Cycloadditions of Cephalosporins. A General Synthesis of Novel 2,3-Fused Cyclobutane and Cyclobutene Cephems

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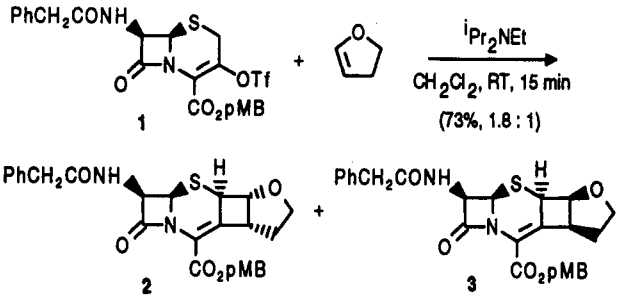
Summary: The cephalosporin triflate (1) reacts with a wide variety of olefins and acetylenes in the presence of a base to give 2,3-fused cyclobutane and cyclobutene derivatives, respectively.

Cephalosporin triflates have recently become extensively used intermediates for the synthesis of carbon–carbon bonds at C(3) of the cephalosporin nucleus. These triflates[1] readily undergo palladium-catalyzed Stille cross-coupling reactions with a wide variety of organostannanes[2] and have also been shown to react with organocuprates.[3]

We were interested in applying the asymmetric Heck olefination methodology[4] to the cephalosporin triflate (1). Treatment of 1 with 2,3-dihydrofuran and diisopropylethylamine in benzene in the presence of palladium acetate and (*R*)-BINAP gave rise to a mixture of two isomeric products (1.8:1 ratio, 73% isolated yield). Detailed NMR studies showed the products to be the fused cyclobutane adducts 2 and 3, and not the expected Heck product. Performing the reaction in CH_2Cl_2 and without the transition metal catalyst resulted in the formation of the same products (eq 1).[5,6]



pMB - p-methoxybenzyl (Eq 1)

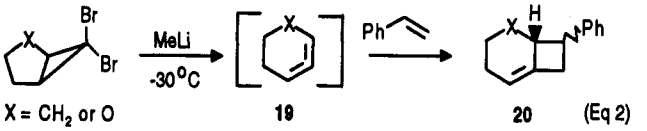
This reaction has proved to be extremely general. A wide variety of olefins were reacted with the triflate (1) in the presence of $^iPr_2NEt$ to give fused cyclobutane products in moderate to good yields (Table I). In some cases the use of a large excess of olefin was required to obtain acceptable yields.

There are a number of regio- and stereochemical features to this reaction which should be highlighted: in the case of terminal olefins the substituent is always found adjacent to the C(2) position of the cephalosporin nucleus and, when only one isomer is observed, this substituent is on the β-face (compounds 8 and 9); the proton at C(2) is always found on the α-face of the molecule.

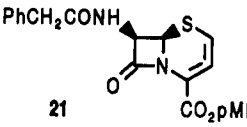
The reaction of 1 with acetylenes has also been investigated and shown to result in the formation of fused cyclobutenes (Table II). Again, in the case of terminal acetylenes, the substituent is found adjacent to C(2). However, in some cases (entries 1 and 4), isomeric mixtures are now obtained at C(2) of the cephalosporin nucleus.

The stereochemistry of the cycloaddition products was determined by NOE difference experiments. Characteristically, strong NOE's were observed from H(6) to H(2) when the latter was on the α-face. When H(2) was on the β-face a stronger NOE was observed between H(2) and the amide proton than between H(2) and H(6). H(6) is known to be on the α-face while the amide at C(7) is on the β-face.

We have shown that 1 equiv of base is required for the reaction to proceed to completion. This presumably effects a formal elimination of trifluoromethanesulfonic acid to produce a reactive species that then undergoes a cycloaddition. Six-membered cyclic allenes (19) have been proposed as intermediates in the formation of the bicyclooctenes 20 (eq 2).[7] The possibility of the bicyclic allene 21 as an intermediate is being investigated.



(Eq 2)



The cycloaddition reaction that we have described is amenable to the rapid production of numerous analogues bearing a wide range of functionality. Current studies on the scope and mechanism will be reported later.

