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Annulated heterocycles through a radical-cation cyclization: synthetic and mechanistic studies

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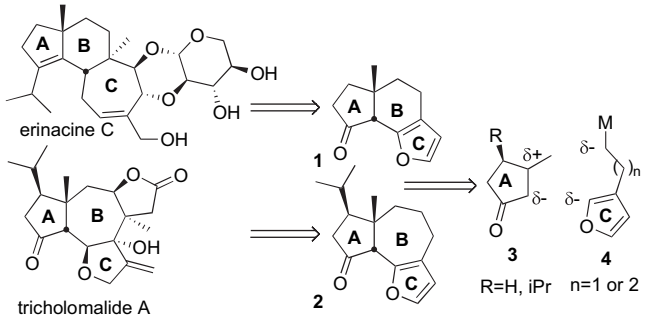
Abstract—The wide range of chemical transformations possible with furans and thiophenes, especially reactions leading to dearomatization of the nucleus, make them highly versatile synthons for complex molecule construction. As part of a program to exploit this intrinsic reactivity, we have developed a convenient method to prepare annulated versions of these heterocycles. The strategy is based on a two-step annulation involving the initial conjugate addition of a heteroaryl organometallic to an enone with trapping of the enolate as the silyl enolether. Anodic oxidation of this molecule leads to the initial formation of a radical-cation that is trapped in a heteroaryl-terminated cyclization to give the annulated products.

1. Introduction

Over the past several years, we have worked on the development of methodology for the synthesis of annulated furans and thiophenes based on the formation and trapping of an intermediate radical-cation generated by electrochemical oxidation at the anode. Our interest in a method of this type has been driven by the recognition that π-excessive heterocycles such as furan and thiophene can serve as versatile precursors to a wide array of non-aromatic functionality.[1] Much of the inspiration for this work has been from erinacine C[2] and tricholomalide A[3], two terpenoid metabolites of fungal origin that act as inducers of nerve growth factor (NGF) expression (Scheme 1).



Scheme 1. Retrosynthetic analysis of terpenoid NGF inducers.

Inducers of NGF have potential for the treatment of neurodegenerative disorders such as Alzheimer's disease and amyotrophic lateral sclerosis.[4]

Retrosynthetic analysis of both structures can lead to a common angular furan framework **1** and **2** where the furan can serve as a precursor to both the carbocyclic seven-membered ring of erinacine C via a [4+3] cycloaddition as well as the furanoid ring of tricholomalide A through adjustment of oxidation states. The initial approach taken to intermediate **1** involved a vinyl furan Diels–Alder reaction between 3-methylcyclopentenone and 3-vinyl furan. Unfortunately, this process was completely ineffective and prompted us to develop new strategies for the construction of annulated furans such as **1** and **2**. We formulated a direct route to such angular-fused heterocycles that would involve the stepwise coupling of simple enone building blocks **3** with alkyl metal derivatives **4** containing a pendant furan. Addition of reagents such as **4** in a conjugate fashion to the enone would form one of the new bonds of the B-ring. The second stage of this annulation protocol was less obvious as it required the polarity reversal of one of the electron-rich carbons either at the silyl enolether or at the C2-position of the furan. Radical-cation chemistry seemed particularly well-suited to trigger the second step of the annulation as removal of one electron from either of the electron-rich π-systems could be followed by nucleophilic attack of the other group to close the central carbocyclic system. In this report, we give a full account of this annulation strategy and an update of the current scope and limitations of this methodology.

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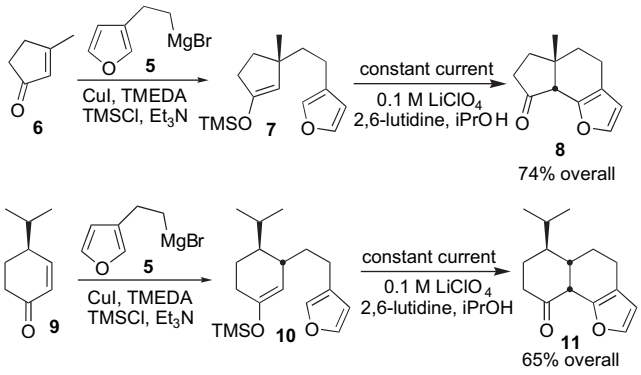
2. Results and discussion

2.1. Six-membered ring annulations with furan

The first efforts centered upon the preparation of six-membered ring systems as would be needed for an approach to the erinacines[5] (Scheme 2).

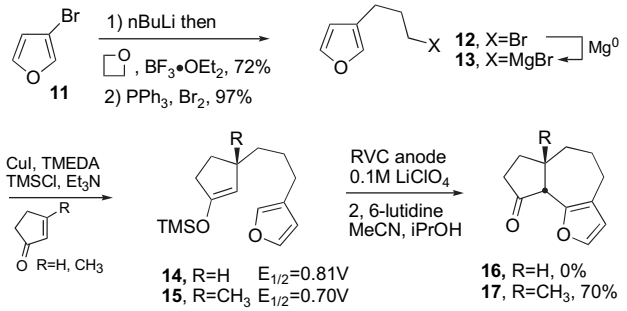


Scheme 2. Six-membered ring annulations.

