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Tin-Free Giese Reaction and the Related Radical Carbonylation Using Alkyl Iodides and Cyanoborohydrides

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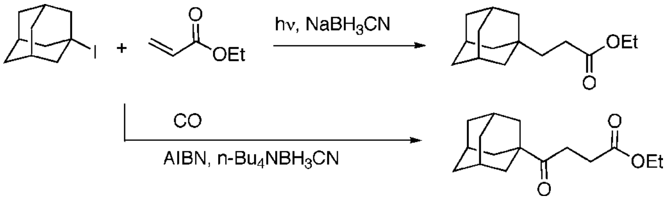
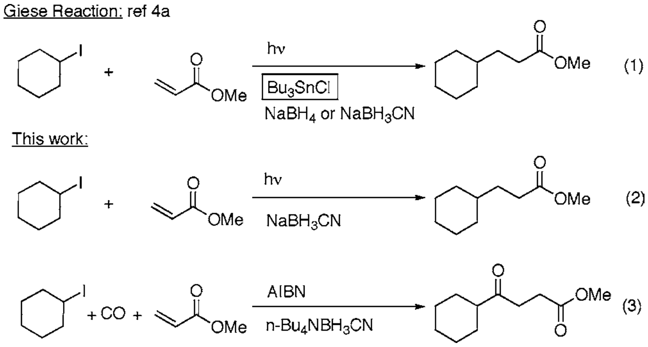
ABSTRACT



Tin-free Giese reaction and the related radical carbonylation process proceeded efficiently in the presence of sodium cyanoborohydride and tetrabutylammonium cyanoborohydride. The reaction took place chemoselectively at the carbon–iodine bond but not at the carbon–bromine and carbon–chlorine bonds. The iodine atom transfer followed by hydride reduction of the resulting carbon–iodine bond is proposed as a possible mechanism.

The carbon−carbon bond-forming reactions by radical addition have found wide applications in modern organic synthesis.[1] Alkyl radicals, which have a nucleophilic character, add to electron-deficient alkenes more smoothly than do ordinary and electron-rich alkenes.[2,3] The Giese reaction, which represents the radical addition of organic halides to electron-deficient alkenes, utilizes this "nucleophilic" radical C−C bond-forming process as a key step and typically uses tributyltin hydride as a radical mediator.[4] In an example shown in eq 1 of Scheme 1, Giese-type addition of iodocyclohexane to methyl acrylate was successfully achieved by using a catalytic amount of tributyltin hydride precursor in the presence of a source of a stoichiometric amount of hydride under photoirradiation conditions.[4] The role of borohydride reagents here is thought to be the conversion of tributyltin halides to tributyltin hydride.[5] Since photoinduced cyclization of *ω*-iodoalkenes using borohydride reagents can work,[6,7] we concluded that the system in which

Scheme 1. Giese Reaction and the Related Tin-Free Processes



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(1) (a) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vols. 1 and 2. (b) Zard, S. Z. *Radical Reactions in Organic Synthesis*; Oxford University Press: Oxford, 2003. (c) Also see a leading review, see: Srikanth, G. S. C.; Castle, S. L. *Tetrahedron* **2005**, *61*, 10377.

(2) (a) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753. (b) Giese, B. *Angew. Chem., Int. Ed.* **1985**, *24*, 553.

(3) For kinetic work, see: Jent, F.; Paul, H.; Roduner, E.; Heming, M.; Fischer, H. *Int. J. Chem. Kinet.* **1986**, *18*, 1113.

(4) (a) Giese, B.; González-Gómez, J. A.; Witzel, T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 69. (b) Curran, D. P.; Hadida, S.; Kim, S.-Y.; Luo, Z. *J. Am. Chem. Soc.* **1999**, *121*, 6607.

(5) (a) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303. (b) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1975**, *40*, 2554. (c) Poupon, J.-C.; Marcoux, D.; Cloarec, J.-M.; Charette, A. B. *Org. Lett.* **2007**, *9*, 3591.

