Sequential Generation and Utilization of Radical and Anionic Species with a Novel Manganese−Lead Reducing Agent. Three-Component Coupling Reactions of Alkyl Iodides, Electron-Deficient Olefins, and Carbonyl Compounds

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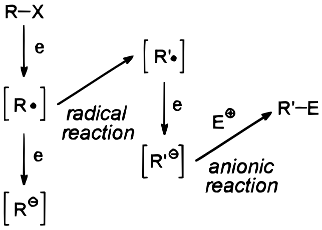
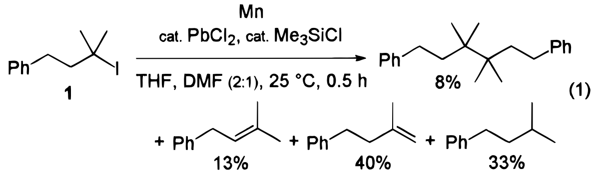
Carbanion and radical chemistry represent integral parts of organic synthesis. However, the reactivities of the two intermediates are sometimes complementary, and so sequential utilization of the two offers great potential for constructing more complex molecules (Scheme 1).[1,2]

Alkyl radicals are usually prepared either by chain methods, the homolytic cleavage of covalent bonds, or by nonchain methods based on redox reactions.[1] One of the latter accesses radicals by reduction of alkyl halides (R−X) with reducing agents; however, the method is not so popular as further reduction of the initial radicals ($R^{\bullet}$) leading to alkyl anions (R^-) normally proceeds faster than the first radical formation under the reduction conditions.[3] Although intramolecular radical cyclization before anionic reactions has been observed in several cases,[2a,3] there are few examples of the intermolecular version due to the above restriction.[4,5] Two requirements exist for a suitable reducing agent to connect the two reactions: (1) The initial radial ($R^{\bullet}$) is not easily reduced to R^- and has a sufficient lifetime to undergo an intermolecular reaction. (2) The final radical ($R'^{\bullet}$) is easily subjected by one-electron reduction to R'^-. Therefore, the desired reductant should be weak enough to be able to discriminate between the two radicals $R^{\bullet}$ and $R'^{\bullet}$. With these considerations in mind, here, a novel manganese−lead reducing agent was utilized, and the above concept was realized as a three-component coupling reaction.

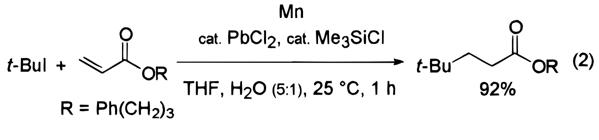
Scheme 1



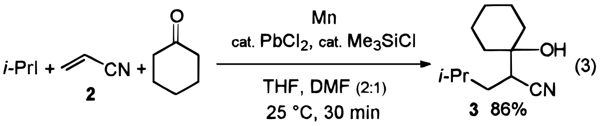
Manganese powder[6] is less reactive toward organic compounds than zinc powder due to a tight layer of manganese oxide on its surface. Recently, it was found that such metal oxide is effectively removed by treatment with Me_3SiCl;[7,8] and moreover, the manganese metal is especially activated by addition of a catalytic amount of $PbCl_2$.[7] Treatment of alkyl iodide **1** with the activated manganese metal afforded four compounds, which suggests the formation of an alkyl radical by reduction of the iodide with the manganese system (eq 1).



Intermolecular 1,4-addition to an α,β-unsaturated ester in a protic solvent was achieved in an excellent yield under mild conditions (eq 2).[9] It is likely, therefore, that the second one-electron reduction leading to an alkylmanganese compound is slower than the first reduction with this manganese system.



When the reaction was conducted in an aprotic solvent, the produced anionic species could be trapped with a carbonyl compound under mild conditions (eq 3).[10] Although the role of $PbCl_2$ is unclear, addition of a catalytic amount of the salt was essential for reducing the alkyl iodide.



The results of three-component coupling of alkyl iodides, electron-deficient olefins, and carbonyl compounds are shown in Table 1. Both 3 mol of an alkyl iodide and a carbonyl compound were used per mole of an olefin.

