Palladium Catalysis in Cephalosporin Chemistry: General Methodology for the Synthesis of Cephem Side Chains†

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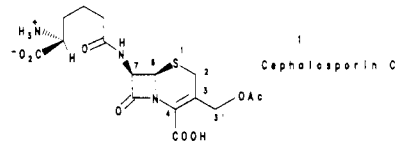
We describe in full the palladium-catalyzed coupling of 3-(triflyloxy)cephems with organotin compounds, leading to the synthesis of 3-alkenyl-, 3-alkynyl-, and 3-arylcephems under exceptionally mild conditions. While this approach was not satisfactory for 3-allylcephems, the related coupling of easily available 3-(chloromethyl)cephems with stannanes provided a high-yielding route to such 3-allylcephems and also to 3-benzyl- and 3-homoallylcephems. The choice of the catalyst was crucial in both cases. It was found that triphenylphosphine-based catalysts were quite unsatisfactory. A much better ligand in this respect was tri(2-furyl)phosphine, which is introduced as a useful new ligand in organopalladium chemistry. The effect of this ligand on coupling rates is discussed. It is suggested that reduced electron density at palladium enhances the rate of the transmetalation, considered to be the rate-determining step in these coupling reactions. In addition, we describe cases of unexpected transfer order among unsymmetrically substituted stannanes, as well as a complex coupling reaction between (chloromethyl)cephems and alkynylstannanes. These new facets of the Stille coupling, as well as the potential of our chemistry for the development of new cephalosporin antibiotics, are discussed in the paper.

Introduction

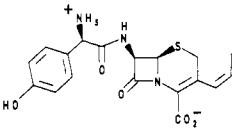
Synthetic modifications of the weak antibacterial cephalosporin C[1] (1) have yielded, during the past two decades, dozens of useful and potent broad-spectrum antibiotics. This has rapidly propelled the cephems to a position of prominence among the many classes of antibacterial agents.[2] Central to the development of novel cephalosporins has been the discovery of a high-yielding process for the chemoselective cleavage of the amide functionality at C-7,[3] which has led to the synthesis of novel and more potent amide derivatives. Chemical modifications at C-3, on the other hand, have been traditionally more difficult and have largely centered on the replacement of the acetoxy group at C-3′ with sulfur- and nitrogen-based nucleophiles. These two types of modifications alone have yielded dozens of useful antibacterials,[4] but in recent years it has become clear that the presence of a leaving group at C-3′ of the cephem nucleus is not a prerequisite for biological activity.[5]



1 Cephalosporin C

Several semisynthetic cephalosporins with a heteroatom directly bound to C-3 have been prepared[5] and some have been shown to be good antibiotics, including the important derivative cefaclor.[5] Recently, several derivatives containing olefinic side chains at C-3 have been described.[6] These side chains usually yield orally active antibiotics with a broad spectrum against gram-positive bacteria and an excellent pharmacokinetic profile.[7] Our interest in these derivatives is in relation to our clinical candidate BMY-28100, 2,[6b] and the need to develop a cost-effective synthesis of this compound.

General methodology for the synthesis of cephems bearing olefinic substituents at C-3 is not available, thereby hindering progress in this medicinally important area.[8]



2 (BMY-28100)

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† This paper is respectfully dedicated to the memory of Prof. John K. Stille.

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(1) 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.

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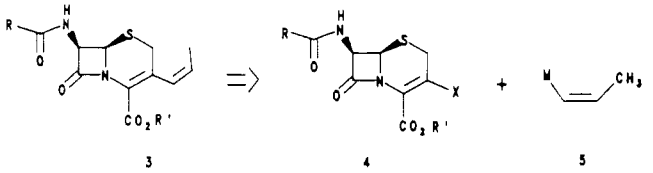
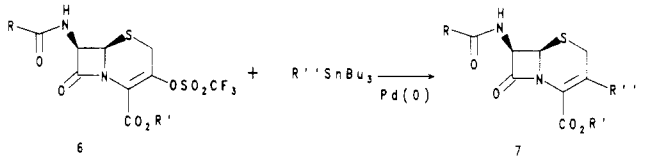
0022-3263/90/1955-5833$02.50/0

Scheme I

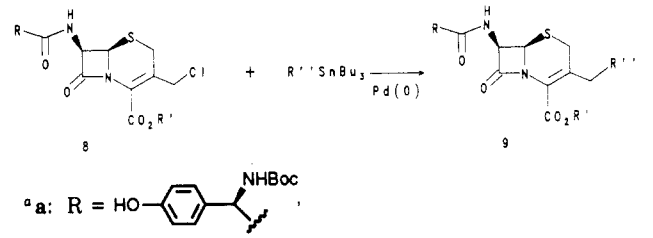


Scheme II[a]



[a] **a**: R = $PhCH_2$, R′ = $CHPh_2$. **b**: R = *t*-BuO, R′ = $CHPh_2$. **c**: R = $PhCH_2$, R′ = *p*-MeO-benzyl. For R″, see Table I.

Scheme III[a]



[a] **a**: R =

R′ = $CHPh_2$. **b**: R = $PhCH_2$, R′ = $CHPh_2$. **c**: R = $PhCH_2$, R′ = *p*-MeO-benzyl. **d**: R = Boc, R′ = $CHPh_2$. For R″, see Table II.

We therefore set as our goal the development of a stereorational and efficient synthesis of BMY-28100 and of a variety of other cephems containing unsaturated side chains. In particular, since the Wittig approach to BMY-28100 is limited to a small group of very reactive aldehydes[6b] and invariably produces *E*/*Z* mixtures,[9] we sought to develop a stereospecific route to our (*Z*)-propenyl derivative, as shown in the retrosynthetic disconnection depicted in Scheme I.

Stereospecific carbon–carbon bond forming reactions using organometallic intermediates are now standard methodology in organic synthesis.[10] In our particular choice of leaving group X and metal M, we were guided by the desire to develop chemistry that would be simple to carry out on a very large scale and would also be suitable to the introduction of many kinds of functionalized side chains at C-3 in a single step, thereby facilitating the drug-discovery effort. Methods that require very low temperatures, hazardous ethereal solvents, scrupulously dry conditions, and/or inert atmosphere were therefore considered less attractive. The palladium-catalyzed reaction between vinyl triflates and organostannanes, recently described by Stille and Scott,[11] appears quite general and mild, can be carried out in a variety of solvents, is not sensitive to traces of moisture, and uses an organometallic substrate, the stannane, that is quite stable to storage and is not air sensitive. Finally, stannanes are available by a variety of synthetic methods[12] and therefore seemed promising reagents in connection with a drug-discovery program.

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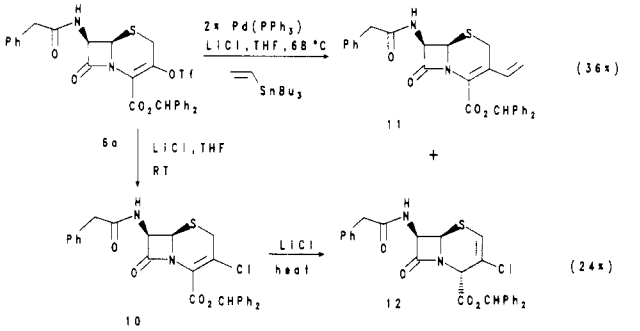
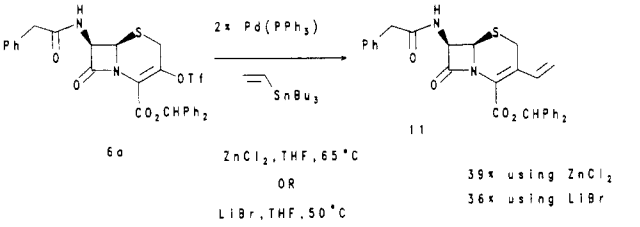
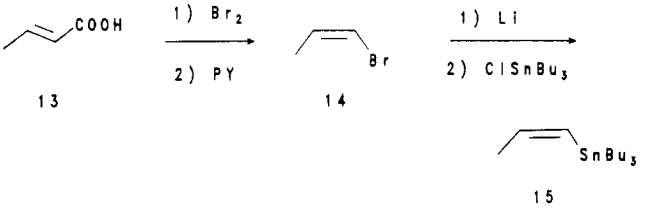
Scheme IV



Scheme V



Scheme VI



We report herein a mild and stereospecific synthesis of BMY-28100 via a modification of the Stille protocol. The coupling reaction was shown to be quite general, as anticipated (Scheme II).

In order to prepare the novel 3-allylcephems, the palladium-based methodology was extended to the coupling of 3-(chloromethyl)cephems with stannanes (Scheme III). This first application of palladium catalysis to cephalosporin chemistry[8f] has made almost any conceivable C-3 carbon substituent available by simple and efficient methodology. A few "abnormal" products have been observed in our coupling reaction, and their possible mode of formation will be briefly discussed.

Results and Discussion

The Stille coupling of triflate **6a**[13] with the commercially available vinyltributyltin was attempted first. The reaction afforded a mixture of two compounds, **11** and **12**, which were not separated (Scheme IV). When **6a** was treated simply with excess LiCl, 3-chlorocephem **10** was obtained; **10** isomerized to **12** upon heating. When mixtures of **10** and **12** were submitted to the coupling conditions, no **11** was produced.

This suggests that, in our system, triflate/chloride exchange and subsequent double-bond migration can compete with the palladium-catalyzed coupling.

The triflate/chloride exchange process probably proceeds by conjugate addition followed by elimination.[13,14] The need for external halide in the coupling reaction of triflates has been discussed by Stille and Scott.[11] In our

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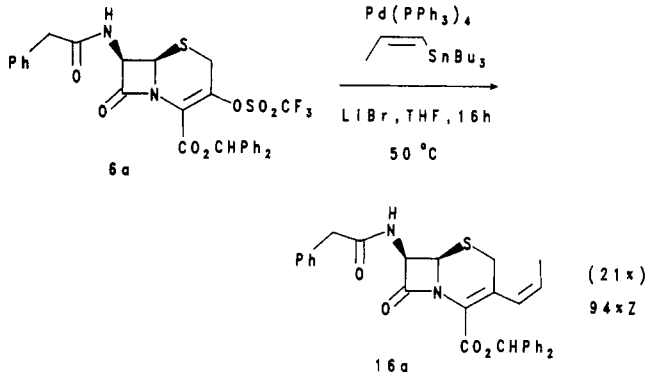
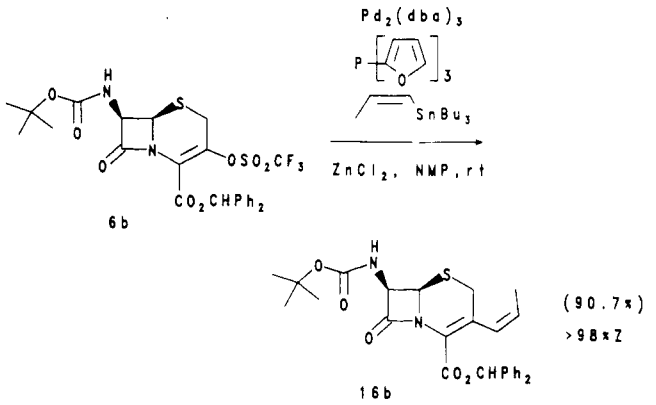
Scheme VII



Scheme VIII



experience also the coupling reaction did not occur in the absence of LiCl.

When other halide salts were examined, it was found that $ZnCl_2$ is a suitable additive (Scheme V). Coupling product **11** was obtained free from any **12**, albeit in only fair yield. We observed that with $ZnCl_2$ instead of LiCl longer reaction times were needed, apparently leading to destruction of the cephem ring. The higher coupling rate observed with LiCl is in agreement with Stille's observations.[11] Also acceptable was lithium bromide (Scheme V), which induced coupling under rather mild conditions, with formation of only a small amount of 3-bromocephem.

Even though the above yields are not high, it was considered likely that the approach could eventually be optimized, and in order to do so we proceeded to the examination of the same coupling with (*Z*)-propenyltributyltin, the stannane of interest. A suitable synthesis of the required stannane **15** is shown in Scheme VI: decarboxydehalogenation of the adduct between *trans*-crotonic acid and bromine stereospecifically yielded (*Z*)-1-bromo-1-propene (>99% *Z*),[15] while lithiation and quenching with chlorotributyltin gave **15** in 98–99% isomeric purity, as described by Seyferth.[16]

Unfortunately, it became clear immediately that the introduction of an alkyl group on the olefinic moiety of the stannane slowed down the coupling rate to an extent that rendered our previously developed coupling conditions unsatisfactory. Thus, triflate **6a** coupled with **15** under the $ZnCl_2$ conditions in only 10% yield. Prolonged refluxing was required, and this caused extensive decomposition of the sensitive triflate. Similarly, use of LiBr led to the desired product, **16a**, in only 21% yield (Scheme VII). Interestingly, the product was 94% *Z* (^{1}H NMR), which suggested that good stereospecificity, under milder conditions, may indeed be attainable.

A study of the effect of solvent, ligands, and halides on the overall coupling rates was undertaken in order to optimize the coupling yield for the synthesis of 3(*Z*)-propenylcephems. In agreement with Stille and Scott,[11] it was found that polar aprotic solvents enhance the coupling rate substantially. The coupling rate increased in the following order:

$$CHCl_3 < THF < CH_3CN < DMF, DMSO, NMP$$

Of the three best solvents, NMP (*N*-methylpyrrolidinone) gave the highest yields. We then investigated the effect of the palladium ligands on the coupling. For convenience, we resorted to in situ formation of our catalysts from tris(dibenzylideneacetonyl)bispalladium(0) (Pd_2dba_3) and the appropriate ligand.[17] Pd_2dba_3 is an intensely colored, air stable, crystalline solid, and its handling does not require special precautions. Addition of Pd_2dba_3 to a degassed solution of the appropriate phosphine in NMP gradually (5–10 min at room temperature) led to yellow solutions containing palladium–phosphine catalysts. With this protocol, it was observed that less sterically demanding, but more electron-rich, phosphines (methyldiphenylphosphine, dimethylphenylphosphine) led to reduced coupling rates. On the other hand, tri(*p*-chlorophenyl)phosphine led to a slight increase of the rate.

