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Palladium-Catalyzed Cyclocoupling of 2-Halobiaryls with Isocyanides via the Cleavage of Carbon−Hydrogen Bonds

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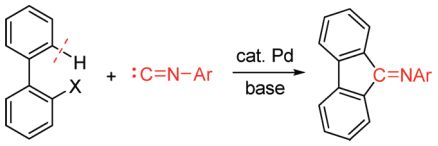

To demonstrate the utility of isocyanides in catalytic C−H bond functionalization reactions, a palladium-catalyzed cyclocoupling reaction of 2-halobiaryls with isocyanides was developed. The reaction afforded an array of fluorenone imine derivatives via the cleavage of a C−H bond at the 2′-position of 2-halobiaryls. The use of 2,6-disubstituted phenyl isocyanide was crucial for this catalytic cyclocoupling reaction to proceed. The reaction was applicable to heterocyclic and vinylic substrates, allowing the construction of a wide range of ring system. The large kinetic isotope effect observed (k_H/k_D = 5.3) indicates that C−H bond activation was the turnover-limiting step in this catalysis.

Introduction

The development of transition-metal-catalyzed methods for the direct functionalization of C−H bonds is currently a vibrant research area, and progress is being made.[1] With respect to C−C bond formation, various carbon-based substituents, such as aryl, alkenyl, and alkyl groups, can be introduced through the catalytic C−H bond functionalization reactions. The installation of carbonyl functionalities has attracted increasing attention, since such methods could serve as atom-efficient and potentially useful pathways to ketones and esters.[2−4] We[2] and others[3] have demonstrated that carbon monoxide can be utilized as an effective carbonyl source in the catalytic C−H bond carbonylation reactions. On the other hand, we have been exploring the utility of isocyanides in organic synthesis and demonstrated that they serve not simply as a carbon monoxide equivalent but also as a unique C1 source, enabling transformations that could not be achieved with carbon monoxide.[5] On the basis of these findings, it may be possible to use isocyanides as a C1 component in C−H bond functionalization reactions. To date, such transition-metal-catalyzed incorporation of isocyanides into C−H bonds has met with limited success. Jones reported that the isomerization of 2,6-xylyl isocyanide to

(1) Representative recent reviews on C−H bond functionalization: (a) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (b) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (c) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (d) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (e) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (f) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, 24. (g) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949. (h) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (i) *Topics in Organometallic Chemistry*; Chatani, N., Ed.; Springer-Verlag: Berlin, 2007; Vol 24. (j) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (k) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (l) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (m) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (n) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

(2) (a) Chatani, N.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1996**, *118*, 493. (b) Chatani, N.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **1997**, *62*, 2604. (c) Fukuyama, T.; Chatani, N.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **1997**, *62*, 5647. (d) Ishii, Y.; Chatani, N.; Kakiuchi, F.; Murai, S. *Organometallics* **1997**, *16*, 3615. (e) Ishii, Y.; Chatani, N.; Kakiuchi, F.; Murai, S. *Tetrahedron Lett.* **1997**, *38*, 7565. (f) Fukuyama, T.; Chatani, N.; Tatsumi, J.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1998**, *120*, 11522. (g) Chatani, N.; Ishii, Y.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **1998**, *63*, 5129. (h) Chatani, N.; Asaumi, T.; Ikeda, T.; Yorimitsu, S.; Ishii, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12882. (i) Ie, Y.; Chatani, N.; Ogo, T.; Marshall, D. R.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2000**, *65*, 1475. (j) Chatani, N.; Fukuyama, T.; Tatamidani, H.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2000**, *65*, 4039. (k) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 10935. (l) Chatani, N.; Yorimitsu, S.; Asaumi, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2002**, *67*, 7557. (m) Asaumi, T.; Chatani, N.; Matsuo, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2003**, *68*, 7538. (n) Asaumi, T.; Matsuo, T.; Fukuyama, T.; Ie, Y.; Kakiuchi, F.; Chatani, N. *J. Org. Chem.* **2004**, *69*, 4433. (o) Chatani, N.; Uemura, T.; Asaumi, T.; Ie, Y.; Kakiuchi, F.; Murai, S. *Can. J. Chem.* **2005**, *83*, 755. (p) Imoto, S.; Uemura, T.; Kakiuchi, F.; Chatani, N. *Synlett* **2007**, 170. (q) Inoue, S.; Shiota, H.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 6898.

