CHEMISTRY
AN ASIAN JOURNAL
www.chemasianj.org

Title: Pd-Catalyzed Decarbonylative C-H Coupling of Azoles and Aromatic Esters

Authors: Kaoru Matsushita, Ryosuke Takise, Tomoya Hisada, Shin Suzuki, Ryota Isshiki, Kenichiro Itami, Kei Muto, and Junichiro Yamaguchi

To be cited as: *Chem. Asian J.* 10.1002/asia.201800478

Link to VoR: http://dx.doi.org/10.1002/asia.201800478

A Journal of
ACES
Asian Chemical Editorial Society

A sister journal of Angewandte Chemie and Chemistry – A European Journal

WILEY-VCH

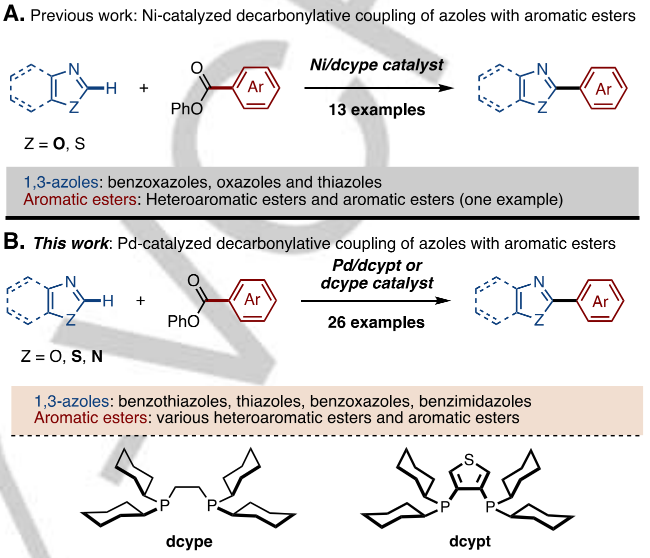
Pd-Catalyzed Decarbonylative C–H Coupling of Azoles and Aromatic Esters

Kaoru Matsushita,[a] Ryosuke Takise,[b] Tomoya Hisada,[a] Shin Suzuki,[b] Ryota Isshiki,[a] Kenichiro Itami,[b] Kei Muto[a] and Junichiro Yamaguchi*[a]

Abstract: A decarbonylative C–H coupling of azoles and aromatic esters by palladium catalysis is described. Our previously reported Ni-catalyzed C–H coupling of azoles and aromatic esters has a significant drawback regarding the substrate scope. Herein, we employ palladium catalysis instead of nickel, resulting in a broader substrate scope in terms of azoles and aromatic esters.

Decarbonylative transformation of aromatic esters with nucleophiles has received significant attention from organic chemists as a way to achieve a unique cross-coupling reaction.[1] Aromatic esters can be converted into functionalized aromatics using transition-metal catalysts *via* decarbonylation. Yamamoto is a pioneer of this phenomenon, as he has discovered and developed these reactions by using nickel complexes.[2] More than 20 years thereafter, Gooßen made a revival of these transformations with carbon nucleophiles by using palladium catalysts in 2002 and 2004.[3]

During our recent development of C–H functionalizations and coupling reactions with phenol derivatives using nickel catalysis,[4,5] we discovered the first Ni-catalyzed decarbonylative coupling in 2012 (Scheme 1A).[6a] 1,3-Azoles reacted with phenyl aromatic esters under a Ni/dcype catalyst to afford 2-arylazoles by formally engaging the ester group as a leaving group. After this reaction, our group and others reported various decarbonylative transformations of esters,[6,7] as well as those of amides[8] and thioesters[9] by mainly using nickel catalysts. However, the original decarbonylative C–H coupling has a drawback in that it has a narrow substrate scope. Benzoxazoles and thiazoles reacted well, but lower yields were observed for benzothiazoles, and benzimidazoles did not work at all. For the aromatic ester component, the reaction was mainly performed using heteroaromatic esters, and only one example employed a simple aromatic phenyl ester. During these efforts, we noticed that palladium catalysts were sometimes better, or at least different, in terms of reactivity when compared with nickel catalysts.[6d, 6e, 6g] Moreover, we discovered a new ligand, dcypt, which was effective for these transformations.[10] In light of these findings, we re-examined the decarbonylative C–H coupling of 1,3-azoles and identified that palladium catalytic systems are also effective for these transformations. Herein, we report the first Pd-catalyzed decarbonylative C–H coupling of 1,3-azoles with aromatic esters (Scheme 1B).



