Communication

Ligand-Enabled Cross-Coupling of C(sp3)–H Bonds with Arylsilanes

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Ligand-Enabled Cross-Coupling of C(sp^3)–H Bonds with Arylsilanes

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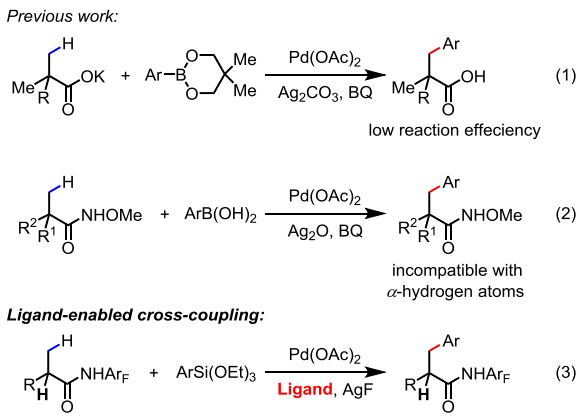
ABSTRACT: Pd(II)-catalyzed cross-coupling of C(sp^3)–H bonds with organosilicon coupling partners has been achieved for the first time. The use of a newly developed quinoline-based ligand is essential for the cross-coupling reactions to proceed.

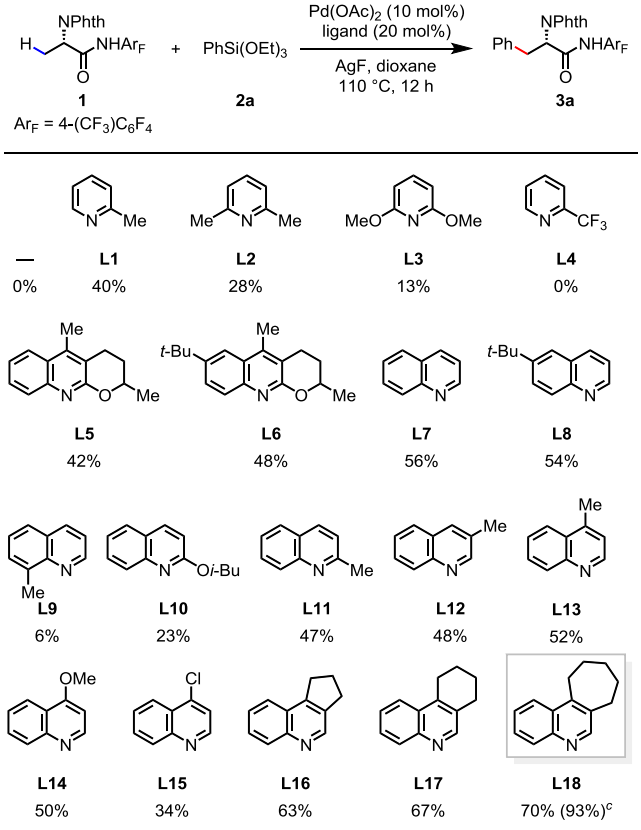
Inspired by the Pd(0)-catalyzed cross-coupling reactions,[1] we embarked on the development of Pd(II)-catalyzed cross-coupling of C–H bonds with organometallic reagents. A Pd(II)/Pd(0) catalytic cycle has been established for the cross-coupling of C(sp^2)–H bonds with organotin[2] and organoboron reagents[3] with limited substrate scopes. Subsequently, C–H cross-coupling with readily available organoboron reagents are expanded to broadly useful substrates including benzoic acids and phenyl acetic acids.[4,5] In contrast, analogous cross-coupling of C(sp^3)–H bonds with organometallic reagents has met with limited success.[6] Although pyridine-directed C(sp^3)–H cross-coupling with alkyl boronic acids is successful,[3] extending this methodology to aliphatic acid substrates affords poor yields (<30%) (Eq 1).[4] The development of an efficient *N*-methoxyamide directing group allowed for a rare cross-coupling of *β*-C(sp^3)–H bonds with boronic acids (Eq 2).[7] Unfortunately, this protocol is incompatible with the substrates containing *α*-hydrogen atoms. Although *β*-C(sp^3)–H arylation with aryl halides via Pd(II)/Pd(IV) catalysis has been developed to accommodate a broader range of substrates,[8] the C(sp^3)–H cross-coupling reaction involving a Pd(II)/Pd(0) catalytic cycle offers a distinct platform for ligand development that will lead to improved catalysis and selectivity. Herein, we report the first example of *β*-C(sp^3)–H cross-coupling of carboxylic acids with arylsilanes using perfluorinated *N*-arylamide auxiliary (Eq 3).[9] The discovery of a new quinoline-based ligand is crucial for the development of this cross-coupling of C(sp^3)–H bonds with arylsilanes.

