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Frustrated Radical Pairs in Organic Synthesis

Minsoo Ju[†],

Zhipeng Lu[†],

Luiz F. T. Novaes,

Jesus I. Martinez Alvarado,

Song Lin*

Department of Chemistry and Chemical Biology, Cornell University, Ithaca, NY 14853, USA.

Abstract

Frustrated radical pairs (FRPs) describe the phenomenon that two distinct radicals—which would otherwise annihilate each other to form a closed-shell covalent adduct—can coexist in solution owing to steric repulsion or weak bonding association. FRPs are typically formed via spontaneous single-electron transfer between two sterically encumbered precursors—an oxidant and a reductant—under ambient conditions. The two components of an FRP exhibit orthogonal chemical properties and can often act in cooperativity to achieve interesting radical reactivities. Initially observed in the study of traditional frustrated Lewis pairs, FRPs have recently been shown to be capable of homolytic activating various chemical bonds. In this Perspective, we will discuss the discovery of FRPs, their fundamental reactivity in chemical bond activation, and recent developments of their use in synthetic organic chemistry including in C—H bond functionalization. We anticipate FRPs will provide new reaction strategies for solving challenging problems in modern organic synthesis.

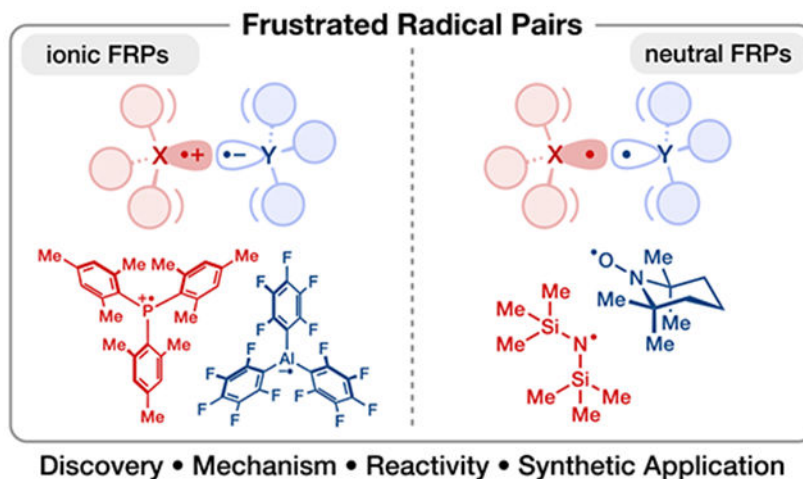
Graphical Abstract

*Corresponding Author Song Lin – Department of Chemistry and Chemical Biology, Cornell University, Ithaca, NY 14853, USA.

songlin@cornell.edu.

[†]Author Contributions

M.J. and Z.L. contributed equally.



INTRODUCTION:

When a Lewis acid donor and a Lewis base acceptor are combined, generally a dative-bonded adduct is formed, but this is not the case when each of the components is too sterically demanding. In 2006, Stephan published a landmark paper describing $\text{Mes}_2\text{P}(\text{C}_6\text{F}_4)\text{B}(\text{C}_6\text{F}_5)_2$ —a sterically encumbered Lewis acid/base pair—does not undergo expected formation of a dative-bond, which can reversibly activate H_2 under metal-free conditions.¹ Such systems that can harness unquenched reactivities of Lewis acidic and basic sites are subsequently named as frustrated Lewis pairs (FLPs) (Scheme 1A).² Since then, the study of FLPs has rapidly expanded into a vibrant subfield at the interface of organic and inorganic chemistry with numerous fascinating discoveries and applications in polymerization, bioinorganic chemistry, materials science, and synthetic organic chemistry.³

The “frustration” between such Lewis acid/base couples are often intuitively attributed to the steric encumbrance making the frontier molecular orbitals (FMOs) of the two species spatially unavailable to form a dative bond (i.e., steric frustration).⁴ Recently, it has also been suggested that energetic mismatching between the acid and base components’ molecular orbitals can lead to weakened bonding interaction between the pair (i.e., electronic frustration),⁵ giving rise to the formation of FLPs from smaller precursors. Notable examples of FLPs make use of triarylboranes as the Lewis acid component, with hindered amines or phosphines comprising the Lewis base component. The coexistence of strong Lewis acidic and basic dyads that would otherwise quench each other often give rise to unique reactivities that are distinct from canonical Lewis acid/base chemistry. Outside of the realm of H_2 activation, FLPs have also been applied to the activation of small molecules such as CO_2 and N_2O ,⁶ as well as organic functional groups such as $\text{C}=\text{N}$, $\text{C}=\text{O}$, and $\text{C}\equiv\text{C}$.⁷

As more and more new reactivities of FLPs are being uncovered, efforts have also been dedicated to elucidating the mechanisms of their formation and transformation. The mode of molecular activation by FLPs was believed to be a heterolytic process, where the Lewis base donates two electrons to the σ^* -orbital of the substrate $\text{X}-\text{Y}$ bond, inducing the cleavage of the $\text{X}-\text{Y}$ σ -bond and subsequent donation of the two bonding electrons to

the empty p -orbital of the Lewis acid acceptor.⁸ Recently, a single-electron transfer (SET) pathway was uncovered in certain FLPs engaging in small molecule activation as evidenced by spectroscopic studies.⁹ In this situation, transfer of a single electron from the Lewis base donor to an empty orbital of the Lewis acid acceptor generates a frustrated radical pair (FRP), a term coined by Stephan in 2013.¹⁰ Analogous to FLPs, an important feature of an FRP is that the two constituent radicals—owing to steric or electronic frustration—either do not undergo recombination or form a very weak adduct that can readily dissociate under ambient conditions (Scheme 2). The phenomenon of SET between Lewis acid/base pairs is reminiscent of electron donor-acceptor (EDA) chemistry. In fact, in several instances we review in this essay, the FRP precursors form EDA complexes (also known as charge-transfer complexes, CTCs) prior to SET.¹¹ However, FRP generation is distinctive in that the SET step does not require photoexcitation and can happen spontaneously at room temperature.

Finally, it is important to note that from a reactivity point of view, an FRP—akin to an FLP—feature two components with distinct chemical properties (e.g., many known FRPs consist of a persistent radical and a transient radical), which thus exhibit orthogonal reactivities and can act in cooperativity in a chemical transformation. In this sense, coexisting radical pairs that do not meet this criterion are not categorized as FRPs in this Perspective, examples including a duo of persistent TEMPO/O₂ radicals and a pair of sterically encumbered *tert*-butyl radicals.

While literature examples remain limited, FRPs have been shown to be capable of cleaving chemical bonds in a homolytic fashion, which may open a new door for bond activation that is not accessible through traditional FLP chemistry. In this Perspective, we will highlight two types of FRPs depending on their charged states: Ionic FRPs consist of a radical cation and a radical anion resulting from SET between two neutral acid-base precursors (Scheme 1B, top); and neutral FRPs comprise of two neutral radicals arising from reactions of a pair of charged species (Scheme 1B, bottom). There are very limited examples of FRPs featuring both a neutral radical and a radical ion, which will also be discussed. We note that due to the nascency of this area of research, several examples discussed herein did not strategically employ FRPs as a mechanistic guiding principle in the reaction development and did not explicitly use the term “frustrated radical pair” to describe the observed open-shell intermediates. Nevertheless, the radical assemblies interrogated in these studies display key properties of FRPs as described in this essay, and they are thus included in the discussion. In the following sections, we will first introduce early studies on the structural properties and electron transfer mechanisms of FRPs, which is followed by case studies in chemical bond activation and their applications in organic synthesis.

FROM FLPS TO FRPS: THE DISCOVERY

The notion of FLPs undergoing a homolytic pathway for molecular activation was first suggested by Pier and co-workers in 2011.¹² It was proposed as one of the four possible mechanisms for H₂ splitting by a ^tBu₃P/B(C₆F₅)₃ FLP system, but this paramagnetic behavior was expected to contribute minimally to the observed reactivity based on a mismatch between the oxidation potential of ^tBu₃P (0.90 V vs Fc⁰/Fc⁺ in MeCN)¹³ and

the reduction potential of $B(C_6F_5)_3$ (-1.17 V vs Fc^0/Fc^+ in THF).¹⁴ Later, Stephan and co-workers proposed that an SET between $Mes_3P/B(C_6F_5)_3$ generates a $[Mes_3P]^+[B(C_6F_5)_3]^-$ FRP on the basis of a weak radical signal detected by electron paramagnetic resonance (EPR) spectroscopy.¹⁵ This FRP is thought to be responsible for homolytic activation of the Sn—H bond of Ph_3SnH affording $[Mes_3PH]^+[HB(C_6F_5)_3]^-$ and $Ph_3Sn-SnPh_3$ as products. However, Slootweg and co-workers later reported that this FRP has a very short lifetime of 237 ps as determined by transient absorption spectroscopy (TAS), which suggested that Sn—H bond cleavage is more likely to be dominated by a $2e^-$ pathway.¹⁶

Interestingly, a clear EPR signal for $[Mes_3P]^+$ was detected when $Mes_3P/B(C_6F_5)_3$ was combined with tetrachloro-1,4-benzoquinone (TCQ),¹⁵ despite the fact that an SET between the phosphine and the borane should be thermodynamically unfavorable. Slootweg and co-workers reasoned that a $TCQ-B(C_6F_5)_3$ complex is formed via a weak borane coordination to a carbonyl group of TCQ, and this in-situ generated adduct is calculated to have an increased electron affinity, allowing for a direct SET with the Mes_3P donor (Scheme 3A/B, substrate-assisted SET).¹⁶ Later discoveries showed that other substrates containing a Lewis basic motif such as peroxides¹⁷ and aryl esters¹⁸ can also participate in FRP generation from FLPs. Stephan and co-workers detected the EPR signal for $[Mes_3P]^+$ when $Mes_3P/B(C_6F_5)_3$ was mixed with benzoyl peroxide derivatives to form radical ion pairs $[Mes_3P]^+[RCOOB(C_6F_5)_3]^-$ ($R = Ph, p-BrC_6H_5, p-CH_3C_6H_5$). Since these initial discoveries, the borane-mediated substrate activation toward radical generation (i.e., substrate-assisted SET) has been employed as a reaction strategy for FRP applications in organic synthesis, a topic that will be described in more detail in the next section.

