Table III. Energies^a of Cations 1–3 and of the Corresponding Hydrocarbons (1-H–3-H) Calculated at RHF/3-21G Geometries with the 3-21G, 3-21G(*), and 6-31G* Basis Sets

molecule	3-21G		3-21G(*)		6-31G*	
	RHF	MP2^b	RHF	MP2^b	RHF	MP2^c
1	–308.5347	–309.2524	–308.5347	–309.2524	–310.2453	–311.2642
1-H	–309.3926	–310.1278	–309.3926	–310.1278	–311.1032	–312.1477
2	–597.0840	–597.8716	–597.1776	–597.9931	–600.3155	–601.4217
2-H	–597.9398	–598.7421	–598.0335	–598.8647	–601.1727	–602.3021
3	–6306.3517		–6306.4284	–6307.2635		
3-H	–6307.2029		–6307.2795	–6308.1282		

^{a} Energies in hartrees. ^{b} Full MP2. ^{c} Frozen core MP2.

from 1c.[17] Moreover, the isotope effects calculated at the MP2/3-21G level (k_H/k_D = 1.063) and the MP2/6-31G* level (k_H/k_D = 1.040) are much larger than at the RHF level and in much better agreement with experiment.[1] The increase in the calculated isotope effect cannot be attributed to an increase in through-space bonding between C_1 and C_4 at the MP2 level, since, on going from the RHF to the MP2 optimized structure for 1, r_{14} increases.[18]

If, as suggested by the results of our calculations on 1, there is some delocalization of the electrons in the C_4–H bond in the carbocation, weakening this bond should provide increased stabilization for the cation. This is what was observed experimentally by Adcock et al. on replacing H at C_4 by metalloidal substituents.[1] That the observed rate accelerations are, in fact, a result of enhanced double hyperconjugation can be seen from comparison of the optimized geometries (Table II) and calculated energies (Table III) for the 4-substituted, bridgehead cations 2 and 3 with those for the corresponding alkanes, 2-H and 3-H.

As in the case for formation of the unsubstituted cation (1), at the RHF level r_{12} decreases and r_{23} increases on formation of 2 and 3. However, when a weak bond to a metalloidal substituent (R = SiH_3 in 2 and R = SnH_3 in 3) replaces the C_4–H bond in 1, even at the RHF level r_{34} decreases and r_{4R} increases. As expected for a larger contribution from structure c in 3 than in 2, the sizes of the changes in these bond lengths are larger for R = SnH_3 than for R = SiH_3. The changes in r_{14} are nearly the same for formation of all three cations, and the small differences in Δr_{14} (1 > 2 > 3) are in the opposite order from those expected for through-space bonding between C_1 and C_4 in the cations. The data in Table II also show that, although the optimized bond lengths change on going from the 3-21G to the 3-21G(*) basis set, the differences between the

bond lengths in 2 and 2-H remain essentially the same.

In agreement with experiment, the energy required for cation formation decreases in the order 1 > 2 > 3. At the RHF level with the 3-21G, 3-21G(*), and 6-31G* basis sets, substitution of R = H at C_4 by R = SiH_3 reduces the energy required for carbocation formation by, respectively, 1.3, 1.3, and 0.4 kcal/mol. Since inclusion of electron correlation increases the importance of the doubly hyperconjugated resonance structure c, it is not surprising that at the MP2 level of theory the magnitudes of these energy reductions increase to 3.1, 2.4, and 1.9 kcal/mol. For R = SnH_3 the RHF energy reductions are 4.2 and 4.3 kcal/mol with, respectively, the 3-21G and 3-21G(*) basis sets and 6.7 kcal/mol at the MP2/3-21G(*) level.

The relative rates of carbocation formation at 25 °C in the gas-phase that are computed from the MP2/3-21G-(*)//RHF/3-21G energies are qualitatively similar to those found in the solvolysis studies.[1] The silyl substituent is calculated to afford a modest rate increase, k_{Si}/k_H = 58; and the stannyl substituent is predicted to yield a substantially larger acceleration, k_{Sn}/k_H = 82 000. The experimental rate ratios in 97% trifluoroethanol at 25 °C are 1:49:2841.[1] Our calculations provide strong support for the interpretation of these rate ratios in terms of increasing stabilization of 1–3 via double hyperconjugation, as depicted by structure c.