Our original hypothesis was that since the transmetalation, presumably the rate-determining step,[10,11] consists of a nucleophilic attack of the stannane at Pd(II),[18] making the palladium species less electron-rich should enhance the rate of the process. The alkylphosphines, even though less sterically demanding, are better donors than triphenylphosphine[19] and appear to slow down the coupling. Unfortunately, triphenyl phosphite, a π-acceptor,[20] failed to provide a significantly faster rate. In our search for phosphines with reduced donicity, we eventually focused our attention on phosphines derived from five-membered heterocycles. In a series of papers,[21] Allen and co-workers describe the reduced nucleophilicity of tri(2-furyl)phosphine[22] and, to a lesser extent, tri(2-thienyl)-phosphine. Their role as donors to transition metals has also been briefly examined,[21,23] but their use in synthetic organometallic chemistry had never been reported.[24]

We were pleased to observe that tri(2-furyl)phosphine appreciably enhanced the rate of coupling of triflates **6** with the (*Z*)-propenylstannane. A measurement of this enhancement, in NMP at room temperature, yielded a factor of ca. 17 over triphenylphosphine (with **6a** as a substrate). The kinetics were cleanly pseudo first order for up to 3 half-lives. A palladium:phosphine ratio of 1:2

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(18) For a general discussion on ligand substitution processes, see: Langford, C. H.; Gray, H. B. *Ligand Substitution Processes*; W. A. Benjamin: New York, 1965.
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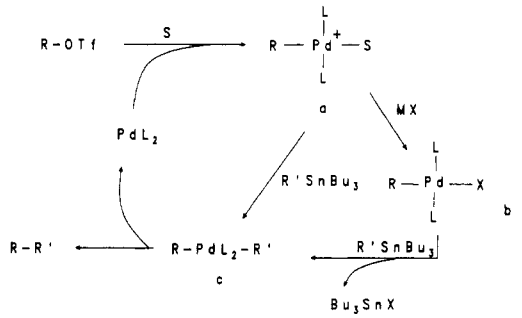
(23) Allen, D. W.; Ashford, D. F. *J. Inorg. Nucl. Chem.* **1976**, *38*, 1953–6.
(24) For a short review on the concept of "catalyst tailoring", see: Henrici-Olivé, G.; Olivé, S. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 105–15.

Scheme IX. Tentative Catalytic Cycle for the Coupling between Cephem Triflates and Unsaturated Stannanes[a]



[a] S = solvent, MX = metal halide, L = ligand (phosphine).

was employed, even though a ratio of 1:4 gave acceptable rates. Excess phosphine slows down the reaction to some extent and, most importantly, a ratio of 1:2 led to a very stable catalyst, capable of at least 100 turnovers.

Under the conditions just described, the coupling could be carried out at room temperature. The stereospecificity was virtually complete (>99%), and the yield was almost quantitative. $ZnCl_2$ was used as halide source in these experiments. Using cephem triflate **6b** as substrate, the (*Z*)-propenylcephem **16b** was obtained in better than 90% yield (Scheme VIII).

A tentative catalytic cycle[25] is shown in Scheme IX. It is likely that the highly coordinatively unsaturated species PdL_2 undergoes a rapid oxidative addition and does not exist as such in appreciable concentration.

Although at the initial stages of our study the requirement for exogenous halide was absolute, our optimized procedure did not seem to require any halide. Indeed, when *no* zinc chloride was employed, the coupling was only 2–3 times slower. When anhydrous zinc chloride that was handled in a dry bag was employed, there was actually *no* enhancement over the experiment without halides, therefore suggesting that the effect of the zinc chloride is due to its water of hydration or to traces of hydrogen chloride.

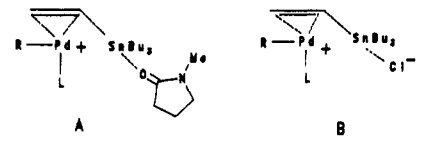
The beneficial effect of traces of water in this type of coupling is precedented.[11] Thus, even though the coupling is slightly faster in the presence of 2 equiv of zinc chloride, we often ran our couplings without any added halide.

The coupling of vinyl triflates with vinyltins *without added halide* finds a precedent in Piers' work[26] on the *intramolecular* triflate–stannane coupling.

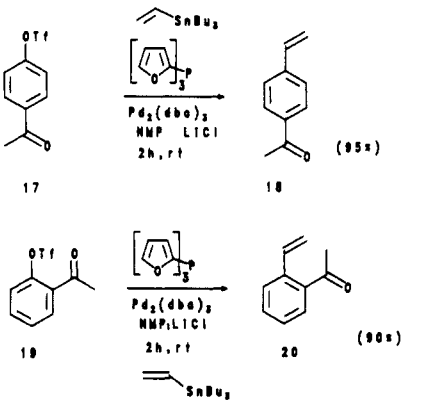
With reference to the catalytic cycle (Scheme IX), it is evident that at least two mechanisms can be operative in these transmetalation reactions. While the catalytic cycle may proceed through b when halide is added,[11] in our case another intermediate (possibly a, where the weak ligand triflate has been replaced by a solvent molecule) must be involved.[27]

In order to identify the structure of the tin-containing coproduct, the reaction was monitored by ^{119}Sn NMR. This indicated smooth conversion from propenyltributyltin to tributyltin chloride when exogenous chloride was used. When no halide was used in NMP, the product showed a

Scheme X



Scheme XI



singlet at δ 17, identical with an authentic sample of tributyltin triflate[28] in NMP. In $CDCl_3$, the tin triflate species displays a singlet at δ 167, which shifts to δ 38 upon addition of 1 equiv of NMP; further addition of NMP gradually shifts the signal to δ 17. These data suggest that tributyltin triflate is pentacoordinated in NMP, as well as in $CDCl_3$ with added NMP, where it is, however, partially dissociated into free NMP and tetracoordinated tin triflate. On the basis of these considerations, the tin-containing coproduct is tributyltin triflate. Pentacoordination is evidenced by the large shift in the ^{119}Sn NMR spectrum.[29]

We make the reasonable proposal that one of the roles for the exogenous halide in typical Stille couplings is to assist tin during the transmetalation. Many examples of S_E2 reactions of organomercurials and organotins[30] that are promoted by nucleophilic attack at the departing metal are known.

While the exact coordination status of the Pd(II) intermediate in the transmetalation is not known, transition state B (Scheme X) is a plausible one for transmetalations with chloride present. In our case, however, the electronic requirements of the reaction are favorable enough that tin may leave unassisted, or perhaps through assistance of a solvent molecule, as in A. It is impossible, simply on the basis of our data, to distinguish between open (as shown) and cyclic transition states; open is better precedented for electrophilic substitution at tin.[30] The slower rate of coupling of propenyltin vs vinyltin suggests that in the transition state the olefinic carbon β to tin bears little or no positive charge. This is in contrast to what is usually observed in electrophilic substitutions of olefinic stannanes, where β-alkyl substituents are responsible for often spectacular rate increases.[31]

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(26) (a) Piers, E.; Friesen, R. W.; Keay, B. A. *J. Chem. Soc., Chem. Commun.* **1985**, 809–10. (b) Piers, E.; Friesen, R. W. *J. Org. Chem.* **1986**, *51*, 3405–6. See also: (c) Stille, J. K.; Tanaka, M. *J. Am. Chem. Soc.* **1987**, *109*, 3785–6.

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(28) Prepared by the procedure of Roesky, H. W.; Wiezer, H. *Chem. Ber.* **1971**, *104*, 2258–65.

(29) Smith, P. J.; Tupciauskas, A. P. *Ann. Rev. NMR Spectrosc.* **1978**, *8*, 291–370.

(30) See: *Comprehensive Chemical Kinetics*; Bamford, C. H., Tipper, C. F. H., Eds.; Elsevier: Amsterdam, 1973; Vol. 12. Also: Reutov, O. A. *J. Organomet. Chem.* **1975**, *100*, 219–35. We note that the solvent effect in our study is qualitatively analogous to the one observed in other studies where cleavage of the Sn–X bond (X = C, S, Se) is rate-limiting. See, for example: Harpp, D. N.; Gingras, M. *J. Am. Chem. Soc.* **1988**, *110*, 7737–45, and references therein.

(31) Baekelmans, P.; Gielen, M.; Malfroid, P.; Nasielski, J. *Bull. Soc. Chim. Belg.* **1968**, *77*, 85–97.

Indeed, the reactivity scale of different olefinic stannanes in this coupling (vide infra) correlates rather well with the ability of the system to stabilize a partial negative charge (carbanion character) at the reacting carbon, further suggesting that nucleophilic assistance at tin (by halide or solvent molecules) may play an important role in the energetics of the reaction. We note that a series of studies[32] on the transmetalation of Pt(II) complexes with stannanes have also been interpreted with a transition state involving substantial negative charge at the tin-bearing carbon. Importantly, a retarding effect of electron-rich phosphines on the reaction rate was reported.[32]

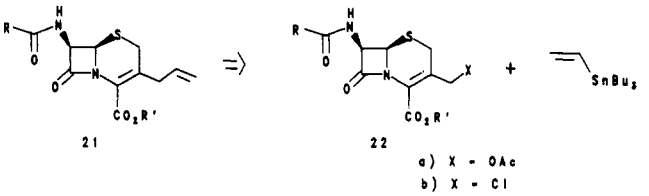
The fact that exogenous halide is not needed in our particular system may be due to the presence of the C-4 carboxyl group in **6**. Such a group may function as an ortho ligand to palladium during the catalytic cycle, therefore eliminating the need for exogenous halide. Isomeric aryl triflates **17** and **19** were prepared (Scheme XI) in order to test this hypothesis. Coupling of **17** with vinyltributyltin under our modified protocol shows the much milder conditions that tri(2-furyl)phosphine allows over triphenylphosphine (2 hr at room temperature vs 4 h at 100 °C for tetrakis[triphenylphosphine]Pd[33]), even though the yield is identical in the two cases. Interestingly, this reaction required LiCl: no coupling took place without it.

Isomeric **19** coupled at a similar rate, but also required LiCl, thereby suggesting the relative unimportance of a "promoting" ortho effect. Indeed, in a competition experiment between **17** and **19** with half an equivalent of vinyltributylin, the para isomer was found to couple 3 times faster than the ortho, showing that an ortho carbonyl has a slightly retarding effect on the coupling. These data do not provide support for the idea that the C-4 carboxylate group in our cephem plays a role as a ligand for palladium in the rate-determining step.

The coupling reaction discussed above can be extended to a variety of unsaturated stannanes (Table I). Vinyltributyltin (entry 1) coupled cleanly under the optimized conditions. Alkyl substitution at the double bond of the stannane slows down the coupling (entries 2–4), but the reaction can still be carried out at room temperature. Functionalized stannanes can also be used (entries 5–7) with remarkably little difference in yields or rates. With (trifluorovinyl)tributyltin the coupling was best carried out in THF, and in this case $ZnCl_2$ was responsible for a large rate enhancement. While less than 5% product was formed in 1 h at room temperature without zinc chloride, addition of 2 equiv of the halide caused the reaction to go to completion in another hour at room temperature. In this case transmetalation from the vinyltin to the vinylzinc species is very likely,[34] while in the other cases the minimal effect of $ZnCl_2$ on the rate suggests that no such transmetalation takes place under our conditions.

A challenging coupling was the one involving (4-*tert*-butylcyclohexen-1-yl)trimethyltin,[35] which is known to be very unreactive in the Stille coupling.[36] Its reactivity was found to be acceptable in our case, but the methyl group was preferentially transfered over the vinylic one (entry 15). This transfer order is surprising in view of the usually slower transfer of methyl groups in typical stannane–triflate couplings.[11]

Scheme XII



The desired cephem **52** was however obtained, albeit in low yield. This represents, to the best of our knowledge, the first example of coupling with cyclohexen-1-yl-stannanes.[36] To our surprise, the homologous (4-*tert*-butylcyclohexen-1-yl)tributylstannane was completely unreactive under the above conditions. The origin of the anomalous reactivity pattern of these stannanes is obscure but also very intriguing in connection with our interest in the mechanism of the transmetalation step. This point will be investigated further in the context of structurally simpler substrates.

The coupling of alkynylstannanes was briefly examined and found to proceed in acceptable yield (entry 8). Reduction occurred when tributyltin hydride was used (entry 9), and aryl substituents could also be introduced at C-3 of the cephem by the use of arylstannanes (entry 10). Alkyl transfer (entries 11 and 12) was found rather difficult: while tetramethyltin, in agreement with the discussion of entry 15, readily coupled in excellent yield, tetrabutyltin only reacted under forcing conditions and in low yield, due to extensive decomposition of the triflate.

Interestingly, a heterocyclic ring could be directly introduced at C-3 of the cephem by using the appropriate stannane[37] (entry 14).

Allyltributyltin (entry 13) gave unsatisfactory results: only in this case did we detect large amounts of a Δ^2 product, as well as the reduction product. This coupling was anomalous since it took place even without palladium. In this case only the Δ^2 product was obtained, and in low yield (15%). When 10% mol of BHT was used in this palladium-catalyzed coupling, the ratio Δ^3/Δ^2 was slightly improved (from 3:1 to ca. 4:1). But by a margin that does not allow us to decide with certainty about the mechanism responsible for the spontaneous (i.e., not palladium-catalyzed) coupling. A radical chain mechanism cannot be ruled out.[38]

The versatility of our coupling reaction is particularly important in connection with structure–activity relationships among 3-substituted cephems. Indeed, our method is the *first general approach* to cephalosporins bearing unsaturated substituents at C-3 and should be very useful in the design of new cephalosporin antibiotics.

The complex results obtained in the allyl coupling led us to explore a better, more general and efficient, approach

(32) See: (a) Eaborn, C.; Odell, K. J.; Pidcock, A. *J. Organomet. Chem.* **1975**, *96*, C38–40. (b) Cardin, C. J.; Cardin, D. J.; Lappert, M. F.; Muir, K. W. *J. Organomet. Chem.* **1973**, *60*, C70–3. (c) Cardin, C. J.; Cardin, D. J.; Lappert, M. F. *J. Chem. Soc., Dalton Trans.* **1977**, 767–79. (d) Eaborn, C.; Odell, K. J.; Pidcock, A. *J. Chem. Soc., Dalton Trans.* **1979**, 758–60. (e) Eaborn, C.; Odell, K. J.; Pidcock, A. *J. Chem. Soc., Dalton Trans.* **1978**, 357–68. (f) Eaborn, C.; Odell, K. J.; Pidcock, A. *J. Organomet. Chem.* **1978**, *146*, 17–21. (g) Eaborn, C.; Odell, K. J.; Pidcock, A. *J. Chem. Soc., Dalton Trans.* **1979**, 134–8.

