Radical-Polar Crossover Catalysis with a d^0 Metal Enabled by a Redox-Active Ligand

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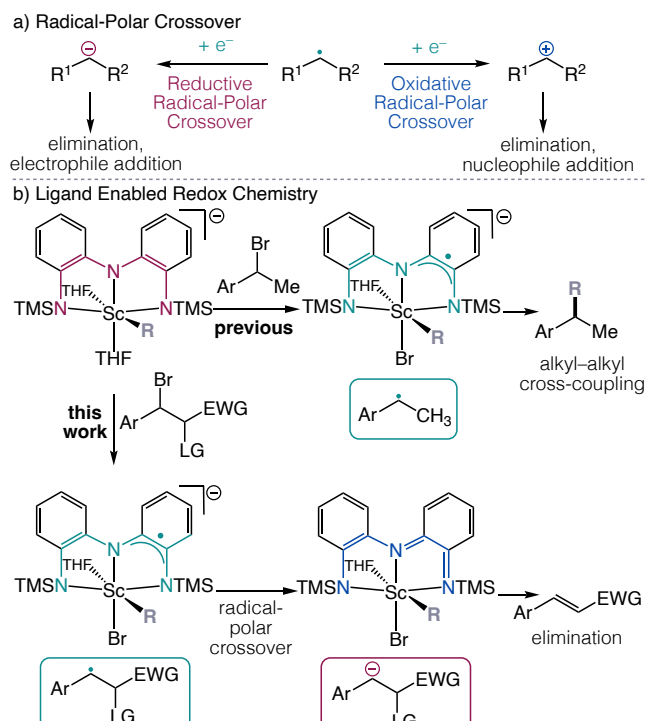*Radical-polar crossover, redox-active ligands, d^0 metals*

ABSTRACT: Radical-polar crossover mechanisms are invoked in numerous late transition metal and photocatalyzed reactions. To the best of our knowledge, reductive radical-polar crossover mechanisms are not invoked for group 3 early transition metals due to their propensity to exist in high oxidation states. Through use of a redox-active (tris)amido ligand we have accessed this mechanism for use with early transition metals. This mechanism is showcased through enabling product formation for a wide variety of elimination products from α-halo substituted benzylic bromides. The mechanism of this new type of reactivity with Sc is explored and Hammett analysis reveals an anionic intermediate. The wide functional group tolerance of this reaction is also demonstrated.

Radical-polar crossover reactions have emerged as an important mechanistic tool in order to harness both radical and polar chemistry and to overcome limitations of both pathways.[1–3] In catalytic examples, a photocatalyst in the presence of light is generally employed in order to either reduce or oxidize the radical to an anion or cation, respectively (**Figure 1a**).[2,3] Alternatively, a late transition metal catalyst, such as Cr, can be used to donate or accept the necessary electrons for the crossover to occur.[1,4–7] Radical-polar crossover is also invoked in electrochemical reactions.[8] A radical-polar crossover mechanism is rarely,

if ever, invoked with group 3 early transition metals.[9,10] This is due to their underexplored redox chemistry. Early transition metals, especially group 3 metals, prefer to stay in their highest oxidation states rendering them d^0 metals with no electrons to donate.[11] If this limitation could be overcome, we hypothesized that these earth abundant and low toxicity metals could be used in this important mechanism without the use of photocatalysts or late transition metals.[12,13]

Recently our group disclosed a report of an alkyl–alkyl cross-coupling reaction catalyzed by a d^0 metal with a redox-active (tris)amido ligand (**Figure 1b**) inspired by the work of Heyduk and coworkers.[14–18] In the mechanism that was previously disclosed, the redox-active ligand mediated the formation of an organic radical intermediate from the alkyl halide through single electron oxidation of the ligand.[19] We hypothesized that a reductive radical-polar crossover mechanism could be harnessed, despite using a d^0 metal, because the (tris)amido ligand can undergo multi electron transfer (**Figure 1b**).[17] Therefore, a test system was designed with an electron withdrawing group (EWG) and leaving group (LG) in the α-position to the radical.


