since we are not aware of a model, i.e., the solvent dependence of an authentic hydride shift. The charge distribution pattern is notably different in the two TSs. A radical ion pair generated by SET offers an alternative. However, it would face the same dilemma of solvent dependence; we have no evidence for a chain reaction. Hydrogen atom transfer should furnish a radical pair, but why should that require the strongest donor and acceptor olefins?

In the controversial debate on the $NAD^+/NADH$ mechanism, more authors in recent years preferred the one-step hydride abstraction[16] rather than a multistep SET-initiated pathway. E.g., according to model calculations by MNDO, the TS for a linear hydride shift from 1,4-dihydropyridine to 1,1-dicyanoethylene resembles the ion pair.[17] Our rate study is a painful reminder that a systematic investigation of solvent effects on the rates of hydride transfer reactions is missing. For the time being, we will emphasize by the term "hydride transfer", irrespective of later specification, the relation to NADH reactions.

Acknowledgment. We are grateful to Drs. W. J. Middleton and H. E. Simmons, Central Research and Development Department, E. I. du Pont de Nemours Co., Wilmington, DE, for a generous gift of hexafluoroacetone. The microanalyses were carried out by Mr. H. Schulz and Mrs. M. Schwarz, and Mr. H. Huber helped in the NMR measurements. We thank the Fonds der Chemischen Industrie, Frankfurt, for support.

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(17) Verhoeven, J. W.; van Gerresheim, W.; Martens, F. M.; van der Kerk, S. M. *Tetrahedron* **1986**, *42*, 975.

2,2-Bis(trifluoromethyl)ethylene-1,1-dicarbonitrile as a Unique Enophile†

Rolf Huisgen* and Reinhard Brückner

Institut für Organische Chemie der Universität München, Karlstr. 23, D-8000 München 2, Germany

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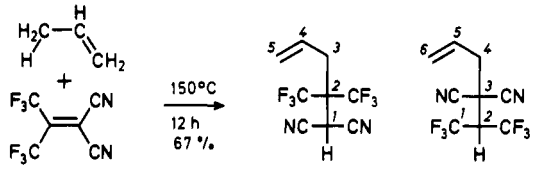
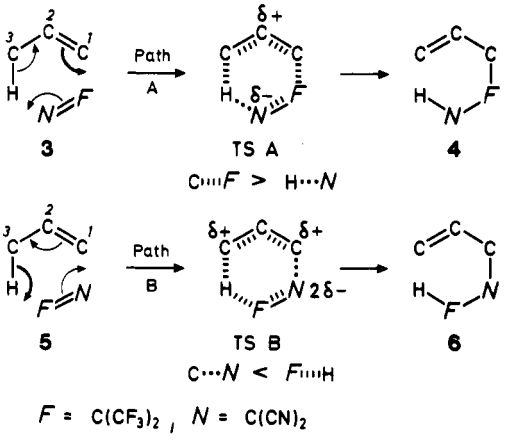
Summary: The title compound (BTF) is the only known electrophilic ethylene derivative which undergoes ene reactions with unactivated alkenes at room temperature. The allylic hydrogen is transferred either to the CF_3- or the CN-bearing carbon of BTF, depending on the structure of the alkene. In a new mechanistic concept, two transition states allow to classify alkenes and to predict the orientation of their ene reactions.

Middleton, the discoverer of the highly electrophilic title olefin (BTF),[1] described its ene reactions with propylene (150 °C, 67% of **1** + **2**) and 2,3-dimethyl-2-butene (room temperature, 72%). He noted with unease that a small portion of the first and all of the second alkene gave rise to ene products with $CH(CF_3)_2$ as terminus. This was unanticipated since cyano groups clearly stabilize carbanionic charge better than trifluoromethyl. The clarification required a systematic study.



The uniqueness of BTF as enophile rests on three phenomena: (1) It is the only C=C-based enophile reacting with *common alkenes at room temperature* without Lewis acid catalysis. (2) BTF is an avid hydride-abstracting reagent.[2] (3) Due to different termini of BTF, the ene products reveal the location of partial negative charge in the transition state.

A mechanistic consideration may precede the results. HCC=C is the reacting section of the alkene in **3** and **5**, and the two moieties of the BTF molecule are abbreviated



by *N* and *F*. The usual enophiles *a*=*b* (maleic anhydride, azodicarboxylic ester, formaldehyde etc.) are *carbophilic*, i.e., the new bond C-*a* is more developed than H-*b* in the transition state (TS). A charge distribution of the pattern of TS A will result. BTF will choose the orientation allowing the cyano groups to stabilize the partial negative charge, and terminal $CH(CN)_2$ will appear in the ene product **4**. The interaction of C-1 with the $C(CF_3)_2$ portion of BTF alone would furnish a zwitterion; the simultaneous H transfer diminishes the ionic charges in TS A.

