JOC The Journal of Organic Chemistry

Note

Copper-Catalyzed Aerobic Cascade Oxidative Coupling/ Cyclization for the Construction of 1,4-Dihydropyridine Derivatives

Zhi-Qiang Zhu, Zong-Bo Xie, and Zhang-Gao Le

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b01736 • Publication Date (Web): 12 Sep 2016

Just Accepted

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

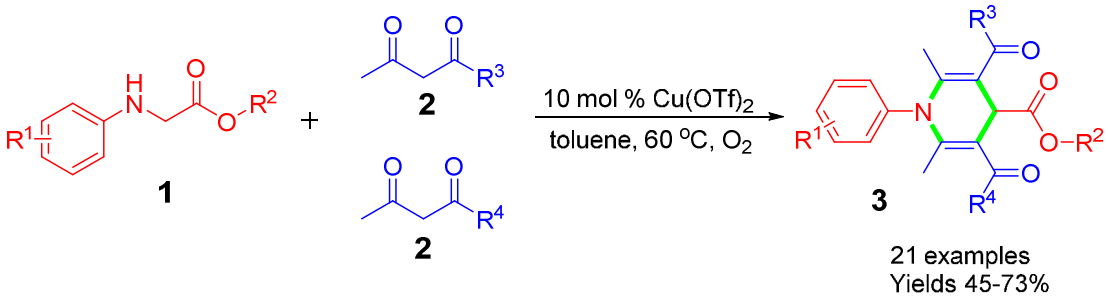
Copper-Catalyzed Aerobic Cascade Oxidative Coupling/Cyclization for the Construction of 1,4-Dihydropyridine Derivatives

Zhi-Qiang Zhu,*[†,‡] Zong-Bo Xie,[†,‡] and Zhang-Gao Le*[†,‡]

[†]Jiangxi 2011 Joint Center for the Innovative Mass Spectrometry and Instrumentation, East China University of Technology, Nanchang 330013, P. R. China

[‡]School of Chemistry, Biology and Material Science, East China University of Technology, Nanchang 330013, P. R. China

ABSTRACT: An efficient copper-catalyzed cascade cyclization reaction for the preparation of polysubstituted 1,4-dihydropyridines between *N*-aryl glycine esters and 1,3-dicarbonyl compounds using molecular oxygen as the terminal oxidant has been described. Various *N*-aryl glycine esters **1** and 1,3-dicarbonyl compounds **2** were able to undergo the cascade reaction smoothly to afford desired products **3** in satisfactory yields. The cascade reaction has the advantages of good functional group tolerance and mild reaction conditions. A possible mechanism has also been proposed based on control experiments.



A cascade reaction can form two or more chemical bonds in a one-pot process without the need to isolate intermediates and change reaction conditions during the reaction. This kind of reaction can decrease resource consumption and environmental impact dramatically, and has been widely used for the synthesis of natural products and pharmaceuticals *etc*.[1] In recent years, the direct oxidative cross-coupling reactions between two C-H centers has emerged as an attractive synthetic strategy for the construction of C-C bonds because this type of reaction avoids prefunctionalization of both substrates efficiently and is more environmentally friendly.[2] Among them, there have been remarkable and instructive advances on the direct coupling of α-C(sp^3)-H bond of glycine derivatives with various nucleophiles.[3-4] For example, in 2008, Li and coworkers reported a novel copper salt-mediated direct oxidative cross-coupling reaction of α-amino acid derivatives with malonates.[3a] In 2010, Huang *et al.* developed an efficient oxidative cross-coupling reaction of α-substituted glycine esters with ketones by the synergistic catalysis of copper salt and pyrrolidine.[3b] In 2011, Wang's group demonstrated an asymmetric oxidative cross-coupling reaction between *N*-aryl α-amino acid esters and α-substituted β-ketoesters under the catalysis of a chiral copper complex.[3c] In 2013, Wu and coworkers revealed a dual catalytic oxidative cross-coupling reaction of *N*-aryl glycine derivatives with β-ketoesters to give desired α-alkylated products by the combination of photocatalysis and transition metal catalysis.[3d] Despite an appealing synthetic strategy, the design and development of novel cascade reactions involving direct oxidative C(sp^3)-H bond transformations is still a challenge.

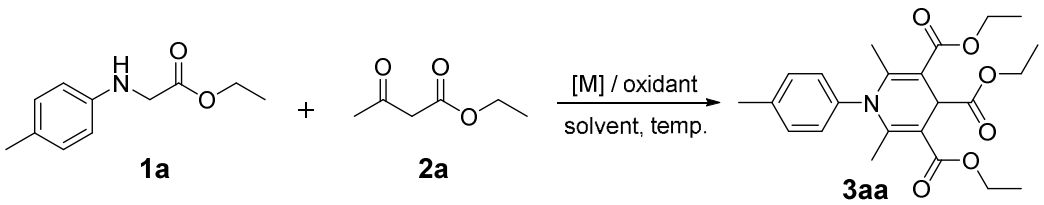
1,4-dihydropyridines represents one of the most important heterocycles in biologically active and naturally occurring molecules.[5-6] Over the past few years, much attention has been attracted on the *N*-substituted 1,4-dihydropyridines with biological activity.[6] For example, *N*-acyloxy 1,4-dihydropyridines were prepared as P-glycoprotein-mediated

MDR-reversing agents,[6a] *N*-aryl substituted 1,4-dihydropyridines were demonstrated to act as sirtuin activators and inhibitors,[6b] and 1-phenyl-4-glycosyl-1,4-dihydropyridines were synthesized as potent antileishmanial agents.[6c] Although a number of methods have been developed for the preparation of 1,4-dihydropyridines, most of them are mainly confined to the Hantzsch synthesis as well as some modified approaches.[7-8] Recently, Jia and coworkers reported a radical cation salt, $TBPA^{+\bullet}$ [tris(4-bromophenyl)aminium hexachloroantim-onate]-catalyzed cascade reaction between glycine derivatives and β-ketoesters for the construction of 1,4-dihydropyridines under aerobic conditions.[9] However, the precusor of the real catalyst $TBPA^{+\bullet}$ is rather expensive, and TMSCl was used as an additive to accelerate the enolization of β-ketoesters in the reaction system. Herein, we wish to present a more economical, efficient, and greener approach to polysubstituted 1,4-dihydropyridines through the cascade reactions of *N*-aryl glycine esters with 1,3-dicarbonyl compounds by using cheap and nontoxic copper salt as a sole catalyst, and molecular oxygen as an environmentally benign oxidant.

