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Troubleshooting a molecular motor: a remarkably stable *N*-acyl pyridinium salt

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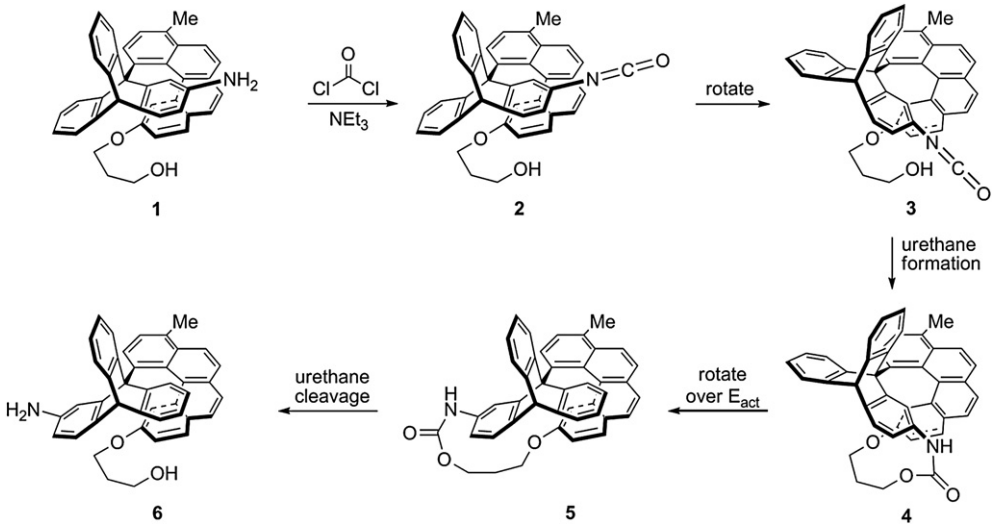
Dedicated to Professor J. Fraser Stoddart in honor of his unusually creative contributions to chemistry and on his receipt of the Tetrahedron Prize

ABSTRACT

With the objective of establishing why reaction of the proposed molecular motors **7** and **22** with carbonyldiimidazole and phosgene does not result in unidirectional rotation, *N*-ethyl-2-[4-(*N*,*N*-dimethylamino)-2-pyridinyl]benzenamine [**28**, 2-(2-(ethylamino)phenyl)DMAP] was examined as a model substrate. The synthesis of **28** is described. Compound **28** was found to react with phosgene to give the unexpectedly stable *N*-acyl pyridinium salt **30**. The latter (**30**) is so stable that it is effectively inert to reaction with methanol. At room temperature the two methyls in the Me_2N-group of **30** are nonequivalent (NMR) and the barrier to rotation around the Me_2N–pyridinium bond is 18.5 kcal/mol. To the authors' knowledge, that is the first quantitative determination of the barrier to rotation around the bond between a 4-(*N*,*N*-dimethylamino) group and an *N*-acyl pyridinium unit. The implications of the findings regarding **30** as to troubleshooting the proposed molecular motor **7**, and possible strategies to follow, are discussed.

1. Introduction

In 1999, we reported a prototype of the first rationally designed, chemically powered, rotary molecular motor.[1,2] The phosgene-fueled system is shown in Scheme 1 and achieves 120° of unidirectional rotation. More recently,[3] we have sought to advance **1** to a continuously rotating motor as summarized conceptually in Figure 1. The system shown in Figure 1 extends the prototype by: (i) having an amino group on each blade of the triptycene; (ii) providing a means for delivering phosgene (or its equivalent) to the amine in the 'firing position'; (iii) achieving a phosgene-powered, 120° rotation of the triptycene by formation of an intramolecular urethane in analogy to Scheme 1; (iv) affording a means for removing the remains of the phosgene by cleavage of the urethane,



Scheme 1. Prototype of a chemically powered, rotary molecular motor.

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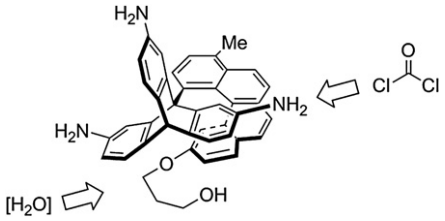


Figure 1. Schematic for a continuously rotating molecular motor involving selective (and repeated) delivery of $Cl_2C{=}O$ to the amino group in the 'firing position' and cleavage of the urethane only after each 120° of rotation has occurred.

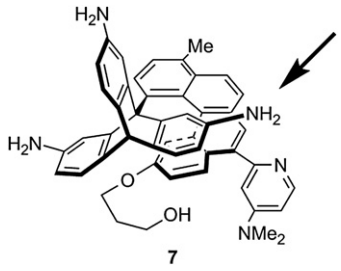


Figure 2. Proposed repeatedly rotating motor.

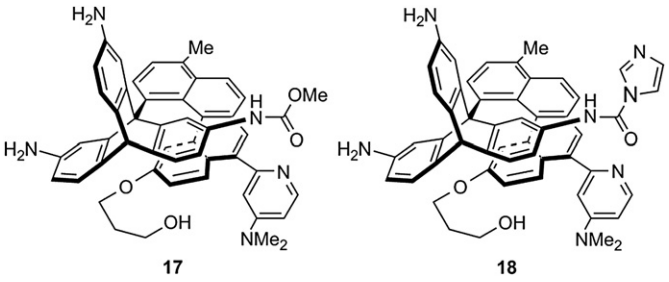
thereby allowing repeated rotation by repetition of the three preceding steps.