In path B *formal hydride transfer*[3] prevails over C–C bond making; the altered regiochemistry in **5** allows TS B to still profit from the stabilizing effect on the CN groups, but now **6** with terminal $CH(CF_3)_2$ will emerge as the product. Path B does not lead to a full allylic cation,

† Dedicated to Professor Richard Neidlein, Heidelberg, on the occasion of his 60th birthday.

(1) Middleton, W. J. *J. Org. Chem.* **1965**, *30*, 1402.

(2) Brückner, R.; Huisgen, R. *J. Org. Chem.*, preceding paper in this issue.

(3) The term "hydride transfer" is introduced although calculations show that the H migrates with little negative charge. E.g., cyclopropane + cyclopropenium ion: Donkersloot, M. C. A.; Buck, H. M. *J. Am. Chem. Soc.* **1981**, *103*, 6549. 1,4-Dihydropyridine + ethylene-1,1-dicarbonitrile: Verhoeven, J. W.; van Gerresheim, W.; Martens, F. M.; van der Kerk, S. M. *Tetrahedron* **1986**, *42*, 975.

0022-3263/91/1956-1679$02.50/0

since C–C bonding in concert reduces the build up of ionic charges (TS B).

Stabilization of partial positive charge at C-2 of the alkene will favor TS A whereas a substituent pattern leading to a good allylic cation should induce pathway B. Both one-step reactions proceed with *obligatory double bond shift*; only these should be called *ene reactions*. The distinction of the product termini, $CH(CN)_2$ or $CH(CF_3)_2$, offers a novel probe and allows to classify the ene reactions of BTF. An additional factor, *steric hindrance by the bulky CF_3 groups*, favors pathway B. The approach of the $C(CF_3)_2$ portion of BTF to the allylic hydrogen is sterically less demanding than that to carbon C-1.

The alkenes were reacted with BTE under the conditions stated in Table I; the reaction times often refer to partial conversions. The distilled products[4] were ^1H NMR analyzed without separation; several ene products were crystalline. Ene products with terminal $CH(CF_3)_2$ show δ(2-H) 3.4–3.8 as septetts with $J_{H,F}$ = 7–8 Hz; the ^{19}F NMR spectra reveal the coupling with 2-H as well as enantiotopic or diastereotopic CF_3 groups. The protons of the $CH(CN)_2$ termini are sharp singlets at δ 4.3–4.8.[5]

Propylene (Table I, entry 1) may serve as calibration point. TS A contains a *sec*-carbocation and TS B the allyl cation as resonance structures; the pathways are used 93:7.[1] Introduction of a 3-isopropyl (no. 2) or phenyl (no. 3) at C-3 contributes to the stability of the quasi-allyl cation, not to that of the *sec*-carbenium ion (C-2); pathway B grows to 33% and 100%, respectively. The rate constant of allylbenzene (no. 3, 10^3k_2 1.7 M^{-1} s^{-1}, benzene, 25 °C) is increased 20-fold in 4-allylanisole. For *p*-$CH_3OC_6H_4CHDCH{=}CH_2$ an *intermolecular* kinetic isotope effect of 4.5, calculated as k_{2H}/k_{2D}, was observed.

A methyl group at C-2 makes the quasi-carbocation of TS A *tertiary* whereas no help comes for TS B. The ene products of isobutene (no. 4, with 96% the highest absol. yield) and of α-methylstyrene (no. 7) are pure terminal dinitriles.[5] So are the products from 2-methyl-1-butene (no. 5) and no. 6; the dichotomy here stems from the involvement of two different hydrogens.

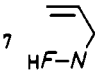
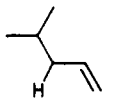
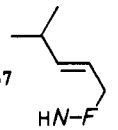
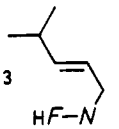
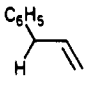
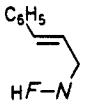
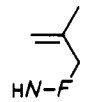
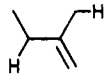
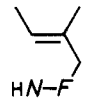
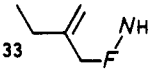
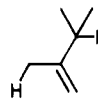
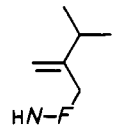
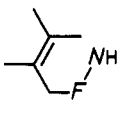
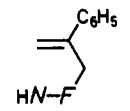
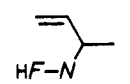
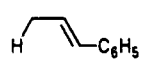
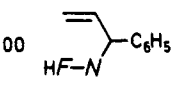
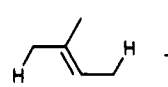
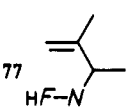
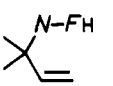
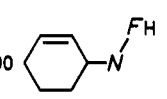
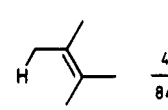
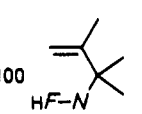
1-Substitution of propylene by alkyl (no. 8, 10–12) or phenyl (no. 9) renders added stability to the quasi-allylic cation of TS B; furthermore, it sterically interferes with the approach of the $C(CF_3)_2$ terminus to C-1. The BTF molecule "turns around" and uses TS B exclusively; all adducts possess terminal $CH(CF_3)_2$. As for 2-methyl-2-butene (no. 10), the quasi-hydride may be 1-H or 4-H affording different ene products.

