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# Novel Chemistry of α-Tosyloxy Ketones: Applications to the Solution- and Solid-Phase Synthesis of Privileged Heterocycle and Enediyne Libraries

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***Abstract:*** New synthetic technologies for the preparation and elaboration of α-tosyloxy ketones in solution- and on solid-phase are described. Both olefins and ketones serve as precursors to these relatively stable chemical entities: olefins via a novel one-pot epoxidation, arylsulfonic acid displacement, and oxidation sequence, and ketones by direct exposure to arylsulfonic acids in the presence of diacetoxy iodobenzene. Reaction of these substrates with O-, S-, or N-centered nucleophiles leads to incorporation of the nucleophile with concomitant expulsion of the sulfonate, while exposure to bis-functional nucleophiles furnishes annulated heterocyclic systems. In addition, the reactions of carbon-centered nucleophiles with α-tosylyloxy ketones are also explored. The collated data for all these nucleophiles provide compelling evidence for the proposal that different reaction pathways are followed when α-tosyloxy ketones are engaged by "hard" versus "soft" nucleophiles. The accessibility and site-selectivity of the chemistry demonstrated herein offer the promise of an expanded use for this moiety in solid-phase library construction, in particular, and in the field of organic synthesis, in general.

## Introduction

The burgeoning number of important biological targets[1] compels the synthetic chemist to face the challenge of producing new molecular diversity for chemical biology and drug discovery purposes.[2] As combinatorial chemistry has increasingly come of age over the past decade,[3] these endeavors can take multiple forms: (a) the discovery and invention of new synthetic methods and cascade reactions for accessing known chemical entities in more efficient ways or to reach new chemical classes; (b) the design and synthesis of unique molecular architectures relevant to biology and medicine; (c) the development of new solid-phase reagents and linkers for applications in library construction;[4] and (d) the development of new methods and technologies that are applicable for the construction of libraries and subsequent biological screening. Taken as a whole, such enabling technologies are considered as a crucial response from chemists to the post-genomic era of drug discovery. Their capacity to expand the role of chemistry in biology and medicine is magnified as synthetic chemists seek rapid access to new areas of chemical space via structural types that complement the molecular diversity obtained from traditional sources such as nature's isolates or single compound-oriented synthesis. Thus, classes of compounds coined as "natural product-like", "privileged structures", or "biologically relevant compounds" are increasingly being designed and targeted for synthesis.[5] With these considerations in mind, we sought new linkers that might enable and facilitate the construction of such libraries containing molecular diversity.

Our criteria for the design of a new linker for solid-phase synthesis included the following considerations: (a) it should be seamless, acting as a reagent during its introduction and imparting no chemical signature upon its departure; (b) simultaneously, it should play a critical role in mediating the reactivity of the substrate; and (c) when applied to solid-phase synthesis, the chemistry involved should be novel, not merely a transfer of previously reported protocols. This rational approach to linker design set the stage for the development of chemistry with applications to both conventional solution-phase organic synthesis and combinatorial chemistry.

In considering the type of substrates to be targeted, we limited ourselves to what we term as "privileged synthons". In other words, the class of organic substrates to be loaded onto the solid-phase should permit the rapid (two steps or less) construction

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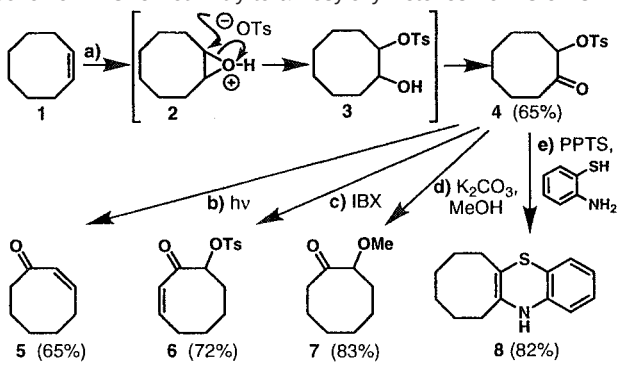
of motifs found in a variety of biologically active molecules (privileged structures). We had originally been attracted by a number of potential candidates[6] accessible through the use of an α-halo ketone scaffold; however, this entity suffers due to a lack of consistency because of the variety of positions and modes of reaction that are available.[7] Conversely, we felt the reactions of α-sulfonyloxy ketones with nucleophiles, which have been rather sporadically explored with the notable exception of the comprehensive work of R. V. Hoffman et al.[7−8] in the arena of α-nosyloxy ketones, may provide a more consistent reaction manifold. In addition, several tantalizing observations[7−10] persuaded us that this was potentially a fertile field to embrace. Thus, by tapping into and elaborating upon the rich chemistry of α-sulfonyloxy ketones, we were afforded an attractive linker that met the stringent requirements of our initial design criteria. Herein, we present a full account of our investigations into the solution- and solid-phase chemistry of α-tosyloxy ketones leading to an array of biologically relevant heterocycles via a cascade "heterocyclic-release" strategy[11] and an approach toward the synthesis of enediynes.

## Results and Discussion

**1. Solution-Phase Chemistry of α-Tosyloxy Ketones and Loading onto Solid Support.** Because of the widespread availability of olefins, we focused our attention on the development of a mild, one-pot protocol for their conversion to α-tosyloxy ketones. Two methods are known for the synthesis of α-sulfonyloxy ketones: (a) treatment of ketones and enol ethers with hypervalent iodine reagents;[12] and (b) oxidation of enol esters, enol ethers, and enamines with arylsulfonyl peroxides.[13] To develop a mild route to α-sulfonyloxy ketones from olefins, we considered the opening of epoxides with *p*-toluenesulfonic acid (*p*-TsOH). Predictably, we found that if excess water was present during the epoxide opening with *p*-TsOH, a 1,2-diol was formed. If, however, there was only very little or no water available, then epoxide opening with *p*-TsOH led smoothly to an α-tosyloxy alcohol which could easily be oxidized to the coveted α-sulfonyloxy ketone. Thus, cyclooctene (**1**) could be easily converted to the α-sulfonyloxy ketone **4** in 65% yield upon sequential treatment with DMDO,[14] *p*-TsOH, and DMP[15] (Scheme 1) (for abbreviations of reagents and protecting groups, see legends in schemes). In contrast to the corresponding α-halo ketone which is known to exhibit lability, **4** was a remarkably stable crystalline solid which could be stored at room temperature unprotected from light.

***Scheme 1.*** One-Pot Entry to α-Tosyloxy Ketones from Olefins[a,b]




[a] Reagents and conditions: (a) DMDO (1.3 equiv, ca. 0.1 M solution in acetone), $CH_2Cl_2$, 1 h, 25 °C; then *p*-TsOH (5.0 equiv), 12 h, 25 °C; then $NaHCO_3$ (6.0 equiv), DMP (2.0 equiv), 25 °C, 65%; (b) benzene (0.05 M), Hanovia (450 W, medium-pressure Hg lamp), 25 °C, 8 h, 65%; (c) IBX (4.0 equiv every 5 h), *p*-TsOH (cat.), DMSO:fluorobenzene (10:1), 85 °C, 15 h, 72%; (d) $K_2CO_3$ (5.0 equiv), MeOH, 25 °C, 1 h, 83%; (e) 2-aminothiophenol (10 equiv), PPTS (cat.), benzene, reflux (Dean−Stark), 24 h, 82%; DMDO = dimethyldioxirane, *p*-TsOH = *p*-toluenesulfonic acid, DMP = Dess−Martin periodinane, PPTS = pyridinium *p*-toluenesulfonate, IBX = *o*-iodoxybenzoic acid, DMSO = dimethyl sulfoxide. [b] Yields refer to chromatographically and spectroscopically homogeneous material.

