Azidomercurations of Alkenes: Mercury-Promoted Schmidt Reactions

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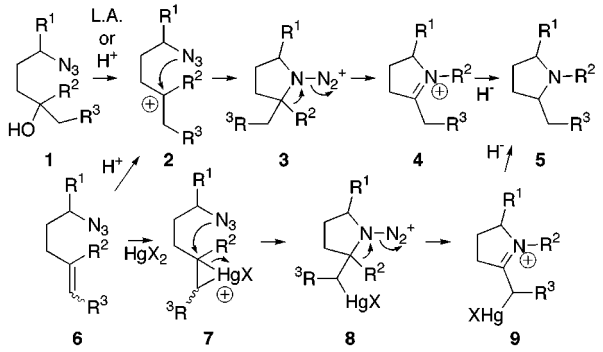
Azides bearing a suitably disposed alkene, when treated with either mercuric perchlorate or mercuric trifluoromethanesulfonate, produce bicyclic iminium ions. This new version of the Schmidt reaction proceeds by capture of the mercuronium ion intermediate by the azide to produce an aminodiazonium ion, which suffers a 1,2-shift to give an iminium ion (e.g., **10** → **16** → **17** → **18**). Reduction of the iminium ion may then be carried out to produce an amine. Compared to earlier work on the protic acid-promoted intramolecular Schmidt reaction of azido-alkenes, the mercury-promoted Schmidt reaction has several advantages. First, the acid-promoted Schmidt reaction of azido-alkenes requires that the intermediate carbocations be tertiary, allylic, benzylic, or propargylic. The mercury-promoted method has no such limitation; thus even 1,2-disubstituted alkenes may be used. Second, the mercury-promoted method is milder, allowing the presence of acid-sensitive functionality. The protic version, typically employing trifluoromethanesulfonic acid, is limited in its functional group tolerance. Third, whereas carbocation rearrangement is often observed prior to cyclization/rearrangement in the acid-promoted Schmidt reaction, the mercury-promoted method avoids this problem. Fourth, the presence of the mercurio group during the rearrangment may alter the regioselectivity of the 1,2-migration. Finally, the mercury-bearing iminium ions that are the result of the Schmidt reaction were found to be sensitive to protodemercuration, precluding their use in other transformations.

Introduction

We have previously shown that the Schmidt reaction of hydrazoic acid (HN_3) with carbocations can be extended to the use of aliphatic azides (RN_3) in both the inter- and intramolecular modes (Scheme 1, **2** → **3** → **4**, intramolecular mode shown).[1,2] Thus, formation of a carbocation **2** from an alcohol **1** or alkene **6** followed by capture by an aliphatic azide generates a secondary aminodiazonium ion **3**. Bond migration to the electron-deficient nitrogen atom results in the formation of an iminium ion **4**, which may be reduced to the amine **5** with sodium borohydride. Other 1,2-migrations of **3** are also possible. Our previous work was limited to benzylic, allylic, or propargylic carbocations; less stabilized cations either failed to produce Schmidt products or suffered rearrangement to a more stable cation prior to the Schmidt reaction.

Scheme 1. Schmidt Reaction Pathways



Furthermore, acid sensitive functionality was not tolerated under the protic or Lewis acidic reaction conditions. We now wish to report the mercury-promoted Schmidt reaction of aliphatic azides with alkenes [Scheme 1, **6** → **7** → **8** → **9** (→ **5**)], a process that avoids some of the limitations of the carbocation method. These are the first examples of azidomercuration reactions involving aliphatic azides.[3,4]

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(1) (a) Pearson, W. H.; Schkeryantz, J. M. *Tetrahedron Lett.* **1992**, *33*, 5291−5294. (b) Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Fang, W.-k.; Blickensdorf, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 10183−10194. (c) Pearson, W. H.; Fang, W.-k.; Kampf, J. W. *J. Org. Chem.* **1994**, *59*, 2682−2684. (d) Pearson, W. H.; Fang, W.-k. *J. Org. Chem.* **1995**, *60*, 4960−4961. (e) Pearson, W. H. *J. Heterocycl. Chem.* **1996**, *33*, 1489−1496. (f) Pearson, W. H.; Fang, W.-k. *Isr. J. Chem.* **1997**, *37*, 39−46.

(2) Aubé has shown that aliphatic azides may participate in Schmidt reactions with ketones and related electrophiles. See: (a) Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965−8966. (b) Aubé, J.; Milligan, G. L.; Mossman, C. J. *J. Org. Chem.* **1992**, *57*, 1635−1637. (c) Aubé, J.; Rafferty, P. S.; Milligan, G. L. *Heterocycles* **1993**, *35*, 1141−1147. (d) Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449−10459. (e) Forsee, J. E.; Aubé, J. *J. Org. Chem.* **1999**, *64*, 4381−4385.

(3) While azidomercurations have not been carried out using aliphatic azides, hydrazoic acid and its salts react with alkenes in the presence of mercuric ion to produce *β*-azidomercurials. See: (a) Heathcock, C. H. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 134−135. (b) Larock, R. C. *Solvomercuration/Demercuration Reaction in Organic Synthesis*; Springer-Verlag: New York, 1986; pp 443−527. (c) Galle, J. E.; Hassner, A. *J. Am. Chem. Soc.* **1972**, *94*, 3930−3933. (d) Sokolova, T. N.; Grishin, Y. K.; Timofeev, I. V.; Kartashov, V. R. *Russ. Chem. B.* **1994**, *43*, 1044−1047. (e) Marchand, A. P.; Sorokin, V. D.; Rajagopal, S. D.; Bott, S. G. *Synth. Commun.* **1994**, *24*, 3141−3147. (f) Kartashov, V. R.; Sokolova, T. N.; Pavinskii, A. Y.; Timofeev, I. V.; Radbil', A. B. *Russ. Chem. B.* **1995**, *44*, 2375−2381.

