

BF₃-Mediated Oxidative Cross-Coupling of Pyridines with Alkynyllithium Reagents and Further Reductive Functionalizations of the Pyridine Scaffold

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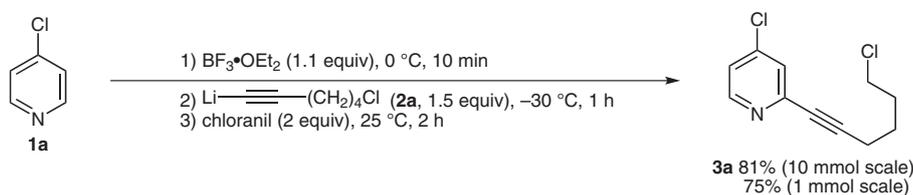
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Abstract: A set of functionalized alkynylpyridines can be readily obtained using Et₂O·BF₃ as promoter. Alkynyllithium reagents undergo an addition reaction at position C-2 of pyridines that are rearomatized by oxidative treatment with chloranil. These substituted pyridines can be easily converted into more valuable intermediates. Examples of applications are given as well. Finally, the synthesis of piperidines and lactams via first an oxidative BF₃-mediated addition reaction followed by a NaBH₄ reduction or acidic workup is also described.

Key words: cross-coupling, pyridines, alkynyllithiums, BF₃, piperidines, lactams



Scheme 1 Typical procedure for the transition-metal-free BF₃-mediated oxidative alkylation of pyridines

Introduction

The pyridine scaffold has been demonstrated to be of utmost interest as building block in many compounds of pharmaceutical and biological interest.¹ The derivatization of pyridines still represents a major challenge and much efforts are made to functionalize them in a straightforward manner.² For example, the addition reaction of alkynyl moieties to the pyridine ring increases the possibility of further chemical transformations of this N-heteroaromatic ring. The introduction of alkynyl groups are usually carried out by Sonogashira cross-coupling protocol.³ These methods are well known for their generality and robustness, but they show some drawbacks, namely, toxicity and high price of the metal catalysts as well as the requirement of sophisticated ligands. A transition-metal-free protocol would be of paramount interest to circumvent these drawbacks. Recently, we have reported the beneficial effect of adding Et₂O·BF₃ to pyridines: a strong activation of the pyridine ring is produced allowing the efficient and regioselective addition of alkyl- and aryl-magnesium or zinc reagents in the absence of a transition metal.⁴ Interestingly, we found that the addition of alkynyllithium derivatives to BF₃-activated pyridines allowed a novel regioselective alkylation process.⁵

Subsequent oxidative treatment with chloranil resulted in rearomatization of the ring. Thus, the activation of pyridines with Et₂O·BF₃ shows high compatibility with lithium species allowing the preparation of a new set of functionalized alkynylpyridines in good yields. Herein, we wish to demonstrate the practicality of this protocol and its scalability.

Scope and Limitations

Typically, 4-chloropyridine (**1a**; 1 equiv) was activated with Et₂O·BF₃ (1.1 equiv, 0 °C, 15 min), followed by the addition of 6-chlorohex-1-ynyllithium (**2a**; 1.5 equiv, -30 °C, 1 h). Subsequent rearomatization by treatment with chloranil (2 equiv, 25 °C, 2 h) afforded the 2,4-disubstituted pyridine (**3a**) in 75% isolated yield on a 1 mmol scale (Scheme 1). This addition reaction was also performed on a larger scale as well. Thus, the upscaling of **3a** to a 10 mmol scale was performed leading to a slightly improved yield of 81% (Scheme 1). With these conditions in hand, the alkylation of a range of pyridines was examined on a 1 mmol and 10 mmol scale (Table 1). Thus, 4-chloropyridine (**1a**) was alkynylated with phenylethynyllithium (**2b**) and with oct-1-ynyllithium (**2c**) to afford the expected pyridines **3b** and **3c** in 65 and 75% yield, respectively, on a 1 mmol scale. Upscaling to 10 mmol of latter reactions gave excellent yields in the range of 55–81% (Table 1, entries 1 and 2). Isonicotinonitrile (**1b**) reacted with (cyclohex-1-en-1-ylethynyl)lithium (**2d**) and with 6-chlorohex-1-ynyllithium (**2a**) affording the corresponding di-

