A Synthetic Approach to 3-Substituted Cephalosporins: Carbon–Carbon Bond Formation at C(3) of the Cephem via Organocuprate Chemistry†

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An efficient approach to the synthesis of 3-substituted cephalosporins is described. 3-Trifloxycephems readily undergo addition–elimination reactions with a variety of organocuprates to form carbon–carbon bonds at the C(3) position of the cephem nucleus. The organocuprates derived from Grignard reagents and copper(I) bromide·dimethyl sulfide complex in THF functioned most effectively in the reaction and did not promote any concurrent Δ^3/Δ^2 isomerization (a problem commonly encountered in cephalosporin chemistry). The chemistry was applied to the synthesis of a variety of 3-substituted cephalosporins bearing carbon substituents including alkyl, cycloalkyl, aryl, alkenyl, and allyl. Precursors for the synthesis of the antibiotics Cefadroxil, Cefixime, and Cefzil are also available via this route.

Introduction

In recent years, considerable interest has been focused on altering the C(3) substituent of the cephem nucleus to obtain a variety of analogues with enhanced biological activities. The discovery of cephalosporin C and 3-methylenecephams spurred the synthesis of useful antimicrobials modified at C(3) by displacement of the acetoxy group with heterocyclic tertiary bases and sulfur nucleophiles or by direct heteroatom substitution at C(3) of the 3-methylenecepham. Both strategies provided 3-substituted cephalosporins, especially 3-norcephalosporins, exhibiting marked antimicrobial properties with oral therapeutic efficacy.[1] In connection with our ongoing research on β-lactam antibiotics, we were interested in forming a carbon–carbon bond at the C(3) position of cephalosporins. Several analogues with carbon substitution at C(3) possess exemplary biological profiles, and some representative examples in this class of antibiotics are Cefadroxil, Cephalexin, Cefixime, and Cefzil (Figure 1).[2] Our interest in developing a cost-effective synthesis of Cefzil prompted us to devise a general and practical approach to synthesize cephems with carbon-based functionality at the C(3) position.

Previous synthetic methodologies to form a C–C bond at C(3) relied on Friedel–Crafts reactions with 3-[(trifluoroacetoxy)methyl]ceph-2-em-4-carboxylic acids,[3] reaction of 3-formylcephems with stabilized phosphoranes,[4] reaction of 3-hydroxycephems with stabilized ylides,[5] conjugate addition of organocuprates to 3-chloro- and 3-vinylcephems,[6] and addition of Grignard reagents to 3-formylcephems.[7] Unfortunately, the scope of the above procedures is limited and often the cephems isolated exist as a mixture of Δ^2 and Δ^3 isomers. Recently, Farina and co-workers reported a general method for the synthesis of C(3)-substituted cephems, based on the Stille reaction.[8] The procedure utilizes palladium(0)-mediated reactions of 3-trifloxycephems with stannanes in the presence of tri(2-furyl)phosphine.

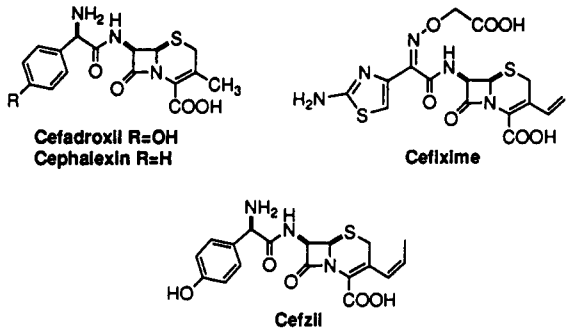


Figure 1.

The ready availability of 3-hydroxycephem 1 from penicillin prompted an interest in using 1 as the key synthon for our target compounds. In analogy to Farina's palladium-based approach, we decided to employ organocuprates and 3-trifloxycephems, as reactions of substrates containing carbon-bound leaving groups with

† The work was carried out at the Chemical Process Development Laboratories, Bristol-Myers Squibb Pharmaceutical Research Institute, Syracuse, N.Y.

(1) (a) Abraham, E. P.; Loder, P. B. In *Cephalosporins and Penicillins; Chemistry and Biology*; Flynn, E. H., Ed.; Academic Press: New York, 1972; pp 1–26. (b) Kukolja, S.; Chauvette, R. R. In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vol. 1, pp 93–198. (c) Durckheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180–202. Trifloxycephems have also been shown to be ideal substrates for the synthesis of 3-norcephems, Farina, V.; Baker, S. R.; Hauck, S. I. *J. Org. Chem.* **1989**, *54*, 4962.

(2) Newall, C. E. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Bently, P. H., Southgate, R., Eds.; The Royal Society of Chemistry: London, 1988; Special Publication No. 70, pp 365–380. For additional biological profile on Cefzil (recently introduced by Bristol-Myers Squibb), see: Tomatsu, K.; Shigeyuki, A.; Masuyoshi, S.; Kondo, S.; Hirano, M.; Miyaki, T.; Kawaguchi, H. *J. Antibiot.* **1987**, *40*, 1175.

(3) Peter, H.; Rodriguez, H.; Muller, B.; Sibral, W.; Bickel, H. *Helv. Chim. Acta* **1974**, *57*, 2024.

(4) Webber, J. A.; Ott, J. L.; Vasileff, R. T. *J. Med. Chem.* **1975**, *18*, 986.

(5) Scartazzini, R. *Helv. Chim. Acta* **1977**, *60*, 1510.

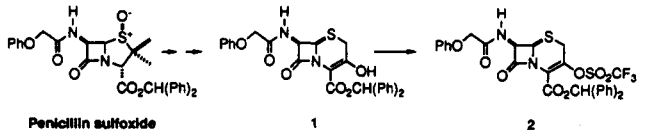
(6) Spry, D. O.; Bhala, A. R. *Heterocycles* **1985**, *23*, 1901.

(7) Spry, D. O.; Bhala, A. R. *Heterocycles* **1986**, *24*, 1799.

(8) Farina, V.; Baker, S. R.; Benigni, D. A.; Hauck, S. I.; Sapino, C. *J. Org. Chem.* **1990**, *55*, 5833 and references cited therein. For similar chemistry employing 3-[(fluorosulfonyl)oxy]cephems, see: Roth, G. P.; Sapino, C. *Tetrahedron Lett.* **1991**, *32*, 4073. For palladium-catalyzed chemistry of β-lactam vinyl triflates in the carbacephem series, see: Blaszczak, L. C.; Brown, R. F.; Cook, G. K.; Hornback, W. J.; Hoying, R. C.; Indelicato, J. M.; Jordan, C. L.; Katner, A. S.; Kinnick, M. D.; McDonald, J. H.; Morin, J. M.; Munroe, J. E.; Pasini, C. E. *J. Med. Chem.* **1990**, *33*, 1656 and references cited therein.