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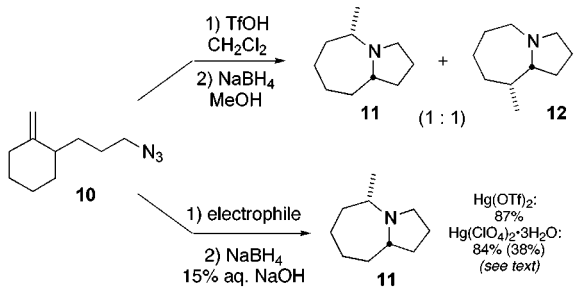
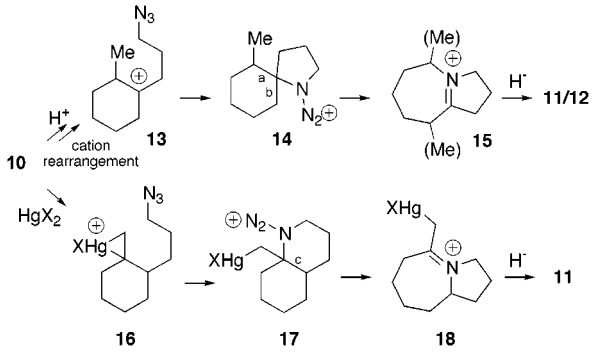
Scheme 2. Proton- vs Mercury-Promoted Schmidt Reactions



Scheme 3. Proposed Mechanisms for Proton- and Mercury-Promoted Schmidt Reactions



Results and Discussion

The proton-initiated intramolecular Schmidt reaction of the azidoalkene **10** had been previously examined in our laboratories, producing a mixture of two regioisomeric products, **11** and **12** (Scheme 2), the result of carbocation rearrangement prior to cyclization (Scheme 3, top pathway).[1b] The yield of **11**/**12** was typically modest (ca. 40%) as a result of isolation problems, although yields as high as 79% could be obtained in larger scale runs. Attempts were made to avoid carbocation rearrangement and thus the lack of regioselectivity by treating **10** with a variety of nonprotic electrophiles. While PhSeCl, PhSeBr, $PdCl_2$, $Pd(OAc)_2$, I_2, *N*-iodosuccinimide, Br_2, $Hg(OAc)_2$, $Hg(O_2CCF_3)_2$, $HgCl_2$, HgI_2, $Hg(NO_3)_2$, and HgO were unsuccessful in promoting Schmidt reactions, generally leaving the starting material untouched, exposure of **10** to a stoichiometric amount of $Hg(ClO_4)_2 \cdot 3H_2O$ or $Hg(OTf)_2$ followed by reduction with sodium borohydride afforded **11** in 84% and 87% yields, respectively, as judged by GC against an internal decane standard, calibrated for relative response.[5] A single stereo- and regioisomer was observed. The isolated yield of **11** was 38% using mercuric perchlorate trihydrate, again reflecting isolation difficulties. The choice of solvent (THF, CH_2Cl_2, or benzene) did not significantly influence the yields. Regarding the stoichiometry of this mercury-promoted Schmidt reaction, at least 1 equiv of the mercury salt is required. In principle, demercuration of an intermediate such as **9** (see Scheme 1) by a nucleophilic counterion could render the reaction catalytic in mercury, but we were unable to promote such a process.

A proposal for the improved regioselectivity of the mercury-promoted Schmidt reaction is shown in Scheme 3. The proton-initiated reaction begins with protonation of the alkene, which is followed by rearrangement to the tertiary carbocation **13**, cyclization to the aminodiazonium ion **14**, and a nonregioselective migration of bond *a* or bond *b* to produce two regioisomeric iminium ions **15**. The mercury-promoted process begins with the formation of the mercuronium ion **16** or its equivalent,[6] which is opened by the azide to produce the aminodiazonium ion **17** without rearrangement. Migration of bond *c* produces the iminium ion **18**, which affords only **11** upon reduction. Other notable differences between these two routes are the positions of the iminium ion functional groups in **15** and **18** and the presence of the organomercury group in **18**.

A variety of azidoalkenes were synthesized (see Supporting Information) and examined in the mercury-promoted Schmidt reaction (Table 1). Treatment of the azidoalkenes **19**−**28** with 2 equiv of $Hg(ClO_4)_2 \cdot 3H_2O$ or $Hg(OTf)_2$ led to gas evolution and the formation of the amines **11** and **29**−**38** after reduction of the intermediate mercury-bearing iminium ion with $NaBH_4$. For comparison, attempted acid-promoted Schmidt reactions of **21**, **22**, and **25**−**27** with TfOH led to decomposition. Entry 1 illustrates the use of a regioisomeric alkene **19** to arrive at the same rearrangement product **11** (cf. Scheme 2, **11** from **10**). Entries 1 and 2 provide additional examples of cyclization without rearrangement; 6-exo ring closure of the azidomercuronium ion is observed rather than five-membered ring formation via a rearranged cation, the observed process using the acidic method. Entries 3−10 show that 1,2-*disubstituted* alkenes may be used in the mercury-promoted Schmidt reaction, which is generally difficult in the acid-promoted method. Especially significant are entries 4−10, reactions that would require a nonstabilized secondary carbocation in the acid-promoted Schmidt reaction. Indeed, treatment of such compounds with acid did not produce Schmidt products, whereas the mercury(II) method was successful. In entry 3, it is unclear whether the mercury-promoted Schmidt reaction proceeds by a 5-exo closure at the secondary nonbenzylic position of the intermediate mercuronium ion followed by migration of the benzylic organomercury group or by a 6-endo closure at the benzylic position followed by ring contraction. Entries 4−6 illustrate functional group tolerance that is not possible in the acid-promoted Schmidt reaction. Entries 4−10 involve hydride migration in the intermediate aminodiazonium ions (i.e., R^2 = H in Scheme 1). As expected, 5-exo (vs 6-endo) and 6-exo (vs 7-endo) closure of the intermediate azidomercuronium ions is apparently involved in entries 4−7. The observation of 5-endo rather than 4-exo closure in entry 10 is also expected on the basis of ring strain issues. The apparent 6-endo closure of the azidomercuronium ions derived from **26** and **27** (entries 8 and 9) is unusual, since 5-exo closure would normally prevail, as was found in entry 5. Related *amino*mercurations[3b] give 5-exo rather than 6-endo products, whether under kinetic or thermodynamic conditions.[7] Perhaps the azidomercuration method inherently favors 6-endo closure over 5-exo (entries 8 and 9) and entry 5 is an exception, e.g., the

