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Functional Group Transposition: A Palladium-Catalyzed Metathesis of Ar−X σ-Bonds and Acid Chloride Synthesis

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Supporting Information

ABSTRACT: We describe the development of a new method to use palladium catalysis to form functionalized aromatics: via the metathesis of covalent σ-bonds between Ar−X fragments. This transformation demonstrates the dynamic nature of palladium-based oxidative addition/reductive elimination and offers a straightforward approach to incorporate reactive functional groups into aryl halides through exchange reactions. The reaction has been exploited to assemble acid chlorides without the use of high energy halogenating or toxic reagents and, instead, via the metathesis of aryl iodides with other acid chlorides.

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Palladium-catalyzed coupling reactions are among the most heavily exploited transformations in synthetic chemistry.[1−3] Central to many of these reactions is the oxidative addition of an organic-halide or pseudohalide substrate to palladium and the ultimate liberation of the functionalized product by reductive elimination. Despite the reversible nature of this oxidative addition/reductive elimination cycle, it has only recently been established that aryl-halogen bond oxidative addition to palladium can itself be reversible and used in synthesis. Hartwig reported in 2001 that the addition of the sterically encumbered P^tBu_3 ligand can facilitate the stoichiometric, reversible reductive elimination of aryl-halogen bonds from palladium (Figure 1a).[4,5] More recently, the importance of this chemistry in catalysis has been demonstrated by Lautens, Buchwald, Tong, and others with a number of efficient palladium-catalyzed transformations.[6−15]

We have reported that palladium-based carbon−halogen reductive elimination can be used in a different direction and drive the synthesis of high energy electrophiles such as acid chlorides from aryl halides and carbon monoxide (Figure 1b).[16−19] Acid chlorides are broadly employed in synthesis due in large part to their high reactivity with a diverse range of nucleophiles, but classically generated with reactive and corrosive chlorinating agents (thionyl chloride, PCl_3, or oxalyl chloride). A key step in this catalytic system is the reductive elimination of the weak and reactive acid chloride bond. The latter is facilitated by a highly sterically encumbered P^tBu_3 ligand, which acts in concert with carbon monoxide coordination to create a strained Pd(II) intermediate for equilibrium acid chloride formation.[20]

One limitation to this catalytic approach to acid chlorides is its reliance upon carbon monoxide as a reagent, which is toxic and requires special handling as a gas. A number of alternative sources of carbon monoxide have been described for use in carbonylation reactions (e.g., metal carbonyls, CO_2, or Skrydstrup's dual chamber systems).[21−27] Unfortunately, many of these can require either specialized equipment or involve reagents/byproducts that are not compatible with the high reactivity of acid chlorides.