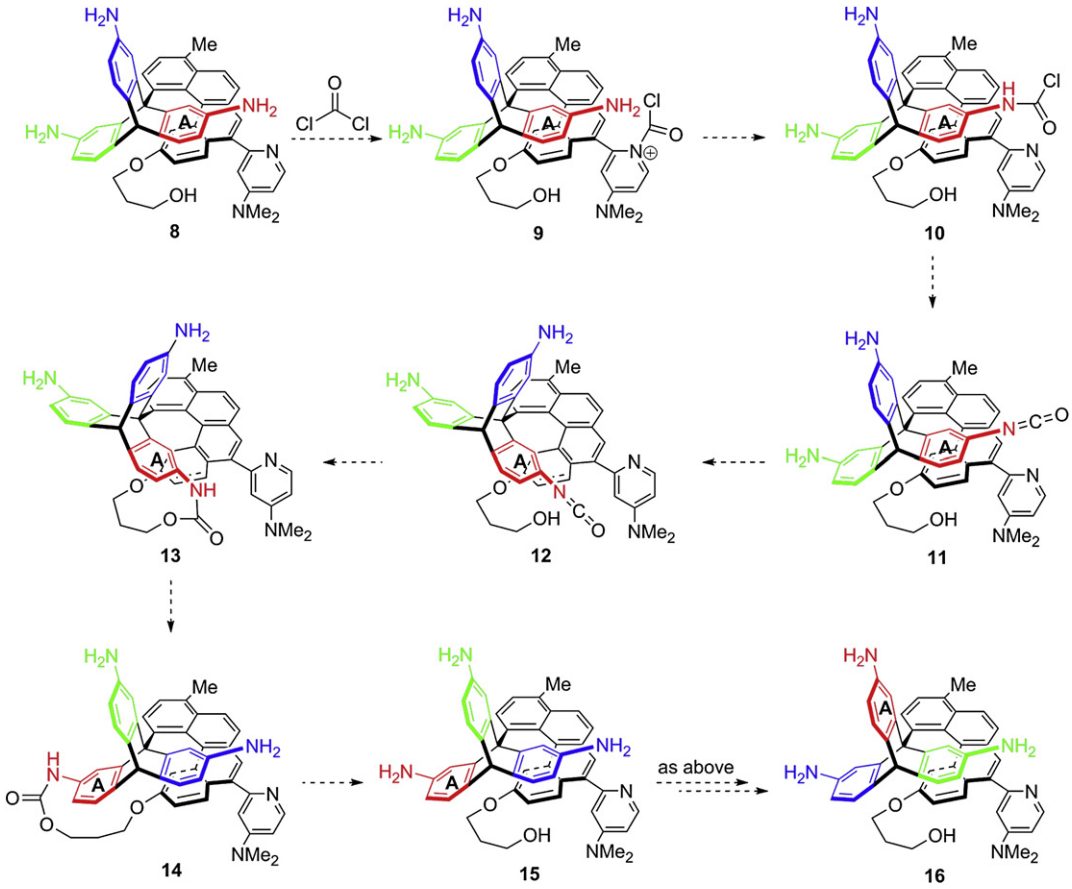
Compound **7** was chosen[3] as a molecular embodiment of the concepts in Figure 1, specifically addressing the first three (i)–(iii) items enumerated above, with the (dimethylamino)pyridine (DMAP) unit intended to capture and deliver the phosgene to the amino group (bold arrow in Fig. 2) in the firing position. The hope was to achieve the sequence of events given in Scheme 2, resulting in a continuously rotating molecular motor.

A major synthetic effort eventually made available limited, but sufficient, quantities of **7** to evaluate the design.[3]

2. Results and discussion

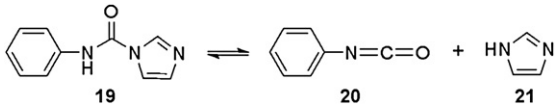
Reaction of **7** with phosgene and triethylamine under the same conditions that were successful with the prototype (Scheme 1) led to immediate polymerization of **7** by polyurea formation. Polymerization could be avoided (at least initially) by conducting the reaction at −78 °C under 100-fold more dilute conditions, but the phosgene seemed too reactive toward the triptycylamines to give the DMAP an opportunity to function as desired, since a mixture of mono-, di-, and tri-'phosgenylation' was observed. In order to give the DMAP time to accomplish its role, the phosgene was replaced with the less reactive 1,1′-carbonyldiimidazole. Reaction between **7** and 1,1′-carbonyldiimidazole gives only monoacylation of **7**, as determined by quenching with methanol to give **17**, whose structure was determined unambiguously. We inferred from the isolation of **17** from the methanol quench that the reaction between **7** and 1,1′-carbonyldiimidazole gave **18**.





Scheme 2. Proposed operation of a continuously rotating, chemically powered molecular motor.

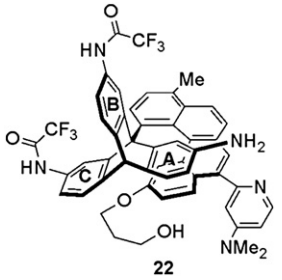
Imidazoyl ureas of primary anilines are reported[4] by Staab to be in equilibrium with the corresponding isocyanates (Eq. 1). If that equilibrium occurred here and if the **7**-based system behaved in analogy to the prototype (Scheme 1), then the sequence of events in Scheme 2 should have unfolded. But it did not.

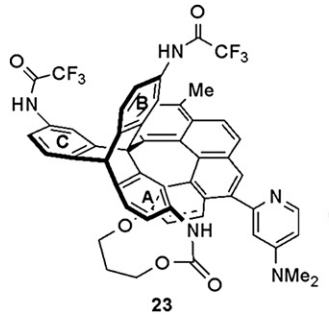


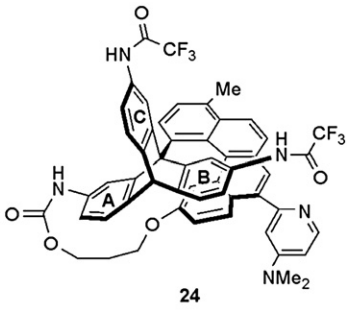
(1)

The system in Scheme 2 differs from that in the prototype (Scheme 1) in two ways. First, the motor molecules are different, and second, the fuels are different (phosgene in Scheme 1; eventually 1,1′-carbonyldiimidazole in Scheme 2). In order to determine whether the failure of the system in Scheme 2 was due to a different motor molecule or a different fuel, it was necessary to examine a case where only one rather than two variables had been changed.