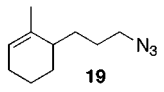
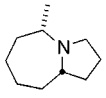
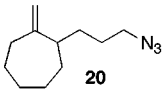
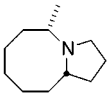
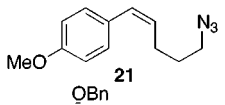
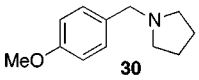
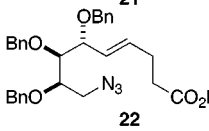
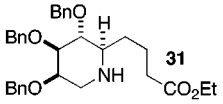
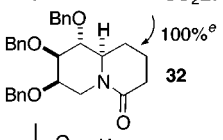
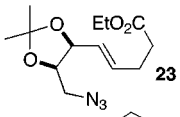
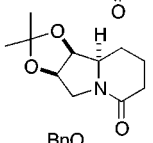
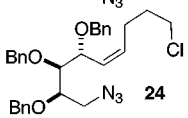
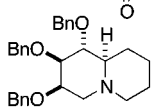
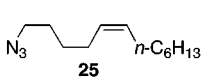
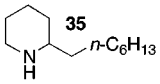
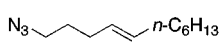
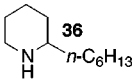
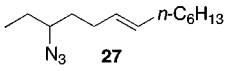
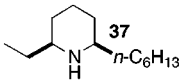
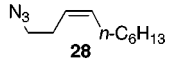
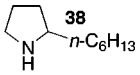
(4) For a review on the related area of alkene cyclofunctionalization, i.e., cyclizations involving electrophile-induced additions of heteronucleophiles to alkenes, see: Harding, K. E.; Tiner, T. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4; pp 363−421.

(5) The results of these studies are presented in the Supporting Information in tabular form.

(6) Varhan, H. B.; Bach, R. D. *J. Org. Chem.* **1992**, *57*, 4948−4954.

(7) (a) Tokuda, M.; Yamada, Y.; Takagi, T.; Suginome, H.; Furusaki, A. *Tetrahedron Lett.* **1985**, *26*, 6085. (b) Tokuda, M.; Yamada, Y.; Suginome, H. *Chem. Lett.* **1988**, 1289.

Table 1. Mercury-Promoted Schmidt Reactions

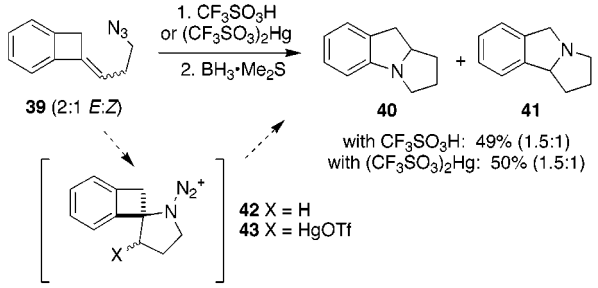
Entry[a]	Azide	Product	Yield[b]
1	 **19**	 **11**	31% 45%[c,d]
2	 **20**	 **29**	31%
3	 **21**	 **30**	43%
4	 **22**	 **31**	41%
		 **32**	100%[e]
5	 **23**	 **33**	34%
6	 **24**	 **34**	63%[f]
7	 **25**	 **35**	73%
8	 **26**	 **36**	58%
9	 **27**	 **37**	44%
10	 **28**	 **38**	37%

[a] Conditons: 2 equiv of $Hg(ClO_4)_2 \cdot 3H_2O$ in THF; $NaBH_4$, 15% NaOH unless otherwise noted. In cases where new chiral centers are formed, only the isomer shown was detected by ^1H NMR. [b] Isolated, chromatographed yields unless otherwise noted. [c] Yield determined by GC against a decane internal standard, calibrated for relative response. [d] Conditions: 2 equiv of $Hg(OTf)_2$ in THF; $NaBH_4$, MeOH. [e] After storage at −5 °C for 2 weeks. [f] Conditons: 2 equiv of $Hg(OTf)_2$ in THF; $NaBH_4$, MeOH; NaOMe, MeOH, reflux.

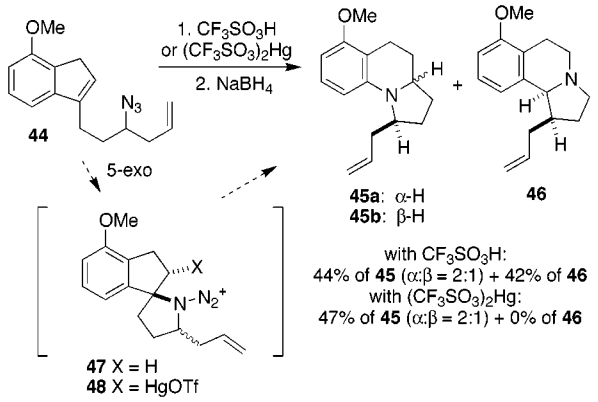
inductive effect of the allylic oxygen on the regioselectivity of the ring-opening of the mercuronium ion derived from **23** might favor 6-endo rather than 5-exo ring closure. Clearly, the 6-endo closures apparently involved in entries 8 and 9 are unexpected and unprecedented in the realm of cyclofunctionalization chemistry. While no explanation is available at this time, this result is a useful one, providing a novel route to piperidines. Finally, the use of the secondary azide **27** (entry 9) is also significant. The *cis*-stereoselectivity observed is likely a result of axial hydride delivery to the best chairlike conformation of the intermediate iminium ion.

When comparing the proton- and mercury-promoted Schmidt reactions, the regioselectivity of the 1,2-shift may be influenced by the presence of the mercury substituent (compare **3** and **8** in Scheme 1 above). Intramolecular Schmidt reactions of the azido-alkenes **39** and **44** (Schemes4 and 5, respectively) serve to illustrate

Scheme 4. 5-endo-trig Cyclizations: Regioselectivity in Proton- vs Mercury-Promoted Schmidt Reactions



