canted from the precipitated solids. After drying, the solvent was removed at reduced pressure to give a viscous oil which on distillation afforded 4.70 g (81%) of enone, bp 85–90 °C (0.45 mm): NMR δ 0.08 (s, 6 H, $(CH_3)_2Si$), 0.91 (s, 9 H, $(CH_3)_3C$), 1–10 (t, 3 H, J = 7 Hz, CH_3CH_2), 2.15 (m, 2 H, CH_3CH_2), 4.30 (m, 2 H, $O—CH_2CH=$), 5.92 (m, 1 H, $CH_2CH=$), 6.70 (d of t, 1 H, J = 15 Hz, J = 3 Hz, $CH=CHCH_2O$); IR 1675. Anal. Calcd for $C_{12}H_{24}O_2Si$: C, 63.12; H, 10.59. Found: C, 62.88; H, 10.65.

5-(Hydroxymethyl)-2,4,4-trimethyl-2-cyclohexen-1-one (5). The reaction of 2.28 g of 6-[(*tert*-butyldimethylsilyl)oxy]-4-hexen-3-one with 1.44 g of 1-[(trimethylsilyl)oxy]-2-methylpropene was carried out by using 1.89 g of $TiCl_4$ according to the general procedure described above to give 2.65 g (88%) of crude keto aldehyde 6. In one run, a small portion of the crude product was purified by chromatography in silica gel: NMR δ 0.09 (s, 6 H, $(CH_3)_2Si$), 0.86 (s, 9 H, $(CH_3)_3C$), 1.0–2, 1.04 (s, 3 H each, $(CH_3)_2C$), 9.5 (s, 1 H, HC=O); IR 1710.

Cyclization of 2.65 g of crude keto aldehyde using the general procedure outlined above afforded 2.33 g of a mixture of enone 5 and its *tert*-butyldimethylsilyl ether (7). The crude mixture was stirred with 7.2 mL of 1 M n-Bu_4NF for 40 min and quenched with water, and the product was isolated using ether. Distillation (bp 97–105 °C, 0.35 mm) gave 1.18 g (70%) of enone 5 as a viscous oil: mass spectrum, m/e (relative intensity) 168 (50), 137 (100), 123 (49), 111 (54), 95 (39), 55 (22); NMR δ 1.02, 1.20, 1.73 (s, 3 H each, CH_3), 2.50 (m, 2 H, CH_2CO), 3.80 (br m, CH_2O), 6.33 (s, 1 H HC=); IR 3660, 1680.[34]

Chromatography of the crude reaction mixture on silica gel resulted in considerable loss of material but indicated an approximately 1:2 ratio of enone 5 and t-$BuMe_4Si$ ether (7), bp 78–82 °C (0.25 mm): NMR δ 0.09 (s, 6 H, $(CH_3)_2$ Si), 0.86 (s, 9 H, $(CH_3)_3C$), 1.05, 1.15 (s, 3 H each $(CH_3)_2C$) 1.60 (s, 3 H, $CH_3C=$), 2.25 (m, 2 H, CH_2CO), 3.60 (t, 2 H, J = 6 Hz, CH_2OSi), 6.30 (m, 1 H, HC=); IR 1680, 1085. Anal. Calcd for $C_{16}H_{30}O_2Si$: C, 68.03; H, 10.70. Found: C, 68.08; H, 10.73.

Acknowledgment. We authors thank John Coates of the Department of Environmental Systems Engineering, Clemson University, for carrying out the capillary GLC analyses and R. Frank Pittman for carrying out the mass spectral determinations.

(34) The analytical data for this compound were consistently and irreproducibly low in carbon although the material was apparently homogenous. Various conversion products (aldehyde, mesylate, and iodide) all had spectral properties consistent with the assigned structures. Also, reaction with *tert*-butyldimethylchlorosilane regenerated the ether which did give acceptable analytical data.

Stereochemical Control of Reductions. 8.[1] Exploration of the Inner Limits of the Haptophilic Effect with 2-Exo-Substituted 7-Methylenenorbornanes[2]

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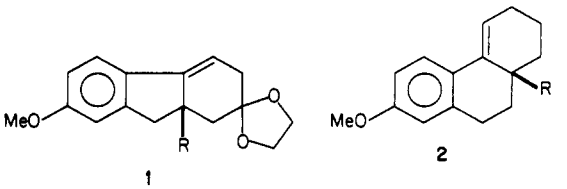
Catalytic hydrogenations over a Pd/C catalyst have been conducted on a series of 2-*endo*-methyl-7-methylenenorbornanes bearing a variable functional group in the 2-exo position. In this system (3), R groups previously found in other systems to have a strong haptophilic attraction to the catalyst surface produced mixtures of reduction products containing 18–63% anti epimer resulting from catalyst adsorption assisted by R ($CH_2OH \sim CHO < CH_2NH_2$). Six carboxyl derivatives used as R groups and previously found to have low to moderate haptophilicities gave pure syn epimers in the hydrogenation of 3. These results are interpretable in terms of a group's ability to bind to the catalyst surface by electron donation vis-à-vis the steric interference to such adsorption generated by the group's bulk. For R = CH_2NH_2 this interpretation is consistent with the known behavior of amines as mild catalyst poisons. However, it is concluded that the geometry of system 3 decreases the effective catalyst-binding properties of all R groups by placing R where it partially blocks one face of the alkene. Attempted reductions of 3, R = CH_2OH, with $LiAlH_4$, with B_2H_6, and with a chelative iridium catalyst are described. The terms proximofacial and distofacial are defined to specify processes occurring at molecular faces respectively nearest to and remote from a reference group.

The stereochemical outcome of a catalytic hydrogenation can be influenced not only by interference with catalyst adsorption arising from bulky groups within the substrate molecule but also, in an opposite sense, by the haptophilic effect[3] of certain substrate groups. This effect, although well documented,[4] is not well understood but is thought to operate by relatively prolonged adsorption of such a group at the catalyst surface, tending to ensure addition of hydrogen to that group's own face of the molecule. We have previously examined this effect in two model systems, 1 and 2, using Pd and Pt[4b,5] catalysts.



1 2

In expanding our original heterogeneous study on the tetrahydrofluorene system 1[3,4a,5] to the related hexa-

(1) Part 7: Thompson, H. W.; Shah, N. V. *J. Org. Chem.* **1983**, *48*, 1325.