The requisite furylethyl bromide could be easily prepared by lithiation of 3-bromofuran followed by addition to ethyleneoxide and conversion of the resultant alcohol to the bromide.[6] Formation of the Grignard reagent **5** under standard conditions was followed by a copper-catalyzed addition to 3-methylcyclopentenone **6** in the presence of trimethylsilyl chloride to give the enolether **7**. The second stage of the annulation would involve the generation of a radical-cation intermediate through a one-electron oxidation of **7**. We initially examined a variety of chemical oxidants including chromium and vanadium reagents but were unable to effect the desired cyclization reaction. Instead, cleavage of the silyl enolether to the corresponding ketone dominated. The seminal work of Moeller[7] on the electrochemical oxidation of electron-rich alkenes inspired us to examine this non-chemical method for generation of the required radical-cation. Gratifyingly, it was found that oxidation of **7** under electrochemical conditions provided high yields of a cyclized product (all annulation yields are reported as the overall yield for the two steps from the enone) as a single diastereomer **8**. The initially formed product is not the furan **8** but an acetal intermediate derived from addition of isopropanol to the intermediate oxocarbenium ion. Brief acid treatment upon work-up converts this intermediate to the furan. A detailed study on the closure of six-membered rings revealed that the reaction was effective, highly diastereoselective, and tolerant to a wide range of functional groups such as ketals, olefins, and carbamates.[8] A related example of the enolether **10** derived from cryptone shows how three contiguous stereogenic centers are set and that groups in the allylic position of the enone **9** can effectively direct the addition of the cuprate. As in other cases, the radical-cation initiated cyclization reaction proceeds under complete kinetic control, yielding only the *cis*-descalin isomer **11**.

2.2. Seven- and five-membered ring annulations with furan

With the successful application of this method to the annulation of six-membered rings, our attention turned to the extension of the process to seven- and five-membered ring annulations. The required furylpropyl bromide **12** needed for the seven-membered ring annulation was conveniently prepared from 3-bromofuran **11** by reaction of the derived organolithium species with trimethyleneoxide[9] followed by bromination (Scheme 3).



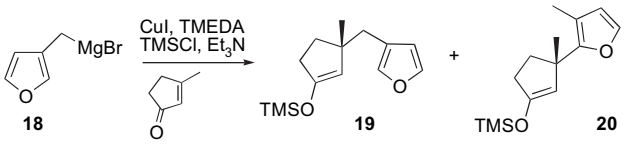
Scheme 3. Seven-membered ring annulations.

Addition of this reagent to cyclopentenone and 3-methylcyclopentenone gave the corresponding silyl enolethers **14** and **15**. A surprising trend emerged during the study of these substrates.[10] Electrochemical oxidation of **14** gave only polymeric materials that precipitated onto the surface of the electrode and caused the consumption of excessive amounts of current. In contrast, electro-oxidation of **15** proceeded smoothly, giving the desired adduct **17** as the exclusive cis-isomer. Slightly better yields could be realized with the use of RVC electrodes in place of graphite, likely due to passivation of the graphite anode. No appreciable difference in yields for six-membered cyclizations between graphite and RVC have been observed.

A more detailed investigation revealed that not only a variety of groups could be used in place of methyl but also in the absence of this quaternary center, the reaction would not proceed. We currently favor a model whereby the full substitution at this center helps to pre-organize the substrate for ring closure, an effect related to the well-known *gem*-dialkyl effect. In the absence of this effect, trapping by the furyl terminator is too slow and the initially generated radical-cation suffers decomposition through bimolecular reactions. This model is based on the substantially different oxidation potential of the two substrate of approximately 100 mV. The oxidation potential is directly related to the energy of activation for the reaction[11] and indicates a more favorable and faster reaction when the additional substitution is present. The pre-organization induced by the alkyl substituent decreases the potential for formation of the radical-cation. Current efforts are focused on incorporating additional control elements into the substrate and enhancing the nucleophilicity of the furan terminator to enhance the rates of cyclization in the absence of this pre-organizing effect.

Five-membered ring closures have thus far proved elusive, owing not to difficulty in the electrochemical cyclization but in the preparation of the required silyl enolether substrates (Scheme 4).

Addition of a furylmethyl Grignard reagent **18** to a typical enone reproducibly gives mixtures of two regioisomeric silyl

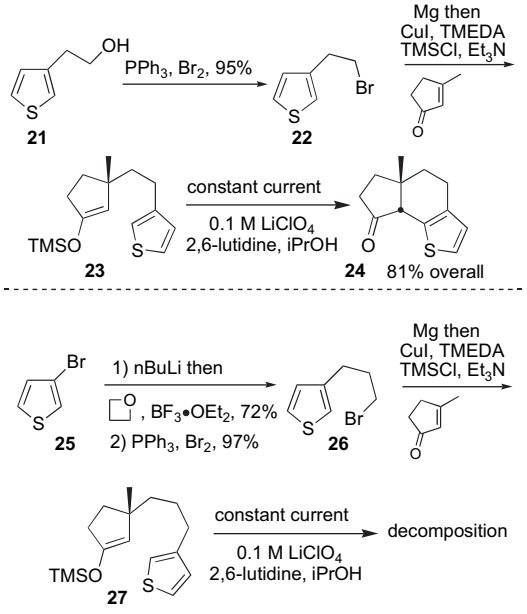


Scheme 4. Attempted application to five-membered rings.

enolethers **19** and **20** in approximately equal ratios. The undesired product **20** apparently arises from addition of the allylic metal at the C2-position of the furan followed by a subsequent isomerization. The distribution of the products has thus far been shown not to be effected by additives, solvent or copper source. Other methods for accessing enolethers such as **19** are currently under investigation.