Initially, *N*-4-methylphenylglycine ester **1a** and ethyl acetoacetate **2a** were used as model substrates to explore and optimize the cascade reaction. When $FeCl_2$ (10 mol %) was used as a catalyst, the reaction of *N*-4-methylphenylglycine ester **1a** with ethyl acetoacetate **2a** occurred under an oxygen atmosphere in CH_3CN at 60 ^oC, giving the desired product **3aa** in 31% yield (entry 1, Table 1). Encourage by this result, other transition-metal salts were probed as catalysts in the reaction. Among various transition-metal catalysts, $Cu(OTf)_2$ was proved to be the best for the yield of **3aa** (compare entries 1-9 with entry 10, Table 1; also see Supporting Information (SI)). No reaction occurred in the absence of a transition-metal catalyst (entry 11, Table 1). Then, a series of oxidants were investigated in the reaction, it was found that lower yields or no formation of **3aa** were observed (compare entries 12-13 with entry 10, Table 1; also see SI). For further screening of different solvents, the

experiment demonstrated that toluene was the best to the yield of **3aa** as compared to CH_3CN, THF, DCE, EtOH, DMF, and DMSO (compare entries 10, 14-18 with entry 19, Table 1). The effect of temperature on the reaction was also tested. The experiment results indicated that lowering temperature to 40 ^oC or raising temperature to 80 ^oC was not beneficial to the yield of **3aa** (compare entry 20 with entry 19, Table 1).

Table 1. Optimization of the reaction conditions[a]



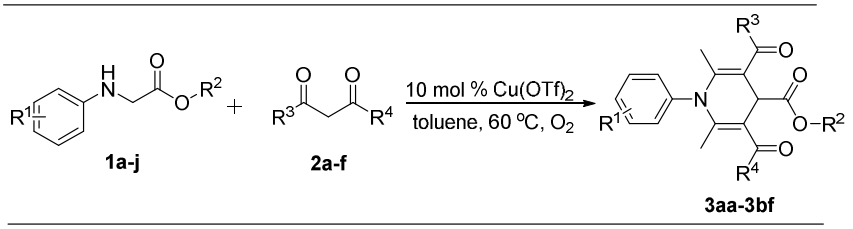
1a + **2a** → **3aa**

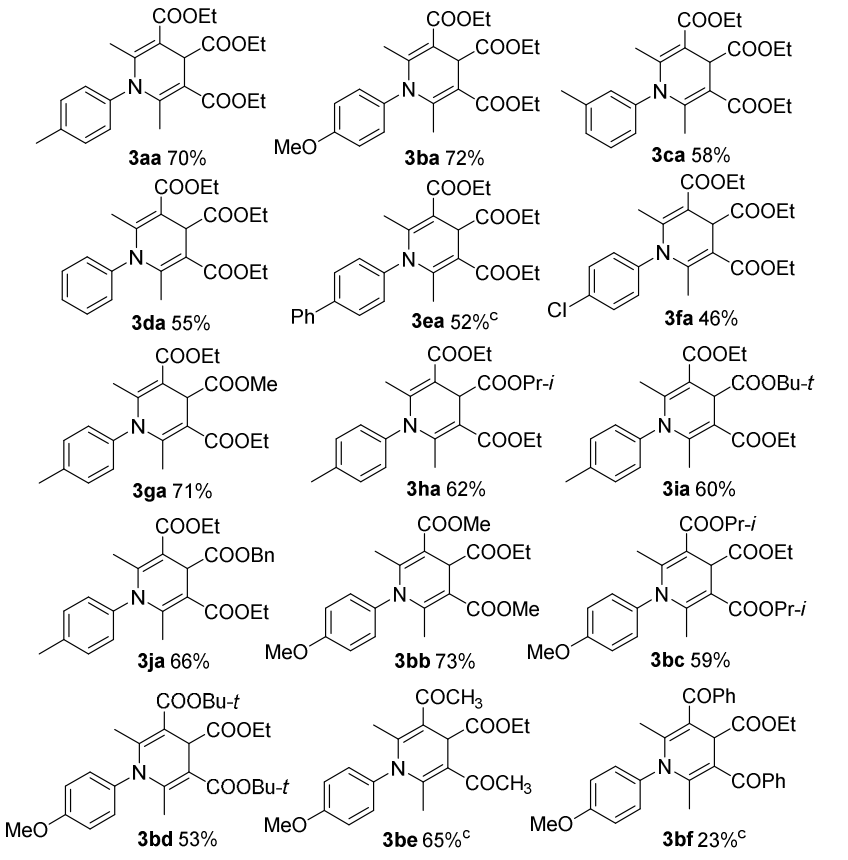
entry	catalyst	oxidant	solvent	yield(%)
1	$FeCl_2$	O_2	CH_3CN	31
2	$FeCl_3$	O_2	CH_3CN	53
3	$InCl_3$	O_2	CH_3CN	22
4	$Sc(OTf)_3$	O_2	CH_3CN	36
5	$Yb(OTf)_3$	O_2	CH_3CN	52
6	$Cu(OAc)_2$	O_2	CH_3CN	12
7	$CuSO_4$	O_2	CH_3CN	38
8	$CuCl_2$	O_2	CH_3CN	58
9	CuO	O_2	CH_3CN	57
10	$Cu(OTf)_2$	O_2	CH_3CN	61
11	--	O_2	CH_3CN	--
12	$Cu(OTf)_2$	DTBP	CH_3CN	42
13	$Cu(OTf)_2$	DCP	CH_3CN	55
14	$Cu(OTf)_2$	O_2	THF	23
15	$Cu(OTf)_2$	O_2	DCE	30
16	$Cu(OTf)_2$	O_2	EtOH	47
17	$Cu(OTf)_2$	O_2	DMF	46
18	$Cu(OTf)_2$	O_2	DMSO	43
19	$Cu(OTf)_2$	O_2	Toluene	70
20[c]	$Cu(OTf)_2$	O_2	Toluene	63(67)[d]

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.44 mmol), catalyst (10 mol %), solvent (1 mL) at 60 ^oC under O_2 (1 atm) or oxidant (2 equiv) for 12 h. [b] Isolated yield based on **1a**. [c] At 80 ^oC. [d] At 40 ^oC for 36 h.