Table I records three "matched pairs" (no. 3/9, 5/10, 6/12), and their ene products demonstrate the obligatory double bond shift. E.g., allylbenzene (no. 3) gives rise to a propenylbenzene derivative and vice versa with no. 9.

We have studied ene reactions of BTF with further alkenes and found them all obeying the same clear-cut rules. Rate measurements were of little help in estimating electronic stabilizations since they are often overpowered by steric effects. For the matched pair no. 6/12, 10^6k_2 (M^{-1} s^{-1}) amounts to 9.1 and 16 (benzene, 25 °C, spectrophotometrically).

Nucleophilic unsaturated systems are converted to carbocations either by electrophilic addition of BTF or by transferring allylic hydride. BTF exceeds TCNE in both functions by far; ordinary monoalkenes do not react with TCNE. The [2 + 2] cycloadditions of BTF with vinyl ethers[6] and styrenes[7] as well as aromatic[1] and vinylic substitutions[8] proceed via 1,4-zwitterions; in these reactions, the quality of the carbocation stabilization makes

Table I. Ene Reactions of BTE with Alkenes (1.0 equiv) in CH_2Cl_2 at Room Temperature[c]

1.		12 h, 67%	[a,b]	93		7 
	3-Substitution					
2.		18 d, 28%		67		33 
3.		141 d, 74%		100		
	2-Substitution					
4.		18 d, 96%	[a]	100		
5.		18 d, 60%		67		33 
6.		4 d, 68%		61		39 
7.		29 d, 59%		100		
	1-Substitution					
8.		26 d, 82%	[a]	100		
9.		66 d, 23%		100		
10.		29 d, 60%		77		23 
11.		129 d, 62%		100		
12.		4 d, 84%		100		

[a] Excess of alkene. [b] 150 °C (ref 1). [c] Relative % by ^1H NMR analysis after high-vacuum distillation. $F = C(CF_3)_2$, $N = C(CN)_2$.

(4) Satisfactory elemental analyses and spectra have been obtained for all new compounds.

(5) Representative ^1H NMR data ($CDCl_3$, J in hertz) are given for some ene products of Table I. No. 3: δ 3.07 (d, $J_{4,5}$ = 7.0, 4-H_2), 3.61 (sept, $J_{H,F}$ = 7.2, 2-H), 6.18 (dt, $J_{4,5}$ = 7.0, $J_{5,6}$ = 15.8, 5-H), 6.81 (d, 6-H), 7.38 (mc, C_6H_5). No. 4: 1.87 (s, 4-CH_3), 2.83 (s, 3-H_2), 4.55 (s, 1-H), 5.19, 3.30 (2 mc, 5-H_2). No. 8: 1.49 (d, J = 6.8, 4-CH_3), 3.12 (br quint, J = 6.8, 4-H), 3.72 (sept, $J_{H,F}$ = 7.3, 2-H), 5.19–6.16 (m, 5-H, 6-H_2).

(6) Huisgen, R.; Brückner, R. *Tetrahedron Lett.* **1990**, *31*, 2553.

(7) Brückner, R.; Huisgen, R.; Schmid, J. *Tetrahedron Lett.* **1990**, *31*, 7129.

(8) Brückner, R.; Huisgen, R., unpublished.

the simultaneous 1,5 H migration unnecessary. The interactions of BTF with isobutenyl, methallyl, and allyl ethers (and sulfides)[2] present the second extreme; only the bond $HC(CF_3)_2$ is established in the first step, and the same allylic ion pair is reached from positional isomers. BTF reactions with 1,3-diarylpropenes and benzylic H follow the same course.[8] *Between these two extremes, BTF combines both functions in a wide range of ene reactions.*

The rate constant for the reaction of ethyl methallyl ether with BTF is only little dependent on solvent polarity;[2] some modifications to the one-step hydride transfer[3] were discussed: H atom transfer giving a radical pair or, in combination with SET, a radical ion pair as intermediate. Although we do not favor these alternatives, they cannot be ruled out on the basis of the substituent effects on the regiochemistry of ene reaction described here.