Figure 1. a) Radical-polar crossover possibilities, b) Use of redox-active ligands and d^0 metals for radical and polar reactivity
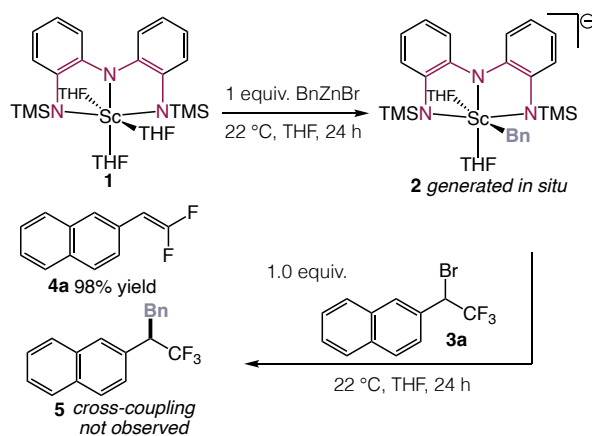
Figure 2. Electron-rich anionic complex **2** generates elimination product **4a**

This would result in an elimination product upon formation of the anion.[20]

These studies were initiated using a benzylic bromide **3a** with a CF$_3$ group in the α-position as the model system (**Figure 2**). These substrates are easily prepared from aryl aldehydes.[21] The trifluoromethyl group is ideal to study as it has the ability to act as an electron withdrawing group and has a leaving group incorporated. The *gem*-difluorostyrene product that is formed is a valuable functional group that is a bioisostere of a carbonyl group.[22–26] These motifs are also relevant to polymer chemistry.[27–31] Finally, these reagents are valuable linchpin reagents for further functionalization.[27,32–36] Based on previous studies, it was known that an electron rich, anionic complex was necessary for reduction of the electrophile to generate a carbon-based radical.[19] Therefore, we hypothesized that using **1** and 1 equivalent of transmetallation reagent BnZnBr, an anionic complex **2**, would be electron rich enough to reduce the benzylic bromide substrate **3a** (**Figure 2**). Excitingly, when *in situ* formed **2** was exposed to 1 equivalent of **3a**, the expected elimination product **4a** was formed in 98% yield based on an a ^{19}F NMR
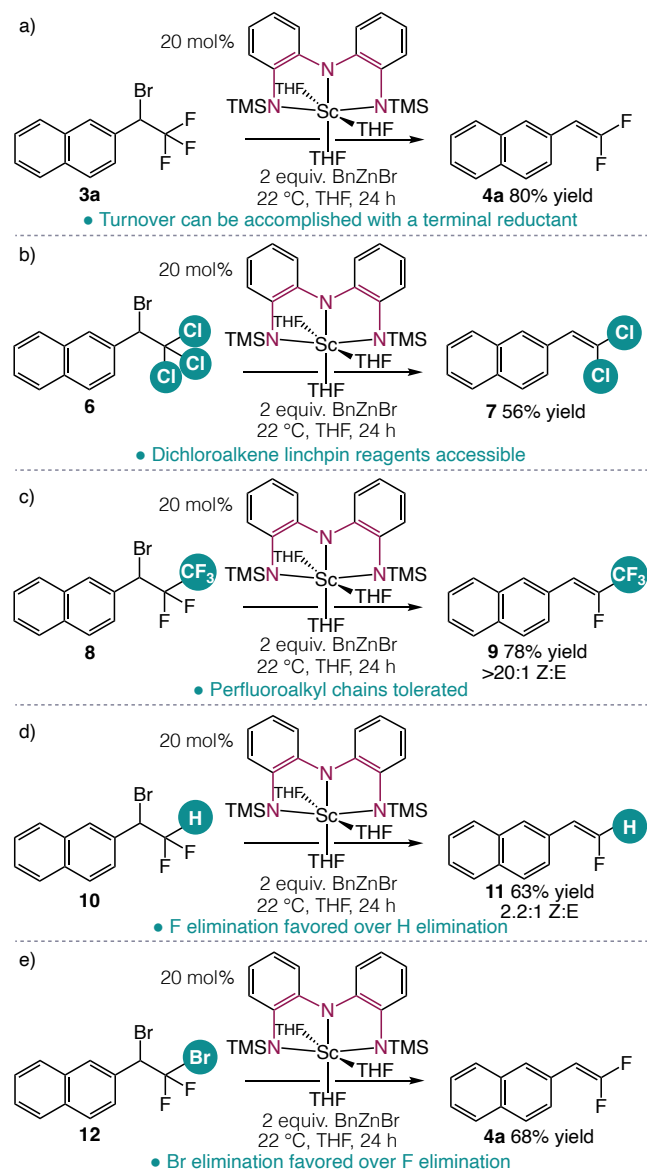

Figure 3. Variety of substrates that will undergo radical-polar crossover catalyzed by **1**

spectroscopy with an internal standard (see SI for isolated yields). No **5**, the product of cross-coupling, was observed.

