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Synthesis of Asymmetrically Substituted Terpyridines by Palladium-Catalyzed Direct C–H Arylation of Pyridine *N*-Oxides

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Dedicated to Professor Hans J. Reich on the occasion of his 70th birthday

Abstract: The synthesis of asymmetrically substituted 2,2′:6′,2″-terpyridines is reported. First, palladium-catalyzed C–H arylation of pyridine *N*-oxides with substituted bromopyridines gave 2,2′-bipyridine *N*-oxides, which were further arylated in a second step to form 2,2′:6′,2″-terpyridine *N*-oxides. Yields of up to 77% were obtained with *N*-oxides bearing an electron-withdrawing ethoxycarbonyl substituent in the 4-position. $Pd(OAc)_2$ with either $P(tBu)_3$ or $P(o\text{-tolyl})_3$ was used as the catalyst. Cyclometalated complexes derived from $Pd(OAc)_2$ and these phosphines were also effective. K_3PO_4 as the base gave better results than K_2CO_3. Subsequent deoxygenation with H_2 and Pd/C as the catalyst gave the asymmetrically substituted 2,2′:6′,2″-terpyridines in near quantitative yield. This reaction sequence significantly reduces the number of steps required in comparison with known cross-coupling methods and therefore allows convenient and scalable access to substituted terpyridines.

Keywords: C–H activation · cross-coupling · heterocycles · palladium · terpyridines

Introduction

Terpyridines[1] have been widely used as chelating ligands for different metal ions, and their complexes[2] have been employed as catalysts,[3] analytical probes,[4] photosensitizers in solar cells,[5] and in artificial photosystems,[6] biomedical applications,[7] and as building blocks for supramolecular architectures.[8,9] Despite their broad utility, relatively few synthetic routes to terpyridines have been described, and most of the discovered routes apply to symmetrically substituted derivatives.[1,10] Apart from by modification of an already existing terpyridine, they can be prepared either by de novo heterocycle synthesis[11] or by cross-coupling[12] of suitably functionalized pyridine building blocks. The synthesis of asymmetrically substituted terpyridines is more challenging and fewer examples have been described.

Although numerous terpyridines have been prepared by the approaches outlined above, all three synthetic strategies are often hampered by inherent limitations with regard to the functionalization pattern and by the need to prepare starting materials with the desired substituents. Particularly, pyridyl organometallic compounds, which are used in cross-coupling reactions, require additional synthetic steps and are frequently unstable.[13] Such multi-step procedures are time consuming, often result in low overall yields, and, consequently, complicate variation and optimization of terpyridine structures for practical applications. Therefore, an efficient and simple synthetic approach to arbitrarily substituted terpyridines would be desirable. To reduce the number of synthetic steps, transition-metal-catalyzed C–H activation reactions offer a powerful route for C–C bond formation as they do not require a functional group at the coupling site.[14] Pyridine *N*-oxides[15] have been established as easily available and stable substrates for direct arylation and related cross-coupling reactions.[16,17] Recently, we reported the preparation of asymmetrically substituted bipyridines by palladium-catalyzed direct arylation of pyridine *N*-oxides with halopyridines.[18] During the course of these studies we observed the formation of symmetrical terpyridine *N*-oxides as side products arising from a second arylation of the initial bipyridine *N*-oxide products. Therefore, we sought to extend this method to the synthesis of substituted terpyridines.

Results and Discussion

Optimization: Starting from our reported reaction conditions, we investigated the double arylation of pyridine *N*-oxide **1a** (Table 1). Whereas previously an excess of *N*-oxide was used, we now employed pyridine *N*-oxide **1a** as the limiting reagent. This substantial change makes full conversion

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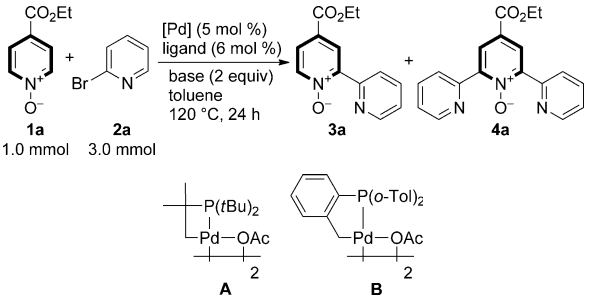
Table 1. Optimization of the reaction conditions.



Entry	[Pd]	Ligand	Base	**3a** [%][a]	**4a** [%][a]
1	$Pd(OAc)_2$	$P(tBu)_3$	K_2CO_3	49	19
2	$Pd(CF_3CO_2)_2$	$P(tBu)_3$	K_2CO_3	33	6
3	$Pd(OAc)_2$	$P(tBu)_2Me$	K_2CO_3	11	0
4	$Pd(OAc)_2$	DavePhos	K_2CO_3	2	2
5	$Pd(OAc)_2$	XPhos	K_2CO_3	19	7
6	$Pd(OAc)_2$	(*t*Bu)XPhos	K_3PO_4	11	6
7	$Pd(OAc)_2$	RuPhos	K_2CO_3	25	7
8	$Pd(OAc)_2$	BrettPhos	K_2CO_3	6	2
9	$Pd(OAc)_2$	XantPhos	K_2CO_3	6	2
10	$Pd(OAc)_2$	$P(o\text{-}Tol)_3$	K_2CO_3	39	10
11	$Pd(OAc)_2$	$P(tBu)_3$	K_3PO_4	47	33
12	$Pd(OAc)_2$	$P(o\text{-}Tol)_3$	K_3PO_4	52	28
13	**A**	–	K_3PO_4	44	35
14[b]	**A** + $[Pd(P(tBu)_3)_2]$	–	K_3PO_4	49	35
15[b]	**A** + $[Pd(PPh_3)_4]$	–	K_3PO_4	50	21
16	**B**	–	K_3PO_4	54	29

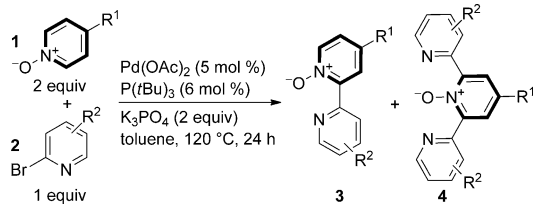
[a] Yields of the isolated products after column chromatography, based on the amount of **1a** used in the reaction. [b] **A** (2.0 mol%) and Pd^0-complex (1.0 mol%) were used. DavePhos = 2-dicyclohexylphosphino-2′-(N,N-dimethyamino)biphenyl; XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl; RuPhos = 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl; BrettPhos = 2-(dicyclohexylphosphino)-3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl; XantPhos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; *o*-Tol = *ortho*-tolyl.

