© 2007 The Chemical Society of Japan Bull. Chem. Soc. Jpn. Vol. 80, No. 5, 809–822 (2007) 809

Vol. 80 Commemorative Accounts

Tin-Free Radical Carbon–Carbon Bond-Forming Reactions Based on α-Scission of Alkylsulfonyl Radicals

Sunggak Kim* and Sangmo Kim

Center for Molecular Design & Synthesis and Department of Chemistry, School of Molecular Science,
Korea Advanced Institute of Science and Technology, Daejeon 305-701, Korea

Received February 14, 2007; E-mail: skim@kaist.ac.kr

Tin-free radical reactions based on α-scission of alkylsulfonyl radicals are very useful for the formation of carbon–carbon bonds and include allylation, acylation, cyanation, vinylation, and carbonylation. For secondary, tertiary, and benzylic radicals, it is possible to use the corresponding iodides as precursors but the primary radicals still require the use of phenyl tellurides or alkyl allyl sulfones. Especially, alkyl allyl sulfones are highly efficient and most reliable primary alkyl radical precursors for the further formation of carbon–carbon bonds. The present approach is very useful for introducing various functional groups such as carbonyl and alkenyl groups under tin-free conditions.

Introduction

Radical-mediated methodology allows reactions to proceed under mild conditions with very high synthetic efficiency[1] but it suffers from a major drawback mainly associated with problems of toxicity of organotin compounds.[2] This disadvantage is a serious problem for industrial applications of radical reactions. Among several approaches including the use of polymer-supported organotin reagents and organosilanes,[2a] organosulfone-mediated tin-free radical reactions are very attractive because they completely eliminate the use of organotin compounds and utilize readily available organosulfone groups as mediators.[3]

Organosulfone-mediated radical allylation[4] and vinylation reactions were originally developed by Zard et al.[5] and are based on facile thermal decomposition of alkylsulfonyl radicals to produce alkyl radicals along with liberation of sulfur dioxide (Eq. 1).[6] The desulfonylation reaction is reversible and the equilibrium favors the formation of alkylsulfonyl radicals. If the alkyl radical is a stabilized radical such as a benzyl or an allyl radical, the liberation of sulfur dioxide occurs readily. Even though the alkylsulfonyl radicals are reluctant to thermal decomposition, the equilibrium can be shifted to the forward direction to generate alkyl radicals by designing the next step highly efficient and/or irreversible.

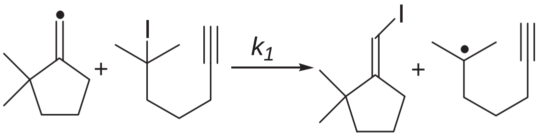
$$\mathrm{RSO_2\bullet} \rightleftharpoons \mathrm{R\bullet} + \mathrm{SO_2} \quad (1)$$

This account focuses on tin-free radical carbon–carbon bond forming reactions based on α-scission of the alkylsulfonyl radicals, in which the alkyl radicals mediate the reactions or directly take part in the reactions. In addition, we describe tin-free radical carbonylation approaches based on the same guiding principle. This account will cover mainly our work together with some reported results from other research groups.

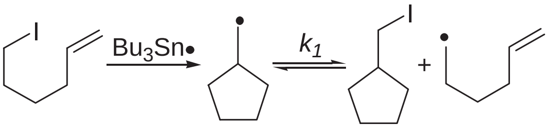
1. Iodine Atom Transfer Approach

An atom-transfer method is one of the fundamental approaches in radical chemistry and mostly involves a halogen atom transfer.[7] In iodine atom transfer approach, a carbon–iodine bond is a good iodine atom donor and the iodine atom transfer between alkyl radicals and alkyl iodides is a well-known process (Eq. 2). The rapid iodine atom transfer can occur whenever an exothermic reaction results in the formation of a more stabilized alkyl radical than the initial alkyl radical.[8] Thus, to accelerate the iodine atom transfer process, it is desirable to generate the radical R′ that is more stable than the initial radical R.

$$\mathrm{R'{-}I} + \mathrm{R\bullet} \rightleftharpoons \mathrm{R{-}I} + \mathrm{R'\bullet} \quad (2)$$



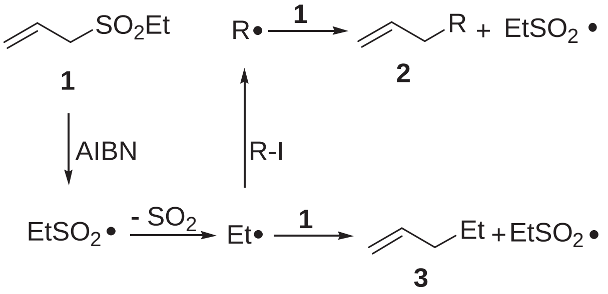
(3)



(4)

Kinetic studies by Curran et al. indicate that iodine atom trans-

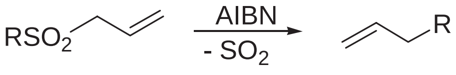
Published on the web May 14, 2007; doi:10.1246/bcsj.80.809



Scheme 1. Mechanism of tin-free radical allylation.

fer from an alkyl iodide to a vinyl radical is very fast and highly efficient. k_1 ranges from about $10^8\,M^{-1}\,s^{-1}$ for primary alkyl iodides to $10^9\,M^{-1}\,s^{-1}$ for tertiary iodides (Eq. 3).[9] Furthermore, iodine atom transfers between alkyl iodides proceed at a rate sufficient ($k_1 = 2 \times 10^5\,M^{-1}\,s^{-1}$) to allow a chain to be maintained (Eq. 4).[10]

1.1 Allylation. Radical allylation reactions proved to be synthetically useful for the formation of carbon–carbon bonds under very mild conditions.[11] Two similar approaches for tin-free radical allylation were reported by Zard et al. The first approach involves sulfur dioxide extrusion from alkyl allyl sulfones to provide allylated products directly (Eq. 5),[4a] whereas the second approach utilizes iodine atom transfer methodology to generate an alkyl radical from an alkyl iodide under tin-free conditions (Eq. 6).[4b]



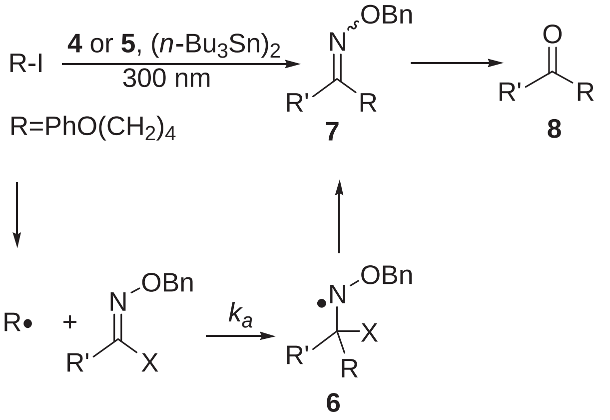
(5)

AIBN=2,2'-azobisisobutyronitrile

(6)

As shown in Scheme 1, the reaction is initiated by generation of an ethylsulfonyl radical and followed by thermal desulfonylation to form an ethyl radical. The ethyl radical can undergo two competing processes, the direct addition of the ethyl radical onto allylsulfone **1** and/or iodine atom transfer from the alkyl iodide to the ethyl radical. The efficiency of the latter process depends critically on the nature of the alkyl iodide. The alkyl radical reacts with allyl sulfone **1** to give the desired allylated product **2**. In allylation, the direct addition of the ethyl radical onto **1** to yield **3** is not a serious problem because the iodine atom transfer process is normally much faster than the direct addition process.[12]

1.2 Acylation. Although acylation is one of the most important organic reactions to introduce the carbonyl group, the radical-mediated acylation reaction has not been well studied because additions of alkyl radicals to C=O bonds are very difficult due to their reversibility and the high π bond strengths of the C=O bonds.[13] In fact, there are no successful methods available for the intermolecular acylation reaction.[14,15] Since the fundamental problem associated with the cleavage of the strong C=O bond could not be readily solved, we turned our attention to the C=N bond rather than the C=O bond. Our approach utilizes an indirect radical acylation reaction involving sulfonyl oxime ether derivatives as carbonyl equivalent radical acceptors (Scheme 2).



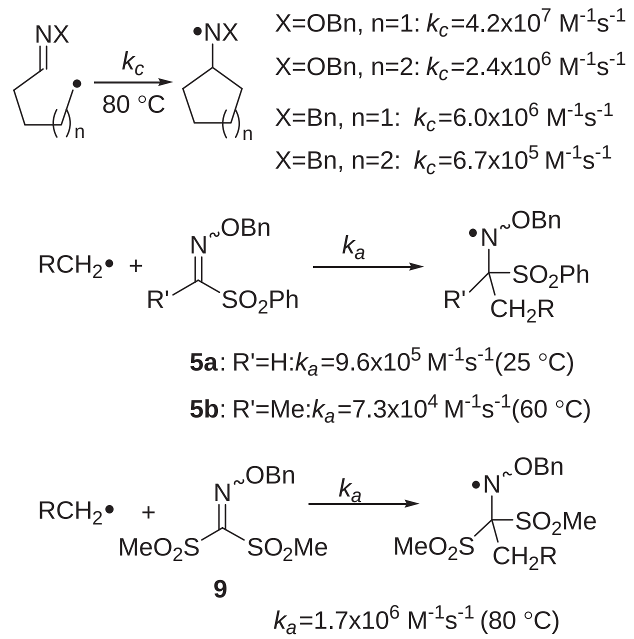
4a: R'=H, X=SPh, 20%
5a: R'=H, X=SO_2Ph, 94%
4b: R'=Me, X=SPh, <5%
5b: R'=Me, X=SO_2Ph, 88%

Scheme 2. Radical reaction of phenylsulfanyl oxime ether **4** and phenylsulfonyl oxime ether **5**.

