JOC The Journal of Organic Chemistry

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Transesterification for Synthesis of Carboxylates Using Aldehydes as Acyl Donors via C−H and C−O Bond Activations

Yong-Sheng Bao,[†] Chao-Yue Chen,[†] and Zhi-Zhen Huang*[,†,‡,§]

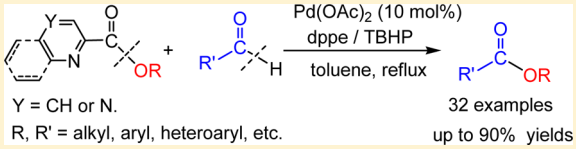
[†]Key Laboratory of Mesoscopic Chemistry of Ministry of Education, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, PR China

[‡]Department of Chemistry, Zhejiang University, Hangzhou 310028, PR China

[§]State Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin 300071, PR China

Supporting Information

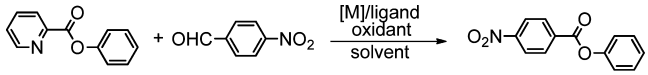
ABSTRACT: A new type of transesterification between aryl, heteroaryl, alkyl *N*-heteroarene-2-carboxylates and various aldehydes by C−H and C−O bond activations has been developed for the synthesis of versatile carboxylates. A possible mechanism containing oxidative addition of acyl−O bond in parent ester and radical cleavage of sp^2 C−H bond in aldehyde is proposed.



Transesterifications as classic organic reactions are widely applied in organic synthesis and chemical industry.[1] In some circumstances for ester syntheses, they are more advantageous than esterification from carboxylic acids and alcohols. For example, some parent carboxylic acids are labile or sparingly soluble in organic solvents.[1a] Transesterifications are performed mainly by the reactions between esters and alcohols under the catalysis of acids or bases. In recent years, main efforts are devoted to develop Lewis acids,[2a] organic and inorganic bases[2b] and *N*-heterocyclic carbene (NHC)[2c] as efficient catalysts for improvement of the transesterifications of carboxylic acids with alcohols. Recently, aldehydes were found to be used as elegant acylating reagents via C−H bond activations.[3] However, to the best of our knowledge, there is no report on the transesterification of esters with aldehydes, while there are numerous literatures on the transesterifications of esters with alcohols.[1,2] Therefore, we envisioned to utilize aldehydes as acyl donors to develop a new type of transesterification for the efficient synthesis of a broad scope of esters under neutral and mild conditions.

Initially, phenyl pyridine-2-carboxylate **1a** with a pyridine moiety as a coordinating group and 4-nitrobenzaldehyde **2a** was chosen as a parent ester and an acyl donor reagent, respectively, exploring and optimizing the new transesterification reaction via C−O and C−H bond activations. We are pleased to find that under the catalysis of $Pd(OAc)_2$ (10 mol %) and PPh_3 using *tert*-butyl peroxide (TBP) as an oxidant, the desired transesterification product, phenyl 4-nitrobenzoate **3aa** was isolated after refluxing the **1a** and **2a** in toluene (Table 1, entry 1). Then, various palladium and other transition metal catalysts were screened in the reaction (entries 2−6). Among them, $Pd(OAc)_2$ proved to be best in the yield of ester **3aa**. Then, *tert*-butyl hydroperoxide (TBHP) and O_2 as an oxidant were examined instead of TBP in the reaction. The experiment indicated that TBHP resulted in better yield than TBP while using O_2 reduced the yields of **3aa** remarkably (entries 7−9). It was noteworthy that no desired ester **3aa** was obtained without any oxidant (entry 8). A series of ligands were also screened in the reaction, and using dppe (15 mol %) led to the best yield of 74% (entry 13). Other solvents, such as *t*-BuOH, 1,4-dioxane or

Table 1. Optimization of Transesterification Reaction between Phenyl 2-Pyridinecarboxylate 1a and 4-Nitrobenzaldehyde 2a[a]



1a 2a 3aa

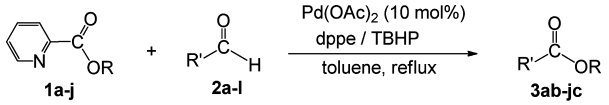
entry	catalyst	ligand	oxidant	solvent	yield (%)[b]
1	$Pd(OAc)_2$	PPh_3	TBP	toluene	35
2	$Pd(PPh_3)_4$	PPh_3	TBP	toluene	0
3	$Pd(PPh_3)_2(OAc)_2$		TBP	toluene	32
4	$Cu(OAc)_2$	PPh_3	TBP	toluene	0
5	$FeCl_3$	PPh_3	TBP	toluene	0
6	$Ru(PPh_3)_3Cl_2$	PPh_3	TBP	toluene	0
7	$Pd(OAc)_2$	PPh_3	O_2	toluene	trace
8	$Pd(OAc)_2$	PPh_3	−	toluene	0
9	$Pd(OAc)_2$	PPh_3	TBHP	toluene	52
10	$Pd(OAc)_2$	PBu_3	TBHP	toluene	49
11	$Pd(OAc)_2$	PCy_3	TBHP	toluene	63
12	$Pd(OAc)_2$	Boc-Val-OH	TBHP	toluene	37
13	$Pd(OAc)_2$	dppe	TBHP	toluene	74
14	$Pd(OAc)_2$	dppe	TBHP	*t*-BuOH	trace
15	$Pd(OAc)_2$	dppe	TBHP	CH_3CN	39
16	$Pd(OAc)_2$	dppe	TBHP	dioxane	trace

