A Novel Approach to Cephalosporins From Allenylazetidinones: A New Cyclization Strategy via Tandem Cuprate Addition–Sulfenylation

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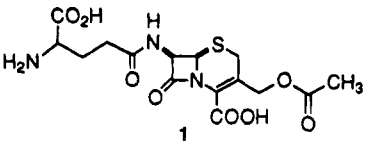
An efficient approach to the synthesis of 3-substituted cephems bearing carbon-based substituents of choice at the C(3) position from inexpensive penicillins is described. The strategy involves the synthesis of an allenylazetidinone from penicillin sulfoxide followed by the addition of an organocuprate at low temperature. Organocuprates undergo 1,4-conjugate addition at the central allenic carbon of the allenylazetidinone to form a carbon–carbon bond which is followed by ring closure *via* an intramolecular sulfenylation reaction. The chemistry has been applied to the synthesis of a variety of 3-substituted cephems bearing substituents such as alkyl, cycloalkyl, aryl, alkenyl, and allyl. Precursors to the synthesis of important antibiotics, *i.e.* Cefadroxil, Cefixime, and Cefzil, are also available from this novel approach. The methodology is not limited to carbon-based 3-substituted cephems, but provides access to some 3-norcephalosporins as well.

Introduction

The unique structural and chemotherapeutic properties of β-lactam antibiotics continue to attract the attention of the synthetic community, since they present a variety of synthetic challenges. In recent years, considerable interest has been focused on the modification of the C(3) position of cephems to obtain cephalosporins with enhanced biological properties. The discovery of cephalosporin C (**1**) , followed by the preparation of 3-methylenecephams **2**, spurred the synthesis of useful antimicrobials modified at C(3′), by displacement of the acetoxy group of **1** with heterocyclic tertiary bases and sulfur nucleophiles, while **2** provided access to a variety of biologically active 3-norcephalosporins.[1] Recently, cephalosporins with all-carbon substituents at the C(3) position have been shown to possess excellent biological profiles,[2] and some representative examples of this class of antibiotics are Cefadroxil (**3**), Cephalexin (**4**), Cefixime (**5**), and Cefzil (**6**). In connection with our studies on β-lactam antibiotics, we were interested in developing a facile methodology toward the synthesis of carbon-based 3-substituted cephems with a major emphasis on developing a practical and cost-effective synthesis of our broad spectrum antibiotic, Cefzil (**6**).[3]



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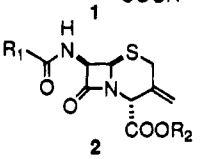

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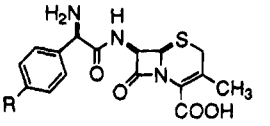
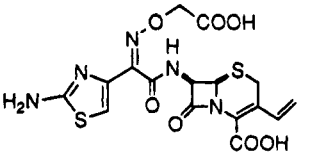


3, R=OH
4, R=H



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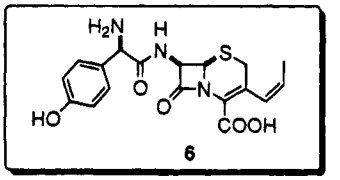

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Previous synthetic methodologies to form a *carbon–carbon* bond at C(3) relied on the following: Friedel–Crafts reactions with 3-[(trifluoroacetoxy)methyl]ceph-2-em-4-carboxylic acids;[4] reactions of 3-formylcephems with stabilized phosphoranes;[5] Wittig reaction of 3-hydroxycephems with stabilized ylides;[6] conjugate additions

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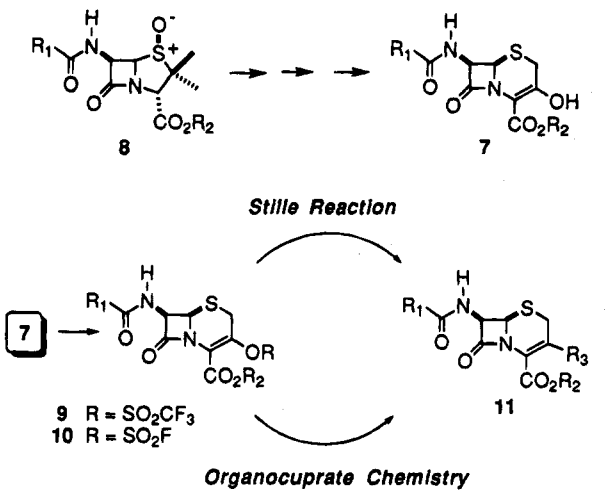
Scheme 1



of organocuprates to 3-chloro- and 3-vinylcephems;[7] and additions of Grignard reagents to 3-formylcephems.[8] Unfortunately, the scope of the above procedures is limited and often cephems are isolated as a mixture of Δ^2 and Δ^3 isomers. Based on the Stille coupling,[9] a general methodology for the synthesis of 3-substituted cephalosporins was reported which utilized 3-trifloxycephems[10] and 3-[(fluorosulfonyl)oxy]cephems[11] as intermediates. Recently, complementary to the palladium approach, we reported the organocuprate-based chemistry to gain access to a variety of 3-substituted cephems.[12] Both strategies employed as their starting material 3-hydroxycephems **7**, readily available from Cephalosporin C or, better from a practical viewpoint, from cheap penicillin sulfoxide (**8**) in a number of steps (Scheme 1).[13]

For a cost-effective synthesis of Cefzil (**6**), we were interested in exploring new chemistry starting from penicillin and bypassing the patented intermediate **7**, while keeping the synthetic steps to a minimum. One of the important reactions in cephalosporin chemistry is the Morin ring expansion of penams into cephems (Scheme 2).[14] This rearrangement, in its several modifications, has allowed the preparation of many semisynthetic cephalosporin antibiotics, including 3-methyl cephems.[15] On the basis of the Morin rearrangement, we envisioned an intramolecular sulfenylation of an allene **14**, as opposed to the alkene moiety in **12**, in conjunction with exogenous nucleophiles. This would allow the introduction of different substituents at C(3), as opposed to the one-carbon fragment that is introduced by the Morin rearrangement. Indeed, the central allenic carbon is susceptible to nucleophilic addition reaction when activated with an electron-withdrawing group,[16] and organocuprates are among the most straightforward reagents for the formation of new carbon–carbon bonds.[17] In view of this, the possibility of adding an organocuprate to the central allenic carbon of **14**, followed by cyclization of copper dienolate **15**, appeared to represent a reasonable strategy for an efficient synthesis of cephems.[18] Herein, we describe the details of this novel approach to synthesize a variety of 3-substituted cephalosporins, including a stereospecific and cost-effective synthesis of Cefzil (**6**), starting from penicillins and utilizing organocuprates.

Results and Discussion

The observation of facile allene formation from vinyl triflates was first described by Stang.[19] Low to moderate yields of allenes were observed when a variety of vinyl triflates were exposed to quinoline at 100 °C. The chemistry was extended by Conway *et al.*, to the synthesis of 3-azido allene **19** from enol triflate **18**, in turn derived from a Staudinger reaction[20] (Scheme 3).

Our synthesis of allenylazetidinones[21] started from the readily available penicillin V (V = phenoxyacetamido) sulfoxide diphenylmethyl ester (**20**). Following Kamiya's procedure,[22] we isolated the disulfide **22** in high yield by refluxing a toluene solution of the sulfoxide **20** and 2-mercaptobenzothiazole in the presence of a Dean–Stark trap. The crystalline disulfide was then treated with ozone followed by reductive workup or under a combination of osmium tetraoxide/sodium periodate oxidative system,[23] to afford amorphous enol azetidinone **24**, as a single geometrical isomer. Treatment of **24** with trifluoromethanesulfonic anhydride (Tf_2O) and Hunig's base (*N,N'*-diisopropylethylamine) in CH_2Cl_2 at low temperature provided isomerically pure enol triflate **26** in high yield. Finally, exposing **26** to 1 mol equiv of triethylamine (TEA) in CH_2Cl_2 at ambient temperature afforded the desired allene **28** in high yield.[24] The NMR spectrum of **28** exhibited a pair of doublets at δ 5.65 and 5.38 with a coupling constant of 15.5 Hz, diagnostic of the cumulene system,[25] and furthermore, the IR spectrum displayed a doublet at 1910 and 1950 cm^{-1}, typical of terminal allenes.[26] Similarly, allene **29** was synthesized from penicillin G (G = phenylacetamido) sulfoxide diphen

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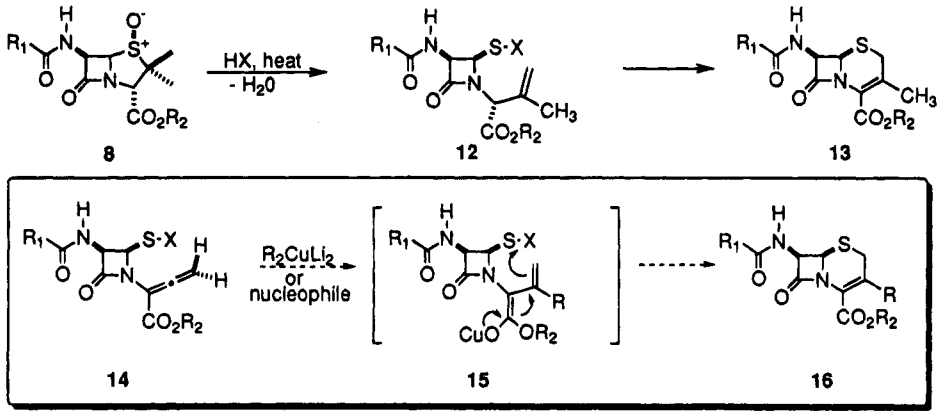
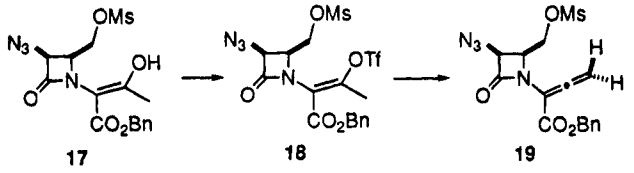
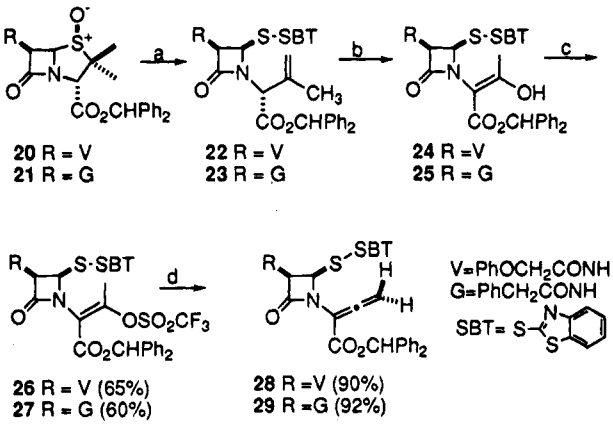
Scheme 2