Direct formation of FRPs in the absence of a substrate could be achieved by pairing the phosphine donor with a more oxidizing acceptor partner, thus allowing for a better alignment of their FMOs (Scheme 3A/B, thermal SET). For instance, an evident EPR signal for phosphonium radical cation $[Mes_3P]^+$ was observed when $Al(C_6F_5)_3$ was used instead of $B(C_6F_5)_3$.¹⁵ The corresponding EPR signal for radical anion $[Al(C_6F_5)_3]^-$ was not observed due to its short lifetime. Similarly, Müller and co-workers reported that silylium and trityl cations are potent single-electron oxidants that readily react with phosphine donors.¹⁹ Electron-rich triaryl phosphines with relatively low ionization potentials (5.00 eV for $Tipp_3P$ and 5.26 eV for Mes_3P) were oxidized by silylium cations such as $[(C_6Me_5)_3Si]^+$ ($E_A = 4.08$ eV), and the resulting phosphonium radical cations were verified by spectroscopic and crystallographic analysis. A trialkylphosphine tBu_3P with higher ionization potential (5.60 eV) required the use of Lewis acids with stronger electron affinities such as $[Ph_3C]^+$ ($E_A = 4.93$ eV) for the SET to occur. Furthermore, Wang and co-workers observed that the formation of stable, deep-blue $N^bAr_3^{*+}$ species when the bridged triphenyl amine N^bAr_3 was treated with $B(C_6F_5)_3$,²⁰ again indicating the redox matching between donor and acceptor is key to FRP formation via direct SET.²¹

Lastly, generation of radical pairs can also be induced photochemically in a manner similar to electron donor-acceptor (EDA) complexes (Scheme 3A/B, photochemical SET). Recent studies from Slootweg and co-workers indicated that a photoexcitation process is necessary to create a radical ion pair from the archetypal $Mes_3P/B(C_6F_5)_3$ FLP system where direct SET is not feasible due to a high thermodynamic barrier.¹⁶ While intense EPR signals were

seen upon visible light irradiation (390–500 nm), no radical formation was observed under dark conditions. The charge transfer interaction between $\text{Mes}_3\text{P}/\text{B}(\text{C}_6\text{F}_5)_3$ was studied via resonance Raman spectroscopy by Ando and co-workers.²² Switching the phosphine donor to ${}^t\text{Bu}_3\text{P}$ also afforded a pair of radical ions with visible light irradiation, although the lifetime of this FRP was significantly shorter than one generated from Mes_3P (6 ps vs 247 ps determined by TAS). The short lifetime was attributed to back-electron transfer (BET) to regenerate the FLP precursors. The photoexcitation mode of activation in radical pair formation closely resembles well-established EDA chemistry.²³ These radical pairs are not categorized as FRPs because they exist predominantly as closed-shell species in the ground state under ambient dark conditions, and thus they will not be discussed in detail in this Perspective.

CHEMICAL BOND ACTIVATION BY FRPS

Section 1. Weak-Bond Activation (Sn—H, O—O bonds)

As discussed in the previous section, Stephan discovered the formation of radical ion pair $[\text{Mes}_3\text{P}]^{*+}[\text{B}(\text{C}_6\text{F}_5)_3]^{*-}$ **4-1** from canonical FLP $\text{Mes}_3\text{P}/\text{B}(\text{C}_6\text{F}_5)_3$ via reversible SET (Scheme 4). This system was shown to activate $\text{Ph}_3\text{Sn—H}$ to afford $\text{Ph}_3\text{Sn—SnPh}_3$, although the mechanism was proposed to be heterolytic in nature by Slootweg (*vide supra*). Later, Stephan reported that the addition of benzoyl peroxides to a solution of $\text{Mes}_3\text{P}/\text{B}(\text{C}_6\text{F}_5)_3$ in CH_2Cl_2 induced an instantaneous color change from light purple to deep purple.¹⁷ This color arose from radical ion salt $[\text{Mes}_3\text{P}]^{*+}[\text{C}_6\text{H}_5\text{COOB}(\text{C}_6\text{F}_5)_3]^-$, which was detected by EPR and UV-Vis spectroscopy along with HR-MS spectrometry. Although crystallization of the FRPs has not been successful, the addition of Ph_3SnH reduced the radical ion pair to the corresponding phosphonium salt $[\text{Mes}_3\text{PH}]^+[\text{C}_6\text{H}_5\text{COOB}(\text{C}_6\text{F}_5)_3]^-$, whose structure was unambiguously confirmed by X-ray crystallography. The formation of $[\text{Mes}_3\text{P}]^{*+}[\text{C}_6\text{H}_5\text{COOB}(\text{C}_6\text{F}_5)_3]^-$ was postulated to arise from SET between $\text{Mes}_3\text{P}/\text{B}(\text{C}_6\text{F}_5)_3$ to give the corresponding FRP $[\text{Mes}_3\text{P}]^{*+}[\text{B}(\text{C}_6\text{F}_5)_3]^{*-}$, which then acts in concert to induce homolysis of the peroxide O—O bond. NMR and DFT studies suggested that the coordination of the peroxide to $\text{B}(\text{C}_6\text{F}_5)_3$ facilitated the said SET process.

Section 2. Strong-Bond Activation (C—H, N—H, O—H, C—O, and C=O)

In 2013, Stephan and co-workers reported that $\text{Al}(\text{C}_6\text{F}_5)_3/\text{R}_3\text{P}$ ($\text{R} = {}^t\text{Bu}, \text{Mes}, \text{Nap}$) FLP systems can capture N_2O to form FLP— N_2O adducts **5-1** (Scheme 5).¹⁰ In the case of $\text{R} = {}^t\text{Bu}$, ${}^t\text{Bu}_3\text{P}(\text{N}_2\text{O})\text{Al}(\text{C}_6\text{F}_5)_3$ was isolated, which can further react with an additional equivalent of $\text{Al}(\text{C}_6\text{F}_5)_3$ to afford ionic FRPs $[\text{R}_3\text{P}]^{*+}[(\mu\text{-O})(\text{Al}(\text{C}_6\text{F}_5)_3)_2]^{*-}$ with the release of N_2 . Interestingly, radical anion $[(\mu\text{-O})(\text{Al}(\text{C}_6\text{F}_5)_3)_2]^{*-}$ is capable of activating C—H bonds via HAT. Various products have been generated depending on the substituents on the phosphine and the solvent. With ${}^t\text{Bu}_3\text{P}$, the ${}^t\text{Bu}$ group on this Lewis base serves as the H donor, which yields $[{}^t\text{Bu}_2\text{PMe}(\text{C}(\text{CH}_2)\text{Me})][(\mu\text{-OH})(\text{Al}(\text{C}_6\text{F}_5)_3)_2]$ salt **5-2**. When $\text{R} = \text{Nap}$, $[(\mu\text{-O})(\text{Al}(\text{C}_6\text{F}_5)_3)_2]^{*-}$ can abstract H from solvent toluene or bromobenzene to yield $[\text{Nap}_3\text{PCH}_2\text{Ph}][(\mu\text{-OH})(\text{Al}(\text{C}_6\text{F}_5)_3)_2]$ **5-3** or $[\text{Nap}_3\text{PC}_6\text{H}_4\text{Br}][(\mu\text{-OH})(\text{Al}(\text{C}_6\text{F}_5)_3)_2]$ **5-4**, respectively. Notably, this is the first example of C—H bond cleavage by FRPs, showcasing the potential of FRPs for the activation of inert chemical bonds.

In 2014, Iwamoto and co-workers reported the synthesis of Bi^{III}-TEMPO complexes from the reaction of TEMPO with dibismuthine (R₂Bi—BiR₂, R = 1,1,4,4-tetrakis-(trimethylsilyl)butane-1,4-diyl) **6-1** (Scheme 6).²⁴ Interestingly, the Bi^{III}-TEMPO complex can dissociate reversibly into a radical pair of Bi^{II} and TEMPO• in solution at room temperature. In this case, the weak Bi—O bond (2.146 Å) is likely caused by the steric repulsion between the bulky bidentate ligand and TEMPO•. To be noted, two neutral radicals were generated concurrently in this case which is different from previously discussed radical ion pairs derived from traditional neutral FLPs. Later, Coles and Fitchett reported the reaction of a bismuth complex from spatially demanding bis(amidodimethyl)disiloxane ligands, [O(SiMe₂NAr)₂]²⁻ (abbreviated as [NONAr]₂, Ar = 2,6-ⁱPr₂C₆H₃ or 2,6-(CHPh₂)-4-^tBuC₆H₂)²⁵ and TEMPO• at equal equivalent to afford Bi(NONAr)(OTEMP) compounds **6-2**.²⁶ This complex has been shown to catalyze oxidative coupling of TEMPO• with phenyl silane (PhSiH₃), which is likely initiated by the dissociation of the Bi—O bond.

Very recently, Cornella and co-workers successfully applied bismuth compounds to the activation of NH₃ and H₂O by making use of the extremely weak Bi—O bond (BDFE = 10.5 kcal/mol). The designer bismuth complex **6-3** has a *N*, *C*, *N* ligand and a bulky alkoxide ligand (2,4,6-tri-*tert*-butylphenolate) and can reversibly dissociate to a radical pair of Bi^{II} and phenoxy radical.²⁷ When the Bi^{II} center coordinates to ammonia, it reduces its N—H BDFE from 100.3 kcal/mol to 47.0 kcal/mol. Similarly, the O—H BDFE of H₂O can be reduced from 113.0 kcal/mol to 52.1 kcal/mol. This bond-weakening effect has also been observed for various simple amines and alcohols. In addition, the resulting Bi^{III}—N complexes **6-4** has been demonstrated to be reactive towards H⁺, H⁻ and H• with reactions occurring at the metal center or ligand. The establishment of such novel reactivities paved the way for future development of transformation of abundant alcohol or amines into value-added products. Although these Bi-oxyl complexes were not referred to as FRPs in their initial reports, they share similar characteristics with other neutral FRPs discussed in this essay. One unique feature, however, is that the Bi-based FRPs consist of two persistent radicals upon homolytic dissociation, which is not commonly seen in early FRPs derived from traditional FLP or new systems that we will cover in the remainder of the Perspective.

