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Au-promoted Pd-catalyzed arylative cyclization of *N,N*-dimethyl-o-alkynylaniline with aryl iodides: Access to 2,3-diaryl indoles and mechanistic insight

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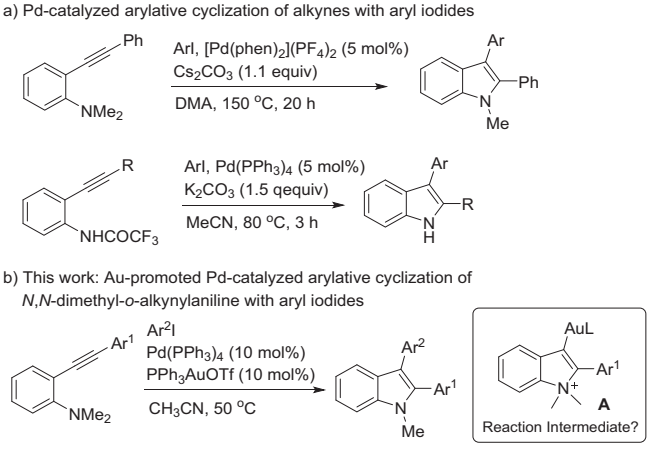
ABSTRACT

We have developed a Au-promoted Pd-catalyzed cyclization/cross-coupling of *N,N*-dimethyl-o-alkynylaniline with aryl iodides to synthesize 2,3-diarylindoles under mild and base-free conditions. A related vinyl-Au species has been isolated through Au-promoted cyclization of *N,N*-dimethyl-o-alkynylaniline and structurally characterized. Further study on its reactivity suggests the vinyl-Au species might be out of catalytic cycle, and $PhPd(OTf)(PPh_3)_2$ is probably the reaction intermediate.

Introduction

Transition metal-catalyzed cross-coupling reactions have been well-established as powerful tools for the formation of C — C bonds in modern synthetic chemistry. [1] Tremendous efforts have been made to develop methods for the access to 2,3-disubstituted indoles, due to the increasing interests in successful biomedical applications of substituted indoles. [2] 2-Substituted 3-arylindoles could be synthesized by Pd-catalyzed cyclization/cross-coupling of either *N,N*-dimethyl-o-alkynylaniline [3a] or *o*-alkynyltrifluoroacetanilides [3b] with aryliodides (Scheme 1a). In both cases, stoichiometric quantities of base are required, and in the former case, a high temperature of 150 °C is also needed. In such process, Pd catalytic cycle starts with oxidative addition of ArI into PdL_n species to form $ArPdXL_2$ intermediate, which is supposed to promote the intramolecular nucleophilic cyclization of alkynes. [4] Because Ag (I) salts are often used as halide abstractor in Pd catalysis, [5] we envision the introduction of Ag(I) salts might accelerate the reaction rate in such transformation. On the other hand, bimetallic catalysis has recently emerged as a promising approach in C — C coupling reactions and provides complementary applications, due to its unique reactivity and selectivity. [6] Among them, Pd/Au bimetallic catalysis is of particular interest and has found to be an efficient catalytic system in several C — C coupling reactions, such as Sonogashira reaction, [7] Stille reaction, [8] and other cou-



Scheme 1. Pd-catalyzed arylative cyclization of *o*-alkynylaniline, and Au-promoted Pd-catalyzed arylative cyclization of *o*-alkynylaniline for the synthesis of 2-substituted 3-arylindoles.