Scheme 3



Scheme 4

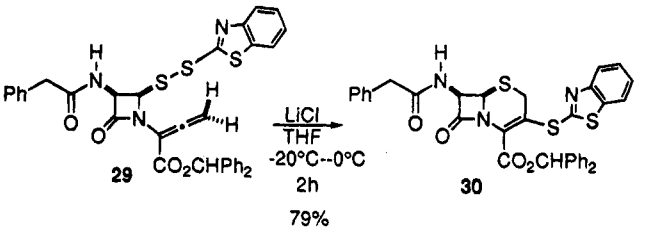


Reagents: (a) 2-mercaptobenzothiazole, toluene, Δ. (b) O_3, CH_2Cl_2, Me_2S, -78°C. (c) Tf_2O, i-Pr_2NEt, CH_2Cl_2, -78°C. (d) TEA, CH_2Cl_2, rt, 40 min.

ylmethyl ester (**21**) (Scheme 4). The allenes **28** and **29** were found to be unstable to silica gel column chromatography. However, a thorough aqueous wash during workup, followed by filtration through a silica pad, afforded pure allenes (free from dissolved ammonium salts). Attempts to crystallize allenyl azetidinones **28** and **29** were unsuccessful under a variety of conditions; nonetheless, these allenes can be stored as amorphous solids at −4 °C for months without decomposition.

With the allene in our hands, we began investigation of its chemistry: allene **29** was treated with 3.0 equiv of

Scheme 5



anhydrous LiCl in THF at low temperature, which afforded 3-(arylthio)cephem **30**, a congener of the new antibiotics endowed with activity against methicillin resistant strains (MRS), in 79% yield (Scheme 5).[27]

Initially, the cyclization step was believed to proceed *via* 3-chlorocephem (**31**), which in the presence of **32** might have undergone *in situ* nucleophilic displacement affording **30**. During the course of reaction, no evidence of **31** was obtained (by HPLC or TLC); furthermore, an attempt to react **31** with **32** under typical cyclization conditions resulted in the isomerization of **31** to its Δ^2 isomer **33**. No trace of cephem **30** was detected.[28] On the other hand, attack of halide on sulfenyl sulfur is precedented in the literature;[29] most likely, under our reaction conditions, chloride reacts at the sulfenyl sulfur to give the azetidinone **34**, which is being attacked by the displaced leaving group (also a good nucleophile) at the central allenic carbon to give the dienolate **35**. The intermediate **35** eventually cyclizes in the absence of a proton source to afford **30** (Scheme 6). Indeed, it is helpful to remove (by aqueous workup) the dissolved triethylammonium triflate salts before subjecting allene to the cyclization conditions, as lower yields of the cephem **30** were obtained when the reaction was run without removing salts. In nucleophilic attack at sulfur, usually the reactivity scale is I > Br > Cl.[29] In our case, chloride seemed to work best, although all halides, including fluoride, yielded some **30**.

To broaden the scope of cyclization, enol triflate **38**, bearing a mercaptobenzoxazole as a leaving group/nucleophile, was synthesized. Upon treatment with 1.0 equiv of TEA, formation of the allene **39** was observed along with a second compound; after completion of the reaction (about 3 h), the allene was not found, and the uncyclized azetidinone **40** was isolated from the reaction

(24) Allene formation strongly depends on the base used (slightly bulkier bases, *e.g.* Hunig's base, reacts extremely slowly), but depends very little on leaving groups, as tosylate, mesylate, triflate all react at similar rates. It follows that in the rate-determining step proton abstraction is important, while C−O bond cleavage is minor or nonexistent. If C−O bond cleavage were rate-determining one would expect the triflate to react 10^5 to 10^7 times more readily than the other sulfonates. Hence, the mechanism is most likely of the E_1CB type. See: (a) Hansen, R. L. *J. Org. Chem.* **1965**, *30*, 4322. (b) Streitwieser, A.; Wilkins, C. L.; Kielman, E. *J. Am. Chem. Soc.* **1968**, *91*, 5386.

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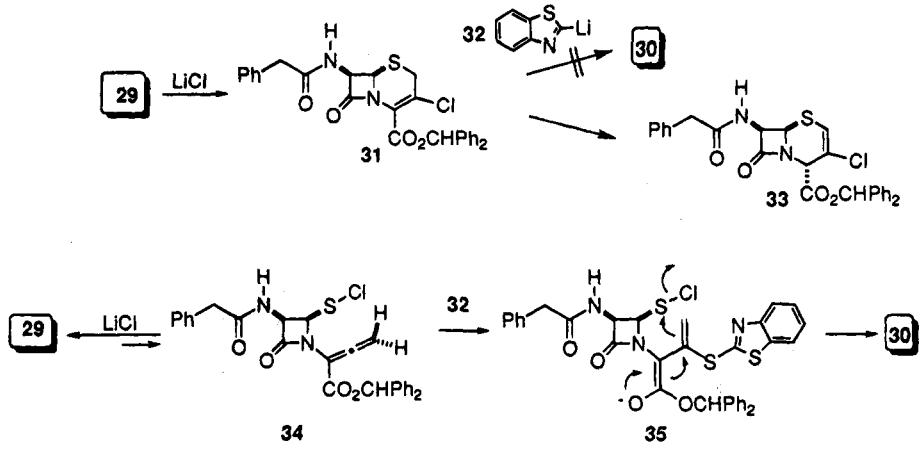
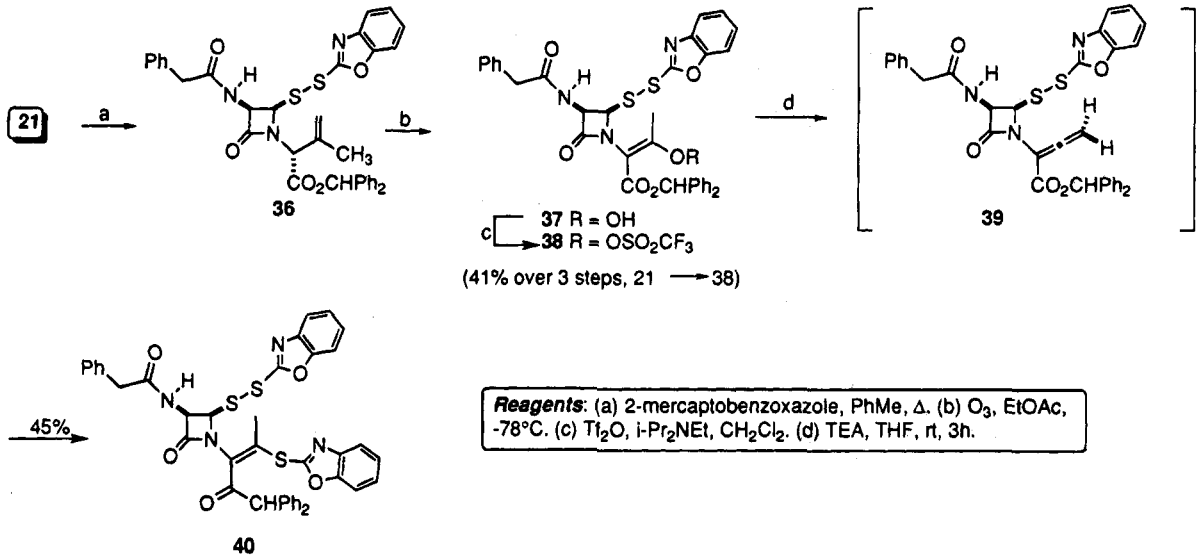
Scheme 6



Scheme 7



mixture in fair yield. The result is rather surprising, as the closely related allene **29** is quite stable under the reaction conditions. It is likely that TEA, in addition to promoting the elimination reaction, can also react at the sulfenyl sulfur by displacing this mercaptide anion (perhaps more reactive as leaving group), which readily reacts with the allene to afford the azetidinone **40** *via* protonation of the intermediate dienolate (Scheme 7). These studies suggest that the mercaptide anion liberated after attack of chloride at sulfur may attack a molecule of allenic disulfide (*e.g.* **29**) or allenic sulfenyl chloride (*e.g.* **34**). The first event can be followed by protonation, if closure is not fast enough. This highlights the fine balance of electronic effects that the allene cyclization rests on and stresses the importance of carefully selecting the reaction conditions. Mechanistically speaking, the reaction is unlikely to be unimolecular, as confirmed by results in the presence of exogenous thiolates (*vide infra*).