Mankad and co-workers reported a heterobinuclear Al—Fe complex L^{dipp}(Me)AlFp (L^{dipp} = HC[(CMe)(2,6-ⁱPr₂C₆H₃N)]₂, Fp = FeCp(CO)₂, Cp = η⁵-C₅H₅) **7-1**, which dissociates into radical pairs instead of ion pairs because homolytic dissociation is favored over heterolytic dissociation by 34.5 kcal/mol (Scheme 7).²⁸ The corresponding radical pairs were able to cooperatively activate CO₂ and epoxide *via* a radical mechanism which is complementary to the traditional 2e⁻ pathway found in FLP chemistry. Interestingly, computational studies showed that the *G*_d (Gibbs free energy barrier for homolytic dissociation) is strongly correlated with the steric hindrance of the R substituents on the ligand of Al (L^R = HC[(CMe)(RN)]₂). In the case of smaller substituents (R = Ph **7-2** or Me **7-3** vs R = dipp), *G*_d is significantly larger, and low reactivity of the Al—Fe complex was expected based on the proposed mechanism. In fact, no reaction with CO₂ was detected when R = Ph, which demonstrates the importance of the steric effect on FRP formation and reactivity. Intriguingly, the radical pair **7-1** can react with benzophenone to afford a new metalloradical

species $L^{\text{dipp}}(\text{Me})\text{Al}(\text{OCPH}_2)$ **7-6**, which was fully characterized by EPR and electron nuclear double resonance (ENDOR) spectroscopies. This mechanistic paradigm based on FRPs grants access to new pathways for functional group activation by heterobimetallic complexes in organic synthesis.

SYNTHETIC APPLICATIONS OF IONIC FRPS

Despite exciting new reactivities being uncovered in homolytic bond activation by means of FRPs, their applications in synthetic contexts are so far limited in number and type of reactions. In 2020, Melen and co-workers reported a seminal contribution, employing the traditional $\text{Mes}_3\text{P}/\text{B}(\text{C}_6\text{F}_5)_3$ FLP towards activating benzhydryl esters **8-1** for C—C bond formation (Scheme 8).¹⁸ The authors initially proposed the generation of ionic FRP $[\text{Mes}_3\text{P}]^{+\bullet}[\text{B}(\text{C}_6\text{F}_5)_3]^{-\bullet}$ via direct SET, followed by homolysis of the ester C—O bond assisted with $[\text{B}(\text{C}_6\text{F}_5)_3]^{-\bullet}$. A concurrently generated benzylic radical **8-5** is trapped by a styrene moiety **8-2**, constructing a new C—C bond. The second C-centered radical intermediate **8-6** is proposed to undergo HAT with $[\text{Mes}_3\text{P}]^{+\bullet}$ to afford a substituted alkene final product **8-3** or **8-4**. Although EPR studies provide a strong evidence for a homolytic pathway being operational, later studies by Slootweg and co-workers suggest that a direct SET between Mes_3P and $\text{B}(\text{C}_6\text{F}_5)_3$ is less likely due to the large energy gap to form radicals.²⁹ In a more recent study, Melen and co-workers further refined the mechanism of benzhydryl ester activation using the $\text{Mes}_3\text{P}/\text{B}(\text{C}_6\text{F}_5)_3$ FLP system.³⁰ In this new transformation employing an arylacetylene as the coupling partner instead of a styrene, DFT studies suggest that the radical species observed by EPR are rapidly equilibrating in solution but are not making a substantial contribution on the reaction pathway to form the product. Rather, a traditional heterolytic pathway by the original FLP was more likely the productive mechanism. However, the possibility of a substrate-assisted FRP formation, as discussed previously, cannot be fully ruled out at this moment.

Ooi and co-workers reported the formation of FRPs from an equimolar mixture of an *N*-methyl-*N*-((trimethylsilyl)methyl)aniline derivative **9-1** and $\text{B}(\text{C}_6\text{F}_5)_3$, yielding an ammonium radical cation **9-5** and $[\text{B}(\text{C}_6\text{F}_5)_3]^{-\bullet}$ (Scheme 9).³¹ EPR signals were detected and assigned to the radical cation (**9-5**) and its stability was attributed to hyperconjugation of the SOMO with the low-lying σ^* orbital of the adjacent C—Si bond. This hyperconjugation results in relatively low oxidation potential of the substrates (e.g., when $\text{Ar} = 4\text{-Me-C}_6\text{H}_4$, $E = 0.10 \text{ V vs Fc/Fc}^+$), allowing SET to happen at ambient temperature generating the FRP. Radical cation **9-5** was proposed to undergo loss of TMS^+ to form α -aminomethyl radical **9-4**. In the presence of a Michael acceptor such as methyl vinyl ketone (MVK) in a protic cosolvent, radical addition takes place to give **9-3**. The authors postulated that that role of $[\text{B}(\text{C}_6\text{F}_5)_3]^{-\bullet}$ is to reduce this electrophilic carbon-centered radical (**9-3**) to form an enolate species. A dramatic increase in yield was observed upon the addition of protic cosolvent MeOH, and deuterium incorporation was evident using MeOD, both of which support the intermediacy of an enolate. Interestingly, when *N,N*-dimethylaniline derivatives **9-8** were used as substrates, the lack of an α -silyl group renders these compounds less reducing. Therefore, photoirradiation with a 405 nm LED light source was necessary to promote their SET with $\text{B}(\text{C}_6\text{F}_5)_3$.

Liu, Wu, and co-workers reported the hydroboration of alkenes **10-1** *via* a pair of radical ions consisting of $\text{BX}_3^{\bullet-}$ ($\text{X} = \text{Br}$ or Cl) and $^i\text{Pr}_2\text{NEt}^{\bullet+}$ (Scheme 10).³² This radical ion duo bears much less internal steric hindrance compared to previously discussed FRP examples due to the use of a smaller Lewis acid precursor. This process is followed by HAT from $^i\text{Pr}_2\text{NEt}^{\bullet+}$ to the resultant C-centered radical (**10-3**), giving rise to hydroboration product **10-2** and an iminium ion byproduct. This method features a broad substrate scope including aryl alkenes and aliphatic alkenes with different substitution patterns from mono- to tetra-substituted. High regioselectivity was observed with internal alkenes where borylation favors the less hindered site. The isomerization issues that are commonly seen in transition-metal catalyzed hydroboration reaction via metal-hydride migration was circumvented. Notably, mechanistic studies by DFT determined a large free energy gap (78.3 kcal/mol) for the SET process between $^i\text{Pr}_2\text{NEt}$ and BCl_3 . Indeed, although the reaction was discovered and carried out under ambient light without additional photoirradiation, control experiments showed substantially lower yield of the hydroboration under dark conditions. This finding suggests that the formation of $[^i\text{Pr}_2\text{NEt}]^{\bullet+}[\text{BCl}_3]^{\bullet-}$ pair was facilitated by photoexcitation.

SYNTHETIC APPLICATIONS OF NEUTRAL FRPS AND RELATED RADICAL PAIRS

As outlined in the previous section, ionic FRPs arising from traditional neutral FLPs have shown interesting homolytic reactivities in various chemical bond activation. In comparison, their counterparts of neutral FRPs, which can be generated from ionic FLPs, have been substantially less explored. Studies in this regard may broaden the scope and synthetic applications of FRPs and open a new mechanistic paradigm for strong bond activation. In this section, we review the limited instances of neutral FRPs reported in the literature and their applications in organic synthesis and catalysis.

A notable early example showcasing the synthetic utility of neutral FRPs was reported by Knowles and co-workers in 2015.³³ A system utilizing a pair of frustrated paramagnetic species consisting of $\text{Cp}^*_2\text{Ti}^{\text{III}}\text{Cl}$ and TEMPO^\bullet was designed to achieve an intramolecular conjugate hydroamination (Scheme 11). The titanocene and aminoxyl radical cooperatively activate strong N—H bonds (BDFE = 99 kcal/mol) that are energetically inaccessible through direct HAT with TEMPO^\bullet (BDEF = 67 kcal/mol) alone. Indeed, the N—H bond is weakened (BDFE = 66 kcal/mol) upon complexation of the amide oxygen to Ti^{III} , to the extent that TEMPO^\bullet can function as a hydrogen-atom acceptor. The HAT results in a Ti^{IV} aza-enolate intermediate **11-4**, which is in valence resonance with a Ti^{III} bond amidyl radical. The closed-shell Ti^{IV} azaenolate then adds to the pendant Michael acceptor intramolecularly, which is followed by Ti migration to form Ti^{IV} enolate (**11-5**). TEMPOH then returns proton to **11-5** to furnish the hydroamination product **11-2**. Finally, SET from the resulting strongly reducing TEMPO^- to dissociated Ti^{IV} species (exergonic by ca. 500 mV)³⁴ regenerates the initial Ti^{III} and TEMPO^\bullet radical pair. Therefore, the overall reaction is catalytic in both the titanocene and TEMPO . The steric frustration between bulky $\text{Cp}^*_2\text{Ti}^{\text{III}}\text{Cl}$ and TEMPO^\bullet was hypothesized to rationalize the unique reactivity of this FRP. Indeed, strong EPR signals were observed for both radical species showing that they can coexist in solution, whereas substituting $\text{Cp}^*_2\text{Ti}^{\text{III}}\text{Cl}$ with smaller $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ resulted in loss

of paramagnetism due to the formation of $\text{Cp}_2\text{Ti}^{\text{IV}}(\text{TEMPO})$ adduct,³⁵ which was shown to be catalytically inactive in the hydroamination reaction. This ingeniously crafted catalytic system is an early example of the application of neutral FRPs in organic synthesis.