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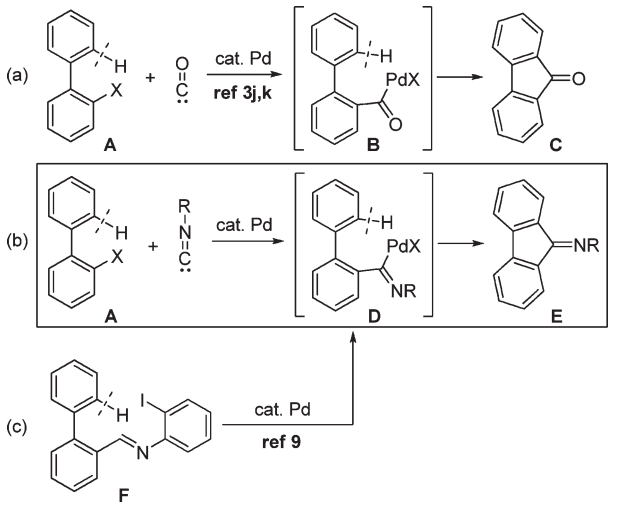
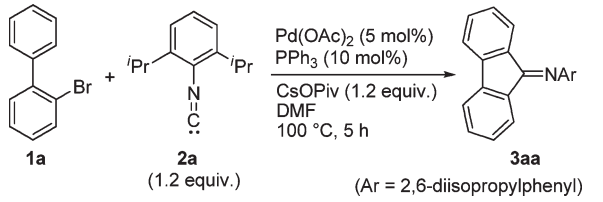
SCHEME 1. Catalytic C−H Bond Functionalization through Acyl and Imidoyl Metal Species



7-methyl-1*H*-indole is catalyzed by a ruthenium complex via the insertion of an isocyanide moiety into the C−H bond of methyl groups.[6] Tanaka and Jones independently reported the catalytic insertion of isocyanides into a C−H bond of benzene under photochemical conditions.[7] The palladium-catalyzed cascade coupling of aryl isocyanides with 6-iodo-*N*-propargylpyridones was reported by Curran.[8] Despite these precedents, there remains a need to develop more general catalytic reactions to assess the utility of isocyanides in C−H bond functionalization reactions.

In the present study, Larock's palladium-catalyzed cyclocarbonylation of 2-halobiaryls **A**, in which fluoren-9-one derivatives **C** are formed through C−H bond cleavage, was chosen as a model reaction (Scheme 1a).[3j,k] The hypothesis is that replacing carbon monoxide with isocyanides in this reaction would lead to the formation of the corresponding imine derivatives **E** if an imidoyl palladium intermediate **D** possesses a reactivity comparable to acyl palladium **B** toward the C−H bonds nearby (Scheme 1b). The feasibility of the hypothesis is supported, in part, by Larock's report that imidoyl palladium **D** that is generated by unique aryl-to-imidoyl palladium migration can undergo cyclization to afford imine **E** (Scheme 1c).[9] This report documents the development of palladium-catalyzed cyclocoupling of 2-halobiaryls with isocyanides, as in Scheme 1b, demonstrating that isocyanides can be utilized as a C1 component in C−H bond functionalization reactions.

TABLE 1. Palladium-Catalyzed Cyclocoupling of 2-Bromobiphenyl (1a) with Isocyanide 2a[a]



entry	variations from "standard" conditions	yield of **3aa** (%)[b]
1	none	95
2	PCy_3 as ligand	94
3	$PdCl_2$ as catalyst precursor	86
4	Cs_2CO_3 as base	54
5	K_2CO_3 as base	80
6	toluene as solvent	42
7	dioxane as solvent	trace
8	80 °C for 20 h	45

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.30 mmol), $Pd(OAc)_2$ (0.0125 mmol), PPh_3 (0.025 mmol), and CsOPiv (0.30 mmol) in DMF (2.0 mL) at 100 °C for 5 h. [b]Isolated yield based on **1a**.

Results and Discussion

A palladium-catalyzed reaction of 2-bromobiphenyl (**1a**) with isocyanide **2a** was initially examined to test the ability of isocyanides to work in Larock's cyclocarbonylation.[3j,k] The expected imine **3aa** was obtained in high yield (Table 1). In reactions using carbon monoxide, PCy_3 has been the optimal ligand and the use of PPh_3 has reduced the yield of the product.[3j,k] However, both PPh_3 and PCy_3 served as an

