Do we really need ligands in Ir-catalyzed C–H borylation?

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Abstract: Direct borylation of C–H bonds is a privileged strategy to access versatile building blocks and valuable derivatives of complex molecules (late-stage functionalization, metabolite synthesis). This perspective aims to provide an overview and classification of the catalytic systems developed in this fast-growing area of research. Unexpected selectivity differences between two established directed-borylation systems have been discovered using high-throughput experimentation highlighting the importance of classical control experiments in catalysis research.

Keywords: C–H activation · Borylation · Iridium · Imine ligand

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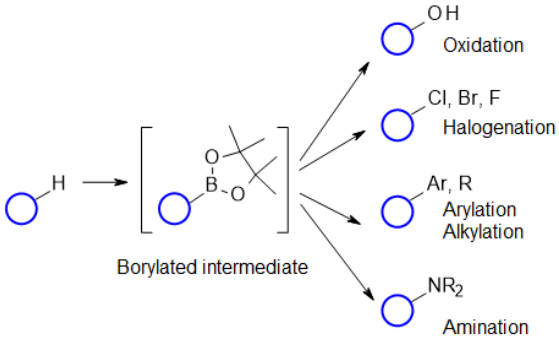
1. Introduction

C–H activation has been called "the holy grail" of organic chemistry, as achieving selective C–H activation in a molecule containing tens of different C–H bonds would give chemists an immense power to modify molecules at will.[1] Among the diversity of bond-forming reactions accessible via C–H activation, iridium catalyzed C–H borylation has gathered particular interest due to the mild reaction conditions, wide functional group tolerance and the synthetic versatility of the resulting C–B bond (Scheme 1).[2]



Scheme 1. C–H Borylation and diversification

Various catalytic systems and strategies to influence the reaction regio- and chemo-selectivity have been designed during the past 20 years. The initial reports spearheaded by Hartwig, Miyaura, Ishiyama as well as Smith focused on sterically or electronically directed C(sp^2) –H borylations (Figure 1a) utilizing *N,N*-bidentate ligands.[3] It is presumed that *N,N*-ligated tris-boryl iridium complex is the key active species catalyzing C–H activation of the substrate. These catalysts, represented by [Ir(COD)OMe]$_2$/**1**, allow for functionalization of the most sterically accessible and/or electronically favored C–H bonds, but often lead to generation of regioisomer mixtures (e.g. *meta*- /*para*- derivatives of mono substituted benzenes). The latest developments in this area include the use of air stable pre-catalysts,[4] improved regioselectivity by the use of sterically encumbered ligands,[5] use of predictive models,[6] and progress towards C(sp^3)–H borylation.[7]

More recently, functional group directed C–H borylations have emerged, in which a coordinating motif (directing group DG) governs the regioselectivity of the C–B coupling.[2c, 8] Generally this is achieved by a clever ligand design allowing for an outer sphere attractive interaction between the ligand and a suitable directing group (DG) of the starting material (Figure 1b) or by an inner sphere chelation of the directing group (DG) to the iridium metal center (Figure 1c). An example of the first approach is urea derived ligand **2** for *meta*-directed borylation of arenes and heteroarenes possessing various DGs such as amides, esters, and phosphonates.[9] Outer-sphere ligand-substrate interactions may play a role in some *ortho*-selective borylations as well. CF_3-substituted bipyridine ligand **3** has been reported to form a highly *ortho*-selective system for amide directed borylation of aryl and heteroaryl substrates. The authors propose the selectivity to originate from dispersion interactions between the carbonyl group of the substrate and the CF_3-pyridine ring of the ligand.[10] The last, inner sphere interaction based approach (Figure 1c), utilizes unsaturated iridium complexes with a vacant coordination site. This enables the direct binding of the directing group to the iridium center, facilitating selective *ortho* C–H functionalization via metalacyclic intermediate. Our team recently reported a new class of bis-cyclometallated iridium catalysts employing imines as *C,N*-ligands (Figure 1, **ImIr-4**).[11] This robust, single component pre-catalyst undergoes HBpin mediated activation with formation of unsaturated iridacycle exhibiting high activity for amide directed borylation of aromatic, heteroaromatic, and acrylic systems.

