A FLEXIBLE ROUTE TO 4-SUBSTITUTED β-LACTAMS

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This paper is dedicated with respect and admiration to Prof. Albert Eschenmoser
on the occasion of his 85th birthday.

Abstract – A variety of 4-substituted β-lactams can be readily prepared by the
radical addition-transfer of 4-*S*-xanthyl-azetidinones to unactivated olefins. For
this radical chain process to operate efficiently it is necessary to place an acyl
group on the nitrogen of the azetidinone ring.

INTRODUCTION

The enormous importance of β-lactam antibiotics and the rich chemistry associated with the strained
lactam ring, especially in its capacity to act as an activated, latent β-aminoacid, have continued to
stimulate the interest of organic chemists.[1,2] In addition to the development of methods for constructing
the β-lactam ring itself, much effort has been expanded for the modification of existing structures. The
introduction of a substituent at position 4 of β-lactams has often been realised by replacement of a
potential leaving group X in structure **1** by various nucleophilic reagents to give derivatives **2** (Scheme
1).[3] Thus, carbanions, organometallics, enol silyl ethers, ketene silyl acetals and allylsilanes can be used
for the substitution reaction, the last three families of nucleophiles usually requiring the mediation of a
Lewis acid. In stark contrast, the introduction of substituents by reactions proceeding by way of radical **3**
and leading to structures **4**, has very seldom been exploited, despite its obvious potential. One rare
example reported a quarter of a century ago by Fliri and Mak and portrayed in Scheme 1 is the radical
allylation of azetidinone **5** with allyltributyltin to provide compound **6** in good yield.[4] This approach is
however limited to very simple allylations and requires the use of organotin derivatives, which are not
acceptable in a pharmaceutical context because of the acute toxicity of organotin derivatives and the
extreme practical difficulty in completely removing tin residues from the products.

Scheme 1. Modification of β-lactams
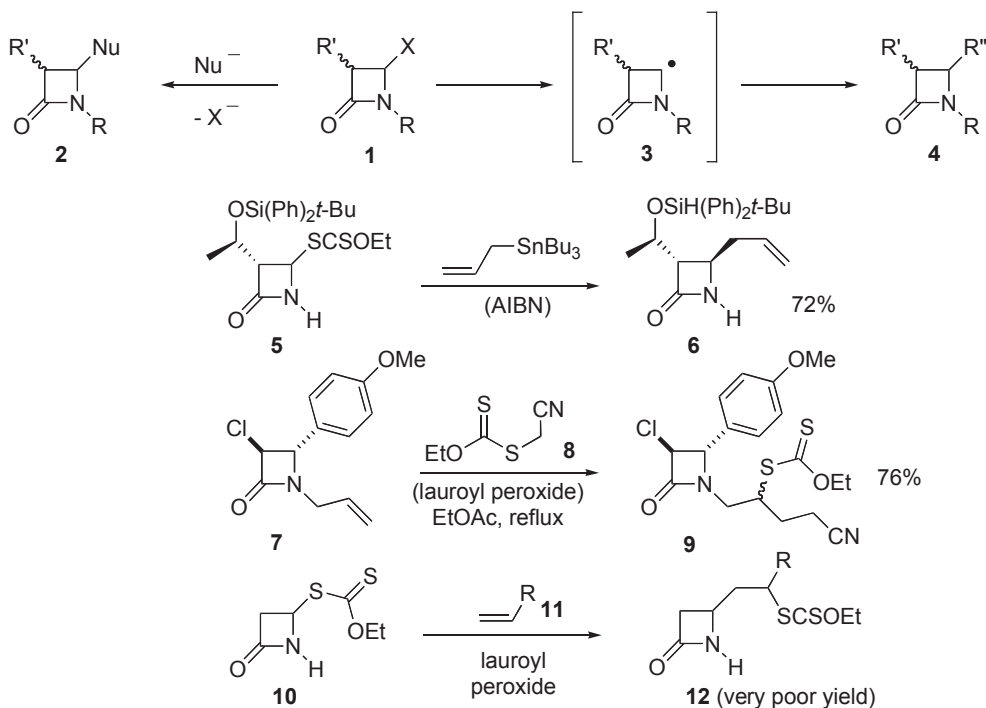
RESULTS AND DISCUSSION