With this promising result, we then pursued making this transformation catalytic in Sc complex **1** by using a terminal reducing agent that could supply 2 equivalents of electrons (see SI for optimization table). After optimization, 20 mol% of **1** and 2 equivalents of terminal reductant BnZnBr generated the product in 80% yield (**Figure 3a**).

Because reductive radical-polar crossover is a mechanism that, to our knowledge, is unknown to be leveraged by group 3 metals and redox-active ligands, we wanted to investigate other scaffolds to see how general the electron withdrawing group and leaving group could be (**Figure 3b-e**). A variety of α-halogenated benzylic bromides were investigated which demonstrates that this reactivity is general for any α-halogenated benzylic bromide. Chloride elimination was demonstrated with compound **6** which undergoes elimination to give the *gem*-dichloroalkene **7** in 56% isolated yield (**Figure 3b**). Pentafluoro compound **8** undergoes fluoride elimination to give **9** in 78% yield with a >20:1 Z:E ratio (**Figure 3c**). Fluoride elimination was also observed with difluoromethyl bromide **10** to afford the mono-fluorinated products in 63% yield with a Z:E ratio of 2.2:1 (**Figure 3d**). Notably, no products of hydride elimination were observed. This is in contrast to some late transition metals processes which have inner sphere competition between β-heteroatom and hydride elimination. Compound **12**, which contains both α-fluoro and α-bromo groups, selectively undergoes bromide elimination instead of fluoride elimination to give **3a** in 68% yield (**Figure 3e**). This selectivity with **12** is consistent with bromide being a better leaving group than fluoride.
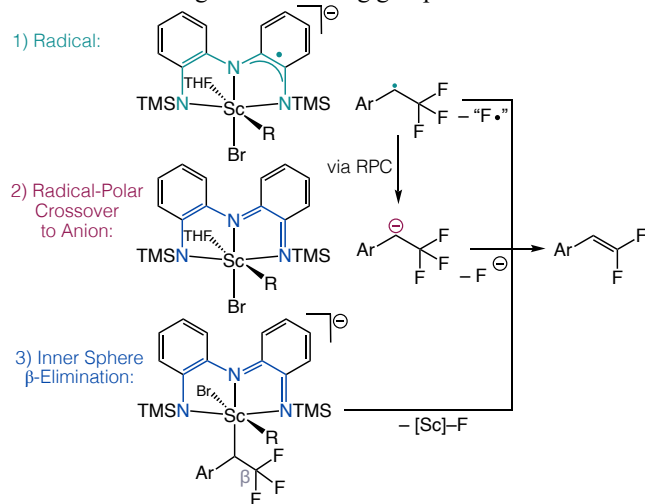
**Figure 4.** Potential mechanistic pathways for product formation

With the generality of this elimination reaction established, we wanted to support our proposed radical-polar crossover mechanism in **Figure 1b** because it lacks precedent with early transition metals. We chose to explore the mechanism using derivatives of **3a** due to the ^{19}F NMR spectroscopy tag and the availability of the starting materials. Three potential intermediates of the organic fragment that could form product are that of 1) a radical intermediate[37], 2) an anionic intermediate formed from radical-polar crossover, and 3) an inner sphere β-halide elimination from an organometallic species[38,39] (**Figure 4**). The results of no competition between elimination of bromide versus fluoride in **Figure 3e** suggest the leaving group ability governs this selectivity. This is despite a 2:1 ratio of F:Br and also

