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Aliphatic C–H activation with aluminium trichloride–acetyl chloride: expanding the scope of the Baddeley reaction for the functionalisation of saturated hydrocarbons†

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The functionalisation of decalin by means of an "aliphatic Friedel–Crafts" reaction was reported over fifty years ago by Baddeley *et al.* This protocol is of current relevance in the context of C–H activation and here we demonstrate its applicability to a range of other saturated hydrocarbons. Structural elucidation of the products is described and a mechanistic rationale for their formation is presented. The "aliphatic Friedel–Crafts" procedure allows for production of novel oxygenated building blocks from abundant hydrocarbons and as such can be considered to add significant synthetic value in a single step.

Introduction

C–H activation is currently of great interest to the synthetic community.[1] In contrast to conventional functional group interconversions, C–H activation represents an alternative paradigm whereby functionality may be introduced where none was present before. Such methodology enables the use of wholly new retrosynthetic approaches to complex molecule synthesis.[2]

Applications of C–H activation in synthesis may be broadly subdivided into those reactions carried out on substrates with extensive existing functionality and those carried out on substrates that have minimal functionality or are entirely unfunctionalised. In the former category, desirable characteristics are chemo- and regioselectivity as well as functional group compatibility, which can restrict the reaction conditions that may be employed.[3] These transformations often employ expensive transition metal catalysts[4] for this "late stage" C–H activation, which can be considered to be justified in terms of the high value products that can be produced.[2b] In contrast, in the latter category, the absence of functionality potentially allows a wider range of reaction conditions to be used without unwanted side reactions. However, since the C–H functionalisation of a saturated hydrocarbon will almost certainly be the first step of a synthetic sequence, it is harder to justify the use of expensive transition metal catalysts. Rather, if the reaction is to be carried out on a significant scale, the cost of the reagents for C–H activation and also the cost of the substrate itself are key considerations if the transformation is to be synthetically useful.

In this latter context, reports from Baddeley on the reaction of decalin with aluminium trichloride and acetyl chloride are noteworthy. When an excess of aluminium trichloride is employed, the reaction furnishes multiple products[5a,c] (Scheme 1a). However, when an excess of acetyl chloride is employed at a lower temperature, tricyclic enol ether **6** is formed cleanly[5b–f] (Scheme 1b).

Such "aliphatic Friedel–Crafts" acetylations have been reported for other unfunctionalised alkanes[6] and alkenes;[7] the products have been used in synthesis and the field has been reviewed.[8] However, the decalin case is uniquely attractive from the standpoint of C–H functionalisation, since not only are the substrate and reagents inexpensive bulk commodity chemicals, but also the product is formed in reasonable yield (30–46%)[5c,6l] and has a boiling point which is distinct from that of the starting material (which constitutes most of the mass balance) and from the boiling points of any byproducts. This permits large-scale purification without recourse to chromatography; we have prepared pure **6** by distillation on a 70 g scale.† Functionalised decalins are key building blocks for terpenoid[9] and steroid[10] natural products and are also important in the fragrance industry;[11] indeed, **6** has seen diverse

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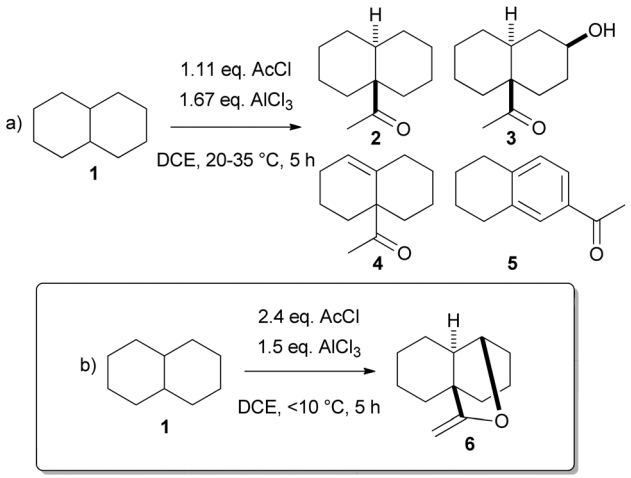
†Electronic supplementary information (ESI) available: NMR spectroscopic data for all novel compounds and for enol ether **6**. Large scale procedure for preparation of **6**. Procedures for preparation of **28** and **30**. CCDC 900347 (**23**), 900348 (**24**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob26765a