Over the past years, we have demonstrated the unique ability of xanthates for creating new carbon-carbon bonds by intermolecular radical addition to *unactivated* alkenes.[5] More generally, relatively slow and otherwise difficult radical transformations can often be accomplished because the xanthate transfer process imparts a comparatively long lifetime to the intermediate radicals, even under concentrated conditions. We exploited this property to construct the β-lactam ring itself, but it seemed interesting to expand the scope to the modification of existing β-lactam structures. However, while the addition of *S*-cyanomethyl xanthate **8** to *N*-allyl β-lactam **7** could indeed be readily accomplished, the addition of β-lactam xanthate **10** to simple unactivated alkenes **11** proceeded in very poor yield (Scheme 1).

The most likely reason underlying this disappointing failure may be traced to the relative stabilities of the various radical intermediates involved in the xanthate addition-transfer, which can be readily understood by a brief examination of the simplified mechanism displayed in Scheme 2. One of the key requirements of the process is that, in the absence of special polar factors, the initial radical, in this case **14**, must be more stable than the adduct radical **15** in order for the equilibrium involving intermediate **16** to favour the forward pathway and thus sustain the desired chain reaction. In other words, the fragmentation of intermediate **16** has to preferentially lead to addition product **17** and starting radical **14**, rather than back to adduct radical **15**. The failure of the desired addition indicated that this is probably not the case, and that the stabilisation of radical **14** by the lone pair of the nitrogen is not sufficient, presumably for reasons related to the strained geometry of the azetidinone structure.

Scheme 2. Simplified mechanistic rationale
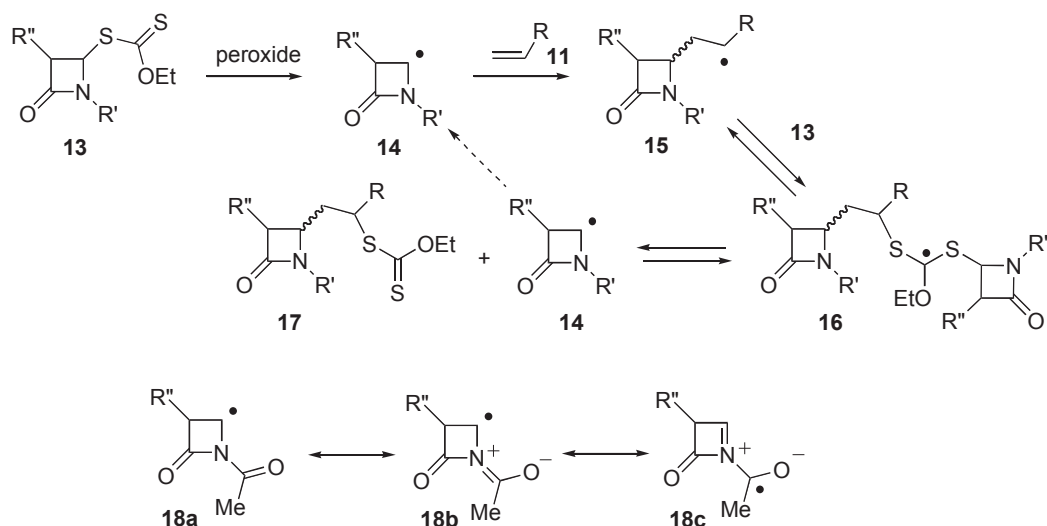
With the aim of enhancing the stability of radical **14** sufficiently to tilt the equilibrium along the forward direction, we contemplated starting with the *N*-acyl derivatives **13** (R' = MeCO-), where we hoped the radical would acquire a certain degree of allylic character through canonical structures **18a-c** of the imide, as pictured in the lower part of Scheme 2. A similar spin delocalization appears to operate in the case of phthalimidomethyl radicals, which we exploited to accomplish a very efficient and broadly applicable radical aminomethylation of alkenes.[6] Because of the strain involved, the extra stabilisation provided by canonical structures **18b** and **18c** would be expected to be less effective than in the case of the much less strained phthalimido analogues, but even a small stabilisation could prove decisive in ensuring success.