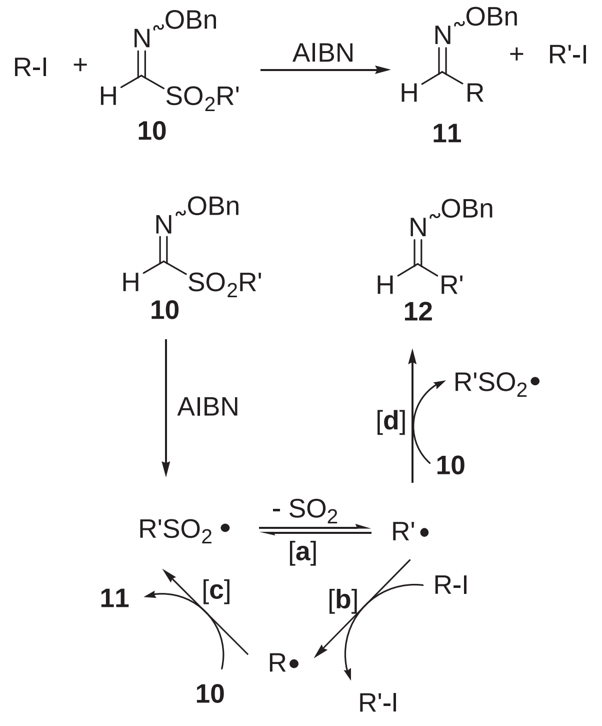
1.2.1 Sulfonyl Oxime Ether Acceptors: The intermolecular additions of alkyl radicals onto the C=N bonds are relatively rare and are expected to be slow.[16] Our approach involves the addition of an alkyl radical onto the C=N bond of oxime ether **4** or **5** and subsequent β-elimination in **6** to afford oxime ether **7** which can be readily hydrolyzed into ketone or aldehyde **8**. To design a highly efficient radical trapping agent, two important features should be considered; (i) an activated C=N bond bearing an electron-withdrawing group and (ii) a facile β-elimination of a leaving group. As shown in Scheme 2, a phenylsulfonyl group is most suitable for our purpose and phenylsulfanyl oxime ether **4a** and **4b** are not effective.[17]

1.2.2 Kinetic Studies: The cyclizations of alkyl radicals onto the C=N bonds are irreversible and are much faster than the additions of alkyl radicals onto the C=C bonds as shown in Scheme 3.[18] In addition, approximate rate constants for intermolecular additions of primary alkyl radicals to phenylsulfonyl oxime ethers were determined as $k_a = 9.6 \times 10^5\,M^{-1}\,s^{-1}$ at 25 °C for **5a** and $k_a = 7.3 \times 10^4\,M^{-1}\,s^{-1}$ at 60 °C for **5b**, indicating that the additions are very fast and highly efficient.[19] We also investigated kinetic data of bis(methanesulfonyl)oxime ether **9**. According to computational data, **9** has a lower LUMO energy and a higher electron density at the iminyl carbon than **5a**. Thus, it is expected that **9** would be more reactive than **5a**. Since we were not sure about our prediction due to a steric effect associated with **9**, an approximate rate constant for the primary alkyl radical addition onto **9** was determined as $k_a = 1.7 \times 10^6\,M^{-1}\,s^{-1}$ at 80 °C.[20]

1.2.3 Tin-Free Acylation Approach: Our tin-free acylation approach is largely based on Zard's tin-free allylation reaction[4b] and utilizes thermal α-scission of an alkylsulfonyl radical (path **a**) and subsequent iodine atom transfer (path **b**) as outlined in Scheme 4.[21] The major problem associated with tin-free acylation approach arises from the fast addition



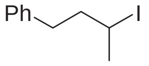
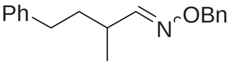
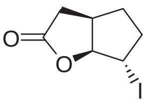
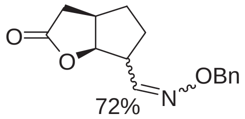
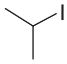
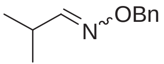
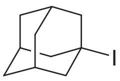
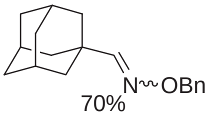
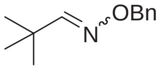
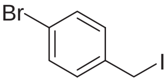
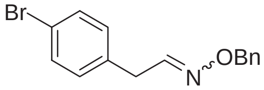
Scheme 3. Kinetic data for the addition of alkyl radicals onto C=N bonds.

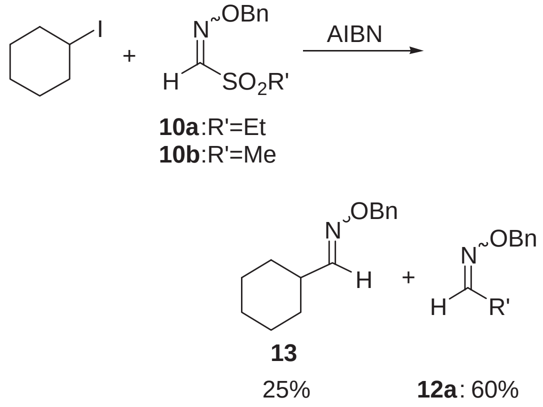


Scheme 4. Tin-free acylation of alkyl iodides.

step (path **d**) unlike the slow addition step in the allylation reaction (Scheme 1). Since the direct addition of the alkyl radical onto sulfonyl oxime ether **10** (path **d**) can compete with iodine atom transfer (path **b**), the efficient iodine atom transfer is a key factor for the success of the present approach. When the efficiency of iodine atom transfer was studied with **10a**, a 25:60 mixture of two oxime ethers **13** and **12a** was obtained (Eq. 7), indicating that **10a** is not suitable for tin-free radical acylation of secondary alkyl iodides. It is evident that the addition of the ethyl radical onto **10a** is more than two times faster than iodine atom transfer from cyclohexyl iodide to the ethyl radical.

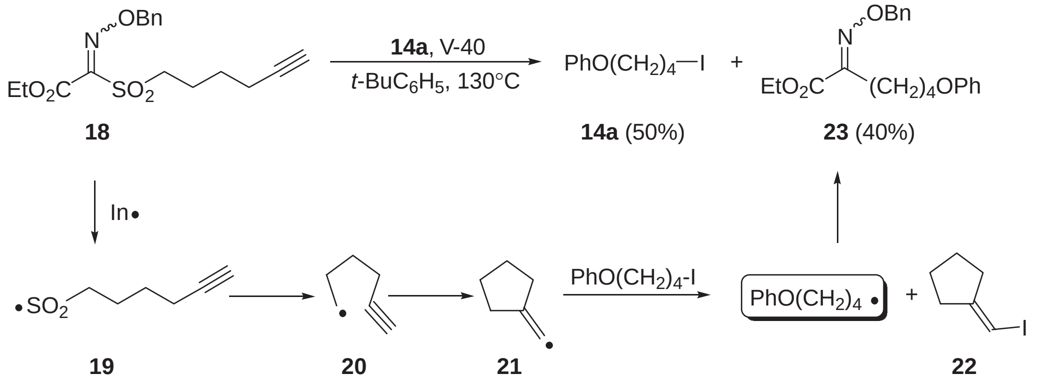
Table 1. Tin-Free Acylation with **10b**

Substrate	Product **11**
	 67%
	 72%
	 67%
	 70%
	 71%
	 80%

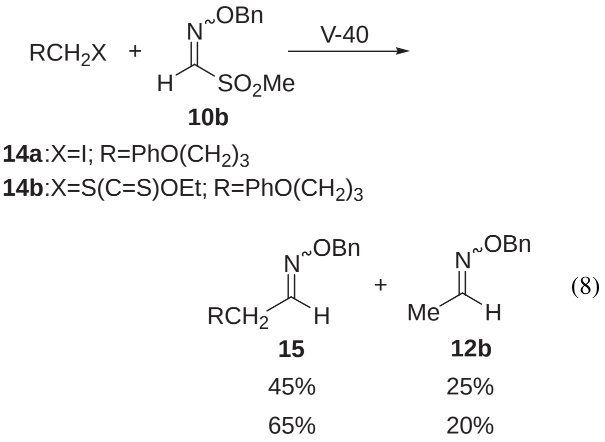


(7)

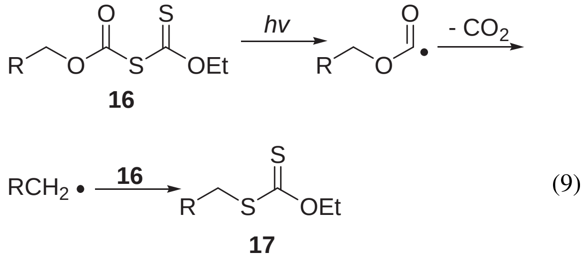
When cyclohexyl iodide was treated with **10b** in refluxing heptane in the presence of AIBN, **13** was isolated in 62% yield along with a trace amount of methyl oxime ether **12b**, indicating that iodine atom transfer process is much faster than the direct addition process. Thus, **10b** obviates the problem we have faced with secondary alkyl iodides due to a large energy difference between a methyl radical and a cyclohexyl radical. As shown in Table 1, the results obtained with **10b** are quite satisfactory, yielding the corresponding oxime ethers in high yield (67–80%).



Scheme 5. Generation of a vinyl radical using **18**.



