Rhodium-catalyzed C–H functionalization of heteroarenes using indoleBX hypervalent iodine reagents

Erwann Grenet, Ashis Das, Paola Caramenti and Jérôme Waser[*]

Abstract

The C–H indolation of heteroarenes was realized using the benziodoxolone hypervalent iodine reagents indoleBXs. Functionalization of the C–H bond in bipyridinones and quinoline *N*-oxides catalyzed by a rhodium complex allowed to incorporate indole rings into aza-heteroaromatic compounds. These new transformations displayed complete regioselectivity for the C-6 position of bipyridinones and the C-8 position of quinoline *N*-oxides and tolerated a broad range of functionalities, such as halogens, ethers, or trifluoromethyl groups.

Introduction

Nitrogen-containing heteroaromatic compounds have valuable properties in medicinal chemistry, pharmacology and functional materials. Among those, pyridinone, sometimes called pyridone, is a key structural motif of well-known active compounds and natural products (Figure 1) [1]. For example, the 2-pyridinone ring is present in milrinone (**1**), used to treat heart failure, while a 4-pyridinone is part of mimosine (**2**), an alkaloid isolated from *Mimosa pudica*. A benzene-fused pyridinone – a quinolone – can be found in brexpiprazole (**3**), a drug used against schizophrenia. In addition, the indole core is also omnipresent in bioactive compounds [2]. It can be directly bound to

other heterocycles, such as a dihydropyrazidinone in hamacanthine A (**4**) (Figure 1) [3]. Due to their occurrence in biologically active compounds, it is therefore attractive to develop new methods to functionalize pyridinones. The introduction of further heterocyclic rings, such as indoles, is particularly attractive.

Most of the methods for indolylpyridinone synthesis involve a condensation cascade process to generate the pyridinone ring [4-6]. These methods usually require an electron-withdrawing group (nitrile, nitro, carbonyl), which ends up on the pyridi-
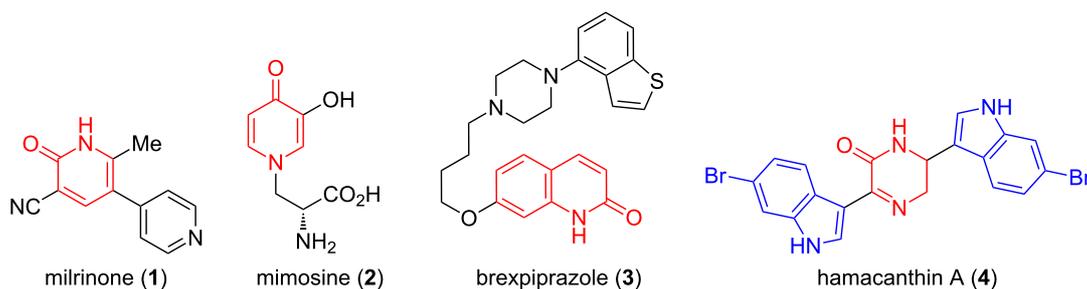
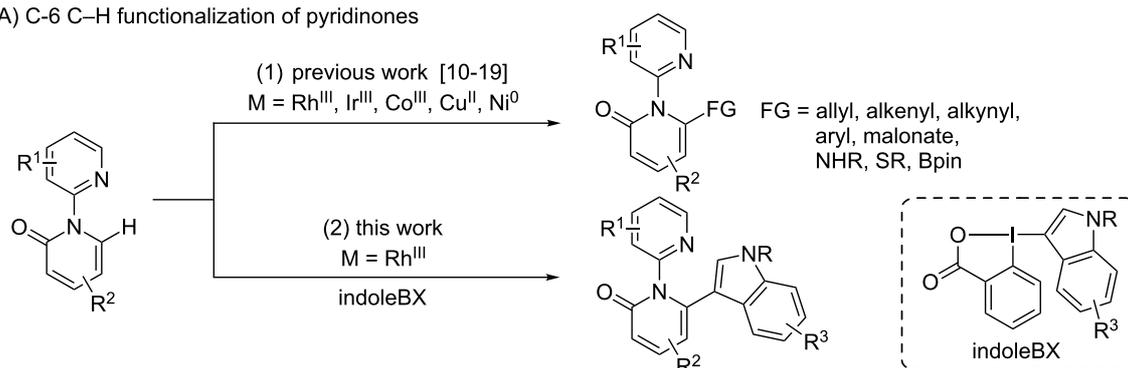**Figure 1:** Bioactive compounds with pyridinone, quinolone and indole cores.

none ring. As alternative, a Suzuki–Miyaura coupling between 3-halogenoindoles and (2-methoxypyridyl)boronic acids followed by a deprotection of the methoxy group [7,8] or transition-metal-catalyzed annulation methods [9] have also been reported.

