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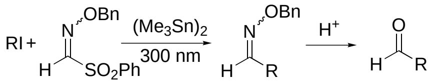
Tin-Free Radical Acylation Reactions with Methanesulfonyl Oxime Ether**

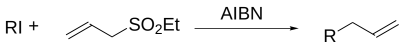
Sunggak Kim,* Hyun-Ji Song, Tae-Lim Choi, and Joo-Yong Yoon

Recent advances in radical reactions have greatly benefited from the efficiency of organotin reagents as mediators. However, organotin reagents are highly toxic, and it is difficult to remove their residues from the products. These disadvantages have proved to be a serious barrier to industrial applications. To solve the problems associated with toxic organotin reagents, several alternative approaches, including the use of polymer-supported organotin reagents and organosilanes, have been utilized with some success.[1] Recently, a few tin-free carbon–carbon bond-forming reactions were reported; they include organosulfone-mediated radical allylation, alkenylation, alkynylation, and azidation reactions.[2–4]

Recently, we reported highly efficient tin-mediated radical acylation reactions with sulfonyl oxime ethers [Eq. (1)].[5] We then studied the possibility of environmentally benign tin-free radical acylation reactions. Our approach is largely based on the tin-free radical allylation reaction of Zard et al. [Eq. (2)][2]

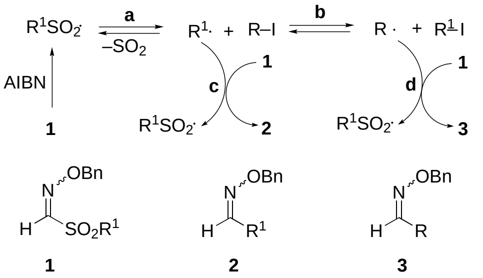


(1)



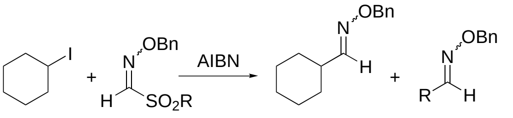
(2)

and involves thermal decomposition of an alkylsulfonyl radical (path a) and subsequent transfer of an iodine atom (path b),[6] as outlined in Scheme 1. The problem with tin-free radical acylation arises from the fast addition of an alkyl radical to sulfonyl oxime ether **1** to afford oxime ether **2**.[7] Since the direct addition of the alkyl radical to sulfonyl oxime ether **1** (path c) would compete with transfer of an iodine atom (path b) in the radical acylation approach, efficient iodine transfer is a key factor for the success of this approach.



Scheme 1. Pathways for the radical reaction of an alkyl iodide with **1**.

We first studied the efficiency of iodine-atom transfer from a secondary alkyl iodide to an ethyl radical relative to the addition of the ethyl radical to ethanesulfonyl oxime ether **4** [Eq. (3)]. Treatment of cyclohexyl iodide with an equimolar amount of **4** and azobisisobutyronitrile (AIBN; 0.1 equiv) in refluxing heptane for 24 h resulted in a 25:60 mixture of two oxime ethers **6** and **7**. Evidently, addition of the ethyl radical to **4** is more than two times faster than the transfer of the iodine atom from cyclohexyl iodide to the ethyl radical. Although the yield of **6** was increased to 48% along with 21% of **7** by using a large excess of cyclohexyl iodide (5 equiv), the serious problem of the formation of **7** could not be solved, and this indicates that **4** is not suitable for tin-free radical acylation with secondary alkyl iodides.



(3)

4 : R = Et　**6**: 25%　**7**: 60%
5 : R = Me　**6**: 62%　**8**: < 3%

We next turned our attention to methanesulfonyl oxime ether **5**. Although it was reported that the methanesulfonyl

