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Progress toward a Rationally Designed, Chemically Powered Rotary Molecular Motor

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Abstract: Building on prototype **1**, which achieves 120° of phosgene-powered unidirectional rotation to rotamer **6** (see Figure 5 in the full article), **7** was designed to accomplish repeated unidirectional rotation (see Scheme 7). Compound **7** contains an amino group on each blade of the triptycene and a 4-(dimethylamino)pyridine (DMAP) unit to selectively deliver phosgene (or its equivalent) to the amine in the "firing position". The synthesis of **7** is described: the key constructive steps are a benzyne addition to an anthracene to generate the triptycene, a stilbene photocyclization to construct the helicene, and a Stille coupling to incorporate the DMAP unit. The DMAP unit was shown to regioselectively relay 1,1′-carbonyldiimidazole (but not phosgene) to the proximal amino group, as designed, but rotation of the triptycene does not occur. Extensive attempts to troubleshoot the problem led to the conclusion that the requisite intramolecular urethane formation, as demonstrated in the prototype (**1** → **4**), does not occur with **7** (to give **85**) or **97** (to give **100**). We speculate that either (i) hydrogen bonding between the hydroxypropyl group and functionality present in **7** but absent from **1** or (ii) a Bürgi−Dunitz (or similar) interaction involving the DMAP (see **106**) prevents achievement of a conformation conducive to intramolecular urethane formation.

The construction of motors of ever smaller sizes has fascinated scientists for decades. In 1959, the Nobel laureate physicist Richard Feynman posted[1] a $1000 reward for the first "operating electric motor [that] is only 1/64 inch cube." The reward was collected within a year (see Figure 1). More recently, microfabrication using photolithography techniques has led to motors whose diameters are about that of a human hair (Figure 2).[2]

The motors illustrated in Figures 1 and 2 are rotary motors. Barring major developments in subatomic physics, the ultimate in miniaturized motors, rotary or otherwise, would be molecular-scale motors. Nature[4] has evolved a number of complex molecular systems that function as rotary motors, including F_1-ATPase (Figure 3)[5] and flagella (Figure 4).[6] Both F_1-ATPase and flagella are chemically powered motors: F_1-ATPase is driven by hydrolysis of ATP, while flagella are fueled by a proton gradient.

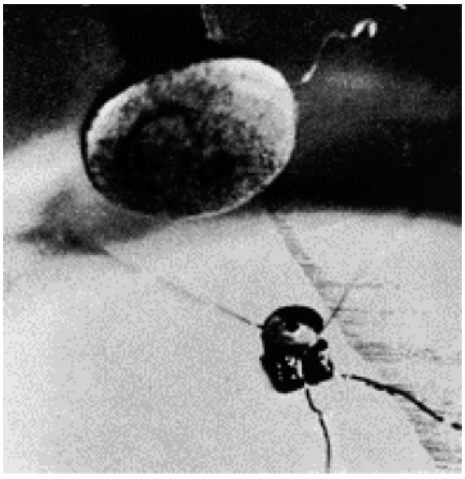

Figure 1. Bottom right: William McLellan's creation that collected Feynman's reward of $1000 for the first "operating electric motor [that] is only 1/64 inch cube." The "scale bar" at the top is the head of a pin. [Reprinted with permission; see ref 3.]

In 1999, we achieved a proof of principle of the first rationally designed, chemically powered rotary molecular motor.[9] In the same year, Koumura, Feringa, and colleagues reported[10] a light-driven rotary molecular motor. In 2005, Feringa and co-workers accomplished[11] a chemically powered rotary molecular motor

(1) Feynman, R. P. There is plenty of room at the bottom. In *Miniaturization*; Gilbert, H. D., Ed.; Reinhold: New York, 1961; Chapter 16, pp 282−296.
(2) Howe, R. T.; Muller, R. S.; Gabriel, K. J.; Trimmer, W. S. N. *IEEE Spectrum* **1990**, *27*, 29−35 and cover. See also: Wise, K. D.; Najafi, K. *Science* **1991**, *254*, 1335−1342.
(3) Figure 1: Photo courtesy of the Archives, California Institute of Technology.
(4) For an overview, see: Berg, J. M.; Tymoczko, J. L.; Stryer, L. Molecular Motors. *Biochemistry*, 6th ed.; W. H. Freeman: New York, 2006; Chapter 34.
(5) (a) Boyer, P. D. *Angew. Chem., Int. Ed.* **1998**, *37*, 2297−2307. (b) Walker, J. E. *Angew. Chem., Int. Ed.* **1998**, *37*, 2308−2319. For a review, see: Noji, H. In *Molecular Motors*; Schliwa, M., Ed.; Wiley-VCH: Weinheim, 2003; pp 141−152.
(6) Berg, H. C. *Annu. Rev. Biochem.* **2003**, *72*, 19−54.
(7) Figure 3: Graphic downloaded with permission from the website www.mech.northwestern.edu/courses/389.S02/intro.html. See also: Wang, H.; Oster, G. *Nature* **1998**, *396*, 279−282.
(8) Figure 4: Graphic reproduced with permission from Berg, J. M.; Tymoczko, J. L.; Stryer, L. *Biochemistry*, 5th ed.; W. H. Freeman: New York, 2002; p 968.

10.1021/ja066044a CCC: $37.00

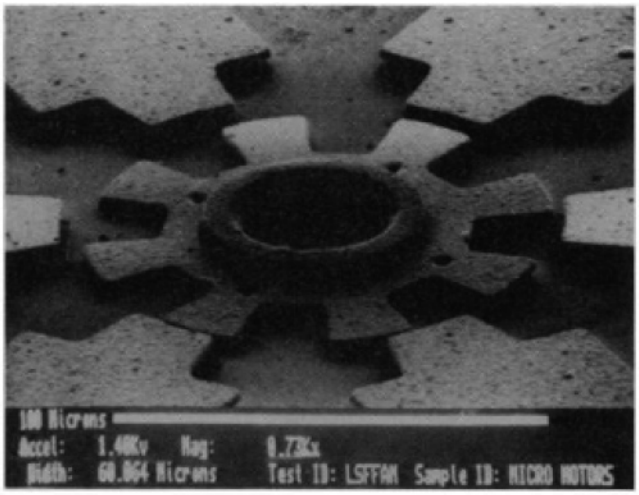

Figure 2. An electric motor created by using photolithography possessing a 100 μm diameter rotor. [Photo courtesy of R. S. Muller, University of California, Berkeley. Reprinted with permission; see ref 2.]

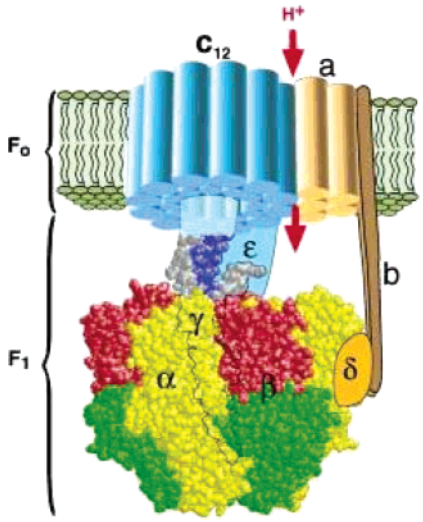

Figure 3. The naturally occurring rotary motor F_1-ATPase. [Reprinted by permission from Macmillan Publishers Ltd.: *Nature*, copyright 1998; see ref 7.]

capable of repeated rotation, and Branchaud et al.[12] have reported related findings. A number of other groups[13] have proffered complementary approaches to achieving rotary motion on a molecular scale, and, as numerous recent reviews attest,[14] much work has also been devoted to constructing other molecular devices.

The operation of our prototype is illustrated in Figure 5; the system is fueled by phosgene and accomplishes a unidirectional, 120° clockwise rotation.

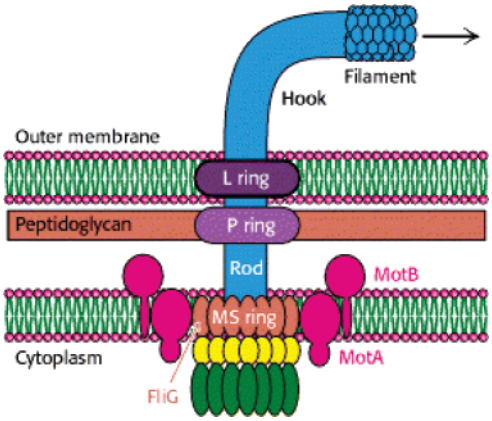

Figure 4. Schematic representation of a flagellum. [Reprinted with permission; see ref 8. Copyright 2002 W. H. Freeman and Co.]

While the demonstration that the prototype behaved as designed was gratifying, much still remained to be addressed. In particular, to advance **1** to a continuously rotating motor, as summarized conceptually in Figure 6, four things need to be achieved:

(i) an amino group must be incorporated on each blade of the triptycene;

(ii) a means for selectively delivering phosgene (or its equivalent) to the amine in the "firing position" must be devised;

(iii) a phosgene-fueled, 120° rotation of the triptycene must be brought about by formation of an intramolecular urethane; and

(iv) the remains of the phosgene must be removed by cleavage of the urethane to allow subsequent repetition of the three preceding steps.

