

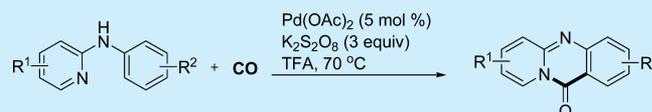
# Palladium-Catalyzed C(sp<sup>2</sup>)-H Pyridocarbonylation of *N*-Aryl-2-aminopyridines: Dual Function of the Pyridyl Moiety

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**S** Supporting Information

**ABSTRACT:** An efficient synthesis of 11*H*-pyrido[2,1-*b*]-quinazolin-11-one through palladium-catalyzed C(sp<sup>2</sup>)-H pyridocarbonylation of *N*-aryl-2-aminopyridines has been developed. The pyridyl group acts as an intramolecular nucleophile for the first time in C-H carbonylation reactions.

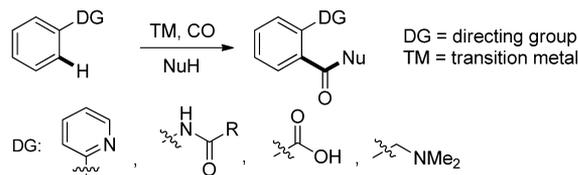


Since seminal work by Heck and co-workers,<sup>1</sup> transition-metal-catalyzed carbonylation reactions of organic (pseudo)halides using carbon monoxide (CO) as a C1 building block have been recognized as a powerful method to synthesize carbonyl derivatives.<sup>2</sup> In the past decade, the development of the direct carbonylation of C-H bonds has resulted in a more straightforward and atom-economic approach to carbonyl-containing compounds.<sup>3</sup> Due to the ubiquity and robustness of C-H bonds, chemo- and regioselective activation of a specific C-H bond is a challenging task. To solve this problem, the strategy of using a directing group is applied to allow selective C-H bond activation by the localized transition-metal catalyst.<sup>4</sup> In this context, a variety of directing groups, including nitrogen-containing heterocycles,<sup>5</sup> amides,<sup>6</sup> carboxylic acids,<sup>7</sup> and tertiary amines,<sup>8</sup> have been developed in C-H carbonylations (Scheme 1a). In some cases when the directing groups need to be removed in intermolecular C-H carbonylations, extra synthetic steps are required, which sacrifices atom economy. On the other hand, the intramolecular version of this process, in which the directing groups act as nucleophiles as well, enables fast construction of heterocycles<sup>9,10</sup> with high step efficiency and atom economy (Scheme 1b).

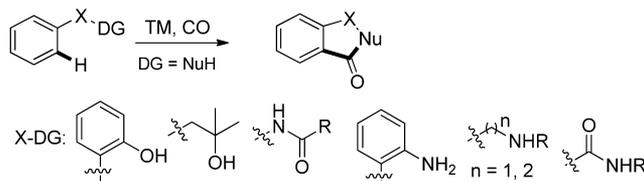
The pyridyl group is widely used as a directing group in transition-metal-catalyzed C-H functionalization reactions, including Pd-, Rh-, or Ru-catalyzed intermolecular carbonylations.<sup>5</sup> A major problem associated with pyridine-directed C-H functionalization is the difficulty of removal or further transformation of the pyridyl moiety. In a previous study, we described a Cu/Fe cocatalyzed intramolecular C-H amination of *N*-aryl-2-aminopyridines for the synthesis of pyrido[1,2-*a*]benzimidazoles, in which the pyridyl group acted as an intramolecular nucleophile as well as a directing group.<sup>11</sup> Herein, we report an unprecedented C-H pyridocarbonylation process by using the same *N*-aryl-2-aminopyridines as substrates. The C-H pyridocarbonylation reaction proceeds efficiently under an atmospheric pressure of CO in the presence of Pd(II) and an oxidant to provide 11*H*-pyrido[2,1-*b*]-quinazolin-11-ones. The pyridyl group acts as both a directing group and an intramolecular nucleophile which is present in the final product (Scheme 1c). The major challenge of this reaction