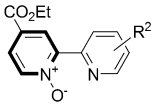
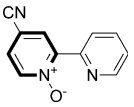
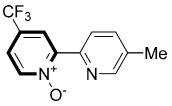
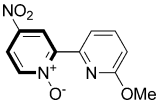
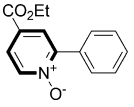
of the *N*-oxide, and thus high yields of the arylated product, considerably more challenging because the rate of the reaction is first-order with respect to *N*-oxide concentration and the C–H activation step is rate-limiting.[16q] Recently, it was shown by Hartwig and co-workers that this C–H bond cleavage can be brought about by use of a cyclometalated palladium complex (see Mechanistic considerations section below).[16t] Although all examined phosphine ligands resulted in some product formation, consistent with the mechanistic proposal, $P(tBu)_3$ and $P(o\text{-}Tol)_3$, both of which are known to form cyclometalated complexes with palladium,[19] gave the highest yields of terpyridine *N*-oxide. Indeed, when we used the cyclometalated complexes **A** and **B** as the catalysts, comparable results to the analogous experiments in which these catalysts were formed in situ were obtained (compare Table 1, entries 13 and 16 with 11 and 12). The combination of cyclometalated complex **A** and a Pd^0 complex worked equally well, but did not provide any further advantage (Table 1, entries 14 and 15). It should be noted, however, that other ligands, which are unlikely to undergo cyclometalation, were found to be effective in related arylation reactions of pyridine *N*-oxides.[16j,m,n,o]

K_3PO_4 as the base resulted in better yields than K_2CO_3. Among the solvents tested, toluene, DMF, *N*-methylpyrrolidone (NMP), and THF gave similar results (see the Supporting Information, Table S1). We chose toluene as the solvent because of its suitably high boiling point and nonpolar nature, which makes separation of the product mixture by column chromatography possible, without additional workup steps for removal of the solvent or the base. THF as the solvent seemed to give slightly higher turnover numbers, but its use was abandoned because superheating the solvent under pressure in a closed vessel was considered inconvenient for routine synthetic applications.

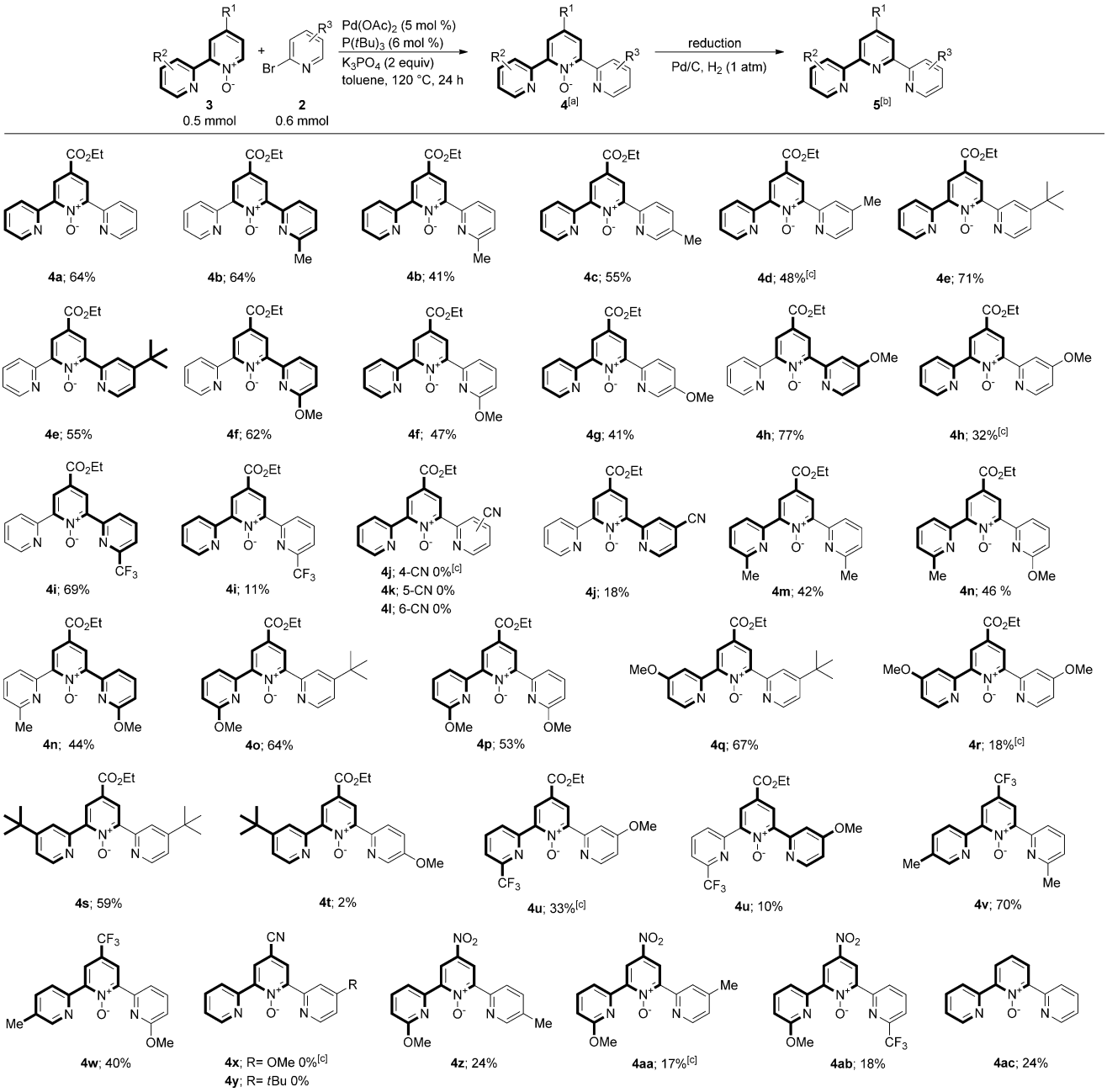
Asymmetrical terpyridines: The bipyridine *N*-oxides **3** used as starting materials for subsequent investigations were prepared, as previously reported, by direct arylation of pyridine *N*-oxides **1** (Table 2).[18] This reaction could be successfully scaled up to 100 mmol. With reasonably large amounts of bipyridine *N*-oxides **3** in hand, we applied the optimized conditions to the synthesis of asymmetrically substituted terpyridine *N*-oxides **4** (Scheme 1). The best results were achieved by starting from bipyridine *N*-oxides with an ethoxycarbonyl substituent in the 4-position, and terpyridine *N*-oxides **4a**–

Table 2. Preparation of bipyridine *N*-oxides.