the greater bond strength of Sc–F versus Sc–Br. This suggests mechanism 3 is inoperable. Similarly, the preference of fluoride versus hydride elimination confirms this.[38] Additionally, no competitive cross-coupling is observed between the organic fragments in the inner sphere mechanism of this coordinatively saturated complex further ruling out mechanism 3. While mechanism 1 is also unlikely, because catalyst **1** is known to induce radical mechanisms, further studies were needed to rule it out.[19,40]
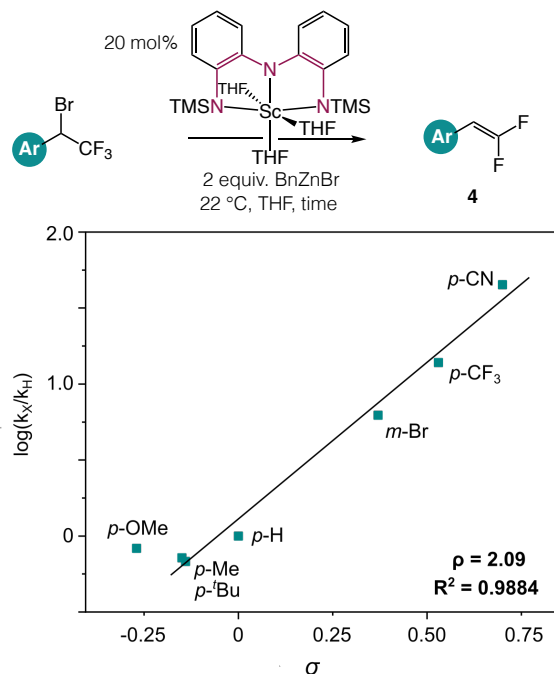

Figure 5. Hammett analysis implicates an anionic intermediate

The importance of an anionic intermediate in the synthesis of *gem*-difluoroalkenes is supported by a Hammett analysis of this reaction which revealed an overall increase in reaction rate with increasingly electron-deficient substrates (**Figure 5**). A linear relationship is observed for the *p*-^{t}Bu, *p*-Me, *p*-H, *m*-Br, *p*-CF$_3$ and *p*-CN substrates. The positive slope (ρ) of 2.09 suggests the mechanism is highly sensitive to the electronic effects of the substituents and that the rate-determining step of the reaction involves the build up of negative charge suggesting, an anionic intermediate. Plotting the data versus Creary radical parameters did not result in any trend (see SI for details). Interestingly, the
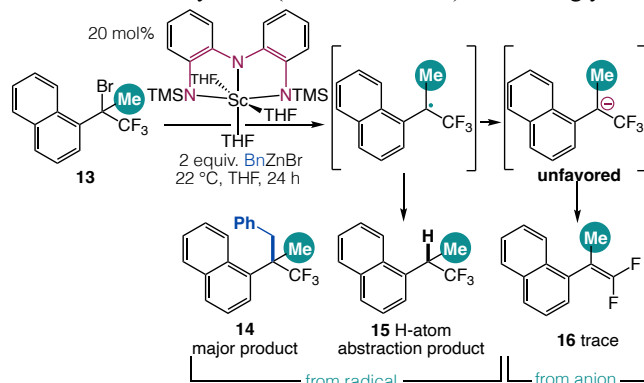
**Figure 6.** Probing intermediacy of a radical and an anion
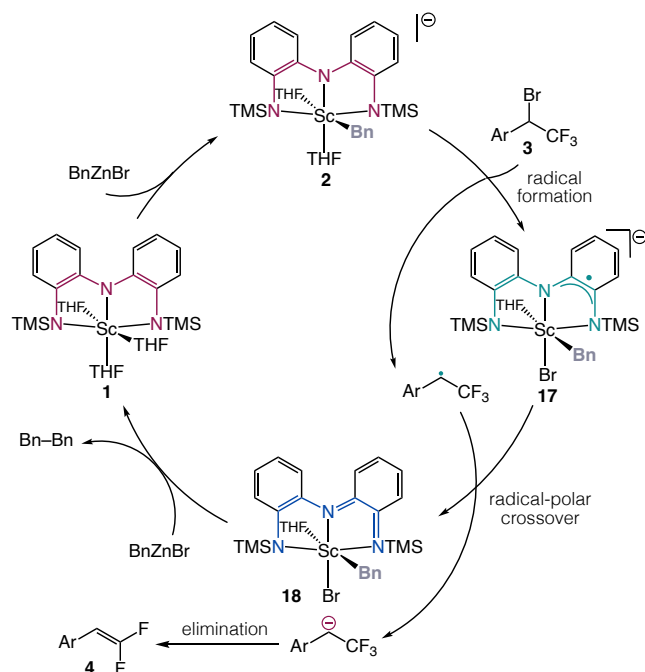
Figure 7. Proposed mechanism for elimination via radical-polar crossover

p-OMe substrate did not fit the trend well, likely due to its electron rich nature.