2.3. Thiophene-based ring annulations

With the successful application of furan terminators to both six- and seven-membered ring annulations, attention was turned to studying the possibility of thiophenes in the annulation (Scheme 5). These adducts would provide access to post-annulation chemistry complimentary to the furans such as Raney nickel desulfurization and access to cyclohexadienes and arenes through Diels–Alder reaction of the derived *S*,*S*-dioxides.[12] The required thiophene fragment **22** was easily prepared by bromination of commercially available thiophene-3-ethanol while **26** was prepared by reaction of 3-lithiothiophene with trimethyleneoxide and bromination.



Scheme 5. Thiophene-based annulations.

Addition of the Grignard reagent derived from **22** to 3-methylcylopentenone gave **23** that smoothly cyclized to the annulated thiophene **24** in excellent overall yield. The reaction generally mimicked that observed for the related furan except that the thiophene ring was regenerated immediately rather than being trapped by alcohol to produce a thioacetal intermediate. In contrast to furan, the seven-membered ring system failed to undergo ring closure, even with the presence of the methyl group that was necessary for a successful furan terminated cyclization. Attempted cyclization of **27** under electrochemical conditions (graphite or RVC) failed to produce any of the desired annulated thiophene. As in the case of other failed reactions, polymeric materials could be observed as coating the electrodes.

2.4. Mechanistic studies

During the course of the synthetic investigations, it was also possible to study various aspects of the mechanism of the key electrochemical step. Two major yet convergent pathways presented themselves that differ primarily to the initial site of oxidation, the silyl enolether or the furan. Unlike chemical oxidation, electrochemical processes can be directly studied by voltammetry to gain insight into the underlying mechanism (Fig. 1).

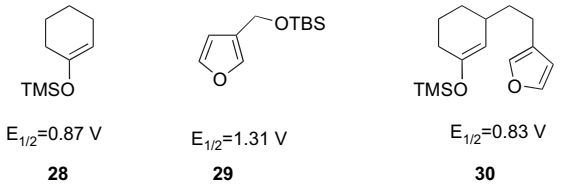
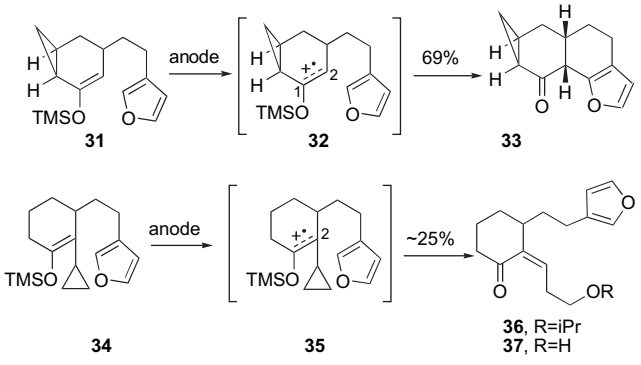


Figure 1. Oxidation potentials of model substrates.

Voltammetry of simple model systems **28** and **29** indicated that, in general, silyl enolethers had a significantly lower oxidation potential than a monoalkyl furan.[8] Moreover, the oxidation potential of intermediate **30** showed two oxidation potentials with the lowest one closely corresponding to the model silyl enolether, thus suggesting this site as the primary position of electron loss. In an attempt to verify the site, two mechanistic probe molecules **31** and **34** were synthesized[8] by typical cuprate chemistry that contained cyclopropanes adjacent to the two carbons of the silyl enolether (Scheme 6).

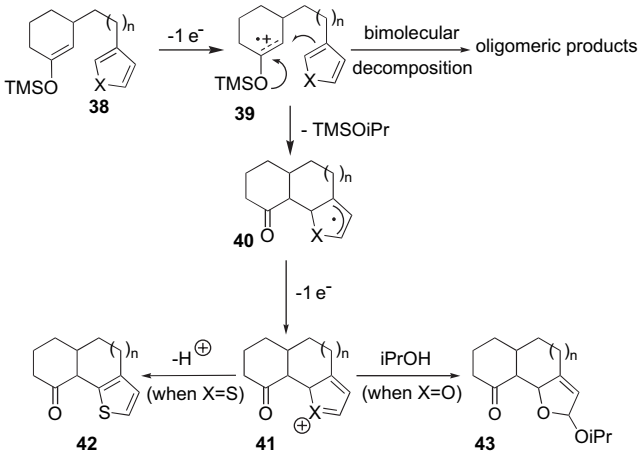


Scheme 6. Mechanistic probe molecules.

It was expected that electrochemical oxidation would generate a cyclopropyl carbinyl radical-cation **32/35** that would undergo rapid ring opening. Surprisingly, oxidation of **31** produce a high yield of the annulated product **33** with no evidence of cyclopropyl cleavage. In contrast, attempted ring closure of **34** led directly to the ring opened products **36** and **37**. These contrasting results suggest that the radical or cation localized at C1 is highly stabilized by the siloxy

group and perhaps that loss of the silyl group to generate an α-carbonyl radical is rapid. If the loss of the silyl group is rapid, then the lifetime of the initial radical-cation may be very short.

Based on these studies, we have developed a working mechanistic model for the electrochemical closure of furans and thiophenes (Scheme 7).

