Organic LETTERS

Letter

pubs.acs.org/OrgLett

Chemo-, Regio- and Stereoselective Heck Arylation of Allylated Malonates: Mechanistic Insights by ESI-MS and Synthetic Application toward 5-Arylmethyl-γ-lactones

Caio C. Oliveira,[†] Marcelo V. Marques,[‡] Marla N. Godoi,[§] Thaís Regiani,[§] Vanessa G. Santos,[§] Emerson A. F. dos Santos,[†] Marcos N. Eberlin,[§] Marcus M. Sá,[‡] and Carlos R. D. Correia*,[†]

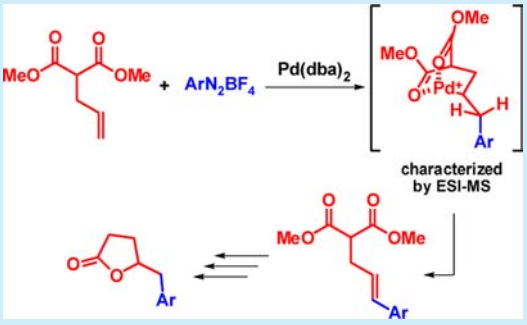
[†]Instituto de Química, Universidade Estadual de Campinas-UNICAMP, Campinas, SP 13083-970, Brazil

[‡]Departamento de Química, Universidade Federal de Santa Catarina, Florianópolis, SC 88040-900, Brazil

[§]Laboratório ThoMSon de Espectrometria de Massas, Universidade Estadual de Campinas-UNICAMP, Campinas, SP 13083-970, Brazil

Supporting Information

ABSTRACT: We describe herein a general method for the controlled Heck arylation of allylated malonates. Both electron-rich and electron-poor aryldiazonium salts were readily employed as the aryl-transfer agents in good yields and in high chemo-, regio-, and stereoselectivity without formation of decarboxylated byproducts. Reaction monitoring via ESI-MS was used to support the formation of chelated Pd species through the catalytic cycle. Additionally, some Heck adducts were successfully used in the total synthesis of pharmacologically active γ-lactones.

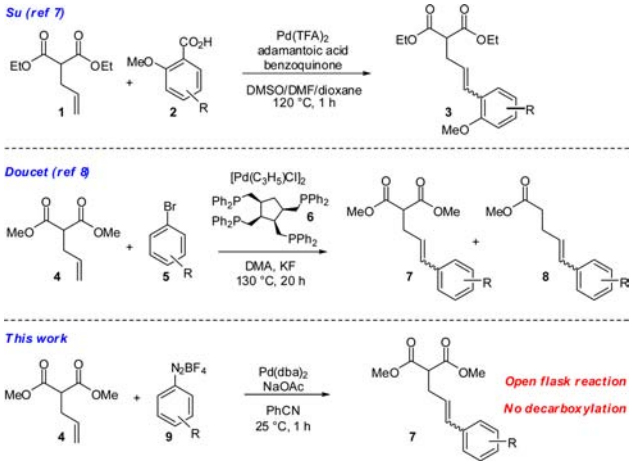


The Heck reaction has been a pivotal tool for the creation of new C−C bonds in chemical synthesis. Its versatility has been demonstrated by many novel methods based on Heck-type reactions as well as its use as a key step in the total synthesis of complex molecules.[1] Despite its broad application, a common feature of this reaction is the low selectivity due to uncontrolled migratory insertion and β-elimination when nonelectronic biased olefins are used.[2] In this context, we have demonstrated that the catalytic pathways involved in the Heck reactions with aryldiazonium salts (Heck−Matsuda reaction)[3] could be successfully controlled by substrates bearing chelating groups, such as the carbonyl group, thus allowing the regio- and stereoselective arylation of allylic acetates and amine derivatives.[4]

We describe herein our efforts to apply the substrate-directable Heck−Matsuda reactions to the synthetically challenging allyl malonates (**1** and **4**, Scheme 1). α-Cinnamylated malonates such as **3** and **7** are useful substrates for the synthesis of carbo- and heterocycles,[5] but somewhat surprisingly, there are a limited number of general methods for their synthesis.[6]

In 2009, Su and co-workers described the combination of **1** with carboxylic acids as a suitable method for the synthesis of cinnamylated malonates **3**. They employed a Pd-catalyzed decarboxylative Heck reaction, although only *ortho*-anisic acids **2** were truly effective.[7] Additionally, Doucet and co-workers have described the Heck reaction of **4** with aryl bromides **5** to give cinnamylated malonates **7** in good yields and selectivity.