To that end, compound **22**, where two of the triptylcylamines are protected as trifluoroacetyl amides, was prepared.[3] In this instance, there is only one free amine, the one in the firing position, so there is no need to enlist the DMAP to deliver the fuel to only one amine. Consequently, it was possible to use phosgene rather than 1,1′-carbonyldiimidazole as the fuel. In this situation, the system differs from that in Scheme 1 by only one variable, the structure of the motor molecule. The reaction of **22** with phosgene would either lead to a functioning motor or indicate that the problem was with the precise structure of the motor molecule. In fact,[3] reaction of **22** with phosgene gave no intramolecular urethane (**23** or **24**) as judged by mass spectrometry. Put briefly, despite the seemingly excellent precedent provided by the prototype system in Scheme 1, the completely developed versions (**7** and **22**) do not function as motors.

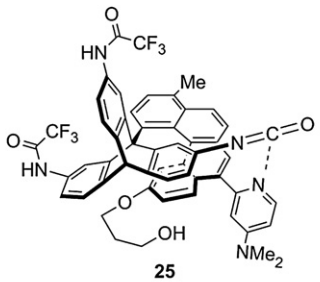


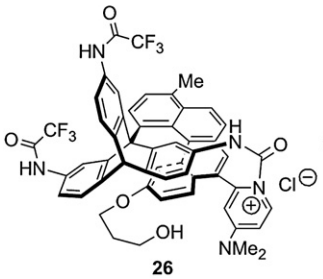


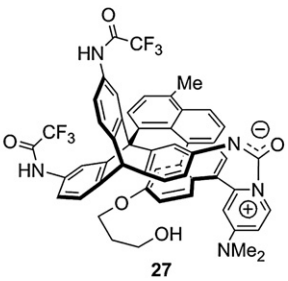


We suggested[3] two explanations for why **7** and **22** do not behave as motors. One explanation was that the hydroxypropyl group adopts a conformation different from that in the prototype, possibly due to hydrogen-bonding interactions with the DMAP or the added substituents on the other two triptycene blades. The second explanation was the intervention of a Bürgi–Dunitz[5] (**25**) or even a covalent interaction, as in **26** and **27**, between the DMAP and either the isocyanate, the carbamoyl chloride **10**, or carbamoyl imidazole **18**. Such an interaction would severely restrict rotation around the triptycene–helicene bond, precluding access to energetically excited rotamers analogous to **3**. Furthermore, such an interaction would attenuate the electrophilic nature of the phosgene-derived (or carbonyldiimidazole-derived) carbonyl in **25**–**27**, making reaction with the hydroxypropyl less likely (if geometric constraints did not make it impossible).

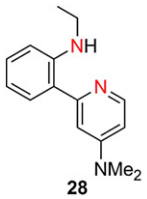
In order to determine if the interactions suggested in **25**–**27** were credible, we chose to examine the reaction of **28** with phosgene to see if there were any indications of analogous interactions, such as those shown in **29** and **30**.

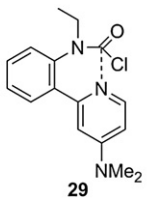


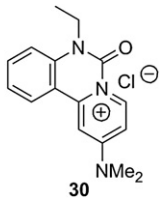




It might be objected that **28** is not a good model[†] for **7**/**22** because the two nitrogens of interest (drawn in red) in **28** are separated by only four bonds, while a dozen or so bonds separate the analogous nitrogens in **7**/**22**. But, because of **7**/**22**′s inherent rigidity, there are no more degrees of freedom associated with **7**/**22** (apart from the triptycene–helicene bond, whose rotation is severely constrained by a ca. 25 kcal/mol barrier[1a,b] to rotation) than with **28**.

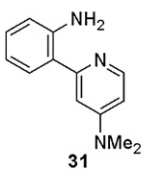


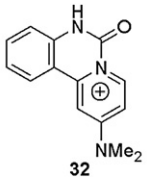


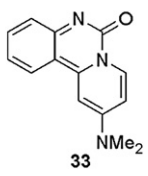


Accordingly, the synthesis of **28** was undertaken and was reduced to practice as shown in Scheme 3. Stille coupling[6] of

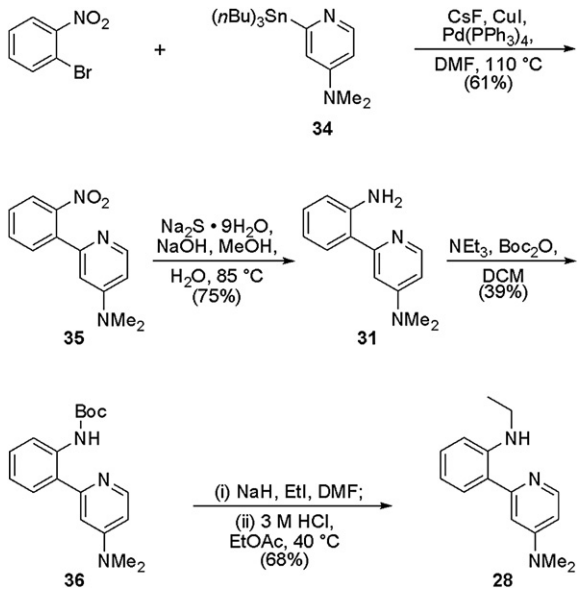
[†] Secondary amine **28** was chosen in preference to the unalkylated primary amine **31** because if **31** was to form **32** (from **31** and phosgene), **32** could suffer loss of a proton and electron reorganization to give pyridoquinazolinone **33**, a compound whose tricyclic ring system is known[9] to be stable.





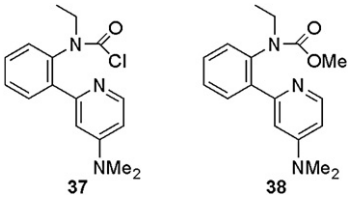


commercially available 1-bromo-2-nitrobenzene with stannane **34**[7] gave biaryl **35**. The nitro group was reduced[8] and the resulting aniline **31** was converted to its *tert*-butoxycarbonyl (BOC) derivative **36**. Treatment of the latter (**36**) with sodium hydride and ethyl iodide and exposure of the crude product to acid cleaved the BOC, affording **28** directly.



Scheme 3. Synthesis of DMAP-substituted aniline **28**.