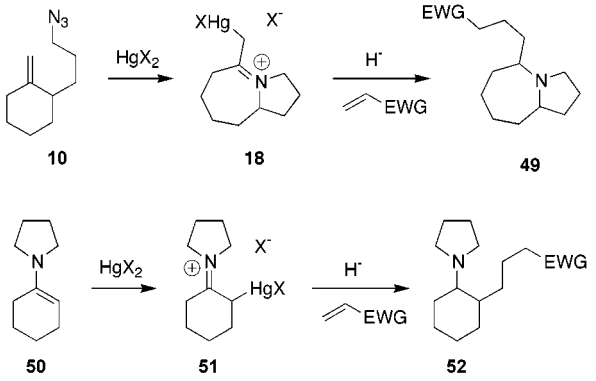
Scheme 5. 5-exo-trig Cyclizations: Regioselectivity in Proton- vs Mercury-Promoted Schmidt Reactions



this point. Treatment of **39**[8] with trifluoromethanesulfonic acid followed by reduction afforded the two benzo-fused pyrrolizidines **40** and **41** in a 1.5:1 ratio, presumably resulting from a 5-endo cyclization to the aminodiazonium ion **42** followed by a 1,2-aryl (rather than alkyl) migration.[8] Using mercuric trifluoromethanesulfonate, **40** and **41** were obtained with the same efficiency and regioselectivity. Apparently, the mercury substituent in the aminodiazonium ion **43** exerted no effect on the migratory preference of the aryl and alkyl groups, a scenario that is reasonable given that the mercury substituent is not directly bonded to the migrating center in the rearrangement step. In contrast, the cyclization of the azido-alkene **44**,[8] proceeding through an initial 5-exo cyclization, shows a clear influence of the mercury substituent. The acid-promoted Schmidt cyclization of **44**,[8] proceeding through the aminodiazonium ion **47**, gave the two benzo-fused indolizidines **45** and **46** in roughly equal amounts, demonstrating that aryl and alkyl migrations occurred to approximately the same extent. The mercury-promoted Schmidt cyclization of **44**, however, produced only the regioisomer **45**. If the mercury-bearing aminodiazonium ion **48** is involved, this experiment indicates that the mercurio group inhibits the migration of the alkyl group, allowing aryl migration to dominate. Examination of the mercury-promoted cyclizations in Scheme 2 and Table 1 reveals a similar observation: with the exception of entry 3 in Table 1, all of these cyclizations proceed by migration of a group that does not bear a mercurio substituent. It is difficult to rationalize entry 3, since it is not known whether the cyclization proceeds in a 5-exo or 6-endo fashion, although it is likely

(8) Pearson, W. H.; Fang, W.-k. *J. Org. Chem.* **2000**, *65*, 7158−7174.

Scheme 6. Proposed Radical Chemistry of the α-Mercurio Iminium Ions

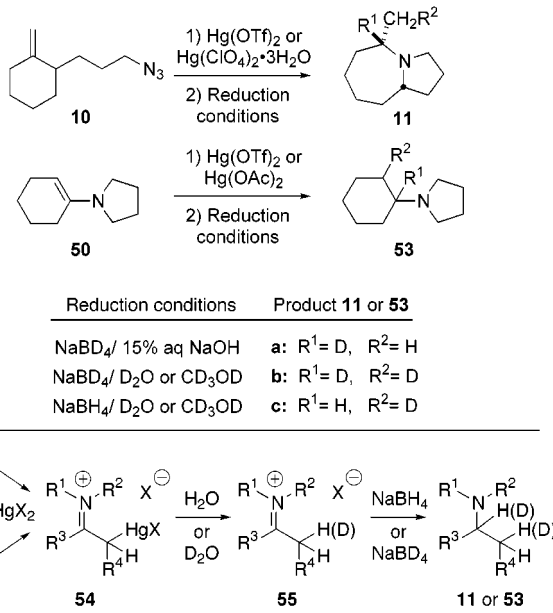


that a mercurio-bearing group migrates in either case, i.e., a mercuriobenzyl group or a mercurioalkyl group must migrate in the 5-exo- or 6-endo-derived aminodiazonium ions, respectively.

While the mercury-promoted Schmidt reaction is a useful complement to the proton-initiated version, this process would be more powerful if the organomercury intermediate (e.g., **3** in Scheme 1 and **18** in Scheme 3) could be used for a subsequent carbon−carbon formation. In particular, upon hydride reduction, *β*-hetero organomercury compounds are known to produce *β*-hetero radicals that can be trapped with electron-poor alkenes.[9] Attempts were therefore made to capture the presumed radical intermediate from the borohydride-promoted demercuration reaction of the intermediate **18** encountered in the mercury-promoted Schmidt reaction of **10** (see Scheme 6) in an attempt to form the chain-extended compounds **49**. Treatment of **10** with $Hg(OTf)_2$ or $Hg(ClO_4)_2 \cdot 3H_2O$ in THF or dichloromethane followed by reduction with $NaBH_4$ or $NaHB(OMe)_3$ in the presence of acrylonitrile or ethyl acrylate failed to induce carbon−carbon bond formation. In related work, 1-(1-pyrrolidinyl)cyclohexene **50** was treated with $Hg(OTf)_2$ or $Hg(OAc)_2$ followed by the same hydrides and traps, also failing to produce the coupling products **52**. Studies on the interaction of enamines with mercury(II) salts have been reported, indicating that α-mercurio iminium ions such as **51** are involved and may be reduced to amines with sodium borohydride.[10−12]

The inability to capture the presumed radical intermediate involved in hydride reductions of the α-mercurio iminium ions led us to seek evidence for the presence of the mercury(II) group in the Schmidt reaction product. Specifically, reduction with sodium borodeuteride should replace the mercury with deuterium (Scheme 7, **54** → **55**-***d*^{1} → **11**-***d*^{2} or **53**-***d*^{2}), a well-known process in organomercury chemistry.[13−15] The mercury-promoted Schmidt reaction of **10** was thus followed by reduction with sodium

Scheme 7. Probing the Nature of the Organomercury Intermediate



borodeuteride, producing only the *monodeuterated* product **11a**, the result of deuteride reduction at the iminium ion carbon (i.e., R^1 = D). No evidence for a second deuterium at R^2, the position presumably occupied by mercury, was found, i.e., no **11b** ($R^1 = R^2$ = D) was formed. When the reduction was carried out with sodium borodeuteride in D_2O (or CD_3OD), two deuteria were incorporated, producing **11b** ($R^1 = R^2$ = D), implying that deuterio-demercuration had occurred prior to iminium ion reduction. Further evidence for this pathway was obtained when sodium borohydride in D_2O (or CD_3OD) was used, leading to **11c** (R^1 = H, R^2 = D). Again, deuterio-demercuration had occurred prior to iminium ion reduction. Similar results were obtained when the enamine **50** was mercurated and subjected to these three sets of reductive conditions, producing **53a**−**c**. Apparently, **10** and **50** are converted to the α-mercurioenamines **54**, which undergo proto- or deuteriodemercuration in the presence of a protic or deuteric solvent, respectively, to produce the iminum ions **55** and thus the amines **11** or **53** after hydride or deuteride reduction. Examples of protodemercuration of organomercury compounds have been reported.[16−18] A consequence of these studies is that α-mercurio iminium ions, while probably present, are too fragile to use in subsequent chemistry.

