

Note

Aerobic Copper-Catalyzed O-Methylation with Methylboronic Acid

Clare E Jacobson, Noelia Martinez-Munoz, and David J. Gorin

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.5b01077 • Publication Date (Web): 26 Jun 2015

Downloaded from <http://pubs.acs.org> on July 2, 2015

Just Accepted

“Just Accepted” manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides “Just Accepted” as a free service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. “Just Accepted” manuscripts appear in full in PDF format accompanied by an HTML abstract. “Just Accepted” manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are accessible to all readers and citable by the Digital Object Identifier (DOI®). “Just Accepted” is an optional service offered to authors. Therefore, the “Just Accepted” Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the “Just Accepted” Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these “Just Accepted” manuscripts.



ACS Publications
High quality. High impact.

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036
Published by American Chemical Society. Copyright © American Chemical Society.
However, no copyright claim is made to original U.S. Government works, or works
produced by employees of any Commonwealth realm Crown government in the course
of their duties.

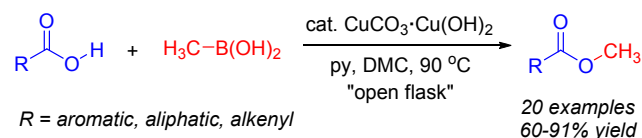
Aerobic Copper-Catalyzed O-Methylation with Methylboronic Acid

Clare E. Jacobson, Noelia Martinez-Muñoz, and David J. Gorin*

Department of Chemistry, Smith College, Northampton, MA 01063

dgorin@smith.edu

Abstract:



The oxidative coupling of alkylboronic acids with oxygen nucleophiles offers a strategy for replacing toxic, electrophilic alkylating reagents. Although the Chan-Lam reaction is widely applied in the arylation of heteroatom nucleophiles, O-alkylation with boronic acids is rare. We report a Cu-catalyzed nondecarboxylative methylation of carboxylic acids with methylboronic acid that proceeds under air with no additional oxidant. An isotope-labeling study supports an oxidative cross-coupling mechanism, in analogy to that proposed for Chan-Lam arylation.

The methylation of oxygen nucleophiles is ubiquitous in contemporary academic and industrial organic synthesis.¹ Typical methods use electrophilic reagents such as methyl iodide, dimethyl sulfate, and diazomethane.² While effective, these reagents are generally unstable and/or hazardous.³ which has motivated chemists to seek safer alternatives. as in the use of trimethylsilyl diazomethane rather than diazomethane.⁴ Unfortunately, trimethylsilyl diazomethane exposure is implicated in two recent laboratory-related deaths,⁵ demonstrating the unmet need for safe, effective methylating reagents.

Therefore, we are pursuing alternate strategies and reagents for O-alkylation.⁶ The use of a nucleophilic methyl source to replace typical reagents would avoid the intrinsic toxicity associated with electrophiles, offering a practical advantage.⁷ Additionally, the selective oxidative cross-coupling of an alkylmetal(loid) reagent and an oxygen nucleophile might enable reaction selectivity and functional group compatibility that complement traditional methods.⁸

The Cu-catalyzed oxidative coupling of heteroatom nucleophiles with arylboronic acids, known as the Chan-Lam reaction, is widely-applied for N- and O-arylation.⁹ In some cases, oxygen present under "open flask" conditions enables catalyst turnover, offering practical and green oxidative conditions.¹⁰ Despite the success of Chan-Lam arylation, the first couplings of alkylboronic acids with heteroatom nucleophiles have emerged only recently.¹¹ Although stoichiometric Cu is often required,^{11b-d,g} the alkylation of phenols, anilines, and amides proceeds with catalytic Cu using an organic peroxide as the terminal oxidant.^{11e,f} To the best of our knowledge, Tsuritani's N-cyclopropylation of indoles is the sole Chan-Lam alkylation that proceeds with catalytic Cu and air as the only added oxidant.^{11a}

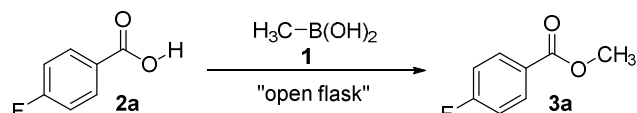
Methylboronic acid (**1**) and related compounds, especially trimethylboroxine and methyltrifluoroborate salts, have been previously employed as methylating reagents.¹² Methyl transfer from **1** to canonical nucleophiles is rare; Cruces used stoichiometric Cu to mediate the N-methylation of anilines,^{11c} but this has not yet been extended to any oxygen nucleophile.

Although an array of oxygen nucleophiles participate in Chan-Lam coupling, most examples use phenols or aliphatic alcohols and carboxylic acids are rarely employed. The use of carboxylic acids is complicated by the potential for decarboxylation, which occurs under an array of conditions.¹³ Non-decarboxylative arylations and alkenylations of carboxylic acids with boronic acids are reported, but the analogous

alkylation has not been demonstrated.¹⁴ We therefore chose to investigate the synthesis of methyl esters by cross-coupling of **1** and carboxylic acids.¹⁵

We report herein an aerobic, Cu-catalyzed methylation of carboxylic acids with **1**. The basic reaction conditions complement those of Fisher esterification and the reaction proceeds open to air without any additional oxidant. Mechanistic studies support a Chan-Lam-type mechanism where the methyl group is transferred from the boronic acid to the substrate.

Table 1. Optimization of Cu-Catalyzed Esterification



entry ^a	[Cu]	additive	solvent	yield (%) ^b
1 ^c	Cu(OTf) ₂	urea	EtOAc	<1
2	Cu(OAc) ₂	py	dioxane	54
3	Cu(OAc) ₂	py	Cl-C ₆ H ₅	64
4	Cu(OAc) ₂	py	DEC	71
5	CuBr ₂	py	DEC	<1
6	Cu(OTf) ₂	py	DEC	47
7	Cu(acac) ₂	py	DEC	46
8	CuCO ₃ ·Cu(OH) ₂ ^d	py	DEC	73
9	CuCO ₃ ·Cu(OH) ₂ ^d	Cs ₂ CO ₃	DEC	<1
10	CuCO ₃ ·Cu(OH) ₂ ^d	Et ₃ N	DEC	10
11	CuCO ₃ ·Cu(OH) ₂ ^d	urea	DEC	13
12	CuCO ₃ ·Cu(OH) ₂ ^d	py	DMC	71 (76) ^e

^a Reaction conditions: [**2a**] = 0.2 M in solvent, 2.5 equiv **1**, 0.2 equiv [Cu], 3.5 equiv additive, 90 °C, 24 h. ^b Determined by ¹⁹F NMR against an internal standard. ^c Temp = 60 °C. ^d 0.1 equiv ^e Isolated yield.