Our initial studies using α-tosyloxy ketone **4** to access novel molecular diversity, as depicted in Scheme 1, gave us a glimpse of the rich chemistry of these species. Application of Schaffner's α-sulfonated ketone fragmentation[16] led to the α,*β*-unsaturated ketone **5** in 65% yield upon irradiation of **4** in benzene for 8 h. Our recently reported IBX-based protocol for oxidation adjacent to carbonyl groups[17] proceeded regioselectively in 72% yield furnishing the unsaturated α-tosyloxy ketone **6**. Upon treatment of **4** with $K_2CO_3$ in MeOH, the α-methoxy ketone **7** was obtained in 83% yield.

Encouraged by reactions of *o*-thioaniline with α-halo ketones,[6c] we proceeded to attempt this heterocyclic annulation reaction with our α-tosyloxy ketone (**4**). In the event, treatment of this scaffold (Scheme 1) with *o*-thioaniline in refluxing benzene in the presence of catalytic amounts of PPTS, and azeotropic removal of water led to thiazine **8** in 82% yield. We reasoned that in a matter similar to the reactions reported for several primary α-mesyloxy ketones,[9] the thiol might initiate reaction by directly displacing the tosylate followed by intramolecular condensation of the amine with the ketone under acid catalysis. Finally, imine to enamine tautomerization would account for the observed product.

In light of these promising results, we decided to seek applications of this chemistry on solid-phase paradigms and, therefore, set out to develop a linker which suitably emulated the tosyloxy group. This end was accomplished by synthesizing the immobilized variant to *p*-TsOH as shown in Scheme 2.[18]

Thus, to obtain a resin with the physical properties required for application in SPOS (solid-phase organic synthesis), we

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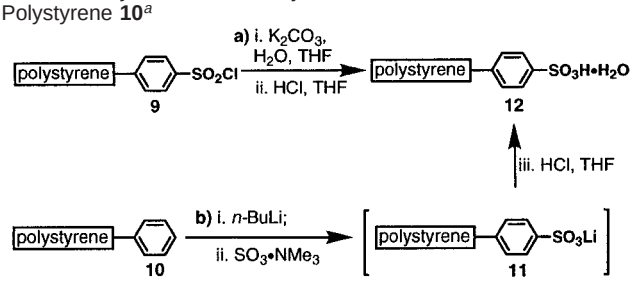
***Scheme 2.*** Synthesis of Resin-bound Sulfonic Acid **12** from Commercially Available Sulfonyl Chloride Resin **9** or from Polystyrene **10**[a]



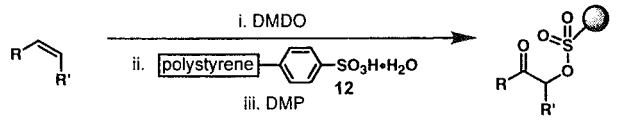

[a] Reagents and conditions: (a) (i) $K_2CO_3$ (2.4 mmol/g of resin, 1.2 equiv), $H_2O$/THF (1:3), 25 °C, 24 h; (ii) 6 N aqueous HCl, THF, 25 °C, 3 h; (b) (i) *n*-BuLi (11.8 mmol/g of resin), TMEDA (9.5 mmol/g of resin), cyclohexane, 65 °C, 4.5 h; (ii) $SO_3•NMe_3$ (5.0 mmol/g of resin), THF, 25 °C, 8 h; (iii) 6 N aqueous HCl, THF, 3 h.

adopted two equally viable methods. In the first approach, polystyrene (**10**) was lithiated with *n*-BuLi and quenched with $SO_3•NMe_3$ [19] to furnish resin salt **11**, which was exposed to 6 N aqueous HCl in THF to afford sulfonic acid resin **12**. Alternatively, commercially available sulfonyl chloride resin **9** was hydrolyzed with $K_2CO_3$ in water/THF, followed by exposure to 6 N aqueous HCl in THF to give resin **12**, identical by IR spectroscopy to the one that was prepared from polystyrene. Elemental analysis revealed a similar content of 1.9−2.1 mmol $SO_3H$ per gram for both resins.

By enlisting the same one-pot protocol as described in the solution-phase for cyclooctene, cyclohexene (**15**) was loaded onto resin **12** to furnish α-sulfonyl ketone **16** (Table 1). As shown in Table 1, a variety of olefins may be loaded onto the solid support in a similar fashion. In addition, cis- and trans-olefins (entries 4 and 5, Table 1) exhibit similar loading efficiencies.

To expand the database of suitable starting materials, the PhI(OAc)$_2$-mediated procedure,[20] presented in Table 2, was efficaciously exploited to smoothly accomplish the loading of a variety of ketones. Thus, by treating the sulfonic acid resin **12** with PhI(OAc)$_2$ in MeCN at ambient temperature, polymer-bound Koser's reagent[20] (**29**) was formed, which upon exposure to various ketones gave the desired α-sulfonyloxy product (Table 2). In addition, through adaptation of the elegant method developed by Moriarty et al.,[12b] we were able to show that in cases where regiospecific generation of the trimethylsilyl enol ether was readily achieved,[21] selective loading of unsymmetrical ketones onto the resin could be attained (Table 2, entry 13). In the entries of both Tables 1 and 2, loading efficiencies were calculated by measuring the amount of product obtained upon cleavage with $K_2CO_3$ in THF/$H_2O$. For nitrogen-containing substrates, loading efficiencies were also determined by elemental analysis. For a number of examples, the loading values obtained by aqueous $K_2CO_3$-mediated cleavage were consistently 5% lower than those obtained by elemental analysis, thus, justifying use of the former method as a conservative measure of loading.

***Table 1.*** One-Pot Loading of α-Sulfonyloxy Ketones onto Sulfonic Acid Resin from Olefins and Epoxides[a]




| Entry | Olefin/Epoxide | Product | Loading(mmol/g)[b] |
|---|---|---|---|
| 1 | 13 | 14 | 0.98 |
| 2 | 15 | 16 | 0.91 |
| 3 | 1 | 17 | 0.88 |
| 4 | 18 | 19 | 0.95 |
| 5 | 20 | 19 | 0.95 |
| 6 | 21 | 22 | 0.89 |
| 7 | 23 | 24 | 0.93[c] |
| 8 | 25 | 26 | 1.14[d] |
| 9 | 27 | 28 | 1.04 |

[a] Reagents and conditions: (i) olefin (2.5 equiv), DMDO (4.0 equiv, ca. 0.1 M solution in acetone), $CH_2Cl_2$, 25 °C, 1 h; (ii) resin **12** (1.0 equiv, based on ca. 1.0 mmol/g loading), 25 °C, 4 h; (iii) $NaHCO_3$ (6.0 equiv), DMP (2.0 equiv), 25 °C, 12 h. [b] Based on yield of α-hydroxy ketone obtained after treatment with $K_2CO_3$ in $H_2O$/THF. [c] 2:1 mixture of regioisomers obtained after cleavage with $K_2CO_3$ in $H_2O$/THF. [d] Loading was estimated by cleavage with $K_2CO_3$ in MeOH in this case.