Conclusion

In conclusion, alkenes undergo azidomercuration with aliphatic azides and mercury(II) salts, resulting in mercury-promoted Schmidt reactions. This mild method complements the proton-initiated Schmidt method, which proceeds under strongly acidic conditions. Evidence for α-mercurio iminium ion intermediates was obtained, which are readily proto- or deuterio-demercurated by

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solvent, producing mercury-free iminium ions that may be reduced to amines.

Experimental Section[19,20]

(2*R,7*R**)-2-Methyl-1-azabicyclo[5.3.0]decane (11). Method A.** A solution of 2-(3-azidopropyl)methylenecyclohexane **10**[20] (0.20 g, 1.1 mmol) in THF (2 mL) was added in a dropwise fashion to a solution of mercuric perchlorate trihydrate (0.51 g, 1.1 mmol) in THF (4 mL) at room temperature. Gas evolution was observed. After 15 min, a solution of sodium borohydride (0.26 g, 6.7 mmol) in 15% aqueous sodium hydroxide (2 mL) was added. After 2 h, the mixture was diluted with ether and decanted away from the bead of mercury. The organic phase was washed twice with brine, dried ($MgSO_4$), and concentrated. Chromatography (20% ethyl acetate/hexanes to 5% MeOH/ethyl acetate gradient) gave 0.065 g (38%) of the title compound as a single diastereomer and regioisomer as judged by proton and carbon NMR spectroscopy: $R_f = 0.15$ (30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.28 (ddd, $J = 9.5$ Hz, 7.4 Hz, 2.9 Hz, 1H), 2.61 (q, $J = 7.7$ Hz, 1H), 2.16−2.41 (m, 2H), 1.37−2.06 (m, 12H), 1.12, (d, $J = 6.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 62.50(+), 60.75(+), 55.77(−), 36.99(−), 35.75(−), 33.68(−), 26.74(−), 23.68(−), 22.82(+), 22.75(−); IR (neat) 1461(m) cm^{-1}; MS (EI, 70 eV) *m*/*z* (rel int) 153 (18.0), 152 (14.8), 138 (100); HRMS (CI with NH_3) calcd for $C_{10}H_{19}N$ 153.1517, found 153.1516. The proton NMR resonances of this compound matched one set of resonances found in an inseparable mixture of **11** and **12** as previously reported.[1b]

Method B. A solution of 2-(3-azidopropyl)methylenecyclohexane **10**[20] (0.100 g, 0.560 mmol) in THF (2 mL) was added in a dropwise fashion to a solution of mercuric perchlorate trihydrate (0.254 g, 0.560 mmol) and decane (internal standard, 0.080 g, 0.560 mmol) in THF (3 mL) at room temperature. Gas evolution was observed. After 15 min, an aliquot was removed from the reaction mixture and quenched with a solution of sodium borohydride (0.05 g, 1.31 mmol) in 1.0 mL of 15% aqueous sodium hydroxide. Ether (3 mL) was added and 1 μL of the organic phase was injected into a GCMS.[19] A product peak having a retention time of 5.56 min was observed. An 84% yield was calculated by comparing the ratio of decane to product, corrected for relative response using a predetermined linear response curve.

Method C. A solution of 2-(3-azidopropyl)methylenecyclohexane **10**[20] (0.100 g, 0.560 mmol) in THF (2 mL) was added in a dropwise fashion to a solution of mercuric trifluoromethanesulfonate (0.278 g, 0.560 mmol) and decane (internal standard, 0.080 g, 0.560 mmol) in THF (3 mL) at room temperature. After 15 min, quenching of an aliquot and analysis by GC as above indicated an 87% yield.

Method D. A solution 1-methyl-6-(3-azidopropyl)cyclohex-1-ene **19** (0.100 g, 0.560 mmol) in THF (2 mL) was added in a dropwise fashion to a solution of mercuric trifluoromethanesulfonate (0.28 g, 0.56 mmol) and decane (internal standard, 0.080 g, 0.560 mmol) in THF (3 mL) at room temperature. Gas evolution was observed. After 15 min, quenching of an aliquot and analysis by GC as above indicated an 45% yield.

Method E. A solution of 1-methyl-6-(3-azidopropyl)cyclohex-1-ene **19** (0.20 g, 1.1 mmol) in THF (2 mL) was added in a dropwise fashion to a solution of mercuric perchlorate trihydrate (0.51 g, 1.1 mmol) in THF (4 mL) at room temperature. Gas evolution was observed. After 15 min, a solution of sodium borohydride (0.26 g, 6.7 mmol) in 15% aqueous sodium hydroxide (2 mL) was added. After 2 h, the mixture was diluted with ether (15 mL) and decanted away from the bead of mercury. The organic phase was washed twice with brine, dried ($MgSO_4$), and concentrated. Chromatography (20% ethyl acetate/hexanes to 5% MeOH/ethyl acetate gradient) gave 0.052 g (31%) of the title compound, identical to the material obtained using Method A.

(2*R,8*R**)-2-Methyl-1-azabicyclo[6.3.0]undecane (29).** A solution of 2-(3-azidopropyl)methylenecycloheptane **20**[20] (0.20 g, 1.0 mmol) in THF (3 mL) was added in a dropwise fashion to a solution of mercuric perchlorate trihydrate (0.94 g, 2.0 mmol) in THF (5 mL) at room temperature. Gas evolution was observed. After 15 min, a solution of sodium borohydride (0.19 g, 5.1 mmol) in 15% aqueous sodium hydroxide (2 mL) was added. After 2 h, the mixture was diluted with ether and decanted away from the bead of mercury. The organic phase was washed twice with brine, dried ($MgSO_4$), and concentrated. Chromatography (1:1 ethyl acetate/hexanes to 20% acetone/ethyl acetate gradient) gave 0.05 g (31%) of a single stereoisomer of the title compound, as tetermined by proton NMR spectroscopy: $R_f = 0.09$ (30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.25 (t, $J = 6.5$ Hz, 1H), 2.96−3.07 (m, 1H), 2.58−2.69 (m, 1H), 2.22−2.34 (m, 2H), 1.24−2.06 (m, 13H), 1.26 (d, $J = 6.4$ Hz, 3H);); ^{13}C NMR ($CDCl_3$, 75 MHz, JMOD) δ 67.5 (+), 64.1 (+), 58.6 (−), 33.5 (−), 33.4 (−), 29.6 (−), 24.2 (−), 23.0 (−), 22.6 (−), 21.7 (−), 17.1 (+); IR (neat) 2785 (s) cm^{-1}; MS (CI with CH_4) *m*/*z* (rel int) 182 (M + CH_3, 14.1), 168 (M + H, 100); HRMS (CI with CH_4) calcd for $C_{11}H_{21}$-NH 168.1752, found 168.1749.