Next, we focused on the cyclization reactions in conjunction with exogenous carbon nucleophiles as the chemistry would enable us to introduce carbon-based substituents of our choice at the C(3) position of cephems. We decided to test our proposal using Gilman's reagent, Me_2CuLi.[30] It was gratifying to find that treatment of **28** with a lower-order (LO) cuprate prepared from methyllithium and copper iodide in THF at low temperature afforded an isomeric mixture of 3-methylcephems (**42a** and **42b**) in 60% yield, along with 3-(arylthio)cephem **41** (Table 1, entry 1). Nonetheless, we were extremely pleased with the outcome as it demonstrated the feasibility of synthesizing cephems using our novel strategy. Isomerization of the olefin to afford the Δ^2 cephem was anticipated, because cuprates are somewhat basic in nature,[17] and cephalosporins tend to isomerize to the Δ^2 isomer under basic conditions.[31] Studies on the composition of Gilman's reagent have clearly demonstrated that the cuprate reagent exists as an equilibrium mixture of different entities along with minute amounts of free MeLi; therefore, it is reasonable to assume that trace amounts of MeLi could very well be responsible for promoting the isomerization.[30,32] The (arylthio)cephem **41** must be arising from **28** during the course of the reaction; as discussed earlier, cleavage of the disulfide bond occurs during the cuprate reaction, consequently freeing some of the mercaptide anion, which attacks the allene affording a cephem. Interestingly, a reactive higher-order (HO) cyanocuprate gave a better yield (70%)

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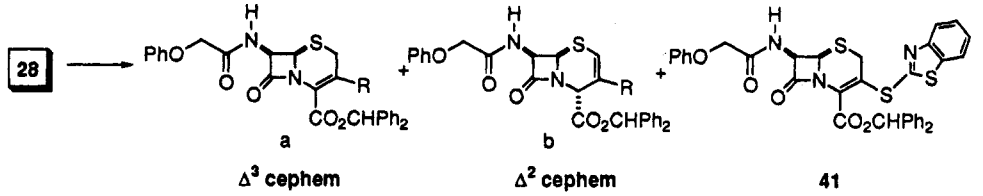
Table 1. Reaction of Allene 28 with Organocuprates



entry	organocuprate	R (% yield)[a]	cephem	Δ^3/Δ^2 cephem[b]	**41** (% yield)
1	Me_2CuLi	R = Me (60)	**42a, 42b**	3:2	10–15
2	$Me_2Cu(CN)Li_2$	R = Me (70)	**42b**	0:100	<5
3	$(Z\text{-}CH_3CH{=}CH)_2CuLi$	R = Z-$CH_3CH{=}CH$ (45)	**43a, 43b**	9:1	<10
4	$(Z\text{-}CH_3CH{=}CH)_2CuLi$[c]	R = Z-$CH_3CH{=}CH$ (30)	**43a, 43b**	95:5	<5
5	$(Z\text{-}CH_3CH{=}CH)_2Cu(CN)Li_2$	R = Z-$CH_3CH{=}CH$ (60)	**43a, 43b**	2:5	10–15
6	$(Z\text{-}CH_3CH{=}CH)(Me)Cu(CN)Li_2$	R = Z-$CH_3CH{=}CH$ (45)	**43a, 43b**	8:2	<10
7	$(Z\text{-}CH_3CH{=}CH)_2CuMgBr$	R = Z-$CH_3CH{=}CH$ (61)	**43a**	100:0	5–10
8	$Me_2CuMgBr$	R = Me (80)	**42a**	100:0	<5

[a] Combined yield of isolated Δ^3 and Δ^2 cephems. [b] Ratio determined by NMR. [c] Prepared by transmetalation reaction.

than did the LO methylcuprate, but promoted isomerization to produce all Δ^2 isomer (Table 1, entry 2).

Next, the synthesis of **43a**, a key intermediate for our target compound Cefzil (**6**), was attempted. Treatment with a LO (*Z*)-1-propenylcuprate, prepared from copper iodide and (*Z*)-1-propenyllithium in THF at −78 °C produced 45% of the desired cephem **43a** along with trace amounts of the Δ^2 isomer **43b** and **41** (Table 1, entry 3). *It is noteworthy that a complete stereoselective transfer of the (Z)-1-propenyl moiety was observed during the organocuprate reaction.*[33] When (*Z*)-1-propenylcuprate was prepared from the corresponding (*Z*)-1-propenyltributyltin via transmetalation reaction,[34] cephem **43a** was obtained in only 30% yield (Table 1, entry 4). As observed previously, the HO cyanocuprate gave a reasonable yield of **43** (60%), but as a 5:2 mixture of Δ^2/Δ^3 isomers (Table 1, entry 5). Little improvement was realized when mixed HO cyanocuprates were employed; **43a** was isolated in low yield along with the Δ^2 isomer **43b** and the undesired cephem **41** (Table 1, entry 6). Interestingly, some transfer of the methyl group (<10%) was observed when (*Z*)-1-propenyl(Me)Cu(CN)Li_2 was used, affording 3-methylcephem **42**.[35]

Grignard reagents have been successfully employed in conjunction with catalytic amounts of copper (Normant's cuprates) to form carbon−carbon bonds in a variety of applications.[17] In view of these studies, addition of (*Z*)-1-propenylmagnesium bromide was attempted in conjunction with 10 mol % of copper iodide. Only trace amounts of **43a** was isolated along with unidentified polar products. Increasing amounts of copper iodide (up to 50 mol %) did not improve the yield.

After unsatisfactory results using catalytic amounts of copper iodide, we decided to use stoichiometric amounts of copper salts and generate magnesiocuprates such as R_2CuMgX. Therefore, organocopper species [(*Z*)-1-propenyl]$_2$CuMgBr was generated by admixing 2.0 equiv of Grignard reagent with 1.0 equiv of copper iodide in THF at −78 °C. A solution of allene **28** in THF was slowly added into the reaction vessel containing the dark-colored cuprate: after 20 min, TLC and HPLC indicated completion of the reaction, and usual workup afforded the desired cephem **43a** in 61% yield, as a pure Δ^3 isomer along with trace amounts of **41** as the only isolable products (Table 1, entry 7). The reaction appeared to be much faster and cleaner compared to the ones with other cuprates; furthermore, it was complete in less than 30 min (*vs* 60 and 90 min observed in the case of other cuprates), thereby minimizing formation of undesired side products. Similarly, the methylcuprate derived from the corresponding Grignard and CuI gave isomerically pure **42a** in 80% yield (Table 1, entry 8).

The composition of Normant's reagent using different stoichiometric amounts of MeMgX and CuX in THF has been studied by Ashby.[36] According to the study, 1.0 equiv of copper bromide and 2.0 equiv of Grignard in THF result in the formation of dimeric species Cu_2MgMe_4 along with $MgBr_2$; involvement of the halide with the complex was not observed in NMR studies. The successful use of Normant's cuprate in our studies could be the consequence of a reaction between Cu_2MgR_4 (*a single entity*) and the allene, which is rather different from the reaction with other LO or HO organocuprates, which often exist as equilibrium mixtures of different entities, probably with differing degrees of reactivity and selectivity.

Normant's cuprates turned out to be ideal reagents for us in order to introduce the desired substituents at the C(3) position of the cephem. The most troublesome Δ^3/Δ^2 isomerization was also avoided with these reagents. In spite of these successful results, we wanted to improve the yield, and we also had to prevent the formation of the unwanted cephem **41**. To address the second problem, *i.e.*, formation of **41**, we decided to replace the mercaptobenzothiazole group (a good nucleophile) with a *sulfinate group*, an excellent leaving group but a poor nucleophile.[37]

The synthesis of our key intermediate **46** started with azetidinone **22**. Treatment of **22** with the sodium salt of

(33) (*Z*)-1-Propenyllithium was prepared in ether according to Whitesides's procedure: Whitesides, G. M.; Casy, C. P.; Krieger, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1379. The solution contained <2% of the *E* isomer. We did not observe any change in the ratio of *Z* and *E* isomers after the cuprate reaction (by HPLC and 360 MHz NMR). For a stereoselective transfer of the (*Z*)-1-propenyl moiety via a higher-order cyanocuprate in the synthesis of polyene macrolide, see: Lipshutz, B. H.; Barton, J. C. *J. Org. Chem.* **1988**, *53*, 4495.

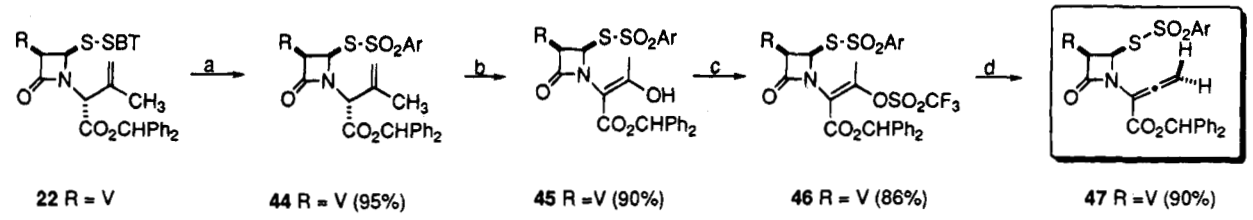
(34) Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H *J. Am. Chem. Soc.* **1988**, *110*, 2641 and references cited therein.

(35) Similar observation has been reported by Lipshutz on the study of ligand transferability, see: Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A.; Parker, D. *J. Org. Chem.* **1984**, *49*, 3928.

(36) Ashby, E. C.; Goel, A. B. *J. Org. Chem.* **1983**, *48*, 2125.

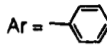
(37) This leaving group has been recently used by Torii in the synthesis of 3-hydroxycephems: Tanaka, H.; Taniguchi, M.; Kameyama, Y.; Monnin, M.; Sasaoka, M.; Shiroi, T.; Nagao, S.; Torii, S. *Chem. Lett.* **1990**, 1867.

Scheme 8

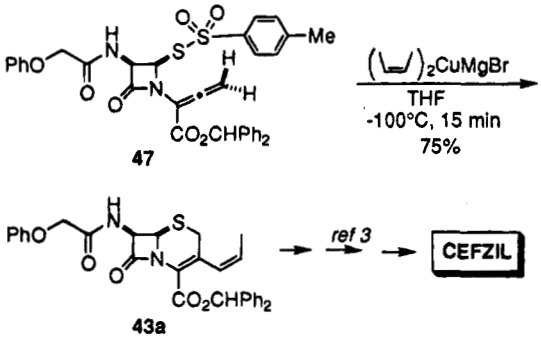


Reagents: (a) $NaSO_2$-*p*-C_6H_4-Me, $AgNO_3$, acetone/H_2O, 4h, rt. (b) O_3, CH_2Cl_2, Me_2S, -78°C. (c) Tf_2O, i-Pr_2NEt, CH_2Cl_2, -78°C. (d) TEA, CH_2Cl_2, rt, 40 min.