(33) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478–86.

(34) Seyferth, D.; Raab, G.; Brändle, K. A. *J. Org. Chem.* **1961**, *26*, 2934–7.

(35) Corey, E. J.; Estreicher, H. *Tetrahedron Lett.* **1980**, *21*, 1113–6.

(36) Scott, W. J., personal communication. We also thank Prof. Scott for a sample of this stannane. Some cycloalkenylstannanes were recently coupled with aryl triflates. See: Laborde, E.; Lesheski, L. E.; Kiely, J. S. *Tetrahedron Lett.* **1990**, *31*, 1837–40.

(37) Very few examples of this class of compounds have been reported. See: (a) Fahey, J. L.; Firestone, R. A.; Chirstensen, B. G. *J. Med. Chem.* **1976**, *19*, 562–5. (b) Sugawara, T.; Matsuya, H.; Matsuo, T.; Miki, T. *Chem. Pharm. Bull.* **1980**, *28*, 2116–28. See also: U.S. Patents 4,496,560 and 4,508,717.

(38) Allylstannanes are excellent radical acceptors. For selected examples, see ref 13.

Table I. Palladium-Catalyzed Coupling of Triflates 6 with Stannanes

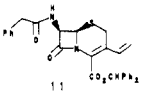
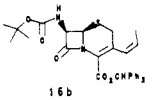
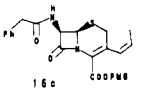
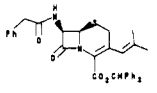
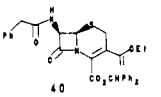
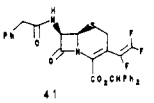
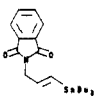
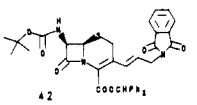
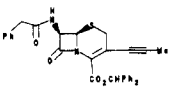
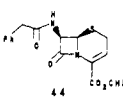
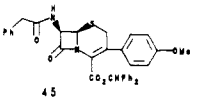
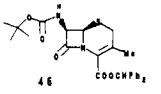
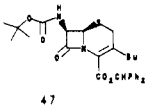
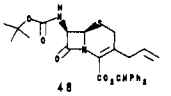
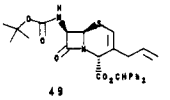
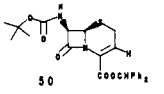
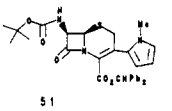
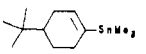
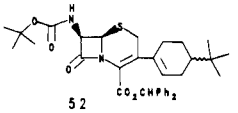
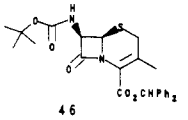
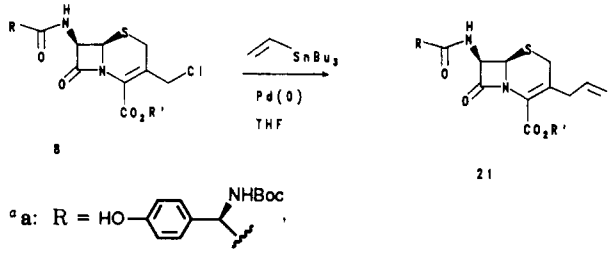
entry	method[a] (triflate)	stannane	product	temp (°C), time (h)	% yield
1	A (**6a**)	CH_2=$CHSnBu_3$	 11	25, 1	79
2	A (**6b**)	(*Z*)-CH_3CH=$CHSnBu_3$	 16b	25, 16	90[b]
3	A (**6c**)	(*Z*)-CH_3CH=$CHSnBu_3$	 16c	25, 20	82[b]
4	A (**6a**)	$(CH_3)_2C$=$CHSnBu_3$	 39	25, 19	66
5	A (**6a**)	CH_2=$C(OEt)SnBu_3$	 40	25, 19	52
6	C (**6a**)	F_2C=$CFSnBu_3$	 41	25, 2	55
7	A (**6b**)		 42	25, 20	73
8	A (**6a**)	MeC≡$CSnBu_3$	 43	25, 16	50
9	C (**6a**)	$HSnBu_3$	 44	65, 1	68
10	A (**6a**)	*p*-$MeOC_6H_4SnBu_3$	 45	50, 6	57
11	B (**6b**)	Me_4Sn	 46	25, 16	85
12	B (**6b**)	Bu_4Sn	 47	50, 7 days	16[c]
13	B (**6b**)	CH_2=$CHCH_2SnBu_3$	 48	50, 40	48[d]
			 49		16
			 50		12
14	B (**6b**)		 51	25, 1	89

Table I (Continued)

entry	method[a] (triflate)	stannane	product	temp (°C), time h	% yield
15	B (**6b**)		 **52**	25, 16	17
			 **46**		74

[a] Method A: Pd_2dba_3, trifurylphosphine, $ZnCl_2$, NMP. Method B: Pd_2dba_3, trifurylphosphine, NMP. Method C: Pd_2dba_3, trifurylphosphine, $ZnCl_2$, THF. [b] The stannane was 98.5% *Z* (NMR), product was 98% *Z* (NMR). [c] The major product was the corresponding 3-hydroxycephem. [d] With 10% BHT the total yield of **48** + **49** was 64% (ratio **48**:**49** = 4:1).

Scheme XIII[a]



[a] **a**: R = HO–; R′ = $CHPh_2$. **b**: R = $PhCH_2$, R′ = $CHPh_2$. **c**: R = $PhCH_2$, R′ = *p*-MeO-benzyl. **d**: R = Boc, R′ = $CHPh_2$.

to this novel class of cephems. A modified synthetic disconnection (Scheme XII) was envisioned, where the intact cephalosporin skeleton could be employed in conjunction with vinylstannanes.

Cephalosporins, being functionalized allylic acetates, should indeed be amenable to Pd-catalyzed coupling reactions, via an η^3-allylpalladium intermediate.[39] Examination of the literature reveals a few scattered examples of reactions were carbon–carbon bonds are formed at C-3′ of the cephalosporin skeleton, none of them being of general utility.[8b,e]

Since both allylic acetates and halides have been successfully coupled with unsaturated stannanes,[40] we proceeded to explore the reactivity of **22a,b** with tributylvinyltin in the presence of tetrakis(triphenylphosphine)-palladium(0). While acetates **22a** were completely inert under all conditions tried, it was found that the readily available chlorides gave, albeit at extremely slow rate and in poor yield, the desired coupling products (Scheme XIII).

Once again, by simply switching to tri(2-furyl)phosphine as palladium ligand a large rate enhancement was observed (the reaction was 45 times faster than with PPh_3 at 65 °C). Use of tri(2-thienyl)phosphine gave a rate enhancement of 8.3 over PPh_3: these data are difficult to explain by invoking the importance of steric effects[41] at palladium in the transmetalation reaction. The order of reactivity seems rather to reflect the extent of electron-withdrawing ability of the substituents at phosphorus. The order of reactivity in the alkaline hydrolysis of the corresponding phosphonium salts[22] follows the same order and is explained with the strong electron-withdrawing power of the heterocyclic moieties.

From a mechanistic viewpoint, the large accelerating effect is quite interesting and could provide an important clue to the mechanism of the transmetalation reaction. This type of rate enhancement was observed in a variety of coupling reactions involving organostannanes.[42] On the practical side, we suggest that these new ligands will be of general use in the Stille-type of coupling.[43]

The reaction in Scheme XIII was quite efficient and general (Table II). The coupling was best carried out in refluxing THF. While reaction also took place at room temperature (usually in 2–3 days with tributylvinyltin), there was no yield improvement over the reactions at reflux, and the faster procedure was usually employed.

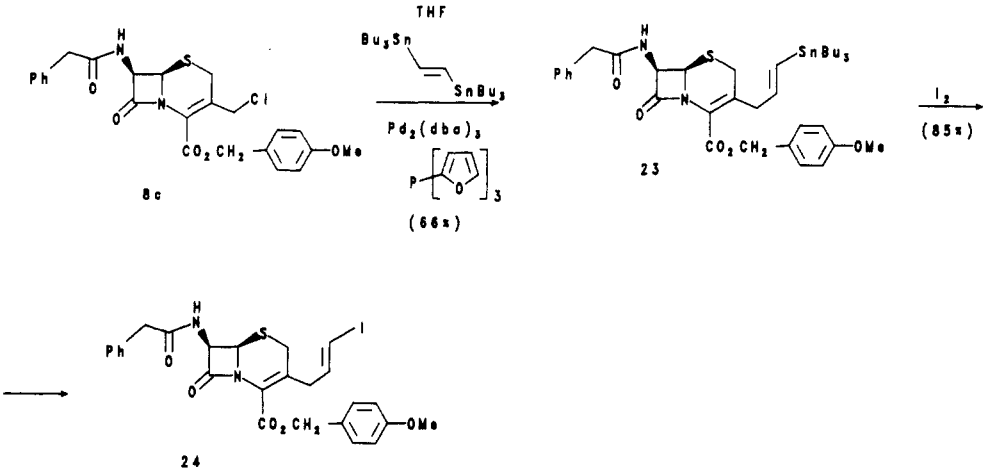
(Bromomethyl)cephems (entry 3) also coupled, but at a slower rate. Cephem 1β-oxides could also be coupled, at a slightly faster rate than the corresponding sulfides (entry 2). Substitution on the vinyltin produced a rate decrease (entries 5 and 6). The stereospecificity was excellent (entry 5). Functionalized stannanes could be employed (entries 7 and 8), and tributyltin hydride gave the reduction product in excellent yield (entry 9). When the palladium catalyst was left out, no reaction occurred under the same conditions, confirming that the reduction reaction is palladium-catalyzed. Tetraalkylstannanes did not couple under the above conditions. Arylstannanes smoothly yielded 3-benzylcephems[8b] (entries 11 and 12). The retarding effect of an electron-withdrawing substituent on the aryl ring suggests some degree of positive charge being carried by the aryl ring in the transition state of the transmetalation.

When (*E*)-1,2-bis(tributylstannyl)ethylene[44] (entry 10) was employed in the coupling, the stannylated cephem **23** was obtained in acceptable yield. This cephem is an ideal intermediate for further side-chain elaboration, in view of the wide range of chemistry displayed by vinylstannanes.[12] For example, addition of 1 equiv of I_2 to **23** produced vinylic iodide **24** in excellent yield (Scheme XIV).

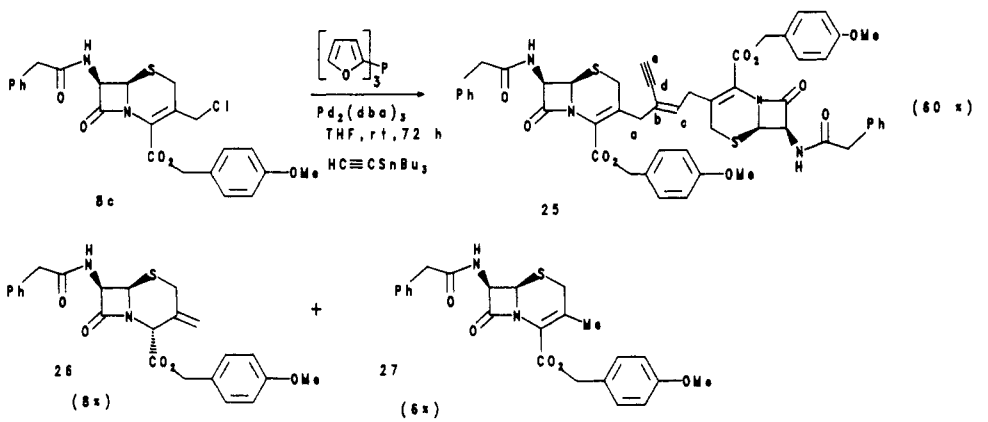
Coupling of allylic halides with alkynyltins is, to the best of our knowledge, unprecedented. One example of an allylic acetate reacting with an alkynyltin is known[45,46] and only yields reduction products, possibly by a single-electron-transfer mechanism. When we used tributylethynyltin with **8c** in our coupling reaction, the dimer **25** was the major product (Scheme XV). Careful chromatography revealed traces of reduction products **26** and **27**, but no trace of the desired 3-propargylcephem. Structural

(39) Trost, B. M.; Verhoeven, T. R. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: New York, Vol. 8, pp 799–938.
(40) (a) Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2595–8. (b) Sheffy, F. K.; Godschalx, J. P.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4833–40.
(41) Stille, J. K.; Simpson, J. H. *J. Am. Chem. Soc.* **1987**, *109*, 2138–52.
(42) V. Farina, Unpublished results.
(43) A comprehensive study on the use of this ligand in palladium-catalyzed couplings is under way and will be reported in due course.
(44) Corey, E. J.; Wollenberg, R. H. *J. Org. Chem.* **1975**, *40*, 3788–9.
(45) Keinan, E.; Roth, Z. *J. Org. Chem.* **1983**, *48*, 1769–72.
(46) For a review on alkynyltins, see: Cauletti, C.; Furlani, C.; Sebald, A. *Gazz. Chim. Ital.* **1988**, *118*, 1–23.