## Scheme 1. C(sp<sup>2</sup>)-H Carbonylation

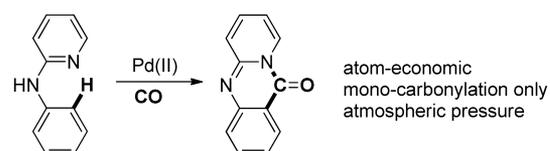
Previous work: (a) intermolecular C-H carbonylation



(b) intramolecular C-H carbonylation



This work: (c) pyridine-directed intramolecular C-H carbonylation



is the potential urea byproduct formation between two aniline moieties under the oxidative conditions.<sup>12</sup>

11*H*-Pyrido[2,1-*b*]quinazolin-11-one is an important scaffold found in many synthetic compounds with various biological activities, including antitumor,<sup>13</sup> anti-allergy,<sup>14</sup> HIV-1 integrase inhibitor,<sup>15</sup> and hypolipemic activities.<sup>16</sup> The general method for the synthesis of this class of molecules is lactamization of 2-(pyridin-2-ylamino)benzoic acid derivatives.<sup>17</sup> In view of recent advances in C-H carbonylations,<sup>4-10</sup> we envisage that the scaffold of 11*H*-pyrido[2,1-*b*]quinazolin-11-one could be read-

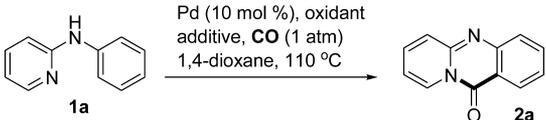
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ily constructed starting from *N*-aryl-2-aminopyridines via palladium-catalyzed C–H pyridocarbonylation. The pyridyl directing group acts as an intramolecular nucleophile as well.

Initially, the reactions of *N*-phenyl-2-aminopyridine **1a** under the previously reported reaction conditions failed to produce any of the desired product **2a**, 11*H*-pyrido[2,1-*b*]quinazolin-11-one (entries 1–2, Table 1).<sup>10d,i</sup> When the oxidant was changed