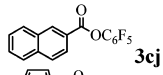
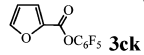
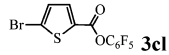
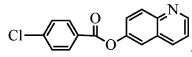
[a]Conditions: **1a** (0.25 mmol), **2a** (1.5 equiv), transition metal catalyst (10 mol %), oxidant (1.5 equiv), 115 °C, 48 h. [b]Isolated yield.

Received: June 21, 2012
Published: August 24, 2012

   dx.doi.org/10.1021/jo3012573 | *J. Org. Chem.* 2012, 77, 8344−8349

Table 2. Transesterification of Pyridine-2-carboxylates 1 with Aromatic or Aliphatic Aldehydes 2 for Versatile Carboxylates 3[a]



entry	R	R'	product 3	yield (%)[b]
1	C_6H_5 **1a**	4-NCC_6H_4 **2b**	4-NCC_6H_4CO-OC_6H_5 **3ab**	69
2	**1a**	4-ClC_6H_4 **2c**	4-ClC_6H_4CO-OC_6H_5 **3ac**	68
3	4-$CH_3COC_6H_5$ **1b**	**2b**	4-NCC_6H_4CO-$OC_6H_4COCH_3$-4 **3bb**	70
4	**1b**	**2c**	4-ClC_6H_4CO-$OC_6H_4COCH_3$-4 **3bc**	75
5	**1b**	4-BrC_6H_4 **2d**	4-BrC_6H_4CO-$OC_6H_4COCH_3$-4 **3bd**	56
6	**1b**	4-$CF_3C_6H_4$ **2e**	4-$CF_3C_6H_4CO$-$OC_6H_4COCH_3$-4 **3be**	75
7	**1b**	4-$CH_3OC_6H_4$ **2f**	4-$CH_3OC_6H_4CO$-$OC_6H_4COCH_3$-4 **3bf**	41
8	**1b**	$CH_3CH_2CH_2$ **2g**	$CH_3CH_2CH_2CO$-$OC_6H_4COCH_3$-4 **3bg**	63
9	C_6F_5 **1c**	**2a**	4-$O_2NC_6H_4CO$-OC_6F_5 **3ca**	90
10	**1c**	**2b**	4-NCC_6H_4CO-OC_6F_5 **3cb**	80
11	**1c**	**2c**	4-ClC_6H_4CO-OC_6F_5 **3cc**	89
12	**1c**	**2e**	4-$CF_3C_6H_4CO$-OC_6F_5 **3ce**	81
13	**1c**	C_6H_5 **2h**	C_6H_5CO-OC_6F_5 **3ch**	72
14	**1c**	4-HOC_6H_4 **2i**	4-HOC_6H_4CO-OC_6F_5 **3ci**	45
15	**1c**	2-naphthyl **2j**	 **3cj**	71
16	**1c**	2-furyl **2k**	 **3ck**	51
17	**1c**	 **2l**	 **3cl**	65
18	$C_6H_5CH_2$ **1d**	**2a**	4-$O_2NC_6H_4CO$-$OCH_2C_6H_5$ **3da**	51
19	**1d**	**2b**	4-NCC_6H_4CO-$OCH_2C_6H_5$ **3db**	53
20	**1d**	**2e**	4-$CF_3C_6H_4CO$-$OCH_2C_6H_5$ **3de**	55
21	4-$CF_3C_6H_4CH_2$ **1e**	**2a**	4-$O_2NC_6H_4CO$-$OCH_2C_6H_4CF_3$-4 **3ea**	53
22	**1e**	**2b**	4-NCC_6H_4CO-$OCH_2C_6H_4CF_3$-4 **3eb**	54
23	2-$ClC_6H_4CH_2$ **1f**	**2a**	4-$O_2NC_6H_4CO$-$OCH_2C_6H_4Cl$-2 **3fa**	54
24	2-$CH_3OC_6H_4CH_2$ **1g**	**2a**	4-$O_2NC_6H_4CO$-$OCH_2C_6H_4OCH_3$-2 **3ga**	58
25	**1g**	**2b**	4-NCC_6H_4CO-$OCH_2C_6H_4OCH_3$-2 **3gb**	56
26	$CH_3CH_2CH_2CH_2$ **1h**	**2a**	4-$O_2NC_6H_4CO$-$OCH_2CH_2CH_2CH_3$ **3ha**	47
27	$C_6H_5CH_2CH_2$ **1i**	**2b**	4-NCC_6H_4CO-$OCH_2CH_2C_6H_5$ **3ib**	50
28	6-quinolyl **1j**	**2c**	 **3jc**	64