**2. The "Heterocycle-Release" Strategy in Solid-Phase Organic Synthesis.** Using scaffold **19** (Scheme 3), we probed the question of whether α-sulfonyloxy ketones could be excised from the solid support as easily as they were dismantled in solution (Scheme 1). As shown in Scheme 3, a variety of simple functionalizing cleavage options were exercised. Thus, carboxylic acids, phenols, thiols, and amines were all successfully employed to furnish the corresponding α-substituted ketones (e.g. **53**−**55**, **58**, and **59**) in high yields. Furthermore, photo-

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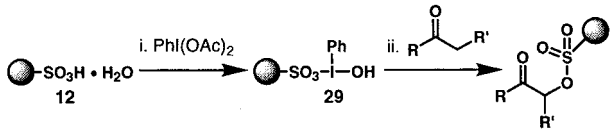
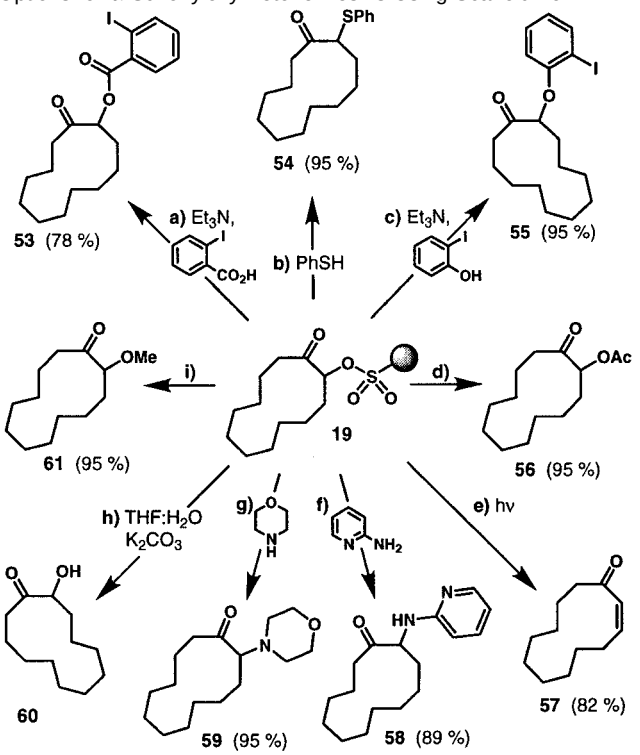
***Table 2.*** Loading of α-Sulfonyloxy Ketones onto Polystyrene Sulfonic Acid Resin **12** from Ketones Using $PhI(OAc)_2$[a]




| Entry | Ketone | Product[a] | Loading(mmol/g)[b] |
|---|---|---|---|
| 1 | **31** | **14** | 1.11 |
| 2 | **30** | **16** | 0.95 |
| 3 | **32** | **33** | 0.74 |
| 4 | **34** | **35** (1 : 2)[d] | 0.38 |
| 5 | **36** | **37** | 1.11[c] |
| 6 | **38** | **39** | 0.71 |
| 7 | **40** | **41** | 0.78 |
| 8 | **42** | **43** | 0.78[e] |
| 9 | **44** | **45** | 0.93 |
| 10 | **46** | **47** | 0.89 |
| 11 | **48** | **49** | 0.90 |
| 12 | **50** | **26** | 0.31 |
| 13 | **51** | **52** | 0.94 |

[a] Reagents and conditions: (i) resin **12** (1.0 equiv), $PhI(OAc)_2$ (2.5 equiv), MeCN, 25 °C, 3 h; (ii) ketone (2.5−10.0 equiv), 8 h. [b] Determined by cleavage by $K_2CO_3$ in $H_2O$/THF. [c] Determined by elemental analysis, value obtained by cleavage = 1.05 mmol/g. [d] Mixture of regioisomers. [e] Estimated by mass gain due to lability under standard cleavage protocols.

***Scheme 3.*** Demonstration of the Functionalizing-Cleavage Options for α-Sulfonyloxy Ketone Resins Using Scaffold **19**[a,b]



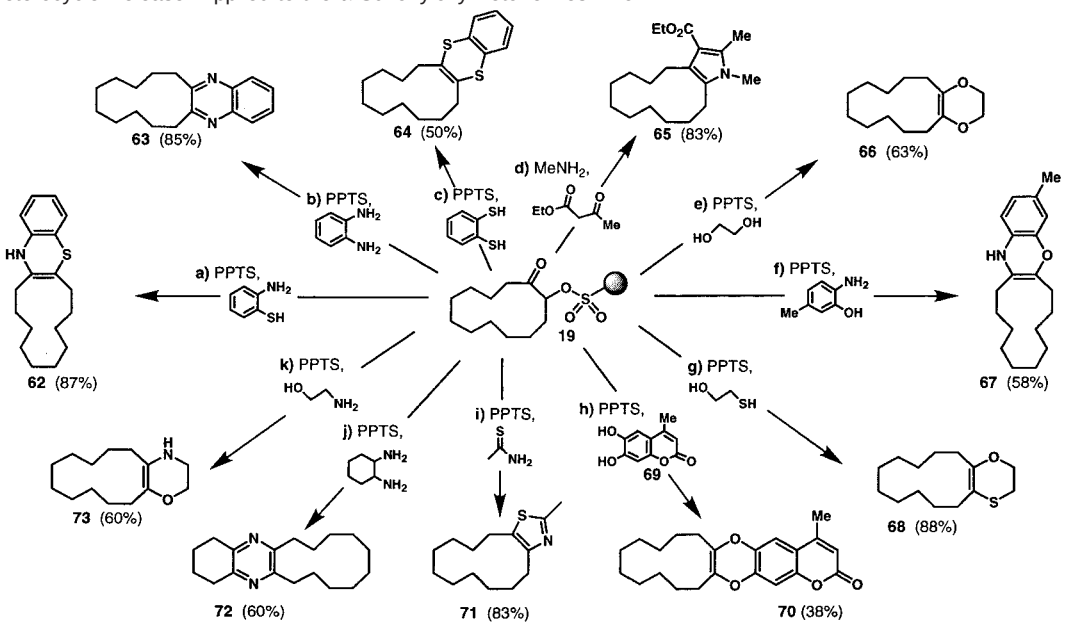

[a] Reagents and conditions: (a) 2-iodobenzoic acid (10 equiv), $Et_3N$ (5.0 equiv), toluene, reflux (Dean−Stark), 16 h, 78%; (b) thiophenol (10 equiv), benzene, reflux, 12 h, 95%; (c) 2-iodophenol (10 equiv), $Et_3N$ (5.0 equiv), toluene, 90 °C, 8 h, 95%; (d) $K_2CO_3$ (10 equiv), MeOH, 25 °C, 8 h; then AcOH, 25 °C, 5 h, 95%; (e) benzene, hanovia (450 W, medium-pressure Hg lamp), 45 °C, 6 h, 82%; (f) 2-aminopyridine (10 equiv), benzene, reflux, 16 h, 89%; (g) morpholine (10 equiv), $CH_2Cl_2$, 25 °C, 12 h, 95%; (h) $K_2CO_3$ (1.0 equiv), THF/$H_2O$ (1:1), reflux, 30 min, 95%; (i) $K_2CO_3$ (5.0 equiv), MeOH, 25 °C, 4 h, 95%. [b] Yields refer to chromatographically and spectroscopically homogeneous material.

release of α,β-unsaturated ketone **57** ensued in 82% yield upon irradiation of **19** in benzene for 6 h. Rapid cleavage to the α-hydroxy ketone **60** was realized upon treatment with $K_2CO_3$ in THF/$H_2O$. Finally, treatment of **19** with $K_2CO_3$ in MeOH led to either the α-methoxy ketone **61** upon filtering through a pad of silica or the α-acetoxy ketone **56** after treatment with 90% AcOH; both products were furnished in near quantitative yields. A mechanistic rationale for the formation of these last two products is shown in Scheme 7.

Confident that our solid-bound α-tosyloxy ketone **19** was emulating its solution-phase relatives, we evaluated a strategy for the release of heterocycles from the solid support based upon the mechanistic analysis depicted in Figure 1.

