Radical carboxylations of iodoalkanes and saturated alcohols using carbon monoxide

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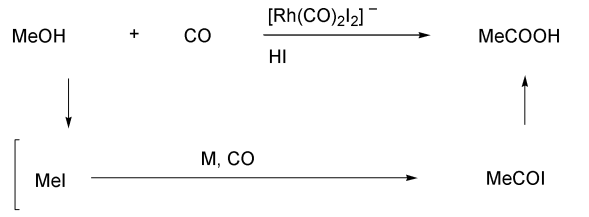
This review covers two radical carboxylation methods using carbon monoxide, both of which were developed by our group. The first method, *atom transfer carbonylation*, converts alkyl iodides into carboxylic acid esters or amides and the second method, *remote carboxylation*, converts saturated alcohols into δ-lactones. Both methods rely upon radical carbonylation chemistry to introduce carbon monoxide, but the key steps are conceptually different. The first method utilizes an atom transfer reaction from an alkyl iodide to an acyl radical leading to an acyl iodide and the latter employs a one-electron oxidation reaction to convert an acyl radical into an acyl cation. The iodine atom transfer carbonylation process is reversible and therefore highly inefficient unless it is performed in concert with an ionic system to shift the equilibrium in the direction of an acyl iodide. In the latter process, a 1,5-translocation scheme to shift the radical from oxygen to the δ-carbon is successfully coupled with the carbonylation–oxidation sequence. Carboxylations of alkyl halides by transition metal catalyzed methods are often problematic because of the inherent weakness of alkyl–metal bonds. Existing methods for carbonylative δ-lactone synthesis using transition metal catalysts are limited to *unsaturated* alcohols. Thus, these two radical carboxylation methods nicely complement existing transition metal catalyzed carboxylations.

1 Introduction

Carboxylation with carbon monoxide is intrinsically important for the synthesis of carboxylic acids and their derivatives. Much effort has been devoted to transition metal catalyzed carboxylation chemistry to date.[1] Monsanto's acetic acid synthesis, which uses CO and methanol as the substrates, is a key example of the industrial importance of the metal catalyzed carboxylation



Scheme 1

processes (Scheme 1).[2] This famous reaction is based on the rhodium catalyzed carbonylation of methyl iodide, which is formed *in situ* from methanol and HI. However, many hurdles still have to be surmounted before the basic reaction can be generally applicable. The formation of regioisomeric products is a serious problem for C_3 and higher alcohols, due to the tendency of the intermediate metal–alkyl species to undergo isomerization. Research into methods to circumvent the undesirable β-elimination is ongoing in the field of transition metal chemistry.[3]

The controlled use of carbon dioxide as a feedstock for the carboxylation of organic substrates represents a holy grail irrespective of whether transition metal species or radical species are the intermediates. With respect to radical processes, to the best of my knowledge, there has been only one recent report from the Curran group documenting the formation of a carboxylic acid by radical carboxylation with carbon dioxide. In this case, the formation of 9-anthracenecarboxylic acid was obtained in 10% yield together with anthracene (71%), when the radical reduction of 9-iodoanthracene with the ethylene-spaced fluorous tin hydride reagent was run at 90 °C using 280 atm of supercritical CO_2 as the reaction medium (Scheme 2).[4] As demonstrated in this rare example, the trapping of CO_2 by radicals is not an efficient process and therefore is of limited synthetic utility.[5]

A surrogate method that relies upon the reaction between radicals and carbon monoxide, in other words, radical carbony-

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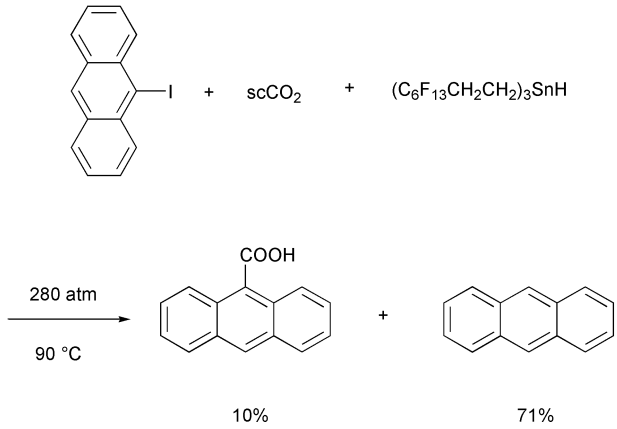
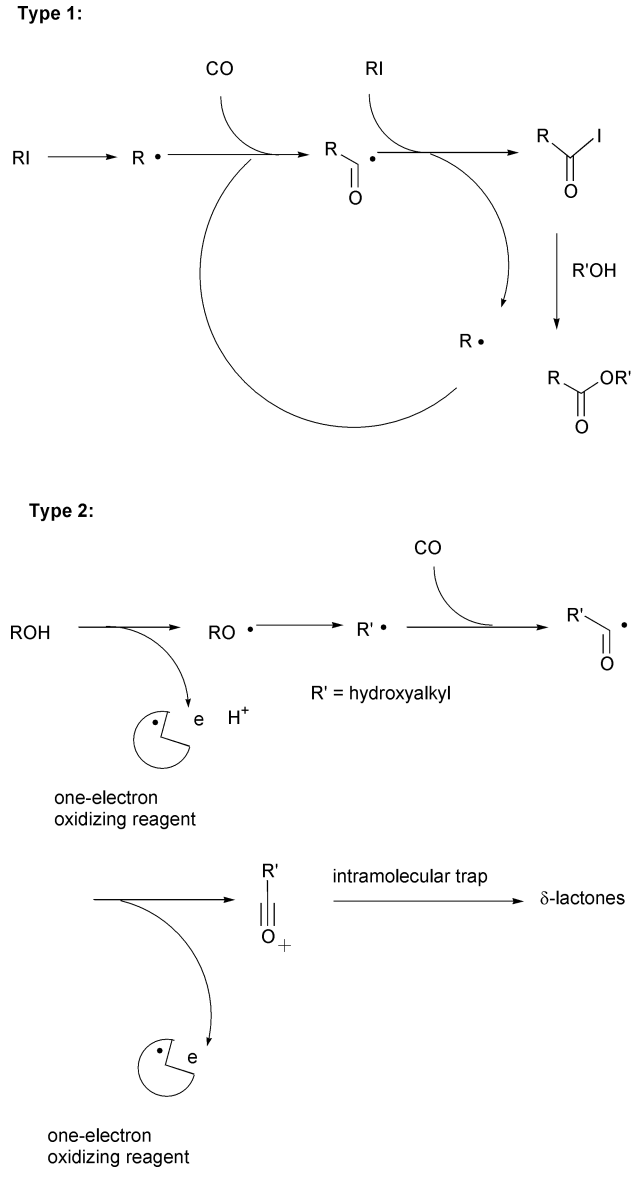


Scheme 2

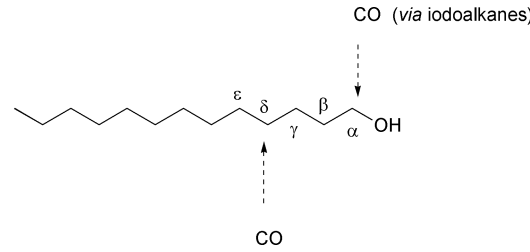
lations,[6–8] can be used. Two methodologies seem to have great potential for radical carboxylation with CO. One promising approach is a radical–ionic hybrid method based on an iodine atom transfer carbonylation that has been invented by us just recently. In this approach, acyl iodides are the precursors for carboxylic acid derivatives *via* ionic nucleophilic substitution reactions (type 1 in Scheme 3).