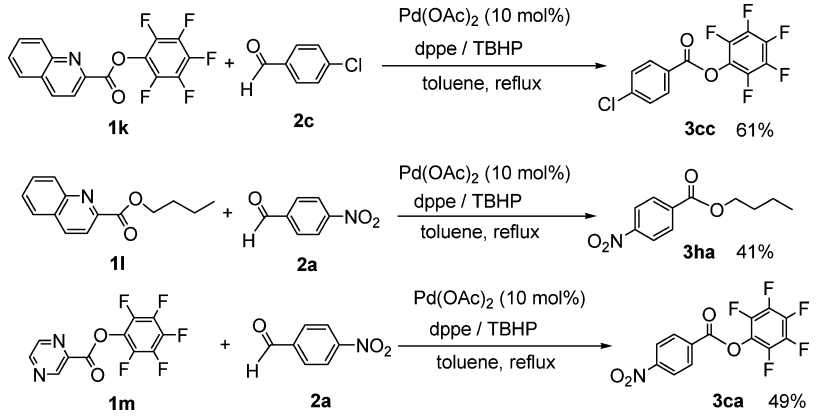
[a]Reaction conditions: **1** (0.25 mmol), **2** (1.5 equiv), $Pd(OAc)_2$ (10 mol %) and TBHP (1.5 equiv), 115 °C, 48 h. [b]Isolated yield.

CH_3CN led to a trace amount of or low yields of ester **3aa** (entries 14−16). Therefore, the optimized reaction should be performed under the catalysis of $Pd(OAc)_2$ (10 mol %) and dppe (15 mol %) using TBHP (1.5 equiv) as an oxidant at reflux in toluene.

Under the optimized reaction conditions, the scope of the transesterification reaction between various pyridine-2-carboxylates **1** and aldehydes **2** was investigated. It was found that not only aryl pyridine-2-carboxylates **1a−c** but also alkyl pyridine-2-carboxylates **1d−i** underwent the transesterification smoothly with both aromatic and aliphatic aldehydes **2a−l** to afford the desired versatile carboxylates **3** up to 90% yield (Table 2). Our experiment indicated that electron-withdrawing groups on the benzene rings of aromatic aldehydes **2a−e** are more beneficial to this reaction than electron-donating groups on those of aromatic aldehydes **2f**, **2i**, and 4-methoxybezaldehyde **2f** led to the lowest yield of the corresponding carboxylic ester **3bf** (41% yield). Although hydroxybenzaldehyde **2i** contains a hydroxy group, it did not conduct the common transesterification reaction with pentafluorophenyl pyridine-2-carboxylate **1c** to exchange pentafluorophenoxy group in **1c** with formylphenoxy group of **2i**. The **2i** kept to perform this new type of transesterification, exchanging 2-picolinyl group in **1c** with 4-hydroxybenzoyl group of **2i**. Naphthaldehyde **2j** as well as benzaldehyde derivatives performed the transesterification reaction expediently to give the corresponding naphthoic ester **3cj** in 71% yield. Using furan-2-carbaldehyde **2k** as a heteroaromatic aldehyde resulted in desired furan-2-carboxylic ester **3ck** albeit in comparatively lower yield. Interestingly, bromo substituted thiophene-2-carbaldehyde **2l**, which contains an easily cleaved C−Br bond by palladium catalysts, still led to 5-bromo-thiophene-2-carboxylic ester **3cl** in a satisfactory yield. Further experiment showed that quinolyl pyridine-2-carbox-

dx.doi.org/10.1021/jo3012573 | J. Org. Chem. 2012, 77, 8344−8349

Scheme 1. Transesterification of Other *N*-Heteroarene-2-carboxylates 1k−m with Aldehydes 2a,2c for Carboxylates 3cc, 3ha, 3ca

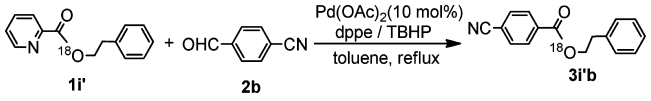


ylate **1j** could also undergo the transesterification smoothly to give desired heteroaryl carboxylic ester **3jc**.

Moreover, when other *N*-heteroarene-2-carboxylates, quinoline-2-carboxylate **1k**, **1l** and pyrazine-2-carboxylate **1m** were employed instead of the corresponding pyridine-2-carboxylate **1c**, **1h**, the transesterification reaction also proceeded expediently to afford the same aryl or alkyl carboxylates **3cc**, **3ha** or **3ca**, respectively (Scheme 1).