Scheme 1. (A) Ni-catalyzed decarbonylative C–H coupling of azoles with aromatic esters. (B) Pd-catalyzed decarbonylative C–H coupling of azoles with aromatic esters. dcype = 1,2-bis(dicyclohexylphosphino)ethane, dcypt = 3,4-bis(dicyclohexylphosphino)thiophene.

To find optimal conditions for the reaction, we selected benzothiazole (**1A**) and phenyl 2-thiophenecarboxylate (**2a**) as model substrates (Table 1). Firstly, we conducted the coupling in the presence of a nickel catalyst [Ni(OAc)$_2$] (5 mol%), dcype or dcypt (10 mol%), and K_3PO_4 (2.0 equiv) in 1,4-dioxane.[6a] As a result, desired coupling product **3Aa** was obtained in 13% and 38% yields, respectively (entries 1 and 2). Changing the transition-metal complex from Ni(OAc)$_2$ to Pd(OAc)$_2$ in toluene increased the yields of **3Aa** to 60% and 73% (entries 3 and 4). Other ligands such as P(n-Bu)$_3$, XPhos, dppe, and IMes shut down the reaction (entries 5–8). 1,4-dioxane was the best solvent to give **3Aa** in 81% yield using dcypt, whereas anisole and DMF gave lower yields (entries 9–11). Although $PdCl_2$ slightly decreased the yield, Pd(acac)$_2$ was superior to Pd(OAc)$_2$, giving **3Aa** in nearly quantitative yield (entries 12–13). Decreasing the loading of the catalyst (1 mol%) was successful, allowing the reaction to afford **3Aa** in 77% yield (entry 14).

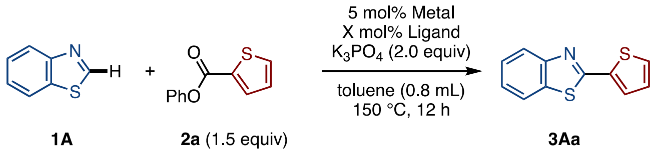
With optimal conditions in hand, we then evaluated the scope of other (hetero)aromatic phenyl esters **2** with benzothiazoles (**1A**) (Scheme 2). It turns out that the optimal conditions in Table 1 were not always the best conditions for this reaction, therefore we changed several parameters for each substrate.[11] Five-membered heterocycles such as thiophene (**2a**), furans (**2b** and **2c**) and thiazole (**2d**) gave the corresponding coupling products in excellent to moderate yields.

---

[a] K. Matsushita, T. Hisada, R. Isshiki, Dr. K. Muto, Prof. Dr. J. Yamaguchi
Department of Applied Chemistry, Waseda University, 3-4-1 Ohkubo, Shinjuku, Tokyo 169-8555, Japan.
E-mail: junyamaguchi@waseda.jp (JY)
[b] Dr. R. Takise, Dr. S. Suzuki, Prof. Dr. K. Itami
Institute of Transformative Bio-Molecules (WPI-ITbM) and Graduate School of Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan

Supporting information for this article is given via a link at the end of the document.