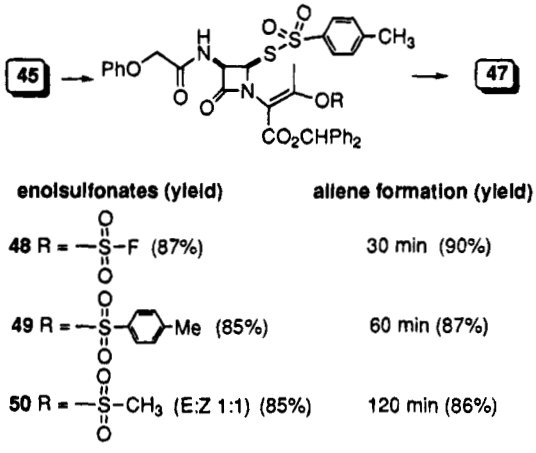
V=$PhOCH_2CONH$

Ar = 

Scheme 9



Scheme 10



p-toluenesulfinic acid and $AgNO_3$ in a mixture of acetone:H_2O (9:1) afforded the sulfone **44** in 95% yield.[13] Alternatively, **45** can also be obtained by the direct ring opening of penicillin sulfoxides employing Torii's conditions, as this would avoid the use of expensive $AgNO_3$.[38] Subsequent steps to synthesize allene **47** employed the following: oxidation of olefin **44** to afford **45**, synthesis of enol triflate **46** from **45**, and transformation of the triflate **46** into allene **47** (Scheme 8). As observed earlier in the mercaptobenzothiazole series, allene **47** was found to be unstable to chromatography. Attempts to purify it by crystallization were also unsuccessful. However, dripping a fairly concentrated CH_2Cl_2 solution of the allene into hexanes at 0 °C afforded pure allene **47**, as an off-white amorphous solid, which can be stored over a longer period of time at 4 °C.

The allene **47** was subjected to the previously developed cuprate addition–cyclization conditions. Interestingly, upon treatment of allene with 2.5 equiv of [(*Z*)-1-(propenyl)]$_2$CuMgBr in THF at −78 °C for 15 min afforded 65% of the cephem **43a** as the only product. No other products were identified. Next, in order to increase the yield of **43a**, the reaction conditions were further optimized and the results can be summarized as follows: after screening a variety of copper sources, recrystallized copper bromide–dimethyl sulfide complex[39] worked effectively; THF appeared to be an ideal solvent for the reaction, since a mixture of THF/ether or ether alone were not suitable; higher yields were realized (75%) when the reaction was performed at −100 °C; 1.5–1.8 equiv of cuprate was sufficient for the reaction. Following our optimized conditions, we were able to achieve the synthesis of isomerically pure **43a** in 75% yield from **47**.

No chromatography or extensive purifications were required, copper salts were removed by filtration through a silica pad, and the desired cephem was isolated simply by triturating the crude product with isopropyl alchohol. The intermediate **43a** can be converted to the antibiotic Cefzil following the standard protocol of acylation and deprotections (Scheme 9).[3] We finally had an effective process for the synthesis of 3-(*Z*)-propenylcephem **43a** from inexpensive penicillin, but to be further cost-efficient, we needed a replacement for the highly priced Tf_2O, employed in the synthesis of enol triflates, key precursors to allenes.

Recently, fluorosulfonic anhydride[40] has been suggested as an inexpensive replacement for Tf_2O; hence, treatment of the enol azetidinone **45** with 1.2 equiv of fluorosulfonic anhydride and Hunig's base at −78 °C in CH_2Cl_2 afforded a single diastereomer of the fluorosulfonate **48** in 95% yield, as an amorphous solid. Further treatment with TEA for 30 min in CH_2Cl_2 afforded the desired allene **47** in high yield and purity. Tosylate **49**, prepared from tosic anhydride, worked equally well and afforded allene in good yield. On the other hand, treatment of **45** with mesyl chloride afforded a 1:1 mixture of *E* and *Z* mesylates **50**, and subsequent treatment with base afforded allene **47** in 86% yield (Scheme 10). The enol triflates can easily be replaced by any of the above-mentioned sulfonates. However, we found the formation of fluorosulfonate **48** and its subsequent transformation to the allene **47** was most convenient and highest yielding for our process.

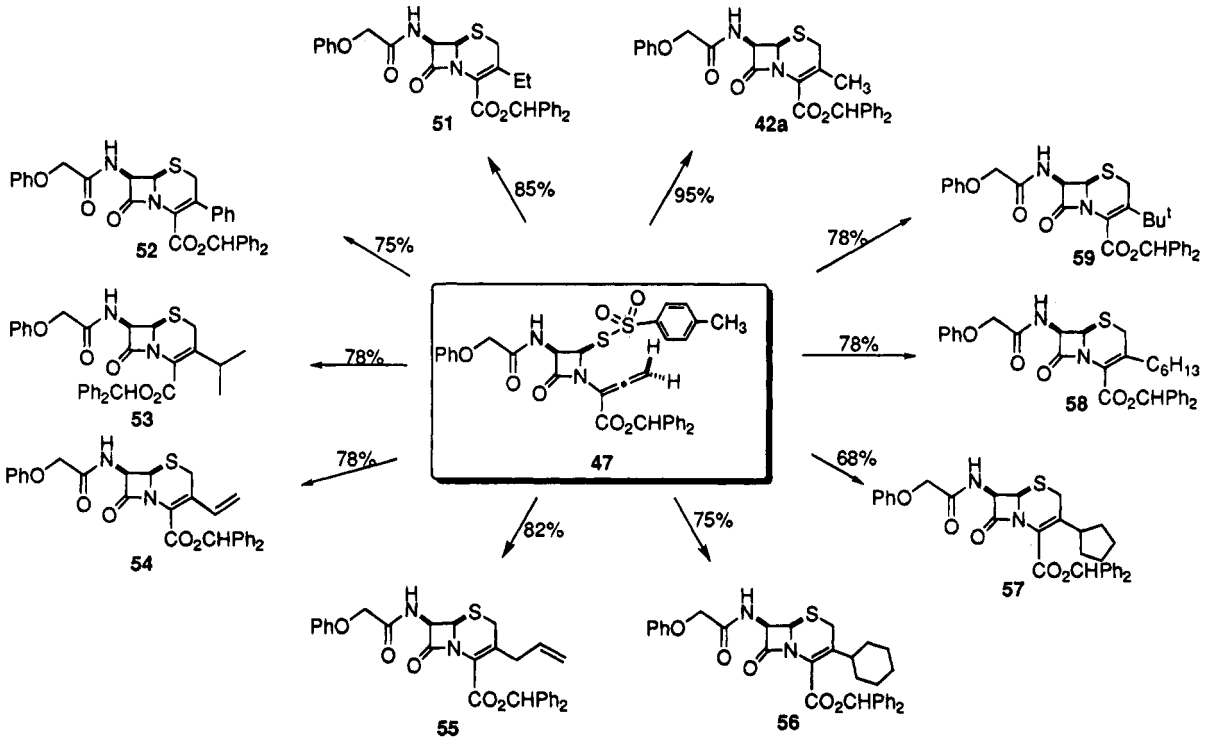
The chemistry was further extended to the synthesis of a variety of structurally diverse 3-substituted cepha-

(38) (a) Torii, S.; Tanaka, H.; Shiroi, H.; Sasaoka, M.; Saito, N.; Matsumura, K. U.S. Patent 4 566 996, 1986. (b) Tanaka, H.; Kameyama, Y.; Yamauchi, T.; Torii, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1793 and references cited therein.

(39) Bertz, S. H.; Gibson, C. P.; Dabbagh, G. J. *Tetrahedron Lett.* **1978**, *28*, 4251 and references cited therein.

(40) Roth, G. P.; Fuller, C. E. *J. Org. Chem.* **1991**, *56*, 3493 and reference cited therein.

Scheme 11



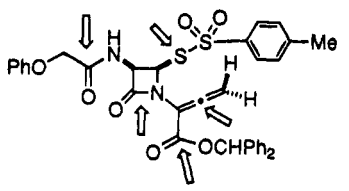


Figure 1. Possible reaction sites of cuprates vs **47**.

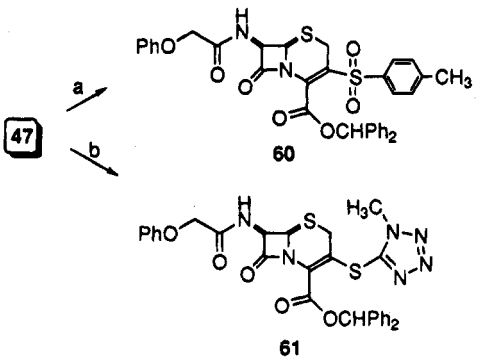
losporins from allene **47** in high yields (Scheme 11), using 1.2−1.5 equiv of organocuprates derived from Grignards and copper bromide−dimethyl sulfide complex in THF.

It is noteworthy to observe a fine balance of reactivity and selectivity between allenyl azetidinones and organocuprates. There are five potential sites on an allenylazetidinone where organocuprate can react (Figure 1); since reactive cuprates (HO or LO lithio cuprates) are less selective, we have observed low yields of isolated cephems along with formation of byproducts. Normant's cuprates are found in our case to be more selective toward the allene, affording higher yields of cephems.

