Preview

Frustrated Radical Pairs in Selective Functionalization of Inert Aliphatic C–H Bonds

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SUMMARY

In this preview, we highlight the recent findings of Lin and co-workers published in *Nature* on the non-directed functionalization of chemically inert aliphatic C–H bonds by utilizing the hexamethyldisilazide anion (HMDS-, a reductant) and an *N*-oxoammonium cation (TEMPO+, an oxidant) as a new class of frustrated radical pair.

Keywords: Frustrated Radical Pairs, Radicals, Alkoxyamines, C–H functionalization.

INTRODUCTION

Frustrated Lewis pair (FLP) chemistry has gained enormous attention in the synthetic community as it can mimic transition metal reactivity and open new avenues in synthesis and catalysis. Frustrated Lewis pairs are mainly explored for H_2 and CO_2 activation and heterolysis (Figure 1A).[1] However, frustrated radical pairs (FRPs) originating from certain FLPs are relatively unexplored, albeit several research groups have recently studied that certain combinations of Lewis acid and Lewis base pairs including phosphorus–borane/alane, nitrogen–borane, and carbon–borane pairs can act as FRPs for the homolysis of Sn–H bonds, the benzhydrylation of alkenes/alkynes, and the α-alkylation of amines (Figure 1B).[2,3] Therefore, the design of novel frustrated radical pairs is highly appealing, and of course, the utilization of this new radical reactivity of frustrated pairs in the activation of inactive bonds can open up new reactivity in both main group catalysis and synthetic chemistry.

The selective functionalization of non-activated aliphatic C–H bonds is an important yet challenging reaction which is useful for the late-stage diversification of biologically active feedstocks and polymer precursors.[4,5] The selective C(sp^3)–H functionalization is documented using transition metal catalysts, directing groups, and a hydrogen atom transfer process,[6] however, the non-directed functionalization of such bonds is very limited and continues to be a synthetic challenge.

The recent discovery of Lin's group in *Nature* demonstrates that the newly designed FRPs originated from the sterically encumbered hexamethyldisilazide anion ($HMDS^-$) and the *N*-oxoammonium cation ($TEMPO^+$) (Figure 1C) could induce the homolysis of inert aliphatic C–H bonds to result in a product having alkyl-TEMPO adduct.[7] Subsequently, the alkyl-TEMPO species having weak C–O and N–O bonds (BDE = 49 and 51 kcal/mol for cyclohexyl–TEMPO) were employed in diverse synthetic modifications as shown in Figure 1E. As illustrated in Figure 1C, the combination of readily accessible reagents lithium hexamethyldisilazide (LiHMDS) and 2,2,6,6-tetramethyl-1-oxo-piperidinium tetrafluoroborate [TEMPO][BF_4^-] could assist in the formation of electronically frustrated radical pairs bearing a transient radical HMDS• and a persistent radical TEMPO• via a single electron transfer process. Following, the potent hydrogen atom acceptor (HAA) capability of the transient radical HMDS• enables the homolytic splitting of less reactive C–H bonds (BDE = 109 kcal/mol for N–H, and 99.5 kcal/mol for cyclohexane) furnishing a carbon-centered radical which subsequently reacted with the persistent aminoxyl radical (TEMPO•) delivered aminoxylation products as alkyl-TEMPO adducts. The addition of 0.2 equivalents of TEMPO was required to facilitate the alkyl radical trapping which aided to improve the yield of the product.

This unique protocol showed success in the aminoxylation of a wide range of hydrocarbons comprising cycloalkanes, linear alkanes, and more complex molecules such as (–)-ambroxide (Figure 1D), (+)-longifolene, protected neomenthol, methyl dehydroabietate, a biflavonoid analogue, and antihistamine loratadine.

The site selectivity was controlled by tuning the steric bulk on the HAA. However, systematic analysis of three different sterically encumbered HAAs including lithium hexaphenyldisilazide (LiHPDS), lithium hexamethyldisilazide (LiHMDS), and potassium *tert*-butoxide (KO^{t}Bu) could help in the selective functionalization of primary, secondary, and tertiary C–H bonds. For instance, primary C–H aminoxylation of isopentane was selectively achieved in the presence of the bulky LiHPDS, whereas the less sterically hindered KO^{t}Bu thermodynamically favored the selective tertiary C–H bond functionalization.