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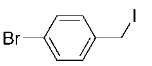
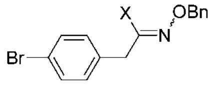
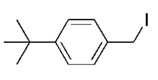
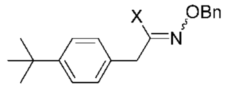
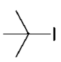
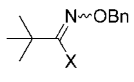
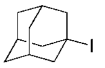
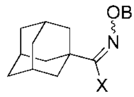
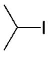
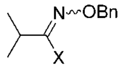
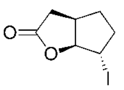
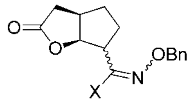
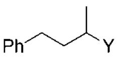
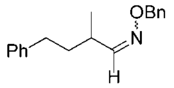
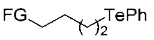
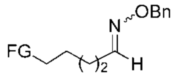
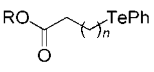
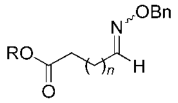
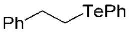
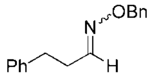
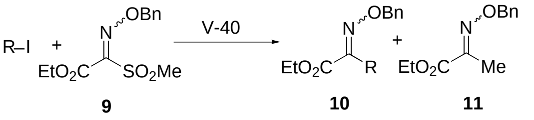
radical hardly decomposes into SO_2 and a methyl radical,[8] we found that decomposition of the methanesulfonyl radical occurred at 120 °C. When cyclohexyl iodide was treated with **5** in refluxing heptane in the presence of AIBN for 40 h, cyclohexyl oxime ether **6** was isolated in 62 % yield along with a trace of methyl oxime ether **8**, that is, transfer of the iodine atom was much faster than the direct addition process. Thus, **5** solved the problem we faced with secondary alkyl iodides. Since the use of AIBN in heptane required 40 h at reflux, the reaction was carried out in octane at 120 °C with V-40 (azobis(cyclohexanecarbonitrile)) as initiator, and this shortened the reaction time to 6 h. As shown in Table 1, the results obtained with **5** were quite satisfactory; the corresponding oxime ethers were obtained in good yields (65–80 %). The present approach was further extended to the synthesis of α-oxime ester **10**, a synthetic equivalent of an α-keto ester, by using ethoxycarbonyl oxime ether **9** [Eq. (4)].[9]

Table 1. Synthesis of oxime ethers from alkyl iodides and tellurides by using **5** and **9**.

Substrate[a]	Product	Yield [%]	
		X = H X = CO_2Et	80 73
		X = H X = CO_2Et	78 75
		X = H X = CO_2Et	71 64
		X = H X = CO_2Et	70 70
		X = H X = CO_2Et	67 64
		X = H X = CO_2Et	72[b] 63[c]
		Y = I, X = H Y = TePh, X = H	67 77
		FG = OPh[d] FG = OTBS[d]	78 77
		FG = OCOPh[d] R = Me, n = 1	72 71
		R = Et, n = 2	71 76

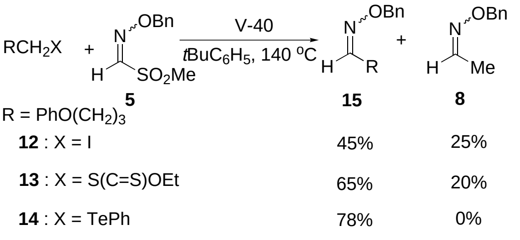
[a] For iodides, in octane at 120 °C for 6 h. For tellurides, in $tBuC_6H_5$ at 140 °C for 24 h. [b] *exo*:*endo* = 4.5:1. [c] *exo*:*endo* = 1.8:1. [d] FG = functional group.



(4)

The reaction was carried out under the same conditions and afforded **10** in good yields (64 to 75 %) without formation of **11** (Table 1).

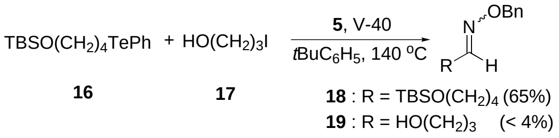
Primary alkyl iodides did not work well with **5** and **9**. Due to the small energy difference between the methyl radical and a primary alkyl radical, iodine-atom transfer competed with the direct addition of the methyl radical to **5** [Eq. (5)]. Treatment of 4-phenoxybutyl iodide (**12**) with an equimolar amount of **5** in *tert*-butylbenzene at 140 °C for 30 h, which gave a 45:25 mixture of the desired oxime ether **15** and **8**, demonstrates the inefficiency of **5** with primary alkyl iodides.



(5)

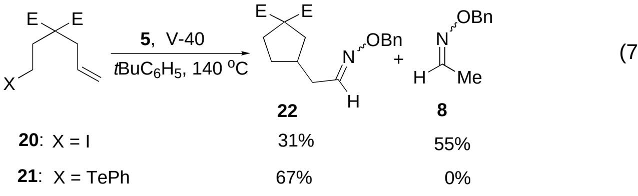
To solve the problem of slow iodine-atom transfer associated with primary alkyl iodides, we searched for better radical-accepting systems than alkyl iodides, and xanthates were our initial choice.[10] The reaction of xanthate **13** with **5** and V-40 under the same conditions afforded a 65:20 mixture of **15** and **8** and indicated that transfer of the xanthate group is slightly faster than that of the iodine atom.