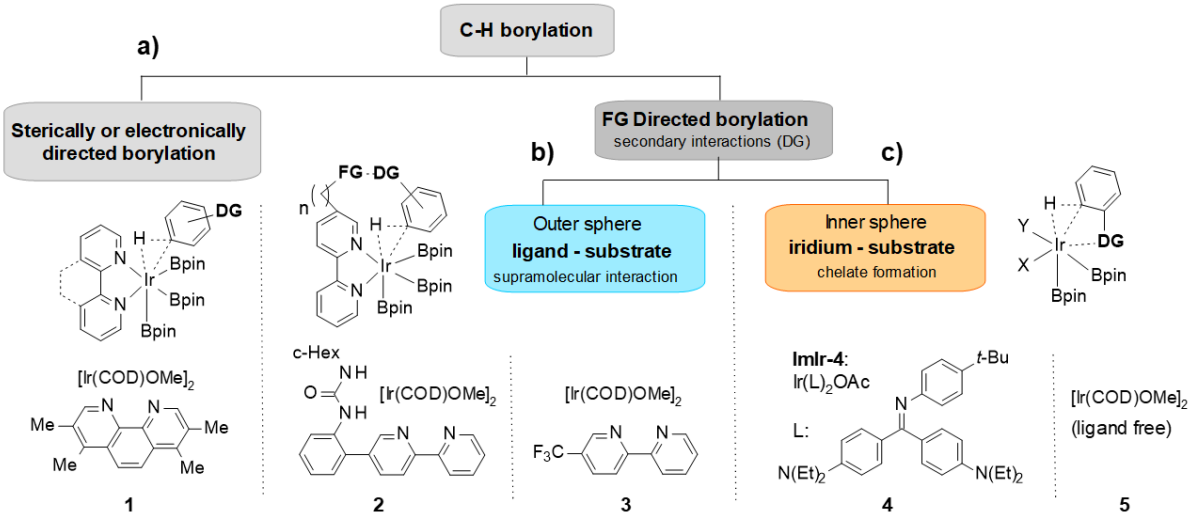
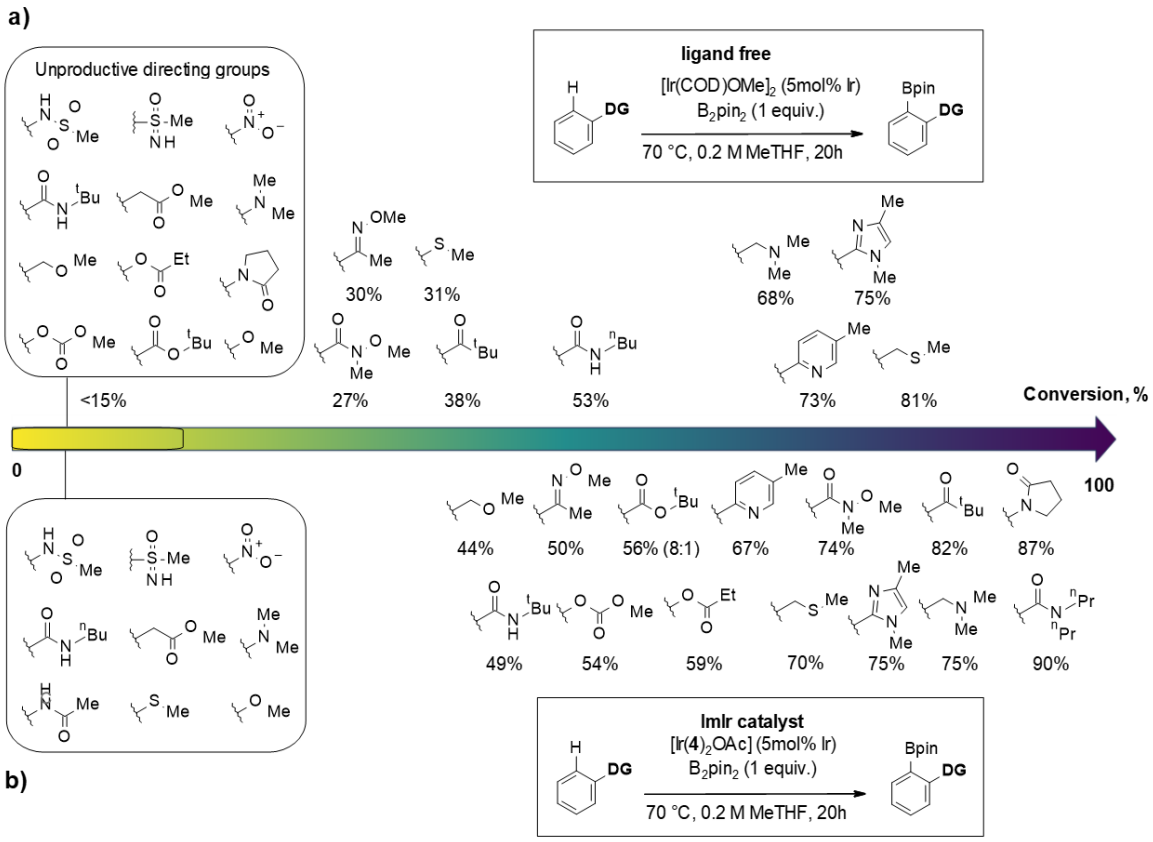


