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HETEROAROMATIC TRAPPING OF TRICYCLIC 2-OXIDOCYCLOPENTENYL CATIONS: A SURPRISINGLY EFFICIENT EXAMPLE OF INTERMOLECULAR INTERRUPTED NAZAROV REACTION†

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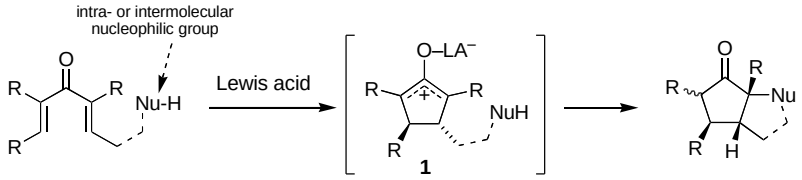
Abstract – Bis(cycloalkenyl) ketones **2a** and **2f** underwent Nazarov cyclization and intermolecular trapping by electrophilic aromatic substitution with furans, thiophenes, pyrroles, indoles and dimethoxybenzene. Only the *cis-anti-cis* diastereomer was isolated with dicyclopentenyl ketone **2a**, whereas a mixture of diastereomers was seen with **2f** (albeit with complete regioselectivity). Comparable interrupted Nazarov trapping was not seen with acyclic dienones **2b-e**, indicating the possible involvement of conformation effects in the polycyclic intermediates derived from **2a** and **2f**.

INTRODUCTION

Introduction of an aryl group adjacent to a ketone is a potentially valuable transformation. A number of methods based on metal catalyzed cross-coupling reactions using aryl halides are available,[1] as well as nucleophilic aromatic substitution[2] and benzyne-mediated[3] strategies. On the other hand, it is difficult to take advantage of straightforward electrophilic aromatic substitution chemistry due to the difficulty in accessing the necessary electrophile. The interrupted Nazarov reaction offers a strategy for gaining *umpollung* type reactivity α to a cyclopentanone carbonyl group (Scheme 1).[4] Cross-conjugated dienones undergo Lewis acid-mediated electrocyclic closure to form 2-oxidocyclopentenyl cations **1** that can be intercepted with a variety of intra- or intermolecular nucleophiles. The resulting cyclopentanone

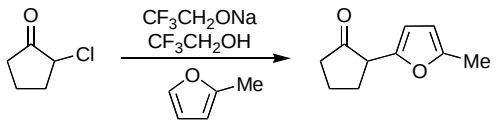
†This paper is dedicated to Professor Emeritus Akira Suzuki on the occasion of his 80th birthday.

products are bonded to the former nucleophile at the 2 position, equivalent to having reacted via a formal α-keto carbocation.



Scheme 1. Nucleophilic trapping of the Nazarov intermediate

While there are several examples of intramolecular trapping by electron-rich arenes,[5] effective intermolecular interception by simple aromatic traps remained elusive until recently. In 2008, we reported that dienone substrates in which both alkenes are encased within 5- or 6-membered rings can be trapped by unsubstituted electron-rich heteroaromatic compounds and 1,3-dimethoxybenzene.[6] Shortly after, Basak and Tius disclosed a related process in which siloxy-substituted dienynes underwent Brønsted acid-mediated Nazarov cyclization with trapping of the intermediate by substituted indoles.[7] A conceptually similar process was also described by Föhlisch and Joachimi, in which an unsubstituted 2-oxidocyclopentenyl cation generated by ionization of 2-chlorocyclopentanone was trapped by 2-methylfuran (eq 1).[8] Here we report a full account of our studies, including the results with a number of substituted heteroaromatic traps.

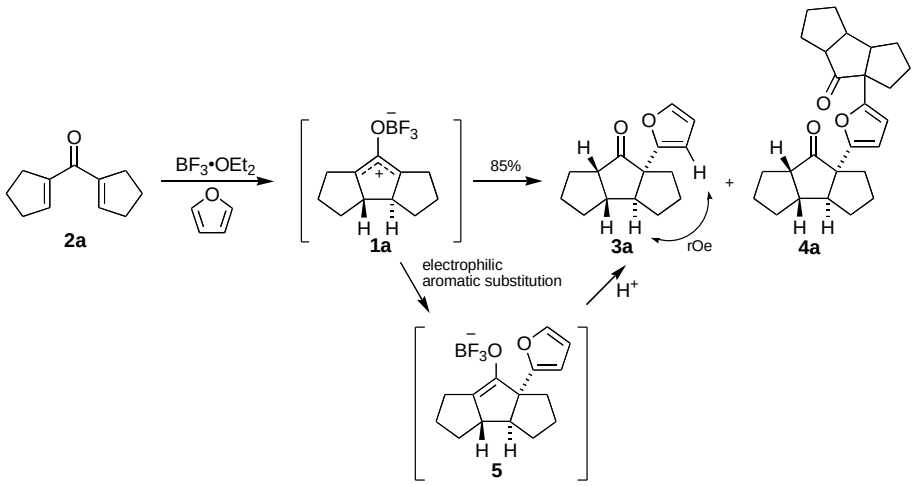


(1)

RESULTS AND DISCUSSION

Our initial studies employed the known dicyclopentenyl ketone **2a** (Scheme 2), a Nazarov substrate that had been successfully trapped with allylsilanes in a formal 3+2 cycloaddition.[9] In an attempt to broaden its reactivity scope to include the corresponding [4+3]-cycloaddition,[10] this dienone was stirred with one equiv each of furan and BF_3•OEt_2 at room temperature, resulting in complete consumption of **2a** after 2 h. Surprisingly, however, neither of the two isolated products was the expected [4+3]-cycloadduct. Instead, products **3a** and **4a** resulting from trapping by simple electrophilic aromatic substitution reaction were obtained in a combined 85% yield. The basic connectivity of these adducts, entailing a bridgehead 2-furyl substituent on a linear triquinane, was determined via standard 2-dimensional NMR experiments. The *cis-anti-cis* relative stereochemistry assigned to the triquinane skeleton was inferred on the basis of the well established conrotatory electrocyclization mechanism of the Nazarov cyclization[11] (leading to *anti* intermediate **1a**), and the previously described preference for nucleophilic attack *cis* to the adjacent bridgehead substituent to provide the less strained ring fusion[9] (confirmed by the observation of TROESY

correlations between the the 3-furyl proton and the neighboring bridgehead proton). Finally, protonation of the resulting enolate **5** *cis* to the neighboring bridgehead proton to furnish the more stable *cis*-fused skeleton is expected to be the major or exclusive stereochemical outcome, due to the large enthalpic advantage. The stereochemical relationship between the two triquinane units in **4a** could not be determined, due to the distance separating them.

