Organic LETTERS

Letter

pubs.acs.org/OrgLett

Nickel-Catalyzed Alkynylation of Anisoles via C–O Bond Cleavage

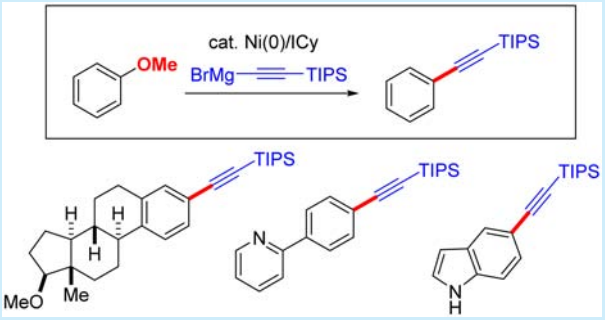
Mamoru Tobisu,*[,‡] Tsuyoshi Takahira,[†] Akimichi Ohtsuki,[†] and Naoto Chatani*[,†]

[†]Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

[‡]Center for Atomic and Molecular Technologies, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

Supporting Information

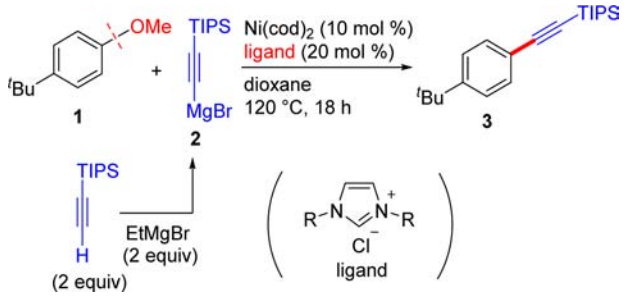
ABSTRACT: A new cross-coupling reaction has been developed for the introduction of an alkyne moiety to an anisole derivative through C–O bond activation using an NHC ligand. This method has been used for direct alkynylation of a broad range of anisole derivatives and provided rapid access to compounds with potential applications in biological and materials science.



Transition-metal-catalyzed cross-coupling reactions for the formation of C–C bonds between organic halides and organometallics have become indispensable tools in organic synthesis.[1] One promising approach for the development of sustainable and environmentally benign cross-coupling processes would be to replace aryl halides with nontoxic and abundant phenol derivatives.[2] Among the many phenol derivatives that could be used as an electrophile in this context, anisoles stand out as being particularly attractive substrates in terms of their availability and atom economy.[3] However, the robust nature of the C(sp^2)–OMe bond has significantly limited the number of nucleophiles capable of undergoing coupling reactions of this type,[4−9] compared with other cross-coupling reactions using activated electrophiles. One of the greatest limitations of cross-coupling involving C–OMe bonds is the current lack of a process for the formation of C(sp^2)–C(sp) bonds, despite the widespread utility of alkyne functionalities in synthetic, biological, and materials chemistry.[10] Herein, we report for the first time the development of a cross-coupling reaction between anisoles and C(sp)–nucleophiles for the construction of C(sp^2)–C(sp) bonds using a Ni(0)/ICy catalyst system.[11]

Our initial investigation was focused on the nickel-catalyzed cross-coupling of anisole **1a** with the alkynylmagnesium reagent **2**, which was readily generated by the treatment of ethynyltriisopropylsilane with EtMgBr, because ArMgX represents one of very few nucleophiles to have been successfully used in the cross-coupling of aryl methyl ethers.[4] However, alkynylMgX is significantly less nucleophilic than ArMgX,[12] making it nontrivial to achieve an alkynylation process of this type. Indeed, the application of the catalytic conditions reported for the cross-coupling of Ar–OMe with Ar–MgX (i.e., Ni(0)/PCy_3)[4] to a reaction using **2** afforded none of the desired product (Table 1, entry 1). Pleasingly, an extensive screening process revealed that the addition of NHC ligands bearing bulky *N*-alkyl groups, such as isopropyl or cyclohexyl groups, to the reaction delivered **3** in excellent yields (entries 5 and 6).[13] The bulkiness of the triisopropylsilyl (TIPS) group in **2** was also found to be critical to the success of the reaction.[14,15] Results using Grignard reagents derived from other alkynes are as follows: 1-octyne (0%), phenylacetylene (0%), ^{t}butylacetylene (22%), triethysilylacetylene (28%). Despite its steric bulk, the TIPS group could be readily removed from the alkynylated products to give the