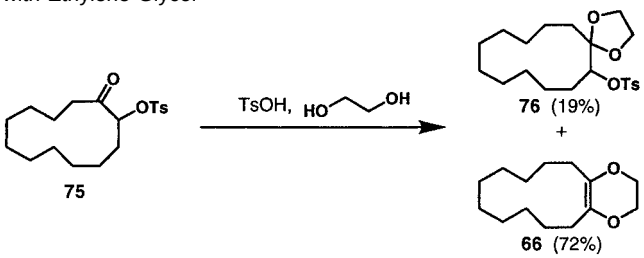
Pleasantly, we found that this heterocycle-release concept allows for the generation of a plethora of ubiquitous and valuable heterocycles. Scheme 4 provides a snapshot of some of the explored possibilities. Thus, dihydrodioxine **66** and dioxine **70** ring systems were released from the resin simply by heating with ethylene glycol or 4-methylesculetin (**69**), respectively, in the presence of catalytic amounts of PPTS in toluene. In the solution-phase version of this cyclo-release reaction employing α-tosyloxy ketone **75** (Scheme 5), significant amounts of a by-product, ketal **76** (19%), were formed in addition to the desired dioxane **77** (72%). In the solid-phase reaction, however, only the heterocycle **66** was obtained (63%), as formation of the ketal

***Scheme 4.*** "Heterocycle-Release" Applied to the α-Sulfonyloxy Ketone Resin **19**[a,b]



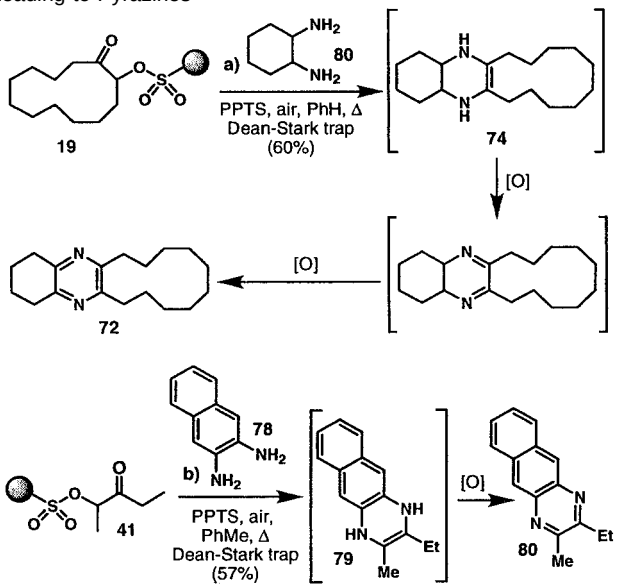

[a] Reagents and conditions: (a) 2-aminothiophenol (10 equiv), PPTS (cat.), benzene, reflux (Dean−Stark), 24 h, 87%; (b) 1,2-diaminobenzene (10 equiv), PPTS (cat.), toluene, reflux (Dean−Stark), 16 h, 85%; (c) 1,2-benzenedithiol (10 equiv), PPTS (cat.), benzene, reflux, 16 h, 50% **64** + ca. 50% of exo-heterocyclic olefin (cis/trans mixture); (d) ethylacetoacetate (20 equiv), $MeNH_2$ (20 equiv, 40% solution in $H_2O$), toluene, 60 °C, 24 h, 83%; (e) ethylene glycol/benzene (1:1), PPTS (cat.), 90 °C, 12 h, 63%; (f) 2-amino-5-methylphenol (10 equiv), PPTS (cat.), benzene, reflux (Dean−Stark), 24 h, 58%; (g) 2-mercaptoethanol (10 equiv), PPTS (cat.), benzene, reflux (Dean−Stark), 16 h, 88%; (h) 4-methylesculetin (**69**) (10 equiv), PPTS (cat.), benzene/DMSO (10:1), 85 °C, 24 h, 38%; (i) thioacetamide (10 equiv), PPTS (cat.), benzene, reflux (Dean−Stark), 36 h, 83%; (j) 1,2-diaminocyclohexane (10 equiv, cis/trans), PPTS (cat.), benzene, reflux (Dean−Stark), 24 h, 60%; (k) ethanolamine (10 equiv), PPTS (cat.), benzene, reflux (Dean−Stark), 36 h, 60%; PPTS = pyridinium *p*-toluenesulfonate; DMSO = dimethyl sulfoxide. [b] Yields refer to chromatographically and spectroscopically homogeneous material.

***Scheme 5.*** Solution-Phase Reaction of α-Tosyloxy Ketone **75** with Ethylene Glycol[a,b]




[a] Reagents and conditions: $TsOH \cdot H_2O$ (0.2 equiv), ethylene:benzene (1:1), 90 °C, 12 h, 19% **76**, 72% **66**. [b] Yields refer to chromatographically and spectroscopically homogeneous materials.

***Scheme 6.*** Proposed Mechanism for the Cascade Reaction Leading to Pyrazines[a,b]




[a] Reagents and conditions: (a) 1,2-diaminocyclohexane (10 equiv), PPTS (cat.), air, benzene, reflux, 24 h, 60%; (b) 2,3-diamino-naphthalene (10 equiv), PPTS (cat.), air, PhMe, reflux, 20 h, 57%. [b] Yields refer to chromatographically and spectroscopically homogeneous materials.

does not result in release from the resin, thus demonstrating an advantage of carrying out this reaction on solid-phase. Dihydro-oxazine ring systems, such as **73**, were similarly accessible from resin **19** upon treatment with 2-aminoethanol in benzene (Scheme 4). The fused thiazole **71** was constructed by heating **19** with excess thioacetamide, while treatment with 1,2-dithio-benzene or 2-mercaptoethanol led to the thianthrene derivative **64** and the 1,4-oxathiene **68**, respectively. Access to the benz-oxazine and benzothiazine systems **67** and **62** was accomplished by exposing resin **19** to 2-amino-5-methylphenol and 2-amino-thiophenol, respectively. Treatment of **19** with ethyl acetoacetate and methyl amine furnished the penta-substituted pyrrole **65** in 83% yield. Remarkably, pyrazine **72** and benzopyrazine **63** were fabricated directly from **19** simply upon treatment with 1,2-diaminocyclohexane and 1,2-diaminobenzene, respectively, in refluxing benzene or toluene and in the presence of air. A plausible mechanistic pathway (see Scheme 6) for this cascade construction of pyrazines involves initial formation of the tetrahydropyrazine **74** followed by aerial oxidation to effect the further conversions ultimately responsible for the formation of pyrazine **72**. In the case of the benzopyrazines, as exemplified by **63** (Scheme 4) and **80** (Scheme 6), only a single oxidation is required to yield the observed product. To the best of our knowledge, the direct synthesis of all of these heterocyclic systems from α-sulfonyloxy ketones is unprecedented.[22] Furthermore, we have found that by utilizing a polymer-bound

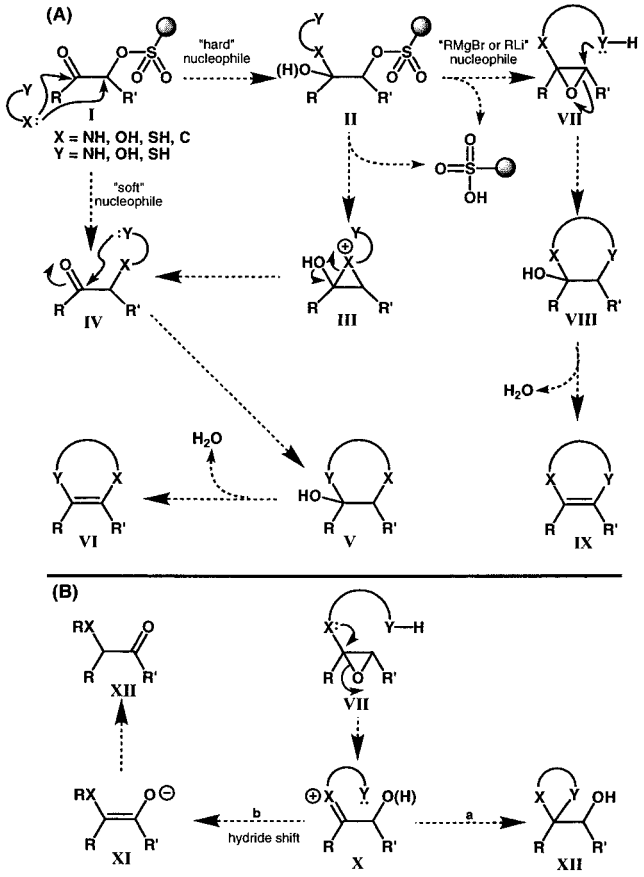
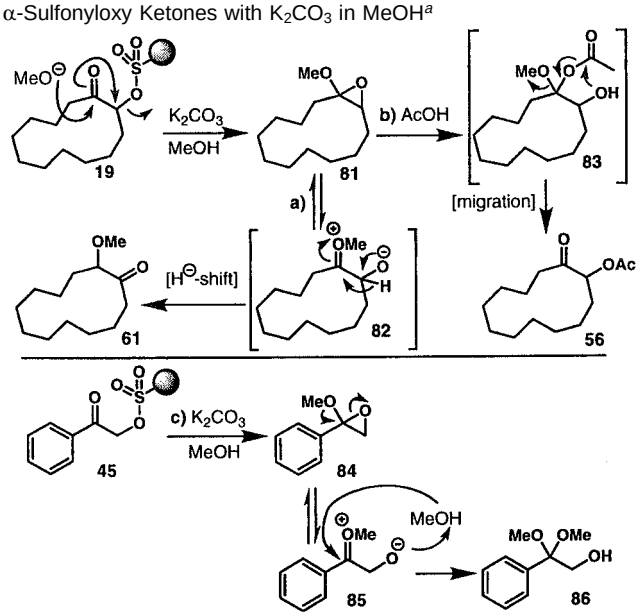


