Table III. ^{13}C NMR Spectral Data[a]

	5a		5b		7a		7b	
C	$CDCl_3$	CD_3OD	$CDCl_3$	CD_3OD	$CDCl_3$	CD_3OD	$CDCl_3$	CD_3OD
16	28.9	30.0	28.9	29.6	28.4	29.3	28.3	29.3
17	55.9	56.8	56.0	56.8	56.4	56.8	56.4	56.8
18	12.4	12.9	12.5	12.9	12.3	12.6	12.3	12.6
19	19.2	19.8	19.3	19.7	19.3	19.7	19.3	19.7
20	40.5	41.7	40.4	41.5	36.2	37.3	36.3	37.5
21	20.9	21.5	20.8	21.4	18.7	19.3	18.9	19.7
22	141.9	141.0	141.6	140.8	34.2	35.3	34.3	35.5
23	126.5	127.9	126.8	127.7	24.3	25.1	24.3	25.5
24	52.5	53.0	52.6	52.9	47.2	50.0	47.5	50.0
25	29.0	29.5	29.1	29.3	28.4	29.1	28.2	29.0
26	19.7	19.1	19.6	18.9	19.3	19.2	19.3	19.3
27	21.1	21.3	20.9	21.4	20.0	20.4	19.6	19.9
28	64.1	65.2	64.3	65.2	63.1	63.8	64.2	64.1
OCH_3	56.5	57.9	56.5	57.8	56.7	57.8	56.7	57.8

[a] At 62.9 MHz; values relative to $CDCl_3$ = 77.00 ppm and CD_3OD = 49.00 ppm (central peaks); assignment aided by DEPT technique and comparison with known reference compounds; carbon signals 1–15 in the Experimental Section.

by HPLC on a Whatman ODS-2 M9 10/50 column eluting with methanol, to afford **6a** (10 mg): $[\alpha]_D$ −51° (*c* 1, $CHCl_3$); mp 194–196 °C; HRMS calcd for $C_{28}H_{46}O_2$ (M^+) *m/z* 414.3498, found 414.3490; ^1H NMR ($CDCl_3$) δ 0.70 (3 H, s, 18-Me), 0.85–0.89 (each 3 H, d, *J* = 7 Hz, 26- and 27-Me), 1.01 (3 H, s, 19-Me), 1.04 (3 H, d, *J* = 7 Hz, 21-Me), 3.35 (1 H, dd, *J* = 9, 11 Hz, 28-H), 3.50 (1 H, m, 3-H), 3.62 (1 H, dd, *J* = 5, 11 Hz, 28-H), 5.10 (1 H, dd, *J* = 9, 15 Hz, 23-H), 5.35 (1 H, m, 6-H), 5.39 (1 H, dd, *J* = 8.5, 15 Hz, 22-H).

(22*E*,24*R*)-Ergosta-5,22-diene-3β,28-diol (6b). The *i*-sterol **5b** (10 mg) was treated as described above to afford **6b** (6 mg): $[\alpha]_D$ −36° (*c* 0.6, $CHCl_3$); mp 196–198 °C; HRMS calcd for $C_{28}H_{46}O_2$ (M^+) *m/z* 414.3498, found 414.3502; ^1H NMR ($CDCl_3$) δ 0.71 (3 H, s, 18-Me), 0.85–0.89 (each 3 H, d, *J* = 7 Hz, 26- and 27-Me), 1.01 (3 H, s, 19-Me), 1.04 (3 H, d, *J* = 7 Hz, 21-Me), 3.34 (1 H, dd, *J* = 9, 11 Hz, 28-H), 3.50 (1 H, m, 3-H), 3.62 (1 H, dd, *J* = 5, 11 Hz, 28-H), 5.10 (1 H, dd, *J* = 9, 15 Hz, 23-H), 5.35 (1 H, m, 6-H), 5.39 (1 H, dd, *J* = 8.5, 15 Hz, 22-H).