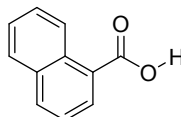
The reaction of 4-fluorobenzoic acid (**2a**) was chosen for preliminary study so that conversion to **3a** could be quantitatively determined by ¹⁹F NMR. Initial screening conditions were adopted from close literature precedent, with the added constraint that only 0.2 equiv of the Cu catalyst was used. The reaction of **2a** and **1** under Cheng's conditions for the arylation of carboxylic acids^{14c} yielded no product (Table 1, entry 1). In contrast, **3a** was formed in 54% yield using modified conditions from Cruces' methylation of anilines (entry 2).^{11c} Surprisingly, this initial result demonstrated catalyst turnover under "open flask" conditions.

Other solvents were screened and found to be effective, including chlorobenzene and diethyl carbonate (DEC) (entries 3-4). Dialkyl carbonates have emerged as non-toxic, green solvents, and therefore DEC was chosen for further optimization studies.¹⁶

Since carboxylic acids are substrates in this chemistry, we sought a catalyst precursor without carboxylate ligands. Although CuBr_2 was ineffective, Cu complexes with oxyanionic ligands of varying basicities, including $\text{Cu}(\text{OTf})_2$ and $\text{Cu}(\text{acac})_2$, catalyzed formation of **3a** (entries 4-8). Ultimately, cupric carbonate $[\text{CuCO}_3 \cdot \text{Cu}(\text{OH})_2]$ emerged as the optimal Cu source (entry 8).¹⁷

Pyridine is essential for the reaction. When Cs_2CO_3 replaced pyridine, no **3a** was observed (entry 9). Low yields also resulted with triethylamine or urea (entries 10-11). In the final, optimized conditions, dimethyl carbonate (DMC) replaced higher-boiling DEC to ease solvent removal, and **3a** was isolated in 76% yield (entry 12).

Table 2. Methylation of Aromatic Carboxylic Acids

$\text{Ar}-\text{C}(=\text{O})\text{OH} \xrightarrow[\text{2.5 equiv 1, py, DMC, air, 90 }^\circ\text{C, 24 h}]{\text{0.1 equiv CuCO}_3 \cdot \text{Cu}(\text{OH})_2} \text{Ar}-\text{C}(=\text{O})\text{OCH}_3$		
2b-I		3b-I
entry	substrate	yield (%)
1	X = 4-tBu 2b	91
2	4-Br 2c	85
3	3-Cl 2d	88
4	4-Ac 2e	66
5	4-CN 2f	79
6	3,4-(-OCH ₂ O-) 2g	74
7	2-CH ₃ 2h	68
8	2-OMe 2i	78
9	 2j	73
10	Y = H 2k	0
11	CH ₃ 2l	67

An array of aromatic carboxylic acids undergo Cu-catalyzed oxidative methylation. Alkyl-substituted **2b** provided ester **3b** in 91% yield. Despite the potential for Cu-mediated reactions of aryl halides,¹⁸ brominated and chlorinated benzoic acid derivatives were smoothly transformed (entries 2-3). However, no methyl ester was observed in the reaction with 4-iodobenzoic acid.

Electron-deficient substrates with ketone and nitrile substituents formed the corresponding methyl esters **3e** and **3f** in 66% and 79% yield, respectively (entries 4-5). Electron-donating substituents are similarly tolerated (entries 1, 6-8). For example, piperonylic acid (**2g**) was methylated in 74% yield (entry 6).

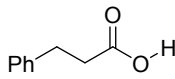
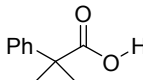
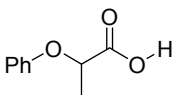
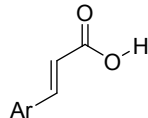
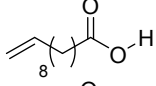
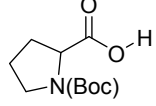
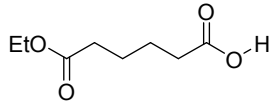
The methylation of 2-substituted benzoic acid derivatives proceeded despite the increased steric demands of the substrates (entries 7-9). Notably, Pd-catalyzed carboxylate-directed C-H methylation of

2h and similar compounds with **1** has been reported.^{12b} This demonstrates that the chemoselectivity of the methylation event may be controlled by the choice of catalyst and reaction conditions.

Given the importance of aromatic heterocycles, the reaction of indole-2-carboxylic acid (**2k**) was investigated. Although no product was observed with the N-H indole, N-methyl derivative **2l** was transformed into **3l** in 67% yield.

The oxidative methylation was applied to aliphatic carboxylic acids to further probe reaction scope. Hydrocinnamic acid (**2m**) was methylated in 80% yield (Table 3, entry 1). Neopentyl ester **3n** was also formed, albeit in reduced yield (entry 2). α -Oxygenated **2o**, which might be susceptible to elimination under the basic reaction conditions, provided **3o** in 78% yield (entry 3). Substrates with alkene functionality are methylated in moderate yields, including cinnamic acid derivatives (entries 4-6) and primary olefin **2s** (entry 7).

