

Sustainability

High-valent bismuth redox catalysis

In the last years, bismuth has transitioned from being considered a mere Lewis acid catalyst to being recognised as an interesting redox catalyst for organic synthesis. A rational design of a ligand scaffold for the Bi center resulted in a robust catalytic system applicable to various bismuth redox processes.

Bismuth is the last non-radioactive element of the periodic table.¹⁾ In addition to its great availability and economical cost, certain Bi compounds have been reported to be non-toxic and non-carcinogenic.²⁾ The presence of Bi in pharmacologically active ingredients such as the antiseptic agent bibrocathol or the antacid medication bismuth subsalicylate exemplifies this low toxicity (Figure 1a).³⁾ It is for these reasons that Bi has been used to develop sustainable chemical processes.⁴⁾

Organic syntheses

In organic syntheses, Bi^{III} salts have been extensively studied as soft Lewis-acid catalysts,⁵⁾ as well as transmetalating reagents in transition-metal-catalysed reactions.⁶⁾ These transformations are examples of redox neutral reactivity and mainly rely on the high Lewis acidity of the Bi^{III} center rather than in its redox properties (Figure 1b).⁷⁾

Bi^{III} salts aren't often engaged in catalytic redox processes. In a series of seminal articles, Barton demonstrated that certain organobismuth(V) compounds of the general structure Ar₃BiX₂ are suited to undergo formal reductive elimination or ligand coupling.⁸⁾ Thermal decomposition of these Bi^V compounds can forge a wide array of Ar-X bonds including Ar-C, Ar-N, Ar-S and Ar-O (Fig-

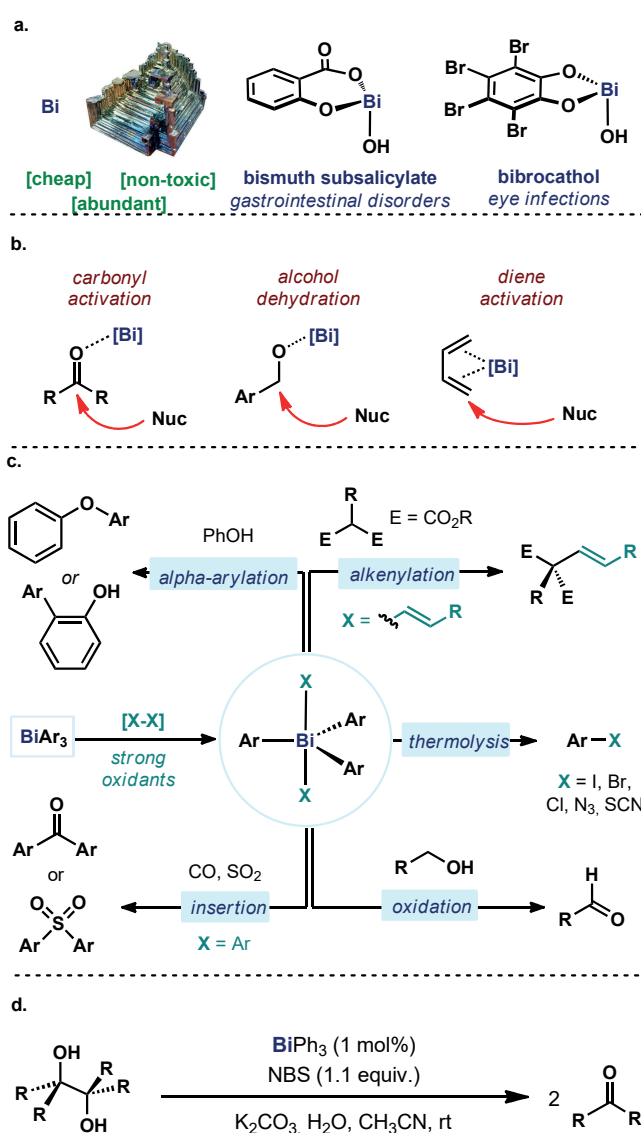


Fig. 1. a) Properties of bismuth and two famous compounds; b) traditional Bi catalysis in organic synthesis: Lewis acid activation; c) stoichiometric applications of the Bi^{III}/Bi^V redox couple in synthesis; d) catalytic oxidation of 1,2-diols reported by Barton.

ure 1c).⁹⁾

Despite this potential for organic synthesis, the field remained dormant for many years due to the necessity of stoichiometric amounts of Bi, which posed a challenge in terms of atom economy and sustainability.