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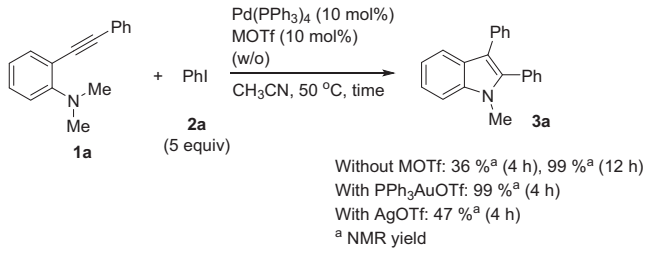
pling reactions. [9] One of the most successful examples of Pd/Au bimetallic catalysis is Au/Pd co-catalyzed cyclization/cross-coupling reaction, which combines the well-established ability of gold to activate C — C multiple bonds for cyclization and the efficient redox turnover of palladium. The process involves a key transmetalation of vinylgold, with RPd^+ intermediate and subsequent reductive elimination at Pd center. [10] Therefore, we speculated Pd catalyst in combination with coinage salt, such as Ag(I) or Au(I) salts, would be an ideal system for the catalytic cyclization/cross-coupling of *o*-alkynylaniline. Herein, we develop a Au-promoted Pd-catalyzed cyclization/cross-coupling of *N,N*-dimethyl-o-alkynylaniline with aryl iodides to efficiently synthesize 2,3-diarylindoles under mild and base-free conditions (Scheme 1b). A related vinyl-Au species **A** has been isolated through the Au-promoted cyclization of *N,N*-dimethyl-o-alkynylaniline, which was structurally characterized by single crystal X-ray diffraction. The study on its reactivity towards aryl iodide under Pd catalysis suggests that the vinyl Au species **A** might be out of catalytic cycle, and PhPd $(OTf)(PPh_3)_2$ is probably the reaction intermediate.

Results and discussion

First, we test the $Pd(PPh_3)_4$-catalyzed cyclization/cross-coupling of *N,N*-dimethyl-o-alkynylaniline **1a** with iodobenzene **2a**. (Scheme 2). The reaction proceeded sluggishly in CH_3CN at 50 °C, as only a low yield of product **3a** (36%, NMR yield) was detected after 4 h, and it took 12 h to achieve a 99% (NMR yield) yield of **3a**. Given these results, we decided to introduce a second metal such as Au complex, which is expected to be highly efficient in the intramolecular cyclization reaction of alkynes. [11] Delightfully, the addition of 10 mol% of PPh_3AuOTf increased considerably the reaction rate. With the assistance of Au(I) it only required 4 h to obtain 99% NMR yield. Using AgOTf as an additive only improved slightly the reaction yield.



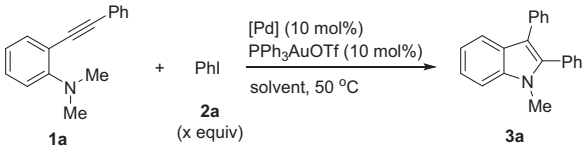
Scheme 2. Pd-catalyzed arylative cyclization of *N,N*-dimethyl-*o*-alkynylaniline **1a** with PhI.

Optimization of various palladium catalysts in different solvents (entries 1 ~ 8, Table 1) was studied. The best result was achieved for **3a** (99% yield; entry 4, Table 1), when using Pd $(PPh_3)_4$ as catalyst in MeCN. Decreasing the amount of substrate **2a** to 1.5 equivalent didn't result in yield loss (entries 9 and 10, Table 1).

We further tested the transformation of **1a** with different aryl iodides (**2**) under the standard reaction conditions (Scheme 3). All of the reactions worked well, giving the desired products **3a** ~ **3 g** in 90 ~ 99% yields. When using different *para*-halogenated and *para*-methyl phenyl iodides, a long reaction time are required to achieve high yields (89 ~ 94% for **3 h** ~ **3j**). For 2-iodonaphthalene, longer reaction time is also required (**3 k**). The reaction was also tolerated with heteroaryl halide (2-iodothiophene), giving the corresponding indole **3 l** in 88% yield. The reactions with different *N,N*-dimethyl-*o*-alkynylanilines were also examined. The desired products **3 m** ~ **3q**, and **3 s** ~ **3 t** were obtained in 80 ~ 93% yields. It should be noted that for the reactions which furnish the 2,3-diarylindole products bearing an orth- groups (methyl or methoxyl) either at 2-aryl or at 3-aryl group, longer reaction time are required (**3 m**, **3n,** and **3r**). When using 2-iodoanisole, a poor yield of 57% was observed for **3r**.