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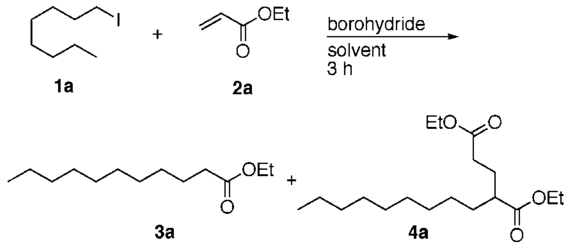
tributyltin reagent is simply eliminated from eq 1 should work, thereby achieving a tin-free Giese reaction (eq 2)[8,9] and the related radical carbonylation (eq 3).[10,11] In this paper, we report that a variety of alkyl iodides can undergo a tin-free Giese reaction and the related radical carbonylation reaction in the presence of sodium cyanoborohydride or tetrabutylammonium cyanoborohydride as a hydrogen source.

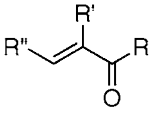
We examined the reaction of 1-iodooctane (**1a**) with ethyl acrylate (**2a**) as a model reaction under a variety of conditions (Table 1). When a mixture of **1a**, **2a**, and $NaBH_4$ in ethanol was irradiated with a 500 W xenon lamp through a Pyrex filter (>280 nm) for 3 h under argon, the expected addition product **3a** was obtained in only 10% yield, in which simple reduction of **1a** became a predominant reaction course (entry 1). Interestingly, however, the use of $NaBH_3CN$ increased the yield of **3a** up to 75%. In this reaction, 1:2 product **4a** was also formed as a byproduct. The thermal reaction conditions using a radical initiator such as V-65 (2,2′-azobis-(2,4-dimethylvaleronitrile)) also gave **3a** and **4a** in 72% and 14% yield, respectively (entry 3). This strongly supported the hypothesis that a radical chain mechanism is involved in this reaction. Tetrabutylammonium cyanoborohydride also gave **3a** in comparable yield (entry 4), whereas sodium triacetoxyborohydride did not give **3a** (entry 5). In the latter case, **1a** was recovered almost unchanged. Interestingly, no reaction took place when the corresponding 1-bromooctane (**1b**) and 1-chlorooctane (**1c**) were used. Thus, in the present Giese-type process iodoalkanes appear to be crucial.

Table 1. Tin-Free Giese Reaction of **1a** with **2a**[a]



entry	borohydride	solvent	conditions	yield[b] (%) 3a	yield[b] (%) 4a
1	$NaBH_4$	EtOH	$h\nu$ (Xe, Pyrex)	10	0
2	$NaBH_3CN$	MeOH	$h\nu$ (Xe, Pyrex)	75	9
3	$NaBH_3CN$	MeOH	V-65[c]	72	14
4	n-Bu_4NBH_3CN	MeOH	$h\nu$ (Xe, Pyrex)	66	16
5	$NaBH(OAc)_3$	C_6H_6	$h\nu$ (Xe, Pyrex)	0	0

[a] Reaction was conducted on a 1 mmol scale with **[1a]** = 0.5 M and **2a** (1.5 equiv), borohydride reagent (5.0 equiv). [b] Isolated yield by flash chromatography on SiO_2. [c] 2,2′-Azobis(2,4-dimethylvaleronitrile).



2a R = OEt, R',R" = H
2b R = OMe, R' = H, R" = CH_3
2c R = OMe, R' = CH_3, R" = H
2d R = OMe, R',R" = H
2e R = CN, R',R" = H
2f R = C_2H_5, R',R" = H
2g R = n-C_8H_{17}, R',R" = H