Scheme 3

The other approach is more traditional, in which the radical carbonylation sequence is combined with a subsequent one electron oxidation process. Acyl cations, thus generated, serve as key precursors for the carboxylated products. The original demonstration of this type of carboxylation reaction dates from reports published in the 1950s, where the Fenton reagent (Fe^{II} plus H_2O_2) was used to create oxidative carbonylation systems.[9] Among the recent studies aiming at carboxylating alkanes by an oxidative carbonylation,[10] Ishii's method using a mixed CO–O_2 gas is quite remarkable, since the key reagent NHPI (*N*-hydroxyphthalimide) is used in a catalytic quantity.[11] Nevertheless, the general problem belying in this alkane functionalization is the marginal regiocontrol, which limits the reaction to symmetrical substrates such as methane, ethane, and cyclohexane. Furthermore, the reaction should be stopped at low conversion to avoid complications associated with the sequential carbonylations. The rare case of regiocontrolled C–H functionalization with CO, which converts saturated alcohols and CO into δ-lactones (type 2 in Scheme 3), also deserves mentioning in the context of radical carboxylation strategies. Thus, two types of recently invented carboxylation methodologies will be the focus of this review.

Since iodoalkanes can be synthesized from saturated alcohols, these carboxylation reactions can be regarded as carboxylations of saturated alcohols, which occur with a high level of regiocontrol at the α- and δ-positions respectively.

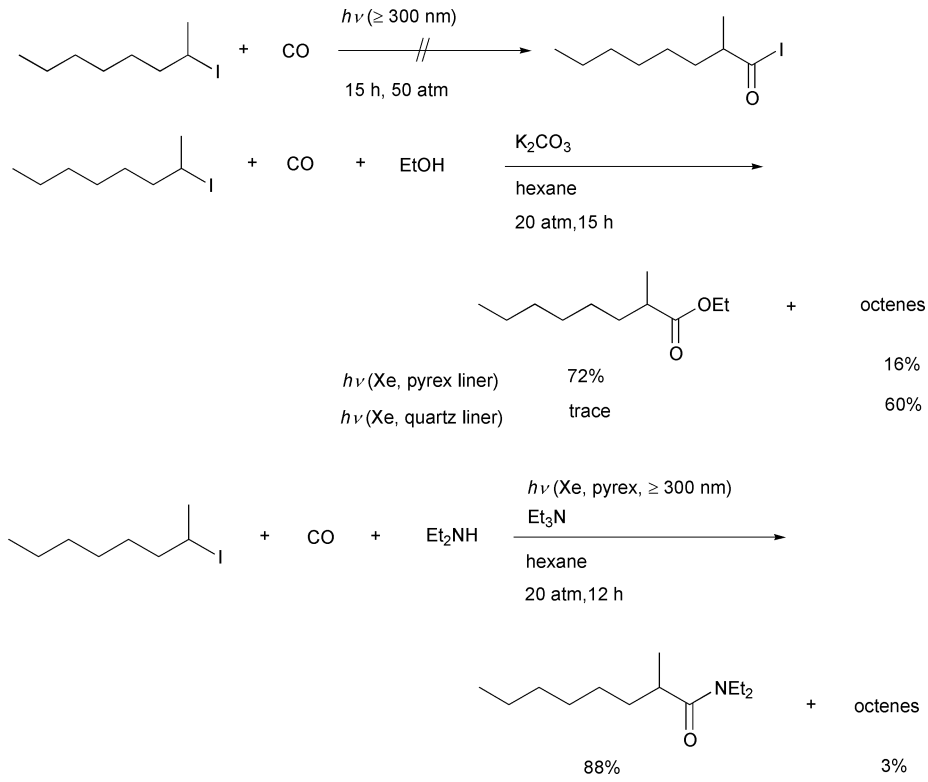


Scheme 4

2 Atom transfer carbonylations of iodoalkanes with CO

2.1 Irradiation system

Our initial idea of atom transfer carbonylation is the simple insertion of carbon monoxide into an alkyl–halogen bond *via* homolysis. To obtain this radical–radical pair, we chose the well known photolytic homolysis of an alkyl iodide,[12] carried out in the presence of pressurized carbon monoxide using a stainless steel autoclave having two quartz windows. Using a 500 W xenon lamp as the light source, a hexane solution of 2-iodooctane was irradiated under 50 atm of CO pressure for 15 h. We were unable to detect the desired acyl iodide *via* this experiment. Since acyl iodides can decompose by photoirradiation, we decided to add an alcohol and potassium carbonate in the hope that the acyl iodide, if formed, would immediately undergo alcoholysis to give an ester that would be stable toward irradiation. This idea is shown in Scheme 5. As we had envisioned, a good yield of the desired carboxylic acid ester was obtained using this reaction system.[13] All of these reactions were carried out using a pyrex glass liner, which appears to be crucial for this catalyst free type of carboxylation reaction. When we examined the reaction of 2-iodooctane using a quartz liner, formation of the ester was completely suppressed. The major products obtained were an isomeric mixture of 1- and 2-octenes. This is a known dehydroiodination pathway iodoalkanes undergo when they are UV-irradiated.[12] Remarkably, inefficient irradiation proved to be crucial for efficient reaction.



Scheme 5

This strongly suggested to us that irradation may simply initiate the process by generating a small amount of an alkyl radical and a radical chain reaction may be involved in the transformation (*vide infra*). Both organic and inorganic bases, such as triethylamine, potassium hydroxide, sodium hydroxide, *etc*. are all effective but in the absence of a base, no carbonylation took place.

Scheme 6 illustrates some examples of ester synthesis by this photo-irradiation reaction. This carboxylation method which is based on atom transfer chemistry can be applied to a wide range of alkyl iodides including tertiary alkyl iodides. Carbonylation of secondary alkyl iodides by transition metals often results in the formation of positional isomers associated with β-elimination of the key metal alkyl species and, for similar reasons, the carbonylation of tertiary iodides is thought to be attainable only with great difficulty. The present carbonylation, however, takes place selectively at the carbon to which the iodine had been attached and, thus, a wide range of aliphatic iodides including tertiary substrates can be used. The reaction of primary alkyl iodides was not fast due presumably to a slow iodine atom transfer. The reaction can be extended to include the amide synthesis by simply changing the trapping nucleophile from alcohols to amines.

