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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Nickel-Catalyzed Site-Selective Alkylation of Unactivated C(sp^3)–H Bonds

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Supporting Information

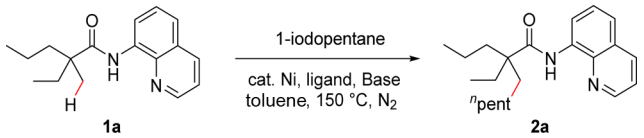
ABSTRACT: The direct alkylation of unactivated sp^3 C–H bonds of aliphatic amides was achieved via nickel catalysis with the assist of a bidentate directing group. The reaction favors the C–H bonds of methyl groups over the methylene C–H bonds and tolerates various functional groups. Moreover, this reaction shows a predominant preference for sp^3 C–H bonds of methyl groups via a five-membered ring intermediate over the sp^2 C–H bonds of arenes in the cyclometalation step.

In the last couple of decades, Ni-catalyzed cross-couplings are of great interest to organic chemists.[1] Along with the extensively studied cross-coupling reactions of aryl halides and pseudohalides, Ni-catalyzed cross-couplings of primary, secondary, and tertiary alkyl halides and surrogates have also been well established.[1f,j,2] Moreover, this first-row transition metal is also capable of catalyzing less reactive electrophiles, such as ethers and phenols, which distinguishes this metal from the second- and third-row elements Pd and Pt in the d^{10} group.[1g,i,3]

Although less studied, Ni-catalyzed cross-couplings via an sp^2 C–H functionalization process have also been documented.[4] Early studies showed that this process could be well performed with a catalytic Ni^0 species on substrates with an acidic C–H bond, such as pyridine,[5] perfluorobenzene,[6] and azole derivatives,[7] and it is believed that the catalytic cycle is initiated by oxidative addition of Ni^0 to the acidic C–H bond. Additionally, Ni^{II}-catalyzed direct arylation of azole derivatives was also demonstrated.[8] In this case, a Ni^{II} species acts as an electrophile for aromatic substitution reaction of azoles. Recently, Ni^0-catalyzed direct funtionalization of benzene derivatives has also been developed.[9] Furthermore, inspired by the reports from the Daugulis' group, the Pd^{II}-catalyzed direct functionalization of unactivated C–H bonds via a bidentate directing group-assisted process,[4b,10] Ni^{II}-catalyzed direct alkylation of benzamide derivatives has also been demonstrated very recently.[11] Additionally, a Ni^0-catalyzed cycloaddition reaction of foramides with alkynes was reported via *in situ* sp^3 C–H bond activation.[12] However, to date, ligand-controlled Ni-catalyzed cross-couplings via an sp^3 C–H functionalization process have not been discovered. It is believed that this process is feasible with the aid of a bidentate directing group, which will lead to the site-selective functionalization on sp^3 carbons.[13] If successful, this process will provide a complementary approach to access α-multisubstituted acid derivatives, the important synthetic intermediates or structural units in biologically active natural products and medicinal compounds.[14]

To verify the proposed strategy, nickel-catalyzed direct alkylation of 2-ethyl-2-methyl-*N*-(quinolin-8-yl)pentanamide (**1a**) with iodopentane was carried out (Table 1). After an initial screening of the catalyst, the alkylated product **2a** was obtained in 63% yield by using catalytic amounts of Ni(acac)$_2$ and PPh$_3$ and excess Cs$_2$CO$_3$ in toluene under atmosphere of N$_2$ (entry 5). It was also noticed that this reaction showed high site selectivity by

Table 1. Optimization of Reaction Conditions[a]