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(1) For some reviews of representative examples of serial processes with different intermediates, see: Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. Malacria, M. *Chem. Rev.* **1996**, *96*, 289; Snider, B. B. *Chem. Rev.* **1996**, *96*, 339.

(2) For some representative examples, see: (a) Cr: Takai, K.; Nitta, K.; Fujimura, O.; Utimoto, K. *J. Org. Chem.* **1989**, *54*, 4732. (b) Sm: Molander, G. A.; Kenny, C. *J. Org. Chem.* **1991**, *56*, 1439. Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 872; Curran, D. P.; Totleben, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 6050. Curran, D. P.; Fevig, T. L.; Jasperse, C. P.; Totleben, M. J. *Synlett* **1992**, 943. Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307. (c) Zn: Bronk, B. S.; Lippard, S. J.; Danheiser, R. L. *Organometallics* **1993**, *12*, 3340.

(3) (a) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8561. (b) Curran, D. P.; Fevig, T. L.; Totleben, M. J. *Synlett* **1990**, 773.

(4) For intermolecular carbon−carbon bond formation with radicals followed by one-electron reduction and protonation, see: Petrier, C.; Dupuy, C.; Luche, J. L. *Tetrahedron Lett.* **1986**, *27*, 3149. RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1989**, *111*, 4525.

(5) For Et_3B-initiated three-component coupling reactions via boron enolate, see: Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 403.

(6) (a) Hiyama, T.; Sawahata, M.; Obayashi, M. *Chem. Lett.* **1983**, 1237; *Nippon Kagaku Kaishi*, **1984**, 1022. (b) Cahiez, G.; Chavant, P.-Y. *Tetrahedron Lett.* **1989**, *30*, 7373. (c) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 2533.

(7) Takai, K.; Ueda, T.; Hayashi, T.; Moriwake, T. *Tetrahedron Lett.* **1996**, *37*, 7049.

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(9) (a) Luche, J. L.; Allavena, C. *Tetrahedron Lett.* **1988**, *29*, 5369. (b) Blanchard, P.; Da Silva, A. D.; El Kortbi, M. S.; Fourrey, J.-L.; Robert-Géro, M. *J. Org. Chem.* **1993**, *58*, 6517.

(10) Addition of Et_2AlCl or anhydrous hydrochloric acid in place of Me_3SiCl was also effective in promoting the reaction.

(11) Shono, T.; Nishiguchi, I.; Sasaki, M. *J. Am. Chem. Soc.* **1978**, *100*, 4314.

(12) Hulce, M.; Chapdellaine, M. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 237.

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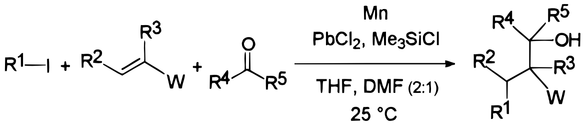
Table 1. Three-Component Coupling of Alkyl Iodides, Electron-Deficient Olefins, and Carbonyl Compounds[a]



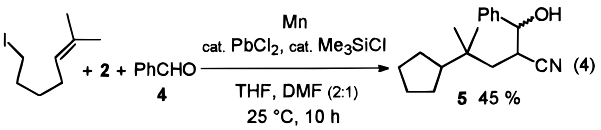
run	R^1	R^2	R^3	W	R^4	R^5	time (h)	yield[b] (%)	diastereomer ratio[c]
1	*i*-Pr	H	H	CN	$-(CH_2)_5-$		0.5	86	
2					Ph	H	0.5	96	57/43
3					Et	H	1	85[d,e]	68/32
4		H	H	CO_2Me	$-(CH_2)_5-$		0.5	83	
5					Ph	H	0.5	81	41/59[f]
6					Et	H	1	77[d,e]	51/49[f]
7		Me	H	CN	Ph	H	6	68[e]	*g*
8		H	Me	CN	Ph	H	0.5	67	52/48
9	*n*-Pr	H	H	CN	Ph	H	6	67[e]	55/45
10		H	H	CO_2Me	$-(CH_2)_5-$		4	61[e]	
11	*t*-Bu	H	H	CN	Ph	H	0.5	86	59/41