In order to determine the behavior of **28** toward phosgene, phosgene—as a solution in toluene—was added to a mixture of a $CDCl_3$ solution of **28** and an excess of an insoluble and polymer-bound tertiary amine.[‡] A precipitate formed immediately. Addition of CH_3OH dissolved the precipitate. The $CDCl_3/CH_3OH$ solution was filtered through a plug of cotton to separate the insoluble polymer (presumably a mixture of polymer-bound tertiary amine and the corresponding amine hydrochloride), and the filtrate was evaporated. The residue (a solid) was dissolved in CD_3OD (it is only slightly soluble in $CDCl_3$), and the ^1H and ^{13}C NMR spectra were recorded. The spectra of the solid show it to be a single compound, but do not unequivocally distinguish between structures **29** and **30**. The spectra do exclude carbamoyl chloride **37** as a possible structure, because the two nitrogen-bound methyl groups are not equivalent in the NMR spectra. Fortunately, diffraction-quality crystals of the solid could be grown from ethanol/diethyl ether. X-ray crystallography revealed the solid to be the cyclic acyl pyridinium salt **30**.



It is remarkable to us[10,11] that **30** is so stable that it can be recrystallized from even initially hot ethanol or isopropanol. In fact, **30** is unchanged by heating in CH_3OH at 100 °C for 19 h, exhibiting no detectable tendency to convert to carbamate **38**.

In order to preclude the possibility that **30** converts to **38** at 100 °C in CH_3OH but that **38** cyclizes back to **30** upon cooling, ^1H NMR spectra of **30** in CD_3OD were recorded first at 25 °C and then at 100 °C. The spectra were identical except that the two sharp peaks for the *N*-methyl protons at 25 °C had coalesced to a broad singlet at 100 °C (Fig. 3). Cooling of the sample back to 25 °C decoalesced the peak for the *N*-methyl protons and restored the 25 °C spectrum. Prompted by this serendipitous observation of coalescence, the actual coalescence temperature was measured and determined to be 95 °C (Fig. 3). That temperature, taken with a difference in the frequencies of the two *N*-methyl resonances of 35.5 Hz (a 500 MHz spectrometer was employed) at 25 °C, allows one to calculate[12] the barrier to rotation about the Me_2N–pyridinium bond in **30** as 18.5 kcal/mol, indicating that there is substantial double bond character (as in **39**) to that bond. To our knowledge, this is the first experimental determination of the barrier to rotation around the Me_2N–pyridinium bond in an *N*-acyl (dimethylamino)pyridinium derivative. NMR spectra of unsymmetrical but neutral DMAP derivatives such as **28**, **31**, **35**, and

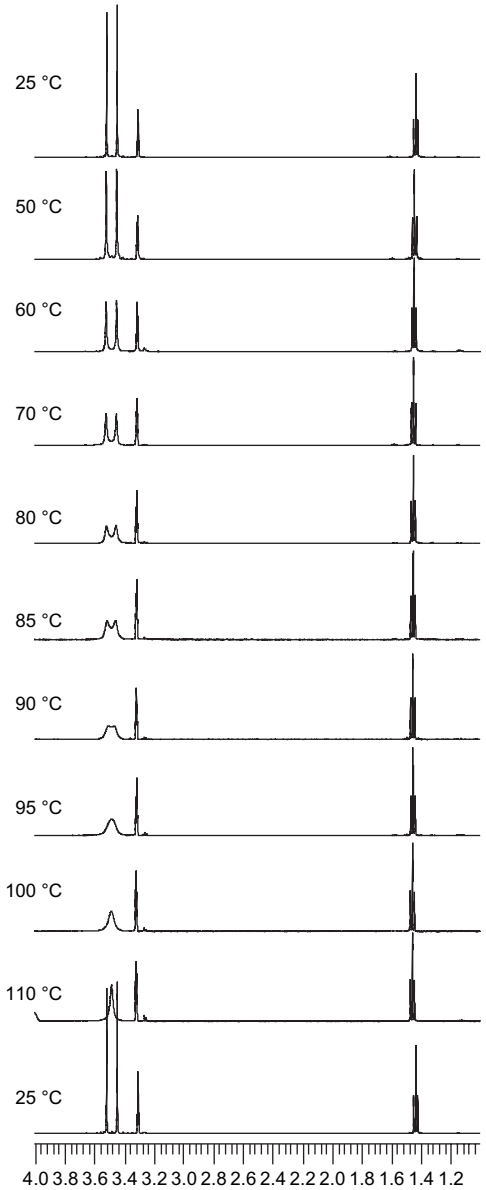
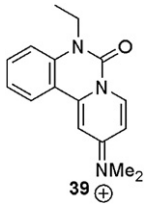


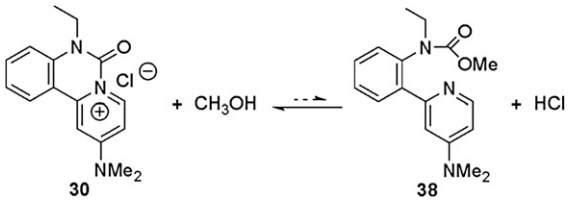
Figure 3. ^1H NMR spectra (500 MHz, CD_3OD) of the two *N*-methyl resonances of **30** at varying temperatures. The bottom 25 °C spectrum was recorded after allowing the 110 °C sample to cool. The peaks from the ethyl group serve as an internal reference.

[‡] A polymer-bound tertiary amine rather than a 'regular' tertiary amine such as Et_3N was used to facilitate separation of amine hydrochloride salts and **28**-derived substances.

36 show (see Section 4) the *N*-methyl protons to be equivalent at room temperature.

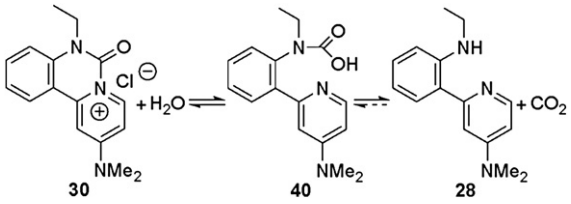


The studies described above indicate that **30** is stable when dissolved in CH_3OH. Put differently, the equilibrium in Eq. 2 lies far to the left.