In the 1980s, Barton reported a method for the cleavage of 1,2-diols with N-bromosuccinimide, where he suggested that an organobismuth complex (Ph_3Bi) was acting as a redox catalyst; yet no mechanistic studies on the intermediates involved were reported (Figure 1d).¹⁰⁾

During the 1990s and early 2000s, Suzuki,¹¹⁾ Akiba,¹²⁾ Mukaiyama¹³⁾ and Finet¹⁴⁾ among others explored the use of bismacyclic scaffolds to enhance the selectivity and facilitate the reductive elimination of C–C, C–O and C–N bonds employing Bi^{III} species in presence of an oxidant, usually *meta*-chloroperoxybenzoic acid (mCPBA). Ball has recently employed a similar strategy to develop an oxidative α -arylation of phenols with arylboronic acids.¹⁵⁾ In the latter report, intense detail was devoted to providing a mechanistic picture of a rather elusive fundamental step, namely the transmetallation of arylboronic acids to Bi^{III} centers.

These methodologies certainly contributed to expanding the scope of processes based on the $\text{Bi}^{\text{III}}/\text{Bi}^{\text{V}}$ redox couple. But the need for stoichiometric amounts of Bi and strong oxidants to regenerate the Bi^{V} species limited its applicability

in catalytic redox transformations.

Design and approach

With the aim of providing solutions to the aforementioned challenges and developing greener and alternative transformations, we have recently implemented a research program that aims at the development of bismuth redox catalysis for the synthesis of organic compounds. To completely unlock its potential, our research programme was initially divided into two main fronts: low-valent bismuth redox catalysis, where Bi^{I} compounds are exploited; and high-valent bismuth redox catalysis, which uses the benefits of the $\text{Bi}^{\text{III}}/\text{Bi}^{\text{V}}$ couple.

Low-valent bismuth redox catalysis capitalises on the reducing power and nucleophilicity of Bi^{I} pincer complexes,¹⁶⁾ which proved to be excellent catalysts for the transfer-hydrogenation of azo- and nitroarenes,¹⁷⁾ as well as the activation and reduction of N_2O .¹⁸⁾ Although rarely investigated, low-valent Bi-catalysis holds potential for synthetically relevant transformations.

Applications in catalysis of the $\text{Bi}^{\text{III}}/\text{Bi}^{\text{V}}$ redox couple have been limited by several factors, mainly

- the difficulty of accessing Bi^{V} from Bi^{III} ,
- the ability of organobismuth compounds to exchange and scramble ligands in solution,
- the dynamic behaviour and unpredictable geometries adopted by Bi^{V} compounds depending on the ligands, and
- the large span of coordination number of Bi cations.

We found initial inspiration in Suzuki's report about a triaryl Bi^{III} complex bearing a tethered diphenylsulfone scaffold (Figure 2a).¹¹⁾ Upon oxidation with strong oxidants, the corresponding Bi^{V} complexes were readily accessed and thermally decomposed via a formal reductive elimination to

selectively forge Ar–X bonds (X = Cl, Br, I). This strategy has also been applied by Fokin in the context of triazole synthesis as a diversification point in click reactions.¹⁹⁾

