New Reagents for the Intermolecular and Intramolecular Pinacolic Coupling of Ketones and Aldehydes

E. J. Corey,* Rick L. Danheiser, and Srinivasan Chandrasekaran

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

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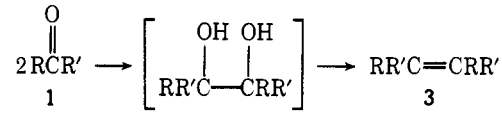
Studies are reported which extend considerably the scope and effectiveness of the pinacolic coupling reaction. Three reagents were found to be most useful: (1) magnesium amalgam–titanium tetrachloride, (2) cyclopentadienyltitanium trichloride–lithium aluminum hydride, and (3) the hexamethylbenzene complex of the well-defined Ti(II) species $(Cl_2AlCl_2)_2Ti$. Examples are given of intermolecular coupling reactions leading to *both* symmetrical and unsymmetrical pinacols. Some uses of the latter products in synthesis are illustrated. Several cases of intramolecular pinacolic reaction to form four-, five-, and six-membered rings are provided. Finally, a brief discussion is presented with regard to possible mechanisms for the titanium mediated pinacolic coupling.

The reductive coupling of carbonyl compounds constitutes an important method for the formation of carbon–carbon bonds.[1] The coupling of carboxylic esters (the acyloin reaction) has long been recognized as a powerful tool for intermolecular condensation and intramolecular cyclization. In contrast, the "pinacolic reduction" of ketones and aldehydes has seen limited application in complex synthetic problems. Aliphatic systems undergo coupling in poor yield and no general method for effective *intramolecular* pinacolic reduction has previously been reported.

Recently, Mc Murry[2] has demonstrated that a reagent (of undefined structure) derived from the interaction of titanium trichloride and lithium aluminum hydride induces coupling of carbonyl compounds. However, this reagent leads not to pinacols, but rather to the corresponding olefins as shown in Scheme I. Other low-valent transition metal reagents[3-5] have been reported to effect pinacolic coupling; however, these reagents do not effectively couple aliphatic ketones.

Scheme I



1 2 3

In connection with our interest in methods for constructing the D ring of gibberellic acid,[6] we have developed several highly efficient and *general* reagents for the pinacolic coupling of ketones and aldehydes. We report herein the results of this investigation, defining the power and scope of the pinacolic coupling process.

Intermolecular Reductive Coupling Reactions. Although Mukaiyama's $TiCl_4$–Zn reagent[4] successfully couples aromatic ketones and aldehydes, we found it less effective in aliphatic systems (vide infra). We have examined a variety of low-valent titanium compounds and have observed the nature and yield of products to be highly dependent on the precise Ti(II) species employed. *However, we have found that ketones and aldehydes are consistently coupled in excellent yield by the Ti(II) species generated by reaction of titanium tetrachloride and amalgamated 70–80 mesh magnesium.* Optimum yields are obtained by reaction at 0° for 1–15 hours in tetrahydrofuran (Table I). Substitution of other forms of aluminum, magnesium, or zinc or other solvent systems resulted in inferior yields. Table II compares our results with previously reported methods.

The potential pinacol rearrangement[8] of these reductive coupling products greatly extends their synthetic utility.

Table I
Intermolecular Reductive Coupling Reactions

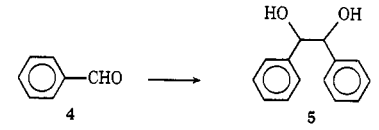
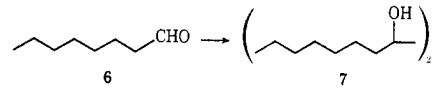
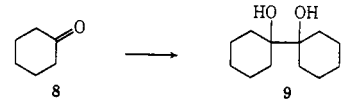
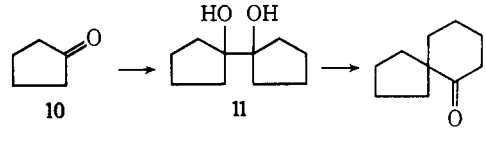
	% isolated yield
 4 → 5	84
 6 → 7	80
 8 → 9	93
 10 → 11	95

Table II
Comparison of Methods for Reductive Coupling of Cyclohexanone

Method	% isolated yield
$Mg(Hg)–TiCl_4$	93
$LiAlH_4–TiCl_3$[2]	(Olefin)
$Zn–TiCl_4$	24[a]
$Mg–TiCl_3$[5]	45
Al(Hg)[7]	55

[a] This result was obtained following the procedure of Mukaiyama and coworkers.[4] The yield is corrected for unreacted starting material.

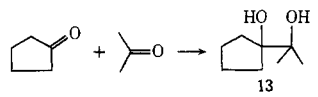
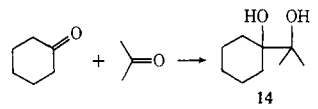
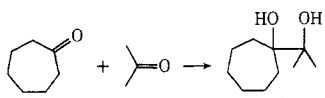
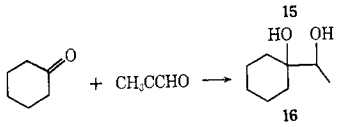
For example, diol 11 undergoes acid-catalyzed rearrangement providing spirodecanone **12,** now available in 82% overall yield from cyclopentanone.[9] This compound served as starting material in a recent total synthesis of perhydrohistrionicotoxin.[10]



10 11 12

We have extended the scope of the reductive coupling method to include the synthesis of *unsymmetrical* pinacols.[11] Thus, reaction of a cyclic ketone and 3 equiv of a low molecular weight carbonyl compound with the Mg(Hg)–$TiCl_4$ reagent affords a mixture from which the unsymmetrical pinacol is easily separated by chromatography in good yield (Table III). Although this method fails with low