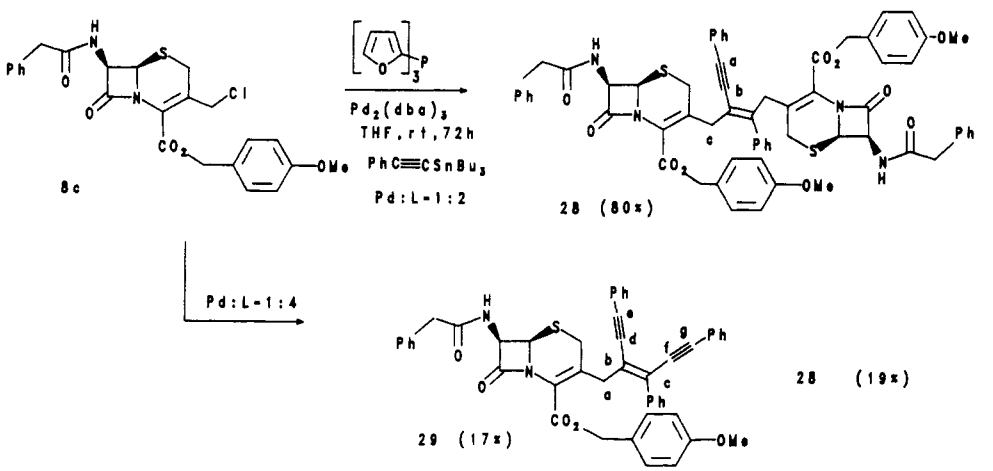
Scheme XIV



Scheme XV



Scheme XVI

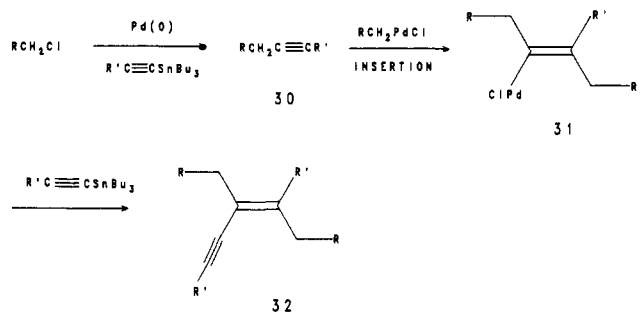


assignment of unsymmetrical dimer **25** was difficult and followed extensive 2D NMR experiments (both proton–proton and proton–carbon correlations) and was corroborated by exact mass determination (FAB method, M + 1 = 953.2890). Especially diagnostic, in the ^{13}C NMR spectrum, were signals at δ 83.4, assigned to acetylenic carbon e, which was coupled to the terminal hydrogen with J = 251.9 Hz.[47] The less intense multiplet at δ 81.0 was assigned to carbon d, with a two-bond carbon–proton coupling of 45.8 Hz and a three-bond coupling of 13.3 Hz. The olefinic carbon c showed a doublet at δ 136.2 (J_{C-H} = 161 Hz), in agreement with expected values. In the ^1H NMR spectrum a doublet of doublets at δ 5.65 ($CDCl_3$) was assigned to the only olefinic proton, which was attached to carbon c according to two-dimensional carbon-proton shift correlation NMR.[47]

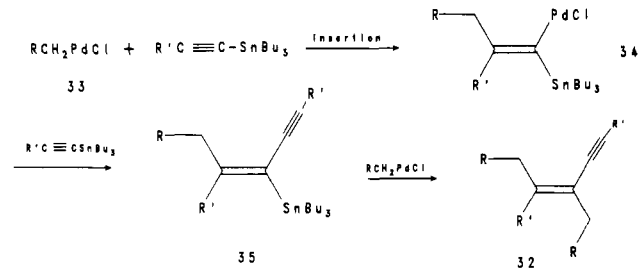
While the production of **25** was quite surprising, it proved not to be an isolated case. Use of (phenylethynyl)tributyltin (entry 14) in the coupling produced the analogous dimer **28** in good yield (Scheme XVI). Once again, the structure was assigned by 2D NMR and confirmed by high-resolution mass spectrometry (M + 1 = 1105.3503, FAB). In the ^{13}C NMR spectrum ($CDCl_3$), the acetylenic carbons gave signals at δ 96.2 (carbon a in **28**) and δ 87.5 (carbon b, long range coupling to methylene

(47) Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*; VCH: New York, 1987.

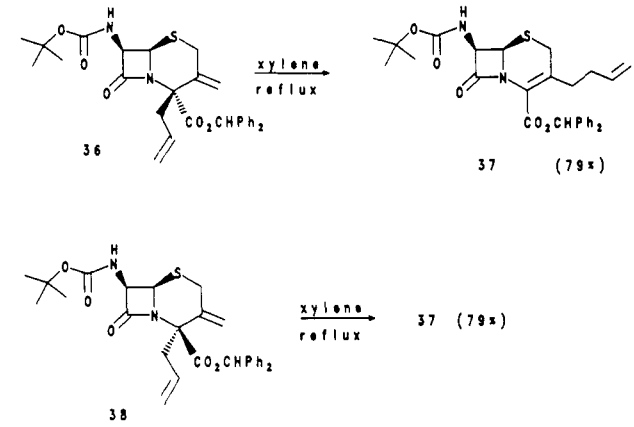
Scheme XVII



Scheme XVIII



Scheme XIX



protons of carbon c of ca. 5 Hz). Only traces of reduction products could be detected in the proton NMR spectrum of the crude.

Experiments where slightly different catalytic systems were used gave more surprising results (Scheme XVI). When the phosphine:palladium ratio was 4:1 instead of 2:1, the reaction proceeded at a similar rate but was more complex. Aside from **28**, the major coproduct was now the enediyne **29**, which is apparently the result of the condensation of one molecule of cephem with three molecules of stannane. The structure was assigned with the aid of mass spectrometry (M = 754) and NMR data. In particular, carbon d in the ^{13}C NMR spectrum gave a multiplet at δ 89.3 with long-range coupling to the methylene protons of a (J = ca. 5 Hz), while carbon f, at δ 90.4, showed no such coupling, therefore ruling out an isomeric structure where both acetylene units are attached to the terminal carbon. The geometric configuration at the double bond, however, could not be established with certainty and is only tentative.

Finally, coupling with tributylpropynyltin gave the product resulting from the expected pathway followed by double-bond migration (entry 15) in rather poor yield. Especially diagnostic in the NMR spectrum were the C-4 proton (singlet at δ 5.11), the downfield shift of the C-6 proton (from ca. δ 5.0 to 5.32), and the reduction in the absolute value of the geminal coupling constant for the C-2 protons (from ca. 18 Hz to 14 Hz), all typical of an exomethylene cepham with α configuration for the C-4 carboxylate. Also noteworthy was the signal for the olefinic proton, which showed the expected long-range coupling (J = 2.3 Hz) with the protons of the terminal methyl group. No other product, with the exception of some reduced materials, could be isolated.

The production of dimers **25** and **28** could be explained by assuming that the intermediate propargyl derivative **30** (Scheme XVII) would suffer fast insertion by the allylpalladium cephem intermediate. Such insertions are precedented.[48] It is also known that insertion of vinylpalladium species across triple bonds is faster than for double bonds,[49] and this would explain the absence of this reaction in all our other couplings involving vinyltins.

When the reaction in entry 13 was run with 10 equiv of the stannane, no difference in the product distribution was observed. If insertion were competitive with transmetalation, excess stannane should tip the balance in favor of transmetalation. Also, exogenous alkynes would be expected to compete with **30** in the (presumed) insertion reaction. To test this hypothesis, the coupling was carried out in the presence of excess 1-hexyne or phenylacetylene, with vinyltins or alkynyltins as traps for vinylpalladium **31**. No incorporation of the alkynes in the products was detected. This strongly suggests that the mechanism in Scheme XVII is not operative. A more reasonable pathway is shown in Scheme XVIII. In this case, an allylpalladium species, **33**, would undergo *insertion* across the triple bond of the stannane, as opposed to the expected *transmetalation*. This would then be followed by two transmetalations at the terminal carbons to yield the observed dimer.

This pathway has the following requirements: (a) Insertion of allylpalladium species across alkynyltins must be much faster than that of vinylpalladium species. (b) Insertion of allylpalladium species across alkynyltins is much faster than across the triple bond of regular terminal alkynes. (c) Insertion across ethynyl- and (phenylethynyl)stannanes is preferred over transmetalation, while the reverse is true for propynylstannane.

Formation of **29** probably requires a third mechanism. One should also note that alkynyltins, unlike vinyltins, undergo ready oxidative addition with Pd(0) complexes,[50] and this pathway may be involved in the reaction to produce **29**.

These intriguing mechanistic issues, as well as possible applications of this chemistry in organic synthesis, deserve a separate, more comprehensive study. We have preliminary evidence that the production of dimers is not limited to cephalosporin substrates.[51]

(48) See: Arcadi, A.; Bernocchi, E.; Burini, A.; Cacchi, S.; Marinelli, F.; Pietroni, B. *Tetrahedron* **1988**, *44*, 481–90, and references therein.
(49) Trost, B. M.; Burgess, K. *J. Chem. Soc., Chem. Commun.* **1985**, 1084–6.
(50) Butler, G.; Eaborn, C.; Pidcock, A. *J. Organomet. Chem.* **1981**, *210*, 403–9.
(51) For example; cinnamyl chloride (i) gave ii in almost quantitative yield under our typical coupling conditions.

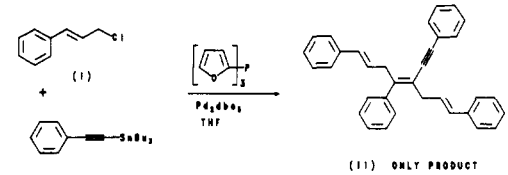


Table II. Palladium-Catalyzed Coupling of 3-(Halomethyl)cephems with Stannanes

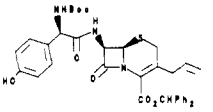
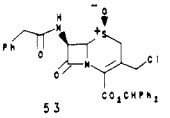
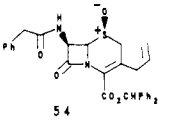
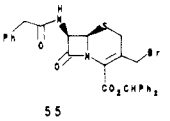
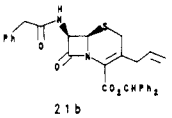
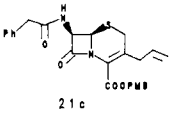
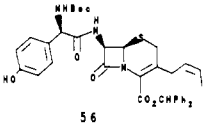
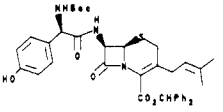
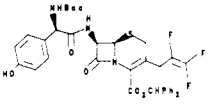
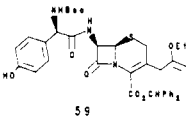
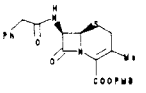
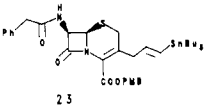
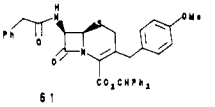
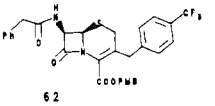
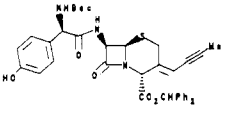
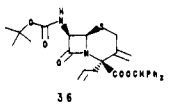
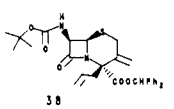
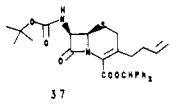
entry	stannane	substrate	product	temp (°C), time (h)	% yield
1	CH_2=$CHSnBu_3$	**8a**	 21a	65, 3	82
2	CH_2=$CHSnBu_3$	 53	 54	65, 40 min	87
3	CH_2=$CHSnBu_3$	 55	 21b	65, 16	80
4	CH_2=$CHSnBu_3$	**8c**	 21c	65, 3	89
5	(*Z*)-CH_3CH=$CHSnBu_3$	**8a**	 56	65, 16	78[a]
6	$(CH_3)_2C$=$CHSnBu_3$	**8a**	 57	65, 72	60
7	F_2C=$CFSnBu_3$	**8a**	 58	65, 72	65
8	CH_2=$C(OEt)SnBu_3$	**8a**	 59	65, 2	71
9	$HSnBu_3$	**8c**	 60	25, 30 min	98
10	(*E*)-Bu_3SnCH=$CHSnBu_3$	**8c**	 23	65, 16	66
11	*p*-$MeOC_6H_4SnBu_3$	**8b**	 61	65, 24	81
12	*p*-$CF_3C_6H_4SnBu_3$	**8c**	 62	65, 72	64
13	HC≡$CSnBu_3$	**8c**	dimer **25**	25, 72	60[b]
14	PhC≡$CSnBu_3$	**8c**	dimer **28**	25, 96	80[c]
15	MeC≡$CSnBu_3$	**8a**	 63	65, 16	32

Table II (Continued)

entry	stannane	substrate	product	temp (°C), time (h)	% yield
16	CH_2=$CHCH_2SnBu_3$	**8d**	 **36**	65, 16	10
			 **38**		54
			 **37**		12

[a] Stereospecificity was >99%. [b] See Scheme XV. [c] See Scheme XVI.

Finally, coupling of 3-chlorocephems with allyltins provided another unexpected result (entry 16 of Table II).

Three products were isolated, and the major one was the result of coupling at the more hindered C-4 position of the cephem ring. The minor products were the expected 3-homoallylic cephem **37** and an isomeric 4-allylcephem.

NOESY experiments proved that the major product **38** bears the newly introduced allyl group in the β position of C-4,[52] which is the more hindered face. Both isomers **36** and **38** could be smoothly converted into the minor isomer **37** by Cope rearrangement (Scheme XIX).

The above results provide a clue as far as the preferred stereochemistry of the intermediate allylpalladium is concerned. The coupling results point to the surprising conclusion that the allylpalladium complex prefers the β configuration, that is the more hindered one. Coupling at C-4 could then be explained by collapse of a bis-π-allylpalladium intermediate, unavailable in the coupling of the other stannanes. β-Alkylation at C-4 of the cephem ring is precedented.[53]

From a preparative point of view, 3-homoallylcephems are therefore readily available by the sequence palladium coupling/Cope rearrangement.

Conclusion

We have described two palladium-based approaches to the synthesis of cephems bearing complex side chains at C-3. The combination of these two methods fills a gap in cephalosporin chemistry, by providing, for the first time, a practical and general approach to almost any conceivable C-3 side chain via 3-(triflyloxy)cephems and 3-(chloromethyl)cephems. New classes of semisynthetic cephalosporins were obtained, and their biological evaluation, as well as the synthesis of new analogues, is under active investigation.

It has been shown that the application of a new ligand, tri(2-furyl)phosphine), consistently speeds up the rate of the Stille coupling reactions, and we plan to provide further evidence that this catalytic system has considerable utility in organic synthesis. While our coupling results mirror to some extent Stille's results for unfunctionalized vinyl triflates, our triflates can be coupled *without* added halides, and this is of mechanistic significance. We have also observed an example of transfer of an alkyl group over a vinyl one in a mixed stannane and the first coupling of the unreactive cyclohexen-1-yl moiety. Whether this can be generalized for other triflates remains to be established. Finally, acetylenic stannanes have been shown to preferentially form dimers with allylic chlorides under our conditions. It is not known whether this observation can yield synthetically useful chemistry, but we are intrigued by the mechanistic picture of this complex reaction, and its extension to other allyl halides is under investigation.