In order to gain insight into the transesterification reaction, we carried out preliminary studies on mechanistic pathway. We prepared ^{18}O-labeled pyridine-2-carboxylate **1i′** by using $H_2{}^{18}O$ as isotopic source. The transesterification reaction of ^{18}O-labeled **1i′** with aromatic aldehyde **2b** led to desired ester **3i′b** without the decrease of ^{18}O-labeling purity in MS under the above optimized conditions (Scheme 2). Such a result means

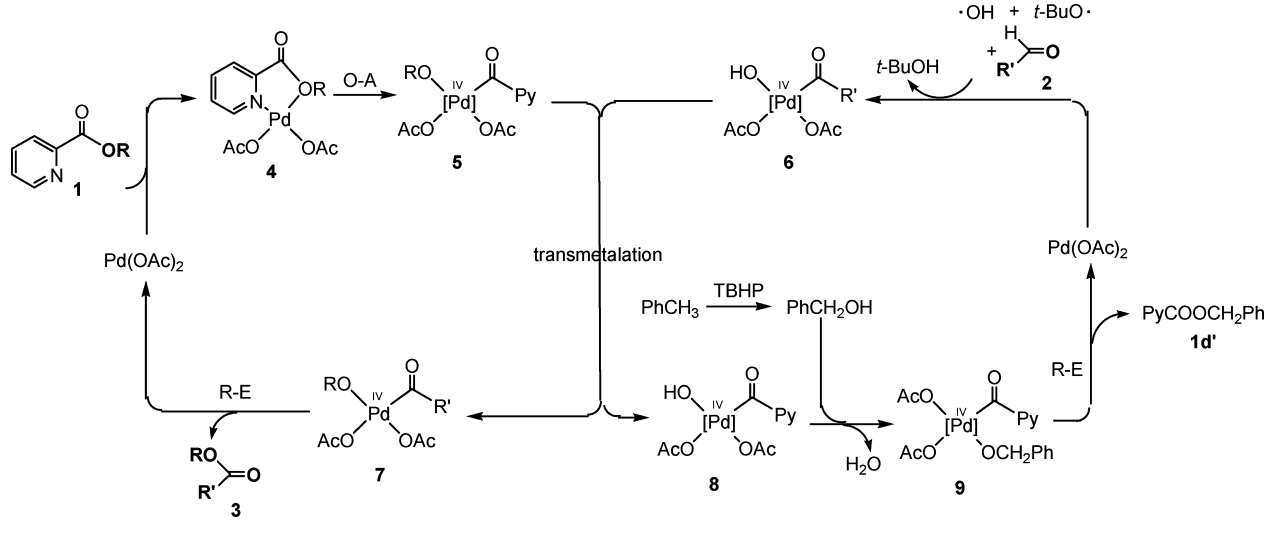
Scheme 2. Transesterification Reaction of ^{18}O-Labeled Pyridine-2-carboxylate 1i′



that the oxygen of alkoxy group in product ester **3** should come from alkoxy group in pyridine-2-carboxylate **1** and rule out that from other oxygen sources. Thus, pyridine-2-carboxylate **1** should be subjected to an oxidative addition of acyl-oxygen bond with palladium catalyst. Our experiment showed that if 2-pyridyl group in **1a** was replaced by 4-pyridyl, 4-nitrophenyl or phenyl group, the transesterification could not occur. This result suggested that nitrogen in this position could promote and control the acyl−oxygen cleavage by palladium catalyst. Moreover, when tetramethylpiperidinyloxy (TEMPO), a radical scavenger, was added into the reaction system of phenyl pyridine-2-carboxylate **1a** with 4-nitrobenzaldehyde **2a**, no desired ester **3aa** was isolated. Instead, we captured most of 4-nitrobenzoyl radical in its ester form with TEMPO.[4] This means that aldehyde should participate in the transesterification reaction in the species of acyl radical.

Therefore, the possible mechanism of the transesterification reaction is postulated as follows (Scheme 3). Initially, $Pd(OAc)_2$ could coordinate with pyridine-2-carboxylate **1** to form an intermediate **4**. In the presence of ligand, palladium in **4** may perform an intramolecular oxidative addition with acyl-oxygen bond, generating a Pd (IV) intermediate **5**. On the other hand, after TBHP dissociates into a butoxy radical and a hydroxy radical, aldehyde **2** is deprived of its hydrogen by the

Scheme 3. Possible Mechanism of the Transesterification



dx.doi.org/10.1021/jo3012573 | J. Org. Chem. 2012, 77, 8344−8349

butoxy radical to generate an acyl radical.[5] The acyl radical and the hydroxy radical undergo an oxidative addition with $Pd(OAc)_2$ to form Pd (IV) intermediate **6**. Subsequently, the intermediate **5** and **6** perform transmetalation to generate Pd (IV) intermediate **7** and **8**, respectively. The reductive elimination of **7** results in the desired ester **3**, with regenerating $Pd(OAc)_2$. MS analysis of the mixture after the reaction of **1c** with **2c** under the optimized conditions indicates that there probably existed benzyl pyridine-2-carboxylate **1d′** and 2-benzylpyridine.[6] Thus, the intermediate **8** may perform a ligand-exchange with benzyl alcohol, which is formed by the oxidation of toluene, generating intermediate **9**. The reductive elimination **9** results in pyridine-2-carboxylate **1d′**, with regenerating $Pd(OAc)_2$.