**Table 1. Optimization of the Reaction Conditions<sup>a</sup>**



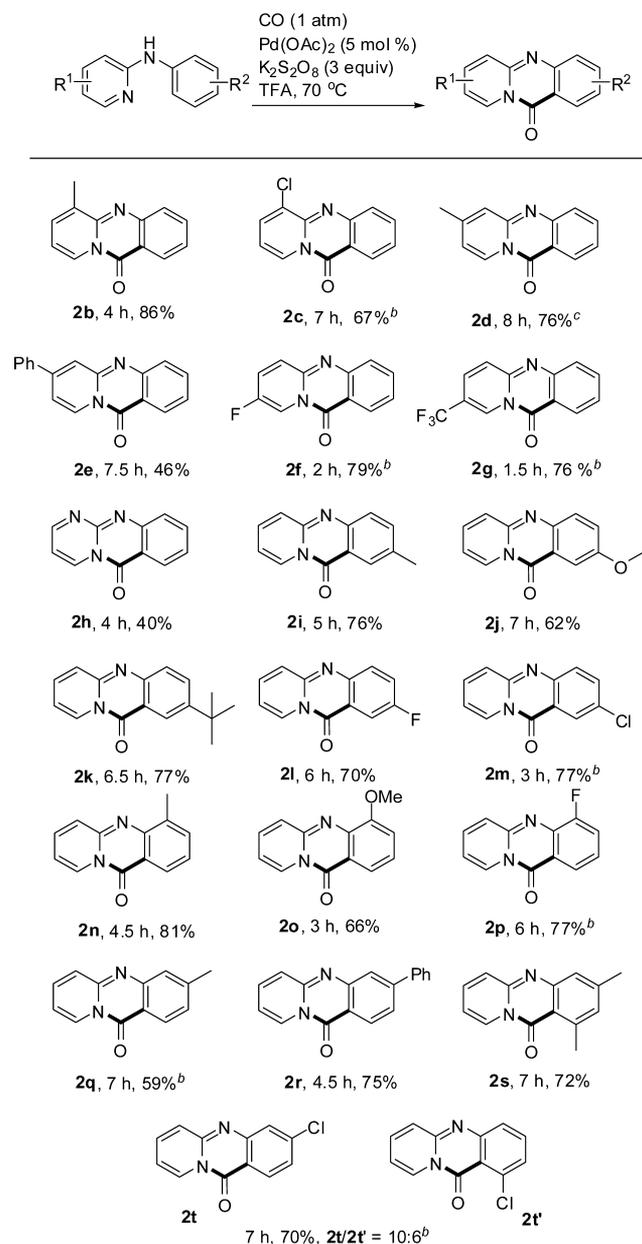
entry	catalyst (10 mol %)	oxidant (1 equiv)	additive (1 equiv)	yield (%) <sup>b</sup>
1 <sup>c</sup>	Pd(OAc) <sub>2</sub>	CuO	–	–
2	Pd(MeCN) <sub>2</sub> Cl <sub>2</sub>	Cu(OAc) <sub>2</sub>	TFA	–
3	Pd(MeCN) <sub>2</sub> Cl <sub>2</sub>	CuCl <sub>2</sub>	–	51
4	Pd(OAc) <sub>2</sub>	CuCl <sub>2</sub>	–	41
5	Pd(TFA) <sub>2</sub>	CuCl <sub>2</sub>	–	26
6	PdCl <sub>2</sub>	CuCl <sub>2</sub>	–	64
7	PdCl <sub>2</sub>	CuCl <sub>2</sub>	TsOH	60
8	PdCl <sub>2</sub>	CuCl <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub>	30
9	PdCl <sub>2</sub>	CuCl <sub>2</sub>	NH <sub>4</sub> Cl	69
10 <sup>d</sup>	PdCl <sub>2</sub>	CuCl <sub>2</sub>	KI	–
11	PdCl <sub>2</sub>	CuBr <sub>2</sub>	–	30
12 <sup>e</sup>	Pd(OAc) <sub>2</sub>	K <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	–	87(78) <sup>f</sup>
13 <sup>e</sup>	Pd(OAc) <sub>2</sub>	Na <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	–	56
14 <sup>e</sup>	Pd(OAc) <sub>2</sub>	NH <sub>4</sub> S <sub>2</sub> O <sub>8</sub>	–	51

<sup>a</sup>Reaction conditions: **1a** (0.2 mmol), Pd (10 mol %), oxidant (1.0 equiv), CO balloon (1 atm), solvent (1.0 mL), 110 °C, 28 h. <sup>b</sup>Isolated yield of **2a**. <sup>c</sup>HOAc as solvent. <sup>d</sup>1,3-Diphenyl-1,3-di(pyridin-2-yl)urea was isolated as major product in 63% yield. <sup>e</sup>TFA (1.0 mL) as solvent, Pd(OAc)<sub>2</sub> (5 mol %), 70 °C, 4 h. <sup>f</sup>In 10 mmol scale of **1a**, 12 h.

to CuCl<sub>2</sub>, **2a** was isolated in 51% yield by applying 10 mol % of Pd(MeCN)<sub>2</sub>Cl<sub>2</sub> as a catalyst under an atmospheric pressure of CO (entry 3). A screening of other Pd(II) species identified PdCl<sub>2</sub> as able to catalyze the reaction in a higher yield of 64% (entries 4–6). Additives such as TsOH, K<sub>2</sub>CO<sub>3</sub>, and NH<sub>4</sub>Cl were also investigated, and no significant improvement in the yields was observed (entries 7–9). It was notable that when KI was added, the major product was changed to 1,3-diphenyl-1,3-di(pyridin-2-yl)urea (entry 10). Fortunately, when the reaction was run in TFA in the presence of 5 mol % of Pd(OAc)<sub>2</sub> as a catalyst and 3.0 equiv of K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> as an oxidant, the yield of **2a** was improved greatly to 87% at much milder conditions (70 °C for 4 h) (entry 12).<sup>18</sup> Other analogous oxidants such as Na<sub>2</sub>S<sub>2</sub>O<sub>8</sub> and (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> proved to be less effective (entries 13–14). Furthermore, the reaction can be run in 10 mmol scale (1.70 g) without a significant loss of the yield (78%, entry 12).