0022-3263/93/1958-2296$04.00/0

Scheme I



organocuprates are among the most conceptually straightforward operations for the formation of new C–C bonds.[9] Several years ago, McMurry and Scott reported the stereoselective coupling reaction of lithium dialkylcuprates with enol triflates affording coupled products in high yields.[10] Based on McMurry's chemistry, we reported our initial study on the reaction of organocuprates with 3-trifloxycephems.[11] Since then we have developed the chemistry further, and herein we disclose the details of our study on the construction of new C–C bonds at the C(3) position in cephalosporins through the use of organocopper chemistry.[12]

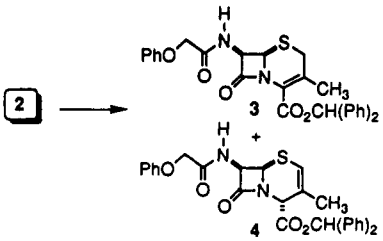
Results and Discussion

Treatment of 3-hydroxycephem **1**, available from penicillin sulfoxide,[13] with trifluoromethanesulfonic anhydride and diisopropylethylamine (Hunig's base) at −78 °C afforded a highly crystalline 3-trifloxycephem **2** (Scheme I).

Reaction of **2** with Gilman's reagent (Me_2CuLi) or a lower-order (LO) cuprate prepared from methyllithium and copper iodide in tetrahydrofuran (THF) afforded **3** (Δ^3) and **4** (Δ^2) as a 1:1 mixture in 65% yield. The isomerization of the olefin was anticipated since cuprates are basic in nature[9a] and cephalosporins are known to isomerize to the thermodynamically more stable Δ^2 isomer under basic conditions.[14] A similar result was observed when a higher-order (HO) cyanocuprate, prepared from copper cyanide and methyllithium, was employed (Scheme II).[9d]

The pioneering work by Ashby[15a] and Lipshutz[15b] on the composition of Gilman's reagent demonstrated that the reagent exists as an equilibrium mixture of different entities along with minute amounts of free MeLi. Hence, the formation of Δ^2-cephem during the course of the reaction could very well be attributed to the presence of free methyllithium in the cuprate solution.[16]

Scheme II



1. Me_2CuLi (ca. 1:1 3/4) 65%
2. $Me_2Cu(CN)Li_2$ (ca. 2:3 3/4) 75%

During the course of our investigations into ways to impede the formation of the undesired Δ^2 isomer, Lipshutz published an interesting study on the role of boron trifluoride etherate ($BF_3{\cdot}Et_2O$) in the reactions of LO organocuprates. The study suggested that $BF_3{\cdot}Et_2O$ was modifying the cuprate by sequestering the alkyllithium species, thereby generating a different and more reactive cuprate/Lewis acid combination (eq 1).[17]

$$2\,(R_2CuLi)_2 \xrightarrow[-78°C]{4\,BF_3} (R_2CuLi)_2 + R_3Cu_2Li + \boxed{RLi{\cdot}BF_3} + 3\,BF_3 \qquad \text{(eq 1)}$$

This chemistry presented a feasible solution to our problem, and we envisioned the possibility of obtaining an isomerically pure 3-methylcephem **3** by employing Me_2CuLi in conjunction with $BF_3{\cdot}Et_2O$, hoping that any free alkyllithium would be trapped by the Lewis acid. Indeed, treatment of **2** with Me_2CuLi in combination with $BF_3{\cdot}Et_2O$ in THF afforded **3** in 85% yield. The strategy was further extended to other organocuprates as well. The methodology worked satisfactorily with the alkyl- and arylcuprates, but low yields were realized with the alkenylcuprates. In particular, we were interested in the successful reaction of (*Z*)-1-propenylcuprate with **2** which would afford **8**, leading to a cost-effective synthesis of the antibiotic Cefzil. However, treatment of **2** with [(*Z*)-1-propenyl]$_2$CuLi afforded **8** in 30% yield along with **1** and decomposition products. In spite of the unsatisfactory yield, we demonstrated the possibility of introducing, *stereospecifically*, the (*Z*)-1-propenyl moiety at the C(3) position by a cuprate-mediated reaction (Scheme III).

We continued our efforts to optimize the methodology in the synthesis of **8**. The challenge was to identify a cuprate reagent which would transfer the alkenyl group stereospecifically without causing any Δ^2/Δ^3 isomerization. A variety of (*Z*)-1-propenylcuprates were screened, and the results are summarized in Table I. The cuprates derived from (*Z*)-1-propenyllithium (entries 2 and 3) or by the transmetalation chemistry[18] using (*Z*)-1-propenyltributyltin (entries 1 and 4) were found to be unsuitable, as low yields or mixtures of **8** (Δ^3) and **9** (Δ^2) were obtained.

(9) (a) Posner, G. H. *Org. React.* **1972**, *19*, 1. (b) Posner, G. H. *Org. React.* **1975**, *22*, 253. (c) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980. (d) Lipshutz, B. H. *Synthesis* **1987**, 325. (e) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005.

(10) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1980**, *21*, 4313. Recently, Lipshutz also demonstrated the coupling of vinyl triflates with a variety of cyanocuprates with allylic ligands, Lipshutz, B. H.; Elworthy, T. R. *J. Org. Chem.* **1990**, *55*, 1695. For examples of additions–eliminations involving organocuprates, see: Posner, G. H.; Brunelle, D. J. *J. Chem. Soc., Chem. Commun.* **1973**, 907. Casey, C. P.; Marten, D. F.; Boggs, R. A. *Tetrahedron Lett.* **1973**, *23*, 2071. Kobayashi, S.; Mukaiyama, T. *Chem. Lett.* **1974**, 705. Dieter, R. K.; Silks, L. A. *J. Org. Chem.* **1986**, *51*, 4687. Back, T. G.; Collins, S.; Krishna, M. J.; Law, K.-W. *J. Org. Chem.* **1987**, *52*, 4258.

(11) For our preliminary communication: Kant, J.; Sapino, C.; Baker, S. *Tetrahedron Lett.* **1990**, *31*, 3389. Also, Kant, J.; Sapino, C. U.S. Pat. 5043439, 1991.

(12) Reaction of the organocuprates (Me_2CuLi and *n*-Bu_2CuLi) with 3-chlorocephem, 3-(iodomethyl)cephem (Δ^2 isomer) and 3-vinylcephem has been reported by Spry; see ref 6. The chemistry afforded, albeit in low yields, mixtures of Δ^2 and Δ^3 cephems.

(13) (a) Woodward, R. B.; Bickel, H. Ger. Offen. 2606196, 1976; *Chem. Abstr.* **1977**, *86*, 29852. (b) Scartazzini, R.; Bickel, H. *Heterocycles* **1977**, *7*, 1165.

