J = 14.7 Hz, 1H), 3.69 (d, J = 14.7 Hz, 1H), 2.72 (m, 4H), 1.28 (d, J = 6.90 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.61, 139.61, 134.91, 134.64, 130.85, 129.05, 128.98, 126.87, 126.43, 125.94, 64.94, 52.23, 47.38, 29.89, 11.02. HRMS (APCI) Calcd for $C_{18}H_{16}ClNO$ $[M + H]^+$ 300.1150, found 300.1144.

2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-1-(thiophen-2-yl)butan-1-one (28a). Yellow liquid, 89% yield (127 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (m, 1H), 7.57 (m, 1H), 7.11 (m, 4H), 7.01 (m, 1H), 3.96 (m, 1H), 3.83 (m, 2H), 2.90 (m, 4H), 1.98 (m, 1H), 1.92 (m, 1H), 0.96 (d, J = 7.50 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.03, 143.28, 135.02, 134.73, 134.32, 133.30, 129.03, 128.08, 126.86, 126.39, 125.90, 72.71, 52.84, 48.03, 29.77, 20.93, 11.58. HRMS (APCI) Calcd for $C_{17}H_{19}NOS$ $[M + H]^+$ 286.1260, found 286.1263.

Methyl 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-2-phenylacetate (29a). Yellow liquid, 86% yield (121 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.37 (m, 3H), 7.10 (m, 3H), 6.95 (m, 1H), 4.25 (s, 1H), 3.74 (s, 3H), 3.70 (m, 2H), 2.82 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.45, 136.36, 134.58, 129.16, 129.05, 128.86, 127.04, 126.57, 126.06, 73.91, 54.26, 52.51, 48.72, 29.20. HRMS (APCI) Calcd for $C_{18}H_{19}NO_2$ $[M + H]^+$ 282.1489, found 282.1487.

Ethyl 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-2-phenylacetate (30a). Yellow liquid, 81% yield (119 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.37 (m, 3H), 7.10 (m, 3H), 6.94 (m, 1H), 4.19 (m, 2H), 4.18 (s, 1H), 3.70 (m, 2H), 2.80 (m, 4H), 1.24 (t, J = 7.08 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ171.79, 136.33, 134.56, 134.48, 129.00, 128.89, 128.82, 128.59, 126.88, 126.38, 125.82, 73.77, 61.18, 54.01, 48.55, 29.06, 14.37. HRMS (APCI) Calcd for $C_{19}H_{21}NO_2$ $[M + H]^+$ 296.1645, found 296.1647.

X-ray crystallography for 1, 2, 3 and 3a

Diffraction data of **1**, **2**, **3** and **3a** were collected on a Bruker Smart CCD diffractometer using graphite-monochromated MoKα radiation (λ = 0.71073 Å). All the data were collected at room temperature and the structures were solved by direct methods and subsequently refined on F^2 by full-matrix least-squares techniques (SHELXL),[21] and SADABS absorption corrections[22] were applied to the data.

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