Since the xanthate could not solve the present problem associated with the direct addition of the methyl radical to **5**, we turned our attention to organic tellurides, which have been utilized to generate alkyl and acyl radicals.[11, 12] Gratifyingly, reaction of phenyl telluride **14** with **5** and V-40 in *tert*-butylbenzene at 140 °C for 24 h gave **15** in 78 % yield without any indication of the formation of **8**. This result is somewhat surprising, because tansfer of an iodine atom and of a phenyl telluride group are known to proceed approximately at the same rate,[13] although there was a previous report that vinyl radicals abstract a phenyl telluride group about ten times faster than an iodine atom.[14] Therefore, we performed a competition experiment [Eq. (6)]. Reaction of an equimolar mixture of phenyl telluride **16**, iodide **17**, and **5** with V-40 (0.2 equiv) in *tert*-butylbenzene at 140 °C for 20 h afforded **18** in 65 % yield along with a small amount of **19** (< 4 %), and this clearly indicates the higher efficiency of transfer of a phenyl



(6)

telluride group relative to that of an iodine atom.[15] Some experimental results are included in Table 1 and demonstrate the efficiency of the phenyl telluride approach. The reaction was successful with secondary and primary alkyl tellurides. We briefly examined a sequential radical reaction involving a cyclization and acylation sequence [Eq. (7)]. Reaction of **21** with **5** under the same conditions afforded the desired oxime ether **22** in 67 % yield, whereas the use of iodide **20** gave **22** in 31 % yield along with **8** (55 %); this demonstrates the efficiency of the phenyl telluride group as a radical precursor.



(7)

Experimental Section

Typical procedure: A degassed solution of 1-bromo-4-iodomethyl-benzene (118 mg, 0.40 mmol), *O*-benzyl-1-(methanesulfonyl)formaldoxime (**5**, 128 mg, 0.60 mmol) and V-40 (20 mg, 0.08 mmol) in freshly distilled octane (2 mL) was heated to reflux under N_2 for 8 h. The solvent was evaporated under reduced pressure, and the residue was purified by chromatography on a silica gel column (*n*-hexane: ethyl acetate 1:15) to yield *O*-benzyl-1-(4-bromobenzyl)formaldehyde (98 mg, 0.32 mmol, 80 % yield, E:Z = 1.1:1). ^{1}H NMR ($CDCl_3$, 200 MHz): E isomer: $\delta = 3.45$ (d, $J = 6.4$ Hz, 2H), 5.08 (s, 2H), 7.06 (d, $J = 2.2$ Hz, 2H), 7.32–7.43 (m, 7H), 7.49 (t, $J = 6.4$ Hz, 1H); Z isomer: $\delta = 3.65$ (d, $J = 5.4$ Hz, 2H), 5.15 (s, 2H), 6.80 (t, $J = 5.4$ Hz, 1H), 7.02 (d, $J = 2.2$ Hz, 2H), 7.32–7.43 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 31.9$, 35.3, 75.8, 76.1, 120.5, 120.8, 127.8, 127.9, 128.2, 128.4, 128.6, 128.8, 130.4, 130.5, 131.7, 131.8, 135.3, 135.8, 137.6, 137.7, 149.0, 149.3; IR (NaCl): $\tilde{\nu} = 3031$, 2928, 1656, 1586, 1488, 1454, 1367, 1276, 1072, 1012 cm^{-1}; HR-MS: [M^+] calcd for $C_{15}H_{14}BrNO$: 303.0259; found: 303.0257.

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Cyclodextrin Cavities as Probes for Ligand-Exchange Processes

Eric Engeldinger, Dominique Armspach,* and
Dominique Matt*

Cyclodextrins (CDs) have attracted a lot of attention as chiral building blocks for the construction of enzyme mimics because of their ability to bind a wide range of organic substrates in water.[1–4] Combining CDs with transition metals has proven a very attractive goal in terms of achieving highly selective and efficient catalysis.[5–11] One of the challenges, so far not met, is to force a metal that is covalently linked to a CD framework to be confined in the cavity where maximum interaction between the first coordination sphere of the metal and the CD walls is expected to take place so as to stabilize unusual coordination modes. In addition, cavities with introverted[12] functionalities could provide new catalysts where a metal center operates inside a spatially restricted environment.[13–15] We report here the first α-CD-based multitopic ligand (**2**) capable of hosting metal–organic fragments. As shown by NMR investigations, the complexes derived from this ligand display unique intra- and intermolecular ligand-exchange phenomena at the included metal center.

We anticipated that an easy way to ensure metal encapsulation in a cavity would be to use an α-CD derivative bearing

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