To support for the intermediacy of both a radical as well as an anionic intermediate in this catalytic reaction, an experiment was designed to see if using tertiary bromide substrate **13** could interrupt the crossover to the anion. This would be due to the tertiary radical being stabilized and the tertiary anion being destabilized (**Figure 6**). This reaction results in the complete consumption of **13** to afford the cross-coupling product **14** as the major product (20%) along with other byproducts, including H-atom abstraction (see Supporting information, page S76). It is known that the cross-coupling product is formed from a benzylic radical intermediate.[19] Since radical-polar crossover to generate the tertiary anion from **13** would be unfavorable compared to the analogous secondary substrate, the fact that only trace amounts of **16** are observed supports the intermediacy of anionic intermediates in the synthesis of gem-difluoroalkenes with **1**. Observation of **14** as the major product also supports the formation of transient benzylic radicals en route to the proposed radical-polar crossover, but in the case of **13** cross-coupling occurs instead via our previously reported mechanism.

Based on these results, we propose that the reaction proceeds via formation of the benzylic radical intermediate via 1-electron reduction of **3** by **2**, which can occur via a variety of mechanisms (e.g. halogen atom abstraction or electron transfer followed by loss of bromide) to generate a benzylic radical and singly oxidized Sc complex **17**. Radical-polar crossover via electron transfer from the resulting paramagnetic complex to the benzylic radical intermediate generates an anionic intermediate that can undergo fluoride elimination to afford the *gem*-difluoroalkenes.
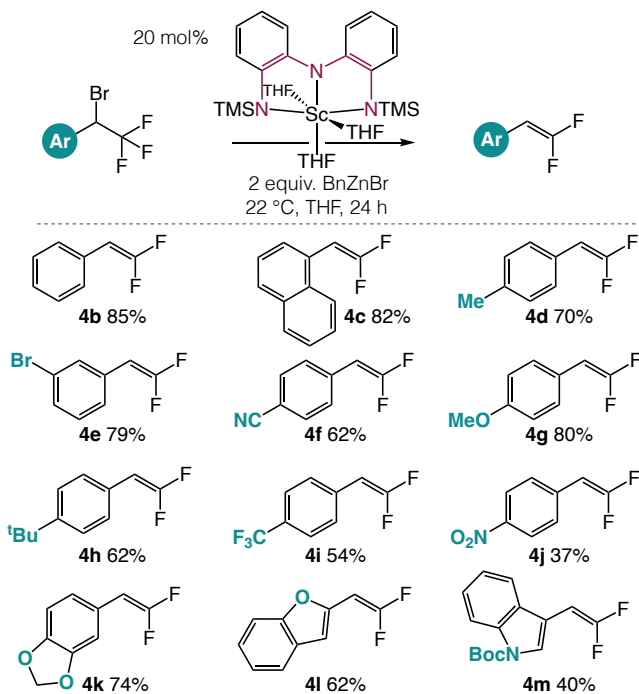
Figure 8. Functional group tolerance and scope

In order to explore the generality of *gem*-difluoroalkene synthesis by fluoride elimination, we pursued exploring the scope of products accessible with Sc complex **1**. Electron-neutral **4b** was formed in excellent yield (85%). 1-naphthyl-substituted **4c** was also efficiently synthesized, displaying tolerance to sterics. Arenes with electron-donating groups were also well tolerated, forming alkyl- and oxygen-substituted products (**4d**, **4g**, **4h**, and **4k**) in 62-80% yields. Further displaying the electronic scope, electron-poor arenes **4e**, **4f**, and **4i** were also formed in good yields (up to 79%); even nitro-substituted **4j** was formed in modest yield (37%). Tolerance of oxygen-containing functional groups is displayed (**4k** and **4l**), and the formation of aryl bromide **4e** displays contrasting reactivity compared to late transition metal complexes. Importantly, use of benzofuran- and indole-based arenes gave *gem*-difluoroalkenes **4l** and **4m**, further enabling access to fluorinated pharmaceutically relevant heterocycles.

In summary, a d^0 metal catalyst supported by a redox-active (tris)amido ligand was demonstrated to participate in a radical-polar crossover mechanism. To our knowledge, this was a previously underutilized mechanism with early transition metals. A wide scope of elimination reactions were explored, demonstrating the far reach of this methodology. Mechanistic investigations indicate the presence of an anionic intermediate, supporting the conclusion that this reaction is operating under a radical-polar crossover mechanism. Finally, a wide functional group tolerance is showcased in the synthesis of a scope of *gem*-difluorostyrenes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and compound characterization (PDF)

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Author Contributions

All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

REFERENCES

(1)   Pitzer, L.; Schwarz, J. L.; Glorius, F. Reductive Radical-Polar Crossover: Traditional Electrophiles in Modern Radical Reactions. *Chem. Sci.* **2019**, *10* (36), 8285–8291. https://doi.org/10.1039/C9SC03359A.