Experimental Section

All reactions were carried out under argon, using a Firestone valve. Oven-dried (130 °C, 24 h) glassware and syringes were used. The glassware was allowed to cool in a desiccator, assembled cold, capped with rubber septa, and filled with argon after removing the air in vacuo. Dry THF was obtained by distillation from Na/benzophenone. Dry NMP (*N*-methylpyrrolidinone) was obtained by distillation from calcium hydride and stored over molecular sieves. All other solvents were obtained from Aldrich (anhydrous grade) and used directly. Unless otherwise stated, all yields refer to materials dried to constant weight and showing the microanalytical data reported below. Melting points were recorded on a Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Bruker WM-360 (at 360 MHz for ^1H) or a Varian Gemini 300 (at 300 MHz) instrument. Accurate mass measurements were obtained with a Kratos MS50RF mass spectrometer in the positive ion FAB mode, with *m*-nitrobenzyl alcohol as the matrix. Elemental analyses were performed on Oneida Research Services in Whitesboro, NY. Preparative chromatography was carried out by the flash technique.[54] HPLC monitoring was carried out on all reactions, using a Perkin-Elmer Series 410 instrument equipped with a BioLC pump, an LC-235 Diode-Array detector, and an LCI-100 Laboratory Computing integrator. A Phenomenex C-18 (300 × 39 mm) column was used, eluting at 1.5 mL/min with mixtures of acetonitrile (typically 50–75%) and 10 mM ammonium phosphate buffer (pH = 6.50). The detector wavelength was set in the range 255–275 nm. Rate estimation of coupling rections was carried out by quantitative HPLC: calibration curves were obtained with standard solutions of starting material and product, and from this a response factor was obtained. Reactions were run in a thermostatic bath, and aliquots were withdrawn at appropriate times and immediately quenched into a large volume of acetonitrile in a volumetric flask. These solutions were injected into the HPLC and concentrations estimated from the observed detector response, each point being the average of two determinations. Pseudo-first-order rate constants were obtained by plotting ln A_0/A vs time, where A_0 is the concentration of substrate at time zero and A is the concentration at time t.

Organostannanes. The following stannanes were prepared according to literature methods: (*Z*)-1-propenyltributyltin,[16] 1-(tributylstannyl)-2-methylprop-1-ene,[55] (trifluorovinyl)tributyltin,[56] 1-(tributylstannyl)-1-propyne,[57] (*p*-methoxyphenyl)-

(52) An intense cross peak between H-6 and the allyl methine proton was observed in the case of **36** but was absent in **38**. The assignments are also consistent with the deshielding of H-6 in the NMR spectrum of 3-exo-methylene cepham 4α-carboxylate esters (e.g., **26**).

(53) Spry, D. O. *Tetrahedron Lett.* **1973**, *14*, 165–8. Also: Bremner, D. H.; Ringan, N. S.; Smith, A. D. M. *Tetrahedron Lett.* **1987**, *28*, 6687–90, and references therein.

(54) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–5.

(55) Saihi, M. L.; Pereyre, M. *Bull. Soc. Chim. Fr.* **1977**, 1251–5.

(56) Kaesz, H. D.; Stafford, S. L.; Stone, F. G. A. *J. Am. Chem. Soc.* **1960**, *82*, 6232–5.

tributyltin,[58] 1-methyl-2-(tributylstannyl)pyrrole,[59] (4-*tert*-butyl-1-cyclohexen-1-yl)trimethyltin and (4-*tert*-butyl-1-cyclohexen-1-yl)tributyltin,[35,60] (*E*)-1,2-bis(tributylstannyl)ethylene,[44] [*p*-(trifluoromethyl)phenyl]tributyltin.[61] Vinyltributyltin, 1-methoxy-1-(tributylstannyl)ethylene, tetramethyltin, tetrabutyltin, allyltributyltin, ethynyltributylin, and (phenylethynyl)tributyltin were obtained from Aldrich. Tributyltin hydride (Aldrich) was distilled in vacuo before use.

Vinyl Triflates. Cephem triflates **6a–c** were prepared as previously described.[13] Aryl triflate **17** was prepared according to Stille.[33]

The **3-(halomethyl)cephems** were prepared according to literature procedures.[6b,62]

Tri(2-furyl)phosphine was prepared according to Allen[22] and recrystallized from benzene/hexane, mp 63 °C.

(*E*)-1-Phthalimido-3-(tributylstannyl)-2-propene. (*E*)-1-(Tributylstannyl)-1-propen-3-ol[63] (102.6 mg, 0.296 mmol) and phthalimide (51.0 mg, 0.346 mmol) were dissolved in anhydrous THF (1 mL), and triphenylphosphine (113 mg, 0.432 mmol) was added all at once. Then diethyl azodicarboxylate (77.3 mg, 0.432 mmol) was added dropwise at room temperature. After 1 h, the solution was evaporated to dryness and the residue chromatographed (5% ethyl acetate in hexane) to yield a white powder, 105.8 mg (76%). NMR ($CDCl_3$): δ 7.85 (m, 2 H), 7.70 (m, 2 H), 6.13 (d, J = 19 Hz, 1 H), 5.94 (dt, J = 19 Hz, J' = 5 Hz, 1 H), 4.30 (m, 2 H), 1.60–1.10 (m, 12 H), 0.95–0.80 (m, 15 H). Anal. ($C_{23}H_{35}NO_2Sn$) C, H, N.

2-Acetylphenyl Trifluoromethanesulfonate (19). To a solution of *o*-hydroxyacetophenone (4.10 g, 0.030 mmol) in dry pyridine (18 mL) was added neat triflic anhydride (5.50 mL, 30 mmol) at 0 °C with stirring. After an overnight period at room temperature, workup with ether–water, then 5% HCl washes, and drying over sodium sulfate gave a crude product that was chromatographed with 5–15% ethyl acetate gradient in hexane. Yield: 6.30 g (78%) of **19** as a yellow oil. NMR ($CDCl_3$): δ 7.79 (dd, 1 H) 7.55 (m, 1 H) 7.45 (m, 1 H) 7.30 (dd, 1 H), 2.58 (s, 3 H). MS: 269 (M + H). Anal. ($C_9H_7SO_4F_3$) C, H, S.

Typical Procedures for the Coupling of Triflates 9a–c with Stannanes. Procedure A: Coupling of Triflate 6c with (*Z*)-1-Propenyltributyltin (Table I, Entry 3). Triflate **6c** (5.860 g, 0.010 mol) was dissolved in dry NMP (20 mL), the solution was degassed with argon, and zinc chloride (2.720 g, 0.020 mol) was added, followed by tri(2-furyl)phosphine (92 mg, 0.397 mmol) and Pd_2dba_3 (90.8 mg, 0.198 mmol Pd). The solution was stirred for 10 min, and then (*Z*)-1-propenyltributyltin (3.640 g, 0.011 mol) was added neat by syringe, rinsing with dry NMP (2 mL). The reaction mixture was stirred at room temperature for 20 h, diluted with ethyl acetate (100 mL), washed three times with water and once with brine, and dried over sodium sulfate. Filtration and concentration gave a crude product that was redissolved in acetonitrile (100 mL) and washed three times with pentane (100 mL each), in order to remove the tin-containing coproducts. Evaporation gave an oil that was recrystallized from warm methanol. Yield: 3.910 g (82%) of tan crystals of **16c**, mp 133–4 °C. NMR ($CDCl_3$): δ 7.4–7.2 (m, 7 H), 6.84 (m, 2 H), 6.1–6.0 (2 overlapping br d; J = 12 Hz, J' = 9 Hz, 2 H), 5.77 (dd, J = 9 Hz, J' = 4.9 Hz, 1 H), 5.62 (m, 1 H), 5.12 (s, 2 H), 4.95 (d, J = 4.9 Hz, 1 H), 3.78 (s, 3 H), 3.60 (m, 2 H), 3.42 (d, J = 18 Hz, 1 H), 3.22 (d, J = 18 Hz, 1 H), 1.51 (dd, J = 7.1 Hz, J' = 1.8 Hz, 3 H). The amount of *E* isomer present was estimated at 2% by NMR integration, by comparison with the NMR spectrum of an authentic sample, prepared according to the literature.[6b] Anal. ($C_{26}H_{26}N_2O_5S$) C, H, N, S.

Procedure B: Coupling of Triflate 6b with 1-Methyl-2-(tributylstannyl)pyrrole (Table I, Entry 14). Triflate **6b** (598 mg, 0.973 mmol) was dissolved in dry NMP (5 mL), the solution was degassed with argon, and then tri(2-furyl)phosphine (9.3 mg, 0.039 mmol) was added, followed by Pd_2dba_3 (9.1 mg, 0.019 mmol Pd) and, after 5 min, 1-methyl-2-(tributylstannyl)pyrrole (516 mg, 1.390 mmol) in NMP (2 mL). The solution was stirred for 1 h at room temperature. Workup as in procedure A gave an oil that was purified by flash chromatography, eluting with a gradient of 20% to 30% ethyl acetate in hexane. The resulting off-white foam (530 mg, 100%) was recrystallized from ether/hexane, to yield white fluffy crystals, 472 mg (89%), of **51**, mp 137–9 °C. NMR ($CDCl_3$): δ 7.31–7.05 (m, 10 H), 6.82 (s, 1 H), 6.48 (m, 1 H), 6.10 (m, 1 H) 6.06 (m, 1 H), 5.67 (dd, J = 9.3 Hz, J' = 4.8 Hz, 1 H), 5.27 (d, J = 9.3 Hz, 1 H), 5.02 (d, J = 4.8 Hz, 1 H), 3.58 (d, J = 18.9 Hz, 1 H), 3.43 (d, J = 18.9 Hz, 1 H), 3.10 (s, 3 H), 1.45 (s, 9 H). Mass spectrum: (M + H) 546. Anal. ($C_{30}H_{31}N_3O_5S$) C, H, N, S.

Procedure C: Coupling of Triflate 6a with (Trifluorovinyl)tributyltin (Table I, Entry 6). Triflate **6a** (188 mg, 0.297 mmol) was dissolved in dry degassed THF (3 mL) and treated with (trifluorovinyl)tributyltin (132 mg, 0.356 mmol), followed by zinc chloride (81.6 mg, 0.60 mmol), tri(2-furyl)phosphine (6.9 mg, 0.030 mmol), and Pd_2dba_3 (6.8 mg, 0.015 mmol of Pd). The mixture was stirred at room temperature for 2 h; then workup as in procedure A gave a crude product that was purified by flash chromatography (20% ethyl acetate in hexane) to yield **41** as a tan amorphous solid, 92.0 mg (55%). NMR ($CDCl_3$): 7.4–7.1 (m, 15 H), 6.99 (s, 1 H), 6.01 (br d, 1 H), 5.92 (dd, J = 9 Hz, J' = 5 Hz, 1 H), 5.01 (d, J = 5 Hz, 1 H), 3.63 (m, 2 H), 3.51 (d, J = 18.9 Hz, 1 H), 3.44 (dd, J = 18.9 Hz, J'_{H-F} = ca. 2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz, CF_3COOH reference): δ 92.4 (dd, J = 116 Hz, J' = 29 Hz, 1 F), 37.5 (dd, J = 116 Hz, J' = 63 Hz, 1 F), 20.4 (dd, J = 63 Hz, J' = 29 Hz, 1 F). Accurate mass determination (M + H): calcd for $C_{30}H_{24}N_2O_4SF_3$ 565.1409, found 565.1399.

Coupling of Triflate 6a with Vinyltributyltin (Table I, Entry 1). Triflate **6a** (464.5 mg, 0.730 mmol) was coupled with vinyltributyltin (279 mg, 0.880 mmol) according to procedure A. After 1 h at room temperature, workup and recrystallization from ethanol yielded **11** (296 mg, 79%). The NMR and IR spectra were identical with those published in the literature.[6c]

Coupling of Triflate 6b with (*Z*)-1-Propenyltributyltin (Table I, Entry 2). Triflate **6b** (999.0 mg, 1.625 mmol) was coupled with (*Z*)-1-propenyltributyltin (556.1 mg, 1.787 mmol) according to procedure A. After 16 h at room temperature, workup and chromatography (ethyl acetate/hexane) gave **16b** as a white foam (746.7 mg, 90%). NMR ($CDCl_3$): δ 7.45–7.20 (m, 10 H), 6.98 (s, 1 H), 6.09 (br d, 1 H), 5.7–5.5 (m, 2 H), 5.30 (br d, 1 H, exch), 5.10 (d, J = 4 Hz, 1 H), 3.55 (d, J = 18 Hz, 1 H), 3.37 (d, J = 18 Hz, 1 H), 1.47 (s, 9 H), 1.42 (dd, J = 7 Hz, J' = 1.8 Hz, 3 H). Anal. ($C_{28}H_{30}N_2O_5S$) C, H, N, S.

Coupling of Triflate 6a with 1-(Tributylstannyl)-2-methylprop-1-ene (Table I, Entry 4). Triflate **6a** (105 mg, 0.166 mmol) was coupled with 1-(tributylstannyl)-2-methylprop-1-ene (70 mg, 0.203 mmol) according to procedure A. After 19 h at room temperature, workup and chromatography (ethyl acetate/hexane) gave pure **39** as a foam (60.3 mg, 66%). NMR ($CDCl_3$): δ 7.5–7.15 (m, 15 H), 6.95 (s, 1 H), 6.14 (br d, 1 H), 5.79 (m, 2 H), 4.98 (d, J = 4.8 Hz, 1 H), 3.65 (m, 2 H), 3.35 (d, J = 18 Hz, 1 H), 3.15 (d, J = 18 Hz, 1 H), 1.59 (s, 3 H), 1.40 (s, 3 H). Anal. Calcd for $C_{32}H_{30}N_2O_4S$: C, 71.35; H, 5.61; N, 5.20; S, 5.95. Found: C, 70.97; H, 5.67; N, 5.07; S, 5.42.