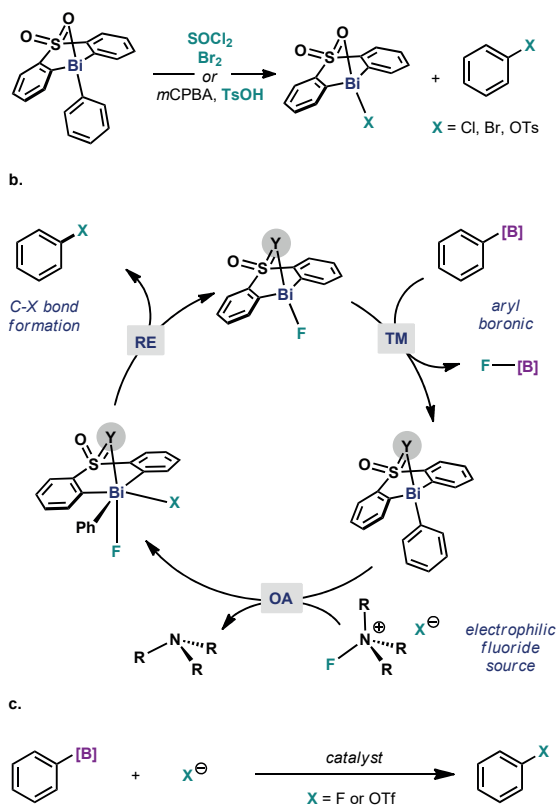
These studies established the foundations of our approach and were an excellent starting point to study the feasibility of $\text{Bi}^{\text{III}}/\text{Bi}^{\text{V}}$ catalysis. Furthermore, the diphenylsulfone scaffold forms a six-membered bismacycle, which helps to control its fluxional behaviour, thus resulting in high selectivity for the pendant aryl group. In addition to its structural advantages, we also hypothesised that the O atoms on the sulfone backbone could influence the Bi center, hence providing an additional modification site if required.

To mimic transition metal catalysis, a simple catalytic cycle based on an hypothetical $\text{Bi}^{\text{III}}/\text{Bi}^{\text{V}}$ couple for the formation of Ar–X bonds was devised (Figure 2b). For this cycle to be unlocked, three fundamental organometallic steps such as transmetalation (TM), oxidative addition (OA), and reductive elimination (RE) should operate in synchrony. With this design in mind, we focused on the oxidative coupling of arylboronic acid derivatives with partners that pose a challenge, such as fluoride or perfluoroalkylsulfonate salts (Figure 2c).

Dissecting high-valent bismuth redox catalysis

The fluorination of aromatic boronic acids is a highly desirable transformation both in medicinal and agrochemical sciences.²⁰⁾ Although transition metals can transform boronic acid derivatives into aryl fluorides, the majority of such methods requires stoichiometric amounts of metal.²¹⁾ Catalytic variants that proceed via outer sphere one-

Oriol Planas joined the group of Josep Cornella as a Post-Doc in 2018. He is developing organic transformations based on the redox properties of bismuth. He received his PhD in 2016 in the group of Xavi Ribas and Anna Company. **Josep Cornella** (Pep) obtained a Max Planck Research Group Leader (MPRGL) in 2017 to start his independent career at Max-Planck-Institut für Kohlenforschung, where he leads the Sustainable Catalysis Laboratory. He earned his PhD in early 2012 in the group of Igor Larrosa. cornella@kofo.mpg.de



[challenging catalytic transformations using transition metals]

Fig. 2. High-valent bismuth catalysis. a) Inspiration: stoichiometric use of organobismuth for C-X bond formation. b) Catalysis: hypothetical $\text{Bi}^{\text{III}}/\text{Bi}^{\text{V}}$ catalytic cycle. c) Benchmark reactions: conversion of arylboronic acids to aryl fluorides and triflates.

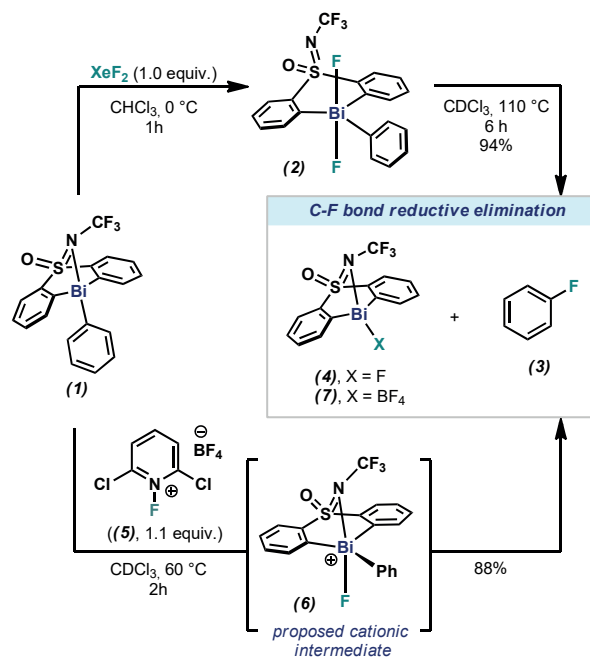


Fig. 3. $\text{C}(\text{sp}^2)\text{-F}$ reductive elimination from Bi^{V} species.