Scheme 3. Radical additions of *S*-azetidinyl xanthates
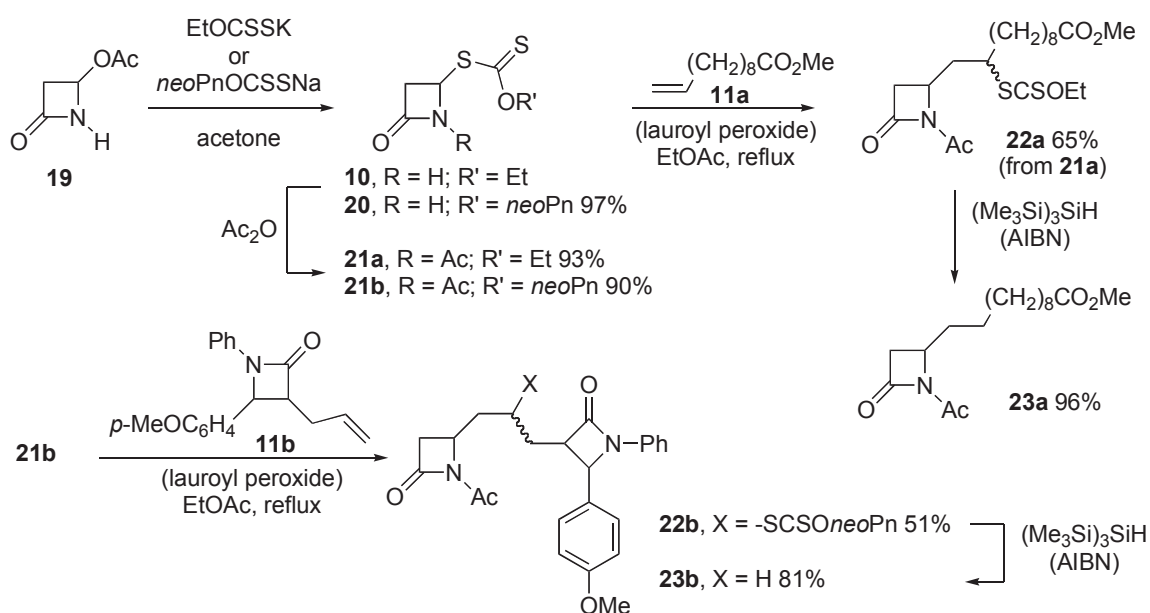
We therefore prepared *N*-acetyl derivative **21a** from known xanthate **10**,[7] itself readily obtained from commercial 4-acetoxyazetidinone **19** (Scheme 3). In the same manner, we prepared the neopentyl analogue **21b** (*neo*Pn = neopentyl). We have observed over the years that *S*-neopentyl xanthates tended to be more crystalline than their ethyl analogues, and this can be advantageous when there is a need to purify delicate structures.[8] Neopentyl derivatives were also much less susceptible to undesired ionic transformations. When a concentrated solution of xanthate **21a** and methyl 10-undecenoate **11a** was heated at reflux in ethyl acetate in the presence of a small amount of lauroyl peroxide, we were gratified to find that a relatively smooth reaction took place to give the desired product **22a** in 65% yield. To simplify the characterization of the product, the xanthate group was removed to give **23a** in near quantitative yield by reduction with tris-(trimethylsilyl)silane and a small amount of AIBN in refluxing 1:1 toluene:cyclohexane (Scheme 3).[9]
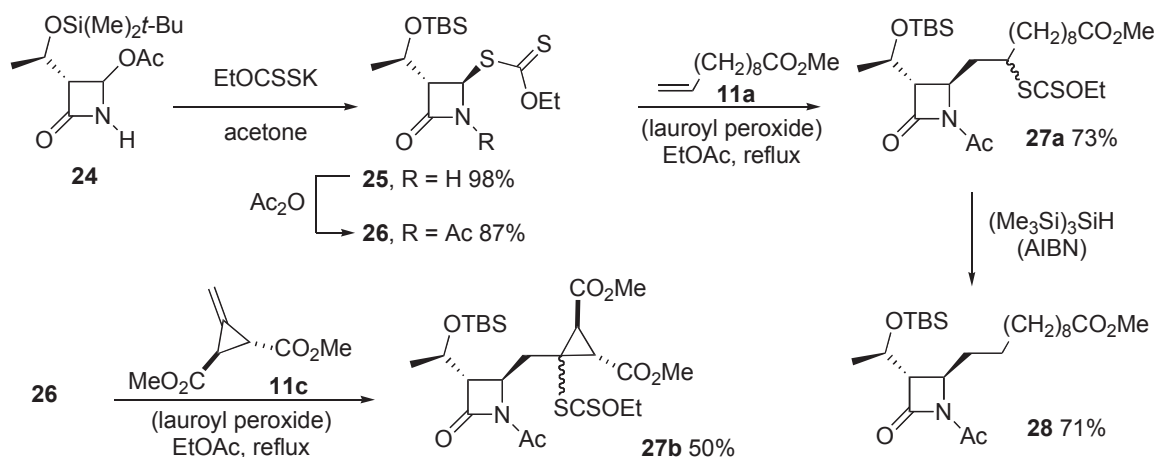
Scheme 4. Radical additions of functionalized *S*-azetidinyl xanthates