In contrast, several procedures have been described for the modification of pyridinones to introduce other substituents, especially based on highly efficient C–H functionalization methods [10]. Very recently, several research groups have selectively functionalized the C-6 C–H bond by using a 2-pyridyl directing group on the nitrogen and a transition metal catalyst (reaction 1, Scheme 1A) [11-19]. In particular, Li and co-workers have used ethynylbenziodoxolone (EBX) hypervalent iodine reagents to achieve a regiodivergent alkynylation of the pyridinone core employing either a gold(I) or a rhodium(III) catalyst for C-5 and C-6 functionalization, respectively [13]. Hypervalent iodine reagents in general [20], and benziodoxole
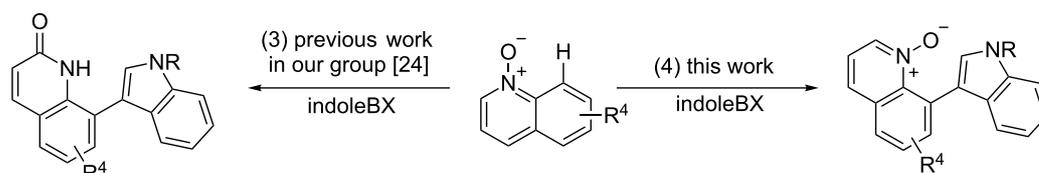
derivatives in particular [21], have found broad application in synthetic chemistry. Aryl iodonium salts have been used successfully in transition-metal-catalyzed transformations [22], but only one application of indole iodonium salts in copper catalysis by You and co-workers had been reported until 2017 [23]. In this context, indole-based benziodoxole hypervalent iodine reagents, recently introduced by Yoshikai's and our group [24-27], appeared ideal partners to develop a new C–H heteroarylation of pyridinones.

Herein, we report the selective C–H heteroarylation of the C-6 position of bipyridinones by a rhodium-catalyzed reaction with indoleBX (reaction 2, Scheme 1A). In addition, we demonstrate that the mild conditions developed allow the heteroarylation of the C-8 position of quinoline *N*-oxides, whereas formation of the quinolinone had been observed in our previous work (Scheme 1B). The obtained products combine up to three classes of privileged heterocycles in medicinal chemistry in a

Scheme 1: C–H functionalization of pyridinones and quinoline *N*-oxides.

single compound, and are therefore expected to be highly use-
ful building blocks in the search for new bioactive compounds.

Results and Discussion

We started the studies on C–H indolation with the optimization
of the reactions conditions (Table 1) for the coupling of [1,2'-
bipyridin]-2-one (**5a**) with Me-indoleBX **6a**, easily obtained
from commercially available 1-methylindole and 2-iodoben-
zoic acid [24]. While the reaction conditions previously de-
veloped in our group for the C–H functionalization of 2-phenyl-
pyridine [24] failed for the coupling of **5a** with **6a** (Table 1,
entry 1), we were pleased to see that addition of 0.15 equiv
Zn(OTf)$_2$ allowed a full conversion to the desired product **7a** in
86% yield (Table 1, entry 2). The Lewis acid is supposed to
weaken the O–I bond by coordination of the carboxy group in
6a. No base was required in this case. The reaction was com-
pletely selective for the C-6 position of the pyridinone ring.
Control experiments pointed out that both Lewis acid (Table 1,
entry 3) and AgSbF$_6$ as additive (Table 1, entry 4) were neces-
sary for an efficient reaction. The transformation was tolerant to
air (Table 1, entry 5). However, more byproducts were ob-
served. Decreasing the temperature (Table 1, entry 6) or the
catalyst loading (Table 1, entry 7) resulted in lower yields.
Finally, three control experiments with 1-methylindole (**8**,
Table 1, entry 8), 3-iodo-1-methylindole (**9**, Table 1, entry 9)

and the poorly stable (1*H*-indol-3-yl)(phenyl)iodonium tetra-
fluoroborate [23] (**10**, Table 1, entry 10) did not lead to the for-
mation of **7a**, highlighting the unique reactivity of the benzio-
doxolone hypervalent iodine reagent.