Having identified optimal conditions, we then studied the generality of the tin-free Giese reaction for a variety of alkyl iodides and electron-deficient alkenes (Table 2). Primary alkyl iodides **1a**, **1f**, **1g**, and **1h** reacted with ethyl acrylate (**2a**) to give the corresponding esters in good yields (entries 1, 6, 7, and 8). The reactions of alkyl iodides **1g** and **1h** were chemoselective to give the corresponding chlorine- and bromine-retaining products **3g** and **3h**, respectively (entries 7 and 8). These products can serve as the second radical precursors, when the ordinary tin hydride mediated system is applied. Under similar conditions, secondary and tertiary iodoalkanes, such as iodocyclohexane (**1d**) and 1-iodoadamantane (**1e**), reacted with **2a** to give the corresponding addition products **3d** and **3e** in good yields (entries 4 and 5). The reaction of **1a** with methyl crotonate (**2b**) gave the corresponding adduct **3b** in 67% yield (entry 2), whereas methyl methacrylate (**2c**) gave a poor yield of adduct **3c** due to the formation of significant amounts of 1:2 and 1:3 products (entry 3). Using a stainless steel autoclave and CO pressure conditions, we applied the thermally induced reaction system using n-Bu_4NBH_3CN-AIBN (2,2′-azobis-(isobutyronitrile)) for the carbonylative three-component coupling reaction (entries 9−11) for which tributyltin hydride or $(TMS)_3SiH$ had to be used in the original procedures.[10] Whereas the procedure A with sodium cyanoborohydride can be applied to the addition of **1a** to acrylonitrile (**2e**) (entry 12), the reaction using ethyl vinyl ketone (**2f**) suffered from undesirable reduction courses of **2f**.[12] Fortunately, this problem was circumvented by the use of a milder reagent, n-Bu_4NBH_3CN, instead of $NaBH_3CN$ (entries 13−16).

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(6) (a) Abe, M.; Hayashikoshi, T.; Kurata, T. *Chem. Lett.* **1994**, 1789. (b) Kurata, T.; Kinoshita, R. *J. Oleo Sci.* **2001**, *50*, 759. (c) Liu, Q.; Han, B.; Zhang, W.; Yang, L.; Liu, A.-L.; Yu, W. *Synlett* **2005**, 2248.

(7) For nickel-catalyzed addition of iodoalkanes to electron-deficient alkenes using borhydride exchange resin, see: Sim, T. B.; Choi, J.; Joung, M. J.; Yoon, N. M. *J. Org. Chem.* **1997**, *62*, 2357. Also see an indium(III) chloride catalyzed system: Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 906.

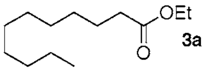
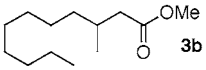
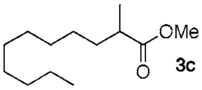
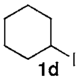
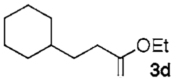
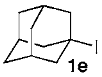
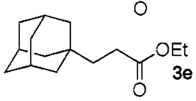
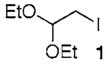
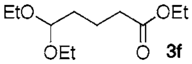
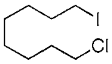
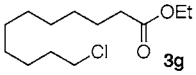
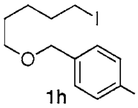
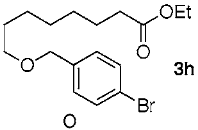
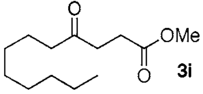
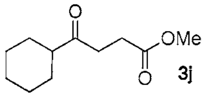
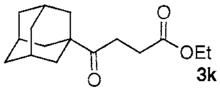
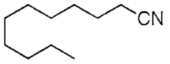
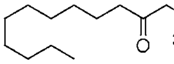
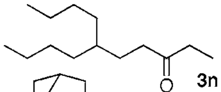
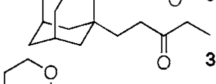
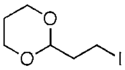
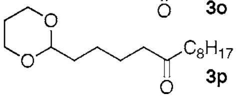
(8) For different approaches of tin-free reactions using organoboron compounds, see: (a) Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 403. (b) Ollivier, C.; Renaud, P. *Chem. Eur. J.* **1999**, *5*, 1468. (c) Ollivier, C.; Renaud, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 925. (d) Yajima, T.; Saito, C.; Nagano, H. *Tetrahedron* **2005**, *61*, 10203.

(9) For reviews on tin-free radical reactions, see: (a) Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3073.(b) Studer, A. *Synthesis* **2002**, 835. (c) Kim, S.; Kim, S. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 809. Also see some recent work: (d) Smith, D. M.; Pulling, M. E.; Norton, J. R. *J. Am. Chem. Soc.* **2007**, *129*, 770. (e) Guin, J.; Mück-Lichtenfeld, C.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2007**, *129*, 4498. (f) Carta, P.; Puljic, N.; Robert, C.; Dhimane, A.-L.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Org. Lett.* **2007**, *9*, 1061. (g) Kim, S.; Lim, K.-C.; Kim, S.; Ryu, I. *Adv. Synth. Catal.* **2007**, *349*, 527.

