



Progress

Tuning radical reactivity for selective radical/radical cross-coupling

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Dedicated to Professor Xiyun Lu on the occasion of his 90th birthday.

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ABSTRACT

Radical/radical cross-coupling represents a straightforward way for the construction of new chemical bonds in theory and has received more and more attention over the past several years. Until now, it is challenging to achieve the selective bond formation between two transient radicals since selective radical cross-coupling usually happens between persistent radical and transient radical. However, the number of persistent radicals is much less than that of transient radicals. These issues limit the application of radical/radical cross-coupling in the construction of new chemical bonds. To solve this, we proposed a novel strategy “tuning radical reactivity” that could tune transient radical into persistent radical. This paper will introduce the concept and recent developments of “tuning radical reactivity”.

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1. Introduction

Radical chemistry laid the foundation for the development of organic synthesis [1–4], biological processes [5,6] and polymerization [7,8]. Generally, radicals with a single electron have a strong tendency to form chemical bonds. Due to the quick reaction rate and low activation energy, radical/radical coupling is an efficient way to construct new chemical compounds [9]. However, radicals are present only under special and limited conditions [10]. It still remains a great scientific challenge to achieve highly selective radical/radical cross-coupling for further application.

In 1936, the persistent radical effect (PRE) provides the theoretical basis for the realization of radical/radical cross-coupling between persistent radical ($\cdot R_p$) and transient radical ($\cdot R_t$) [11]. Subsequently, the research on polyoxometalates that could achieve the homolysis of inert alkane C–H bonds under photo-induced electron transfer (PET) appreciably expanded the scope of radical cross coupling [12]. Recently, a few radical/radical cross-coupling reactions have been realized between R–H and R–X (X = CN, F, Cl, Br, I, etc.) via photocatalysis [13–17]. Although, the photo-induced radicals generation became a useful method [18], most studies were still limited in the reaction between $\cdot R_p$ and $\cdot R_t$. Therefore, it is still a great challenge to achieve the selective bond formation between two transient radicals that may be more commonly used in chemical transformations [19]. It is reasonable to

assume that if methods could be developed to stabilize one of reactive radicals, it will provide a solution for the direct cross-coupling between two transient radicals. In this paper, we would like introduce the concept of “tuning radical reactivity” and its applications in oxidative cross-coupling.

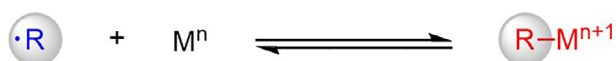
2. The concept of “tuning radical reactivity”

Based on previous researches in X-ray absorption fine structure (XAFS), we found that the equilibrium between organocuprates and radicals could serve as persistent radical [20–22]. This reveals that transient radical could be translated into persistent radical in special conditions. Inspired by that, we proposed “tuning radical reactivity”: through transforming $\cdot R_t$ into a more stable intermediate, radical/radical cross-coupling could be realized more easily. This novel strategy has been achieved by the following ways: Method **a**) by tuning $\cdot R_t$ into $R-M^{n+1}$ via oxidative addition (Scheme 1a); Method **b**) by tuning $\cdot R_t$ into $\cdot R-M^n$ via metal chelation (Scheme 1b); Method **c**) by tuning $\cdot R_t$ into C–X bond (X = I, Br, Cl) (Scheme 1c) and; Method **d**) by tuning $\cdot R_t$ into \cdot (R-Arene) intermediates (Scheme 1d). Approximately, the principle of Method **a** and Method **c** is to create a radical pool, in which there is an equilibrium between $\cdot R_t$ and $R-M^{n+1}$ or R–X. While $\cdot R_t$ is involved in the reaction, $R-M^{n+1}$ or R–X will produce another $\cdot R_t$. Therefore method **a** and method **c** could promote radical/radical cross-coupling via increasing the concentration of $\cdot R_t$. Otherwise, the principle of Method **b** and Method **d** is to enhance the stability of $\cdot R_t$ via conjugation.

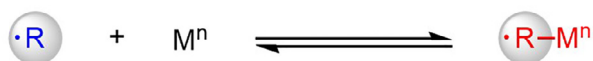
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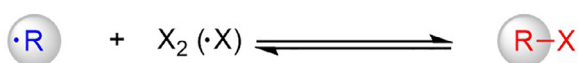
a) Tuning $\cdot R_t$ into $R-M^{n+1}$ via oxidative addition