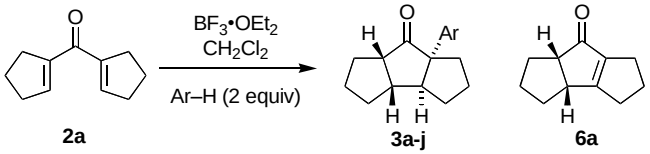


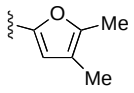
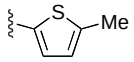
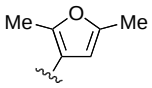
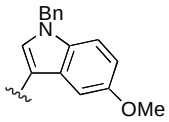
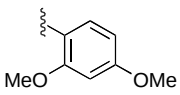
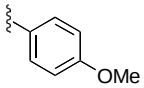
Scheme 2. Electrophilic aromatic substitution of furan by the cationic intermediate from **2a**

While 2:1 adduct **4a** possesses a unique and potentially useful structure, the simple 1:1 adduct **3a** was of more immediate interest, as this was the first observation of intermolecular arene trapping of a Nazarov intermediate. To optimize the formation of the 1:1 adduct, we increased the amount of furan to 10 equiv, and under these conditions only **3a** was obtained. These conditions were then applied to dienone **2a** and a variety of simple heteroarenes (Table 1), although with traps other than furan 2 equiv was sufficient to assure exclusive formation of 1:1 adducts **3**. Thiophene, N-tosylpyrrole and N-benzylpyrrole cleanly trapped intermediate **1a** to provide adducts **3b-d**. Substituted thiophenes and furans also provided arylated products (**3e-g**) as single regioisomers, although in only modest yields in the case of 2,5-dimethylfuran (entry 7). In analogy to the results described by the Tius group,[7] N-protected indole and 5-methoxyindole underwent trapping at the 3 position in high yields (entries 8 and 9). To further test the limits of this method, we also examined two electron-rich benzene systems (entries 10 and 11). 1,3-Dimethoxybenzene proved to be a highly effective trap, providing 2,4-dimethoxyphenyl-substituted triquinane **3j** in good yield. However, no trapping was seen with the less activated anisole. Instead, the simple eliminative Nazarov product **6a** was obtained in good yield.

The generally efficient formation of adducts **3a-j** raised a question: why did the cationic intermediate **1a** derived from dienone **2a** consistently undergo bimolecular arene trapping? Nazarov intermediates from acyclic dienones were already known to react with furan in [4+3]-cycloadditions.[10] For example, dienones **2b-d** all furnished keto-bridged cyclooctenes **7b-d** in good yield, with no evidence of simple

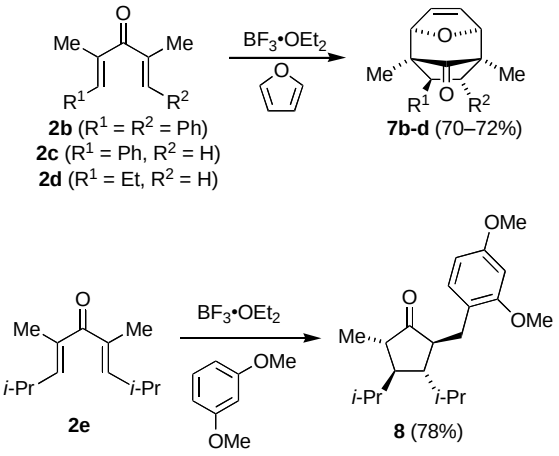
Table 1. Arene trapping of **2a** with electron rich arenes



entry[a]	Ar	product	yield (%)[b]
1[c,d]		**3a**	79
2[d]		**3b**	79
3[d,e]		**3c**	78
4		**3d**	64
5		**3e**	81
6		**3f**	82
7		**3g**	31
8		**3h**	84
9		**3i**	85
10[d]		**3j**	79
11		**6a**	81

[a]Standard procedure: BF_3•OEt_2 (1.1 equiv) was added to a solution of dienone **1** and arene (2 equiv) in CH_2Cl_2 at rt. After 30 min, reaction was quenched with sat. $NaHCO_3$. Crude product was purified by flash chromatography. [b]All stated yields given are for homogeneous material following chromatographic purification. [c]Excess furan was used (10 equiv). [d]Results from entries 1-3 and 10 and characterization data for the products were previously described in reference 6. [e]Excess BF_3•OEt_2 (3.1 equiv) was required to effect the transformation.

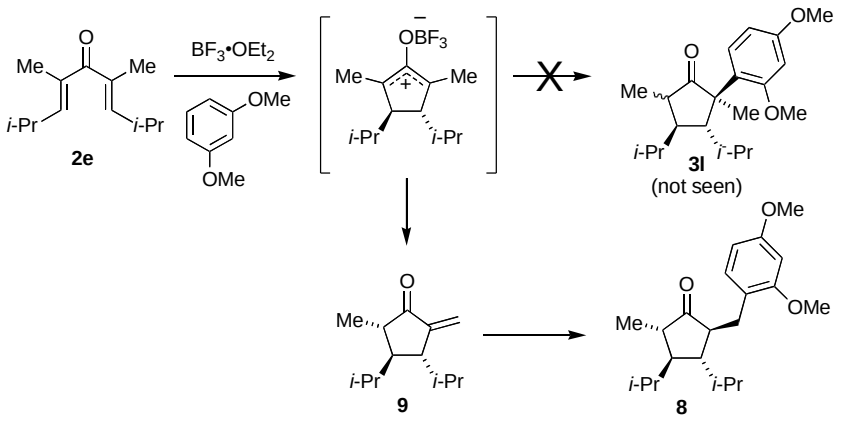
arene trapping (Scheme 3). However, treatment of **2b** with heteroarenes possessing less diene character such as thiophene or N-tosylpyrrole did not result in any simple arylation products analogous to **3**, as was also the case with dimethoxybenzene. A possible rationale for the differing reactivity of **2a** and **2b** with these arenes centers on the lifetime of the cationic intermediate following Nazarov electrocyclization. The polycyclic **1a** may persist long enough to undergo bimolecular trapping because the conventional elimination pathway is disfavored as a result of diminished conformational mobility.[12] On the other hand, with furan **1a** may not be able to undergo [4+3]-cycloaddition due to the greater steric demand likely to be present in the transition state for this concerted process.