Table 1. Ni-Catalyzed Cross-Coupling of 1a with 2a: Effect of Selected Ligands[a]



entry	ligand	GC yield of **3** (%)
1	PCy_3	0
2	IMes·HCl (R = 2,4,6-$Me_3C_6H_3$)	8
3	IPr·HCl (R = 2,6-$^i Pr_2C_6H_4$)	<5
4	IMe·HCl (R = Me)	7
5	I^{i}Pr·HCl (R = ^{i}Pr)	38
6	ICy·HCl (R = Cy)	76 (70)[b]
7	I^{t}Bu·HCl (R = ^{t}Bu)	45

[a]Reaction conditions: **1a** (0.25 mmol), **2** (0.50 mmol), $Ni(cod)_2$ (0.025 mmol), and ligand (0.050 mmol) in dioxane (0.50 mL) at 120 °C for 18 h. [b]Isolated yield.

Received: December 24, 2014
Published: January 13, 2015

DOI: 10.1021/ol503707m
Org. Lett. 2015, 17, 680–683

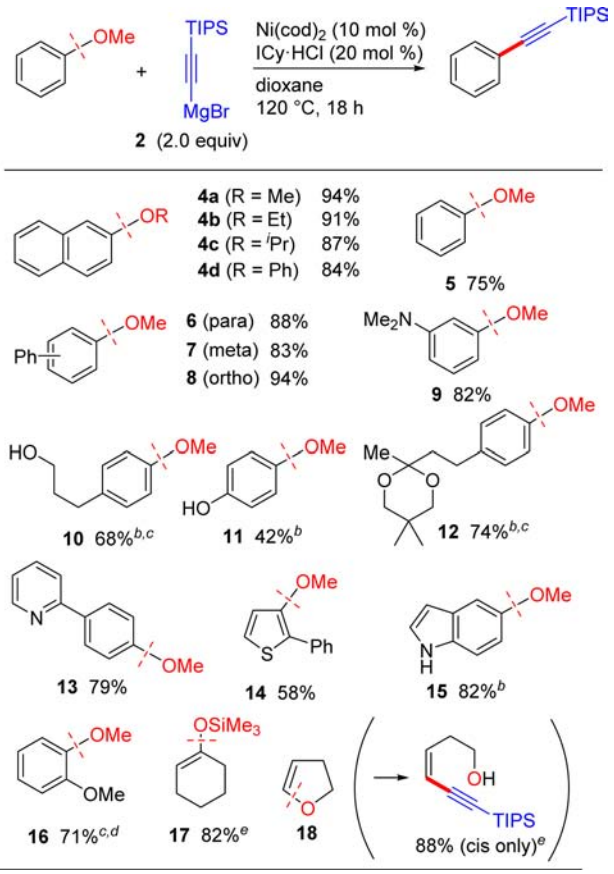
corresponding terminal alkynes, which could be used as versatile intermediates for the construction of complex scaffolds (see Scheme 4).