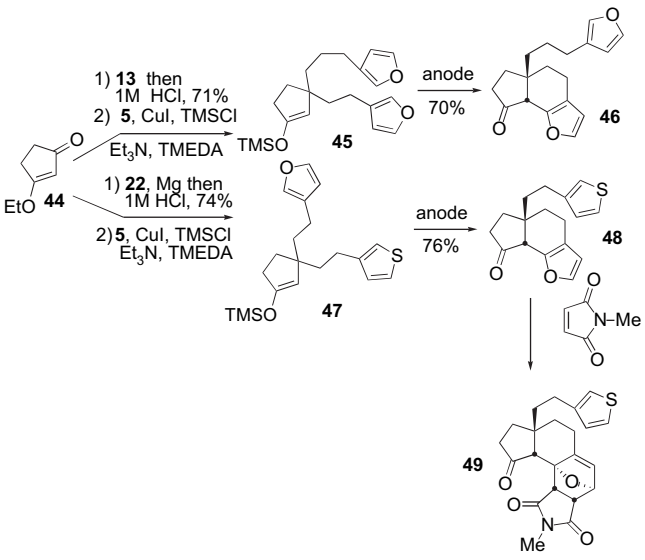


Scheme 7. Proposed mechanism for oxidative ring closure.

Loss of the first electron from the generic substrate **38** is believed to occur from the silyl enolether to produce radical-cation **39**. Rapid loss of the trimethylsilyl group as suggested by probe **31** generates an α-carbonyl radical. The furyl trap could cyclize on the radical (before or after loss of TMS) prior to a second oxidation. Attack of the heterocycle on the initial radical could lead directly to delocalized radical **40** that suffers a second electron loss to generate carbenium ion **41**. Nucleophilic trapping by an alcohol scavenger (furan case) or proton loss (thiophene case) neutralizes the final cation, giving initial products **42** and **43**. Several variations on this model are possible relating to the timing of the loss of the second electron. For example, a second oxidation to a highly reactive α-carbonyl cation could precede cyclization and attack of the heterocycle would directly give the carbenium ion **41**.

The interesting differences between six- and seven-membered ring closures is also rationalized by a mechanism that involves a highly unstable intermediate such that ring closure on the radical-cation intermediate **39** must be sufficiently fast to compete with decomposition pathways that likely involve bimolecular processes or even polymerization. The seven-membered closure illustrates this fine line as the kinetically slower cyclization competes poorly in the absence of pre-organization. Likewise, the failure of the thiophene seven-membered ring closure can be attributed to the decreased nucleophilicity of the heterocycle. To examine the potential of kinetic differences in the radical-cation cyclization, two competition substrates have been prepared and examined for competing cyclizations (Scheme 8).

Addition of heteroaryl substituted Grignard reagents to the vinylogous ester **44** followed by hydrolysis gave substituted enones that undergo a second addition to yield substrates **45**



Scheme 8. Competitive cyclizations.

and **47**. The bis-furan **45** sets up a direct competition between a six- and seven-membered ring closure with the sole product **46** arising from cyclization of the smaller ring.[10] This complete selectivity is consistent with attack of the furan on the radical-cation derived from oxidation of the silyl enolether. Primary oxidation of the furan would not be expected to show significant selectivity and products arising from both closures would be observed. At this time, the possibility of initial oxidation at the heterocycle followed by rapid electron transfer from the silyl enolether cannot be ruled out. The second competition probed the difference between the two heterocycles. Again, the reaction was completely selective with the only product observed being that of closure of the furan, consistent with the greater nucleophilicity of this heterocycle. The assignment of the adduct **48** was easily made by a subsequent Diels–Alder reaction[13] to give **49** (tentative assignment of stereochemistry). It is noteworthy that although thiophene closes slower than furan, the yields of the six-membered thiophene closure are higher than the furan. This seems to relate primarily to the sensitivity of the furan adduct, which undergoes some oxidation at the bridgehead position. The thiophene seems not to suffer from this problem.

3. Conclusions

The generation of radical-cation reactive intermediates by electrochemical oxidation forms the basis of a selective, high-yielding, and mild method for the formation of angularly fused heterocycles. Through this method, we have been able to develop routes for six-membered annulations involving both furans and thiophenes and seven-membered ring cyclizations involving furans. Mechanistic studies involving voltammetry, probe molecules, and competition reactions strongly point to a mechanism that involves primary oxidation of the silyl enolether. The radical-cation cyclization is extremely sensitive to structural effects and features that slow the rate of ring closure result in the formation of oligomeric products to the complete exclusion of the cyclic product. Several challenges for the methodology remain including the development of a five-membered ring annulation

and annulation of seven-membered ring systems in the absence of geminal disubstitution. Current efforts are also focused on the synthesis of erinacine C and tricholomalide A.

4. Experimental

4.1. General experimental

All reactions were carried out in flame-dried glassware under an atmosphere of argon unless otherwise noted. Tetrahydrofuran was freshly distilled from Na/benzophenone and dichloromethane from calcium hydride. Mixtures of TMSCl and Et_3N refer to the supernatant liquid from a centrifuged 1:1 (v/v) solution made in a flame-dried distillation receiver under argon. These solutions can be kept up to 3 days in a −20 °C freezer. All commercially available enones were distilled prior to use and kept in a freezer under an atmosphere of argon. Copper(I) iodide was either purchased at 99.999% purity (Aldrich) or purified by Soxhalet extraction with CH_2Cl_2. NMR spectra were either obtained on a Varian 300 or a Varian Inova 500 in $CDCl_3$ with residual chloroform as the internal standard. Elemental analyses were performed by Atlantic Microlab, Inc., and high-resolution mass spectrometry was performed by the Washington University Resource for Biomedical and Bio-organic Mass Spectrometry.