(3) (a) Murahashi, S. *J. Am. Chem. Soc.* **1955**, *77*, 6403. (b) Murahashi, S.; Horiie, S. *J. Am. Chem. Soc.* **1956**, *78*, 4816. (c) Hong, P.; Yamazaki, H. *Chem. Lett.* **1979**, *8*, 1335. (d) Fisher, B. J.; Eisenberg, R. *Organometallics* **1983**, *2*, 764. (e) Sakakura, T.; Tanaka, M. *Chem. Lett.* **1987**, *16*, 1113. (f) Sakakura, T.; Sodeyama, T.; Sasaki, K.; Wada, K.; Tanaka, M. *J. Am. Chem. Soc.* **1990**, *112*, 7221. (g) Moore, E. J.; Pretzer, W. R.; O'Connell, T. J.; Harris, J.; LaBounty, L.; Chou, L.; Grimmer, S. S. *J. Am. Chem. Soc.* **1992**, *114*, 5888. (h) Taniguchi, Y.; Yamaoka, Y.; Nakata, K.; Takaki, K.; Fujiwara, Y. *Chem. Lett.* **1995**, *24*, 345. (i) Lu, W.; Yamaoka, Y.; Taniguchi, Y.; Kitamura, T.; Takaki, K.; Fujiwara, Y. *J. Organomet. Chem.* **1999**, *580*, 290. (j) Campo, M. A.; Larock, R. C. *Org. Lett.* **2000**, *2*, 3675. (k) Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 5616. (l) Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. *J. Am. Chem. Soc.* **2004**, *126*, 14342. (m) Orito, K.; Miyazawa, M.; Nakaura, T.; Horibata, A.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Yamazaki, T.; Tokuda, M. *J. Org. Chem.* **2006**, *71*, 5951. (n) Funk, J. K.; Yennawar, H.; Sen, A. *Helv. Chim. Acta* **2006**, *89*, 1687. (o) Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14082. (p) Guan, Z. H.; Ren, Z. H.; Spinella, S. M.; Yu, S.; Liang, Y. M.; Zhang, X. *J. Am. Chem. Soc.* **2009**, *131*, 729. (q) 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. (r) Giri, R.; Lam, J. K.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 686.

(4) Carbonyl sources other than CO have also been utilized in transition-metal-catalyzed C−H bond functionalization reactions. Aldehydes: (a) Jia, X.; Zhang, S.; Wang, W.; Luo, F.; Cheng, J. *Org. Lett.* **2009**, *11*, 3120. (b) Baslé, O.; Bidange, J.; Shuai, Q.; Li, C.-J. *Adv. Synth. Catal.* **2010**, *352*, 1145. Acid halides and derivatives: (c) Kochi, T.; Urano, S.; Seki, H.; Mizushima, E.; Sato, M.; Kakiuchi, F. *J. Am. Chem. Soc.* **2009**, *131*, 2792. Isocyanates and ketenes: (d) Hong, P.; Yamazaki, H.; Sonogashira, K.; Hagihara, N. *Chem. Lett.* **1978**, *8*, 535. (e) Kuninobu, Y.; Tokunaga, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2005**, *128*, 202. CO_2: (f) Sugimoto, H.; Kawata, I.; Taniguchi, H.; Fujiwara, Y. *J. Organomet. Chem.* **1984**, *266*, C44. (g) Choi, J.-C.; Kobayashi, Y.; Sakakura, T. *J. Org. Chem.* **2001**, *66*, 5262. Formic acid: (h) Sugimoto, H.; Kawata, I.; Taniguchi, H.; Fujiwara, Y. *J. Organomet. Chem.* **1984**, *266*, C44. (i) Shibahara, F.; Kinoshita, S.; Nozaki, K. *Org. Lett.* **2004**, *6*, 2437. Azidocarboxylates: (j) Yu, W. Y.; Sit, W. N.; Lai, K. M.; Zhou, Z. Y.; Chan, A. S. C. *J. Am. Chem. Soc.* **2008**, *130*, 3304.

(5) (a) Chatani, N.; Oshita, M.; Tobisu, M.; Ishii, Y.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 7812. (b) Oshita, M.; Yamashita, K.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 761. (c) Yoshioka, S.; Oshita, M.; Tobisu, M.; Chatani, N. *Org. Lett.* **2005**, *7*, 3697. (d) Tobisu, M.; Oshita, M.; Yoshioka, S.; Kitajima, A.; Chatani, N. *Pure Appl. Chem.* **2006**, *78*, 275. (e) Tobisu, M.; Yamaguchi, S.; Chatani, N. *Org. Lett.* **2007**, *9*, 3351. (f) Tobisu, M.; Kitajima, A.; Yoshioka, S.; Hyodo, I.; Oshita, M.; Chatani, N. *J. Am. Chem. Soc.* **2007**, *129*, 11431. (g) Tobisu, M.; Ito, S.; Kitajima, A.; Chatani, N. *Org. Lett.* **2008**, *10*, 5223.

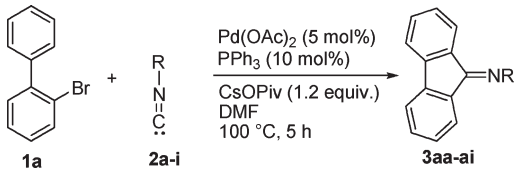
(6) (a) Jones, W. D.; Kosar, W. P. *J. Am. Chem. Soc.* **1986**, *108*, 5640. (b) Hsu, G. C.; Kosar, W. P.; Jones, W. D. *Organometallics* **1994**, *13*, 385.