Entry	Product		Yield [%][a]	Amount of **2** [mmol]
1[b]		**3a** R^2 = H	61 (**4a** 18)	100
2		**3p** R^2 = 6-OMe	66 (**4p** 13)	10
3		**3ai** R^2 = 6-CF_3	46 (**4ai** 9)	2.5
4		**3s** R^2 = 4-*t*Bu	57	9
5[c]		**3r** R^2 = 4-OMe	54	10
6[c]		**3aj** R^2 = 4-CN	31	4
7		**3ae**	51 (**4ae** 20)	4
8		**3ak**	68	4
9		**3al**	57	4
10		**6d**	67 (**9d** 18)	10

[a] Yields of the isolated products after column chromatography, based on the amount of halopyridine used in the reaction. [b] $Pd(OAc)_2$ (2.0 mol%) and $P(tBu)_3$ (2.4 mol%) were used. The reaction time was 48 h. [c] The corresponding chloropyridine, instead of bromopyridine **2**, was used.



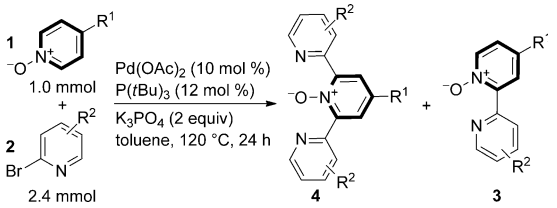
Scheme 1. The scope of the arylation of bipyridine *N*-oxides and the reduction of the products to the corresponding terpyridines. [a] Yields of the isolated products after column chromatography, based on the amount of **3** used in the reaction. [b] For yields of the deoxygenated products **5**, see Figure 2. [c] The corresponding chloropyridine, instead of the bromopyridine, was used.

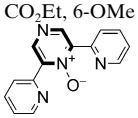
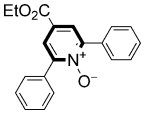
u were obtained in up to 77% yield. However, substrates containing a cyano substituent gave no, or only a little, product regardless of the position of the cyano group. The most effective arylating agents were 2-bromopyridine and 2-bromo-4-(*tert*-butyl)pyridine. In several examples, the yields depended on the order of the introduction of the pyridyl rings (Scheme 1, **4b**, **4e**, **4f**, **4h–j**, **4n**, and **4u**).

Although direct arylation of a 4-CF_3-bipyridine *N*-oxide gave the terpyridine *N*-oxides in yields comparable to the ester-substituted bipyridine *N*-oxides (Scheme 1, **4v**, **4w**), 4-NO_2-bipyridine *N*-oxides resulted in much lower yields (Scheme 1, **4z**, **4aa**, **4ab**), and 4-CN-bipyridine *N*-oxide **3ae** was completely unreactive and the starting material was recovered (Scheme 1, **4x**, **4y**). This disappointing reactivity of CN- or NO_2-substituted bipyridine *N*-oxides is surprising considering that the corresponding pyridine *N*-oxides underwent satisfactory coupling with bromopyridine.[18,20]

Symmetrical terpyridines: The synthesis of a variety of symmetrical terpyridine *N*-oxides by one-pot direct arylation of pyridine *N*-oxides was also investigated (Table 3). Such symmetrical terpyridine *N*-oxides had already been observed as

Table 3. Double arylation of pyridine *N*-oxides.



Entry	Substituents R^1, R^2	Yield of **4** [%][a]	Yield of **3** [%][a]
1	CO_2Et, H	**4a** 40	**3a** 44
2	CF_3, H	**4ad** 47	**3ad** 37
3	CN, H	**4ae** 12	**3ae** 55
4	NO_2, H	**4af** 3	**3af** 22
5	H, H	**4ac** 26	**3ac** 50
6	CO_2Et, 4-*t*Bu	**4s** 9	**3s** 50
7	CO_2Et, 6-Me	**4m** 9	**3m** 39
8[b]	CO_2Et, 6-Me	**4m**10	**3m** 43
9	CO_2Et, 6-OMe	**4p** 23	**3p** 53
10[b]	CO_2Et, 6-OMe	**4p** 22	**3p** 45
11		**7** 24	**6**[c] 29
12		**9d** 30	**8d**[c] 45

[a] Yields of the isolated products after column chromatography, based on the amount of **1** used in the reaction. [b] $Pd(OAc)_2$ (5 mol%) and P(*t*Bu)$_3$ (6 mol%) were used. [c] Refers to the corresponding monoarylated product.

byproducts in the synthesis of bipyridine *N*-oxides, as these still contain a C–H bond available for activation. In the one-pot reaction with pyridine *N*-oxide **1** as the limiting reagent, terpyridine *N*-oxides were obtained in low to moderate yields. The main product was usually the bipyridine *N*-oxide **3**, except for **4a** and **4ad**, which were obtained in relatively good yields (Table 3, entries 1 and 2). In the arylation of unsubstituted pyridine *N*-oxide, a 26% yield of **4ac** was isolated (Table 3, entry 5). These yields, however, cannot be directly compared with the yields previously reported for the preparation of bipyridine *N*-oxides because they are based on the use of *N*-oxide as the limiting reagent, whereas the previous experiments were based on the aryl halide as the limiting reagent and use of an excess of pyridine *N*-oxide as the starting material. Thus, despite the relatively low yield, the one-step double arylation might still be the most economic way to access a specific, symmetrically substituted, terpyridine.

Other teraryl compounds: We briefly investigated the formation of related teraryl compounds by direct arylation of pyridine *N*-oxides (Figure 1). Thus, 3- and 4-bromopyridines were found to be significantly less reactive than 2-bromopyridine (Figure 1, **9a** and **9b**), and 2-bromopyrimidine and 2-bromoquinoline did not give any cross-coupling product (Figure 1, **9c** and **9f**). The double arylation of bipyridine

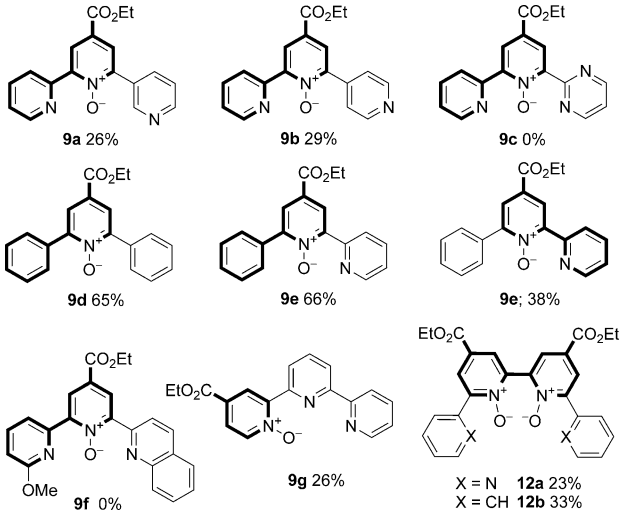


Figure 1. The arylation of related *N*-oxides. Yields of the isolated products, based on the amount of the pyridine *N*-oxide derivative used in the reaction. For the reaction conditions, see Scheme 1. For yields of the deoxygenated products, see Figure 2.

N,*N*′-dioxide **11** with either bromopyridine or bromobenzene gave the corresponding quateraryls **12** in modest yields.