Table 1. Metal-catalyzed decarbonylative C–H coupling of azoles **1A** with aromatic esters **2a**.[a]

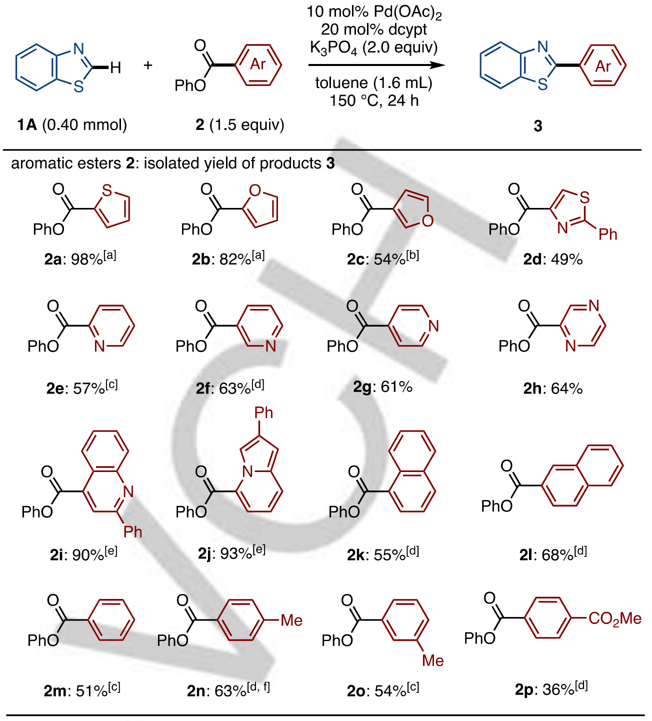


Entry	Metal	Ligand/X mol%	Solvent	Yield of 3/%[b]
1	$Ni(OAc)_2$	dcype (10)	1,4-dioxane	13
2	$Ni(OAc)_2$	dcypt (10)	1,4-dioxane	38
3	$Pd(OAc)_2$	dcype (10)	toluene	60
4	$Pd(OAc)_2$	dcypt (10)	toluene	73
5	$Pd(OAc)_2$	P(*n*-Bu)$_3$ (20)	toluene	0
6	$Pd(OAc)_2$	XPhos (20)	toluene	0
7	$Pd(OAc)_2$	dppe (10)	toluene	0
8[c]	$Pd(OAc)_2$	IMes·HCl (20)	toluene	0
9	$Pd(OAc)_2$	dcypt (10)	1,4-dioxane	81
10	$Pd(OAc)_2$	dcypt (10)	anisole	44
11	$Pd(OAc)_2$	dcypt (10)	DMF	43
12	$PdCl_2$	dcypt (10)	1,4-dioxane	76
13	$Pd(acac)_2$	dcypt (10)	1,4-dioxane	<99
14[d]	$Pd(acac)_2$	dcypt (2)	1,4-dioxane	77

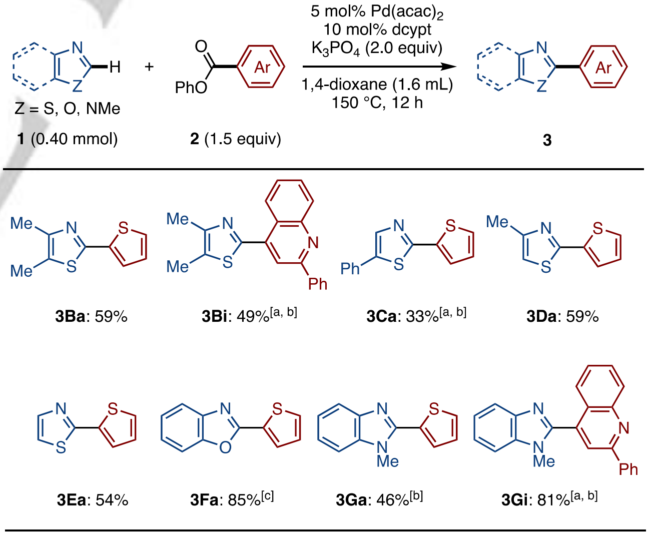
[a] Conditions: **1A** (0.2 mmol), **2a** (0.3 mmol), metal catalyst (5 mol%), ligand (10–20 mol%), K_3PO_4 (0.4 mmol), solvent (0.8 mL), 150 ºC, 12 h. [b] Yield was determined by GC analysis using *n*-decane as an internal standard. [c] NaO*t*-Bu (20 mol%) was added. [d] $Pd(acac)_2$ (1 mol%), dcypt (2 mol%) were used.