In summary, we found an unprecedented transesterification reaction of *N*-heteroarene-2-carboxylates **1** with aldehydes **2** by C−H and C−O bond activations for the synthesis of a broad scope of carboxylates **3** under neutral and mild conditions. By using $Pd(OAc)_2$ as a catalyst and TBHP as an oxidant, various aryl, heteroaryl, alkyl *N*-heteroarene-2-carboxylates **1a−m** could perform the transesterification smoothly with aromatic, heteroaromatic and aliphatic aldehydes **2a−l** to furnish versatile carboxylates **3** up to 90% yield. The transesterification reaction has good generality and tolerates various functional groups, such as nitro, cyno, hydroxy, acetyl, fluoro, chloro, bromo, trifluoromethyl and methoxy group. Neither *N*-heteroarene-2-carboxylate **1** nor aldehyde **2** is necessary to be largely excess in this reaction. ^{18}O-isotopic labeling and radical inhibiting experiments indicate that the mechanistic pathway may undergo the two key steps of oxidative addition of acyl−O bond in parent ester **1** and radical cleavage of sp^2 C−H bond in aldehyde **2**.

EXPERIMENTAL SECTION

Preparation of *N*-Heteroarene-2-carboxylates (1a−m). A mixture of *N*-heteroarene-2-carboxylic acid (10 mmol), alcohol or phenol (10 mmol), DMAP (4-(dimethylamino)pyridine, 1 mmol) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiamide hydrochloride (EDC·HCl, 10 mmol) in THF (50 mL) was stirred overnight at 25 °C. The resulting mixture was filtered, and the filtrate was evaporated in vacuo. The residue was purified by flash column chromatography (silica gel, ethyl ether/petroleum ether = 1:3 as eluent), affording a corresponding *N*-heteroarene-2-carboxylic ester **1a−m**.

General Procedure for the Transesterification Reaction. A mixture of *N*-heteroarene-2-carboxylate **1** (0.25 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol %) and dppe (14.9 mg, 0.0375 mmol, 15 mol %) in toluene (1 mL) was sealed in a 40 mL-vial. The reaction mixture was heated at 115 °C for 10 min. Then, aldehyde **2** (0.375 mmol) and TBHP (33.8 mg, 0.375 mmol) were added, and the resulting mixture was refluxed for 36−48 h. After cooling to room temperature, the mixture was filtered, and the filtrate was evaporated in vacuo. The residue was purified by flash column chromatography (silica gel, ethyl acetate/petroleum ether = 1:3 to 1:8 as an eluent) to afford the desired carboxylic ester **3**.

Phenyl 4-Nitrobenzoate ***3aa***.[7] Yield: 74% (44.9 mg); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.44−8.33 (m, 4H), 7.52−7.42 (m, 2H), 7.37−7.28 (m, 1H), 7.26−7.20 (m, 2H); MS (EI) *m*/*z* (%) 242.9 (M^+, 6), 149.9(100), 119.9(88), 103.9(20), 93.9(12), 91.9(13), 75.9(9).

Phenyl 4-Cyanobenzoate ***3ab***.[7] Yield: 69% (38.4 mg); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.32 (d, *J* = 8.5 Hz, 2H), 7.83 (d, *J* = 8.5 Hz, 2H), 7.50−7.41 (m, 2H), 7.36−7.27 (m, 1H), 7.25−7.18 (m, 2H); MS (EI) *m*/*z* (%) 222.9 (M^+, 20), 129.9(77), 101.9 (100), 93.9(7).

Phenyl 4-Chlorobenzoate ***3ac***.[7] Yield: 68% (39.4 mg); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.15 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.7 Hz, 2H), 7.48−7.39 (m, 2H), 7.33−7.27 (m, 1H), 7.25−7.18 (m, 2H); MS (EI) *m*/*z* (%) 231.9 (M^+, 2), 140.9(31), 138.8 (100), 110.9(23).

4-Acetylphenyl 4-Cyanobenzoate ***3bb***.[8] Yield: 70% (46.4 mg); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.32 (d, *J* = 8.5 Hz, 2H), 8.08 (d, *J* = 8.7 Hz, 2H), 7.85 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 2H), 2.64 (s, 3H); MS (EI) *m*/*z* (%) 264.9 (M^+, 3), 136.0(4), 129.9 (100), 120.9(17), 101.9(33), 42.9(2).

4-Acetylphenyl 4-Chlorobenzoate ***3bc***.[9] Yield: 75% (51.4 mg); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.14 (d, *J* = 8.6 Hz, 2H), 8.06 (d, *J* = 8.7 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.33 (d, *J* = 8.7 Hz, 2H), 2.63 (s, 3H); MS (EI) *m*/*z* (%) 273.9 (M^+, 1), 140.9(50), 138.8 (100), 135.9(3), 120.9(14), 110.9(48), 42.9(3).

4-Acetylphenyl 4-Bromobenzoate ***3bd***. Yield: 56% (44.5 mg); mp 150−152 °C; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.08 (d, *J* = 2.4 Hz, 2H), 8.05 (d, *J* = 2.5 Hz, 2H), 7.68 (d, *J* = 8.6 Hz, 2H), 7.33 (d, *J* = 8.7 Hz, 2H), 2.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 196.9, 164.0, 154.5, 135.0, 132.1, 131.7, 130.1, 129.3, 128.0, 121.9, 26.6; Anal. Calcd. For $C_{15}H_{11}BrO_3$: C, 56.45; H, 3.47%. Found: C, 56.27; H, 3.64%; MS (EI) *m*/*z* (%) 317.9(M^+, 0.33), 184.8(80), 182.8 (100), 154.8(13), 135.9(2), 120.9(7).