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substituted pyridines **3d** and **3e** in 77–86% yield on a 10 mmol scale. Similar results were obtained on a 1 mmol scale (entries 3 and 4). Picolinonitrile (**1c**) was also satis-

factorily alkynylated with oct-1-ynyllithium (**2c**) to give the 2,6-disubstituted pyridine **3f** in moderate yields of 52–55% (entry 5).

Table 1 Direct Alkynylation of Pyridine Derivatives **1** Using Various Alkynyllithiums **2** Leading to Products **3**

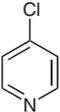
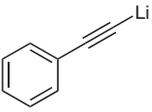
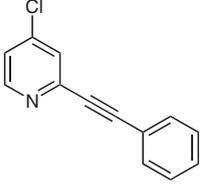
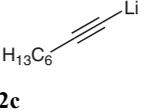
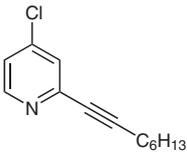
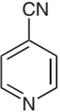
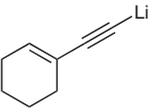
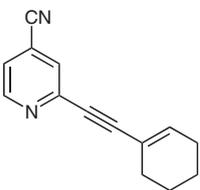
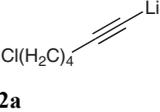
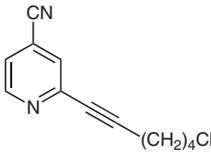
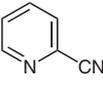
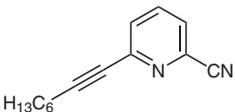
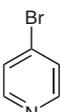
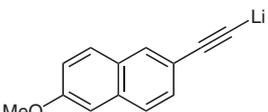
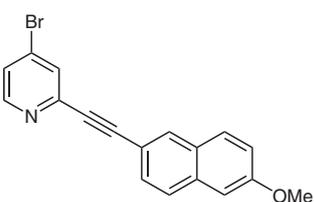
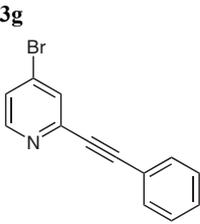
Entry	Substrate 1	RLi 2	Product 3	Scale (mmol)	Yield (%) ^a
1	 1a	 2b	 3b	10 1	81 75
2	1a	 2c	 3c	10 1	55 65
3	 1b	 2d	 3d	10 1	77 76
4	1b	 2a	 3e	10 1	86 89
5	 1c	2c	 3f	10 1	52 55
6	 1d	 2e	 3g	6 1	52 63
7	1d	2b	 3h	10 1	73 76

Table 1 Direct Alkynylation of Pyridine Derivatives **1** Using Various Alkynyllithiums **2** Leading to Products **3** (continued)

Entry	Substrate 1	RLi 2	Product 3	Scale (mmol)	Yield (%) ^a
8	1d	2f	3i	10 1	61 65
9	1e	2b	3j	10 1	75 82
10 ^b	1f	2a	3k	10 1	60 66
11 ^b	1g	2g	3l	8 1	60 68
12 ^b	1h	2b	3m	10 1	54 50

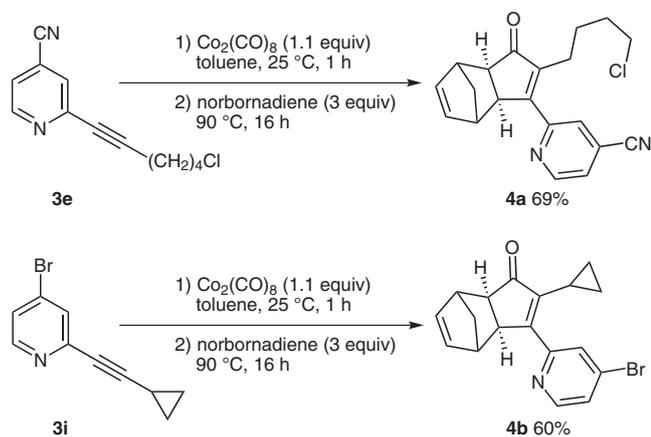
^a Yield of isolated analytically pure compounds.^b Reaction time: 2 h.