(10) (a) Ryu, I.; Kusano, K.; Yamazaki, H.; Sonoda, N. *J. Org. Chem.* **1991**, *56*, 5003.(b) Ryu, I.; Hasegawa, M.; Kurihara, A.; Ogawa, A.; Tsunoi, S.; Sonoda, N. *Synlett* **1993**, 143. (c) Kishimoto, Y.; Ikariya, T. *J. Org. Chem.* **2000**, *65*, 7656.

(11) For reviews on radical carbonylation, see: (a) Ryu, I.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1050. (b) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (c) Ryu, I. *Chem. Soc. Rev.* **2001**, *30*, 16. Also see a review on acyl radicals: (d) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991.

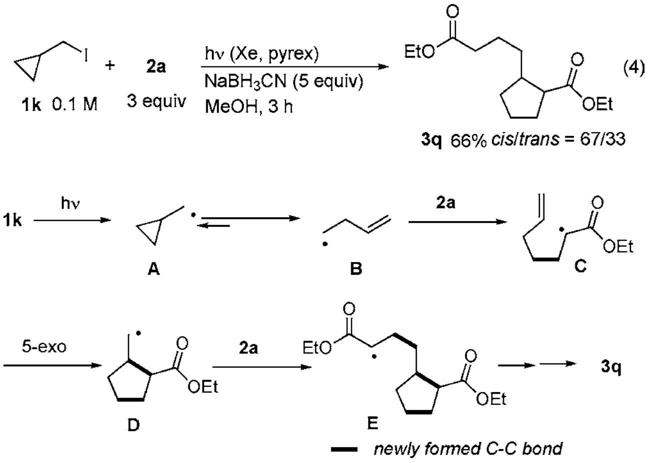
Table 2. Tin-Free Giese Reaction and Radical Carbonylation[a]

entry	1	procedure[a]	2	product 3	yield [b]
1	**1a**	A	**2a**	 **3a**	75%
2	**1a**	A	**2b**	 **3b**	67%
3	**1a**	A	**2c**	 **3c**	21%[c]
4	 **1d**	A	**2a**	 **3d**	70%
5	 **1e**	A	**2a**	 **3e**	73%
6	 **1f**	A	**2a**	 **3f**	70%
7	 **1g**	A	**2a**	 **3g**	67%
8	 **1h**	A	**2a**	 **3h**	67%
9	**1a**	B	**2d**	 **3i**	62%
10	**1d**	B	**2d**	 **3j**	60%
11	**1e**	B	**2a**	 **3k**	54%
12[d]	**1a**	A	**2e**	 **3l**	69%
13	**1a**	C	**2f**	 **3m**	67%
14	**1i**	C	**2f**	 **3n**	66%
15	**1e**	C	**2f**	 **3o**	55%
16	 **1j**	C	**2g**	 **3p**	67%

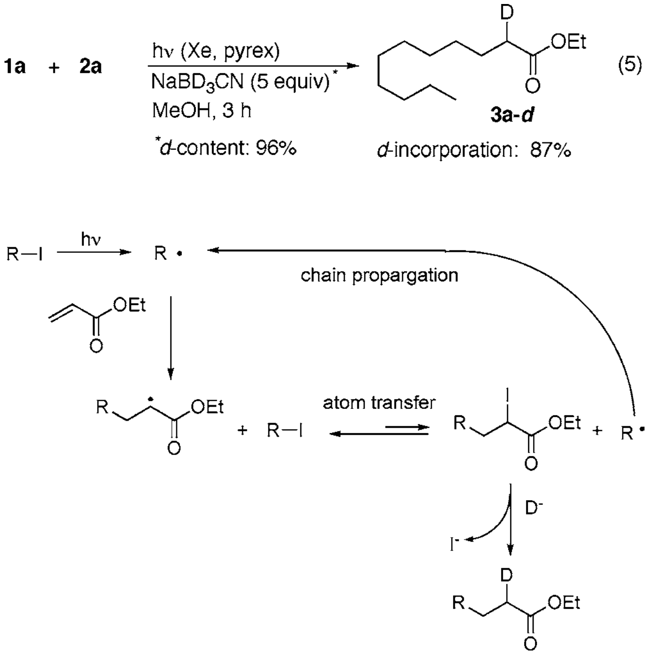
[a] Procedure A: **[1]** = 0.5 M, **2** (1.5−2.0 equiv), $NaBH_3CN$ (4.9−5.4 equiv), MeOH, 3 h, light (500 W xenon lamp, Pyrex). Procedure B: **[1]** = 0.017 M, **2** (2−4 equiv), *n*-Bu_4NBH_3CN (5−5.6 equiv), AIBN (10 mol %), benzene (MeOH for entry 9), CO (90 atm), 10−19 h, 80 °C. Procedure C: **[1]** = 0.5 M, **2** (3.0 equiv), *n*-Bu_4NBH_3CN (3 equiv), MeOH, 6 h, light (500 W xenon lamp, Pyrex). [b] Isolated yield by flash chromatography on SiO_2. [c] Products containing two and three molecules of **2c** were also formed. [d] Acrylonitrile (3 equiv), 20 h, (3 h, 57% yield).