After screening the reaction conditions, it can be concluded that the optimized reaction should be performed in the presence of 10 mol % $Cu(OTf)_2$ at 60 °C in toluene using molecular oxygen as an oxidant. Under the optimized conditions, a range of *N*-aryl glycine esters **1** were investigated in the reaction, it was found that various *N*-aryl glycine esters **1a-j** were able to undergo the cascade reaction smoothly with ethyl acetoacetate **2a** to afford desired products **3aa-ja** in the yields of 46-72% (Table 2). The experimental results indicated

Table 2. Scope of the cascade reaction[a,b]



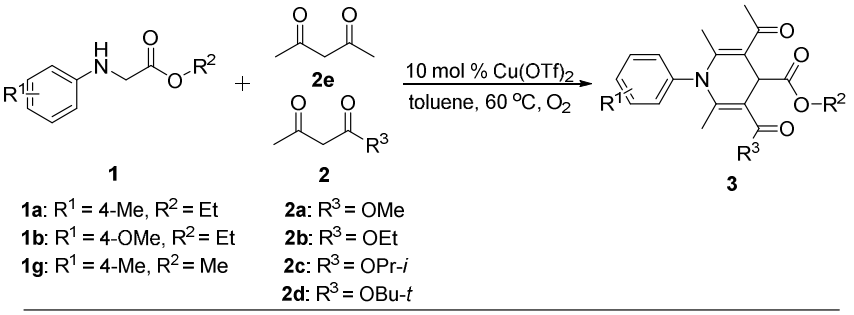


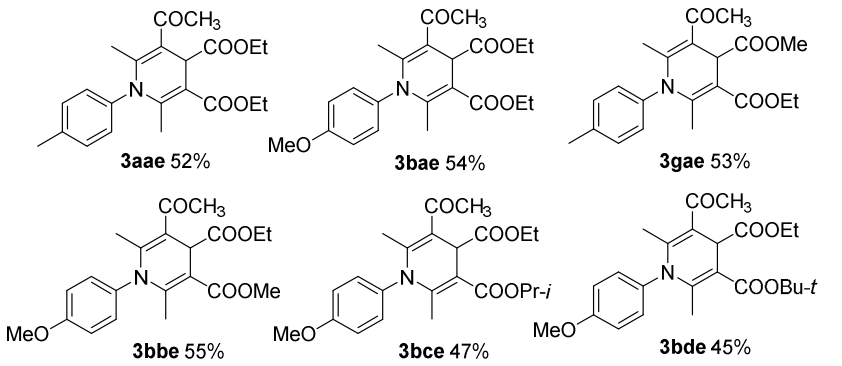
Reaction Conditions: (a) **1** (0.2 mmol), **2** (0.44 mmol), $Cu(OTf)_2$ (10 mol %), toluene (1 mL), at 60 °C under O_2 (1 atm) for 12 h. (b) Isolated yield based on **1**. (c) 18 h.

that this cascade reaction is not very sensitive to the groups connected with carbonyl groups, such as ethyl, methyl, isopropyl, *tert*-butyl, and benzyl ester **1**. The electron-donating groups on *N*-benzene rings of glycine esters **1a-c** seem to be more beneficial to the cascade reaction as compared to the electron-withdrawing groups on *N*-benzene rings of glycine esters. Then, various 1,3-dicarbonyl compounds **2** were examined in the cascade reaction with *N*-aryl glycine esters **1b**. As shown in Table 2, a series of β-carbonyl esters **2a-d** were able to undergo the cascade reaction smoothly to give the corresponding products **3ba-3bd** in satisfactory yields. The 1,3-diketone compound **2e** was also suitable to this transformation, which gave desired product **3be** in good yield. The experimental results also indicated that the steric hindrance of 1,3-dicarbonyl compounds **2** had significant impact on the reaction yields. When 1-phenylbutane-1,3-dione **2f**, which has a bulky phenyl group at α-position was employed instead of ethyl acetoacetate **2a**, low yield of desired product **3bf** was obtained. When 1,3-diphenylpropane-1,3-dione was used instead of ethyl acetoacetate, no expected product was observed.

For further examining the generality of this protocol, three component cascade cyclization reactions were probed for the synthesis of unsymmetrical 1,4-dihydropyridines (Table 3). The experiment results demonstrated that a series of *N*-aryl glycine esters **1a-b,g** were able to perform the cascade cyclization reactions smoothly with acetoacetate esters **2a** and acetylacetone **2e** to afford desired products **3aae**, **3bae** and **3gae** in moderate yields under optimized conditions. The experiment also demonstrated that a series of β-carbonyl esters **2a-d** were able to perform the cascade cyclization reactions smoothly with *N*-aryl glycine esters **1b** and acetylacetone **2e** to provide desired products **3bae-3bde** in moderate yields. It seems that the cascade cyclization reaction is sensitive to steric hindrance of the groups connected with carbonyl groups, such as ethyl, methyl, isopropyl, and *tert*-butyl esters **2**.

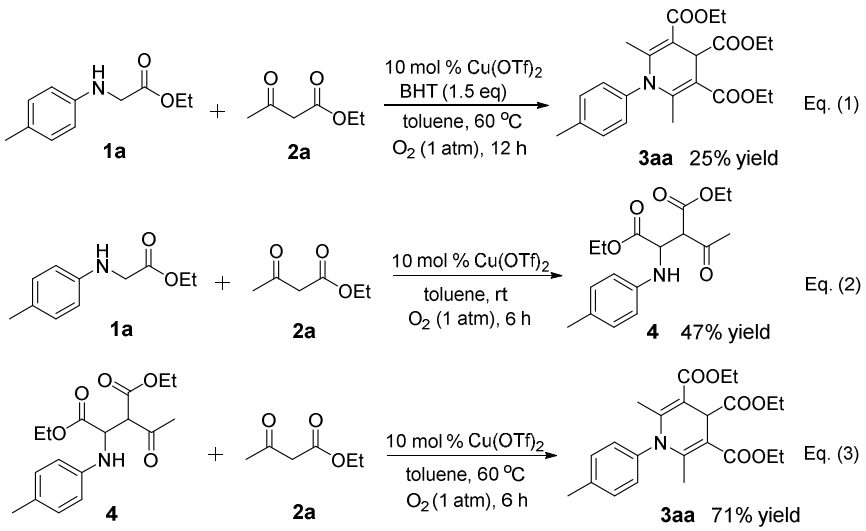
Table 3. Synthesis of unsymmetrical 1,4-dihydropyridines[a,b]