The success of this preliminary reaction opens up numerous possibilities for rapidly constructing highly functional and indeed quite complex azetidinones. One such example, also pictured in Scheme 3, is the synthesis of di-β-lactam **23b** by the addition of *S*-azetidinyl xanthate **21b** to 3-allyl azetidinone **11b** and reductive removal of the xanthate group from the intermediate adduct **22b**. One of the main features of the present radical process is its tolerance for numerous functional groups because of the extreme mildness of the experimental conditions. This is illustrated by the addition reactions of 3-substituted xanthate **26**, derived from commercially available 4-acetoxyazetidinone derivative **24** (Scheme 4). Thus, the addition reaction of **26** with methyl 10-undecenoate **11a** proceeded as effectively as with the simpler xanthate **21a** leading finally to compound **28** following the removal of the xanthate group. Only one isomer is obtained since the bulky protected hydroxyethyl substituent on C-3 of the azetidinone forces the new carbon-carbon bond to form from the opposite side of the ring. The addition of **26** to the dimethyl ester **11c** of Feist's acid is another example of the degree of complexity that can be swiftly attained.
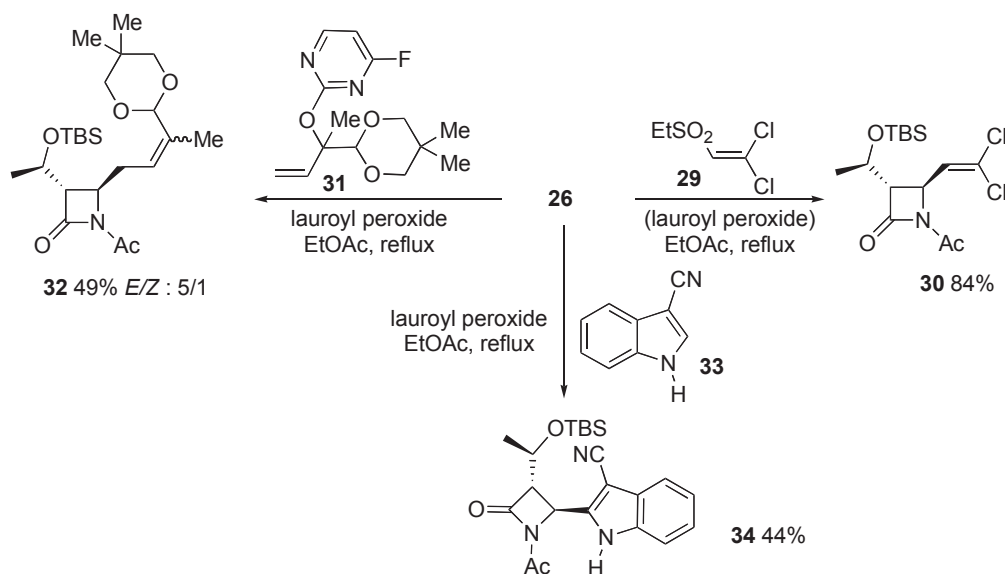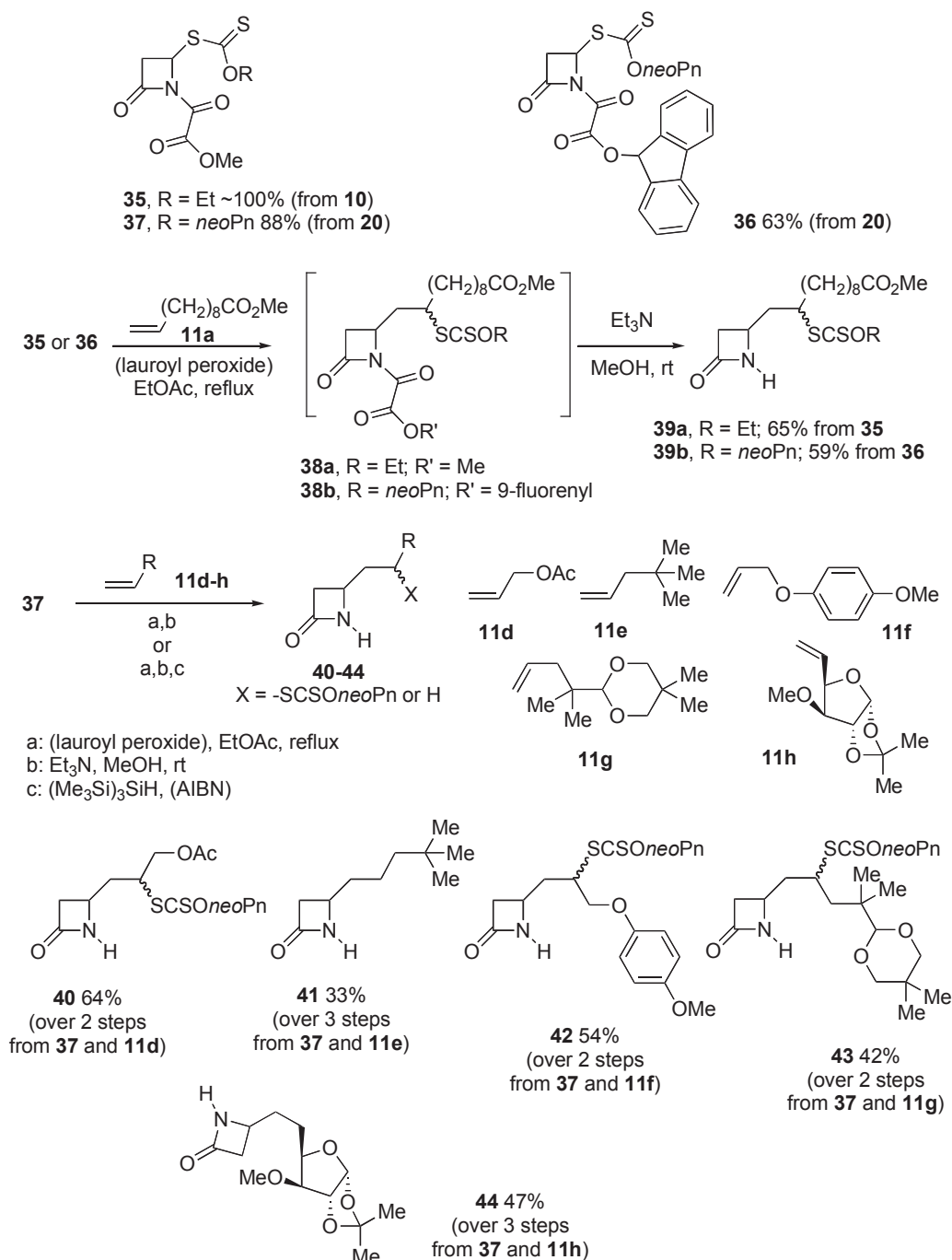
Scheme 5. Radical vinylation, allylation and heteroarylation of functionalised *S*-azetidinyl xanthates