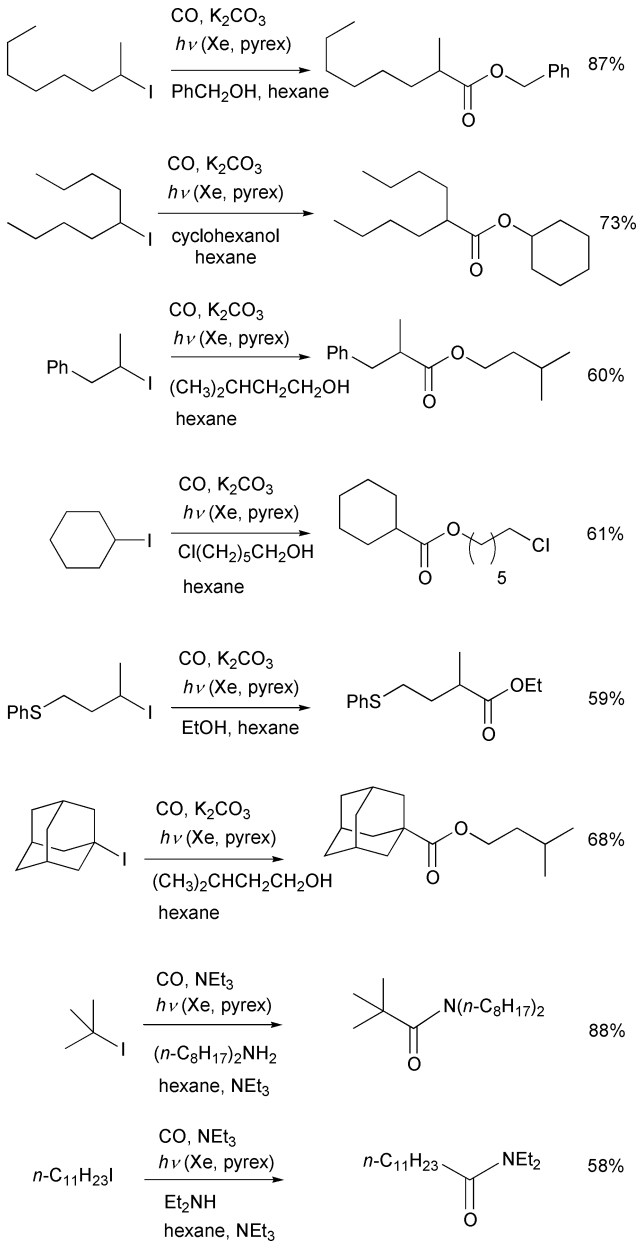
It should be noted that the general idea of atom transfer carbonylation originated from mechanistic considerations surrounding the unexpected observation of lactone formation in the double carbonylation of 4-pentenyl iodide using a slow radical mediator such as tributylgermane or $(TMS)_3SiH$ (Scheme 7).[14] Bicyclic lactone formation did not occur with 4-pentenyl bromide as the substrate and this clearly speaks against a rare 5-*endo* reaction mechanism.

Group transfer ability of a phenylseleno functionality[15,16] to an acyl radical was tested in the photolysis of α-phenylselenoacetate and related compounds in the presence of an alkene and CO. This three-component coupling reaction involves the addition of an α-(alkoxycarbonyl)methyl radical to an alkene, the trapping of the produced alkyl free radical by CO, and termination of the reaction by a phenylseleno group transfer from the starting material which leads to acyl selenides *via* group transfer carbonylation. (Scheme 8).[17] Unlike the case of the iodine atom transfer system discussed above, the system shown in Scheme 8 does not need the following ionic process, since the product acyl selenide is reasonably stable under the irradiation conditions and group transfer is designed to take place easily by employment of α-phenylseleno carbonyl compounds. However, the fact that the reverse reaction was involved was determined by photolyzing the product, which yielded the parent olefin (Scheme 8). This competing process obviously lowers the yields of the product.

2.2 Thermal initiation system

What is the role of photo-irradiation? We suspected that the role is merely to initiate the hybrid radical–ionic reaction by effecting the homolysis of an R–I bond in a small quantity. If this was the case, the thermal initiation process would allow the same reaction to take place. We tested a variety of thermal initiation systems (Scheme 9),[18] and found that the AIBN–allyltributyltin system was quite promising. If the avoidance of toxic tin compounds is preferred, tris(trimethylsilyl)silane is equally effective.

In these two systems, the abstraction of iodine by a tin or silyl radical serves as the source of small amounts of an alkyl radical, which participates in the subsequent chain reaction system comprised of (i) radical carbonylation and (ii) iodine atom transfer reactions from an iodoalkane to give an acyl radical. The latter does not necessarily appear to be thermodynamically favorable. For example, a low level *ab initio* MO calculation using UHF/3-21G* as a basis set suggests that the conversion of isopropyl iodide and CO into the corresponding acyl iodide is 1.92 kcal mol^{-1} endothermic. The most likely mechanism involves (i) radical initiation *via* either irradiation or thermal initiation, (ii) radical chain propagation, composed of two reversible radical reactions (carbonylation and iodine atom transfer) and (iii) ionic quenching to shift the equilibria of the



Scheme 6 *Conditions*: 20–50 atm, Xe irradiation through a pyrex tube, 12–14 h.

reversible reactions (Scheme 10). In the hands of a tin mediated radical carbonylation process, tertiary substrates require high CO pressure to compete with the very rapid back decarbonylation reaction, compared with secondary and primary alkyl radicals.[19] However, the unique radical–ionic cooperation to drive the carbonylation–decarbonylation equilibrium in the forward direction could give an advantage for the carbonylation of tertiary radicals.

Scheme 11 illustrates examples of atom transfer carbonylation using allyltin–AIBN as the radical initiator system. Generally, the amide synthesis proceeds more rapidly than the corresponding ester synthesis. Indeed, even in the case where methanol was used as the solvent, the amide was the only product derived from the carbonylation reaction. Both primary amines and secondary amines were useful. We also tested trapping of an acyl iodide by an enamine, which gave a mixture of a 1,3-diketone and an amide (Scheme 12).[20]

An intramolecular variant of the atom transfer based radical carboxylation was examined using ω-iodo alcohols as the substrate (Scheme 13). Thus, five- to seven-membered lactones were prepared successfully in good yields by this method.[21] One easy way to prepare the starting ω-iodo alcohols is carboiodination of unsaturated alcohols.[22] Scheme 13 also illustrates an example where the three carbon components were combined *via* successive carboiodination, atom transfer carbonylation, and intramolecular ionic trap.