1a **2a**

entry	Ni source (10 mol %)	ligand (mol %)	base (equiv)	yield (%)[b]
1	Ni(OTf)$_2$	PPh$_3$ (20)	Cs$_2$CO$_3$ (5.0)	<5
2	Ni(COD)$_2$	PPh$_3$ (20)	Cs$_2$CO$_3$ (5.0)	<5
3	NiBr$_2$	PPh$_3$ (20)	Cs$_2$CO$_3$ (5.0)	28
4	NiCl$_2$·6H$_2$O	PPh$_3$ (20)	Cs$_2$CO$_3$ (5.0)	41
5	Ni(acac)$_2$	PPh$_3$ (20)	Cs$_2$CO$_3$ (5.0)	63
6	Ni(acac)$_2$	–	Cs$_2$CO$_3$ (5.0)	10
7	Ni(acac)$_2$	P(2-furyl)$_3$ (20)	Cs$_2$CO$_3$ (5.0)	71
8	Ni(acac)$_2$	PCy$_3$ (20)	Cs$_2$CO$_3$ (5.0)	82
9	Ni(acac)$_2$	dppe (10)	Cs$_2$CO$_3$ (5.0)	71
10	Ni(acac)$_2$	dppp(10)	Cs$_2$CO$_3$ (5.0)	69
11	Ni(acac)$_2$	xantphos (10)	Cs$_2$CO$_3$ (5.0)	79
12	Ni(acac)$_2$	BINAP (10)	Cs$_2$CO$_3$ (5.0)	74
13	Ni(acac)$_2$	dppbz(10)	Cs$_2$CO$_3$ (5.0)	89(86)[c]
14	Ni(acac)$_2$	dppbz(10)	K$_2$CO$_3$ (5.0)	70
15	Ni(acac)$_2$	dppbz(10)	Na$_2$CO$_3$ (5.0)	<5
16	Ni(acac)$_2$	dppbz(10)	K$_3$PO$_4$ (5.0)	<5
17	Ni(acac)$_2$	dppbz(10)	Cs$_2$CO$_3$ (3.0)	65

[a]Reaction conditions: **1a** (0.3 mmol), Ni source (10 mol %), ligand, base, N$_2$ (1 atm), 1.2 mL of toluene, 150 °C, 24 h. [b]Yields and conversions are based on **1a**, determined by ^{1}H NMR using dibromomethane as the internal standard. [c]Isolated yields. Dppbz = 1,2-bis(diphenylphosphino)benzene.

Received: December 25, 2013
Published: January 14, 2014

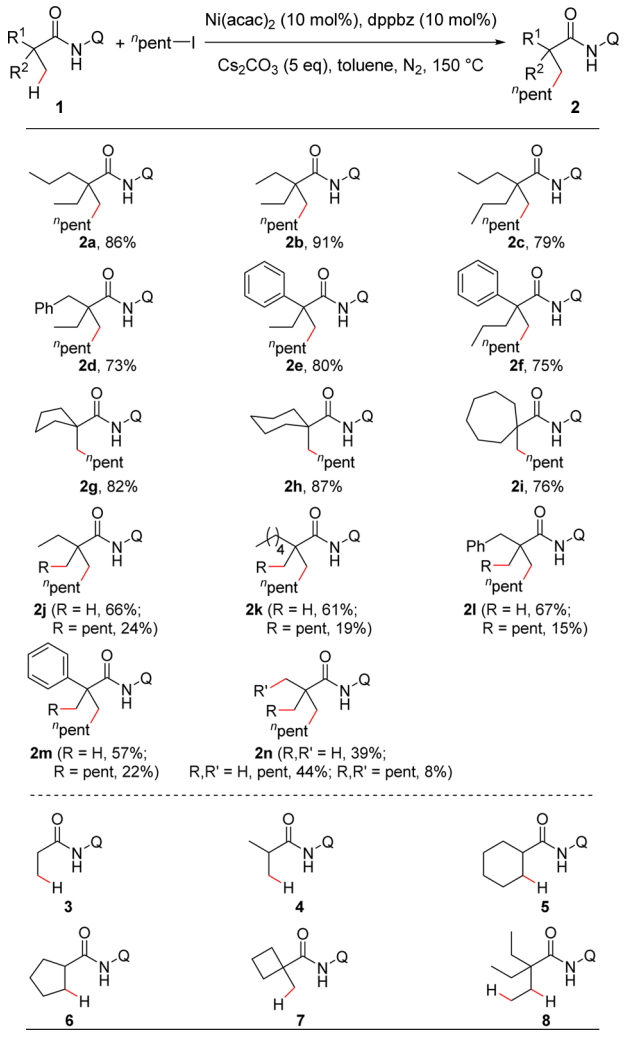
dx.doi.org/10.1021/ja413131m | J. Am. Chem. Soc. 2014, 136, 1789–1792