With the optimized conditions in hand, we proceeded to evaluate the scope of the reaction using a range of aryl ethers (Scheme 1).[16] In addition to methoxy (**4a**) and ethoxy (**4b**) groups, even a bulky isopropoxy group in **4c** was similarly substituted by **2** in an efficient manner. Interestingly, 2-phenoxynaphthalene (**4d**) also reacted smoothly under the optimized alkynylation conditions to form 2-alkynylnaphthalene selectively, which indicated that a naphthyl-oxygen bond is more reactive than a phenyl-oxygen bond.[17] This result, however, does not mean that the current protocol is not amenable to benzene derivatives. The application of the current conditions to anisole (**5**) afforded the corresponding alkynylated product in a synthetically useful yield. Ortho-substitution of anisole did not have a significant impact on the efficiency of the reaction, as exemplified by the excellent yield obtained with **8**. The reaction conditions were found to be compatible with several functional groups, including amines (e.g., **9**). Notably, the reaction was also tolerant of OH and NH groups, which allowed for the direct conversion of a methoxy group to the corresponding TIPS-alkyne using an additional equivalent of the Grignard reagent, as evidenced by the reactions of compounds **10**, **11**, and **15**. In particular, a phenolic hydroxyl group in **11** is potentially reactive toward the nickel-catalyzed cross-coupling;[3a] none of such an undesired byproduct (i.e., dehydroxylative alkynylation and reduction) was observed under these conditions, and 46% of **11** was recovered. Although ketones were not compatible with the current conditions, they can be used by protecting it as an acetal, as in **12**. This method was also successfully applied to the cross-coupling of heteroarenes, including the electron-deficient pyridine **13**, the electron-rich thiophene **14**, and indole **15**. 1,2-Dimethoxybenzene (**16**) also reacted smoothly under the optimized conditions to give the monoalkynylated product. The current method was also successfully applied to the alkynylation of vinylic C−O bonds. For example, the silyl enol ether **17** underwent this cross-coupling to provide the corresponding conjugated enyne. Furthermore, the use of cyclic ether **18** as a substrate allowed for the stereoselective synthesis of a homoallylic alcohol bearing a conjugated alkyne.

Since nickel complexes have been successfully used to activate several other inert bonds, including C−F[18] and C−CN bonds,[19] we thought that it would be interesting to determine the order of the reactivity of these groups under the current conditions (Scheme 2). The nickel-catalyzed reaction of 4-fluoroanisole (**19**) with **2** afforded alkyne **20**, where the C−F bond was cleaved exclusively with the C−OMe bond remaining intact. It is noteworthy that this reaction represents, to the best of our knowledge, the first reported example of the catalytic alkynylation of a simple, electron-rich aryl fluoride.[20] 4-Methoxybenzonitrile (**21**) reacted in a similar manner to **19**, with the alkynylation occurring exclusively at the cyanide site to form **20**.[21] These results therefore demonstrated that a C−OMe bond is less reactive than a C−F or C−CN bond toward the alkynylation reaction, and this difference in the reactivity could be used for the sequential functionalization of arenes.

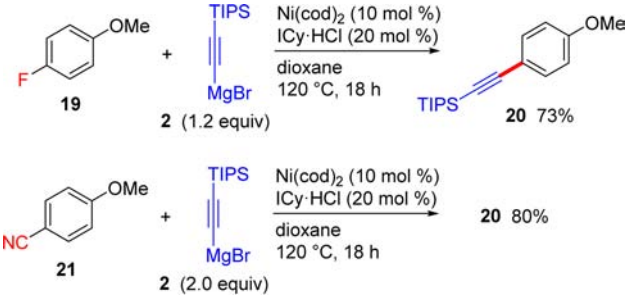
Our newly developed nickel-catalyzed alkynylation reaction also performed well in a series of complex systems (Scheme 3). For example, the alkynylated derivatives of estradiol, serotonin, and dextromethorphan (i.e., **22**, **23**, and **24**, respectively) were readily synthesized. These products could also be subjected to further transformations, such as azide/alkyne cycloaddition reactions, to allow for the synthesis of increasingly complex and biologically interesting molecules. Furthermore, the current alkynylation protocol was successfully applied to the extension of the π-conjugated systems of various aromatic motifs that are frequently used in organic materials (i.e., **25**−**28**). The robust nature of the methoxy group (i.e., its tolerance toward organolithium reagents and the conditions required for conventional palladium-catalyzed cross-coupling reactions) represents a

Scheme 1. Ni/ICy-Catalyzed Alkynylation of Aryl Methyl Ethers[a]