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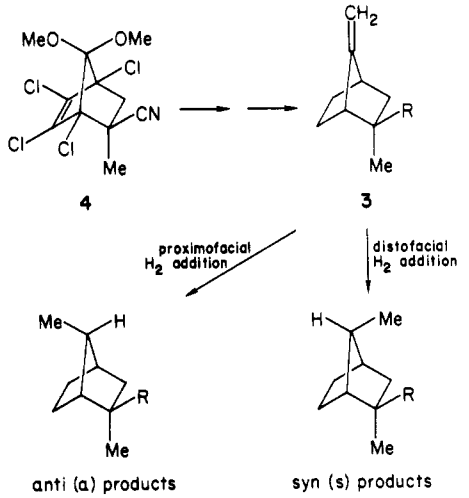
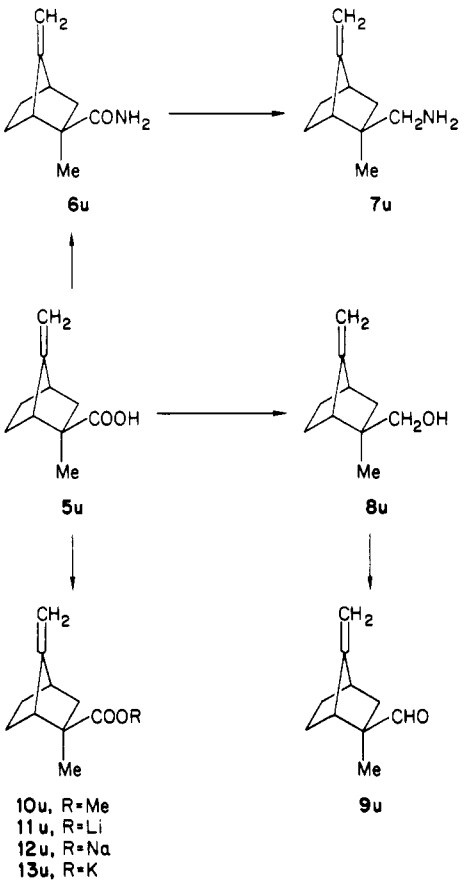
hydrophenanthrene 2,[4b,6] we were able to examine the haptophilic behavior of several groups of prospective interest originally unavailable to us (e.g., CH_2NH_2 and CH_2CH_3).[7] However, we wished also to study a molecule with fundamentally different geometry to assess the relevance to other systems of the group haptophilicities we had determined. In the present report we examine both the heterogeneous and homogeneous catalytic hydrogenation of 3.



In addition to possessing attributes we have previously discussed as desirable for testing haptophilic effects,[3] system 3 is conformationally and spectroscopically simple and has a double bond which cannot migrate under catalytic conditions, a worrisome general possibility with the Pd catalyst we intended to use.[8] However, 3 also differs from our previously studied systems in having a di- rather than a trisubstituted alkene and in presenting the groups of concern in a less planar format. Although the alkene and the functional group of haptophilic potential are separated in 3 by an additional intervening carbon atom compared to systems 1 and 2, the rigid three-dimensional arrangement of 3 appears from models to be able to hold any atom beyond the first in the R group approximately as close to the alkene as in 1 or 2. Since R's first atom is farther from the alkene in 3 but more nearly opposite the alkene's face, it was not clear what net effect upon group haptophilicities was to be expected when 3 was reduced.

It seems worthwhile here to call attention to some potentially confusing points of nomenclature regarding these reductions. The increasing tendency is to use the terms cis and trans only for configurational assignments, with syn and anti referring to the stereochemistry of processes. However in norbornanes syn and anti are still used, even by *Chemical Abstracts*, for the configurations of substituents at C7. Moreover, in system 3 the stereochemistry of the two added hydrogens relative to each other is not determinable or of interest, although the usual process is syn. What is at issue is the stereochemistry of the substrate–catalyst engagement relative to the influencing group R, a stereochemical distinction for which no discrete terminology exists. Until now the kind of description most often used for haptophilic or chelative effects has referred to adsorption (or addition, or reaction) "cis (or syn) with respect to" or "at the same face as" the influencing group.

Scheme I



In systems 1 and 2 adsorption which was cis or syn in this sense led, with seeming logic, to cis products, but the analogous process in 3 leads to products designated as anti.

Therefore we define a process occurring at the same molecular face as a group of potential influence as proximofacial, and one occurring at the remote face as distofacial . These terms are entirely independent of cis/trans and syn/anti and express no sense of transfer or conveyance from one site to another, as do suprafacial and antarafacial. They merely specify at which face reaction occurs and neither require nor imply the operation of chelative effects (e.g., utilization of proximofacial/distofacial ratios for B_2H_6 addition to pinenes); however, their proper use does require that the reference group be specified. In 3, the (presumably syn) addition of hydrogen by the proximofacial route (relative to R) leads to anti products; the (presumably syn) addition of hydrogen by the distofacial route gives syn products.

Results and Discussion

Our entry point into this system was the compound 4, whose synthesis and conversion into **5u** and **10u** we have previously described.[9] The transformation of **5u** into the other desired compounds in this unsaturated (u) series was uncomplicated and proceeded as outlined in Scheme I.

For comparison with the anticipated hydrogenation products of this series, we wished to have samples of both syn (s) and anti (a) compounds bearing these functional groups and having verified stereochemistry. In practice, the acquisition of stereochemically pure samples of all the desired compounds in what was shown to be the syn series presented few difficulties. Catalytic hydrogenation of any

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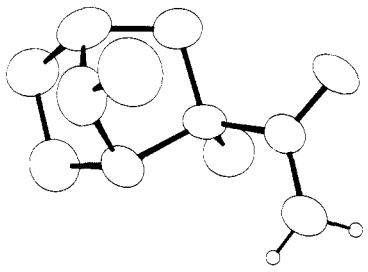

Figure 1. X-ray crystallographic structure of **6s**.