Coupling of Triflate 6a with 1-Ethoxy-1-(tributylstannyl)ethylene (Table I, Entry 5). Triflate **6a** (200 mg, 0.310 mmol) was coupled with 1-ethoxy-1-(tributylstannyl)ethylene (90 mg, 0.660 mmol) according to procedure A. After 19 h at room temperature, workup and chromatography (ethyl acetate/hexane) gave **40** as a foam (92 mg, 52%). NMR ($CDCl_3$): δ 7.5–7.1 (m, 15 H), 6.99 (s, 1 H), 6.03 (d, J = 9 Hz, 1 H, exch), 5.92 (dd, J = 9 Hz, J' = 5 Hz, 1 H), 4.97 (d, $J \mp$ 5 Hz, 1 H), 4.00 (d, J = ca. 2 Hz, 1 H), 3.82 (d, J = ca. 2 Hz, 1 H), 3.60 (m, 3 H), 3.41 (d, J = 18 Hz, 1 H), 3.36 (m, 2 H), 1.04 (t, J = 7 Hz, 3 H). Anal. ($C_{32}H_{30}N_2O_5S$) C, H, N.

Coupling of Triflate 6b with 1-Phthalimido-3-(tributylstannyl)-2-propene (Table I, Entry 7). Triflate **6b** (72 mg, 0.117 mmol) was coupled with 1-phthalimido-3-(tributylstannyl)-2-

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propene (61.2 mg, 0.128 mmol) according to procedure A. After 20 h at room temperature, workup and chromatography (ethyl acetate/hexane) gave **42** as a foam (55.6 mg, 73%). NMR ($CDCl_3$): δ 7.82 (m, 2 H), 7.71 (m, 2 H), 7.46–7.24 (m, 10 H), 7.02 (d, J = 16 Hz, 1 H), 6.98 (s, 1 H), 5.91 (dt, J = 16 Hz, J' = 6.6 Hz, 1 H), 5.57 (br m, 1 H), 5.19 (br d, J = ca. 9 Hz, 1 H), 4.94 (d, J = 4.8 Hz, 1 H), 4.25 (m, 2 H), 3.57 (d, J = 17.7 Hz, 1 H), 3.46 (d, J = 17.7 Hz, 1 H), 1.43 (s, 9 H). Accurate mass determination: calcd for $C_{36}H_{33}N_3O_7S$ (M + H) 652.2117, found 652.2126.

Coupling of Triflate 6a with 1-(Tributylstannyl)-1-propyne (Table I, Entry 8). Triflate **6a** (103 mg, 0.162 mmol) was coupled with 1-(tributylstannyl)-1-propyne (53 mg, 0.162 mmol) according to procedure A. After 16 h at room temperature, workup and chromatography (ethyl acetate/hexane) gave **43** as a foam (44 mg, 50%). NMR ($CDCl_3$): δ 7.5–7.2 (m, 15 H), 6.97 (s, 1 H), 6.02 (br d, 1 H), 5.82 (dd, J = 9 Hz, J' = 5 Hz, 1 H), 4.92 (d, J = 5 Hz, 1 H), 3.65 (m, 3 H), 3.35 (d, J = 18 Hz, 1 H), 1.90 (s, 3 H). Mass spectrum: 539 (M + H). Anal. ($C_{31}H_{26}N_2O_4S$) C, H, N, S.

Coupling of Triflate 6a with Tributyltin Hydride (Table I, Entry 9). Triflate **6a** (100 mg, 0.158 mmol) was reacted with tributyltin hydride (216 mg, 0.740 mmol) according to procedure C. After 1 h at 65 °C, workup and chromatography (ethyl acetate/hexane) gave the known **44** (53 mg, 68%), mp 159–60 °C (lit.[64] mp 160–2 °C). NMR ($CDCl_3$): δ 7.5–7.2 (m, 15 H), 6.95 (s, 1 H), 6.60 (dd, J = 6.2 Hz, J' = 2.5 Hz, 1 H), 6.1 (br d, J = 9 Hz), 5.91 (dd, J = 9 Hz, J' = 5 Hz, 1 H), 4.92 (d, J = 5 Hz, 1 H), 3.55 (m, 2 H), 3.51 (dd, J = 19 Hz, J' = 2.5 Hz, 1 H), 3.33 (dd, J = 19 Hz, J' = 6.2 Hz, 1 H).

Coupling of Triflate 6a with (*p*-Methoxyphenyl)tributyltin (Table I, Entry 10). Triflate **6a** (102.9 mg, 0.163 mmol) was coupled with (*p*-methoxyphenyl)tributyltin (77.5 mg, 0.195 mmol) according to procedure A. After 6 h at 50 °C, workup and chromatography (ethyl acetate/hexane) yielded **45** as a foam (54.8 mg, 57%). NMR ($CDCl_3$): δ 7.5–7.2 (m, 13 H), 6.95 (d, J = 8 Hz, 2 H), 6.87 (m, 2 H), 6.82 (s, 1 H), 6.62 (d, J = 8 Hz, 2 H), 6.03 (br d, J = 9 Hz, 1 H), 5.87 (dd, J = 9 Hz, J' = 5 Hz, 1 H), 5.04 (d, J = 5 Hz, 1 H), 3.72 (s, 3 H), 3.65 (dd, 2 H), 3.55 (s, 2 H). Mass spectrum: 591 (M + H). Anal. ($C_{35}H_{30}N_2O_5S$) C, H, N.

Coupling of Triflate 6b with Tetramethyltin (Table I, Entry 11). Triflate **6b** (154.8 mg, 0.252 mmol) was reacted with tetramethyltin (50 μL, 0.361 mmol) according to procedure B. After 16 h at room temperature, workup and chromatography (ethyl acetate/hexane) gave pure **46** as a foam (102.5 mg, 85%). NMR ($CDCl_3$): δ 7.5–7.2 (m, 10 H), 6.89 (s, 1 H), 5.57 (br m, 1 H), 5.25 (br d, J = 9 Hz, 1 H), 4.93 (d, J = 4.8 Hz, 1 H), 3.47 (d, J = 18.5 Hz, 1 H), 3.19 (d, J = 18.5 Hz, 1 H), 2.09 (s, 3 H), 1.44 (s, 9 H). Accurate mass determination: calcd for $C_{26}H_{29}N_2O_5S$ (M + H) 481.1797, found 481.1788. Anal. Calcd for $C_{26}H_{28}N_2O_5S$: C, 64.98; H, 5.87; N, 5.83. Found, C, 64.47; H, 5.71; N, 5.76.

Coupling of Triflate 6b with Tetrabutyltin (Table I, Entry 12). Triflate **6b** (533 mg, 0.867 mmol) was coupled with tetrabutyltin (570 μL, 1.734 mmol) according to procedure B. After 7 days at 50 °C, workup and chromatography (ethyl acetate/hexane) gave **47** as a foam (73.2 mg, 16%). NMR ($CDCl_3$): δ 7.45–7.25 (m, 10 H), 6.93 (s, 1 H), 5.55 (br m, 1 H), 5.21 (br d, J = 9 Hz, 1 H), 4.94 (d, J = 4.8 Hz, 1 H), 3.45 (d, J = 18 Hz, 1 H), 3.25 (d, J = 18 Hz, 1 H), 2.46 (m, 2 H), 2.28 (m, 2 H), 1.21 (m, 2 H), 0.80 (t, J = 7.2 Hz, 3 H). Accurate mass determination: calcd for $C_{29}H_{35}N_2O_5S$ (M + H) 545.2087, found 545.2074. Anal. Calcd for $C_{29}H_{34}N_2O_5S$: C, 66.64; H, 6.56; N, 5.36. Found: C, 66.14; H, 6.47; N, 5.05.

Coupling of Triflate 6b with Allyltributyltin (Table I, Entry 13). (A) Blank Run. Triflate **6b** (68.5 mg, 0.111 mmol) in dry NMP (1 mL) was treated with allyltributyltin (38.4 mg, 0.111 mmol) at 50 °C for 24 h. Workup and chromatography (ethyl acetate/hexane) gave the Δ^2 isomer **49**, 8.7 mg (15%), as a foam. The NMR spectrum of the crude showed no evidence of Δ^3 isomer **48**. NMR ($CDCl_3$): δ 7.4–7.2 (m, 10 H), 6.86 (s, 1 H), 6.01 (s, 1 H), 5.61 (m, dd when dcpl m at δ 2.8, J_{trans} = ca. 17 Hz, J_{cis} = ca. 9 Hz, 1 H), 5.38 (br m, 1 H), 5.30 (br m, 1 H), 5.22 (d, J = 4.8 Hz, 1 H), 5.09 (br d, J = 9 Hz, 1 H), 4.99 (br d, J = 17 Hz, 1 H), 2.80 (m, 2 H), 1.42 (s, 9 H). Accurate mass determination: calcd for $C_{28}H_{30}N_2O_5S$ (M + H) 507.1954, found 507.1949.

(B) Palladium Catalyzed. Triflate **6b** (113.4 mg, 0.185 mmol) in dry NMP (1.2 mL) was coupled with allyltributyltin (64.1 mg, 0.185 mg) according to procedure B. After 40 h at 50 °C, workup and careful chromatography (20% ethyl acetate in hexane) afforded two fractions: the first (59.8 mg, 64%) was a 3:1 mixture of **48** and **49** (by NMR integration, vide infra), the second (10 mg, 12%) was the reduction product **50**. NMR ($CDCl_3$): δ 7.5–7.2 (m, 10 H), 6.94 (s, 1 H), 6.65 (dd, J = 6.2 Hz, J' = 2.4 Hz, 1 H), 5.67 (dd, J = 9.5 Hz, J' = 5.1 Hz, 1 H), 5.24 (br d, J = 9.5 Hz, 1 H), 4.92 (d, J = 5.1 Hz, 1 H), 3.60 (dd, J = 19.3 Hz, J' = 2.4 Hz, 1 H), 3.41 (dd, J = 19.3 Hz, J' = 6.2 Hz, 1 H), 1.44 (s, 9 H). Accurate mass determination: calcd for $C_{25}H_{26}N_2O_5S$ (M + H) 467.1641, found 467.1630.

When the above coupling was repeated in the presence of 0.0185 mmol (10 mol %) of 2,6-di-*tert*-butyl-4-methylphenol (BHT), **48** and **49** were obtained in the same yield in a ratio of 4:1 (NMR integration).

An authentic sample of **48** was obtained as follows: 3-chlorocephem **8d** (643.6 mg, 1.250 mmol) was dissolved in dry THF (10 mL) and treated with tri(2-furyl)phosphine (23 mg, 0.100 mmol), Pd_2dba_3 (22.9 mg, 0.025 mmol Pd), and vinyltributyltin (434.4 mg, 1.370 mmol). After being refluxed overnight, the dark mixture was evaporated to dryness, redissolved in acetonitrile (50 mL) and washed four times with equal volumes of hexane, and then evaporated and chromatographed (20% ethyl acetate in hexane) to yield **48** as a white solid, 506 mg (80%). The analytical sample was obtained after trituration with hexane. NMR ($CDCl_3$): δ 7.45–7.25 (m, 10 H), 6.93 (s, 1 H), 5.71 (m, 1 H), 5.59 (br dd, 1 H), 5.21 (br d, J = ca. 9 Hz, 1 H), 5.11–5.01 (m, 2 H), 4.95 (d, J = 4.7 Hz, 1 H), 3.69 (d, J = 18.8 Hz, 1 H), 3.45 (m overlapping d at 3.29, 1 H), 3.29 (d, J = 18.8 Hz, 1 H), 2.89 (dd, J = 14.3 Hz, J' = 7.5 Hz, 1 H), 1.44 (s, 9 H). Anal. Calcd for $C_{28}H_{30}N_2O_5S$: C, 66.38; H, 5.97; N, 5.53; S, 6.33. Found: C, 65.78; H, 6.17; N, 5.17; S, 5.97. Accurate mass determination: calcd for $C_{28}H_{31}N_2O_5S$ (M + H) 507.1954, found 507.1944.

Coupling of Triflate 6b with (4-*tert*-Butyl-1-cyclohexen-1-yl)trimethyltin (Table I, Entry 15). Triflate **6b** (195 mg, 0.317 mmol) was coupled with (4-*tert*-butyl-1-cyclohexen-1-yl)trimethyltin (105 mg, 0.349 mmol) according to procedure B. Workup and chromatography (20% to 30% ethyl acetate in hexane) gave two fractions. The first yielded a white solid, **52** (31.9 mg, 17%, 1:1 mixture of diastereomers). NMR ($CDCl_3$): δ 7.4–7.2 (m, 10 H), 6.92 and 6.88 (two s, 0.50 H each), 5.56 (br dd, 1 H), 5.40 (m, 1 H), 5.19 (br d, 1 H), 4.97 (two overlapping d, 1 H overall), 3.37 (m, 2 H), 2.0–1.2 (m, 16 H, incl. s at 1.44), 0.72 and 0.71 (two s, 9 H overall). Anal. Calcd for $C_{35}H_{42}N_2O_5S$: C, 69.73; H, 7.02; N, 4.65. Found: C, 69.25; H, 6.89; N, 4.70. Accurate mass determination: calcd for $C_{35}H_{43}N_2O_5S$ (M + H) 603.2893, found 603.2887.

The second fraction was identical by NMR with the coupling product between **6b** and tetramethyltin (entry 11 in Table I), cephem **46** (113.8 mg, 74%).

Coupling between Aryl Triflates and Vinyltributyltin (Scheme XI). (A) *p*-(Triflyloxy)acetophenone (204.8 mg, 0.763 mmol) in dry NMP (3 mL) was treated with lithium chloride (94 mg, 2.217 mmol), tri(2-furyl)phosphine (7.1 mg, 0.031 mmol), Pd_2dba_3 (7.0 mg, 0.015 mmol), and, after 5 min, vinyltributyltin (266 mg, 0.839 mmol). The degassed solution was stirred at room temperature for 2 h, then worked up (ethyl acetate, three water washes), and dried. The crude product was chromatographed (5% ethyl acetate in hexane) to yield pure *p*-acetylstyrene (18)[33] (106.6 mg, 95%), which solidified on standing. Mp: 29–31 °C (lit.[33] mp 29–30 °C).

(B) *o*-(Triflyloxy)acetophenone was reacted with vinyltributyltin as above to yield *o*-acetylstyrene[65] in 90% yield. MS: 147 (M + H). Bp (Kugelrohr): 110–8 °C/4 mmHg (lit.[65] bp 97–8 °C at 3 mmHg).