Scheme 1. Palladium-Catalyzed C(sp^3)–H Activation/Cross-Coupling Reactions of Carboxylic Acid Derivatives



A wide range of organosilicon reagents have been successfully used as coupling partners in the Hiyama cross-coupling reactions of aryl halides.[1f,10] Important advances have also been made in the cross-coupling of alkyl halides with arylsilanes.[11] Despite significant progress of Pd-,[12,13] Rh-,[14] and Ni-catalyzed[15] C(sp^2)–H cross-coupling with arylsilanes, cross-coupling of inert C(sp^3)–H bonds with organosilicon reagents remains to be reported. Encouraged by our recent observation that pyridine- and quinoline-based ligands promote C(sp^3)–H olefination via a Pd(II)/Pd(0) catalytic cycle,[16] we launched our efforts to develop new ligands that could promote *β*-C(sp^3)–H cross-coupling of carboxylic acid derivatives with organosilicon reagents.

Table 1. Screening of Ligand for C(sp^3)–H Cross-Coupling with Arylsilanes[a,b]



[a] Reaction conditions: substrate **1** (0.1 mmol), **2a** (2.0 equiv.), Pd(OAc)$_2$ (10 mol%), ligand (20 mol%), AgF (3.0 equiv.), 1,4-dioxane (1.0 mL), 110 °C, 12 h. [b] The yield was determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as the internal standard. [c] After 8 h, the second batch of **2a** (2.0 equiv.) and AgF (3.0 equiv.) was added, and the reaction proceeded for another 10 h.

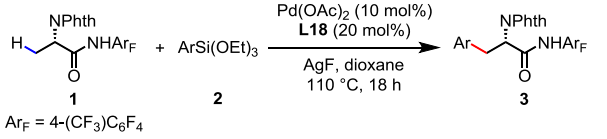
Our experiments commenced by investigating the coupling of an alanine-derived amide **1** with various organosilicon reagents (see supporting information). We examined various oxidants and solvents, as well as those additives previously proven to be beneficial to the Hiyama cross-coupling. We found the reaction of amide **1** with 2 equiv. of triethoxyphenylsilane (**2a**) in the presence of 10 mol% of Pd(OAc)$_2$, 20 mol% of 2-picoline (**L1**), and 3 equiv. of AgF in 1,4-dioxane at 110 °C afforded the desired product **3a** in 40% yield. AgF proves to be the only effective additive which has dual functions in this transformation: 1) silver salts are one of the most efficient and commonly used oxidants to reoxidize Pd(0) to Pd(II) in Pd(II)/Pd(0) catalytic cycles;[17] 2)