***N*-(4-Methoxybenzyl)pyrrolidine (30).** This compound has been previously synthesized by the coupling of an arylstannane with an iminium ion.[21] Our mercury-promoted Schmidt method was carried out as follows. A solution of (*Z*)-1-azido-5-(*p*-methoxyphenyl)pent-4-ene **21**[20] (0.17 g, 0.81 mmol) in THF (2 mL) was added in a dropwise fashion to a solution of mercuric perchlorate trihydrate (0.73 g, 1.6 mmol) in THF (5 mL) at room temperature. Gas evolution was observed. After 15 min, a solution of sodium borohydride (0.290 g, 7.50 mmol) in 15% aqueous sodium hydroxide (2 mL) was added. After 2 h, the mixture was diluted with ether and decanted away from the bead of mercury. The organic phase was washed twice with brine, dried ($MgSO_4$), and concentrated. Chromatography (1:1 ethyl acetate/hexanes to 20% acetone/ethyl acetate gradient) gave 0.66 g (43%) of the title compound: $R_f = 0.21$ (30% ethyl acetate/hexanes); proton and carbon NMR data for this compound matched the literature values.[21]

(2*R*,3*R*,4*R*,5*R*)-2-[3-(Carboethoxy)propyl]-3,4,5-tri(benzyloxy)piperidine (31) and (1*R*,2*R*,3*R*,9a*R*)-1,2,3-Tri(benzyloxy)quinolizidin-6-one (32). A solution of methyl(2*R*,3*S*,4*R*,5*E*)-9-azido-6,7,8-tri(benzyloxy)non-5-enoate **22**[22] (0.431 g, 0.950 mmol) in THF (2 mL) was added in a dropwise fashion to a solution of mercuric perchlorate trihydrate (0.200 g, 0.368 mmol) in THF (2 mL) at room temperature. Gas evolution was observed. After 15 min, a solution of sodium borohydride (0.072 g, 1.90 mmol) in 15% aqueous sodium hydroxide (2 mL) was added. After 2 h, the mixture was diluted with ether and decanted away from the bead of mercury. The organic phase was washed twice with brine, dried ($MgSO_4$), and concentrated. Chromatography (1:1 ethyl acetate/hexanes to 25% acetone/ethyl acetate gradient) gave 0.078 g (41%) of a single stereoisomer of the title compound **31** as a colorless oil: $R_f = 0.66$ (50% ethyl acetate/acetone); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23−7.44 (m, 15H), 4.98 (d, $J = 3.8$ Hz, 1H), 4.69 (s, 2H), 4.59 (q, $J = 1.4$ Hz, 2H), 4.07 (q, $J = 2.9$ Hz, 2H),3.56 (br. s, 1H), 3.45 (d, $J = 2.4$ Hz, 2H), 3.12 (dd, $J = 5.0$ Hz, $J = 1.3$ Hz,

(19) Proton NMR spectral assignments were based on two-dimensional correlated off-resonance spectroscopy (COSY) experiments, nuclear Overhauser and exchange spectroscopy (NOESY) experiments, or comparisons with analogous compounds reported in the literature. J-Modulated spin−echo Fourier transform (JMOD) ^{13}C NMR experiments are reported as (+) for CH_3 and CH or (−) for CH_2 and quarternary carbon and are used as an alternative to off-resonance decoupling. GC and GC/MS data were obtained on a Hewlett-Packard 6890 series gas chromatograph equipped with a 5973 mass selective detector. The column was a Hewlett-Packard 5-MS comprising 5% phenyl methyl siloxane with a film thickness of 0.25 μM, internal diameter of 0.25 mm, and a length of 30 m. Temperature program: 50 °C for 4 min, then increase to 200 °C at 40 °C/min, then hold 10 min. For exploratory experiments, accurate yields were obtained by gas chromatography against an internal decane standard, where a calibration curve was used to correct for relative response factors.

(20) See the Supporting Information for the preparation of the Schmidt substrates.

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1H), 2.12−2.53 (m, 6H), 1.53−1.97 (m, 3H), 1.23 (t, J = 3.1 Hz, 3H). Upon standing at −5 °C for 2 weeks, this material cyclized quantitatively to give 74 mg of the lactam **32** after removal of a trace of ethanol in vacuo: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29−7.44 (m, 15H), 5.14 (dd, J = 14.3 Hz, J = 3.3 Hz, 1H), 5.04 (d, J = 11.0 Hz. 1H), 4.81 (d, J = 12.8, 1H), 4.49−4.65 (m, 5H), 3.83 (t, J = 2.6 Hz, 1H), 3.73 (t, 9.5 Hz, 1H), 3.50 (dd, J = 9.2 Hz, J = 2.9 Hz, 1H), 3.16−3.22 (m, 1H), 2.39 (t, J = 6.2 Hz, 1H), 2.32 (d, J = 14.3 Hz, 1H), 2.10−2.16 (m, 1H), 1.76−1.89 (m, 2H), 1.60−1.67 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 138.3, 138.1, 138.0, 128.4, 128.3, 128.2, 128.0, 127.8, 127.7, 127.6, 83.3, 79.0, 75.7, 71.2, 70.4, 70.1, 59.2, 41.7, 32.7, 25.4, 18.5; IR (neat) 1695 (s) cm^{-1}; MS (CI with NH_4^+) m/z (rel int) 472 (M + H, 100); HRMS (CI with NH_3) calcd for $C_{30}H_{34}NO_4$ 472.2487, found 472.2473. The configuration of the title lactam was assigned based on its similarity to the quinolizidine **34** synthesized below, a compound we had previously made and whose configuration had been assigned by 2-D NOESY NMR spectroscopy.[22]