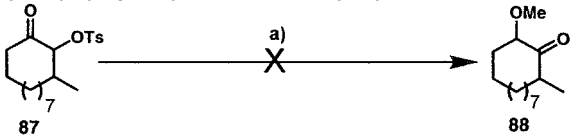

***Figure 1.*** (A) Mechanistic rationale for the different pathways available by which nucleophiles can attack α-tosyloxy ketones which is dependent on the nature of the nucleophile. (B) Rationale to explain observation of anomalous products **7**, **61** (path b), and **76** (path a).

***Scheme 7.*** Mechanistic Rationale for the Reaction of α-Sulfonyloxy Ketones with $K_2CO_3$ in MeOH[a]




[a] Reagents and conditions: (a) see Scheme 4; (b) see Scheme 4; (c) $K_2CO_3$, MeOH, 25 °C, 12 h, 90%.

***Scheme 8.*** Attempt to Confirm Involvement of a Hydride Shift in the Mechanism for the Formation of **61** from α-Tosyloxy Ketone **19** by Employing Unsymmetrical α-Tosyloxy Ketone **87**[a]




[a] Reagents and conditions: (a) $K_2CO_3$ (1.0 equiv), anhydrous MeOH, 25−40 °C, 12 h.

isocyanate (Aldrich) or liquid−liquid extraction, excess reagents can be easily removed, thus potentially facilitating high throughput applications of this method.

Returning to the observed products obtained upon treatment of **4** or **19** with $K_2CO_3$ in MeOH which furnished the α-methoxy ketones **7** and **61** in yields of 83 and 95%, respectively (Schemes 1 and 3), we reasoned that the formation of **61** involved initial attack of methoxide at the ketone followed by displacement of the tosylate to furnish epoxide **81** (Scheme 7). Indeed, the latter compound could be isolated by removal of methanol and immediate dissolution into $CDCl_3$, and characterized by NMR and IR spectroscopy. However, epoxide **81** proved unstable, rearranging on silica, or within 24 h upon storage, to the α-methoxy ketone **61**, presumably via a mechanism involving a hydride shift. This mechanistic rationale, which is supported by previously reported observations of hydride shifts under similar circumstances,[23] is illustrated in Scheme 7. In a quest to substantiate this postulate, the unsymmetrical methyl-substituted α-tosyloxycyclododecanone (**87**, Scheme 8) was synthesized and subjected to the action of potassium carbonate in methanol for 24 h. However, no significant reaction was observed in this scenario even upon warming the mixture to 40 °C, suggesting that substitution at the 3-position critically undermines the expected reaction progress (see Scheme 8).

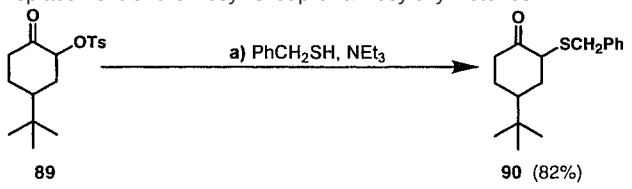
The reactivity profile observed in this case was slightly surprising on a number of levels. First it had been proposed[7,24] that α-tosyloxy and α-mesyloxy ketones were not generally the subject of nucleophilic attack at the carbonyl, but instead were attacked via an $S_N2$ displacement at the site of attachment of the activated α-leaving group. Second, our later investigations utilizing this reaction as a means to assess resin loading revealed that all other substrates, encompassing a range of cyclic, acyclic, and activated examples, afforded exclusively the α-hydroxy dimethylketal instead of the α-methoxy ketone. For example, exposure of **45** (Scheme 7) to $K_2CO_3$ in MeOH led to the isolation of **86**. It is these observed products that are consistent with the previously reported reactions of 2-nosyloxy ketones that were also shown to proceed via the methoxy epoxides such as **81** (Scheme 7),[7b,8] to afford α-hydroxy dimethylketals when treated with methanolic $K_2CO_3$. Hence, we were faced with questions that sought to probe the scope and generality of reactions observed in larger (8- to 12-membered) ring α-tosyloxy ketones where transannular strain provides an additional feature in guiding reactions down a particular

(22) Several of these compounds have been accessed from (i) α-hydroxy ketones: Fjeldskaar, I. R.; Rongved, P.; Skattebøl, L. *Acta Chem. Scand.* **1987**, 477; or (ii) α-haloketones.[6c]

(23) Stevens, C. L.; Dykstra, S. J. *J. Am. Chem. Soc.* **1954**, *76*, 4402. House, H. O.; Prabhu, A. V.; Wilkins, J. M.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 3067. Philipson, N.; Anson, M. S.; Montana, J. G.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2821.

(24) Creary, X.; Rollin, A. J. *J. Org. Chem.* **1977**, *42*, 4226. It should be noted that for an irreversible reaction to occur at the carbonyl site, in this particular case, the nucleophile would be required to attack the more hindered face of the molecule so that an anti-periplanar arrangement of the resultant alkoxide with the tosylate leaving group could be attained. The $sp^2$ carbons in bicycles of this nature are well known to be pyramidalized, and as such nucleophiles are precluded from attacking the more congested face.

***Scheme 9.*** Thiols React Rapidly and Chemoselectively by Direct Displacement of the Tosyl Group of α-Tosyloxy Ketones[a,b]

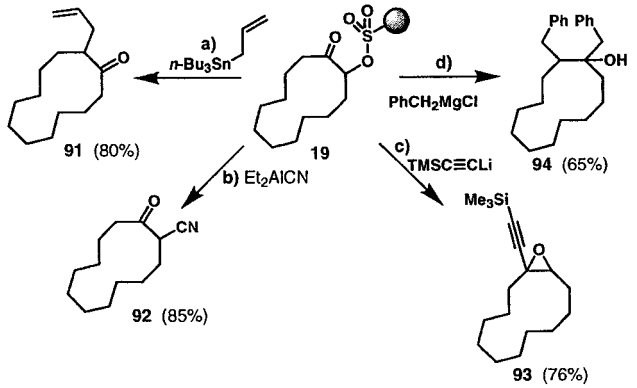



[a] Reagents and conditions: (a) $PhCH_2SH$ (1.5 equiv), $NEt_3$ (1.5 equiv), acetone, room temperature, 2 h. [b] Yield refers to chromatographically and spectroscopically homogeneous material.

pathway. At the same time, we were also aware of the results of Simmons et al.[9] which had demonstrated that on a steroid scaffold the α-mesyloxy ketone moiety reacted very rapidly with thiols to furnish the products of $S_N2$ displacement of the primary mesylate. It was in the context of these disparate and sometimes conflicting findings that we sought to establish a greater degree of understanding of the reactivity of α-tosyloxy ketones with nucleophiles through a systematic study of other examples, including an unsymmetrical substrate.