Scheme 1. Heck Reactions with Allylated Malonates



However, formation of decarboxylated byproducts **8** was often observed, especially when *ortho*-substituted bromides were employed.[8]

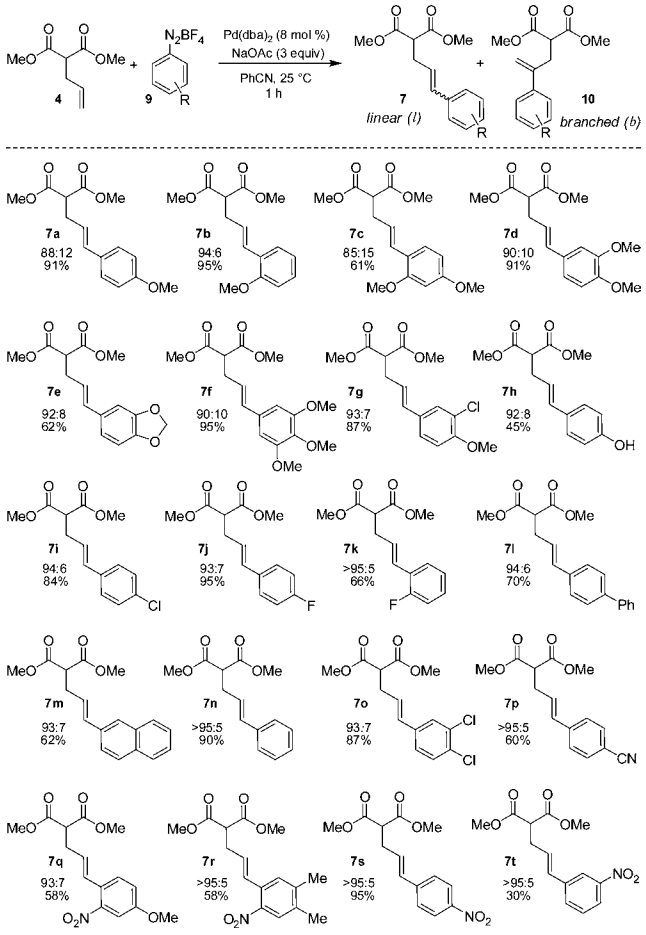
To our delight, our previous reaction conditions optimized for the arylation of allylic esters[4a] also proved suitable for the allylated malonate **4**. Treatment of **4** in an open-flask vessel with 1.2 equiv of 4-methoxyphenyldiazononium salt (**9a**), 8

Received: August 27, 2014
Published: September 23, 2014

   dx.doi.org/10.1021/ol502529v | Org. Lett. 2014, 16, 5180−5183

mol % of $Pd(dba)_2$ in benzonitrile, and freshly powdered NaOAc as the base, at room temperature for 1 h, furnished the cinnamylated malonate **7a** in 91% yield with an 88:12 ratio in favor of the *linear* (*l*) versus the *branched* (*b*) regioisomer **10**. After crystallization, the *E*-isomer **7a** could be isolated in pure form (Scheme 2).

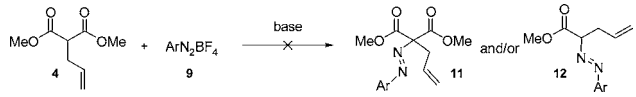
Scheme 2. Stereoselective Heck–Matsuda Reaction for 7



To evaluate the scope of the substrate-directable Heck–Matsuda reaction, we extended the conditions described above to several electronically and sterically distinct aryldiazonium salts **9** (Scheme 2). In general, arylations were highly selective when electron-deficient and/or *ortho*-substituted aryldiazonium salts were used. These results support our previous hypothesis[4] that more electrophilic cationic arylpalladium species provides more tightly chelated intermediates, thus resulting in higher selectivities. Functional groups amenable to further derivatization, such as nitro (**7q–t**), cyano (**7p**), hydroxyl (**7h**), and halogen (**7g,i–k,o**), were well tolerated. The corresponding Heck products were obtained in good yields and stereoselectivity higher than 92:8 in favor of the *linear* isomer with *E*-configuration, although formation of the *Z*-isomer in very small amounts could be inferred from the analysis of the crude reaction by ^{1}H NMR spectroscopy.