Unfortunately the system cannot be applied to tandem double carbonylation reactions even when 5-pentenyl iodide was used as the starting substrate. It is probable that the iodine atom transfer–ionic quenching protocol is not efficient enough to capture the product over a multi-step equilibrium. However, we have recently found that a Pd–light system enables us to execute such a reaction.[23] Judging from the stereochemical outcome of the cyclized product, it is concluded that the reaction includes an acyl radical cyclization step.

It is interesting to note that recently the Yoon[24] and Curran[25] groups independently have also reported that the use of a hybrid radical–ionic system effected successful atom transfer reactions which had been thought to be difficult (Schemes 14, 15). All these new achievements based on a hybrid system may be a stimulus to reconsider some other reactions whose potential has yet to be developed.

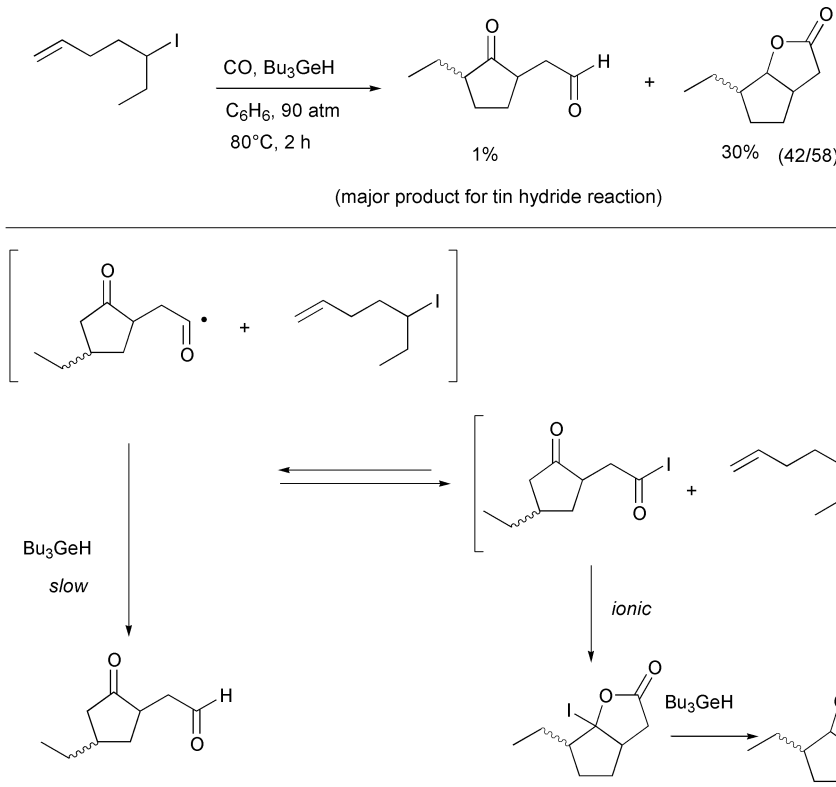
3 Remote carboxylations of saturated alcohols

3.1 One-electron oxidation system

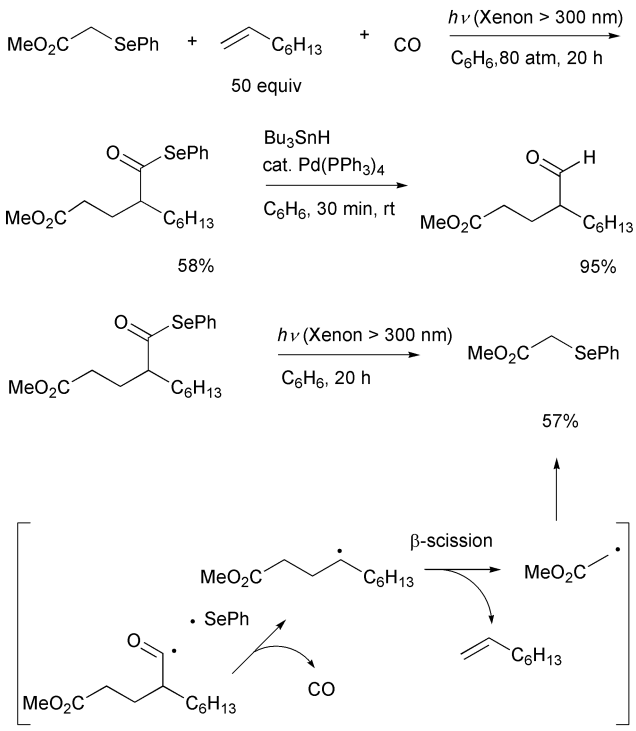
Alkoxy radical mediated δ-functionalization reactions of saturated alcohols based on the 1,5-H shift have a long history.[26,27] However, the examples of δ-functionalization reactions have been largely restricted to cases of heteroatom introducing reactions that occur at δ-carbons, represented by the Barton reaction[26d] and a select few intramolecular cyclization reactions. We became interested in the carboxylative version of the Barton reaction, a regioselective δ-carboxylation of saturated alcohols, which includes carbonylation plus one-electron transfer (Scheme 16). The initial discovery in collaboration with Howard Alper that radical carboxylation with CO can be carried out in a Mn^{III} induced one-electron oxidation system,[28] encouraged us to embark on this challenging C–H functionalization project. After screening a variety of one-electron oxidizing systems, we determined that a lead tetraacetate ($Pb(OAc)_4$, LTA) promoted oxidative cyclization system[29] can be successfully applied to the envisioned process. Thus, δ-hydroxyalkyl radicals can be generated in high selectivity from the corresponding methanols *via* alkoxy radicals. Subsequent trapping of the resulting radicals with CO results in a δ-selective carbonylation. One-electron oxidation of the resulting acyl radical generates an acyl cation which cyclizes to form the δ-lactone ring.

The results of control experiments using 1-octanol showed that lower concentrations of 1-octanol, smaller amounts of LTA (1.5 mol equiv.), higher pressures of CO (80–100 atm), and lower reaction temperatures (40 °C) all favored carbonylation of the δ-hydroxyalkyl radical over the undesirable direct oxidation leading to THF ring formation.[30]

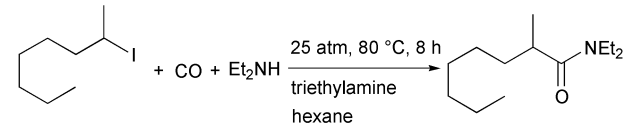
In Scheme 17, examples of carboxylation of primary and secondary alcohols having 2° δ-carbons are provided. In all cases, the major competing reaction is oxidation to give THF derivatives. On the other hand, small quantities (< 5%) of ε-lactones (*via* 1,6-H shifts) were occasionally observed. These by-products can be eliminated by flash chromatography on silica gel to afford pure δ-lactones. In general, the yields of δ-lactones from secondary alcohols are higher than those from primary alcohols. This may be due to a decrease in the rate of reaction leading to THF derivatives from these secondary alcohols due to additional steric congestion at the cyclization step.