Supplementary Material Available: Optimized geometries of 1–3 and 1-H–3-H (15 pages). This material is contained in many 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.

(17) The MP2/6-31G* optimized C_4–H bond length in 1 is 0.0005 Å longer than that in 1-H.

(18) Flattening of C_1 on carbocation formation results in the decrease in r_{14} that is calculated on going from 1-H to 1.

Ruthenium-Catalyzed Hydration of Nitriles and Transformation of δ-Keto Nitriles to Ene–Lactams

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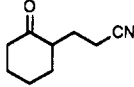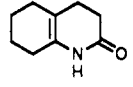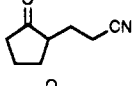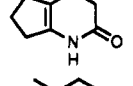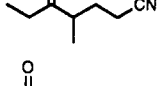
Received January 22, 1992
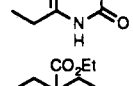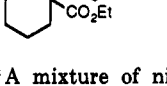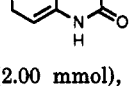
Summary: Hydration of nitriles and transformation of δ-keto nitriles to ene–lactams can be performed efficiently by using $RuH_2(PPh_3)_4$ catalyst under mild conditions. The effectiveness of the reaction is illustrated by the short-step synthesis of (–)-pumiliotoxin C.
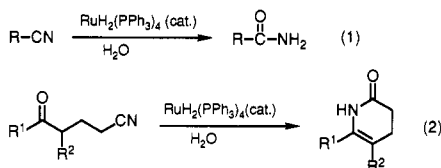
The hydration of nitriles under mild and neutral reaction conditions is of importance from both an enzymatic[1]

Table I. Ruthenium-Catalyzed Hydration of Nitriles and Cyclization of Keto Nitriles[a]

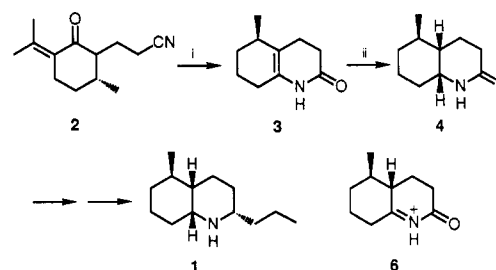| nitrile	product[b]	isolated yield, %
CH_3CN	CH_3CONH_2	92
$n\text{-}C_5H_{11}CN$	$n\text{-}C_5H_{11}CONH_2$	94
PhCN	$PhCONH_2$	92
NC⁀⁀CO₂Me	H₂NCO⁀⁀CO₂Me	93
(cyclohexanone with CN chain)	(bicyclic ene-lactam)	94
(cyclopentanone with CN chain)	(bicyclic ene-lactam)	97
(ethyl methyl ketone with CN chain)	(methyl ene-lactam)	51
(cyclohexanone with CN and CO₂Et)	(bicyclic ene-lactam with CO₂Et)	85

[a] A mixture of nitrile (2.00 mmol), water (4.00 mmol), and $RuH_2(PPh_3)_4$ (0.06 mmol) in 1,2-dimethoxyethane (0.5 mL) was reacted at 120 °C for 24 h in a sealed tube under argon. [b] The product gives satisfactory IR, NMR, and mass spectrum data and analysis.

and a synthetic[2] point of view. Although metal complex-induced hydration of nitriles has been studied extensively, the reported methods are still unsatisfactory with respect to catalytic cycle and removal of excess water.[3,4] We have found that ruthenium-catalyzed hydration of nitriles proceeds highly efficiently upon treatment with 2 equiv of water under neutral conditions (eq 1). The principle

$$R\text{--}CN \xrightarrow[\text{H}_2\text{O}]{RuH_2(PPh_3)_4 \text{ (cat.)}} R\text{--}\overset{\displaystyle O}{\underset{}{C}}\text{--}NH_2 \quad (1)$$

$$\quad (2)$$

of the present hydration reaction can be extended for the catalytic transformation of δ-keto nitriles to ene–lactams, which are highly versatile synthetic intermediates (eq 2).[5]

The ruthenium-catalyzed hydration proceeds generally, and highly efficiently, under neutral conditions. In a typical case, the reaction of benzonitrile with 2 equiv of water in 1,2-dimethoxyethane in the presence of 3 mol % of $RuH_2(PPh_3)_4$ at 120 °C gave benzamide in 93% yield after filtration over Florisil short column. The representative results of the hydration of nitriles are summarized in Table I. $RuH_2(PPh_3)_4$ was the most effective catalyst among those examined.[6] The present hydration