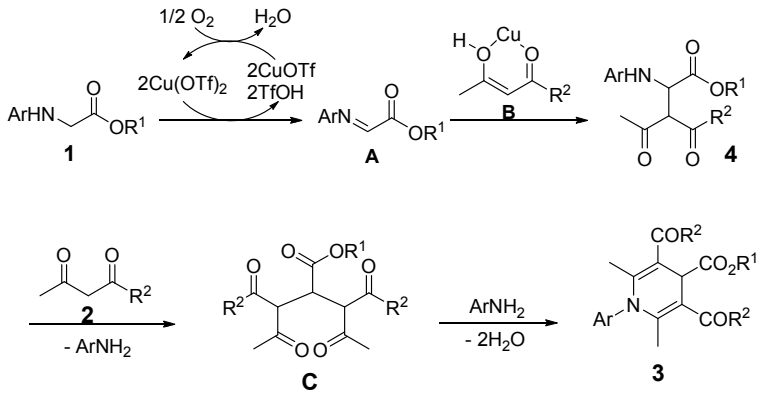
Reaction Conditons: (a) **1** (0.2 mmol), **2e** (0.22 mmol) and **2** (0.22 mmol), $Cu(OTf)_2$ (10 mol %), toluene (1 mL), at 60 °C under O_2 (1 atm) for 12 h. (b) Isolated yield based on **1.**

To gain insight into this cascade cyclization reaction, we carried out several control experiments on the mechanistic pathway (Scheme 1). Firstly, when a radical inhibitor, 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added to the standard reaction conditions, the yield of the desired product **3aa** decreased dramatically from 70% to 25% [Eq. (1)]. This result suggests that free radical intermediate might be involved in this cascade cyclization reaction. Secondly, intermediate **4** was obtained in 47% yield from the oxidative cross-coupling reaction of **1a** and **2a** under room temperature after a relatively short reaction time [Eq. (2)]. Moreover, we found that the isolated intermediate **4** was able to undergo cyclization reaction with **2a** successfully to provide desired product **3aa** in good yield [Eq. (3)]. The experiment results indicate that the oxidative cross-coupling product **4** is the key intermediate of this copper-catalyzed cascade cyclization.



Scheme 1. Control experiments

Based on the experiment results and previous literature,[3-4,10] a plausible mechanism for the cascade reaction is depicted in Scheme 2. Initially, iminium intermediate **A** and copper (I) were generated form the oxidation of glycine ester **1** by two moleculars of $Cu(OTf)_2$.[4d,f] Immediately, copper (I) can be oxidized to copper (II) for catalytic recycle by molecular oxygen.[10] In the presence of $Cu(OTf)_2$ as a Lewis acid, the electrophilic addition of iminium intermediate **A** to the Lewis acid-bonded nucleophile **B** gives intermediate **4**.[3c-d] Subsequently, the second 1,3-dicarbonyl compound **2** reacts with intermediate **4** to provide intermediate **C**. Finally, intermediate **C** undergoes condensation reaction with aryl amine and loss of water to afford desired polysubstituted 1,4-dihydropyridines **4**.



Scheme 2. Plausible mechanism.

In conclusion, we have developed a novel and facile copper-catalyzed cascade reaction between *N*-aryl glycine esters and 1,3-dicarbonyl compounds for the efficient synthesis of polysubstituted 1,4-dihydropyridine derivatives by using molecular oxygen as the terminal oxidant. Various *N*-aryl glycine esters **1** and 1,3-dicarbonyl compounds **2** were able to perform the cascade reaction smoothly to give desired products **3** in satisfactory yields. A possible mechanism has also been proposed based on control experiments. This synthetic method has the advantages of good functional group tolerance, simple operation and mild reaction conditions. The cascade cyclization reaction may have potential to be used for the synthesis of natural products and biologically active molecules.

EXPERIMENTAL SECTION

General procedure for synthesis of 1,4-dihydropyridines 3aa-3bf. To a solution of *N*-aryl glycine esters **1** (0.2 mmol) in toluene (1 mL) was added 1,3-dicarbonyl compounds **2** (0.44 mmol) and $Cu(OTf)_2$ (7.4 mg, 0.02 mmol). The reaction mixture was stirred at 60 ^oC under oxygen atmosphere for 12-18 hrs. After the reaction was finished, the resulting mixture was concentrated under vacuum and the residue was subjected to column chromatography (silica gel, 15:1 petroleum ether/ethyl acetate as an eluent) to afford the corresponding products **3**.

Triethyl 1,4-dihydro-2,6-dimethyl-1-*p*-tolylpyridine-3,4,5-tricarboxylate (3aa):[8f] Yield 70% (58.1 mg); yellow oil; ^1H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.21 (d, J = 8.0 Hz, 2H), 7.04 (dd, J = 6.8 Hz, J = 2.0 Hz, 2H), 4.87 (s, 1H), 4.27-4.11 (m, 6H), 2.39 (s, 3H), 2.05 (s, 6H), 1.30 (t, J = 7.0 Hz, 6H), 1.25 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 173.9, 167.6, 149.0, 138. 7, 137.5, 130.1, 130.0, 101.0, 60.6, 60.1, 40.1, 21.2, 18.2, 14.3, 14.2; MS (EI) *m/z* 415 $(M)^+$, 342(100), 314, 286, 91.

Triethyl 1,4-dihydro-1-(4-methoxyphenyl)-2,6-dimethylpyridine-3,4,5-tricarb-oxylate (3ba): Yield 72% (62.1 mg); yellowish solid; mp 106-107 ^oC (lit.[8f]

108.2-109.5 °C); ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.09 (d, J = 9.2 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 4.87 (s, 1H), 4.27-4.11 (m, 6H), 3.84 (s, 3H), 2.06 (s, 6H), 1.30 (t, J = 7.0 Hz, 6H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 173.9, 167.5, 159.4, 149.3, 132.8, 131.3, 114.4, 101.1, 60.6, 60.1, 55.5, 40.1, 18.2, 14.3, 14.2; MS (EI) *m/z* 431 $(M)^+$, 358(100), 330, 302, 77.