Table 3. Esterification of Aliphatic and Alkenyl Substrates

$\text{R}-\text{C}(=\text{O})\text{OH} \xrightarrow[\text{air, 90 } ^\circ\text{C, 24 h}]{\text{0.1 equiv CuCO}_3 \cdot \text{Cu(OH)}_2, \text{ 2.5 equiv } \mathbf{1}, \text{ py, DMC}} \text{R}-\text{C}(=\text{O})\text{OCH}_3$		
entry	substrate	yield (%)
1	 2m	80
2	 2n	65
3	 2o	78
4	Ar = Ph 2p	66
5	4-OMe-Ph 2q	67
6	4-Cl-Ph 2r	67
		
7	 2s	60
8	 2t	73
9	 2u	78

As demonstrated by the transformation of acid-sensitive N-Boc-proline (**2t**), this O-methylation is complementary to Fisher esterification. Ester **2u** was methylated to see if the ethyl ester would endure.

Mixed diester **3u** was exclusively observed, demonstrating that transesterification does not occur under the basic reaction conditions.

The coupling of **1** with a carboxylic acid requires an oxidation event and we next investigated the terminal oxidant. Since the catalytic reaction proceeds under "open flask" conditions, we propose that molecular oxygen from air serves as the ultimate electron acceptor. To test this, oxygen was excluded from the reaction, which resulted in only trace formation of **3a** (Table 4, entry 1). To exclude the possibility that the combination of atmospheric water and methylboronic acid is the oxidant,¹⁹ water was added to the reaction. Low product yield was observed, suggesting that oxygen is necessary (entry 2).

Other oxidants were also screened. While use of HOOTBu and PhI(OAc)₂ resulted in low yields, tBuOOTBu provided **3a** in yield comparable to the "open-flask" reaction. A control experiment in which **1** was omitted resulted in no product formation, suggesting that the peroxide is not the methyl source under these conditions (See SI, eq S1).²⁰ While practically the use of air is advantageous, it is noteworthy that the successful reaction observed with tBuOOTBu parallels previous non-aerobic Cu-catalyzed Chan-Lam alkylations.^{11e,f}

Table 4. Terminal Oxidant Screen

2a	$\xrightarrow[\text{N}_2 \text{ atmosphere}]{[\text{Cu}], 1}$	3a
entry ^a	additive (2 equiv)	NMR yield (%)
1	none	<1
2	H ₂ O	8
3	PhI(OAc) ₂	<1
4	aqueous HOOtBu	12
5	tBuOOTBu	73

^a Conditions: 0.1 equiv CuCO₃·Cu(OH)₂, 3.5 equiv py, 2.5 equiv **1**, DEC, 90 °C, 24 h.

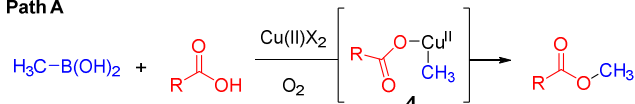
We next considered possible reaction mechanisms. The O-methylation may proceed similarly to Chan-Lam O-arylation, which has recently been studied (Scheme 1, path A).²¹ In accord with Stahl's studies, intermediate **4** may be formed by ligand exchange with the carboxylic acid and transmetalation with **1**. Reductive elimination, likely from a Cu(III) species, and oxidation with O₂ would yield the product and regenerate the Cu(II) catalyst.

Given the single prior report of aerobic Cu-catalyzed Chan-Lam alkylation,^{11a} alternate mechanistic pathways were considered. Oxidation of aryl- or alkyl-boronic acids to the corresponding phenols and

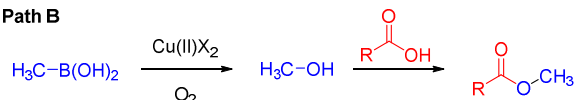
alcohols occurs under a variety of conditions,²² and methanol formed *in situ* might react with the carboxylic acid to form the product (Scheme 1, path B).²³

Scheme 1. Possible Mechanistic Pathways

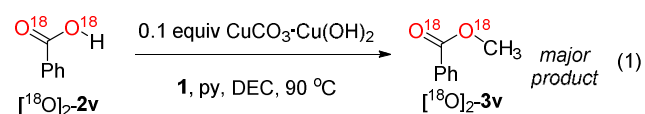
Path A



Path B



An isotope-labeling experiment was used to differentiate between the mechanistic proposals. The reaction of ¹⁸O-labeled benzoic acid ([¹⁸O]₂-**2v**) resulted in the formation of ester [¹⁸O]₂-**3v** with both labeled atoms retained (eq 1). This is inconsistent with a carbonyl substitution mechanism (path B). Additionally, no product was observed upon substitution of methanol for **1** (see SI, eq S2). Taken together, these experiments suggest that Cu-catalyzed O-methylation proceeds via a cross-coupling mechanism analogous to that proposed for Chan-Lam arylation (path A).²¹



In conclusion, a Cu-catalyzed Chan-Lam methylation of carboxylic acids has been developed. The esterification of aryl, aliphatic, and alkenyl carboxylic acids with **1** proceeds under air without any additional oxidant. The basic reaction conditions complement those of Fisher esterification, and mechanistic studies support a methyl transfer mechanism from **1** to the substrate. This reaction expands the scope of Chan-Lam coupling to include nondecarboxylative alkylation of carboxylic acids and demonstrates a strategy to replace toxic electrophilic reagents in O-alkylation.

Experimental Section.

General Information. Unless otherwise noted, all reagents were obtained commercially and used without further purification. Basic cupric carbonate ($\text{CuCO}_3\cdot\text{Cu(OH)}_2$, CAS: 12069-69-1) was obtained from Fisher Scientific. TLC analysis of reaction mixtures was performed on silica gel 60 F254 TLC plates using KMnO_4 stain and UV light to visualize the reaction components. Column chromatography was carried out

on 60 Å, 40-63 µm silica gel using mixtures of ethyl acetate and hexanes as eluent. ^1H NMR spectra were referenced to chloroform and obtained at a frequency of 300 MHz or 500 MHz, as noted. ^1H -decoupled ^{19}F NMR spectra were referenced to 4-methoxy-3-nitro-benzotrifluoride and obtained at 470 MHz. GCMS analysis was performed using a J&W DB5-ms GC capillary column (0.25 mm x 30 m, 0.25 µm film thickness).