The versatility of these allenes was further demonstrated by the synthesis of 3-norcephems. Treatment of **47** with 3.8 equiv of LiBr in NMP for 16 h at ambient temperature afforded the sulfone **60** in 61% yield. Similar to organocopper chemistry, external non-carbon nucleophiles can also be added to afford 3-(arylthio)-cephems; for example, treatment of allene **47** with the sodium salt of 1-methyl-2-mercaptotetrazole in the presence of LiBr in THF afforded the (arylthio)cephem **61** in modest yield (Scheme 12). These reactions were not further optimized, as the synthetic scope of the cuprate addition was obviously more important for the preparation of the latest generation of cephem antibiotics. Torii and co-workers have also independently reported similar approaches to 3-norcephems and *exo*-methylenepenams using allenic intermediates.[41]

In conclusion, we have presented a novel approach to the synthesis 3-substituted cephalosporins. The starting

Scheme 12



Reagents: a. LiBr, NMP, rt, 16h, 61%.
b. sodium salt of 1-methyl-2-mercaptotetrazole, LiBr, THF, 32%.

magnesiocuprates are easily prepared from the corresponding Grignard reagents, which are readily accessible, being either available commercially or easily prepared. The allene is readily available from penicillin, yet another inexpensive substrate available from the natural chiral pool. Since organocuprates are extremely versatile reagents, this chemistry can be utilized to attach many side chains to the C(3) position of cephalosporins and therefore should prove extremely valuable to medicinal chemists engaged in the field of cephalosporin research. Our strategy highlights the high reactivity of allenyl esters with cuprates, even in the presence of other functionalities which might potentially interfere, thus suggesting that annelating strategies based on these intermediates and other electrophilic traps may be of general use in organic synthesis. Work to explore these possibilities is in progress.

(41) (a) Tanaka, H.; Kameyama, Y.; Yamada, T.; Tokumaru, Y.; Shiroi, T.; Sasaoka, M.; Taniguchi, M.; Torii, S. *Synlett* **1991**, 888. (b) Tanaka, H.; Kameyama, Y.; Sumida, S-I.; Shiroi, T.; Sasaoka, M.; Taniguchi, M.; Torii, S. *Synlett* **1992**, 351. (c) Tanaka, H.; Kameyama, Y.; Sumida, S-I.; Torii, S. *Tetrahedron Lett.* **1992**, *46*, 7029.

Experimental Section

General Methods. All reactions were carried out under argon in glassware dried overnight at 120 °C and cooled under argon. THF was distilled from benzophenone/sodium ketyl prior to use. Azetidinones **20**–**25**, **44**, and **45** were synthesized according to the literature procedures.[42] Unless stated otherwise, Grignard reagents and organolithiums were purchased from Aldrich or Organometallics, Inc., and were titrated before use by the method of Watson and Eastham.[43] (*Z*)-1-Propenyllithium was prepared according to Whitesides.[33] (*Z*)-1-Propenylmagnesium bromide was prepared following the procedures of Beak and Seyferth.[44,45] (*Z*)-1-Propenyltributyltin was prepared following the protocol of Seyferth.[45] Copper(I) bromide–dimethyl sulfide complex was purchased from Aldrich and was further purified by the procedure of House.[46] Other solvents and reagents employed were of commercial grade. Analytical thin-layer chromatography was performed on EM 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and/or ethanolic phosphomolybdic acid solution followed by heating. Purification of the products were carried out by flash chromatography[47] using silica (EM reagent 60, 230–400 mesh). Combustion analyses and infrared measurements were performed by the Analytical Department of Bristol-Myers Squibb in Syracuse and Wallingford.

Diphenylmethyl 2-[(3*R*,4*R*)-4-[(Benzothiazol-2-yl)dithio]-3-(phenoxyacetamido)-2-oxoazetidin-1-yl]-3-[(trifluoromethanesulfonyl)oxy]-2-butenoate (26). To a solution of **24** (0.50 g, 0.65 mmol) in dry CH_2Cl_2 (15 mL) at −78 °C was added *i*-Pr_2NEt (0.12 mL, 0.66 mmol) followed by Tf_2O (0.11 mL, 0.66 mmol) under argon. The reaction mixture was stirred at −78 °C for 1 h and poured into a 1:1 mixture of EtOAc and aqueous saturated NH_4Cl (50 mL). The organic layer was washed with brine (10 mL) and 25% $NaHCO_3$ solution (10 mL), dried ($MgSO_4$), and evaporated *in vacuo* to afford the crude compound which was purified by flash chromatography (30% EtOAc in hexanes) to give **26** (0.35 g, 65%) as a white foam: ^1H NMR ($CDCl_3$) δ 7.87 (d, J = 7.7 Hz, 1H), 7.70 (d, J = 7.7 Hz, 1H), 7.64–7.04 (m, 17H), 6.93 (d, J = 7.3 Hz, 1H), 6.87 (s, 1H), 5.43 (d, J = 5.2 Hz, 1H), 5.04 (dd, J = 5.2 Hz; J' = 7.3 Hz, 1H), 4.62 (AB q, 2H), 2.53 (s, 3H); HRMS (FAB) calcd for $C_{36}H_{28}F_3N_3O_8S_4$ (MH^+) 816.8756, found 816.8750. Anal. Calcd for $C_{36}H_{27}F_3N_3O_8S_4$: C, 53.02; H, 3.43; N, 5.15. Found: C, 53.12; H, 3.52; N, 5.25.

Diphenylmethyl 2-[(3*R*,4*R*)-4-[(Benzothiazol-2-yl)dithio]-3-(phenylacetamido)-2-oxoazetidin-1-yl]-3-[(trifluoromethanesulfonyl)oxy]-2-butenoate (27). Following the procedure for the preparation of **26**, azetidinone **25** (1.46 g, 2.19 mmol) afforded **27** (1.05 g, 60%) as a white foam. A portion was recrystallized from ether–hexanes to afford white crystals: mp 132–3 °C; ^1H NMR ($CDCl_3$) δ 7.82 (d, J = 8.1 Hz, 2H), 7.69 (d, J = 8.1Hz, 2H), 7.49–7.03 (m, 15 H), 6.83 (s, 1H), 6.19 (d, J = 7.2 Hz, 1H), 5.34 (d, J = 5.2 Hz, 1H), 4.79 (dd, J = 5.2 Hz; J' = 7.2 Hz, 1H), 3.71 (m, 2H), 2.52 (s, 3H); MS (FAB, MH^+) 800. Anal. Calcd for $C_{36}H_{27}F_3N_3O_7S_4$: C, 54.05; H, 3.53; N, 5.25; F, 7.13. Found: C, 53.76; H, 3.50; N, 5.10; F, 7.09.

Diphenylmethyl 2-[(3*R*,4*R*)-4-[(*p*-Toluenesulfonyl)thio]-3-(phenoxyacetamido)-2-oxoazetidin-1-yl]-3-[(trifluoromethanesulfonyl)oxy]-2-butenoate (46). Following the procedure for the preparation of **26**, azetidinone **45** (8.35 g, 12.3 mmol) afforded **46** (8.82 g, 86.5%) as a white foam: ^1H NMR ($CDCl_3$) δ 7.50–7.00 (m, 18H), 6.98 (s, 1H), 6.82 (br d, 2H), 5.90 (d, J = 5.2 Hz, 1H), 5.00 (dd, J = 5.2 Hz; J' = 7.2 Hz, 1H), 4.48 (m, 2H), 2.32 (s, 3H); HRMS (FAB) calcd for $C_{36}H_{31}F_3N_2O_{10}S_3$ (MH^+) 805.8314, found 805.8309. Anal. Calcd for $C_{36}H_{30}F_3N_2O_{10}S_3$: C, 53.73; H, 3.85; N, 3.47. Found: C, 53.85; H, 3.95; N, 3.50.

Diphenylmethyl 2-[(3*R*,4*R*)-[(*p*-Toluenesulfonyl)thio]-3-(phenoxyacetamido)-2-oxoazetidin-1-yl]-3-[(fluorosulfonyl)oxy]-2-butenoate (48). To a solution of **45** (10.00 g, 14.8 mmol) in dry CH_2Cl_2 (90 mL) at −78 °C was added *i*-Pr_2-NEt (2.84 mL, 16.3 mmol) followed by fluorosulfonic anhydride[48] (1.69 mL, 16.3 mmol) under argon. The reaction mixture was stirred for 2.5 h and poured into brine (50 mL). The organic layer was washed with more brine (10 mL) and 25% $NaHCO_3$ solution (10 mL), dried (Na_2SO_4) and evaporated *in vacuo* to afford the crude compound which was purified by flash chromatography (40% EtOAc in hexanes) to give **48** (8.82 g, 86.5%) as a white foam: ^1H NMR ($CDCl_3$) δ 7.00–7.50 (m, 19H), 6.93 (s, 1H), 6.88 (d, J = 7.8 Hz, 1H), 5.99 (d, J = 5.3 Hz, 1H), 5.05 (dd, J = 5.5 Hz; J' = 7.8 Hz, 1H), 4.50 (d, J = 2.8 Hz, 2H), 2.42 (s, 3H), 2.30 (s, 3H); HRMS calcd for $C_{35}H_{31}$-$FN_2O_{10}S_3$ (MH^+) 755.8236, found 755.8228. Anal. Calcd for $C_{35}H_{30}FN_2O_{10}S_3$: C, 55.53; H, 4.42; N, 3.70. Found: C, 55.29; H, 4.15; N, 3.63.