Table I. Percent Proximofacial H_2 Addition Observed in Heterogeneous Catalytic Hydrogenation of Systems 1–3

	Pt[a]	Pd/C		
R	1	1[b]	2[c]	3[d]
CH_2NH_2			100	63
CHO		93	95	18
CH_2OH	98	95	9	19
COOK	41	(28)[a]	75	0
COONa	39	55 (29)[a]	70	0
COOLi	45	23	60	0
COOH	25	18	26	0
COOMe	20	15	9	0
$CONH_2$		10		0

[a] Reference 5; solvent, 2-methoxyethanol. [b] Reference 3; solvent, 2-methoxyethanol. [c] Reference 6; solvent, ethanol. [d] This work; solvent, ethanol; values determined by a combination of GC and ^1H NMR on unfractionated products and considered accurate to ±3% for CH_2NH_2 and CHO and to ±4% for CH_2OH, tolerances which incorporate factors for both measurement precision and reaction variability.

of the unsaturated compounds bearing carboxyl derivatives gave stereochemically pure product and routes similar to those outlined in Scheme I served to interconvert all the compounds in this series. Because several of these carboxyl derivatives had been observed in systems 1 and 2 to have low haptophilicities[3,4b,6] and give predominantly distofacial reduction, we believed the stereochemistry of this reduced series to be syn, an assignment supported by the extraordinary stability found for the imidazolide intermediate prepared in converting **5s** to **6s**, compared to the corresponding imidazolide of the u series.

However, obtaining pure samples of contrasting stereochemistry proved more difficult, since no method of reduction we applied ever produced even a 2:1 preponderance of the putative anti epimer. Moreover, in the best case (**7**), the functional group was one which, even assuming isolation of the major component, would have been quite difficult to retroconvert to the other desired groups. For the more readily convertible groups (CHO, CH_2OH), the most favorable mixture we ever obtained, in terms of isolating anti compound, held only ca. 20% of that isomer. Because of the potential problems involved in separation, purification, interconversion, and proof of relative stereochemistry on the small quantities involved, we chose rather to rely for this proof on a single-crystal X-ray analysis[10] of compound **6s** (Figure 1), which was easily obtained in pure form, and the demonstrated interconvertibility of the compounds of the s series. This, coupled with NMR and GC analysis of the hydrogenation products and the interconvertibility of anti epimers within mixtures, sufficed to identify unequovically both the syn and anti products.

The stereochemical results of all our hydrogenations are summarized in Table I, where the proximofacial/distofacial

(10) Analysis carried out by Prof. R. A. Lalancette and J. A. Boyko of this department.

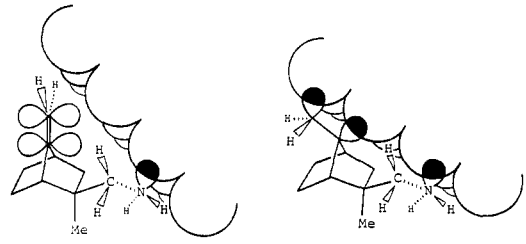

Figure 2.

product ratios obtained with 3 are contrasted with those for the same functional groups in systems 1 and 2. As may be seen, only functional groups which were strongly haptophilic in one of the previously tested systems were at all effective haptophilically in 3. The order of haptophilicity for those groups here is $CH_2OH \sim CHO < CH_2NH_2$, comparable in part to system 1, where $CH_2OH \sim CHO$, and in part to 2, in which $CHO < CH_2NH_2$. However in the present system, the preference for proximofacial adsorption with these functional groups is generally much lower and their steric bulk more important than with 1 or 2.

What is most immediately striking is that, while haptophilic effects clearly do operate, most of the functional groups which have low or even moderate haptophilicities in 1 and 2 have no haptophilic effect at all here. In systems 1 and 2 these carboxyl derivatives gave proximofacial/distofacial product ratios ranging from 9:91 to 75:25, but in the present system no proximofacial adsorption products were observed.

Clearly when a group R in one of these systems leads to a product which is entirely either one epimer or the other, that group is effectively "off-scale", and one has incomplete information about its place in the sequence. In series 2 the aminomethyl group (100% proximofacial) was off the high end of our scale, but each of the other dozen-plus groups examined fell within the 0–100 range,[4b,6] which is therefore rich in information on relative haptophilicities. In effect, with system 3, the entire sequence is found to have undergone a sort of register shift, which brings CH_2NH_2 on-scale but pushes all the carboxyl derivatives off-scale at the low end, giving us information about the former at the expense of the latter.

When a given group's tendency either to induce or to inhibit proximofacial adsorption under given experimental conditions is found to change from one system to another, this must be due to the molecular context. Because the "register shift" we have noted increases the observed amount of distofacial adsorption in 3 systematically for all R groups, we conclude that some aspect of the geometry of 3 magnifies the steric effect of *any* substituent at C2. In 1 and 2 the point of attachment of the group R is a carbon atom directly connected to the alkene and therefore in its plane; hence, R projects outward from that plane and away from the near end of the alkene at a 109.5° angle. However in 3 the point of attachment of R is the homoallylic C2 carbon already about 1.2 Å removed from the alkene plane, and R projects both outward from that plane and upward, with a vector toward the alkene, so that R lies more nearly opposite the face of the alkene than is the case for 1 or 2. Clearly one might examine the "outer" extremes of the haptophilic effect with a system in which groups of interest are either so remote from the alkene or so obstructed that their haptophilicity is greatly attenuated. The system 3 appears to be near the "inner" limit of behavior, where the groups of interest would be so close to the alkene as to block its proximal face completely.

Measurements from molecular models suggest that the

rigid three-dimensional norbornane skeleton attached to one end of our alkene increases the distance of nearest approach to the catalyst so as to make adsorption at that end of the alkene inherently more difficult than in systems 1 and 2. Moreover, when R is changed from H to CH_2 or C=O in these systems, the effect is greatest in 3, in terms of distancing the alkene from the catalyst surface. In fact, when an exo substituent is present at C2, attachment of a trigonal C7 atom to the catalyst surface (i.e., π-complexation) appears to be so difficult that such an adsorption seems much more favorable as a σ-process (Figure 2).

The precise role of π-adsorbed species in heterogeneous catalytic hydrogenation is unclear, but mechanisms have often depicted progressions from π- to σ-bonding involving rehybridization at carbon. Although we have no evidence concerning such a sequence of events in 3, a reasonable role for haptophilic groups would be proximofacial facilitation of this process, which in 3 might otherwise be quite difficult because of steric hindrance. Specifically, the contribution of such a group may be to hold the molecule at the catalytic surface until a site of appropriate geometry is found and sufficient activation energy for the necessary rehybridization is acquired. Of the functionalities we have studied, amino seems best suited to this role by virtue of its willingness to form bonds by electron-pair donation. The principal reason we wished to examine the case R = CH_2NH_2 was that amines are known in the context of heterogeneous hydrogenation to be catalyst poisons,[11] albeit mild ones, which is to say, poisons whose association constants are not overwhelmingly large.[4e] Such relatively long term but reversible surface adsorption accords perfectly with the haptophilic behavior we have observed for CH_2NH_2, and our presumption is that other haptophiles may operate by the same mechanism.