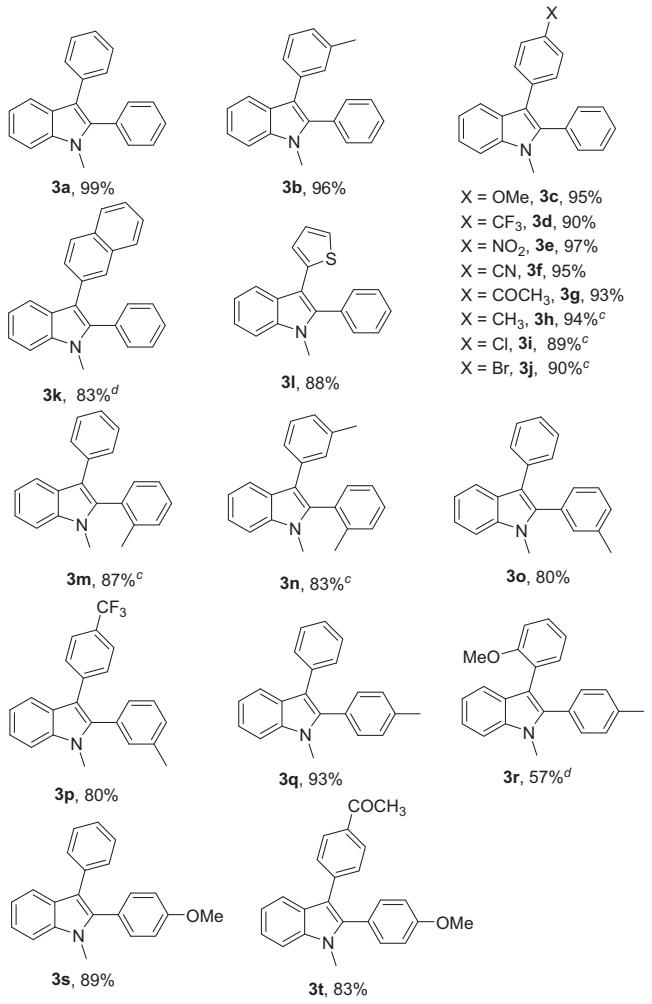
Considering the unique ability of gold to activate alkynes towards nucleophilic attack, we assume that a vinyl gold intermediate might be involved in the catalytic cycle. We have recently reported the isolation of several vinyl Au intermediates through intramolecular nucleophilic attack on Au-activated alkynes. [12] To our delight, the treatment of **1a** with one equivalent of PPh_3-AuOTf resulted in the formation of a vinyl gold complex **4** with a high yield (94%) in 5 min (Eqn 1, Scheme 4). The structure of **4** was determined by single crystal X-ray diffraction, which exhibits the expected linear coordination geometry (Fig. 1). The Au-C bond distances [Au-C7, 2.046(3Å] in **4** is similar with that of a $C(sp^2)$-Au

Table 1
Optimization of Reaction Conditions[a].



entry[a]	Pd	**2a** (x equiv)	sovent	yield[b](%)
1	$Pd(PPh_3)Cl_2$	5	CH_3CN	trace
2	$Pd(OAc)_2$	5	CH_3CN	14
3	$PdCl_2$	5	CH_3CN	11
4	$Pd(PPh_3)_4$	5	CH_3CN	99
5	$Pd(PPh_3)_4$	5	CH_3OH	96
6	$Pd(PPh_3)_4$	5	DMF	25
7	$Pd(PPh_3)_4$	5	toluene	7
8	$Pd(PPh_3)_4$	5	THF	trace
9	$Pd(PPh_3)_4$	3	CH_3CN	99
10	**$Pd(PPh_3)_4$**	**1.5**	**CH_3CN**	**99**

[a]Unless otherwise stated, reactions were performed with 0.45 mmol of **1a**, 10 mol% palladium catalyst and 10 mol% PPh_3AuOTf in 4 mL of solvent under a nitrogen atmosphere for 4 h. [b]NMR yields.