(14) Cocker, J. D.; Eardley, S.; Gregory, G. I.; Hall, M. E.; Long, A. G. *J. Chem. Soc. C* **1966**, 1142.

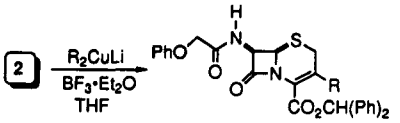
(15) (a) Ashby, E. C.; Watkins, J. J. *J. Am. Chem. Soc.* **1977**, *99*, 5312. (b) Lipshutz, B. H.; Kozlowski, J. A.; Breneman, C. M. *J. Am. Chem. Soc.* **1985**, *107*, 3197.

(16) The presence of free alkyllithium most likely promotes the Δ^3/Δ^2 isomerization by abstracting the C(2) proton from the cephem. However, as proposed by one of the reviewers, it is also possible that the amide side chain is deprotonated and the basic nitrogen then abstracts the proton from C(2) in a six-centered transition state to enolize the conjugated ester. I thank the reviewer for helpful comments.

(17) Lipshutz, B. H.; Ellsworth, E. L.; Siahaan, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 1351.

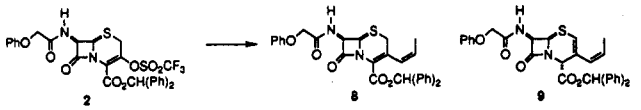
(18) Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. *J. Am. Chem. Soc.* **1988**, *110*, 2641 and references cited therein.

Scheme III



Cephem	R	Yield (%)
3	Me	85
5	Et	75
6	Ph	65
7	vinyl	35
8		30

Table I



entry	source	cuprates	% yield[a]
1	 CuI MeLi BF_3·OEt_2	$(\text{vinyl})_2\text{CuLi}$	34
2	 CuCN	$(\text{vinyl})_2\text{Cu(CN)Li}_2$	64 (ca. 3:2 8/9)
3	 CuCN BF_3·OEt_2	$(\text{vinyl})_2\text{Cu(CN)Li}_2$	62 (ca. 7:2 8/9)
4	 CuCN MeLi	$(\text{vinyl})(\text{Me})\text{Cu(CN)Li}_2$	60 (ca. 2:3 8/9)[b]
5	 $CuBr\cdot Me_2S$	$(\text{vinyl})_2\text{CuMgBr}$	80

[a] Isolated yield of cephem 8. Combined isolated yield where Δ^3 and Δ^2 isomers are observed. [b] Also isolated 10% of 3-methylcephem as a mixture of Δ^3 and Δ^2 isomers.

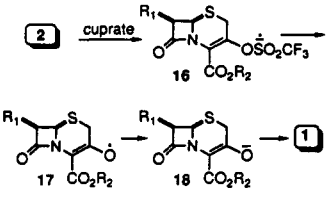
The cuprate generated from copper iodide, (*Z*)-1-propenyltributyltin, and methyllithium in the presence of BF_3·Et_2O afforded only 34% of **8** along with **1**[19] and decomposition products (entry 1). Similar results were observed earlier with a LO cuprate derived from (*Z*)-1-propenyllithium (Scheme III). The HO cyanocuprate with or without Lewis acid complex gave a modest yield but promoted Δ^3/Δ^2 isomerization (entries 2 and 3). Treatment of **2** with a mixed HO cyanocuprate, derived via in situ transmetalation between 1.0 equiv of stannane and 2.0 equiv of $Me_2Cu(CN)Li_2$, afforded **8** and **9** along with a mixture of 3-methylcephems **3** and **4** (ca. 10%) (entry 4). The formation of the 3-methylcephems probably occurred as a result of transfer of the methyl group from $[(Z)\text{-1-propenyl(Me)Cu(CN)Li}_2]$[20] or from incomplete transmetalation.

In addition to undergoing reaction at C(3), the cuprate could also attack the carbonyl group of a β-lactam ring or the amide side chain. These reactions could readily afford a variety of products, most likely polymers. However, low yields of the expected products **8** and **9** and the observed decomposition products could also be due to lack of chemoselectivity of (*Z*)-1-propenylcuprates toward the potential reactive sites on the cephem **2**.[21]

After initial screening of a number of propenyl cuprates, we turned our attention toward copper-catalyzed additions of Grignard reagents.[22] Treatment of **2** with (*Z*)-1-propenylmagnesium bromide in THF along with 10 mol % of copper iodide or copper chloride at low temperature for 1–4 h afforded only trace amounts of **8**, along with recovered starting material and some decomposition products. Prolonged reaction times resulted in additional degradation. No improvement was realized by increasing the amount of copper salt from 10 to 30 mol %. Nonetheless, after a few unsuccessful attempts, we returned to the cuprate chemistry and generated $[(Z)\text{-1-propenyl}]_2\text{CuMgBr}$ from the corresponding Grignard and copper iodide in THF. Treatment with **2** in THF at −78 °C cleanly afforded the desired cephem **8** in 60% yield. The transfer of the (*Z*)-1-propenyl group was stereospecific (>99%)[23] as no *E* isomer was detected by ^{1}H NMR. Further optimization of the reaction and replacement of copper iodide with copper(I) bromide–dimethyl sulfide complex[24] furnished the target cephem **8** in 80% yield (entry 5, Table I). The intermediate **8** was eventually converted to Cefzil following standard deprotection and acylation protocols.[25]

The scope of this chemistry was further examined by preparing a variety of structurally diverse alkyl, cycloalkyl, aryl, alkenyl, and allyl organocuprates from the corresponding Grignard reagents and copper(I) bromide–dimethyl sulfide complex at −78 °C in THF. Reactions with **2** for 15–30 min afforded isomerically pure 3-substituted (Δ^3) cephems in high yields (Table II). Following this procedure we also synthesized the cephems **3** and **7**,

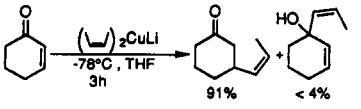
(19) The mechanism of cuprate addition is widely believed to proceed via a single electron-transfer process.[9] Copper can also donate an electron to the sulfonate ester to form the radical anion intermediate **16** which in turn might fragment into an alkoxy radical **17** and the sulfinate anion. The alkoxy radical could be reduced to the alkoxy anion **18** which upon quenching with a proton source would afford 3-hydroxycephem **1**. We do not believe that the formation of 3-hydroxycephem is simply due to hydrolysis of the triflate, arising from quenching of the reaction mixture with saturated NH_4Cl solution.



The rationale is based on the work described by Closson on the regeneration of alcohols from sulfonates employing arene radicals anion. Closson, W. D.; Ganson, J. R.; Rhee, S. W.; Quaal, K. S. *J. Org. Chem.* **1982**, *47*, 2476.