Alternative Reductions of Alcohol 8u. In our attempts to produce pure materials of the anti series, we have carried out several reactions of **8u**, which, in spite of their failure to give major amounts of **8a**, provide insight into the processes involved and into the geometry of 3. Our first such attempt was to improve the proportion of **8a** in our heterogeneous reduction system by changing the solvent,[4b] but we found that pentane gave mixtures only slightly enriched in **8a** compared to those we had already obtained using ethanol.

Several systems are known in which $LiAlH_4$ may be added to alkenes with the internal assistance of hydroxyl[12] or other groups.[13] However, the attempted reduction of **8u** by $LiAlH_4$ at temperatures up to 162 °C led in every instance to recovery or detection only of starting material. During any proximofacial alkene reduction process in 3, as the bonding at C7 changes from trigonal to tetrahedral, the extreme inflexibility of 3 dictates that the entire range of movement in the anti direction must be accommodated by the carbon attached to C7, while C7 itself remains fixed as part of the rigid norbornane skeleton. In the case of $LiAlH_4$ this requires a high degree of mobility for the Al and its associated hydride, evidently more than is allowed by the oxymethylene tether at C2. Our previous results[12] with internal delivery of $LiAlH_4$ by means of a hydroxyl hinge suggested that the success of this process is extremely sensitive to the specific geometry of the system involved, and the present results with 3 bear this out.

Although several reports exist of the intramolecular delivery of hydride to polar unsaturated functions by either tetravalent or trivalent boron species,[14] we do not know of any instance of intramolecular alkoxyboron hydride delivery to an unactivated alkene.[15] Presumably geometrical constraints similar to those cited above would apply to the addition of BH across the double bond of 3. When we attempted to carry out such an internal BH delivery by using 1 molar equiv of BH_3·THF, initial evolution of gas was observed; however, NMR showed that the vinyl absorption of **8u** was undiminished even after reaction temperatures of 80 °C. Only after another molar equivalent of BH_3·THF had been added at 25 °C did the vinyl absorption disappear.

Our original extension of the principal of haptophilic control of reduction stereochemistry to homogeneous catalysis[16] has recently been significantly improved upon with the iridium catalyst introduced by Crabtree.[17] However our reduction of **8u** with this iridium catalyst led to a mixture containing a ca. 10:90 ratio of saturated alcohols, with only the minor component as the product of proximofacial hydrogen addition. Reduction by simple alkene chelation with this catalyst is evidently not an extremely fast process. Stork, Crabtree, and Evans[17] have provided examples in which hydroxyl-assisted proximofacial reduction proceeds at rates up to 1000 times faster than the distofacial process. Since the latter is faster in **8u** by ca. 10:1, the rate of proximofacial reduction here is evidently so low, compared to typical hydroxyl-assisted proximofacial reductions with this catalyst, that we cannot even be confident that this case involves hydroxyl assistance at all. The small amount of proximofacial reduction may be occurring in spite of the presence of hydroxyl. In either case it is clear that **8u** and this catalyst are geometrically mismatched and that the hydroxyl function is, in some sense, too close to the alkene—failure, again, at the inner limits of the method.

With the results from system 3 we have gained several important insights. (1) Because we have confirmed the high haptophilicity previously found for CH_2NH_2, we have increased our confidence in our depiction of haptophilic effects as part of the spectrum of catalyst interactions which includes both chemisorption and poisoning.[3] (2) Because CH_2NH_2 is on-scale with 3, we have obtained an admittedly limited but improved quantitative measure of the superiority of this group as a haptophile. (3) We have obtained some glimpses into the practical consequences of the geometry of 2-exo-substituted 7-methylenenorbornanes and into the geometrical inner limits of the haptophilic effect.

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Experimental Section[18]

2-*endo*-Methyl-7-methylenebicyclo[2.2.1]heptane-2-*exo*-carboxamide (6u). A solution of 500 mg (3.0 mmol) of **5u**[9] in 7 mL of dry DMF was stirred during addition of 740 mg (4.56 mmol) of 1,1'-carbonyldiimidazole and subsequently for 30 min at 25 °C and 30 min at 40 °C (until gas evolution ceased). This warm solution was treated with 1 mL of concentrated NH_4OH in 2 mL of DMF and heated for 30 min with an oil bath at 80 °C. After acidification, the usual extraction and isolation procedure yielded crude solid recrystallized from *i*-Pr_2O to give 439 mg (88%) of **6u** as white crystals: mp 102–103 °C; MS, *m/e* (relative intensity) 166.1 (0.93), 165.1 (M^+, 7.7), 121.1 (15.0), 111.1 (13.4), 110.0 (100); IR 3480, 3380, 3200, 3080, 1650, 1600, 890 cm^{-1}; ^1H NMR δ 6.01 (2 H, br s, exchangeable with D_2O), 4.68 (2 H, s), 2.40 (2 H, complex), 2.22 (1 H, m), 1.98–1.22 (4 H, complex), 1.30 (3 H, s), 1.11 (1 H, d, J = 12 Hz, H_{3N}).

Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.99; H, 9.13; N, 8.38.

2-*exo*-(Imidazolylcarbonyl)-2-*endo*-methyl-7-methylenebicyclo[2.2.1]heptane was isolated when a mixture similar to that described above was treated with concentrated NH_4OH in DMF for 1 h at only 25 °C. Aqueous dilution, extraction with CH_2Cl_2, chromatography (SiO_2, 2:3 EtOAc/hexane), and concentration in vacuo gave 82% of yellowish liquid: MS, *m/e* (relative intensity) 217.1 (2.0), 216.1 (M^+, 10.0), 149.1 (6.1), 121.0 (100), 105.0 (12.1), 93.0 (61.3); IR 3115, 3080, 1720, 1680, 890 cm^{-1}; ^1H NMR δ 8.20 (1 H, s), 7.44 (1 H, s), 7.05 (1 H, s), 4.63 (2 H, dd), 2.98 (1 H, br s) 2.5 (2 H, complex), 2.0–1.2 (5 H, complex), 1.54 (3 H, s).