(8)



(9)

The present method reaches a limit with primary alkyl iodides. Due to a small energy difference (4 kcal mol^{-1}) between a methyl radical and a primary alkyl radical, iodine atom transfer becomes less efficient and competes with the direct addition of the methyl radical onto **10b**. When the reaction was carried out with 4-phenoxybutyl iodide (**14a**) and an equimolar amount of **10b** in *tert*-butylbenzene at 140 °C for 30 h, a 45:25 mixture of the desired oxime ether **15** and **12b** was obtained, showing the inefficiency of **10b**. Our attempt to solve the problem using alkyl xanthate **14b** was also unsatisfactory (Eq. 8).[22] Furthermore, *S*-alkoxycarbonyl dithiocarbonate **16** is known to be a suitable precursor for the generation of the primary alkyl radical under tin-free conditions but it can not be applied to carbon–carbon bond formations owing to the rapid formation of the corresponding xanthate **17** (Eq. 9).[23]

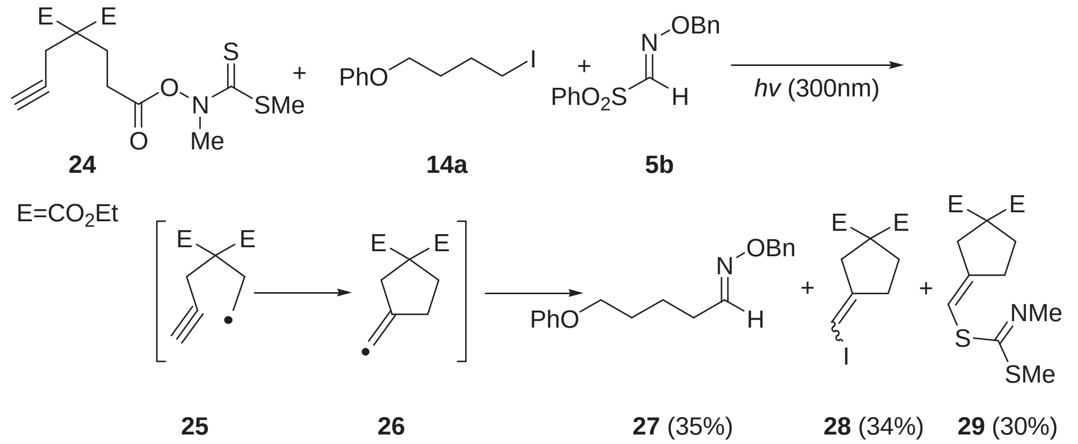
For the more efficient iodine atom transfer, an obvious solution is to utilize a vinyl radical, which is more reactive than the methyl radical. To generate the vinyl radical under tin-free conditions, we devised sulfonyl oxime ether **18** not only to mediate the reaction but also to generate the vinyl radical via radical cyclization of **20** (Scheme 5). The key feature of the present approach is the generation of intermediate **20** through the desulfonylation of **19**. When alkyl iodide **14a** was treated with **18** using V-40 (1,1′-azobis(cyclohexane-1-carbonitrile) initiator in refluxing *tert*-butylbenzene for 12 h, the reaction did not go to completion and the desired product **23** was isolated in 40% yield together with recovery of starting iodide **14a** (50%). Although the reason for this observation is not clear, it is assumed that the vinyl radical would react with sulfur dioxide to form a vinylsulfonyl radical to terminate the radical chain propagation.

In order to avoid liberation of sulfur dioxide in the present approach, we devised **24** to generate an alkyl radical via decarboxylation under photochemically initiated conditions (Scheme 6). We developed a new Barton-type thiohydroxamate ester **24**,[24] which is more stable and less reactive, and has several advantages than Barton ester.[25] Upon irradiation at 300 nm alkyl radical intermediate **25** is cleanly generated and undergoes cyclization to generate vinyl radical intermediate **26**. However, in addition to iodine atom transfer to yield oxime ether **27**, the vinyl radical reacts with a thiocarbonyl group of **24** to produce **29** roughly in an equal ratio.

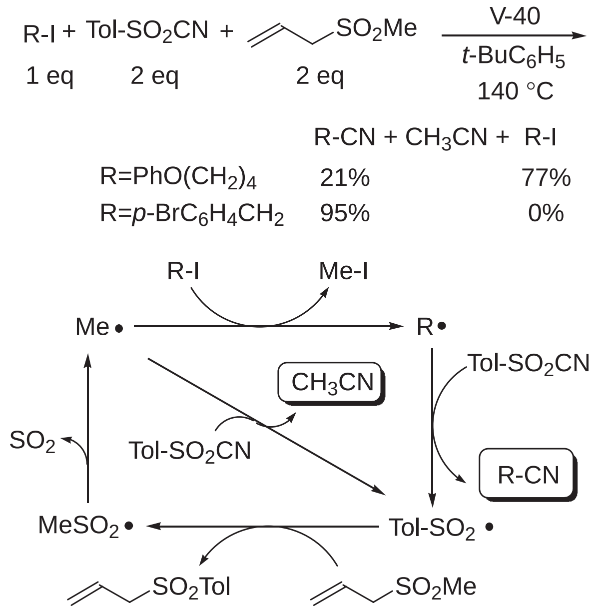
2. Alkyl Allyl Sulfone Approach

Since tin-free radical acylation approach using methanesulfonyl oxime ether **10b** does not work with primary alkyl iodides and xanthates, alternative radical precursors are needed to accommodate all the structurally different substrates including primary alkyl substrates. During our studies on the tin-free radical cyanation using allyl methyl sulfone as a mediator, we have found that the yields depended very much on the nature of the starting iodides.[26] Evidently, a fast and efficient iodine atom transfer from *p*-bromobenzyl iodide to the methyl radical proceeded rapidly to generate a stable benzylic radical, whereas the iodine atom transfer from 4-phenoxybutyl iodide competed with the addition of the methyl radical onto a tosyl cyanide to produce acetonitrile (Scheme 7). To obviate the problem of the competition between the iodine atom transfer and the direct addition, we came up with a simple idea which was to eliminate those two competition reactions by using an alkyl allyl sulfone precursor.

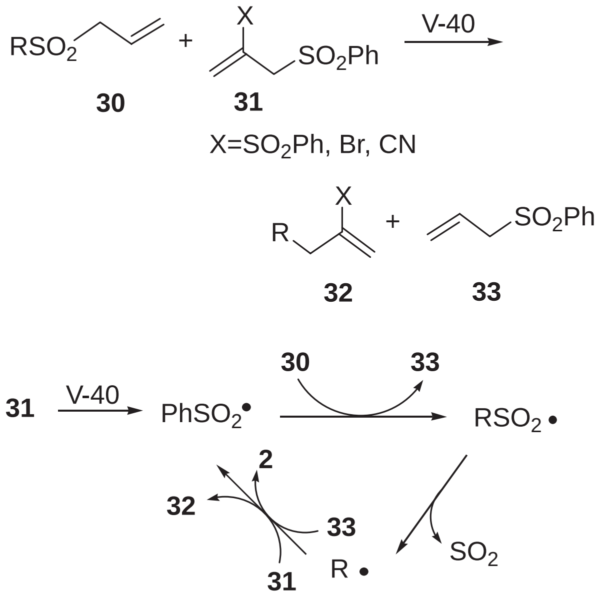
We have found that alkyl allyl sulfones are the solution for a



Scheme 6. Generation of a vinyl radical using **24**.



Scheme 7. Radical cyanation using methyl allyl sulfone as a mediator.

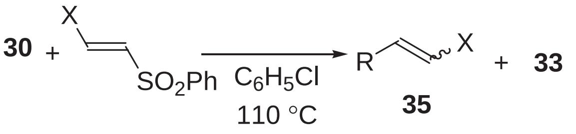


Scheme 8. Radical allylation using **30**.

longstanding problem to generate primary alkyl radicals under tin-free conditions and are highly efficient and reliable primary alkyl radical precursors for the further formation of carbon–carbon bonds. The use of alkyl allyl sulfone precursors does not require an atom or a group transfer step for generation of alkyl radicals. Hence, they can be successfully applied to various carbon–carbon bond formation reactions under tin-free conditions.

2.1 Allylation, Vinylation, and Cyanation. As shown in Scheme 8, the addition of a phenylsulfonyl radical onto alkyl allyl sulfone **30** would produce an alkylsulfonyl radical along with the formation of phenyl allyl sulfone (**33**). Although the alkylsulfonyl radical would add to **30** and **33**, the former is a degenerate process and the latter produces the phenylsulfonyl radical. Thus, both reactions do not interfere with the desired process. Since the addition of an alkyl radical onto **30** and **33** is relatively slow, the alkyl radical should preferentially add to activated allyl sulfones **31** along with regeneration of the phenylsulfonyl radical for the propagation of a radical chain reaction.

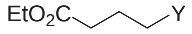
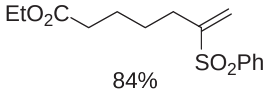
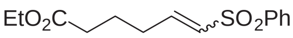
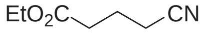
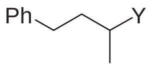
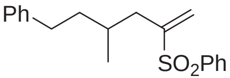
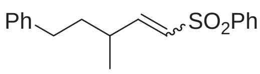
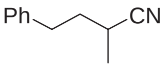
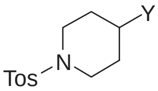
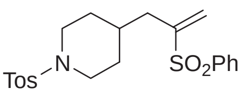
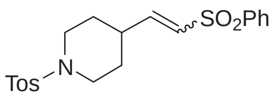
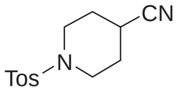
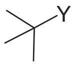
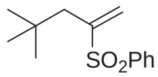
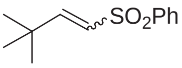
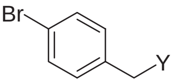
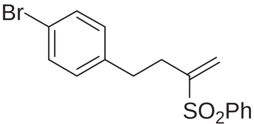
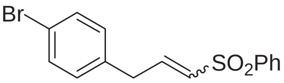
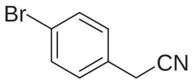
When radical allylations with several C2-substituted allyl sulfones **31** were performed, the allylated products **32** were isolated in high yields regardless of the nature of the C2 substituents.[27] As shown in Table 2, the method accommodates all the structurally different substrates, ranging from primary alkyl radicals to benzylic radicals. The same approach can be applied to radical vinylation reactions.[27]

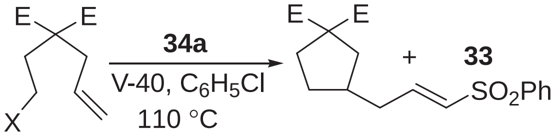


(10)

34a: X=SO_2Ph	**35a** (82%, V-40)
34b: X=Ph	**35b** (72%, lauroyl peroxide)
34c: X=CO_2Et	**35c** (65%, lauroyl peroxide)

Table 2. Tin-Free Radical Allylation, Vinylation, and Cyanation Using Alkyl Allyl Sulfone Precursor **30**

Alkyl allyl sulfone **30** ($Y = SO_2CH_2CH{=}CH_2$)	Product **32**	 **35a**	 **38**
	 84%	 88%	 93%
	 90%	 96%	 98%
	 88%	 98%	 98%
	 98%	 98%	
	 97%	 97%	 98%