We now report the achievement of the first two objectives: construction of a triaminotriptycene assembly and incorporation of a 4-(dimethylamino)pyridine (DMAP) unit to selectively deliver the phosgene equivalent to the proximal amino group. Those achievements were accomplished with **7** (Figure 7).[15]

(9) (a) Kelly, T. R.; De Silva, H.; Silva, R. A. *Nature* **1999**, *400*, 150−152. (b) Kelly, T. R.; Silva, R. A.; De Silva, H.; Jasmin, S.; Zhao, Y. *J. Am. Chem. Soc.* **2000**, *122*, 6935−6949. (c) Kelly, T. R. *Acc. Chem. Res.* **2001**, *34*, 514−522. (d) Kelly, T. R.; Sestelo, J. P. In *Molecular Machines and Motors*; Sauvage, J.-P., Ed.; Structure & Bonding 99; Springer-Verlag: Berlin, 2001; pp 19−53.

(10) Koumura, N.; Zijlstra, R. W. J.; van Delden, R. A.; Harada, N.; Feringa, B. L. *Nature* **1999**, *401*, 152−155. For more recent, related work, see: (a) Vicario, J.; Walko, M.; Meetsma, A.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 5127−5135. (b) Eelkema, R.; Pollard, M. M.; Vicario, J.; Katsonis, N.; Ramon, B. S.; Bastiaansen, C. W. M.; Broer, D. J.; Feringa, B. L. *Nature* **2006**, *440*, 163 and references therein.

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(12) (a) Dahl, B. J.; Branchaud, B. P. *Tetrahedron Lett.* **2004**, *45*, 9599−9602. (b) Lin, Y.; Dahl, B. J.; Branchaud, B. P. *Tetrahedron Lett.* **2005**, *46*, 8359−8362.

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(14) (a) Balzani, V.; Credi, A.; Raymo, F. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2000**, *39*, 3348−3391. (b) *Molecular Machines and Motors*; Sauvage, J.-P., Ed.; Structure & Bonding 99; Springer-Verlag: Berlin, 2001. (c) Stoddart, J. F., Guest Ed. Molecular Machines Special Issue. *Acc. Chem. Res.* **2001**, *34*, 409−522. (d) Balzani, V.; Venturi, M.; Credi, A. *Molecular Devices and Machines: A Journey into the Nanoworld*; Wiley-VCH: Weinheim, 2003. (e) *Molecular Motors*; Schliwa, M., Ed.; Wiley: Weinheim, 2003. (f) *Molecular Machines*; Kelly, T. R., Ed.; Topics in Current Chemistry 262; Springer: Berlin, 2005; pp 1−227. (g) Kottas, G. S.; Clarke, L. I.; Horinek, D.; Michl, J. *Chem. Rev.* **2005**, *105*, 1281−1376. (h) Kelly, T. R. *Angew. Chem., Int. Ed.* **2005**, *44*, 4124−4127.

(15) Note: The work on **7** did not lend itself to preliminary communications, so there are no earlier papers.

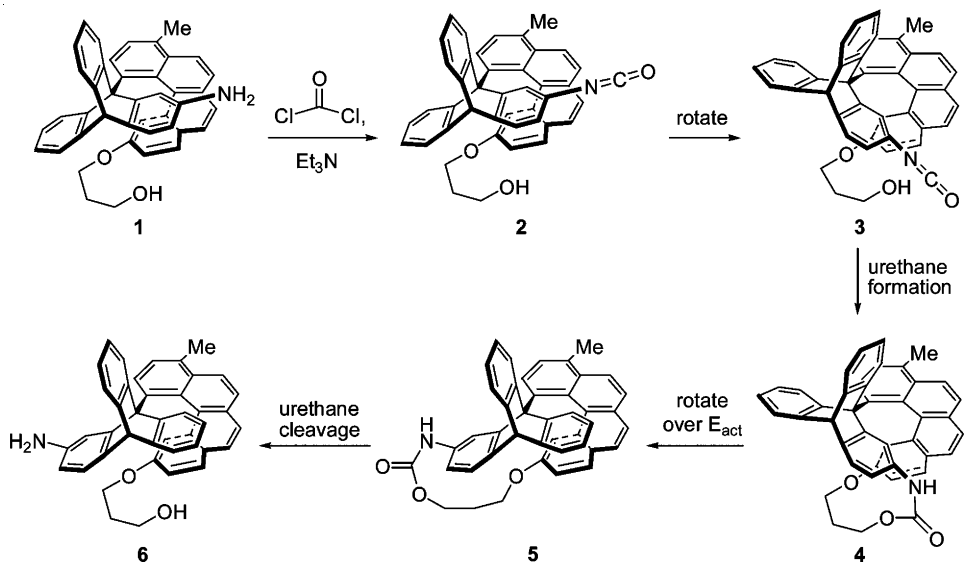


Figure 5. Sequence of events in the chemically powered rotation of **1** to **6**.

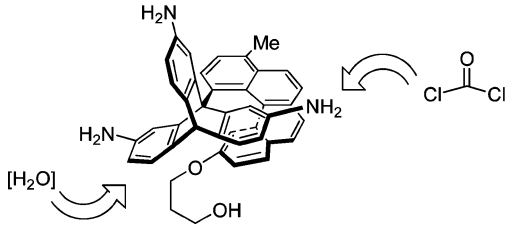


Figure 6. Schematic for a continually rotating molecular motor involving selective (and repeated) delivery of $Cl_2C{=}O$ to the amino group in the "firing" position and cleavage of the urethane only after each 120° of rotation has occurred.

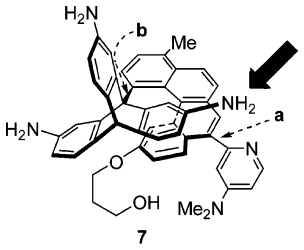
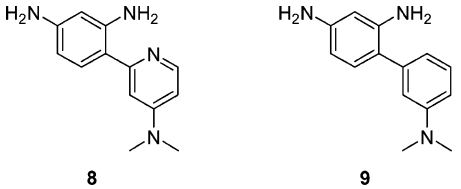


Figure 7. Proposed repeatedly rotating motor.

Model studies with **8** had previously[16] demonstrated that the presence of the DMAP unit in **8** directs monoacylation exclusively to the adjacent amino group. In the case of the non-pyridine control (**9**), a mixture of both possible monoacylation products was obtained.



A DMAP unit was enlisted as a delivery vehicle because DMAP and other 4-(dialkylamino)pyridines are frequently employed as catalysts for the acylation of sterically hindered alcohols and phenols.[17,18] The process usually takes place via the reaction of DMAP with the acylating agent (typically an acid chloride or anhydride), followed by attack of the nucleophile on the *N*-acylpyridinium salt. The acylation of amines with acyl chlorides is usually so fast that it does not require the addition of a catalyst. However, it has been documented[19] that the DMAP-catalyzed reaction of *m*-chloroaniline with benzoyl chloride is about 10^6 times faster than the noncatalyzed reaction, suggesting a decidedly higher reactivity of acid chlorides toward DMAP than toward anilines. We thus envisioned[16] that inclusion of a suitably positioned DMAP group in our design of a molecular motor would allow for selective intramolecular delivery of phosgene to only the amino group in the firing position, i.e., the one situated proximate to the DMAP moiety (see bold arrow in Figure 7). The design of **7**, i.e., the placement of the DMAP unit, was arrived at using Spartan-based (pBP/DN**//AM1) molecular modeling.[20] Modeling of **7** shows that once the DMAP unit has reacted with the phosgene, the carbonyl carbon of the resulting acylated species (acylpyridinium ion) is in very close proximity to the nearby aniline for conformations that are close in energy to the ground-state conformation by rotation around bond **a** and/or low-energy rotation around bond **b** in Figure 7 (on the basis of earlier work,[21] the barrier to full rotation around bond **b** is estimated to be 20−25 kcal/mol).

Synthesis. Given the foregoing rationale, the synthesis of **7** was undertaken. The synthesis of **7** was patterned as closely as

(16) Kelly, T. R.; Cavero, M. *Org. Lett.* **2002**, *4*, 2653−2656.

(17) For reviews, see: (a) Sheinkman, A. K.; Suminov, S. I.; Kost, A. N. *Russ. Chem. Rev.* **1973**, *42*, 642−661. (b) Hassner, A.; Krespki, L. R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069−2076. (c) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569−583. (d) Ragnarsson, U.; Grehn, L. *Acc. Chem. Res.* **1998**, *31*, 494−501. (e) Spivey, A.; Maddaford, A.; Redgrave, A. J. *Org. Prep. Proced. Int.* **2000**, *32*, 333−365. (f) Murugan, R.; Scriven, E. F. V. *Aldrichim. Acta* **2003**, *36*, 21−27. (g) Spivey, A. C.; Arseniyadis, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5436−5441.