Fig. 1. Iridium catalyzed C–H borylation. Common strategies to influence the regioselectivity: a) Sterically or electronically directed, b) Outer sphere (ligand – substrate) directed, and c) Inner sphere (metal – substrate) directed. Mechanistic proposals representing the common strategies and selected examples of Iridium catalyst and ligand structure developed within each class. DG = Directing group, FG = functional group, COD = 1,5-Cyclooctadiene, X = represents an anionic ligand, Y = represents a neutral ligand.

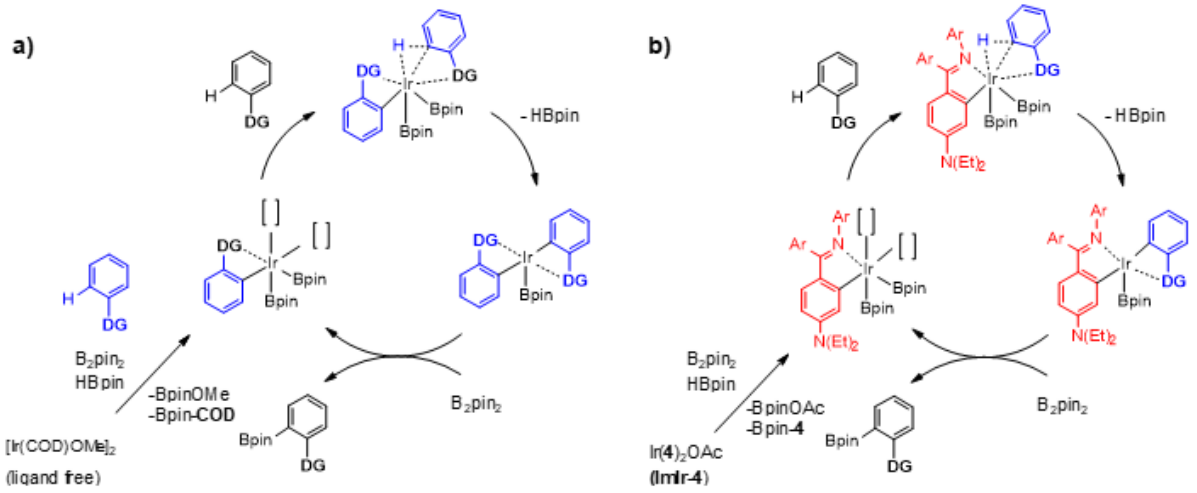
As the number of newly reported iridium-ligand systems continues to rise, there is a concurrent increase in the number of reports detailing the simplest system: ligand-free C–H borylation. Typically, these processes only require $[Ir(COD)OMe]_2$ and a boron source (Figure 1, **5**).[12] The boundaries between the mentioned categories of borylation catalysts and their mechanistic modes of action are not always clear-cut. For instance, *N,N*-bidentate ligands such as **2**, or **3** could undergo rollover cyclometallation to form a *C,N* bidentate ligand.[13] Likewise, the possibility of competition between ligated and ligand-free borylation cannot be ruled out, especially for catalysts formed *in situ* from $[Ir(COD)OMe]_2$. In view of these ambiguities, we considered that the field would benefit from direct, side-by-side comparison studies between different C–H borylation methods and substrates bearing various directing groups. These studies would help to provide guidance for the application of these methods to complex substrates.[14]