Table III
Unsymmetrical Reductive Coupling Reactions

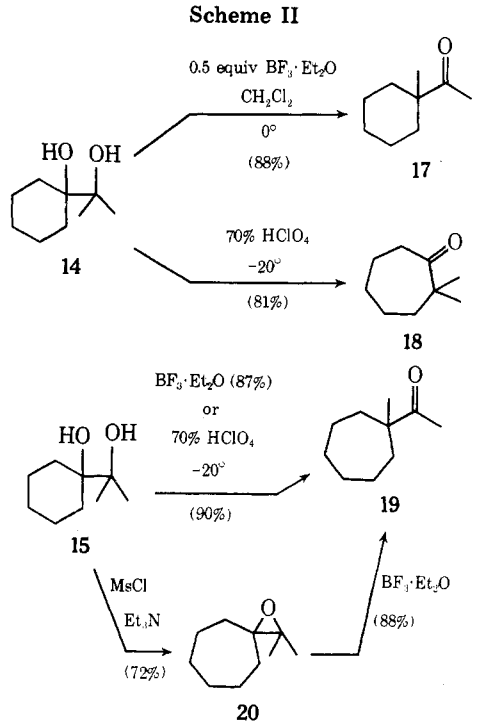
	% isolated yield[a]
 13	65[b]
 14	76[b]
 15	75[b]
 16	72[c]

[a] The yields are based on cyclic ketone. [b] The Mg(Hg)–$TiCl_4$ reagent was employed for this reaction. [c] The $CpTiCl_3$–$LiAlH_4$ reagent was employed for this reaction.

molecular weight aldehydes, excellent results are obtained using the reagent formed by reaction of cyclopentadienyltitanium trichloride and lithium aluminum hydride (vide infra).[12]

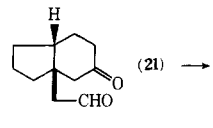
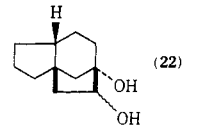
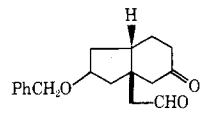
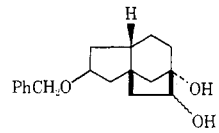
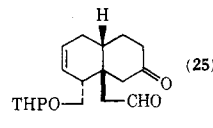
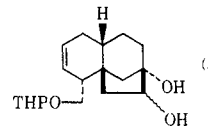
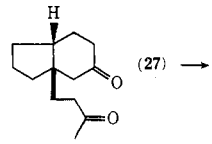
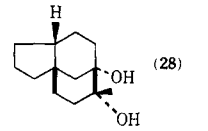
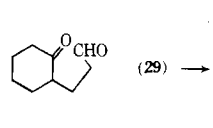
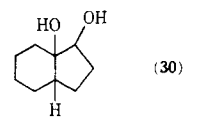
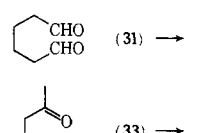
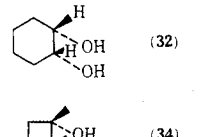
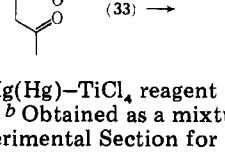
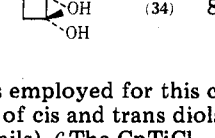
The unsymmetrical pinacols **13–16** are useful synthetic intermediates. Treatment with methanesulfonyl chloride and triethylamine affords epoxides in excellent yield. Both the pinacols and epoxides undergo ring expansion reactions and/or methyl group migration in high yields under mild conditions.[13] Scheme II details some of our results.

Scheme II



Intramolecular Reductive Coupling Reactions. Compounds **23** and **25** are key intermediates in studies directed toward the total synthesis of gibberellic acid being pursued in these laboratories. Our interest in methods for the intramolecular coupling of these molecules initiated this investigation. Classical conditions[6,7] proved totally ineffective for these reactions. Mc Murry's reagent succeeds only for pinacolic cyclizations in which deoxygenation of the initially

Table IV
Intramolecular Reductive Coupling Reactions

	% isolated yield
 (21) →  (22)	90[a,b]
 (23) →  (24)	50[c,d]
 (25) →  (26)	55[c,d]
 (27) →  (28)	43[a,e]
 (29) →  (30)	49[b,c]
 (31) →  (32)	32[a,e]
 (33) →  (34)	81[a,e]

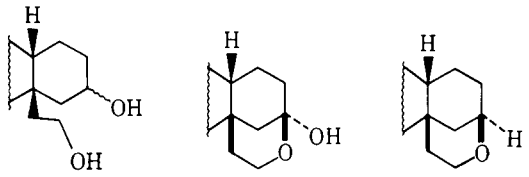
[a] The Mg(Hg)–$TiCl_4$ reagent was employed for this cyclization. [b] Obtained as a mixture of cis and trans diols (see Experimental Section for details). [c] The $CpTiCl_3$–$LiAlH_4$ reagent was employed for this cyclization. [d] Obtained in somewhat lower yield (40–45%) using Mc Murry's reagent ($TiCl_3$–$LiAlH_4$). [e] No trans diol could be detected.

formed pinacol would lead to highly strained bridgehead olefins. *We have found that reduction of cyclopentadienyltitanium trichloride with lithium aluminum hydride provides a new reagent which induces the intramolecular coupling of carbonyl compounds in fair to excellent yields.*[14] The Mg(Hg)–$TiCl_4$ reagent supplements this new species in less difficult cyclizations. Table IV illustrates our results.