Several control experiments aided to understand the involvement of FRPs in the inert C–H bond activation. Cyclic Voltammetry (CV) studies of donors LiHMDS, LiHPDS, and acceptor TEMPO indicated that LiHMDS, LiHPDS, and TEMPO were oxidized at $E_{p/2}$ ~ 0.44–0.46 V, thus expected to undergo thermodynamically feasible single electron transfer (SET) between disilazide anion and oxoammonium cation. Again, electron paramagnetic resonance (EPR) studies of FRPs could reveal the possibility of the formation of TEMPO•. Of note, disilylaminyl or *t*-butoxyl radicals could not be detectable due to the short lifetimes of the radicals. The addition of styrene as a radical trap ensued a difunctionalization of styrene indicating the formation of HMDS• and TEMPO• radicals in the reaction profile. The product derived from the decomposition of transient radicals also further supported the existence of radical pairs. Radical clock experiments showed the ring opening of cyclopropane rather than a ring-retained product which confirmed hydrogen atom transfer assisted generation of a carbon centered radical. Computational insights showed that the TEMPO-HMDS and TEMPO-^{t}BuO adducts suffered from steric repulsion which promoted the species to be dissociated as frustrated radical pairs.

Post-synthetic modifications of alkoxyamine products with the help of traditional synthetic routes were carried out to obtain chemically useful substrates. For instance, the substrate (–)-ambroxide described earlier led to the aminoxylated ambroxide intermediate which could be treated with *m*-chloroperoxybenzoic acid (*m*CPBA) or zinc powder to lead to the corresponding ketone or alcohol respectively, as the final useful products in a one pot reaction (Figure 1D). In the follow up reactions (Figure 1E), *m*CPBA or magnesium monoperoxyphthalate (MMPP) mediated oxidative N–O bond cleavage of secondary aminoxylated products to corresponding ketones, whereas reductive cleavage of the N–O bond by Zn led to the corresponding alcohols. Alternatively, homolysis of a benzylic C–O bond in the presence of deuterated thiophenol rendered the hydrogen isotope exchange product. Also, by applying Knowles[8] and Coote's[9] photo- and electro-chemical methods, a variety of nucleophilic substitution reactions were implemented. Furthermore, benzylic halogenation of alkyl-TEMPO adducts in the presence of Selectfluor™ or trichloroisocyanuric acid (TCCA) provided fluorinated or chlorinated products with reasonable yields.

In conclusion, Lin and co-workers have discovered unconventional and novel frustrated radical pairs consisting of a transient HAA and a persistent aminoxyl radical from the combination of lithium hexamethyldisilazide (LiHMDS) and TEMPO$^+BF_4^-$. This was utilized for the inert C–H bond activation of aliphatic hydrocarbon feedstocks and complex organic architectures. The site-selectivity of C–H bond activation was also controlled by the structural modification of the HAA. The synthesized C–H aminoxylation products were then further converted to a variety of synthetically useful organic skeletons via traditional synthetic procedures. Overall, we envision that this work will lead to the further development of frustrated radical pair chemistry to unlock new transformations directed towards synthetic challenges.

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AUTHOR CONTRIBUTIONS

M.P. and R.L.M. jointly wrote and edited the article.

DECLARATION OF INTERESTS

The authors declare no competing financial interests. R.L.M. is a member of the journal's advisory board.