We had previously reported the use of allyl and vinyl ethylsulfones as tin-free allylating and vinylating reagent for both aliphatic iodides and xanthates.[10] An example of the latter transformation is shown in Scheme 5, whereby *S*-azetidinyl xanthate **26** is converted in high yield into nicely crystalline (mp: 85-86 °C) dichlorovinyl derivative **30** upon reaction with sulfone **29**. Very recently, we discovered that allylic alcohols become highly versatile radical allylating agents when they are converted into their 6-allyloxy-2-fluoropyridinyl derivatives.[11] This process has an enormous potential for synthesis in view of the central position played by alkenes in organic chemistry. An illustration in the present case is the formation of protected enal **32**, as a 5:1 mixture of geometrical isomers by addition-fragmentation of xanthate **26** to derivative **31**. It is worth noting that in this case, the lauroyl peroxide must be used in stoichiometric amounts since the departing fluoropyridinyloxy radical is unable to propagate the chain. Another process, which also requires the use of stoichiometric peroxide, is the intermolecular addition of xanthates to certain heteroaromatic derivatives, as illustrated by the formation in moderate yield of compound **34** by reaction of xanthate **26** with 3-cyanoindole **33**. While this approach is somewhat limited in scope as far as the heteroaromatic component is concerned, it can nevertheless furnish in one step some very interesting structures.[12]