Scheme I[a]

[a] Key: (i) $RuH_2(PPh_3)_4/H_2O$; (ii) $H_2/Pd\text{-}C$.

is advantageous over the previous methods[2–4] because of its simple operation, neutral reaction conditions, and high efficiency. The ruthenium-catalyzed reaction of δ-keto nitriles, which are obtained readily by cyanoethylation of ketones, proceeds highly efficiently with 2 equiv of water under similar reaction conditions. Representative results of the transformation of δ-keto nitriles to ene–lactams are shown in Table I. Keto nitriles derived from both cyclic and aliphatic ketones can be converted into the corresponding ene–lactams in excellent yields. The formation of ene–lactams can be rationalized by assuming nucleophilic attack of water to the coordinated nitriles[7] to give amides, which undergo further ruthenium-induced cyclization to give ene–lactams.

The effectiveness of the present reaction is illustrated by the synthesis of (−)-pumiliotoxin C (1), which is an interesting toxic skin alkaloid produced by Central American frogs *Dendrobates pumilio* and *D. auratus*.[8] Although racemic pumiliotoxin C has been synthesized by various methods,[9] natural (−)-1 has been synthesized by two methods; intramolecular Diels–Alder reaction[9c] and cyclization of piperidine enamines.[9h] Our strategy for the synthesis of (−)-1 is shown in Scheme I, in which the ruthenium-catalyzed cyclization and diastereoselective catalytic hydrogenation are key steps. Ruthenium-catalyzed deisopropylidenation of (3R)-2-(2-cyanoethyl)-6-isopropylidene-3-methylcyclohexanone (2), which was derived from cyanoethylation of optically pure (R)-(+)-pulegone,[10] and subsequent cyclization gave (5R)-5-methyl-3,4,5,6,7,8-hexahydro-2(1H)-quinolinone (3) in 56% yield (mp 127.5–128.5 °C (hexane–^{i}PrOH); [α]$^{26}_D$ +45.2° (c 1.01, $CHCl_3$)). Although diastereoselective reduction of ene-lactams has never been reported probably because of difficulty of hydrogenation under the usual conditions,[12]

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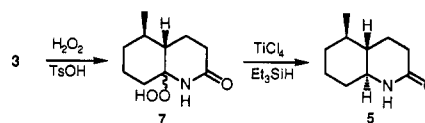
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(6) Hydration of acetonitrile with 2 equiv of H_2O in 1,2-dimethoxyethane was carried out at 120 °C using 3 mol % of a catalyst. RuH_2(PPh₃)₄ (conv 100%, yield 92%); Rh(OH)(CO)(PPh₃)₂ (76%, 78%); however, other known catalysts such as Pd(OH)₂(bipy)(H₂O)₂ and Ni-(piaH)₂Cl₂·H₂O show no catalytic activity under the reaction conditions.

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(10) Pure (R)-(+)-pulegone was obtained by recrystallization of the corresponding semicarbazone[11] followed by hydrolysis ([α]$^{23}_D$ +23.2° (neat)).

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(12) The hydrogenation of 3 using catalysts such as Pd/C, Ru/C (room temperature, 24 h, H_2 (1 atm), EtOH) gave the 40–50% yields, and the diastereomeric ratio of 4/5 was 58–73/42–27.
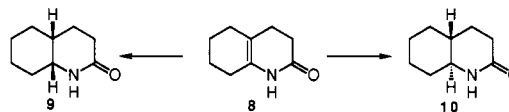
we have found that hydrogenation of ene–lactam **3** occured over 5% palladium on charcoal in EtOH/AcOH (5/1) in the presence of a catalytic amount of HCl at 60 °C under H_2 (80 atm) to give (4a*S*,5*R*,8a*R*)-5-methyl-2,3,4a,5,6,7,8,8a-octahydro-2(1*H*)-quinolinone (**4**) (mp 146.5–147.5 °C; $[\alpha]^{25}_D$ –60.4° (*c* 1.00, CHCl₃) highly selectively. The diastereomeric ratio of **4** (4a*S*,5*R*,8a*R*)/its isomer **5** (4a*S*,5*R*,8a*S*) was determined to be 98/2 by GLC analysis (capillary column, PEG-20M, 25 m). The lactam **4** thus obtained was converted into **1** ([$\alpha]^{21}_D$ –16.2° (*c* 1.00, CH₃OH))[13] by the reported method.[9b]