Scheme 3. Scope of cyclization reactions.[a,b] [a] Unless otherwise stated, reactions were performed with 0.45 mmol of **1**, 1.5 equiv **2** and 10 mmol% $Pd(PPh_3)_4$, 10 mmol% PPh_3AuOTf in 5 mL of CH_3CN at 50 °C under a nitrogen atmosphere for 4 h. [b]Isolated yields. [c]8 h. [d]24 h.

single bond (e.g., 2.045(6) Å). [13] Under catalysis of $Pd(PPh_3)_4$, vinyl gold **4** could react with excess PhI in MeCN at 50 °C to give arylation product **3a** in 85% yield (Eqn 2, Scheme 4). However, the transformation is sluggish, requiring 12 h to obtain complete conversion, while in catalytic reaction, it only takes 4 h to give desired product **3a** in 99%. Interestingly, when treatment of vinyl gold **4** in the presence of $Pd(PPh_3)_4$ and PhI at the room temperature, **1a**, ring-opening product of **4** was observed after 2 h, and arylation product **3a** was finally obtained in 99% yield. This finding suggests the formation of the vinyl gold **4** is reversible.

Next, we examined the reaction between PPh_3AuOTf and *trans*-[PdPhI(PPh_3)$_2$] (**5**) formed by oxidative addition of $Pd(PPh_3)_4$ with PhI. A new major species appearing at 21.54 ppm was observed by ^{31}P NMR (Scheme 5). We assigned it as $PhPd(OTf)(PPh_3)_2$ (**6**) by comparison with the ^{31}P NMR data of an authentic complex, $C_6F_5Pd(OTf)(PPh_3)_2$ which appears at 23.50 ppm [14]. The observation suggests Au salt (PPh_3AuOTf) probably acts as an iodide abstractor, and $PhPd(OTf)(PPh_3)_2$ might be the reaction intermediate.

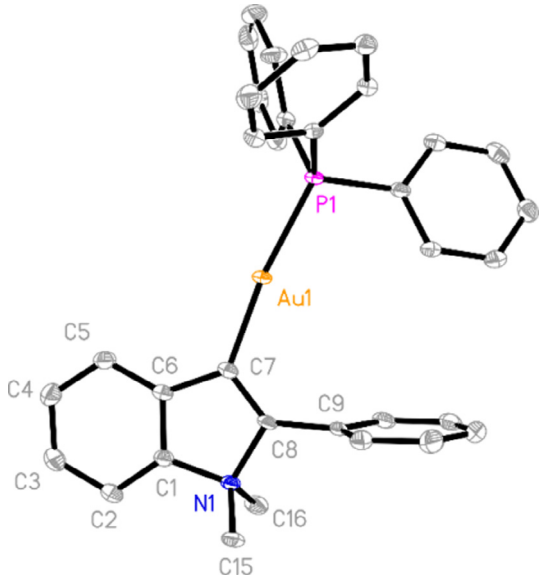
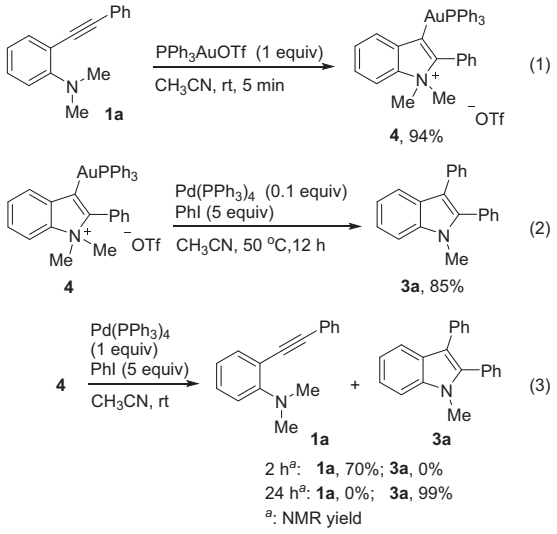
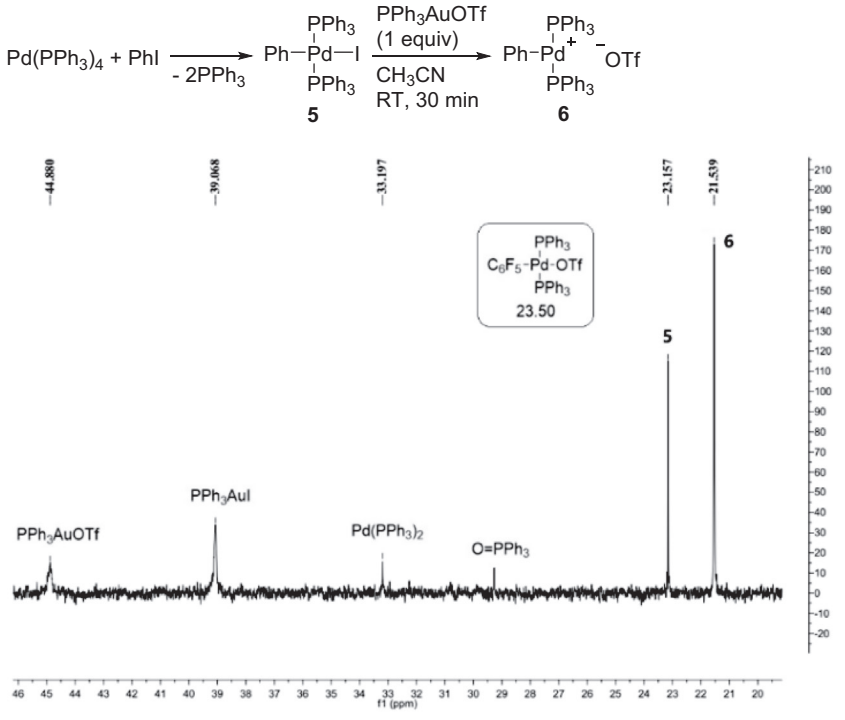