First, the observation of Simmons et al.[9] regarding the specificity of attack by thiols at the carbon bearing the primary mesylate of α-mesyloxy ketones was found to extend to our more substituted α-tosyloxy ketones, such as **89**, that reacted smoothly with benzyl mercaptan in the presence of triethylamine at room temperature to afford **90** in high yield (see Scheme 9). In addition to the other examples where sulfur acts as the nucleophile (e.g., formation of **8**, **54**, **62**, **64**, **68**, and **71**, Schemes 1, 3, and 4), the formation of **53** also likely results from a simple $S_N2$ mode of attack because the alternatives involving intermediates of type **III** or **X** (illustrated in Figure 1) would both place a positively charged oxygen next to a carbonyl group, a species which represents a rather high energy option. The reaction of other "soft" nucleophiles (e.g., furnishing products **55**, **56**, **58**, and **71**, Schemes 3 and 4) has the possibility of reacting through direct displacement of the tosylate or the alternative pathways described in Figure 1 via either intermediate **III** or intermediate **X**. The resin-bound ketone **19** was also reacted with carbon-centered nucleophiles in a study delineated in the following section. In the case of an organostannane-derived radical and Nagata's reagent ($Et_2AlCN$), a direct displacement of the tosyl function was once again observed exclusively, yielding compounds **91** and **92** (Scheme 10), respectively. In combination, these results clearly indicate that nucleophiles with "soft" character react quite specifically by direct displacement of the tosyl group (Figure 1). At the opposite end of the spectrum, "hard" carbon-centered nucleophiles, such as Grignard reagents and lithium acetylides, react at low temperatures exclusively at the carbonyl carbon to afford α-hydroxytosylates in high yields (see Table 3). In this context, Reitz et al.[25] have reported work on simple unactivated resin-bound tosylates, indicating that scission of the tosyl function is not seen upon exposure to Grignard reagents, sodium borohydride, or Suzuki couplings. Collation of the combined results obtained when using the broad array of nucleophiles in this method led us to propose the alternate pathways illustrated in Figure 1, with key intermediates isolated and characterized in a number of instances. In addition, we highlight two cases where

***Scheme 10.*** Functionalizing-Cleavage Options by Carbon−Carbon Bond-Forming Reactions with the α-Sulfonyloxy Ketone Resin **19**[a]




[a] Reagents and conditions: (a) allyltri(*n*-butyl)tin (5.0 equiv), AIBN (cat.), benzene, 80 °C, 24 h, 80%; (b) $Et_2AlCN$ (5.0 equiv), toluene, 0−25 °C, 1 h, 85%; (c) lithium trimethylsilylacetylide (5.0 equiv), THF, 0−25 °C, 3 h, 76%; (d) benzylmagnesium chloride (5.0 equiv), THF, 0−25 °C, 2 h, 65%. [b] Yields refer to chromatographically and spectroscopically homogeneous materials.

the combination of an oxygen-centered nucleophile attacking an 8- or 12-membered α-tosyloxy ketone leads to anomalous reactivity patterns (Figure 1B). The exact mechanistic intricacies of the species residing closer to the boundary between hard and soft character require further investigation, potentially on a case by case basis, but the selectivity and the switch in chemoselectivity seen as one approaches either of the opposing dipoles of nucleophilic character endow this motif with remarkable versatility.

**3. Formation of Carbon−Carbon Bonds from α-Tosyloxy Ketones: Synthesis of Enediynes and Related Systems.** To expand the scope of the α-tosyloxy ketones as substrates for organic synthesis, we focused our attention on carbon nucleophiles. Our first foray into the development of carbon−carbon bond-forming reactions with α-sulfonyloxy ketones as substrates is shown in Scheme 10. Gratifyingly, treatment of **19** with allyltri(*n*-butyl)tin in the presence of catalytic amounts of AIBN resulted in the release of α-allyl ketone **91** in 80% yield. Reaction of the Nagata reagent ($Et_2AlCN$) with resin **19** afforded the α-cyano ketone **92** in 85% yield, while treatment with TMSC≡CLi gave rise to the epoxide **93** in 76% yield. Isolation of the epoxide once again demonstrated the viability of the mechanistic analysis outlined in Figure 1 by providing support for the intermediacy of **VII**. Treatment of resin-bound α-sulfonyloxy ketone **19** with $PhCH_2MgCl$ at 0 °C led to carbinol **94** in 65% yield.

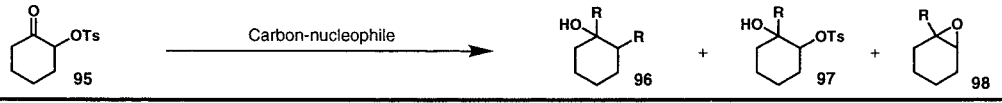
Encouraged by the efficiency of these carbon−carbon bond-forming reactions, and given the importance of enediynes and related systems, we set out to explore conditions which would enable the synthesis of such compounds. Enediynes represent an intriguing class of compounds whose antitumor properties have been extensively investigated.[26] Libraries of enediynes and precursors thereof might, therefore, be useful synthetic intermediates and biological tools, with some small molecule members of this class already known as photoactive agents against certain proteins.[27] In an effort to develop enabling

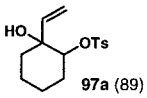
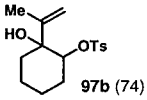
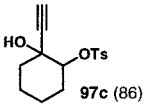
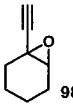
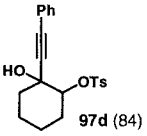
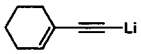
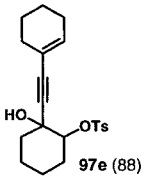
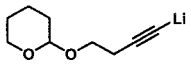
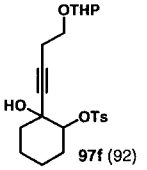
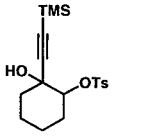
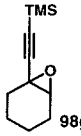
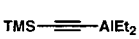
(25) (a) Teuter, J. K.; Nortey, S. O.; Baxter, E. W.; Leo, G. C.; Reitz, A. B. *Tetrahedron Lett.* **1998**, *39*, 975. (b) Baxter, E. W.; Reuter, J. K.; Nortey, S. O.; Reitz, A. B. *Tetrahedron Lett.* **1998**, *39*, 979.

(26) (a) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387. (b) Smith, A. L.; Nicolaou, K. C. *J. Med. Chem.* **1996**, *39*, 2103.

(27) Jones, G. B.; Wright, J. M.; Plourde, G.; Purohit, A. D.; Wyatt, J. K.; Hynd, G.; Fouad, F. *J. Am. Chem. Soc.* **2000**, *122*, 9872.

***Table 3.*** Exploration of the Reactivity of α-Sulfonyloxy Ketone **95** toward Carbon-Nucleophiles[a]




| Entry | Carbon-nucleophile | Equivalents | Conditions | Products (Yield%)[b] | | |
|---|---|---|---|---|---|---|
| 1 |  | 1.25 | THF, -40 to 0 °C, 0.5 h |  **97a** (89) | | |
| 2 |  | 2.0 | THF, 0 °C, 0.5 h |  **97b** (74) | | |
| 3 |  | 1.25 | THF, -40 to 0 °C, 0.5 h |  **97c** (86) | | |
| 4 |  | 2.0 | THF, -78 to 25 °C, 1 h | **97c** (77) |  **98c** (20) | |
| 5 |  | 5.0 | THF, 25 °C, 12 h | **96c** (40) | **97c** (20) | **98c** (15) |
| 6 |  | 1.2 | THF, -40 to -10 °C, 0.5 h |  **97d** (84) | | |
| 7 |  | 1.2 | THF, -40 to -10 °C, 0.5 h |  **97e** (88) | | |
| 8 |  | 1.2 | THF, -40 to -10 °C, 0.5 h |  **97f** (92) | | |
| 9 |  | 1.2 | THF, -40 to -10 °C, 0.5 h |  **97g** (71) | | |
| 10 |  | 2.0 | THF, -78 to 25 °C, 1 h | **97g** (58) |  **98g** (41) | |
| 11 |  | 2.0 | THF, -78 to 25 °C, 3 h | **97g** (10) | **98g** (85) | |
| 12 |  | 5.0 | THF/PhMe, -78 to 25 °C, 12 h | **97g** (65) | **98g** (0) | |

[a] Reactions were carried out on 1.0−11.2 mmol scale. [b] Yields refer to chromatographically and spectroscopically homogeneous compounds.

methods for constructing libraries of such compounds, we targeted stable enediyne precursors to be released from the solid-phase and converted to enediynes by a single subsequent step; the concept is shown in Figure 2.