General procedure for optimizing the methylation of **2a**

To a 2 dram screw-top vial equipped with a magnetic stir bar was added **2a** (31 mg, 0.22 mmol), 4-methoxy-3-nitro-benzotrifluoride (internal standard, 16 mg, 0.07 mmol), and the appropriate solvent (1.1 mL). The appropriate amine was added (3.5 equiv, 0.77 mmol). An aliquot (100 µL) was removed and used as the T = 0 sample for quantifying reaction progress. To the remaining solution was added the copper complex (0.2 equiv, 0.04 mmol) and methylboronic acid (**1**) (30 mg, 0.5 mmol). (For the reactions with $\text{CuCO}_3 \cdot \text{Cu}(\text{OH})_2$, 0.1 equiv of the copper complex was used.) A rubber septa with a vent needle was placed over the top of the screw top vial and the reaction mixture was heated to 90 °C. After stirring for 24 hours, the reaction was cooled and a second aliquot was removed. The T=0 and T=24 hour aliquots were each diluted in CDCl_3 and analyzed by ^1H -decoupled ^{19}F NMR.

General procedure for the methylation of carboxylic acids (2a-2u) with 1. To a 10 mL round bottom flask equipped with magnetic stir bar and reflux condenser was added the appropriate carboxylic acid (**2a-2u**, 0.6 mmol), DMC (3 mL, 0.2 M substrate concentration) and pyridine (0.17 mL, 2.1 mmol). Cupric carbonate ($\text{CuCO}_3 \cdot \text{Cu}(\text{OH})_2$, 13.3 mg, 0.06 mmol) was added, followed by methylboronic acid (**1**, 90 mg, 1.5 mmol). The heterogenous reaction mixture was left open to ambient air and heated to 90 °C. After 24 hours, the reaction was cooled to room temperature, filtered through celite, and concentrated *en vacuo*. Pure methyl ester was obtained from the crude residue by flash column chromatography.

Methyl 4-fluorobenzoate (3a, CAS Registry: 403-33-8). Carboxylic acid **2a** (84 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (50:1 hexanes/ethyl acetate eluent), methyl ester **3a** was isolated as a clear oil (70.0 mg, 76% yield). The spectral data were

consistent with reported values.²⁴ ¹H NMR (CDCl₃, 300 MHz) δ 8.06 (dd, 2 H, *J* = 9.0, 5.4 Hz), 7.11 (dd, 2 H, *J* = 8.7, 8.7 Hz), 3.91 (s, 3 H).

Methyl 4-*tert*-butylbenzoate (3b, CAS Registry: 26537-19-9). Carboxylic acid **2b** (107 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (50:1 hexanes/ethyl acetate eluent), methyl ester **3b** was isolated as a clear oil (104.9 mg, 91% yield). The spectral data were consistent with reported values.²⁵ ¹H NMR (CDCl₃, 300 MHz) δ 8.00 (d, 2 H, *J* = 8.4 Hz), 7.47 (d, 2 H, *J* = 8.4 Hz), 3.92 (s, 3 H), 1.36 (s, 9 H).

Methyl 4-bromobenzoate (3c, CAS Registry: 619-42-1). Carboxylic acid **2c** (121 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (50:1 hexanes/ethyl acetate eluent), methyl ester **3c** was isolated as a white solid (109.7 mg, 85% yield). The spectral data were consistent with reported values.²⁶ ¹H NMR (CDCl₃, 300 MHz) δ 7.88 (d, 2 H, *J* = 8.7 Hz), 7.56 (d, 2 H, *J* = 8.7 Hz), 3.90 (s, 3 H).

Methyl 3-chlorobenzoate (3d, CAS Registry: 2905-65-9). Carboxylic acid **2d** (94 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (50:1 hexanes/ethyl acetate eluent), methyl ester **3d** was isolated as a clear oil (89.8 mg, 88% yield). The spectral data were consistent with reported values.²⁷ ¹H NMR (CDCl₃, 300 MHz) δ 8.02 (dd, 1 H, *J* = 1.8, 1.8 Hz), 7.92 (ddd, 1 H, *J* = 7.8, 1.5, 1.5 Hz), 7.53 (ddd, 1 H, *J* = 8.1, 2.1, 1.2 Hz), 7.38 (dd, 1 H, *J* = 7.8, 7.8 Hz), 3.93 (s, 3 H).

Methyl 4-acetylbenzoate (3e, CAS Registry: 3609-53-8). Carboxylic acid **2e** (98 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (50:1 hexanes/ethyl acetate eluent), methyl ester **3c** was isolated as a white solid (70.0 mg, 66% yield). The spectral data were consistent with reported values.²⁸ ¹H NMR (CDCl₃, 300 MHz) δ 8.10 (d, 2 H, *J* = 8.4 Hz), 7.99 (d, 2 H, *J* = 8.4 Hz), 3.94 (s, 3 H), 2.63 (s, 3 H).

Methyl 4-cyanobenzoate (3f, CAS Registry: 1129-35-7). Carboxylic acid **2f** (88 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (19:1 hexanes/ethyl acetate eluent), methyl ester **3f** was isolated as a white solid (76.3 mg, 79% yield). The spectral data were consistent with reported values.²⁹ ¹H NMR (CDCl₃, 300 MHz) δ 8.13 (d, 2 H, *J* = 8.7 Hz), 7.74 (d, 2 H, *J* = 8.7 Hz), 3.95 (s, 3 H).

Methyl piperonylate (3g, CAS Registry: 326-56-7). Carboxylic acid **2g** (100 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (19:1 hexanes/ethyl acetate eluent), methyl ester **3g** was isolated as a white solid (80.4 mg, 74% yield). The spectral data were consistent with reported values.³⁰ ¹H NMR (CDCl₃, 300 MHz) δ 7.65 (dd, 1 H, *J* = 8.1, 1.5 Hz), 7.47 (d, 1 H, *J* = 1.8 Hz), 6.83 (d, 1 H, *J* = 8.1 Hz), 6.04 (s, 2 H), 3.88 (s, 3 H).