Fig. 1. Molecular structure of **4**. The counter anion and hydrogen atoms have been omitted for clarity. Selected bond distances (Å) and angles (deg): Au(1)-C(7) 2.046 (3), Au(1)-P(1) 2.2920(7), C(6)-C(7) 1.469(4), C(7)-C(8) 1.331(4), C(1)-C(6) 1.385(4), N(1)-C(1) 1.481(4), N(1)-C(8) 1.523(3), C(7)-Au(1)-P(1) 172.01(8), C(8)-C(7)-Au(1) 122.6(2), C(6)-C(7)-Au(1) 129.8(2), C(8)-C(7)-C(6) 107.4(2).

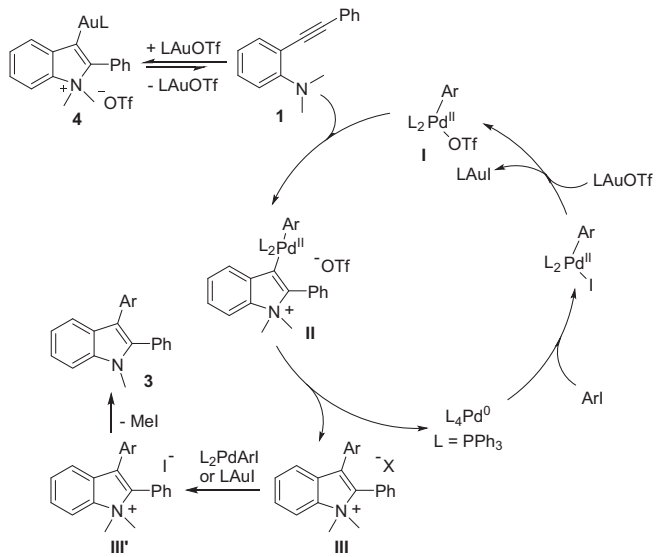


Scheme 4. Isolation of key Au species **4** and its reactivity with PhI under catalysis of Pd.

Based on the observations, we propose a plausible mechanism (Scheme 6). Oxidative addition of $Pd(PPh_3)_4$ with ArI forms PdArI(PPh_3)$_2$, which reacts with PPh_3AuOTf to form $ArPd(OTf)(PPh_3)_2$ (**I**). Pd species **I** promotes the cyclization of **1** to form vinyl Pd(II) complex **II**. Pd(II) complex **II** further undergoes reductive elimination to give the indolium intermediate **III**, and release Pd^0. **III** further undergoes the anion exchange with $Ar(PPh_3)_2PdI$ or $(PPh_3)AuI$ to give **III'**, which undergoes elimination of MeI to give the final product **3**.