We also noted that running the Heck–Matsuda reaction in shorter times at room temperature avoids the occurrence of two intrinsic and undesired side reactions, namely, the decarboxylation of cinnamylated malonates **7** to furnish esters **8** and the nucleophilic addition of malonate derivatives to aryldiazonium salts (the Japp–Klingemman reaction) which provides the azo products **11** and **12** (Scheme 3).[9] Therefore, these observations place the current method in a privileged position regarding the synthesis of structurally diverse cinnamylated malonates.

Scheme 3. Undesired Japp–Klingemman Reaction



To rationalize the mechanism of this substrate-directable Heck–Matsuda reaction, the reaction outcome was monitored by electrospray ionization–mass spectrometry (ESI-MS).[10] Because arylation proceeds by a cationic mechanism, it is possible to follow the transformation by ESI-MS without the need of additives or charge tags. The reaction between allylated malonate **4** and the aryldiazonium **9a**, catalyzed by $Pd(dba)_2$, in benzonitrile was monitored periodically until the starting material **4** was consumed. Aliquots of the reaction medium (1 μL) were taken and diluted in acetonitrile (1 mL) with 0.1% of formic acid and ESI(+)-MS recorded every 5 min (Figure 1).[11] A very clean ESI mass spectrum was observed 5 min after

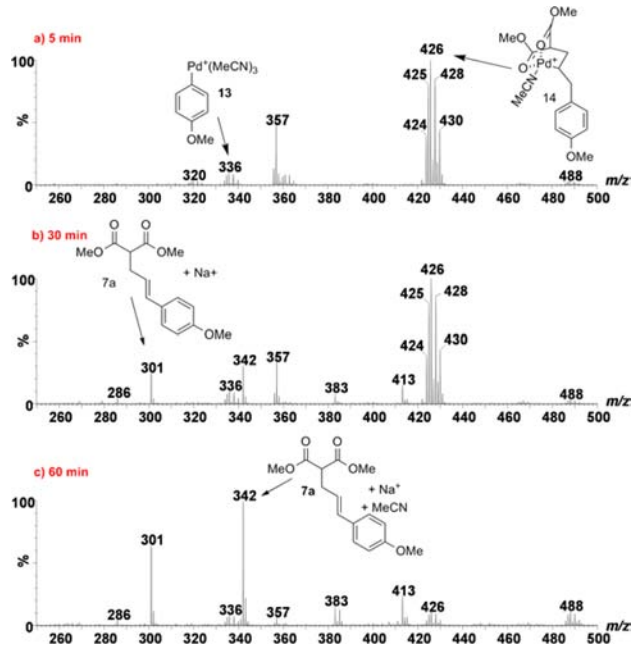


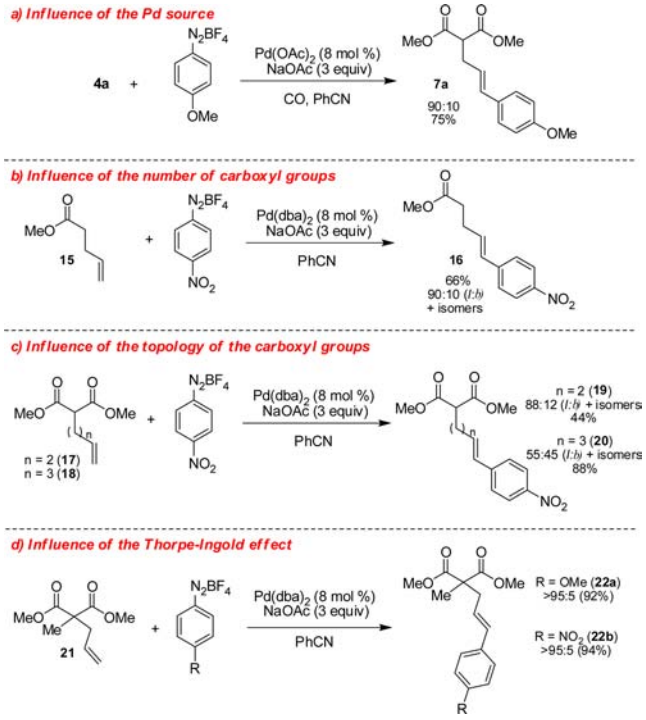
Figure 1. Monitoring the Heck–Matsuda reaction by ESI-MS.