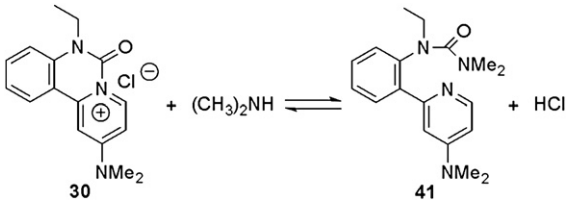
(2)

The reactivity of **30** toward two nucleophiles other than CH_3OH, namely water and dimethylamine, was also examined. When a solution of **30** in water is heated at 55 °C for 16 h, about 20% is converted to **28**, presumably by way of an unfavorable equilibrium to give carbamic acid **40** (Eq. 3) followed by decarboxylation[13] of **40** to give **28**. The decarboxylation provides a means for driving the conversion of **30** to **28** to completion; no comparable driving force is available to drive the conversion of **30** and CH_3OH to **38** (Eq. 2).



(3)

In contrast to the situation with **30** and CH_3OH, where equilibrium (e.g., Eq. 2) favors *N*-acyl pyridinium species **30** and CH_3OH rather than urethane **38**, reaction of **30** with dimethylamine in CD_3OD to give urea **41** proceeds virtually to completion in 3 h at room temperature (Eq. 4), reflecting the greater stability of amides (ureas) versus esters (urethanes). Here too, however, the proximity of the DMAP unit to the urea carbonyl in **41** bestows reactivity on the urea unlike that of typical ureas: the equilibrium in Eq. 4 can be driven to the left at room temperature simply by several cycles of dissolving the mixture of **30** and **41** in CD_3OD and removing volatiles under vacuum, with all of **41** being converted back to **30**.

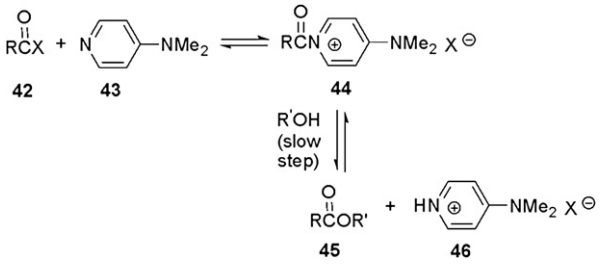


(4)

3. Conclusions

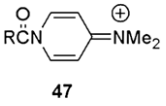
As mentioned previously, the work described above was carried out with the aim of troubleshooting the non-functioning molecular motor of Scheme 2. The discovery of the unexpected stability of **30** leads us to conclude that the problem is the intrusion into Scheme 2 of the Bürgi–Dunitz or covalent interactions depicted in **25**, **26**, and **27**. The obvious question is: 'how might one modify **7** to achieve a functioning motor?'

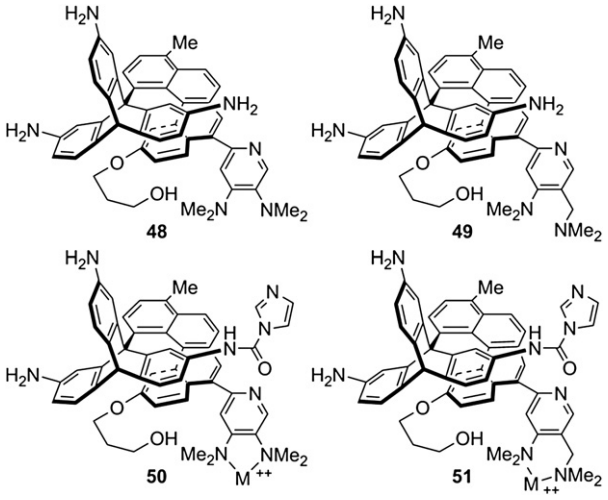
The consensus mechanism for the catalytic role of DMAP in the acylation of alcohols (and, presumably, other substrates) is shown in Scheme 4.[11g,14]



Scheme 4. Generally accepted mechanism for the catalytic role of DMAP in the acylation of alcohols by acylating agents.

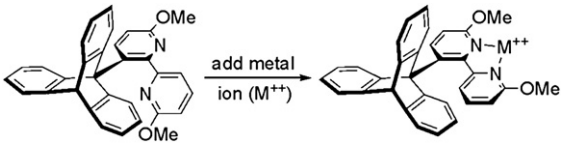
The second step, the reaction of the acyl pyridinium salt **44** with R′OH, is the rate-determining step.[11g,14] According to Hassner et al.[11b] and Spivey and Arseniyadis,[11g] 4-amino-substituted pyridines such as DMAP are more effective catalysts than pyridine itself because they are better at stabilizing the intermediate acyl pyridinium species **44** (by a contribution from resonance structure **47**). It may seem counterintuitive that stabilizing the starting material for a rate-determining step would accelerate the rate for the overall reaction. But stabilizing **44** results in more **44** being present, because the position of the **42**+**43**⇌**44** equilibrium is shifted to the right. Evidently, the increased concentration of **44** plays a greater role in accelerating the overall reaction than the stabilization of **44** does in decelerating the rate-limiting step.





From the standpoint of 'repairing' the molecular motor, it would appear that replacing the DMAP in **7** with a less participatory unit, perhaps just a pyridine, would be sufficient to attenuate the interfering Bürgi–Dunitz (**25**) or covalent (**26** or **27**) interaction. The concern with adopting such an approach is that it might also diminish the system's ability to capture and deliver the carbonylimidazole unit to the requisite aniline group. Perhaps a better way to walk this molecular tightrope is to include a unit that can interfere with the behavior of the DMAP unit, but only after the DMAP

has delivered the carbonylimidazole group. Two possibilities are **48** and **49**, where, after the carbonylimidazole moiety has been delivered, one adds a metal ion (M^{++}), with metal-ion coordination—as in **50** and **51**—disengaging the dimethylamine group from stabilizing the Bürgi–Dunitz (**25**) or covalent (**26** or **27**) interaction. Whether such a metal-coordination strategy would be effective in the current instance remains to be determined, but the use of metal-ion coordination stood us in good stead in effectively engaging a molecular brake (Eq. 5).[15]



52 (brake off) **53** (brake on) (5)

In conclusion, the foregoing studies appear to have identified the source of the problem with the non-functioning of **7** and **22**. Unfortunately, however, for reasons that have been given elsewhere,[16] it is unlikely that the proposed cures will ever be examined.