2. Comparison of Ligand-free and Imine-Ligated C–H Borylation

Our investigation commenced with a comprehensive exploration of ligand-free C–H borylation, comparing it side-by-side with our recently published **ImIr-4** catalyst system. To evaluate the reactivity of various directing groups, a high-throughput screening of 24 substrates bearing functional groups, commonly found in bioactive molecules, was conducted. Subsequently, we organized the substrates based on their reactivity, with substrate conversion determined via quantitative GC analysis (Scheme 2). Regioselectivity was assessed by GC and GCMS analysis of the crude reaction mixtures, where the assignment of minor *meta*-/*para*-isomers was aided by comparison with reference reactions catalysed by the unselective $[Ir(COD)OMe]_2$/**1** (tetramethyl-phenanthroline) system. For all performing substrates presented in Scheme 2, but *t*Bu-ester, an excellent *ortho*-selectivity was observed for both directed borylation methods (sum *ortho* + bis-*ortho*-borylation product vs. other isomers > 20:1 GC-FID ratio). The results revealed interesting differences between the two methods. Notably, the substrate scope of the **ImIr-4** C–H borylation (Scheme 2b) is broader, providing superior conversions for substrates that coordinate through oxygen directing group such as esters, carbamates, and bulky ketones.

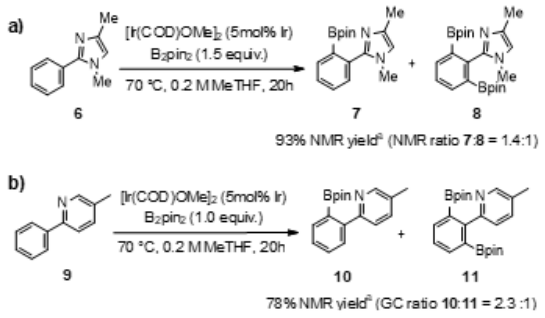


Scheme 2. Evaluation of substrate reactivity with different directing groups (DG) under a) ligand-free C–H borylation conditions and b) **Imlr-4** conditions. Reactions were conducted in 96-well Paradox plates at a 0.08 mmol scale. Conversion of starting material was determined using quantitative GC FID. Regioselectivity (*ortho* : *meta/para*) for productive examples was >20:1 unless otherwise indicated.



Scheme 4. Proposed reaction mechanism of directed C–H borylation a) ligand-free conditions and b) **ImIr-4** conditions.

An interesting observation pertains to amide directing groups, where the **ImIr-4** system excels with tertiary amides but encounters challenges with secondary amides, particularly when the substituents are less bulky (*t*Bu > *n*Bu). Conversely, the ligand-free system (Scheme 2a) exhibits better acceptance of less bulky *N*-substituents. We posit that this shift in reactivity may results from the N vs. O coordination preferences of the corresponding catalyst. Certain directing groups, such as heterocycles, benzyl thioethers (as previously reported by Li[15]), and benzyl amines (as previously reported by Chattopadhyay[12d]) demonstrated very high reactivity under our ligand-free screening conditions. In general, directing groups containing softer Lewis basic heteroatoms (N, S) proved to be more reactive compared to those with harder oxygen-containing directing groups. To the best of our knowledge, only heterocycles connected to the phenyl group through a linker (forming a 6-iridacycle) have previously been reported to perform under the ligand-free borylation conditions.[12c, 12d, 16]
To validate our initial screening results, borylation of aryl-heteroaryl type substrates has been scaled up, and the resulting products have been characterized (Scheme 3).



Scheme 3. Borylation of heterocyclic substrates. Yield determined by ^{1}H NMR analysis of the crude reaction mixture using 1,2,4,5-tetramethylbenzene as internal standard..[a]NMR yield refers to the combined yield of mono- and bis-borylated product.

Mechanistic studies on ImIr catalysis have revealed the formation of a key bis-cyclometallated species with imine ligand and substrate bound to the metal (Schem 4b).[11] In analogy, we propose that substrates performing well under the ligand-free conditions may modify the catalyst and act as its own ligand in the process (Scheme 4a),[17] drawing parallels to a similar mechanism observed in ruthenium catalyzed C–H functionalization of phenylpyridine derivatives.[18]

3. Conclusions

We have used high throughput experimentation to study the iridium catalyzed borylation of substates bearing diverse directing groups in the presence and absence of an exogenous ligand for the iridium catalyst. While the imine ligated iridium catalyst generally proved more effective, our results uncover that 'ligand free' conditions can be a simple and synthetically practical method for directed *ortho*-borylation of a number of substrates, notably those bearing S or N based directing groups.
The presented report highlights the importance of running test reactions in the absence of ligands (control experiments), especially when exploring new substrate classes or developing new ligands. Studies focusing on the application of directed and non-directed C–H borylation methods for late-stage functionalization of biologically active compounds are currently underway in our laboratory, and we will share the results in due course.