addition of 4-methoxybenzenediazonium salt (**9a**), which supported the formation of a cationic arylpalladium species coordinated to three molecules of acetonitrile (**13**, *m/z* 336) and an interesting alkylpalladium intermediate whose cationic Pd seems chelated by both carboxyl groups of the malonate moiety (**14**, *m/z* 426). More informative was the observation of a qualitative relationship between the consumption of **14** and an increase of relative abundance of the ions corresponding to the Heck–Matsuda adduct **7a** (*m/z* 301 and *m/z* 342, due to simultaneous detection of Na^+ or Na^+/acetonitrile, respectively). Finally, after 60 min, the ion attributed to **14** (*m/z* 426) nearly disappeared, in accordance with the reaction time observed in the laboratory (Figure 1)

dx.doi.org/10.1021/ol502529v | Org. Lett. 2014, 16, 5180–5183

To support the role of intermediate **14** in the Heck–Matsuda reaction, and its assignment as species chelated by both carboxyl groups, a few control experiments were performed as described in Scheme 4. Because the dba ligand

Scheme 4. Probing the Role of Intermediate 14 in the Substrate-Directable Heck–Matsuda Reaction

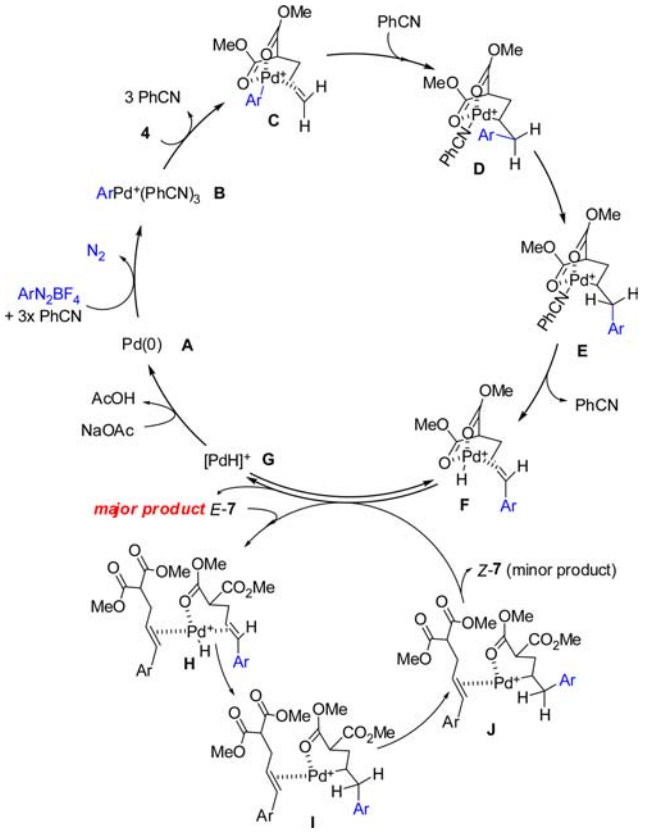


seems to have no effective role in the reaction, the catalyst $Pd(dba)_2$ was replaced by $Pd(OAc)_2$ (reduced to Pd(0) with a CO atmosphere). As expected, the Heck product **7a** was isolated in 75% yield with virtually the same selectivity (90*l*:10*b*) (Scheme 4a).