The scope and limitations of the reaction were then studied
(Scheme 2). The diversification of the directing group was ex-
amined first. The unsubstituted pyridine group led to the forma-
tion of product **7a** in 86% yield. The electron-rich 5-methoxy-
pyridine and the electron-poor 5-trifluoromethylpyridine
directing groups gave products **7b** and **7c** in 82% and 72%
yield, respectively. When a nitro group was present on the pyri-
dine (**5d**), the product was not observed, probably due to a
weaker coordination of the nitrogen on the pyridine. Pyrimi-
dine could not be used as directing group (**5e**), confirming what
has already been reported by others authors [13]. Quinoline **7f**
was obtained in 79% yield. Concerning the pyridinone core,
both an electron-donating methyl group and electron-with-
drawing trifluoromethyl and fluoro groups (**7g–i**) were well
tolerated in the C-3 position. However, the strong electron-with-
drawing CF$_3$ group resulted in a lower 65% yield (**7h**). This ob-
servation is also true for the C-4 position. Indeed, products **7j–l**
were synthesized in 78% yield for a methyl, 66% yield for a tri-
fluoromethyl and 84% yield for a benzyloxy substituent. As
previously reported [13], 5-substituted pyridinone **5m** could not

---

Table 1: Optimization of the C–H heteroarylation[a,b].
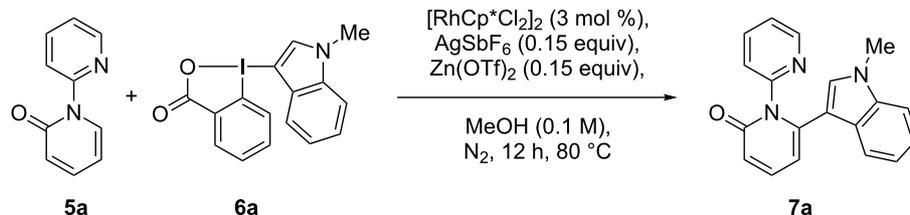
| Entry	Changes from conditions	Yield (%)
1	[RhCp*Cl$_2$]$_2$ (2.5 mol %), AgSbF$_6$ (0.10 equiv), NaOPiv (0.10 equiv), DCE, 12 h, 50 °C	no reaction
2	–	86
3	without Zn(OTf)$_2$	no reaction
4	without AgSbF$_6$	60
5	under air atmosphere	80
6	60 °C	48
7	1 mol % of [RhCp*Cl$_2$]$_2$	75
8	1-methylindole (**8**)	no reaction
9	3-iodo-1-methylindole (**9**)	0[c]
10	iodonium salt **10**	0[c]

