Synthetic Methods

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Radicals and Transition-Metal Catalysis: An Alliance Par Excellence to Increase Reactivity and Selectivity in Organic Chemistry**

*Leigh Ford and Ullrich Jahn**

cross-coupling · elimination · homogeneous catalysis · hydrogen transfer · radicals

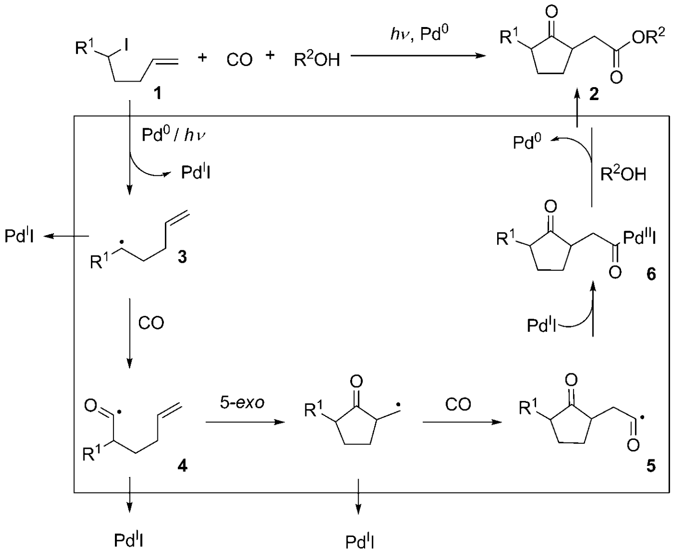
Only a decade ago, a review by Zard was titled: "*Riding the tiger: Using degeneracy to tame wild radical reactions*".[1] This perception of radical reactions being wild and hard to control is linked to the short lifetime of radicals and the widely varying kinetics of the individual radical reaction steps. Thanks to the ground-breaking studies by Ingold, Beckwith, Fischer, and Newcomb, the kinetics of radical reactions are known today.[2,3] Free radical chemistry represents an attractive alternative to its ionic counterpart with several advantages including high functional group tolerance and the use of mild reaction conditions.[4] Another advantage of applying free radicals is their central position among reactive intermediates, since they can be easily reduced to carbanions or oxidized to carbocations. A critical point remains, however, that radical reactions require a stoichiometric amount of a chain carrier, oxidant, or reductant.

Transition-metal catalysis offers an excellent and complementary potential to solve synthetic problems.[5] As the fundamental reactivity patterns are known, reactivity can be tuned by the proper choice of substrate, metals, and ligands utilized. Cross-coupling reactions, in particular, enjoy a wide popularity, although optimization can be quite cumbersome. A major disadvantage of a number of coupling reactions is that they are often sluggish and thus require quite harsh conditions to accomplish the transformation.

Recently, a novel strategy has emerged that combines the advantages of transition-metal catalysis and free radicals in organic chemistry, and it is proving to be very useful for the development of new efficient synthetic methodology.

Although radicals were recognized early on to be involved in various transition-metal-catalyzed processes including palladium-catalyzed reactions,[6] Kharasch-type reactions,[7] and several nickel-catalyzed cross-coupling reactions,[8] an initial study in merging transition-metal catalysis with radical chemistry was first published in 2002 by Ryu and co-workers (Scheme 1).[9] They reported a photolytic palladium-catalyzed cascade starting from homoallyl halides **1** and leading to diverse cyclopentanone derivatives **2** in good yields. The proposed mechanism involves the photolytic formation of a homoallyl radical **3** and a Pd^{I}I species upon irradiation of the homoallyl halide in the presence of the Pd^{0} catalyst. Radical **3** undergoes addition to CO to generate the acyl radical intermediate **4**. 5-*exo* Cyclization followed by further carbonylation leads to radical **5**, which can couple with the Pd^{I}I species to give the acylpalladium intermediate **6**. In the last step the palladium unit is displaced in the presence of a nucleophile to generate the final product.

Pd^{I} complexes, though currently not very common, are isolable dimeric species, which have been used in Buchwald–Hartwig aminations[10] and enolate arylations;[11] however, their role is most likely that of a precatalyst. Hor and co-workers summarized the use of Pd^{I} catalysts in Suzuki–



Scheme 1. Photolytic Pd-catalyzed radical carbonylation/cyclization/carbonylation cascade. The arrows to the outside Pd^{I}I indicate that reversible combination may occur, thus modulating the lifetime of the radicals.