A library of dialkynyl alcohols (**C**) could be synthesized in a stepwise fashion from resin-bound α-sulfonyloxy ketones (**A**) via monoalkynyl derivatives (**B**). After additional diversity introduction and release from the resin, dehydration of the tertiary alcohol would complete the enediyne library (**D**). A number of solution-phase studies were carried out to gauge the feasibility of the concept and to determine the exact conditions required for each step. As shown in Table 3, using the α-sulfonyloxy ketone **95**, a variety of carbon nucleophiles were screened under several different conditions. It was our hope that

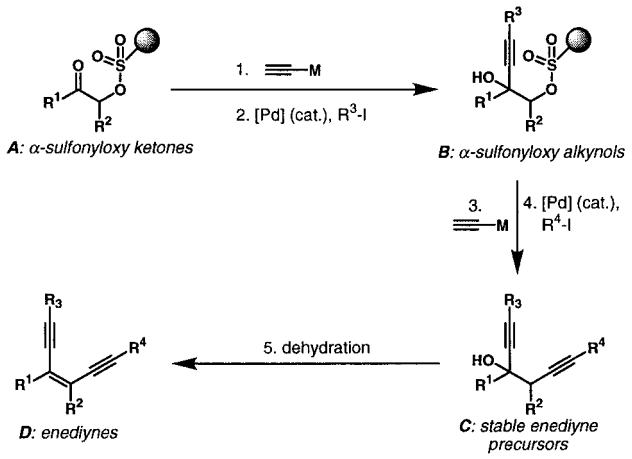


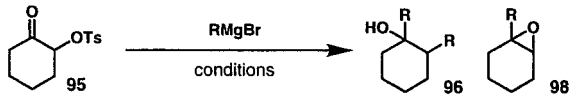

***Figure 2.*** General concept for the synthesis of enediyne libraries from α-sulfonyloxy ketone resins.

we could develop conditions to access compounds of type **96** or **97** selectively and at will (Table 3).

Gratifyingly, the products obtained upon treatment of **95** with a range of Grignard reagents or lithium acetylides at temperatures from −40 to 0 °C were the result of clean monoaddition of the organometallic reagent to the carbonyl; yields of **97a**−**g** ranged from moderate to high. As expected, the lithium acetylides (entries 6−9, Table 3) reacted at lower temperatures than did the related Grignard reagents (entries 1−3, Table 3), and increasing substitution also required a rise in operating temperature (entry 2, Table 3). These products (**97a**−**g**) were readily isolated, purified by column chromatography, and stored without decomposition. However, if the reactions were quenched above 0 °C, the fidelity of the reaction was significantly sacrificed with increasing amounts of the epoxide (**98**) being produced (entries 4 and 10, Table 3). In our preliminary studies, the reactions of cuprates with α-tosyloxy ketones were found to be unsuccessful with almost quantitative recovery of the starting material even after extended reaction times. In an effort to explore further possibilities, the reaction of an organoaluminum species was investigated. Although the use of diethylaluminum trimethylsilylacetylide (entry 12, Table 3) successfully furnished the α-tosyloxy alkynol **97g** in 65% yield, reaction times were longer, and the product was contaminated with trace amounts of a chlorohydrin byproduct (presumably formed via displacement of the tosylate with residual chloride ions from the initial preparation of the organoaluminum species).

Having established a viable route to the α-tosyloxy alkynols (**97**), we focused our attention on finding optimum conditions for the displacement of the tosylate group to form the second desired carbon−carbon bond. This reaction, however, proved to be capricious. After examination of a broad range of conditions, it was determined that refluxing **95** with various Grignard reagents for a short period in ether allowed isolation of the desired dialkynols, but only as a component of a complex mixture (see Table 4). No products arising from an oxyanion-accelerated Cope rearrangement were observed when a vinylic Grignard reagent was utilized (see entries 5 and 6, Table 4). Unfortunately, there was no improvement in the outcome of this reaction when α-tosylhydroxyalkynes (**97**) were employed in the reaction in an attempt to access the mixed dialkynols (**105**). At lower temperatures, substantial starting material was recovered in addition to the product of exchange of alkyne

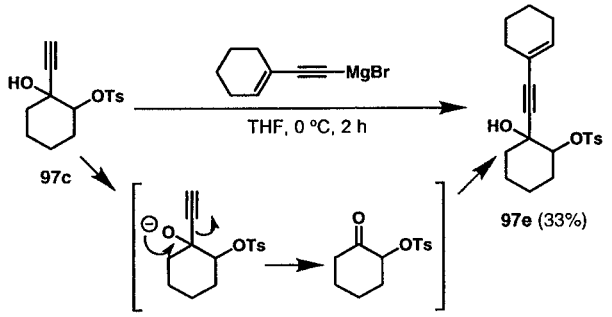
***Table 4.*** Reactions of Grignard Reagents with α-Tosyloxy Ketones[a]




| Entry | RMgBr | Reagent (equiv) | Conditions | Products (Yield)[b] |
|---|---|---|---|---|
| 1 |  | 2.0 | Ether, 50 °C, 120 min | decomposition |
| 2 |  | 3.0 | Ether, 50 °C, 40 min | **96c** (31) |
| 3 |  | 2.0 | Ether, 0 to 25 °C, 105 min | **96c** (5), **98c** (12)[c] |
| 4 |  | 2.0 | THF, reflux, 15 min | **96c** (8)[d] |
| 5 |  | 4.0 | THF, reflux, 30 min | **96a** (45) |
| 6 |  | 4.0 | THF, reflux, 30 min | **96b** (28) |

[a] Reactions were carried out on 1−5 mmol scale. [b] Yields refer to chromatographically and spectroscopically homogeneous compounds. [c] 51% of **95** recovered. [d] 16% of **95** recovered.

***Scheme 11.*** Alkyne Groups Exchange under Reaction Conditions[a,b]

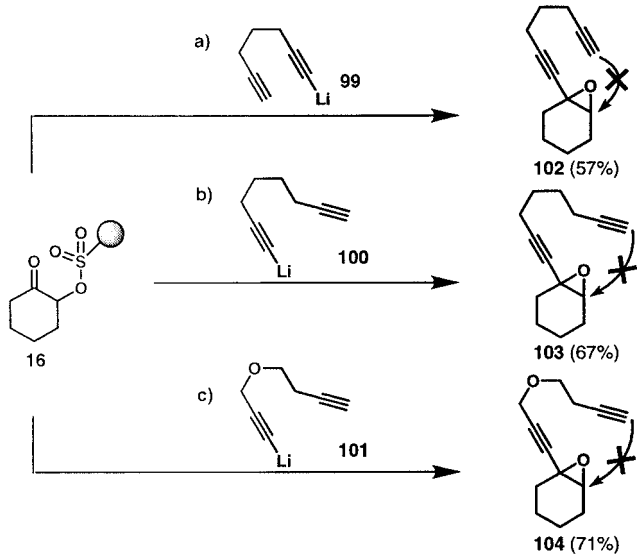



[a] Reagents and conditions: (a) RMgBr (1.5 equiv), 0 °C, 2 h. [b] Yield refers to chromatographically and spectroscopically homogeneous material.

groups (see Scheme 11), and higher temperatures led to complete decomposition. Seeking to overcome this hurdle to directly access the desired cyclic enediynes, the resin-bound α-tosyloxy ketone **14** was treated with a series of bis-alkynes. However, despite repeated attempts, we were unable to access these structural types. Our efforts included use of a variety of bis-alkynes with different metals, with both dimetal diynes in one step, and with mono-metal diynes in two steps via the epoxide. For example, the lithiated alkynes **99**−**101** (Scheme 12) furnished only the corresponding epoxides **102**−**104**. All efforts to close these alkynes to the cyclic carbinols failed, presumably due to geometrical constraints which precluded the bis-alkynes from undergoing the requities 9-*exo*-tet and 10-*exo*-tet cyclizations. The failure to optimize this second step precluded transfer of this chemistry to the solid-phase except in the example described below (Scheme 13). The limitation imposed by this difficulty has encouraged us to envision beginning our next generation of studies by widening the search for alternative strategies to effect the second functionalization and to include an investigation of direct displacement of the tosylate by a softer organometallic reagent such as a stannane (vide infra).