Interestingly, the described protocol showed a compatibility with the use of bromopyridines such as 4-bromopyridine (**1d**) or 3-bromopyridine (**1e**). Thus, when **1e** was submitted to the standard reaction conditions with arylethynyllithium species **2b** and **2e**, the corresponding 2,4-disubstituted pyridines **3g,h** were obtained in 52–76% yield (entries 6 and 7). When cyclopropylethynyllithium reagent **2f** was used, 4-bromo-2-(cyclopropylethynyl)pyridine (**3i**) was produced in 61–65% yield (entry 8). 3-Bromopyridine (**1e**) was treated with phenylethynyllithium (**2b**) leading to the corresponding 2,3-disubstituted pyridine **3j** in 82% isolated yield on a 1 mmol scale, although a slight erosion was seen on a larger scale (entry 9). Remarkably, electron-rich alkylpyridines, such as 4-*tert*-butylpyridine (**1f**) and 3-picoline (**1g**), also react well under the described reaction conditions. Thus, alkylpyridines **1f** and **1g** were independently treated with alkynyllithium reagents **2a** and **2g**, affording the 2,4- and 2,3-disubstituted

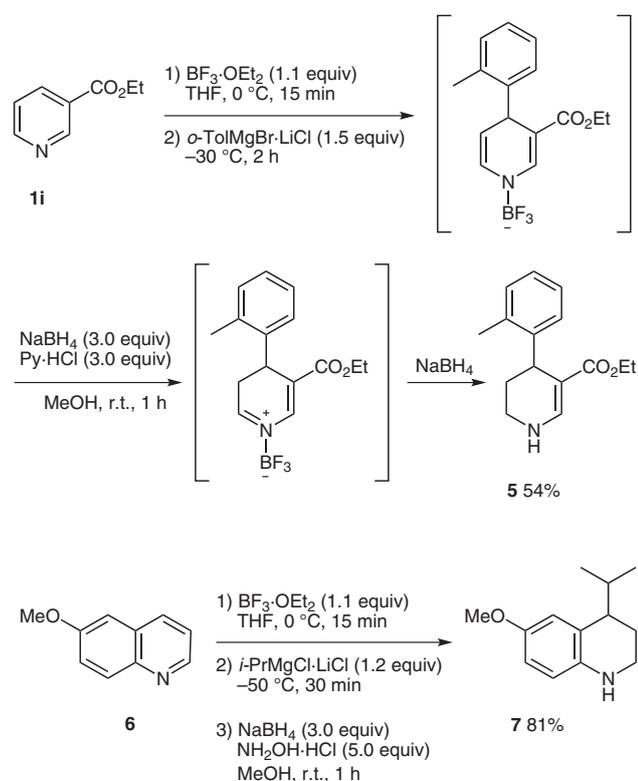
products **3k** and **3l** in 60–68% yield (entries 10 and 11). Finally, the reaction of pyridine **1h** with phenylethynyllithium (**2b**) allowed the formation of 2-(phenylethynyl)pyridine (**3m**) in 50–54% yield (entry 12). It should be noted that alkylpyridines and unsubstituted pyridines required longer reaction time (2 h) to achieve almost full conversion, showing that they are probably less activated as substrates.