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[*] Dr. L. Ford, Priv.-Doz. Dr. U. Jahn
Institute of Organic Chemistry and Biochemistry
Academy of Sciences of the Czech Republic
Flemingovo namesti 2, 16610 Prague 6 (Czech Republic)
Fax: (+420) 220-183-578
E-mail: jahn@uochb.cas.cz
Homepage: http://www.uochb.cz/web/structure/616.html

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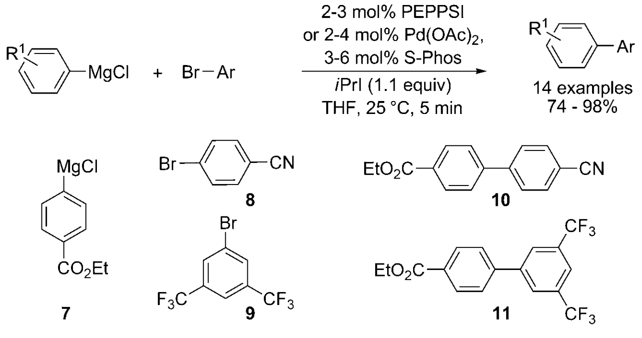
Miyaura couplings and mentioned a potential Pd^I/Pd^{III} manifold and thus a radical pathway in these reactions.[12]

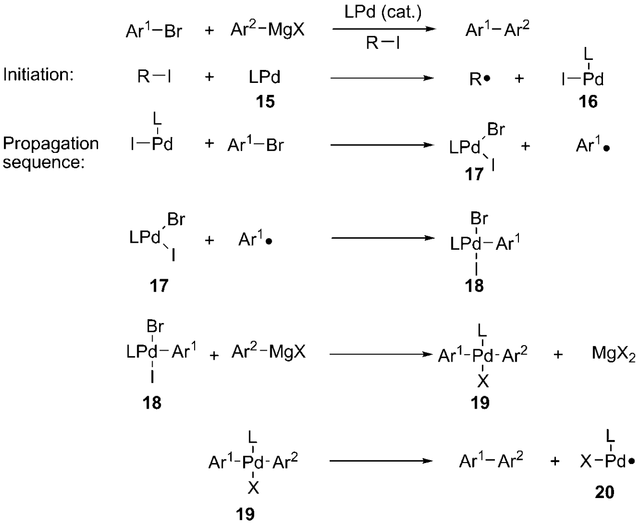
Manolikakes and Knochel provided the first evidence for a Pd^I/Pd^{III} catalytic cycle involving a radical chain reaction in Kumada cross-coupling reactions of aryl Grignard reagents with aryl bromides (Scheme 2).[13] The coupling was slow when the Grignard reagent was generated classically by the oxidative addition of magnesium. The reaction was significantly more facile and occurred at room temperature in only a few minutes when the aryl Grignard reagent was generated by iodine–magnesium exchange of aryl iodides with the *i*PrMgCl/LiCl complex and then added to a mixture of the aryl bromide and catalytic Pd(OAc)$_2$ and S-Phos (2-dicyclohexylphosphanyl-2′,6′-dimethoxybiphenyl) or PEPPSI ([1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride). This acceleration can be traced to the isopropyl iodide generated along with the Grignard reagent. Deliberate addition of other alkyl iodides displayed the same accelerating effect. This procedure was used to couple a wide variety of functionalized aryl and heteroaryl Grignard compounds with various aryl bromides in excellent yields after only 5 min. Even the highly unstable ester-substituted organomagnesium compound **7** could be coupled with bromobenzenes **8** and **9** to give biphenyls **10** and **11** in 82 and 84 % yield, respectively.



Scheme 2. Scope of the radical-catalyzed Kumada coupling.

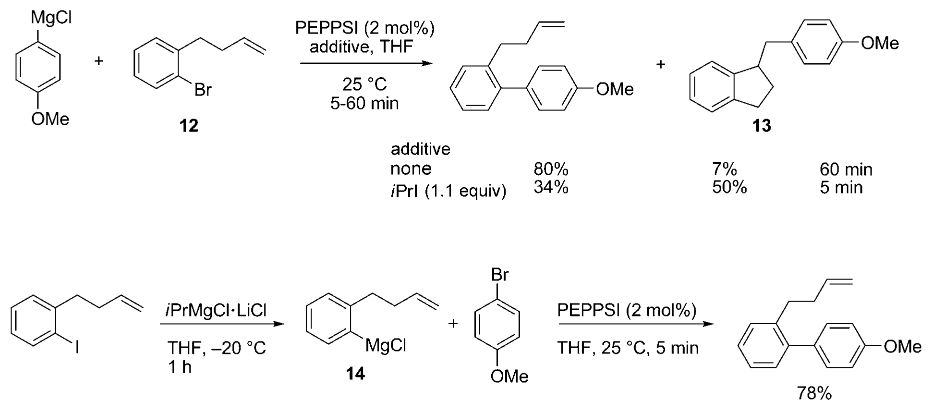
Significantly, the cyclized product **13** was isolated from the coupling with aryl bromide **12**, whereas no cyclized product was observed with the *ortho*-alkenyl Grignard reagent **14** (Scheme 3).