2-*endo*-Methyl-2-*exo*-(aminomethyl)-7-methylenebicyclo[2.2.1]heptane (7u). Compound **6u** (200 mg, 1.2 mmol) was treated with 605 mg (15.9 mmol) of $LiAlH_4$ in 9 mL of dry Et_2O in a manner similar to that described below for the preparation of **8u**. The usual workup afforded 180 mg (98%) of **7u** as a yellowish oil, which was ninhydrin-positive on TLC and was distilled at a bath temperature of 65–70 °C (131 mm); IR 3370, 3300, 1675, 1585, 880, no absorption at 1650 cm^{-1}; MS, *m/e* (relative intensity) 152.1 (1.0), 151.1 (M^+, 3.30), 150.1 (6.7), 136.1 (18.7), 122.1 (15.5), 96.1 (100); ^1H NMR δ 4.59 (2 H, s), 2.52 (1 H, d, J = 12 Hz), 2.33 (1 H, d, J = 12), 2.32–1.05 (9 H, complex), 1.01 (3 H, s), 0.89 (1 H, d, J = 12, H_{3N}).

Anal. Calcd for $C_{17}H_{19}N_3O_5$ (3,5-dinitrobenzamide derivative): C, 59.12; H, 5.55; N, 12.17. Found: C, 59.10; H, 5.49; N, 12.29.

2-*endo*-Methyl-2-*exo*-(hydroxymethyl)-7-methylenebicyclo[2.2.1]heptane (8u). A solution of 783 mg (4.7 mmol) of compound **5u**[9] in 7 mL of dry Et_2O was added dropwise to an ice-cooled mixture of 1.0 g (26.3 mmol) of $LiAlH_4$ in 15 mL of dry Et_2O. After the mixture had been stirred at room temperature for 1 h, 1 mL of water was added dropwise with cooling, followed by 3 mL of 15% aqueous NaOH and another 1 mL of water. Filtration led to 682 mg (95%) of **8u** as a white solid, recrystallized from petroleum ether, to afford an analytically pure sample: mp 51–52 °C; MS, *m/e* (relative intensity) 153.1 (0.26), 152.1 (M^+, 1.3), 121.1 (24.8), 119.1 (28.9), 105.1 (19.6), 79.0 (100); IR (CH_2Cl_2) 3620, 1675, 880 cm^{-1}; ^1H NMR δ 4.64 (2 H, s), 3.39 (1 H, d, J = 10.4 Hz), 3.23 (1 H, d, J = 10.4), 2.32 (1 H, t, J = 4), 2.11 (1 H, d, J = 3.5), 1.83–1.29 (6 H, complex), 1.08 (3 H, s), 0.95 (1 H, d, J = 12, H_{3N}).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.79; H, 10.43.

2-*endo*-Methyl-7-methylenebicyclo[2.2.1]heptane-2-*exo*-carboxaldehyde (9u). A mixture of 682 mg (4.48 mmol) of compound **8u** and 2.25 g (6.0 mmol) of pyridinium dichromate in 15 mL of dry CH_2Cl_2 was stirred at 25 °C under N_2 for 16 h. The mixture was diluted with Et_2O and filtered through Celite. The residue was concentrated and filtered through a short SiO_2 column and eluted with petroleum ether, to give, upon reconcentration, 452 mg (67%) of **9u** as a colorless liquid: MS, *m/e* (relative intensity) 151.2 (1.1), 150.1 (M^+, 7.8), 135.1 (8.7), 121.1 (16.9), 103.0 (11.2), 43.0 (100); IR 3075, 2805, 2705, 1725, 1680, 890 cm^{-1}; ^1H NMR δ 9.47 (1 H, s), 4.61 (2 H, d), 2.37 (2 H, m), 2.12–1.20 (5 H, complex), 1.13 (3 H, s), 0.96 (1 H, d, J = 12 Hz, H_{3N}). This material was air-sensitive and was best preserved from decomposition by refrigerating under N_2.

Conversion of 5u to Its Lithium Salt (11u). A solution of 253 mg (1.52 mmol) of **5u**[9] in 3 mL of dry PhH was treated with LiOEt (0.4 M in absolute EtOH; 3.7 mL, 1.48 mmol) and stirred at 25 °C for 30 min. Solvent was removed in vacuo to give white solid, to which 50 mL of petroleum ether was added. After 15 min of stirring, filtration yielded 242 mg (89%) of **11u**: IR 3080, 1670, 1570, 1435, 880, no absorption at 1700 cm^{-1}.

Conversion of 5u to Its Sodium Salt (12u). A solution of 213.5 mg (1.28 mmol) of **5u**[9] in 3 mL of dry PhH was treated with NaOH (0.4 M in absolute EtOH; 3.15 mL, 1.26 mmol) and stirred at 25 °C for 45 min. Solvent was removed in vacuo, and moisture was azeotroped from the residual oil twice with dry PhH. The resulting white solid was washed with petroleum ether and filtered to give 222.5 mg (94%) of **12u**: IR 3080, 1675, 1550, 1435, 880, no absorption at 1700 cm^{-1}.

Conversion of 5u to Its Potassium Salt (13u). A solution of 266 mg (1.60 mmol) of **5u**[9] in 3 mL of dry PhH was treated with KOH (0.4 M in absolute EtOH; 3.9 mL, 1.56 mmol) and stirred at 25 °C for 45 min. Solvent was removed in vacuo and moisture was azeotroped from the residual oil twice with dry PhH to give a white solid which was washed with petroleum ether. Filtration gave 301 mg (94%) of **13u**: IR 3080, 1657, 1560, 1435, 880, no absorption at 1700 cm^{-1}.

2-*endo*-7-*syn*-Dimethylbicyclo[2.2.1]heptane-2-*exo*-carboxylic Acid (5s). Catalytic hydrogenation of **5u**[9] under the standard conditions subsequently described provided **5s** directly upon concentration of the filtered reaction mixture: mp 127–128 °C; IR 3300–2500, 1690 cm^{-1}; MS, *m/e* (relative intensity) 169.1 (0.32), 168.1 (M^+, 0.52), 123.1 (17.8), 82.0 (100); ^1H NMR δ 12.05 (1 H, s, $w_{1/2}$ = 6 Hz, exchangeable with D_2O), 2.65–2.30 (2 H, complex), 1.80–1.35 (6 H, complex), 1.28 (3 H, s), 0.98 (1 H, d, J = 12), 0.85 (3 H, d, J = 7).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.25; H, 9.51.