Optimum reaction conditions involve reduction of 6 equiv of $CpTiCl_3$ with 4.5 equiv of $LiAlH_4$ at 50° in tetrahydrofuran followed by rapid addition of 1 equiv of carbonyl compound. High-dilution techniques are not necessary to inhibit intermolecular condensation. Other reactant ratios and solvent systems resulted in inferior yields. We have examined a large number of systems involving $TiCl_3$, $TiCl_4$, and $CpTiCl_3$ in combination with various reducing reagents for the coupling reaction of **21**. In addition to the previously described reagents, $TiCl_3$–*t*-BuLi, $TiCl_3$–*n*-BuLi, and $TiCl_3$–DIBAL furnish **22**, although in inferior yields. Some low-valent forms of other transition metals (Mo, W, Zr) were investigated but were found ineffective for intramolecular coupling.

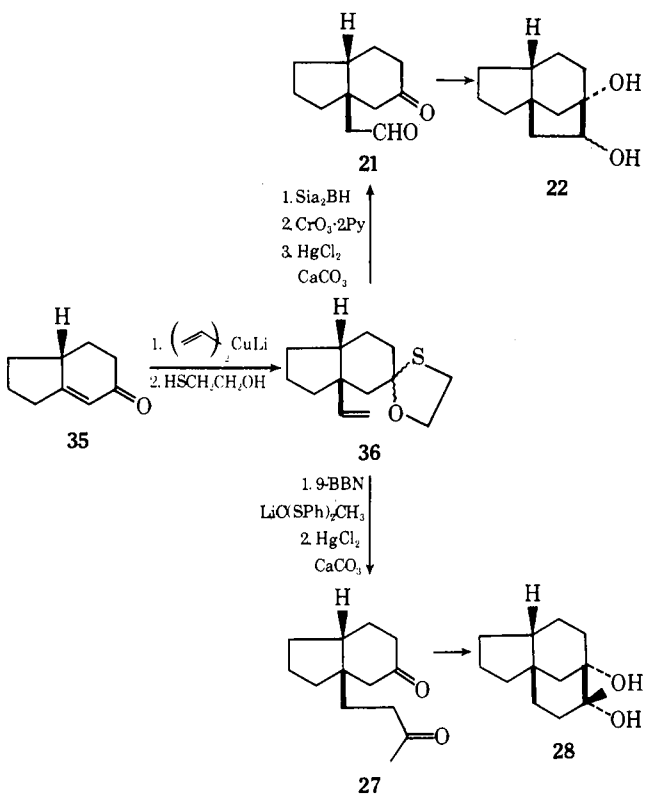
A complication encountered in applying previously described coupling conditions to the dicarbonyl substrates indicated in Table IV is competing intramolecular aldol condensation. This facile side reaction, which is particularly serious in the case of keto aldehydes **21**, **23**, and **25**, is mini-

mized by employing the $CpTiCl_3$–$LiAlH_4$ reagent. However, significant quantities of other products (both polar and nonpolar relative to pinacol) have been observed in certain instances. In the case of substrate **25**, these byproducts were shown to possess the following diol, ketol, and cyclic ether structures.



In conjunction with the conjugate addition of vinyl Gilman reagent,[6] the reductive coupling reaction provides a sequence for the *1,3 bridging of α,β-unsaturated ketones and aldehydes* (Scheme III). For example, functionalization of the vinyl appendage in **36** through hydroboration and oxidation allows the addition of a two-carbon 1,3 bridge (e.g., **35** → **22**). Alternatively, treatment of **36** with 9-BBN followed by an α-lithio thioacetal[15] leads to the addition of a three-carbon 1,3 bridge (e.g., **35** → **28**).

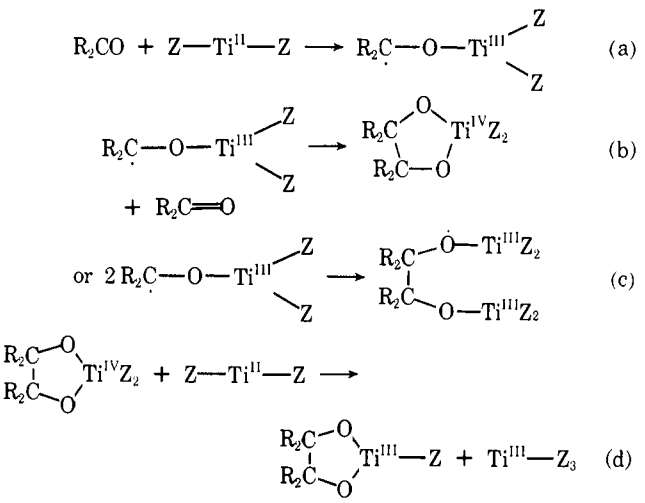
Scheme III



Of special note is the synthesis of a four-membered ring in high yield. Classical methods give cyclobutanediols in only very low yields.[17] Conia[18] has demonstrated the synthetic utility of these pinacols; thermal rearrangement of **34** affords 1,1-dimethylcyclobutanone while acid-catalyzed ring contraction provides methyl 1-methylcyclopropyl ketone in quantitative yield.

Mechanism of the Reductive Coupling Reaction. Mc Murry[2] has suggested that Ti(II) is the reactive species in these reductive coupling reactions. Based on this assumption a family of plausible mechanisms may be devised (Scheme IV). Reduction of the carbonyl group by the Ti(II) reagent gives a Ti(III) intermediate (eq a); two alternative paths for the coupling of this intermediate are shown. In eq b the Ti(III) intermediate participates in a cycloaddition

Scheme IV



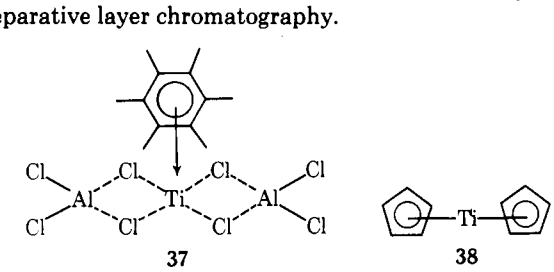
process to form a cyclic Ti(IV) derivative of the pinacolic product, whereas in eq c a pinacol bis-Ti(III) complex is formed by the coupling of two Ti(III) species.