With the optimized conditions in hand, the scope of substituents on the pyridyl ring of *N*-aryl-2-aminopyridines **1** was investigated first (Scheme 2). A range of functional groups with varied electronic properties, including Me, F, Cl, CF<sub>3</sub>, and Ph, were well-tolerated, providing corresponding substituted 11*H*-pyrido[2,1-*b*]quinazolin-11-ones **2b–2g** in 46–87% yields. However, when a Me group was present in the C6 position of the pyridine, only a trace amount of the desired product was detected. It was notable that a pyrimidine motif was also compatible with the reaction conditions, providing the corresponding 6*H*-pyrimido[2,1-*b*]quinazolin-6-one **2h** in

**Scheme 2. Scope of *N*-Aryl-2-aminopyridines<sup>a</sup>**



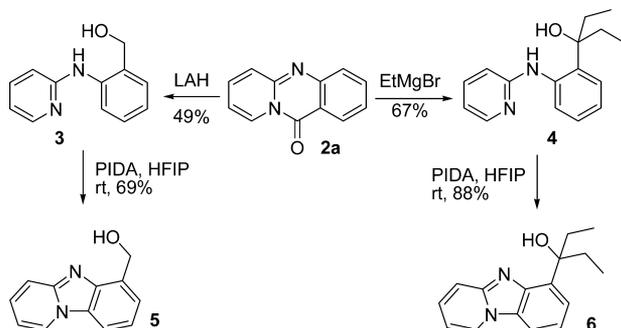
<sup>a</sup>Reaction conditions: **1** (0.2 mmol), Pd(OAc)<sub>2</sub> (5 mol %), K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (3.0 equiv), CO balloon (1 atm), TFA (1.0 mL), 70 °C, isolated yields of **2**. <sup>b</sup>K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (5.0 equiv). <sup>c</sup>At 60 °C.

moderate yield. Then, the effect of the substituents on the phenyl ring of *N*-aryl-2-aminopyridines was studied. Substrates with both electron-donating groups (Me, MeO, and *t*-Bu) and electron-withdrawing ones (F, Cl) on the *para*-position of the phenyl ring were carbonylated smoothly to provide corresponding products **2i–2m** in 62 to 77% yields. Substitution on the *ortho* position was usually unfavorable for aromatic C–H functionalization due to the steric hindrance. However, in this C–H pyridocarbonylation reaction, the steric influence was neglectable (**2n–2p**). When *meta*-substituted *N*-aryl-2-aminopyridines were applied to the reaction, the regioselectivity between the two C–H bonds to be activated was dependent on the size of the substituent. When the substituent was a methyl or phenyl group, only the sterically less hindered C–H bond was reacted, furnishing the sole product **2q** and **2r** in 59% and

75% yields, respectively. However, in the case of a smaller Cl, two isomers in a ratio of 5:3 in favor of **2t** were obtained.

Further transformation of the pyridoquinazolinone product **2a** was also explored (Scheme 3). The reduction of **2a** with

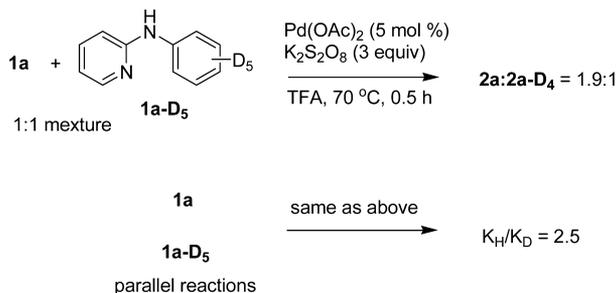
### Scheme 3. Diversification of **2a**



$\text{LiAlH}_4$  gave 2-aminopyridine substituted phenylmethanol **3** as a result of the amide bond cleavage. The released pyridyl moiety can act as an intramolecular nucleophile again in a PIDA-promoted C–H amination reaction, providing C6 hydroxymethyl substituted pyrido[1,2-*a*]benzimidazole **5**.<sup>19</sup> A similar lactam opening and reclosing process was realized by Grignard addition followed by C–H cycloamination to give a tertiary alcohol substituted pyrido[1,2-*a*]benzimidazole derivative **6**. These transformations demonstrated that the current C–H pyridocarbonylation products can be served as precursors of C6 hydroxymethyl substituted pyrido[1,2-*a*]benzimidazoles.