2-*endo*-7-*syn*-Dimethylbicyclo[2.2.1]heptane-2-*exo*-carboxamide (6s). A solution of 346 mg (2.05 mmol) of **5s** in 6 mL of dry DMF was stirred during addition of 434 mg (2.68 mmol) of 1,1'-carbonyldiimidazole and subsequently for 1 h at 25 °C and 2 h at 35 °C. After this warm solution was treated with 0.5 mL of concentrated NH_4OH in 2 mL of DMF and heated under N_2 at 78 °C for 4 h, TLC of an aliquot showed the presence of imidazolide but negligible formation of amide. Addition of another 0.5 mL of concentrated NH_4OH and 8 h of heating under N_2 at 120 °C, followed by a further 1.0 mL of concentrated NH_4OH and 10 more h of heating at 120 °C, appeared (TLC) to have provided appreciable amide. Aqueous dilution and extraction gave an organic phase washed successively with 2 N HCl, dilute Na_2CO_3, water, and brine, providing finally 115 mg of solids. Isolation by preparative TLC (3:2 EtOAc/hexane) gave 83.5 mg (24%) of **6s** as a white solid, mp 153–154 °C, identical by ^1H NMR and mixed mp with material produced directly by hydrogenation of **6u**: IR 3400, 3200, 1630 cm^{-1}; MS, *m/e* (relative intensity) 168.0 (1.9), 167.1 (M^+, 14.5), 123.0 (100); ^1H NMR δ 6.0–5.3 (2 H, br s, exchangeable ith D_2O), 2.6–2.15 (2 H, complex), 2.0–1.3 (6 H, complex), 1.28 (3 H, s), 0.99 (1 H, overlapped), 0.87 (3 H, d, J = 7 Hz).

Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.37. Found: C, 71.83; H, 10.09; N, 8.29.

(18) Melting points were determined with a Thomas-Hoover Uni-Melt apparatus and are uncorrected as are boiling points. IR spectra were taken with Perkin-Elmer 727B, 1320, or 180 IR spectrometers, using neat liquids and KBr pellets for solids unless otherwise specified. ^1H NMR spectra were recorded at 60, 79.5, and 90 MHz with Varian T60A, CFT-20, and EM-390 spectrometers, respectively; at 100 MHz with a Varian XL-100 or a JEOL JNM-PS-FT-100 spectrometer; and at 200 MHz with a Bruker WP-200-SY or a Varian XL-200 spectrometer, utilizing $CDCl_3$ ($SiMe_4$) as the solvent. ^{13}C NMR spectra were recorded at 20 and 25.16 MHz with Varian FT-80A and XL-100 spectrometers, respectively, utilizing $CDCl_3$ as solvent unless otherwise specified. Low and high resolution mass spectra were determined with Varian CH-5 and MAT-312 spectrometers, respectively. Data for the single-crystal X-ray structure determination of compound **6s** were collected with a Syntex Model $P2_1$ automatic X-ray diffractometer. Gas chromatographic analyses were carried out with a Varian 3700 series instrument, utilizing columns packed with 10% OV-17 (**9a,s**) and 10% Carbowax 1540 (**8a,s**) on solid supports and with 10% Carbowax 1540 on a support washed with 5% KOH (**7a,s**). Elemental analyses were carried out with a Perkin-Elmer 240 elemental analyzer. E. Merck G60 and Baker 60–200-mesh SiO_2 were used for preparative and flash column chromatography, respectively.

2-*exo*-(Imidazolylcarbonyl)-2-*endo*-7-*syn*-dimethylbicyclo[2.2.1]heptane was isolated when a mixture similar to that described above was treated with concentrated NH_4OH in DMF only for 1 h at 25 °C. Aqueous dilution, extraction with CH_2Cl_2, clean-up chromatography (SiO_2), and concentration in vacuo gave 83% of yellowish liquid: MS, *m/e* (relative intensity) 219.0 (0.3), 218.2 (M^+, 1.6), 151.1 (13.9), 123.1 (100), 95.1 (10.3), 67.1 (40); IR 3120, 1715 cm^{-1}; ^1H NMR δ 8.23 (1 H, s), 7.49 (1 H, s), 7.07 (1 H, s), 2.9–2.3 (2 H, complex), 2.2–1.1 (7 H, complex), 1.50 (3 H, s), 0.79 (3 H, d, J = 7 Hz).

X-ray Crystal Structure of 6s.[10] A single-crystal X-ray diffraction experiment was carried out at room temperature (22 °C) to determine the stereochemistry of the apical methyl group relative to the amido group. The unit cell parameters found are a = 15.990 (5) Å, b = 12.182 (4) Å, c = 20.789 (6) Å, β = 100.57 (2)°, and V = 3981 (2) Å^3 in the centrosymmetric space group $C2/c$ (Z = 16, D_c = 1.12 g cm^{-3}). Intensity data were measured up to 110° by the θ–2θ technique with monochromatized CuK_α radiation. Of a total of 2506 unique reflections collected, 1377 were considered observed at a level $I > 3\sigma(I)$. A trial structure consisting of all 24 non-hydrogen atoms of the two molecules in the asymmetric unit was obtained by the multiple tangent formula using MULTAN80. The residual index $R = [\sum(||F_o| - |F_c||)/\sum|F_o|]$ was 0.114. Hydrogen atom positions were either calculated in their idealized positions or found in difference electron density syntheses; they were assigned an isotropic temperature factor of 3.80 Å^2 and refined for positional parameter variation only. Full-matrix refinement of non-hydrogen atoms was carried out with anisotropic temperature factors. The final residual was 0.068 (R_w = 0.089).