favoring the methyl group over the methylene groups, which is believed to be arisen from the steric effect. Additionally, the formation of a five-membered ring intermediate in the cyclometalation step is preferred over the six- or seven-membered ring intermediates since the alkylation of the C−H bonds of methyl groups on the ethyl or propyl group was not observed. Further optimization showed that this reaction was improved by using the bidentate ligand dppbz (entry 13). Additionally, the reaction could also be effectively performed in other solvents (see Supporting Information).

With the optimized conditions in hand, the scope of amides was studied. As shown in Table 2, 2,2-disubstituted propanamides bearing both the linear and cyclic chains provided the desired products in good to excellent yields (**2a**−**i**). Surprisingly, with the 2-phenyl-substituted substrates, the reaction showed a predominant preference for the sp^3 C−H bonds of methyl group over the sp^2 C−H bonds of phenyl group (**2e** and **2f**), indicating that in the metalation step, a five-membered intermediate should be favored than a six-membered intermediate. It is noteworthy that in the Pd-catalyzed direct alkylation of amides, sp^3 C−H bond functionalization was disfavored in the presence of a competing sp^2 C−H bond. As expected, with two methyl groups on the α-position of the amide, both mono- and dialkylated products were observed, favoring the mon-alkylation (**2j**−**m**). Furthermore, the 2,2-dimethyl-substituted propanamide provided three products with the mono- and dialkylated products as the major isomers (**2n**). It was also noticed that a tertiary α-carbon is necessary for this process to reach an efficient cyclometalation since amides **3**−**6** failed to this reaction. In addition, cyclobutanecaroxamide **7** did not provide the desired product. As suggested by the report from Nakamura's group, the CH_3−C−C(=O) bond angle of **7** is much wider than its cyclopentyl or cyclohexyl derivative,[15] and thus the cyclometalation of this substrate with a Ni^{II} species is less feasible. Furthermore, 2,2-diethyl-*N*-(quinolin-8-yl)butanamide (**8**) also failed to provide any C-alkylated products on either the primary or secondary carbon.

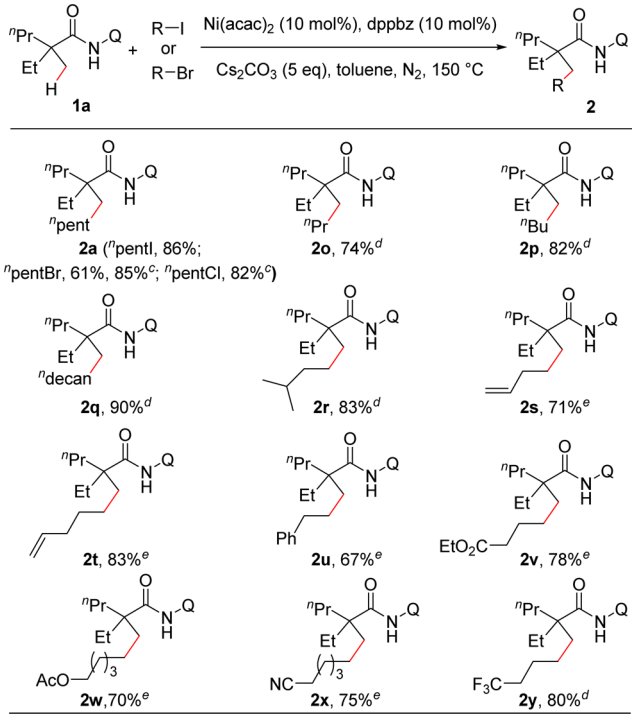
Next, we carried out the substrate scope study on alkyl halides (Table 3). As expected, linear alkyl halides showed great compatibility with the reaction conditions, and this reaction tolerated a variety of functional groups, such as the alkene, cyano, ester, and trifluoromethyl groups (**2a**−**y**). It was also found that alkyl iodides could be replaced with alkyl bromides or chlorides with the addition of CsI. Furthermore, there is an apparent steric effect for this reaction since both isopropyl and isobutyl iodides failed to give the desired products. In addition, benzylic and allylic halides were not compatible with the current reaction conditions. Unfortunately, secondary alkyl halides and benzyl bromide failed to provide the desired products, presumably due to the steric effect or the unstability of the intermediate.