In the case of intramolecular processes forming four- to six-membered carbocyclic systems, reaction by eq b would be expected to lead to cis 1,2-diols whereas the alternative pathway (eq c) could produce either cis or trans diols. The data in Table IV are consistent with the operation of either pathway for intramolecular coupling reactions, but suggest that in some instances (e.g., exclusive formation of cis diols **32** and **34**) the cycloaddition mechanism (eq b) may be favored.

In order to test the hypothesis embodied in Scheme IV, we examined the possibility of accomplishing pinacolic coupling using well-defined Ti(II) species. *We have found Ti(II) complexes of known structure which are capable of effecting the reductive coupling of carbonyl compounds.* The complex **37**,[19] prepared by reaction of Al–$AlCl_3$, $TiCl_4$, and hexamethylbenzene, is especially effective. Good yields of pinacols are obtained by reaction of **37** with acetone, cyclohexanone, and also the dicarbonyl compounds **21** and **33**.[20]

At least 2 molar equiv of **37** are required for complete reaction of carbonyl compound. This observation is consistent with pathways in which the Ti(II) reagent is transformed eventually into Ti(III) species. Such mechanisms include reaction by eq a and c and also the pathway expressed by eq a and b followed by reduction of the cyclic Ti(IV) pinacol ester by the Ti(II) reagent to two Ti(III) species (eq d).

Titanocene (**38**) was less effective as a pinacolic coupling reagent than **37** and therefore was not studied in any detail. For example, reaction of diketone **33** with titanocene, prepared by the method of Rausch and Alt,[21,22] gave a complex mixture from which **34** was isolated in 10% yield by preparative layer chromatography.



We are continuing to examine new titanium complexes in order to extend further the scope and efficiency of the reductive coupling reaction and to clarify the mechanism of these coupling reactions. The methods already described in

this report provide the chemist with powerful new synthetic tools for the formation of rings and chains.

Experimental Section

Instrumentation. Infrared spectra were obtained using a Perkin-Elmer Model 267 diffraction grating spectrophotometer. Proton magnetic resonance spectra were measured with Varian Associates T-60 and HA-100 spectrometers; chemical shifts are expressed in parts per million downfield from internal trimethylsilane. Mass spectra were observed with an AEI MS-9 spectrometer at an ionizing voltage of 70 eV. Melting points and boiling points are uncorrected.

Materials. Cyclopentadienyltitanium trichloride was obtained from Alfa Products and was stored and transferred under argon atmosphere in a glove bag. Titanium tetrachloride, methanesulfonyl chloride, and 2-mercaptoethanol were distilled under argon. Boron trifluoride etherate, diisopropyl sulfide, and acetonitrile were distilled from calcium hydride. Triethylamine was distilled from sodium hydride. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl. All reactions were carried out in flame-dried glassware under an atmosphere of argon.

Procedure for Intermolecular Reductive Coupling. Cyclohexanone. To a solution of mercuric chloride (0.044 g, 0.16 mmol) in 3 ml of distilled THF was added 70–80 mesh magnesium (0.144 g, 6.0 mmol), and the resulting mixture was stirred at room temperature under argon for 0.25 hr. The turbid supernatant liquid was withdrawn by syringe and the remaining amalgam was washed with three 2-ml portions of THF. The resulting dull gray amalgam was taken up in 5 ml of THF, cooled to −10°, and treated dropwise with titanium tetrachloride (330 μl, 0.570 g, 3.0 mmol) to give a yellow-green mixture. A solution of cyclohexanone (0.196 g, 2.0 mmol) in 5 ml of THF was added, and the purple reaction mixture was stirred at 0° for 0.5 hr. The reaction was quenched with 0.5 ml of saturated K_2CO_3 solution and stirred at 0° for 0.25 hr. The resulting dark blue mixture was diluted with ether and filtered through Celite. The filtrate was washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.197 g of colorless crystals. Recrystallization from ether–petroleum ether gave 0.186 g (93% yield) of **9** as colorless crystals, mp 124–125° (lit.[23] mp 124.5–126.5°).

Reductive Coupling of Cyclopentanone. This reaction was carried out as described for cyclohexanone. Recrystallization of the crude product from ether–petroleum ether gave **11** as colorless crystals (95% yield), mp 111–112° (lit. mp 109–111° [23] and 111.4–112.4° [24]).

Reductive Coupling of Benzaldehyde. In an identical manner 1,2-diphenyl-1,2-ethanediol (**5**) was obtained in 84% yield.

Reductive Coupling of Octanal. This reaction was performed as described for cyclohexanone but required 13 hr at 0°. Recrystallization of the crude product from ether gave **7** (80% yield) as a white solid, mp 53–54° (lit.[25] mp 59–63°); an exact mass determination gave *m/e* 258.2558 (calcd for $C_{16}H_{34}O_2$, 258.2559).

Procedure for Unsymmetrical Reductive Coupling. Cyclohexanone and Acetone. To a solution of mercuric chloride (0.600 g, 2.21 mmol) in 10 ml of THF was added 70–80 mesh magnesium (1.92 g, 80.0 mmol), and the resulting mixture was stirred at room temperature under argon for 0.25 hr. The turbid supernatant liquid was withdrawn by syringe, and the remaining amalgam was washed with three portions of THF. Tetrahydrofuran (30 ml) was added, and the mixture was cooled to −10° and treated dropwise with titanium tetrachloride (4.4 ml, 7.6 g, 40.0 mmol). The walls of the reaction flask were washed with 10 ml of THF, and a solution of cyclohexanone (0.980 g, 10 mmol) and acetone (1.74 g, 30.0 mmol) in 10 ml of THF was added. The purple mixture was stirred for 1.5 hr at 0°, treated with 1.5 ml of saturated aqueous K_2CO_3 solution, and stirred for 0.25 hr further at 0°. Ether (100 ml) was added, and the mixture was filtered through Celite. The filtrate was washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 2.81 g of a viscous oil. Column chromatography on silica gel (elution with 40% ether–petroleum ether) gave 1.160 g (76% yield) of **14** as colorless crystals: mp 82–83° (lit.[26] mp 83°); ^1H NMR ($CDCl_3$) δ 1.23 (s, 6 H) and 1.2–2.1 (m, 12 H); ir ($CHCl_3$) λ_{max} 2.76, 2.80, 2.9, 3.35, 3.40, and 3.49 μ; an exact mass determination gave *m/e* 158.1298 (calcd for $C_9H_{18}O_2$, 158.1306).