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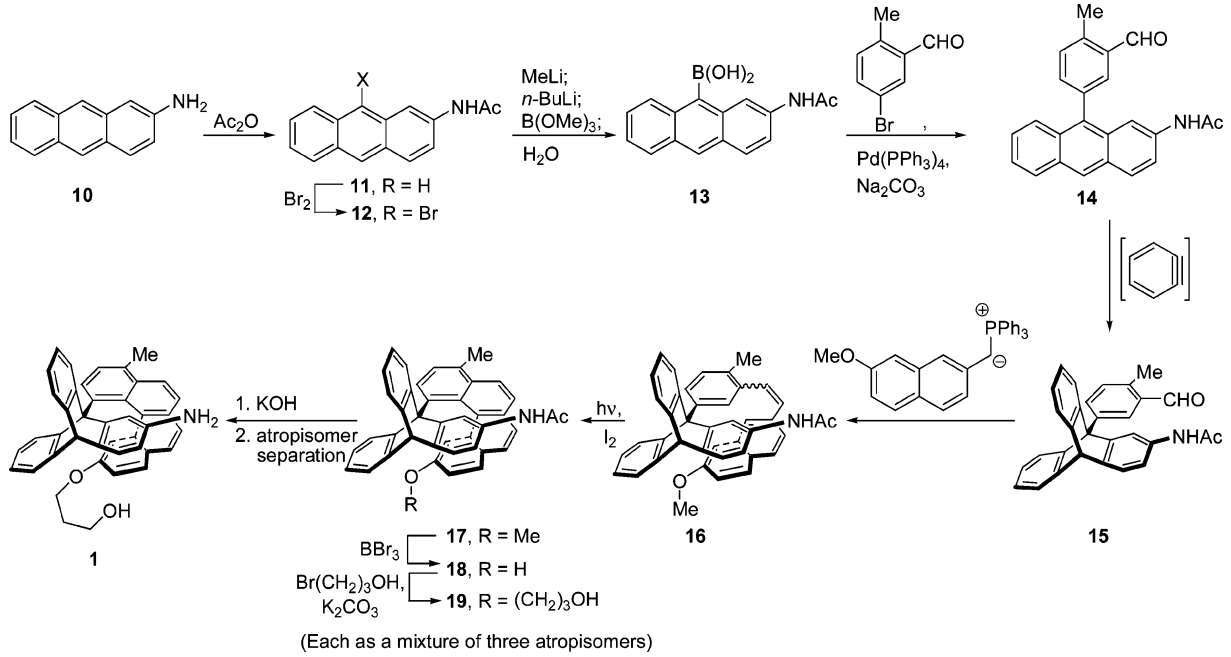
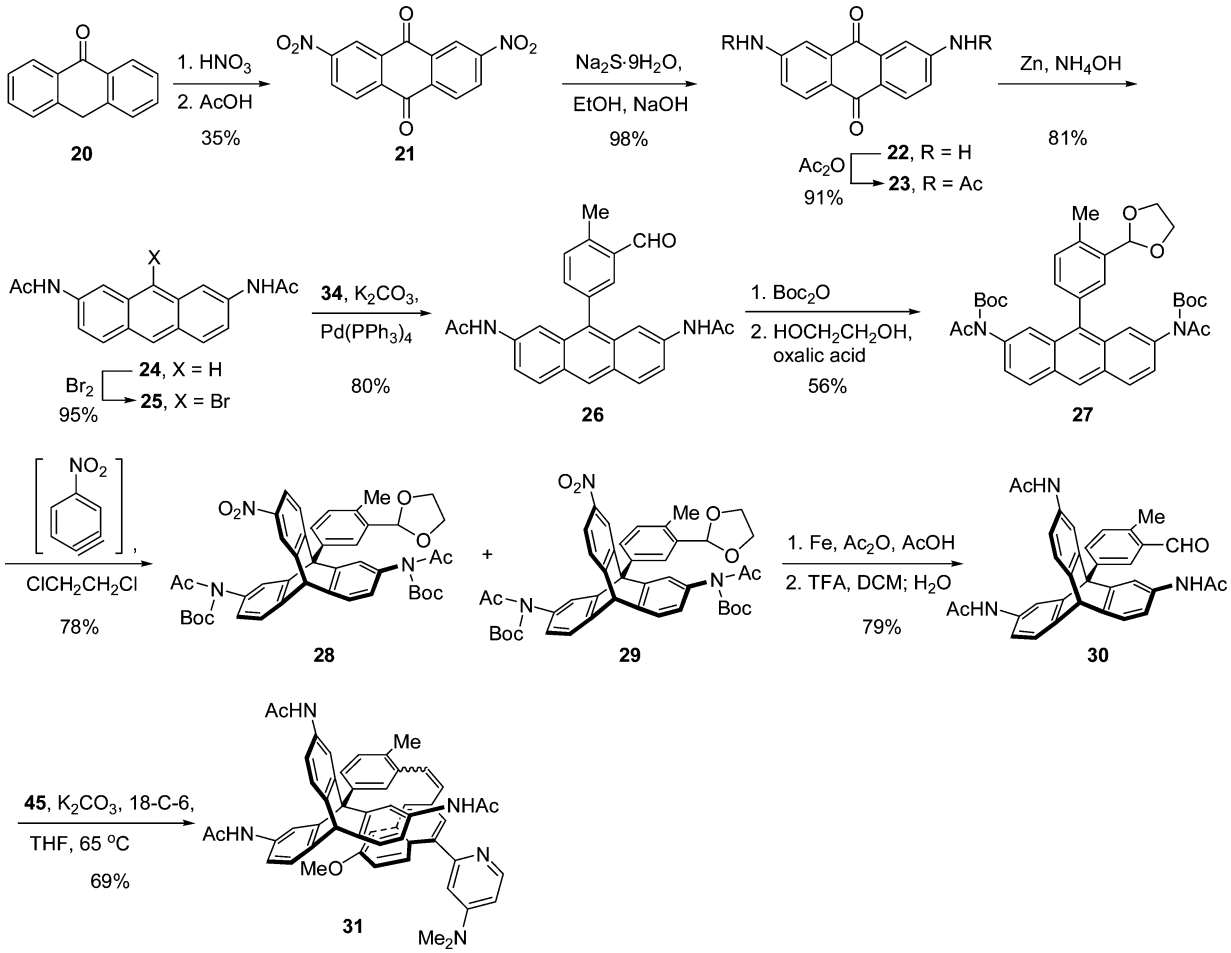
(19) Litvinenko, L. M.; Kirichenko, A. I. *Dokl. Akad. Nauk SSSR* **1967**, *176*, 97−100; *Dokl. Chem. Engl. Transl.* **1967**, 763−766.

(20) Software used: *Spartan*, Version 4.0; Wavefunction, Inc.: Irvine, CA, 1999 (for Silicon Graphics computers).

Scheme 1

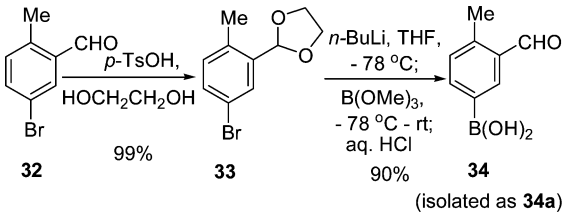


Scheme 2

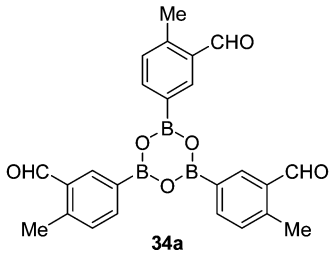


possible after the synthesis[9,22] of prototype **1** (Scheme 1), with the hope that the fewer deviations from the earlier route (Scheme 1), the better the chances for success. The synthesis of **7** commenced (Scheme 2) with the known preparation[23] of diaminoanthraquinone **22** from commercially available anthrone (**20**), and the two amines were acetylated. The anthraquinone unit was then converted[24] to an anthracene (**24**), which, under carefully controlled conditions, can be brominated to **25** in high yield.[25] The regiochemistry of the bromination is that anticipated on the basis of the reinforcing directing effects of the two

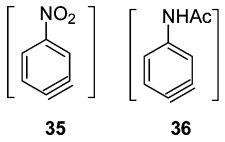
acetamido groups in the electrophilic aromatic substitution. Suzuki coupling[26,27] of bromide **25** with boronic acid **34** provided aldehyde **26**. Boronic acid **34**, isolated as the trimeric anhydride **34a**, was prepared from the known[28] bromotoluldehyde **32** as shown in eq 1.