Based on these observations, a radical catalysis mechanism involving a Pd^I/Pd^{III} system was proposed (Scheme 4). The initiation step is reaction of the Pd^0 catalyst **15** with the alkyl iodide (R−I) to give an alkyl radical (R$^•$) and the Pd^I species **16**. The latter abstracts bromine from aryl bromide (Ar^1−Br) to release aryl radical (Ar$^{1•}$), which is trapped by palladium(II) halide **17** to give the Pd^{III} complex **18**, which undergoes transmetalation with the aryl Grignard reagent (Ar^2−MgX) affording the diarylpalladium(III) halide **19**. Reductive elimination of **19** generates the cross-coupled product (Ar^1−Ar^2) and regenerates the LPd^{I}X radical chain carrier **20**.



Scheme 4. Chain reaction of radical-catalytic Kumada couplings.

The effect of radical catalysis in the Kumada reaction is highly beneficial from several points of view. The slow transition-metal-catalyzed reaction is accelerated dramatically, which allows the reaction to be conducted under very mild

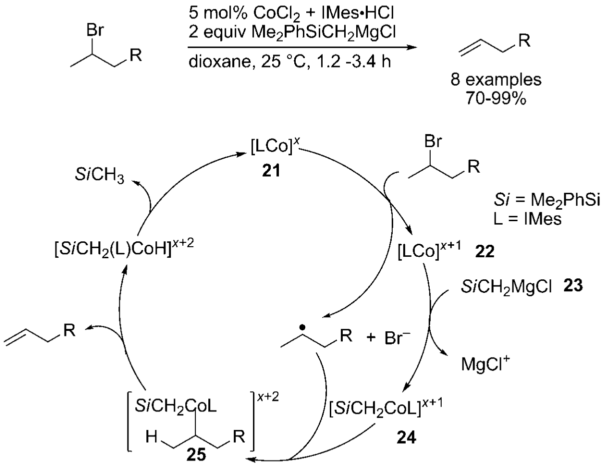


Scheme 3. Mechanistic experiments indicating radical catalysis.

conditions and enhances the functional group tolerance of the organometallic reaction considerably. This obviates the transmetalation of the Grignard reagents to zinc or boron intermediates, which greatly improves the atom economy of the process. In addition, the ability of palladium (in its various oxidation states) to mediate the radical chain reaction process of the highly reactive aryl radicals is quite efficient, resulting in high yields of the cross-coupled products.[14]

Palladium is not the only metal suitable for radical catalysis. Recent studies highlight the versatility of other metal complexes and illustrate how textbook reactions, which historically often gave poor results under polar reaction conditions, can be vastly improved under free radical conditions.

Oshima and co-workers have shown that a cobalt(II) salt, in combination with an N-heterocyclic carbene ligand (IMes·HCl), mediates the regioselective dehydrohalogenation of alkyl halides by dimethylphenylsilylmethylmagnesium chloride effectively and under mild conditions to give terminal alkenes almost exclusively (Scheme 5).[15] In contrast, the corresponding ionic elimination produces a mixture of regio- and stereoisomers.

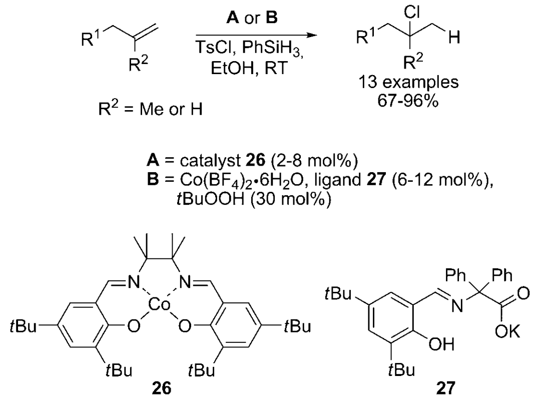


Scheme 5. Cobalt-catalyzed synthesis of terminal alkenes by radical-catalyzed dehydrobromination.