To gain insight into the mechanism of this C–H pyridocarbonylation process, reactions with isotope labeled *N*-phenyl-2-aminopyridine **1a-D<sub>5</sub>** were investigated (Scheme 4). When a 1:1 mixture of **1a** and **1a-D<sub>5</sub>** was subjected to the

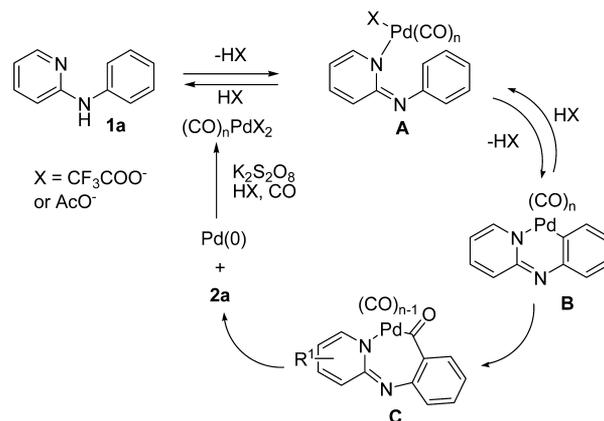
### Scheme 4. Isotope Labeling Experiments



standard conditions, a 1.9:1 mixture of **2a** and **2a-D<sub>4</sub>** was obtained in 0.5 h as determined by <sup>1</sup>H NMR. In parallel reactions using **1a** and **1a-D<sub>5</sub>** as substrates respectively, a significant  $K_{\text{H}}/K_{\text{D}}$  (2.5) value was obtained.<sup>20</sup> Partial deuterium scrambling was also observed in the recovered **1a-D<sub>5</sub>**, showing that a reversible rate-limiting C–H cleavage was likely involved in the reaction (see SI).

Based on the observations described above, a plausible reaction mechanism is proposed in Scheme 5. Initial chelation of the pyridine nitrogen with the CO ligated Pd(II) complex and the following electrophilic cyclopalladation on the phenyl ring form intermediate **B**, which is probably a rate-limiting step. Migratory insertion of a coordinated CO into the aryl–Pd bond produces a seven-membered palladocycle **C**. Reductive elimination leads to the corresponding pyridocarbonylation

### Scheme 5. Plausible Mechanism



product with the concurrent formation of a Pd(0) species, which is reoxidized to the Pd(II) complex by  $\text{K}_2\text{S}_2\text{O}_8$  in the presence of CO and TFA.

In summary, we have developed an efficient catalytic protocol for the synthesis of 11*H*-pyrido[2,1-*b*]quinazolin-11-ones starting from readily available *N*-aryl-2-aminopyridines. This is the first example of using a pyridyl group as both a directing group and an intramolecular nucleophile in a Pd-catalyzed  $\text{C}(\text{sp}^2)$ –H carbonylation reaction. The C–H pyridocarbonylation reaction takes place smoothly under an atmospheric pressure of CO in the presence of  $\text{Pd}(\text{OAc})_2$  and  $\text{K}_2\text{S}_2\text{O}_8$  as an oxidant in TFA. A range of substituted 11*H*-pyrido[2,1-*b*]quinazolin-11-ones which can be further transformed to C6 substituted pyrido[1,2-*a*]benzimidazoles are obtained in moderate to good yields.

### ■ ASSOCIATED CONTENT

#### Supporting Information

Experimental procedures and full analytical data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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#### Notes

The authors declare no competing financial interest.