Scheme 5. The reaction of PPh_3AuOTf and *trans*-[PdPhI(PPh_3)$_2$] (**5**).



Scheme 6. Proposed reaction mechanism.

Conclusion

To summarize, we present a Au-promoted Pd-catalyzed cyclization/cross-coupling of *N,N*-dimethyl-o-alkynylanilines with aryl iodides to prepare 2-substituted 3-arylindoles. A related vinyl-Au intermediate has been isolated through PPh_3AuOTf-promoted cyclization of *N,N*-dimethyl-o-alkynylaniline. Reactivity of the vinyl-Au species with aryl iodide in the presence of Pd catalyst has been investigated, suggesting that the Au intermediate might be out of catalytic cycle, and PhPd(OTf)(PPh_3)$_2$ is probably the reaction intermediate.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152766.

References

[1] (a) W. Shi, C. Liu, A. Lei, Chem. Soc. Rev. 40 (2011) 2761;
(b) S.H. Cho, J.Y. Kim, J. Kwak, S. Chang, Chem. Soc. Rev. 40 (2011) 5068;
(c) F. Chen, T. Wang, N. Jiao, Chem. Rev. 114 (2014) 8613;
(d) A.H. Cherney, N.T. Kadunce, S.E. Reisman, Chem. Rev. 115 (2015) 9587;
(e) H. Yang, X. Yang, W. Tang, Tetrahedron 72 (2016) 6143;
(f) Y. Xia, D. Qiu, J. Wang, Chem. Rev. 117 (2017) 13810;
(g) G.C. Fu, ACS Cent. Sci. 3 (2017) 692;
(h) C.S. Wang, P.H. Dixneuf, J.F. Soule, Chem. Rev. 118 (2018) 7532;
(i) I.P. Beletskaya, F. Alonso, V. Tyurin, Coord. Chem. Rev. 385 (2019) 137.
[2] (a) T. Kawasaki, K. Higuchi, Nat. Prod. Rep. 22 (2005) 761;
(b) G.R. Humphrey, J.T. Kuethe, Chem. Rev. 106 (2006) 2875;
(c) A.J. Kochanowska-Karamyan, M.T. Hamann, Chem. Rev. 110 (2010) 4489;
(d) V. Sharma, P. Kumar, D. Pathak, Heterocycl. Chem. 47 (2010) 491;
(e) M.Z. Zhang, Q. Chen, G.F. Yang, Eur. J. Med. Chem. 89 (2015) 421;
(f) Y. Zou, A.B. Smith, J. Antibiot. 71 (2018) 185.
[3] (a) T. Yamauchi, F. Shibahara, T. Murai, Tetrahedron Lett. 57 (2016) 2945;
(b) S. Cacchi, G. Fabrizi, L.M. Parisi, Synthesis 2004 (1889) 11.
[4] (a) B. Yao, Q. Wang, J. Zhu, Angew. Chem. Int. Ed. 51 (2012) 5170;
(b) B. Yao, Q. Wang, J. Zhu, Angew. Chem. Int. Ed. 51 (2012) 12311;
(c) B. Yao, Q. Wang, J. Zhu, Angew. Chem. Int. Ed. 52 (2013) 12992;
(d) B. Yao, Q. Wang, J. Zhu, Chem. Eur. J. 20 (2014) 12255.