(24*R*)-3α,5-Cyclo-6β-methoxy-5α-ergostan-28-ol (7a). Alcohol **5a** (15 mg) was hydrogenated at atmospheric pressure over 10% Pt/C in 10 mL of ethanol for 5 h. Removal of the catalyst by filtration and evaporation of solvent gave the noncrystalline saturated alcohol **7a** (13 mg): $[\alpha]_D$ +45° (*c* 1, $CHCl_3$); HRMS calcd for $C_{29}H_{50}O_2$ (M^+) *m/z* 430.3798, found 430.3794; ^1H NMR ($CDCl_3$) δ 0.42 (1 H, m, 4-H), 0.64 (1 H, m, 4-H), 0.71 (3 H, s, 18-Me), 1.02 (3 H, s, 19-Me), 2.77 (1 H, t, *J* = 3 Hz, 6-H), 3.32 (3 H, s, OMe), remaining side chain signals in Tables I and II; ^{13}C NMR C-1 to C-15 as in **5a** ±0.1 ppm, remaining signals in Table III.

(24*S*)-3α,5-Cyclo-6β-methoxy-5α-ergostan-28-ol (7b). Alcohol **5a** (15 mg) was converted to **7b** as described above: $[\alpha]_D$ +39° (*c* 1, $CHCl_3$); HRMS calcd for $C_{29}H_{50}O_2$ (M^+) *m/z* 430.3798, found 430.3789; ^1H NMR ($CDCl_3$) δ 0.42 (1 H, m, 4-H), 0.64 (1 H, m, 4-H), 0.71 (3 H, s, 18-Me), 1.02 (3 H, s, 19-Me), 2.77 (1 H, t, *J* = 3 Hz, 6-H), 3.32 (3 H, s, OMe), remaining side chain signals in Tables I and II; ^{13}C NMR C-1 to C-15 as in **5a** ±0.1 ppm, remaining signals in Table III.

Enzymic Hydrolysis of Coscinasteroside C (8) and Preparation of MTPA Derivative for NMR Measurement. The glycoside sulfate **8** (5 mg), after solvolysis at 130 °C in pyridine–dioxane, 1:1, was incubated at 37 °C with a glycosidase mixture (5 mg) from *Charonia lampas* in citrate buffer (2.0 mL; pH 4.5). After reaction for 24 h, TLC analysis (SiO_2 with 1-butanol–acetic acid–water, 60:15:25) showed that the starting material had disappeared. The mixture was then extracted with 1-butanol and evaporated, and the residue was fractionated by hplc on a C-18 μ-Bondapack column (30 cm × 3.9 mm i.d.) using methanol–water (70:30) as eluent to give 24-methyl-5α-cholest-22(*E*)-ene-3β,6α,8,15β,16β,28-hexol (1 mg): negative ion FABMS *m/z* 479 ($[M - H]^-$); ^1H NMR (CD_3OD) δ 0.88 (3 H, d, *J* = 6.5 Hz, 26- or 27-H_3), 0.94 (3 H, d, *J* = 6.5 Hz, 27- or 26-H_3), 1.03 (3 H, s, 19-H_3), 1.09 (3 H, d, *J* = 6.5 Hz, 21-H_3), 1.32 (3 H, s, 18-H_3), 1.64 (1 H, m, 25-H), 2.18 (1 H, m, 24-H), 2.43 (1 H, dd, *J* = 5, 12 Hz, 7-H), 3.46 (1 H, dd, *J* = 9, 10 Hz, 28-H), 3.50 (1 H, m, 3α-H), 3.67 (1 H, dd, *J* = 5, 10 Hz, 28-H), 3.73 (1 H, td, *J* = 3, 12 Hz, 6β-H), 4.16 (1 H, t, *J* = 6.5 Hz, 16α-H), 4.39 (1 H, dd, *J* = 5.6, 6.7 Hz, 15α-H), 5.29 (1 H, dd, *J* = 9, 15 Hz, 23-H), 5.49 (1 H, dd, *J* = 9, 15 Hz, 22-H).

The polyhydroxylated sterol was then treated with (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) chloride (3 μL) as described above for preparation of **5a**$_1$–**5b**$_2$ to give (+)-MPTA triester; negative ion FABMS *m/z* 1127 ($[M - H]^-$); ^1H NMR (CD_3OD) δ 0.88 (3 H, d, *J* = 6.5 Hz, 26- or 27-H_3), 0.92 (3 H, d, *J* = 6.5 Hz, 27- or 26-H_3), *1.06 (3 H, d, J = 6.5 Hz, 21-H3)*, 1.12 (3 H, s, 19-H_3), 1.31 (3 H, s, 18-H_3), 2.64 (1 H, m, 20-H), *4.37 (2 H, d, J = 6.5 Hz, 28-H$_2$)*, 5.37 (1 H, dd, *J* = 9, 15 Hz, 23-H), 5.79 (1 H, dd, *J* = 9, 15 Hz, 22-H).