4.2. Synthesis of heteroaryl ethyl and propyl bromides

4.2.1. General trimethyleneoxide opening conditions. To a solution of either 3-bromofuran or 3-bromothiophene (137 mmol) in 137 mL of THF was added *n*-BuLi (137.5 mmol, 55 mL in hexanes) dropwise at −78 °C. After 45 min, trimethyleneoxide (137 mmol, 8.0 g) was added via syringe. Immediately following, $BF_3{\cdot}OEt_2$ (137 mmol, 17.2 mL) was added dropwise over 30 min, keeping the reaction temperature below −70 °C. The mixture was stirred for 5 h at −78 °C and quenched by the dropwise addition of saturated sodium bicarbonate. The mixture was allowed to warm slowly overnight and the aqueous layer extracted three times with ethyl acetate. The combined organic layers were washed with water, brine, and dried over sodium sulfate. The product was concentrated in vacuo and vacuum distilled (bulb-to-bulb, ~0.1 mmHg) to provide the desired alcohol.

4.2.1.1. 3-Furan-3-yl-propan-1-ol. Isolated as a colorless oil (12.5 g, 99 mmol, 72%). IR (thin film) λ_{max} (cm^{-1}): 3359, 2936, 2862, 1502, 1449, 1382, 1157; ^1H NMR (500 MHz, $CDCl_3$): δ 7.35 (d, J=1.2 Hz, 1H), 7.23 (m, 1H), 6.28 (d, J=1.3 Hz, 1H), 3.65 (t, J=7.7 Hz, 2H), 2.52 (t, J=6.3 Hz, 2H), 1.82 (m, 2H), 1.29 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.1, 139.1, 124.7, 111.2, 33.0, 32.1, 21.2. HRMS: Anal. Calcd for $C_7H_{10}O_2$: 126.0681; found: 126.0688.

4.2.1.2. 3-Thiophen-3-yl-propan-1-ol. Isolated as a colorless oil (13.6 g, 95 mmol, 69%). IR (thin film) λ_{max} (cm^{-1}): 3366, 3011, 2982, 1455; ^1H NMR (500 MHz, $CDCl_3$): δ 7.20 (dd, J=1.2 Hz, 1H), 7.23 (m, 1H), 6.28 (d, J=1.3 Hz, 1H), 3.54 (t, J=7.6 Hz, 2H), 2.62 (t, J=6.9 Hz, 2H), 1.80 (m, 2H), 1.34 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.3, 127.5, 125.3, 123.8, 34.6, 33.4, 22.2. EI-HRMS: Anal. Calcd for $C_7H_{10}OS$ (M^+): 142.0452; found: 142.0463.

4.2.2. General bromination conditions. To a solution of triphenylphosphine (12.85 g, 49 mmol) in 80 mL of dichloromethane was added bromine (2.51 mL, 49 mmol) via syringe at 0 °C. The suspension was allowed to stir for 10 min and 2,6-lutidine (7 mL, 60 mmol) was added dropwise. After 15 min, a solution of the alcohol (44.6 mmol) in 20 mL of dichloromethane was added slowly via syringe. The now homogeneous solution was stirred for 5 h at 0 °C and monitored by TLC until complete. *It is imperative that excess bromine need not be added to the reaction mixture due to over-bromination of the heterocyclic ring*. Once complete, the solvent was removed in vacuo (25 °C water bath) and the slurry treated with 300 mL of pentane. The resulting slurry was passed through a plug of 6 cm Celite and 6 cm silica gel to remove the triphenylphosphine oxide. Once all of the bromide had passed through the plug, the pentane (total pentane volume=1.5 L) was removed to provide the desired bromide as colorless oils. Typical yields ranged from 90–97%. *Caution: these bromides are volatile and are serious lachrymators*.

4.2.2.1. 3-(3-Bromo-propyl)-furan, 12. Isolated as a colorless oil (8.14 g, 43.3 mmol, 97%). IR (thin film) λ_{max} (cm^{-1}): 3132, 2936, 2854, 1572, 1501, 1435, 1258; ^1H NMR (500 MHz, $CDCl_3$): λ 7.39 (d, J=1.5 Hz, 1H), 7.28 (m, 1H), 6.30 (d, J=1.6 Hz, 1H), 3.43 (t, J=6.6 Hz, 2H), 2.62 (t, J=7.3 Hz, 2H), 2.11 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): λ 143.3, 139.5, 123.4, 111.1, 33.4, 33.0, 23.3. EI-HRMS m/z calcd for C_7H_9BrO (M^+): 187.9837; found: 187.9845.

4.2.2.2. 3-(2-Bromo-ethyl)-thiophene, 22. Isolated as a colorless oil (8.05 g, 42.4 mmol, 95%). IR (thin film) λ_{max} (cm^{-1}): 3100, 2962, 1423, 1411, 1270, 1210; ^1H NMR (500 MHz, $CDCl_3$): δ 7.32 (dd, J=4.9, 2.9 Hz, 1H), 7.10 (m, 1H), 7.00 (dd, J=4.9, 1.2 Hz, 1H), 3.60 (t, J=7.6 Hz, 2H), 3.24 (t, J=7.6 Hz, 2H); ^{13}C (125 MHz, $CDCl_3$): δ 139.4, 128.1, 126.1, 122.1, 34.1, 32.6. EI-HRMS m/z calcd for C_6H_7BrS (M^+): 189.9452; found: 189.9455.

4.2.2.3. 3-(3-Bromo-propyl)-thiophene, 26. Isolated as a colorless oil (8.28 g, 40.6 mmol, 91%). IR (thin film) λ_{max} (cm^{-1}): 3105, 3069, 2935, 2848, 1732, 1437, 1254; ^1H NMR (500 MHz, $CDCl_3$): δ 7.19 (dd, J=5.2, 1.2 Hz, 1H), 6.98 (dd, J=5.9, 5.1 Hz, 1H), 6.88–6.89 (m, 1H), 3.48 (t, J=7.4 Hz, 2H), 3.06 (t, J=7.5 Hz, 2H), 2.25 (pentet, J=7.4 Hz, 2H); ^{13}C (125 MHz, $CDCl_3$): δ 143.3, 127.2, 125.2, 123.8, 34.6, 33.0, 28.3. EI-HRMS m/z calcd for C_7H_9BrS (M^+): 203.9608; found: 203.9611.