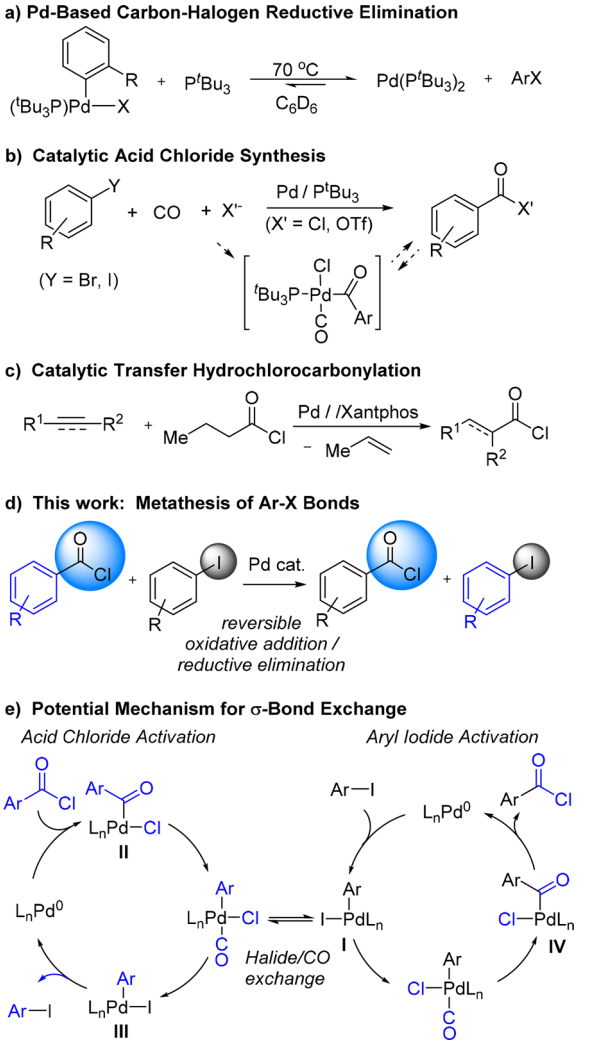

Figure 1. Reversible oxidative addition/reductive elimination of C−X Bonds.

In light of the ability of palladium catalysts to mediate oxidative addition and reductive elimination reactions, we questioned if

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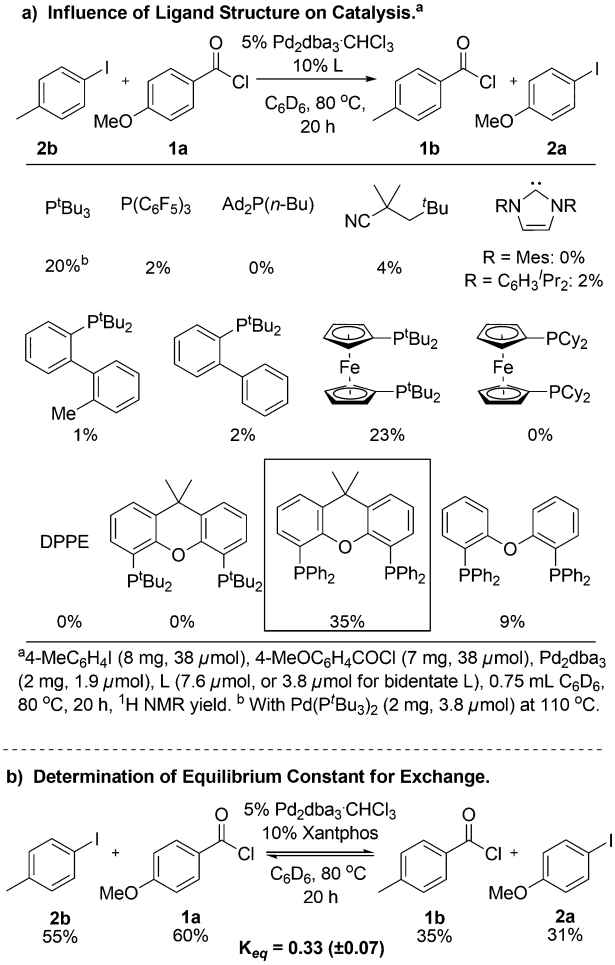
they might offer a fundamentally different way to generate functionalized aromatics: via the metathesis of Ar−X σ-bonds. As noted above, aryl halide oxidative addition/reductive elimination can be reversible with the use of sterically encumbered ligands.[6,7] Similarly, the reductive elimination of acid chlorides from palladium has been found to be a dynamic, equilibrium process with P^tBu_3 as ligand, while carbon monoxide insertion is also reversible with palladium catalysis and exploited in decarbonylative coupling reactions, as well as a route to generate CO.[26,28,29] Together, these suggest the potential to exploit reversible oxidative addition/reductive elimination reactions to perform the overall metathesis of Ar−X σ-bonds and thereby form acid chlorides from simply other acid chlorides. In this regard, Morandi has recently described the use of shuttle catalysis for the efficient transfer of acid chlorides (or nitriles) between alkenes and alkynes via dehydrochlorocarbonylation (Figure 1c).[30−33] As an alternative, we report here what is to our knowledge the first example of how palladium-catalyzed reversible oxidative addition/reductive elimination chemistry can itself allow the dynamic exchange of different σ-bonded functional groups between two Ar−X substrates (Figure 1d). The transformation demonstrates the dynamic nature of palladium oxidative addition/reductive elimination chemistry, as well as interpalladium exchange, and offers a method to synthesize a diverse array of (hetero)aryl acid chlorides in high yield, with no corrosive byproducts or intermediates and without the use of carbon monoxide itself as a reagent.