[a]Reactions conditions: **5** (0.20 mmol), **6** (0.20 mmol), [RhCp*Cl$_2$]$_2$ (3.7 mg, 6.0 μmol, 3 mol %), AgSbF$_6$ (10.3 mg, 30.0 μmol, 0.15 equiv), Zn(OTf)$_2$ (10.9 mg, 30.0 μmol, 0.15 equiv), methanol (2.0 mL) at 80 °C for 12 h. [b]Isolated yield after preparative TLC. [c]Decomposition.
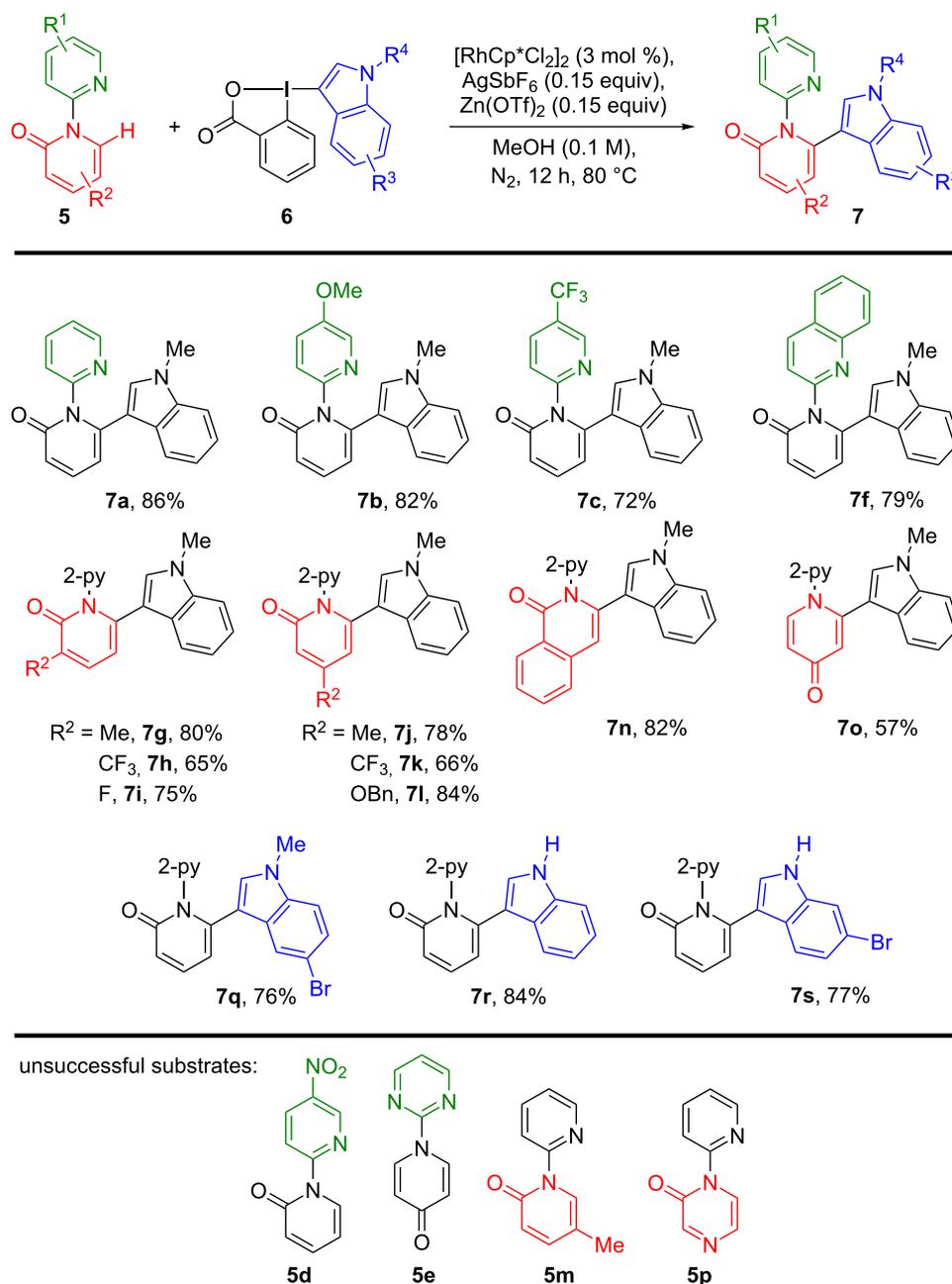
Scheme 2: Scope and limitations of the Rh-catalyzed C–H activation of [1,2'-bipyridin]-2-one.

be functionalized. Isoquinolone **7n** was prepared in 82% yield. The methodology could also be applied to 4-pyridone in a moderate 57% yield for product **7o**. Unfortunately, pyrazin-2-one **5p** could not be functionalized. Modification of the hypervalent iodine reagent was then investigated with three selected compounds only. A bromo substituent on the benzene ring was well tolerated (**7q**). The coupling could be also performed with N–H unprotected indoleBX reagents to afford products **7r** and **7s** in 84% and 77% yield, respectively.