4-Acetylphenyl 4-(Trifluoromethyl)benzoate ***3be***. Yield: 75% (57.7 mg); mp 102−104 °C; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.33 (d, *J* = 8.2 Hz, 2H), 8.07 (d, *J* = 8.7 Hz, 2H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 2H), 2.64 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)196.8, 163.5, 154.3, 135.6, 135.1, 132.3, 130.7, 130.1, 125.8, 125.7, 125.3, 121.8, 26.6; MS (EI) *m*/*z* (%) 307.9 (M^+, 4), 289.0(5), 172.9 (100), 144.9(84), 120.9(7), 94.9(6), 42.9(2). Anal. Calcd. For $C_{16}H_{11}F_3O_3$: C, 62.34; H, 3.60%. Found: C, 62.44; H, 3.81%.

4-Acetylphenyl 4-Methoxybenzoate ***3bf***.[9] Yield: 41% (27.7 mg); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.16 (d, *J* = 8.9 Hz, 2H), 8.05 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 7.00 (d, *J* = 9.0 Hz, 2H), 3.91 (s, 3H), 2.63 (s, 3H); MS (EI) *m*/*z* (%) 270.0(M^+, 0.15), 135.9(6), 134.9 (100), 120.9(8), 106.9(6).

4-Acetylphenyl Butyrate ***3bg***.[10] Yield: 63% (32.4 mg); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.00 (d, *J* = 8.7 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 2.62−2.54 (m, 5H), 1.89−1.72 (m, 2H), 1.06 (t, *J* = 7.4 Hz, 3H); MS (EI) *m*/*z* (%) 206.0 (M^+, 4), 136.9(64), 135.9(13), 120.9 (100), 70.9(94), 43.0(53).

2,3,4,5,6-Pentafluorophenyl 4-Nitrobenzoate ***3ca***.[11] Yield: 90% (74.9 mg); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.42−8.39 (m, 4H); MS (EI) *m*/*z* (%) 183.9(18), 154.9(9), 149.9(100), 135.9(10), 119.9(62), 116.9(7), 103.9(97), 75.9(41).

2,3,4,5,6-Pentafluorophenyl 4-Cyanobenzoate ***3cb***.[12] Yield: 80% (62.6 mg); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.32 (d, *J* = 8.5 Hz, 2H), 7.87 (d, *J* = 8.5 Hz, 2H); MS (EI) *m*/*z* (%) 183.8(5), 154.8(6), 129.9(100), 101.9(63), 74.9(6).

2,3,4,5,6-Pentafluorophenyl 4-Cholrobenzoate ***3cc***.[13] Yield: 89% (71.6 mg); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.15 (d, *J* = 8.7 Hz, 2H), 7.54 (d, *J* = 8.7 Hz, 2H); ^{19}F NMR (400 MHz, $CDCl_3$) δ (ppm) −152.23 to −152.63 (m, 2F), −157.60 (t, *J* = 21.7 Hz, 1F), −161.94 to −162.38 (m, 2F); MS (EI) *m*/*z* (%) 184.0(0.22), 141.0(17), 139.0(100), 111.0(49).

2,3,4,5,6-Pentafluorophenyl 4-(Trifluoromethyl)benzoate ***3ce***.[14] Yield: 81% (72.1 mg); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.34 (d, *J* = 8.2 Hz, 2H), 7.83 (d, *J* = 8.3 Hz, 2H); MS (EI) *m*/*z* (%) 336.8(5), 172.9(100), 154.8(7), 144.9(90), 124.9(7), 94.9(9), 74.9(5).

2,3,4,5,6-Pentafluorophenyl Benzoate ***3ch***.[15] Yield: 72% (51.8 mg); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.27−8.16 (m, 2H), 7.77−7.67 (m, 1H), 7.62−7.51 (m, 2H). ; MS (EI) *m*/*z* (%) 183.8(100), 154.8(8), 135.9(82), 116.9(38), 104.9(20).

2,3,4,5,6-Pentafluorophenyl 4-Hydroxybenzoate ***3ci***.[16] Yield: 45% (34.2 mg); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.11 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 8.5 Hz, 2H); MS (EI) *m*/*z* (%) 184.0(58), 136.0(38), 121.1 (100), 93.1(16).

2,3,4,5,6-Pentafluorophenyl 2-Naphthoate ***3cj***.[17] Yield: 71% (60.1 mg); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.82 (s, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 8.08−7.85 (m, 3H), 7.76−7.51 (m, 2H);^{19}F NMR (400 MHz, $CDCl_3$) δ (ppm) −152.25 to −152.49 (m, 2F), −157.97 (t, *J* = 21.7 Hz, 1F), −162.14 to −162.57 (m, 2F);MS (EI) *m*/*z* (%) 155.1(100), 127.1(99), 101.1(2), 77.1(3).

dx.doi.org/10.1021/jo3012573 | J. Org. Chem. 2012, 77, 8344−8349

2,3,4,5,6-Pentafluorophenyl Furoate ***3ck***.[11] Yield: 51% (35.4 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.76 (d, J = 0.9 Hz, 1H), 7.51 (d, J = 3.6 Hz, 1H), 6.66 (dd, J = 3.6, 1.7 Hz, 1H); MS (EI) m/z (%) 183.8(100), 135.8(56), 116.9(25), 94.9(38).