In the case of phenyl picolinate (**2e**) and phenyl nicotinate (**2f**), dcype was better than dcypt to give coupling products in 57% and 63% yields, respectively. 4-Pyridyl (**2g**), 2-pyrazinyl (**2h**) and other phenyl azinecarboxylates (**2i** and **2j**) worked under basic conditions (Table 1, entry 4) to give the corresponding coupling products **3** in moderate to good yields. Aromatic esters containing 1-naphthyl (**2k**) 2-naphthyl (**2l**), and phenyl (**2m**) groups were also effective with dcype, providing the corresponding 2-arylbenzothiazoles in good yields. Substrates containing *para*- and *meta*-tolyl (**2n** and **2o**) groups, as well as methoxycarbonyl (**2p**), also afforded the coupled products.

Next, the scope of 1,3-azoles was also investigated (Scheme 3). 4,5-Dimethylthiazole, 5-phenylthiazole, and 4-methylthiazole were reacted with phenyl aromatic esters to give the corresponding coupling products (**3Ba**, **3Bi**, **3Ca**, **3Da**, and **3Ea**) in moderate yields. Only one example of benzoxazoles was attempted to provide 2-arylbenzoxazole (**3Fa**) in good yield, since oxazoles were already investigated in a previously reported Ni-catalyzed reaction.[6a] To our delight, benzimidazoles also worked under palladium catalysis to give the corresponding coupling products (**3Ga** and **3Gi**).

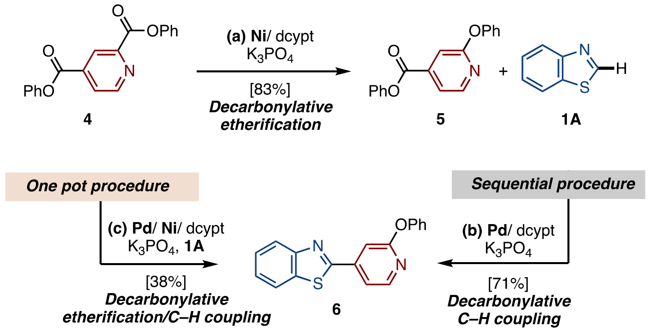


Scheme 2. Substrate scope of benzothiazoles (**1A**) with various aromatic esters **2**. [a] $Pd(acac)_2$ (5 mol%), dcypt (10 mol%) in 1,4-dioxane (1.6 mL) for 12 h; [b] $Pd(OAc)_2$ (5 mol%), dcypt (10 mol%) for 12 h; [c] $Pd(OAc)_2$ (10 mol%), dcype (20 mol%); [d] $Pd(OAc)_2$ (10 mol%), dcype (20 mol%) in 1,4-dioxane; [e] **1A** (0.2 mmol); [f] 170 °C.



Scheme 3. Substrate scope of azole **1** and phenyl ester **2**. [a] **1** (0.2 mmol); [b] $Pd(OAc)_2$ (10 mol%), dcypt (20 mol%) in toluene (1.6 mL) for 24 h; [c] $Pd(acac)_2$ (10 mol%), dcype (20 mol%) for 24 h

To showcase the utility of the present C–H coupling method, we set out to achieve a sequential decarbonylative reaction using both palladium and nickel catalysis (Scheme 4). To this end, diphenyl ester **4** was subjected to decarbonylative etherification under Ni/dcypt catalysis to give ether **5** in good yield.[6f] Subsequently, the decarbonylative C–H coupling of ester **5** with benzothiazole (**1A**) under Pd/dcypt catalysis provided 2-arylbenzothiazole **6**. Instead of a sequential procedure, a one-pot procedure can also be performed to make **6**: diphenyl ester **4** was reacted with **1A** in the presence of both palladium and nickel catalysts to afford the same product **6** in 38% yield.



Scheme 4. Pd/Ni sequential decarbonylative transformations. (a) $Ni(cod)_2$ (5 mol%), dcypt (10 mol%), K_3PO_4 (1.5 equiv), toluene, 150 ºC, 18 h, 83%; (b) $Pd(OAc)_2$ (10 mol%), dcypt (20 mol%), K_3PO_4 (2.0 equiv), toluene, 170 ºC, 24 h, 71%; (c) $Ni(OAc)_2$ (5 mol%), $Pd(OAc)_2$ (10 mol%), dcypt (30 mol%), K_3PO_4 (2.0 equiv), toluene, 170 ºC, 24 h, 38%.