Reductive Coupling of Cyclopentanone and Acetone. Cyclopentanone (1.68 g, 20.0 mmol) was coupled with acetone (4.06 g, 70.0 mmol) according to the above procedure to afford **13** in 65% yield: mp 60–61° (lit.[27] 62°).

Reductive Coupling of Cycloheptanone and Acetone. Cycloheptanone (2.24 g, 20.0 mmol) was coupled with acetone (4.64 g, 80.0 mmol) according to the above procedure to afford 5.61 g of a viscous oil. Column chromatography on silica gel (elution with 40% ether–petroleum ether) gave 2.572 g (75% yield) of **15** as colorless crystals: mp 51–52°; ^1H NMR ($CDCl_3$) δ 1.23 (s, 6 H), 1.67 (broad s, 12 H), and 2.1–2.4 (m, 2 H); ir ($CHCl_3$) λ_{max} 2.76, 2.81, 2.9, 3.32, 3.40, and 3.49 μ; an exact mass determination gave *m/e* 172.1459 (calcd for $C_{10}H_{20}O_2$, 172.1463).

Reductive Coupling of Cyclohexanone and Acetaldehyde. To a solution of cyclopentadienyltitanium trichloride (1.315 g, 6.0 mmol) in 4 ml of distilled THF at 0° under argon was cautiously added lithium aluminum hydride (0.171 g, 4.5 mmol) in portions. The dark mixture was stirred at 50° for 1 hr, cooled to room temperature, and treated with a solution of cyclohexanone (0.098 g, 1.0 mmol) and acetaldehyde (0.176 g, 4.0 mmol) in 3 ml of THF. The resulting mixture was stirred for 2.5 hr at room temperature and then quenched with 0.5 ml of saturated aqueous K_2CO_3 solution. The blue mixture was stirred for 0.25 hr, diluted with ether, and filtered through Celite. The filtrate was washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.251 g of a colorless oil. Preparative layer chromatography on silica gel (elution with ethyl acetate) gave 0.103 g (72% yield) of **16** as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.15 (d, 3 H, J = 6 Hz), 1.3–2.2 (m, 10 H), 2.98 (broad s, 2 H, –OH), and 3.58 (q, 1 H, J = 6 Hz); ir (CCl_4) λ_{max} 2.94, 3.35, 3.41, and 3.49 μ; an exact mass determination gave *m/e* 144.1149 (calcd for $C_8H_{16}O_2$, 144.1150).

Ring Expansion of Diol 14. To 70% perchloric acid (15 ml) cooled to −20° was added in portions the diol **14** (0.158 g, 1.0 mmol), and the resulting solution was stirred for 0.25 hr at −20° under argon. Water was added, and the solution was extracted with ether. The combined organic layers were washed with saturated $NaHCO_3$ solution and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.144 g of a pale yellow oil. Filtration through silica gel (elution with 5% ether–petroleum ether) gave 0.114 g (81% yield) of **18** as a colorless oil with spectral data identical with that previously reported.[28]

Rearrangement of Diol 14. To a solution of the diol **14** (0.158 g, 1.0 mmol) in 5 ml of CH_2Cl_2 at 0° under argon was added boron trifluoride etherate (0.071 g, 0.5 mmol), and the resulting solution was stirred for 0.25 hr at 0°. Ether was added, and the solution was washed with saturated $NaHCO_3$ solution, water, and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to yield 0.142 g of a pale yellow oil. Filtration through silica gel (elution with 5% ether–petroleum ether) gave 0.123 g (88% yield) of **17** as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.10 (s, 3 H), 1.2–2.6 (m, 10 H), and 2.33 (s, 3 H); ir ($CHCl_3$) λ_{max} 3.23, 3.35, 3.43, and 5.86 μ.

Rearrangement of Diol 15. Exposure of diol **15** to 70% perchloric acid as described for diol **14** gave, after filtration through silica gel, the ketone **19** (90% yield) as a colorless oil. Similarly, treatment of **15** with BF_3·Et_2O as described above for **14** afforded **19** in 87% yield: ^1H NMR ($CDCl_3$) δ 1.10 (s, 3 H), 1.1–2.3 (m, 12 H), and 2.14 (s, 3 H); ir ($CHCl_3$) λ_{max} 3.39, 3.45, and 5.85 μ.

Preparation of Epoxide 20. To a solution of the diol **15** (0.344 g, 2.0 mmol) and triethylamine (1.01 g, 10.0 mmol) in 6 ml of methylene chloride at −20° under argon was added methanesulfonyl chloride (0.920 g, 8.0 mmol), and the resulting solution was stirred for 1.5 hr at −20° and 15 hr at 0°. The solution was washed with 5% aqueous acetic acid, water, and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.282 g of yellow oil. Preparative layer chromatography on silica gel (elution with 50% ether–petroleum ether) gave 0.222 g (72% yield) of **20** as a colorless oil. The spectral data were identical with that previously reported for this compound.[28]

Rearrangement of the Epoxide 20. Treatment of the epoxide **20** with boron trifluoride etherate as described above for the diol **14** gave the ketone **19** in 88% yield.