Methyl 2-methylbenzoate (3h, CAS Registry: 89-71-4). Carboxylic acid **2h** (82 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (50:1 hexanes/ethyl acetate eluent), methyl ester **3h** was isolated as a clear oil (61.6 mg, 68% yield). The spectral data were consistent with reported values.²⁸ ¹H NMR (CDCl₃, 300 MHz) δ 7.93 (dd, 1 H, *J* = 8.1, 1.2 Hz), 7.41 (ddd, 1 H, *J* = 7.5, 7.5, 1.5 Hz), 7.27 (m, 2 H), 3.91 (s, 3 H), 2.63 (s, 3 H).

Methyl 2-methoxybenzoate (3i, CAS Registry: 606-45-1). Carboxylic acid **2i** (91 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (19:1 hexanes/ethyl acetate eluent), methyl ester **3i** was isolated as a white solid (77 mg, 78% yield). The spectral data were consistent with reported values.³¹ ¹H NMR (CDCl₃, 300 MHz) δ 7.81 (d, 1 H, *J* = 7.9, 1.9 Hz), 7.50 (m, 1H), 7.00 (m, 2 H), 3.90 (s, 3 H), 3.89 (s, 3 H).

Methyl 1-naphthoate (3j, CAS Registry: 2459-24-7). Carboxylic acid **2j** (103 mg, 0.60 mmol) was reacted according to the general procedure.³² After column chromatography (50:1 hexanes/ethyl acetate eluent), methyl ester **3j** was isolated as a clear oil (81.4 mg, 73% yield). The spectral data were consistent with reported values.³³ ¹H NMR (CDCl₃, 300 MHz) δ 8.98 (d, 1 H, *J* = 8.7 Hz), 8.22 (dd, 1 H, *J* = 7.2, 1.2 Hz),

8.04 (d, 1 H, $J = 8.1$ Hz), 7.91 (d, 1 H, $J = 8.1$ Hz), 7.69 - 7.49 (m, 3 H), 4.04 (s, 3 H). Peaks corresponding to methyl 2-napthoate (CAS Registry: 2459-25-8)²⁸ were also observed:³² δ 8.66 (s, 1 H), 8.11 (m, 1 H), 7.98 (m, 1 H), 7.90 (m, 2 H), 7.69 - 7.49 (m, 2 H), 4.02 (s, 3 H).

Methyl 1-methylindole-2-carboxylate (3l, CAS Registry: 37493-34-8). Carboxylic acid **2l** (105 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (50:1 hexanes/ethyl acetate eluent), methyl ester **3l** was isolated as a white solid (76.5 mg, 67% yield). The spectral data were consistent with reported values.³⁴ ^1H NMR (CDCl_3 , 300 MHz) δ 7.72 (d, 1 H, $J = 7.8$ Hz), 7.40 (m, 3 H), 7.20 (m, 1 H), 4.11 (s, 3 H), 3.96 (s, 3 H).

Methyl 3-phenylpropanoate (3m, CAS Registry: 103-25-3). Carboxylic acid **2m** (90 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (50:1 hexanes/ethyl acetate eluent), methyl ester **3m** was isolated as a clear oil (78.7 mg, 80% yield). The spectral data were consistent with reported values.³⁵ ^1H NMR (CDCl_3 , 300 MHz) δ 7.39 - 7.18 (m, 5 H), 3.71 (s, 3 H), 3.00 (t, 2 H, $J = 8.1$ Hz), 2.68 (t, 2 H, $J = 8.1$ Hz).

2-Methyl-2-phenylpropionate methyl ester (3n, CAS Registry: 57625-74-8). Carboxylic acid **2n** (99 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (100:1 hexanes/ethyl acetate eluent), methyl ester **3n** was isolated as a clear oil (69.4 mg, 65% yield). The spectral data were consistent with reported values.³⁶ ^1H NMR (CDCl_3 , 300 MHz) δ 7.43 - 7.25 (m, 5 H), 3.69 (s, 3 H), 1.64 (s, 6 H).

Methyl 2-phenoxypropanoate (3o, CAS Registry: 2065-24-9). Carboxylic acid **2o** (100 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (50:1 hexanes/ethyl acetate eluent), methyl ester **3o** was isolated as a clear oil (84.6 mg, 78% yield). The spectral data were consistent with reported values.³⁷ ^1H NMR (CDCl_3 , 300 MHz) δ 7.30 (m, 2 H), 7.00 (t, 1 H, $J = 7.5$ Hz), 6.91 (m, 2 H), 4.80 (q, 1 H, $J = 6.9$ Hz), 3.77 (s, 3 H), 1.65 (d, 3 H, $J = 6.9$ Hz).

Methyl cinnamate (3p, CAS Registry: 103-26-4). Carboxylic acid **2p** (89 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (50:1 hexanes/ethyl acetate eluent), methyl ester **3p** was isolated as a white solid (64.1 mg, 66% yield). The spectral data were consistent with reported values.²⁸ ¹H NMR (CDCl₃, 300 MHz) δ 7.72 (d, 1 H, *J* = 15.9 Hz), 7.54 (m, 2 H), 7.40 (m, 3 H), 6.47 (d, 1 H, *J* = 16.2 Hz), 3.83 (s, 3 H).

Methyl 4-methoxycinnamate (3q, CAS Registry: 943-89-5). Carboxylic acid **3q** (107mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (50:1 hexanes/ethyl acetate eluent), methyl ester **3q** was isolated as a white solid (76.8 mg, 67% yield). The spectral data was consistent with reported values.³⁸ ¹H NMR (CDCl₃, 300 MHz) δ 7.65 (d, 1 H, *J* = 15.9 Hz), 7.47 (d, 2 H, *J* = 8.6 Hz), 6.90 (d, 2 H, *J* = 8.8 Hz), 6.32 (d, 1 H, *J* = 15.9 Hz), 3.83 (s, 3H), 3.80 (s, 3 H).

Methyl 4-chlorocinnamate (3r, CAS Registry: 7560-44-3). Carboxylic acid **2r** (110 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (50:1 hexanes/ethyl acetate eluent), methyl ester **3p** was isolated as a white solid (79.6 mg, 67% yield). The spectral data were consistent with reported values.³⁹ ¹H NMR (CDCl₃, 300 MHz) δ 7.64 (d, 1 H, *J* = 16.2 Hz), 7.44 (d, 2 H, *J* = 8.4 Hz), 7.35 (d, 2 H, *J* = 8.7 Hz), 6.40 (d, 1 H, *J* = 15.9 Hz), 3.81 (s, 3 H).