(1)



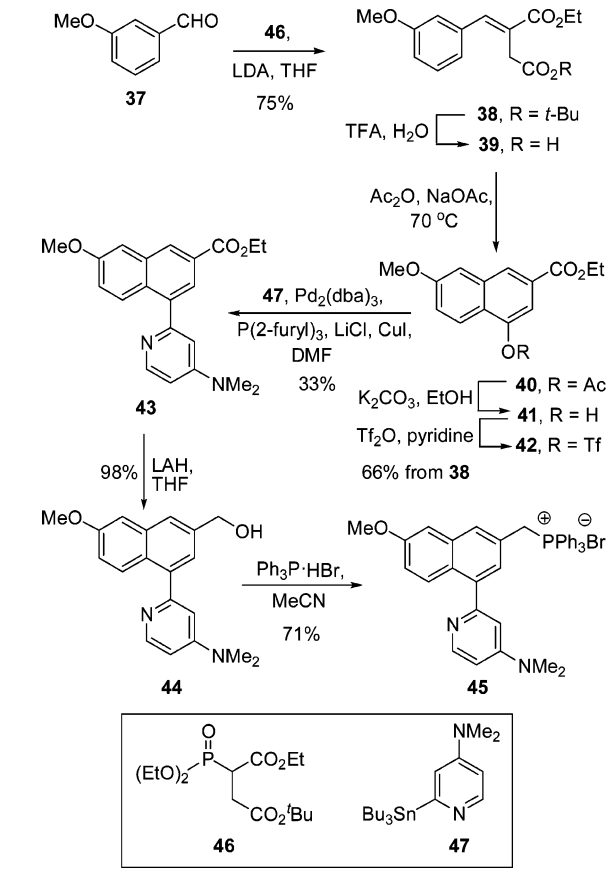
Because the ensuing benzyne addition proceeds in higher yield if the amide NH's and the aldehyde are protected, those groups were converted to their Boc and dioxolane derivatives, respectively, to give **27** (Scheme 2). Reaction of **27** with 4-nitrobenzyne,[29] prepared by diazotization of the corresponding 5-nitroanthranylic acid, gave an approximately 1:1 regioisomeric mixture of the two triptycenes **28** and **29** in a combined yield of 78%. The two regioisomers could be separated by careful chromatography. Assignment of the regiochemistry to the two benzyne adducts was accomplished after reduction[30] of the nitro group and acetylation of the resulting amine. Partial cleavage of the Boc and acetal groups occurs during this sequence, and it is completed by treatment with trifluoroacetic acid and water. Assigning the structure of the desired regioisomer (**30**) at that stage was then elementary because the ^{1}H NMR spectrum of **30** reveals the three-fold symmetry of the triptycene unit. It warrants mention that attempts to go directly from **26** to **30** using 4-acetamidobenzyne (**36**, from diazotization of 5-acetamidoanthranylic acid) in place of nitrobenzyne **35** failed. Even after a sample of authentic **30** was available (via **29**) to help search for **30** in the crude **26** + **36** product, no significant amount of **30** could be detected. It was a surprise to us that the



nature of a substituent would have such a profound impact on the reactivity of species as inherently reactive as benzynes are.

Wittig reaction between aldehyde **30** and the ylide derived from phosphonium salt **45** gave stilbene **31** as a 10:1 mixture of *E*/*Z* isomers. Phosphonium salt **45** was obtained by the sequence summarized in Scheme 3. The known naphthol **41** was prepared by the indicated route developed by Boger.[31] Reaction of the naphthol **41** with triflic anhydride gave triflate **42**. Stille coupling of triflate **42** with DMAP-stannane **47**[16] generated **43**. Reduction of the ester in **43** to the benzylic alcohol **44** and reaction of the latter with 2.5 equiv of triphenylphosphine hydrobromide afforded phosphonium salt **45** directly.

Scheme 3



With stilbene **31** in hand, we were optimistic that the synthesis of the final target (**7**) would soon be achieved, because the three remaining tasks (Scheme 4), stilbene photocyclization,[32] hydroxypropyl installation, and acetamide hydrolysis, had strong precedent in the synthesis of the prototype (Scheme 1). Unfortunately, our hopes for a swift conclusion were soon dashed, as we were unable to accomplish the photocyclization. Extremely extensive efforts that examined solvent, temperature, filters, lamps, and pH (to protonate the DMAP), all failed to generate any detectable amount of desired product. Comparison of the unsuccessful photocyclization of **31** to **48** with the previously successful photocyclization of **16** to **17** implicated

(21) See ref 9 and (a) Kelly, T. R.; Tellitu, I.; Sestelo, J. P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1866−1868. (b) Kelly, T. R.; Sestelo, J. P.; Tellitu, I. *J. Org. Chem.* **1998**, *63*, 3655−3665. (c) Davis, A. P. *Angew. Chem., Int. Ed.* **1998**, *37*, 909−910.
(22) The purpose of the methyl group is to block stilbene photocyclization from occurring on the otherwise less sterically encumbered position para to the triptycene.
(23) Perry, P. J.; Reszka, A. P.; Wood, A. A.; Read, M. A.; Gowan, S. A.; Dosanjh, H. S.; Trent, J. O.; Jenkins, T. C.; Kelland, L. R.; Neidle, S. *J. Med. Chem.* **1998**, *41*, 4873−4889.
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(26) (a) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513−519. (b) Sato, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1989**, 1405−1408. (c) Sasaki, M.; Fuwa, H. *Synlett* **2004**, 1851−1874. (d) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633−9695.
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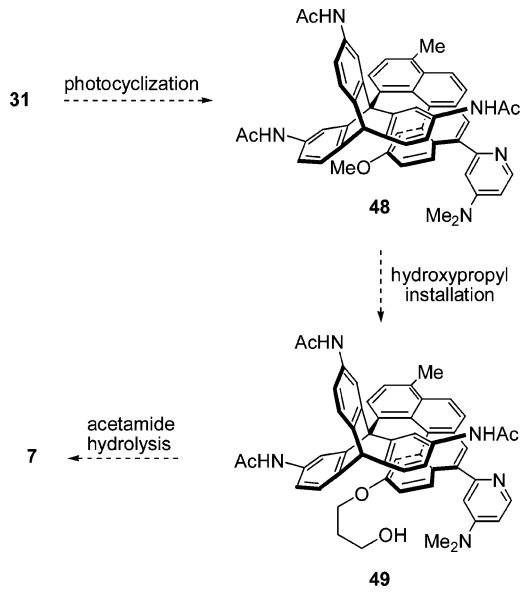
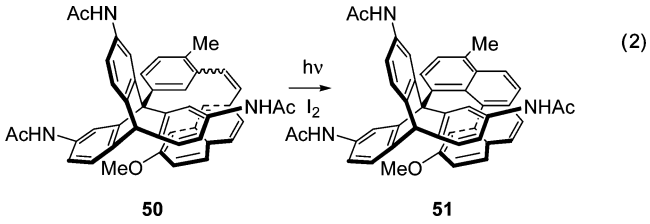
(30) Makosza, M.; Winiarski, J. *J. Org. Chem.* **1984**, *49*, 1494−1499.

Scheme 4

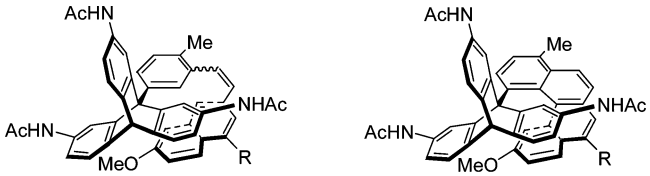


two possible culprits: the presence of a DMAP or the two extra acetamides on the triptycene. A control photolysis experiment with **50**, which lacks the DMAP but retains the three acetamides, led to the formation of the desired photoproduct **51** (eq 2), revealing that it was apparently the presence of the DMAP in **31** that was responsible for the difficulty.



(2)

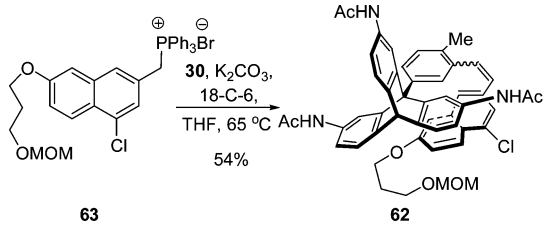
Protracted efforts (not detailed here) to identify a functional group that would allow both the photocyclization and the subsequent incorporation of the DMAP were conducted. Substrates that were synthesized and examined are **52**-**56**. Triflate **52** and bromide **53** failed in the photocylization; ethers **54** and **55** underwent the photocyclization adequately (20−25% yield) to **57** and **58** but could not be advanced to **59** (**59** appears unexpectedly unstable; attempts to convert **58** to **59** in the presence of a triflating agent (Tf_2O) in order to trap **59** as **60** failed).