(1*S*,2*R*,8a*R*)-1,2-*O*-Isopropylidene-1,2-dihydroxyindolizidin-5-one (33). A solution of ethyl (4*E*,6*S*,7*R*)-6,7-*O*-isopropylidine-6,7-dihydroxyoct-4-enoate **23**[22] (0.100 g, 0.371 mmol) in THF (3 mL) was added in a dropwise fashion to a solution of mercuric perchlorate trihydrate (0.338 g, 0.743 mmol) in THF (2 mL) at room temperature. Gas evolution was observed. After 30 min, a solution of sodium borohydride (0.056 g, 1.48 mmol) in MeOH (2 mL) was added. After 18 h, MeOH (3 mL) and NaOMe (0.004 g, 0.074 mmol) were added and the solution was heated at reflux for 3 h. The reaction mixture was then cooled and concentrated. Chromatography (1:1 ethyl acetate/hexanes to 25% acetone/ethyl acetate gradient) of the residue gave 0.027 g (34%) of a single isomer of the title compound: R_f = 0.12 (10% MeOH/$CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.73 (t, J = 5.1 Hz, 1H), 4.60 (dd, J = 6.0 Hz, J = 4.4 Hz, 1H), 4.2 (d, J = 13.6 Hz, 1H), 3.4 (m, 1H), 3.09 (dd, J = 13.6 Hz, J = 5.1 Hz, 1H), 2.22−2.46 (m, 2H), 1.61−2.07 (m, 4H), 1.41 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, JMOD) δ 168.8 (−), 81.3 (+), 77.8 (+), 77.4 (+), 76.6 (−), 61.3 (+), 50.3 (−), 31.4 (−), 26.6 (+), 24.9 (+), 22.7 (−), 21.1 (−). The configuration of the title compound was assigned by comparison to the known compound (1*S*,2*R*,8*R*,8a*R*)-1,2-*O*-isopropylidene-1,2,8-trihydroxyindolizidin-5-one.[23]

(1*R*,2*R*,3*R*,9a*R*)-1,2,3-Tri(benzyloxy)quinolizidine (34). This compound has been prepared in our laboratories by the thermal cyclization of (2*R*,3*S*,4*R*,5*Z*)-1-azido-2,3,4-tri(benzyloxy)-9-chloro-5-nonene and the reduction of the resultant iminium ion.[22] Our mercury-promoted Schmidt method for the preparation of this compound was carried out as follows. A solution of (2*R*,3*S*,4*R*,5*Z*)-1-azido-2,3,4-tri(benzyloxy)-9-chloro-5-nonene **24**[22] (0.374 g, 0.721 mmol) in THF (2 mL) was added in a dropwise fashion to a solution of mercuric trifluoromethanesulfonate (0.720 g, 1.44 mmol) in THF (5 mL) at room temperature. Gas evolution was observed. After 15 min, a solution of sodium borohydride (0.164 g, 4.32 mmol) in methanol (3 mL) was added. After 4 h, sodium methoxide (0.116 g, 2.16 mmol) was added and the solution was warmed to reflux for 4 h. After cooling, the contents of the flask were diluted with ether and decanted away from the bead of mercury. The solution was washed twice with brine, dried ($MgSO_4$), and concentrated. Chromatography (100% dichloromethane to 5% methanol in dichloromethane gradient) gave 0.213 g (63%) of a single isomer of the title compound as a colorless oil: R_f = 0.45 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24−7.42 (m, 15H), 4.99 (d, J = 10.6 Hz, 1H), 4.80 (ABq, J_{AB} = 13.2 Hz, $\Delta\nu$ = 25.6 Hz, 2H), 4.57−4.67 (m, 4H), 3.73−3.78 (m, 1H), 3.66 (t, J = 9.3 Hz, 1H), 3.39 (dd, J = 9.3 Hz, J = 3.3 Hz, 1H), 2.89 (dd, J = 12.5 Hz, J = 2.9 Hz, 1H), 2.82 (br. d, J = 11.4 Hz, 1H), 2.16 (br. d, J = 12.5 Hz, 2H), 1.84−1.95 (m, 2H), 1.67−1.74 (m, 2H), 1.52−1.58 (m, 1H), 1.13−1.38 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.8, 138.6, 128.5, 128.3, 128.2, 128.1, 127.6, 127.5, 126.9, 83.9, 80.4, 75.7, 71.9, 71.6, 71.2, 66.1, 57.6, 55.8, 28.2, 25.1, 23.7; IR (neat) 1496 (w), 1453 (m) cm^{-1}; MS (CI with NH_4^+) m/z (rel int) 458 (M^+, 7), 212 (100); HRMS (CI with NH_3) calcd for $C_{30}H_{36}NO_3$ (M + H) 458.2695, found 458.2717. The proton and carbon NMR data for this compound matched the values we had obtained previously.[22]

2-Heptylpiperidine (35). This compound has been made by Meyers and co-workers by the alkylation of a metalated formamidine derivative of piperidine.[24] The mercury-promoted Schmidt method was carried out as follows: A solution of (*Z*)-1-azidododec-5-ene **25**[20] (0.26 g, 0.560 mmol) in THF (2 mL) was added in a dropwise fashion to a solution of mercuric perchlorate trihydrate (1.13 g, 2.50 mmol) in THF (5 mL) at room temperature. Gas evolution was observed. After 15 min, a solution of sodium borohydride (0.290 g, 7.50 mmol) in 15% aqueous sodium hydroxide (2 mL) was added. After 2 h, the mixture was diluted with ether and decanted away from the bead of mercury. The organic phase was washed twice with brine, dried ($MgSO_4$), and concentrated. Chromatography (1:1 ethyl acetate/hexanes to 20% acetone/ethyl acetate gradient) gave 0.167 g (73%) of the title compound, R_f = 0.13 (30% ethyl acetate/hexanes), which was found to have proton and carbon NMR spectroscopic data and MS data that matched the literature values.[24]

2-Hexylpiperidine (36). This compound has been made by Meyers and co-workers by the alkylation of a metalated formamidine derivative of piperidine.[25] Our mercury-promoted Schmidt method was carried out as follows. A solution of (*E*)-1-azidoundec-4-ene **26**[20] (0.250 g, 1.28 mmol) in THF (2 mL) was added in a dropwise fashion to a solution of mercuric perchlorate trihydrate (1.16 g, 2.56 mmol) in THF (8 mL) at room temperature. Gas evolution was observed. After 45 min, a solution of sodium borohydride (0.290 g, 7.68 mmol) in 15% aqueous sodium hydroxide (2 mL) was added. After 2 h, the reaction mixture was diluted with ether and decanted away from the bead of mercury. The organic phase was washed twice with brine, dried ($MgSO_4$), and concentrated. Chromatography (1:1 ethyl acetate/hexanes to 20% acetone/ethyl acetate gradient) gave 0.126 g (58%) of the title compound, R_f = 0.16 (30% ethyl acetate/hexanes), which was found to have proton and carbon NMR spectroscopic data and MS data that matched the literature values.[25]