In summary, we have developed a Pd-catalyzed C–H coupling of 1,3-azoles and aromatic esters. Adding to our previously established Ni-catalyzed transformation, palladium catalysts were also effective for this transformation, and exhibited a considerably broad substrate scope. Further studies to expand the scope of ester-based coupling by palladium catalysis are ongoing in our group and will be reported in due course.

Experimental Section

General Information

Unless otherwise noted, all reactants or reagents including dry solvents were obtained from commercial suppliers and used as received. $Pd(OAc)_2$, K_3PO_4 and thiazole (**1E**) were obtained from Wako Chemicals. $Ni(OAc)_2{\cdot}4H_2O$ and 3,4-bis(dicyclohexylphosphino)thiophene (dcypt) were obtained from KANTO Chemical. 1,2-Bis(dicyclohexylphosphino)ethane (dcype) was obtained from Sigma-Aldrich. $Pd(acac)_2$, benzothiazole (**1A**), 4,5-dimethylthiazole (**1B**), 4-methylthiazole (**1D**), benzoxazole (**1F**), 1-methylbenzimidazole (**1G**) and phenyl benzoate (**2m**) were obtained from TCI Chemical. Other substrates were synthesized according to procedures and the spectra matched with those of compounds reported in the literature.[11] Unless otherwise noted, all reactions were performed with dry solvents under an atmosphere of N_2 in dried glassware using standard vacuum-line techniques. All C–H coupling reactions were performed in 20-mL glass vessel tubes equipped with a J. Young® O-ring tap and heated (YMC EX-Thermo Stirring, AR-HSC) in a 9-well aluminum reaction block (IKA H 135.103 Block 9 x 16 ml) unless otherwise noted. All work-up and purification procedures were carried out with reagent-grade solvents in air.

General Procedure for Pd-catalyzed Decarbonylative C–H coupling

A 20-mL glass vessel equipped with a J. Young® O-ring tap containing a magnetic stirring bar and K_3PO_4 (169.8 mg, 0.80 mmol, 2.0 equiv) was dried with a heat gun *in vacuo* and filled with N_2 after cooling to room temperature. To this vessel were added aromatic ester **2** (0.60 mmol, 1.5 equiv), $Pd(acac)_2$ (6.09 mg, 0.02 mmol, 5.0 mol%) and 3,4-bis(dicyclohexylphosphino)thiophene (dcypt: 19.1 mg, 0.04 mmol, 10 mol%). The vessel was evacuated *in vacuo* and refilled N_2 gas three times. To this vessel were added azole **1** (0.40 mmol) and dry 1,4-dioxane (1.6 mL). The vessel was sealed with the O-ring tap and then heated at 150 °C for 12 h in a 9-well aluminum reaction block with stirring. After cooling the reaction mixture to room temperature, the mixture was passed through a short silica gel pad with EtOAc as an eluent. The filtrate was concentrated and the residue was purified by Isolera® or PTLC to afford the corresponding C–H coupling product **3**.

Acknowledgements

This work was supported by JSPS KAKENHI Grant Number JP16H01011, JP16H04148 (to J. Y.), and JP17K14453 (to K.M.), the ERATO program from JST (to K. I.), and a JSPS research fellowship for young scientists (to T. R. and S. S.). Materials Characterization Central Laboratory in Waseda University is acknowledged for HRMS measurement. ITbM is supported by the World Premier International Research Center (WPI) Initiative, Japan.

Keywords: C–H coupling • palladium • nickel • decarbonylation • heteroarenes

References:

[1] a) A. Correa, J. Cornella, R. Martin, *Angew. Chem. Int. Ed.* **2013**, *52*, 1878. b) R. Takise, K. Muto, J. Yamaguchi, *Chem. Soc. Rev.* **2017**, *46*, 5864.