(20) On the study of ligand transferability, Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A.; Parker, D. *J. Org. Chem.* **1984**, *49*, 3928.

(21) To remove any doubts regarding the formation of $[(Z)\text{-1-propenyl}]_2\text{CuLi}$, it was decided to examine the reactivity of the cuprate toward a simple enone system. The desired cuprate was prepared according to the procedure described earlier and on treatment with 2-cyclohexen-1-one at −78 °C for 3 h afforded the 1,4-addition product in 91% yield along with a trace of 1,2-addition product.



ratio by ^{1}H NMR

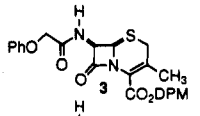
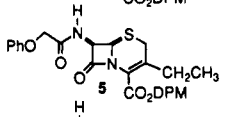
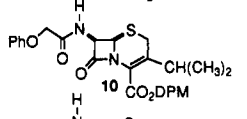
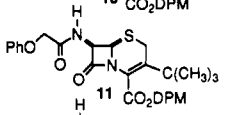
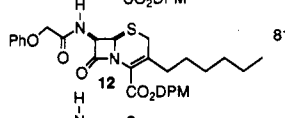
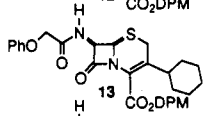
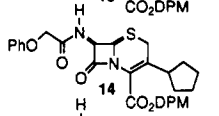
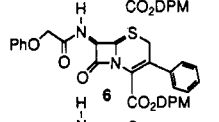
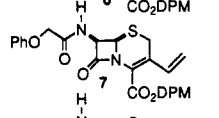
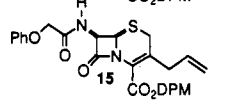
(22) (a) Erdik, E. *Tetrahedron* **1984**, *40*, 641. (b) Normant, J. F. *Pure Appl. Chem.* **1978**, *50*, 709.

(23) The solution of (*Z*)-1-propenylmagnesium bromide in THF contained <4–5% of the corresponding *E* isomer. We did not observe any change in the ratio of *Z* and *E* isomers after the cuprate reaction (by 360-MHz NMR). For a literature precedent on the stereoselective transfer of the (*Z*)-1-propenyl moiety via a HO cyanocuprate in the synthesis of a polyene macrolide, see: Lipshutz, B. H.; Barton, J. C. *J. Org. Chem.* **1988**, *53*, 4495.

(24) $CuBr\cdot Me_2S$ complex has been found to be superior to CuI in the cuprate reactions. Bertz, S. H.; Gibson, C. P.; Dabbagh, G. J. *Tetrahedron Lett.* **1978**, *28*, 4251.

(25) Naito, T.; Hoshi, H.; Aburaki, S.; Abe, Y.; Okumura, J.; Tomatsu, K.; Kawaguchi, H. *J. Antibiot.* **1987**, *40*, 991.

Table II

cuprate	time (−78 °C)	cephem	% yield
$Me_2CuMgBr$	15 min		95
$Et_2CuMgBr$	20 min		89
$i\text{-}Pr_2CuMgBr$	15 min		73
$t\text{-}Bu_2CuMgBr$	15 min		78
$hexyl_2CuMgBr$	15 min		81
$(\bigcirc)_2CuMgBr$	10 min		62
$(\bigcirc)_2CuMgBr$	15 min		82
$Ph_2CuMgBr$	20 min		85
$vinyl_2CuMgBr$	15 min		85
$allyl_2CuMgBr$	30 min		82

DPM = $CH(C_6H_5)_2$

precursors to the antibiotics Cefadroxil, Cephalexin, and Cefixime, respectively.

The composition of Normant's reagent using different stoichiometric amounts of MeMgX and CuX in THF was studied in detail by Ashby and Goel.[26] According to their studies, 1.0 equiv of copper bromide and 2.0 equiv of methylmagnesium bromide in THF results in the formation of a dimeric species Cu_2MgMe_4 along with $MgBr_2$. Involvement of the halide with the complex was not observed in NMR studies by Ashby. The successful implementation of Normant's cuprates (derived from Grignards and copper salt) in our studies could be the consequence of a reaction between Cu_2MgR_4 (a single entity) and **2**, which is quite different when compared to the reaction with LO or HO cuprates, which usually exist as an equilibrium mixture of different entities, probably with differing degrees of reactivity and selectivity as well.

In conclusion, we have presented a practical approach to the synthesis of carbon-based 3-substituted cephalosporins. The starting Grignards are readily accessible, being either available commercially or easily prepared. The 3-trifloxycephem is readily synthesized from penicillin, yet another inexpensive substrate available from the natural chiral pool. The chemistry can be utilized to attach many desirable carbon tethers to the C(3) position of cephalosporins and therefore should prove valuable to medicinal chemists engaged in the field of cephalosporin chemistry. Furthermore, the methodology nicely overcomes the troublesome problem of Δ^3/Δ^2 isomerization, frequently experienced in working with the cephalosporins.

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

Experimental Section

General Methods. All reactions were carried out under an atmosphere of argon in glassware dried overnight at 120 °C and cooled under argon. THF was distilled from benzophenone/sodium ketyl prior to use. Unless stated otherwise, Grignard reagents and organolithiums were purchased from Aldrich and Organometallics, INC., and were titrated before use by the method of Watson and Eastham.[27] (*Z*)-1-Propenyllithium was prepared according to the protocol of Whitesides in ether.[28] (*Z*)-1-Propenylmagnesium bromide was prepared in THF at ambient temperature following the protocol of Beak[29a] and Seyferth.[29b] (*Z*)-1-Propenyltributyltin was prepared following the protocol of Seyferth.[30] Copper(I) bromide–dimethyl sulfide complex was purchased from Aldrich and was further purified by the procedure of House.[31] Other solvents and reagents employed were of commercial grade.

Analytical thin-layer chromatography was performed on EM Reagent 0.25-mm silica gel 60-F plates. Visualization was accomplished with UV light and ethanolic phosphomolybdic acid solution followed by heating. Purification of the products was carried out by flash chromatography[32] using silica (EM reagent 60, 230–400 mesh) and the appropriate solvent system.

^1H NMR spectra were recorded on a Brucker WM-360 (360 MHz) instrument at ambient temperature. Data are reported as follows: chemical shift in ppm from internal standard tetramethylsilane on the δ scale, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, m = multiplet, AB q = AB system quartet), coupling constant (Hz), and integration. Combustion analyses, GC analysis, and infrared measurements were performed at the Analytical Department, Bristol-Myers Squibb, PRI, Syracuse, NY.