Procedure for Intramolecular Reductive Coupling. Coupling of Keto Aldehyde 21. To 70–80 mesh magnesium (0.195 g, 8.0 mmol) in 3 ml of distilled THF under argon was added mercuric chloride (0.060 g, 0.22 mmol), and the mixture was stirred for 0.25 hr at room temperature. The solvent was withdrawn by syringe, and the amalgam was washed with three portions of THF. An additional 4 ml of THF was added, the mixture was cooled to −10°, and titanium tetrachloride (0.33 ml, 0.570 g, 3.0 mmol) was added dropwise. A solution of keto aldehyde[6] **21** (0.180 g, 1.0 mmol) in 4 ml of THF was introduced, and the mixture was stirred at 0° for 1.25 hr. The reaction mixture was treated with 0.5 ml of saturated K_2CO_3 solution at 0° for 0.25 hr, and the resulting blue-black mixture was filtered through Celite with the aid of ether.

The filtrate was washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.165 g (90% yield) of **22** as colorless crystals (80:20 mixture of cis and trans diols). The cis and trans diols were separated by column chromatography on silica gel: trans diol, mp 107–109°; cis diol, mp 85–86°; ^1H NMR ($CDCl_3$) δ 1.3–2.0 (m, 15 H), 3.45 (broad m, –OH, 2 H), and 3.69 (d of d, 1 H, J = 3.5, 6.5 Hz); ir (tf) λ_{max} 2.95, 3.41, and 3.49 μ.

Reductive Coupling of Diketone 27. This compound was cyclized over 5 hr at 0° according to the above procedure to afford 0.281 g of a pale yellow oil. Preparative layer chromatography on silica gel (elution with ethyl acetate) gave the cis diol **28** (43% yield) as colorless crystals: mp 95–96°; ^1H NMR ($CDCl_3$) δ 1.18 (s, 3 H), 1.2–2.0 (m, 17 H), and 2.8 (broad s, –OH, 2 H); ir (tf) λ_{max} 2.93, 3.40, and 3.49 μ.

Reductive Coupling of Keto Aldehyde 25. To a solution of cyclopentadienyltitanium trichloride (0.207 g, 0.99 mmol) in 4 ml of distilled THF under argon was cautiously added a solution of lithium aluminum hydride in THF (1.12 *M*, 0.665 ml, 0.75 mmol). The reaction mixture was stirred at 50° for 1 hr and then a solution of keto aldehyde **25**[29] (0.050 g, 0.165 mmol) in 2 ml of THF was introduced. The mixture was stirred for 2 hr at 50°, cooled to room temperature, treated with 0.5 ml of saturated K_2CO_3 solution, and stirred for an additional 0.25 hr. The resulting dark blue mixture was filtered through Celite with the aid of ether, and the filtrate was washed with saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford 0.048 g of a yellow oil. Preparative layer chromatography on silica gel (elution with ethyl acetate) gave 0.008 g of trans diol **26b**, mp 97–99° (15% yield), and 0.020 g of cis diol **26a** (40% yield): mp 87.5–89°; ^1H NMR ($CDCl_3$) δ 1.1–2.7 (m, 20 H), 3.0–4.2 (m, 5 H), 4.55 (s, 1 H), and 5.65 (s, 2 H); ir ($CHCl_3$) λ_{max} 3400, 3020, 1140, 1120, 1075, and 1035 cm^{-1}; an exact mass determination gave *m/e* 308.4184 (calcd for $C_{18}H_{28}O_4$, 308.4182).

Reductive Coupling of Keto Aldehyde 29. To a solution of cyclopentadienyltitanium trichloride (1.97 g, 9.0 mmol) in 10 ml of distilled THF at 0° under argon was cautiously added in portions lithium aluminum hydride (0.256 g, 6.75 mmol). The black mixture was stirred for 1 hr at 50°, and then a solution of keto aldehyde **29**[30] in 10 ml of THF was added dropwise. The resulting mixture was stirred for 2.5 hr at 50°, cooled to 0°, and treated with 1.0 ml of saturated K_2CO_3 solution, and stirred at room temperature for 0.5 hr. The reaction mixture was filtered through Celite with the aid of ether, and the filtrate was washed with saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford 0.203 g of a yellow oil. Column chromatography on silica gel (elution with 10–60% tetrahydrofuran–hexanes) of this material and the product of another run gave four isomeric diols **30**[31] in yields of 12, 20, 11, and 6% (combined yield, 49%). The major isomer: mp 60.5–61°; ^1H NMR ($CDCl_3$) δ 1.3–2.6 (m, 15 H) and 3.7–4.0 (m, 1 H); ir ($CHCl_3$) λ_{max} 2.94, 3.41, and 3.50 μ; an exact mass determination gave *m/e* 156.1145 (calcd for $C_9H_{16}O_2$ 156.1150).

Reductive Coupling of Dialdehyde 31. The dialdehyde **31** was treated with the Mg(Hg)–$TiCl_4$ reagent at 0° for 2.5 hr according to the procedure described for keto aldehyde **21**. Preparative layer chromatography of the crude product on silica gel (elution with ethyl acetate) gave **32** (32% yield) as colorless crystals, mp 94–96° (lit.[32] mp 98°).

Reductive Coupling of Diketone 33. The diketone **33** was coupled with the Mg(Hg)–$TiCl_4$ reagent at 0° for 2.5 hr according to the procedure described for keto aldehyde **21**. Preparative layer chromatography of the crude product on silica gel (elution with ethyl acetate) gave **34** (81% yield) as colorless crystals, mp 29–30° (lit.[18a] mp 14°). The ^1H NMR, ir, and mass spectral data were identical with those reported;[18b] the bistrimethylsilyl ether was prepared and an exact mass determination gave *m/e* 260.1628 (calcd for $C_{12}H_{28}O_2Si_2$, 260.1628).