(2)   Wiles, R. J.; Molander, G. A. Photoredox-Mediated Net-Neutral Radical/Polar Crossover Reactions. *Isr. J. Chem.* **2020**, *60* (3–4), 281–293. https://doi.org/10.1002/ijch.201900166.

(3)   Sharma, S.; Singh, J.; Sharma, A. Visible Light Assisted Radical-Polar/Polar-Radical Crossover Reactions in Organic Synthesis. *Adv. Synth. Catal.* **2021**, *363* (13), 3146–3169.

(4)   Matos, J. L. M.; Vásquez-Céspedes, S.; Gu, J.; Oguma, T.; Shenvi, R. A. Branch-Selective Addition of Unactivated Olefins into Imines and Aldehydes. *J. Am. Chem. Soc.* **2018**, *140* (49), 16976–16981. https://doi.org/10.1021/jacs.8b11699.

(5)   Ni, S.; Padial, N. M.; Kingston, C.; Vantourout, J. C.; Schmitt, D. C.; Edwards, J. T.; Kruszyk, M. M.; Merchant, R. R.; Mykhailiuk, P. K.; Sanchez, B. B.; Yang, S.; Perry, M. A.; Gallego, G. M.; Mousseau, J. J.; Collins, M. R.; Cherney, R. J.; Lebed, P. S.; Chen, J. S.; Qin, T.; Baran, P. S. A Radical Approach to Anionic Chemistry: Synthesis of Ketones, Alcohols, and Amines. *J. Am. Chem. Soc.* **2019**, *141* (16), 6726–6739. https://doi.org/10.1021/jacs.9b02238.

(6)   Schwarz, J. L.; Schäfers, F.; Tlahuext-Aca, A.; Lückemeier, L.; Glorius, F. Diastereoselective Allylation of Aldehydes by Dual Photoredox and Chromium Catalysis. *J. Am. Chem. Soc.* **2018**, *140* (40), 12705–12709. https://doi.org/10.1021/jacs.8b08052.

(7)   Mitsunuma, H.; Tanabe, S.; Fuse, H.; Ohkubo, K.; Kanai, M. Catalytic Asymmetric Allylation of Aldehydes with Alkenes through Allylic C(Sp3)–H Functionalization Mediated by Organophotoredox and Chiral Chromium Hybrid Catalysis. *Chem. Sci.* **2019**, *10* (12), 3459–3465. https://doi.org/10.1039/C8SC05677C.

(8)   Zhang, W.; Lin, S. Electroreductive Carbofunctionalization of Alkenes with Alkyl Bromides via a Radical-Polar Crossover Mechanism. *J. Am. Chem. Soc.* **2020**, *142* (49), 20661–20670. https://doi.org/10.1021/jacs.0c08532.

(9)   McCallum, T.; Wu, X.; Lin, S. Recent Advances in Titanium Radical Redox Catalysis. *J. Org. Chem.* **2019**, *84* (22), 14369–14380. https://doi.org/10.1021/acs.joc.9b02465.

(10)   Wu, X.; Chang, Y.; Lin, S. Titanium Radical Redox Catalysis: Recent Innovations in Catalysts, Reactions, and Modes of Activation. *Chem* **2022**. https://doi.org/10.1016/j.chempr.2022.06.005.

(11)   Beaumier, E. P.; Pearce, A. J.; See, X. Y.; Tonks, I. A. Modern Applications of Low-Valent Early Transition Metals in Synthesis and Catalysis. *Nat. Rev. Chem.* **2019**, *3* (1), 15–34. https://doi.org/10.1038/s41570-018-0059-x.

(12)   Egorova, K. S.; Ananikov, V. P. Toxicity of Metal Compounds: Knowledge and Myths. *Organometallics* **2017**, *36* (21), 4071–4090. https://doi.org/10.1021/acs.organomet.7b00605.

(13) Rim, K. T.; Koo, K. H.; Park, J. S. Toxicological Evaluations of Rare Earths and Their Health Impacts to Workers: A Literature Review. *Saf. Health Work* **2013**, *4* (1), 12–26. https://doi.org/10.5491/SHAW.2013.4.1.12.