Organic radicals are highly reactive and often transient in nature. This characteristic provides opportunities to uncover new reactivities through the activation of strong chemical bonds, but it also poses issues in reaction design due to the tendency of radicals to decompose unselectively. Thus, employing FRPs in organic synthesis is especially challenging when the radicals involved are short-lived. In the Knowles example describe above, both radical species in the FRP are persistent. While such approaches provide a solution to the aforementioned selectivity issue, it also limits the types of transformations that FRPs can promote. One way to overcome this challenge is to utilize the persistent radical effect (PRE)³⁶ in the FRP reaction design. The PRE is a kinetic phenomenon observed when the two radicals feature significantly different self-reaction rate constants (e.g., one radical has a much longer lifetime than the other), which can render a radical bond cleavage/formation step selective and therefore synthetically useful.

Given the criteria of steric encumbrance for generating FRP and radical persistency for implementing the principle of PRE, 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO[•]) stands out.³⁷ In fact, this highly persistent aminoxyl radical has seen many applications in organic synthesis as a scavenger for transient radicals.³⁸ The simultaneous generation of a pair of persistent TEMPO[•] and a transient radical X[•] can be achieved in two different modes; oxidation of TEMPO⁻ by X⁺ or reduction of TEMPO⁺ by X⁻. The use of a cationic oxidant or anionic reductant partner would lead to a pair of neutral radicals that may avoid recombination owing to steric or electronic frustration (i.e., neutral FRPs). In this situation, the transient radical X[•] can undergo a substrate activation step such as radical addition or homolytic bond cleavage, leading to a second, substrate-derived transient radical species. This radical can be trapped by persistent TEMPO[•], affording an aminoxylated product. In this fashion, the FRPs may split chemical bonds in a way akin to bond activation by FLPs but via a homolytic pathway.

Recently, Chen and co-workers leveraged the PRE of TEMPO[•] to achieve the dioxygenation of alkenes. In this reaction, the combination of TEMPO⁺ and deprotonated *N*-hydroxyphthalimide (NHPI) provides a pair of aminoxyl radicals with disparate levels of persistency, which can undergo selective sequential addition to an alkene (Scheme 12).³⁹ The NHPI is initially transformed to a quasi-persistent phthalimide *N*-oxyl radical (PINO[•])⁴⁰ upon deprotonation and single-electron oxidation by TEMPO⁺, concurrently furnishing persistent TEMPO[•]. Subsequent addition of PINO[•] to an alkene **12-1** generates a *C*-centered radical **12-3** that is immediately captured by TEMPO[•]. Since direct TEMPO[•] addition to alkene is unfavorable, the cross dioxygenation is highly regio- and chemoselective. The observed regioselectivity has useful synthetic implications, as the N—O bond of the ONPhth group can be cleaved under milder reduction conditions, serving as a derivatization handle orthogonal to the OTMP group. We note that in this work, the authors did not explicitly name the TEMPO[•]/PINO[•] couple an FRP. In this particular case, TEMPO[•] and PINO[•] do not react with each other owing to the exceedingly weak O—O bond in the would-be complex,⁴¹ which thus constitutes an example of an electronically frustrated radical pair.

While studying the reaction mechanism of electrocatalytic alkene diazidation that our group previously developed,⁴² we found that the electrolysis of a mixture of NaN_3 , TEMPO^\bullet , and an alkene gave rise to azidoaminoxylated products (Scheme 13).⁴³ Cyclic voltammetry and UV-vis studies showed that electrochemically generated TEMPO^+ forms a metastable charge-transfer complex (CTC) with N_3^- , the structure of which was elucidated via X-ray crystallography.⁴⁴ The CTC in a MeCN solution dissociates into a pair of persistent TEMPO^\bullet and transient azidyl radical (N_3^\bullet) with a half-life of about 7 min. The transient N_3^\bullet can add to an alkene **13-1**, generating a *C*-centered radical intermediate **13-3** that can then be trapped by persistent TEMPO^\bullet , accomplishing alkene difunctionalization. Despite the small size of N_3^\bullet , the $\text{TEMPO}^\bullet/\text{N}_3^\bullet$ radical pair forms spontaneously at ambient temperature from the $\text{TEMPO}-\text{N}_3$ CTC as a result of weak bonding interactions between the two radical components³⁹ (association energy about 10.6 kcal/mol estimated by DFT).

During the azidoaminoxylation reaction, minor amounts of vicinal diazide side products were often observed when sterically hindered alkenes are used. This finding led us to discover that by employing a new aminoxyl radical CHAMPO^\bullet with greater steric encumbrance as the electrocatalyst, the diazide can be generated selectively (Scheme 13D).⁴⁵ We hypothesized that CHAMPO^\bullet is too sterically hindered to react with *C*-centered radical intermediate **13-3**; thus, a second N_3 group transfer from the $\text{CHAMPO}-\text{N}_3$ CTC becomes possible.

Encouraged from previous work on the formation and reactivity of the $\text{TEMPO}^\bullet/\text{N}_3^\bullet$ radical pair, we became interested in exploring new FRPs of a similar nature that may enable challenging organic transformations. Even though highly reactive FRPs have been shown to be capable of activating strong chemical bonds such as C—H bonds (see Section 2 of “Chemical Bond Activation by FRPs”), this proof of concept has yet to be implemented in the context of organic synthesis; As summarized in this section, the most predominant applications of FRPs are within the realm of alkene functionalization. It has been reported in the literature that N_3^\bullet can effect homolytic aliphatic C—H activation but only at activated sites such as benzylic positions ($\text{BDFE}_{\text{H}-\text{N}(\text{azide})} = 94$ kcal/mol in DMSO).⁴⁶ We envisioned that by systematically tuning the structure and substituents of the transient radical of the $\text{TEMPO}^\bullet/\text{X}^\bullet$ pair, we could construct FRPs that will not only form rapidly from its precursors but also display sufficient reactivity towards unactivated C—H bonds.

Achieving an efficient and selective $\text{C}(sp^3)\text{—H}$ bond functionalization would provide a powerful platform for an efficient upgrading of simple precursors and late-stage diversification of complex molecules. The main challenge in this goal, however, arises from the strong and ubiquitous nature of the C—H bonds in organic molecules. Recently, we developed a new class of FRPs composed of persistent TEMPO^\bullet and transient hexamethyldisilazide radical (HMDS^\bullet), which are formed readily from lithium hexamethyldisilazide (LiHMDS) and TEMPO^+ precursors (Scheme 14A).⁴⁷ Upon formation, HMDS^\bullet is highly electrophilic and an excellent hydrogen-atom acceptor (HAA) ($\text{BDE}_{\text{N—H}} = 109$ kcal/mol), whereas TEMPO^\bullet shows high affinity to transient radicals and can capture *C*-centered radicals at rates often near diffusion limit. Indeed, we showed that this radical pair is strongly reactive yet frustrated due to their sizes and weak bonding interactions, which is able to split aliphatic C—H bonds via a homolytic pathway, giving rise

to C—H aminoxylated product **14-2** along with hexamethyldisilazane (Scheme 14B). An attractive feature in this reaction design is that structural modulation of the HAA can provide regioselectivity control. For instance, when using bulkier lithium hexaphenyldisilazide (LiHPDS) as the base precursor, the sterically most accessible but thermodynamically unfavorable primary C—H bonds can be selectively functionalized. In contrary, when substituting LiHMDS with KO^tBu—which we showed can also react with TEMPO⁺ to form an FRP consisting of TEMPO[•] and a smaller HAA ^tBuO[•]—sterically encumbered but thermodynamically weak C—H bonds were preferentially activated. The new C—H functionalization method enabled by FRP chemistry grants access to a variety of functional organic molecules from simple feedstock hydrocarbons as well as complex molecular scaffolds through post-synthetic diversifications (Scheme 14C). We note that this reaction design is reminiscent of radical initiated C—H functionalization via photoexcitation of covalent radical precursors,⁴⁸ but the modes of activation and mechanistic principles are distinct.

CONCLUSION

Originally discovered during the studies of canonical frustrated Lewis pairs, the concept of frustrated radical pairs has begun to show promise as a new way to break and make chemical bonds in organic synthesis. Development of this nascent research is built on the foundation of seminal early studies that unequivocally established the formation of coexisting FRPs via spectroscopic and crystallographic analysis, combined with experimental and computational work that dove into the mechanisms of FRP generation. In addition, effort has been made toward studying the reactivity of various types FRPs towards the activation of strong and weak chemical bonds. In fact, since the inception of this concept, the radical behavior of FRPs has been reviewed in several recent publications.⁹ This Perspective provides an expanded overview of this promising research area by including latest developments as well as several closely relevant literature examples that were not previously categorized as FRPs.

Owing to steric encumbrance and/or orbital energy mismatch, radical pairs may not annihilate each other. Instead, they are capable of homolytically activating myriad chemical bonds including Sn—H, O—O, C—O, C=C, N—H, O—H, and even unactivated C—H bonds. These fundamental reactivities of FRPs have begun to show promising applications in organic synthesis including the cross-coupling of diarylmethyl esters with styrene, hydroboration of simple alkene, hydroamination of α,β -unsaturated carbonyl compounds, and most recently, aminoxylation of aliphatic C—H bonds. One general principle that has proven effective in reaction design of FRPs is based on the PRE, wherein the incorporation of a persistent radical and a transient radical act in synergy to achieve bond activation. Like the ever-expanding field of FLPs, we anticipate the discovery of new varieties and new reaction strategies of FRPs will continue to open new opportunities for innovations in organic synthesis.