Acknowledgment. Financial support was provided by MPI (Roma) and CNR (Roma) "Contributo No. 88.00127.03". Mass spectral data were provided by "Servizio di Spettrometria di Massa del CNR e dell'Università di Napoli". The assistance of the staff is acknowledged.

Registry No. **1**, 25819-77-6; **2a**, 91535-67-0; **2b**, 91509-33-0; **3a**, 91509-34-1; **3b**, 91509-36-3; **4a** (isomer 1), 125413-89-0; **4a** 26-ol derivative (isomer 1), 125413-90-3; **4a** *p*-toluenesulfonate derivative (isomer 1), 125413-91-4; **4a** (isomer 2), 125413-94-7; **4a** 26-ol derivative (isomer 2), 125413-92-5; **4a** *p*-toluenesulfonate derivative (isomer 2), 125413-93-6; **4b**, 125473-23-6; **4b** (isomer 2), 125473-24-7; **5a**, 125413-95-8; **5a1**, 125413-95-8; **5a2**, 125473-26-9; **5b**, 125473-25-8; **5b1**, 125514-81-0; **5b2**, 125473-27-0; **6a**, 125413-97-0; **6b**, 125473-28-1; **7a**, 68844-34-8; **7b**, 68889-65-6; **8**, 105377-96-6; (+)-MTPA chloride, 20445-33-4; (−)-MTPA chloride, 39637-99-5; 3β,6α,28-(*R*)-(+)-MTPA, 125413-98-1; 3-((*tert*-butyldimethylsilyl)oxy)propyne, 76782-82-6; triethyl orthopropionate, 115-80-0; (22*E*,24*S*)-24-(((*tert*-butyldimethylsilyl)oxy)methyl)-3α,5-cyclo-6β-methoxy-5α-cholest-22-ene, 125413-99-2; 24-methyl-2α-cholest-22(*E*)-ene-3β,6α,8,15β,16β,28-hexol, 125414-00-8; pisasteroside A, 123154-33-6.

An Improved Method for Reductive Alkylation of Amines Using Titanium(IV) Isopropoxide and Sodium Cyanoborohydride[1]

Ronald J. Mattson,* Kahnie M. Pham, David J. Leuck,[2] and Kenneth A. Cowen[3]

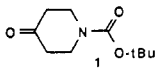
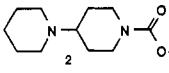
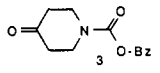
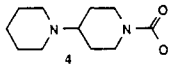
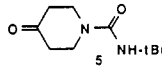
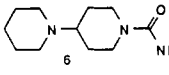
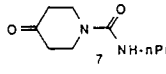
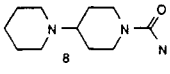
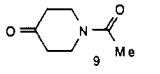
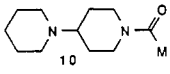
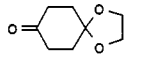
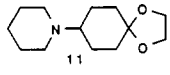
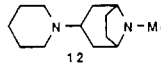
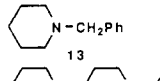
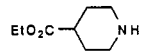
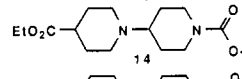
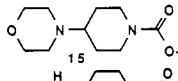
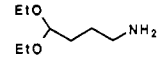
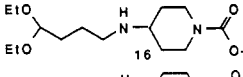
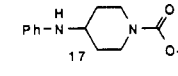
CNS Chemistry, Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492-7660

Received August 29, 1989

The reductive alkylation of amines is one of the fundamental reactions of synthetic organic chemistry. The