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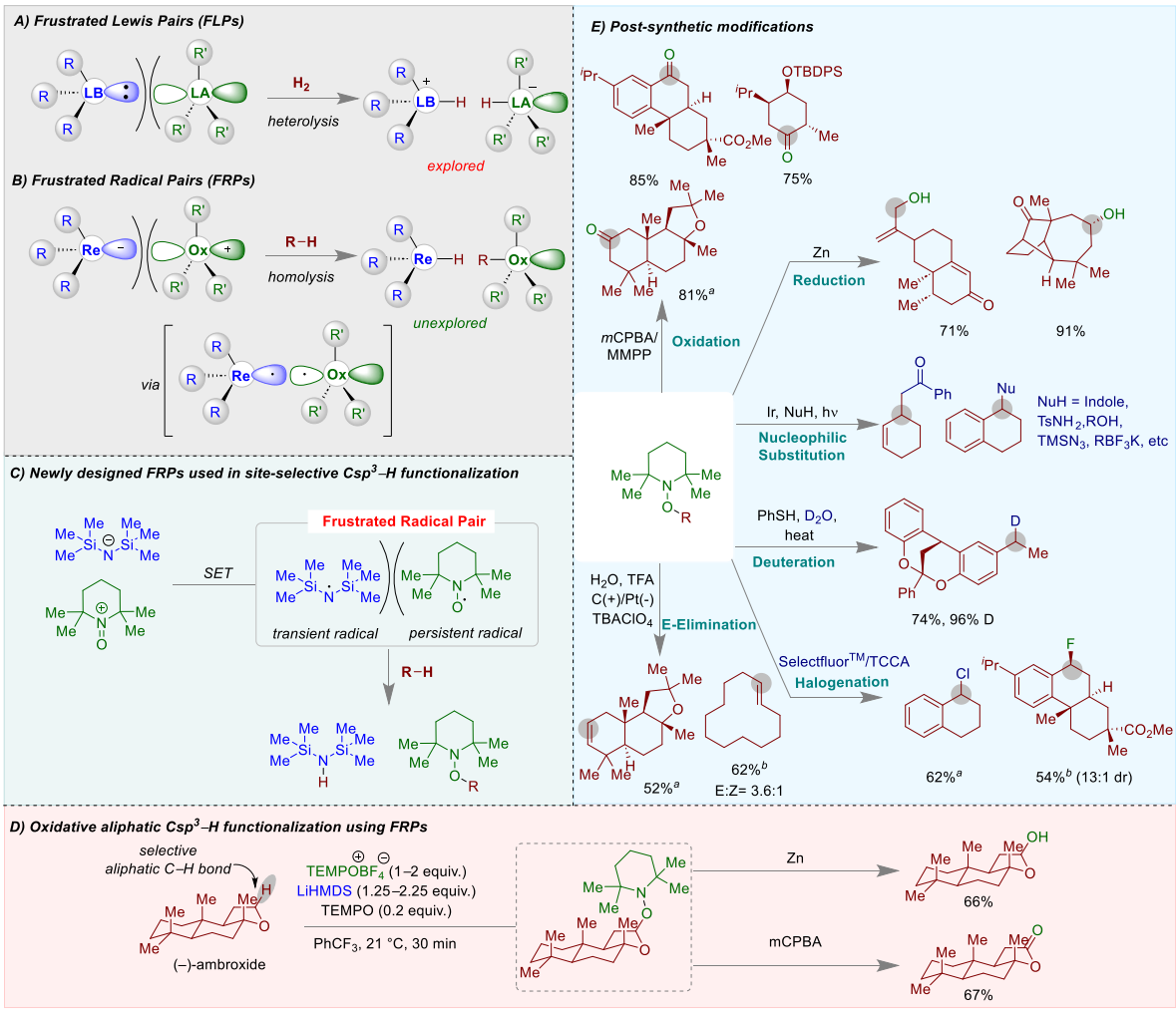

Figure 1. Frustrated Radical Pairs in Selective Functionalization of Inert Aliphatic C–H Bonds: (A) Classical frustrated Lewis pairs, (B) frustrated radical pairs using reductant and oxidant, (C) and (D) Lin's work using the hexamethyldisilazide anion ($HMDS^-$) and the *N*-oxoammonium cation ($TEMPO^+$) as frustrated radical pairs in the regioselective activation of highly non-activated C–H bonds. (E) Post synthetic modifications of alkoxyamines, yield[a] from ^1H NMR spectroscopy, and yield[b] from gas chromatography.