The development of the catalytic exchange of acid chloride and aryl iodide functional groups presents several reaction design challenges. First, the oxidative addition/reductive elimination chemistry of two different functionalities, aryl iodide and acid chloride, must be sufficiently competitive to allow exchange, despite the established high reactivity of acid chlorides toward palladium (Figure 1e). The exchange of halides and carbon monoxide between palladium catalysts must also occur and do so faster than reductive elimination. Finally, unproductive, yet precedented steps such as aryl chloride reductive elimination and carbon monoxide displacement must not occur, as these could be irreversible and block the reaction.

We first examined the exchange of aryl iodide and acid chloride with the $Pd(P^tBu_3)_2$ catalyst previously employed in catalytic acid chloride synthesis. No exchange is observed at ambient temperature, and instead, acid chloride simply undergoes stoichiometric oxidative addition to palladium (Table S1). The latter is consistent with previous reports of the rapid and favored addition of acid chloride to Pd(0). Heating the catalytic reaction to 110 °C results in the formation of a new acid chloride **1b** in low yield (20%, Scheme 1a). Unfortunately, this exchange is incomplete, and there is catalyst degradation at temperatures above 110 °C as well as the unproductive aryl chloride reductive elimination.[34]

We postulated that the slow exchange of acid chloride/iodide functionalities is likely related to inhibited acid chloride reductive elimination. While P^tBu_3 can facilitate ambient temperature reductive elimination of acid chlorides during carbonylations, this requires CO coordination to lower the barrier to elimination.[24] We therefore probed if other ligands may be better suited to favor reductive elimination in the absence of CO. Although many mono- and bidentate ligands lead to minimal exchange, we were pleased to find that the large bite angle Xantphos ligand leads to a significant increase in yield and forms **1b** in 35% yield under more mild conditions (80 °C, Scheme 1a). Importantly, there is minimal generation of decarbonylated

Scheme 1. Catalyst Development for Aryl−X Exchange



products with Xantphos, and most of the other products are the starting acid chloride (**1a**, 60%), aryl iodide (**2b**, 55%), and the aryl iodide byproduct (**2a**, 31%). Decreasing the catalyst loading leads to analogous results (Table S2).

The exchange of functional groups between the *p*-methoxyphenyl and *p*-tolyl units is a pseudoderivative metathesis reaction. Performing the reaction in reverse with acid chloride **1b** and aryl iodide **2a** leads to the generation of the near identical mixture of products. The Pd/Xantphos catalyst can therefore fully scramble Ar−X functional groups to form an equilibrium mixture of products. Variation of the concentration of reagents allows the determination of the equilibrium constant for exchange ($K_{eq} = 0.33 \pm 0.07$, Scheme 1b). The latter is consistent with the expected ability of the *p*-methoxy substituent in **1a** to stabilize the acid chloride functionality.

Much as with olefin metathesis or other exchange reactions, this palladium-catalyzed equilibrium exchange of Ar−X functional groups can, in principle, be directed toward product formation by modification of the reaction parameters, such as the steric/electronic properties in the reagents. One approach to favor exchange is with *ortho*-substituted acid chlorides, which leads to the favored formation of *p*-methoxybenzoyl chloride (e.g., **3a**,**b**, Scheme 2 and Table S3). This reaction is presumably driven by the slow oxidative addition of the sterically encumbered aryl iodide byproduct to palladium. Even more dramatic influences can be attained by electronic effects, where strong electron withdrawing units such as *p*-COCl (**3e**) and *p*-