(2*R,5*S**)-2-Ethyl-5-hexylpiperidine (37).** A solution of (*E*)-3-azidotridec-6-ene **27**[20] (0.350 g, 01.57 mmol) in THF (2 mL) was added in a dropwise fashion to a solution of mercuric perchlorate trihydrate (1.42 g, 3.14 mmol) in THF (8 mL) at room temperature. Gas evolution was observed. After 20 min, a solution of sodium borohydride (0.360 g, 9.42 mmol) in 15% aqueous sodium hydroxide (3 mL) was added. After 2 h, the mixture was diluted with ether and decanted away from the bead of mercury. The organic phase was washed twice with brine, dried ($MgSO_4$), and concentrated. Chromatography (1:1 ethyl acetate/hexanes to 20% acetone/ethyl acetate gradient) gave 0.136 g (44%) of the title compound as a single stereoisomer as judged by proton and carbon NMR: R_f = 0.13 (30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 2.43−2.49 (m, 1H), 2.34−2.43 (m, 1H), 1.73−1.82 (m, 1H), 1.61−1.72 (m, 2H), 1.27−1.40 (m, 14H), 0.94−1.07 (m, 2H), 0.91 (t, J = 7.48 Hz 3 H), 0.88 (t, J = 6.87 Hz, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 58.76 (+), 57.16 (+), 37.44 (−), 32.69 (−), 32.19 (−), 31.79 (−), 30.11 (−), 29.48 (−), 25.92 (−), 24.81 (−), 22.58 (−), 14.06 (+), 10.43 (+); IR (neat) 3286 (br. w), 2794 (w), 2717 (w) cm^{-1}; MS (CI with CH_4) m/z (rel int) 198 (9.6), 112 (100); HRMS (CI with CH_4) calcd for $C_{13}H_{27}NH$ 198.2222, found 198.2214. The configuration of this compound was assigned as 2,5-*cis* on the basis of a comparison of the chemical shifts of carbons C(2) and C(5) in the ^{13}C NMR spectrum (δ 58.8, 57.2, order not known) to the values reported for *cis*- and *trans*-2-methyl-5-undecylpiperidine (δ 52.6, 57.2 and δ 45.9, 50.9, respectively).[26]

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2-Hexylpyrrolidine (38). This compound has previously been synthesized by Buchwald and co-workers by a titanocene-mediated reduction of 2-hexyl-1-pyrroline.[27] Our mercury-promoted Schmidt method was carried out as follows. A solution of (*Z*)-1-azidododec-5-ene **28**[20] (0.269 g, 1.38 mmol) in THF (2 mL) was added in a dropwise fashion to a solution of mercuric perchlorate trihydrate (1.25 g, 2.76 mmol) in THF (10 mL) at room temperature. Gas evolution was observed. After 20 min, sodium borohydride (0.31 g, 8.3 mmol) in 15% aqueous sodium hydroxide (3 mL) was carefully added. The solution instantly became gray in color and after 14 h, the fine black particles coalesced into a bead of mercury. The mixture was diluted with ether and decanted away from the bead of mercury. The organic phase was separated and washed with brine, then dried ($MgSO_4$) and concentrated. Chromatography (1:1 ethyl acetate/hexanes to 20% acetone/ethyl acetate gradient) gave 0.079 g (37%) of the title compound as a pale yellow oil. The proton and carbon NMR data for this compound matched the literature values.[27]

2,3,8,8a-Tetrahydro-1*H*-3a-azacyclopenta[*a*]indene (40) and 2,3,5,9b-Tetrahydro-1*H*-pyrrolo[2,1-*a*]isoindole (41). Mercuric trifluoromethanesulfonate (1.00 g, 2.01 mmol) was added to a solution of 7-(3-azidopropylidene)bicyclo[4.2.0]octa-1(6),2,4-triene **39**[8] (280 mg, 1.51 mmol, 2:1 *E*:*Z*) in THF (25 mL) at room temperature. After 1 h, the mixture was cooled to 0 °C and treated with borane dimethyl sulfide complex (4.50 mL of a 2.0 M in THF, 9.00 mmol). After 14 h, 15% aqueous sodium hydroxide was added and the mixture was extracted with ether (3x). The combined organic phases were washed with brine (3x), dried ($MgSO_4$) and concentrated. Chromatography (1:7 ether/hexanes) gave 120 mg (50%) of an inseparable 1.5:1 mixture of **40**[28,29] and **41**[30] as judged by ^{1}H NMR. The ^{1}H NMR, ^{13}C NMR, and MS data for these compounds matched the values we had previously observed[8] and the literature values.[28−30]

(1*R,3a*S**)-6-Methoxy-1-(2-propenyl)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline (45a) and (1*R**,3a*R**)-6-Methoxy-1-(2-propenyl)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline (45b).**[8] Mercuric trifluoromethanesulfonate (300 mg, 0.60 mmol) was added to a solution of 3-(3-azido-5-hexenyl)-7-methoxy-1*H*-indene **44**[8] (100 mg, 0.37 mmol) in THF (8 mL) at room temperature. After 30 min, the reaction mixture was cooled to 0 °C and sodium borohydride (84 mg, 2.22 mmol) in methanol (3 mL) was added. After the mixture warmed to room temperature for 14 h, 15% aqueous sodium hydroxide was added and the mixture was extracted with ether (3x). The combined organic phases were washed twice with brine, dried (Na_2SO_4), and concentrated. Chromatography (1:7 ether/hexanes) gave 42 mg (47%) of an inseparable 2:1 mixture of **45a** and **45b** as a clear oil, R_f = 0.61, as judged by integration of the hydrogens at δ 3.12−3.04 (m, 0.5H) and 2.96 (dd, J = 17.3, 5.6 Hz, 1H) in the ^{1}H NMR spectrum. The ^{1}H NMR, ^{13}C NMR, and MS data for these compounds matched the values we had previously observed.[8]

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Supporting Information Available: Experimental details and spectral data for compounds not reported in the Experimental Section, deuterium labeling studies, copies of ^{1}H and/or ^{13}C NMR spectra for all new compounds without elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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