We also applied these conditions to different quinoline *N*-oxides (Scheme 3). This class of substrates had also been used for C–H alkynylation using EBX reagents [28]. During our previous work, we had attempted the C8-heteroarylation of quinoline *N*-oxide with Me-indoleBX **6a**. However, the transformation required a temperature of 100 °C, leading to the formation of the corresponding isoquinolone in only 38% yield [24]. By employing the milder conditions developed for pyridinones, we were pleased to see that the *N*-oxide group could be preserved and
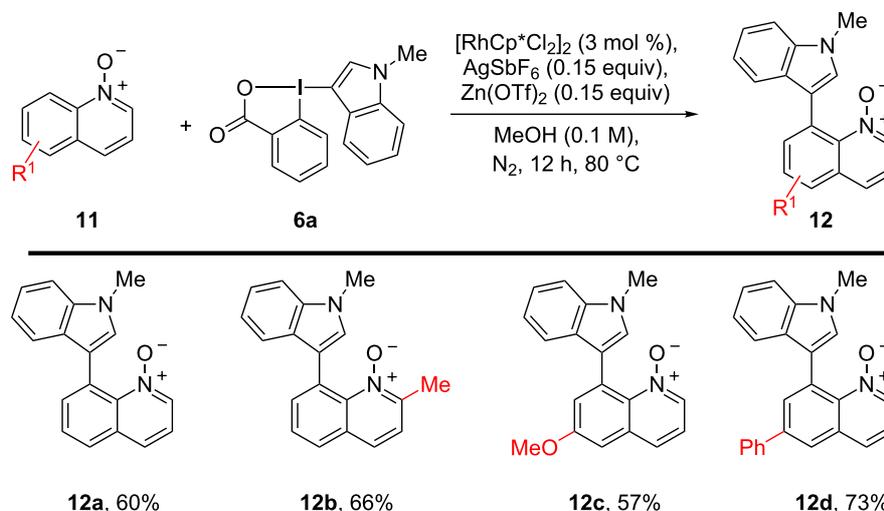
Scheme 3: Scope of the Rh-catalyzed *peri* C–H activation of quinoline *N*-oxides.

product **12a** was obtained in 60% yield. A methyl substitution in C-2 position gave the product **12b** in 66% yield. In C-6 position both a methoxy and a phenyl group were well tolerated giving 57% and 73% yield of products **12c** and **12d**.

The pyridine directing group could be cleaved by alkylation of the pyridine nitrogen using methyl triflate followed by reduction with sodium cyanoborohydride to deliver the N–H unprotected pyridinone **13** in 74% yield (Scheme 4) [29]. A rearrangement of the *N*-oxide furnished the corresponding isoquinolone **14** in 62% yield.

Conclusion

In summary, we have developed the C-6 selective C–H heteroarylation of pyridin-2-ones using indoleBXs as coupling partners, [RhCp*Cl$_2$]$_2$ as catalyst, AgSbF$_6$ as co-catalyst and Zn(OTf)$_2$ as Lewis acid. The reaction could also be applied to functionalize one pyridin-4-one in C-6 position, one isoquinolinone in C-3 position and quinoline *N*-oxides in C-8 position. After cleavage of the directing group or rearrangement of the *N*-oxide function, we were able to access 6-(indol-3-yl)pyridinone and 8-(indol-3-yl)quinolone. The developed transformations give access to important heterocyclic building blocks for synthetic and medicinal chemistry and set the stages for the development of other C–H heteroarylation processes based on indoleBX reagents.