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(1) Farina, V.; Baker, S. R.; Hauck, S. I. *J. Org. Chem.* **1989**, *54*, 4962.
(2) Farina, V.; Baker, S. R.; Benigni, D. A.; Hauck, S. I., Sapino, C. *J. Org. Chem.* **1990**, *55*, 5833 and references cited therein. For similar chemistry utilizing 3-[(fluorosulfonyl)oxy]cephems, see: Roth, G. P.; Sapino, C. *Tetrahedron Lett.* **1991**, *32*, 4073. For palladium-catalyzed reactions of carbacephem triflates, see: Cook, G. K.; Hornback, W. J.; Jordan, C. L.; McDonald, J. H.; Munroe J. E. *J. Org. Chem.* **1989**, *54*, 5828.
(3) Kant, J. *J. Org. Chem.* **1993**, *58*, 2296.
(4) Ozawa, F.; Kobatake, Y.; Hayashi, T. *Tetrahedron Lett.* **1993**, *34*, 2505. Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417.
(5) Typical procedure for the preparation of the cycloadducts: To a solution of triflate 1 (1 equiv) and alkene or alkyne (see Tables I and II) in CH_2Cl_2 was added $^iPr_2NEt$ (1 equiv). After being stirred for 15 min the mixture was chromatographed to afford the cycloadducts.
(6) The mixture of 2 and 3 was converted to the sulfoxides 4 and 5 (*m*-CPBA, CH_2Cl_2, 0 °C, 5 min) which could be separated by chromatography. Reduction of 4 and 5 (PCl_3, DMF, −30 °C, 30 min) gave 2 and 3, respectively.
(7) Harnos, S.; Tivakornpannarai, S.; Waali, E. E. *Tetrahedron Lett.* **1986**, *27*, 3701. Christl, M.; Braun, M. *Chem. Ber.* **1989**, *122*, 1939. Christl, M.; Braun, M.; Müller, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 473.

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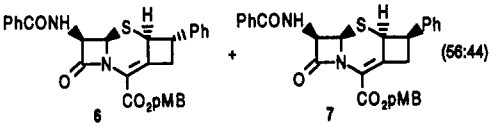
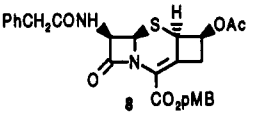
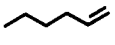
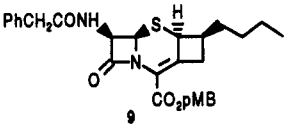
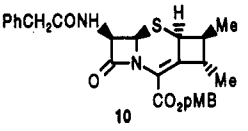
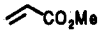
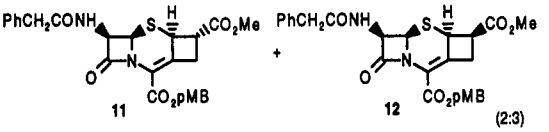
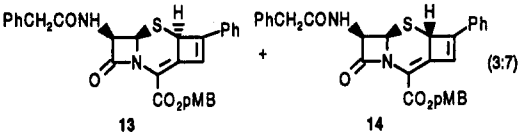
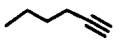
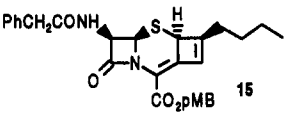
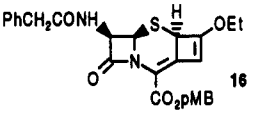
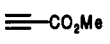
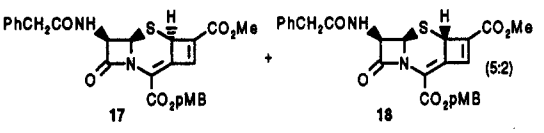
Table I. Reaction of 1 with Olefins[a]

olefin	equiv used	products (ratio)	yield, %
	3	 (56:44)	73
	5		72
	5		54
	c		88
	50	 (2:3)	76

[a] Reaction conditions: triflate 1 (1 equiv), alkene, $^{i}Pr_2NEt$ (1 equiv), CH_2Cl_2, 15 min. [b] The benzamide derivative was used to simplify the NMR of the products 6 and 7. [c] *trans*-2-Butene condensed into solution at −10 °C prior to adding base.

Table II. Reaction of 1 with Acetylenes[a]

acetylene	equiv used	products (ratio)	yield, %
	30	 (3:7)	95
	87		50
	10		36
	10	 (5:2)	35

[a] Reaction conditions as in Table I.

Supplementary Material Available: Typical experimental procedures, data for all prepared compounds, and NMR spectra of 2 and 3 (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.