Methyl 10-undecenoate (3s, CAS Registry: 111-81-9). Carboxylic acid **2s** (110 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (50:1 hexanes/ethyl acetate eluent), methyl ester **3s** was isolated as a clear oil (70.5 mg, 60% yield). The spectral data were consistent with reported values.⁴⁰ ¹H NMR (CDCl₃, 300 MHz) δ 5.80 (m, 1 H), 4.95 (m, 2 H), 3.66 (s, 3 H), 2.30 (t, 2 H, *J* = 7.5 Hz), 2.03 (m, 2 H), 1.62 (m, 2 H), 1.29 (m, 10 H).

Boc-Pro-OMe (3t, CAS Registry: 145681-01-2). Carboxylic acid **2t** (129 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (10:1 hexanes/ethyl acetate eluent), methyl ester **3t** was isolated as a clear oil (100.1 mg, 73% yield). The spectral data were consistent with

reported values and indicated the presence of conformational isomers.⁴¹ ¹H NMR (CDCl₃, 300 MHz) δ 4.27 - 4.15 (m, 1 H), 3.68 (s, 3 H), 3.54 - 3.30 (m, 2 H), 2.28 - 1.71 (m, 4 H), 1.43 - 1.36 (m, 9 H).

Ethyl methyl adipate (3u, CAS Registry: 18891-13-9). Carboxylic acid **2u** (105 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (19:1 hexanes/ethyl acetate eluent), methyl ester **3u** was isolated as a clear oil (88.8 mg, 78% yield). The spectral data were consistent with reported values.⁴² ¹H NMR (CDCl₃, 500 MHz) δ 4.08 (2 H, q, J = 7.0 Hz), 3.62 (s, 3 H), 2.28 (m, 4 H), 1.62 (m, 4 H), 1.21 (t, 3 H, J = 7.0 Hz).

Procedure and GCMS data for the Isotope-Labeling Experiment (eq 1).

[¹⁸O]₂-**2v** was prepared from benzotrichloride (Acros) and ¹⁸O-water (97%, Cambridge Isotope) as previously reported.⁴³ The ¹H NMR spectral data were consistent with the values observed for **2v**. GCMS m/z (% relative intensity, ion): 126.2 (81%, M), 107.2 (100%, M - (¹⁸OH)), 77.1 (94%, M - (C[¹⁸O]₂H)). The molecular ion peak corresponding to [¹⁸O]-**2v** was also identified: 124.1 (3.6%, M). The molecular ion peak corresponding to unlabeled **2v** was also identified: 122.1 (1.3%, M). The percentage of ¹⁸O in synthetic [¹⁸O]₂-**2v** was therefore calculated to be 96.5%.

[¹⁸O]₂-**2v** was reacted with **1** according to the general methylation procedure. An aliquot was taken from the reaction at T = 24 h and analyzed by GCMS. [¹⁸O]₂-**3v** was identified. GCMS m/z (% relative intensity, ion): 140.2 (28.8%, M), 107.2 (100%, M - (¹⁸OCH₃)). The molecular ion peak corresponding to [¹⁸O]-**3v** was also identified: 138.2 (10.2%, M). The molecular ion peak corresponding to unlabeled **3v** was also identified: 136.2 (1.2%, M). The calculated percentages of product formed are 72% [¹⁸O]₂-**3v**, 25% [¹⁸O]-**3v**, and 3% **3v**. A peak for the benzoic acid ([¹⁸O]₂-**2v**) was also observed. m/z (% relative intensity, ion): 126.2 (71.8%, M), 107.2 (100%, M - (¹⁸OCH₃)). The molecular ion peak corresponding to [¹⁸O]-**2v** was also identified: 124.2 (28.5%, M). The molecular ion peak corresponding to unlabeled **2v** was also identified: 122.2 (12.6%, M). The calculated percentages of **2v** epitopes are 64% [¹⁸O]₂-**2v**, 25% [¹⁸O]-**2v**, and 11% **2v**.

Acknowledgment We gratefully acknowledge financial support from the donors of the American Chemical Society Petroleum Research Fund (#52706-UNI1) and Smith College for a Jean Picker Fellowship (DG) and a McKinley Fellowship (NM). We thank Dr. Charles Amass (Smith College) for assistance with instrumentation and Dr. Craig F. Gorin (Dow) for helpful discussions.

Supporting Information Available Control experiments with tBuOOtBu (eq S1) and MeOH (eq S2).

Copies of ^1H NMR spectra for **3a-3u**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References:

- (1) Recent examples in natural product synthesis: a) Deng, J.; Zhou, S.; Zhang, W.; Li, J.; Li, R.; Li, A. *J. Am. Chem. Soc.* **2014**, *136*, 8185. b) Qin, T.; Porco, J. A. *Angew. Chem. Int. Ed.* **2014**, *53*, 3107. In reaction development: c) Mita, T.; Higuchi, Y.; Sato, Y. *Org. Lett.* **2014**, *16*, 14. d) Neufeld, K.; Henßen, B.; Pietruszka, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 13253. In medicinal chemistry: e) Deng, Y.; Shipps, G. W.; Cooper, A.; English, J. M.; Annis, D. A.; Carr, D.; Nan, Y.; Wang, T.; Zhu, H. Y.; Chuang, C.-C.; Dayananth, P.; Hruza, A. W.; Xiao, L.; Jin, W.; Kirschmeier, P.; Windsor, W. T.; Samatar, A. A. *J. Med. Chem.* **2014**, *57*, 8817. f) Zheng, P.; Somersan-Karakaya, S.; Lu, S.; Roberts, J.; Pingle, M.; Warriar, T.; Little, D.; Guo, X.; Brickner, S. J.; Nathan, C. F.; Gold, B.; Liu, G. *J. Med. Chem.* **2014**, *57*, 3755.
- (2) For a review, see: Lamoureux, G.; Agüero, C. *ARKIVOC* **2009**, 251.
- (3) a) Hite, M.; Rinehart, W.; Braun, W.; Peck, H. *Am. Ind. Hyg. Assoc. J.* **1979**, *40*, 600. b) Rippey, J. C. R.; Stallwood, M. I. *Emerg. Med. J.* **2005**, *22*, 878. c) Mileson, B. E.; Sweeney, L. M.; Gargas, M. L.; Kinzell, J. *Inhal. Toxicol.* **2009**, *21*, 583.
- (4) a) Hodnett, N. S. *Synlett* **2003**, 2095. b) de Boer, T. J.; Backer, H. J. *Org. Synth.* **1956**, *4*, 16.
- (5) Kemsley, J. N. *Chem. Eng. News* **2011**, *89*, 15.
- (6) Ji, Y.; Sweeney, J.; Zoglio, J.; Gorin, D. J. *J. Org. Chem.* **2013**, *78*, 11606.
- (7) (a) Schwöbel, J. A. H.; Koleva, Y. K.; Enoch, S. J.; Bajot, F.; Hewitt, M.; Madden, J. C.; Roberts, D. W.; Schultz, T. W.; Cronin, M. T. D. *Chem. Rev.* **2011**, *111*, 2562. (b) Enoch, S. J.; Ellison, C. M.; Schultz, T. W.; Cronin, M. T. D. *Crit. Rev. Toxicol.* **2011**, *41*, 783.
- (8) For a review of cross-coupling reactions of two nucleophiles, see: Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780.
- (9) For reviews, see: a) Qiao, J.; Lam, P. *Synthesis* **2011**, 2011, 829. b) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozłowski, M. C. *Chem. Rev.* **2013**, *113*, 6234. For recent catalytic, aerobic examples, see: c) Kumar, K. A.; Kannaboina, P.; Dhaked, D. K.; Vishwakarma, R. A.; Bharatam, P. V.; Das, P. *Org. Biomol. Chem.* **2015**, *13*, 1481. d) El Khatib, M.; Molander, G. A. *Org. Lett.* **2014**, *16*, 4944. e) Liu, C.-Y.; Li, Y.; Ding, J.-Y.; Dong, D.-W.; Han, F.-S. *Chem. Eur. J.* **2014**, *20*, 2373. f) Rasheed, S.; Rao, D. N.; Reddy, K. R.; Aravinda, S.; Vishwakarma, R. A.; Das, P. *RSC Advances* **2014**, *4*, 4960.
- (10) Reviews of aerobic metal catalysis: a) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381. b) Campbell, A. N.; Stahl, S. S. *Acc. Chem. Res.* **2012**, *45*, 851. Also see ref 9b.
- (11) Cyclopropylboronic acid: a) Tsuritani, T.; Strotman, N. A.; Yamamoto, Y.; Kawasaki, M.; Yasuda, N.; Mase, T. *Org. Lett.* **2008**, *10*, 1653. b) Bénard, S.; Neuville, L.; Zhu, J. *Chem. Commun.* **2010**, *46*, 3393. Methylboronic acid: c) González, I.; Mosquera, J.; Guerrero, C.; Rodríguez, R.; Cruces, J. *Org. Lett.* **2009**, *11*, 1677. Other alkylboronic acids: d) Larrosa, M.; Guerrero, C.; Rodríguez, R.; Cruces, J. *Synlett* **2010**, 2101. e) Rossi, S. A.; Shimkin, K. W.; Xu, Q.; Mori-Quiroz, L. M.; Watson, D. A. *Org. Lett.* **2013**, *15*, 2314. Alkylboronic esters: f) Sueki, S.; Kuninobu, Y. *Org. Lett.* **2013**, *15*, 1544. Alkylboranes: g) Naya, L.; Larrosa, M.; Rodríguez, R.; Cruces, J. *Tetrahedron Lett.* **2012**, *53*, 769.