4. Experimental

4.1. General

All reactions were carried out under an atmosphere of argon in flame-dried glassware. The reaction solvent dichloromethane (CH_2Cl_2) was purified by passage through activated alumina columns.[17] Anhydrous *N*,*N*-dimethylformamide (DMF) was purchased from ACROS and stored over activated 4 Å molecular sieves. All other reagents and solvents were used as received from the manufacturer unless otherwise stated. Flash column chromatography was carried out using Bodman reagent silica gel 60 Å or Alfa Aesar activated neutral aluminum oxide 58 Å. Prior to use, activated Brockman I neutral aluminum oxide was adjusted[18] to Brockman III activity by adding 6% (w/w) water (H_2O). Reactions were monitored by thin layer chromatography (TLC) using Whatman 250 micron silica gel plates with aluminum backing and UV254 nm fluorescent indicator or Analtech 200 micron neutral aluminum oxide plates with aluminum backing and UV254 nm fluorescent indicator. All TLC plates were visualized by UV fluorescence quenching. All solution pHs were measured using EM colorpHast pH strips (Fisher, catalog number M95903). The phrase 'removal of solvents in vacuo' means that solvents were removed on a rotary evaporator using a diaphragm pump (ca. 8 Torr) and that remaining traces of volatiles were then removed on a high-vacuum oil pump (ca. 0.05 Torr). Melting points were recorded on a Fisher-Johns melting point apparatus or Lab Devices Mel-Temp II (mp>300 °C) and are uncorrected. Infrared spectra were recorded using a Nicolet Avatar 360 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Varian Gemini-400 (400 MHz) spectrometer or a Varian Unity INOVA-500 (500 MHz) spectrometer and are reported in parts per million using TMS (0.00 ppm) or residual solvent protons ($CDCl_3$=7.26 ppm, CD_3OD=3.30 ppm) as an internal standard. Data are reported as: [δ shift] ([s=singlet, d=doublet, ap d=apparent doublet, dd=doublet of doublets, t=triplet, q=quartet, m=multiplet, br=broad], [J= coupling constant in Hz], and [integration]). Proton-decoupled ^{13}C NMR spectra were recorded on a Varian Gemini-400 (100 MHz) spectrometer or a Varian Unity INOVA-500 (125 MHz) spectrometer and are reported in parts per million using solvent ($CDCl_3$= 77.0 ppm and CD_3OD=49.0 ppm) as an internal standard. High resolution mass spectra were obtained at the Boston College mass spectrometry laboratory. X-ray crystallography and structure analysis for **30** were performed at the Boston College X-ray facility. Crystallographic data (excluding structure factors) for the structural analysis has been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 670092. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk). Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA).

4.2. Synthesis of 6*H*-9(*N*,*N*-dimethylamino)-5-(*N*-ethyl)-6-oxopyrido[1,2-*c*]quinazolinium chloride (30)

*4.2.1. 4-(N,N-Dimethylamino)-2-(2-nitrophenyl)pyridine (**35**)*

Commercially available cuprous iodide (Aldrich, catalog number 20,554-0) was purified following Dieter's procedure.[19] For a typical case, 5.00 g of cuprous iodide was added in one portion, open to the air, to a saturated aqueous NaI solution (20 mL) immersed in a hot oil bath (100 °C). The homogenous solution was maintained in the oil bath (100 °C) for 30 min, then removed from the bath, diluted with H_2O (20 mL), and allowed to cool to room temperature. Upon cooling, a precipitate formed. The precipitate was collected by vacuum filtration and washed sequentially with H_2O, ethanol, ethyl acetate (EtOAc), diethyl ether (Et_2O), and finally hexanes. The purified cuprous iodide was both dried (ca. 24 h) and stored over P_2O_5 in a vacuum desiccator (ca. 0.05 Torr).

For a related procedure see Ref. 7. A 100 mL airfree® round-bottomed flask (Chemglass, catalog no. AF-0528-02) was charged with cesium fluoride (1.62 g, 10.7 mmol, purchased from Strem), a rubber septum, and a stir bar. The flask and its contents were flame-dried under vacuum and backfilled with Ar. To the flask were added 1-bromo-2-nitrobenzene (1.08 g, 5.35 mmol), **34**[7] (2.20 g, 5.35 mmol), and DMF (50 mL). The mixture was freeze–pump–thaw degassed three times under vacuum and backfilled with Ar. To the mixture was added tetrakis(triphenylphosphine)palladium(0) (310 mg, 0.268 mmol, purchased from Strem) followed by purified (see above) cuprous iodide (153 mg, 0.803 mmol), each in a single portion. The flask was fitted with an Ar balloon and the mixture was heated to 110 °C. After stirring at 110 °C for 19 h, the black mixture was cooled to room temperature and passed through a plug of Celite™. The Celite™ was rinsed with EtOAc (100 mL). The combined filtrate and rinse were added to 9 M NH_4OH (150 mL) and transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (3×50 mL). The organics were pooled, washed with 9 M NH_4OH (50 mL portions; washed until the blue/green color no longer persisted in the aqueous layer), H_2O (2×150 mL), and saturated NaCl solution (1×100 mL), dried with $MgSO_4$, and filtered. Removal of the solvent in vacuo gave a red oil. The oil obtained was purified by flash column chromatography (12 cm×4 cm; Brockman III neutral aluminum oxide) with 40% EtOAc in hexanes to afford 795 mg (61%) of **35** (R_f=0.4; 1:1 hexanes/EtOAc; neutral aluminum oxide) as a brown solid. Mp 110–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J=6.0 Hz, 1H), 7.85 (d, J=8.0 Hz, 1H), 7.63–7.61 (m, 2H), 7.53–7.48 (m, 1H), 6.64 (d, J=2.4 Hz, 1H), 6.51 (dd, J=6.0, 2.4 Hz, 1H), 3.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 154.6, 149.5, 149.4, 136.3, 131.9, 131.0, 128.5, 123.8, 105.7, 105.2, 39.1; IR (KBr) ν 3447, 2917, 1601, 1539, 1456, 1374, 1303 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{14}N_3O_2$ (MH^+) 244.1086, found 244.1089.