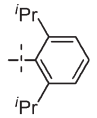
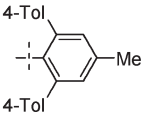
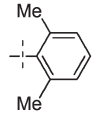
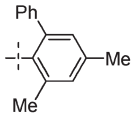
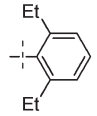
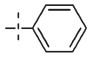
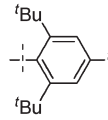
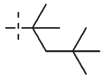
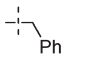
(7) (a) Tanaka, M.; Sakakura, T.; Tokunaga, Y.; Sodeyama, T. *Chem. Lett.* **1987**, *16*, 2373. (b) Jones, W. D.; Foster, G. P.; Putinas, J. M. *J. Am. Chem. Soc.* **1987**, *109*, 5047. (c) Jones, W. D.; Hessell, E. T. *Organometallics* **1990**, *9*, 718.

(8) Curran, D. P.; Du, W. *Org. Lett.* **2002**, *4*, 3215.

(9) Zhao, J.; Yue, D.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2007**, *129*, 5288.

TABLE 2. Scope of Isocyanides[a]



entry	R	yield (%)[b]	entry	R	yield (%)[b]
1		**3aa** 95	5		**3ae** 93
2		**3ab** 86[c]	6		**3af** 87
3		**3ac** 83	7		**3ag** 0
4		**3ad** 46	8		**3ah** 0
			9		**3ai** 0

[a]Reaction conditions: **1a** (0.25 mmol), isocyanide (0.30 mmol), $Pd(OAc)_2$ (0.0125 mmol), PPh_3 (0.025 mmol), and CsOPiv (0.30 mmol) in DMF (2.0 mL) at 100 °C for 5 h. [b]Isolated yield based on **1a**. [c]Run for 10 h.

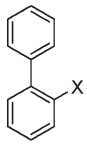
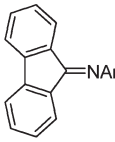
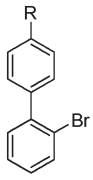
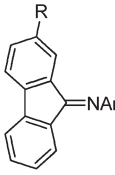
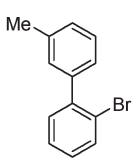
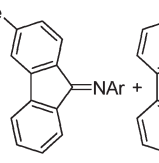
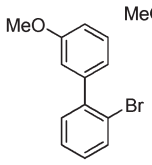
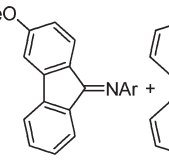
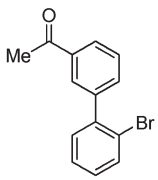
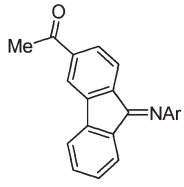
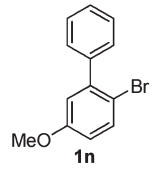
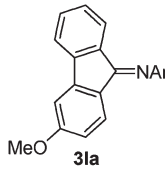
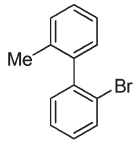
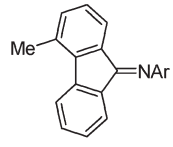
effective ligand (entries 1 and 2). $PdCl_2$ can be used as a palladium source in place of $Pd(OAc)_2$ (entry 3). CsOPiv proved to be the optimal base (entries 4 and 5). The solvent employed had a major effect on the yield, and DMF was the solvent of choice (entries 6 and 7). Lowering the reaction temperature below 100 °C resulted in a significant loss of the efficiency of the catalysis (entry 8).

The effect of the structure of isocyanides on the palladium-catalyzed cyclocoupling of **1a** was then examined (Table 2). We found that 2,6-xylyl isocyanide (**2b**), which is less bulky than **2a**, required a longer reaction time (10 h) to complete the reaction (entry 2). Other phenyl isocyanides bearing 2,6-substituents, such as ethyl (entry 3) and aryl (entry 5), and asymmetrically substituted phenyl isocyanide **2f** (entry 6) all furnished the corresponding cyclocoupling product in good yield, whereas the introduction of highly congested *tert*-butyl groups had a detrimental effect on the reaction (entry 4). The substituents at the 2,6-positions were crucial for this cyclocoupling reaction to proceed: no corresponding product was observed when phenyl isocyanide (**2g**) was used (entry 7). This is presumably due to the decomposition of **2g** under the catalytic conditions in the present study, through polymerization,[10] for example, and/or catalyst deactivation by multiple coordination of **2g** to a palladium center.[11] Aliphatic isocyanides **2h** and **2i** were unable to undergo this cyclocoupling reaction under these conditions (entries 8 and 9). On the basis of these results, isocyanide **2a** was used for the subsequent studies.

(10) Reviews on the polymerization of isocyanides: (a) Millich, F. *Chem. Rev.* **1972**, *72*, 101. (b) Millich, F. *J. Polym. Sci. Macromol. Rev.* **1980**, *15*, 207. (c) Suginome, M.; Ito, Y. *Adv. Polym. Sci.* **2004**, *171*, 77.

(11) $Pd(CNR)_n$ are known to aggregate into higher nuclearity clusters. See: Yamamoto, Y. *Coord. Chem. Rev.* **1980**, *32*, 193.