52, R = OTf
53, R = Br
54, R = OEt
55, R = OTIPS
56, R = Cl

57, R = OEt
58, R = OTIPS
59, R = OH
60, R = OTf
61, R = Cl

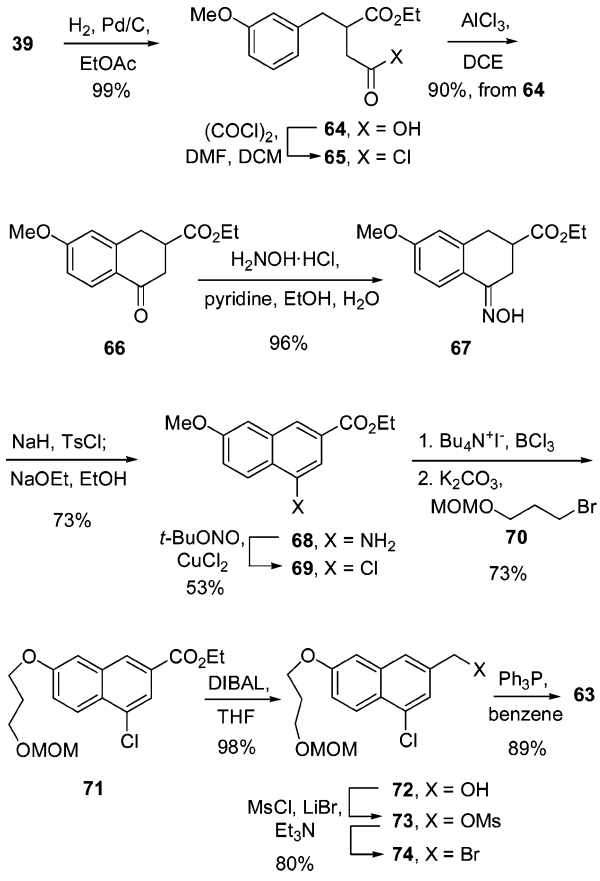
As a last resort, we examined the photocyclization of chlorostilbene **56** to chlorohelicene **61**. Aryl chlorides have historically been inferior partners in palladium-catalyzed couplings, but we hoped that recent advances in the couplings of aryl chlorides, notably due to Fu[33] and Buchwald,[34] might save the day. Chloride **56**, unlike bromide **53** (which suffered rapid decomposition upon photolysis), proved a competent substrate for photocyclization. Consequently, chlorostilbene **62** was prepared (eq 3) as a 10:1 *E*/*Z* mixture by a Wittig reaction between the ylide derived from phosphonium salt **63** and aldehyde **30**.



(3)

The synthesis of **63** is summarized in Scheme 5. The aforementioned unsaturated acid **39** was hydrogenated to **64** over Pd/C. The latter was converted with oxalyl chloride to the corresponding acid chloride **65**, which, without isolation, underwent $AlCl_3$-induced intramolecular Friedel−Crafts acylation to give tetralone **66**. Semmler−Wolff rearrangement[35] of the derived oxime **67** then gave naphthylamine **68**, which was converted to chloride **69** through application[36] of a Sandmeyer

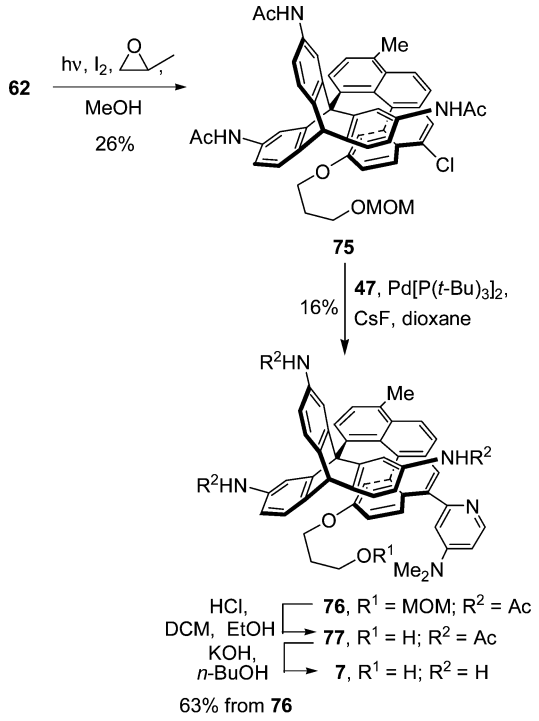
Scheme 5



(31) Boger, D. L.; McKie, J. A.; Cai, H.; Cacciari, B.; Baraldi, P. G. *J. Org. Chem.* **1996**, *61*, 1710−1729.
(32) For a review, see: Mallory, F. B.; Mallory, C. W. *Org. React.* **1984**, *30*, 1−456.
(33) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343−6348.
(34) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028−13032.

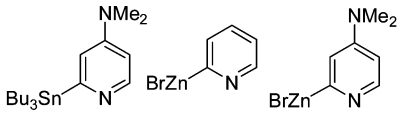
reaction. A methoxymethyl (MOM)-protected version of the hydroxypropyl side chain was installed by cleavage[37] of the methyl ether and alkylation of the resulting phenol with bromide **70**[38] to give **71**. The ester group in **71** was reduced, and the resulting benzylic alcohol **72** was converted to the bromide **74** by way[39] of unisolated mesylate **73**. Reaction of bromide **74** with triphenylphosphine then gave phosphonium salt **63**.

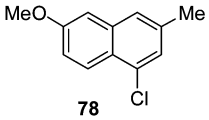
Scheme 6



As expected (Scheme 6) on the basis of the successful conversion of **56** to **61**, photocyclization of **62** afforded helicene **75** (26% yield). But the continuing inferiority of aryl chlorides (compared to aryl bromides) in some demanding palladium-catalyzed coupling reactions was soon manifested.[40] Model studies with chloromethoxynaphthalene **78** as a surrogate for **75** were promising (Table 1) with DMAP-stannane **47** using Fu's[33] conditions, and with commercially available 2-pyridylzinc bromide using Buchwald's[34] protocol for the Negishi coupling. Unfortunately, despite the very generous assistance of Professors Fu, Buchwald, and others (see Acknowledgments), extension of the model studies to the real system was disappointing. The Negishi coupling of **80** with **75** gave no identifiable **76**, an outcome presaged by the difference in yields of the reactions of **78** with **79** and **80**. In contrast to the 75% yield of the reaction of **78** and **47** with Fu's catalyst, the yield in the real system (**75** + **47** → **76**) plummeted to a single digit. After 4 months of

Table 1. Yields of Coupling Reactions of Chlorides **78** and **75** with Pyridine Derivatives



	47	**79**	**80**
 **78**	75%	60%	28%
75	7%	not determined	no useful reaction

attempted optimization, the yield was only about 7%. Nonetheless, despite extreme limitations in material, we elected to push forward to **7**, as shown in Scheme 6, since only two deprotection steps remained; they were in due course reduced to practice.[41]

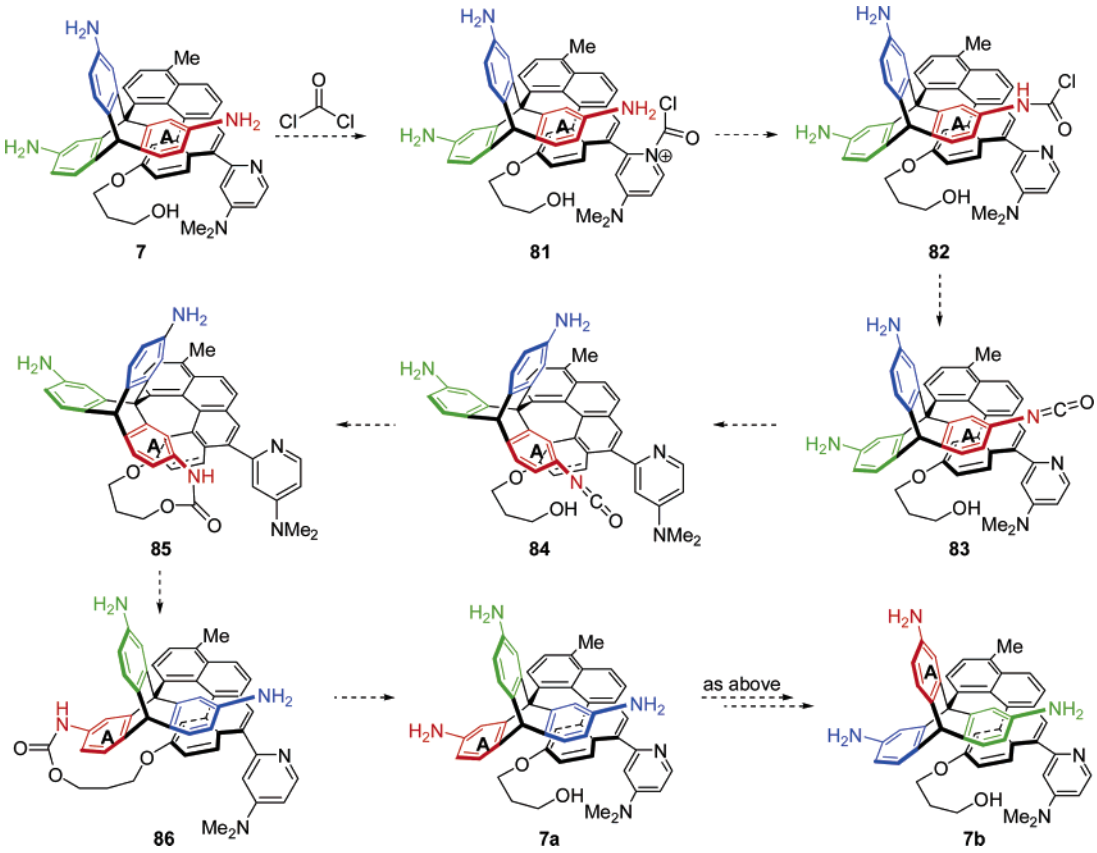
Notwithstanding the limited quantities of **7** available (during the course of the several months devoted to the following studies, the yield[42] of the Stille coupling of **75** with **47** to give **76** was raised to 16%), it was still possible to evaluate whether **7** functioned as designed. The plan (or at least the desire) was that the sequence of events summarized in Scheme 7 would happen. Specifically, the hope was that the DMAP unit would capture a phosgene molecule to give **81** and pass it to the proximal triptycylamino group, giving **82**. If subsequent events proceeded in analogy to Figure 5, then unidirectional rotation would ensue, but in a manner that could be repeated *ad infinitum*.