In order to show the usefulness of this method, the alkynyl groups of several alkynylpyridines obtained by our protocol were derivatized (Scheme 2). Thus, alkynes **3e** and **3i** were submitted to cobalt-mediated intermolecular Pauson–Khand reaction⁶ and the resulting adducts **4a,b** were obtained in 60–69% yield.⁷

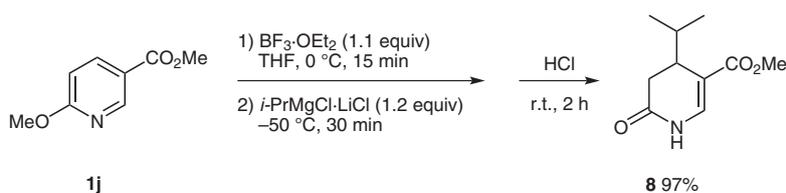
Furthermore, the derivatization of BF₃-pyridine adducts obtained by oxidative addition of alkyl- or arylmagnesium reagents was studied briefly.⁴ Lately, the preparation of 1,2,5,6-tetrahydropyridines through a C-2 regioselective



Scheme 2 Cobalt-mediated intermolecular Pauson–Khand reactions of alkynes **3e** and **3i**



Scheme 3 Oxidative BF₃-mediated cross-coupling of ethyl nicotinate (**1i**) and 6-methoxyquinoline (**6**) and their subsequent reduction by NaBH₄, affording **5** and **7**



Scheme 4 Oxidative BF₃-mediated cross-coupling of 6-methoxynicotinate (**1j**) and subsequent acidic workup, affording **8**

addition of organomagnesium reagents to *N*-benzoyliminopyridinium ylides⁸ and pyridine *N*-oxides⁹ followed by a NaBH₄ in methanol reduction protocol was reported. By taking advantage of these described protocols, we applied the NaBH₄ reduction to our system. After screening several proton sources, NH₂OH·HCl and pyridine·HCl were found to be the best acid promoting a selective reduction. As a typical example, ethyl nicotinate (**1i**) was successfully treated with Et₂O·BF₃ and *o*-TolMgBr·LiCl. Subsequent treatment with NaBH₄/pyridine·HCl allowed the partial reduction to the 1,4,5,6-tetrahydropyridine derivative **5** in 54% yield (Scheme 3). It should be noted that the double bond conjugated to the ester was not reduced under these conditions. It was found that these reductive conditions can also be applied to quinolines. For instance, when 6-methoxyquinoline (**6**) was submitted to the latter reaction conditions, 4-isopropyl-6-methoxy-1,2,3,4-tetrahydroquinoline (**7**) was obtained in 81% yield (Scheme 3). In this particular case, the use of NH₂OH·HCl as proton source gave the best results.

Acidic hydrolysis of BF₃-pyridine intermediates bearing a methoxy group can be also carried out, allowing the efficient synthesis of γ -lactams.¹⁰ 6-Methoxynicotinate (**1j**) was successfully reacted with *i*-PrMgCl·LiCl in the presence of Et₂O·BF₃, subsequent workup with HCl in aqueous solution allowed the formation of the methyl 4-isopropyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (**8**) in 97% yield (Scheme 4).

Conclusion

In summary, a practical and direct oxidative cross-coupling of pyridines with alkynyllithium species is described. The absence of transition metals makes this synthesis an amenable protocol for larger preparatory scales. The method also shows a good compatibility with various functional groups. Additionally, we have also reported reductive or hydrolytic conditions to derivatize the BF₃-pyridine intermediates formed by our addition protocol leading to piperidine or lactam derivatives. We are currently extending this methodology to other heterocycles in our laboratories.

Procedures

All reactions were carried out under argon atmosphere in dried glassware. Commercially available starting materials were purchased from commercial suppliers and used without further purification, unless otherwise stated. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under N₂. Yields refer to isolated compounds estimated to be >95% pure as determined by ¹H NMR and capillary GC analyses.