[2] a) J. Ishizu, T. Yamamoto, A. Yamamoto, *Chem. Lett.* **1976**, *5*, 1091; b) T. Yamamoto, J. Ishizu, T. Kohara, S. Komiya, A. Yamamoto, *J. Am. Chem. Soc.* **1980**, 102, 3758.

[3] a) L. J. Gooßen, J. Paetzold, *Angew. Chem. Int. Ed.* **2002**, *41*, 1237; b) L. J. Gooßen, J. Paetzold, *Angew. Chem. Int. Ed.* **2004**, *43*, 1095.

[4] For a review of Ni-catalyzed C–H functionalizations, see: a) J. Yamaguchi, K. Muto, K. Itami, *Eur. J. Org. Chem.* **2013**, 19; b) S. Z. Tasker, E. A. Standley, T. F. Jamison, *Nature* **2014**, *509*, 299; c) L. C. M. Castro, N. Chatani, *Chem. Lett.* **2015**, *44*, 410; d) G. Pototschnig, N. Maulide, M. Schnürch, *Chem. Eur. J.* **2017**, *23*, 9206. e) J. Yamaguchi, K. Muto, K. Itami, *Top Curr. Chem,* **2016**, *374*, 55.

[5] a) K. Muto, J. Yamaguchi, K. Itami, *J. Am. Chem. Soc.* **2012**, *134*, 169; b) L. Meng, Y. Kamada, K. Muto, J. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2013**, *52*, 10048; c) K. Muto, J. Yamaguchi, A. Lei, K. Itami, *J. Am. Chem. Soc.* **2013**, *135*, 16384; d) H. Xu, K. Muto, J. Yamaguchi, C. Zhao, K. Itami, D. G. Musaev, *J. Am. Chem. Soc.* **2014**, *136*, 14834; e) K. Muto, T. Hatakeyama, J. Yamaguchi, K. Itami, *Chem. Sci.* **2015**, *6*, 6792; f) R. Takise, K. Itami, J. Yamaguchi, *Org. Lett.* **2016**, *18*, 4428.

[6] a) K. Amaike, K. Muto, J. Yamaguchi, K. Itami, *J. Am. Chem. Soc.* **2012**, *134*, 13573; b) K. Muto, J. Yamaguchi, D. G. Musaev, K. Itami, *Nat. Commun.* **2015**, *6*, 7508; c) K. Amaike, K. Itami, J. Yamaguchi, *Chem. Eur. J.* **2016**, *22*, 4384; d) K. Muto, T. Hatakeyama, K. Itami, J. Yamaguchi, *Org. Lett.* **2016**, *18*, 5106; e) T. Okita, K. Kumazawa, R. Takise, K. Muto, K. Itami, J. Yamaguchi, *Chem. Lett.* **2017**. *46*, 218; f) R. Takise, R. Isshiki, K. Muto, K. Itami, J. Yamaguchi, *J. Am. Chem. Soc.* **2017**, *139*, 3340; g) R. Isshiki, R. Takise, K. Itami, K. Muto, J. Yamaguchi, *Synlett* **2017**, *28*, 2599; h) R. Isshiki, K. Muto, J. Yamaguchi, *Org. Lett.* **2018**, *20*, 1150.

[7] a) N. A. LaBerge, J. A. Love, *Eur. J. Org. Chem.* **2015**, 5546. b) L. Guo, A. Chatupheeraphat, M. Rueping, *Angew. Chem. Int. Ed.* **2016**, *55*, 11810. c) X. Pu, J. Hu, Y. Zhao, Z. Shi, *ACS Catal.* **2016**, *6*, 6692. d) H. Yue, L. Guo, H.-H. Liao, Y. Cai, C. Zhu, M. Rueping, *Angew. Chem. Int. Ed.* **2017**, *56*, 4282. e) X. Liu, J. Jia, M. Rueping, *ACS Catal*. **2017**, *7*, 4491. f) H. Tatamidani, F. Kakiuchi, N. Chatani, *Org. Lett.* **2004**, *6*, 3597. g) A. Chatupheeraphat, H. H. Liao, W. Srimontree, L. Guo, Y. Minenkov, A. Poater, L. Cavallo, M. Rueping, *J. Am. Chem. Soc.* **2018**, *140*, 3724. For related nondecarbonylative couplings of aromatic esters,