Scheme 3. Behavior of acyclic dienones

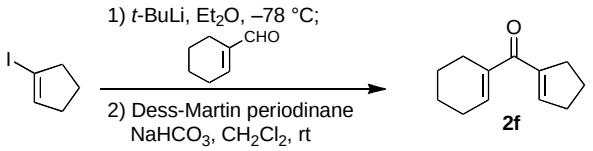
With these differences in mind, we also examined the more hindered dienone **2e**, a substrate which had shown broad generality in a variety of trapping processes. In the event, no adducts were seen with the heteroarene traps. However, with dimethoxybenzene an interesting new product was isolated in good yield. This product clearly contained elements of both reactants, with one fewer arene proton suggesting some sort of aromatic substitution process. Notably, there was no quaternary center adjacent to the cyclopentanone carbonyl, suggesting that trapping in analogy to **2a** to give **3l** had not occurred. Moreover, one of the former methyl groups flanking the carbonyl was missing, and an unexpected benzylic methylene was present, adjacent to one of the cyclopentanone α carbons. Based on these data, we assigned structure **8** to this adduct. The all-*trans* relative configuration was supported by ^{1}H NMR coupling constants.[6]

Adduct **8** may arise via conjugate addition of dimethoxybenzene to methylidenecyclopentanone **9**, formed by exocyclic elimination of the cyclized intermediate **1e** (Scheme 4). In general, elimination of the Nazarov intermediate occurs in an endocyclic mode to form the most substituted (Saytzeff) alkene. However, in this case the alternative elimination may be favored to avoid the severe steric congestion resulting from enone **6e**.[13] The lack of enone β substituents on **9** would then permit the subsequent conjugate addition to occur.[14,15]



Scheme 4. Formation of adduct **8**

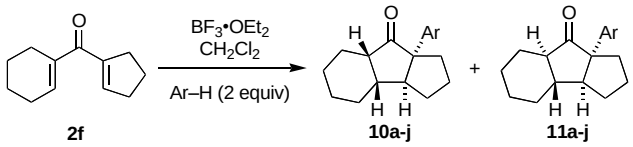
Since arene effective trapping of the Nazarov intermediate was not possible with acyclic dienones, we next chose to examine the higher homologue of **2a**, cyclohexenyl cyclopentenyl ketone **2f**, prepared in two steps from cyclohexenecarboxaldehyde (eq 2). This unsymmetrical example was expected to address several interesting questions. First, would the presence of one larger ring shorten the lifetime of the cationic intermediate through greater conformational mobility, and hence cause decreased efficiency in the bimolecular trapping process? Second, if trapping occurred, would any regioselectivity be observed (i.e., trapping at the diquinane or the hydrindan bridgehead)? Finally, would there be any erosion in the complete stereoselectivity in favor of the *cis-anti-cis* ring-fusion stereochemistry observed with **2a**?



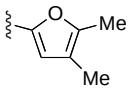
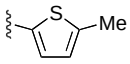
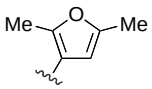
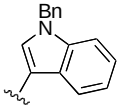
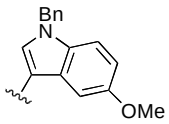
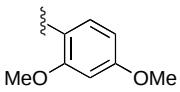
(2)

Treatment of **2f** with the same heteroarenes used with **2a** furnished good yields of the adducts **10** and **11** (Table 2), except in the case of 2,5-dimethylfuran (entry 7). As before, complete regioselectivity was observed with respect to substitution on the arene. However, in all successful cases, inseparable mixtures of adducts were obtained, in ratios of 2:1–5:1. Two possibilities were considered for the source of the mixtures: (1) regioisomeric trapping of **1f** at the two bridgehead positions (i.e., **A** vs. **B**, Scheme 5), or diastereomeric mixtures of a single regioisomer (i.e., **A** vs. **A'**). Fortuitously, with 1,3-dimethoxybenzene, the adducts (**10j** and **11j**) were separable. Examination of the mass spectral fragmentation patterns of these compounds revealed an important correlation with that of **3j**. Specifically, **3j** (and other triquinane adducts derived from **2a**) undergo loss of a neutral C_5H_8CO fragment, presumably producing arylcyclopentenyl cation radical **12j** (*m/z* 204.115). Both **10j** and **11j** displayed the same fragment (the base peak) in their mass spectra, corresponding to loss of $C_6H_{10}CO$. With the observation of the same aryl-containing cation radical from all three adducts, it can be inferred that both **10j** and **11j** are substituted with a dimethoxyphenyl group at the diquinane bridgehead rather than the hydrindan bridgehead, and hence must differ in their ring fusion relative configuration. Given