Scheme 7

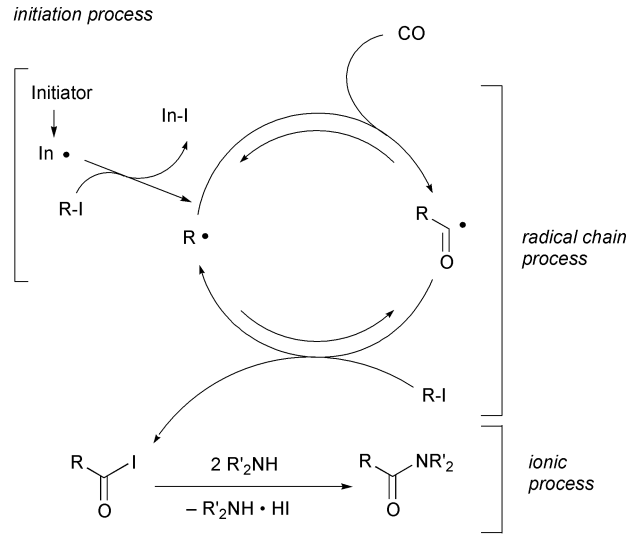


Scheme 8



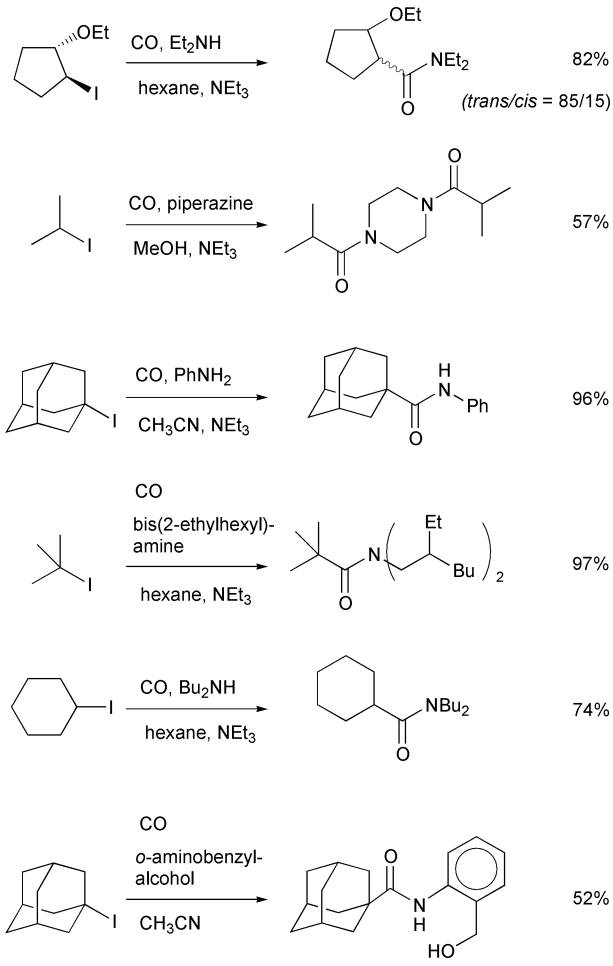
none	0%
AIBN (30 mol%)	10%
BPO (20 mol%)	17%
AIBN (25 mol%), allyltributyltin (10 mol%)	91%
AIBN (25 mol%), allyltributyltin (10 mol%), galvinoxyl (20 mol%)	5%
AIBN (25 mol%), $(TMS)_3SiH$ (20 mol%)	80%
AIBN (30 mol%), Bu_3SnH (30 mol%)	43%

Scheme 9

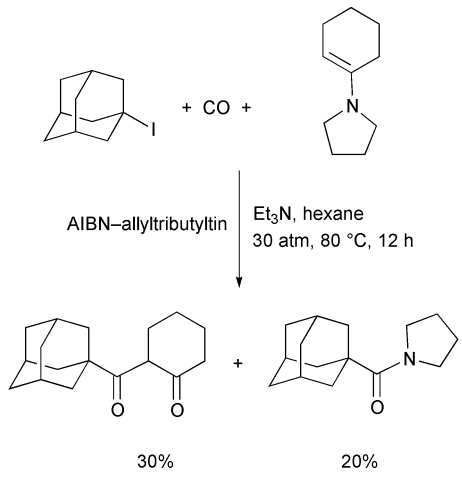


Scheme 10

This δ-carboxylation method was successfully applied to a concise synthesis of carpenter bee pheromone from optically pure (*R*)-(–)-2-hexanol (Scheme 17). Preparative HPLC separation of the product mixture composed of *cis*- and *trans*-2-methyl-5-hexanolide afforded pure *cis*-(2*S*,5*R*)-2-methyl-5-hexanolide (ee ~ 100%), a sex pheromone of the carpenter bee *Xylocopa hirutissima*. The observed quantitative optical yield confirmed that the absolute configuration at the hydroxy-bearing carbon was completely retained. However, in some

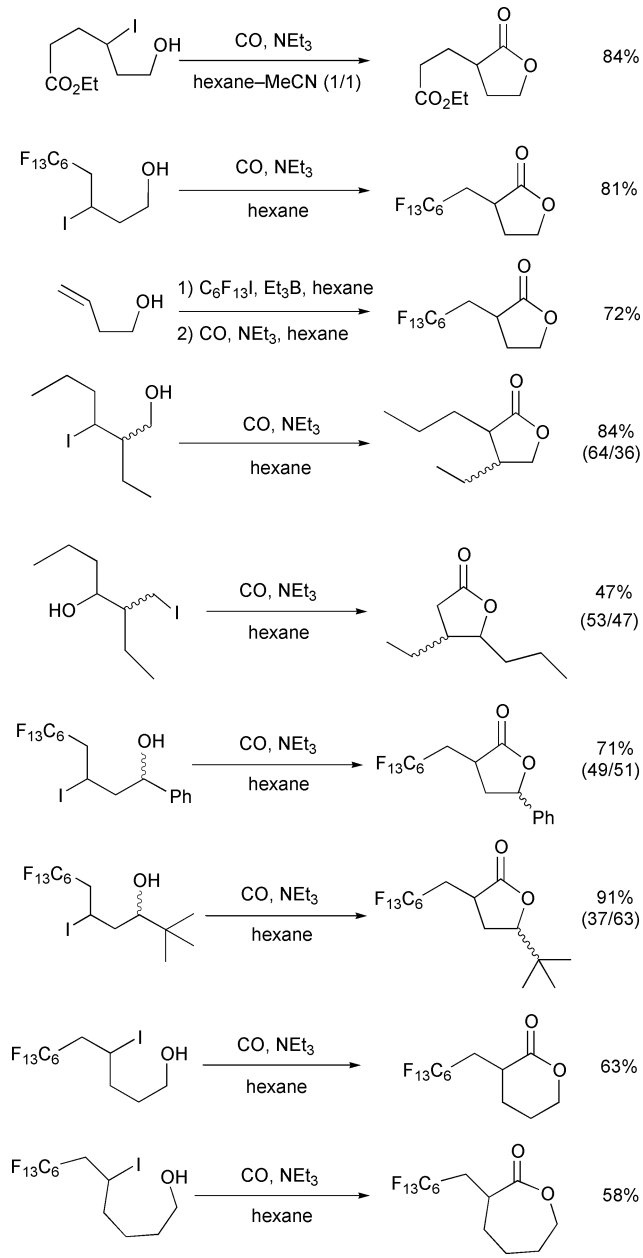


Scheme 11 *Conditions*: 20–25 atm, allyltributyltin (10 mol%)–AIBN (30 mol%), 80 °C, 8 h.