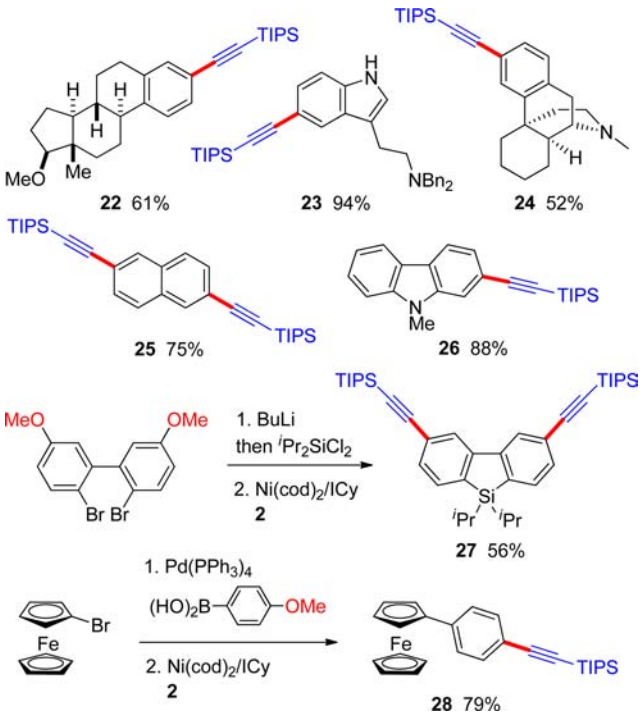
[a]Reaction conditions: aryl ether (0.50 mmol), **2** (1.0 mmol), $Ni(cod)_2$ (0.050 mmol), and ICy·HCl (0.10 mmol) in dioxane (1.0 mL) at 120 °C for 18 h. Isolated yield is shown. [b] Grignard reagent (1.5 mmol) was used. [c] $Ni(cod)_2$ (0.10 mmol) was used. [d] **2** (2.0 mmol) was used. [e] Run at 80 °C.

Scheme 2. Comparison of the C−OMe Bond with Other Unreactive Electrophiles



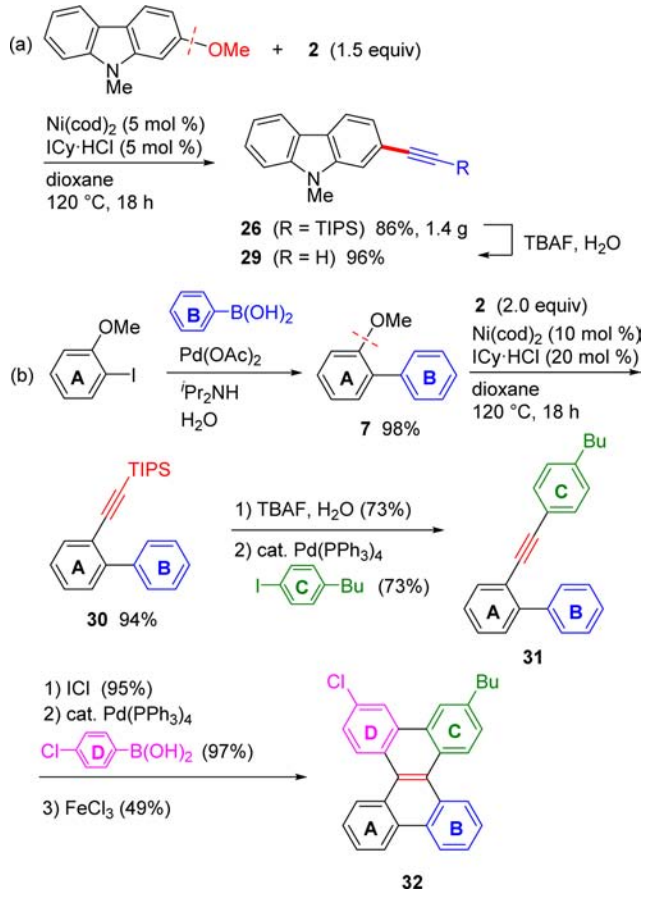
DOI: 10.1021/ol503707m
Org. Lett. 2015, 17, 680−683

Scheme 3. Alkynylation of Molecules Relevant to Biology and Materials Science[a]



[a]See Supporting Information for detailed conditions.

Scheme 4. Synthetic Applications



significant advantage to this method, because it would allow for the late-stage introduction of alkyne functionalities into elaborate aromatic systems.