Table 2. Scope of Aliphatic Amides[a,b]



[a]Reaction conditions: **1** (0.3 mmol), iodopentane (5.0 equiv), $Ni(acac)_2$ (10 mol %), dppbz (10 mol %), Cs_2CO_3 (5.0 equiv), N_2 (1 atm), 1.2 mL toluene, 150 °C, 12−24 h. [b]Isolated yield. Q = 8-quinolinyl.

Table 3. Scope of Alkyl Halides[a,b]

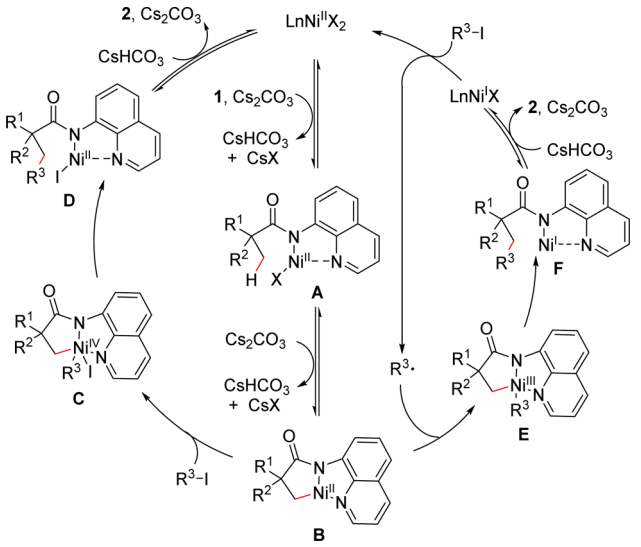


[a]Reaction conditions: **1** (0.3 mmol), alkyl halide (5.0 equiv), $Ni(acac)_2$ (10 mol %), dppbz (10 mol %), Cs_2CO_3 (5.0 equiv), N_2 (1 atm), 1.2 mL toluene, 150 °C, 24 h. [b]Isolated yield. [c]With CsI (5.0 equiv). [d]Alkyl iodide. [e]Alkyl bromide with CsI (5.0 equiv).

dx.doi.org/10.1021/ja413131m | J. Am. Chem. Soc. 2014, 136, 1789−1792

On the basis of the above results and the previous reports,[11,16] a plausible reaction mechanism is proposed (Scheme 1).