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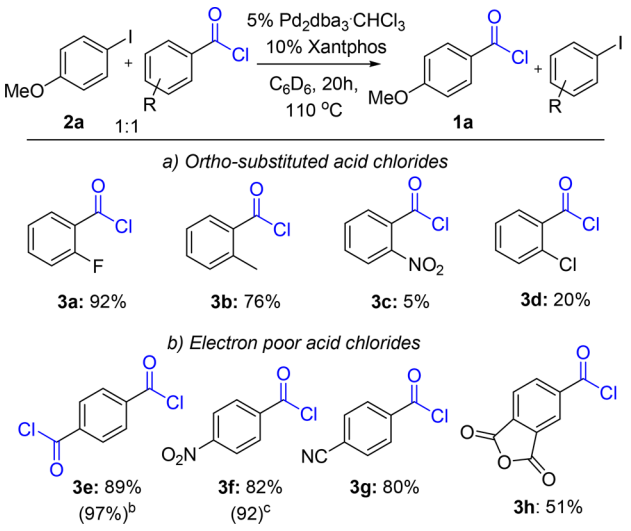
Scheme 2. Influence of Acid Chloride on Equilibrium[a]



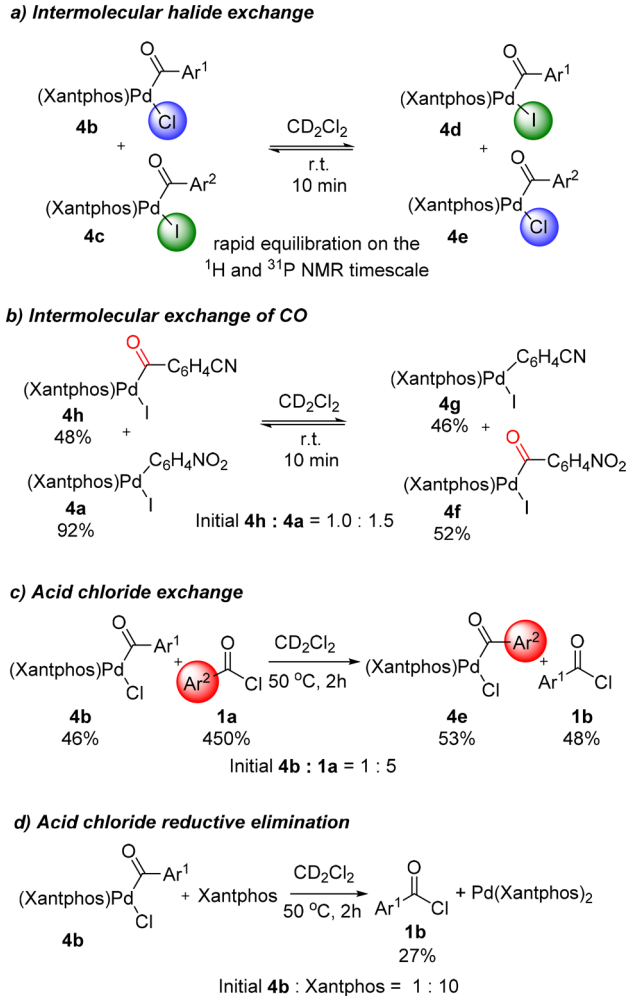
[a] *p*-MeOC$_6$H$_4$I (9 mg, 38 μmol), ArCOCl (38 μmol), Pd$_2$dba$_3$·CHCl$_3$ (2 mg, 1.9 μmol), Xantphos (2 mg, 3.8 μmol), 0.75 mL C$_6$D$_6$, 110 °C, 20 h, NMR yield. [b] 56 μmol of acid chloride. [c] 56 μmol of aryl iodide.

NO$_2$ (**3f**) on the acid chloride can drive the exchange to form **1a** in high yield. These transformations can be made nearly quantitative with a slight excess of either the aryl iodide or acid chloride. These latter acid chlorides are attractive as reagents: *p*-nitrobenzoyl chloride is a commonly employed chromophoric labeling reagent,[35] while terephthaloyl chloride is a high-volume monomer in polyamide synthesis. They therefore represent broadly available and inexpensive sources of the acid chloride functionality to incorporate into products by exchange.