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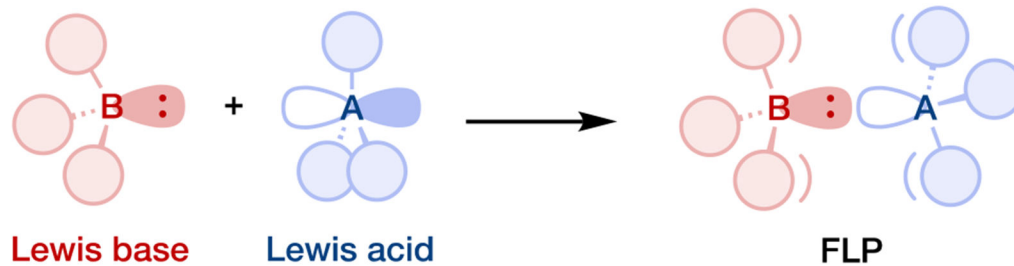
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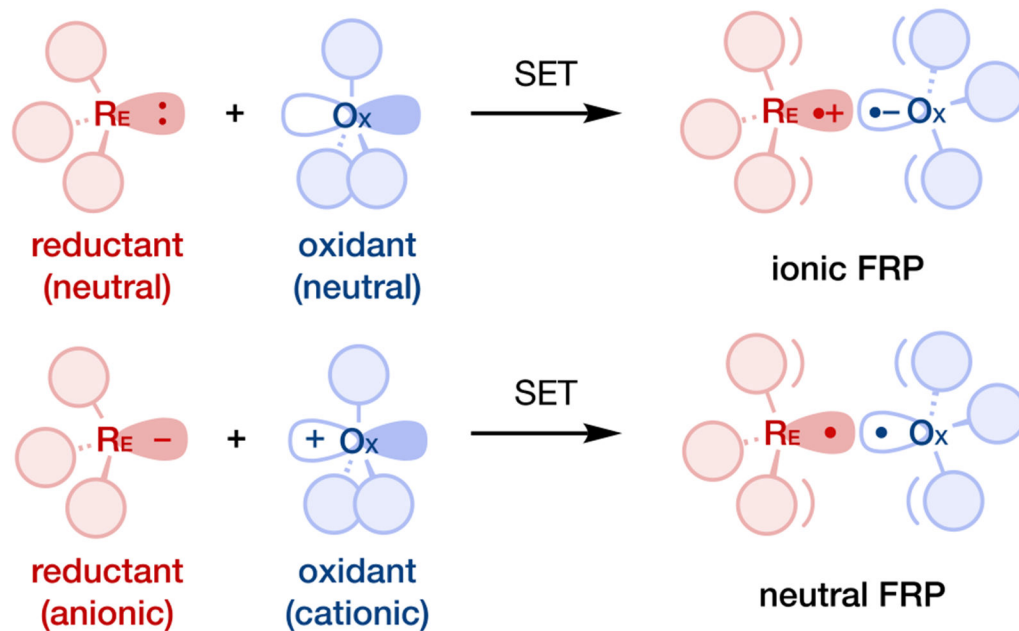
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48. For a selected recent article, see: (a) Schmidt VA; Quinn RK; Brusoe AT; Alexanian EJ Site-selective aliphatic C—H bromination using *N*-bromoamides and visible light. *J. Am. Chem. Soc* 2014, 136, 14389–14392; [PubMed: 25232995] (b) Shu C; Noble A; Aggarwal VK Metal-free photoinduced C(sp^3)—H borylation of alkanes. *Nature* 2020, 586, 714–719; [PubMed: 33116286] (c) An Q; Wang Z; Chen Y; Wang X; Zhang K; Pan H; Liu W; Zuo Z Cerium-Catalyzed C—H Functionalizations of Alkanes Utilizing Alcohols as Hydrogen Atom Transfer Agents. *J. Am. Chem. Soc* 2020, 142, 6216–6226; [PubMed: 32181657] (d) Stateman LM; Nakafuku KM; Nagib DA Remote C-H Functionalization via Selective Hydrogen Atom Transfer. *Synthesis (Stuttg)* 2018, 50, 1569–1586; [PubMed: 29755145] (e) Wang F; Stahl SS Merging Photochemistry with Electrochemistry: Functional-Group Tolerant Electrochemical Amination of C(sp^3)—H Bonds. *Angew. Chem. Int. Ed* 2019, 58, 6385–6390.

A) Frustrated Lewis pairs (FLPs)

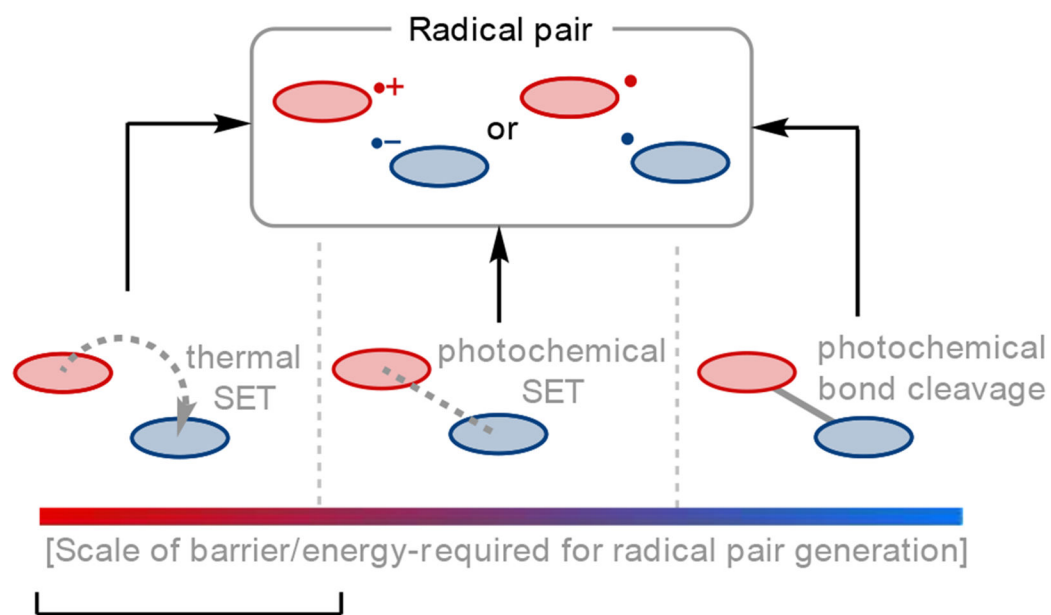


B) Frustrated radical pairs (FRPs)



Scheme 1.
Introduction to Frustrated Radical Pairs.

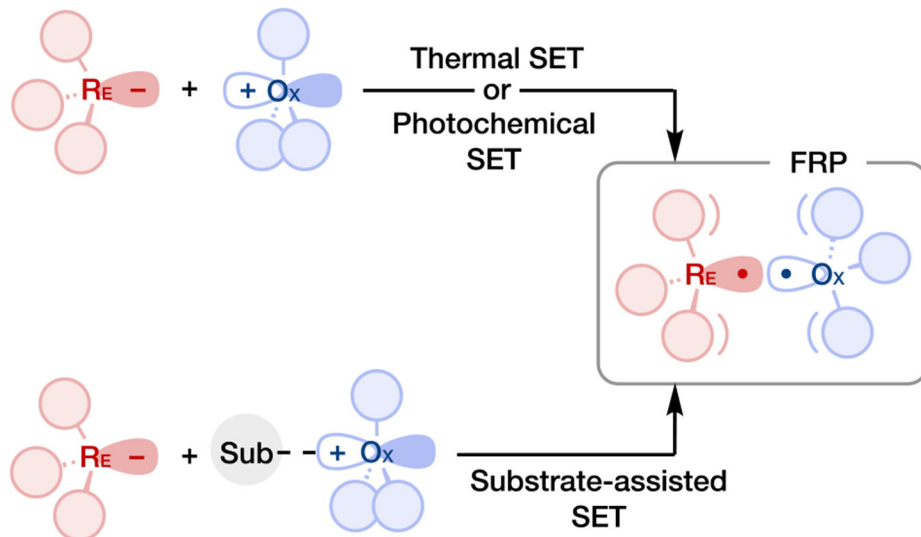
Mechanistic paradigms for radical pair generation



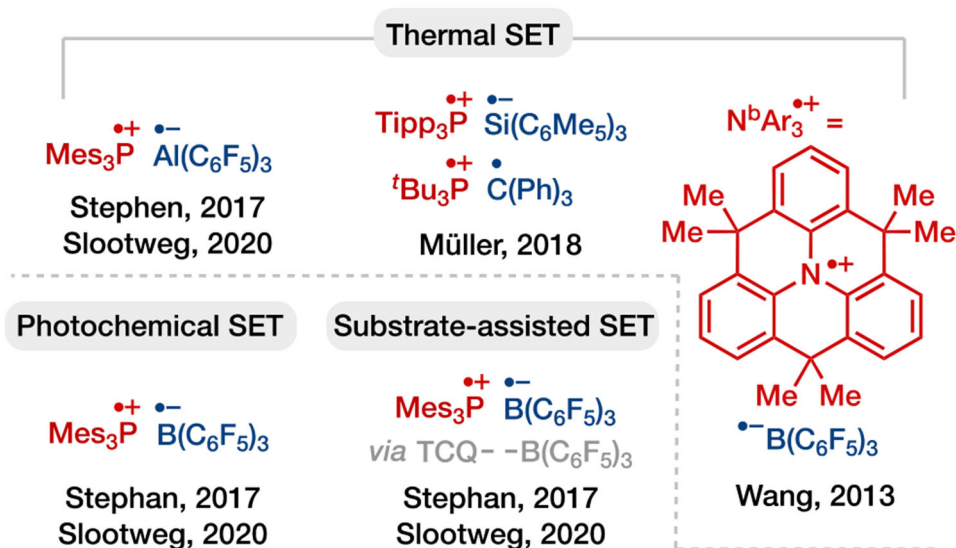
Where the formation of FRPs typically falls on the scale

Scheme 2.
Different Modes of Radical Pair Generation.