Scheme 1. Proposed Reaction Mechanism

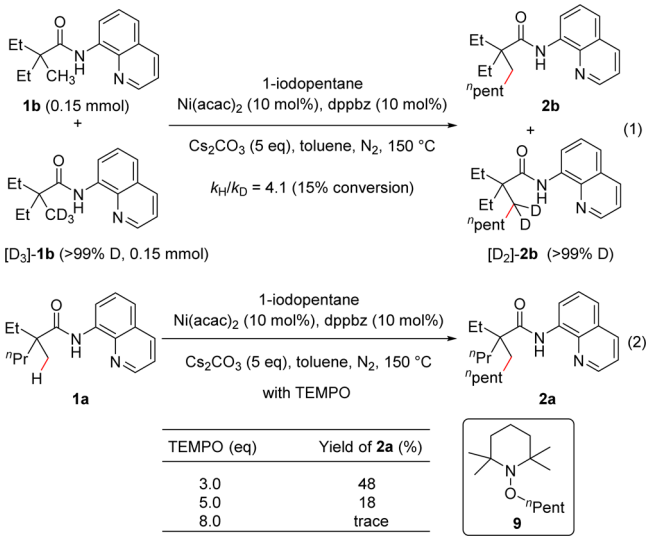


Coordination of amide **1** to a Ni^{II} species followed by a ligand exchange process under basic conditions generates nickel complex **A**, which gives rise to the intermediate **B** via a reversible cyclometalation process.[17] Oxidative addition of intermediate **B** with an alkyl halide followed by reductive elimination generates the intermediate **D**,[18] which produces the desired product **2** upon protonation and regenerates the Ni^{II} species. Alternatively, the Ni^{III} complex **E** could be involved in this process by oxidation of intermediate **B** with an alkyl radical.[19] Reductive elimination of the intermediate **E** followed by protonation generates the desired product **2** and a Ni^{I} species. Treatment of the Ni^{I} species with an alkyl halide produces the alkyl radical and Ni^{II} species. It is noteworthy that in the reaction of **1a** with 1-iododecane, a small amount of decene, the β-H eliminated product of the alkylmetal intermediate, was detected by GC/mass, which indirectly supports the formation of the intermediate **C** or **E**. It should be mentioned that although this process could potentially begin with a Ni^{0} species,[9d] the extremely low yield of **2a** with a catalytic amount of $Ni(COD)_2$ indicates that the catalytic cycle is unlikely initiated by a Ni^{0} species.

To further probe the reaction mechanism, a deuterium-labeling experiment was carried out, and an apparent isotope effect was observed [Scheme 2, (1)]. This indicates that the cyclometalation of amide **1** with a nickel species is the rate-determining step in the process. Furthermore, a radical trapping experiment was also carried out, and it was found that the addition of TEMPO resulted in the decreased yield of this reaction [Scheme 2, (2)]. Additionally, 2,2,6,6-tetramethyl-1-(pentyloxy)piperidine (**8**) was isolated along with the desired product. Notably, in the absence of a nickel species, this compound was not produced. On the basis of the above observations, it is believed that this reaction performed through the Ni^{II}/Ni^{III} catalytic cycle.

In summary, a highly regioselective alkylation of 2,2-disubstituted propionamide with 8-aminoquinolinyl group as the amide moiety was developed via a nickel-catalyzed sp^3 C–H bond functionalization process. This reaction shows a great preference for sp^3 C–H bonds of methyl groups over the methylene C–H bonds with good functional group tolerance.

Scheme 2. Deuterium Labeling and Radical Trapping Experiments



TEMPO (eq)	Yield of **2a** (%)
3.0	48
5.0	18
8.0	trace

Unexpectedly, the preference for sp^3 C–H bonds of methyl groups via a five-membered ring intermediate in the cyclometalation step was also observed over the sp^2 C–H bonds of arenes via a six-membered ring intermediate, which constitutes a unique phenomenon of nickel catalysis. The detailed mechanistic study of this transformation is currently undergoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization 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.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge financial support for this research from Indiana University Purdue University Indianapolis. The Bruker 500 MHz NMR was purchased using funds from an NSF-MRI award (CHE-0619254).

■ REFERENCES

(1) For selected recent reviews, see: (a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 2. (b) Takahashi, T.; Kanna, K.-i. *Modern Organonickel Chemistry*, Wiley-VCH: Weinheim, Germany, 2005, p 41. (c) Negishi, E.-i.; Hu, Q.; Huang, Z.-H.; Wang, G.-W.; Yin, N. *Chemistry of Organozinc Compounds*, John Wiley & Sons Ltd.: Chichester, UK, 2006, p 457. (d) Nakao, Y.; Hiyama, T. *Pure Appl. Chem.* **2008**, *80*, 1097. (e) Denmark, S. E.; Butler, C. R. *Chem. Commun.* **2009**, 20. (f) Phapale, V. B.; Cardenas, D. J. *Chem. Soc. Rev.* **2009**, *38*, 1598. (g) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346. (h) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417. (i) Mesganaw, T.; Garg, N. K. *Org. Process Res. Dev.* **2013**, *17*, 29. (j) Han, F.-S. *Chem. Soc. Rev.* **2013**, *42*, 5270.