electron processes, thus avoiding the intermediacy of purely organometallic intermediates, are rare.²²⁾

We combined the high oxidation potential of Bi^{V} species, the lability of Bi-X bonds, and a sulfone-based bismacyle to fluorinate aryl boronic esters.²³⁾ After a thorough screening of sulfone-based complexes, we identified a sulfoximine-bearing bismuth complex with a S=N-CF_3 (1) moiety that proved key for the reactivity (Figure 3).

Oxidation of (1) with XeF_2 provides (2) in quantitative yields. Thermolysis of (2) resulted in a $\text{C}(\text{sp}^2)\text{-F}$ reductive elimination, affording 94 % yield of fluorobenzene (3) with concomitant formation of the corresponding $\text{Bi}^{\text{III}}\text{-F}$ (4). The milder N-flu-

oro-2,6-dichloropyridinium tetrafluoroborate (5) can replace XeF_2 , providing 88 % yield of fluorobenzene after the oxidation/reductive elimination sequence. In the latter thermolysis, a cationic Bi^{V} is postulated to be an intermediate (6), although further studies to fully elucidate its exact structure are currently underway.

Turning it catalytic

In the combination of aryl boronic acid derivatives and the newly designed bismine ((7) and (8), Figure 4, p. XX), additional KF as an activator provides $\text{Ar-Bi}^{\text{III}}$ compounds with various functional groups on the aryl ring. A two-step method for fluorination is possible with (5) at

60°C (Figure 4a, (9) – (14)). Since the individual fundamental organometallic steps postulated in Figure 2b had been demonstrated to be feasible, we wanted to merge them in one catalytic cycle.

IN A NUTSHELL

The recent advancements in bismuth redox catalysis make it possible to develop chemical transformations using a sustainable, cheap, and abundant element.

Bi is able to undergo transmetalation, oxidative addition, and reductive elimination, resulting in reactivity that outperforms and reaches beyond the limits for the elements of the d-block.

For broader use, mild oxidants and lower catalyst loadings are required.

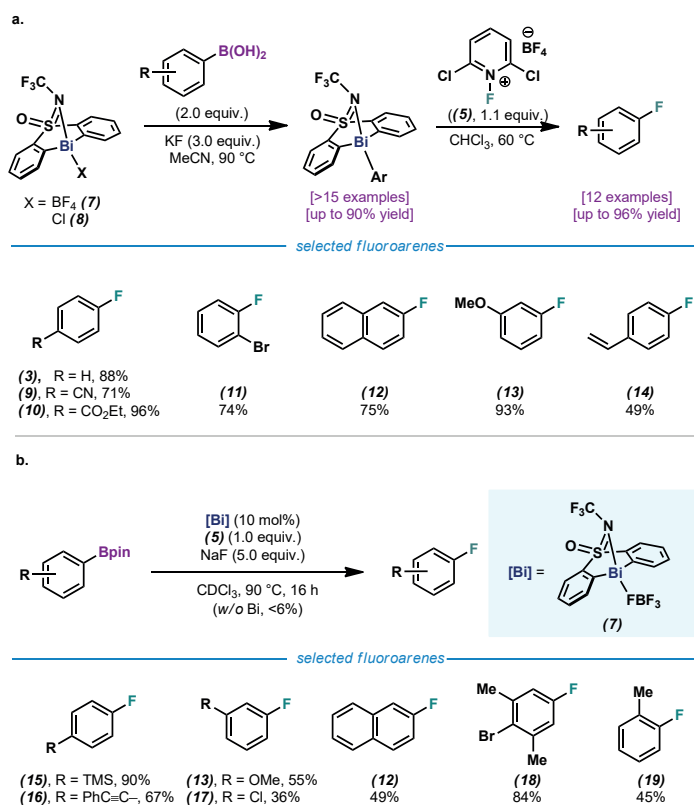


Fig. 4. Fluorination of arylboronic acid derivatives through bismuth redox processes. a) Bismuth-mediated fluorination of arylboronic acids. b) Catalytic fluorination of boronic esters through a Bi^{III}/Bi^V redox cycle.