BF₃-Mediated Direct Alkynylation of Pyridine Derivatives Using Alkynyllithium Reagents General Procedure

A dry and argon-flushed flask, equipped with a magnetic stirring bar and a rubber septum was charged with a solution of a pyridine derivative **1** (1 equiv) in anhydrous THF (0.5 M) and cooled to 0 °C. Et₂O·BF₃ (1.1 equiv) was added dropwise and stirred for 15 min at the same temperature. Then, the reaction mixture was cooled to –30 °C. An alkynyllithium **2** [1.5 equiv; prepared by adding *n*-BuLi (1.5 equiv) to a 0.75 M solution of the alkyne in THF at 0 °C and stirring for 30 min] was cannulated to the reaction flask and the resulting mixture was stirred at the same temperature for 1 h. Then, chloranil (2 equiv) was added and the mixture was warmed to r.t. and continuously stirred for 2 h. Finally, the mixture was quenched with sat. aq NH₄Cl/NH₃ (4:1) solution and extracted with EtOAc (2 × 20 mL). The organic phases were combined and filtered through a layer of silica gel. The filtrate was concentrated in vacuo. Purification by flash chromatography furnished the desired product **3** (see Supporting Information for further details).

4-Chloro-2-(6-chlorohex-1-yn-1-yl)pyridine (3a)

To a solution of 4-chloropyridine (**1a**; 1.14 g, 10 mmol) in THF (20 mL) was added Et₂O·BF₃ (1.56 g, 11 mmol) dropwise at 0 °C. The reaction mixture was stirred for 15 min and reacted with the lithium reagent **2a** [15 mmol; prepared by adding *n*-BuLi (15 mmol) to a 0.75 M solution of 6-chlorohex-1-yne in THF (1.75 g, 15 mmol) at –10 °C and stirring for 30 min]. The crude product was purified by flash chromatography (SiO₂, EtOAc–*i*-hexane, 1:3) furnishing the compound **3a** (1.85 g, 81%) as a light reddish oil.

IR (Diamond-ATR, neat): 2953, 2233, 1543, 1454, 1380, 1101, 825 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.43 (d, *J* = 5.4 Hz, 1 H), 7.38 (dd, *J* = 2.0, 0.5 Hz, 1 H), 7.21 (dd, *J* = 5.4, 2.0 Hz, 1 H), 3.59 (t, *J* = 6.4 Hz, 2 H), 2.50 (t, *J* = 6.9 Hz, 2 H), 2.01–1.90 (m, 2 H), 1.84–1.72 (m, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 2.00, 80.51, 44.70, 31.73, 25.53, 18.75.

MS (EI, 70 eV): *m/z* (%) = 227 (5), 192 (90), 164 (100), 151 (25).

HRMS (EI): *m/z* (M⁺) calcd for C₁₁H₁₁Cl₂N: 227.0269; found: 227.0262.

Cobalt-Mediated Intermolecular Pauson–Khand Reaction; 2-[(3aS,7aR)-2-(4-chlorobutyl)-1-oxo-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-3-yl]isonicotinonitrile (4a); Typical Procedure

A dry and argon flushed flask, equipped with a magnetic stirring bar and a rubber septum was charged with Co₂(CO)₈ (0.464 g, 1.36 mmol, 1.1 equiv), alkyne **3e** (0.270 g, 1.23 mmol, 1 equiv), and anhydrous toluene (4 mL) at r.t. during 1 h. Then, norbornadiene (0.38 mL, 3.69 mmol, 3 equiv) was added via a syringe and the reaction mixture was heated to 90 °C. The resulting mixture was stirred at the same temperature for 16 h. Finally, the crude was concentrated in vacuo and purified by flash chromatography (SiO₂, EtOAc–*i*-hexane, 2:8) furnishing the compound **4a** (0.287 g, 69%) as a beige solid; mp 119.3–121.8 °C.

IR (Diamond-ATR, neat): 2941, 1688, 1584, 1353, 667 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.94 (br s, 1 H), 7.76 (br s, 1 H), 7.53 (br s, 1 H), 6.35 (br s, 1 H), 6.29 (br s, 1 H), 3.54 (m, 2 H), 3.27 (br s, 1 H), 3.02 (br s, 1 H), 2.65 (br s, 1 H), 2.59 (m, 2 H), 2.49 (br s, 1 H), 1.86–1.76 (m, 2 H), 1.71–1.56 (m, 2 H), 1.43 (m, 1 H), 1.25 (m, 1 H).