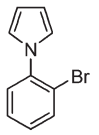
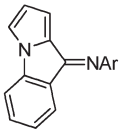
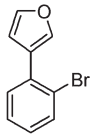
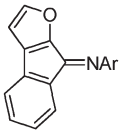
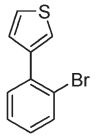
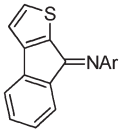
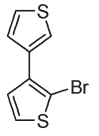
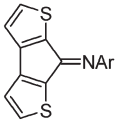
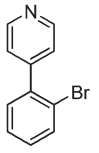
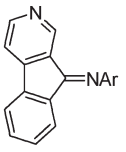
TABLE 3. Palladium-Catalyzed Cyclocoupling of 2-Bromobiphenyls with Isocyanide 2a[a]

entry	substrate	product	yield (%)[b]
1	 X = Br (**1a**)		**3aa** 95
2	X = I (**1b**)		**3aa** 95
3	X = OTf (**1c**)		**3aa** 92
4[c]	X = Cl (**1d**)		**3aa** 0
5	 R = Me (**1e**)		**3ea** 87
6[d]	R = OMe (**1f**)		**3fa** 90
7	R = CF_3 (**1g**)		**3ga** 95
8	R = CO_2Me (**1h**)		**3ha** 82
9	R = CHO (**1i**)		**3ia** 85
10	R = CN (**1j**)		**3ja** 92
11	 **1k**	 **3ka** + **4ka**	88 (17:1)[e]
12	 **1l**	 **3la** + **4la**	97 (2.1:1)[e]
13	 **1m**	 **3ma**	87
14	 **1n**	 **3la**	97
15	 **1o**	 **3oa**	98

[a]Reaction conditions: 2-halobiaryl (0.25 mmol), **2a** (0.30 mmol), $Pd(OAc)_2$ (0.0125 mmol), PPh_3 (0.025 mmol), and CsOPiv (0.30 mmol) in DMF (2.0 mL) at 100 °C for 5 h. [b]Isolated yield based on 2-halobiaryl. [c]PCy_3 was used in place of PPh_3. [d]Run for 20 h. [e]Determined by ^1H NMR.

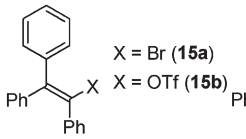
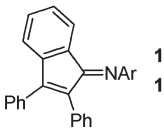
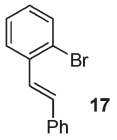
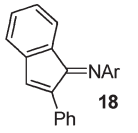
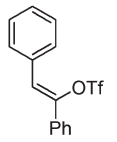
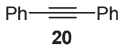
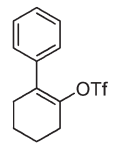
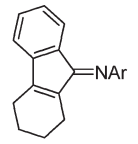
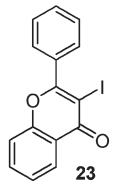
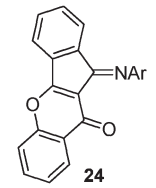
The reaction conditions optimized for the palladium-catalyzed reaction of **1a** with **2a** have successfully been applied to a wide range of 2-halobiphenyls (Table 3). In addition to bromides (entry 1), iodides (entry 2) and triflates (entry 3) serve as good substrates, whereas the corresponding chlorides

TABLE 4. Palladium-Catalyzed Cyclocoupling of 2-Bromoheterobiaryls with Isocyanide 2a[a]

entry	substrate	product	yield (%)[b]
1	 **5**	 **6**	99
2	 **7**	 **8**	93
3	 **9**	 **10**	89
4	 **11**	 **12**	95
5	 **13**	 **14**	53

[a]Reaction conditions: 2-halobiaryl (0.25 mmol), **2a** (0.30 mmol), $Pd(OAc)_2$ (0.0125 mmol), PPh_3 (0.025 mmol), and CsOPiv (0.30 mmol) in DMF (2.0 mL) at 100 °C for 5 h. [b]Isolated yield based on 2-haloheterobiaryl.

TABLE 5. Palladium-Catalyzed Cyclocoupling of 2-Bromostyrene Derivatives with Isocyanide 2a[a]

entry	substrate	product	yield (%)[b]
1	 X = Br (**15a**) X = OTf (**15b**)	 **16**	**16** 80
2			**16** 30
3	 **17**	 **18**	0
4	 **19**	**18**	0
		 **20**	83
5	 **21**	 **22**	62
6	 **23**	 **24**	40

[a]Reaction conditions: substrate (0.25 mmol), **2a** (0.30 mmol), $Pd(OAc)_2$ (0.0125 mmol), PPh_3 (0.025 mmol), and CsOPiv (0.30 mmol) in DMF (2.0 mL) at 100 °C for 5 h. [b]Isolated yield based on the substrate.

remained intact even in the presence of an electron-rich PCy_3 ligand.[12] Functional group compatibility was assessed by the reactions of a series of 2-bromobiphenyls bearing a substituent at the 4′-position (entries 5−10). Both electron-donating and -withdrawing groups were tolerated, and even a reactive formyl group survived (entry 9).