(2) (a) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525. (b) Guan, B.-T.; Xiang, S.-K.; Wang, B.-Q.; Sun, Z.-P.; Wang, Y.; Zhao,

K.-Q.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 3268. (c) Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2011**, *133*, 389. (d) Hu, X.-L. *Chem. Sci.* **2011**, *2*, 1867. (e) Maity, P.; Shacklady-McAtee, D. M.; Yap, G. P. A.; Sirianni, E. R.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 280. (f) Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 624. (g) Zhou, Q.; Srinivas, H. D.; Dasgupta, S.; Watson, M. P.; Watson. *J. Am. Chem. Soc.* **2013**, *135*, 3307. (h) Nielsen, D. K.; Huang, C.-Y.; Doyle, A. G. *J. Am. Chem. Soc.* **2013**, *135*, 13605.

(3) (a) Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Acc. Chem. Res.* **2010**, *43*, 1486. (b) Yu, D.-G.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7097. (c) Yu, D.-G.; Wang, X.; Zhu, R.-Y.; Luo, S.; Zhang, X.-B.; Wang, B.-Q.; Wang, L.; Shi, Z.-J. *J. Am. Chem. Soc.* **2012**, *134*, 14638.

(4) (a) Yamaguchi, J.; Muto, K.; Itami, K. *Eur. J. Org. Chem.* **2013**, 19. (b) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726.

(5) (a) Kanyiva, K. S.; Nakao, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 8872. (b) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 2448. (c) Tobisu, M.; Hyodo, I.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 12070. (d) Nakao, Y.; Yamada, Y.; Kashihara, N.; Hiyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 13666. (e) Tsai, C.-C.; Shih, W.-C.; Fang, C.-H.; Li, C.-Y.; Ong, T.-G.; Yap, G. P. A. *J. Am. Chem. Soc.* **2010**, *132*, 11887. (f) Hyodo, I.; Tobisu, M.; Chatani, N. *Chem. Commun.* **2012**, *48*, 308. (g) Hyodo, I.; Tobisu, M.; Chatani, N. *Chem.—Asian J.* **2012**, *7*, 1357. (h) Liu, S.; Sawicki, J.; Driver, T. G. *Org. Lett.* **2012**, *14*, 3744. (i) Nakao, Y.; Idei, H.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 15996. (j) Tamura, R.; Yamada, Y.; Nakao, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 5679.

(6) (a) Nakao, Y.; Kashihara, N.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 16170. (b) Kanyiva, K. S.; Kashihara, N.; Nakao, Y.; Hiyama, T.; Ohashi, M.; Ogoshi, S. *Dalton Trans.* **2010**, *39*, 10483. (c) Doster, M. E.; Hatnean, J. A.; Jeftic, T.; Modi, S.; Johnson, S. A. *J. Am. Chem. Soc.* **2010**, *132*, 11923. (d) Hatnean, J. A.; Beck, R.; Borrelli, J. D.; Johnson, S. A. *Organometallics* **2010**, *29*, 6077. (e) Guihaumé, J.; Halbert, S.; Eisenstein, O.; Perutz, R. N. *Organometallics* **2012**, *31*, 1300. (f) Doster, M. E.; Johnson, S. A. *Organometallics* **2013**, *32*, 4174.