Acknowledgements
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[1] B. A. Arndtsen, R. G. Bergman, T. A. Mobley, T. H. Peterson, *Acc. Chem. Res.* **2002**, *28*, 154, DOI: 10.1021/ar00051a009.

[2] a) I. A. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890, DOI: 10.1021/cr900206p; b) R. Bisht, C. Haldar, M. M. M. Hassan, M. E. Hoque, J. Chaturvedi, B. Chattopadhyay, *Chem. Soc. Rev.* **2022**, *51*, 5042, DOI: 10.1039/d1cs01012c; c) M. M. M. Hassan, S. Guria, S. Dey, J. Das, B. Chattopadhyay, *Sci. Adv.* **2023**, *9*, eadg3311, DOI: 10.1126/sciadv.adg3311.
[3] a) J. Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka, Jr., M. R. Smith, 3rd, *Science* **2002**, *295*, 305, DOI: 10.1126/science.1067074; b)T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, N. R. Anastasi, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 390, DOI: 10.1021/ja0173019; c) T. Ishiyama, J. Takagi, J. F. Hartwig, N. Miyaura, *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 3056−3058; d) T. M. Boller, J. M. Murphy, M. Hapke, T. Ishiyama, N. Miyaura, J. F. Hartwig, *J. Am. Chem. Soc.* **2005**, *127*, 14263, DOI: 10.1021/ja053433g; e) M. A. Larsen, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 4287, DOI: 10.1021/ja412563e; f) J. S. Wright, P. J. H. Scott, P. G. Steel, *Angew. Chem. Int. Ed. Engl.* **2021**, *60*, 2796, DOI: 10.1002/anie.202001520; g) S. Rej, N. Chatani, *J. Am. Chem. Soc.* **2021**, *143*, 2920, DOI: 10.1021/jacs.0c13013; h) C. N. Iverson, M. R. Smith, *J. Am. Chem. Soc.* **1999**, *121*, 7696, DOI: 10.1021/ja991258w; i) J.-Y. Cho, C. N. Iverson, M. R. Smith, *J. Am. Chem. Soc.* **2000**, *122*, 12868, DOI: 10.1021/ja0013069.
[4] a) C. C. C. J. Seechurn, V. Sivakumar, D. Satoskar, T. J. Colacot, *Organometallics* **2014**, *33*, 3514, DOI: 10.1021/om500420d; b) E. D. Slack, T. J. Colacot, *Org. Lett.* **2021**, *23*, 1561, DOI: 10.1021/acs.orglett.0c04210.
[5] B. Ramadoss, Y. Jin, S. Asako, L. Ilies, *Science* **2022**, *375*, 658, DOI: 10.1126/science.abm7599.
[6] a) D. F. Nippa, K. Atz, R. Hohler, A. T. Muller, A. Marx, C. Bartelmus, G. Wuitschik, I. Marzuoli, V. Jost, J. Wolfard, M. Binder, A. F. Stepan, D. B. Konrad, U. Grether, R. E. Martin, G. Schneider, *Nat Chem* **2024**, *16*, 239, DOI: 10.1038/s41557-023-01360-5; b) E. Caldeweyher, M. Elkin, G. Gheibi, M. Johansson, C. Skold, P. O. Norrby, J. F. Hartwig, *J. Am. Chem. Soc.* **2023**, *145*, 17367, DOI: 10.1021/jacs.3c04986.
[7] I. F. Yu, K. A. D'Angelo, A. D. Hernandez-Mejias, N. Cheng, J. F. Hartwig, *J. Am. Chem. Soc.* **2024**, *146*, 7124, DOI: 10.1021/jacs.3c12981.