see: h) L. Hie, N. F. Fine Nathel, X. Hong, Y.-F. Yang, K. N. Houk, N. K. Garg, *Angew. Chem. Int. Ed.* **2016**, *55*, 2810. i) T. Ben Halima, W. Zhang, I. Yalaoui, X. Hong, Y.-F. Yang, K. N. Houk, S. G. Newman, *J. Am. Chem. Soc*. **2017**, *139*, 1311.

[8] For a review, see: a) G. Meng, S. Shi, M. Szostak, *Synlett* **2016**, *27*, 2530. For selected examples, see: b) Y. Kajita, S. Matsubara, T. Kurahashi, *J. Am. Chem. Soc.* **2008**, *130*, 6058. c) G. Meng, M. Szostak, *Angew. Chem. Int. Ed.* **2015**, *54*, 14518. d) S. Shi, G. Meng, M. Szostak, *Angew. Chem. Int. Ed*. **2016**, *55*, 6959. e) J. Hu, Y. Zhao, J. Liu, Y. Zhang, Z. Shi, *Angew. Chem. Int. Ed.* **2016**, *55*, 8718. f) X. Liu, H. Yue, J. Jia, L. Guo, M. Rueping, *Chem. Eur. J.* **2017**, *23*, 11771. g) C. Liu, M. Szostak, *Angew. Chem. Int. Ed.* **2017**, *57*, 3939. h) W. Srimontree, A. Chatupheeraphat, H. H. Liao, M. Rueping, *Org. Lett.* **2017**, *19*, 3091. For related nondecarbonylative couplings of aromatic amides, see: i) L. Hie, N. F. Fine Nathel, T. K. Shah, E. L. Baker, X. Hong, Y.-F. Yang, P. Liu, K. N. Houk, N. K. Garg, *Nature* **2015**, *524*, 79. j) N. A. Weires, E. L. Baker, N. K. Garg, *Nat. Chem.* **2016**, *8*, 75. k) J. E. Dander, N. K. Garg, *ACS Catal.* **2017**, *7*, 1413.

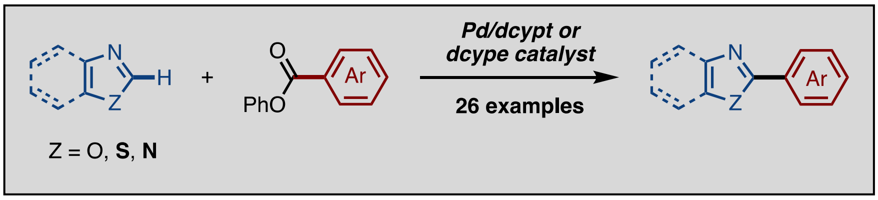
[9] a) H. Ochiai, Y. Uetake, T. Niwa, T. Hosoya, *Angew. Chem. Int. Ed.* **2017**, *56*, 2482; b) T. Niwa, H. Ochiai, M. Isoda, T. Hosoya, *Chem. Lett.* **2017**, *46*, 1315; c) N. Ichiishi, C. A. Malapit, Ł. Woźniak, M. S. Sanford, *Org. Lett.* **2018**, *20*, 44; d) S.-C. Lee, H.-H. Liao, A. Chatupheeraphat, M. Rueping, *Chem. Eur. J.* **2018***, 24*, 3608; e) C. Liu, M. Szostak, *Chem. Commun.* **2018**, *54*, 2130.

[10] a) R. Takise, K. Muto, J. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2014**, *53*, 6791; b) E. Koch, R. Takise, A. Studer, J. Yamaguchi, K. Itami, *Chem. Commun.* **2014**, *51*, 855.

[11] See supporting information for detail.

10.1002/asia.201800478

Entry for the Table of Contents



Changing from Ni to Pd in the decarbonylative C–H coupling of azoles and aromatic esters.