[a] Reaction was conducted on a 2.0 mmol scale. An alkyl iodide (3.0 mol), a carbonyl compound (3.0 mol), Mn (6.0 mol), $PbCl_2$ (0.06 mol), and Me_3SiCl (0.10 mol) were used per mol of an electron-deficient olefin. [b] Isolated yields. [c] Diastereomer ratios were determined by isolation, GLPC, or NMR. [d] An aldehyde (1.2 mol) was used per mol of an electron-deficient olefin. [e] $PbCl_2$ (0.3 mol) was used per mol of an olefin. [f] *anti*/*syn* ratio. [g] Mixture of four isomers of undetermined structures.

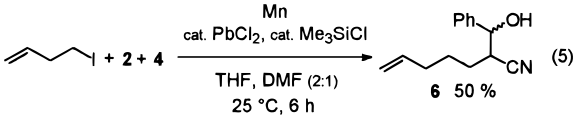
The reaction proceeded with primary, secondary, and tertiary alkyl iodides, but in the case of primary iodide, the amount of $PbCl_2$ was increased from 1 to 5 mol % of manganese to accelerate the process (Table 1, runs 9 and 10). Both acrylonitrile and acrylic esters could be employed as activated olefins, while the reaction with an alkyl vinyl ketone gave a complex mixture. A substituent at the β-position of the electron-deficient olefin decreased the reactivity of the olefin, and the reaction also required 5 mol % of $PbCl_2$ (Table 1, run 7). Ketones and aldehydes could be used as the third component, and the diastereoselectivity of the anionic addition was approximately 1:1 ~ 2:1 ratio.

In 1978, Shono and Nishiguchi reported a similar three-component coupling of alkyl iodides, α,β-unsaturated nitriles (or esters), and carbonyl compounds using zinc metal,[11] but the mechanism of such coupling reactions with metal is still uncertain.

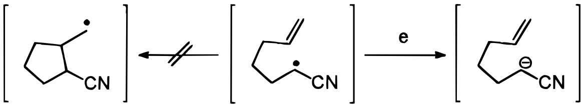
When 7-iodo-2-methyl-2-octene was used as an alkyl iodide, intramolecular radical cyclization occurred before intermolecular addition to acrylonitrile (eq 4). A three-component coupling product without the cyclization, however, was not detected.



Hydroxynitrile **6** was obtained in 50% yield in the case of 4-iodo-1-butene (eq 5), although no coupling product was obtained from further cyclization. The results suggests that the second one-electron reduction of radical **7** to a nitrile anion **8** proceeds very quickly (Scheme 2).

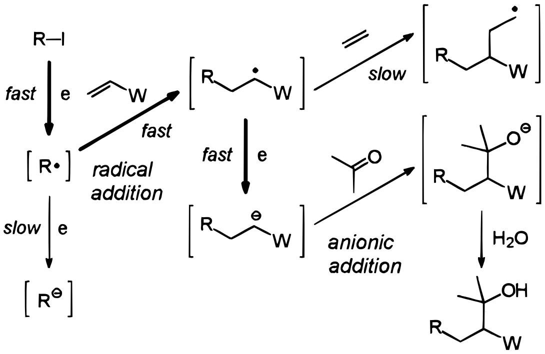


Scheme 2



7 **8**

Scheme 3



Consequently, the three-component coupling is realized by a subtle balance of the reaction rates (Scheme 3). The reduction rate of an alkyl radical to an alkyl anion is slower than 1,4-addition of the radical to an activated olefin. However, one-electron transfer to the resulting radical having an electron-withdrawing group proceeds faster than addition to a different unsaturated bond. Sequential generation and utilization of radical and anionic species, therefore, are the essential factors in the coupling reaction of iodoalkanes, α,β-unsaturated nitriles (or esters), and ketones (or aldehydes), and the protocol itself can provide a new access to similar coupling products that are difficult to obtain with organocuprates in one-pot reactions due to their complex nature.[12]

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Supporting Information Available: General procedure and spectroscopic and analytical data of all compounds in Table 1 and compounds **5** and **6** (7 pages).

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