2,3,4,5,6-Pentafluorophenyl 5-Bromo-2-thiophenecarboxylate ***3cl***.[18] Yield: 65% (60.4 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.81 (d, J = 4.1 Hz, 1H), 7.21 (d, J = 4.1 Hz, 1H); ^{19}F NMR (400 MHz, $CDCl_3$) δ (ppm) −152.06 to −152.35 (m, 2F), −157.28 (t, J = 21.7 Hz, 1F), −161.90 to −162.21 (m, 2F); MS (EI) m/z (%) 190.9(85), 188.9(100), 184.0(6), 160.9(5).

Benzyl 4-Nitrobenzoate ***3da***.[19] Yield: 51% (32.8 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.33−8.18 (m, 4H), 7.50−7.30 (m, 5H), 5.41 (s, 2H); MS (EI) m/z (%) 257.1 (M^+, 44), 227.1(9), 150.0 (100), 134.0(17), 120.0(68), 91.1(95).

Benzyl 4-Cyanobenzoate ***3db***.[20] Yield: 53% (31.4 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.17 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 7.48−7.34 (m, 5H), 5.39 (s, 2H); MS (EI) m/z (%) 236.9 (M^+, 45), 129.9 (100), 101.9(19), 90.9(45).

Benzyl 4-(Trifluoromethyl)benzoate ***3de***.[21] Yield: 55% (38.5 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.19 (d, J = 8.1 Hz, 2H), 7.71 (d, J = 8.2 Hz, 2H), 7.50−7.33 (m, 5H), 5.40 (s, 2H); MS (EI) m/z (%) 280.1 (M^+, 15), 173.0 (100), 145.0(43), 91.1(41).

4-(Trifluoromethyl)benzyl 4-Nitrobenzoate ***3ea***. Yield: 53% (43.1 mg); mp 95−97 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.35−8.20 (m, 4H), 7.68 (d, J = 8.1 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H), 5.46 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 164.4, 150.8, 139.2, 135.1, 130.9, 130.8 (q, J_{C-F} =32.6 Hz)), 128.8, 128.4, 125.8(q, J_{C-F} = 3.75 Hz), 123.9 (q, J_{C-F} =272 Hz), 123.7, 66.6; Anal. Calcd. For $C_{15}H_{10}F_3NO_4$: C, 55.39; H, 3.10; N, 4.31%. Found: C, 55.59; H, 3.40; N, 4.21%; MS (EI) m/z (%) 324.9 (M^+, 3), 308.9(5), 294.9(17), 158.9(61), 149.9 (100), 119.9(46).

4-(Trifluoromethyl)benzyl 4-Cyanobenzoate ***3eb***. Yield: 54% (41.2 mg); mp 77−79 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.18 (d, J = 8.6 Hz, 2H), 7.77 (d, J = 8.6 Hz, 2H), 7.67 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 8.1 Hz, 2H), 5.45 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 164.6, 139.3, 133.6, 132.3, 130.8 (q, J_{C-F} =32.6 Hz), 130.2, 128.4, 125.7 (q, J_{C-F} = 3.75 Hz), 123.9 (q, J_{C-F} =272 Hz), 117.8, 116.8, 66.5; Anal. Calcd. For $C_{16}H_{10}F_3NO_2$: C, 62.96; H, 3.30; N, 4.59%. Found: C, 63.16; H, 3.50; N, 4.37%; MS (EI) m/z (%) 304.9 (M^+, 24), 158.9(60), 129.9 (100), 101.9(32).

2-Chlorobenzyl 4-Nitrobenzoate ***3fa***.[22] Yield: 54% (39.3 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.38−8.16 (m, 4H), 7.54−7.48 (m, 1H), 7.47−7.41 (m, 1H), 7.39−7.28 (m, 2H), 5.51 (s, 2H); MS (EI) m/z (%) 290.9(M^+, 0.09), 255.9(100), 225.9(15), 149.9(54), 126.9(16), 124.9(73), 119.9(65).

2-Methoxybenzyl 4-Nitrobenzoate ***3ga***.[22] Yield: 58% (41.6 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.33−8.18 (m, 4H), 7.46−7.30 (m, 2H), 7.04−6.89 (m, 2H), 5.46 (s, 2H), 3.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.67, 157.75, 150.51, 135.84, 130.81, 130.05, 129.97, 123.49, 120.50, 110.62, 63.22, 55.48; MS (EI) m/z (%) 286.9 (M^+, 11), 149.9(7), 136.9 (100), 120.9(40), 119.9(11), 90.9(73).

2-Methoxybenzyl 4-Cyanobenzoate ***3gb***.[22] Yield: 56% (37.4 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 6.8 Hz, 2H), 7.73 (d, J = 6.8 Hz, 2H), 7.43−7.30 (m, 2H), 7.04−6.86 (m, 2H), 5.44 (s, 2H), 3.86 (s, 3H); MS(EI) m/z (%) 266.9 (M^+, 9), 136.9(100), 129.9(72), 120.9(17), 101.9(24), 90.9(55).