(7) (a) Clement, N. D.; Cavell, K. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3845. (b) Kanyiva, K. S.; Nakao, Y.; Hiyama, T. *Heterocycles* **2007**, *72*, 677. (c) Canivet, J.; Yamaguchi, J.; Ban, I.; Itami, K. *Org. Lett.* **2009**, *11*, 1733. (d) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 1737. (e) Mukai, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 6410. (f) Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 4156. (g) Kanyiva, K. S.; Löbermann, F.; Nakao, Y.; Hiyama, T. *Tetrahedron Lett.* **2009**, *50*, 3463. (h) Nakao, Y.; Kashihara, N.; Kanyiva, K. S.; Hiyama, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 4451. (i) Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 12307. (j) Yamamoto, T.; Muto, K.; Komiyama, M.; Canivet, J.; Yamaguchi, J.; Itami, K. *Chem.—Eur. J.* **2011**, *17*, 10113. (k) Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 775. (l) Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 169. (m) Shih, W.-C.; Chen, W.-C.; Lai, Y.-C.; Yu, M.-S.; Ho, J.-J.; Yap, G. P. A.; Ong, T.-G. *Org. Lett.* **2012**, *14*, 2046. (n) Jiang, Y.-Y.; Li, Z.; Shi, J. *Organometallics* **2012**, *31*, 4356. (o) Amaike, K.; Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 13573. (p) Lee, W.-C.; Wang, C.-H.; Lin, Y.-H.; Shih, W.-C.; Ong, T.-G. *Org. Lett.* **2013**, *15*, 5358. (q) Meng, L.; Kamada, Y.; Muto, K.; Yamaguchi, J.; Itami, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 10048. (r) Muto, K.; Yamaguchi, J.; Lei, A.-W.; Itami, K. *J. Am. Chem. Soc.* **2013**, *135*, 16384.

(8) (a) Truong, T.; Alvarado, J.; Tran, L. D.; Daugulis, O. *Org. Lett.* **2010**, *12*, 1200. (b) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *ChemCatChem* **2010**, *2*, 1403. (c) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2202. (d) Matsuyama, N.; Kitahara, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 2358. (e) Vechorkin, O.; Proust, V.; Hu, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 3061. (f) Qu, G.-R.; Xin, P.-Y.; Niu, H.-Y.; Wang, D.-C.; Ding, R.-F.; Guo, H.-M. *Chem. Commun.* **2011**, *47*, 11140.

(9) (a) Kleiman, J. P.; Dubeck, M. *J. Am. Chem. Soc.* **1963**, *85*, 1544. (b) Shacklady-McAtee, D. M.; Dasgupta, S.; Watson, M. P. *Org. Lett.* **2011**, *13*, 3490. (c) Ogata, K.; Atsumi, Y.; Shimada, D.; Fukuzawa, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 5896. (d) Shiota, H.; Ano, Y.; Ahihara, Y.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 14952. (e) Beaulieu, L.-P. B.; Sustac Roman, D.; Vallee, F.; Charette, A. B. *Chem. Commun.* **2012**, *48*, 8249. (f) Song, W.-F.; Ackermann, L. *Chem. Commun.* **2013**, *49*, 6638.

(10) (a) Dangel, B. D.; Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856. (b) Zaitsev, V.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (c) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391. (d) Giri, R.; Maugel, N.; Foxman, B. M.; Yu, J.-Q. *Organometallics* **2008**, *27*, 1667. (e) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (f) He, G.; Chen, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 5192. (g) Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 12984. (h) Ano, Y.; Tobisu, M.; Chatani, N. *Org. Lett.* **2012**, *14*, 354. (i) Tran, L. D.; Daugulis, O. *Angew. Chem., Int. Ed.* **2012**, *124*, 5278. (j) Rodríguez, N.; Romero-Revilla, J. A.; Fernández-Ibáñez, M. Á.; Carretero, J. C. *Chem. Sci.* **2013**, *4*, 175. (k) Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124. (l) Chen, K.; Hu, F.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 3906.

(11) Ahihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2013**, *135*, 5308.

(12) Nakao, Y.; Morita, E.; Idei, H.; Hiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 3264.

(13) (a) Koo, K.; Hilhouse, G. L. *Organometallics* **1995**, *14*, 4421. (b) Koo, K.; Hilhouse, G. L. *Organometallics* **1996**, *15*, 2669. (c) Lu, Z.-L.; Abbina, S.; Sabin, J. R.; Nemykin, V. N.; Du, G.-D. *Inorg. Chem.* **2013**, *52*, 1454.