After optimisation of the reaction conditions, a variety of aryl boronic esters could be converted to the corresponding aryl fluorides using 10 mol% of (**7**) (Figure 4b). Whereas substitution in *para*-position posed no difficulties ((**15**), (**16**), (**18**)), *meta*-substituted aryl boronic esters were more difficult ((**13**), (**17**)). Polyaromatic systems and sterically crowded compounds were also amenable for fluorination ((**12**) and (**19**), respectively). It is important to note that the reaction does not proceed without Bi.

So, Bi not only mimics organometallic transition-metal-like behaviour, but also unveils alternative reactivity that is beyond their scope. With a view towards expanding this reactivity to other coupling partners, an example by Mukaiyama (Figure 5a) inspired us, where a stoichiometric oxidative coupling between phe-

nylbismine species (**20**) and triflic acid afforded phenyl triflate (**22**) in 29% yield.^{12b,c} Presumably, this reaction proceeded via the intermediacy of (**21**), which delivers the C–OTf product after reductive elimination/ligand coupling. This example is a pioneer concept, as it represents a unique example for the construction of C(sp²)–OTf bonds through cross-coupling. This feature is currently inaccessible to transition metals due to the weak nucleophilic character of the triflate ion.

Uncommon partners

It was hence envisaged that our redox platform could provide a catalytic variant that forges C–O bonds using rather uncommon coupling partners such as perfluoroalkylsulfonate salts (Figure 5b).²⁴ Optimisation of the reac-

tion conditions led us to use a bismine catalyst featuring a diarylsulfone backbone decorated with electron withdrawing CF₃ groups (**23**), (**5**) as oxidant, sodium phosphate as base, and 5 Å molecular sieves. Under these conditions, aryl boronic acids with various substitution patterns were converted to their corresponding triflates using NaOTf as a coupling partner ((**25**) – (**29**)). Replacing NaOTf by KONf afforded even better yields of the corresponding aryl nonaflates ((**30**) – (**34**)).

Crucial information on the operating mechanism for the C–OTf bond formation was obtained when phenylbismine (**35**) was oxidised with (**5**) in the presence of NaOTf and formed phenyl triflate (**22**) quantitatively (Figure 5c).

This outcome points to the formation of a highly electrophilic Bi^V intermediate (**36**) bearing a OTf moiety, in agreement with the intermediate proposed by Mukaiyama. Indeed, this species was detected in high-resolution mass spectrometry (HRMS), suggesting its presence during the catalytic transformation. Together with preliminary DFT studies, this indicates that the reaction also follows a catalytic cycle based on fundamental organometallic steps, resembling the one in Figure 2. In this case, reductive elimination is proposed to proceed through a transition state involving a five-membered cycle, in which the triflate ion acts as a nucleophile to deliver the desired product.

Recently, elements of the group 15 have been at the center of attention as they have been shown to be applicable as catalysts in a myriad of organic transformations.²⁵ Indeed, strategies exploiting the use of their redox properties have recently been reported,²⁶ and even one-electron processes for Bi are beginning to have an impact in organic synthesis.²⁷ Multinuclear complexes,²⁸ ligand design, and in-