(14) Belli, R. G.; Tafuri, V. C.; Joannou, M. V.; Roberts, C. C. D0 Metal-Catalyzed Alkyl–Alkyl Cross-Coupling Enabled by a Redox-Active Ligand. *ACS Catal.* **2022**, *12* (5), 3094–3099. https://doi.org/10.1021/acscatal.1c06002.

(15) Haneline, M. R.; Heyduk, A. F. C−C Bond-Forming Reductive Elimination from a Zirconium(IV) Redox-Active Ligand Complex. *J. Am. Chem. Soc.* **2006**, *128* (26), 8410–8411. https://doi.org/10.1021/ja061107a.

(16) Blackmore, K. J.; Ziller, J. W.; Heyduk, A. F. "Oxidative Addition" to a Zirconium(IV) Redox-Active Ligand Complex. *Inorg. Chem.* **2005**, *44* (16), 5559–5561. https://doi.org/10.1021/ic050997c.

(17) Nguyen, A. I.; Blackmore, K. J.; Carter, S. M.; Zarkesh, R. A.; Heyduk, A. F. One- and Two-Electron Reactivity of a Tantalum(V) Complex with a Redox-Active Tris(Amido) Ligand. *J. Am. Chem. Soc.* **2009**, *131* (9), 3307–3316. https://doi.org/10.1021/ja808542j.

(18) Munhá, R. F.; Zarkesh, R. A.; Heyduk, A. F. Tuning the Electronic and Steric Parameters of a Redox-Active Tris(Amido) Ligand. *Inorg. Chem.* **2013**, *52* (19), 11244–11255. https://doi.org/10.1021/ic401496w.

(19) Belli, R. G.; Tafuri, V. C.; Roberts, C. C. Improving Alkyl–Alkyl Cross-Coupling Catalysis with Early Transition Metals through Mechanistic Understanding and Metal Tuning. *ACS Catal.* **2022**, 9430–9436. https://doi.org/10.1021/acscatal.2c02785.

(20) Lang, S. B.; Wiles, R. J.; Kelly, C. B.; Molander, G. A. Photoredox Generation of Carbon-Centered Radicals Enables the Construction of 1,1-Difluoroalkene Carbonyl Mimics. *Angew. Chem. Int. Ed.* **2017**, *56* (47), 15073–15077. https://doi.org/10.1002/anie.201709487.

(21) Kuang, C.; Zhou, X.; Xie, Q.; Ni, C.; Gu, Y.; Hu, J. Generation of Carbocations under Photoredox Catalysis: Electrophilic Aromatic Substitution with 1-Fluoroalkylbenzyl Bromides. *Org. Lett.* **2020**, *22* (21), 8670–8675. https://doi.org/10.1021/acs.orglett.0c03258.

(22) Magueur, G.; Crousse, B.; Ourévitch, M.; Bonnet-Delpon, D.; Bégué, J.-P. Fluoro-Artemisinins: When a Gem-Difluoroethylene Replaces a Carbonyl Group. *J. Fluor. Chem.* **2006**, *127* (4), 637–642. https://doi.org/10.1016/j.jfluchem.2005.12.013.

(23) Meanwell, N. A. Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. *J. Med. Chem.* **2018**, *61* (14), 5822–5880. https://doi.org/10.1021/acs.jmedchem.7b01788.

(24) Meanwell, N. A. The Influence of Bioisosteres in Drug Design: Tactical Applications to Address Developability Problems. In *Tactics in Contemporary Drug Design*; Meanwell, N. A., Ed.; Topics in Medicinal Chemistry; Springer: Berlin, Heidelberg, 2015; pp 283–381. https://doi.org/10.1007/7355_2013_29.

(25) Ma, Y.; Reddy, B. R. P.; Bi, X. Coupling of Trifluoroacetaldehyde N-Triftosylhydrazone with Organoboronic Acids for the Synthesis of Gem-Difluoroalkenes. *Org. Lett.* **2019**, *21* (24), 9860–9863. https://doi.org/10.1021/acs.orglett.9b03740.

(26) Leriche, C.; He, X.; Chang, C. T.; Liu, H. Reversal of the Apparent Regiospecificity of NAD(P)H-Dependent Hydride Transfer: The Properties of the Difluoromethylene Group, A Carbonyl Mimic. *J. Am. Chem. Soc.* **2003**, *125* (21), 6348–6349. https://doi.org/10.1021/ja021487+.