(14) (a) Scott, K. R.; Kennedy, P. G.; Kemp, M.; Telang, V. G.; Matthews, H. W. *J. Pharm. Sci.* **1983**, *72*, 183. (b) Scott, K. R.; Moore, J. A.; Zalucky, T. B.; Nicholson, J. M.; Lee, J. A. M.; Hinko, C. N. *J. Med. Chem.* **1985**, *28*, 413. (c) Tarver, M. L.; Nicholson, J. M.; Scott, K. R. *J. Pharm. Sci.* **1985**, *74*, 785. (d) Hoffman, W. F.; Alberts, A. W.; Anderson, P. S.; Chen, J. S.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1986**, *29*, 849. (e) Huang, Z.; Poulter, C. D.; Wolf, F. R.; Somers, T. C.; White, J. D. *J. Am. Chem. Soc.* **1988**, *110*, 3959. (f) Kenda, B. M.; Matagne, A. C.; Talaga, P. E.; Pasau, P. M.; Differding, E.; Lallemand, B. I.; Frycia, A. M.; Moureau, F. G.; Klitgaard, H. V.; Gillard, M. R.; Fuks, B.; Michel, P. *J. Med. Chem.* **2004**, *47*, 530. (g) Werstuck, G. H.; Kim, A. J.; Brenstrum, T.; Ohnmacht, S. A.; Panna, E.; Capretta, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5465. (h) Pryde, D. C.; Maw, G. N.; Planken, S.; Platts, M. Y.; Sanderson, V.; Corless, M.; Stobie, A.; Barber, C. G.; Russell, R.; Foster, L.; Barker, L.; Wayman, C.; Van Der Graaf, P.; Stacey, P.; Morren, D.; Kohl, C.; Beaumont, K.; Coggon, S.; Tute, M. *J. Med. Chem.* **2006**, *49*, 4409. (i) Pryde, D. C.; Cook, A. S.; Burring, D. J.; Jones, L. H.; Foll, S.; Platts, M. Y.; Sanderson, V.; Corless, M.; Stobie, A.; Middleton, D. S.; Foster, L.; Barker, L.; Van Der Graaf, P.; Stacey, P.; Kohl, C.; Coggon, S.; Beaumont, K. *Bioorg. Med. Chem.* **2007**, *15*, 142. (j) Obniska, J.; Kaminski, K.; Hondo, L.; Zejc, A. *Arch. Pharm.* **2007**, *340*, 404. (k) Arbour, A.; Roy, S.; Godbout, C.; Spino, C. *J. Org. Chem.* **2009**, *74*, 3806.

(15) Shang, R.; Ilies, L.; Matsumoto, A.; Nakamura, E. *J. Am. Chem. Soc.* **2013**, *135*, 6030.

(16) (a) Terao, J.; Kambe, N. *Acc. Chem. Res.* **2008**, *41*, 1545. (b) Higgs, A. T.; Zinn, P. J.; Sanford, M. S. *Organometallics* **2010**, *29*, 5446.

(17) A stoichiometric amount of $Ni(dppbz)I_2$ or $Ni(acac)_2$ was used to try to identify the formation of the intermediate **A** or **B**. Unfortunately, neither of the two intermediates was detected by ^1H NMR.

(18) For the Ni^{IV} or Ni^{III} intermediate **C** or **E**, the metal could coordinate six ligands in maximum, and there are two potential coordination methods. In the first one, only one phosphine atom in the phosphine ligand may be involved in this coordination process since the monodentate phosphine ligands also worked efficiently for the reaction. In the second one, the coordination between the nickel and pyridine nitrogen is displaced by the bidentate phosphine ligand.

(19) (a) Higgs, A. T.; Zinn, P. J.; Simmons, S. J.; Sanford, M. S. *Organometallics* **2009**, *28*, 6142. (b) Breitenfeld, J.; Ruiz, J.; Wodrich, M. D.; Hu, X. *J. Am. Chem. Soc.* **2013**, *135*, 12004. (c) Biswas, S.; Weix, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16192.