The use of electron deficient acid chlorides offers a broadly applicable method to convert an array of aryl iodides to acid chlorides. In order to avoid challenges with catalyst initiation, the air stable (Xantphos)Pd(4-C$_6$H$_4$NO$_2$)(I) **4a** was employed as catalyst, which leads to clean exchange at 100 °C within 10 h (Table S4).[36−39] As shown in Table 1, the use of *p*-nitrobenzoyl chloride with an excess of aryl iodide allows the conversion of a range of electron neutral or electron rich aryl iodides to acid chlorides **1a−c,l** in good yield (Method I). In each of these, we observe the formation of aryl iodide as the main byproduct. This transformation can also allow the transfer acid chloride to electron deficient aryl iodides (**1d−k**). The latter are presumably driven by the strong electron withdrawing nature of the *p*-nitro unit in **3f**. The reaction shows good functional group compatibility and can be performed with various halide, aldehyde, ether, ester, or nitrile aromatics. Heteroaryl iodides are also viable reagents, with examples including indole, dioxolane, dioxole, and thiophenes (**1t−x**). However, sterically encumbered *ortho*-substituted aryl iodides are less reactive (**1q,r**), and vinyl iodides do not participate in the equilibrium under these conditions. The aryl iodide can also be used as the limiting reagent in concert with terephthaloyl chloride (Method 2). Of note, this leads to improved yields in cases where the aryl iodide contains a potentially coordinating functionality (e.g., **1o−p,w−x**). Coupling this transformation to subsequently react with nucleophiles can provide a platform to generate a diverse range of acylated products from aryl iodides via exchange (Table S5).

We have performed preliminary mechanistic experiments to probe how this palladium catalyzed Ar−X σ-bond exchange

Scheme 3. Mechanism Studies on Ar−X Exchange (Ar^1 = 4-C$_6$H$_4$Me; Ar^2 = 4-C$_6$H$_4$OMe)



proceeds. Xantphos/Pd-aryl and -aroyl complexes **4** can be generated via oxidative addition reactions (see SI for details). The combination of palladium-chloride and -iodide complexes **4b** and **4c** results in the near immediate equilibration of the halide ligands between palladium centers to form a time average of products on the ^{1}H and ^{31}P NMR time scale (Scheme 3a). Similarly, the reaction of palladium complexes **4h** and **4a** leads to the exchange of carbon monoxide within minutes at ambient temperature to form four separate complexes (Scheme 3b), demonstrating that CO deinsertion and exchange between palladiums is also dynamic. While these results suggest the bimolecular exchange steps in Scheme 1 are viable, a single palladium cycle involving the oxidative addition of Ar−X to Pd(II) cannot be ruled out as a possibility. In order to probe the viability of acid chloride reductive elimination from **4**, a second acid chloride was added to complex **4b**, which results in the exchange of acyl fragments at 50 °C (Scheme 3c). Similarly, the addition of excess Xantphos to **4b** to trap Pd(0) as (Xantphos)$_2$Pd also generates acid chloride under similar conditions (Scheme 3d), supporting the viability of a Pd(0/II) cycle. Preliminary kinetic analysis of the catalytic metathesis reaction shows a second order rate dependence of palladium catalyst concentration (Figure S1), which is also suggestive of the role of two (Xantphos)Pd fragments in the exchange. There is a first order rate dependence on aryl iodide concentration, and an

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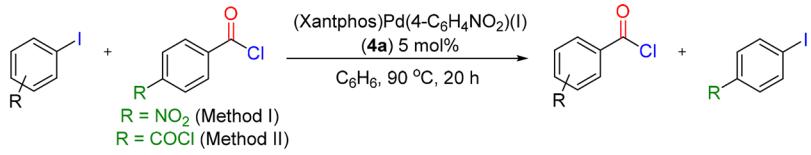
Table 1. Palladium-Catalyzed Acid Chloride Synthesis via Metathesis[a]



1a I: 95% II: 97%[c]	**1b** I: 94% II: 92%[c]	**1c** I: 80% II: 73%	**1d** I: 82%[b] II: 65%	**1e** I: 82%[b] II: 76%	**1f** I: 94%[b] II: 80%[c]
1g I: 63%[b] II: 90%	**1h** I: 91%[b] II: 87%	**1i** I: 93%[b] II: 92%[c]	**1j** I: 93%[b] II: 92%[c]	**1k** I: 95%[b] II: 81%	**1l** I: 91%[b] II: 70%
1m I: 91%[b] II: 83%[c]	**1n** I: 93%[b] II: 90%[c]	**1o** I: 62%[b] II: 90%[c]	**1p** I: 63%[b] II: 84%[c]	**1q** I: 68%[b] II: 53%[c]	**1r** I: 71%[b] II: 63%[c]
1s I: 95%[b] II: 89%[c]	**1t** I: 85%[b] II: 70%	**1u** I: 90% II: 91%[c]	**1v** I: 92% II: 96%[c]	**1w** I: 52%[d] II: 92%[c]	**1x** I: 63%[d] II: 90%