Diphenylmethyl (6*R*,7*S*)-7-(Phenoxyacetamido)-3-[[(trifluoromethyl)sulfonyl]oxy]ceph-3-em-4-carboxylate (2). To a stirred solution of **1** (15.5 g, 30 mmol) was added diisopropylethylamine (6.09 mL, 35 mmol) followed by trifluoromethanesulfonic anhydride (10 g, 35 mmol) in anhydrous CH_2Cl_2 (275 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1.45 h and quenched by pouring into a solution of brine (30 mL). The organic layer was separated and washed with brine (25 mL), dried ($MgSO_4$), and evaporated to give a thick yellow oil. On triturating with diethyl ether and standing for 30 min, a colorless crystalline compound was isolated (needles). Recrystallization (diethyl ether/hexanes) afforded 17.5 g (90%) of **2**: mp 140–141 °C; ^1H NMR ($CDCl_3$) δ 7.45–7.26 (m, 13 H), 7.07–6.90 (m, 4 H), 5.97 (dd, J = 5.04 and 9.25 Hz, 1 H), 5.10 (d, J = 5.04 Hz, 1 H), 4.57 (s, 2 H), 3.79 and 3.47 (AB q, J = 18.4 Hz, 2 H). Anal. Calcd for $C_{29}H_{23}N_2O_8S_2F_3$: C, 53.67; H, 3.62; N, 4.32. Found: C, 53.60; H, 3.60; N, 4.14.

Representative Coupling Procedures. Procedure A. Reaction of 2 with LO Cuprate. In a two-necked flask was placed copper(I) iodide (0.38 mmol) followed by THF (1.5 mL). The flask was cooled to −78 °C (dry ice–acetone), and RLi (0.76 mmol) was slowly added. The ice bath was removed, and the suspension was stirred for 15–20 min. The cuprate was recooled to −78 °C,

(27) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.
(28) Whitesides, G. M.; Casy, C. P.; Krieger, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1379.
(29) (a) Beak, P.; Yamamoto, J.; Upton, C. *J. Org. Chem.* **1975**, *40*, 3052. (b) Seyferth, D.; Vaughan, L. G. *J. Am. Chem. Soc.* **1964**, *86*, 883. (*Z*)-1-Propenylmagnesium bromide was prepared from magnesium turnings and (*Z*)-1-bromopropene in THF at ambient temperature. The isomeric purity of ±96% was determined by ^{13}C NMR (360 MHz at ambient temperature) or by quenching the Grignard solution with tributyltin chloride and analyzing the product by GC. During the preparation care must be exercised to keep internal temperature of the reaction mixture between 20–25 °C in order to keep the ratio of *E* isomer to a minimum (<4%). For a stereoselective preparation of (*Z*)-1-bromopropene, see: Fuller, C. E.; Walker, D. G. *J. Org. Chem.* **1991**, *56*, 4066.
(30) Seyferth, D.; Vaughan, L. G. *J. Organomet. Chem.* **1963**, *1*, 138.
(31) House, H. O.; Chu, C.-Y.; Wilkins, J. M.; Umen, M. *J. Org. Chem.* **1975**, *40*, 1460.
(32) Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

and a solution of **2** (0.15 mmol) in THF (2 mL) was added. After being stirred for 60 min, the reaction mixture was poured into a solution of saturated NH_4Cl and ethyl acetate (ca. 1:1, 10 mL). The organic layer was separated and further washed with brine (2 mL) and 10% $NaHCO_3$ (2 mL), dried ($MgSO_4$), and evaporated to give the crude cephem which was further purified by flash chromatography.

Procedure B. Reaction of 2 with HO Cyanocuprate. The HO cyanocuprate was prepared following procedure A and using copper cyanide instead of copper iodide.

Procedure C. Reaction of 2 with LO Cuprate in Conjunction with BF_3·Et_2O. In a two-necked flask was placed copper(I) iodide (1.54 mmol) followed by THF (2.5 mL). The flask was cooled to −78 °C (dry ice–acetone), and RLi (3.08 mmol) was slowly added. The ice bath was removed, and the suspension was stirred for 15–20 min. The cuprate solution was recooled to −78 °C, and BF_3·Et_2O (3.08 mmol) was added followed by a solution of **2** (0.77 mmol) in THF (3 mL). After stirring for 60 min, the reaction mixture was poured into a solution of saturated NH_4Cl and ethyl acetate (ca. 1:1, 20 mL). The organic layer was separated and further washed with brine (5 mL) and $NaHCO_3$ (5 mL), dried ($MgSO_4$), and evaporated to give the crude cephem. Further purification was achieved by flash chromatography.

Procedure D. General Procedure for Reaction of 2 with Cuprate Derived from Grignard Reagent. In a two-necked flask copper(I) bromide–dimethyl sulfide complex (1.0 mmol) was placed followed by THF (2 mL), and the flask was cooled to −78 °C (dry ice–acetone). A solution of Grignard reagent (2.0 mmol) was added dropwise to the stirred suspension. The ice bath was removed, and the suspension was stirred until a dark-colored homogeneous solution was observed (ca. 10–15 min). The cuprate solution was recooled to −78 °C, and a solution of **2** (0.5 mmol dissolved in 2 mL of THF) was added. The dark-colored solution was stirred until completion of reaction and quenched into a solution of saturated NH_4Cl. The aqueous layer was extracted with ethyl acetate, washed with 10% of $NaHCO_3$ solution (5 mL) and brine (5 mL), dried ($MgSO_4$), and evaporated to afford the cephem which was purified by flash chromatography.

Preparation of Cephems. Diphenylmethyl (6*R*,7*S*)-7-(Phenoxyacetamido)-3-methylceph-3-em-4-carboxylate (3). (a) Following Procedure A. The cuprate was prepared from CuI (72 mg, 0.38 mmol) and methyllithium (0.59 mL, 0.76 mmol, 1.29 M solution in hexanes) in THF (1.5 mL). Treatment with **2** (93 mg, 0.15 mmol) in THF (2 mL) afforded cephem (49.7 mg, 65% combined, as a 1:1 mixture of **3** and **4**). Isomers were separated by flash chromatography (30% ethyl acetate in hexanes). Cephem **3** (Δ^3 isomer, foam): TLC R_f 0.40 (40% ethyl acetate in hexanes); IR (KBr) 1780, 1722, 1683 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.52–6.91 (m, 17 H), 5.9 (dd, J = 5.0 and 9.8 Hz, 1 H), 5.05 (d, J = 5.0 Hz, 1 H), 4.57 (s, 2 H), 3.45 and 3.20 (AB q, J = 19.0 Hz, 2 H), 2.12 (s, 3 H). Anal. Calcd for $C_{29}H_{26}N_2O_5S$: C, 67.49; H, 5.09; N, 5.44. Found: C, 67.55; H, 5.09; N, 5.40. Cephem **4** (Δ^2 isomer, foam): TLC R_f 0.50 (40% ethyl acetate in hexanes); IR (KBr) 1780, 1722, 1683 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.47–6.86 (m, 17 H), 5.92 (d, J = 1.6 Hz, 1 H), 5.70 (dd, J = 9.22 and 4.09 Hz, 1 H), 5.25 (d, J = 4.9 Hz, 1 H), 4.86 (s, 1 H), 4.56 (s, 2 H), 1.81 (s, 3 H). Anal. Calcd for $C_{29}H_{26}N_2O_5S$: C, 67.49; H, 5.09; N, 5.44. Found: C, 67.39; H, 5.29; N, 5.20.