(C) Competition Experiment. *o*- and *p*-(triflyloxy)acetophenone (110 mg each, 0.410 mmol) were treated with vinyltributyltin (107.8 mg, 0.340 mmol) as above. After 2 h at room temperature,

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workup gave a crude product, which showed (NMR) **18** and **20** in a 73:27 ratio.

General Procedure for the Coupling of 3-(Chloromethyl)cephems and Stannanes. Coupling of 3-(Chloromethyl)cephem 8a with Vinyltributyltin (Table II, Entry 1). A mixture of vinyltributyltin (2.860 g, 9.019 mmol), 3-(chloromethyl)cephem (**8a**) (5.000 g, 7.530 mmol), and tri(2-furyl)phosphine (70 mg, 0.302 mmol) in dry THF (40 mL) was degassed with argon, and Pd_2dba_3 (69 mg, 0.152 mmol Pd) was added. After being refluxed for 3 h, the mixture was cooled, evaporated to dryness, and partitioned between acetonitrile and pentane, washing the acetonitrile with two more batches of pentane. After evaporation, the crude product was chromatographed (ethyl acetate/hexane) to yield a white foam, **21a** (4.240 g, 82%). NMR ($CDCl_3$): δ 7.4–7.2 (m, 10 H), 7.14 (d, J = 8 Hz, 2 H), 6.94 (s, 1 H), 6.69 (d, J = 8 Hz, 2 H), 6.56 (br d, 1 H), 5.97 (br s, 1 H), 5.78 (dd, J = 9 Hz, J' = 5 Hz, 1 H), 5.72 (m, 1 H), 5.57 (br s, 1 H), 5.15–5.0 (m, 3 H), 4.93 (d, J = 5 Hz, 1 H), 3.35 (d, J = 18 Hz, 1 H), 3.33 (m, 1 H), 3.20 (d, J = 18 Hz, 1 H), 2.87 (dd, J = 14 Hz, J' = 7.5 Hz, 1 H), 1.42 (s, 9 H). Anal. ($C_{36}H_{37}N_3O_7S$) C, H, N, S. Accurate mass determination: calcd for $C_{36}H_{38}N_3O_7S$ (M + H) 656.2430, found 656.2379.

Coupling of 3-(Chloromethyl)cephem 1β-Oxide 53 with Vinyltributyltin (Table II, Entry 2). 3-(Chloromethyl)cephem 1β-oxide **53** (161.5 mg, 0.294 mmol) was coupled with vinyltributyltin (102 mg, 0.320 mmol) according to the general procedure. After 40 min at reflux, workup and chromatography (ethyl acetate/hexane) gave **54** as a white solid, 138 mg (87%). NMR ($CDCl_3$): δ 7.4–7.1 (m, 15 H), 6.88 (s, 1 H), 6.65 (d, J = 9.5 Hz, 1 H), 6.00 (dd, J = 9.5 Hz, J' = 5 Hz, 1 H), 5.61 (m, 1 H), 5.02 (m, 2 H), 4.38 (d, J = 5 Hz, 1 H), 3.6–3.5 (m, 3 H), 3.23 (dd, J = 14 Hz, J' = 6 Hz, 1 H), 2.99 (d, J = 18.3 Hz, 1 H), 2.91 (dd, J = 14 Hz, J' = 7 Hz, 1 H). Anal. Calcd for $C_{31}H_{28}N_2O_5S$: C, 68.70; H, 5.22; N, 5.18; S, 5.93. Found: C, 69.03; H, 5.35; N, 5.09; S, 5.45. Accurate mass determination: calcd for $C_{31}H_{29}N_2O_5S$ (M + H) 541.1797, found 541.1735.

Coupling of 3-(Bromomethyl)cephem 55 with Vinyltributyltin (Table II, Entry 3). 3-(Bromomethyl)cephem **55** (200 mg, 0.350 mmol) was coupled with vinyltributyltin (110 mg, 0.350 mmol) according to the general procedure. After 16 h at reflux, workup and chromatography (ethyl acetate/hexane) gave **21b** as a white solid (148 mg, 80%). NMR ($CDCl_3$): δ 7.5–7.2 (m, 15 H), 6.88 (s, 1 H), 6.11 (d, J = 9 Hz, 1 H), 5.81 (dd, J = 9 Hz, J' = 5 Hz, 1 H), 5.72 (m, 1 H), 5.10 (m, 2 H), 5.02 (d, J = 5 Hz, 1 H), 3.62 (m, 2 H), 3.48 (d, J = 18 Hz, 1 H), 3.32 (m, 1 H), 3.29 (d, J = 18 Hz, 1 H), 2.89 (dd, J = 14 Hz, J' = 7 Hz, 1 H). Anal. ($C_{31}H_{28}N_2O_4S$) C, H, N, S.

Coupling of 3-(Chloromethyl)cephem 8c with Vinyltributyltin (Table II, Entry 4). 3-(Chloromethyl)cephem **8c** (305 mg, 0.626 mmol) was coupled with vinyltributyltin (217 mg, 0.684 mmol) according to the general procedure. After 3 h at reflux, workup and chromatography (40% ethyl acetate in hexane) gave **21c** as a white solid, 267.7 mg (89%). NMR ($CDCl_3$): δ 7.4–7.2 (m, 7 H), 6.83 (d, J = 8 Hz, 2 H), 5.98 (br d, 1 H exch.), 5.8–5.6 (m, 2 H), 5.13 (s, 2 H), 5.1–5.0 (m, 2 H), 4.88 (d, J = 5 Hz, 1 H), 3.76 (s, 3 H), 3.61 (m, 2 H), 3.35 (m, 2 H incl. d, J = 18 Hz, 1 H), 3.20 (d, J = 18 Hz, 1 H), 2.81 (dd, J = 14 Hz, J' = 7 Hz, 1 H). Anal. Calcd for $C_{26}H_{26}N_2O_5S$: C, 65.25; H, 5.48; N, 5.85. Found: C, 64.70; H, 5.40; N, 5.74. Accurate mass determination: calcd for $C_{26}H_{27}N_2O_5S$ (M + H) 479.1653, found 479.1633.

Coupling of 3-(Chloromethyl)cephem 8a with (*Z*)-1-Propenyltributyltin (Table II, Entry 5). 3-(Chloromethyl)-cephem **8a** (1.000 g, 1.506 mmol) was coupled with (*Z*)-1-propenyltributyltin (595 mg, 1.792 mmol, 98.5% Z) according to the general procedure. After 16 h at reflux, workup and chromatography (ethyl acetate/hexane) gave **56** as a white solid (>98% *Z* by NMR), 790 mg (78%). NMR ($CDCl_3$): δ 7.5–7.2 (m, 10 H), 7.14 (d, J = 8 Hz, 2 H), 6.95 (s, 1 H), 6.69 (d, J = 8 Hz, 2 H), 6.56 (br d, 1 H), 5.92 (br s, 1 H), 5.76 (dd, J = 9 Hz, J' = 5 Hz, 1 H), 5.57 (m, 2 H), 5.28 (m, 1 H), 5.10 (br s, 1 H), 4.94 (d, J = 5 Hz, 1 H), 3.35 (d, J = 18 Hz, 1 H), 3.14 (d, J = 18 Hz, 1 H), 3.20–3.05 (m, 2 H), 1.58 (d, J = 7 Hz, 3 H), 1.42 (s, 9 H). Anal. ($C_{37}H_{39}N_3O_7S$) C, H, N.

Coupling of 3-(Chloromethyl)cephem 8a with 1-(Tributylstannyl)-2-methylprop-1-ene (Table II, Entry 6). 3-(Chloromethyl)cephem **8a** (664.2 mg, 1.000 mmol) was coupled with 1-(tributylstannyl)-2-methylprop-1-ene (380 mg, 1.100 mmol) according to the general procedure. After 72 h at reflux, workup and chromatography (ethyl acetate/hexane) gave **57** as a foam, 411 mg (60%). NMR ($CDCl_3$): δ 7.5–7.2 (m, 10 H), 7.15 (d, J = 8 Hz, 2 H), 6.94 (s, 1 H), 6.69 (d, J = 8 Hz, 2 H), 6.49 (br d, 1 H), 5.76 (dd, J = 9 Hz, J' = 5 Hz, 1 H), 5.60 (br s, 2 H), 5.10 (br s, 1 H), 5.00 (br t, 1 H), 4.93 (d, J = 5 Hz, 1 H), 3.36 (d, J = 18 Hz, 1 H), 3.14 (d, J = 18 Hz, 1 H), 3.20–3.10 (m, 1 H), 3.00 (dd, J = 14 Hz, J' = 9 Hz, 1 H), 1.66 (s, 3 H), 1.56 (s, 3 H), 1.42 (s, 9 H). Anal. ($C_{38}H_{41}N_3O_7S$) C, H, N.

Coupling of 3-(Chloromethyl)cephem 8a with (Trifluorovinyl)tributyltin (Table II, Entry 7). 3-(Chloromethyl)cephem **8a** (1.250 g, 1.882 mmol) was coupled with (trifluorovinyl)tributyltin (1.040 g, 2.800 mol) according to the general procedure. After 72 h at reflux, workup and chromatography (ethyl acetate/hexane) gave **58** as a foam, 868 mg (65%). NMR ($CDCl_3$): δ 7.4–7.2 (m, 10 H), 7.10 (d, J = 8 Hz, 2 H), 6.95 (s, 1 H), 6.80 (br d, 1 H), 6.66 (d, J = 8 Hz, 2 H), 5.80 (dd, J = 9 Hz, J' = 5 Hz, 1 H), 5.59 (br s, 1 H), 5.10 (br s, 1 H), 4.95 (d, J = 5 Hz, 1 H), 3.68 (br t, J = 15 Hz, 1 H), 3.41 (d, J = 19 Hz, 1 H), 3.31 (br t, J = 15 Hz, 1 H), 3.15 (d, J = 19 Hz, 1 H), 1.42 (s, 9 H). Anal. ($C_{36}H_{34}N_3O_7SF_3$) C, H, N, S.

Coupling of 3-(Chloromethyl)cephem 8a with 1-Methoxy-1-(tributylstannyl)ethylene (Table II, Entry 8). 3-(Chloromethyl)cephem **8a** (1.070 g, 1.611 mmol) was coupled with 1-methoxy-1-(tributylstannyl)ethylene (700 mg, 1.940 mmol) according to the general procedure. After 2 h at reflux, workup and chromatography (ethyl acetate/hexane) gave **59** (799 mg, 71%), which was somewhat unstable on silica and was contaminated by traces of the hydrolysis product. NMR ($CDCl_3$): δ 7.5–7.2 (m, 10 H), 7.15 (d, J = 8 Hz, 2 H), 6.95 (s, 1 H), 6.72 (d, J = 8 Hz, 2 H), 6.52 (br d, 1 H), 5.75 (dd, J = 9 Hz, J' = 5 Hz, 1 H), 5.60 (br s, 2 H), 5.10 (br s, 1 H), 4.95 (d, J = 5 Hz, 1 H), 3.90 (d, J = 2 Hz, 1 H), 3.80 (d, J = 2 Hz, 1 H), 3.65 (q, 2 H), 3.5–3.00 (m, 4 H), 1.42 (s, 9 H), 1.22 (t, 3 H). Anal. Calcd for $C_{38}H_{41}N_3O_8S$: C, 65.22; H, 5.91; N, 6.00. Found: C, 64.39; H, 5.36; N, 5.93. Mass (M + H) 700.

Coupling of 3-(Chloromethyl)cephem 8c with Tributyltin Hydride (Table II, Entry 9). 3-(Chloromethyl)cephem **8c** (199 mg, 0.410 mmol) was couled with tributyltin hydride (0.220 mL, 0.820 mmol) according to the general procedure. After 30 min at room temperature, workup and trituration with ether gave pure **60** (182 mg, 98%) as a white solid. NMR ($CDCl_3$): δ 7.4–7.2 (m, 7 H), 6.82 (d, J = 8.7 Hz, 2 H), 6.31 (br d, J = 9 Hz, 1 H), 5.71 (dd, J = 9 Hz, J' = 4.8 Hz, 1 H), 5.14 (s, 2 H), 4.86 (d, J = 4.8 Hz, 1 H), 3.76 (s, 3 H), 3.60 (m, 2 H), 3.39 (d, J = 18.3 Hz, 1 H), 3.09 (d, J = 18.3 Hz, 1 H), 2.05 (s, 3 H). Accurate mass determination: calcd for $C_{24}H_{25}N_2O_5S$ (M + H) 453.1481, found 453.1475.

Coupling of 3-(Chloromethyl)cephem 8c with (*E*)-1,2-Bis(Tributylstannyl)ethylene (Table II, Entry 10). 3-(Chloromethyl)cephem **8c** (209 mg, 0.440 mmol) was coupled with (*E*)-1,2-bis(tributylstannyl)ethylene (532.8 mg, 0.880 mmol) according to the general procedure. After 16 h at reflux, workup and chromatography (ethyl acetate/hexane) gave **23** as an oil (225 mg, 66%). NMR ($CDCl_3$): δ 7.20–7.00 (m, 7 H), 6.69 (d, J = 8.7 Hz, 2 H), 5.92–5.80 (m, 2 H), 5.65 (ddd, partially overlapping dd at 5.57, J = 19 Hz, J' = 6.6 Hz, J'' = 4.9 Hz, 1 H), 5.57 (dd, J = 9 Hz, J' = 4.8 Hz, 1 H), 5.01 (s, 2 H), 4.70 (d, J = 4.8 Hz, 1 H), 3.60 (s, 3 H), 3.44 (m, 2 H), 3.31 (dd, J = 14 Hz, J' = 4.9 Hz, 1 H), 3.16 (d, J = 18.2 Hz, 1 H), 3.03 (d, J = 18.2 Hz, 1 H), 2.74 (dd, J = 14 Hz, J' = 6.6 Hz, 1 H), 1.4–1.0 (m, 12 H), 0.8–0.6 (m, 15 H). Anal. ($C_{38}H_{52}N_2O_5SSn$) C, H, N, S. Accurate mass determination: calcd for $C_{38}H_{53}N_2O_5SSn$ (M + H) 768.2619, found 768.2618.