Heck arylation of the unsaturated monoester **15** showed decreased *l*:*b* selectivity, providing compound **16** along with several isomeric products originated from double bond migration (Scheme 4b). Similar behavior was observed when the distance between the alkene moiety and the carboxyl groups was increased by using the homologous analogues **17** and **18** (Scheme 4c). Finally, introduction of an α-methyl group in the malonate portion favored formation of a chelate-type intermediate by a Thorpe–Ingold effect to give the expected arylated malonates **22** with excellent *l*:*b* selectivity regardless of the electronic nature of the aryldiazonium salt employed (Scheme 4d).

Based on the data collected, we propose a catalytic cycle for this Heck reaction as summarized in Scheme 5 starting with the oxidative addition of Pd(0) to the aryldiazonium salt followed by N_2 extrusion to generate the cationic arylpalladium **B** [similar to the intermediate **13** (*m*/*z* 336) in Figure 1]. Chelation of **13** by allylated malonate **7** leads to palladabicycle **C**, which then directs the insertion of the aryl group to the terminal carbon-forming **D**, which is analogous to **14** (*m*/*z* 426) in Figure 1. Rotation of the benzylic center followed by a favored β-elimination of Pd–H from *syn*-**E** produces the linear Heck product (*E*)-**7a** and the palladium hydride **G**, which is decomposed by the base to regenerate the catalyst.

Scheme 5. Catalytic Cycle for the Formation of 7 Based on ESI-MS



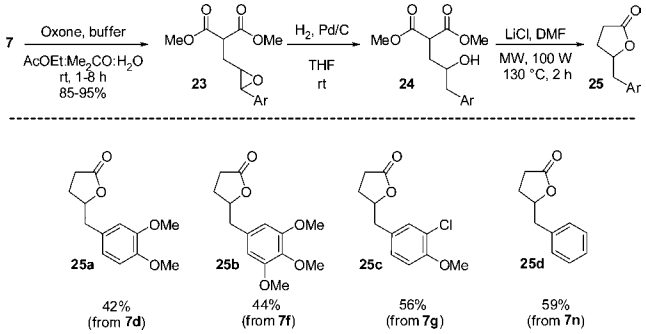
In the present study, dba do not seem to have any relevant stabilization role because of the coordinating groups present in the olefin. Indeed, an ion of *m*/*z* 341 [PdH(dba)], previously identified by us as an important intermediate for the Heck–Matsuda reaction with 2,3-dihydrofuran,[10a] was not intercepted in the present reaction. This apparent low influence of dba can be explained by the preferential transference of PdH species to a previously formed Heck adduct **7** (**H** – characterized by ESI (+)-MS, see the Supporting Information).[4c] We hypothesize that PdH transference might operate as a potential route for the isomerization of the major linear *E* product into the very minor *Z* isomer. Formation of the *branched* isomer **10** in minor amounts can be rationalized by the noncarbonyl-assisted insertion of the cationic arylpalladium **13** onto allylated malonate **4**, which is in accordance with the expected regioselectivity in the carbopalladation of alkyl-substituted olefins.[12]

To demonstrate further the synthetic and strategic potential of this method to prepare useful compounds, we use it to developed a straightforward route to pharmacologically active 5-arylmethyl-γ-lactones **25**. The synthesis started with the epoxidation of the cinnamylated malonates **7** with aqueous Oxone[13] in a two-phase system (to avoid byproducts from overoxidation) to give the corresponding epoxides **23** cleanly with yields ranging from 85 to 95% (^{1}H NMR yield). To prevent decomposition of epoxides **23**, in particular those containing electron-donating groups in the aryl moiety, the routes were optimized using the crude reaction products in the next two steps. They consisted of hydrogenolysis of the benzylic C–O bond with H_2–Pd/C in THF followed by a microwave-assisted tandem lactonization/Krapcho decarboxy-

dx.doi.org/10.1021/ol502529v | Org. Lett. 2014, 16, 5180–5183

lation of the resulting secondary alcohols **24** to provide the 5-arylmethyl-γ-lactones **25** after a single column chromatography purification, in overall yields ranging from 42 to 59% starting from the cinnamylated malonates **7** (Scheme 6). Lactones **25a**