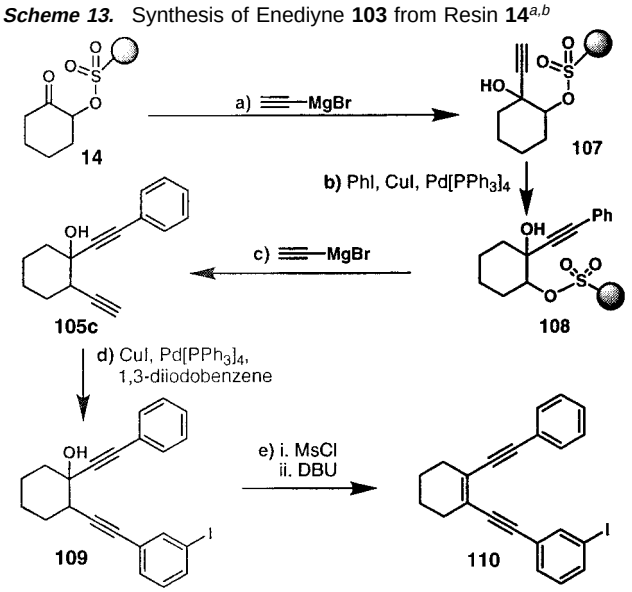
Despite the unsatisfactory outcome of the second organometallic addition step, we wanted to assess the viability of the critical conversion of dialkynols (**98**) to the coveted acyclic enediynes (**106**) for inclusion in a future revised strategy. This

***Scheme 12.*** Attempted Construction of Cyclic Dialkynols from Resin **16**[a,b]




[a] Reagents and conditions: (a) alkynyllithium (3.0 equiv), THF, −78 to 25 °C, 3 h. [b] Yields refer to chromatographically and spectroscopically homogeneous materials.

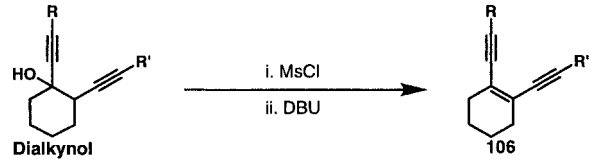
***Scheme 13.*** Synthesis of Enediyne **103** from Resin **14**[a,b]




[a] Reagents and conditions: (a) ethynyl magnesium bromide (1.5 equiv), THF, −40 to 0 °C, 3 h; (b) PhI (1.2 equiv), CuI (0.08 equiv), $Pd[PPh_3]_4$ (0.04 equiv), $Et_3N$ (1.5 equiv), $CH_2Cl_2$, 25 °C, 1 h, estimated by mass gain 73%; (c) ethynyl magnesium bromide (5.0 equiv), PhMe:THF (10:1), reflux, 0.5 h, 15% over three steps; (d) 1,3-diiodobenzene (1.2 equiv), CuI (0.08 equiv), $Pd[PPh_3]_4$ (0.04 equiv), $Et_3N$ (1.5 equiv), $CH_2Cl_2$, 25 °C, 1 h, 95%; (e) (i) MsCl (3.0 equiv), $Et_3N$ (3.5 equiv), $CH_2Cl_2$, 0 °C, 15 min; (ii) DBU (10.0 equiv), 0−25 °C over 12 h, 71%. [b] Yields refer to chromatographically and spectroscopically homogeneous materials.

transformation could be accomplished upon sequential treatment with mesyl chloride followed by DBU as shown in Table 5. Interestingly, some of the prepared enediynes exhibited unexpectedly high lability toward ordinary light. This feature was especially true for the symmetrical enediyne **106a**, which required careful manipulation to avoid decomposition during the work-up and purification procedures. Finally, we sought access to more complex enediyne derivatives by enlisting additional reactions that would permit functionalization and diversification of the terminal alkyne, such as the Sonagashira

***Table 5.*** Synthesis of Enediynes (**106**) from Dialkynols (**96c** and **105a**−**c**)[a,b]




| Entry[a] | Dialkynol | Yield (%) |
|---|---|---|
| 1 | **96c:** R = R' = H | **106a:** 78 |
| 2 | **105a:** R = H, R' = $CH_2CH_2OTBS$ | **106b:** 67 |
| 3 | **105b:** R = TMS, R' = H | **106c:** 54 |
| 4 | **105c:** R = Ph, R' = H | **106d:** 98 |

[a] Reagents and conditions: (i) MsCl (3.0 equiv), $Et_3N$ (3.5 equiv), $CH_2Cl_2$, 0 °C, 15 min; (ii) DBU (10.0 equiv), 0−25 °C over 12 h. [b] Reactions were carried out on 0.05−1.0 mmol scale. Yields refer to chromatographically and spectroscopically homogeneous product.

reaction.[28] Thus, this strategy was tested on the solid-phase by reaction of resin **14** with ethynyl magnesium bromide to afford resin **107** which was subsequently treated with iodobenzene in the presence of catalytic amounts of $Pd[PPh_3]_4$, CuI, and triethylamine to afford resin **108** (which exhibited an IR spectrum identical to the product obtained by treating resin **14** with lithium phenylacetylide). The material was then released from the resin by treatment with ethynyl magnesium bromide to furnish the corresponding dialkynol **105c** in a yield of 15% over three steps. Compound **105c** was further elaborated by a second Sonagashira coupling with 1,3-diiodobenzene to afford **109** (95%), which was successfully dehydrated following the established protocol to yield enediyne **103** in good yield (71%, Scheme 13).

## Conclusion

In this article, we have described a number of synthetically useful aspects of the chemistry of α-tosyloxy carbonyl compounds both in solution- and on solid-phase. The ease of preparation of these substrates either from olefins or ketones, their relative stability, and their chemical versatility allowed the development of several methods for the construction of a variety of compounds. Among the synthetic technologies leading to heterocyclic systems, the construction of pyrazines, phenoxazines, morpholines, thiazoles, and phenthiazines stands out in particular. Unique among the carbon−carbon bond-forming reactions of α-sulfonyloxy ketones are those with acetylenic nucleophiles, which lead selectively and sequentially to monoalkynol, alkyne-epoxy products. Despite a poor result in the further elaboration of these compounds to the dialkynol congeners, a notable aspect of this sequence is its ability to deliver stable enediyne precursors which can easily be converted to the often labile enediyne compounds just prior to their use. The principle of introducing and expanding diversity by elaboration of terminal alkyne functionality using Sonagashira methodology was established for use in a second-generation approach to the synthesis of libraries of enediynes. Of particular interest is the solid-phase version of this chemistry, which utilizes the α-sulfonyloxy carbonyl moiety as both a substrate and a linker. This unique property allows these resins to serve

(28) Sonagashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 3, p 521.

admirably well in a plethora of cyclization, release-based schemes for the construction of molecular diversity and as an enabling technology for combinatorial chemistry. Applications of these enabling technologies to the synthesis of compound libraries for biological screening purposes are anticipated, as are more general uses of this chemistry in the field of organic synthesis.

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**Supporting Information Available:** Experimental details and characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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