4.3. Synthesis of enones from 44

4.3.1. 3-(3-Furan-3-yl-propyl)-cyclopent-2-one. To a degassed solution of bromide (**12**) (5 mmol, 945 mg) in THF (5 mL) was added magnesium turnings (5 mmol, 122 mg). The reaction was allowed to stir for 2 h, then cooled to 0 °C. A solution of 3-ethoxy-2-cyclopenten-1-one **44** (4 mmol, 504 mg) in 5 mL of THF was then added dropwise and the bright orange solution was stirred for 2 h at 0 °C and 2 h at 25 °C. The reaction was quenched by adding 20 mL of 1 M HCl and stirred for 4 h. The aqueous layer was extracted twice with 50 mL of EtOAc. The combined organic layers were washed with 20 mL of saturated $NaHCO_3$, 20 mL of

water, and 20 mL of brine. After drying over sodium sulfate and concentrating, the crude enone was subjected to flash silica gel chromatography (5:1 Hex/EtOAc → 1:1 Hex/EtOAc) to provide the enone as a pale-yellow oil (2.84 mmol, 504 mg, 71%) which solidified in a −20 °C freezer. IR (neat) λ_{max} (cm^{-1}) 2930, 1667, 1622, 1251; ^1H NMR (500 MHz) δ 7.37 (dd, J=2.9, 1.7 Hz, 1H), 7.23 (s, 1H), 6.27 (d, J=2.8 Hz, 1H), 5.96 (s, 1H), 2.57 (m, 2H), 2.49 (t, J=7.6 Hz, 2H), 2.44 (t, J=7.6 Hz, 2H), 2.40 (m, 2H), 1.86 (pentet, J=7.6 Hz, 2H); ^{13}C NMR (125 MHz) δ 210.3, 182.7, 143.2, 139.2, 129.8, 124.3, 111.0, 35.5, 33.1, 31.8, 27.5, 24.6; EI-HRMS m/z calcd for $C_{12}H_{14}O_2$ (M^+): 190.0994; found 190.0996.

4.3.2. 3-(2-Thiophen-3-yl-ethyl)-cyclopent-2-enone. To a degassed solution of bromide (**22**) (23.7 mmol, 4.5 g) in THF (24 mL) was added magnesium turnings (23.7 mmol, 492 mg). The reaction was allowed to stir for 2 h, then cooled to 0 °C. A solution of 3-ethoxy-2-cyclopenten-1-one **44** (15.8 mmol, 2.0 g) in 10 mL of THF was then added dropwise and the bright orange solution was stirred for 2 h at 0 °C and 2 h at 25 °C. The reaction was quenched by adding 60 mL of 1 M HCl and stirred for 4 h. The aqueous layer was extracted twice with 100 mL of EtOAc. The combined organic layers were washed with 50 mL of saturated $NaHCO_3$, 50 mL of water, and 50 mL of brine. After drying over sodium sulfate and concentrating, the crude enone was subjected to flash silica gel chromatography (5:1 Hex/EtOAc → 1:1 Hex/EtOAc) to provide the enone as a white solid (3.37 g, 17.5 mmol, 74%). Isolated as a white solid (mp 91.5–93 °C). IR (neat) λ_{max} (cm^{-1}) 2930, 1667, 1622, 1251; ^1H NMR (500 MHz): δ 7.29 (dd, J=4.9, 2.8 Hz, 1H), 6.99 (m, 1H), 6.97 (dd, J=4.9, 1.5 Hz, 1H), 6.00 (m, 1H), 2.96 (t, J=7.3 Hz, 2H), 2.77 (t, J=8.1 Hz, 2H), 2.61 (m, 2H), 2.42 (m, 2H); ^{13}C NMR (125 MHz): δ 210.2, 181.9, 141.1, 130.1, 128.0, 126.1, 120.8, 35.5, 34.4, 31.9, 27.9. Anal. Calcd for $C_{11}H_{12}OS$: C, 68.71; H, 6.29; O, 8.32; S, 16.68; found: C, 68.94; H, 6.47; O, 8.23; S, 16.57.

4.4. General cuprate conditions

A solution of the bromide (6 mmol) in 6 mL of THF was degassed by sonication for 10 min. Magnesium turnings (previously washed with 1 M HCl, water, acetone, and diethyl ether) (144 mg, 6 mmol) were added and stirred for 2.5 h or until mostly dissolved. The dark solution was cooled to 0 °C and CuI (1.2 mmol, 228 mg) was added. The black slurry was stirred for 20 min then cooled to −78 °C. A 1:1 solution of Et_3N/TMSCl (6 mL) was added dropwise followed by TMEDA (0.98 mL, 6 mmol). After 10 min, a solution of the desired enone (4.6 mmol) in 3 mL of THF was added dropwise at −78 °C. If done correctly, the slurry will turn yellow upon addition of enone. The mixture was allowed to stir for 4 h and allowed to warm to room temperature over 1 h. The now black solution was placed into a −20 °C freezer overnight. The reaction was quenched by pouring the mixture into ice-cold saturated ammonium chloride (30 mL) and pentane (60 mL) in a separatory funnel. The organic layer was washed with saturated sodium bicarbonate and brine and dried over sodium sulfate. The crude enolether was concentrated in vacuo and taken forward without further purification.