*4.2.2. 2-[4-(N,N-Dimethylamino)-2-pyridinyl]benzenamine (**31**)*

For a related procedure see Ref. 7. To a 100 mL round-bottomed flask fitted with a reflux condenser were added **35** (795 mg, 3.27 mmol) and methanol (45 mL). To the flask was added, in one portion, a freshly prepared solution of sodium sulfide nonahydrate (3.15 g, 13.1 mmol) and sodium hydroxide (1.30 g, 32.7 mmol) in H_2O (15 mL). The flask was heated to 85 °C, stirred open to the air, and maintained at 85 °C as the progress of the reaction was monitored by TLC (R_f of **31**=0.3; 1:1 Et_2O/hexanes; neutral aluminum

oxide). Once the reaction was complete (ca. 5 h), the solution was cooled to room temperature and the solvents were removed in vacuo to give a yellow residue. The residue obtained was dissolved in a mixture of CH_2Cl_2 (50 mL) and 1 M NaOH (50 mL). The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The organics were pooled, washed with 1 M NaOH (2×75 mL), dried with $MgSO_4$, and filtered. Removal of the solvent in vacuo gave a yellow residue. The residue was purified by flash column chromatography (12 cm×4 cm; Brockman III neutral aluminum oxide) with 55% EtOAc in hexanes to afford 527 mg (75%) of **31** as a white solid. Mp 88–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J=6.0 Hz, 1H), 7.43 (dd, J=7.6, 1.6 Hz, 1H), 7.16–7.11 (m, 1H), 6.78–6.72 (m, 3H), 6.44 (dd, J=6.0, 2.6 Hz, 1H), 5.45 (br s, 2H), 3.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 155.2, 148.2, 146.2, 129.3, 129.2, 124.3, 117.5, 116.7, 105.4, 104.8, 39.2; IR (KBr) ν 3451, 3326, 2922, 1597, 1537, 1492, 1445 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{16}N_3$ (MH^+) 214.1344, found 214.1353.

4.2.3. 1,1-Dimethylethyl [2-[4-(N,N-dimethylamino)-2-pyridinyl]phenyl]carbamate (**36**)

A 100 mL round-bottomed flask was charged with **31** (1.04 g, 4.88 mmol), triethylamine (3.45 mL, 24.4 mmol), and CH_2Cl_2 (35 mL). To the solution was added di-*tert*-butyl dicarbonate (1.13 g, 5.12 mmol) in six portions (ca. 200 mg each) over a 5 min period. The solution was allowed to stir at room temperature. After stirring for 20 h, the yellow precipitate, which had formed was collected by vacuum filtration and washed with CH_2Cl_2 (3×10 mL). The combined filtrate and washes were diluted with CH_2Cl_2 (50 mL), transferred to a separatory funnel, washed with H_2O (2×50 mL) and saturated NaCl solution (1×50 mL), dried with $MgSO_4$, and filtered. Removal of the solvent in vacuo gave an oil. The oil obtained was purified by flash column chromatography (12 cm×3 cm; silica gel) with 40% Et_2O in hexanes to afford 600 mg (39%) of **36** (R_f=0.4; 2:3 hexanes/Et_2O; silica) as a white solid. Mp 114–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.99 (br s, 1H), 8.28–8.27 (ap d, 2H), 7.54 (dd, J=8.0, 1.6 Hz, 1H), 7.36–7.32 (m, 1H), 7.07–7.03 (m, 1H), 6.79 (d, J=2.4 Hz, 1H), 6.48 (dd, J=6.4, 2.4 Hz, 1H), 3.05 (s, 6H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 155.3, 153.3, 147.8, 137.9, 129.2, 128.7, 127.0, 121.8, 119.9, 105.7, 105.0, 79.4, 39.2, 28.4; IR (KBr) ν 3227, 2974, 2560, 2252, 1917, 1715, 1600, 1538, 1435 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{23}N_3O_2Na$ (MNa^+) 336.1688, found 336.1685. Anal. Calcd for $C_{18}H_{23}N_3O_2$: C, 68.98; H, 7.40; N, 13.41. Found: C, 69.01; H, 7.50; N, 13.36.

The precipitate collected (239 mg, 21%) was tentatively identified as *9-(N,N-Dimethylamino)-6H-pyrido[1,2-c]quinazolin-6-one* (**33**). Compound **33** (R_f=0.38; 1:5 methanol/DCM; neutral aluminum oxide) was obtained as a yellow solid. Mp 290 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (d, J=8.0 Hz, 1H), 7.82 (d, J=8.0 Hz, 1H), 7.52 (t, J=6.8 Hz, 1H), 7.42 (d, J=8.0 Hz, 1H), 7.07–7.03 (m, 2H), 6.68 (dd, J=8.0, 2.8 Hz, 1H), 3.29 (s, 6H). The compound was too insoluble to obtain a ^{13}C NMR spectrum. IR (KBr) ν 3421, 1638, 1607, 1555, 1522, 1468, 1437 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{14}N_3O$ (MH^+) 240.1137, found 240.1131.