Triethyl 1,4-dihydro-2,6-dimethyl-1-*m*-tolylpyridine-3,4,5-tricarboxylate (3ca): Yield 58% (48.2 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.32-7.27 (m, 1H), 7.20 (d, J = 7.6 Hz, 1H), 6.98 (d, J = 6.0 Hz, 2H), 4.87 (s,1H), 4.27-4.12 (m, 6H), 2.37 (s, 3H), 2.05 (s, 6H), 1.30 (t, J = 7.0 Hz, 6H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 173.9, 167.6, 148.8, 140.1, 139.6, 130.9, 129.4, 129.0, 127.5, 101.0, 60.6, 60.1, 40.1, 21.2, 18.2, 14.3, 14.2; HRMS (EI-TOF) *m/z* calcd for $C_{23}H_{29}NO_6$ 415.1995, found 415.1982.

Triethyl 1,4-dihydro-2,6-dimethyl-1-phenylpyridine-3,4,5-tricarboxylate (3da):[8f] Yield 55% (44.1 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.45-7.38 (m, 3H), 7.19 (d, J = 6.4 Hz, 2H), 4.88 (s, 1H), 4.27-4.12 (m, 6H), 4.14 (m, 2H), 2.05 (s, 6H), 1.30 (t, J = 7.0 Hz, 6H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$)), δ (ppm): 173.8, 167.5, 148.8, 140.2, 130.5, 129.4, 128.7, 101.2, 60.6, 60.1, 40.1, 18.2, 14.3, 14.2; MS (EI) *m/z* 401 $(M)^+$, 328(100), 300, 272, 77.

Triethyl 1-([1,1'-biphenyl]-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (3ea): Yield 52% (49.6 mg); light yellow solid; mp 108-109 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.45 (d, J = 7.6 Hz, 2H), 7.61 (d, J = 7.6 Hz, 2H), 7.47 (t, J = 7.6 Hz, 2H), 7.39 (t, J = 7.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 2H), 4.89 (s, 1H), 4.28-4.14 (m, 6H), 2.11 (s, 6H), 1.31 (t, J = 7.2 Hz, 6H), 1.27 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 173.3, 167.0, 148.3, 141.2, 139.3, 138.9, 130.3, 128.4, 127.5, 127.4, 126.6, 100.9, 60.1, 59.6, 39.7, 17.8, 13.8, 13.7; HRMS (EI-TOF) *m/z* calcd for $C_{28}H_{31}NO_6$ 477.2151, found 477.2149.

Triethyl 1-(4-chlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,4,5-tricarboxylate (3fa):[8f] Yield 46% (40.0 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.41 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 4.85 (s, 1H), 4.27-4.11 (m, 6H), 2.04 (s, 3H), 1.30 (t, J = 7.0 Hz, 6H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz,

$CDCl_3$), δ (ppm): 173.8, 167.3, 148.3, 138.8, 134.7, 131.8, 129. 7, 101.8, 60.7, 60.2, 40.1, 18.20, 14.3, 14.2; MS (EI) *m/z* 435 $(M)^+$, 362(100), 334, 306, 77.

3,5-Diethyl 4-methyl 1,4-dihydro-2,6-dimethyl-1-*p*-tolylpyridine-3,4,5-tricarboxylate (3ga):[8d] Yield 71% (56.9 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.22 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 4.90 (s, 3H), 4.27-4.17 (m, 4H), 3.69 (s, 3H), 2.39 (s, 3H), 2.05 (s, 6H), 1.29 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 174.4, 167.5, 149.2, 138.7, 137.4, 130.1, 130.0, 100.9, 60.2, 52.0, 40.0, 21.2, 18.2, 14.3; HRMS (EI-TOF) *m/z* calcd for $C_{22}H_{27}NO_6$ 401.1838, found 401.1833.

3,5-Diethyl 4-isopropyl 1,4-dihydro-2,6-dimethyl-1-*p*-tolylpyridine-3,4,5-tricarboxylate (3ha): Yield 62% (53.2 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.22 (d, J = 8.0 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 5.02-4.95 (m, 1H), 4.82 (s, 1H), 4.28-4.14 (m, 4H), 2.39 (s, 3H), 2.04 (s, 6H), 1.30 (t, J = 7.0 Hz, 6H), 1.22 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 173.4, 167.6, 148.9, 138.6, 137.6, 130.1, 130.0, 101.1, 67.8, 60.0, 40.3, 21.8, 21.1, 18.2, 14.4; HRMS (EI-TOF) *m/z* calcd for $C_{24}H_{31}NO_6$ 429.2151, found 429.2155.

4-*tert*-Butyl 3,5-diethyl 1,4-dihydro-2,6-dimethyl-1-*p*-tolylpyridine-3,4,5-tricarboxylate (3ia):[8d] Yield 60% (53.2 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.21 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 4.77 (s, 1H), 4.25-4.17 (m, 4H), 2.39 (s, 3H), 2.04 (s, 6H), 1.43 (s, 9H), 1.31 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 172.8, 167.7, 148.4, 138.6, 137.6, 130.1, 130.0, 101.5, 80.1, 60.0, 40.9, 28.0, 21.1, 18.1, 14.4; HRMS (EI-TOF) *m/z* calcd for $C_{25}H_{33}NO_6$ 443.2308, found 443.2313.

4-Benzyl 3,5-diethyl 1,4-dihydro-2,6-dimethyl-1-*p*-tolylpyridine-3,4,5-tricarboxylate (3ja): Yield 66% (63.0 mg); yellowish solid; mp 116-118 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.33-7.27 (m, 5H), 7.15 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 7.6 Hz, 2H), 5.14 (s, 2H), 5.00 (s, 1H), 4.21-4.15 (m, 4H), 2.37 (s, 3H), 2.04 (s, 6H), 1.24 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 173.4, 167.4, 149.3, 138.6, 137.3, 136.5, 130.1, 130.0, 128.3, 127.9, 127.8, 100.8, 80.1, 66.3, 60.2, 40.0, 21.1, 18.2, 14.3; HRMS (EI-TOF) *m/z* calcd for $C_{28}H_{31}NO_6$ 477.2151, found 477.2140.