Table 2. Arene trapping of **2f** with electron rich arenes



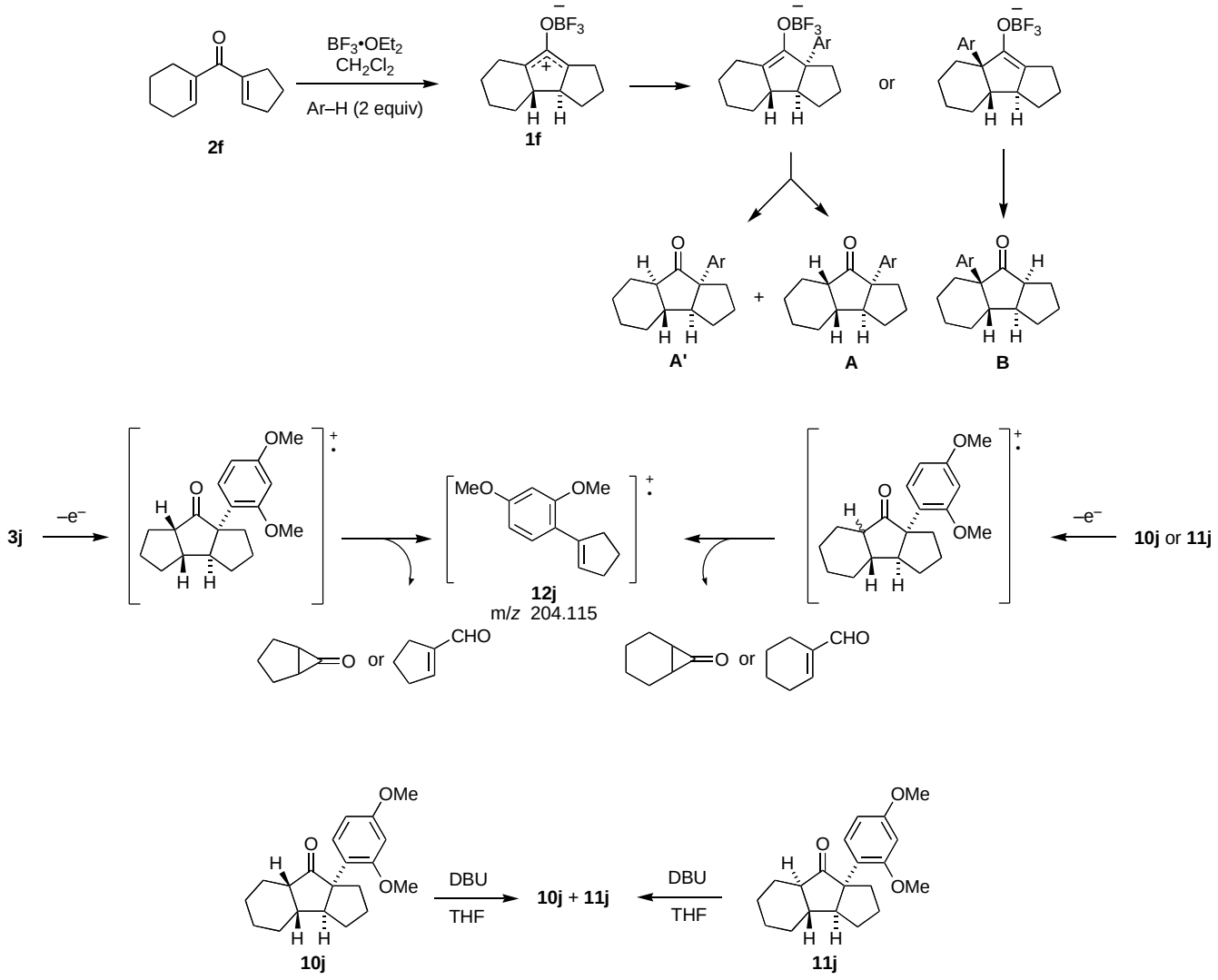
2f **10a-j** **11a-j**

entry[a]	Ar	products (ratio)	combined yield (%)[b]
1[c, d]		**10a** + **11a** (2:1)	76
2[d]		**10b** + **11b** (4:1)	80
3[d,e]		**10c** + **11c** (2:1)	29
4		**10d** + **11d** (2:1)	78
5		**10e** + **11e** (2:1)	85
6		**10f** + **11f** (2:1)	86
7		--[f]	--
8		**10h** + **11h** (2:1)	82
9		**10i** + **11i** (5:1)	82
10[d]		**10j** + **11j** (2:1; separable)	80

[a]See Table 1 for standard procedure. [b]All stated yields given are for homogeneous material following chromatographic purification. [c]Excess furan was used (10 equiv). [d]Results from entries 1-3 and 10 and characterization data for the products were previously described in reference 6. [e]Excess BF_3•OEt_2 (3.1 equiv) was required to effect the transformation. [f]Starting material was decomposed without formation of any discernable adduct of 2,5-dimethylfuran.

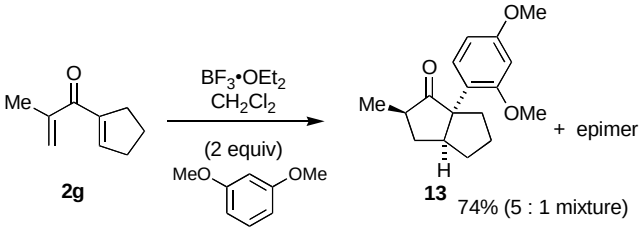
the low likelihood of a *trans* diquinane ring fusion, a mixture of *cis*- and *trans*-fused hydrindans, arising from protonation of either face of the enolate precursor, was considered. If this position were the only point of difference, it might be possible to interconvert **10j** and **11j** through base-mediated epimerization.[16] In the event, treatment of either pure isomer with DBU resulted in identical equilibrium

mixtures of **10j** and **11j**, offering strong evidence for the structural assignment. The same fragmentation pattern was seen in the mass spectra of all of the other adduct **10** and **11**, and they were also assigned as epimers in analogy to **10j** and **11j**.



Scheme 5. Possible origins of isomeric mixtures from **2f** and evidence for epimeric relationship of **10j** and **11j**

Finally, the contrast between dienones **2a** and **2f** vs acyclic dienones **2b-e** prompted the examination of a hybrid substrate **2g** with a single cyclopentene ring[17] (eq 3). Although the cationic intermediate in this case would not be tricyclic, it would possess the electrophilic diquinane bridgehead site that was crucial for trapping in **2a** and **2f**. In the event, when **2g** was treated with 1,3-dimethoxybenzene under the standard conditions, two adducts were obtained in good yield, and in a ratio of 5:1. While the minor isomer could not be obtained in sufficient purity to be characterized, the major product **13** was found to be a single diastereomer from trapping at the diquinane bridgehead position.[18] The minor product is inferred to be the epimer of **13**, in analogy to the mixtures obtained from **2f**.



Scheme 6. Trapping of **2g** with 1,3-dimethoxybenzene

CONCLUSIONS

Cross-conjugated dienones **2a** and **2f** were found to undergo a high-yielding and general interrupted Nazarov process, in which the tricyclic cationic intermediates were trapped by a variety of heteroaromatic nucleophiles. Both substrates were also trapped by 1,3-dimethoxybenzene. This process entails a direct α-arylation adjacent to a cyclopentanone carbonyl group, giving rise to linearly fused bridgehead-arylated products. For the unsymmetrical substrate **2f**, complete regioselectivity was seen in favor of attack at the diquinane bridgehead. Acyclic dienones did not undergo an analogous trapping process, but in one case a novel adduct resulting from conjugate addition of dimethoxybenzene to an α-methylenecyclopentanone resulting from conventional Nazarov elimination was observed. A monocyclic substrate, **2g**, also underwent trapping with dimethoxybenzene, again at the diquinane bridgehead.