0022-3263/90/1955-2552$02.50/0

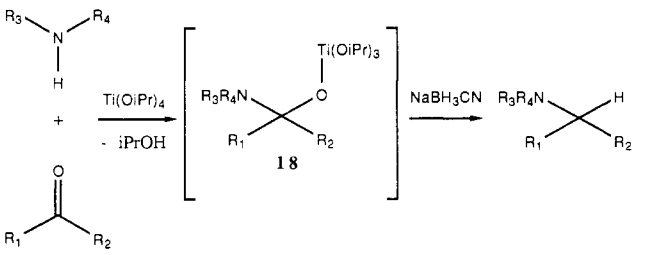
Table I

amine	ketone	product	yield
Piperidine			78%
Piperidine			54%
Piperidine			50%
Piperidine			56%
Piperidine			69%
Piperidine			49% (4% via Borch)
Piperidine	Tropinone		58% (0% via Borch)
Piperidine	Benzaldehyde		71%
	1		82% (24% via Borch)
Morpholine	1		65%
	1		86%
Aniline	1		59%

Borch reductive alkylation method[4] works well provided the intermediate iminium adduct forms readily. For this reason the Borch procedure usually requires an excess of amine to favor the formation of the iminium intermediates. When both the ketone and amine starting materials are valuable or the iminium intermediate is difficult to form, the Borch method can be less than satisfactory. Titanium(IV) chloride has been used as a Lewis acid catalyst in cases when the formation of enamines has proven to be difficult;[5] however, an excess of amine is still needed[6] and the presence of acid-sensitive functionality is limited. Titanium(IV) isopropoxide has been used as a trans-esterification catalyst compatible with a variety of functional groups, such as lactam, acetonide, and *tert*-butyldimethylsilyl ether.[7] We now report that titanium(IV) isopropoxide is a mild and effective Lewis acid catalyst for the reductive alkylation of amines with ketones and aldehydes in the presence of acid-sensitive functional groups.

To evaluate the utility of this methodology, an equimolar ratio of various amines and ketones, bearing potentially acid sensitive or reducible functional groups, were reacted with an excess of titanium(IV) isopropoxide and sodium cyanoborohydride via the general procedure to give the results shown in Table I. The solvent and reducing agent were added only after the intermediate titanium/ketone/amine adduct had been allow to form for 1 h. This one-pot procedure proved to be compatible with carbamate, urea, acetal, ketal, ester, and amide groups. The yields for this method were acceptable for all examples, but the Borch method gave lower yields of the three examples which were tried for comparison (products **11**, **12**, and **14**; 49%, 58%, and 82%, respectively, by the present method, and 4%, 0%, and 24%, respectively, by the Borch method). Consistent with the ability of titanium(IV) isopropoxide to catalyze transesterification, a small amount of isopropyl ester was seen in the NMR and mass spectra of product **14**; however, this small amount was not enough to affect the elemental analysis.

Initially we presumed that the titanium(IV) isopropoxide was performing as a dehydrating agent as well as a Lewis acid to generate enamines which were then reduced by the sodium cyanoborohydride. We were not able, however, to isolate enamines from a mixture of amine, ketone, and titanium(IV) isopropoxide, nor were we able to visualize imine or enamine functionality in the IR spectra of the amine/ketone/titanium(IV) isopropoxide mixtures. This suggests that an iminium species is, at most, a transient intermediate in this reaction. In one possible mechanism, the stable complex **18** is formed, which then is reduced either directly or via a transient iminium species. Reetz[8] has observed that diisobutylaluminum hydride (DIBAL-H) will reduce the similar titanium adducts formed from ketones and titanium amides. Complex **18** is similar to those recently proposed as intermediates in the formation of phenethylamines via the addition of benzylmagnesium chloride to similar titanium complexes.[9] Work is now underway to further investigate the mechanism of this reaction and to extend its utility.