The regioselectivity of the present cyclocoupling was investigated next using a 3′-substituted system in which two different C−H bonds could participate in the reaction. When methyl-substituted substrate **1k** was subjected to the catalytic conditions, the cyclocoupling reaction occurred almost exclusively at the less-hindered site (entry 11). However, both regioisomers **3la** and **4la** were obtained in a ratio of 2.1:1 in the case of methoxy-substituted substrate **1l** (entry 12). The relatively facile formation of the sterically demanding isomer **4la**, compared to **4ka**, might be attributed to the coordinating ability of an oxygen atom of the methoxy group, which directs a palladium catalyst to the congested C−H bond.[2i] In anticipation of regioselective formation of the hindered isomer by using such directing effect, a substrate bearing an acetyl group at the 3′-position was examined next. However, the cyclocoupling reaction proceeded exclusively at the less-hindered position, indicating that the steric bulkiness of the acetyl group was dominant over the directing effect (entry 13).

2-Halobiaryl bearing a substituent at the 4-position also underwent a cyclocoupling reaction to afford the corresponding imine **3la** in good yield (entry 14). The selective formation of **3la** provides an insight into the reaction mechanism (vide infra). Introduction of a methyl group at the 2′-position did not interfere with the cyclocoupling reaction, and the corresponding imine **3oa** was efficiently furnished (entry 15).

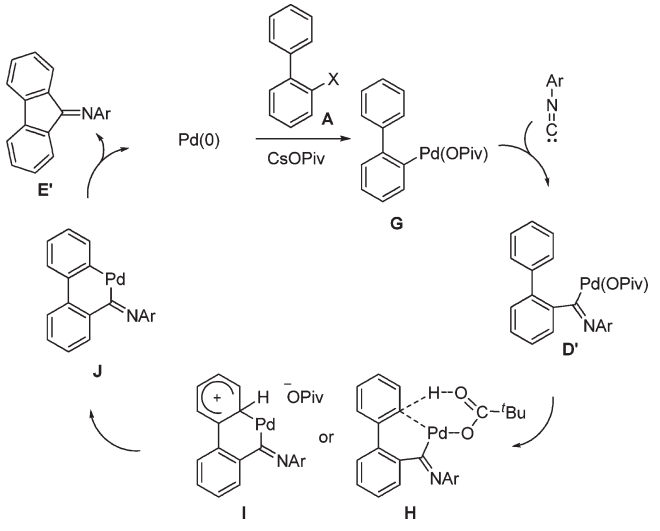
To further investigate the reactivity of the postulated imidoyl palladium intermediate, as in **D** in Scheme 1, toward an aromatic C−H bond, heteroaromatic substrates were then applied to this catalytic cyclocoupling reaction (Table 4). C−H bonds in electron-rich heteroaryls, including pyrroles (entry 1), furans (entry 2), and thiophenes (entries 3 and 4), successfully participated in the cyclocoupling reaction to form the corresponding products with unique ring systems. Especially noteworthy was the effective construction of a strained ring system **12**, in which three five-membered rings were fused (entry 4). In the case of furans and thiophenes (entries 2−4), the reaction selectively proceeded at the 2-position of the heteroaryls, rather than at the 3-position. The

(12) PCy_3 is one of the effective ligands for the activation of Ar−Cl bonds. For a leading reference, see: Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555.

observed regioselectivity agreed with that observed in other palladium-catalyzed C−H bond functionalization reactions through electrophilic substitution[1e] and concerted metalation/deprotonation mechanism.[13] In addition to electron-rich heteroaryls, the C−H bond in electron-deficient pyridines could also be used in the present cyclocoupling reaction (entry 5).

We next turned our attention to the issue of whether a vinylic system can be applied to the present cyclocoupling reaction in place of an aromatic one (Table 5). Commercially available 2-bromo-1,1,2-triphenylethylene (**15a**) was initially examined as a substrate for palladium-catalyzed cyclocoupling with **2a**. The expected indenone imine **16**[14] was obtained in 80% yield under conditions optimized for 2-halobiaryl substrates (entry 1). The use of the corresponding triflate **15b** significantly decreased the yield of **16**, although **15b** was consumed completely (entry 2). Bromide **17** did not afford the cyclocoupling product, however, indicating that a vinylic C−H bond cannot participate in the catalytic reaction (entry 3). When triflate **19** was subjected to the catalytic conditions, the corresponding product **18** was not formed, but diphenylacetylene (**20**, 83% yield) was obtained instead through the elimination of TfOH (entry 4). Thus, the presence of two substituents at the β-position of vinyl halides (or triflates) is required to suppress the undesired elimination pathway. For example, halides and triflates connected to unsaturated cyclic systems, as in **21** and **23**, underwent the cyclocoupling reaction, allowing isocyanide **2a** to be incorporated into polycyclic systems (entries 5 and 6).