[5] (a) M. Weber, S. Jautze, W. Frey, R. Peters, J. Am. Chem. Soc. 132 (2010) 12222; (b) K.E. Roth, A.S. Blum, Organometallics 30 (2011) 4811; (c) M. Weber, W. Frey, R. Peters, Chem. Eur. J. 19 (2013) 8342; (d) J.M. Bauer, W. Frey, R. Peters, Angew. Chem. Int. Ed. 53 (2014) 7634; (e) K.R. Garrison, J. Tjuttrins, G.M. Torres, N.J. Liu, O. Kulkarni, B.A. Arndtsen, Nat. Chem. 10 (2018) 193.
[6] (a) J.J. Hirner, Y. Shi, S.A. Blum, Acc. Chem. Res. 44 (2011) 603;
(b) M.H. Pérez-Temprano, J.A. Casares, P. Espinet, Chem. Eur. J. 2012 (1864) 18;
(c) J. Park, A. Hong, Chem. Soc. Rev. 41 (2012) 6931;
(d) C. Cordovilla, C. Bartolome, J.M. Martínez-Ilarduya, P. Espinet, ACS Catal. 5 (2015) 3040;
(e) D.R. Pye, N.P. Mankad, Chem. Sci. 8 (2017) 1705;
(f) M.M. Lorion, K. Maindan, A.R. Kapdi, L. Ackermann, Chem. Soc. Rev. 46 (2017) 7399;
(g) N.P. Mankad, Chem. Commun. 54 (2018) 1291.
[7] For selected Sonogashira reaction examples, see: (a) L.A. Jones, S. Sanz, M. Laguna, Catal. Today 122 (2007) 403; (b) T. Lauterbach, M. Livendahl, A. Rosellón, P. Espinet, A.M. Echavarren, Org. Lett. 12 (2010) 3006; (c) B. Panda, T. K. Sarkar, Chem. Commun. 46 (2010) 3131; (d) B. Panda, T.K. Sarkar, Tetrahedron Lett. 51 (2010) 301; (e) P. Venkatesan, J. Santhanalakshmi, Langmuir 26 (2010) 12225; (f) S. Pankajakshan, T.P. Loh, Chem.-Asian J. 6 (2011) 2291; (g) B. Panda, T.K. Sarkar, Synthesis 45 (2013) 817.
[8] For selected Stille reaction examples, see: (a) Y. Shi, S.M. Peterson, W.W. Haberaecker, S.A. Blum, J. Am. Chem. Soc. 130 (2008) 2168; (b) A. Duschek, S.F. Kirsch, Angew. Chem. Int. Ed. 47 (2008) 5703; (c) J. Pozo, D. Carrasco, M.H. Perez-Temprano, M. García-Melchor, R. Álvarez, J.A. Casares, A. Espinet, Angew. Chem., Int. Ed. 52 (2013) 2189.
[9] For selected other reaction examples, see: (a) Y. Shi, S.D. Ramgren, S.A. Blum, Organometallics, 28 (2009) 1275; (b) A.S.K. Hashmi, C. Lothschütz, R. Döpp, M. Rudolph, T.D. Ramamurthi, F. Rominger, Angew. Chem., Int. Ed., 48 (2009) 8243; (c) A.S.K. Hashmi, R. Döpp, C. Lothschütz, M. Rudolph, D. Riedel, F. Rominger, Adv. Synth. Catal. 352 (2010) 1307; (d) M. Peña-López, M. Ayán-Varela, L.A. Sarandeses, J. Pérez Sestelo, Chem.-Eur. J., 16 (2010) 9905; (e) W.Y. Man, S. Bock, N.N. Zaitseva, M.I. Bruce, P.J. Low, J. Organomet. Chem. 696 (2011) 2172; (f) K.E. Roth, S.A. Blum, Organometallics 30 (2011) 4811; (g) D. Weber, M.R. Gagne, Chem. Commun. 47 (2011) 5172; (h) M. Peña-López, M. Ayán-Varela, L.A. Sarandeses, J. Pérez Sestelo, Org. Biomol. Chem. 10 (2012) 1686; (i) A.S.K. Hashmi, C. Lothschütz, R. Döpp, M. Ackermann, J.D.B. Becker, M. Rudolph, C. Scholz, F. Rominger, Adv. Synth. Catal. 