4-Ethyl 3,5-dimethyl 1,4-dihydro-1-(4-methoxyphenyl)-2,6-dimethylpyridine-3,4,5-tricarboxylate (3bb): Yield 73% (58.9 mg); yellowish solid; mp 101-102 ^{o}C (lit.[8f] 101.6-103.1 ^{o}C); ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.08 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 4.87 (s, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.84 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 2.07 (s, 6H), 1.25 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 173.6, 167.9, 159.5, 149.7, 132.6, 131.2, 114.5, 100.7, 60.7, 55.5, 51.4, 39.9, 18.2, 14.2; MS (EI) *m/z* 403 $(M)^+$, 344, 330(100), 212, 77.

4-Ethyl 3,5-diisopropyl 1,4-dihydro-1-(4-methoxyphenyl)-2,6-dimethylpyridine -3,4,5-tricarboxylate (3bc):[8f] Yield 59% (54.2 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.09 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.4 Hz, 2H), 5.11-5.05 (m, 2H), 4.85 (s,1H), 4.14 (q, J = 7.2 Hz, 2H), 3.84 (s, 3H), 2.04 (s, 6H), 1.29-1.26 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 174.0, 167.1, 159.4, 148.9, 132.9, 131.4, 114.4, 101.5, 67.4, 60.6, 55.5, 40.2, 22.0, 21.9, 18.1, 14.3; MS (EI) *m/z* 459 $(M)^+$, 386(100), 302, 212, 77.

3,5-Di-*tert*-butyl 4-ethyl 1,4-dihydro-1-(4-methoxyphenyl)-2,6-dimethylpyridine-3,4,5-tricarboxylate (3bd):[8f] Yield 53% (51.5 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.08 (dd, J = 6.8 Hz, J = 2.0 Hz, 2H), 6.90 (dd, J = 6.8 Hz, J = 2.0 Hz, 2H), 4.79 (s, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.83 (s, 3H), 2.01 (s, 6H), 1.50 (s, 18H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 174.2, 166.9, 159.3, 148.3, 133.0, 131.5, 114.3, 102.4, 79.9, 60.5, 55.5, 40.9, 28.2, 18.0, 14.4; MS (EI) *m/z* 487 $(M)^+$, 414(100), 358, 303, 212.

Ethyl 3,5-diacetyl-1,4-dihydro-1-(4-methoxyphenyl)-2,6-dimethylpyridine-4-carboxylate (3be):[8f] Yield 65% (48.3 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.08 (d, J = 8.4 Hz, 2H), 6.94 (d, J = 8.4 Hz, 2H), 4.74 (s,1H), 4.16 (q, J = 7.2 Hz, 2H), 3.85 (s, 3H), 2.42 (s, 6H), 2.03 (s, 6H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 197.9, 173.0, 159.6, 148.5, 132.3, 131.1, 114.6, 110.3, 61.1, 55.5, 41.0, 30.2, 18.9, 14.2; MS (EI) *m/z* 371 $(M)^+$, 299(100), 240, 212, 77.

Ethyl 3,5-dibenzoyl-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-4-carboxylate (3bf):[8f] Yield 23% (22.8 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.81 (d, J = 6.8 Hz, 4H), 7.50-7.47 (m, 2H), 7.41 (t, J = 7.4 Hz, 4H), 7.17 (d, J

= 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 4.65 (s, 1H), 4.06 (q, *J* = 7.2 Hz, 2H), 3.83 (s, 3H), 1.65 (s, 6H), 1.13 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 197.1, 172.7, 159.5, 145.4, 139.8, 132.5, 131.9, 131.2, 128.8, 128.5, 114.5, 109.3, 61.1, 55.5, 44.0, 19.7, 14.0; MS (EI) *m/z* 495 $(M)^+$, 422(100), 362, 105, 77.

General procedure for the synthesis of unsymmetrical 1,4-dihydropyridines 3. To a solution of *N*-aryl glycine esters **1** (0.2 mmol) in toluene (1 mL) was added 1,3-dicarbonyl compounds **2** (0.22 mmol), acetylacetone 2e (22 mg, 0.22 mmol) and $Cu(OTf)_2$ (7.4 mg, 0.02 mmol). The reaction mixture was stirred at 60 ^{o}C under oxygen atmosphere for 12 hrs. After the reaction was finished, the resulting mixture was concentrated under vacuum and the residue was subjected to column chromatography (silica gel, 10:1 petroleum ether/ethyl acetate as an eluent) to afford the corresponding products **3**.

Diethyl 5-acetyl-1,4-dihydro-2,6-dimethyl-1-*p*-tolylpyridine-3,4-dicarboxylate (3aae): Yield 52% (40.1 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.22 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 4.79 (s, 1H), 4.27-4.13 (m, 4H), 2.43 (s, 3H), 2.40 (s, 3H), 2.09 (s, 3H), 1.98 (s, 3H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 198.9, 173.3, 167.3, 149.5, 147.9, 138.8, 137.3, 130.0, 129.9, 109.3, 101.0, 60.9, 60.2, 40.9, 29.8, 21.2, 18.7, 18.2, 14.4, 14.2; HRMS (EI-TOF) *m/z* calcd for $C_{22}H_{27}NO_5$ 385.1889, found 385.1896.

Diethyl 5-acetyl-1,4-dihydro-1-(4-methoxyphenyl)-2,6-dimethylpyridine-3,4-dicarboxylate (3bae):[8f] Yield 54% (43.3 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.07 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 4.79 (s, 1H), 4.24-4.12 (m, 4H), 3.84 (s, 3H), 2.42 (s, 3H), 2.09 (s, 3H), 1.99 (s, 3H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 198.9, 173.3, 167.2, 159.5, 149.7, 148.1, 132.5, 131.2, 114.5, 109.4, 101.1, 60.9, 60.3, 55.5, 40.8, 29.8, 18.7, 18.2, 14.4, 14.2; MS (EI) *m/z* 401 $(M)^+$, 328(100), 300, 212, 77.

Ethyl 4,5-diacetyl-1,4-dihydro-2,6-dimethyl-1-*p*-tolylpyridine-3-carboxylate (3gae): Yield 53% (39.3 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.23 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 4.83 (s, 1H), 4.24-4.21 (m, 2H), 3.71 (s, 3H), 2.42 (s, 3H), 2.40 (s, 3H), 2.09 (s, 3H), 1.99 (s, 3H), 1.30 (t, *J* = 7.0 Hz, 3H); ^{13}C

NMR (100 MHz, $CDCl_3$), δ (ppm): 198.8, 173.8, 167.2, 149.6, 148.0, 138.9, 137.2, 130.0, 129.9, 109.2, 100.9, 60.3, 52.2, 40.7, 29.9, 21.6, 18.8, 18.2, 14.4; HRMS (EI-TOF) *m/z* calcd for $C_{21}H_{25}NO_5$ 371.1733, found 371.1737.