Experimental Section

The starting materials were used as commercially supplied, except for ketones **1**, **3**, and **5**, which were prepared via literature procedures.[10] All IR spectra were recorded on a Perkin-Elmer Model 1800 FT-IR spectrometer. The 200-MHz NMR spectra were determined on a Varian VXR-200 spectrometer and the 300-MHz spectra on a Bruker AM300 spectrometer using deuteriochloroform with 2% (v/v) tetramethylsilane as the internal reference. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. All products were purified by flash chromatography on silica gel using 5% methanol/ethyl acetate as the eluent, except for **16** (10% methanol/ethyl

(1) Mattson, R. J.; Pham, K. M.; Leuck, D. J. Presented at the 196th National Meeting of the American Chemical Society, Los Angeles, CA, Sept 25–30, 1988; Division of Organic Chemistry Abstract 57.
(2) Current address: Chemsyn Science Laboratories, 13605 W. 96th Terrace, Lenexa, KS 66215.
(3) Current address: The Ohio State University, Columbus, OH 43210.
(4) (a) Borch, R. F. *Org. Synth.* **1972**, *52*, 124. (b) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2987. (c) Borch, R. F.; Hassid, A. I. *J. Org. Chem.* **1972**, *37*, 1673.
(5) (a) White, W. A.; Weingarten, H. *J. Org. Chem.* **1967**, *32*, 213. (b) Weingarten, H.; White, W. A. *J. Org. Chem.* **1966**, *31*, 4041. (c) Weingarten, H.; Miles, M. G.; Byrn, S. R.; Hobbs, C. F. *J. Am. Chem. Soc.* **1967**, *89*, 5974. (d) Oruri, T.; Kawai, N.; Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* **1978**, *26*, 803. (e) Hirsh, H. V. *Chem. Ber.* **1967**, *100*, 1289. (f) Nelson, P.; Pelter, A. *J. Chem. Soc.* **1965**, 5142.
(6) Carlson, R.; Nilsson, A. *Acta Chem. Scand. B* **1984**, *38*, 49.
(7) Seebach, D.; Hungerbuhler, E.; Haef, R.; Schnurrenberger, P. *Synthesis* **1982**, 138.
(8) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986; p 107.
(9) Takahashi, H.; Tasubuki, T.; Higashiyama, K. *Synthesis* **1988**, 238.
(10) (a) Labouta, I. M.; Falch, E.; Krogsgaard-Larsen, P. *Eur. J. Med. Chem.* **1982**, *17*, 531. (b) Maschler, H. Eur. Patent 0,097,000, Feb 6, 1983. (c) Takemura, S.; Kiki, Y.; Kuroda, M.; Ozaki, T.; Suzuki, A. *Chem. Pharm. Bull.* **1982**, *30*, 1084.