SCHEME 2. Possible Mechanism



A possible mechanism for the palladium-catalyzed cyclocoupling of 2-halobiaryls with isocyanides, found in the present study, is depicted in Scheme 2. Oxidative addition of 2-halobiaryl **A** to Pd(0), followed by the ligand exchange from halide to pivalate, affords aryl palladium intermediate **G**. The aryl palladium **G** subsequently forms imidoyl palladium species **D′** via the insertion of isocyanide into an aryl−palladium bond. Activation of a C−H bond at the 2′-position by imidoyl palladium **D′** then affords a palladacycle **J**, presumably either through electrophilic aromatic substitution, as in **I**,[1e] or through a concerted metalation-deprotonation mechanism, as in **H**,[13] analogous to the C−H bond activation by aryl palladium species. The final product **E′** is released from **J** by reductive elimination, and Pd(0) is regenerated.

It is widely recognized that aryl palladium **G** can also activate the C−H bond at the 2′-position, leading to 1,4-migration of a palladium center.[15,16] Even if such a migration process is involved in the present cyclocoupling reaction, the reaction would afford an identical product with all substrates shown in Table 3 except for **1n**. As shown in Scheme 3, aryl palladium **25** initially formed from **1n** could rapidly isomerize to **26** via the 1,4-migration. The involvement of the intermediate **26** would lead to the formation of a mixture of isomeric products **3la** and **4la**, on the basis of the fact that 2-bromobiaryl **1l** afforded **3la** and **4la** (entry 12 in Table 3). However, the isomerized product **4la** was not detected at all in the palladium-catalyzed reaction of **1n** (entry 14 in Table 3). This observation indicates that insertion of isocyanide into aryl palladium **G** and the subsequent C−H bond activation by the resultant imidoyl palladium **D′** are relatively fast processes compared with 1,4-palladium migration.

To gain further insight into the C−H bond activation process by imidoyl palladium species, an intramolecular kinetic isotope effect was investigated by conducting a catalytic reaction of **29** (Scheme 4). The observed product distribution suggests that a C−H bond is activated significantly faster than a C−D bond (k_H/k_D = 5.3). This observation does not serve to discriminate among the possible mechanisms for the C−H bond activation step (S_EAr[17] or concerted metalation-deprotonation[18]) but does indicate that C−H bond activation is a turnover-limiting step in the present catalysis.

Conclusions

In summary, we have demonstrated the utility of isocyanides in catalytic C−H bond functionalization reactions by developing a palladium-catalyzed cyclocoupling of 2-halobiaryls with isocyanides. The use of 2,6-disubstituted phenyl isocyanides is crucial for efficient catalysis. Scope and limitation studies revealed that the postulated imidoyl palladium species exhibited reactivity in aromatic C−H bond activation comparable to that observed for the corresponding acyl palladium species.[3j,k] Although the precise mechanism for the C−H bond activation by imidoyl palladium remains elusive, the process proved to be a turnover-limiting step in the present catalysis. We expect that the

(13) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826.

(14) For other catalytic methods for the synthesis of indenone imine derivatives via C−H bond cleavage, see: (a) Hu, Q.; Lu, J.; Wang, C.; Wang, C.; Xi, Z. *Tetrahedron* **2007**, *63*, 6614. (b) Fukutani, T.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Commun.* **2009**, 5141.

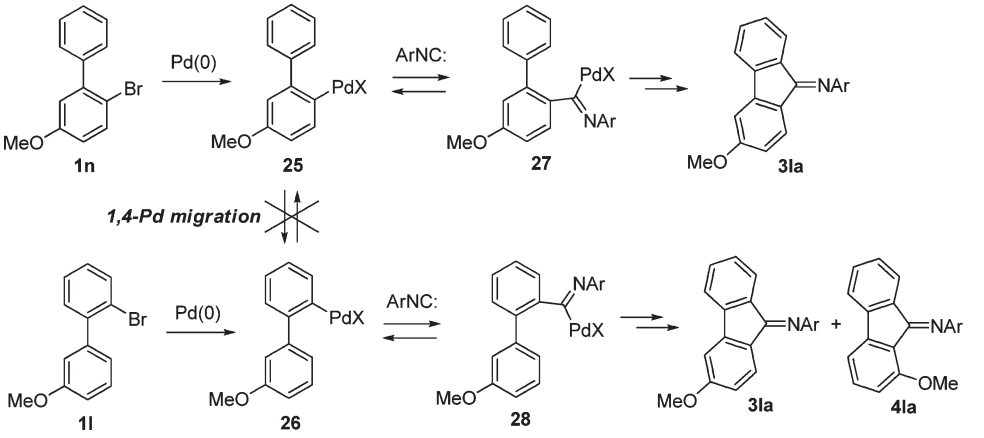
(15) (a) Karig, G.; Moon, M.-T.; Thasana, N.; Gallagher, T. *Org. Lett.* **2002**, *4*, 3115. (b) Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2002**, *124*, 14326. (c) Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 11506. (d) Huang, Q.; Campo, M. A.; Yao, T.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2004**, *69*, 8251. (e) Campo, M. A.; Zhang, H.; Yao, T.; Ibdah, A.; McCulla, R. D.; Huang, Q.; Zhao, J.; Jenks, W. S.; Larock, R. C. *J. Am. Chem. Soc.* **2007**, *129*, 6298.