Deoxygenation: The reduction of pyridine *N*-oxides to the corresponding pyridines is a reaction with considerable precedent.[16d,18,21] For this final step, we found reduction with hydrogen and palladium on charcoal as the catalyst to be the most convenient method, which generally gave the corresponding terpyridines **5** in high yields (Figure 2).

Mechanistic considerations: The kinetics of the palladium-catalyzed arylation of pyridine *N*-oxides has been investigated in some detail and two different mechanisms have been proposed.[16p–t] Fagnou's group experimentally found that the arylation of 4-nitropyridine *N*-oxide with 3,5-bromobenzene exhibits first-order behavior in *N*-oxide, zero-order behavior in aryl bromide, and half-order behavior in the palladium catalyst.[16q] They proposed a catalytic cycle in which fast oxidative addition of the aryl halide to a palladium(0) complex **C** leads to a palladium(II) aryl intermediate **D** (Scheme 2). After exchange of the halide ion for an acetate ion, aryl palladium complex **E** induces the rate-limiting C–H activation of the pyridine *N*-oxide, resulting in a bisaryl palladium complex **F**, which undergoes fast reductive elimination of the coupling product, regenerating the palladium(0) catalyst.

Hartwig and co-workers found that the isolated proposed aryl palladium intermediate **E** reacts with pyridine *N*-oxide only after an induction period and is therefore not kinetically competent for activating the C–H bond.[16t] However, reaction of $Pd(OAc)_2$ and P(*t*Bu)$_3$ rapidly forms cyclometaled complex **A**, which was found to react with pyridine *N*-oxide without an induction period. They proposed a revised mechanism involving two interlocking catalytic cycles (Scheme 3). Dimeric cyclometalated complex **A** is in equilibrium with an undetected monomeric species **A′**, which induces C–H acti-

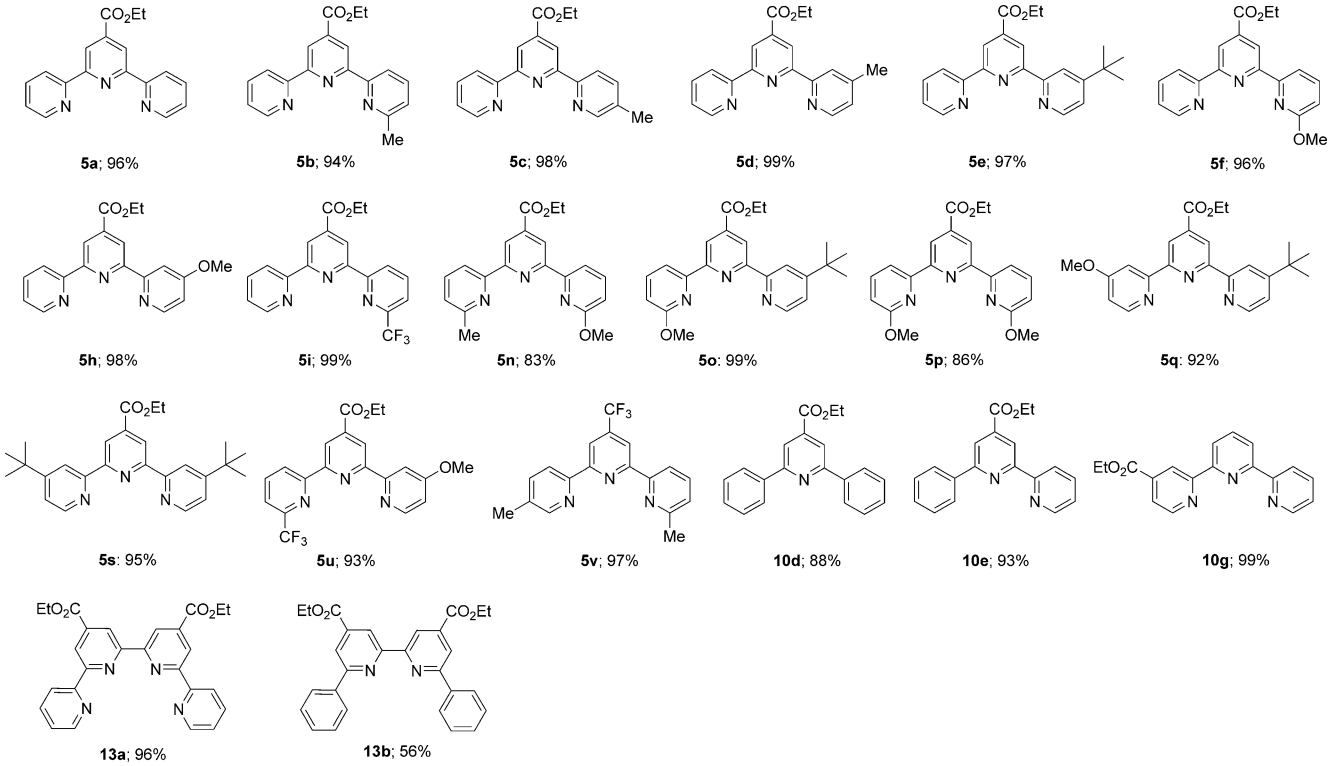
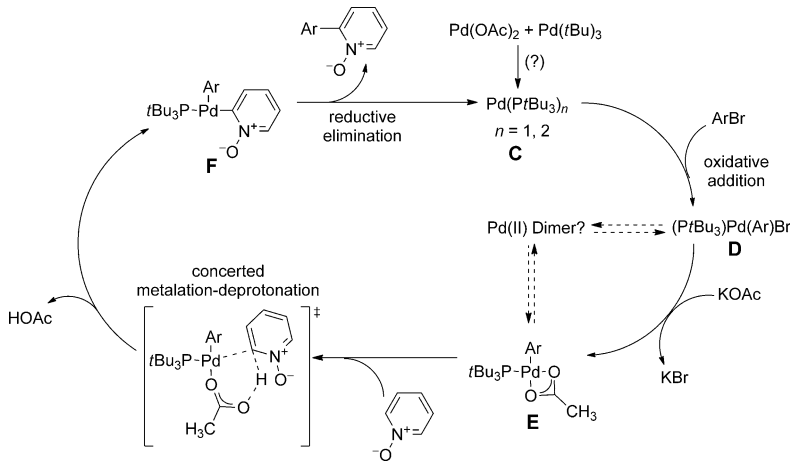


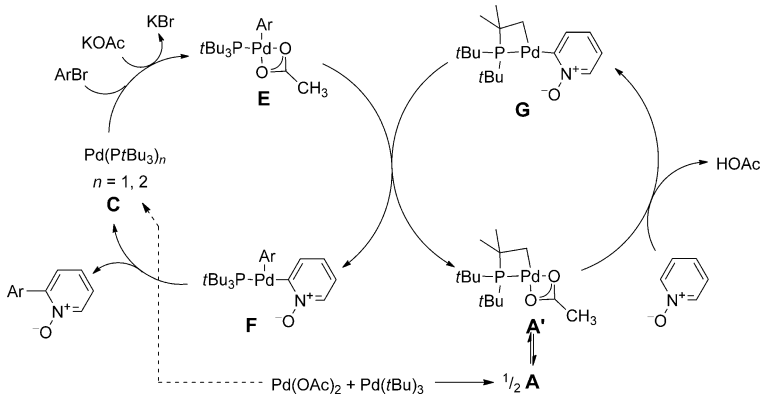
Figure 2. Yields of the deoxygenated *N*-oxides. Reaction conditions: Pd/C (10 mol%), H_2 (1 atm), ethanol, RT.