Scheme 12

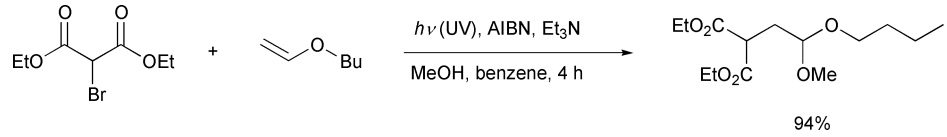
cases, for example *trans*-2-cyclohexyl-1-cyclohexanol, the stereochemistry at the hydroxy-bearing carbon was not retained (Scheme 18). Tricyclic δ-lactone **A** was obtained as a mixture of eight diastereomers, despite the fact that only four diastereomers were considered to be possible if the configuration of hydroxy-bearing carbon was retained. The four major diastereomers were assigned as *trans* isomers with retention of ordinal stereochemistry, in a ratio of 55:15:12:6 and four minor diastereomers assigned as *cis* isomers with inversion of ordinal stereochemistry, in a 4:3:3:2 ratio. The initially generated alkoxyl radical having a *trans* configuration may undergo β-



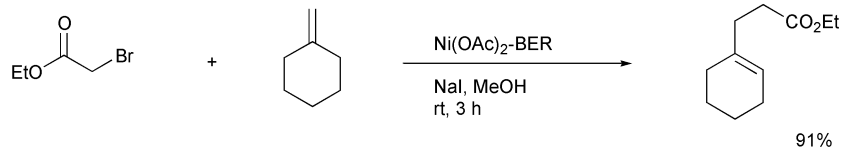
Scheme 13 *Conditions*: 45–90 atm, allyltributyltin (10 mol%)–AIBN (20–30 mol%), 80 °C, 12 h.

scission, and cyclization of the resulting radical back onto the internal aldehyde would afford an isomerized radical with *cis* configuration. The isomerized radical undergoes 1,5-hydrogen transfer, CO trapping, and oxidation to give the four minor products. This result is supported by kinetic data which show that the cyclization–fragmentation process is in equilibrium.[31] The complete retention of stereochemistry observed in the case of (*R*)-(–)-2-hexanol can be explained in this context since β-scission yields two fragments, whose recombination is entropically unlikely. In strained cyclic alcohols like cyclobutanols, β-scission is irreversible and carbonylation–oxidation of the resulting ring opened radicals leads to carboxylic acids (Scheme 18).[32]

The carboxylation of alcohols having 1° δ-carbons was also successful. In this case, the reaction was not accompanied by the two types of by-products that were observed with alcohols having 2° δ-carbons. ε-Lactones were not formed, since 1,6-H shifts are no longer possible and very little competitive oxidation leading to the tetrahydrofuran derivative was observed, which is ascribed to the slower oxidation of primary radicals compared to secondary radicals. The slow side reaction

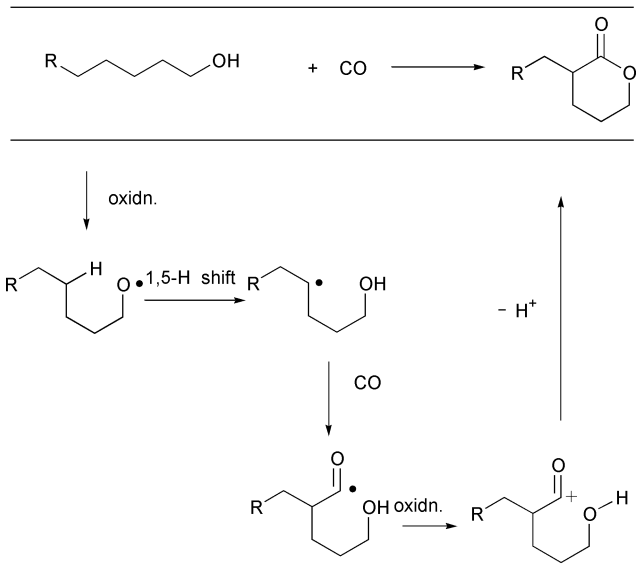


Scheme 14[25]



BER = borohydride exchange resin

Scheme 15[24]



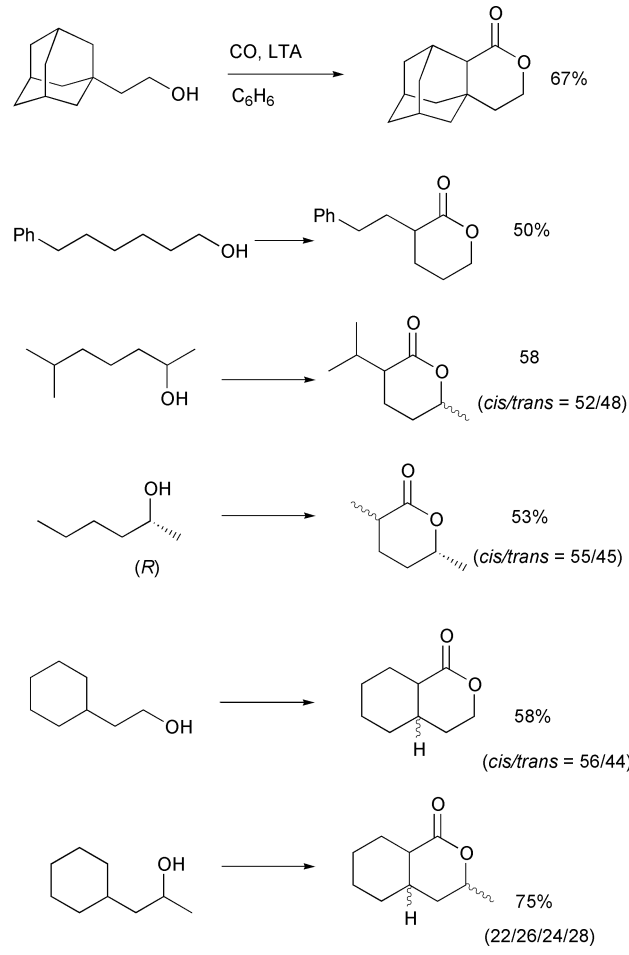
Scheme 16

may enable us to carbonylate alcohols which have 1° δ-carbons at relatively low CO pressures (20–80 atm) and at high temperatures (60–80 °C). Indeed in the first example shown in Scheme 19, when 2,6-dimethyl-4-heptanol was treated with 20 atm of CO, the δ-lactone was obtained in 62% yield along with only 2% of the corresponding THF derivative. The relatively low reactivity of the 1° δ-carbon systems with carbon monoxide can, however, often lead to slightly reduced conversions and recovery of the starting alcohols.