36 **37** (92%) (11)

$E = CO_2Et$
$X = SO_2CH_2CH{=}CH_2$

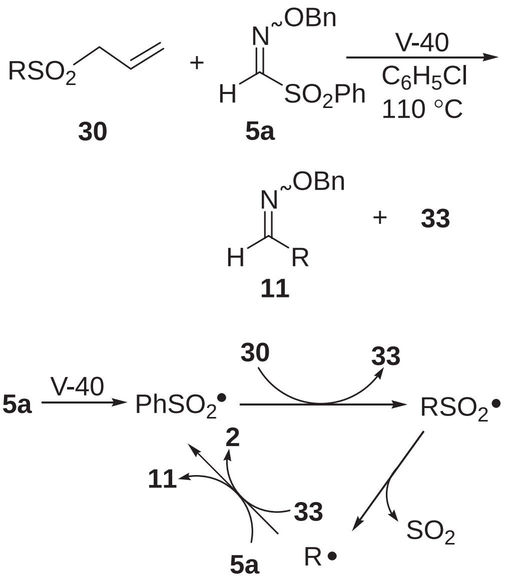
$$\mathbf{30} + \text{TolSO}_2\text{-CN} \xrightarrow[\text{C}_6\text{H}_5\text{Cl, 110 °C}]{\text{V-40}} \underset{\mathbf{38}}{\text{R–CN}} + \mathbf{33} \qquad (12)$$

For radical vinylations, when (*Z*)- and (*E*)-1,2-bis(phenylsulfonyl)ethene (**34a**) were used as radical acceptors, vinyl sulfones were obtained in good yields (Eq. 10). In the case of **34b**, the choice of a radical initiator was important. The reaction of **30** with **34b** using V-40 initiator gave the desired alkene **35b** in 21% yield, whereas **35b** was isolated in 72% yield using lauroyl peroxide initiator. Tandem radical reactions involving cyclization and vinylation worked efficiently. When **36** was treated with **34a** under the similar conditions, the desired product **37** was isolated in 92% yield (Eq. 11). The present approach can be efficiently applied to the tin-free radical cyanation using tosyl cyanide (Eq. 12). The additional experimental results obtained for the allylation, vinylation, and cyanation are presented in Table 2. The yields are excellent for each of these reactions, indicating that the alkyl allyl sulfones are a good source of alkyl radicals, especially primary alkyl radicals.

2.2 Acylation. Radical acylation using alkyl allyl sulfone precursors follows the same guiding principle of the radical allylation.[28] Reaction of allyl sulfone **30** with **5a** (1.5 molar amount) and V-40 (0.2 molar amount) as initiator in chlorobenzene at 110 °C proceeded cleanly and was complete within 6 h, yielding **11** in high yield. In the present approach, the direct allylation of an alkyl radical onto starting allyl sulfone **30** was much slower than the addition of the alkyl radical onto **5a** and did not cause any problems (Scheme 9).[12]

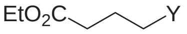
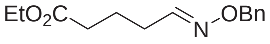
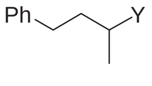
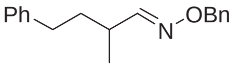
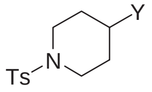
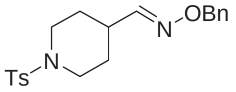
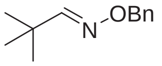
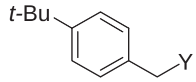
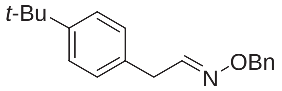
This method is quite general and highly efficient for radical acylation of a variety of structurally different substrates as shown in Table 3. For example, it always works well not only with reactive primary and secondary alkyl radicals but also with stable tertiary and benzylic radicals. The reactions with secondary, tertiary alkyl, and benzylic sulfones can be conducted at lower temperatures due to the facile decomposition of the corresponding sulfonyl radicals but the reactions with primary alkyl sulfones typically require elevated temperatures (>100 °C).

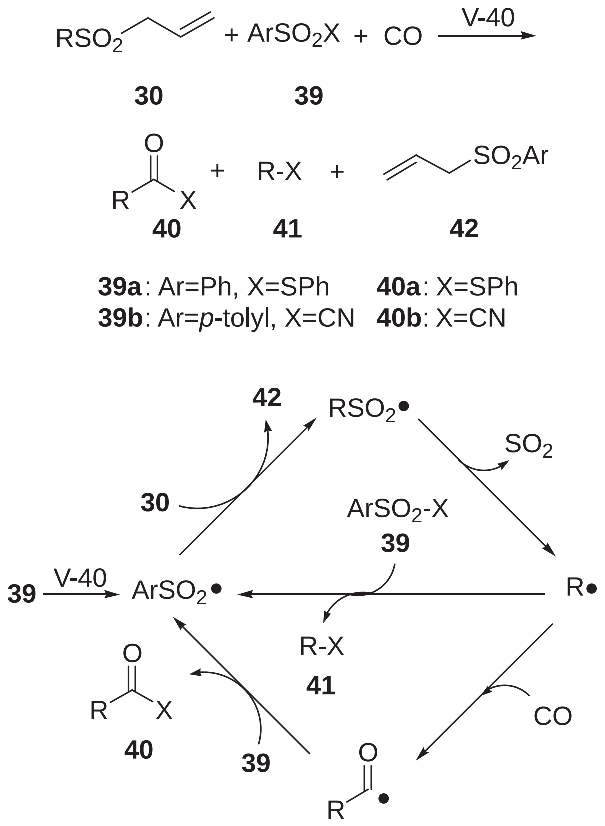
2.3 Thioalkoxycarbonylation. Free radical carbonylation is synthetically very useful in preparing various carbonyl compounds.[29] Synthetic methods based on free radical carbonylation utilize mainly highly toxic organotin compounds as mediators. Based on our successful results using alkyl allyl sulfone precursors, we studied tin-free radical carbonylations. To uncover efficient radical-trapping agents of acyl radicals,[30]



Scheme 9. Radical acylation using **30**.

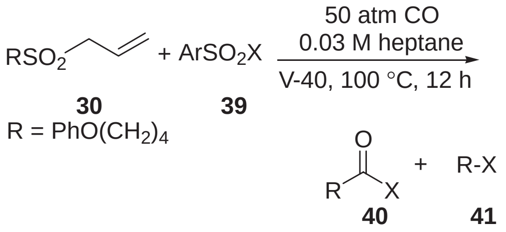
Table 3. Tin-Free Acylation Using Alkyl Allyl Sulfones with **5a**

Alkyl allyl sulfone **30** (Y = $SO_2CH_2CH=CH_2$)	Product **11**
	 86%
	 98%
	 98%
	 95%
	 95%



Scheme 10. Tin-free radical carbonylation of alkyl allyl sulfone **30** with $ArSO_2X$ **39**.

Table 4. Radical Carbonylation of Alkyl Allyl Sulfone **30** with **39**

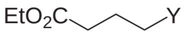
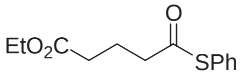
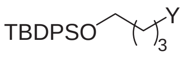
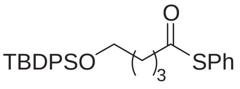
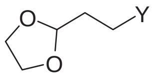
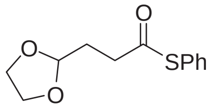
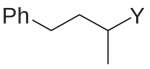
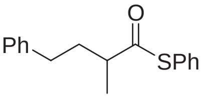
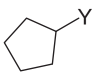
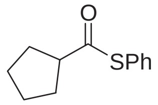
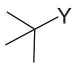
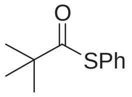


39		Yield/%		
		40	**41**	**30**
Ar = Ph	X = Cl	10[a)]	0	76
Ph	Br	0	75	20
Ph	SePh	0	84	0
p-Tol	CN	58[a)]	27	0
Ph	SPh	75	12	7

a) Isolated as methyl ester.

we screened several arylsulfonyl derivatives **39**.[31] As shown in Scheme 10, the addition of an arylsulfonyl radical to alkyl allyl sulfone **30** produces an alkyl radical through the thermal desulfonylation of the initially generated alkylsulfonyl radical along with formation of aryl allyl sulfone **42**. The alkyl radical can react with CO and/or **39** to yield the acyl radical and/or by-product **41**. Therefore, the success of this approach depends critically on obviating the formation of **41**. As shown in Table 4, phenylsulfonyl bromide and phenyl benzeneselenosulfonate react with the alkyl radical prior to the carbonylation of the alkyl radical, whereas phenylsulfonyl chloride is too unreactive toward the alkyl radical. The best result was obtained with phenyl benzenethiosulfonate, giving a mixture of thiol ester (75%) along with some phenyl sulfide (12%). Further optimization of the reaction condition increased the yield of thiol ester **40a** at the higher pressure of CO and at the lower concentration of **30**. A somewhat less satisfactory

Table 5. Thioalkoxycarbonylation Using Alkyl Allyl Sulfones

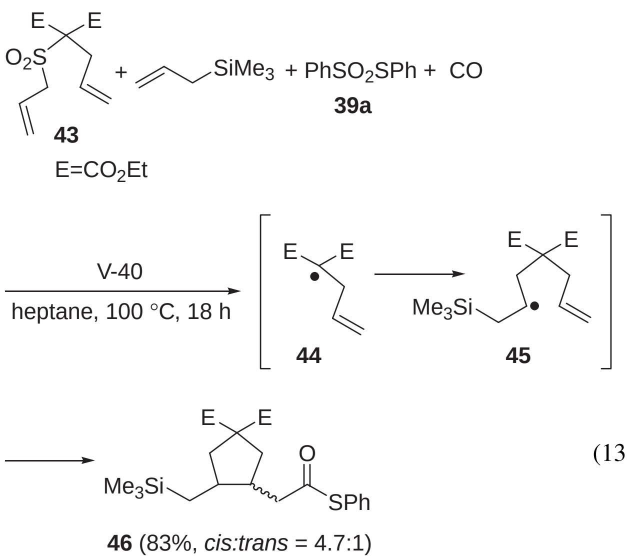
Alkyl allyl sulfone **30** ($Y = SO_2CH_2CH{=}CH_2$)	Product **40a**
	 94%
	 98%
	 95%
	 64%(26%)[a]
	 83%(13%)[a]
	 33%(57%)[a]

a) RSPh **41a**.