EXPERIMENTAL

General Information. Reactions were carried out in flame-dried glassware under a positive nitrogen atmosphere unless otherwise stated. Transfer of anhydrous solvents and reagents was accomplished with oven-dried syringes or cannulae. Solvents were distilled before use: methylene chloride from calcium hydride, tetrahydrofuran, diethylether and benzene from sodium/benzophenone ketyl, toluene from sodium metal. Thin layer chromatography was performed on glass plates precoated with 0.25 mm Kieselgel 60 F254 (Merck). Liquid chromatography-mass spectrometry (LC-MS) was carried out using Agilent-1100 series. Flash chromatography column were packed with 230-400 mesh silica gel (Silicycle). Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 300 MHz, 400 MHz, or 500 MHz on Varian Inova 300, Inova 400, Mercury 400, Inova 500 and Unity 500 instruments. Coupling constants (J) are reported in Hertz (Hz). The chemical shifts are reported on the δ scale (ppm) and the spectra are referenced to tetramethylsilane (0 ppm, ^{1}H; ^{13}C) or to deuteriochloroform (7.26 ppm, 1H; 77.23 ppm, ^{13}C) as internal standard. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on the same instruments at 100 MHz or 125 MHz. Infrared (IR) spectra were measured with a Mattson Galaxy Series FT-IR 3000 spectrophotometer. Mass spectra were determined on a PerSeptive Biosystem Mariner high-resolution electrospray spectrometer in the positive mode.

Standard Procedure for Arene Trapping. $BF_3{\cdot}OEt_2$ (0.11 mmol) was added to a stirred solution of dienone (0.10 mmol) and arene (0.20 mmol) in CH_2Cl_2 (at a concentration of 10 mM) at room temperature. After 30 minutes the reaction was worked up with aq. saturated $NaHCO_3$ (5 mL). The organic layer was drawn off and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phase was then dried over $MgSO_4$, concentrated and purified via flash chromatography (10% EtOAc in hexanes).[19]

3d: 20mg (64%): pale yellow oil; IR (film) 3100, 30.62, 3029, 2952, 2866, 1730, 1605, 1469, 1477, 1452, 1420, 1329, 1298, 1086, 1030, 713 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$) δ 7.31 (m, 2H), 7.25 (m, 1H), 7.05 (d, 2H, J = 7.4 Hz), 6.51 (dd, 1H, J = 2.7, 1.9 Hz), 6.07 (dd, 1H, J = 3.5, 3.0 Hz), 6.00 (dd, 1H, J = 3.6, 1.8 Hz), 5.26 (d, 1H, J = 16.2 Hz), 5.21 (d, 1H, J = 16.2 Hz), 2.91 (ddd, 1H, J = 9.6, 4.9, 4.9 Hz), 2.66 (m, 1H), 2.35 (dddd, 1H, J = 9.0, 9.0, 4.5, 4.5 Hz), 2.13 (m, 1H), 2.04 (m, 2H), 1.84 (m, 3H), 1.74 (m, 3H), 1.57 (m, 2H), 1.46 (m, 1H); ^{13}C NMR (125MHz, $CDCl_3$) δ 221.9, 139.2, 132.8, 128.5, 127.2, 126.8, 123.6, 106.9, 106.9, 62.8, 53.6, 52.3, 51.8, 45.3, 37.8, 34.1, 33.4, 30.2, 25.7, 25.1; HRMS calc for $C_{22}H_{25}NO$ (M^+) 319.1936; found 319.1932 (68%), 223.1361 [M-C_6H_8O]$^+$ (100%).

3e: 21mg (81%): pale yellow oil; IR (film) 2950, 2868, 1736, 1679, 1612, 1448, 1223, 1153, 945, 801 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 5.91 (s, 1H), 2.86 (ddd, 1H, J = 9.4, 9.4, 4.6 Hz), 2.67 (ddd, 1H, J = 7.3, 3.3, 3.3), 2.33 (m, 1H), 2.16 (s, 3H), 2.07 (m, 3H), 1.93 (m, 3H), 1.90 (s, 3H), 1.77 (m, 1H), 1.68 (m, 2H), 1.58 (m, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 222.9, 153.6, 146.8, 114.5, 109.1, 63.0, 53.4, 52.6, 46.7, 37.9, 35.3, 34.6, 30.4, 26.1, 26.0, 11.6, 10.1; HRMS calc for $C_{17}H_{22}O_2$ (M^+) 258.1620; found 258.1615 (40%), 162.1045 [M-C_6H_8O]$^+$ (100%).

3f: 21mg (81%): pale yellow oil; IR (film) 3060, 2950, 2866, 1734, 1653, 1552, 1470, 1448, 1230, 1166, 1107, 1060, 769 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 6.68 (d, 1H, J = 3.6 Hz), 6.58 (m, 1H), 2.90 (ddd, 1H, J = 8.7, 5.6, 5.6 Hz), 2.69 (ddd, 1H, J = 7.3, 3.3, 3.3 Hz), 2.44 (s, 3H), 2.38 (dddd, 1H, J = 8.1, 8.1, 4.3, 4.3 Hz), 2.19 (m, 2H), 2.04 (ddd, 1H, J = 13.6, 7.0, 7.0 Hz), 1.89 (m, 3H), 1.74 (m, 3H), 1.55 (m, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 222.7, 145.0, 138.5, 124.9, 123.6, 64.3, 55.3, 53.1, 46.7, 42.4, 35.2, 34.2, 30.6, 26.1, 26.0, 15.5; HRMS calc for $C_{16}H_{20}OS$ (M^+) 260.1235; found 260.1236 (44%), 164.0660 [M-C_6H_8O]$^+$ (100%).