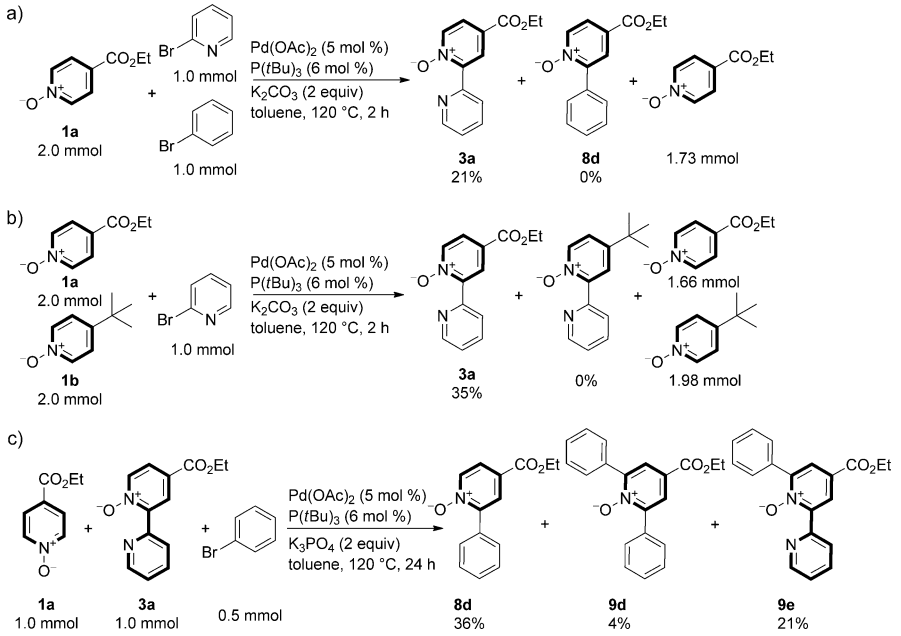
Scheme 2. The catalytic cycle for the direct arylation of pyridine *N*-oxides proposed by Fagnou et al.[16q]

We initially conducted competition experiments to probe whether changing the starting material from bromobenzene to bromopyridine would cause a significant change in the reaction pathway. When pyridine *N*-oxide **1a** was subjected to reaction with an equimolar mixture of bromobenzene and bromopyridine, only incorporation of the pyridine ring into the product was observed, when the reaction was stopped before going to completion (Scheme 4a). This result was expected since the more electrophilic bromopyridine undergoes faster oxidative addition than bromobenzene and, therefore, the pyridyl ring should be incorporated into the product faster, irrespective of the order of the elementary steps. When an equimolar mixture of pyridine *N*-oxides **1a** and **1b** was reacted with bromopyridine, only the coupling product **3a**, derived from **1a**, was observed (Scheme 4b). This result is in agreement with the positive Hammett correlation previously observed for the reaction rate of substituted pyridine *N*-oxides,[16q] and also conforms with our own observation that *N*-oxides with electron-withdrawing groups led to higher yields than *N*-oxides with electron-donating substituents.[18] To

vation of the pyridine *N*-oxide, giving intermediate **G**. At the same time, a second aryl palladium complex **E** is formed by oxidative addition of the aryl bromide to palladium(0) complex **C**. These two aryl palladium complexes, **G** and **E**, react with each other, probably in a transmetalation reaction, transferring the pyridine *N*-oxide ring to **E**, which regenerates the cyclometalated complex **A**. The concomitantly formed bisaryl palladium complex **F** undergoes fast reductive elimination to form the biaryl product and regenerate the palladium(0) catalyst **C**.



Scheme 3. The cooperative catalysis mechanism for the direct arylation of pyridine *N*-oxides proposed by Hartwig et al.[16t]



Scheme 4. Competition experiments a) between bromopyridine and bromobenzene, b) between pyridine *N*-oxides **1a** and **1b**, and c) between pyridine *N*-oxide **1a** and bipyridine *N*-oxide **3a**.

probe the influence of the 2-pyridyl substituent of bipyridine *N*-oxides on the reactivity, an equimolar mixture of pyridine *N*-oxide **1a** and bipyridine *N*-oxide **3a** was subjected to direct arylation with bromobenzene (Scheme 4c). Products **8d** and **9d**, both arising from arylation of pyridine *N*-oxide **1a**, and product **9e**, arising from bipyridine *N*-oxide **3a**, were formed in a 2:1 ratio. This result indicates that pyridine *N*-oxides and bipyridine *N*-oxides exhibit the same reactivity towards C–H activation, taking into account the number of potential coupling sites. We had previously drawn this same conclusion from the product ratios of bipyridine *N*-oxides and terpyridine *N*-oxides observed in the arylation of pyridine *N*-oxides.[18]

Additionally, we wanted to compare the reaction rate of the coupling of pyridine *N*-oxide with either bromobenzene or with bromopyridine because the pyridine nitrogen atom might coordinate to the palladium and, therefore, decrease the effective catalyst concentration. If the bromopyridine starting material, as well as the bipyridine *N*-oxide product, inhibited the reaction, we would expect the reaction with bromopyridine to be slower than the corresponding reaction with bromobenzene. If only the bipyridine *N*-oxide product, and not the bromopyridine starting material, inhibited the reaction, we would expect the reaction with bromopyridine to slow down as the bipyridine *N*-oxide product is formed. We performed the arylation of pyridine *N*-oxide **1a** with bromopyridine and bromobenzene in side-by-side reactions, monitoring the consumption of aryl halide by GC-FID (Figure 3). Apart from in the first few minutes, both reactions exhibit similar profiles. Independent of the nature of the aryl bromide, the starting material is consumed after approximately 220 min. A nearly linear decay of the concentration of aryl bromide was observed, as expected because of the known zero-order behavior of the reaction. This result clearly shows that the rate-determining step, the C–H activation,[16q] is not inhibited by either the bromopyridine substrate or by the *N*-