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### ■ REFERENCES

- (1) (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318. (b) Schoenberg, A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 7761. (c) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327.
- (2) For general reviews, see: (a) Barnard, C. F. *J. Organometallics* **2008**, *27*, 5402. (b) Brennfürer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114. (c) Grigg, R.; Mutton, S. P. *Tetrahedron* **2010**, *66*, 5515. (d) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 4986. (e) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Rev.* **2013**, *113*, 1.
- (3) For recent reviews on C–H carbonylation reactions, see: (a) Brennfürer, A.; Neumann, H.; Beller, M. *ChemCatChem* **2009**, *1*, 28. (b) Liu, Q.; Zhang, H.; Lei, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 10788.

- (4) For examples of nondirected C–H carbonylation reactions, see: (a) Lang, R.; Wu, J.; Shi, L.; Xia, C.; Li, F. *Chem. Commun.* **2011**, 47, 12553. (b) Zhang, H.; Liu, D.; Chen, C.; Liu, C.; Lei, A. *Chem.—Eur. J.* **2011**, 17, 9581. (c) Zhang, H.; Shi, R.; Gan, P.; Liu, C.; Ding, A.; Wang, Q.; Lei, A. *Angew. Chem., Int. Ed.* **2012**, 51, S204. (d) Xie, R.; Xie, Y.; Qian, B.; Zhou, H.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2012**, 134, 9902. (e) Gadge, S. T.; Khedkar, M. V.; Lanke, S. R.; Bhanage, B. R. *Adv. Synth. Catal.* **2012**, 354, 2049. (f) Lang, R.; Shi, L.; Li, D.; Xia, C.; Li, F. *Org. Lett.* **2012**, 14, 4130. (g) Xie, P.; Xia, C.; Huang, H. *Org. Lett.* **2013**, 15, 3370. (h) Zeng, F.; Alper, H. *Org. Lett.* **2013**, 15, 2034.
- (5) (a) Chatani, N.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **1997**, 62, 2604. (b) Guan, Z.-H.; Ren, Z.-H.; Spinella, S. M.; Yu, S.; Liang, Y.-M.; Zhang, X. *J. Am. Chem. Soc.* **2009**, 131, 729. (c) Liu, B.; Shi, B.-F. *Synlett* **2013**, 24, 2274. (d) Liu, B.; Jian, H.-Z.; Shi, B.-F. *Org. Biomol. Chem.* **2014**, 12, 2538.
- (6) (a) Houlden, C. E.; Hutchby, M.; Bailey, C. D.; Ford, J. G.; Tyler, S. N. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem., Int. Ed.* **2009**, 48, 1830. (b) Giri, R.; Lam, J. K.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, 132, 686.
- (7) Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, 130, 14082.
- (8) Li, H.; Cai, G.-X.; Shi, Z.-J. *Dalton Trans.* **2010**, 39, 10442.
- (9) (a) Lu, Y.; Leow, D.; Wang, X.; Engle, K. E.; Yu, J.-Q. *Chem. Sci.* **2011**, 2, 967. (b) Ferguson, J.; Zeng, F.; Alwis, N.; Alper, H. *Org. Lett.* **2012**, 14, 5602. (c) Inamoto, K.; Kadokawa, J.; Kondo, Y. *Org. Lett.* **2013**, 15, 3962. (d) Lee, T.-H.; Jayakumar, J.; Cheng, C.-H.; Chuang, S.-H. *Chem. Commun.* **2013**, 49, 11797. (e) Luo, S.; Luo, F.-X.; Zhang, X.-S.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2013**, 52, 10598. (f) Chen, M.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Angew. Chem., Int. Ed.* **2013**, 52, 14196.