[a]Method I: aryl iodide (0.45 mmol), 4-nitro-benzoyl chloride (56 mg, 0.30 mmol), **4a** (14 mg, 15 μmol), 6 mL of C_6H_6, 90 °C, 20 h, isolated as an amide (see SI). Method II: aryl iodide (38 μmol), terephthaloyl chloride (11 mg, 56 μmol), **4a** (1.8 mg, 1.9 μmol), NMR yield. [b]0.90 mmol of ArI. [c]110 °C. [d]In addition to unreacted thiophenyl iodide, we observe 10−15% of PhCOCl and PhI arising from aryl exchange with the ligand (ref 36).

inverse first influence of acid chloride concentration (Figures S2 and S3). Together these imply that elimination of acid chloride from **IV** for aryl iodide oxidative addition also contributes to the rate determining step.

Overall, while there are several pathways possible for this reaction, the data is consistent with a mechanism similar to that in Figure 1e. In this, the Xantphos/Pd(0) catalyst undergoes reversible oxidative addition of both aryl iodide and acid chloride to generate the corresponding palladium-aryl (**I**) and−acyl complexes (**II**). While both are favored steps, acid chloride oxidative addition appears more rapid, and aryl iodide concentration can favor the competitive buildup of **I**, which can undergo exchange of CO and halide, followed by dynamic reductive elimination. The large, bidentate Xantphos ligand presumably lowers the barrier to this reductive elimination by both steric strain in **IV** and stabilization of Pd(0),[40] and build-up from this new acid chloride and aryl iodide products.

In conclusion, we have described above what is to our knowledge the first example of the metathesis of Ar−X σ-bonded functionalities. This proceeds via the reversible Ar−X oxidative addition/reductive elimination on palladium with the large bite angle Xantphos ligand and offers a platform to synthesize acid chlorides from aryl iodides without carbon monoxide or the use of caustic reagents or intermediates and, instead, from simply other inexpensive and broadly available acid chlorides. The approach of using palladium catalysis to achieve exchange of σ-bonds opens the potential to develop mild methods to form various functionalized aromatics from stable Ar−X reagents. Studies directed toward exploiting the latter are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b06605.