354 (2012) 133; (j) J.J. Hirner, K.E. Roth, Y. Shi, S.A. Blum, Organometallics 31 (2012) 6843; (k) H. Wu, Y.P. He, L.Z. Gong, Adv. Synth. Catal., 354 (2012) 975; (l) M. Peña-López, L.A. Sarandeses, J. Pérez Sestelo, Eur. J. Org. Chem. (2013) 2545; (m) M. Al-Amin, J.S. Johnson, S.A. Blum, Organometallics 33 (2014) 5448; (n) D. Carrasco, M.H. Pérez-Temprano, J.A. Casares, P. Espinet, Organometallics 33 (2014) 3540; (o) R. Tanimoto, S. Suzuki, M. Kozaki, K. Okada, Chem. Lett. 43 (2014) 678; (p) A. Verlee, T. Heugebaert, T. van der Meer, P. Kerchev, K.V. Hecke, F.V. Breusegem, C.V. Stevens, ACS Catal. 9 (2019) 7862.
[10] (a) Y. Shi, K.E. Roth, S.D. Ramgren, A.S. Blum, J. Am. Chem. Soc. 131 (2009) 18022; (b) M. Al-Amin, K.E. Roth, S.A. Blum, ACS Catal. 4 (2014) 622; (c) M. Al-Amin, J.S. Johnson, S.A. Blum, Organometallics 33 (2014) 5448.
[11] (a) A.S.K. Hashmi, Chem. Rev. 107 (2007) 3180;
(b) Z.G. Li, C. Brouwer, C. He, Chem. Rev. 108 (2008) 3239;
(c) A. Arcadi, Chem. Rev. 108 (2008) 3266;
(d) E.J. Núñez, A.M. Echavarren, Chem. Rev. 108 (2008) 3326;
(e) A.S.K. Hashmi, M. Rudolph, Chem. Soc. Rev. 37 (2008) 1766;
(f) A. Corma, A.L. Pérez, M.J. Sabater, Chem. Rev. 111 (2011) 1657;
(g) M. Rudolph, A.S.K. Hashmi, Chem. Commun. 47 (2011) 6536;
(h) N. Krause, C. Winter, Chem. Rev. 2011 (1994) 111;
(i) M. Rudolph, A.S.K. Hashmi, Chem. Soc. Rev. 41 (2012) 2448;
(j) Y. Zhang, T. Luo, Z. Yang, Nat. Prod. Rep. 31 (2014) 489;
(k) A. Furstner, Acc. Chem. Res. 47 (2014) 925;
(l) A. Stephen, K. Hashmi, Acc. Chem. Res. 47 (2014) 864;
(m) L. Fensterbank, M. Malacria, Acc. Chem. Res. 47 (2014) 953;
(n) H.S. Yeom, S. Shin, Acc. Chem. Res. 47 (2014) 966;
(o) W.-B. Yang, A.S.K. Hashmi, Chem. Soc. Rev. 43 (2014) 2941;
(p) E. Soriano, I. Fernandez, Chem. Soc. Rev. 43 (2014) 3041;
(q) B. Ranieri, I. Escofet, A.M. Echavarren, Org. Biomol. Chem. 13 (2015) 7103;
(r) R. Dorel, A.M. Echavarren, Chem. Rev. 115 (2015) 9028;
(s) R.J. Harris, R.A. Widenhoefer, Chem. Soc. Rev. 45 (2016) 4533.
[12] (a) S. Lv, J. Wang, C. Zhang, S. Xu, M. Shi, J. Zhang, Angew. Chem. Int. Ed. 54 (2015) 14941;
(b) J. Wang, X.-M. Cao, S. Lv, C. Zhang, S. Xu, M. Shi, J. Zhang, Nat. Commun. 8 (2017) 14625;
(c) H. Chen, J. Wang, Z. Hu, S. Xu, M. Shi, J. Zhang, Chem. Commun. 53 (2017) 10835;
(d) J. Wang, L. Zhan, G. Wang, Y. Wei, M. Shi, J. Zhang. Chem. Commun. 56 (2020) 6213;
(e) C. Zhang, G. Wang, L. Zhan, J. Wang, Y. Wei, S. Xu, M. Shi, J. Zhang, ACS Catal. 10 (2020) 6682.
[13] E.J. Fernández, A. Laguna, M.E. Olmos, Adv. Organomet. Chem. 52 (2005) 77.
[14] A.L. Casado, P. Espinet, A.M. Gallego, J. Am. Chem. Soc. 122 (48) (2000) 11771.