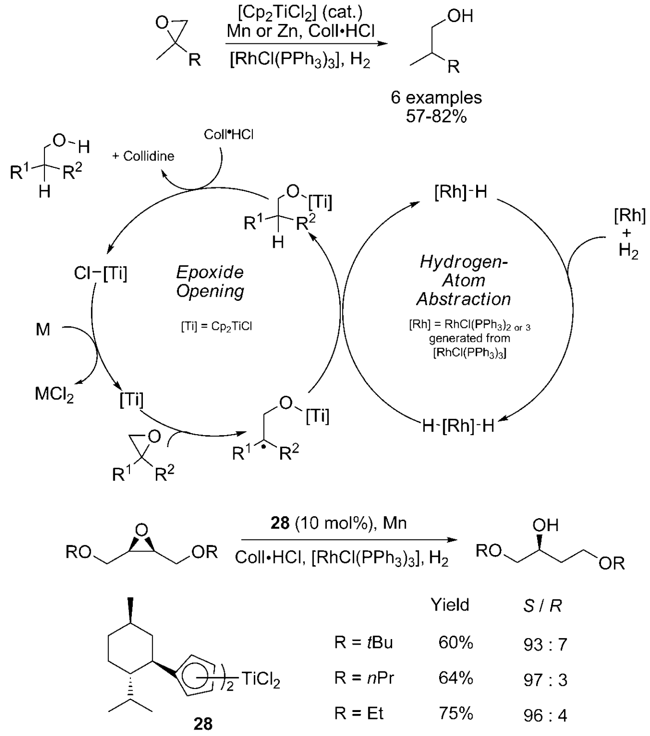
A plausible mechanism for the reaction involves electron transfer from cobalt complex **21** to the alkyl halide, resulting in formation of an alkyl radical. The Grignard reagent **23**, which functions as a hydrogen acceptor, is transmetalated by cobalt complex **22** to give intermediate **24**. The capture of the alkyl radical by cobalt complex **24** generates alkylcobalt complex **25**, which undergoes β-hydride elimination through a synperiplanar conformation to afford the 1-alkene selectively.

The reverse reaction, the polar Markovnikov addition of HCl to olefins is rarely utilized synthetically, despite the usefulness of alkyl chlorides. Carreira and Gaspar reported a cobalt-catalyzed addition that is thought to involve radical intermediates (Scheme 6).[16]

Recently Gansäuer and co-workers developed a method for the catalytic reductive ring opening of epoxides (Scheme 7).[17] A synergistic system was used consisting of catalytic $[Cp_2TiCl_2]$ to mediate the radical ring opening of the epoxide along with a rhodium hydride, derived from Wilkinson's catalyst in an atmosphere of H_2, to promote the hydrogen-atom transfer. In this way variously substituted epoxides can be cleaved to alcohols at ambient temperature in good yields. The reaction produces the less-substituted alcohol since the epoxide opening generates the most stable radical. The versatility of transition metals in radical chemistry is demonstrated with this catalytic system.



Scheme 6. Cobalt-catalyzed Markovnikov hydrochlorination of olefins.



	Yield	S / R
R = tBu	60%	93 : 7
R = nPr	64%	97 : 3
R = Et	75%	96 : 4

Scheme 7. Radical catalysis with a bimetallic system for the ring opening of epoxides.

Hydrogen-atom transfer from transition-metal hydrides represents an exciting alternative to classical hydrogen atom donors in radical chemistry. The low M–H bond strength (BDE Rh^{III}-H is about 58 kcal mol^{-1})[18] indicates that such transfers could occur with rate constants of up to $10^9\,M^{-1}\,s^{-1}$.[19]

The method has been extended to the enantioselective opening of *meso*-epoxides with Ti complex **28**.

It must be mentioned that MacMillan's work on "SOMO catalysis"[20] is similar in principle to the chemistry highlighted here. It is worthwhile to compare MacMillan's "SOMO catalysis" with "radical catalysis". Both concepts refer to the combination of a radical reaction for the key bond formation (or breaking) with a catalytic polar process that controls the radical process in a favorable way. The generation and fate of the radical is determined by the quantity and nature of the transition-metal complex in "radical catalysis", and by the quantity of organocatalyst used to generate the enamine intermediate in "SOMO catalysis". In the latter method, the stereoselectivity of the process is, of course, also efficiently controlled. Thus, in both processes the catalyst secures the desired low radical concentration during the overall process, guaranteeing that undesired side reactions of the reactive radicals are minimal.

In summary, radical reactions initiated and controlled by transition-metal catalysis show great promise in mediating a variety of reactions in excellent yields and under mild conditions. By utilizing transition-metal complexes in catalytic amounts for the generation and transformation of radicals, these reactions have distinct advantages over standard methods of radical chemistry and transition-metal catalysis. In addition, radical catalysis can greatly improve reactions that perform poorly under polar conditions. Thus transition-metal-"tamed" radicals represent powerful and versatile intermediates in organic chemistry.

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