3g: 16mg (31%): pale yellow oil; IR (microscope) 2950, 2868, 1732, 1679, 1623, 1577, 1450, 1328, cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 5.77 (s, 1H), 2.89 (ddd, 1H, J = 8.2, 8.2, 8.2 Hz), 2.46 (m, 1H), 2.34 (dddd, 1H, J = 8.7, 8.7, 4.4, 4.4 Hz), 2.26 (s, 3H), 2.21 (s, 3H), 2.15 (m, 1H), 2.00 (m, 2H), 1.87 (m, 3H), 1.76 (m,3H), 1.58 (m, 1H), 1.52 (m, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ 223.6, 148.6, 146.0, 121.5, 107.1, 61.1, 54.1, 52.7, 46.0, 39.4, 34.4, 34.3, 30.4, 26.0, 25.5, 14.0, 13.6; HRMS calc for $C_{17}H_{22}O_2$ (M^+) 258.1620; found 258.1615 (56%), 162.1045 [M-C_6H_8O]$^+$ (100%).

3h: 31mg (84%): pale yellow oil; IR (film) 3087, 3061, 3031, 2949, 2865, 1728, 1612, 1542, 1496,

1481, 1467, 1453, 1371, 1355, 1335, 1199, 1180, 1017, 736, 696 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 7.69 (d, 1H, J = 7.9 Hz), 7.28 (m, 4H), 7.17 (ddd, 1H, J = 4.2, 6.9, 8.1 Hz), 7.12 (m, 1H), 7.08 (m, 2H), 6.88 (s, 1H), 5.29 (d, 1H, J = 16.2 Hz), 5.26 (d, 1H, J = 16.2 Hz), 2.91 (m, 2H), 2.46 (dddd, 1H, J = 8.7, 8.7, 4.4, 4.4 Hz), 2.28 (m, 3H), 1.82 (m, 6H), 1.47(m, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 225.4, 137.9, 137.8, 128.9, 127.7, 126.9, 126.6, 125.8, 122.0, 121.2, 119.2, 117.3, 110.2, 62.2, 53.2, 52.8, 50.2, 46.7, 39.7, 35.4, 34.8, 31.1, 26.2, 26.1; HRMS calc for $C_{26}H_{27}NO$ (M^+) 369.2093; found 369.2096 (50%), 273.1518 $[M\text{-}C_6H_8O]^+$ (100%).

3i: 34mg (85%): brown oil; IR (film) 3063, 3030, 2948, 2866, 1228, 1621, 1575, 1487, 1451, 1355, 1343, 1288, 1258, 1222, 1180, 1043, 1030, 793, 731, 705 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 7.28 (m, 3H), 7.13 (m, 2H), 7.07 (m, 2H), 6.87 (s, 1H), 6.84 (dd, 1H, J = 8.9, 2.4 Hz), 5.53 (br s, 2H), 3.88 (s, 3H), 2.93 (ddd, 1H, J = 9.2, 9.2, 5.1 Hz), 2.85 (ddd, 1H, J = 7.3, 3.2, 3.2 Hz), 2.46 (dddd, 1H, J = 8.5, 8.5, 4.2, 4.2 Hz), 2.25 (m, 3H), 1.85 (m, 6H), 1.51 (m, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 225.2, 153.7, 137.9, 133.3, 128.9, 127.7, 127.0, 126.8, 126.5, 116.6, 111.9, 110.9, 103.5, 62.3, 56.1, 53.1, 52.8, 50.4, 46.5, 39.1, 35.2, 34.8, 31.1, 26.2, 25.9; HRMS calc for $C_{27}H_{29}NO_2$ (M^+) 399.2198; found 399.2196 (28%), 303.1623 $[M\text{-}C_6H_8O]^+$ (69%), 91.0548 $[M\text{-}C_{20}H_{22}NO_2]^+$ (100%).

10d and **11d:** 52 mg (78%) isolated as a 2:1 mixture of diastereomers. Small quantities of pure diastereomers were obtained using radial chromatography.

10d: off-white solid; IR (film) 3108, 3037, 2997, 2930, 2861, 1727, 1686, 1498, 1477, 1466, 1457, 1447, 1376, 1264, 1236, 1087, 1028, 773, 708 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$) δ 7.31 (m, 2H), 7.25 (m, 1H), 7.06 (m, 2H), 6.52 (dd, 1H, J = 2.3, 2.3 Hz), 6.07 (d, 2H, J = 2.3 Hz), 5.51 (d, 1H, J = 16.1 Hz), 5.43 (d, 1H, J = 16.1 Hz), 3.07 (ddd, 1H, J = 8.3, 4.9, 4.4 Hz), 2.57 (dddd, 1H, J = 6.5, 6.5, 6.5, 6.5 Hz), 2.07 (m, 2H), 1.98 (m, 2H), 1.83 (m, 1H), 1.65 (m, 4H), 1.52 (m, 2H), 1.34 (m, 4H); ^{13}C NMR (125MHz, $CDCl_3$) δ 219.3. 139.7, 134.7, 128.5, 127.0, 126.7, 123.8, 106.8, 106.6, 59.6, 52.2, 50.6, 48.9, 39.3, 39.1, 32.5, 28.3, 26.6, 23.7, 23.4, 23.1; HRMS calc for $C_{23}H_{27}NO$ (M^+) 333.2093; found 333.2093 (40%), 223.1364 $[m\text{-}C_7H_{10}O]^+$ (100%).

11d: pale yellow oil; IR (film) 3063, 3030, 2930, 2856, 1733, 1605, 1496, 1476, 1450, 1359, 1294, 1157, 1086, 1076, 1029, 727 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$) δ 7.30 (m, 2H), 7.24 (m, 1H), 7.04 (m, 2H), 6.50 (dd, 1H, J = 2.8, 1.8 Hz), 6.10 (dd, 1H, J = 3.7, 1.9 Hz), 6.07 (dd, 1H, J = 3.7, 2.8 Hz), 5.53 (d, 1H, J = 16.1 Hz), 5.28 (d, 1H, J = 16.1 Hz), 2.85 (dd, 1H, = 10.1, 7.2 Hz), 2.39 (m, 1H), 2.23 (ddd, 1H, J = 14.0, 10.8, 3.4 Hz), 2.11 (m, 1H), 1.91 (m, 1H), 1.81 (m, 2H), 1.68 (m, 4H), 1.47 (m, 1H), 1.16 (m, 4H), 0.90 (m, 1H); ^{13}C NMR (125MHz, $CDCl_3$) δ 215.6, 139.4, 134.8, 128.5, 127.1, 126.8, 124.1, 107.0, 106.4, 60.2, 52.4, 52.1, 51.5, 43.4, 35.4, 32.1, 29.7, 26.2, 25.9, 25.1, 25.0; HRMS calc for $C_{23}H_{27}NO$ (M^+) 333.2093; found 333.2093 (40%), 223.1362 $[m\text{-}C_7H_{10}O]^+$ (100%).