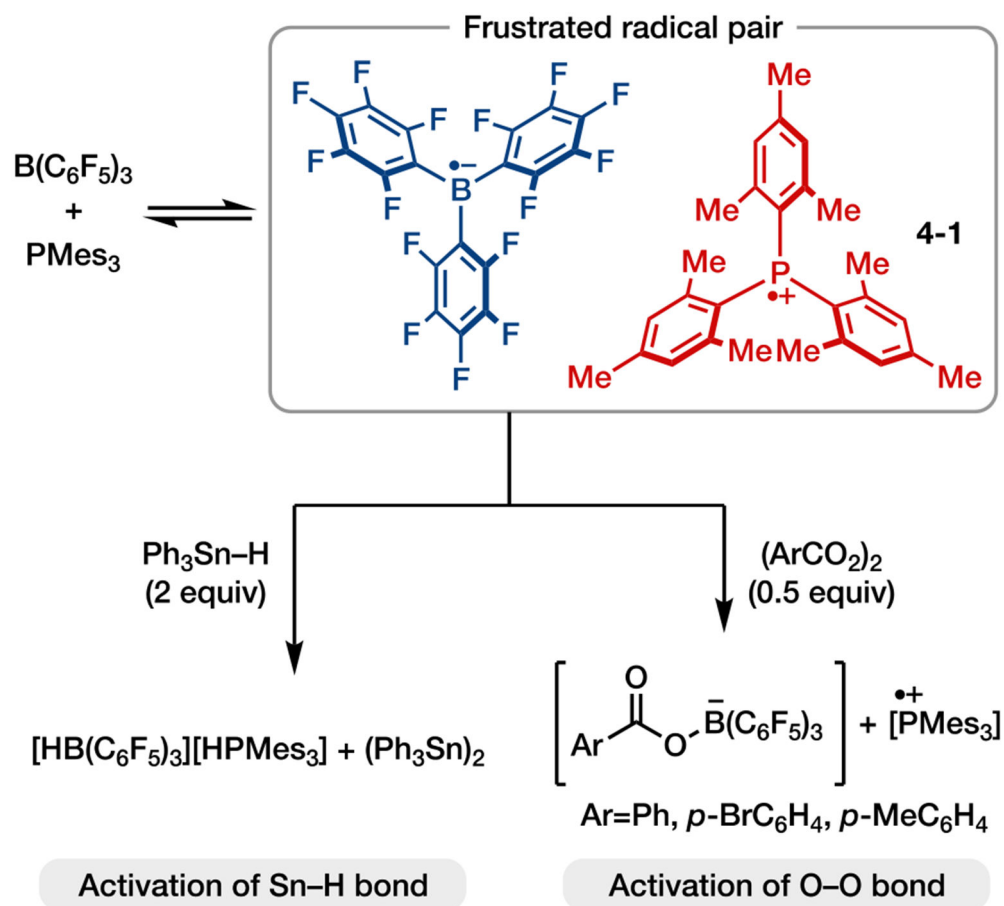
A) Generation of Frustrated Radical Pairs



B) Early examples of ionic FRPs and related radical pair systems

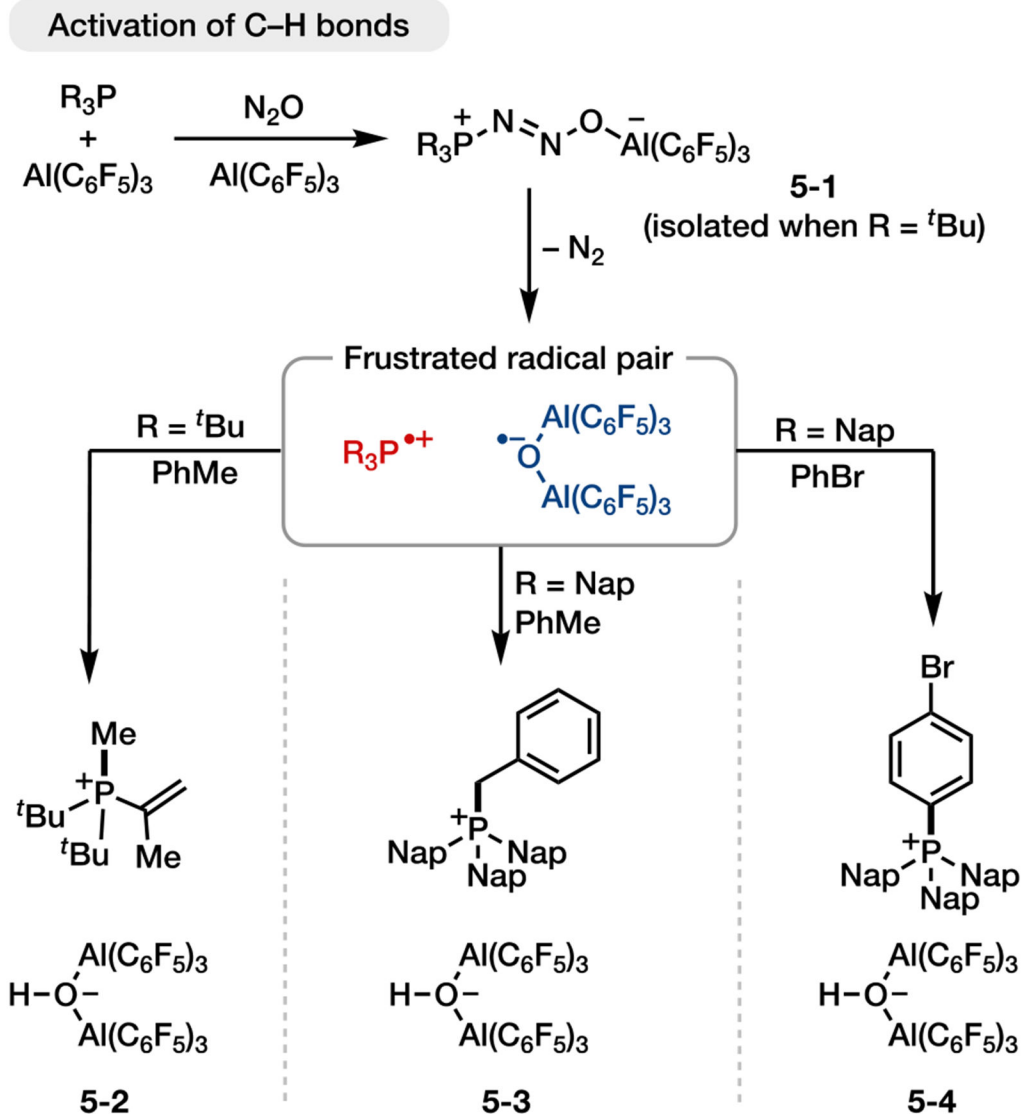


Scheme 3. Generation of Frustrated Radical Pairs and Select Early Examples.



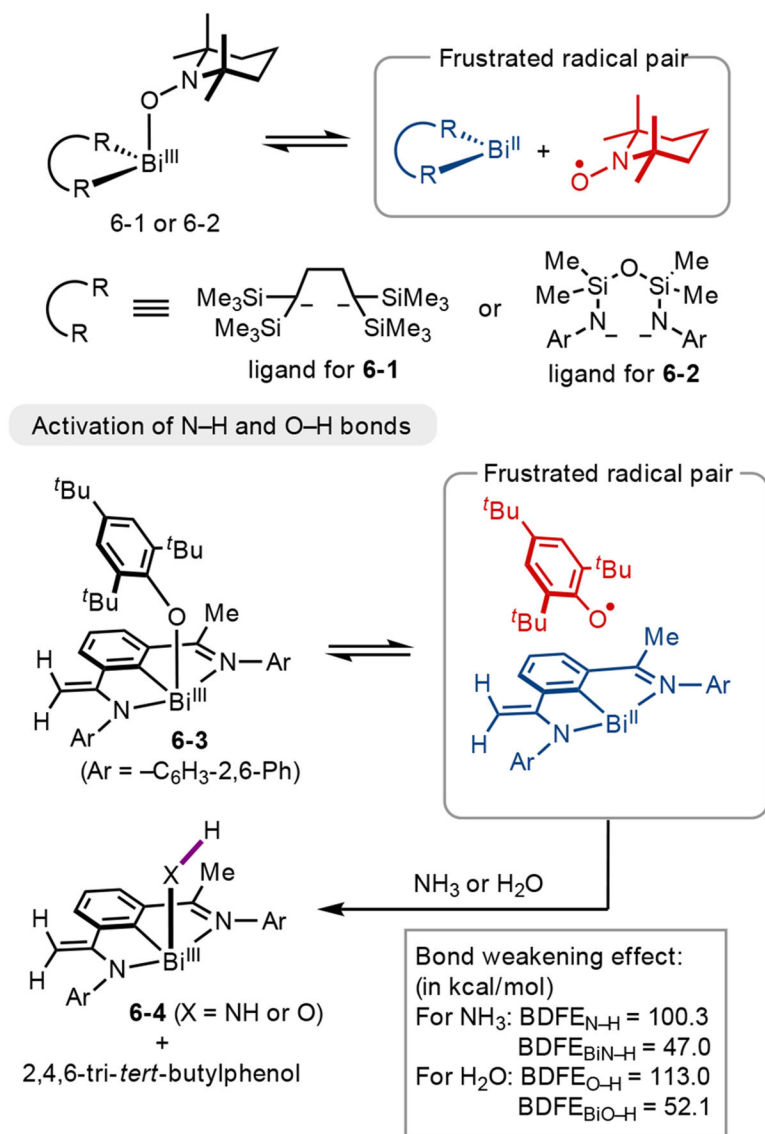
Scheme 4.

Sn-H and O-O Bond Activation with $[Mes_3P]^{\bullet+}[B(C_6F_5)_3]^{\bullet-}$ FRP.

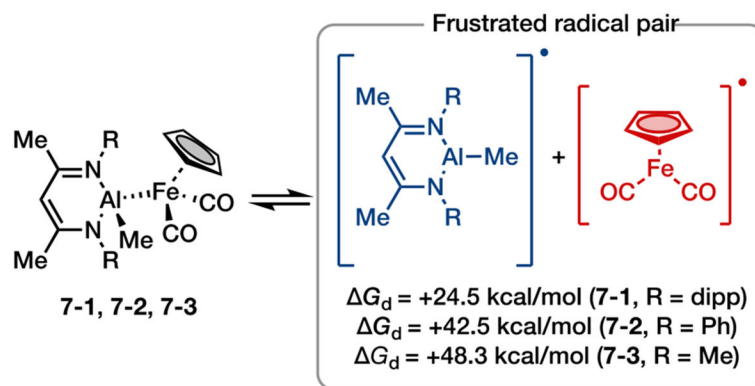


Scheme 5.