Selective formation of cis-fused lactam **4** can be rationalized by assuming diastereoselective protonation of **3** to give acyl iminium ion **6** which undergoes subsequent hydrogenation. Consequently, trapping of **6** with suitable nucleophiles and subsequent selective transformation would give trans-fused products. Indeed, treatment of **3** with H_2O_2 in the presence of TsOH catalyst gave unstable (4a*S*,5*R*)-8a-hydrodioxy-5-methyl-3,4,4a,5,6,7,8,8a-octahydro-2(1*H*)-quinolinone (**7**) [77%, 4a*S*,5*R*,8a*R*/ 4a*S*,5*R*,8a*S* = 2/1], which was converted into (4a*S*,5*R*,8a*S*)-lactam **5** (mp 180–180.5 °C, $[\alpha]^{25}_D$ + 14.7°

(13) The HCl salt of (–)-**1**, mp 286–288 °C (sealed capillary) (lit.[9c] mp 288–290 °C (sealed capillary)); [$\alpha]^{21}_D$ –16.2° (*c* 1.00, CH₃OH) (lit.[9c] [$\alpha]^{20}_D$ –14.5° (*c* 1.00, CH₃OH)). (+)-**1** HCl: [$\alpha]^{25}_D$ +16.2° (*c* 1.00, CH₃OH),[9c] [$\alpha]^{20}_D$ +16.4° (*c* 1.00, CH₃OH),[9c] [$\alpha]^{20}_D$ +16.1° (*c* 1.00, CH₃OH).[9i]

(*c* 1.06, CHCl₃)) upon treatment with Et₃SiH in CH₂Cl₂ in the presence of TiCl₄ [72% yield, 5/4 = 90/10]. We

are in a position to be able to prepare either cis- or trans-fused decahydroquinolines selectively by the acid-promoted catalytic hydrogenation of ene–lactams or the acid-promoted reaction of ene–lactams with H_2O_2 followed by treatment with Et₃SiH in the presence of TiCl₄. Simply, *cis*- and *trans*-3,4,4a,5,6,7,8,8a-octahydro-2(1*H*)-quinolinone (**9** and **10**) can be prepared selectively (9/10 = 92/8, 9/10 = 7/93) from 3,4,5,6,7,8-hexahydro-2(1*H*)-quinolinone (**8**) by using our methods. The details of the mechanism and the extension of the useful catalytic reactions to the other systems are under active study.

Supplementary Material Available: Experimental procedures and spectral data for all compounds (11 pages). Ordering information is given on any current masthead page.

A Convergent Method for the Stereoselective Synthesis of Trisubstituted Alkenes

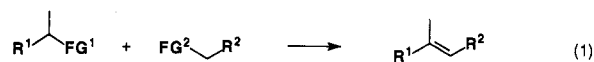Stephen F. Martin,* Dilon Daniel, Robert J. Cherney, and Spiros Liras

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Received February 6, 1992

Summary: A method for the stereoselective, convergent synthesis of trisubstituted alkenes has been developed. The procedure features the synthesis of allylic alcohols **9** by coupling an aldehyde with a vinyl organometallic reagent. Treatment of **9** with carbon disulfide and methyl iodide gave the intermediate allylic xanthates **10** that underwent facile [3,3]-sigmatropic rearrangement to give the dithiocarbonates **11** and **12**, radical reduction of which gave the (*E*)-alkenes **13** as the major products.

A common functional element present in a large number of natural products is a trisubstituted carbon–carbon double bond. Consequently, the convergent, stereoselective construction of trisubstituted alkenes constitutes an important problem in synthetic organic chemistry.[1] Indeed, while we were formulating strategies for the total syntheses of several natural products, it became apparent that known methods for coupling two fragments with the stereoselective formation of a trisubstituted double bond according to eq 1 were somewhat limited in scope.[2–5] We therefore

set to the task of devising solutions to this problem.

After considering a number of possible connective routes to alkenes, we concluded that the sequence of reactions

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