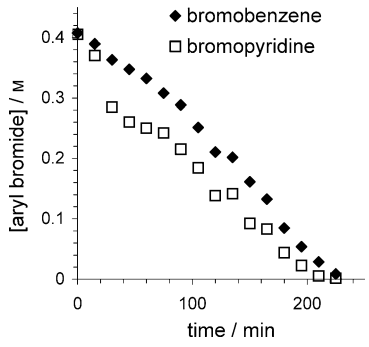


Figure 3. Comparison of the reaction of pyridine *N*-oxide **1a** with bromopyridine (□) or bromobenzene (◆). Reaction conditions: Pyridine *N*-oxide (2 equiv), aryl bromide (1 equiv), K_3PO_4 (2 equiv), $Pd(OAc)_2$ (5 mol%), $PtBu_3$ (6 mol%), toluene, 120°C. The consumption of aryl halide was monitored by GC-FID, quantified against *n*-decane as the internal standard.

oxide product. Furthermore, this result might be interpreted as an indication that aryl palladium complex **E** is not taking part in the C–H activating step because in this case one would expect a dependence of the rate of the reaction on the nature of the aryl ligand. Although our observations are consistent with the mechanism proposed by Hartwig and co-workers for the direct arylation of pyridine *N*-oxide,[16t] they do not explain the observed limitations of the reaction with regard to the aryl halide or the *N*-oxide substrate.

Conclusion

We successfully extended the palladium-catalyzed direct arylation of pyridine *N*-oxides to the synthesis of asymmetrically substituted terpyridines. Compared with known methods, this approach, based on C–H activation, significantly reduces the number of steps, and therefore offers rapid access to substituted terpyridines in useful yields by applying stable, readily available, and inexpensive starting materials. The best yields were obtained, when the *N*-oxide was functionalized with an electron-withdrawing ethoxycarbonyl substituent in the 4-posititon. Competition experiments and simple kinetic studies are in agreement with a cooperative catalysis mechanism proposed by Hartwig and co-workers. Future work will need to be performed to expand the substrate scope to *N*-oxides bearing electron-donating substituents and possibly provide a mechanistic understanding of the reasons for the current limitations.

Experimental Section

General procedure A: Preparation of bipyridine *N*-oxide derivatives: Pyridine *N*-oxide (2 equiv), $Pd(OAc)_2$ (5.0 mol%), and K_3PO_4 (2 equiv) were weighed into a Teflon-capped vial or a Schlenk flask. Under an argon atmosphere (glovebox), $P(tBu)_3$ (6.0 mol%) dissolved in toluene (0.5 M, based on the amount of halopyridine) was added. The halopyridine (1 equiv) was added through a syringe (if solid, the halopyridine was added in the beginning) and the reaction mixture was stirred for 15 min at RT and then for 24 h at 120 °C. After cooling to RT, the reaction mixture was directly purified by column chromatography ($d=6$ cm, $l=35$ cm SiO_2 for 10 mmol halopyridine, deactivated, acetone/hexane, 0:100–100:0 v/v in 10% increments).

General procedure B: One-pot preparation of terpyridine *N*-oxides from pyridine *N*-oxides: Pyridine *N*-oxide (1 equiv), $Pd(OAc)_2$ (10 mol%), and K_3PO_4 (2 equiv) were weighed into a Teflon-capped vial. Under an argon atmosphere (glovebox), $P(tBu)_3$ (12 mol%) dissolved in toluene (0.5 M, based on pyridine *N*-oxide) was added. The halopyridine (2.4 equiv) was added through a syringe (if solid, the halopyridine was added in the beginning) and the reaction mixture was stirred for 15 min at RT and then for 24 h at 120 °C. After cooling to RT, the reaction mixture was directly purified by column chromatography ($d=2.5$ cm, $l=25$ cm SiO_2 for 1 mmol pyridine *N*-oxide, deactivated, acetone/hexane, 0:100–100:0 v/v in 10% increments).

General procedure C: Preparation of terpyridine *N*-oxides from bipyridine *N*-oxides: Bipyridine *N*-oxide (1 equiv), $Pd(OAc)_2$ (5.0 mol%), and K_3PO_4 (2 equiv) were weighed into a Teflon-capped vial. Under an argon atmosphere (glovebox), $P(tBu)_3$ (6.0 mol%) dissolved in toluene (0.5 M, based on bipyridine *N*-oxide) was added. The halopyridine (1.2 equiv) was added through a syringe (if solid, the halopyridine was added in the beginning) and the reaction mixture was stirred for 15 min at RT and then for 24 h at 120 °C. After cooling to RT, the reaction mixture was directly purified by column chromatography ($d=2.5$ cm, $l=25$ cm SiO_2 for 0.5 mmol bipyridine *N*-oxide, deactivated, acetone/hexane, 0:100–100:0 v/v in 10% increments).

General procedure D: Preparation of quarterpyridine *N′,N″*-dioxides from bipyridine *N,N′*-dioxides: Bipyridine *N,N′*-dioxide (1 equiv), $Pd(OAc)_2$ (10 mol%), and the base (3 equiv) were weighed into a Teflon-capped vial. Under an argon atmosphere (glovebox), $P(tBu)_3$ (12 mol%) dissolved in toluene (0.5 M, based on bipyridine *N*-oxide) was added. The halopyridine (4.0 equiv) was added through a syringe (if solid, the halopyridine was added in the beginning) and the reaction mixture was stirred for 15 min at RT and then for 24 h at 120 °C. After cooling to RT, the reaction mixture was directly purified by column chromatography ($d=2.5$ cm, $l=25$ cm SiO_2 for 1 mmol bipyridine *N,N′*-dioxide, deactivated, acetone/hexane, 0:100–100:0 v/v in 10% increments).

General procedure E: Deoxygenation of pyridine *N*-oxides: The terpyridine *N*-oxide (1 equiv) was dissolved in ethanol, and Pd/C (10 wt%, 0.1 equiv) was added. The flask was evacuated and filled with argon (3× vacuum/argon), evacuated again, and H_2 (1 atm) was added from a balloon. After full conversion of the substrate was achieved, as judged by TLC, the reaction mixture was filtered over Celite and washed with ethanol (100 mL). Evaporation of the solvent gave the corresponding terpyridine.

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[1] U. S. Schubert, H. Hofmeier, G. R. Newkome, *Modern Terpyridine Chemistry* Wiley-VCH, Weinheim, **2006**.

[2] For selected reviews, see: a) L. Hammarström, O. Johansson, *Coord. Chem. Rev.* **2010**, *254*, 2546–2559; b) I. M. Dixon, E. Lebon, P. Sutra, A. Igau, *Chem. Soc. Rev.* **2009**, *38*, 1621–1634; c) K. M.-C. Wong, V. W.-W. Yam, *Acc. Chem. Res.* **2011**, *44*, 424–434.