Table II. Physical and Spectral Data

product	mp, °C	IR R_f	IR cm^{-1}	MS	NMR
2	oil	0.22,[a] 0.68[b]	2865, 1700, 1414	269 (M + H)$^+$	200 MHz: δ 1.3–1.5 (m, 4 H), 1.45 (s, 9 H), 1.5–1.65 (m, 4 H), 1.8 (br d, J = 12 Hz, 2 H), 2.25–2.45 (m, 1 H), 2.5 (t, J = 6 Hz, 4 H), 2.67 (t, J = 12 Hz, 2 H), 4.16 (br d, J = 12 Hz, 2 H)
4	oil	0.13,[a] 0.58[b]	1702	303 (M + H)$^+$	200 MHz: δ 1.3–1.5 (m, 4 H), 1.5–1.65 (m, 4 H), 1.8 (br d, J = 12 Hz, 2 H), 2.3–2.5 (m, 1 H), 2.5 (t, 4 H), 2.75 (t, J = 12 Hz, 2 H), 4.25 (br d, J = 12 Hz, 2 H), 5.1 (s, 2 H), 7.25 (m, 5 H)
6	112–113	0.29[b]	1625, 1534	268 (M + H)$^+$	200 MHz: δ 1.35 (s, 9 H), 1.35–1.55 (m, 4 H), 1.55–1.7 (m, 4 H), 1.85 (d, J = 12 Hz, 2 H), 2.3–2.5 (m, 1 H), 2.54 (t, J = 6 Hz, 4 H), 2.72 (d of t, 2 H), 3.94 (d, J = 12 Hz, 2 H), 4.3 (s, 1 H)
8	175–176	0.18[b]	1618, 1547	254 (M + H)$^+$	200 MHz: δ 0.9 (t, J = 6 Hz, 3 H), 1.3–1.7 (m, 10 H), 1.85 (br d, J = 12 Hz, 2 H), 2.3–2.5 (m, 1 H), 2.52 (t, 4 H), 2.75 (d of t, 2 H), 3.2 (q, J = 6 Hz, 2 H), 3.98 (br d, J = 12 Hz, 2 H), 4.5 (br s, 1 H)
10	oil	0.13[b]	1655	211 (M + H)$^+$	200 MHz: δ 1.35–1.5 (m, 4 H), 1.5–1.65 (m, 4 H), 1.7–1.95 (m, 2 H), 2.1 (s, 3 H), 2.35–2.6 (m, 6 H), 3.03 (d of t, 1 H), 3.95 (br d, 1 H), 4.75 (br d, 1 H)
11	oil	0.56[b]	2935, 1119, 1108	226 (M + H)$^+$	200 MHz: δ 1.4–2.0 (m, 14 H), 2.3–2.5 (m, 1 H), 2.55 (t, 4 H), 3.95 (s, 4 H)
12	oil	0.34[c]	2933, 1111	209 (M + H)$^+$	200 MHz: δ 1.3–1.6 (m, 10 H), 1.75 (d of t, 2 H), 1.9–2.1 (m, 2 H), 2.1 (s, 3 H), 2.45 (t, 4 H), 2.5–2.7 (m, 1 H), 3.2 (t, 2 H)
13	oil	0.40[d]	2935, 1455	176 (M + H)$^+$	200 MHz: δ 1.3–1.5 (m, 2 H), 1.5–1.65 (m, 4 H), 2.37 (t, 4 H), 3.45 (s, 2 H), 7.3 (m, 5 H)
14	oil	0.36[a,b]	1732, 1695	341 (M + H)$^+$	300 MHz: δ 1.07 (t, 3 H), 1.15–1.3 (m, 2 H), 1.27 (s, 9 H), 1.5–1.65 (m, 4 H), 1.75 (br d, 2 H), 2.0–2.3 (m, 4 H), 2.5 (br t, 2 H), 2.7 (br d, 2 H), 3.9–4.05 (m, 4 H) (small amt iPr ester at δ 4.8)
15	76–78	0.16,[a] 0.82[b]	1695	271 (M + H)$^+$	200 MHz: δ 1.25–1.55 (m, 4 H), 1.46 (s, 9 H), 1.82 (br d, J = 12 Hz, 2 H), 2.2–2.4 (m, 1 H), 2.55 (t, J = 6 Hz, 4 H), 2.68 (t, J = 12 Hz, 2 H), 3.68 (t, J = 6 Hz, 4 H), 4.15 (br d, J = 12 Hz, 2 H)
16	oil	0.12,[a] 0.66[b]	1700	345 (M + H)$^+$	300 MHz: δ 1.2 (t, J = 6 Hz, 6 H), 1.2–1.7 (m, 7 H), 1.45 (s, 9 H), 1.95 (br d, J = 12 Hz, 2 H), 2.5–2.95 (br s, 1 H, NH), 2.65 (t, J = 6 Hz, 2 H), 2.77 (t, J = 12 Hz, 2 H), 3.4–3.75 (m, 4 H), 4.05 (br d, J = 12 Hz, 2 H), 4.50 (t, J = 6 Hz, 1 H)
17	139–141	0.45[d]	1680	249 M$^+$	300 MHz: δ 1.24–1.37 (m, 2 H), 1.47 (s, 9 H), 2.01 (d of d, 2 H), 2.91 (t, J = 12 Hz, 2 H), 3.37–3.44 (m, 1 H), 3.56 (br s, 1 H, NH), 4.03 (br d, J = 9 Hz, 2 H), 6.59 (d, 2 H), 6.68 (t, 1 H), 7.15 (d of t, 2 H)

[a] Ethyl acetate. [b] Acetone. [c] 1:1 methanol/CH_2Cl_2. [d] 4:1 hexanes/ethyl acetate.