Addition of phosgene followed by triethylamine to a solution of **7** in $CDCl_3$ according to the reaction conditions that accomplished the unidirectional rotation of the prototype (Figure 5) instead led to near-instantaneous precipitation of the vast majority of the material. That precipitation was originally attributed to insolubility of amine hydrochloride salts, but the same problem persisted when tetrahydrofuran (THF) was used as solvent. Mass spectrometry (MS) of the crude reaction mixture revealed that it contained virtually no volatiles, even under conditions where amine hydrochloride salts of **7**, **85**, **86**, etc. would be volatilized. The problem was not insolubility, but polymerization, presumably due to intermolecular urea formation. Intermolecular urea formation did not complicate the study of the prototype (Figure 5), although, *a priori*, it loomed as a possible concern.

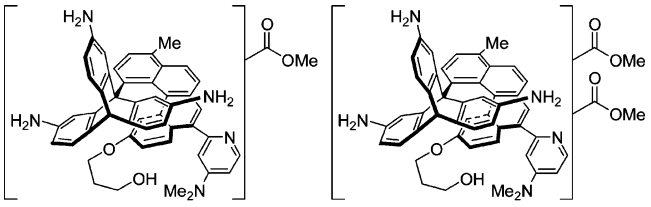
Dilution of the initial concentration of **7** by a factor of 100 (which should diminish the rate of a bimolecular reaction by a factor of 10 000) and lowering the reaction temperature to −78 °C effectively suppressed polymerization (at least during the

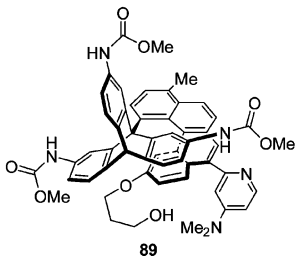
(35) For a review, see: (a) Conky, R. T.; Ghosh, S. In *Mechanisms of Molecular Migrations*; Thyagarajan, B. S., Ed.; Interscience: New York, 1971; Vol. 4, pp 197−308. See also: (b) Garst, M. E.; Cox, D. D.; Harper, R. W.; Kemp, D. S. *J. Org. Chem.* **1975**, *40*, 1169−1170.
(36) (a) Doyle, M. P.; Siegfried, B.; Dellaria, J. F. *J. Org. Chem.* **1977**, *42*, 2426−2431. (b) Cadogan, J. I.; Roy, D. A. *J. Chem. Soc. C* **1966**, *14*, 1249−1250.
(37) Brooks, P. R.; Wirtz, M. C.; Vetelino, M. G.; Rescek, D. M.; Woodworth, G. F.; Morgan, B. P.; Coe, J. W. *J. Org. Chem.* **1999**, *64*, 9719−9721.
(38) Sato, T.; Kumagawa, T.; Sugimoto, A.; Yamakawa, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 301−310.
(39) Andrus, M. B.; Hicken, E. J.; Meredith, E. L.; Simmons, B. L.; Cannon, J. F. *Org. Lett.* **2003**, *5*, 3859−3862.
(40) For a recent review of the Stille reaction, see: Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704−4734.
(41) Strictly speaking, since **7** is chiral, it would be necessary to resolve **7** to have a system capable of truly unidirectional rotation. But since enantiomers in an achiral environment give identical NMR, MS, and IR spectra, carrying out the resolution would not have increased the information generated and, therefore, would not have warranted the investment of effort required to develop a resolution of **7**.
(42) Yields of palladium-catalyzed couplings are reported to often improve substantially when the couplings are conducted in a microwave reactor [(a) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717−727. (b) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250−6284 and references therein]. Due to the paucity of **75**, we were not able to extensively study the effect of microwave-promoted reactions, but in our one attempt (a CEM Discovery microwave reactor was utilized), the microwave-promoted reaction gave results inferior to those obtained under optimized non-microwave conditions.

Scheme 7



initial reaction period). Because of the conditions of high dilution we were forced to employ, MS was used to monitor reaction progress. Operationally, that was accomplished by quenching aliquots of the reaction mixture into methanol and recording the mass spectrum of the resulting mixture. But a new problem surfaced: The mass spectrum showed not only a peak for the expected monomethylurethane **87**, but also smaller, although still significant peaks for bi- (**88**) and triurethanes (**89**), even

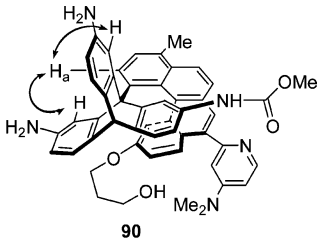




when only 1 equiv of phosgene was used. MS is not able to determine whether the monourethane was derived from **82** (or **83**) or from "phosgenylation" of one of the other two triptycene-based amino groups, or whether the peak represented a mixture of all three possible monourethanes. But the formation of significant amounts of bi- and triurethanes when only 1 equiv of phosgene was used strongly implied that the DMAP was not performing its intended role of capturing and delivering one—and only one—phosgene molecule. It appeared that the phosgene was too reactive toward the triptycyl amines to give the DMAP time to function as desired.

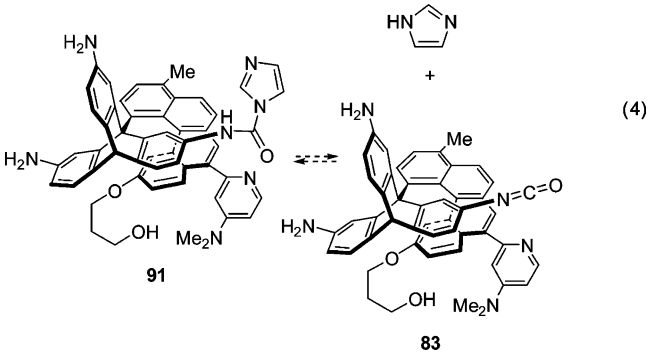
A less reactive surrogate for phosgene was sought, and 1,1′-carbonyldiimidazole was chosen. Reaction between **7** and 1,1′-carbonyldiimidazole only gives monoacylation (monitored as before by methanol quench/mass spectrometry). As judged by ^{1}H NMR, the methanol quench led to the clean formation of a single monomethylurethane. That finding suggests that only one of the triptycylamines is being converted to the corresponding imidazolyl urea, but it does not establish which amine is being acylated.

The structure of the methanol-quenched product from monoacylation of **7** with 1,1′-carbonydiimidazole was assigned unambiguously as **90** by careful and extensive 2-D NMR studies on both **90** and **7**. The ^{1}H NMR chemical shift assignments for



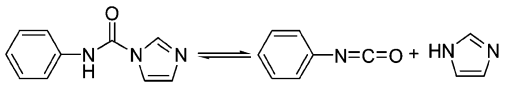
the protons in **90** and **7** are given in the Supporting Information. A long-range correlation, between H_a on the helicene and

protons on two blades of the triptycene in both **90** and **7**, allowed for the identification of which blade of the triptycene in **90** bore the methyl urethane. It is the one blade that does not exhibit a long-range correlation with H_a; that one blade corresponds to the blade proximate to the DMAP. Comparison of the chemical shifts in **90** and **7** (see Supporting Information) indicates that it is only in the triptycene blade proximate to the DMAP that there is a significant difference in the ^{1}H chemical shifts for **90** and **7**. *We conclude that the strategy of using the DMAP to selectively deliver the 1,1′-carbonyldiimidazole to only one of the three aminotriptycene blades to give* ***91*** *has succeeded*. All that remains is for **91** to convert, à la eq 4, to isocyanate **83** to trigger (Scheme 7) unidirectional rotation to **86** as in the prototype.



(4)

Imidazolyl ureas of primary anilines are reported by Staab[43] to be in equilibrium with the corresponding isocyanates (eq 5). If (i) that equilibrium occurs here and (ii) the **7**-based system behaves in analogy to the prototype (Figure 5), then the sequence of events in Scheme 7 should unfold. But it does not. In the prototype (Figure 5), so-called prebarrier urethane **4** forms so fast upon addition of phosgene and triethylamine to **1** that the formation of isocyanate **2** cannot be detected by ^{1}H NMR. Rather, **4** is the first detectable intermediate, and it is the rotation of **4** to **5** that is the rate-determining step. But in the present case of **7**, MS of the methanol-quenched reaction mixture shows no significant peak for either **85** or **86** (being isomers, **85** and **86** would give molecular ions of the same mass).