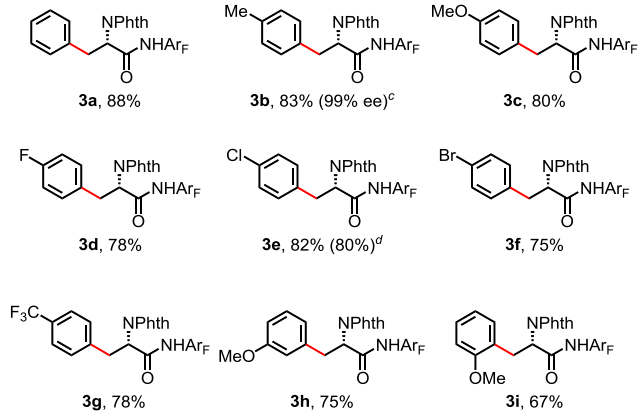
fluoride sources are known to activate organosilicon coupling partners, promoting transmetallation of aryl groups to Pd(II).[18] Analysis of the reaction mixture showed that a substantial amount of organosilicon reagents were homo-coupled to give the biaryl side product. In the absence of ligands, the desired coupling reaction did not proceed, indicating a significant ligand effect. We therefore began to examine a variety of substituted pyridine ligands that could potentially accelerate the C(sp^3)–H cross-coupling further in order to outcompete the homo-coupling process (Table 1). 2,6-Lutidine (**L2**) and 2,6-dimethoxypyridine (**L3**) gave the desired product in lower yields (28% and 13% respectively), demonstrating that the increase of steric bulk and electron-donating ability of pyridine-based ligands has negative impact on the reaction. However, replacement of 2-picoline (**L1**) with electron-deficient 2-trifluoromethylpyridine (**L4**) resulted in a complete loss of reactivity.

While these pyridine ligands have been previously shown to promote arylation of C(sp^3)–H bonds with aryl iodides,[19] the failed attempts to improve the reaction suggest that the transmetallation and reductive elimination at the Pd(II) centers require a different type of ligands. The tricyclic quinoline ligands (**L5**, **L6**) were therefore chosen because they were previously used to promote Pd-catalyzed C(sp^3)–H olefination reactions via Pd(II)/Pd(0) catalysis.[16] We found that the use of **L6** increased the yield of **3a** to 48%. Based on this finding, we systematically surveyed different types of quinoline-based ligands. Gratifyingly, the simple quinoline (**L7**) further improved the reactivity, giving **3a** in 56% yield. While the substituent at the 6-position of quinoline **L8** did not affect the yield, installation of a methyl group at the 8-position (**L9**) drastically decreased the reaction efficiency. Any substitution at the 2-positions of quinoline-based ligands (**L10**, **L11**) was detrimental to the cross-coupling reactions. These investigations showed that this Hiyama-type cross-coupling is very sensitive to the steric effect of quinoline-based ligands. In terms of electronic effects, electron-donating groups at the 3- or 4-positions of quinolines (**L12–L14**) gave moderate yields from 48% to 52% whereas electron-deficient 4-chloroquinoline (**L15**) afforded only 34% yield. Given that quinolines containing fused carbocylic rings could have distinct steric and electronic properties, we introduced 5-, 6-, and 7-membered rings to the ligands (**L16–L18**), and found **L18** provided the highest yield of 70%. The yield was further increased to 93% when a second batch of **2a** and AgF was added after 8 hours.

Cross-coupling reactions of alanine-derived amide **1** with a broad range of electron-rich and electron-poor triethoxyarylsilanes were carried out under the standard conditions (Table 2). Triethoxyarylsilanes containing methyl and methoxy groups on the aryl ring afforded desired products in excellent yields (**3b**, **3c**). *para*-Fluoro, chloro, bromo, and trifluoromethyl groups are well tolerated, furnishing phenylalanine derivatives in yields from 75% to 82% (**3d–3g**). This reaction is also compatible with *meta*- and *ortho*-substituted triethoxyarylsilanes (**3h**, **3i**). Furthermore, the cyclobutyl C(sp^3)–H bond in amide substrate **4** derived from 1-aminocyclobutane-1-carboxylic acid was successfully functionalized to afford the corresponding *β*-alkyl-*β*-aryl-*α*-amino acid derivatives in 72% yield with high levels of diastereoselectivity (Scheme 2). The cross-coupling reaction was also carried out on a gram scale without a noticeable decrease in yield (**3e**). Importantly, in the absence of external inorganic bases, complete retention of *α*-chirality (**3b**) was observed in the *β*-C(sp^3)–H cross-coupling using amide **1** (99% ee) as the substrate.