Diphenylmethyl 2-[(3*R*,4*R*)-[(*p*-Toluenesulfonyl)thio]-3-(phenoxyacetamido)-2-oxoazetidin-1-yl]-3-[(*p*-toluenesulfonyl)oxy]-2-butenoate (49). To a solution of **45** (1.00 g, 1.48 mmol) in dry CH_2Cl_2 (10 mL) at −78 °C was added *i*-Pr_2NEt (0.28 mL, 1.63 mmol) followed by *p*-toluenesulfonic anhydride (0.53 g, 1.63 mmol) under argon. The reaction mixture was stirred for 2 h and poured into a 1:1 mixture of EtOAc:saturated NH_4Cl (50 mL). The organic layer was separated and washed with brine, dried (Na_2SO_4), and evaporated *in vacuo* to afford the crude compound, which was purified by flash chromatography (40% EtOAc in hexanes) to give **49** (1.04 g, 85%) as a white foam: ^1H NMR ($CDCl_3$) δ 7.81 (d, J = 7.5 Hz, 2H), 7.52 (d, J = 7.5 Hz, 2H), 7.40–7.00 (m, 19H), 6.95 (s overlapping with d, 2H), 5.65 (d, J = 4.7 Hz, 1H), 5.36 (dd, J = 4.7 Hz; J' = 9.4 Hz, 1H), 4.39 (AB q, J = 15 Hz, 2H), 2.47 (s, 3H), 2.39 (br s, 6H); HRMS calcd for $C_{42}H_{38}N_2O_{10}S_3$ (MH^+) 827.9575, found 827.9569. Anal. Calcd for $C_{42}H_{37}$-$N_2O_{10}S_3$: C, 61.06; H, 4.59; N, 3.38. Found: C, 60.95; H, 4.50; N, 3.46.

Diphenylmethyl 2-[(3*R*,4*R*)-[(*p*-Toluenesulfonyl)thio]-3-(phenoxyacetamido)-2-oxoazetidin-1-yl]-3-[(methanesulfonyl)oxy]-2-butenoate (50). To a solution of **45** (0.20 g, 0.29 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C was added TEA (55.0 μL, 0.40 mmol) followed by methanesulfonyl chloride (34.0 μL, 0.40 mmol) under argon. The ice bath was removed, the mixture was stirred for 2.0 h, and then it was poured into a 1:1 mixture of EtOAc:saturated NH_4Cl (50 mL). The organic layer was washed with brine, dried (Na_2SO_4), and evaporated *in vacuo* to afford the crude compound, which was purified by flash chromatography (40% EtOAc in hexanes) to give **50** (0.18 g, 85%) as a 1:1 mixture of (*E*) and (*Z*) isomers: ^1H NMR ($CDCl_3$) δ 7.49–6.88 (m, 42 H), 5.87 (d, J = 5.4 Hz, 1H), 5.77 (d, J = 5.4 Hz, 1H), 5.08 (dd, J = 7.7 Hz; J' = 5.4 Hz, 1H), 5.04 (dd, J = 7.7 Hz; J' = 5.4 Hz, 1H), 4.55–4.47 (m, 4H), 3.34 (s, 3H), 2.92 (s, 3H), 2.50 (s, 3H), 2.44 (s, 3H), 2.38 (s, 3H), 2.34 (s, 3H); MS (FAB) 750. Anal. Calcd for $C_{36}H_{34}$-$N_2O_{10}S_3$: C, 57.62; H, 4.53; N, 3.73. Found: C, 57.39; H, 4.59; N, 3.89.

A Representative Procedure for Allene Preparation: Diphenylmethyl 2-[(3*R*,4*R*)-4-[(Benzothiazol-2-yl)dithio]-3-(phenoxyacetamido)-2-oxoazetidin-1-yl]-2,3-butadienoate (28). To a solution of **26** (0.26 g, 0.32 mmol) in dry CH_2Cl_2 (5.0 mL) was added TEA (53.0 μL, 0.38 mmol) at room temperature. The solution was stirred for 45 min, after which HPLC indicated consumption of **26** and showed a new peak at retention time 4.74 (C-18, 2.0 mL/min, λ = 254 nm, 70%

(42) Woodward, R. B.; Bickel, H. U.S. Patent 4 550 162, 1985. Also refs 22 and 23.

(43) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

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acetonitrile and 30% water). The solution was poured into a flask containing brine (5 mL). The organic layer was washed thoroughly with H_2O (2 × 5 mL) and 10% HCl solution (2 × 5 mL), dried ($MgSO_4$), and concentrated to give the allene **28** (0.19 g, 90%) as a light yellow foam. The foam was redissolved in CH_2Cl_2 (1.0 mL) and added dropwise to cold hexanes with magnetic stirring. The pure allene precipitated out as an amorphous solid which could be filtered and stored at 4 °C for several weeks: ^1H NMR ($CDCl_3$) δ 7.82 (d, J = 9.5 Hz, 1H), 7.60–6.90 (m, 18H), 6.83 (s, 1H), 5.86 (d, J = 5.1 Hz, 1H), 5.65 (d, J = 15.5 Hz, 1H), 5.60 (dd, J = 5.1 Hz; J' = 8.0 Hz, 1H), 5.23 (d, J = 15.5 Hz, 1H), 4.45 (AB q, J = 17 Hz, 2H); MS (FAB) 665. Anal. Calcd for $C_{35}H_{27}N_3O_5S_3$: C, 63.13; H, 4.05; N, 6.30. Found: C, 63.31; H, 4.21; N, 6.05.

Diphenylmethyl 2-[(3*R*,4*R*)-4-[(Benzothiazol-2-yl)dithio]-3-(phenylacetamido)-2-oxoazetidin-1-yl]-2,3-butadienoate (29). Following the representative procedure, enol triflate **27** (0.50 g, 0.65 mmol) upon treatment with TEA (92.0 μL, 0.65 mmol) afforded allene **29** (0.38 g, 92%) as a beige powder: ^1H NMR ($CDCl_3$) δ 7.81 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.50–7.01 (m, 17 H), 6.78 (s, 1H), 6.51 (d, J = 8.0 Hz, 1H), 5.76 (d, J = 4.8 Hz, 1H), 5.41 (dd, J = 4.8 Hz; J' = 8.0 Hz, 1H), 5.40 (AB q, J = 15.3 Hz, 2H), 3.65 (s, 2H); HRMS calcd for $C_{35}H_{27}N_3O_4S_3$ (MH^+) 650.1242, found 650.1244.

Diphenylmethyl 2-[(3*R*,4*R*)-4-[(*p*-Toluenesulfonyl)thio]-3-(phenoxyacetamido)-2-oxoazetidin-1-yl]-2,3-butadienoate (47). (a) Following the representative procedure, enol triflate **46** (0.30 g, 0.36 mmol) upon treatment with TEA (77.0 μL, 0.36 mmol) in CH_2Cl_2 (3 mL) for 1 h afforded allene **47** (0.24 g, 100%) as a colorless foam: ^1H NMR (CDCl3) δ 7.60 (d, J = 8.4 Hz, 1H), 7.41–7.25 (m, 16 H), 7.16 (d, J = 8.4 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.84 (s, 1H), 5.60 (d, J = 8.4 Hz, 1H), 5.45 (dd, J = 5.0 Hz; J' = 8.4 Hz, 1H), 4.46 (AB q, J = 14.7 Hz, 2H); HRMS calcd for $C_{35}H_{30}N_2O_7S_2$ (MH^+) 655.7591, found 655.7586. Anal. Calcd for $C_{35}H_{29}N_2O_7S_2$: C, 64.27; H, 4.77; N, 4.27. Found: C, 64.45; H, 5.07; N, 4.33.

(b) Following the representative procedure, **48** (4.03 g, 5.34 mmol) upon treatment with TEA (0.78 mL, 5.66 mmol) in CH_2Cl_2 (20 mL) for 30 min afforded **47** (3.15g, 90%) as a colorless foam.

(c) Following the representative procedure, **49** (25.0 mg, 0.03 mmol) upon treatment with TEA (4.40 μL, 0.03 mmol) in CH_2Cl_2 (1.0 mL) for 1 h afforded **47** (17.1 mg, 87%) as a colorless foam.

(d) Following the representative procedure, **50** (as a *E* and *Z* mixture) (0.60 g, 0.79 mmol) upon treatment with TEA (0.11 mL, 0.79 mmol) in CH_2Cl_2 (6 mL) for 1 h afforded **47** (0.45 g, 86%) as a colorless foam.

Diphenylmethyl (6*R*,7*S*)-7-(Phenylacetamido)-3-[(benzothiazol-2-yl)thio]-3-cephem-4-carboxylate (30). To a solution of allene **29** (0.11 g, 0.17 mmol) in dry THF (5 mL) at −20 °C was added LiCl (0.64 mL, 0.51 mmol, 0.8 M THF solution). The yellow solution was allowed to reach 0 °C over 2.0 h and kept at 0 °C for another 2.0 h. The reaction mixture was poured into saturated NH_4Cl and EtOAc. The organic phase was washed with water, brine, dried ($MgSO_4$), and evaporated *in vacuo* to afford the crude cephem. Flash chromatography yielded the pure cephem **30** (87.0 mg, 79%) as a white solid which was crystallized from ether/hexanes. The compound was identical (mp, NMR) with a literature sample.[28]

Diphenylmethyl 2-[(3*R*,4*R*)-4-[(Benzoxazol-2-yl)dithio]-3-(phenylacetamido)-2-oxoazetidin-1-yl]-3-[(trifluorosulfonyl)oxy]-2-butenoate (38). A solution of **21** (5.00 g, 9.67 mmol) in toluene (100 mL) was refluxed in the presence of 2-mercaptobenzoxazole (1.68 g, 10.6 mmol) using a Dean–Stark trap to remove the water. After 3 h the solution was cooled and evaporated to dryness, and the crude product was filtered through a pad of silica gel (40% ethyl acetate–hexane) to yield crude **36** as an oil (4.10 g): ^1H NMR ($CDCl_3$) δ 7.55–7.21 (m, 19 H), 6.82 (s, 1H), 6.75 (br d, 1H), 5.55 (d, J = 5.1 Hz, 1H), 5.47 (dd, J = 7.3 Hz; J' = 5.1 Hz, 1H), 3.64 (s, 2H), 1.86 (s, 3H).