[3] For a review, see: a) A. Winter, G. R. Newkome, U. S. Schubert, *ChemCatChem* **2011**, *3*, 1384–1406; Selected examples: b) T. Wada, H. Maki, T. Imamoto, H. Yuki, Y. Miyazato, *Chem. Commun.* **2013**, *49*, 4394–4396; c) C. M. Moore, N. K. Szymczak, *Chem. Commun.* **2013**, *49*, 400–402; d) N. Kaveevivitchai, R. Zong, H.-W. Tseng, R. Chitta, R. P. Thummel, *Inorg. Chem.* **2012**, *51*, 2930–2939; e) Z. Chen, C. Chen, D. R. Weinberg, P. Kang, J. J. Concepcion, D. P. Harrison, M. S. Brookhart, T. J. Meyer, *Chem. Commun.* **2011**, *47*, 12607–12609.

[4] a) C. Bazzicalupi, A. Bencini, S. Puccioni, B. Valtancoli, P. Gratteri, A. Garau, V. Lippolis, *Chem. Commun.* **2012**, *48*, 139–141; b) A. Wild, A. Winter, M. D. Hager, U. S. Schubert, *Chem. Commun.* **2012**, *48*, 964–966; c) Z. Huang, J. Du, J. Zhang, X.-Q. Yu, L. Pu, *Chem. Commun.* **2012**, *48*, 3412–3414.

[5] a) B. Bozic-Weber, E. C. Constable, N. Hostettler, C. E. Housecroft, R. Schmitt, E. Schonhofer, *Chem. Commun.* **2012**, *48*, 5727–5729; b) M. Kimura, J. Masuo, Y. Tohata, K. Obuchi, N. Masaki, T. N. Murakami, N. Koumura, K. Hara, A. Fukui, R. Yamanaka, S. Mori, *Chem. Eur. J.* **2013**, *19*, 1028–1034; c) E. C.-H. Kwok, M.-Y. Chan, K. M.-C. Wong, W. H. Lam, V. W.-W. Yam, *Chem. Eur. J.* **2010**, *16*, 12244–12254; d) M. K. Nazeeruddin, P. Pechy, M. Grätzel, *Chem. Commun.* **1997**, *0*, 1705–1706.

[6] a) P. D. Frischmann, K. Mahata, F. Würthner, *Chem. Soc. Rev.* **2013**, *42*, 1847–1870; b) L. Flamigni, J.-P. Collin, J.-P. Sauvage, *Acc. Chem.*

Res. **2008**, *41*, 857–871; c) D. Chao, W.-F. Fu, *Chem. Commun.* **2013**, *49*, 3872–3874.

[7] a) S. D. Cummings, *Coord. Chem. Rev.* **2009**, *253*, 1495–1516; b) I. Eryazici, C. N. Moorefield, G. R. Newkome, *Chem. Rev.* **2008**, *108*, 1834–1895; c) B. Boff, C. Gaiddon, M. Pfeffer, *Inorg. Chem.* **2013**, *52*, 2705–2715; d) A. Wild, K. Babiuch, M. Konig, A. Winter, M. D. Hager, M. Gottschaldt, A. Prokop, U. S. Schubert, *Chem. Commun.* **2012**, *48*, 6357–6359.

[8] a) A. Wild, A. Winter, F. Schlutter, U. S. Schubert, *Chem. Soc. Rev.* **2011**, *40*, 1459–1511; b) K. A. Williams, A. J. Boydston, C. W. Bielawski, *Chem. Soc. Rev.* **2007**, *36*, 729–744; c) E. C. Constable, *Chem. Soc. Rev.* **2007**, *36*, 246–253.

[9] Example for terpyridine *N*-oxides as ligand: A. J. Amoroso, M. W. Burrows, A. A. Dickinson, C. Jones, D. J. Willock, W.-T. Wong, *J. Chem. Soc. Dalton Trans.* **2001**, 225–227.

[10] a) M. Heller, U. S. Schubert, *Eur. J. Org. Chem.* **2003**, 947–961; b) R.-A. Fallahpour, *Synthesis* **2003**, 155–184.

[11] For examples of condensation methods, see: a) F. Kröhnke, *Synthesis* **1976**, 1–24; b) I. Sasaki, J. C. Daran, G. G. A. Balavoine, *Synthesis* **1999**, 815–820; c) F. Dumur, C. R. Mayer, E. Dumas, J. Marrot, F. Sécheresse, *Tetrahedron Lett.* **2007**, *48*, 4143–4146; d) F. S. Han, M. Higuchi, D. G. Kurth, *Org. Lett.* **2007**, *9*, 559–562; e) J. Dash, H.-U. Reissig, *Chem. Eur. J.* **2009**, *15*, 6811–6814; f) J. Hummel, A. Winter, A. Baumgaertel, N. Risch, U. S. Schubert, *Synlett* **2010**, 61–66; g) E. C. Constable, E. L. Dunphy, C. E. Housecroft, M. Neuburger, S. Schaffner, F. Schaper, S. R. Batten, *Dalton Trans.* **2007**, 4323–4332; h) T. R. Kelly, R. L. Lebedev, *J. Org. Chem.* **2002**, *67*, 2197–2205; i) V. Duprez, F. C. Krebs, *Tetrahedron Lett.* **2006**, *47*, 3785–3789; j) I. Eryazici, C. N. Moorefield, S. Durmus, G. R. Newkome, *J. Org. Chem.* **2006**, *71*, 1009–1014; for examples for hetero-Diels–Alder cycloadditions, see: k) A. Gehre, S. P. Stanforth, B. Tarbit, *Tetrahedron* **2009**, *65*, 1115–1118; l) J. Sauer, D. K. Heldmann, G. R. Pabst, *Eur. J. Org. Chem.* **1999**, 313–321; for an example of metal-catalyzed [2+2+2] cycloaddition, see: m) G. Onodera, Y. Shimizu, J.-N. Kimura, J. Kobayashi, Y. Ebihara, K. Kondo, K. Sakata, R. Takeuchi, *J. Am. Chem. Soc.* **2012**, *134*, 10515–10531.

[12] a) T. Kauffmann, J. König, A. Woltermann, *Chem. Ber.* **1976**, *109*, 3864–3868; b) M. Heller, U. S. Schubert, *J. Org. Chem.* **2002**, *67*, 8269–8272; c) R.-A. Fallahpour, *Synthesis* **2000**, 1665–1667; d) S.-H. Yang, K.-L. Wu, Y. Chi, Y.-M. Cheng, P.-T. Chou, *Angew. Chem.* **2011**, *123*, 8420–8424; *Angew. Chem. Int. Ed.* **2011**, *50*, 8270–8274; e) J. Li, T. Sato, H. Li, M. Higuchi, *Synthesis* **2011**, 1361–1364; f) G. D. Harzmann, M. Neuburger, M. Mayor, *Eur. J. Inorg. Chem.* **2013**, 3334–3347.