10e and **11e:** 46 mg (84%) as an inseparable mixture of diastereomers (2:1): brown oil; IR (film) 2930,

2858, 1741, 1640, 1561, 1448, 1386, 1361, 1293, 1271, 1224, 1158, 1030, 949, 810 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$) δ 5.90 (s, 1H), 5.84 (s, 0.5H), 2.72 (ddd, 1H, J = 8.9, 4.8, 4.8 Hz), 2.59 (ddd, 1H, J = 6.1, 6.1, 6.1 Hz), 2.54 (dd, 0.5H, J = 10.2, 6.4 Hz), 2.17 (m, 1.9H), 2.15 (s, 3.3H), 2.13 (2, 1.7H), 2.09 (m, 1.3H), 1.97 (m, 2.5H), 1.88 (s, 3.6H), 1.86 (s, 2.0H), 1.72 (m, 6.4H), 1.54 (m, 4H), 1.39 (m, 1H), 1.20 (m, 5.7H); ^{13}C NMR (125MHz, $CDCl_3$) δ 218.6, 215.2, 153.7, 153.3, 146.6, 146.3, 114.4, 114.2, 108.6, 108.0, 60.9, 60.0, 54.1, 52.1, 50.5, 47.7, 44.0, 39.8, 38.7, 33.6, 33.3, 31.8, 30.1, 28.8, 26.9, 26.3, 25.4, 25.3, 25.2, 23.6, 23.3, 22.9, 11.4, 11.4, 9.9, 9.8; HRMS calc for $C_{18}H_{24}O_2$ (M^+) 272.1776; found 272.1777 (40%), 162.1043 $[M\text{-}C_7H_{10}O]^+$ (100%).

10f and **11f:** 47 mg (86%) as an inseparable mixture of diastereomers (2:1): brown oil; IR (film) 2930, 2857, 1739, 1551, 1448, 1330, 1293, 1227, 1661, 1029, 796 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$) δ 6.75 (d, 1H, J = 3.5 Hz), 6.65 (d, 0.5H, J = 3.5 Hz), 6.57 (m, 1.4H), 2.82 (ddd, 1H, J = 9.0, 4.6, 4.6 Hz), 2.61 (m, 1.6H), 2.45 (d, 3H, J = 1.1 Hz), 2.43 (d, 1.5H, J = 1.1 Hz), 2.37 (ddd, 0.6H, J = 12.2, 7.8, 4.0 Hz), 2.18 (m, 2.2H), 2.04 (m, 3.3H), 1.87 (m, 3.4H), 1.71 (m, 4.6H), 1.52 (m, 1.6H), 1.39 (m, 1H), 1.24 (m, 4.6H); ^{13}C NMR (125MHz, $CDCl_3$) δ 219.0, 215.1, 146.1(appears to be two overlapping signals), 138.1, 138.0, 124.9, 124.5, 123.0, 122.7, 62.3, 61.3, 54.5, 53.3, 52.8, 47.9, 44.5, 43.5, 40.0, 38.0, 33.1, 31.8, 30.4, 28.9, 26.8, 26.3, 25.7, 25.3, 25.2, 23.4, 23.3, 23.2, 15.2, 15.2; HRMS calc for $C_{17}H_{22}OS$ (M^+) 274.1391; found 274.1390 (38%), 164.0657$[M\text{-}C_7H_{10}O]^+$ (100%); Anal. Calc. for $C_{17}H_{22}OS$: C, 74.40; H, 8.08, S, 11.68. Found: C, 74.48; H, 8.42; S, 11.81.

10h and **11h:** 63 mg (82%) isolated as a 2:1 mixture of diastereomers. Small quantities of the major diastereomer were obtained pure using radial chromatography while **11h** was enriched to a 3:5 mixture.

10h: pale yellow oil; IR (film) 3062, 3031, 2931, 2857, 1730, 1611, 1496, 1480, 1466, 1453, 1356, 1335, 1179, 909, 737, 696 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$) δ 7.81 (d, 1H, J = 8.0 Hz), 7.26 (m, 4H), 7.16 (ddd, 1H, J = 7.0, 7.0, 1.2 Hz), 7.11 (ddd, 1H, J = 7.0, 7.0, 1.2 Hz), 7.07 (m, 2H), 7.00 (s, 1H), 5.29 (d, 1H, J = 16.2 Hz), 5.24 (d, 1H, J = 16.2Hz), 3.03, (ddd, 1H, J = 9.3, 3.6, 3.6 Hz), 2.56 (ddd, 1H, J = 6.3, 6.3, 6.3 Hz), 2.39 (dddd, 1H, J = 13.0, 9.1, 9.1, 7.8 Hz), 2.32 (ddd, 1H, J = 13.1, 9.4, 7.1 Hz), 2.21 (ddd, 1H, J = 11.6, 6.8, 4.6 Hz), 2.10, (m, 1H), 2.04 (dddd, 1H, J = 13.8, 4.6, 4.6, 4.6 Hz), 1.86 (m, 1H), 1.76 (ddd, 1H, J = 11.6, 7.7, 4.2 Hz), 1.63 (m, 2H), 1.50 (dddd, 1H, J = 17.4, 10.7, 6.1, 4.1 Hz), 1.42 (m, 2H), 1.17 (m, 1H), 1.09 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$) δ 222.9, 138.0, 137.9, 129.0, 127.8, 126.9, 126.8, 125.9, 122.0, 121.4, 119.2, 118.8, 110.3, 59.7, 50.4, 50.3, 49.4, 41.6, 41.4, 34.3, 29.9, 27.5, 24.3, 23.8, 23.8; HRMS calc for $C_{27}H_{29}NO$ (M^+) 383.2249; found 383.2247 (82%), 273.1525 $[M\text{-}C_7H_{10}O]^+$ (100%).