4-Ethyl 3-methyl 5-acetyl-1,4-dihydro-1-(4-methoxyphenyl)-2,6-dimethylpyridine-3,4-dicarboxylate (3bbe):[8f] Yield 55% (42.6 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.07 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 4.78 (s, 1H), 4.16 (qd, J = 7.6 Hz, J = 2.4 Hz, 2H), 3.84 (s, 3H), 3.76 (s, 3H), 2.43 (s, 3H), 2.10 (s, 3H), 1.99 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 198.9, 173.2, 167.7, 159.5, 150.2, 148.0, 132.5, 131.2, 114.5, 109.5, 100.6, 61.0, 55.5, 51.6, 40.8, 29.9, 21.6, 18.7, 18.2, 14.2; MS (EI) *m/z* 387 $(M)^+$, 330, 314(100), 212, 77.

4-Ethyl 3-isopropyl 5-acetyl-1,4-dihydro-1-(4-methoxyphenyl)-2,6-dimethylpyridine-3,4-dicarboxylate (3bce):[9] Yield 47% (39.8 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.07 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 5.13-5.06 (m, 1H), 4.78 (s, 1H), 4.15 (qd, J = 6.8 Hz, J = 2.8 Hz, 2H), 3.84 (s, 3H), 2.42 (s, 3H), 2.08 (s, 3H), 1.99 (s, 3H), 1.30-1.24 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 198.9, 173.4, 166.8, 159.5, 149.3, 148.2, 132.6, 131.2, 114.5, 109.3, 101.6, 67.6, 60.9, 55.5, 40.9, 29.8, 22.0, 21.9, 18.7, 18.1, 14.3; MS (EI) *m/z* 415 $(M)^+$, 342(100), 300, 212, 77.

3-*tert*-Butyl 4-ethyl 5-acetyl-1,4-dihydro-1-(4-methoxyphenyl)-2,6-dimethylpyridine-3,4-dicarboxylate (3bde):[9] Yield 45% (38.6 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.07 (dd, J = 6.8 Hz, J = 2.0 Hz, 2H), 6.92 (dd, J = 6.8 Hz, J = 2.0 Hz, 2H), 4.74 (s, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.84 (s, 3H), 2.41 (s, 3H), 2.05 (s, 3H), 1.99 (s, 3H), 1.51 (s, 9H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 198.8, 173.4, 166.6, 159.4, 148.5, 148.4, 132.6, 131.3, 114.4, 109.1, 102.9, 80.4, 60.8, 55.5, 41.2, 29.8, 28.3, 18.7, 18.1, 14.3; MS (EI) *m/z* 429 $(M)^+$, 356, 300(100), 212, 77.

Diethyl 2-acetyl-3-(*p*-tolylamino)succinate (4): Light yellow oil, dr = 1:1. Mixture of two diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 6.99 (d, J = 6.8 Hz, 2H), 6.64-6.61 (m, 2H), 4.71-4.67 (m, 1H), 4.40-4.37 (m, 1H), 4.27-4.13 (m, 4H),

4.11 (d, J = 5.6 Hz, 0.5H), 4.07 (d, J = 6.0 Hz, 0.5H), 2.32 (s, 1.5H), 2.27 (s, 1.5H), 2.23 (s, 3H), 1.30-1.18 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 202.2, 201.3, 171.5, 171.4, 168.0, 167.9, 144.2, 143.9, 129.8, 129.8, 128.4, 114.4, 114.2, 61.9, 61.9, 61.8, 61.7, 61.0, 60.8, 57.3, 56.7, 30.0, 29.9, 20.4, 14.0, 14.0; MS (EI) *m/z* 321 $(M)^+$, 206, 192, 160(100), 91.

AUTHOR INFORMATION

Corresponding Author

*E-mail: zhuzq@ecit.cn; zhgle@ecit.edu.cn

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Financial supports from the National Natural Science Foundation of China (21602027, 21262002 and 21465002) and the Program for Changjiang Scholars and Innovative Research Team in University (IRT13054) are gratefully acknowledged.

ASSOCIATED CONTENT

Supporting Information. Optimization of reaction conditions and spectra of ^{1}H NMR, ^{13}C NMR and HRMS for products. This material is available free of charge via the internet at http://pubs.acs.org.).

REFERENCES

(1) For reviews on cascade reactions, see: (a) Nicolaou, K. C.; Edmonds D. J.; Bulger, P. G. *Angew. Chem. Int. Ed,* **2006**, *45*, 7134; (b) Nicolaou, K. C.; J. S. Chen, *Chem. Soc. Rev.* **2009**, *38*, 2993; (c) Grondal, C.; Jeanty M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167; (d) Westermann, B.; Ayaz M.; Berkel, S. S. *Angew. Chem. Int. Ed.* **2010**, *49*, 846; (e) Volla, C. M. R.; Atodiresei I.; Rueping, M. *Chem. Rev.* **2014**, *114*, 2390; (f) Smith, J. M.; Moreno, J.; Boal B. W.; Garg, N. K. *Angew. Chem. Int. Ed.* **2015**, *54*, 400.

(2) For reviews on oxidative coupling reactions, see: (a) Ashenhurst, J. A. *Chem. Soc. Rev.* **2010**, *39*, 540; (b) Cho, S. H.; Kim, J. Y.; Kwak J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40,* 50683; (c) Yeung C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215; (d) Liu, C.; Zhang, H.; Shi W.; Lei, A. *Chem. Rev.* **2011**, *111*, 17804; (e) Zhang, C.; Tang C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464; (f) Girard, S. A.; Knauber T.; Li, C.-J. *Angew. Chem. Int. Ed.* **2014**, *53*, 74; (g) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. *Chem. Rev.* **2015**, *115*, 12138.