92 93

(5)

In seeking to troubleshoot the situation, it was essential to identify the entity actually present in solution after the DMAP-achieved delivery of the 1,1′-carbonyldiimidazole to the adjacent aminotriptycene blade. MS indicated that, prior to the methanol quench (to give **90**), the molecule had a mass of 760, consistent with isocyanate **83**, the isomeric intramolecular urethane **85** (or **86**), or possibly **91**, which might fragment to **83** in the mass spectrometer. While appropriate infrared spectroscopy measurements might have provided the answer, we enlisted ^{13}C NMR labeling studies. ^{13}C-Labeling of the carbonyl carbon of 1,1′-carbonyldiimidazole has been reported.[44] Using commercially available 99% ^{13}C-labeled phosgene, ^{13}C-carbonyl labeled 1,1′-carbonyldiimidazole was prepared and substituted for the 1,1′-carbonyldiimidazole used to prepare **91**.

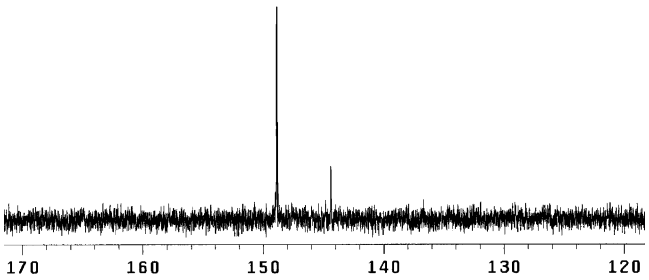


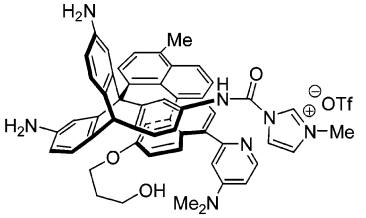
Figure 8. ^{13}C NMR spectrum of the crude product of the reaction between **7** and 99% ^{13}C-carbonyl-labeled 1,1′-carbonyldiimidazole. The peak at δ 144 Hz is from excess ^{13}C-carbonyl-labeled 1,1′-carbonyldiimidazole. The peak at δ 149 Hz corresponds to ^{13}C-carbonyl-labeled **91** (see text).

Since the natural abundance of ^{13}C is approximately 1%, the carbonyl-derived ^{13}C-labeled (from 99% ^{13}C-phosgene) peak for the yet-undetermined **83**, **85**, or **91** stands out in the ^{13}C NMR spectrum of the unknown (Figure 8) like a telephone pole in a recently mown hayfield. The chemical shift of the peak (δ 149 Hz) is substantially downfield of the chemical shift range (ca. δ 125 Hz) for *N*-aryl isocyanates, but well within the range expected for the carbonyl carbon in **85** and **91**.[45] Heteronuclear multiple bond correlation (HMBC) NMR spectroscopy served to distinguish between **85** and **91** because it shows a strong correlation between the ^{13}C carbonyl carbon and two imidazole hydrogens (and none to a tether methylene), thereby establishing that the species in hand was **91**.

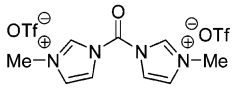
As mentioned above, Staab's documentation of the equilibrium in eq 5 had led us to anticipate a similar equilibrium between imidazole urea **91** and isocyanate **83** plus imidazole (eq 4). But apparently that equilibrium was not being established, because the expected cascade of events (Scheme 7) that would be unleashed upon the formation of **83** did not occur. Attempts to activate the imidazole by protonation[46] by addition of one or several equivalents of methanesulfonic acid, or metal ion[47] (Hg^{2+}) coordination [several equivalents of Hg(triflate)$_2$ were added in case of competing coordination by other nitrogens in **91**], did not provoke any reaction. Not surprisingly, attempts to methylate[48] the imidazole with methyl triflate to give **94** led to a complex mixture of products. Efforts to promote the conversion of **91** to **83** by using the phosphazene base known as P_1-*t*-Bu-tris(tetramethylene)[49] and the guanidine base 2-*tert*-butyl-1,1,3,3-tetramethylguanidine[50] also failed. The thermal instability of **91** severely constrained other options: a $CDCl_3$

(43) Staab, H. A. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 351−367.
(44) Nelson, V. C. *J. Labelled Compd. Radiopharm.* **1996**, *38*, 713−723.
(45) Evident from examination of ^{13}C NMR spectra of *N*-aryl isocyanates, urethanes, and ureas in *The Aldrich Library of ^{13}C & ^{1}H FT NMR Spectra*, 1st ed.; Pouchet, C. J., Behnke, J., Eds.; Aldrich Chemical Co., Inc.: Milwaukee, WI, 1993; Vols. 1−3.
(46) (a) Staab, H. A.; Wendel, K.; Datta, A. P. *Justus Liebigs Ann. Chem.* **1966**, *694*, 78−85. (b) Oakenfull, D. G.; Jencks, W. P. *J. Am. Chem. Soc.* **1971**, *93*, 178−188. (c) Oakenfull, D. G.; Salvesen, K.; Jencks, W. P. *J. Am. Chem. Soc.* **1971**, *93*, 188−194.
(47) Of common metal ions, mercuric ion has the strongest affinity for imidazole [(a) Brooks, P.; Davidson, N. *J. Am. Chem. Soc.* **1960**, *82*, 2118−2123. (b) Smith, R. M.; Martell, A. E. *Critical Stability Constants*; Plenum Press: New York and London, 1975; Vol. II, pp 144−145, 208]. Ley has used zinc-ion coordination to activate *N*-acylimidazoles to hydrolysis (Ford, M. J.; Ley, S. V. *Synlett* **1990**, 255−256), but at somewhat elevated temperatures.
(48) Ulibarri, U.; Choret, N.; Bigg, D. C. H. *Synthesis* **1996**, 1286−1288.
(49) Schwesinger, R.; Hasenfratz, C.; Schlemper, H.; Walz, L.; Peters, E. M.; Peters, K.; von Schnering, H. G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1361−1363. Reagent obtained from Fluka.
(50) Barton, D. H. R.; Chen, M.; Jaszberenyi, J. C.; Taylor, D. K. *Org. Synth.* **1997**, *74*, 101−107. Reagent obtained from Fluka.

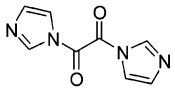
solution of **91** is stable for ca. 3 days at −25 °C but decomposes overnight at room temperature. Attempts to prepare **94** directly by use of Rapoport's[51] 1,1′-carbonylbis(3-methylimidazolium) ditriflate (**95**) were thwarted because the very reactive **95** behaves toward **7** like the unselective phosgene rather than like 1,1′-carbonyldiimidazole itself. Oxalyldiimidazole (**96**) was also examined as a possible fuel but failed (as judged by MS, giving monoacylation but no further reaction).



94



95

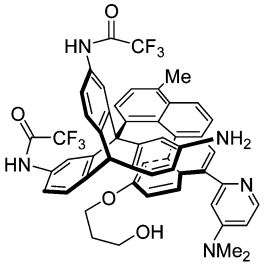


96

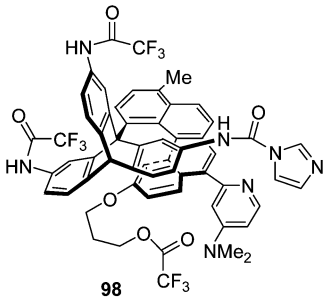
Two explanations for our failure to implement Scheme 7 presented themselves. One possibility was that, despite the seemingly apt precedent of Figure 5 for Scheme 7, there was some unrecognized design flaw that doomed Scheme 7 to failure. The other possibility was that our problems were due to limitations inherent in the fuels examined.

To resolve the question, we sought to re-examine phosgene, the fuel that was successful in powering the prototype (Figure 5), under circumstances where lack of selectivity for monoacylation would not be a problem. The hope was to use a molecule such as **97**, where the two anilines we wished to keep uninvolved are removed from the action by acylation. It might be regarded as far-fetched to imagine that **7** could be selectively converted to **97**. But in **91**, the one aniline we do not seek to protect is already masked. As events unfolded, exploratory experiments involving reaction of *in situ*-generated **91** with ostensibly 2 equiv of trifluoroacetic anhydride (TFAA, as a solution in $CDCl_3$) gave, as established by mass spectrometric monitoring of the reaction, a mixture of mono-, bis-, and tristrifluoroacetyl derivatives of **91**. The formation of a tristrifluoroacetate, presumably **98**, was an unexpected complication, but perhaps a result of inaccurate measurements of the amount of **7** or TFAA resulting from conducting the exploratory, moisture-sensitive experiment on submilligram amounts of **91** due to the paucity of **7**. Fortunately, a simple solution presented itself: use excess TFAA to convert all of **91** to **98**.

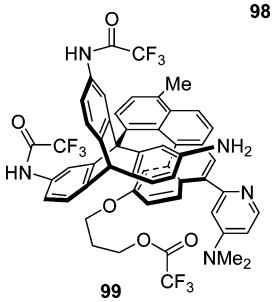
Trifluoroacetate esters are exceptionally labile to hydrolysis.[52] Evaporation of volatiles from **98** (to remove residual TFAA that might trifluoroacetylate the unmasked aniline NH_2 in **99**)



97



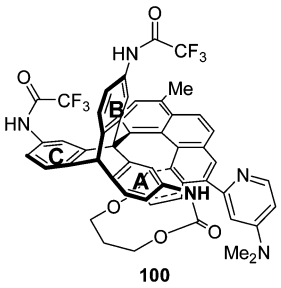
98



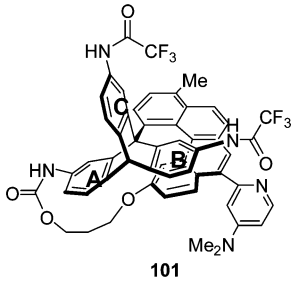
99

and stirring the crude residue first for 4 h with a mixture of water and CH_2Cl_2 (which, as evidenced by MS, cleaved the imidazolylurea in **98** to give **99**) and then with aqueous THF (which hydrolyzed the sole trifluoroacetyl ester in **99**) gave monoamine **97**.