(b) Following Procedure B. The cuprate was prepared from CuCN (55 mg, 0.61 mmol) and methyllithium (0.95 mL, 1.23 mmol, 1.3 M solution in hexanes) in THF (1.5 mL). Treatment with **2** (200 mg, 0.30 mmol) in THF (2 mL) afforded cephem (118 mg, 75% combined, as a 2:3 mixture of **3** and **4**).

(c) Following Procedure C. The cuprate was prepared from CuI (293 mg, 1.54 mmol), methyllithium (2.05 mL, 3.08 mmol, 1.5 M solution in hexanes), and BF_3·Et_2O (0.38 mL, 3.08 mmol) in THF (2.5 mL). Treatment with **2** (500 mg, 0.77 mmol) in THF (2 mL) for 60 min afforded, after flash chromatography (40% ethyl acetate in hexanes), cephem **3** (336 mg, 85%).

(d) Following Procedure D. The cuprate was prepared from methylmagnesium bromide (0.20 mL, 0.62 mmol, 3.0 M solution in ether) and CuBr·Me_2S (63 mg, 0.31 mmol) in THF (1 mL). Treatment with **2** (100 mg, 0.15 mmol) for 15 min followed by workup and flash chromatography (30% ethyl acetate/hexanes) afforded **3** (75 mg, 95%).

Diphenylmethyl (6*R*,7*S*)-7-(Phenoxyacetamido)-3-ethylceph-3-em-4-carboxylate (5). (a) Following Procedure C. The cuprate was prepared from CuI (366 mg, 1.92 mmol), ethyllithium (7.68 mL, 3.84 mmol, 0.5 M solution in benzene), and BF_3·Et_2O (0.47 mL, 3.84 mmol) in THF (3 mL). Treatment with **2** (500 mg, 0.77 mmol) afforded **5** (306 mg, 75%) as a foam after flash chromatography (40% ethyl acetate in hexanes): IR (KBr) 1781, 1723, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41–6.90 (m, 17 H), 5.83 (dd, J = 5.0 & 9.8 Hz, 1 H), 5.00 (d, J = 5.0 Hz, 1 H), 4.55 (s, 2 H), 3.40 and 3.26 (AB q, J = 18.9 Hz, 2 H), 2.60 (m, 1 H), 2.20 (m, 1 H), 1.05 (t, J = 8.5 Hz, 3 H). Anal. Calcd for $C_{30}H_{28}N_2O_5S$: C, 68.16; H, 5.34; N, 5.30. Found: C, 68.15; H, 5.27; N, 5.36.

(b) Following Procedure D. The cuprate was prepared from ethylmagnesium bromide (0.22 mL, 0.68 mmol, 3.0 M solution in ether) and CuBr·Me_2S (69 mg, 0.34 mmol) in THF (2 mL). Treatment with **2** (100 mg, 0.154 mmol) for 20 min followed by workup and flash chromatography (silica, 30% ethyl acetate/hexanes) afforded the cephem **5** as a foam (73 mg, 89%).

Diphenylmethyl (6*R*,7*S*)-7-(Phenoxyacetamido)-3-phenylceph-3-em-4-carboxylate (6). (a) Following Procedure C. The cuprate was prepared from CuI (366 mg, 1.92 mmol), phenyllithium (1.92 mL, 3.84 mmol, 2.0 M solution in THF), and BF_3·Et_2O (0.47 mL, 3.84 mmol) in THF (3 mL). Treatment with **2** (500 mg, 0.77 mmol) for 2 h afforded **6** (288 mg, 65%) as a foam after flash chromatography (40% ethyl acetate in hexanes): IR (KBr) 1772, 1720, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36–6.81 (m, 22 H), 5.96 (dd, J = 5.1 and 9.8 Hz, 1 H), 5.10 (d, J = 5.0 Hz, 1 H), 4.58 (s, 2 H), 3.62 (s, 2 H). Anal. Calcd for $C_{34}H_{28}N_2O_5S$: C, 70.82; H, 4.89; N, 4.85. Found: C, 70.75; H, 4.90; N, 4.72.

(b) Following Procedure D. The cuprate was prepared from phenylmagnesium bromide (1.36 mL, 1.36 mmol, 1.0 M solution in THF) and CuBr·Me_2S (139 mg, 0.68 mmol) in THF (2 mL). Treatment with **2** (200 mg, 0.31 mmol) for 20 min followed by workup and flash chromatography (silica, 35% ethyl acetate/hexanes) afforded the cephem **6** as a foam (151 mg, 85%).

Diphenylmethyl (6*R*,7*S*)-7-(Phenoxyacetamido)-3-vinylceph-3-em-4-carboxylate (7). (a) Following Procedure C. The cuprate was prepared from CuI (175 mg, 0.92 mmol), vinyllithium (0.85 mL, 1.84 mmol, 2.15 M solution in THF), and BF_3·Et_2O (0.23 mL, 1.84 mmol) in THF (2 mL). Treatment with **2** (200 mg, 0.31 mmol) for 2.5 h afforded **7** (56 mg, 35%) as a glass after flash chromatography (40% ethyl acetate in hexanes): IR (KBr) 1781, 1723, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44–7.20 (m, 13 H), 7.05–6.83 (m, 5 H), 5.90 (dd, J = 4.8 and 9.5 Hz, 1 H), 5.62 (d, J = 11.2 Hz, 1 H), 5.41 (d, J = 17.2 Hz, 1 H), 5.05 (d, J = 4.8 Hz, 1 H), 4.55 (s, 2 H), 3.62 and 3.47 (AB q, J = 17.8 Hz, 2 H). Anal. Calcd for $C_{30}H_{26}N_2O_5S$: C, 67.45; H, 4.90; N, 5.24. Found: C, 67.45; H, 5.02; N, 5.35.

(b) Following Procedure D. The cuprate was prepared by the addition of vinylmagnesium bromide (2.3 mL, 2.30 mmol, 1.0 M solution in THF) and CuBr·Me_2S (237 mg, 1.15 mmol) in THF (2 mL). Treatment with **2** (500 mg, 0.77 mmol) for 15 min followed by workup and flash chromatography (silica, 40% ethyl acetate/hexanes) afforded the cephem **7** (344 mg, 85%).