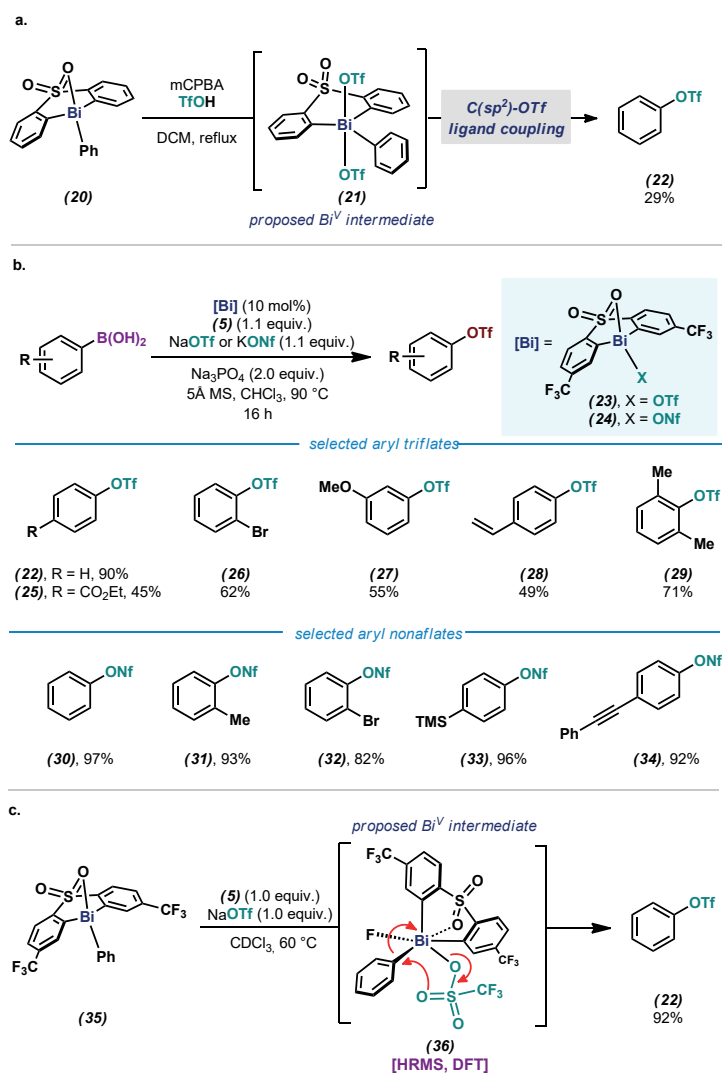


Fig. 5. a) Precedent: Bi-mediated C-OTf bond formation reported by Mukaiyama. b) Catalytic triflation and nonaflation of arylboronic acids via bismuth redox catalysis. c) Detection of high-valent intermediate by HRMS.

depth mechanistic studies will be essential to fully understand the underlying mechanisms of these transformations, leading to further discoveries through high-valent Bi redox catalysis. ■

- 1) P. de Marcillac, N. Coron, G. Dambier, J. Leblanc, J.-P. Moalic, *Nature* 2003, 422, 876–878
- 2) R. Mohan, *Nat. Chem.* 2010, 2, 336–336
- 3) a) G. G. Briand, N. Burford, *Chem. Rev.* 1999, 99, 2601–2658; b) D. M. Keogan, D. M. Griffith, *Molecules* 2014, 19, 15258–15297
- 4) a) J. M. Bothwell, S. W. Krabbe, R. S. Mohan, *Chem. Soc. Rev.* 2011, 40, 4649–4707; b) A. Gagnon, J. Dansereau, A. Le Roch, *Synthesis* 2017, 49, 1707–1745; c) K. Ruffell, L. T. Ball, *Trends Chem.* 2020, 2, 867–869

- 5) T. Ollevier, ed. *Bismuth-Mediated Organic Reactions*, Springer, 2012
- 6) M. Hébert, P. Petitot, E. Benoit, J. Dansereau, T. Ahmad, A. Le Roch, X. Ottenwaelder, A. Gagnon, *J. Org. Chem.* 2016, 81, 5401–5416
- 7) C. Lichtenberg, *Chem. Commun.* 2021, 57, 4483–4495
- 8) a) D. H. R. Barton, D. J. Lester, W. B. Motherwell, M. T. B. Papoula, *J. Chem. Soc., Chem. Commun.* 1980, 246–247; b) D. H. R. Barton, J.-C. Blazejewski, B. Charpiot, D. J. Lester, W. B. Motherwell, M. T. B. Papoula, *J. Chem. Soc., Chem. Commun.* 1980, 827–829; c) D. H. R. Barton, J. P. Kitchin, D. J. Lester, W. B. Motherwell, M. T. B. Papoula, *Tetrahedron* 1981, 37, 73–79; d) D. H. R. Barton, N. Y. Bhatnagar, J.-P. Finet, W. B. Motherwell, *Tetrahedron* 1986, 42, 3111–3122.
- 9) a) J.-P. Finet, ed. *Ligand Coupling Reac-*

tions with Heteroatomic Compounds, Elsevier, 1998; b) F. Zhao, X.-F. Wu, *J. Catal.* 2021, 397, 201–204