2-*endo*-7-*syn*-Dimethyl-2-*exo*-(aminomethyl)bicyclo[2.2.1]heptane (7s). Carboxamide **6s** (123 mg, 0.74 mmol) in 10 mL of dry Et_2O was added to a slurry of 533 mg (14.0 mmol) of $LiAlH_4$ in 5 mL of Et_2O at 0 °C under N_2. The mixture was then refluxed under N_2 for 3.5 h. The usual workup, described previously for **7u**, yielded 110 mg (97%) of **7s** as a yellowish liquid, which was ninhydrin-positive on TLC: IR 3380, 3300, 1600, no absorption at 1630 cm^{-1}; ^1H NMR δ 2.60 (2 H, s), 2.0–1.1 (10 H, complex), 1.07 (3 H, d, J = 7 Hz), 0.99 (3 H, s), 0.83 (1 H, d, J = 12).

Anal. Calcd for $C_{17}H_{21}N_3O_5$ (3,5-dinitrobenzamide derivative): C, 58.78; H, 6.09; N, 12.10. Found: C, 58.64; H, 5.98; N, 11.80.

2-*endo*-7-*syn*-Dimethyl-2-*exo*-carbomethoxybicyclo[2.2.1]heptane (10s). Carboxylic acid **5s** (77 mg, 0.46 mmol) was treated with CH_2N_2 as previously described for **10u**[9] to give 82 mg (99%) of yellowish liquid. The ^1H NMR (90, 200 MHz) was essentially identical with that of material produced directly by hydrogenation of **10u**, which had indicated that any epimeric material, if present, was $\ll$1%: $n^{24.5}_D$ 1.4644; bp 85–90 °C bath temp (143 mm); IR 1720, no absorption at 1690 or 880 cm^{-1}; MS, *m/e* (relative intensity) 183.3 (1.0), 182.3 (M^+, 2.8), 124.3 (11.2), 123.3 (100), 82.2 (96.1); exact mass calcd for $C_{11}H_{18}O_2$ 182.1307, found 182.1321; ^1H NMR δ 3.66 (3 H, s), 2.57–2.47 (2 H, complex), 1.9–1.35 (5 H, complex), 1.22 (3 H, s), 1.18–1.05 (2 H, complex), 0.99 (3 H, d, J = 13 Hz).

2-*endo*-7-*syn*-Dimethyl-2-*exo*-(hydroxymethyl)bicyclo[2.2.1]heptane (8s). Ester **10s** (145 mg, 0.80 mmol) was treated with 100 mg (2.64 mmol) of $LiAlH_4$ in 5 mL of dry Et_2O, essentially as previously described for the reduction of **5u**, to give 105 mg (86%) of **8s** as a white solid, mp 65–68 °C; ^1H NMR showed only one doublet, at δ 1.07 (J = 7 Hz), in contrast to material produced by hydrogenation of **8u**. An analytical sample was obtained by recrystallization from petroleum ether: mp 66–68 °C; IR (CH_2Cl_2) 3610, 3490, no abstraction at 1720 cm^{-1}; MS, *m/e* (relative intensity) 125.1 (1.1), 124.1 (18.8), 123.1 (100); ^1H NMR δ 3.49 (1 H, d, J = 10.6 Hz), 3.46 (1 H, d, J = 10.6), 1.90–1.11 (8 H, complex; 1 H exchangeable with D_2O), 1.07 (3 H, d, J = 7), 1.05 (3 H, s), 0.90 (1 H, d, J = 12.3).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.93; H, 11.76.

2-*endo*-7-*syn*-Dimethylbicyclo[2.2.1]heptane-2-*exo*-carboxaldehyde (9s). Alcohol **8s** (249 mg, 1.6 mmol) was treated with 911 mg (2.4 mmol, 1.5 equiv) of pyridinium dichromate in 8 mL of dry CH_2Cl_2 by stirring at 25 °C for 16 h under N_2. The mixture was diluted with 50 mL of Et_2O, filtered through a short SiO_2 column, and concentrated to afford 135 mg (55%) of **9s** as a colorless liquid, which was air-sensitive and was best preserved from decomposition by refrigerating under N_2: IR 2800, 1715 cm^{-1}; ^1H NMR δ 9.60 (1 H, s), 2.4–1.1 (8 H, complex), 1.05 (3 H, s), 0.95 (1 H, d, J = 12 Hz), 0.73 (3 H, d, J = 7).

Hydrogenations, General Procedure. Hydrogenations were carried out with a low-pressure apparatus at a pressure of 76 ± 1.5 cm, using 10 mL of absolute EtOH and 30 mg of a single lot of 5% Pd/C catalyst per 1.0 mmol of olefin. A 50-mL, round-bottomed, male-jointed flask, equipped with a Teflon-coated stirring bar and containing the catalyst and the solution of olefin (0.40–0.82 mmol) was connected without stirring to the apparatus, which was then alternately evacuated and filled with H_2 several times to remove air. The pressure of H_2 was adjusted to ca. 1 atm by means of the Hg leveling-bulb of the gas buret, and stirring was begun and conninued until uptake of H_2 ceased (20–45 min). Filtration of the mixture through a pad of Celite removed catalyst, which was washed with several portions of CH_2Cl_2 (except in the case of **7**[19]), followed by concentration under vacuum. In the case of **9** the filtrate was washed 3× with distilled water to remove EtOH before concentration under vacuum at room temperature. For the carboxylate salts, the dry residue was dissolved in 40–60 mL of water, acidified with 2 N HCl, and extracted 4× with CH_2Cl_2; these extracts were combined, dried, filtered, and concentrated. Recovered yields were 91–99% except for the case of **9u**, whose products were especially volatile (83%).

The reduction of **5u**, **6u**, and **10u**, as described above, as well as of **11u–13u**, provided crude, unfractionated products in which anti epimers were undetectable and less than 1%. The corresponding reductions of **7u–9u** gave crude, unfractionated products whose ^1H NMR spectra displayed the following clearly differentiable peaks attributable to the anti epimers; some of these peaks could be used for quantitation.

7a: δ 2.62 (d, J = 12.5 Hz, NCH), 2.40 (d, J = 12.5, NCH, 2.01 (q, J = 7, MeCH), 0.97 (s, Me), 0.88 (d, J = 7, Me).

8a: δ 3.45 (d, J = 10.5 Hz, OCH), 3.23 (d, J = 10.5, OCH), 1.02 (s, Me), 0.88 (d, J = 7, Me). A typical sample of this mixture melted 59–63 °C before recrystallization.

9a: δ 9.47 (s, CHO), 0.84 (d, J = 7 Hz, Me). The product (350 mg) from one such hydrogenation of **9u** was subjected to ^1H NMR to determine the **9s**/**9a** ratio and was then reduced with excess $LiAlH_4$ in Et_2O at 0 °C. The **8s**/**8a** ratio observed by ^1H NMR in the resulting mixture of alcohols (63% yield) was unchanged.