4.5. General electrolysis conditions

Electrolyses were carried out with either a custom-made electrode system consisting of alternating carbon (anode) and stainless steel (cathode) electrodes, or with reticulated vitreous carbon (RVC) fixed onto a carbon rod serving as the anode and another carbon rod serving as the cathode. No attempts were made to exclude air from the prior example, but the latter requires degassing by sonication for reproducible yields. All solvents were purchased at the highest purity and used without further purification. Lithium perchlorate and 2,6-lutidine were also used without further purification. RVC was purchased from Electrolytica, Inc.

4.5.1. Electrolysis with carbon/stainless steel electrodes. To the crude enolether generated from the cuprate addition (4.6 mmol) was added a 4:1 CH_3CN/*i*-PrOH (230 mL) and 2,6-lutidine (18.4 mmol, 2.14 mL). Lithium perchlorate (2.48 g, 23 mmol) was then added and allowed to dissolve. An electrode system consisting of alternating carbon and stainless steel plates (five stainless steel and four carbon) was submerged and connected to the potentiostat so that the stainless steel plates acted as the cathode and the carbon plates as the anode. In order to determine the surface area of the electrode (anode), the carbon plates were measured to the depth of the solution and the width of the plate and multiplied by four. The potentiostat was then activated and the current necessary for a current density=1 mA/cm^2 was dialed in and locked. The reaction was checked by TLC once 2.2 F/mol were consumed and, if complete, the current was stopped. If the reaction was not yet complete, then the reaction was closely monitored by TLC until completion (usually every 10 min). The reaction was worked up by concentrating the reaction solution and partitioning the crude product between ether (100 mL) and 1 M HCl (60 mL). The aqueous layer was extracted three times and the combined organic layers washed again with 1 M HCl, water, saturated sodium bicarbonate, brine, and dried over sodium sulfate. After concentrating, the product was purified by flash chromatography (typical gradient elution conditions were 20:1 hexanes/ethyl acetate → 10:1 hexanes/ethyl acetate). *It is imperative that the silica gel be degassed before chromatography to obtain reported yields* (for procedure, see Ref. 8).

4.5.2. Electrolysis with RVC/carbon electrodes. To the crude enolether generated from the cuprate addition (4.6 mmol) was added a 4:1 CH_3CN/*i*-PrOH (230 mL) and 2,6-lutidine (18.4 mmol, 2.14 mL). Lithium perchlorate (2.48 g, 23 mmol) was then added and allowed to dissolve. An electrode system consisting of two carbon rods (diameter=7 mm, serving as the cathode) and one carbon rod with an approximately 1 cm^3 piece of RVC (serving as the anode) attached at the end was submerged and purged with argon. After 5 min, the solution was degassed by sonication for 15 min. The carbon rods were connected to the potentiostat accordingly, via alligator clips. The optimized current must be determined through several experimental trials and is dependent upon scale and substrate. On this scale (4.6 mmol), 8 mA was passed until 2.3 F/mol were consumed. The reaction was worked up by concentrating the reaction solution and partitioning the crude product between ether (100 mL) and 1 M HCl (60 mL). The aqueous layer was extracted

three times and the combined organic layers washed again with 1 M HCl, water, saturated sodium bicarbonate, brine, and dried over sodium sulfate. After concentrating, the product was purified by flash chromatography (typical gradient elution conditions were 20:1 hexanes/ethyl acetate → 10:1 hexanes/ethyl acetate). *Again, It is imperative that the silica gel be degassed before chromatography to obtain reported yields*.

4.5.2.1. *cis*-5a-Methyl-4,5,5a,6,7,8a-hexahydro-1-oxa-as-indacen-8-one, 8. Isolated as a white solid (mp 42–43 °C, 74%); IR (KBr pellet) λ_{max} (cm^{-1}) 2959, 2862, 1742, 1625, 1550, 1050; ^1H NMR (300 MHz): δ 7.35 (dd, J=1.9 Hz, 1H), 6.21 (J=1.9 Hz, 1H), 3.00 (s, 1H), 2.51 (m, 2H), 2.41 (m, 2H), 2.00 (m, 1H), 1.81 (m, 1H), 1.62 (m, 2H), 1.19 (s, 3H); ^{13}C NMR (125 MHz): δ 215.1, 144.7, 142.6, 116.7, 110.0, 54.9, 40.2, 35.5, 33.1, 31.7, 25.5, 19.0. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42; found: C, 75.64; H, 7.51.

4.5.2.2. *cis*-6-Isopropyl-4,5a,6,7,8,9a-hexahydro-5H-naphtho[1,2-b]furan-9-one, 11. Isolated as a colorless oil that solidified in a −20 °C freezer, (65%). IR (neat) λ_{max} (cm^{-1}): 2927, 1717, 1634, 1511; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (dd, J=2.0, 0.9 Hz, 1H), 6.21 (d, J=2.0 Hz, 1H), 3.59 (d, J=11.2 Hz, 1H), 2.43–2.60 (m, 4H), 2.10–2.23 (m, 3H), 1.87 (qd, J=11.5, 2.2 Hz, 1H), 1.78 (tt, J=11.5, 3.4 Hz, 1H), 1.54–1.63 (m, 1H), 1.39 (dddd, J=30.5, 24.4, 11.7, 5.6 Hz, 1H), 1.03 (d, J=6.9 Hz, 3H), 0.80 (d, J=7.1 Hz, 3H); ^{13}C NMR: δ 208.9, 146.8, 142.6, 119.4, 110.1, 52.9, 46.5, 46.1, 41.4, 27.4, 26.8, 26.5, 22.1, 21.7, 15.0. EI-HRMS m/z calcd for $C_{15}H_{20}O_2$ (M^+): 232.1463; found: 232.1465.