(27) Wang, Z.; Sun, Y.; Shen, L.-Y.; Yang, W.-C.; Meng, F.; Li, P. Photochemical and Electrochemical Strategies in C–F Bond Activation and Functionalization. *Org. Chem. Front.* **2022**, *9* (3), 853–873. https://doi.org/10.1039/D1QO01512E.

(28) Cardoso, V. F.; Correia, D. M.; Ribeiro, C.; Fernandes, M. M.; Lanceros-Méndez, S. Fluorinated Polymers as Smart Materials for Advanced Biomedical Applications. *Polymers* **2018**, *10* (2). https://doi.org/10.3390/polym10020161.

(29) Guerre, M.; Lopez, G.; Améduri, B.; Semsarilar, M.; Ladmiral, V. Solution Self-Assembly of Fluorinated Polymers, an Overview. *Polym. Chem.* **2021**, *12* (27), 3852–3877. https://doi.org/10.1039/D1PY00221J.

(30) Dolui, S.; Kumar, D.; Banerjee, S.; Ameduri, B. Well-Defined Fluorinated Copolymers: Current Status and Future Perspectives. *Acc. Mater. Res.* **2021**, *2* (4), 242–251. https://doi.org/10.1021/accountsmr.1c00015.

(31) *Fluorinated Polymers*; 2016. https://doi.org/10.1039/9781782629368.

(32) Feng, Z.; Geng, S.; Zhang, J. Advances in Silylation and Borylation of Fluoroarenes and Gem-Difluoroalkenes via C-F Bond Cleavage. *Chem. Commun.* **2021**. https://doi.org/10.1039/D1CC04729A.

(33) Zhu, W.; Xi, H.; Jiao, W.; Huang, L.; Wang, L.; Wu, J. Difunctionalization of Gem-Difluoroalkenes via Photoredox Catalysis: Synthesis of Diverse α,α-Difluoromethyl-β-Alkoxysulfones. *Org. Lett.* **2022**. https://doi.org/10.1021/acs.orglett.1c04165.

(34) Wang, J.; Gao, H.; Shi, C.; Chen, G.; Chen, X.; Xu, L.; Cai, X.; Huang, B.; Li, H.; Tan, X. Recent Advances in Radical-Based C-F Bond Activation of Polyfluoroarenes and Gem-Difluoroalkenes. *Chem. Commun.* **2021**. https://doi.org/10.1039/D1CC04189D.

(35) Koley, S.; Altman, R. A. Recent Advances in Transition Metal-Catalyzed Functionalization of Gem-Difluoroalkenes. *Isr. J. Chem.* **2020**, *60* (3–4), 313–339. https://doi.org/10.1002/ijch.201900173.

(36) Jouffroy, M.; Pye, P.; Jerhaoui, S.; Chen, W.; Surkyn, M. Development of a Concise and Robust Route to a Key Fragment of MCL-1 Inhibitors via Stereoselective Defluoroborylation. *J. Org. Chem.* **2021**. https://doi.org/10.1021/acs.joc.1c01666.

(37) Yao, C.; Wang, S.; Norton, J.; Hammond, M. Catalyzing the Hydrodefluorination of CF3-Substituted Alkenes by PhSiH3. H• Transfer from a Nickel Hydride. *J. Am. Chem. Soc.* **2020**, *142* (10), 4793–4799. https://doi.org/10.1021/jacs.9b13757.

(38) Bogdos, M.; Stepanovic, O.; Bismuto, A.; Luraschi, M.; Morandi, B. β-X vs. β-H Elimination. Selection Rules for Chemoselectivity Enabled by Mechanistic Studies. **2022**. https://doi.org/10.26434/chemrxiv-2022-50fd0.

(39) Chen, W.; Ni, S.; Wang, Y.; Pan, Y. Electrochemical-Promoted Nickel-Catalyzed Reductive Allylation of Aryl Halides. *Org. Lett.* **2022**. https://doi.org/10.1021/acs.orglett.2c01247.

(40) Wu, J.; Wu, H.; Liu, X.; Zhang, Y.; Huang, G.; Zhang, C. Nickel-Catalyzed Cross-Coupling of Acyl Chloride with Racemic α-Trifluoromethyl Bromide to Access Chiral α-Trifluoromethyl Ketones. *Org. Lett.* **2022**. https://doi.org/10.1021/acs.orglett.2c01208.

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