This oil was dissolved in EtOAc (150 mL) and was ozonized at −78 °C until the solution was pale blue. The excess ozone was purged by bubbling N_2 gas, and the ozonide was reduced with methyl sulfide (5 mL). The cooling bath was removed and the mixture was allowed to reach room temperature. Evaporation and filtration through a pad of silica gel (50% ethyl acetate/hexane) afforded **37** as a yellow oil (2.51 g): ^1H NMR ($CDCl_3$) δ 12.2 (s, 1H), 7.58–7.04 (m, 19 H), 6.80 (s, 1H), 6.10 (br d, 1H), 5.47 (d, J = 5.0 Hz, 1H), 4.96 (br m, 1H), 3.67 (s, 2H), 2.29 (s, 3H).

This crude oil (1.04 g, 1.59 mmol) was dissolved in CH_2Cl_2 (20 mL) at −78 °C and treated with *i*-Pr_2NEt (0.31 mL, 1.1 equiv) and TF_2O (0.27 mL, 1.0 equiv). After 1 h at −78 °C, the solution was quenched with saturated aqueous NH_4Cl and EtOAc. The organic phase was washed with water and brine and dried over Na_2SO_4. Flash chromatography (30–40% ethyl acetate/hexane) gave **38** as a foam (0.51 g, 41%) which could not be recrystallized from a variety of solvents: ^1H NMR ($CDCl_3$) δ 7.58–7.00 (m, 19H), 6.89 (s, 1H), 6.16 (d, J = 7.1 Hz, 1H), 5.50 (d, J = 5.2 Hz, 1H), 4.85 (dd, J = 7.1 Hz; J' = 5.2 Hz, 1H), 3.69 (s, 2H), 2.49 (s, 3H); HRMS calcd for $C_{36}H_{29}F_3N_3O_8S_3$ (MH^+) 784.1069, found 784.1052.

Diphenylmethyl 2-[(3*R*,4*R*)-4-[(Benzoxazol-2-yl)dithio]-3-(phenylacetamido)-2-oxoazetidin-1-yl]-3-[(benzoxazol-2-yl)thio]-2-butenoate (40). The triflate **38** (0.12 g, 0.15 mmol) in CH_2Cl_2 (3.0 mL) was treated with TEA (22 μL, 1.1 equiv), monitoring by HPLC. Allene **39** was detected initially, but another product was also evident within 5 min. After *ca.* 3 h all starting material and allene had disappeared, and the major product was isolated by workup (aqueous NH_4Cl and ethyl acetate) followed by flash chromatography (40% EtOAc/hexane) as a yellow oil (55.0 mg, 45%), identified as **40** by NMR and MS: ^1H NMR ($CDCl_3$) δ 7.73–6.95 (m, 23 H), 6.85 (s, 1H), 6.14 (d, J = 7.1 Hz, 1H), 5.59 (d, J = 5.2 Hz, 1H), 4.88 (dd, J = 7.1 Hz; J' = 5.2 Hz, 1H), 3.65 (s, 2H), 2.40 (s, 3H); HRMS calcd for $C_{42}H_{33}N_4O_6S_3$ (MH) 785.1562, found 785.1587.

Reaction of Allenes with Cuprates. Procedure A. Reaction of Allenes with LO Cuprates. To copper(I) iodide (0.48 mmol) under argon was added THF (1.5 mL). The mixture was cooled to −78° C and RLi (0.96 mmol) was slowly added. The cooling bath was removed and the suspension was stirred for 15–20 min until a homogeneous mixture was observed. The cuprate was recooled to −78 °C and a solution of the allene (0.30 mmol) in THF (2.0 mL) was added. After stirring for 1 h, the reaction mixture was poured into a 1:1 solution of saturated NH_4Cl and ethyl acetate (10 mL). The organic layer was washed with brine (2 mL) and 10% $NaHCO_3$ (2 mL), dried (MgSO4), and evaporated to give the crude cephem which was further purified by flash chromatography.

Procedure B. Reaction of Allenes with HO Cyanocuprates. Copper cyanide (0.77 mmol) and RLi (1.54 mmol) in THF (2 mL) were reacted to generate the cuprate in the same fashion as above. The allene (0.30 mmol) in THF (2 mL) was added to the stirred homogeneous cuprate solution at −78 °C. The reaction was quenched after 60 min. Workup and purification as above afforded the cephems.

Procedure C. Reaction of Allenes with Cuprates Derived from Grignards. Copper(I) bromide–dimethyl sulfide complex or copper iodide (1.00 mmol) was suspended in dry THF (2.0 mL) under argon and the flask was cooled to −78 °C. To the stirred suspension was added the Grignard solution (2.0 mmol) dropwise. The cooling bath was removed and the suspension was stirred until a dark homogenous solution was obtained (*ca.* 10–15 min). The cuprate solution was recooled to −78 °C and a solution of allene (0.50 mmol in 2 mL of THF) was added. The dark solution was stirred until completion of reaction was observed (as indicated by TLC or HPLC) and then poured into a saturated NH_4Cl solution/ethyl acetate. The organic phase was washed with 10% $NaHCO_3$ (5 mL) and brine (5 mL), dried ($MgSO_4$), and evaporated to afford the crude cephem.

Diphenylmethyl (7*S*,6*R*)-7-(Phenoxyacetamido)-3-methyl-3-cephem-4-carboxylate (42). Following Procedure A. The cuprate was prepared from CuI (190 mg, 0.37 mmol) and MeLi (0.57 mL, 0.74 mmol, 1.3 M solution in hexanes) in THF (1.5 mL). Treatment with **28** (153 mg, 0.23 mmol, dissolved in 2.0 mL of THF) afforded a mixture of cephems **42a** and **42b**

(*ca.* 3:2, 0.11 g, 60%) after flash chromatography (30% ethyl acetate/hexanes). These cephems were identical to the literature samples.[12a] Also isolated was **41** (15 mg, 10%) as an amorphous solid, identical to a literature sample.[28]

Following Procedure B. The cuprate was prepared from CuCN (69.0 mg, 0.77 mmol) and MeLi (1.19 mL, 1.54 mmol, 1.29 M solution in hexanes) in THF (1.5 mL). Treatment with **28** (200 mg, 0.30 mmol) in THF (2.0 mL) afforded **42b** (280 mg, 70%) and **41** (6.0 mg, 4%).

Following Procedure C. The cuprate was prepared from MeMgBr (0.32 mL, 0.97 mmol, 3.0 M solution in ether) and CuI (93.0 mg, 0.48 mmol) in THF (1.0 mL). Treatment of **28** (200 mg, 0.30 mmol) with the cuprate for 15 min followed by workup and flash chromatography (30% EtOAc/hexanes) afforded **42a** (120 mg, 80%) and trace amounts of **41**.

Following Procedure C. The cuprate was prepared from MeMgBr (0.32 mL, 0.97 mmol, 3.0 M solution in ether) and CuI (92.9 mg, 0.48 mmol) in THF (1.0 mL). Treatment of **47** (0.20 g, 0.30 mmol) with the cuprate for 15 min followed by workup and flash chromatography (30% EtOAc/hexanes) afforded **42a** (147 mg, 95%).

Diphenylmethyl (7*S*,6*R*)-7-(Phenoxyacetamido)-3-(*Z*)-propenyl-3-cephem-4-carboxylate (43a). Following Procedure A. (a) The cuprate was prepared from CuI (67.4 mg, 0.35 mmol) and (*Z*)-1-propenyllithium (0.71 mL, 0.69 mmol, 0.98 M solution in ether) in THF (2.0 mL). Treatment with **28** (116 mg, 0.17 mmol) for 20 min at −78 °C followed by flash chromatography (30% EtOAc/hexanes) afforded a mixture of **43a** and **43b**, *ca.* 9:1 by ^{1}H NMR (41 mg, 45%) as a foam. The compounds were identical to literature samples.[12a] Also isolated from the reaction mixture was cephem **41** (9.0 mg, 8%).

(b) CuI (72.0 mg, 0.33 mmol) was suspended in dry THF (1.5 mL). The flask was cooled to −78 °C and (*Z*)-1-propenyltributyltin (249 mg, 0.75 mmol) followed by MeLi (0.54 mL, 0.75 mmol, 1.4 M solution in ether) was added and the solution was stirred for 3 h. To the dark cuprate suspension was added a solution of **28** (110 mg, 0.16 mmol) in THF (1.5 mL). After stirring for 1 h at −78 °C, the solution was poured into a 1:1 mixture of saturated NH_4Cl and EtOAc (10 mL). The organic layer was washed with brine (3 mL) and 10% $NaHCO_3$ (3 mL), dried ($MgSO_4$), and evaporated to give the crude cephem. Purification was carried out by flash chromatography (30% EtOAc/hexanes) to give a mixture of **43a** and **43b**, 95:5 by ^{1}H NMR (53.0 mg, 30%) as a foam. Trace amounts of **41** were also isolated.

Following Procedure B. (a) The cuprate was prepared from CuCN (44.0 mg, 0.49 mmol) and (*Z*)-1-propenyllithium (98.0 μL, 0.98 mmol, 1.0 M solution in ether) in THF (2 mL). Treatment with **28** for 1 h at −78 °C afforded, after flash chromatography (30% EtOAc/hexanes), **43a** and **43b**, *ca.* 2:5 by ^{1}H NMR (62.0 mg, 60%).

(b) CuCN (44.0 mg, 0.49 mmol) was treated by THF (4.0 mL) under argon. The flask was cooled to −78 °C and (*Z*)-1-propenyllithium was slowly added (0.49 mL, 0.49 mmol, 1.0 M solution in ether) followed by MeLi (0.24 mL, 0.49 mmol, 2.0 M solution in ether). The cooling bath was removed and the suspension was stirred for 30 min, yielding a homogeneous solution. The cuprate solution was recooled to −78 °C and a solution of **28** (128 mg, 0.196 mmol) in THF (1.5 mL) was added. After stirring for 35 min, the reaction mixture was poured into a 1:1 mixture of saturated NH_4Cl and EtOAc (10 mL). The organic layer was washed with brine (3 mL) and 10% $NaHCO_3$ (3 mL), dried ($MgSO_4$), and evaporated to give the crude cephems. Flash chromatography (40% EtOAc/hexanes) afforded **43a** and **43b** (48.0 mg, 45%) in a ratio of *ca.* 8:2 by ^{1}H NMR. By chromatography, **41** (10.0 mg, 8%) as well as a mixture of **42a** and **42b** (11.0 mg, 10%) were also isolated.