Efficient and Practical Asymmetric Synthesis of the Taxol C-13 Side Chain, *N*-Benzoyl-(2*R*,3*S*)-3-phenylisoserine, and Its Analogues via Chiral 3-Hydroxy-4-aryl-β-lactams through Chiral Ester Enolate–Imine Cyclocondensation

Iwao Ojima,* Ivan Habus, and Mangzhu Zhao

Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794

Gunda I. Georg and Lalith R. Jayasinghe

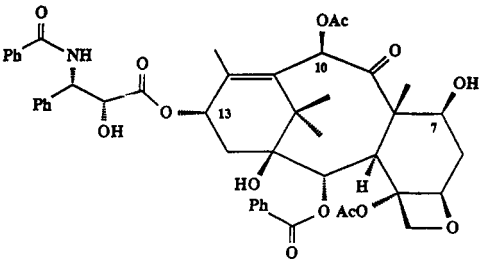
Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas 66045

Received November 16, 1990

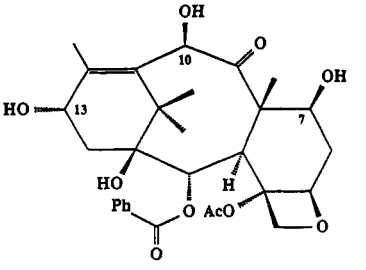
Summary: A highly efficient chiral ester enolate–imine condensation giving 3-hydroxy-4-aryl-β-lactams with >96% ee is successfully applied to the asymmetric synthesis of the enantiomerically pure taxol C-13 side chain, *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine, and its analogues.

Taxol (1), a complex diterpene[1] isolated from the bark of *Taxus brevifolia* (Western Yew), is currently considered the most exciting lead in cancer chemotherapy. Taxol (1) possesses high cytotoxicity and strong antitumor activity and is currently in phase II clinical trials in the United States.[2,3] Significant activity against cisplatin refractory advanced ovarian cancer has been established.[3b,c] A recent report has now shown that a more readily available taxol precursor can be isolated from the leaves of *Taxus baccata*.[4] Extraction of the fresh leaves yields 10-deacetyl baccatin III (2), (1 g/1 kg), which has been converted to 1.[4]

With the availability of 2, it appears that sufficient supplies of 1 can now be produced in a semisynthetic fashion. It should be noted that the C-13 side chain, i.e., the *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine (9) moiety, is crucial for the strong antitumor activity of 1.[5] The first enantioselective synthesis of the important side chain 9 was achieved in eight steps and 23% yield via a Sharpless epoxidation from *cis*-cinnamyl alcohol with an enantiomeric excess of 76–80%.[6] A recent publication describes the chemoenzymatic synthesis of a derivative of 9, in which the racemic mixture was resolved by enzymatic hydrolysis with lipases.[7]



1



2

We describe here our preliminary results on the successful application of lithium chiral ester enolate–imine cyclocondensation strategy[8,9] to the asymmetric synthesis of the C-13 side chain of taxol, 9, and its derivatives using 3-hydroxy-4-aryl-β-lactams as the key intermediates. With this approach, 9 and its derivatives can be obtained in three steps in good yields with virtually 100% ee.

First, we carried out the reactions of chiral lithium ester enolates (4), generated in situ from (silyloxy)acetates (3), with *N*-(trimethylsilyl)imines (5), which gave the corresponding chiral β-lactams 6 (eq 1). Results are summarized in Table I.

As Table I shows, the chiral auxiliary and the O-protecting group exert marked effects on the enantioselectivity

(1) E.g., for a review: Miller, R. W. *J. Nat. Prod.* **1980**, *43*, 425.
(2) E.g., for a review: Zee-Cheng, R. K.-Y.; Cheng, C. C. *Drugs Future* **1986**, *11*, 45.
(3) (a) Wiernik, P. H.; Schwartz, E. L.; Strauman, J. J.; Dutcher, J. P.; Lipton, R. B.; Paietta, E. *Cancer Res.* **1987**, *47*, 2486. (b) *Annual Report to the Food and Drug Administration: Taxol*, IND 22850. NSC 125973; February 1989; Division of Cancer Treatment, NCI, Bethesda. (c) Workshop on Taxol and Taxus: *Current and Future Perspectives*; June 1990; Division of Cancer Treatment, NCI, Bethesda.
(4) Denis, J.-N.; Greene, A. E.; Guenard, D.; Gueritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917.
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