(3) (a) Zhao L.; Li, C.-J. *Angew. Chem. Int. Ed.* **2008**, *47*, 7075; (b) Xie J.; Huang, Z.-Z. *Angew. Chem. Int. Ed.* **2010**, *49*, 10181; (c) Zhang, G.; Zhang Y.; Wang, R. *Angew. Chem. Int. Ed.* **2011**, *50*, 10429; (d) Gao, X.-W.; Meng, Q.-Y.; Xiang, M.; Chen, B.; Feng, K.; Tung C.-H.; Wu, L.-Z. *Adv. Synth. Catal.* **2013**, *355*, 2158; (e) Gao, X.-W.; Meng, Q.-Y.; Li, J.-X.; Zhong, J.-J.; Lei, T.; Li, X.-B.; Tung, C.-H.; Wu, L.-Z. *ACS Catal.* **2015**, *5*, 2391.

(4) (a) Zhao, L.; Basle O.; Li, C.-J. *Proc. Natl. Acad. Sci. USA.* **2009**, *11*, 4106; (b) Li, K.; Tan, G.; Huang, J.; Song F.; You, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 12942-12945; (c) Huo, C.; Yuan, Y.; Wu, M.; Jia, X.; Wang, X.; Chen, F.; Tang, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 13544; (d) Zhu, Z.-Q.; Bai P.; Huang, Z.-Z. *Org. Lett.* **2014**, *16*, 4881; (e) Salman, M.; Zhu Z.-Q.; Huang, Z.-Z. *Org. Lett.* **2016**, *18*, 1526; (f) Xie, Z.; Jia, J.; Liu X.; Liu, L. *Adv. Synth. Catal.* **2016**, *358*, 919; (g) Xie, Z.; Liu X.; Liu, L. *Org. Lett.* **2016**, *18*, 2982.

(5) (a) Guengerich, F. P.; Brain, W. R.; Iwasaki, M.; Sari M. A.; Berntsson, P. *J. Med. Chem.* **1991**, *34*, 1838; (b) Baindur, N.; Rutledge A.; Triggle, D. J. *J. Med. Chem.* **1993**, *36*, 3743; (c) van Rhee, A. M.; Jiang, J. L.; Melman, N.; Olah, M. E.; Stiles G. L.; Jacobson, K. A. *J. Med. Chem.* **1996**, *39*, 2980; (d) Peri, R.; Padmanabhan, S.; Rutledge, A.; Singh S.; Triggle, D. J. *J. Med. Chem.* **2000**, *43*, 2906; (e) Hilgeroth A.; Lilie, H. *Eur. J. Med. Chem.* **2003**, *38*, 495; (f) Shan, R.; Velaskez, C.; Knaus, E. *J. Med. Chem.* **2004**, *47*, 254; (g) Cosconati, S.; Marinelli, L.; Lavecchia A.; Novellino, E. *J. Med. Chem.* **2007**, *50*, 1504; (h) Coburger, C.; Lage, H.; Molnar J.; Hilgeroth, A. *Pharm. Res.* **2009**, *26*, 182; (i) Schade, D.; Lanier, M.; Willems, E.; Okolotowicz, K.; Bushway, P.; Wahlquist, C.; Gilly, G.; Mercola M.; Cashman, J. R. *J. Med. Chem.*

2012, *55*, 9946.

(6) (a) Voigt, B.; Coburger, C.; Monar J.; Hilgeroth, A. *Bioorg. Med. Chem.* **2007**, *15*, 5110; (b) Mai, A.; Valente, S.; Meade, S.; Carafa, V.; Tardugno, M.; Bebbioso, A.; Galmozzi, A.; Mitro, N.; Fabiani, E. D.; Altucci L.; Kazantsev, A. *J. Med. Chem.* **2009**, *52*, 5496; (c) Pandey, V. P.; Bisht, S. S.; Mishra, M.; Kumar, A.; Siddiqi, M. I.; Verma, A.; Mittal, M.; Sane, S. A.; Gupta S.; Tripathi, R. P. *Eur. J. Med. Chem.* **2010**, *45*, 2381; (d) Coburger, C.; Wollmann, J.; Krug, M.; Baumert, C.; Seifert, M.; Molnar, J.; Lage H.; Hilgeroth, A. *Bioorg. Med. Chem.* **2010**, *18*, 4983.

(7) For reviews, see: (a) Stout, D. M. *Chem. Rev.* **1982**, *82*, 223; (b) Lavilla, R. *J. Chem. Soc. Perkin Trans. 1* **2002**, 1141; (c) Wan J.-P.; Liu, Y. *RSC Adv.* **2012**, *2*, 9763.

(8) (a) Ishar, M. P. S.; Kumar, K.; Kaur, S.; Kumar, S.; Girdhar, N. K.; Sachar, S.; Marwaha A.; Kapoor, A. *Org. Lett.* **2001**, *3*, 2133; (b) Cui, S.-L.; Wang, J.; Lin X.-F.; Wang, Y.-G. *J. Org. Chem.* **2007**, *72*, 7779; (c) Wen, L. R.; Sun, J. H.; Li, M.; Sun E. T.; Zhang, S. S. *J. Org. Chem.* **2008**, *73*, 1852; (d) Chen, X.; Huang, X.; Chen, Y.; He, F.; Li, X. *Lett. Org. Chem.* **2009**, *6*, 213; (e) Sun, J.; Xia, E. Y.; Wu Q.; Yan, C. G. *Org. Lett.* **2010**, *12*, 3678; (f) Sun, J.; Sun, Y.; Gao H.; Yan, C. G. *Eur. J. Org. Chem.* **2011**, *42*, 6952; (g) Liu, Y.-P.; Liu, J.-M.; Wang, X.; Cheng T.-M.; Li, R.-T. *Tetrahedron* **2013**, *69*, 5242; (h) Sharma P.; Gupta, M. *Green Chem.* **2015**, *17*, 1100.

(9) Jia, X.; Wang, Y.; Peng, F.; Huo, C.; Yu, L.; Liu J.; Wang, X. *Adv. Synth. Catal.* **2014**, *356*, 1210.

(10) For reviews, see: (a) Caron, S.; Dugger, R.; Ruggeri, S. G.; Ragan J. A.; Ripin, D. H. B. *Chem. Rev.* 2006, **106**, 2943; (b) Que L.; Tolman, W. B. *Nature* **2008**, *455*, 333; (c) Wendalndt, A. E.; Suess A. M.; Stahl, S. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 11062; (d) Shi, Z.; Zhang, C.; Tang C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381.