Scheme 6. Synthesis of 5-Arylmethyl-γ-lactones 25



and **25b** have anti-inflammatory properties, and their fully *O*-demethylated derivatives are metabolites from green tea, which are associated with preventive cancer properties.[14]

In summary, we have developed an efficient and straightforward method for the arylation of allylated malonates using the Pd-catalyzed Heck−Matsuda reaction with aryldiazonium salts. All transformations were carried out under open flask conditions, and the products were obtained with high chemo-, regio-, and stereocontrol. Mechanistic investigations by ESI-MS reation monitoring supported the involvement of an interesting chelated intermediate consisted of $Pd(II)^+$ bound to both carboxyl groups present in the substrate. Finally, the Heck adducts **7** were readily transformed into 5-arylmethyl-γ-lactones **25** possessing relevant pharmacological properties.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data for the new compounds, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: roque@iqm.unicamp.br.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the São Paulo Research Foundation (FAPESP, Gran Nos. 2011/23832-6 and 2013/07600-3), the Brazilian National Research Council (CNPq), and the Brazilian Coordination for the Improvement of Higher Education Level Personnel (CAPES) for financial support and fellowships.

■ REFERENCES

(1) (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. (c) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11771. (d) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; Wiley-Interscience: New York, 2002. (e) Tsuji, J. *Palladium Reagents and Catalyst*; Wiley: Chichester, U.K., 2004. (f) *The Mizoroki−Heck Reaction*, Oestreich, M., Ed.; Wiley: Chichester, U.K., 2009.

(2) For selective β-eliminations in Heck reactions, see: (a) Werner, E. W.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 9692. (b) Correia, C. R. D.; Oliveira, C. C.; Salles, A. G., Jr.; dos Santos, E. A. F. *Tetrahedron Lett.* **2012**, *53*, 3325. (c) Wu, X.; Zhou, J. *Chem. Commun.* **2013**, *49*, 4794. (d) Oliveira, C. C.; Angnes, R. A.; Correia, C. R. D. *J. Org. Chem.* **2013**, *78*, 4373. (e) Angnes, R. A.; Oliveira, J. M.; Oliveira, C. C.; Martins, N. C.; Correia, C. R. D. *Chem.—Eur. J.* **2014**, DOI: 10.1002/chem.201404159. (f) Gigant, N.; Bäckvall, J.-E. *Org. Lett.* **2014**, *16*, 4432. For a review, see (e) Le Bras, J.; Muzart, J. *Tetrahedron* **2012**, *68*, 10065.

(3) For recent accomplishments, see: (a) Perez, C. C.; Pena, J. M.; Correia, C. R. D. *New J. Chem.* **2014**, *38*, 3933. (b) Oger, N.; Le Callonnec, F.; Jacquemin, D.; Fouquet, E.; Le Grognec, E.; Felpin, F.-X. *Adv. Synth. Catal.* **2014**, *356*, 1065. (c) Canto, K.; da Silva Ribeiro, R.; Biajoli, A. F. P.; Correia, C. R. D. *Eur. J. Org. Chem.* **2013**, 8004. (d) El Bakouri, O.; Fernández, M.; Brun, S.; Pla-Quintana, A.; Roglans, A. *Tetrahedron* **2013**, *69*, 9761. (e) Schmidt, B.; Elizarov, N.; Berger, R.; Petersen, M. *Synthesis* **2013**, *45*, 1174. (f) Saini, V.; Liao, L.; Wang, Q.; Jana, R.; Sigman, M. S. *Org. Lett.* **2013**, *15*, 5008. (g) Schmidt, B.; Elizarov, N.; Berger, R.; Hölter, F. *Org. Biomol. Chem.* **2013**, *11*, 3674. For reviews, see: (h) Taylor, J. G.; Moro, A. V.; Correia, C. R. D. *Eur. J. Org. Chem.* **2011**, 1403. (i) Felpin, F.-X.; Nassar-Hardy, L.; Le Callonnec, F.; Fouquet, E. *Tetrahedron* **2011**, *67*, 2815. (j) Roglans, A.; Pla-Quintana, A.; Moreno-Manas, M. *Chem. Rev.* **2006**, *106*, 4622.