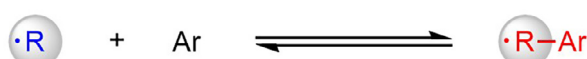
b) Tuning $\cdot R_t$ into $\cdot R-M^n$ via metal chelation



c) Tuning $\cdot R_t$ into C-X bond (X = I, Br, Cl)



d) Tuning $\cdot R_t$ into $\cdot(R-Ar)$ intermediates

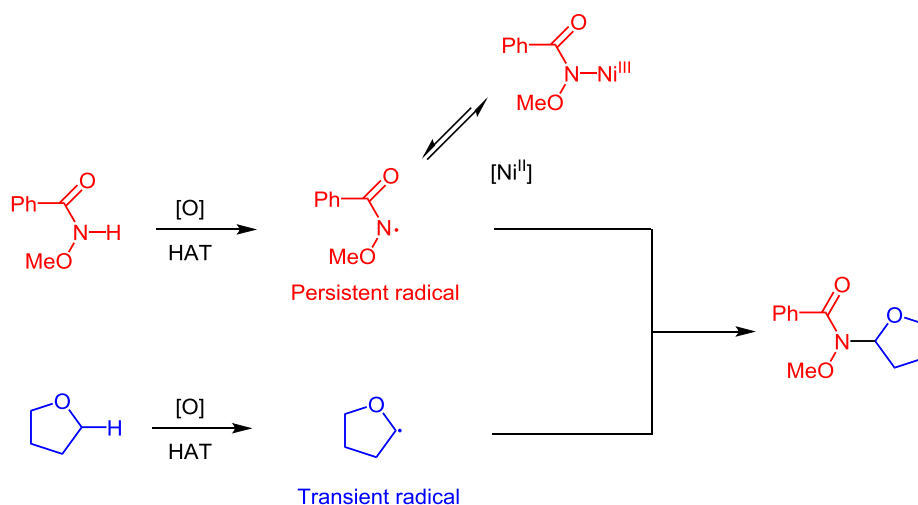


Scheme 1. (Color online) Four paths of tuning $\cdot R_t$ reactivity.

3. Recent developments of tuning the reactivity of transient radical

3.1. Tuning $\cdot R_t$ into $R-M^{n+1}$ via oxidative addition

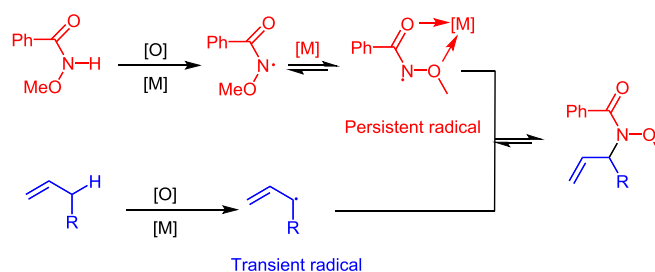
Generally, tuning $\cdot R_t$ into metal complex (M^{n+1}) via oxidative addition is an effective method to increase the concentration of $\cdot R_t$ owing to the forming of radical pool, which is caused by the equilibrium between $\cdot R_t$ and radical-metal complex ($R-M^{n+1}$). In 2014, we have developed a $C(sp^3)$ -H/N-H cross-coupling of *N*-alkoxyamides with aliphatic hydrocarbons in the same way [23] (Scheme 2). Mechanistic studies showed that the coordination of the nitrogen radical ($\cdot R_t$) to nickel exists as a fast equilibrium with a tendency toward the side of complexation. Therefore, the generated complex plays an important role of nitrogen radical pool which is the key to achieve nitrogen radical/ sp^3 carbon radical cross-coupling. Similarly, we have achieved inert $C(sp^3)$ -H arylation from arylboronic acid through this novel strategy [24].



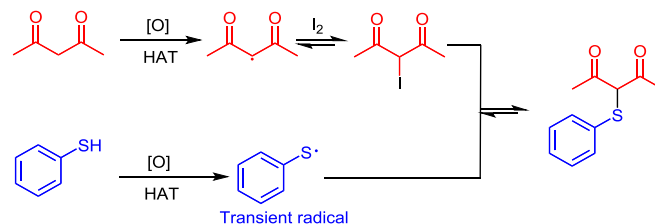
Scheme 2. (Color online) Oxidative $C(sp^3)$ -H/N-H cross-coupling by tuning $\cdot R_{tra}$ into $R-M^{n+1}$ via oxidative addition.