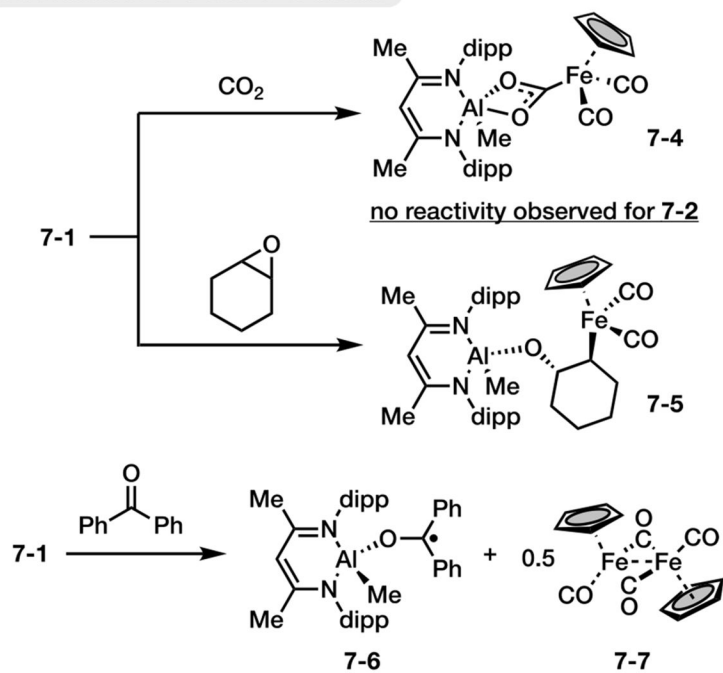
Aliphatic C–H Bond Activation with $[\text{R}_3\text{P}]^+[(\mu\text{-O})(\text{Al}(\text{C}_6\text{F}_5)_3)_2]^-$ FRP.



Scheme 6.
 N—H and O—H Bond Activation by a Bi^{III}-TEMPO Complex.

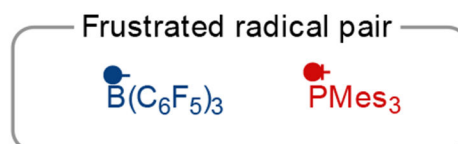


Activation of C—O and C=O bonds

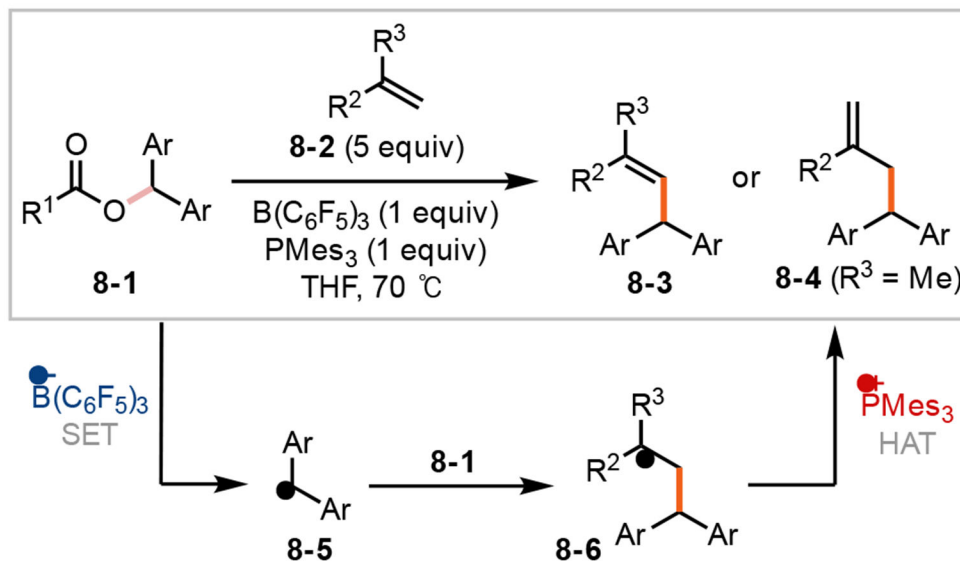


Scheme 7.
 C=O and C—O Bond Activation with a Heterobinuclear Al—Fe Complex.

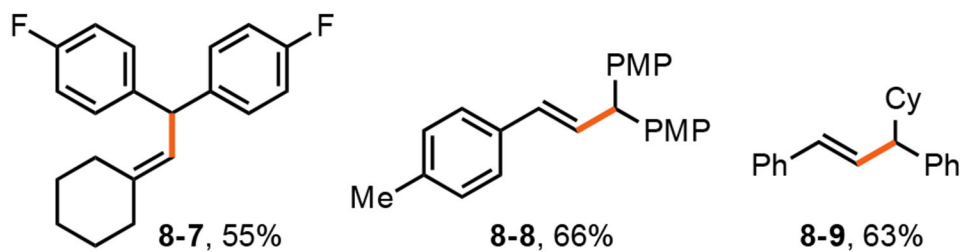
A) FRP generation



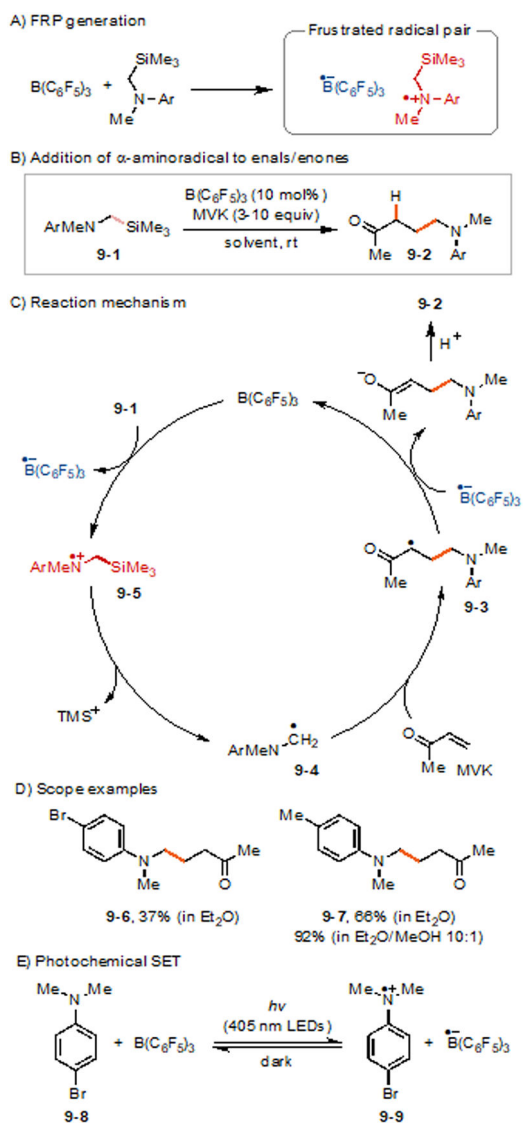
B) Alkylation of alkenes



C) Selected scope examples

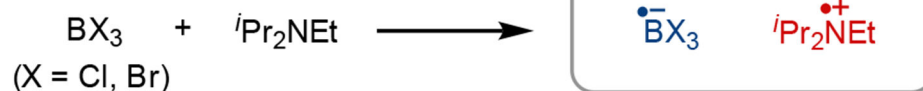
**Scheme 8.**

Cross-Coupling of Benzhydryl Ester with Alkene with $[\text{Mes}_3\text{P}]^+[\text{B}(\text{C}_6\text{F}_5)_3]^-$ FRP.

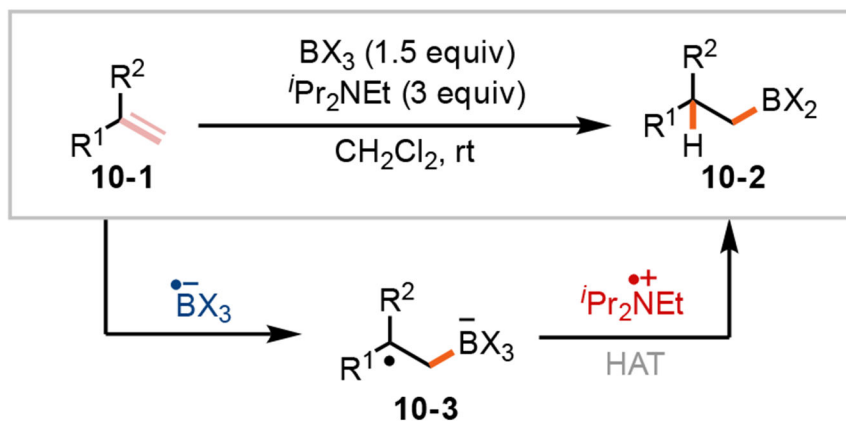
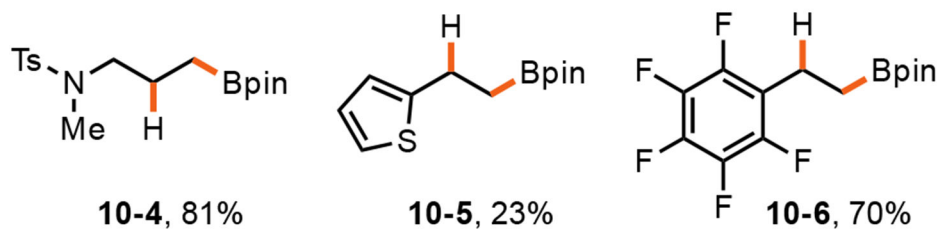


Scheme 9.
Desilylative Alkylation of *N*-Methyl-*N*-((Trimethylsilyl)methyl)anilines.

A) Radical ion pair generation



B) Alkylation of alkenes

C) Selected scope examples (RBBr₂ was converted to RBPin)**Scheme 10.**Hydroboration of Alkenes with $\text{}^i\text{Pr}_2\text{NEt}^{\oplus}/\text{BX}_3^{\ominus}$ Radical Ion Pair.