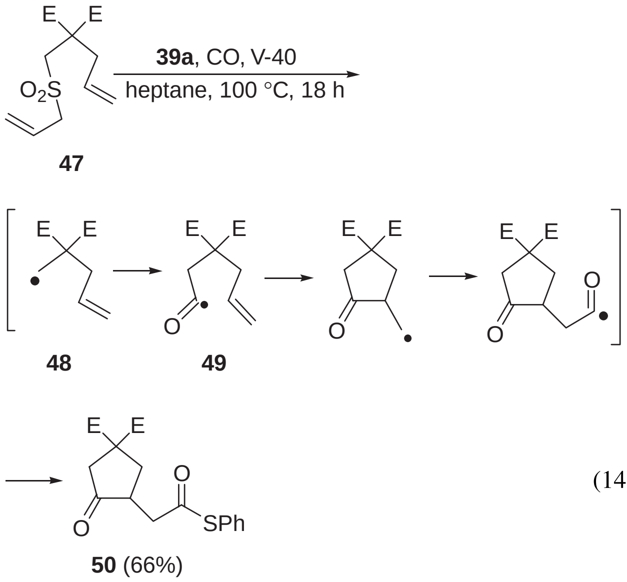
result was also obtained with tosyl cyanide under the same conditions.

Some experimental results are summarized in Table 5. Primary alkyl radicals work well, yielding the corresponding thiol esters in high yields. Since the radical carbonylation of secondary alkyl radicals is less efficient and slower than that of primary alkyl radicals, secondary alkyl radicals lead to a significant amount of the formation of **41a** (X = SPh). As we anticipated, tertiary alkyl radicals give more direct addition products. Furthermore, a stable benzylic radical does not undergo carbonylation, yielding the dimeric product.

We briefly studied sequential radical reactions. When a four-component coupling reaction using alkyl allyl sulfone precursor **43**, allyl trimethylsilane, CO, and **39a** was carried out under the same conditions, the desired product **46** was isolated in 83% yield (Eq. 13). Apparently, the electrophilic alkyl radical **44** failed to undergo carbonylation and reacted with allyl trimethylsilane to yield the radical intermediate **45**. The subsequent cyclization followed by thioalkoxycarbonylation provided **46**. Our next attention was given to the possibility of a double carbonylation (Eq. 14).[32] Reaction of **47** with **39a** and CO yielded acyl radical **49** through carbonylation of the radical intermediate **48**. The subsequent 5-*exo* ring closure of **49** and CO trapping followed by quenching with **39a** afforded cyclopentanone **50** in 66% yield.

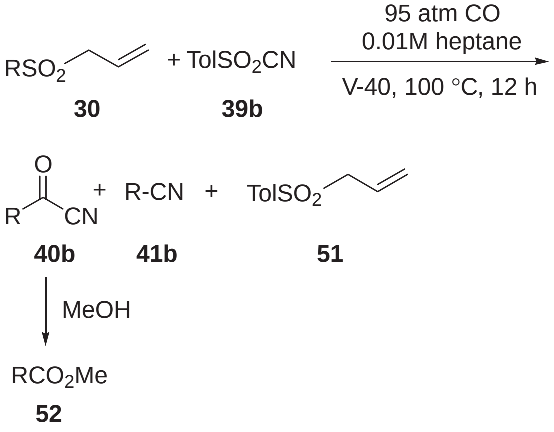


(13)



(14)

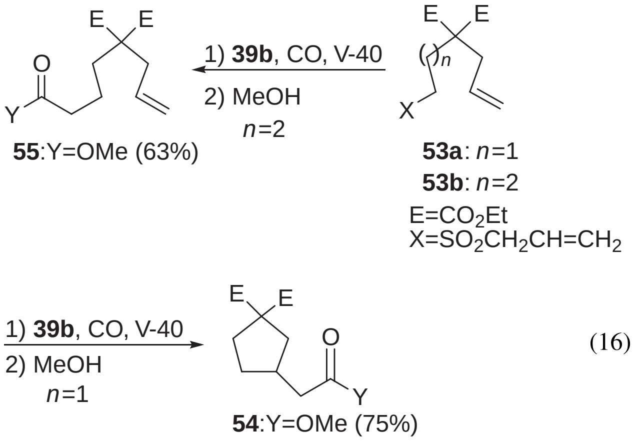
2.4 Cyanocarbonylation. As the extension of tin-free radical thioalkoxycarbonylation, we studied the feasibility of tin-free cyanocarbonylation reactions involving two one-carbon radical synthons, CO and CN using alkyl allyl sulfone precursors (Eq. 15).[33]



(15)

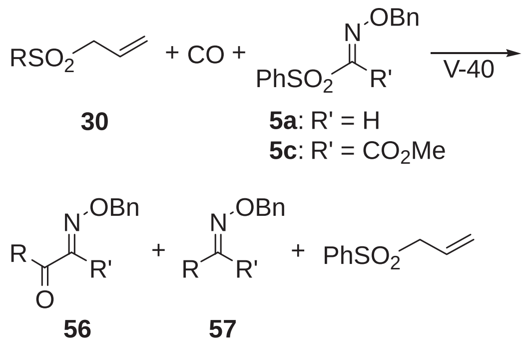
As indicated from Table 4, a significant amount of alkyl cyanide **41b** was formed by the direct cyanation of the alkyl radical prior to radical carbonylation of the alkyl radical. The formation of alkyl cyanide **41b** was reduced at the higher pressure of CO and at the more diluted concentration. The scope and limitation of the present method parallel with those of the previously observed thioalkoxycarbonylation. Primary alkyl radicals work well, yielding acyl cyanides **40b** in high yields. On the other hand, secondary alkyl radicals are much less effective, yielding a significant amount of the corresponding alkyl cyanides (Table 6).

We have studied tandem radical reactions involving cyclization and cyanocarbonylation (Eq. 16). Treatment of **53a** with **39b** and V-40 in heptane under 95 atm of CO at 100 °C for 24 h afforded cyclopentane derivative **54** after quenching the reaction mixture with methanol. However, when **53b** was subjected to the same conditions, the cyclization did not occur and **55** was isolated in 63% yield, clearly indicating that radical carbonylation must be much faster than 6-*exo* ring closure under the present condition.



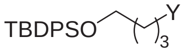
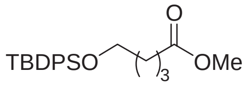
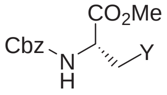
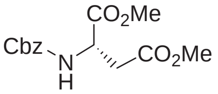
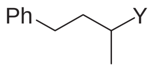
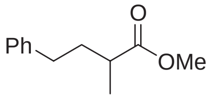
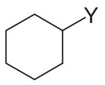
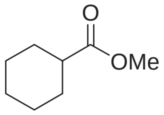
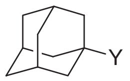
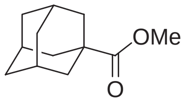
(16)

2.5 *N*-Alkoxyiminocarbonylation. In our continued efforts to develop tin-free radical carbonylation reactions, we have studied radical reactions of phenylsulfonyl oxime ether **5** with alkyl allyl sulfone precursors under CO pressure to achieve consecutive radical acylations in an indirect manner (Eq. 17).[34] Previously, the organotin-mediated version of the same reaction was reported and was very useful for the synthesis of vicinal dicarbonyl and tricarbonyl compounds (Eq. 18)[35,36]



(17)

Table 6. Cyanocarbonylation Using Alkyl Allyl Sulfones

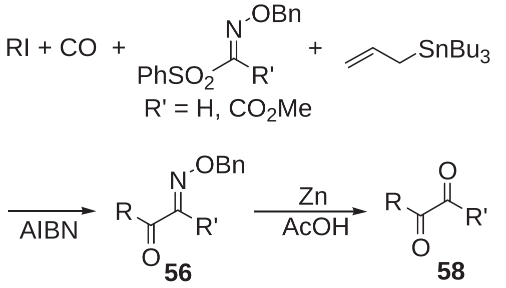
Alkyl allyl sulfone **30** ($Y = SO_2CH_2CH{=}CH_2$)	Product **52**[a)]
	 83%(10%)[b]
	 85%
	 52%(33%)[c]
	 80%(15%)[c]
	 83%(8%)[c]

a) Acyl cyanides were converted in situ with methanol to the methyl esters. b) Recovered starting material. c) RCN **41b**.

Table 7. The Effect of CO Pressure and Concentration of **30**

$$\mathbf{30} + \mathbf{5a} \text{ or } \mathbf{5c} + \text{CO} \xrightarrow[100\ °\text{C},\ 18\ \text{h}]{\text{V-40},\ C_6H_6} \mathbf{56} + \mathbf{57}$$

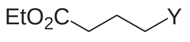
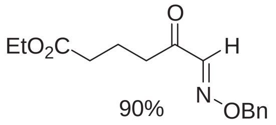
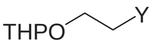
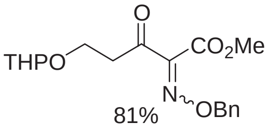
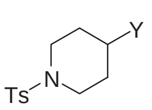
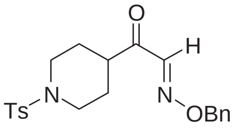
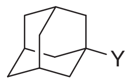
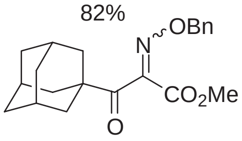
	Conc. of **30** /M	CO /atm	Yield/%		
			56	**57**	**30**
5a	0.03	95	93	0	0
5a	0.05	50	58	19	17
5a	0.03	50	64	12	19
5c	0.03	50	93	0	0
5c	0.03	30	94	0	0



(18)

The present approach follows the same mechanism as we observed in the thioalkoxycarbonylation (Scheme 10). To search for optimum conditions, we briefly studied the effect of CO pressure and the concentration of **30** as shown in Table 7. Several features are noteworthy. First, the direct addition product **57** forms at the lower pressure of CO (95 atm

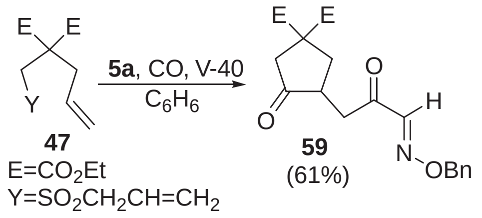
Table 8. *N*-Alkoxyiminocarbonylation of Alkyl Allyl Sulfones with **5a** or **5c**

Alkyl allyl sulfone **30** ($Y = SO_2CH_2CH{=}CH_2$)	Product **56**
	 90%
	 81%
	 82%
	 32% (62%)[a]

a) Oxime ester **57**.

versus 50 atm). Second, at the more concentrated solution (0.05 M versus 0.03 M), the amount of **57** is increased. This observation also is parallel to the previous thioalkoxycarbonylation and cyanocarbonylation reactions. Finally, **5a** requires the higher pressure of CO (95 atm versus 30 atm) than **5c**, suggesting that **5c** is more reactive than **5a** toward the acyl radical.