- (12) Suzuki-Miyaura coupling: a) Gray, M.; Andrews, I. P.; Hook, D. F.; Kitteringham, J.; Voyle, M. *Tetrahedron Lett.* **2000**, *41*, 6237. C-H methylation: b) Giri, R.; Mangel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. Addition to carbonyl electrophiles: c) Wang, D.; Ge, B.; Ju, A.; Zhou, Y.; Xu, C.; Ding, Y. *J. Organomet. Chem.* **2015**, *780*, 30. d) Takatsu, K.; Shintani, R.; Hayashi, T. *Angew. Chem. Int. Ed.* **2011**, *50*, 5548. For an overview of the reactivity of alkylboronic acids, see: e) Hall, D. G. In *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA, 2011; pp 13-15, 61.
- (13) a) Jiang, Y.; Pan, S.; Zhang, Y.; Yu, J.; Liu, H. *Eur. J. Org. Chem.* **2014**, 2014, 2027. b) Bhadra, S.; Dzik, W. I.; Gooßen, L. J. *J. Am. Chem. Soc.* **2012**, *134*, 9938. For a review of carboxylic acids in metal catalysis, see: c) Gooßen, L. J.; Rodríguez, N.; Gooßen, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 3100.
- (14) a) Huang, F.; Quach, T. D.; Batey, R. A. *Org. Lett.* **2013**, *15*, 3150. b) Popovic, S.; Bieräugel, H.; Detz, R. J.; Kluwer, A. M.; Koole, J. A. A.; Streefkerk, D. E.; Hiemstra, H.; van Maarseveen, J. H. *Chem. Eur. J.* **2013**, *19*, 16934. c) Zhang, L.; Zhang, G.; Zhang, M.; Cheng, J. *J. Org. Chem.* **2010**, *75*, 7472. d) Dai, J.-J.; Liu, J.-H.; Luo, D.-F.; Liu, L. *Chem. Commun.* **2011**, 47, 677. e) Luo, F.; Pan, C.; Qian, P.; Cheng, J. *Synthesis* **2010**, 2005.
- (15) For a mechanistically distinct esterification with methylboronic acid, see: a) Lu, W.; Chen, J.; Liu, M.; Ding, J.; Gao, W.; Wu, H. *Org. Lett.* **2011**, *13*, 6114. For a review of transition-metal catalyzed esterification, see: b) Luo, F.; Pan, C.; Cheng, J. *Synlett* **2012**, 23, 357.
- (16) a) Schöffner, B.; Schöffner, F.; Verevkin, S. P.; Börner, A. *Chem. Rev.* **2010**, *110*, 4554. b) ACS GCI Pharmaceutical Roundtable Solvent Selection Guide, version 2.0, 2011. [Online] <http://www.acs.org/content/dam/acsorg/greenchemistry/industrialinnovation/roundtable/acs-gci-pr-solvent-selection-guide.pdf> (accessed June 2, 2015).
- (17) For the use of $\text{CuCO}_3 \cdot \text{Cu}(\text{OH})_2$ in aerobic catalysis, see: Sang, P.; Xie, Y.; Zou, J.; Zhang, Y. *Adv. Synth. Catal.* **2012**, *354*, 1873.
- (18) For an overview of Cu-catalyzed reactions of aryl halides, see: a) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2010**, *1*, 13. For examples with aryl bromides and/or chlorides, see: b) Mormino, M. G.; Fier, P. S.; Hartwig, J. F. *Org. Lett.* **2014**, *16*, 1744. c) Maiti, D.; Buchwald, S. L. *J. Org. Chem.* **2010**, *75*, 1791.
- (19) a) Van Berkel, S. S.; van den Hoogenband, A.; Terpstra, J. W.; Tromp, M.; van Leeuwen, P. W. N. M.; van Strijdonck, G. P. F. *Tetrahedron Lett.* **2004**, *45*, 7659. b) Tromp, M.; van Strijdonck, G. P. F.; van Berkel, S. S.; van den Hoogenband, A.; Feiters, M. C.; de Bruin, B.; Fiddy, S. G.; van der Eerden, A. M. J.; van Bokhoven, J. A.; van Leeuwen, P. W. N. M.; Koningsberger, D. C. *Organometallics* **2010**, *29*, 3085.
- (20) For Cu-catalyzed methyl transfer from alkylperoxides, see: Xia, Q.; Liu, X.; Zhang, Y.; Chen, C.; Chen, W. *Org. Lett.* **2013**, *15*, 3326.
- (21) a) King, A. E.; Ryland, B. L.; Brunold, T. C.; Stahl, S. S. *Organometallics* **2012**, *31*, 7948. b) Huffman, L. M.; Casitas, A.; Font, M.; Canta, M.; Costas, M.; Ribas, X.; Stahl, S. S. *Chem. Eur. J.* **2011**, *17*, 10643. c) King, A. E.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 5044.
- (22) Cu-catalyzed boronic acid oxidation: Xu, J.; Wang, X.; Shao, C.; Su, D.; Cheng, G.; Hu, Y. *Org. Lett.* **2010**, *12*, 1964. Also see ref 12e; pp 79–81.
- (23) For metal-free esterification with arylboronic acids via path B, see: a) Ruso, J. S.; Rajendiran, N.; Kumaran, R. S. *Tetrahedron Lett.* **2014**, *55*, 2345. For Cu-catalyzed Fisher esterification, see: b) Ho, T.-L. *Synth. Commun.* **1989**, *19*, 2897. c) Iranpoor, N.; Firouzabadi, H.; Zolfigol, M. A. *Synth. Commun.* **1998**, *28*, 1923.
- (24) Irfan, M.; Glasnov, T. N.; Kappe, C. O. *Org. Lett.* **2011**, *13*, 984.
- (25) Dumur, F.; Contal, E.; Wantz, G.; Phan, T. N. T.; Bertin, D.; Gimes, D. *Chem. Eur. J.* **2013**, *19*, 1373.
- (26) Lerebours, R.; Wolf, C. *J. Am. Chem. Soc.* **2006**, *128*, 13052.
- (27) Molander, G. A.; Cavalcanti, L. N. *J. Org. Chem.* **2011**, *76*, 7195.
- (28) Heller, S. T.; Sarpong, R. *Org. Lett.* **2010**, *12*, 4572.
- (29) Leduc, A. B.; Jamison, T. F. *Org. Proc. Res. Dev.* **2012**, *16*, 1082.
- (30) Zhang, J.; Zhang, Y.; Zhang, Y.; Herndon, J. W., *Tetrahedron Lett.* **2003**, *59*, 5609.
- (31) Huang, S.; Hsei, I.; Chen, C. *Bioorg. Med. Chem.* **2006**, *14*, 6106.
- (32) **2j** was obtained from Aldrich as a 94:6 mixture of 1-napthoic acid:2-napthoic acid, as confirmed by ^1H NMR. An identical ratio of methyl 1-napthoate (**3j**):methyl 2-napthoate was obtained from the reaction.
- (33) De Sarkar, S.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.*, **2010**, *132*, 1190.

- (34) Sechi, M.; Derudas, M.; Dallochio, R.; Dessì, A.; Bacchi, A.; Sannia, L.; Carta, F.; Palomba, M.; Ragab, O.; Chan, C.; Shoemaker, R.; Sei, S.; Dayam, R.; Neamati, N. *J. Med. Chem.* **2004**, *47*, 5298.
- (35) Black, P. J.; Edwards, M. G.; Williams, J. M. J. *Eur. J. Org. Chem.* **2006**, 4367.
- (36) Liu, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 5182.
- (37) Chen, C.; Zhu, S.-F.; Liu, B.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 12616.
- (38) Hesse, M.; Li, Y. *Helv. Chim. Acta* **2003**, *86*, 321.
- (39) Wang, X.-R.; Chen, F. *J. Chem. Res.* **2010**, *34*, 714.
- (40) Wu, F.-L.; Ross, B. P.; McGearry, R. P. *Eur. J. Org. Chem.* **2010**, 1989.
- (41) Barker, G.; O'Brien, P.; Campos, K. R. *Org. Lett.* **2010**, *12*, 4176.
- (42) Iwasawa, N.; Hayakawa, S.; Funahashi, M.; Isobe, K.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 819.
- (43) a) Ponticorvo, L.; Rittenberg, D. *J. Am. Chem. Soc.* **1954**, *76*, 1705. b) Kobayashi, M.; Minato, H.; Ogi, Y. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 905.