(4) (a) Moro, A. V.; Cardoso, F. S. P.; Correia, C. R. D. *Org. Lett.* **2009**, *11*, 3642. (b) Prediger, P.; Barbosa, L. F.; Génisson, Y.; Correia, C. R. D. *J. Org. Chem.* **2011**, *76*, 7737. (c) Oliveira, C. C.; dos Santos, E. A. F.; Nunes, J. H. B.; Correia, C. R. D. *J. Org. Chem.* **2012**, *77*, 8182. (d) Prediger, P.; da Silva, A. R.; Correia, C. R. D. *Tetrahedron* **2014**, *70*, 3333. For a personal account, see: (e) Oliveira, C. C.; Correia, C. R. D. In *Strategies and Tactics in Organic Synthesis*; Harmata, M., Ed.; Academic Press: Amsterdam, 2014; Vol. *10*, pp 1−32.

(5) (a) Mauleón, P.; Zeldin, R. M.; González, A. Z.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 6348. (b) Teller, H.; Corbet, M.; Mantilli, L.; Gopakumar, G.; Goddard, R.; Thiel, W.; Fürstner, A. *J. Am. Chem. Soc.* **2012**, *134*, 15331. (c) Noucti, N. N.; Alexanian, E. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 8424.

(6) (a) Williams, J. M. J.; Acemoglu, L. *Adv. Synth. Catal.* **2001**, *343*, 75. (b) Blacker, A. J.; Clarke, M. L.; Loft, M. S.; Williams, J. M. J. *Org. Lett.* **1999**, *1*, 1969.

(7) Hu, P.; Kan, J.; Su, W.; Hong, M. *Org. Lett.* **2009**, *11*, 2341.

(8) Doucet, H.; Lemhadri, M.; Battace, A.; Zair, T.; Santelli, M. *J. Organomet. Chem.* **2007**, *692*, 2270.

(9) (a) Bessard, Y. D.; Imwinkelried, R. D. Production. of 5-alkoxy-indole-2-carboxylic acid compounds useful as intermediates. CH687327 (A5), Nov 15, 1996. (b) Isaad, J.; Achari, A. E. *Tetrahedron* **2011**, *67*, 5678. (c) Alvarado, M.; Decara, J.; Luque, M. J.; Hernandez-Folgado, L.; Gómez-Cañas, M.; Gómez-Ruiz, M.; Fernández-Ruiz, J.; Elguero, J.; Jagerovic, N.; Serrano, A.; Goya, P.; de Fonseca, F. R. *Bioorg. Med. Chem.* **2013**, *21*, 1708.

(10) (a) Sabino, A. A.; Machado, A. H. L.; Correia, C. R. D.; Eberlin, M. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 2514; *Angew. Chem.* **2004**, *116*, 2568. (b) Machado, A. H. L.; Milagre, H. M. S.; Eberlin, L. S.; Sabino, A. A.; Correia, C. R. D.; Eberlin, M. N. *Org. Biomol. Chem.* **2013**, *11*, 3277. (c) Fiebig, L.; Schlörer, N.; Schmalz, H.-G.; Schäfer, M. *Chem.—Eur. J.* **2014**, *20*, 4906. (d) Santos, V. G.; Godoi, M. N.; Regiani, T.; Gama, F. H. S.; Coelho, M. B.; de Souza, R. O. M. A.; Eberlin, M. N.; Garden, S. J. *Chem.—Eur. J.* **2014**, *20*, 12808.

(11) Acetonitrile was used to dilute the reaction samples due to the high boiling point of benzonitrile (191 °C).

(12) (a) Ruan, J.; Xiao, J. *Acc. Chem. Res.* **2011**, *44*, 614. (b) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2.

(13) Marques, M. V.; Sá, M. M. *J. Org. Chem.* **2014**, *79*, 4650.

(14) Lambert, J. D.; Rice, J. E.; Hong, J.; Hou, Z.; Yang, C. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 873.