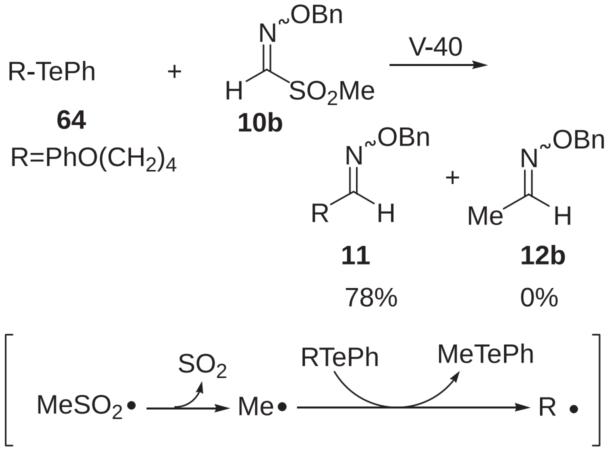
Some experimental results are summarized in Table 8. Primary alkyl allyl sulfone precursors work well with **5a** and **5c**, yielding the acylated oxime ethers in high yields. As we expected, secondary alkyl allyl sulfone precursors require a high CO pressure (130 atm) to obviate the problem of the formation of a by-product and tertiary alkyl radicals give even more by-product. Furthermore, a double carbonylation is successfully achieved as seen in Eq. 19.



(19)

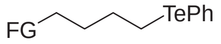
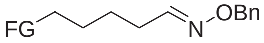
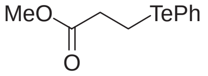
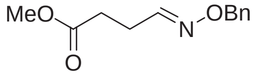
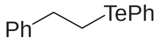
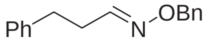
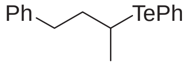
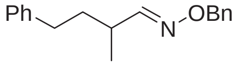
3. Phenyl Telluride Group Transfer Approach

3.1 Acylation. Organic tellurides have been utilized as alkyl and acyl radical precursors.[37,38] Previously, the transfer of an iodine atom and of a phenyl telluride group are known to proceed approximately at the same rate,[39] although a vinyl radical abstracts a phenyl telluride group about ten times faster than an iodine atom.[40] The efficiency of phenyl telluride group transfers has been demonstrated in living radical polymerization.[41]

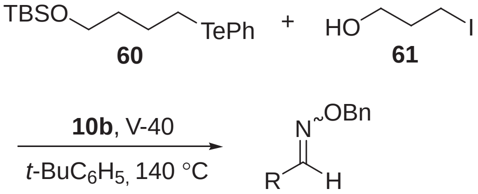


Scheme 11. Radical reaction of alkyl phenyl telluride with **10b**.

Table 9. Radical Acylation of Alkyl Phenyl Tellurides

Substrate **64**	Product **11**
	 FG=OTBS ;77% =OCOPh;72%
	 71%
	 76%
	 77%

Somewhat surprisingly, the problem of a slow iodine atom and xanthate group transfers could be solved by using alkyl phenyl telluride precursors (Scheme 11).[21] When an equimolar mixture of **60** and **61** was treated with **10b** using V-40 initiator in *tert*-butylbenzene at 140 °C for 20 h, **62** was isolated in 65% yield along with a small amount of **63** (<3%) (Eq. 20). This result clearly indicates the higher efficiency of the phenyl telluride group transfer relative to the iodine atom transfer.



(20)

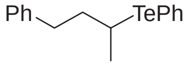
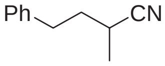
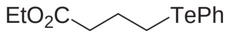
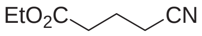
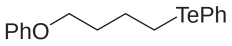
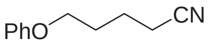
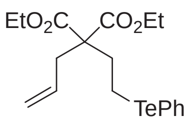
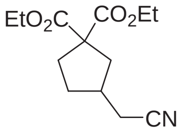
62: $R=TBSO(CH_2)_4$: 65%

63: $R=HO(CH_2)_3$: <3%

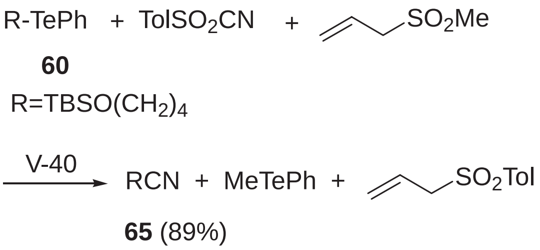
Based on this observation, phenyl telluride **64** was treated with **10b** and V-40 in *tert*-butylbenzene at 140 °C for 24 h and **11** was isolated in 78% yield without any indication of the formation of **12b** (Scheme 11). Additional experimental results are listed in Table 9.

3.2 Cyanation. We also studied the possibility of radical cyanation of alkyl iodides using methyl allyl sulfone as a me-

Table 10. Radical Cyanation of Alkyl Phenyl Telluride with Tosyl Cyanide

Substrate **64**	Product **38**
	 90%
	 86%
	 78%
	 66%

diator.[26] According to our competition experiment, an alkyl radical addition onto tosyl cyanide is approximately two times faster than the same addition onto phenylsulfonyl oxime ether **5a**. Thus, radical cyanations with primary and secondary alkyl iodides would be expected to give less satisfactory results. As shown in Scheme 7, the method worked well with benzylic iodides but was not satisfactory with primary alkyl iodides because the direct addition process involving the methyl radical addition to tosyl cyanide was much faster than the iodine atom transfer process.



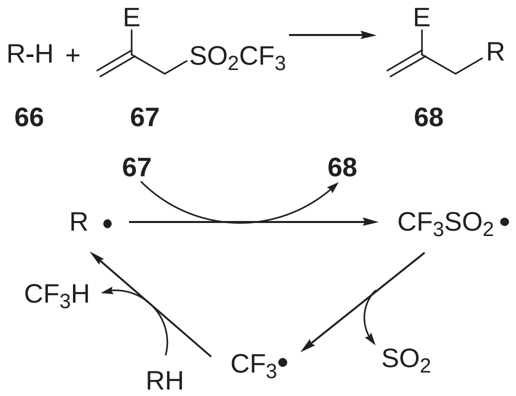
(21)

As we expect from the results obtained in the acylation, primary alkyl phenyl tellurides are exceedingly effective for tin-free radical cyanation. For instance, treatment of **60** with tosyl cyanide and methyl allyl sulfone using V-40 initiator in *tert*-butylbenzene at 140 °C for 12 h afforded **65** in 89% yield (Eq. 21). Further examples are shown in Table 10.

4. Unactivated C–H Bonds

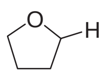
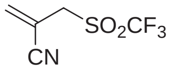
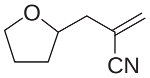
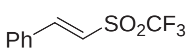
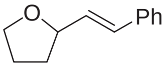
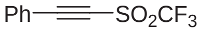
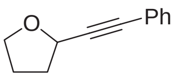
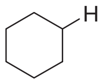
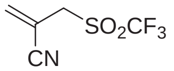
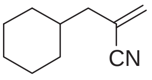
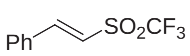
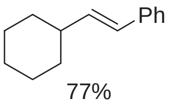
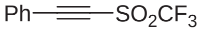
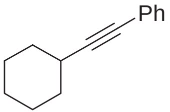
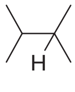
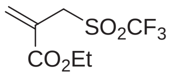
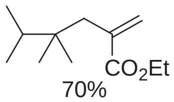
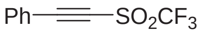
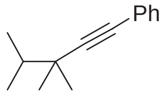
α-Scission of alkylsulfonyl radicals can be utilized to functionalize the unactivated C–H bonds. To achieve this goal, highly electrophilic radicals such as a trifluoromethyl radical[42] and a bromine atom[43] should be generated to abstract a hydrogen atom from the unactivated C–H bond to form an alkyl radical. Based on very rapid α-scission of trifluoromethanesulfonyl radicals, Fuchs developed allylation,[44] vinylation,[45] and alkynylation of C–H bonds.[46]

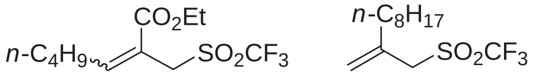
4.1 Allylation. The mechanism is the same as in the allylation discussed previously (Scheme 12). The strong electrophilicity of the trifluoromethyl radical ensures faster abstraction of a hydrogen atom from the solvent than the direct addition of trifluoromethyl radical to the allylic triflones **67**. Some reported experimental results are listed in Table 11. The reaction is very sensitive to the structure of allylic triflones. For examples, substituted activated allyl triflone **69** and an unactivated allyl triflone **70** do not provide any allylation products (Chart 1).



Scheme 12. Radical allylation of unactivated C–H bonds.