Table 2. Synthesis of Phenylalanine Derivatives using Ligand-Enabled C(sp^3)–H Cross-Coupling with Arylsilanes[a,b]





[a] Reaction conditions: substrate **1** (0.1 mmol), **2** (2.0 equiv.), Pd(OAc)$_2$ (10 mol%), **L18** (20 mol%), AgF (3.0 equiv.), 1,4-dioxane (1.0 mL), 110 °C. The second batch of **2** (2.0 equiv.) and AgF (3.0 equiv.) was added at 8 h. The reactions were run for 18 h total. [b] Isolated yields. [c] The ee value was determined by chiral HPLC. [d] Isolated yield of a gram-scale reaction in the parenthesis.

Scheme 2. Cross-Coupling of Cyclobutyl C(sp^3)–H Bonds

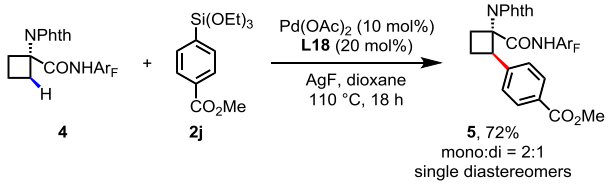
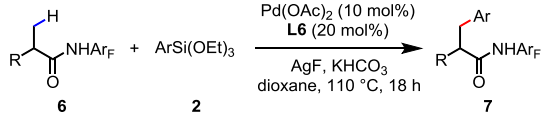
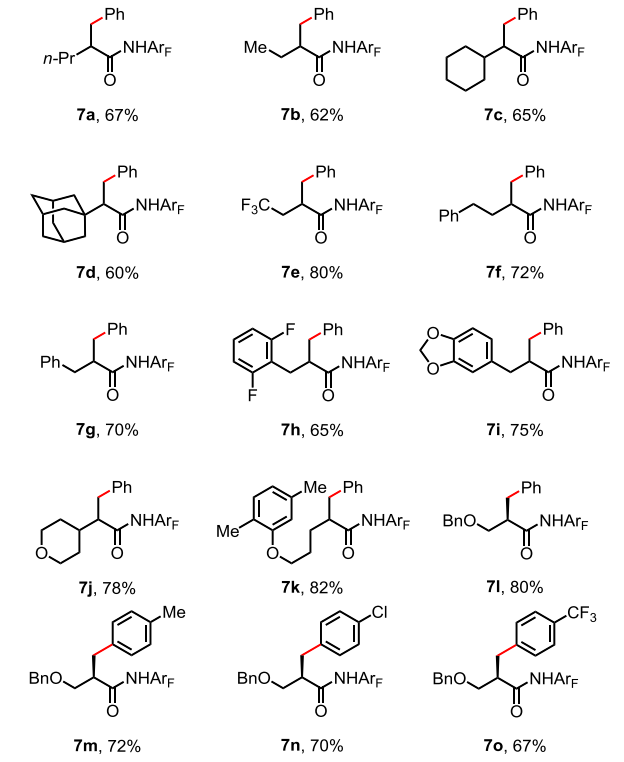


Table 3. *β*-C(sp^3)–H Cross-Coupling of Carboxylic Acid Derivatives with Arylsilanes[a,b]



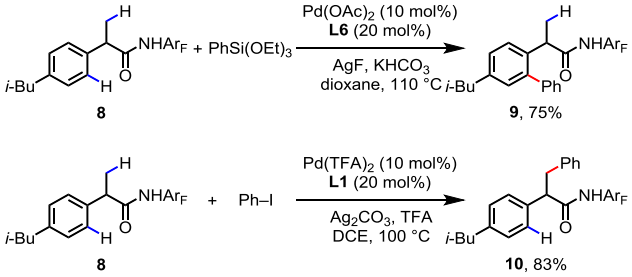


[a] Reaction conditions: substrate **6** (0.1 mmol), **2** (2.0 equiv.), $Pd(OAc)_2$ (10 mol%), **L6** (20 mol%), $KHCO_3$ (2.0 equiv.), AgF (3.0 equiv.), 1,4-dioxane (1.0 mL), 110 °C. The second batch of **2a** (2.0 equiv.) and AgF (3.0 equiv.) was added at 8 h. The reactions were run for 18 h total. [b] Isolated yields.