Compound **23** (133 mg, 0.173 mmol) was then dissolved in dry THF (2 mL) and cooled to −78 °C. Iodine (44 mg, 0.173 mmol) was added in one lot under argon. The mixture was allowed to reach room temperature over 1 h; then it was quenched with 5% sodium bisulfite solution and extracted with ethyl acetate. The organics were dried, evaporated, and redissolved in acetonitrile. Four hexane washes were used to remove tributyltin iodide. Evaporation gave almost pure **24** (106 mg, 100%). Recrystallization from a small amount of ethyl acetate gave white crystals, 89 mg (85%) of pure material, mp 169–75 °C. NMR ($CDCl_3$): δ 7.38–7.23 (m, 7 H), 6.86 (d, J = 8.7 Hz, 2 H), 6.42 (ddd, J = 14.6

Hz, J' = 8 Hz, J'' = 6 Hz, 1 H), 6.12 (d, J = 14.6 Hz, 1 H), 6.00 (br d, J = 9 Hz, 1 H), 5.76 (dd, J = 9 Hz, J' = 4.8 Hz, 1 H), 5.16 (s, 2 H), 4.88 (d, J = 4.8 Hz, 1 H), 3.78 (s, 3 H), 3.62 (m, 2 H), 3.37 (d, J = 18.3 Hz, 1 H), 3.31 (dd, J = 14.4 Hz, J' = 6 Hz, 1 H), 3.16 (d, J = 18.3 Hz, 1 H), 2.81 (dd, J = 14.4 Hz, J' = 8 Hz, 1 H). Anal. ($C_{26}H_{25}N_2O_5SI$) C, H, N. Accurate mass determination: calcd for $C_{26}H_{26}N_2O_5SI$ (M + H) 605.0607, found 605.0594.

Coupling of 3-(Chloromethyl)cephem 8b with (*p*-Methoxyphenyl)tributyltin (Table II, Entry 11). 3-(Chloromethyl)cephem **8b** (638 mg, 1.197 mmol) was coupled with (*p*-methoxyphenyl)tributyltin (523 mg, 1.200 mmol) according to the general procedure. After 24 h at reflux, workup and chromatography (ethyl acetate/hexane) gave the known cephem **61** as a white solid, 586 mg (81%), mp 194–7 °C (lit.[86] mp 198.5–99.5 °C). NMR ($CDCl_3$): δ 7.4–7.2 (m, 15 H), 7.05 (d, J = 8.5 Hz, 2 H), 6.99 (s, 1 H), 6.79 (d, J = 8.5 Hz, 2 H), 6.07 (br d, J = 9 Hz, 1 H), 5.84 (dd, J = 9 Hz, J' = 4.6 Hz, 1 H), 4.97 (d, J = 4.6 Hz, 1 H), 3.89 (d, J = 14.7 Hz, 1 H), 3.79 (s, 3 H), 3.67 (m, 2 H), 3.44 (d, J = 14.7 Hz, 1 H), 3.32 (d, J = 18 Hz, 1 H), 3.12 (d, J = 18 Hz, 1 H).

Coupling of 3-(Chloromethyl)cephem 8c with [*p*-(Trifluoromethyl)phenyl]tributyltin (Table II, Entry 12). 3-(Chloromethyl)cephem **8c** (328.3 mg, 0.674 mmol) was coupled with [*p*-(trifluoromethyl)phenyl]tributyltin (322.7 mg, 0.742 mmol) according to the general procedure. After 72 h at reflux, workup and chromatography (ethyl acetate/hexane) gave **62** as a white solid, 257 mg (64%). Recrystallization from ethyl acetate–hexane gave a microcrystalline solid, mp 177–8 °C. NMR ($CDCl_3$) δ 7.51 (d, J = 8.1 Hz, 2 H), 7.35–7.21 (m, 9 H), 6.83 (d, J = 8.7 Hz, 2 H), 6.04 (br d, J = 9 Hz, 1 H), 5.79 (dd, J = 9 Hz, J' = 4.8 Hz, 1 H), 5.18 (m, 2 H), 4.91 (d, J = 4.8 Hz, 1 H), 4.11 (d, J = 14.9 Hz, 1 H), 3.77 (s, 3 H), 3.60 (m, 2 H), 3.44 (d, J = 14.9 Hz, 1 H), 3.33 (d, J = 18.3 Hz, 1 H), 3.02 (d, J = 18.3 Hz, 1 H). Anal. ($C_{31}H_{27}N_2O_5SF_3$) C, H, N, S, F. Accurate mass determination: calcd for $C_{31}H_{28}N_2O_5SF_3$ (M + H) 597.1671, found 597.1658.

Coupling of 3-(Chloromethyl)cephem 8c with Ethynyltributyltin (Table II, Entry 13). 3-(Chloromethyl)cephem **8c** (163.3 mg, 0.344 mmol) was coupled with ethynyltributyltin (108.4 mg, 0.344 mmol) according to the general procedure. After 72 h at room temperature, workup and careful chromatography (gradient of 40–60% ethyl acetate in hexane) gave 21.8 mg (14%) of a mixture of reduction products **26**[66] and **27**, identical with the material obtained by tin hydride reduction (entry 9) in a ratio (NMR) of 57:43. The major product, a yellow glass (95.9 mg, 60%), was identified as dimer **25**. NMR ($CDCl_3$, 500 MHz): δ 7.4–7.15 (m, 14 H), 6.83 (m, 6 H, incl. 2 H exch.), 5.77 and 5.75 (two overlapping dd, 2 H overall), 5.67 (dd, J = 8.5 Hz, J' = 5.5 Hz, 1 H), 5.13 (m, 4 H), 4.88 and 4.87 (two overlapping d, J = 4.8 Hz, 2 H overall), 3.76 (s, 6 H), 3.59 (m, 4 H), 3.6–2.95 (m, 9 H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): 171.5, 171.4, 165.7, 164.9, 161.7, 161.4, 158.7, 136.2, 134.1, 134.0, 131.6, 130.4, 129.5, 129.2, 128.8, 128.7, 127.3, 127.2, 126.9, 126.8, 124.2, 122.8, 121.7, 114.0, 113.9, 83.4, 81.0, 67.6, 59.0, 58.95, 57.8, 57.2, 55.2, 43.0, 42.9, 39.4, 34.7, 28.9, 27.8. Anal. Calcd for $C_{52}H_{48}N_4O_{10}S_2$: C, 65.52; H, 5.08; N, 5.88. Found: C, 64.98; H, 5.00; N, 5.69. Accurate mass determination: calcd for $C_{52}H_{49}N_4O_{10}S_2$ (M + H) 953.2890, found 953.2903.

Coupling of 3-(Chloromethyl)cephem 8c with (Phenylethynyl)tributyltin (Table II, Entry 14). 3-(Chloromethyl)-cephem **8c** (227 mg, 0.467 mmol) was coupled with (phenylethynyl)tributyltin (201 mg, 0.514 mmol) according to the general procedure. After 96 h at room temperature, workup and chromatography (ethyl acetate/hexane) gave dimer **28** as a yellow glassy solid, 206 mg, 80%. NMR ($CDCl_3$): δ 7.3–6.7 (m, 28 H), 6.16 (two overl. d, J = ca. 9 Hz, 2 H), 5.69 and 5.60 (two dd, J = 9 Hz, J' = 4.6 Hz for both, 2 H), 5.10 (m, 2 H), 4.95 (m, 2 H), 4.80 (d, J = 4.6 Hz, 1 H), 4.66 (d, J = 4.6 Hz, 1 H), 4.25 (d, J = 14.4 Hz, 1 H), 4.02 (d, J = 14.4 Hz, 1 H), 3.74 (s, 3 H), 3.72 (s, 3 H), 3.60 (m, 4 H), 3.55–3.20 (m, 5 H), 3.00 (d, J = 18 Hz, 1 H). Anal. Calcd for $C_{64}H_{56}N_4O_{10}S_2$: C, 69.54; H, 5.11; N, 5.07; S, 5.80. Found: C, 68.81; H, 4.98; N, 4.93; S, 5.59. Accurate mass determination: calcd for $C_{64}H_{57}N_4O_{10}S_2$ (M + H) 1105.3516, found 1105.3503.

When the coupling was repeated using 5 molar equiv of Pd and 20 molar equiv of tri(2-furyl)phosphine as the catalytic system, along with a 19% yield of **28**, careful gradient chromatography (30% ethyl acetate in hexane) gave **29** (28 mg, 17%) as a yellow glass. NMR ($CDCl_3$): δ 7.5–7.1 (m, 22 H), 6.81 (d, J = 8.8 Hz, 2 H), 6.01 (br d, J = 9.3 Hz, 1 H), 5.75 (dd, J = 9.3 Hz, J' = 4.8 Hz, 1 H), 5.14 (m, 2 H), 4.83 (d, J = 4.8 Hz, 1 H), 3.98 (d, J = 18 Hz, 1 H), 3.78 (s, 3 H), 3.75–3.40 (m, 4 H), 3.00 (d, J = 18 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 76.1 MHz): δ 170.2, 163.7, 161.0, 159.1, 136.4, 133.1, 131.2, 130.5, 130.1, 129.4, 129.0, 128.7 128.4, 128.2, 128.1, 128.0, 127.9, 127.2, 126.6, 125.6, 123.9, 122.7, 122.5, 113.6, 97.9, 96.1, 90.3, 89.3, 67.8, 59.1, 57.4, 55.4, 43.6, 36.3, 28.7. Accurate mass determination: calcd for $C_{48}H_{39}N_2O_5S$ (M + H) 755.2580, found 755.2575.

Coupling of 3-(Chloromethyl)cephem 8a with 1-(Tributylstannyl)-1-propyne (Table II, Entry 15). 3-(Chloromethyl)cephem **8a** (1.000 g, 1.506 mmol) was coupled with 1-(tributylstannyl)-1-propyne (740 mg, 2.249 mmol) according to the general procedure. After 16 h at reflux, workup and careful chromatography (16% ethyl acetate in dichloromethane) gave **63** as a pale yellow solid, 320 mg (32%). NMR ($CDCl_3$): δ 7.45–7.20 (m, 10 H), 7.12 (d, J = 8.4 Hz, 2 H), 6.82 (s, 1 H), 6.69 (d, J = 8.4 Hz, 2 H), 6.60 (d, J = 9.7 Hz, 1 H exch.), 5.79 (br s, 1 H exch.), 5.66 (d, J = 2.3 Hz, 1 H), 5.64 (dd, J = 9.7 Hz, J' = 4.5 Hz, 1 H), 5.55 (br s, 1 H exch.), 5.32 (d, J = 4.5 Hz, 1 H), 5.11 (s, 1 H), 5.07 (br s, 1 H), 3.71 (d, J = 14 Hz, 1 H), 3.24 (d, J = 14 Hz, 1 H), 2.02 (d, J = 2.3 Hz, 3 H), 1.42 (s, 9 H). Mass spectrum (M + H): 668. Anal. Calcd for $C_{37}H_{37}N_3O_7S$: C, 66.54; H, 5.59; N, 6.29. Found: C, 65.38; H, 5.62; N, 6.05.

Coupling of 3-(Chloromethyl)cephem 8d with Allyltributyltin (Table II, Entry 16). 3-(Chloromethyl)cephem **8d** (647 mg, 1.256 mmol) was coupled with allyltributyltin (457 mg, 1.381 mmol) according to the general procedure. After 16 h at reflux, workup and chromatography (18% ethyl acetate in hexane) gave a number of fractions containing the three isomeric cephems **36**, **37**, and **38** (overall, 497 mg, 76%). Cephem **38**, the fastest eluting and major product, was obtained pure by combining the first three fractions of the chromatography. Its epimer **36**, the slowest eluting, was isolated by pooling the final three fractions, while **37**, contained in most of the middle fractions, was characterized (vide infra) by separately subjecting pure **36** or **38** to thermal Cope rearrangement. The yields of each compound were calculated by weighing each of the three chromatographic pools and then calculating the composition of the middle one by NMR integration.

For **36** (foam): NMR ($CDCl_3$) δ 7.4–7.2 (m, 10 H), 6.80 (s, 1 H), 5.81 (m, 1 H), 5.29 (s, 1 H), 5.1–5.0 (m, 5 H), 4.92 (m, 1 H), 3.54 (d, J = 13.5 Hz, 1 H), 3.24 (d, J = 13.5 Hz, 1 H), 2.98 (dd, J = 14.2 Hz, J' = 7.1 Hz, 1 H), 2.71 (dd, J = 14.2 Hz, J' = 7.2 Hz, 1 H), 1.41 (s, 9 H). Accurate mass determination: calcd for $C_{29}H_{33}N_2O_5S$ (M + H) 521.2110, found 521.2103.

For **38** (foam): NMR ($CDCl_3$) δ 7.4–7.2 (m, 10 H), 6.86 (s, 1 H), 5.74 (m, 1 H), 5.35–5.27 (m, 5 H), 4.92 (d, J = 10.3 Hz, 1 H), 4.85 (d, J = 17 Hz, 1 H), 3.43 (dd, J = 13.8 Hz, J' = 5.4 Hz, 1 H), 3.13 (s, 2 H), 2.86 (dd, J = 13.8 Hz, J' = 8.7 Hz, 1 H), 1.41 (s, 9 H). Accurate mass determination: calcd for $C_{29}H_{33}N_2O_5S$ (M + H) 521.2110, found 521.2116.

Preparation of 37. Cephem **38** (68.5 mg, 0.132 mmol) was refluxed in xylene (5 mL) for 24 h. Evaporation and chromatography (20% ethyl acetate in hexane) gave **37** (54.1 mg, 79%). The same experiment using **36** as a substrate produced **37** in identical yield. NMR ($CDCl_3$): δ 7.4–7.2 (m, 10 H), 5.65–5.57 (m, 2 H), 5.23 (br d, 1 H), 4.93–4.90 (m, 2 H), 3.46 (d, J = 18.1 Hz, 1 H), 3.26 (d, J = 18.1 Hz, 1 H), 2.60 (m, 1 H), 2.38 (m, 1 H), 2.24 (m, 1 H), 2.12 (m, 1 H), 1.44 (s, 9 H). Accurate mass determination: calcd for $C_{29}H_{33}N_2O_5S$ (M + H) 521.2110, found 521.2112.

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(66) Identical with a commercial sample of **32** obtained from Otsuka Chemical Co. For a literature procedure, see: Chauvette, R. R.; Pennington, P. A. *J. Med. Chem.* **1975**, *18*, 403–8, and references therein.