Diphenylmethyl (6*R*,7*S*)-7-(Phenoxyacetamido)-3-[(*Z*)-1-propenyl]ceph-3-em-4-carboxylate (8). (a) Following Procedure C. The cuprate was prepared from CuI (73 mg, 0.38 mmol), (*Z*)-1-propenyllithium (0.82 mL, 0.77 mmol, 0.95 M solution in ether), and BF_3·Et_2O (0.09 mL, 0.77 mmol) in THF (2 mL). Treatment with **2** (100 mg, 0.15 mmol) in THF (1 mL) for 2 h at −78 °C followed by flash chromatography (30% ethyl acetate in hexanes) afforded **8** (25 mg, 30%) as a foam: IR (KBr) 1779, 1728, 1633 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51–6.90 (m, 17 H), 6.10 (d, J = 11.7 Hz, 1 H), 5.90 (dd, J = 4.5 and 9.8 Hz, 1 H), 5.56 (m, 1 H), 5.07 (d, J = 4.5 Hz, 1 H), 4.58 (s, 2 H), 3.47 and 3.27 (AB q, J = 17.5 Hz, 2 H), 1.43 (d, J = 7.0 Hz, 3 H). Anal. Calcd for $C_{31}H_{28}N_2O_5S$: C, 68.87; H, 5.22; N, 5.18. Found: C, 69.05; H, 5.23; N, 5.22. Also isolated from the reaction mixture was cephem **1** (24 mg, 30%). The spectral properties were in agreement with the reported values.[13]

(b) Following Procedure B. The cuprate was prepared from CuCN (34 mg, 0.38 mmol) and (*Z*)-1-propenyllithium (0.80 mL, 0.76 mmol, 0.95 M solution in ether) in THF (1 mL). Treatment with **2** (50 mg, 0.07 mmol) in THF (1 mL) for 2 h at −78 °C afforded after flash chromatography (45% ethyl acetate in

hexanes) 8 and 9 (26 mg, 64% combined as a 3:2 mixture of Δ^3 and Δ^2 isomers). The isomers were separated by flash chromatography: ^{1}H NMR ($CDCl_3$) 9 (Δ^2 isomer, foam) δ 7.51–6.90 (m, 17 H), 6.10 (s, 1 H), 5.71 (m, 2 H), 5.56 (m, 1 H), 5.33 (d, J = 4.05 Hz, 1 H), 4.92 (s, 1 H), 4.58 (s, 2 H), 1.62 (d, J = 7.0 Hz, 3 H). Anal. Calcd for $C_{31}H_{28}N_2O_5S$: C, 68.87; H, 5.22; N, 5.18. Found: C, 69.01; H, 5.18 N, 5.01.

When the above reaction was run in the presence of BF_3·Et_2O (0.09 mL, 0.76 mmol), 8 and 9 were isolated (25 mg, 62% as 7:2 mixture of Δ^3 and Δ^2 isomers).

(c) Transmetalation Reaction. In a two-necked flask was placed CuCN (33 mg, 0.37 mmol) followed by THF (2 mL). The flask was cooled to 0 °C, and MeLi (0.58 mL, 0.74 mmol, 1.27 M solution in hexanes) was slowly added. The ice bath was removed, and (*Z*)-1-propenyltributyltin (201 mg, 0.60 mmol) was added. The solution was stirred at ambient temperature for 3.0 h. The cuprate solution was recooled to −78 °C, and a solution of 2 (250 mg, 0.38 mmol) in THF (1.5 mL) was added. After stirring for 60 min, the reaction mixture was poured into a solution of saturated NH_4Cl and ethyl acetate (ca. 1:1, 10 mL). The organic layer was separated and further washed with brine (3 mL) and 10% $NaHCO_3$ (3 mL), dried ($MgSO_4$), and evaporated to give the crude cephems which after flash chromatography (40% ethyl acetate in hexanes) afforded 8 and 9 (123 mg, 60% combined ca. 2:3). Also isolated were the cephems 3 and 4 (19 mg, 10% combined ca. 1:1).

(d) Transmetalation Reaction II. In a two-necked flask under an argon atmosphere was placed copper iodide (73 mg, 0.38 mmol) followed by THF (1.5 mL). The flask was cooled to −78 °C, (*Z*)-1-propenyltributyl tin (255 mg, 0.77 mmol) followed by MeLi (0.58 mL, 0.77 mmol, 1.29 M solution in hexanes) was added, and the solution was stirred for 3.0 h. To the dark-colored cuprate suspension was added BF_3·Et_2O (0.09 mL, 0.77 mmol), followed by a solution of 2 (100 mg, 0.15 mmol) in THF (1.5 mL). After being stirred for 2.0 h at −78 °C, the solution was poured into a mixture of saturated NH_4Cl and ethyl acetate (ca. 1:1, 10 mL). The organic layer was separated and further washed with brine (3 mL) and 10% $NaHCO_3$ (3 mL), dried ($MgSO_4$) and evaporated to give the crude cephem. Further purification was achieved by flash chromatography (40% ethyl acetate in hexanes) to give 8 (27 mg, 34%).

(e) Following Procedure D. The cuprate [(*Z*)-1-propenyl]$_2$CuMgBr was prepared by the addition of (*Z*)-1-propenylmagnesium bromide (0.68 mL, 0.68 mmol, 1.0 M solution in THF) to CuBr·Me_2S (69 mg, 0.34 mmol) in THF (1.5 mL). Treatment with 2 (100 mg, 0.15 mmol) for 1.5 h followed by workup and flash chromatography (40% ethyl acetate/hexanes) afforded the cephem 8 as a foam (67 mg, 80%).

Diphenylmethyl (6*R*,7*S*)-7-(Phenoxyacetamido)-3-isopropylceph-3-em-4-carboxylate (10). Following Procedure D. The cuprate was prepared by the addition of isopropylmagnesium bromide (0.57 mL, 1.14 mmol, 2.0 M solution in THF) to CuBr·Me_2S (117 mg, 0.57 mmol) in THF (2 mL). Treatment with 2 (250 mg, 0.38 mmol) for 15 min followed by workup and flash chromatography (35% ethyl acetate/hexanes) afforded the cephem 10 as a foam (152 mg, 73%): IR (KBr) 1780, 1723, 1687 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.40–7.20 (m, 14 H), 7.05–6.89 (m, 3 H), 5.82 (dd, J = 4.8 and 9.5 Hz, 1 H), 5.0 (d, J = 4.8 Hz, 1 H), 4.55 (s, 2 H), 3.40–3.17 (m, 3 H), 1.05 (d, J = 7.0 Hz, 3 H), 0.97 (d, J = 7.0 Hz, 3 H). Anal. Calcd for $C_{31}H_{30}N_2O_5S$: C, 68.62; H, 5.57; N, 5.16. Found: C, 68.78; H, 5.53; N, 5.14.