This lower reactivity of the primary carbon can be used to our advantage in the selective carbonylation of an alcohol which has both 2° and 1° δ-carbons, *a* and *b*. In this case, carbon monoxide could be incorporated at the 2° δ-carbon *a*, with high regiochemical selectivity (Scheme 20). For example, 2-propyl-5-octanolide was formed predominantly over 5-undecanolide in a 24 : 1 ratio. Purification to eliminate the minor product was easily accomplished by flash chromatography on silica gel. The preferential formation of the secondary carbonylation product is reasonable in light of the weaker C–H bond strength of methylene relative to that of methyl (ΔE = *ca.* 3 kcal mol^{-1}).[33] The efficiency of the 1,5-hydrogen transfer correlates well with the C–H bond dissociation energies.

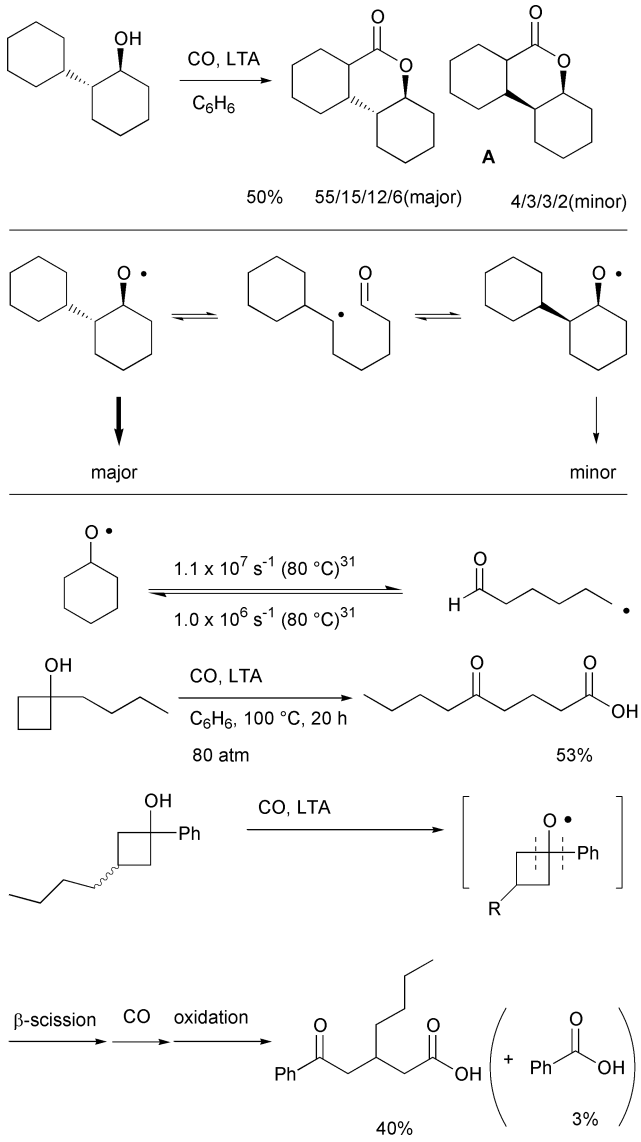
3.2 Irradiation system through alkyl benzenesulfenates

In contrast to primary and secondary alcohols, tertiary alcohols were virtually inert under the reaction conditions employed. This is presumably because of the difficulty of the formation of alkoxylead species due to steric congestion at the initial step under the standard conditions.

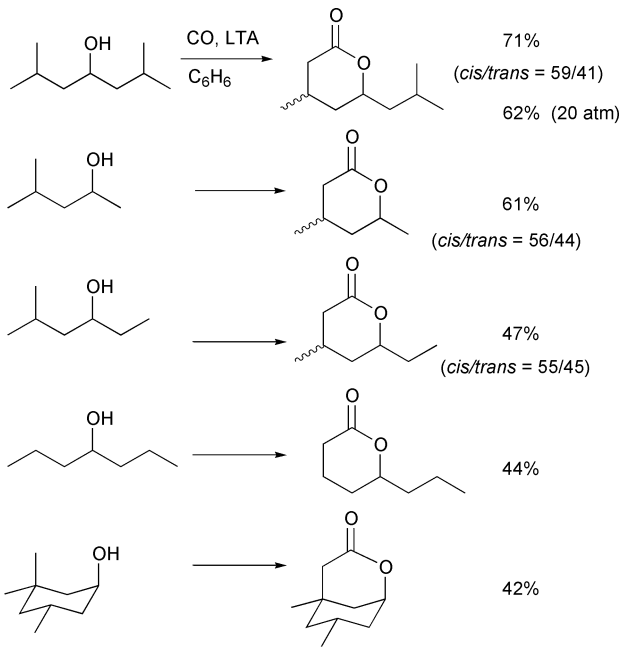


Scheme 17 *Conditions*: ROH (0.4–0.8 mmol), LTA (1.5–2.0 equiv.), C_6H_6 (20–40 mL), CO (80 atm), 40 °C, 3–7 days.

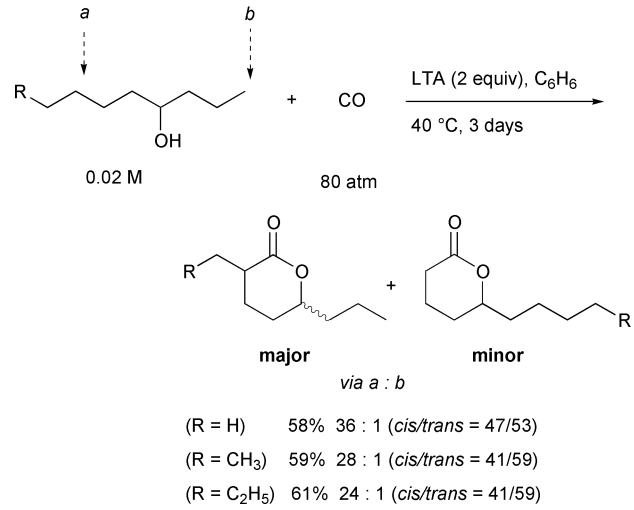
In order to circumvent this limitation, we considered generating the alkoxyl radical without LTA and we were particularly interested in the methods involving photolytic cleavage of O–X bonds.[34] It is well known that O–S bonds undergo homolytic cleavage to give alkoxyl radicals,[35] as does O–O homolysis. It has recently been reported that photolytic cleavage of the O–S bond in alkyl 4-nitrobenzenesulfenates,[36] which are readily prepared by the reaction of the alcohols with 4-nitrobenzenesulfenyl chloride, provides a convenient method for the generation of alkoxyl radicals. Thus, the reaction of an alkyl 4-nitrobenzenesulfenate derived from a tertiary alcohol and 4-nitrobenzenesulfenyl chloride with CO was conducted under sunlamp irradiation in the hope of effecting δ-carboxylation to give a thioester. The requisite lactone was formed in 52% yield (Scheme 21).[30b] The formation of the lactone can be