In all the preceding examples, the *N*-acetyl group serves to stabilize the radical and, even if this stabilization is presumably relatively small in absolute terms, it has proved essential for implementing the chain process, which does not operate in its absence. The drawback is that it is very difficult to remove this acetyl group without destroying the azetidinone ring, and this obliterates to a large extent the utility of this approach. In order to circumvent this rather serious problem, we examined the replacement of the acetyl by an oxalyl group. It was known by researchers in the β-lactam field that an *N*-oxalyl group could

be removed under extremely mild conditions that did not affect the fragile azetidinone ring.[13] We therefore prepared xanthate **35** from β-lactam xanthate **10** and, indeed, found that the addition and removal of the oxalyl group could be readily accomplished, as demonstrated by the synthesis of compounds **39a,b** possessing a free N-H group on the β-lactam ring (Scheme 6).

35, R = Et ~100% (from **10**)
37, R = *neo*Pn 88% (from **20**)

36 63% (from **20**)

38a, R = Et; R' = Me
38b, R = *neo*Pn; R' = 9-fluorenyl

39a, R = Et; 65% from **35**
39b, R = *neo*Pn; 59% from **36**

a: (lauroyl peroxide), EtOAc, reflux
b: Et₃N, MeOH, rt
c: (Me₃Si)₃SiH, (AIBN)

40-44
X = -SCSO*neo*Pn or H

11d   **11e**   **11f**

11g   **11h**

40 64%
(over 2 steps
from **37** and **11d**)

41 33%
(over 3 steps
from **37** and **11e**)

42 54%
(over 2 steps
from **37** and **11f**)

43 42%
(over 2 steps
from **37** and **11g**)

44 47%
(over 3 steps
from **37** and **11h**)

Scheme 6. Synthesis of *N*-unsubstituted β-lactams

The intermediate adduct **38a** was not purified in this sequence but immediately converted into **39a** by exposure to triethylamine in methanol. In fact, the purification of *N*-oxalyl azetidinones proved rather

tricky and some decomposition was observed upon chromatographic separation. We attempted to overcome this hurdle by replacing the *O*-ethyl xanthate group in **35** with an *O*-neopentyl xanthate and the methyl oxalate with the much bulkier 9-fluorenyl ester.[14] However, the resulting derivative **36** did not prove superior in relation to the synthetic effort need to prepare it, as shown by the formation of analogous product **39b** in similar overall yield (59% vs 65%). The remainder of the study was therefore performed using azetidinyl xanthate **37**, which was readily obtained and proved easy to purify by crystallisation.

Xanthate **37** was reacted with a selection of five olefins, **11d-h**, to give the corresponding adducts **40-44** in useful overall yield. In two instances (**41** and **44**), the xanthate group was reductively removed. In the case of **41**, the volatility of the olefin caused a significant lowering of the yield. The attachment of a β-lactam motif to a glucose residue as in **44** is noteworthy and further demonstrates the synthetic potential of this novel chemistry

In summary, we have developed a flexible approach to highly substituted azetidinones. While the radical additions of the β-lactam xanthates are slightly less efficient than the phthalimido substituted xanthates we described previously, many of the compounds reported in this preliminary work would be exceedingly tedious, if not impossible, to make by more traditional routes. Indeed, the xanthate transfer technology represents a quite general solution to a longstanding problem in organic synthesis, namely the creation of a carbon-carbon bond in an *intermolecular* fashion starting with *non-activated* alkenes.

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