With **97** in hand, we now had a species where we could, as with the prototype, use phosgene/triethylamine as fuel. The system thus differs from the prototype by only a single variable: the precise structure of the motor molecule. If our failure to achieve rotation of **7** with 1,1′-carbonyldiimidazole and oxalyldiimidazole was a consequence of a difference in the fuel, then reaction of **97** with phosgene/triethylamine should result in unidirectional rotation (via **100** and **101**). On the other hand, if the problem is with the precise structure of the motor molecule, then use of the same fuel (phosgene/triethylamine) as works with the prototype will still not produce rotation.



100

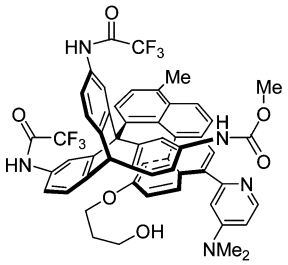


101

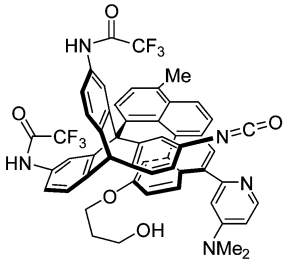
With the opportunity for achieving a clear-cut answer finally secured, **97** was treated with phosgene/triethylamine exactly as was done with the prototype. Quenching of an aliquot of the reaction mixture into methanol and mass spectrometric examination showed a strong molecular ion peak for monomethylurethane **102**, indicating that the reaction of **97** with phosgene to give **103** (and/or **104**) was definitely successful. But the mass spectrum showed no peak attributable to intramolecular urethane **100** or **101**. (The mass spectrum of the reaction mixture prior to a methanol quench also showed no peak for **100** or **101**, excluding the possibility that the desired intramolecular urethanes were formed initially but then were being cleaved to **97** or **105** in the methanol quench.) In short, despite the seemingly compelling precedent provided by the prototype system (Figure 5), the completely developed versions do not rotate.

(51) Saha, A. K.; Schultz, P.; Rapoport, H. *J. Am. Chem. Soc.* **1989**, *111*, 4856−4859. This paper reports a ^{1}H NMR spectrum for **95** of δ 8.86 (s, 2H), 7.44 (m, 2H), 7.16 (m, 2H), 4.00 (s, 6H), but the solvent is not explicitly indicated. The general section says that NMR spectra were recorded in $CDCl_3$ unless otherwise indicated. In our hands, **95** is not sufficiently soluble in $CDCl_3$ to permit recording of a ^{1}H NMR spectrum. The ^{1}H NMR spectrum for **95** in CD_3CN shows δ 9.18 (s, 2H), 7.98 (m, 2H), 7.72 (m, 2H), 4.00 (s, 6H), in agreement with a spectrum of **95** in CD_3CN kindly provided by Dr. S. Sabesan (see: Sabesan, S. *Tetrahedron Lett.* **1997**, *38*, 3127−3130).

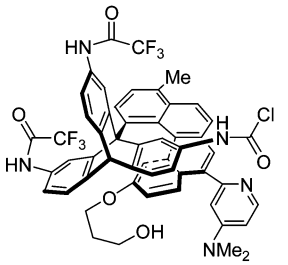
(52) Cramer, F.; Bär, H. P.; Rhaese, H. J.; Sänger, W.; Scheit, K. H.; Schneider, G.; Tennigkeit, J. *Tetrahedron Lett.* **1963**, *16*, 1039−1042.



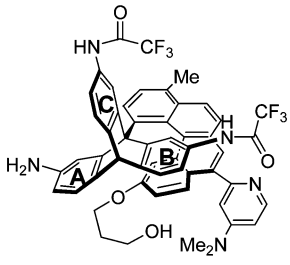
102



103

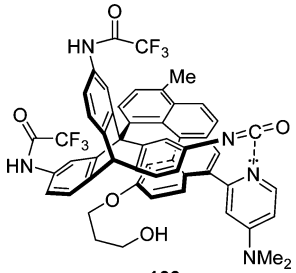


104



105

We are surprised that the fully elaborated systems **7** and **97**[53] are not successful. It is true that models are only models, but Figure 5 appears to be a compelling model, especially given that the DMAP unit functions as designed. We suggest two explanations for why **7** and **97** do not behave as motors. Perhaps in **7** and **97**, the hydroxypropyl group adopts a conformation different from that in the prototype, possibly due to hydrogen-bonding interactions with the DMAP or the added substituents on the other two triptycene blades. Alternatively, rotation around the triptycene/helicene bond in **7** and **97** may be so constrained [perhaps by hydrogen bonding or a Bürgi−Dunitz (or similar) interaction[54] as in **106**] that access to a rotationally excited rotamer (compare **3** in Figure 5) that brings the hydroxyl group on the propyl side chain within reach of the isocyanate is not possible.[55,56]



106

While we would, of course, have preferred to see Scheme 7 unfold as planned, we still believe we have two significant achievements to report: (i) success in the construction of **7**, a challenging synthetic target in and of itself, and (ii) the demonstration that the DMAP-based delivery strategy works. We also believe that a relatively easy solution exists for transforming **7** from a near miss to a fully functional, repeatedly rotating, chemically powered molecular motor. But a confluence of circumstances, including the principal investigator's (PI's) decision 4 years ago not to submit new grant applications, the ending of currently funded grants, and the consequent planned gradual winding down of his research program, render it unlikely that further work on this program will be accomplished at Boston College. It has been an exciting time and, as indicated in the lists of coauthors (present and past) and the Acknowledgments, the PI is grateful to many for helping make it happen.

Acknowledgment. We are grateful to the National Institutes of Health (grant no. GM56262) for support of this work. We thank Professors Greg Fu[33] (MIT), Steve Buchwald[34] (MIT), John Verkade[57] (Iowa State), and Antonio Echavarren[40] (Institut Català d'Investigació Química, Tarragona, Spain) for exchange of information about palladium-catalyzed couplings, Professors Sally Mallory[32] (U. Penn) and Frank Mallory[32] (Bryn Mawr) for discussions of stilbene photocyclizations, and Dr. Subramaniam Sabesan[51] (Dupont) for information regarding **95**. We also thank Dr. Eric L. Elliott for countless mass spectra, and Justin Pine, Meaghan O'Malley, Agata Sajkiewicz, Jack Beierle, Matt Demers, and Agnes Bak for assistance with the preparation of starting materials. Finally, we acknowledge numerous Boston College colleagues (faculty, postdocs, students and staff) for helpful suggestions and assistance, and Dr. John Schwab (NIGMS) for his interest.

Supporting Information Available: General experimental procedures, details of preparations/characterizations of all compounds, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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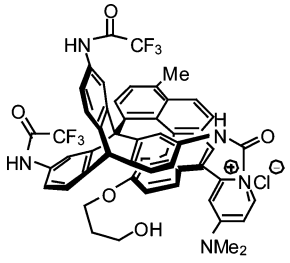
(53) Had **97** rotated, cleavage of the two relatively labile trifluoroacetamides—which can be achieved with methanol containing triethylamine—and urethane cleavage as with **101** → **105** would also have given a repeatedly rotating molecular motor system, although a somewhat more convoluted one.

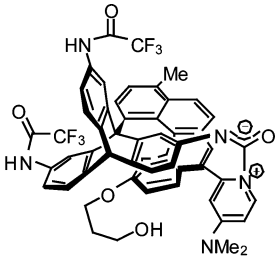
(54) Bürgi, H. B.; Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153−161.

(55) It has been suggested that use of excess phosgene may disrupt the Bürgi−Dunitz interaction, but excess phosgene does not change the outcome. MS indicated that the alcohol is not phosgenylated by excess phosgene under the conditions examined.

(56) We were unable to establish exactly what **97** is converted to ("**X**") upon addition of phosgene and triethylamine. Possibilities for **X** include **103**, **104**, **106**, **i**, and **ii**. Use of 99% ^{13}C-labeled phosgene in place of normal phosgene and ^{13}C NMR spectroscopy might have distinguished among those possibilities. But **X**, whatever it is, completely decomposes in less than 30 min at room temperature (see Experimental Section for preparation of **102**). Given the very limited quantities of **97** available, it would not have been possible to record a ^{13}C NMR spectrum of ^{13}C-labeled **X** before it decomposed.



i



ii

(57) Su, W.; Urgaonkar, S.; McLaughlin, P. A.; Verkade, J. G. *J. Am. Chem. Soc.* **2004**, *126*, 16433−16439.