11h: pale yellow oil; ^1H NMR (500MHz, $CDCl_3$) δ 7.91 (d, 1H, J = 8.0 Hz), 7.33-7.21 (m, 4H), 7.16 (m, 1H), 7.11 (m, 2H), 7.07 (m, 1H), 6.92 (s, 1H), 5.29 (d, 1H, J = 16.2), 5.24 (d, 1H, J = 16.2), 2.78 (dd, 1H, J = 9.7, 7.6), 2.56 (m, 1H), 2.23 (m, 1H), 2.11 (m, 1H), 2.06-1.95 (m, 1H), 1.89-1.72 (m, 4H), 1.54-1.37

(m, 2H), 1.29 (m, 1H), 1.25-1.03 (m, 5H); ^{13}C NMR (125MHz, $CDCl_3$), minor product signals only, δ 216.9, 137.9, 137.8, 128.0, 127.9, 127.0, 126.7, 125.0, 122.3, 121.7, 119.6, 119.4, 110.2, 60.3, 52.9, 51.6, 50.3, 45.2, 36.6, 32.4, 31.2, 26.7, 26.1, 25.6, 25.5.

10i and **11i:** 68 mg (82%) as an inseparable 5:1 mixture of diastereomers): pale yellow oil; IR (film) 3063, 3030, 2933, 2857, 1731, 1621, 1575, 1486, 1450, 1356, 1343, 1290, 1217, 1180, 1030, 839, 794, 736, 704 cm^{-1}; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.45 (d, 0.2H, J = 2.4 Hz), 7.34 (d, 1H, J = 2.4 Hz), 7.28 (m, 3.3H), 7.13 (d, 1H, J = 9.0 Hz), 7.08 (m, 2.4 Hz), 7.00 (s, 1H), 6.93 (s, 2H), 6.85 (m, 1.2H), 5.26 (d, 1H, J = 16.2Hz) 5.21 (d, 1.4H, J = 16.2 Hz), 3.91 (s, 0.6H), 3.90 (s, 3H), 3.03 (ddd, 1H, J = 9.0, 3.6, 3.6 Hz), 2.78 (dd, 0.2H, J = 9.2, 7.8 Hz), 2.59 (dd, 1.2H, J = 11.7, 5.9 Hz), 2.36 (m, 2H), 2.23 (m, 1.2H), 2.16 (m, 0.2H), 2.11 (m, 1H), 2.05 (m, 1.2H), 1.98 (m, 0.6H), 1.86 (m, 1.5H), 1.78 (m, 1.5H), 1.66 (m, 2.6H), 1.48 (m, 3.3), 1.19 (m, 3.9H); ^{13}C NMR (125MHz, $CDCl_3$) δ 222.4, 216.9, 153.8, 153.4, 153.4, 137.8, 137.6, 133.0, 128.7, 128.7, 127.5, 127.5, 126.8, 126.6, 126.5, 126.3, 125.2, 118.4, 117.9, 112.1, 111.4, 110.6, 110.5, 103.7, 103.5, 59.9, 59.4, 56.0, 55.9, 52.6, 51.1, 50.2, 50.1, 49.9, 49.1, 44.9, 41.1, 40.7, 36.0, 33.9, 32.1, 31.6, 30.8, 29.5, 27.1, 26.4, 25.8, 25.3, 25.2, 23.9, 23.5, 23.5; HRMS calc for $C_{28}H_{31}NO_2$ (M^+) 413.2355; found 413.2358 (30%), 303.1628 $[M\text{-}C_7H_{10}O]^+$ (100%).

13: 17 mg (64%): colorless oil; IR (microscope) 2955, 2870, 2837, 1734, 1612, 1584, 1505, 1464, 1208, 1164, 1134, 1032 cm^{-1}; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.06 (d, 1H, J = 8.2 Hz), 6.45 (dd, 1H, J = 8.2, 2.5 Hz), 6.44 (d, 1H, J = 2.5 Hz), 3.79 (s, 3H), 3.71 (s, 3H), 2.74 (m, 1H), 2.68 (ddq, 1H, J = 11.8, 9.3, 7.1 Hz), 2.38 (ddd, 1H, J = 12.7, 9.2, 8.1 Hz), 2.18 (m, 1H), 1.84 - 1.95 (m, 2H), 1.75 – 1.84 (m, 2H), 1.58 (m, 1H), 1.21 (d, 3H, J = 7.1 Hz), 1.18 (ddd, 1H, J = 12.8, 11.8, 10.4 Hz); ^{13}C NMR (125MHz, $CDCl_3$) δ 221.6, 159.8, 157.4, 127.7, 124.0, 104.0, 99.6, 62.7, 55.3, 55.1, 47.9, 43.8, 36.4, 31.5, 30.5, 24.0, 15.8; HRMS calc for $C_{17}H_{22}O_3$ (M^+) 274.1569; found 274.1568 (23%), 204.1149 $[M\text{-}C_4H_6O]^+$ (100%).

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14. Related alkylations of indoles via conjugate addition have been described: W. Chen, W. Du, L. Yue, R. Li, Y. Wu, L.-S. Ding, and Y.-C. Chen, *Org. Biomol. Chem.*, 2007, **5**, 816; (b) L.-W. Xu, W. Zhou, L. Yang, and C.-G. Xia, *Synth. Commun.*, 2007, **37**, 3095.
15. A structurally similar compound to **9** had been reported, prepared via arylcuprate 1,4-addition to a methylenecyclopentanone: A. B. Smith, III, B. A. Wexler, and J. S. Slade, *Tetrahedron Lett.*, 1980, **21**, 3237.
16. Epimers **10j** and **11j** were distinguished by analysis of the coupling constants for the hydrindan bridgehead proton adjacent to the ketone. For the *cis* isomer **10j**, two small couplings and one large *trans*-diaxial coupling were observed, while for *trans* isomer **11j**, two large *trans*-diaxial couplings were observed.
17. See reference 10 for the preparation of **2g**.
18. Major product **13** was assigned the indicated relative stereochemical configuration based upon vicinal coupling constants and the observation of several unambiguous rOe correlations in the 2D-TROESY spectrum.

19. Spectral data for **2f, 3a-c**, **3j**, **8**, **10a-c**, **11a-c**, **10j** and **11j** are found in the electronic supplementary information accompanying reference 6.