¹³C NMR (100 MHz, CDCl₃): δ = 209.16, 162.70, 155.67, 150.88, 149.11, 138.21, 137.66, 124.59, 124.20, 121.14, 116.24, 52.33, 48.92, 44.57, 43.97, 43.29, 41.77, 32.47, 25.33, 23.43.

MS (EI, 70 eV): *m/z* (%) = 341 (75), 273 (31), 209 (35), 66 (100).

HRMS (EI): *m/z* (M⁺) calcd for C₂₀H₁₉ClN₂O: 338.1186; found: 338.1188.

Piperidine Derivatives; Ethyl 4-(*o*-Tolyl)-1,4,5,6-tetrahydropyridine-3-carboxylate (5); Typical Procedure

A dry and argon flushed 10 mL flask, equipped with a magnetic stirring bar and a rubber septum was charged with a solution of ethyl nicotinate (**1i**; 149 mg, 1.0 mmol) in anhydrous THF (2 mL) and cooled to 0 °C. Et₂O·BF₃ (156 mg, 1.1 mmol) was added dropwise and stirred for 15 min at the same temperature. The reaction mixture was cooled to –30 °C followed by the dropwise addition of a THF solution of *o*-TolMgBr·LiCl (1.29 mL, 1.16 M, 1.5 mmol), the mixture was stirred at the same temperature for 2 h. A solution of NaBH₄ (114 mg, 3.0 mmol in 2 mL MeOH) and a solution of pyridine·HCl (347 mg, 3.0 mmol in 1 mL MeOH) were added and the mixture was warmed up to r.t. and continuously stirred for 1 h. Finally, the mixture was quenched with aq 1 M NaOH (1 mL) and extracted with EtOAc (3 × 20 mL). The organic phases were combined and filtered through a layer of silica gel. The filtrate was concentrated in vacuo. The crude product was purified by flash chromatography (SiO₂, EtOAc–*i*-hexane, 1:4) furnishing the compound **5** (131 mg, 54%) as a white solid; mp 131.0–133.1 °C.

IR (Diamond-ATR, neat): 3293, 1644, 1599, 1218, 1064, 742 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.74 (d, *J* = 6.4 Hz, 1 H), 7.19–6.93 (m, 4 H), 4.74 (br s, 1 H), 4.21 (d, *J* = 5.0 Hz, 1 H), 4.00 (q, *J* = 7.0 Hz, 2 H), 3.16–2.90 (m, 2 H), 2.44 (s, 3 H), 2.00–1.81 (m, 1 H), 1.68 (d, *J* = 13.0 Hz, 1 H), 1.12 (t, *J* = 7.0 Hz, 3 H).

¹³C NMR (75 MHz, CDCl₃): δ = 168.30, 144.39, 143.53, 134.92, 130.20, 127.59, 125.68, 125.26, 97.31, 58.82, 36.25, 32.39, 26.57, 19.17, 14.37.

MS (70 eV, EI): *m/z* (%) = 245 (55), 216 (68), 200 (39), 172 (100), 154 (41).

HRMS: *m/z* (M⁺) calcd for C₁₅H₁₉NO₂: 245.1416; found: 245.1406.

γ-Lactam Derivatives; Methyl 4-Isopropyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (8); Typical Procedure

A dry and argon flushed 10 mL flask, equipped with a magnetic stirring bar and a rubber septum was charged with a solution of methyl 6-methoxynicotinate (**1j**; 167 mg, 1.0 mmol) in anhydrous THF (2 mL) and cooled to 0 °C. Et₂O·BF₃ (156 mg, 1.1 mmol) was added dropwise and stirred for 15 min at the same temperature. The reaction mixture was cooled to –50 °C followed by dropwise addition of a THF solution of *i*-PrMgCl·LiCl (0.93 mL, 1.29 M, 1.2 mmol), and the mixture was stirred at the same temperature for 30 min. Then, aq 2 M HCl (1 mL) was added and the mixture was warmed up to r.t., and stirred for another 2 h. Finally, the mixture was extracted with EtOAc (3 × 20 mL). The organic phases were combined and filtered through a layer of silica gel. The filtrate was concentrated in vacuo. The crude product was purified by flash chromatography (SiO₂, EtOAc–*i*-hexane 1:2), furnishing the compound **8** (192 mg, 97%) as a white solid; mp 159.2–161.7 °C.