[13] a) E. Tyrrell, P. Brookes, *Synthesis* **2003**, 469–483; b) G. A. Molander, B. Biolatto, *J. Org. Chem.* **2003**, *68*, 4302–4314; c) B. M. Coleridge, C. S. Bello, D. H. Ellenberger, A. Leitner, *Tetrahedron Lett.* **2010**, *51*, 357–359; for the development of stable pyridyl boron reagents, see: d) A. Bouillon, J.-C. Lancelot, J. Sopkova de Oliveira Santos, V. Collot, P. R. Bovy, S. Rault, *Tetrahedron* **2003**, *59*, 10043–10049; e) P. B. Hodgson, F. H. Salingue, *Tetrahedron Lett.* **2004**, *45*, 685–687; f) D. M. Knapp, E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2009**, *131*, 6961–6963.

[14] For selected recent reviews, see: a) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem.* **2012**, *124*, 10382–10401; *Angew. Chem. Int. Ed.* **2012**, *51*, 10236–10254; b) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879–5918; c) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215–1292; d) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169; e) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624–655; f) X. Chen, K.-M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196–5217; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115; g) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976–10011; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826; h) F. Bellina, R. Rossi, *Tetrahedron* **2009**, *65*, 10269–10310.

[15] For a review on *N*-activated pyridines, see: J. A. Bull, J. J. Mousseau, G. Pelletier, A. B. Charette, *Chem. Rev.* **2012**, *112*, 2642–2713.

[16] a) L.-C. Campeau, S. Rousseaux, K. Fagnou, *J. Am. Chem. Soc.* **2005**, *127*, 18020–18021; b) J.-P. Leclerc, K. Fagnou, *Angew. Chem.* **2006**, *118*, 7945–7950; *Angew. Chem. Int. Ed.* **2006**, *45*, 7781–7786; c) S. H. Cho, S. J. Hwang, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 9254–9256; d) L.-C. Campeau, D. R. Stuart, J.-P. Leclerc, M. Bertrand-Laperle, E. Villemure, H.-Y. Sun, S. Lasserre, N. Guimond, M. Lecavallier, K. Fagnou, *J. Am. Chem. Soc.* **2009**, *131*, 3291–3306; e) M. P. Huestis, K. Fagnou, *Org. Lett.* **2009**, *11*, 1357–1360; f) D. J. Schipper, M. El-Salfiti, C. J. Whipp, K. Fagnou, *Tetrahedron* **2009**, *65*, 4977–4983; g) P. Xi, F. Yang, S. Qin, D. Zhao, J. Lan, G. Gao, C. Hu, J. You, *J. Am. Chem. Soc.* **2010**, *132*, 1822–1824; h) X. Gong, G. Song, H. Zhang, X. Li, *Org. Lett.* **2011**, *13*, 1766–1769; i) D. Lapointe, T. Markiewicz, C. J. Whipp, A. Toderian, K. Fagnou, *J. Org. Chem.* **2011**, *76*, 749–759; j) L. Ackermann, S. Fenner, *Chem. Commun.* **2011**, *47*, 430–432; k) J. R. Fulton, J. E. Glover, L. Kamara, G. J. Rowlands, *Chem. Commun.* **2011**, *47*, 433–435; l) W. Mai, J. Yuan, Z. Li, G. Sun, L. Qu, *Synlett* **2012**, 145–149; m) L. Zhao, C. Tsukano, E. Kwon, Y. Takemoto, M. Hirama, *Angew. Chem.* **2013**, *125*, 1766–1769; *Angew. Chem. Int. Ed.* **2013**, *52*, 1722–1725; n) J. T. Myers, J. M. Hanna Jr, *Tetrahedron Lett.* **2013**, *54*, 612–615; o) E. Kaneko, Y. Matsumoto, K. Kamikawa, *Chem. Eur. J.* **2013**, *19*, 11837–11841; for mechanistic studies, see: p) S. I. Gorelsky, D. Lapointe, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 10848–10849; q) H.-Y. Sun, S. I. Gorelsky, D. R. Stuart, L.-C. Campeau, K. Fagnou, *J. Org. Chem.* **2010**, *75*, 8180–8189; r) S. I. Gorelsky, D. Lapointe, K. Fagnou, *J. Org. Chem.* **2012**, *77*, 658–668; s) S. I. Gorelsky, *Organometallics* **2012**, *31*, 4631–4634; t) Y. Tan, F. Barrios-Landeros, J. F. Hartwig, *J. Am. Chem. Soc.* **2012**, *134*, 3683–3686.

[17] For examples of related C–C bond formation reactions with pyridine *N*-oxides, see: a) J. Wu, X. Cui, L. Chen, G. Jiang, Y. Wu, *J. Am. Chem. Soc.* **2009**, *131*, 13888–13889; b) B. Xiao, Z.-J. Liu, L. Liu, Y. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 616–619; c) S. Zhang, L.-Y. Liao, F. Zhang, X.-F. Duan, *J. Org. Chem.* **2013**, *78*, 2720–2725; d) M. Hussain, T. S.-L. Banchelin, H. Andersson, R. Olsson, F. Almqvist, *Org. Lett.* **2013**, *15*, 54–57; e) F. Gosselin, S. J. Savage, N. Blaquiere, S. T. Staben, *Org. Lett.* **2012**, *14*, 862–865; for examples of direct arylation of pyridines, see: f) B. Liu, Y. Huang, J. Lan, F. Song, J. You, *Chem. Sci.* **2013**, *4*, 2163–2167; g) A. M. Berman, R. G. Bergman, J. A. Ellman, *J. Org. Chem.* **2010**, *75*, 7863–7868.

[18] S. Duric, C. C. Tzschucke, *Org. Lett.* **2011**, *13*, 2310–2313.

[19] a) W. H. Henderson, J. M. Alvarez, C. C. Eichman, J. P. Stambuli, *Organometallics* **2011**, *30*, 5038–5044; b) W. A. Herrmann, C. Brossmer, K. Öfele, C.-P. Reisinger, T. Priermeier, M. Beller, H. Fischer, *Angew. Chem.* **1995**, *107*, 1989–1992; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1844–1848.

[20] There are numerous examples of similar C–H arylation reactions that tolerate cyano-substituents, compare refs. [16d–h], and Table 3, entry 3.

[21] a) D. Wenkert, R. B. Woodward, *J. Org. Chem.* **1983**, *48*, 283–289; b) T. Q. Nguyen, F. Qu, X. Huang, A. F. Janzen, *Can. J. Chem.* **1992**, *70*, 2089–2093; c) R. Balicki, M. Cybulski, G. Maciejewski, *Synth. Commun.* **2003**, *33*, 4137–4141; d) R. Balicki, *Synthesis* **1989**, 645–646; e) Y. Mikami, A. Noujima, T. Mitsudome, T. Mizugaki, K. Jitsukawa, K. Kaneda, *Chem. Eur. J.* **2011**, *17*, 1768–1772.

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