To investigate the compatibility of this protocol with other aliphatic acids, amide **6a** derived from 2-methylpentanoic acid was subjected to standard conditions to afford the arylated product **7a** in 45% yield. Extensive optimization including changing ligands and bases (see SI) improved the yield to 67% (Table 3). Under these new conditions, a variety of amides derived from aliphatic acids were arylated in good yields (**7b–7d**). The cross-coupling of amide **6e** containing a trifluoromethyl group afforded the desired product **7e** in 80% yield. A number of aryl groups on the β- and γ-positions of amide substrates are tolerated (**7e–7i**). The reaction is also tolerant of different types of ether groups including a benzyl protected β-hydroxyl group (**7j–7l**). Various triethoxyarylsilane partners containing methyl, chloro, and trifluoromethyl groups were coupled with substrate **6l** to give the desired products in good yields (**7m–7o**). It should be noted that arylation of alanine-derived amide **1** under these conditions also proceeds, albeit leading to substantial racemization of the product.

While the β- and γ-aryls did not interfere with the β-C(sp^3)–H activation, the α-aryl group in the ibuprofen-derived substrate was preferentially *ortho*-arylated under these conditions (Scheme 3). To achieve the site-selective β-C–H arylation of **8**, we turned to our previously developed arylation protocol with aryl iodides and successfully obtained the β-arylated product **10** in 83% yield.[16] The observed opposite site selectivity with Pd(II)/Pd(IV)[16] and Pd(II)/Pd(0) catalysis speaks to the importance of developing different catalytic cycles for C–H activation reactions. We anticipate the ability to arylate C–H bonds at different positions using two different protocols will be highly useful in synthesis.

Scheme 3. C–H Functionalizations of an Ibuprofen-Derived Amide



In conclusion, ligand-enabled cross-coupling of β-C(sp^3)–H bonds in carboxylic acid derivatives with arylsilanes has been achieved using a new quinoline-based ligand. The development of this coupling reaction further demonstrates the potential utility of quinoline-based ligands in Pd-catalyzed C–H activation reactions.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds (PDF). 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) Stille, J. K. *Angew. Chem. Int. Ed.* **1986**, *25*, 508. (b) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. (c) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461. (d) Suzuki, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 6722. (e) Negishi, E.-i. *Angew. Chem. Int. Ed.* **2011**, *50*, 6738. (f) Nakao, Y.; Hiyama, T. *Chem. Soc. Rev.* **2011**, *40*, 4893.

(2) Chen, X.; Li, J.-J.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 78.

(3) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634.

(4) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510.

(5) Wang, D.-H.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 17676.

(6) Wasa, M.; Engle, K. M.; Yu, J.-Q. *Isr. J. Chem.* **2010**, *50*, 605.

(7) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190.

(8) For representative examples of C–C bond forming reactions using aryl and alkyl halides, see: (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (c) Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124. (d) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 12135.

(9) (a) Wasa, M.; Engle, K. M.; Lin, D. W.; Yoo, E. J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19598. (b) Wasa, M.; Chan, K. S. L.; Zhang, X.-G.; He, J.; Miura, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 18570. (c) He, J.; Wasa, M.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 3387.