- (10) (a) Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. *J. Am. Chem. Soc.* **2004**, 126, 14342. (b) Inoue, S.; Shiota, H.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2009**, 131, 6898. (c) Yoo, E. J.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, 132, 17378. (d) Ma, B.; Wang, Y.; Peng, J.; Zhu, Q. *J. Org. Chem.* **2011**, 76, 6362. (e) López, B.; Rodríguez, A.; Santos, D.; Albert, J.; Ariza, X.; García, J.; Granell, J. *Chem. Commun.* **2011**, 47, 1054. (f) Haffemayer, B.; Gulias, M.; Gaunt, M. J. *Chem. Sci.* **2011**, 2, 312. (g) Hasegawa, N.; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, 133, 8070. (h) Wrigglesworth, J. W.; Cox, B.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Org. Lett.* **2011**, 13, 5326. (i) Ferguson, J.; Zeng, F.; Alwis, N.; Alper, H. *Org. Lett.* **2013**, 15, 1998. (j) Rajeshkumar, V.; Lee, T.-H.; Chuang, S.-C. *Org. Lett.* **2013**, 15, 1468. (k) Liang, Z.; Zhang, J.; Liu, Z.; Wang, K.; Zhang, Y. *Tetrahedron* **2013**, 69, 6519. (l) Liang, D.; Hu, Z.; Peng, J.; Huang, J.; Zhu, Q. *Chem. Commun.* **2013**, 49, 173. (m) Li, W.; Liu, C.; Zhang, H.; Ye, K.; Zhang, G.; Zhang, W.; Duan, Z.; You, S.; Lei, A. *Angew. Chem., Int. Ed.* **2014**, 53, 2443.
- (11) Wang, H.; Wang, Y.; Peng, C.; Zhang, J.; Zhu, Q. *J. Am. Chem. Soc.* **2010**, 132, 13217.
- (12) (a) Didgikara, M. R.; Joshi, S. S.; Gupta, S. P.; Diwakara, M. M.; Deshpandeb, R. M.; Chaudhari, R. V. *J. Mol. Catal. A: Chem.* **2011**, 334, 20. (b) Guan, Z.-H.; Lei, H.; Chen, M.; Ren, Z.-H.; Bai, Y.; Wang, Y.-Y. *Adv. Synth. Catal.* **2012**, 354, 489.
- (13) (a) Smith, J. R.; Evans, K. J.; Wright, A.; Willows, R. D.; Jamie, J. F.; Griffith, R. *Bioorg. Med. Chem.* **2012**, 20, 1354. (b) Ebeid, M. Y.; Aly, S. M. E. M.; Mikhael, A. N.; Eissa, A. A. H. *Egypt. J. Pharm. Sci.* **1992**, 33, 293.
- (14) (a) Schwender, C. F.; Sunday, B. R.; Decker, V. L. *J. Med. Chem.* **1982**, 25, 742. (b) Schwender, C. F.; Sunday, B. R.; Herzig, D. J.; Kusner, E. K.; Schumann, P. R.; Gawlak, D. L. *J. Med. Chem.* **1979**, 22, 748.
- (15) (a) Saiz-Urra, L.; Gonzalez, M. P.; Fall, Y.; Gomez, G. *Eur. J. Med. Chem.* **2007**, 42, 64. (b) Yuan, H.; Parrill, A. L. *Bioorg. Med. Chem.* **2002**, 10, 4169.
- (16) Matzkies, F.; Stechert, R.; Rauber, G.; Matzkies, F. *Arzneim.-Forsch.* **1989**, 39, 1171.
- (17) (a) Pellón, R. F.; Martín, A.; Docampo, M. L.; Mesa, M. *Synth. Commun.* **2006**, 36, 1715. (b) Docampo, M. L.; Pellón, R. F. *Synth. Commun.* **2003**, 33, 1777. (c) Pellón, R. F.; Carrasco, R.; Rodés, L. *Synth. Commun.* **1996**, 26, 3869. (d) Kovač, T.; Oklobđžija, M.; Comisso, G.; Decorte, E.; Fajdiga, T.; Moimas, F.; Angeli, C.; Zonno, F.; Toso, R.; Šubjić, V. *J. Heterocycl. Chem.* **1983**, 20, 1339.
- (18) Lu, W.; Yamaoka, Y.; Taniguchi, Y.; Kitamura, T.; Takaki, K.; Fujiwara, Y. *J. Organomet. Chem.* **1999**, 580, 290.
- (19) He, Y.; Huang, J.; Liang, D.; Liu, L.; Zhu, Q. *Chem. Commun.* **2013**, 49, 7352.
- (20) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, 51, 3066.