Addition of Vinyl Gilman Reagent to Enone 35. To a solution of 2.13 *M* vinyllithium (45.0 ml, 96 mmol) in 100 ml of ether at −50° under argon was added dropwise over 0.25 hr a solution of CuI[33] (9.90 g, 52 mmol) in diisopropyl sulfide (34.0 ml, 27.6 g, 234 mmol). This mixture was stirred for 0.25 hr at −25°, then cooled to −78°, and a solution of the enone **35** (5.45 g, 40.0 mmol) in 11 ml of ether was added dropwise over 0.25 hr. The resulting dark green mixture was stirred for 0.5 hr at −55° and then allowed to warm to −40° over 1 hr. The reaction mixture was poured into 200 ml of saturated aqueous NH_4Cl solution buffered to pH 8 with NH_4OH, stirred for 0.5 hr, and filtered through Celite with the aid of ether. The organic layer of the filtrate was extracted with saturated buffered aqueous NH_4Cl solution, water, and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 12.481 g of a pale yellow oil. Chromatography on silica gel (elution with 5–15% THF–hexanes) gave 5.670 g (87% yield)[34] of the vinyl ketone **39** as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.5–2.5 (m, 11 H), 2.37 (broad s, 2 H), 4.8–5.2 (m, 2 H), and 5.81 (d of d, 1 H, J = 10, 18 Hz); ir (tf) λ_{max} 3.21, 3.36, 3.45, 5.82, and 6.09 μ; GLC t_r 9.0 min (155°, 10 ft 5% Carbowax 20M); an exact mass determination gave *m/e* 164.1199 (calcd for $C_{11}H_{16}O$; 164.1201).

Preparation of Hemithioketal 36. A solution of the vinyl ketone **39** (4.00 g, 24.4 mmol) in 40 ml of ether was treated with distilled 2-mercaptoethanol (1.97 ml, 2.09 g, 26.8 mmol) and boron trifluoride etherate (3.0 ml, 3.46 g, 24.4 mmol) and then stirred at room temperature under argon for 1.5 hr. The reaction mixture was diluted with ether, extracted with half-saturated $NaHCO_3$ solution and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 5.087 g (94% yield) of **36** (ca. 1:1 mixture of hemithioketal epimers) as a colorless oil used in the next step without purification: ^1H NMR ($CDCl_3$) δ 1.4–2.2 (m, 13 H), 3.00 and 3.04 (each a t, 2 H total, J = 6 Hz), 4.14 (t, 2 H, J = 6 Hz), 4.8–5.2 (m, 2 H), and 5.90 and 6.17 (each a d of d, 1 H total, J = 10, 18 Hz); ir (tf) λ_{max} 3.24, 3.40, 3.49, and 6.10 μ.

Hydroboration of 36. Disiamylborane was prepared by adding 2-methyl-2-butene (4.95 ml, 3.28 g, 46.8 mmol) to 1.17 *M* borane solution (in THF, 19 ml, 22.3 mmol) in 20 ml of THF at 0° under argon and stirring the resulting solution for 1 hr at 0° and 1 hr at room temperature. A solution of the hemithioketals **36** (2.50 g, 11.1 mmol) in 10 ml of THF was added, and the resulting solution was stirred for 14 hr at room temperature. The reaction mixture was cooled to 0° and treated dropwise with 15% NaOH solution (13.2 ml, 55.5 mmol) and 30% H_2O_2 solution (9.6 ml, 111 mmol). The mixture was then stirred for 1.5 hr at room temperature, poured into 10% Na_2SO_3–saturated NaCl solution, and extracted with ether. The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated with the aid of toluene to afford 2.69 g of a colorless oil. Evaporative distillation (oven temperature 180°, 0.25 mm) gave 2.736 g (100% yield) of the alcohols **40** (mixture of hemithioketal epimers) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.4–2.0 (m, 16 H), 3.03 (broad t, 2 H, J = 6 Hz), 3.72 (broad t, 2 H, J = 6 Hz), and 4.13 (broad t, 2 H, J = 6 Hz); ir (tf) λ_{max} 3.00, 3.40, and 3.49 μ.

Oxidation of the Alcohol 40. To a mechanically stirred mixture of dipyridinechromium(VI) oxide[35] (4.14 g, 16 mmol) and purified, anhydrous Celite[36] (8.28 g) in 70 ml of CH_2Cl_2 at −20° under argon was added a solution of the alcohols **40** (0.373 g, 1.54 mmol) in 5 ml of CH_2Cl_2. The mixture was stirred for 1 hr at −20°, treated with powdered $NaHSO_4 \cdot H_2O$ (8.28 g, 60 mmol), and stirred for 0.5 hr at −20°. The resulting mixture was filtered through $MgSO_4$ with the aid of ether and CH_2Cl_2 and concentrated to afford 0.311 g (84% yield) of aldehyde **41** used in the next step without purification: ^1H NMR ($CDCl_3$) δ 1.5–2.2 (m, 15 H), 3.0 (m, 2 H), 4.10 (broad t, 2 H, J = 6 Hz), and 9.80 (m, 1 H); ir (tf) λ_{max} 3.40, 3.46, 3.65, and 5.80 μ.

Preparation of the Keto Aldehyde 21. A solution of hemithioketals **41** (0.115 g, 0.48 mmol) in 1.5 ml of H_2O and 6 ml of CH_3CN under argon was treated with $HgCl_2$ (0.287 g, 1.05 mmol) and $CaCO_3$ (0.120 g, 1.2 mmol) and stirred at room temperature for 10 min. The mixture was filtered through Celite with the aid of ether, and the filtrate was extracted with ice-cooled NH_4OAc solution (pH 7), ice–water, and saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford 0.067 g (80% yield) of **21** as a colorless oil used in the next step without purification: ^1H NMR ($CDCl_3$) δ 1.7–2.7 (m, 15 H) and 10.0 (broad t, 1 H); ir (tf) λ_{max} 3.37, 3.41, 3.48, 3.65, and 5.82 μ.