Experimental
General procedure for C–H heteroarylation

In a sealed tube, [RhCp*Cl$_2$]$_2$ (3.7 mg, 6.0 μmol, 3 mol %), AgSbF$_6$ (10.3 mg, 30.0 μmol, 0.15 equiv), Zn(OTf)$_2$ (10.9 mg, 30.0 μmol, 0.15 equiv), the corresponding pyridinone or quino-
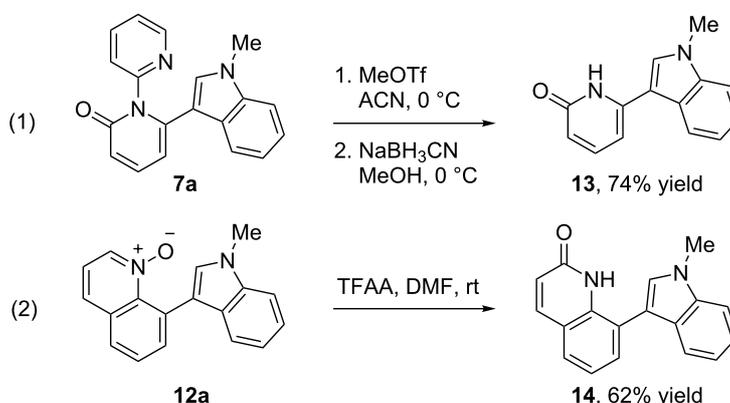
Scheme 4: Product modifications.

line *N*-oxide (0.20 mmol, 1.00 equiv) and the corresponding hypervalent iodine reagent (0.20 mmol, 1.00 equiv) were solubilized in dry MeOH (2.0 mL, 0.1 M) under N_2 atmosphere. The mixture was stirred at 80 °C for 12 h. The mixture was then diluted with DCM (5 mL) and quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL). The two layers were separated and the aqueous layer was extracted twice with DCM (5 mL). The organic layers were combined, dried over magnesium sulfate dehydrate, filtered and concentrated under reduced pressure. The crude residue was purified by preparative TLC using DCM/MeOH to afford the pure desired compound.

Supporting Information

Supporting Information File 1
Detailed experimental procedures, analytical data for all compounds and copies of the NMR spectra of new compounds.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-102-S1.pdf]

Acknowledgements

ORCID® iDs

Erwann Grenet - https://orcid.org/0000-0002-5249-8766
Jérôme Waser - https://orcid.org/0000-0002-4570-914X