4.2.4. N-Ethyl-2-[4-(N,N-dimethylamino)-2-pyridinyl]-benzenamine (**28**)

To a 50 mL round-bottomed flask equipped with an Ar mineral oil bubbler were added **36** (600 mg, 1.92 mmol) and DMF (15 mL). To the stirred homogenous solution was added (*CAUTION*: rapid evolution of H_2 gas!) NaH (60% dispersed in mineral oil, 112 mg, 2.87 mmol) in three portions (ca. 40 mg each) followed by heating to 30 °C. The solution was maintained at 30 °C for 2 h and then cooled to room temperature. To the solution was added ethyl iodide (158 μL, 2.02 mmol) in one portion and the progress of the reaction was monitored by TLC (desired product R_f=0.2; 3:2 hexanes/Et_2O; neutral aluminum oxide). Once the reaction was complete (ca. 30 min), the mixture was quenched (*CAUTION*: residual NaH may be present!) with H_2O (50 mL) and extracted with EtOAc (3×50 mL). The organics were pooled, washed with H_2O (4×100 mL) and saturated NaCl solution (1×200 mL), dried with $MgSO_4$, and filtered. Removal of the solvent in vacuo gave 650 mg of a white solid. The white solid obtained was dissolved in EtOAc (10 mL) and transferred to a 50 mL round-bottomed flask. To the solution was added 3 M HCl (10 mL) and the biphasic mixture was allowed to stir open to the air. The mixture was placed in a 40 °C oil bath and the progress of the reaction was monitored by TLC (stirring was stopped and the EtOAc layer was spotted; R_f of **28**=0.5; 1:1 EtOAc/hexanes; silica). Once complete (ca. 4 h), 10 M NaOH was slowly added to the mixture until (ca. 5 mL) the pH of the aqueous layer was approximately 10. The contents of the flask were transferred to a separatory funnel, the EtOAc layer was separated, and the aqueous layer was extracted with EtOAc (3×40 mL). The organics were pooled, washed with H_2O (2×40 mL) and saturated NaCl solution (1×50 mL), dried with $MgSO_4$, and filtered. Removal of the solvent in vacuo gave an oil. The oil obtained was purified by flash column chromatography (12 cm×3 cm; Brockman III neutral aluminum oxide) with 15% EtOAc in CH_2Cl_2 to afford 316 mg (68% from **36**) of **28** as a white solid. Mp 94–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J=5.6 Hz, 1H), 7.43 (dd, J=7.6, 1.6 Hz, 1H), 7.39 (br s, 1H), 7.25–7.21 (m, 1H), 6.76 (d, J=2.8 Hz, 1H), 6.71–6.67 (m, 2H), 6.44 (dd, J=5.6, 2.8 Hz, 1H), 3.19 (q, J=7.2 Hz, 2H), 3.04 (s, 6H), 1.27 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 155.1, 147.9, 147.4, 129.6, 129.3, 123.6, 115.4, 110.8, 105.6, 104.6, 39.2, 37.9, 14.7; IR (KBr) ν 3314, 2970, 2849, 1894, 1609, 1506, 1437 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{20}N_3$ (MH^+) 242.1657, found 242.1666.

4.2.5. 6H-9-(N,N-Dimethylamino)-5-(N-ethyl)-6-oxopyrido-[1,2-c]quinazolinium chloride (**30**)

Chloroform ($CHCl_3$) was purified according to Perrin and Armarego.[20] For a typical case, $CHCl_3$ (180 mL, ACS grade purchased from Mallinckrodt) was washed with H_2O (3×100 mL), dried over anhydrous potassium carbonate (10 g), refluxed with $CaCl_2$ (35 g), and distilled prior to use.

To a 25 mL round-bottomed flask were added polymer-supported diisopropylamine (PS-DIA) beads (669 mg, 0.336–1.00 mmol; 50–90 mesh, 1% cross-linked, 0.5–1.5 mmol/g, purchased from Aldrich, catalog number 538469) and distilled $CHCl_3$ (6 mL, see above). After stirring for 10 min under Ar, the $CHCl_3$ was removed with a syringe and a narrow (21 gauge) needle. This process was repeated a total of three times after which the beads were dried under vacuum (ca. 0.05 Torr) for 30 min. To the flask were added **28** (75.0 mg, 0.311 mmol) and distilled $CHCl_3$ (10 mL, see above). The mixture was allowed to stir for 30 min at room temperature and then phosgene (327 μL, 0.62 mmol; purchased as a 20% w/w solution in toluene from Fluka, catalog number 79830; *CAUTION*: extremely toxic!) was added in one portion. The mixture initially took on a deep yellow color and then quickly (ca. 2 min) turned to a cloudy white color. After stirring for 30 min at room temperature, the flask was quenched with methanol (10 mL), turning the reaction mixture from a cloudy white suspension to a clear mixture. The mixture was filtered through a plug of cotton and the beads were rinsed with methanol (3×5 mL). The combined filtrate and rinses were transferred to a 50 mL round-bottomed flask and removal of the solvents in vacuo gave 110 mg of a white solid. This white solid was crystallized from isopropanol (ca. 10 mL) to give 76 mg (81%) of **30** as white prisms. X-ray quality crystals were obtained by slow vapor diffusion using ethanol as the dissolving solvent and diethyl ether as the precipitating solvent. Mp 306–309 °C (dec); ^{1}H NMR (500 MHz, CD_3OD) δ 9.12 (d, J=8.5 Hz, 1H), 8.62 (d, J=8.5 Hz, 1H), 7.86 (t, J=8.0 Hz, 1H), 7.71 (s, 1H), 7.66 (d, J=8.5 Hz, 1H), 7.51 (t, J=8.0 Hz, 1H), 7.34 (dd, J=8.5, 2.5 Hz, 1H), 4.42

(q, J=7.0 Hz, 2H), 3.52 (s, 3H), 3.45 (s, 3H), 1.43 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 158.7, 146.1, 145.5, 137.4, 136.1, 136.0, 127.1, 125.9, 116.7, 114.6, 109.5, 100.2, 41.8, 41.3, 41.2, 12.4; IR (KBr) ν 3404, 3084, 2972, 1728, 1705, 1651, 1645, 1607, 1574, 1556, 1504, 1470, 1446 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{18}N_3O$ (M^+) 268.1444, found 268.1448. Anal. Calcd for $C_{16}H_{18}N_3OCl\cdot{}^1/_2\,H_2O$: C, 61.44; H, 6.12; N, 13.43. Found: C, 61.16; H, 6.04; N, 13.29.

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Supplementary data

Contains copies of ^{1}H and ^{13}C NMR spectra for compounds **28**, **30**, **31**, **35**, **36** and ^{1}H NMR spectrum of **33**. Also, X-ray diffraction data for compound **30** is included (13 pages). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.04.101.

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