Table III. Elemental Analysis

compd	formula	analysis
2	$C_{15}H_{28}N_2O_2$	calcd: C, 67.13; H, 10.52; N, 10.44 found: C, 67.07; H, 10.47; N, 10.30
4	$C_{18}H_{26}N_2O_2 \cdot 0.1H_2O$	calcd: C, 71.07; H, 8.69; N, 9.21 found: C, 71.04; H, 8.70; N, 9.11
6	$C_{15}H_{29}N_3O$	calcd: C, 67.37; H, 10.93; N, 15.71 found: C, 67.40; H, 10.95; N, 15.71
8	$C_{14}H_{27}N_3O \cdot 0.1H_2O$	calcd: C, 65.90; H, 10.75; N, 16.47 found: C, 65.90; H, 10.78; N, 16.62
10	$C_{12}H_{22}N_2O$	calcd: C, 66.53; H, 10.55; N, 13.32 found: C, 66.88; H, 10.49; N, 13.03
11	$C_{13}H_{23}NO_2$	calcd: C, 69.30; H, 10.29; N, 6.22 found: C, 69.22; H, 10.31; N, 6.18
12	$C_{13}H_{24}N_2$	calcd: C, 74.54; H, 11.61; N, 13.45 found: C, 74.15; H, 11.73; N, 13.38
13	$C_{12}H_{17}N$	calcd: C, 82.23; H, 9.78; N, 7.99 found: C, 81.82; H, 9.78; N, 7.99
14	$C_{18}H_{32}N_2O_4$	calcd: C, 63.51; H, 9.48; N, 8.23 found: C, 63.41; H, 9.51; N, 8.15
15	$C_{14}H_{26}N_2O_3$	calcd: C, 62.20; H, 9.70; N, 10.37 found: C, 62.17; H, 9.66; N, 10.44
16	$C_{18}H_{36}N_2O_4$	calcd: C, 62.76; H, 10.54; N, 8.14 found: C, 62.86; H, 10.60; N, 8.14
17	$C_{16}H_{24}N_2O_2$	calcd: C, 69.54; H, 8.76; N, 10.14 found: C, 69.83; H, 8.81; N, 10.14

acetate) and 17 (7:1 hexanes/ethyl acetate). All yields given are of analytically pure material, and all compounds had NMR and IR spectra and elemental analyses (±0.4%) consistent with the assigned structures.

General Procedure. A mixture of the ketone (10 mmol), amine (10 mmol), and titanium(IV) isopropoxide (3.72 mL, 12.5 mmol) was stirred at room temperature in a 100-mL round-bottom flask under a drying tube. After 1 h, the IR spectrum of the mixture showed no ketone band, and the viscous solution was diluted with absolute ethanol (10 mL). Sodium cyanoborohydride (0.42 g, 6.7 mmol) was added, and the solution was stirred for 20 h. Water (2 mL) was added with stirring, and the resulting inorganic precipitate was filtered and washed with ethanol. The filtrate was then concentrated in vacuo. The crude product was dissolved in ethyl acetate, filtered to remove the remaining inorganic solids, and concentrated in vacuo. The products were then purified by flash chromatography.

Registry No. **1**, 79099-07-3; **2**, 125541-12-0; **3**, 19099-93-5; **4**, 125541-13-1; **5**, 125541-11-9; **6**, 125541-14-2; **7**, 89805-08-3; **8**, 125541-15-3; **9**, 32161-06-1; **10**, 125541-16-4; **11**, 125541-17-5; **12**, 125541-18-6; **13**, 2905-56-8; **14**, 125541-19-7; **15**, 125541-20-0; **16**, 125541-21-1; **17**, 125541-22-2; titanium(IV) isopropoxide, 546-68-9; piperidine, 110-89-4; ethyl piperidine-4-carboxylate, 1126-09-6; 4,4-diethoxybutanamine, 6346-09-4; aniline, 62-53-3; tropinone, 532-24-1; benzaldehyde, 100-52-7; morpholine, 110-91-8; 1,2-dioxaspiro[4.5]decan-8-one, 4746-97-8.

Nickel(0)-Catalyzed Hydroacylation of Alkynes with Aldehydes to α,β-Enones

Tetsuo Tsuda,* Takao Kiyoi, and Takeo Saegusa*

Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Yoshida, Kyoto 606, Japan

Received August 29, 1989

Transition metal catalyzed reaction of alkynes with aldehydes has not been well known. By taking advantage of the nickel(0)-catalyzed cycloaddition reaction of diynes with carbon dioxide to bicyclic α-pyrones,[1] we have found

(1) Tsuda, T.; Morikawa, S.; Sumiya, R.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 3140.

0022-3263/90/1955-2554$02.50/0