References

1. Jessen, H. J.; Gademann, K. *Nat. Prod. Rep.* **2010,** *27,* 1168–1185. doi:10.1039/b911516c
2. Gribble, G. W. *Indole Ring Synthesis: From Natural Products to Drug Discovery;* John Wiley & Sons: Chichester, 2016.
3. Gunasekera, S. P.; McCarthy, P. J.; Kelly-Borges, M. *J. Nat. Prod.* **1994,** *57,* 1437–1441. doi:10.1021/np50112a014
4. Mohamed, S. F.; Hosni, H. M.; Amr, A. E.; Abdalla, M. M. *Russ. J. Gen. Chem.* **2016,** *86,* 672–680. doi:10.1134/S1070363216030269
   See for a C-4 substituted example.
5. Krichevskii, É. S.; Alekseeva, L. M.; Kuleshova, E. F.; Granik, V. G. *Pharm. Chem. J.* **1995,** *29,* 132–133. doi:10.1007/BF02226526
   See for a C-5 substituted example.
6. El-Sayed, N. S.; Shirazi, A. N.; El-Meligy, M. G.; El-Ziaty, A. K.; Rowley, D.; Sun, J.; Nagib, Z. A.; Parang, K. *Tetrahedron Lett.* **2014,** *55,* 1154–1158. doi:10.1016/j.tetlet.2013.12.081
   See for a C-6 substituted example.
7. Chen, K. X.; Vibulbhan, B.; Yang, W.; Sannigrahi, M.; Velazquez, F.; Chan, T.-Y.; Venkatraman, S.; Anilkumar, G. N.; Zeng, Q.; Bennet, F.; Jiang, Y.; Lesburg, C. A.; Duca, J.; Pinto, P.; Gavalas, S.; Huang, Y.; Wu, W.; Selyutin, O.; Agrawal, S.; Feld, B.; Huang, H.-C.; Li, C.; Cheng, K.-C.; Shih, N.-Y.; Kozlowski, J. A.; Rosenblum, S. B.; Njoroge, F. G. *J. Med. Chem.* **2012,** *55,* 754–765. doi:10.1021/jm201258k
   See for a C-3 example.
8. Kaila, N.; Follows, B.; Leung, L.; Thomason, J.; Huang, A.; Moretto, A.; Janz, K.; Lowe, M.; Mansour, T. S.; Hubeau, C.; Page, K.; Morgan, P.; Fish, S.; Xu, X.; Williams, C.; Saiah, E. *J. Med. Chem.* **2014,** *57,* 1299–1322. doi:10.1021/jm401509e
9. Krieger, J.-P.; Lesuisse, D.; Ricci, G.; Perrin, M.-A.; Meyer, C.; Cossy, J. *Org. Lett.* **2017,** *19,* 2706–2709. doi:10.1021/acs.orglett.7b01051
10. Hirano, K.; Miura, M. *Chem. Sci.* **2018,** *9,* 22–32. doi:10.1039/c7sc04509c
11. Odani, R.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2014,** *53,* 10784–10788. doi:10.1002/anie.201406228
12. Miura, W.; Hirano, K.; Miura, M. *J. Org. Chem.* **2017,** *82,* 5337–5344. doi:10.1021/acs.joc.7b00682
    and references cited therein.
13. Li, Y.; Xie, F.; Li, X. *J. Org. Chem.* **2016,** *81,* 715–722. doi:10.1021/acs.joc.5b02410
14. Kong, L.; Yu, S.; Tang, G.; Wang, H.; Zhou, X.; Li, X. *Org. Lett.* **2016,** *18,* 3802–3805. doi:10.1021/acs.orglett.6b01806
15. Peng, P.; Wang, J.; Jiang, H.; Liu, H. *Org. Lett.* **2016,** *18,* 5376–5379. doi:10.1021/acs.orglett.6b02755
16. Das, D.; Poddar, P.; Maity, S.; Samanta, R. *J. Org. Chem.* **2017,** *82,* 3612–3621. doi:10.1021/acs.joc.7b00135
17. Kumar, K. A.; Kannaboina, P.; Das, P. *Org. Biomol. Chem.* **2017,** *15,* 5457–5461. doi:10.1039/c7ob01277b
18. Wang, H.; Pesciaioli, F.; Oliveira, J. C. A.; Warratz, S.; Ackermann, L. *Angew. Chem., Int. Ed.* **2017,** *56,* 15063–15067. doi:10.1002/anie.201708271
19. Das, D.; Samanta, R. *Adv. Synth. Catal.* **2018,** *360,* 379–384. doi:10.1002/adsc.201701244
    and references cited therein.
20. Yoshimura, A.; Zhdankin, V. V. *Chem. Rev.* **2016,** *116,* 3328–3435. doi:10.1021/acs.chemrev.5b00547
21. Li, Y.; Hari, D. P.; Vita, M. V.; Waser, J. *Angew. Chem., Int. Ed.* **2016,** *55,* 4436–4454. doi:10.1002/anie.201509073
22. Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009,** *48,* 9052–9070. doi:10.1002/anie.200904689
23. Liu, C.; Yi, J.-C.; Liang, X.-W.; Xu, R.-Q.; Dai, L.-X.; You, S.-L. *Chem. – Eur. J.* **2016,** *22,* 10813–10816. doi:10.1002/chem.201602229
24. Caramenti, P.; Nicolai, S.; Waser, J. *Chem. – Eur. J.* **2017,** *23,* 14702–14706. doi:10.1002/chem.201703723
25. Caramenti, P.; Waser, J. *Helv. Chim. Acta* **2017,** *100,* e1700221. doi:10.1002/hlca.201700221
26. Grenet, E.; Waser, J. *Org. Lett.* **2018,** *20,* 1473–1476. doi:10.1021/acs.orglett.8b00337
27. Wu, B.; Wu, J.; Yoshikai, N. *Chem. – Asian J.* **2017,** *12,* 3123–3127. doi:10.1002/asia.201701530
28. Kwak, J.; Kim, M.; Chang, S. *J. Am. Chem. Soc.* **2011,** *133,* 3780–3783. doi:10.1021/ja111670s
29. Smout, V.; Peschiulli, A.; Verbeeck, S.; Mitchell, E. A.; Herrebout, W.; Bultinck, P.; Vande Velde, C. M. L.; Berthelot, D.; Meerpoel, L.; Maes, B. U. W. *J. Org. Chem.* **2013,** *78,* 9803–9814. doi:10.1021/jo401521y