3.2. Tuning $\cdot R_t$ into $\cdot R-M^n$ via metal chelation

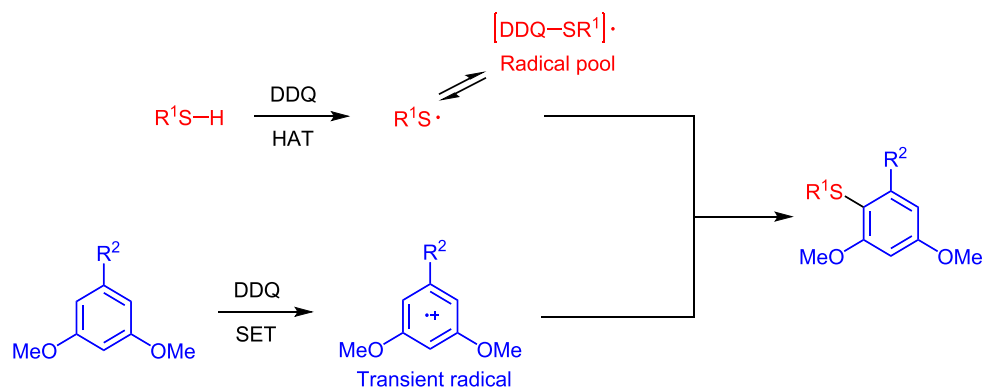
Commonly, tuning $\cdot R_t$ into $\cdot R-M^n$ via metal chelation is another method to enhance the stability of $\cdot R_t$ by conjugation. In 2016, we have achieved the synthesis of allylic amine by another novel strategy that metal (M^n) tunes $\cdot R_t$ (nitrogen-centered radical) into $\cdot R-M^n$ (persistent radical complex) via metal chelation [25]. The key to this reaction is that nitrogen-centered radical is stabilized through a triplet diradical Cu(II) complex (Scheme 3). This process was proven by a variety of methods. Basically, EPR research showed the existence of nitrogen-centered radical generated from *N*-methoxybenzamide. Moreover, DFT calculations revealed that a triplet diradical Cu(II) complex is a persistent radical species, and nitrogen-centered radical Cu(II) complex was detected by high-resolution electrospray ionization mass spectrometry (ESI-MS). In addition, this method was also used in asymmetric synthesis based on the steric effects [26].



Scheme 3. (Color online) Tuning the reactivity of radical through a triplet diradical Cu(II) intermediate.



Scheme 4. (Color online) Tuning the reactivity of radical via using iodine in C-H/S-H oxidative coupling.



Scheme 5. (Color online) DDQ-controlled radical-radical cross-coupling for C–S bond formation.

3.3. Tuning $\cdot R_t$ into C–X bond ($X = I, Br, Cl$)

Due to low dissociation energy and high reactivity of C–X bond, tuning $\cdot R_t$ into C–X bond is an efficient way to achieve radical/radical cross-coupling by generating relatively stable and reactive C–X intermediate. In 2015, we have developed an iodine catalyzed oxidative coupling for the synthesis of β -dicarbonyl thioethers [27] (Scheme 4). In this reaction, diketone radical generated by oxidation could be quickly iodinated to form R–I intermediate. Then a sulfur-center radical would be transformed to target product via a radical substitution pathway. Moreover, radical addition is also could be achieved by this strategy smoothly. Through tuning radical reactivity by iodine, we have achieved the synthesis of furans, dihydrofurans and indolizines from β -keto esters or 2-pyridinyl- β -esters with alkenes and alkynes [28,29].

3.4. Tuning $\cdot R_t$ into $\cdot(R$ -Arene) intermediates

Tuning $\cdot R_t$ into $\cdot(R$ -Arene) intermediates is another way to enhance $\cdot R_t$ stability. The key to this method is generating a suitable $\cdot(R$ -Arene) intermediate. If the intermediate is too stable, it's hard to get cross-coupling product. On the other hand, overactive intermediate could not play the role of radical pool. In 2016, we successfully synthesized non-symmetric diaryl thioethers through radical/radical cross-coupling (Scheme 5) [30]. The preliminary mechanistic studies showed that the C–S bond formation achieved through the cross-coupling of thyl radical and aryl radical. The key to this reaction is that thyl radical combined with DDQ plays a role of $\cdot R_p$ and aryl radical plays a role of $\cdot R_t$. Subsequently, we have achieved the construction of C–S bond by more universal method that radical species were induced by anodic oxidation [31]. This strategy avoided the use of catalyst and stoichiometric oxidant. Furthermore, the combination of $\cdot R_t$ and arene (Ar) is widely used in boron chemistry where boron radical is easily combined with pyridine derivatives [32].

4. Conclusion and outlook

During recent years, several radical/radical oxidative cross-coupling have been achieved. Tuning radical reactivity offers a new sight and it may significantly expand the scope of radical cross-coupling in the near future. Furthermore, the metal-radical synergy provides an important potential application in asymmetric synthesis [33,34] and fluorochemistry [35,36] with chiral metal complexes. However, the use of stoichiometric radical initiators to produce radicals has led to a lot of waste. The methods of generating radical from R–H bond are still limited under mild condition. Fortunately, generating radical by oxidation-induced from

R–H bond, which have been widely explored during these past years, is a fascinating and unconventional approach with high atom- and step-economy [37–41]. Combined with the strategy of oxidation induction, great chances still remain in radical/radical cross-couplings and further exciting developments are expected.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.scib.2018.06.004>.

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