IR (Diamond-ATR, neat): 2955, 2852, 1616, 1364, 1204, 1172, 804 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 8.34 (br s, 1 H), 7.36 (d, *J* = 5.5 Hz, 1 H), 3.74 (s, 3 H), 2.86–2.72 (m, 1 H), 2.65–2.51 (m, 2 H), 1.96–1.76 (m, 1 H), 0.93 (d, *J* = 6.9 Hz, 3 H), 0.85 (d, *J* = 6.9 Hz, 3 H).

¹³C NMR (75 MHz, CDCl₃): δ = 172.30, 167.02, 135.07, 111.16, 51.49, 36.74, 31.89, 31.12, 19.93, 17.82.

MS (70 eV, EI): *m/z* (%) = 198 (12), 155 (100), 123 (40).

HRMS: *m/z* (M⁺) calcd for C₁₀H₁₅NO₃: 197.1052; found: 197.1056.

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Supporting Information for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synthesis>.

References

- (1) (a) Glorius, F.; Spielkamp, N.; Holle, S.; Goddard, R.; Lehmann, C. W. *Angew. Chem. Int. Ed.* **2004**, *43*, 2850. (b) *Modern Heterocyclic Chemistry*; Alvarez-Builla, J.; Vaquero, J. J.; Barluenga, J., Eds.; Wiley-VCH: Weinheim, **2011**. (c) Hardin Narayan, A. R.; Sarpong, R. *Org. Biomol. Chem.* **2012**, *10*, 70.
- (2) (a) *Organotransition Metal Chemistry*; Hartwig, J. F., Ed.; University Science Books: Sausalito (CA, USA), **2010**. (b) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; de Meijere, A., Eds.; Wiley-VCH: Weinheim, **2004**.
- (3) For few examples, see: (a) Carvalho, J. F. S.; Louvel, J.; Doornbos, M. L. J.; Klaasse, E.; Yu, Z.; Brussee, J.; Ijzerman, A. P. *J. Med. Chem.* **2013**, *56*, 2828. (b) Moulton, B. E.; Whitwood, A. C.; Duhme-Klair, A. K.; Lynam, J. M.; Fairlamb, I. J. S. *J. Org. Chem.* **2011**, *76*, 5320.
- (4) Chen, Q.; Mollat du Jourdin, X.; Knochel, P. *J. Am. Chem. Soc.* **2013**, *135*, 4958.
- (5) Chen, Q.; León, T.; Knochel, P. *Angew. Chem. Int. Ed.* **2014**, *53*, in press; DOI: 10.1002/anie.201400750.
- (6) (a) For a recent review of Pauson–Khand reaction, see: *The Pauson–Khand Reaction: Scope, Variations and Applications*; Ríos Torres, R., Ed.; Wiley-VCH: Weinheim, **2012**. For examples of application, see: (b) Vázquez-Romero, A.; Cárdenas, L.; Blasi, E.; Verdaguer, X.; Riera, A. *Org. Lett.* **2009**, *11*, 3104. (c) Kizirian, J.-C.; Aiguabella, N.; Pesquer, A.; Fustero, S.; Bello, P.; Verdaguer, X.; Riera, A. *Org. Lett.* **2010**, *12*, 5620.
- (7) Only one regioisomer was detected by GC analysis. For a study of regioselectivities in cobalt-mediated intermolecular Pauson–Khand reaction, see ref. 3b.
- (8) (a) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012**, *112*, 2642. (b) Legault, C.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 6360.
- (9) Hussain, M.; Sainte-LuceBanchelin, T.; Andersson, H.; Olsson, R.; Almqvist, F. *Org. Lett.* **2013**, *15*, 54.
- (10) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986**, *27*, 4549.