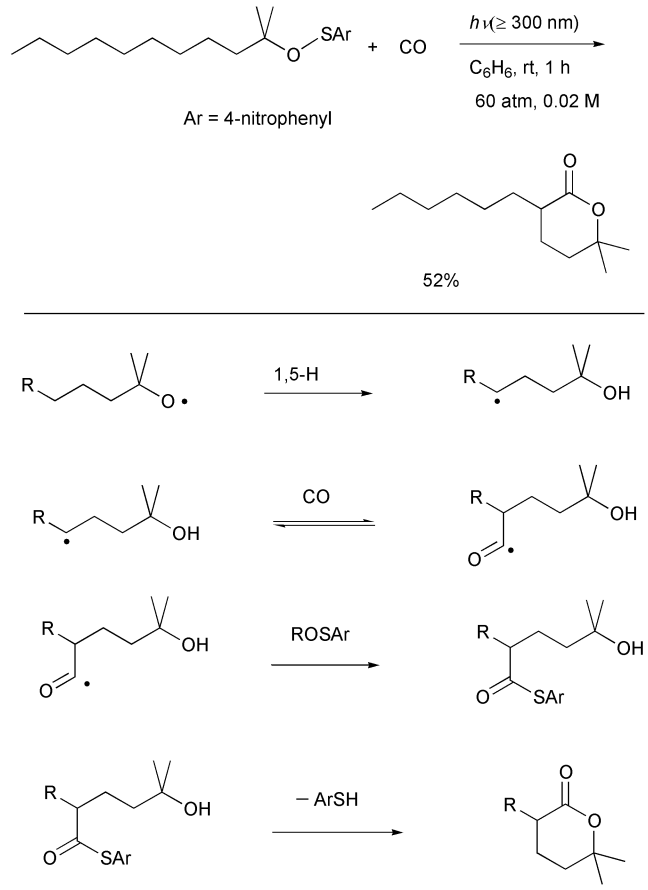
Scheme 18



Scheme 19 *Conditions*: ROH (0.4–0.8 mmol), LTA (1.5–2 equiv.), C_6H_6 (20 mL), CO (80 atm), 60 °C, 2–5 days.



Scheme 20

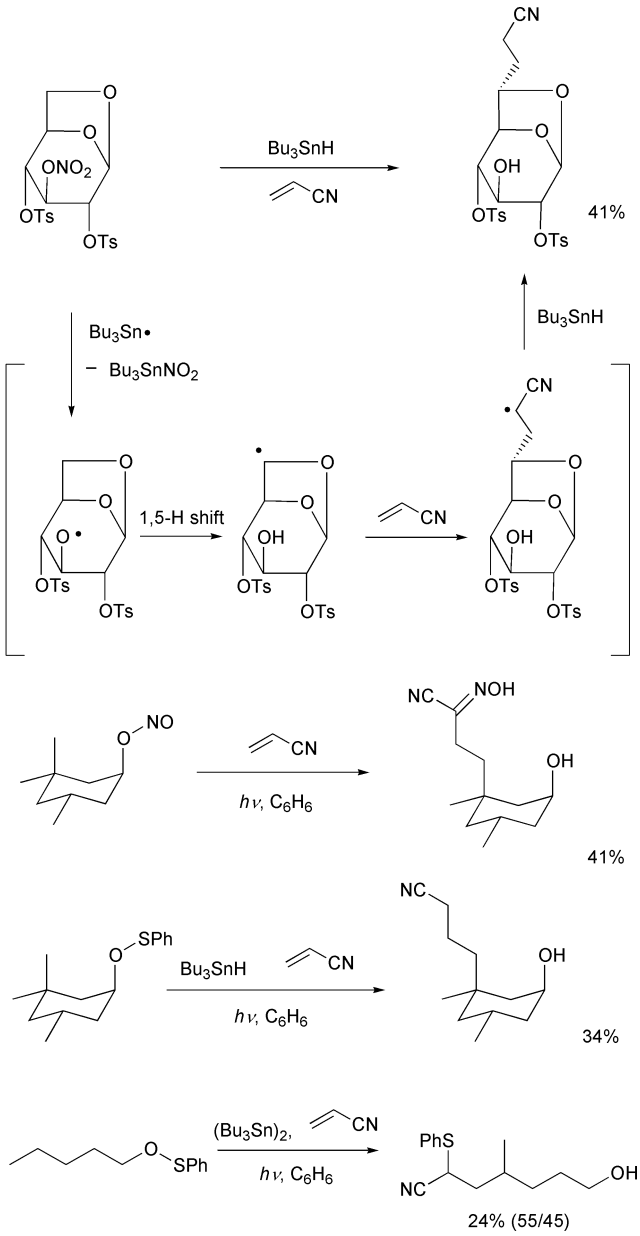


Scheme 21

rationalized as being derived from an initially produced thioester which is formed *via* an S_H2 reaction at sulfur. Therefore, group transfer from a benzenesulfenate to an acyl radical is a key step for this reaction. Although the system requires optimization in terms of the yields of the δ-lactones, we believe that the photolytic δ-carbonylation of alkyl 4-nitrobenzenesulfenates is complementary to our LTA-induced oxidation system.

Finally, though quite restricted, some interesting examples of intermolecular C–C bond forming reactions using an alkene are listed in Scheme 22. The first example was reported by Fraser-Reid and co-workers in 1989,[37] and the latter three examples

were recently reported by Cekovic and co-workers.[38,39] These results are a proof of the continuing vitality of remote-carbon-functionalization.



Scheme 22

4 Conclusion

Two types of radical carboxylation methods are described in this account. Radical carboxylations based on iodine atom transfer chemistry are found to be particularly useful for the conversion of a wide variety of alkyl iodides into the one carbon homologated carboxylic acid derivatives. This work demonstrated that thermodynamically unfavorable radical chain reactions can be carried out if they are performed in conjunction with ionic reaction systems. Remote carboxylation provides a convenient one-step synthesis of δ-lactones from a cheap and readily available feedstock, *saturated* alcohols. Carboxylation of tertiary alcohols, although unsuccessful with the LTA-induced system, can be achieved *via* photolysis of alkyl 4-nitrobenzenesulfenates, which may prove to be a highly efficient alternative to the LTA system. We believe that these two topics will stimulate further developments in carboxylation chemistry.

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