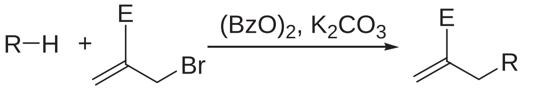
Table 11. Radical Allylation, Vinylation, and Alkynylation of Unactivated C–H Bonds

Substrate **66**	Triflone	Product
		 91%
		 71%
		 92%
		 84%
		 77%
		 83%
		 70%
		 78%



69 **70**

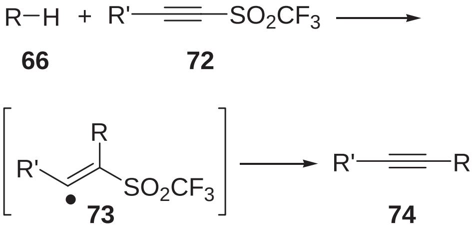
Chart 1.



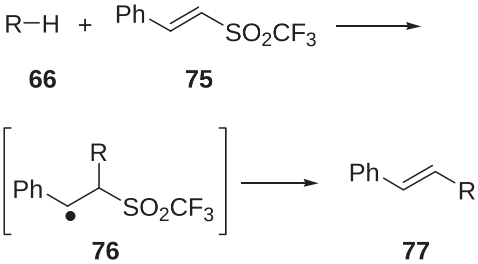
66 **71** **68** (22)

Tanko and Sadeghipour also reported the radical allylation reaction of unactivated C–H bonds based on the previously known abstraction of the hydrogen atom from C–H bonds during NBS bromination (Eq. 22).[43,47] The present approach works well with activated allylic bromide **71** and benzylic C–H bonds.

4.2 Alkynylation and Vinylation. Fuchs and Gong accidentally found the alkynylation reaction by adding acetylenic triflones in tetrahydrofuran.[46a] This exciting observation prompted the discovery of the alkynylation and the vinylation reaction of unactivated hydrocarbons under radical conditions. The alkynylation reaction involves addition of an alkyl radical to the α-carbon of the acetylenic triflone **72** followed by elimination of the vinyl radical **73** to alkyne **74** and the trifluoromethanesulfonyl radical (Eq. 23). Similarly, addition of the alkyl radical to the vinyl sulfone **75** provides alkene **77** via a similar addition-elimination process (Eq. 24). As shown in Table 11, several alkyne and vinyl groups can be introduced and the yields are generally high. The scope and the limitation of the alkynylation and vinylation are very similar to those of the allylation reaction. Furthermore, it is noteworthy that the alkynylation of alkyl iodides requires a stoichiometric amount of hexabutylditin because the trifluoromethyl radical does not abstract an iodine atom to propagate the radical chain.[48]

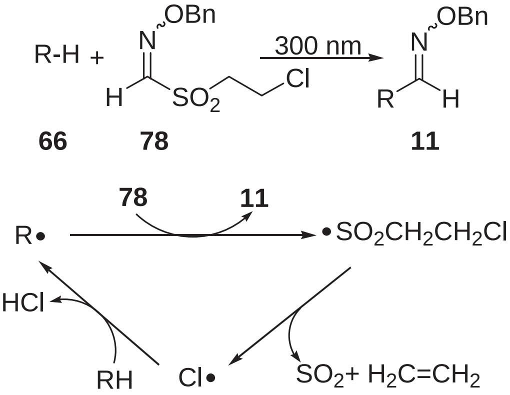


66 **72** **73** **74** (23)



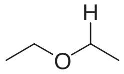
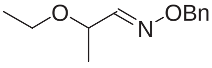
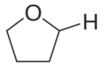
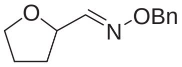
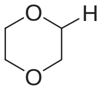
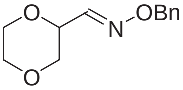
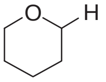
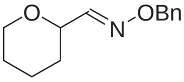
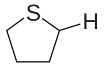
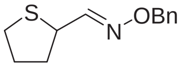
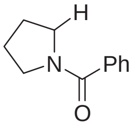
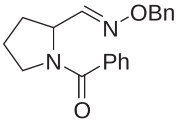
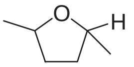
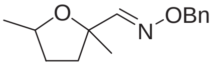
66 **75** **76** **77** (24)

4.3 Acylation. Radical acylation follows the similar guiding principle of the alkynylation and the vinylation reaction but utilizes a chlorine atom to abstract a hydrogen atom from a C–H bond. The chlorine atom should be more effective than the bromine atom in abstracting the hydrogen atom due to a stronger H–Cl bond than H–Br bond. To generate the chlorine atom, 2-chloroethylsulfonyl oxime ether **78** was designed to achieve the radical acylation of the C–H bond (Scheme 13).[49] When a solution of **78** in diethyl ether was irradiated at 300 nm for 12 h, the desired oxime ether **11** was isolated in 83% yield (Table 12). This reaction can be carried out under thermal conditions. This approach involves an alkyl radical addition to **78** followed by β-elimination of 2-chloroethylsulfonyl radical which undergoes thermal decomposition to generate the chlorine atom along with the liberation of sulfur dioxide and ethene. Finally, the chlorine atom abstracts hydrogen atom from dioxane to produce the alkyl radical. This approach is attractive because it not only avoids the use of highly toxic organotin compounds but also introduces an oxime ether group to α-carbon to the heteroatom with cleaving C–H bonds in a single step. Furthermore, the present approach works with unactivated tertiary and benzylic C–H bonds to introduce the oxime ether group but fails with unactivated secondary and primary alkyl C–H bonds.



Scheme 13. Radical acylation of C–H bonds using **78**.

Table 12. Radical Acylation of C–H Bonds with **78**

Substrate **66**	Product **11**	
		83%
		81%
		79%
		81%
		57%
		75%
		69%

Conclusion

Organosulfone-mediated tin-free radical reactions are very useful for carbon–carbon bond formations and include allylation, acylation, cyanation, vinylation, and carbonylation reactions. For secondary, tertiary and benzylic radicals, it is possible to use the corresponding iodides as precursors but the primary radicals still require the use of phenyl tellurides or alkyl allyl sulfones. Especially, alkyl allyl sulfones are highly efficient and most reliable primary alkyl radical precursors for the further formation of carbon–carbon bonds. The reactions with secondary or tertiary alkyl sulfones could be conducted at lower temperatures due to the facile decomposition of the corresponding sulfonyl radicals but the reactions with primary alkyl sulfones typically require elevated temperatures. The present approaches will find useful applications for introducing various functional groups such as carbonyl and alkenyl groups and have great synthetic potential because these methods proceed under mild conditions, where more conventional methods would be inappropriate.

We are grateful for financial support from Korea Science and Engineering Foundation. I thank my co-workers for their experimental and intellectual contributions to this research.

References

1 a) D. P. Curran, in *Comprehensive Organic Synthesis*, ed. by B. M. Trost, I. Fleming, M. F. Semmelhack, Pergamon, Oxford, **1991**, Vol. 4. pp. 715–831. b) *Radicals in Organic Synthesis*, ed. by P. Renaud, M. P. Sibi, Wiley-VCH, Weinheim, **2001**, Vols. 1 and 2.

2 For reviews, see: a) P. A. Baguley, J. C. Walton, *Angew. Chem., Int. Ed.* **1998**, *37*, 3072. b) A. Studer, S. Amrein, *Synthesis* **2002**, 835. c) B. Quiclet-Sire, S. Z. Zard, *Chem. Eur. J.* **2006**, *12*, 6002.

3 F. Bertrand, F. L. Guyader, L. Liguori, G. Ouvry, B. Quiclet-Sire, S. Seguin, S. Z. Zard, *C. R. Acad. Sci., Ser. IIc: Chim.* **2001**, *4*, 547.

4 a) B. Quiclet-Sire, S. Z. Zard, *J. Am. Chem. Soc.* **1996**, *118*, 1209. b) F. L. Guyader, B. Quiclet-Sire, S. Seguin, S. Z. Zard, *J. Am. Chem. Soc.* **1997**, *119*, 7410. c) B. Quiclet-Sire, S. Seguin, S. Z. Zard, *Angew. Chem., Int. Ed.* **1998**, *37*, 2864.

5 F. Bertrand, B. Quiclet-Sire, S. Z. Zard, *Angew. Chem., Int. Ed.* **1999**, *38*, 1943.

6 a) C. Chatgilialoglu, in *The Chemistry of Sulfones and Sulfoxides*, ed. by S. Patai, Z. Rappoport, C. J. M. Stirling, Wiley, Chicheser, **1988**, pp. 1089–1113. b) C. Chatgilialoglu, L. Lunazzi, K. Ingold, *J. Org. Chem.* **1983**, *48*, 3588. c) R. S. Givens, B. Hrinczenko, J. H.-S. Liu, B. Matuszewski, J. Tholen-Collison, *J. Am. Chem. Soc.* **1984**, *106*, 1779.

7 For a review of halogen atom abstraction, see: a) W. C. Danen, in *Methods in Free Radical Chemistry*, ed. by E. S. Huyser, Marcel Dekker, New York, **1974**, Vol. 5, pp. 1–100. b) J. Byers, in *Radicals in Organic Synthesis*, ed. by P. Renaud, M. P. Sibi, Wiley-VCH, Weinheim, Germany, **2001**, Vol. 1, pp. 72–83.

8 a) N. O. Brace, *J. Org. Chem.* **1966**, *31*, 2879. b) R. Hiatt, S. W. Benson, *J. Am. Chem. Soc.* **1972**, *94*, 25. c) A. L. Castelhano, D. Griller, *J. Am. Chem. Soc.* **1982**, *104*, 3655.

9 a) D. P. Curran, M.-H. Chen, D. Kim, *J. Am. Chem. Soc.* **1986**, *108*, 2489. b) D. P. Curran, M.-H. Chen, *J. Am. Chem. Soc.* **1987**, *109*, 6558.

10 a) D. P. Curran, D. Kim, *Tetrahedron Lett.* **1986**, *27*, 5821. b) M. Newcomb, R. M. Sanchez, J. Kaplan, *J. Am. Chem. Soc.* **1987**, *109*, 1195. c) D. P. Curran, E. Bosch, J. Kaplan, M. Newcomb, *J. Org. Chem.* **1989**, *54*, 1826.

11 For reviews, see: a) D. P. Curran, *Synthesis* **1988**, 489. b) C. P. Jasperse, D. P. Curran, T. L. Fevig, *Chem. Rev.* **1991**, *91*, 1237. c) I. J. Rosenstein, in *Radicals in Organic Synthesis*, ed. by P. Renaud, M. P. Sibi, Wiley-VCH, Weinheim, Germany, **2001**, Vol. 1, pp. 50–71.