- 10) a) D. H. R. Barton, W. B. Motherwell, A. Stobie, *J. Chem. Soc., Chem. Commun.* 1981, 1232–1233
- 11) H. Suzuki, T. Murafuji, N. Azuma, *J. Chem. Soc., Perkin Trans.* 1992, 1, 1593–1600
- 12) K. Ohkata, S. Takemoto, M. Ohnishi, K.-y. Akiba, *Tetrahedron Lett.* 1989, 30, 4841–4844
- 13) a) K. Ikegai, T. Mukaiyama, *Chem. Lett.* 2005, 34, 1496–1497; b) N. Sakurai, T. Mukaiyama, *Heterocycles* 2007, 74, 771–790; c) S. Naoto, M. Teruaki, *Chem. Lett.* 2007, 36, 928–929. d) S. Imachi, T. Mukaiyama, *Chem. Lett.* 2007, 36, 718–719
- 14) A. Y. Fedorov, J.-P. Finet, *J. Chem. Soc., Perkin Trans.* 2000, 1, 3775–3778
- 15) M. Jurrat, L. Maggi, W. Lewis, L. T. Ball, *Nat. Chem.* 2020, 12, 260–269
- 16) P. Šimon, F. de Proft, R. Jambor, A. Růžicka, L. Dostál, *Angew. Chem Int. Ed.* 2010, 49, 5468–5471
- 17) F. Wang, O. Planas, J. Cornella, *J. Am. Chem. Soc.* 2019, 141, 4235–4240
- 18) Y. Pang, M. Leutzsch, N. Nöthling, J. Cornella, *J. Am. Chem. Soc.* 2020, 142, 19473–19479
- 19) B. T. Worrell, S. P. Ellery, V. V. Fokin, *Angew. Chem Int. Ed.* 2013, 125, 13275–13279
- 20) G. Pattison, *Org. Biomol. Chem.* 2019, 17, 5651–5660
- 21) a) P. S. Fier, J. Luo, J. F. Hartwig, *J. Am. Chem. Soc.* 2013, 135, 2552–2559; b) Y. Ye, M. S. Sanford, *J. Am. Chem. Soc.* 2013, 135, 4648–4651; c) M. Tredwell, S. M. Preshlock, N. J. Taylor, S. Gruber, M. Huiban, J. Passchier, J. Mercier, C. Génicot, V. Gouverneur, *Angew. Chem. Int. Ed.* 2014, 53, 7751–7755; d) T. Furuya, H. M. Kaiser, T. Ritter, *Angew. Chem. Int. Ed.* 2008, 47, 5993–5996; e) T. Furuya, T. Ritter, *Org. Lett.* 2009, 11, 2860–2863
- 22) A. R. Mazzotti, M. G. Campbell, P. Tang, J. M. Murphy, T. Ritter, *J. Am. Chem. Soc.* 2013, 135, 14012–14015
- 23) O. Planas, F. Wang, M. Leutzsch, J. Cornella, *Science* 2020, 367, 313–317
- 24) O. Planas, V. Peciukenas, J. Cornella, *J. Am. Chem. Soc.* 2020, 142, 11382–11387.
- 25) J. M. Lipshultz, G. Li, A. T. Radosevich, *J. Am. Chem. Soc.* 2021, 143, 1699–1721
- 26) a) P. P. Power, *Nature* 2010, 463, 171–177; b) C. Weetman, S. Inoue, *ChemCatChem* 2018, 10, 4213–4228; c) R. L. Melen, *Science* 2019, 363, 479–484
- 27) a) R. J. Schwamm, M. Lein, M. P. Coles, C. M. Fitchett, *Chem. Commun.* 2018, 54, 916–919; b) J. Ramler, I. Krummenacher, C. Lichtenberg, *Chem. Eur. J.* 2020, 26, 14551–14555
- 28) M. Magre, J. Kuziola, N. Nöthling, J. Cornella, *Org. Biomol. Chem.* 2021, 19, 4922–4929