Attempted Isomerization of 7s to 7a under Hydrogenation Conditions. Compound **7s** (111 mg, 0.734 mmol) in 7.3 mL of absolute EtOH, along with 22 mg of 5% Pd/C, was treated with H_2 under the conditions of the general procedure, in order to establish its stability toward epimerization. Only 0.4 mL of H_2 was absorbed after 35 min. Upon isolation, 100 mg (90%) of **7s** was recovered, in which the 7-*anti*-methyl doublet of **7a** at δ 0.88 could not be detected by ^1H NMR.

Homogeneous Hydrogenation of 8u with Ir(cod)py(PCy$_3$)PF$_6$ Catalyst.[17] To a solution of 200 mg (1.3 mmol) of **8u** in 15 mL of purified CH_2Cl_2 (degassed and distilled from CaH_2) was added 10–11 mg (1.0 mol %) of Ir(cod)py(PCy_3)PF_6 catalyst in 4 mL of purified CH_2Cl_2 under H_2 at 1 atm pressure. The mixture was stirred and within 2 min turned from reddish to yellowish, but within about 25 min no H_2 had been absorbed. Then a solution of 14.5 mg (1.4 mol %[17c]) of catalyst in 2 mL of purrified CH_2Cl_2 was introduced directly into the reaction solution by syringe. The reddish color persisted during the 50-min course of the subsequent hydrogenation, with 30 mL of H_2 absorbed. An additional 5.7 mg (0.5 mol %) of catalyst in 1 mL of purified CH_2Cl_2 was syringed into the solution, which was allowed to stir for a further 25 min, but no more H_2 was absorbed. Solvent was removed under vacuum, and the residue was diluted with petroleum ether and filtered through a pad of Celite, which was washed with petroleum ether. Concentration gave 201 mg (99%) of yellowish solid, whose ^1H NMR spectrum was identical with that of **8s** except for the presence of ca. 10% of **8a**, indicated by the 7-*anti*-methyl doublet at δ 0.88. Recrystallization from pe-

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troleum ether gave 130 mg (64%) of pure **8s** as a white solid: mp 68–69 °C, mmp 68–69 °C.

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Supplementary Material Available: Tables of atomic positional and thermal parameters and of bond distances and angles for **6s** (4 pages). Ordering information is given on any current masthead page.

Oxidative Cyclization of Unsaturated Aminoquinones. Synthesis of Quinolinoquinones. Palladium-Catalyzed Synthesis of Pyrroloindoloquinones

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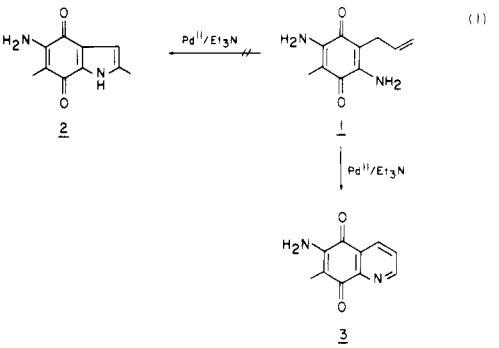
2-Allyl-3,6-diamino-5-methyl-1,4-benzoquinone (**1**) underwent a facile oxidative cyclization to produce quinolinoquinone **3** in the presence of a variety of oxidizing agents, including palladium(II) salts. Chloranil was the most efficient oxidizing agent and produced **3** in high yield. Under hydrolysis conditions, (hydroxyethyl)benzobis(oxazole) **4** underwent a retroaldol reaction, followed by an aldehyde amine condensation and an electrocyclic cyclization to form quinolinoquinones. In contrast, 2-allyl-3,6-bis(benzylamino)-5-methyl-1,4-benzoquinone (**13**) underwent smooth, palladium(II)-catalyzed cyclization to form the corresponding indoloquinone. The corresponding bis(allylamino)benzoquinone **17** underwent a similar cyclization, followed by an olefin insertion reaction to form pyrroloindoloquinones **20** and **21**.

The palladium-catalyzed intramolecular amination of olefins has recently been developed into an efficient process for the conversion of *o*-allylanilines to indoles.[1] The process involves coordination of the olefin to palladium(II) followed by nucleophilic attack at the *most substituted* olefin terminus. When the cyclization was carried out with *N*-acryloyl-*o*-allylaniline, a cyclization–insertion process ensued to give a tricyclic material, a pyrroloindole.[2] With the intent of using this chemistry to synthesize the pyrroloindoloquinone ring system common to the mitomycin antibiotics,[3] a general synthetic approach to 2,5-disubstituted 3,6-diamino-1,4-benzoquinones was recently developed in these laboratories.[4] Herein we report the results of the palladium-catalyzed cyclization reactions of various allyl-containing diaminobenzoquinones.

Results and Discussion

Initial studies centered on the palladium(II)-assisted cyclization of allylbenzoquinone **1** with the intent of producing indoloquinone **2** (eq 1). Treatment of **1** with a stoichiometric amount of $PdCl_2(CH_3CN)_2$ followed by sequential addition of 2 equiv of triethylamine (standard stoichiometric cyclization conditions[1]) resulted in exclusive formation of quinoline **3**, in modest yield (46%). No trace



(1)

of indole **2** was detected. Quinoline **3**, resulting from amination of the *less substituted* olefin terminus, was unexpected but not unprecedented in cyclizations using stoichiometric quantities of palladium(II) salts.[5] This reaction was then repeated under standard catalytic cyclization conditions (3 × 3% Pd(II) catalyst, 3 equiv of benzoquinone/equiv of substrate, THF, 110 °C). Again only quinoline **3** was obtained. Furthermore, in contrast to other palladium(II)-catalyzed cyclization reactions, this reaction was remarkably insensitive to the nature of the palladium catalyst, and all catalysts studied [Li_2PdCl_4, $Pd(OAc)_2$, $PdCl_2(CH_3CN)_2$, $PdCl_2(PhCN)_2$] gave the same product and the same conversion (~75% by NMR of the crude reaction mixture). Finally, the reaction was repeated in the absence of any palladium catalyst, using 4 equiv of benzoquinone per equiv of substrate. Again, quinoline **3**

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