Diphenylmethyl (6*R*,7*S*)-7-(Phenoxyacetamido)-3-*tert*-butylceph-3-em-4-carboxylate (11). Following Procedure D. The cuprate *t*-Bu_2CuMgBr was prepared by the addition of *tert*-butylmagnesium bromide (1.92 mL, 3.84 mmol, 2.0 M solution in THF) to CuBr·Me_2S (395 mg, 1.92 mmol) in THF (3 mL). Treatment with 2 (500 mg, 0.77 mmol) for 15 min followed by workup and flash chromatography (35% ethyl acetate/hexanes) afforded the cephem 11 as a foam (334 mg, 78%): IR (KBr) 1777, 1723, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.40–7.20 (m, 15 H), 7.02 (s, 1 H), 6.91 (d, J = 9.5 Hz, 1 H), 5.83 (dd, J = 4.8 and 9.5 Hz, 1 H), 4.95 (d, J = 4.8 Hz, 1 H), 4.35 (s, 2 H), 3.45 and 3.30 (AB q, J = 18.9 Hz, 2 H), 1.05 (s, 9 H). Anal. Calcd for $C_{34}H_{32}N_2O_5S$: C, 70.08; H, 5.88; N, 4.80. Found: C, 70.04; H, 6.00; N, 4.72.

Diphenylmethyl (6*R*,7*S*)-7-(Phenoxyacetamido)-3-hexylceph-3-em-4-carboxylate (12). Following Procedure D. The cuprate (hexyl)$_2$CuMgBr was prepared by the addition of hexylmagnesium bromide (1.92 mL, 3.84 mmol, 2.0 M solution in THF) to CuBr·Me_2S (395 mg, 1.92 mmol) in THF (3 mL). Treatment with 2 (500 mg, 0.77 mmol) for 15 min followed by workup and flash chromatography (35% ethyl acetate/hexanes) afforded the cephem 12 as a foam (364 mg, 81%): IR (KBr) 1773, 1722, 1687 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45–6.80 (m, 17 H), 5.84 (dd, J = 4.8 and 9.5 Hz, 1 H), 5.00 (d, J = 4.8 Hz, 1 H), 4.55 (s, 2 H), 3.40 and 3.24 (AB q, J = 18.9 Hz, 2 H), 2.47 (m, 1 H), 2.26 (m, 1 H), 1.60–0.94 (m, 8 H), 0.87 (t, J = 7.5 Hz, 3 H). Anal. Calcd for $C_{34}H_{36}N_2O_5S$: C, 69.84; H, 6.20; N, 4.79. Found: C, 69.44; H, 6.22; N, 4.71.

Diphenylmethyl (6*R*,7*S*)-7-(Phenoxyacetamido)-3-cyclohexylceph-3-em-4-carboxylate (13). Following Procedure D. The cuprate (cyclohexyl)$_2$CuMgBr was prepared by the addition of cyclohexylmagnesium bromide (1.54 mL, 3.08 mmol, 2.0 M solution in THF) to CuBr·Me_2S (316 mg, 1.54 mmol) in THF (2 mL). Treatment with 2 (500 mg, 0.77 mmol) for 10 min followed by workup and flash chromatography (35% ethyl acetate/hexanes) afforded the cephem 13 as a foam (282 mg, 62%): IR (KBr) 1777, 1723, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.40–6.90 (m, 17 H), 5.80 (dd, J = 4.8 and 9.5 Hz, 1 H), 5.00 (d, J = 4.8 Hz, 1 H), 4.55 (s, 2 H), 3.37 and 3.24 (AB q, J = 18.9 Hz, 2 H), 2.92 (br t, 1 H), 0.94–1.91 (m, 10 H). Anal. Calcd for $C_{34}H_{34}N_2O_5S$: C, 70.08; H, 5.88; N, 4.80. Found: C, 70.04; H, 6.00; N, 4.72.

Diphenylmethyl (6*R*,7*S*)-(Phenoxyacetamido)-3-cyclopentylceph-3-em-4-carboxylate (14). Following Procedure D. The cuprate (cyclopentyl)$_2$CuMgBr was prepared by the addition of cyclopentylmagnesium bromide (1.54 mL, 3.08 mmol, 2.0 M solution in THF) to CuBr·Me_2S (316 mg, 1.54 mmol) in THF (2 mL). Treatment with 2 (500 mg, 0.77 mmol) for 15 min followed by workup and flash chromatography (silica, 35% ethyl acetate/hexanes) afforded the cephem 14 as a foam (359 mg, 82%): IR (KBr) 1778, 1723, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45–7.20 (m, 14 H), 7.08–6.90 (m, 3 H), 5.80 (dd, J = 4.8 and 9.5 Hz, 1 H), 5.02 (d, J = 4.8 Hz, 1 H), 4.53 (s, 2 H), 3.40–3.10 (m, 3 H), 1.92–1.21 (m, 8 H). Anal. Calcd for $C_{33}H_{32}N_2O_5S$: 69.69; H, 5.67; N, 4.93. Found: C, 69.34; H, 5.67; N, 4.83.

Diphenylmethyl (6*R*,7*S*)-7-(Phenoxyacetamido)-3-allylceph-3-em-4-carboxylate (15). Following Procedure D. The cuprate (allyl)$_2$CuMgBr was prepared by the addition of allylmagnesium bromide (1.14 mL, 1.14 mmol, 1.0 M solution in ether) to CuBr·Me_2S (117 mg, 0.57 mmol) in THF (2 mL). Treatment with 2 (250 mg, 0.38 mmol) for 30 min followed by workup and flash chromatography (35% ethyl acetate/hexanes) afforded the cephem 15 as a glass (170 mg, 82%): IR (KBr) 1780, 1720, 1683 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.41–7.20 (m, 14 H), 7.05 (t, J = 7.5 Hz, 1 H), 6.95 (s, 1 H), 6.89 (d, J = 8.5 Hz, 1 H), 5.89 (dd, J = 7.5 and 14.0 Hz, 1 H), 5.80–5.60 (m, 1 H), 5.18–4.9 (m, 3 H), 4.56 (s, 2 H), 3.44–3.24 (m, 3 H), 2.86 (dd, J = 7.5 and 14.2 Hz, 1 H). Anal. Calcd for $C_{31}H_{28}N_2O_5S$: C, 68.87; H, 5.22; N, 5.18. Found: C, 69.02; H, 5.02; N, 5.30.

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