Butyl 4-Nitrobenzoate ***3ha***.[23] Yield: 47% (26.2 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.34−8.16 (m, 4H), 4.38 (t, J = 6.6 Hz, 2H), 1.87−1.69 (m, 2H), 1.58−1.39 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H); MS (EI) m/z (%) 222.9 (M^+, 0.76), 149.9(79), 119.9 (100), 103.9(21), 91.9(26), 75.9(14), 56.0(38).

Phenethyl 4-Cyanobenzoate ***3ib***.[24] Yield: 50% (31.4 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.09 (d, J = 8.5 Hz, 2H), 7.72 (d, J = 3.0 Hz, 2H), 7.36−7.30 (m, 2H), 7.30−7.19 (m, 3H), 4.57 (t, J = 6.9 Hz, 2H), 3.09 (t, J = 6.9 Hz, 2H). MS (EI) m/z (%) 130.0(60), 119.1(3), 104.1 (100), 102.0(27), 91.1(45), 77.0(16), 44.0(5).

Quinolin-6-yl 4-Chlorobenzoate ***3jc***.[25] Yield: 64% (45.3 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.95 (d, J = 2.9 Hz, 1H), 8.26−8.13 (m, 4H), 7.72 (d, J = 2.4 Hz, 1H), 7.60 (dd, J = 9.1, 2.5 Hz, 1H), 7.53 (d, J = 8.5 Hz, 2H), 7.47 (dd, J = 8.2, 4.3 Hz, 1H); MS (EI) m/z (%) 283.1 (M^+,9), 141.0(55), 139.0 (100), 127.9(44), 126.9(35), 111.0(59); MS (ESI) m/z 284.05 $[M + H]^+$.

^{18}O-Isotopic Labeling and Radical Inhibiting Experiments. *^{18}O-Isotopic Labeling Experiment. Preparation of (^{18}O) Phenethyl 2-Pyridinecarboxylate* ***1i′***. A mixture of phenethyl bromide (9.2 g, 50 mmol), $AgNO_3$ (4.25 g, 25 mmol) and $H_2{}^{18}O$ (1.0 g, about 50 mmol) was stirred at 50 °C for 12 h. The resulting mixture was filtered, and the filtrate was purified by flash column chromatography (silica gel, ethyl ether/petroleum ether = 1:3 as eluent), affording ^{18}O-isotopic phenethyl alcohol. Then the mixture of the phenethyl alcohol (1.24 g, 10 mmol), pyridine-2-carboxylic acid (1.23 g, 10 mmol), DMAP (0.12 g, 1 mmol) and EDC·HCl (1.92 g, 10 mmol) in THF (50 mL) was stirred overnight at 25 °C. The resulting mixture was filtered, and the filtrate was evaporated in vacuo. The residue was purified by flash column chromatography (silica gel, ethyl ether/petroleum ether = 1:3 as eluent), affording the desired ^{18}O-phenethyl pyridine-2-carboxylate **1i′**.

The experimental procedure is similar to the general procedure of the transesterification reaction, affording desired ^{18}O-phenethyl 4-cyanobenzoate **3i′b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.09 (d, J = 8.5 Hz, 2H), 7.72 (d, J = 3.0 Hz, 2H), 7.36−7.30 (m, 2H), 7.30−7.19 (m, 3H), 4.57 (t, J = 6.9 Hz, 2H), 3.09 (t, J = 6.9 Hz, 2H); MS (EI) m/z (%) 130.0(100), 104.1(61), 91.1(23), 77.0(4); MS (ESI) m/z: 252.05 $[M - H]^-$.

Radical Inhibiting Experiment. A mixture of phenyl 2-pyridinecarboxylate **1a** (60.8 mg, 0.25 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol %), dppe (14.9 mg, 0.0375 mmol, 15 mol %) in toluene (1 mL) was sealed in a 40-mL vial. The reaction mixture was heated at 115 °C for 10 min. Then 4-nitrobenzaldehyde **2a** (56.6 mg, 0.375 mmol), TEMPO (58.9 mg, 0.375 mmol) and TBHP (33.8 mg, 0.375 mmol) were added, and the resulting mixture was refluxed for 48 h. After cooling to room temperature, the mixture was filtered, and the filtrate was evaporated in vacuo. The residue was purified by flash column chromatography (silica gel, ethyl ether/petroleum ether = 1:5), affording 4-nitrobenzoyl-TEMPO ester **11** in about 70% yield.

2,2,6,6-Tetramethyl-piperidin-1-yl 4-Nitrobenzoate ***11***.[26] ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.40−8.29 (m, 2H), 8.29−8.17 (m, 2H), 1.85−1.44 (m, 6H), 1.28 (s, 6H), 1.12 (s, 6H); MS(ESI) m/z 329.05 $[M + Na]^+$.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectra of ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and MS. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Fax: (+86)25-83686231. E-mail: huangzz@nju.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from National Natural Science Foundation of China (No. 21072091) and MOST of China (973 program 2011CB808600) is gratefully acknowledged.

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