We then examined a radical cascade sequence using cyclopropylmethyl iodide (**1k**) as the substrate (eq 4). When the reaction of **1k** with **2a** was carried out, **3q**, originating from one molecule of **1k** and two molecules of **2a** was formed as the major product (66% yield, *cis/trans* = 67/33) (Scheme 2). The result can be rationally explained by the formation of cyclopropylcarbinyl radical **A** and its rapid ring-opening to give homoallyl radical **B**,[13] which then undergoes addition to **2a**. The resulting radical **C** would undergo 5-exo cyclization to give **D**, which would add to a second molecule of **2a** to give **E**, a precursor radical for **3q**.

Scheme 2. Tandem Radical Processes Leading to **3q**



Scheme 3. Radical/Ionic Hydrid Reaction Mechanism



To gain insight into the mechanism of the final hydrogen-delivering process, we conducted a deuterium-labeling

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(12) We checked the background reaction by treating octyl vinyl ketone (**2g**) with 1 equiv of $NaBH_3CN$ in MeOH at rt for 6 h, which gave a mixture of 1-undecen-3-ol (17%), 3-undecanone (31%), and 3-undecanol (5%).

(13) (a) Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 5699. (b) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151.

experiment. When we used $NaBD_3CN$, 87% of deuterium incorporation at the carbon α to carbonyl group was observed (eq 5). This result led us to postulate a radical/ionic hybrid reaction mechanism, in which α-iodo ester forms via iodine atom transfer from alkyl iodide to the Giese adduct radical (Scheme 3).[14] This is an reversible process; however, the subsequent facile hydride reduction at iodine α to a carbonyl shifts the reaction to give the final adduct.[15] Thus, borohydride reagents likely act as a hydride source in the final step but not as a hydrogen source.[16] The failure of bromides and chlorides may be due to the less capable atom transfer ability in the energetically unfavorable atom transfer step.

In summary, we have demonstrated that the Giese reaction using alkyl iodides as starting materials and cyanoborohydrides as reducing reagents proceeds without the use of tin hydride or its precursors. The process can be applied to carbonylative three-component coupling and tandem radical reactions. We are now applying the present radical/ionic reaction concept to some other radical reactions.

Acknowledgment. I.R. acknowledges a Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Tansformation of Carbon Resources" from MEXT Japan and Scientific Research (B) from JSPS.

Supporting Information Available: Experimental procedures and characterization of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] For radical/ionic hybrid mechanism in other radical reactions involving atom transfer radical addition, see: (a) Curran, D. P.; Ko, S. B. *Tetrahedron Lett.* **1998**, *39*, 6629. (b) Joung, M. J.; Ahn, J. H.; Lee, D. W.; Yoon, N. M. *J. Org. Chem.* **1998**, *63*, 2755. (c) ref. 11c

[15] In a separate experiment, ethyl α-iodododecanoate was reduced very smoothly with $NaBH_3CN$/MeOH at rt (98%, 30 min).

[16] We have not precluded fully an alternative $S_{RN}1$ mechanism that involves direct hydrogen abstraction of the α-keto radical from BH_3CN^-. Cf. Kropp, M.; Schuster, G. B. *Tetrahedron Lett.* **1987**, *28*, 5295. Also see ref 5c.