(16) For 1,4-migration of other metals, see: Ma, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2005**, *44*, 7512.

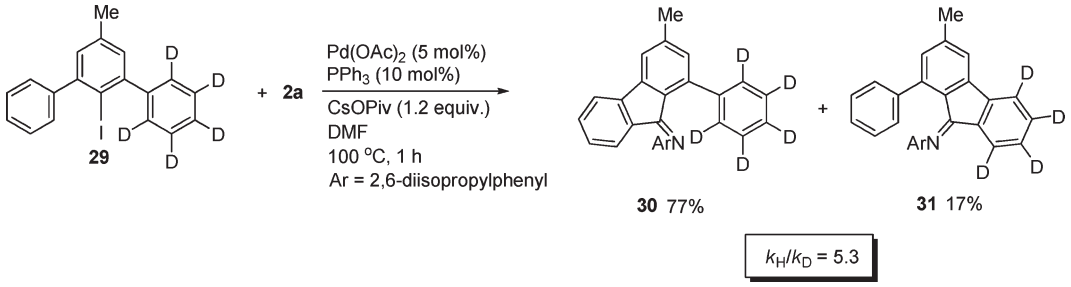
(17) For discussion on large kinetic isotope effect in S_EAr process, see: Zhao, X.; Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 5837and references therein.

(18) For discussion on large kinetic isotope effect in concerted metalation-deprotonation process, see: Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *128*, 581.

SCHEME 3. Fate of Aryl Palladium Intermediate: Formation and Cyclization of Imidoyl Palladium versus 1,4-Migration



SCHEME 4. Intramolecular Kinetic Isotope Effect



fundamental knowledge gained in the present study will aid the further development of new catalytic reactions using isocyanides, particularly those that cannot be achieved with carbon monoxide. Related studies are underway in our laboratory.

Experimental Section

General Procedure for the Palladium-Catalyzed Cyclocoupling of 2-Halobiaryls. To a flame-dried 10 mL two-necked flask were added 2-halobiaryl (0.25 mmol), isocyanide (0.30 mmol), $Pd(OAc)_2$ (0.0125 mmol), PPh_3 (0.025 mmol), CsOPiv (0.30 mmol), and DMF (2 mL) under a gentle stream of nitrogen. The mixture was stirred at 100 °C for 5 h under N_2 atmosphere. The reaction mixture was then cooled to room temperature, diluted with diethyl ether, and washed with brine. The organic layer was dried ($MgSO_4$). After removing the volatiles in vacuo, the residue was subjected to column chromatography on silica gel to afford the desired product.

***N*-(9*H*-Fluoren-9-ylidene)-2,6-diisopropylaniline (3aa).** Yellow solid. Mp = 101−102 °C. R_f = 0.43 (hexane/EtOAc = 4:1). ^{1}H NMR ($CDCl_3$): δ 0.94 (d, J = 7.0 Hz, 6H), 1.17 (d, J = 6.5 Hz, 6H), 2.82−2.92 (m, 2H), 6.41 (d, J = 7.6 Hz, 1H), 6.89 (td, J = 7.8 Hz, 0.8 Hz, 1H), 7.18−7.50 (m, 6H), 7.58 (t, J = 8.4 Hz, 2H), 8.03 (d, J = 7.3 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 23.2, 23.3, 28.4, 119.5, 120.0, 123.1, 123.2, 123.9, 126.4, 127.8, 128.3, 131.57, 131.64, 135.2, 137.2, 141.8, 143.0, 147.0, 162.9. IR (KBr): 3060 m, 2962 s, 2868 m, 2360 w, 1651 s, 1606 m, 1450 s, 1382 m, 1361 m, 1328 m, 1306 s, 1253 m, 1190 m, 1144 m, 1103 m, 1059 w, 1043 w, 941 m, 908 m, 795 m, 771 m, 734 s, 656 m, 434 w. MS *m*/*z* (relative intensity, %): 340 (M^+, 28), 339 ($M^+ - 1$, 100), 325 (14), 324 (54), 310 (20), 309 (70), 294 (24), 282 (27), 281 (26), 280 (40), 279 (12), 278 (21), 267 (16), 175 (13), 174 (89), 165 (46), 161 (25), 147 (13), 146 (46), 139 (11), 132 (50), 117 (11), 115 (10), 77 (10). Exact mass calcd for $C_{25}H_{25}N$ 339.1987, found 339.1991.

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