Experimental procedures and compound characterization (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Biffis, A.; Centomo, P.; Del Zotto, A.; Zecca, M. *Chem. Rev.* **2018**, *118*, 2249−2295.
(2) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062−5085.
(3) Molnár, A. R. D. *Palladium-Catalyzed Coupling Reactions: Practical Aspects and Future Developments*; Wiley-VCH: Weinheim, Germany, 2013.
(4) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 1232−1233.
(5) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 13944−13945.
(6) Petrone, D. A.; Ye, J.; Lautens, M. *Chem. Rev.* **2016**, *116*, 8003−8104.
(7) Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14844−14845.
(8) Shen, X.; Hyde, A. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14076−14078.
(9) Newman, S. G.; Lautens, M. *J. Am. Chem. Soc.* **2010**, *132*, 11416−11417.
(10) Newman, S. G.; Howell, J. K.; Nicolaus, N.; Lautens, M. *J. Am. Chem. Soc.* **2011**, *133*, 14916−14919.
(11) Liu, H.; Li, C.; Qiu, D.; Tong, X. *J. Am. Chem. Soc.* **2011**, *133*, 6187−6193.
(12) Sather, A. C.; Buchwald, S. L. *Acc. Chem. Res.* **2016**, *49*, 2146−2157.
(13) Ye, Y.; Takada, T.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2016**, *55*, 15559−15563.
(14) Petrone, D. A.; Franzoni, I.; Ye, J.; Rodríguez, J. F.; Poblador-Bahamonde, A. I.; Lautens, M. *J. Am. Chem. Soc.* **2017**, *139*, 3546−3557.
(15) Sperger, T.; Le, C. M.; Lautens, M.; Schoenebeck, F. *Chem. Sci.* **2017**, *8*, 2914−2922.
(16) Quesnel, J. S.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2013**, *135*, 16841−16844.
(17) Quesnel, J. S.; Kayser, L. V.; Fabrikant, A.; Arndtsen, B. A. *Chem. - Eur. J.* **2015**, *21*, 9550−9555.
(18) Tjutrins, J.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2015**, *137*, 12050−12054.
(19) Garrison Kinney, R.; Tjutrins, J.; Torres, G. M.; Liu, N. J.; Kulkarni, O.; Arndtsen, B. A. *Nat. Chem.* **2017**, *10*, 193.
(20) Quesnel, J. S.; Moncho, S.; Ylijoki, K. E. O.; Torres, G. M.; Brothers, E. N.; Bengali, A. A.; Arndtsen, B. A. *Chem. - Eur. J.* **2016**, *22*, 15107−15118.
(21) Gautam, P.; Bhanage, B. M. *Catal. Sci. Technol.* **2015**, *5*, 4663−4702.
(22) Więckowska, A.; Fransson, R.; Odell, L. R.; Larhed, M. *J. Org. Chem.* **2011**, *76*, 978−981.
(23) Lescot, C.; Nielsen, D. U.; Makarov, I. S.; Lindhardt, A. T.; Daasbjerg, K.; Skrydstrup, T. *J. Am. Chem. Soc.* **2014**, *136*, 6142−6147.
(24) Natte, K.; Dumrath, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 10090−10094.
(25) Ueda, T.; Konishi, H.; Manabe, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 8611−8615.
(26) Friis, S. D.; Lindhardt, A. T.; Skrydstrup, T. *Acc. Chem. Res.* **2016**, *49*, 594−605.
(27) Qi, X.; Li, C.-L.; Wu, X.-F. *Chem. - Eur. J.* **2016**, *22*, 5835−5838.
(28) Malapit, C. A.; Ichiishi, N.; Sanford, M. S. *Org. Lett.* **2017**, *19*, 4142−4145.
(29) Keaveney, S. T.; Schoenebeck, F. *Angew. Chem., Int. Ed.* **2018**, *57*, 4073−4077.
(30) Fang, X.; Cacherat, B.; Morandi, B. *Nat. Chem.* **2017**, *9*, 1105.
(31) Yu, P.; Morandi, B. *Angew. Chem., Int. Ed.* **2017**, *56*, 15693−15697.
(32) Bhawal, B. N.; Morandi, B. *ACS Catal.* **2016**, *6*, 7528−7535.
(33) Lian, Z.; Bhawal, B. N.; Yu, P.; Morandi, B. *Science* **2017**, *356*, 1059−1063.
(34) 4-Chloroanisole and 4-chlorotoluene are observed in 2% and 5%, respectively, along with phosphine decomposition. See SI for details.
(35) Tobiszewski, M.; Namiesnik, J.; Pena-Pereira, F. *Green Chem.* **2017**, *19*, 5911−5922.
(36) There is imperfect mass balance arising from the aryl exchange of aromatic units on the Xantphos ligand itself at high temperatures, which leads to ca. 5−10% phenyl iodide and phenyl acid chloride formation.[37−39]
(37) Segelstein, B. E.; Butler, T. W.; Chenard, B. L. *J. Org. Chem.* **1995**, *60*, 12−13.
(38) Goodson, F. E.; Wallow, T. I.; Novak, B. M. *J. Am. Chem. Soc.* **1997**, *119*, 12441−12453.
(39) Klingensmith, L. M.; Strieter, E. R.; Barder, T. E.; Buchwald, S. L. *Organometallics* **2006**, *25*, 82−91.
(40) van Leeuwen, P. W. N. M.; Kamer, P. C. J. *Catal. Sci. Technol.* **2018**, *8*, 26−113.

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