12 D. P. Curran, P. A. van Elburg, B. Giese, S. Gilges, *Tetrahedron Lett.* **1990**, *31*, 2861.

13 a) A. L. J. Beckwith, B. P. Hay, *J. Am. Chem. Soc.* **1989**, *111*, 230. b) A. L. J. Beckwith, B. P. Hay, *J. Am. Chem. Soc.* **1989**, *111*, 2674. c) R. Walton, B. Fraser-Reid, *J. Am. Chem. Soc.* **1991**, *113*, 5791.

14 For intramolecular acylation reactions, see: a) S.-I. Kiyooka, Y. Kaneko, H. Matsue, M. Hamada, R. Fujiyama, *J. Org. Chem.* **1990**, *55*, 5562. b) S. Kim, S. Y. Jon, *Chem. Commun.* **1996**, 1335. c) D. P. Curran, U. Diederichsen, M. Palovich, *J. Am. Chem. Soc.* **1997**, *119*, 4797. d) S. Kim, C. H. Cho, C. J. Lim, *J. Am. Chem. Soc.* **2003**, *125*, 9574. e) C. H. Cho, S. Kim, *Can. J. Chem.* **2005**, *83*, 917. f) C. H. Cho, S. Kim, M. Yamane, H. Miyauchi, K. Narasaka, *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1665.

15 For a review, see: S. Kim, *Adv. Synth. Catal.* **2004**, *346*, 19.

16 a) D. J. Hart, F. L. Seely, *J. Am. Chem. Soc.* **1988**, *110*, 1631. b) A. Citterio, L. Filippini, *Synthesis* **1986**, 473.

17 S. Kim, I. Y. Lee, J.-Y. Yoon, D. H. Oh, *J. Am. Chem. Soc.* **1996**, *118*, 5138.

18 S. Kim, K. S. Yon, Y. S. Kim, *Tetrahedron* **1997**, *53*, 73.

19 S. Kim, I. Y. Lee, *Tetrahedron Lett.* **1998**, *39*, 1587.

20 S. Kim, Y. Song, *C. R. Acad. Sci. Paris, Chim.* **2001**, *4*, 431.

21 S. Kim, H.-J. Song, T.-L. Choi, J.-Y. Yoon, *Angew. Chem., Int. Ed.* **2001**, *40*, 2524.

22 a) J. Boivin, J. Camara, S. Z. Zard, *J. Am. Chem. Soc.* **1992**, *114*, 7909. b) B. Quiclet-Sire, S. Z. Zard, *J. Am. Chem. Soc.* **1996**, *118*, 9190. c) B. Quiclet-Sire, S. Seguin, S. Z. Zard, *Angew. Chem., Int. Ed.* **1998**, *37*, 2864.

23 J. E. Forbes, S. Z. Zard, *J. Am. Chem. Soc.* **1990**, *112*, 2034.

24 a) S. Kim, C. J. Lim, S.-E. Song, H.-Y. Kang, *Chem. Commun.* **2001**, 1410. b) S. Lee, C. J. Lim, S. Kim, *Bull. Korean Chem. Soc.* **2004**, *25*, 1611.

25 For reviews, see: a) D. Crich, L. Quintero, *Chem. Rev.* **1989**, *89*, 1413. b) D. H. R. Barton, *Tetrahedron* **1992**, *48*, 2529. c) S. Z. Zard, *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672.

26 S. Kim, H.-J. Song, *Synlett* **2002**, 2110.

27 S. Kim, C. J. Lim, *Angew. Chem., Int. Ed.* **2002**, *41*, 3265.

28 S. Kim, C. J. Lim, *Bull. Korean Chem. Soc.* **2003**, *24*, 1219.

29 For reviews, see: a) I. Ryu, N. Sonoda, *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1050. b) I. Ryu, N. Sonoda, D. P. Curran, *Chem. Rev.* **1996**, *96*, 177. c) I. Ryu, *Chem. Soc. Rev.* **2001**, *30*, 16. d) I. Ryu, *Chem. Rec.* **2002**, *2*, 249.

30 For a review on acyl radicals, see: C. Chatgilialoglu, D. Crich, M. Komatsu, I. Ryu, *Chem. Rev.* **1999**, *99*, 1991.

31 S. Kim, S. Kim, N. Otsuka, I. Ryu, *Angew. Chem., Int. Ed.* **2005**, *44*, 6183.

32 a) S. Tsunoi, I. Ryu, S. Yamasaki, H. Fukushima, M. Tanaka, M. Komatsu, N. Sonoda, *J. Am. Chem. Soc.* **1996**, *118*, 10670. b) I. Ryu, S. Krrimerman, F. Araki, S. Nishitani, Y. Oderaotoshi, S. Minakata, M. Komatsu, *J. Am. Chem. Soc.* **2002**, *124*, 3812.

33 S. Kim, C. H. Cho, S. Kim, Y. Uenoyama, I. Ryu, *Synlett* **2005**, 3160.

34 S. Kim, K.-C. Lim, S. Kim, *Adv. Synth. Catal.* **2007**, *349*, 527.

35 I. Ryu, H. Kuriyama, S. Minakata, M. Komatsu, J.-Y. Yoon, S. Kim, *J. Am. Chem. Soc.* **1999**, *121*, 12190.

36 I. Ryu, H. Kuriyama, H. Miyazato, S. Minakata, M. Komatsu, J.-Y. Yoon, S. Kim, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1407.

37 a) D. H. R. Barton, J. C. Jaszberenyi, E. A. Theodorakis, *J. Am. Chem. Soc.* **1992**, *114*, 5904. b) M. A. Lucas, C. H. Schiesser, *J. Org. Chem.* **1996**, *61*, 5754.

38 a) C. Chen, D. Crich, A. Papadatos, *J. Am. Chem. Soc.* **1992**, *114*, 8313. b) C. Chen, D. Crich, *Tetrahedron Lett.* **1993**, *34*, 1545. c) D. Crich, C. Chen, J.-T. Hwang, H. Yuan, A. Papadatos, R. I. Walter, *J. Am. Chem. Soc.* **1994**, *116*, 8937. d) S. Yamago, H. Miyazoe, T. Sawazaki, R. Goto, J.-I. Yoshida, *Tetrahedron Lett.* **2000**, *41*, 7517.

39 D. P. Curran, A. A. Martin-Esker, S.-B. Ko, M. Newcomb, *J. Org. Chem.* **1993**, *58*, 4691.

40 L.-B. Han, K.-I. Ishihara, N. Kambe, A. Ogawa, I. Ryu, N. Sonoda, *J. Am. Chem. Soc.* **1992**, *114*, 7591.

41 a) S. Yamago, K. Iida, M. Nakajima, J.-I. Yoshida, *J. Am. Chem. Soc.* **2002**, *124*, 13666. b) S. Yamago, K. Iida, M. Nakajima, J.-I. Yoshida, *Macromolecules* **2003**, *36*, 3793.

42 a) B. R. Langlois, E. Laurent, N. Roidot, *Tetrahedron Lett.* **1992**, *33*, 1291. b) C.-M. Hu, F.-L. Qing, W.-Y. Huang, *J. Org. Chem.* **1991**, *56*, 2801. For a review on fluoroalkyl radicals, see: c) W. R. Dolbier, *Chem. Rev.* **1996**, *96*, 1557.

43 a) G. A. Russell, C. DeBoer, *J. Am. Chem. Soc.* **1963**, *85*, 3136. b) S. S. Friedrich, E. C. Friedrich, L. J. Andrews, R. M. Keefer, *J. Org. Chem.* **1969**, *34*, 900.

44 J. Xiang, J. Evarts, A. Rivkin, D. P. Curran, P. L. Fuchs, *Tetrahedron Lett.* **1998**, *39*, 4163.

45 a) J. Xiang, P. L. Fuchs, *J. Am. Chem. Soc.* **1996**, *118*, 11986. b) J. Xiang, W. Jiang, J. Gong, P. L. Fuchs, *J. Am. Chem. Soc.* **1997**, *119*, 4123.

46 a) J. Gong, P. L. Fuchs, *J. Am. Chem. Soc.* **1996**, *118*, 4486. b) J. S. Xiang, P. L. Fuchs, *Tetrahedron Lett.* **1996**, *37*, 5269. c) J. Xiang, W. Jing, P. L. Fuchs, *Tetrahedron Lett.* **1997**, *38*, 6635.

47 M. Tanko, M. Sadeghipour, *Angew. Chem., Int. Ed.* **1999**, *38*, 159.

48 J. Xiang, P. L. Fuchs, *Tetrahedron Lett.* **1998**, *39*, 8597.

49 S. Kim, N. Kim, J.-Y. Yoon, D. H. Oh, *Synlett* **2000**, 1148.

Sunggak Kim was born on March 17, 1946 in Kyungbuk province, Korea. He received his B.S. in 1969 from Seoul National University. After he had served in Korean Army, he went to Canada in 1972 to receive his graduate training at McGill University in Montreal, where he did his Ph.D. research with Prof. G. Just. He moved to Harvard in 1976, where he spent three years for post-doctoral studies with Professor E. J. Corey. In 1979, he returned to Korea to join the chemistry faculty at the Korea Advanced Institute of Science. He was promoted to Professor of Chemistry at KAIST in 1986. His major scientific awards include the Korea Science Prize in Chemistry (1994), the Korean Chemical Society Award for Young Chemists (1985), and the Korean Federation of Science and Technology Societies Award (1991). His research interests focus on the design and the development of new reactions and strategies with general utility in organic synthesis. Although he continues his interest in new synthetic methodologies utilizing carbenes, cations, and anions, his major research emphasis in recent years has been on the development of new free radical reactions.

Sangmo Kim was born in 1975 in Andong, Kyungbuk province, Korea. He graduated from Hanyang University in 2002 with B.S. degree in Industrial Chemistry and Chemical Engineering and received his M.S. degree in organic chemistry from KAIST in 2004 and continued his Ph.D. studies under the guidance of Prof. Sunggak Kim. His present research topic involves tin-free radical carbonylation.