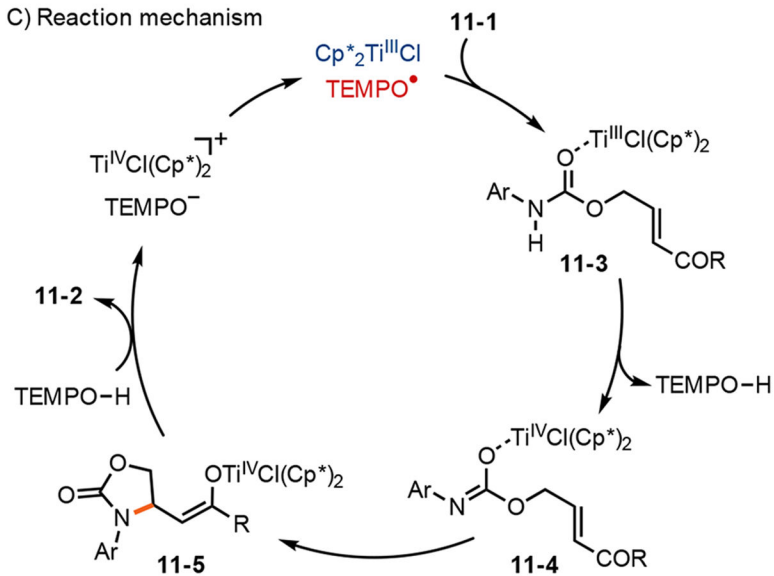
A) FRP Generation



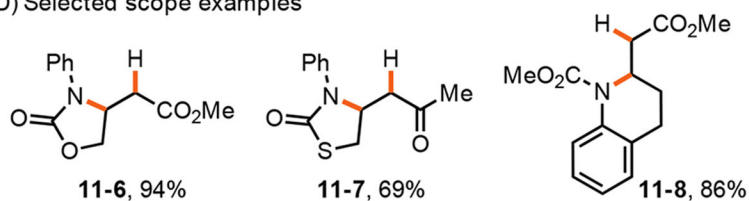
B) Conjugate amination of alkenes



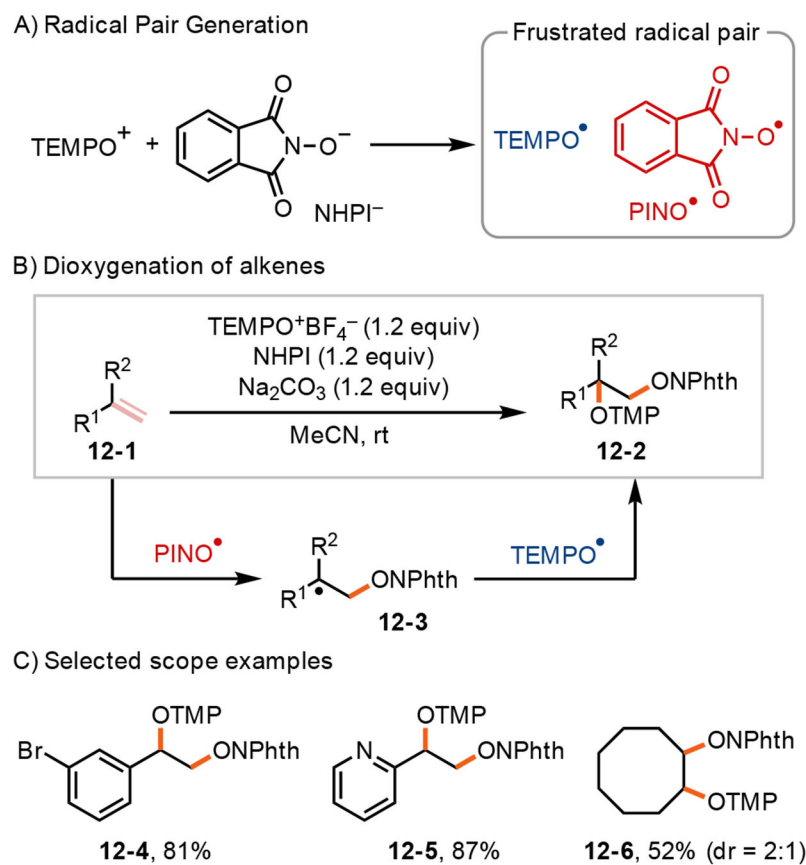
C) Reaction mechanism



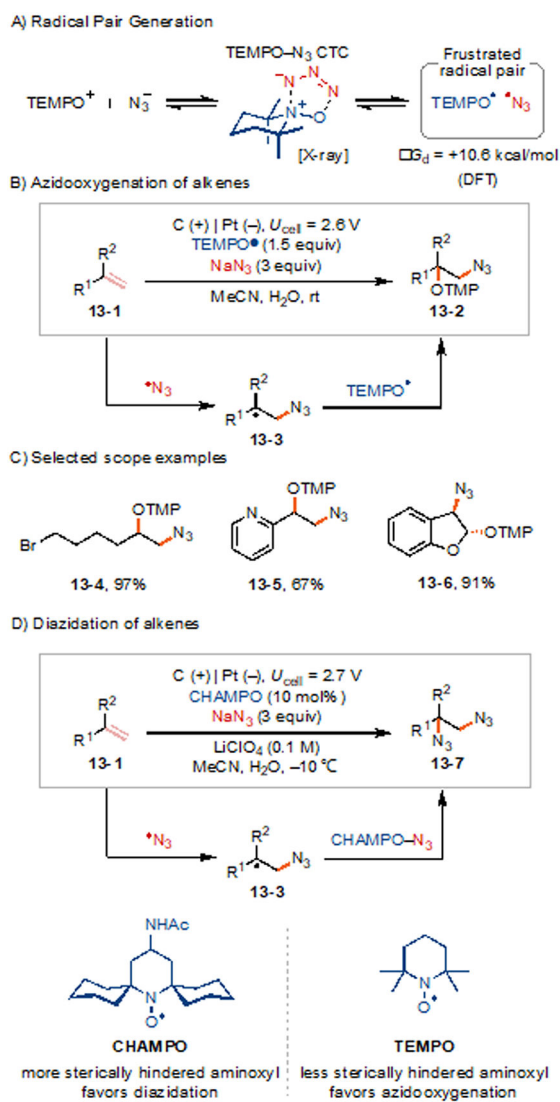
D) Selected scope examples



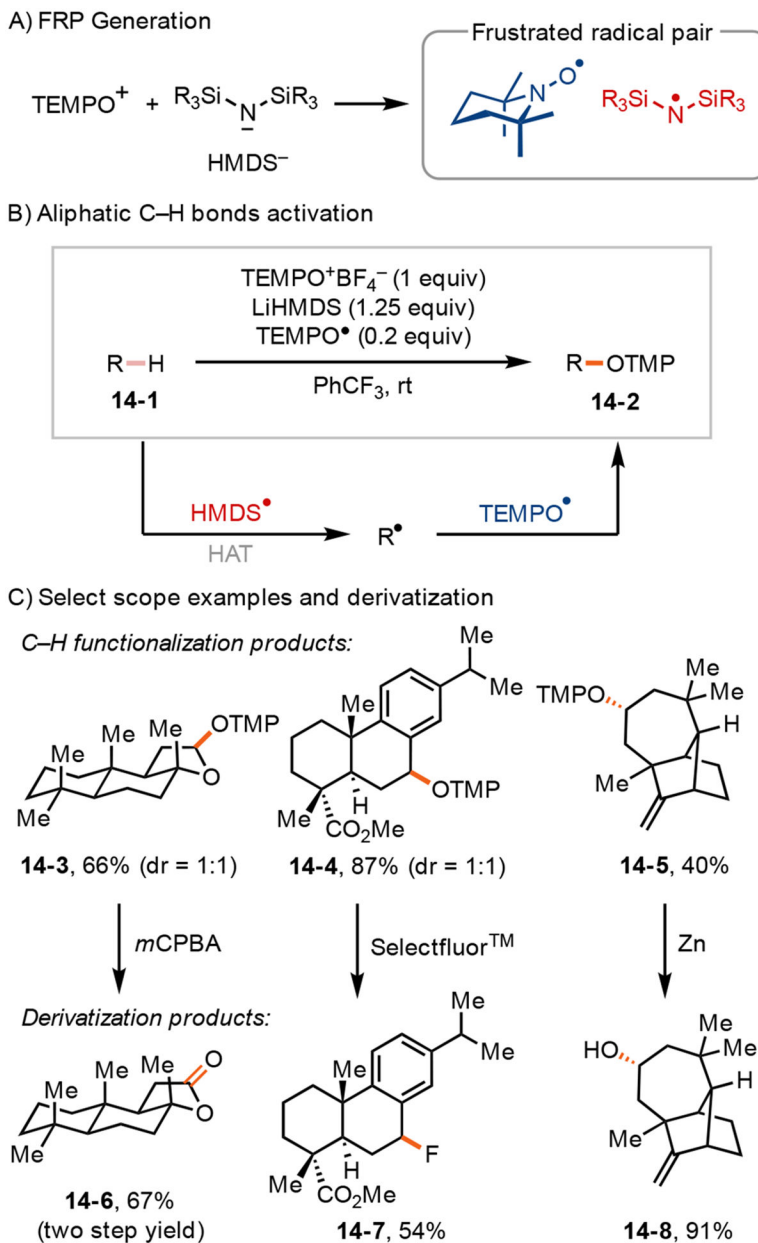
Scheme 11.
Intramolecular Conjugate Amination with $\text{Cp}^*_2\text{Ti}^{\text{III}}\text{Cl}/\text{TEMPO}^*$ FRP.



Scheme 12.
Dioxygenation of Alkenes with PINO[•]/TEMPO[•] FRP.



Scheme 13.
 Azidoxygenation of Alkenes with TEMPO-N₃ CTC and Diazidation of Alkenes with CHAMPO-N₃ CTC.



Scheme 14.
Aliphatic C–H Aminoxylation with HMDS[•]/TEMPO[•] FRP.