Preparation of the Methyl Ketone 42. To a solution of the vinyl hemithioketals **36** (1.95 g, 8.7 mmol) in 50 ml of THF at room temperature under argon was added 0.5 *M* 9-borabicyclo[3.3.1]nonane (19.7 ml, 9.85 mmol). The resulting solution was stirred for 1.5 hr at room temperature and then cooled to −40°. To a solution of acetaldehydediphenylthioacetal[37] (2.64 g, 10.7 mmol) in 20 ml of THF at −40° under argon was added 2.13 *M* *n*-butyllithium solution (5.0 ml, 11.6 mmol). The yellow solution produced was added dropwise (using a cold finger cooled addition funnel at −50°) over 20 min to the borane solution. The reaction mixture was allowed to warm to 0° over 0.75 hr and was then treated with 15% NaOH solution (14 ml, 59 mmol) and 30% H_2O_2 solution (7.2 ml, 83.5 mmol) and stirred for 1 hr at 60° and 1 hr at room temperature. Ether, saturated NaCl solution, and 10% Na_2SO_3 solution were added, and the aqueous phase was extracted with ether. The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 4.984 g of a yellow oil. Column chromatography on silica gel (elution with 5–15% THF–

hexanes) gave 1.53 g (68% yield) of **42** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.5–2.6 (m, 17 H), 2.17 (s, 3 H), 3.04 (two t, total 2 H, J = 6 Hz), and 4.14 (broad t, 2 H); ir (tf) λ_{max} 3.40, 3.49, and 5.83 μ.

Preparation of Diketone 27. A mixture of the hemithioketals **42** (1.53 g, 5.7 mmol), $HgCl_2$ (3.39 g, 12.5 mmol), and $CaCO_3$ (1.43 g, 14.3 mmol) in 52 ml of CH_3CN and 13 ml of distilled water was stirred at room temperature under argon for 10 min. The reaction mixture was filtered through Celite with the aid of ether, extracted with ice-cooled NH_4OAc solution, ice–water, and saturated NaCl solution, and then dried over $MgSO_4$, filtered, and concentrated to afford 1.17 g (99% yield) of **27** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.4–2.5 (m, 17 H) and 2.12 (s, 3 H); ir (tf) λ_{max} 3.40, 3.49, and 5.84 μ; an exact mass determination gave m/e 208.1459 (calcd for $C_{13}H_{20}O_2$, 208.1463).

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Registry No.—**4,** 100-52-7; **6,** 124-13-0; **8,** 108-94-1; **10,** 120-92-3; **14,** 1124-96-5; **15,** 57132-07-7; **16,** 1123-26-8; **17,** 2890-62-2; **20,** 42393-59-9; **21,** 35730-87-1; *cis*-**22,** 35730-88-2; *trans*-**22,** 35730-89-3; **25,** 57132-08-8; **26a,** 57132-09-9; **27,** 57132-10-2; *cis*-**28,** 57132-11-3; **29,** 2568-20-9; **30** isomer a, 57132-12-4; **30** isomer b, 57132-13-5; **30** isomer c, 57527-69-2; **30** isomer d, 57527-70-5; **31,** 1072-21-5; **33,** 110-13-4; **35,** 1489-28-7; **36** isomer a, 57132-14-6; **36** isomer b, 57173-49-6; **37,** 12312-06-0; **39,** 35730-86-0; **40** isomer a, 57132-15-7; **40** isomer b, 57173-50-9; **41** isomer a, 57132-16-8; **41** isomer b, 57173-51-0; **42** isomer a, 57132-17-9; **42** isomer b, 57173-52-1; acetone, 67-64-1; cycloheptanone, 502-42-1; acetaldehyde, 75-07-0; methanesulfonyl chloride, 124-63-0; 2-mercaptoethanol, 60-24-2; diisoamylborane, 6838-83-1; mercuric chloride, 7487-94-7; magnesium, 7439-95-4; cyclopentadienyltitanium trichloride, 1270-98-0; lithium aluminum hydride, 16853-85-3; boron trifluoride etherate, 109-63-7; titanium tetrachloride, 7550-45-0.

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(37) Prepared in 94% yield by treatment of acetaldehyde with 5 equiv of thiophenol and 1 equiv of boron trifluoride etherate (ether, 0°, 9 hr).

A Palladium-Catalyzed Arylation of Allylic Alcohols with Aryl Halides

John B. Melpolder and Richard F. Heck*

Department of Chemistry, University of Delaware, Newark, Delaware 19711

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A convenient reaction for preparing 3-arylaldehydes and ketones from allylic alcohols and aryl halides is described. In some instances 3-arylallylic alcohols may also be obtained in varying yields depending upon the aryl halide used and the catalyst employed. The effects of substituents in both reactants on the reaction course are discussed. Homoallylic alcohols react similarly, giving substantial amounts of aryl ketones or aldehydes.

The previously reported allylic alcohol arylation with organopalladium compounds[1] was shown to be useful for the synthesis of 3-arylaldehydes and ketones when primary or secondary allylic alcohols, respectively, were allowed to react. The reaction required a molar amount of an organomercury compound to prepare, in situ, the organopalladium reagent with either an equivalent amount of a palladium(II) salt or a catalytic amount of this salt plus an equivalent amount of cupric chloride to regenerate the palladium after each reaction cycle. The addition of a hindered tertiary amine to the reaction mixtures also proved beneficial. Even under the most favorable conditions found, however, yields were never over 53% and were often considerably lower.