In terms of the scalability of the reaction, carbazole **26** was successfully synthesized on the gram scale using the current protocol (Scheme 4a). Furthermore, the TIPS group of **26** could be readily removed with TBAF/H_2O to give the terminal alkyne **29**, which could be used as a versatile building block. The orthogonal reactivity of halides and methyl ethers in cross-coupling reactions promises numerous synthetic applications. For example, the sequential palladium- and nickel-catalyzed cross-coupling reactions of 1-iodo-2-methoxybenzene allowed for the sequential introduction of aryl and alkynyl groups in a completely predictable manner to give **30** (Scheme 4b). Compound **30** was then subjected to sequential Sonogashira arylation, electrophilic cyclization,[22] Suzuki–Miyaura arylation, and oxidative cyclization[23] to give the dibenzo[*g*,*p*]chrysene skeleton in **32**.[24] Our newly developed method therefore allows for the modular, catalytic synthesis of dibenzo[*g*,*p*]chrysene derivatives with four aryl rings A to D being assembled with complete control.

In summary, we have developed the first cross-coupling reaction for the formation of C(sp^2)–C(sp) bonds that uses an anisole as the electrophilic component. The addition of an NHC ligand (i.e., ICy) was critical to the success of the reaction and allowed for the synthesis of an array of elaborate aromatic alkynes from simple anisole derivatives. We believe that the inert nature of the methoxy group and the ease with which this functionality can be generated render this alkynylation not only merely unprecedented but also a powerful means of enabling new synthetic strategies, including the direct structural modification of complex molecules, as well as orthogonal cross-coupling reactions. Further studies toward the application of this Ni/ICy system to other catalytic transformations through the activation of unreactive σ-bonds are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and details pertaining to the characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: tobisu@chem.eng.osaka-u.ac.jp.
*E-mail: chatani@chem.eng.osaka-u.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Molecular Activation Directed toward Straightforward Synthesis" from MEXT, Japan and ACT-C from JST, Japan. We also thank the Instrumental Analysis Center, Faculty of Engineering, Osaka University, for their assistance with HRMS.

■ REFERENCES

(1) (a) *Topics in Current Chemistry*; Miyaura, N., Ed.; Wiley: Chichester, 2001; Vol. *219*. (b) De Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2004.

DOI: 10.1021/ol503707m
Org. Lett. 2015, 17, 680–683

(2) Reviews: (a) Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Acc. Chem. Res.* **2010**, *43*, 1486. (b) Li, B.-J.; Yu, D.-G.; Sun, C.-L.; Shi, Z.-J. *Chem.—Eur. J.* **2011**, *17*, 1728. (c) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346. (d) Mesganaw, T.; Garg, N. K. *Org. Process Res. Dev.* **2013**, *17*, 29. (e) Tobisu, M.; Chatani, N. *Top. Organomet. Chem.* **2013**, *44*, 35. (f) Yamaguchi, J.; Muto, K.; Itami, K. *Eur. J. Org. Chem.* **2013**, 19. (g) Han, F.-S. *Chem. Soc. Rev.* **2013**, *42*, 5270. (h) Cornella, J.; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081.

(3) Phenols represent another class of ideal electrophilic coupling partners: (a) Yu, D.-G.; Li, B.-J.; Zheng, S.-F.; Guan, B.-T.; Wang, B.-Q.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4566. (b) Yu, D.-G.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7097. (c) Murai, M.; Origuchi, K.; Takai, K. *Org. Lett.* **2014**, *16*, 3828.