(10) (a) Yoshida, J.; Tamao, K.; Yamamoto, H.; Kakui, T.; Uchida, T.; Kumada, M. *Organometallics* **1982**, *1*, 542. (b) Tamao, K.; Kobayashi, K.; Ito, Y. *Tetrahedron Lett.* **1989**, *30*, 6051. (c) Hagiwara, E.; Gouda, K.-i.; Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1997**, *38*, 439. (d) Mowery, M. E.; DeShong, P. *Org. Lett.* **1999**, *1*, 2137. (e) Denmark, S. E.; Choi, J. Y. *J. Am. Chem. Soc.* **1999**, *121*, 5821. (f) Itami, K.; Nokami, T.; Yoshida, J.-i. *J. Am. Chem. Soc.* **2001**, *123*, 5600. (g) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835. (h) Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2004**, *126*, 4876. (i) Denmark, S. E.; Smith, R. C. *J. Am. Chem. Soc.* **2010**, *132*, 1243. (j) Cheng, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2015**, *137*, 592.

(11) A seminal example of Pd-catalyzed Hiyama cross-coupling with alkyl halides: Lee, J.-Y.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 5616.

(12) (a) Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066. (b) Zhou, H.; Xu, Y.-H.; Chung, W.-J.; Loh, T.-P. *Angew. Chem. Int. Ed.* **2009**, *48*, 5355. (c) Li, W.; Yin, Z.; Jiang, X.; Sun, P. *J. Org. Chem.* **2011**, *76*, 8543.

(13) (a) Liang, Z.; Yao, B.; Zhang, Y. *Org. Lett.* **2010**, *12*, 3185. (b) Bi, L.; Georg, G. I. *Org. Lett.* **2011**, *13*, 5413. (c) Funaki, K.; Kawai, H.; Sato, T.; Oi, S. *Chem. Lett.* **2011**, *40*, 1050. (d) Han, W.; Mayer, P.; Ofial, A. R. *Chem. Eur. J.* **2011**, *17*, 6904. (e) Kawasumi, K.; Mochida, K.; Kajino, T.; Segawa, Y.; Itami, K. *Org. Lett.* **2012**, *14*, 418.

(14) Senthilkumar, N.; Parthasarathy, K.; Gandeepan, P.; Cheng, C.-H. *Chem. Asian. J.* **2013**, *8*, 2175.

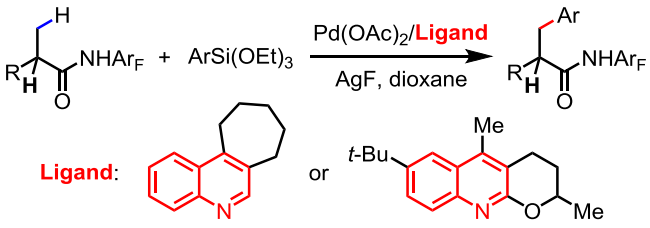
(15) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 2202.

(16) He, J.; Li, S.; Deng, Y.; Fu, H.; Laforteza, B. N.; Spangler, J. E.; Homs, A.; Yu, J.-Q. *Science* **2014**, *343*, 1216.

(17) (a) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (b) Wei, Y.; Kan, J.; Wang, M.; Su, W.; Hong, M. *Org. Lett.* **2009**, *11*, 3346. (c) Zhang, X.; Fan, S.; He, C.-Y.; Wan, X.; Min, Q.-Q.; Yang, J.; Jiang, Z.-X. *J. Am. Chem. Soc.* **2010**, *132*, 4506.

(18) (a) Hatanaka, Y.; Fukushima, S.; Hiyama, T. *Chem. Lett.* **1989**, *18*, 1711. (b) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1989**, *54*, 268. (c) Sugiyama, A.; Ohnishi, Y.-y.; Nakaoka, M.; Nakao, Y.; Sato, H.; Sakaki, S.; Nakao, Y.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 12975.

(19) DFT computational studies on ligand-promoted C(sp^3)–H arylation, see: Dang, Y.; Qu, S.; Nelson, J. W.; Pham, H. D.; Wang, Z.-X.; Wang, X. *J. Am. Chem. Soc.* **2015**, *137*, 2006.


H
R
H
NHArF
O
+
ArSi(OEt)3
Pd(OAc)2/Ligand
AgF, dioxane
Ar
R
H
NHArF
O
Ligand:
N
or
t-Bu
Me
N
O
Me