Procedure C. (a) The cuprate was prepared by the addition of (*Z*)-propenylmagnesium bromide (4.81 mL, 3.66 mmol, 1.0 M solution in THF) to CuI (348 mg, 1.83 mmol) in THF (15 mL). Treatment of allene **28** (1.00 g, 1.53 mmol) with the cuprate for 15 min followed by workup afforded cephem **43a** (0.50 g, 61%) which was purified by crystallization (2-propanol). HPLC indicated <4% of the *E* isomer.

(b) The cuprate was prepared by the addition of (*Z*)-propenylmagnesium bromide (0.68 mL, 0.68 mmol, 1.0 M solution in THF) to CuBr·Me_2S (69.0 mg, 0.34 mmol) in THF (1.5 mL). Treatment of allene **28** (155 mg, 0.23 mmol) with the cuprate at −100 °C for 15 min followed by workup afforded cephem **43a** (93.0 mg, 75%) which was purified by crystallization (2-propanol). HPLC indicated <4% of the *E* isomer.

Diphenylmethyl (7*S*,6*R*)-7-(Phenoxyacetamido)-3-ethyl-3-cephem-4-carboxylate (51). Following Procedure C. The cuprate was prepared from EtMgBr (0.16 mL, 0.46 mmol, 3.0 M solution in ether) to CuI (43.6 mg, 0.23 mmol) in THF (2.0 mL). Treatment with **47** (100 mg, 0.15 mmol) for 20 min followed by workup and flash chromatography (30% EtOAc/hexanes) afforded the cephem **51** as a foam (68.0 mg, 85%). The compound was identical to a literature sample.[12a]

Diphenylmethyl (7*S*,6*R*)-7-(Phenoxyacetamido)-3-phenyl-3-cephem-4-carboxylate (52). Following Procedure C. The cuprate was prepared from PhMgBr (0.98 mL, 0.98 mmol, 1.0 M solution in THF) to CuI (93.0 mg, 0.49 mmol) in THF (2.0 mL). Treatment of **47** (200 mg, 0.31 mmol) with the cuprate for 20 min followed by workup and flash chromatography (35% EtOAc/hexanes) afforded cephem **52** as a foam (128 mg, 75%). The compound was identical to a literature sample.[12a]

Diphenylmethyl (7*S*,6*R*)-7-(Phenoxyacetamido)-3-isopropyl-3-cephem-4-carboxylate (53). Following Procedure C. The cuprate was prepared by the addition of *i*-PrMgBr (0.45 mL, 0.92 mmol, 2.0 M solution in THF) to CuI (87.0 mg, 0.46 mmol) in THF (2.0 mL). Treatment of **47** (200 mg, 0.31 mmol) with the cuprate for 15 min followed by workup and flash chromatography (35% EtOAc/hexanes) afforded cephem **53** as a foam (127 mg, 78%). The compound was identical to a literature sample.[12a]

Diphenylmethyl (7*S*,6*R*)-7-(Phenoxyacetamido)-3-vinyl-3-cephem-4-carboxylate (54). Following Procedure C. The cuprate was prepared by the addition of vinylmagnesium bromide (0.67 mL, 0.67 mmol, 1.0 M solution in THF) to CuI (64.0 mg, 0.34 mmol) in THF (2.0 mL). Treatment of **47** (0.10 g, 0.15 mmol) with the cuprate for 15 min followed by workup and flash chromatography (35% EtOAc/hexanes) afforded cephem **54** (62 mg, 78%). The compound was identical to a literature sample.[12a]

Diphenylmethyl (7*S*,6*R*)-7-(Phenoxyacetamido)-3-allyl-3-cephem-4-carboxylate (55). Following Procedure C. The cuprate was prepared by the addition of allylmagnesium bromide (0.67 mL, 0.67 mmol, 1.0 M solution in ether) to CuI (64 mg, 0.33 mmol) in THF (2.0 mL). Treatment of **47** (100 mg, 0.15 mmol) with the cuprate for 30 min followed by workup and flash chromatography (35% EtOAc/hexanes) afforded the cephem **55** as a glass (67.0 mg, 82%). The compound was identical to a literature sample.[12a]

Diphenylmethyl (7*S*,6*R*)-7-(Phenoxyacetamido)-3-cyclohexyl-3-cephem-4-carboxylate (56). Following Procedure C. The cuprate was prepared by the addition of cyclohexylmagnesium bromide (0.45 mL, 0.90 mmol, 2.0 M solution in THF) to CuI (86.0 mg, 0.45 mmol) in THF (2.0 mL). Treatment of **47** (200 mg, 0.31 mmol) with the cuprate for 10 min followed by workup and flash chromatography (35% EtOAc/hexanes) afforded the cephem **56** as a foam (134 mg, 75%). The compound was identical to a literature sample.[12a]

Diphenylmethyl (7*S*,6*R*)-7-(Phenoxyacetamido)-3-cyclopentyl-3-cephem-4-carboxylate (57). Following Procedure C. The cuprate was prepared by the addition of cyclopentylmagnesium bromide (1.54 mL, 3.08 mmol, 2.0 M solution in THF) to CuBr·Me_2S (312 mg, 1.54 mmol) in THF (2.0 mL). Treatment of **47** (505 mg, 0.77 mmol) with the cuprate for 15 min followed by workup and flash chromatography (35% EtOAc/hexanes) afforded cephem **57** (298 mg, 68%). The compound was identical to a literature sample.[12a]

Diphenylmethyl (7*S*,6*R*)-7-(Phenoxyacetamido)-3-*n*-hexyl-3-cephem-4-carboxylate (58). Following Procedure C. The cuprate was prepared by the addition of *n*-hexylmagnesium bromide (1.92 mL, 3.84 mmol, 2.0 M solution in THF) to CuBr·Me_2S (0.39 g, 1.92 mmol) in THF

(3.0 mL). Treatment of **47** (0.63 g, 0.96 mmol) with the cuprate for 15 min followed by workup and flash chromatography (35% EtOAc/hexanes) afforded cephem **58** as a foam (0.44 g, 78%). The compound was identical to a literature sample.[12a]

Diphenylmethyl (7*S*,6*R*)-7-(Phenoxyacetamido)-3-*tert*-butyl-3-cephem-4-carboxylate (59). Following Procedure C. The cuprate was prepared by the addition of *t*-BuMgBr (0.45 mL, 0.92 mmol, 2.0 M solution in THF) to CuI (87.0 mg, 0.46 mmol) in THF (3.0 mL). Treatment of **47** (200 mg, 0.31 mmol) with the cuprate for 15 min followed by workup and flash chromatography (35% EtOAc/hexanes) afforded cephem **59** as a foam (135 mg, 78%). The compound was identical to a literature sample.[12a]

Diphenylmethyl (7*S*,6*R*)-7-(Phenoxyacetamido)-3-(*p*-toluenesulfonyl)-3-cephem-4-carboxylate (60). To a solution of allene **47** (0.24 g, 0.36 mmol) in dry *N*-methylpyrrolidinone (3 mL) was added anhydrous LiBr (0.12 g, 1.38 mmol), and the resulting mixture was stirred for 16 h at room temperature. The mixture was poured into a solution containing water and EtOAc (1:1). The organic phase was washed with brine, water, and 0.1 N HCl solution, dried ($MgSO_4$), and evaporated to afford the crude cephem. Crystallization with EtOAc/hexanes afforded **60** (149 mg, 61%): mp 192–3 °C; ^{1}H NMR ($CDCl_3$) δ 7.72 (d, 2H), 7.50–7.1 (m, 14 H), 7.10 (s, 1H), 7.00 (t, 1H), 6.88 (d, 2H), 5.92 (dd, J = 5.2 Hz; J' = 6.8 Hz, 1H), 5.0 (d, J = 5.2 Hz, 1H), 4.52 (s, 2H), 3.59 (d, J = 17.7 Hz, 1H), 3.38 (d, J = 17.7 Hz, 1H), 2.40 (s, 3H). Anal. Calcd for $C_{35}H_{30}N_2O_7S_2$: C, 64.20; H, 4.62; N, 4.78; S, 9.79. Found: C, 63.16; H, 4.48; N, 4.48; S, 9.80.

Diphenylmethyl (7*S*,6*R*)-7-(Phenoxyacetamido)-3-[(1-methyl-1,2,3,4-tetrazol-5-yl)thio]-3-cephem-4-carboxylate (61). To a solution of allene **47** (100 mg, 0.15 mmol) in dry *N*-methylpyrrolidinone (2 mL) was added anhydrous LiBr (26.0 mg, 0.30 mmol) followed by the sodium salt of the *N*-methyl-1,2,3,4-tetrazole (41.4 mg, 0.30 mmol). The resulting mixture was stirred for 16 h at room temperature. The mixture was poured into a solution containing water and EtOAc (1:1). The organic phase was washed with brine, water, and 0.1 N HCl solution, dried ($MgSO_4$), and evaporated to afford the crude cephem which was further purified by flash chromatography (silica: 30% EtOAc/hexanes) to afford **60** (28 mg, 31%) as a foam: ^{1}H NMR ($CDCl_3$) δ 7.58–6.94 (m, 16 H), 6.89 (d, J = 7.2 Hz, 1H), 6.00 (dd, J = 5.2 and 7.1 Hz, 1H), 5.15 (d, J = 5.2 Hz, 1H), 4.52 (s, 2H), 3.81 (d, J = 17.5 Hz, 1H), 3.77 (s, 3H), 3.41 (d, J = 17.5 Hz, 1H); HRMS (FAB) calcd for $C_{30}H_{27}N_6O_5S_2$ (MH^+) 616.7084, found 616.7075.

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