(4) Cross-coupling with Grignard reagents: (a) Wenkert, E.; Michelotti, E. L.; Swindell, C. S. *J. Am. Chem. Soc.* **1979**, *101*, 2246. (b) Wenkert, E.; Michelotti, E. L.; Swindell, C. S.; Tingoli, M. *J. Org. Chem.* **1984**, *49*, 4894. (c) Dankwardt, J. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2428. (d) Guan, B.-T.; Xiang, S.-K.; Wu, T.; Sun, Z.-P.; Wang, B.-Q.; Zhao, K.-Q.; Shi, Z.-J. *Chem. Commun.* **2008**, 1437. (e) 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. (f) Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2011**, *133*, 389. (g) Xie, L.-G.; Wang, Z.-X. *Chem.—Eur. J.* **2011**, *17*, 4972. (h) Zhao, F.; Yu, D.-G.; Zhu, R.-Y.; Xi, Z.; Shi, Z. J. *Chem. Lett.* **2011**, *40*, 1001. (i) Iglesias, M. J.; Prieto, A.; Nicasio, M. C. *Org. Lett.* **2012**, *14*, 4318. (j) Zhao, F.; Zhang, Y.-F.; Wen, J.; Yu, D.-G.; Wei, J.-B.; Xi, Z.; Shi, Z.-J. *Org. Lett.* **2013**, *15*, 3230. (k) Cornella, J.; Martin, R. *Org. Lett.* **2013**, *15*, 6298. (l) Yonova, I. M.; Johnson, A. G.; Osborne, C. A.; Moore, C. E.; Morrissette, N. S.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 2422. (m) Iwasaki, T.; Miyata, Y.; Akimoto, R.; Fujii, Y.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2014**, *136*, 9260.

(5) Cross-coupling with trimethylsilyl lithium: Leiendecker, M.; Hsiao, C.-C.; Guo, L.; Alandini, N.; Rueping, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 12912.

(6) Cross-coupling with organozinc reagents: Wang, C.; Ozaki, T.; Takita, R.; Uchiyama, M. *Chem.—Eur. J.* **2012**, *18*, 3482.

(7) Cross-coupling with organoboron reagents: (a) Kakiuchi, F.; Usui, M.; Ueno, S.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2004**, *126*, 2706. (b) Ueno, S.; Mizushima, E.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2006**, *128*, 16516. (c) Tobisu, M.; Shimasaki, T.; Chatani, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4866. (d) Shimasaki, T.; Konno, Y.; Tobisu, M.; Chatani, N. *Org. Lett.* **2009**, *11*, 4890. (e) Tobisu, M.; Yasutome, A.; Kinuta, H.; Nakamura, K. *Org. Lett.* **2014**, *16*, 5572.

(8) Amination: (a) Tobisu, M.; Shimasaki, T.; Chatani, N. *Chem. Lett.* **2009**, *38*, 710. (b) Tobisu, M.; Yasutome, A.; Yamakawa, K.; Shimasaki, T.; Chatani, N. *Tetrahedron* **2012**, *68*, 5157.

(9) Reductive cleavage: (a) Álvarez-Bercedo, P.; Martin, R. *J. Am. Chem. Soc.* **2010**, *132*, 17352. (b) Tobisu, M.; Yamakawa, K.; Shimasaki, T.; Chatani, N. *Chem. Commun.* **2011**, *47*, 2946. (c) Sergeev, A. G.; Hartwig, J. F. *Science* **2011**, *332*, 439. (d) Cornella, J.; Gómez-Bengoa, E.; Martin, R. *J. Am. Chem. Soc.* **2013**, *135*, 1997.

(10) (a) Diederich, F., Stang, P. J., Tykwinski, R. R., Eds. *Acetylene Chemistry*; Wiley-VCH: Weinheim, 2005. A themed issue on click chemistry: (b) Finn, M. G.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1231 and articles therein. A review on alkyne metathesis: (c) Zhang, W.; Moore, J. S. *Adv. Synth. Catal.* **2007**, *349*, 93.

(11) A review on recent advances in nickel catalysis: Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature* **2014**, *509*, 299.

(12) pK_a values of C−H bonds in benzene and acetylene are approximately 43 and 25, respectively: (a) Streitwieser, A., Jr.; Scannon, P. J.; Niemeyer, H. M. *J. Am. Chem. Soc.* **1972**, *94*, 7936. (b) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.

(13) Although the steric nature of the NHC ligand is likely to be one critical factor for promoting this cross-coupling, correlation between the yield and the buried volume of the effect of the ligand is weak. See Supporting Information for detailed analysis of the effect of the ligand and other results of optimization of reaction conditions.