4.5.2.3. *cis*-6a-Methyl-5,6,6a,7,8,9a-hexahydro-4H-azuleno[4,5-*b*]furan-9-one, 17. Isolated as a colorless oil, which solidified in a −20 °C freezer, (61% carbon/stainless steel, 70% RVC/carbon) IR (neat) λ_{max} (cm^{-1}) 2930, 1715, 1631, 1505, 1251, 1107; ^1H NMR (500 MHz) δ 7.28 (d, J=1.7 Hz, 1H), 6.18 (d, J=1.7 Hz, 1H), 3.37 (s, 1H), 2.49–2.55 (m, 1H), 2.43 (ddd, J=8.7, 2.7, 1.0 Hz, 1H), 2.41 (dd, J=10.6, 8.4 Hz, 1H), 2.31–2.36 (m, 1H), 1.84–1.99 (m, 2H), 1.70–1.72 (m, 4H), 1.27 (s, 3H); ^{13}C NMR (125 MHz) δ 215.4, 145.3, 141.3, 121.9, 113.4, 62.0, 40.2, 39.3, 37.6, 35.1, 26.1, 25.9, 22.5. EI-HRMS m/z calcd for $C_{13}H_{16}O_2$ (M^+): 204.1150; found: 204.1137.

4.5.2.4. *cis*-5a-Methyl-4,5,5a,6,7,8a-hexahydro-1-thia-as-indacen-8-one, 24. Isolated as a white solid (mp 70.1–70.8 °C, 81%). IR (neat) λ_{max} (cm^{-1}): 2922, 2855, 17,454, 1454, 1433, 1381; ^1H NMR (500 MHz, $CDCl_3$): δ 7.19 (dd, J=5.1, 0.5 Hz, 1H), 6.80 (dd, J=5.1, 0.5 Hz, 1H), 3.04 (s, 1H), 2.68–2.71 (m, 2H), 2.39–2.47 (m, 2H), 2.02 (ddd, J=17.5, 8.7, 4.4 Hz, 1H), 2.01 (dt, J=13.1, 9.5 Hz, 1H), 1.60–1.72 (m, 2H), 1.24 (s, 3H); ^{13}C NMR (125 MHz): δ 215.8, 134.3, 129.4, 126.6, 124.2, 56.5, 39.4, 35.2, 33.5, 31.2, 25.4, 22.4. Anal. Calcd for $C_{12}H_{14}OS$: C, 69.86; H, 6.84; O, 7.76; S, 15.54; found: C, 69.83; H, 6.85; O, 7.78; S, 15.46.

4.5.2.5. *cis*-5a-(3-Furan-3-yl-propyl)-4,5,5a,6,7,8a-hexahydro-1-oxa-as-indacen-8-one, 46. Isolated as a viscous colorless oil. IR (neat) λ_{max} (cm^{-1}) 2933, 1717, 1630, 1505, 1107; ^1H NMR (500 MHz) δ 7.35–7.36 (m, 2H), 7.21–7.22 (m, 1H), 6.27 (s, 1H), 6.22 (d, J=1.6 Hz, 1H), 3.03 (s, 1H), 2.39–2.47 (m, 6H), 1.97 (ddd, J=13.2, 7.9, 5.1 Hz, 1H), 1.83–1.89 (m, 1H), 1.75 (dt, J=13.7, 4.4 Hz, 1H), 1.57–1.69 (m, 4H) 1.37–1.44 (m, 1H); ^{13}C NMR (125 MHz) δ 215.4, 145.2, 143.1, 142.9, 139.1, 124.9, 116.9, 111.0, 110.2, 55.0, 43.4, 37.4, 35.5, 31.0, 28.7, 25.5, 24.5, 19.0. EI-HRMS m/z calcd for $C_{18}H_{20}O_3$ (M^+): 284.1412; found: 284.1412.

4.5.2.6. *cis*-5a-(2-Thiophen-3-yl-ethyl)-4,5,5a,6,7,8a-hexahydro-1-oxa-as-indacen-8-one, 48. Isolated as a viscous, pale-yellow oil (1.00 g, 3.5 mmol, 76%), which solidified in a −20 °C freezer. IR (thin film) λ_{max} (cm^{-1}): 3104, 2920, 2856, 1745, 1502, 1453; ^1H NMR (500 MHz): δ 7.37 (dd, J=1.9, 0.7 Hz, 1H), 7.26–7.27 (m, 1H), 6.94–6.95 (m, 2H), 6.24 (d, J=1.7 Hz, 1H), 3.10 (s, 1H), 2.71–2.75 (m, 2H), 2.52–2.64 (m, 2H), 2.44–2.48 (m, 2H), 1.93–2.07 (m, 3H), 1.85 (dt, J=13.9, 4.7 Hz, 1H), 1.64–1.76 (m, 2H), 1.17–1.28 (m, 1H); ^{13}C NMR (125 MHz): δ 215.1, 145.2, 143.0, 142.4, 128.3, 125.9, 120.2, 116.9, 110.3, 55.1, 43.5, 38.6, 35.6, 31.1, 28.6, 24.9, 19.1. EI-HRMS m/z calcd for $C_{17}H_{18}O_2S$: 286.1028; found: 286.1040.

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