[8] a) A. Ros, R. Fernandez, J. M. Lassaletta, *Chem. Soc. Rev.* **2014**, *43*, 3229, DOI: 10.1039/c3cs60418g; b) L. Xu, G. Wang, S. Zhang, H. Wang, L. Wang, L. Liu, J. Jiao, P. Li, *Tetrahedron*, *73*, 7123, DOI: https://doi.org/10.1016/j.tet.2017.11.005; c) M. R. Smith, 3rd, R. Bisht, C. Haldar, G. Pandey, J. E. Dannatt, B. Ghaffari, R. E. Maleczka, Jr., B. Chattopadhyay, *ACS Catal.* **2018**, *8*, 6216, DOI: 10.1021/acscatal.8b00641; d) P. C. Roosen, V. A. Kallepalli, B. Chattopadhyay, D. A. Singleton, R. E. Maleczka, Jr., M. R. Smith, 3rd, *J. Am. Chem. Soc.* **2012**, *134*, 11350, DOI: 10.1021/ja303443m.
[9] a) Y. Kuninobu, H. Ida, M. Nishi, M. Kanai, *Nat. Chem.* **2015**, *7*, 712, DOI: 10.1038/nchem.2322; bY. Y. Xu Lu, Haruka Ida, Mitsumi Nishi, Motomu Kanai, Yoichiro Kuninobu, *ACS Cat.* **2019**, *9*, 1705, DOI: https://doi.org/10.1021/acscatal.8b05005.
[10] D. Marcos-Atanes, C. Vidal, C. D. Navo, F. Peccati, G. Jimenez-Oses, J. L. Mascarenas, *Angew. Chem. Int. Ed. Engl.* **2023**, *62*, e202214510, DOI: 10.1002/anie.202214510.
[11] J. M. Zakis, A. M. Messinis, L. Ackermann, T. Smejkal, J. Wencel-Delord, *Adv. Synth. Catal.* **2024**, DOI: 10.1002/adsc.202301411.
[12] a) K. M. Crawford, T. R. Ramseyer, C. J. Daley, T. B. Clark, *Angew. Chem. Int. Ed. Engl.* **2014**, *53*, 7589, DOI: 10.1002/anie.201402868; b) S. Mao, B. Yuan, X. Wang, Y. Zhao, L. Wang, X. Y. Yang, Y. M. Chen, S. Q. Zhang, P. Li, *Org. Lett.* **2022**, *24*, 3594, DOI: 10.1021/acs.orglett.2c00994; c) J. S. Scott, T. A. Moss, B. Barlaam, P. R. J. Davey, G. Fairley, E. T. Gangl, R. D. R. Greenwood, H. Hatoum-Mokdad, A. S. Lister, D. Longmire, R. Polanski, S. Stokes, M. J. Tucker, J. G. Varnes, B. Yang, *ACS Med. Chem. Lett.* **2020**, *11*, 2519, DOI: 10.1021/acsmedchemlett.0c00505; d) M. M. M. Hassan, B. Mondal, S. Singh, C. Haldar, J. Chaturvedi, R. Bisht, R. B. Sunoj, B. Chattopadhyay, *J. Org. Chem.* **2022**, *87*, 4360, DOI: 10.1021/acs.joc.2c00046; e) S. Xu, R. Du, L. Liu, *Chinese J. Org. Chem.* **2021**, *41*, DOI: 10.6023/cjoc202101009.
[13] B. Butschke, H. Schwarz, *Chem. Sci.* **2012**, *3*, 308, DOI: 10.1039/c1sc00651g.
[14] P. S. Kutchukian, J. F. Dropinski, K. D. Dykstra, B. Li, D. A. DiRocco, E. C. Streckfuss, L. C. Campeau, T. Cernak, P. Vachal, I. W. Davies, S. W. Krska, S. D. Dreher, *Chem. Sci.* **2016**, *7*, 2604, DOI: 10.1039/c5sc04751j.
[15] L. Liu, G. Wang, J. Jiao, P. Li, *Org. Lett.* **2017**, *19*, 6132, DOI: 10.1021/acs.orglett.7b03008.
[16] Y. Yang, Q. Gao, S. Xu, *Adv. Synth. Catal.* **2018**, *361*, 858, DOI: 10.1002/adsc.201801292.
[17] J. M. Zakis, T. Smejkal, J. Wencel-Delord, *Chem. Commun.* **2022**, *58*, 483, DOI: 10.1039/d1cc05195d.
[18] a) M. Simonetti, D. M. Cannas, X. Just-Baringo, I. J. Vitorica-Yrezabal, I. Larrosa, *Nat. Chem.* **2018**, *10*, 724, DOI: 10.1038/s41557-018-0062-3; b) M. T. Findlay, P. Domingo-Legarda, G. McArthur, A. Yen, I. Larrosa, *Chem. Sci.* **2022**, *13*, 3335, DOI: 10.1039/d1sc06355c.