(14) Selected transition-metal catalyzed reactions in which TIPS-protected alkynes exhibit superior performance: (a) Tsukada, N.; Ninomiya, S.; Aoyama, Y.; Inoue, Y. *Org. Lett.* **2007**, *9*, 2919. (b) Nishimura, T.; Guo, X.-X.; Uchiyama, N.; Katoh, T.; Hayashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 1576. (c) Shirakura, M.; Suginome, M. *J. Am. Chem. Soc.* **2008**, *130*, 5410. (d) Ogata, K.; Murayama, H.; Sugasawa, J.; Suzuki, N.; Fukuzawa, S.-i. *J. Am. Chem. Soc.* **2009**, *131*, 3176. (e) Nicolai, S.; Erard, S.; González, D. F.; Waser, J. *Org. Lett.* **2010**, *12*, 384. (f) Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9346. (g) Ogata, K.; Sugasawa, J.; Fukuzawa, S.-i. *Angew. Chem., Int. Ed.* **2009**, *48*, 6078. (h) Tobisu, M.; Ano, Y.; Chatani, N. *Org. Lett.* **2009**, *11*, 3250. (i) Brand, J. P.; Waser, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 7304. (j) Ogata, K.; Atsuumi, Y.; Fukuzawa, S.-i. *Org. Lett.* **2011**, *13*, 122. (k) Nicolai, S.; Piemontesi, C.; Waser, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 4680. (l) Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 12984. (m) Shibata, Y.; Tanaka, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 10917. (n) Ano, Y.; Tobisu, M.; Chatani, N. *Org. Lett.* **2011**, *14*, 354. (o) Ano, Y.; Tobisu, M.; Chatani, N. *Synlett* **2012**, *23*, 2763. (p) Li, Y.; Brand, J. P.; Waser, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 6743.

(15) Note: Use of the Ni(II) precatalyst was also possible for relatively reactive substrates, such as **4a** (90% with 10 mol% of $NiCl_2$). However, $Ni(cod)_2$ was employed throughout this study since it generally provided better results. See Supporting Information for details.

(16) Note: (a) The use of aryl pivalates and carbamates in place of aryl ethers under the current conditions resulted in a complicated mixture. (b) An attempt to use terminal alkynes along with a catalytic amount of copper salts, instead of **2**, was unsuccessful.

(17) A similar selectivity was also observed in the reaction using MeMgBr. See ref 4d.

(18) Reviews on catalytic C−F bond activation: (a) Torrens, H. *Coord. Chem. Rev.* **2005**, *249*, 1957. (b) Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119. (c) Sun, A. D.; Love, J. A. *Dalton Trans.* **2010**, *39*, 10362.

(19) Reviews on catalytic C−CN bond activation: (a) Nakao, Y.; Hiyama, T. *Pure Appl. Chem.* **2008**, *80*, 1097. (b) Tobisu, M.; Chatani, N. *Chem. Soc. Rev.* **2008**, *37*, 300. (c) Nakao, Y. *Bull. Chem. Soc. Jpn.* **2012**, *85*, 731. (d) Wang, R.; Falck, J. R. *RSC Adv.* **2014**, *4*, 1062.

(20) Alkynylation of highly activated 2-nitrofluroarenes is known: Cargill, M. R.; Sandford, G.; Kilickiran, P.; Nelles, G. *Tetrahedron* **2013**, *69*, 512.

(21) Penney, J. M.; Miller, J. A. *Tetrahedron Lett.* **2004**, *45*, 4989.

(22) Yao, T.; Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3511.

(23) Wang, K.; Lü, M.; Yu, A.; Zhu, X.; Wang, Q. *J. Org. Chem.* **2009**, *74*, 935.

(24) Selected examples for catalytic synthesis of dibenzo[*g*,*p*]chrysene derivatives: (a) Li, C.-W.; Wang, C.-I.; Liao, H.-Y.; Chaudhuri, R.; Liu, R.-S. *J. Org. Chem.* **2007**, *72*, 9203. (b) Shimizu, M.; Nagao, I.; Tomioka, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 8096. (c) Tsuji, H.; Ueda, Y.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2010**, *132*, 11854. (d) Mochida, K.; Kawasumi, K.; Segawa, Y.; Itami, K. *J. Am. Chem. Soc.* **2011**, *133*, 10716.

DOI: 10.1021/ol503707m
Org. Lett. 2015, 17, 680−683