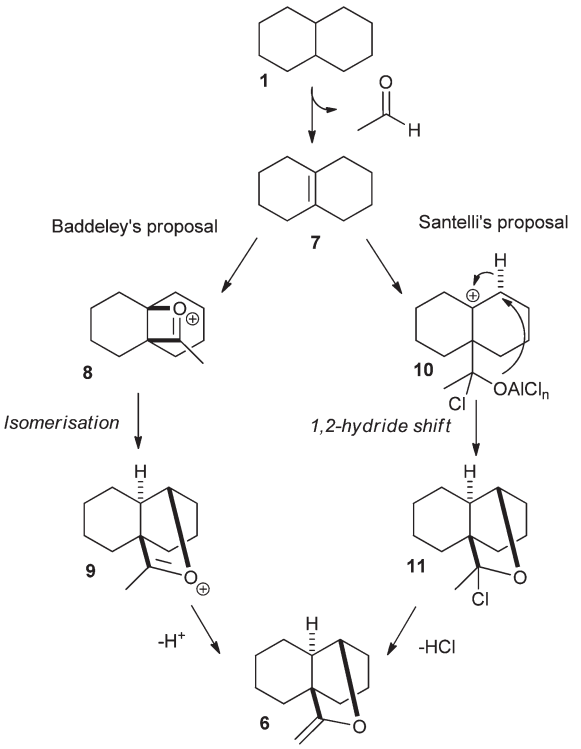


Scheme 1 C–H activation of decalin with aluminium trichloride and acetyl chloride.

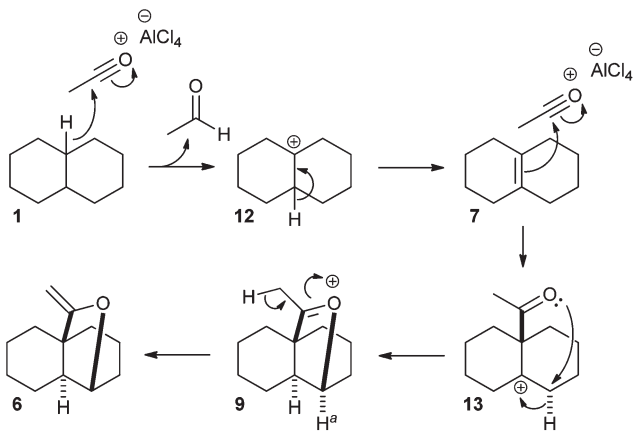
synthetic applications.[12] Other examples of the functionalisation of decalin with aluminium trichloride include the use of benzenesulfonyl chloride to form several mono substituted chlorodecalins.[13] We identified several saturated hydrocarbon substrates for which such aliphatic Friedel–Crafts reactions have not been reported and from which synthetically valuable products might be accessed. Products that were obtained from these substrates are described in this paper.

Results and discussion

Mechanistic rationalisation of Baddeley's transformation is important to aid in the structural elucidation of any products that form from its application to other substrates. Baddeley's original proposal[5b] invoked an oxonium intermediate incorporated into a 4-membered ring (**8**, Scheme 2). Such an intermediate would be exceedingly strained; subsequently, Santelli *et al.* were the first to propose[6m] a variant on this mechanism which did not include such a strained oxonium. Our mechanistic proposal (Scheme 3) has several features in common with the previous proposals. In the absence of unsaturation for the acylating agent to react with, it instead acts as a hydride sink (such reactivity is precedented[8]), leading to the formation of a tertiary cation at the decalin ring junction. Loss of a proton affords $\Delta^{9,10}$-octalin **7**. A second equivalent of acylating agent reacts with the newly introduced unsaturation to give cation **13**. Rather than formation of a 4-membered ring, we propose a [1,2]-hydride shift and attack of the oxygen at the position α- to the ring junction, as in Santelli's proposal. Such a process may be concerted or stepwise. Finally on work up, loss of a proton affords enol ether **6**. Overall, our proposal differs from Santelli's in that **13** and **9** possess an sp^2 carbon (Santelli proposes this carbon to be sp^3 with a bond to a chlorine, *cf.* **10** and **11**). *In situ* reaction monitoring by NMR spectroscopy shows formation of **9** prior to work up. Key proton H^a is observed at



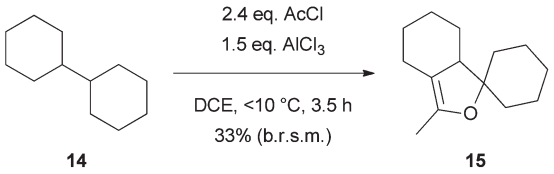
Scheme 2 Baddeley's and Santelli's mechanistic proposals.



Scheme 3 Our mechanistic proposal.

6.08 ppm in the ^{1}H-NMR spectrum, a comparable shift to similar compounds in the literature.[14]

The proposal that the initial C–H activation step proceeds by hydride abstraction guided our choice of other hydrocarbon substrates for Baddeley's protocol. Specifically, we selected only those able to form tertiary carbocations by hydride abstraction, *i.e.* those possessing (non-bridgehead) methines. In the first instance, we sought commercially available and inexpensive substrates. Bicyclohexyl meets these criteria,[15] being produced by hydrogenation of the kerosene fraction of coal distillate.[16] Thus, in the first instance, bicyclohexyl was subjected to the reaction conditions determined by Baddeley to be optimal for production of **6** from decalin. Gratifyingly,

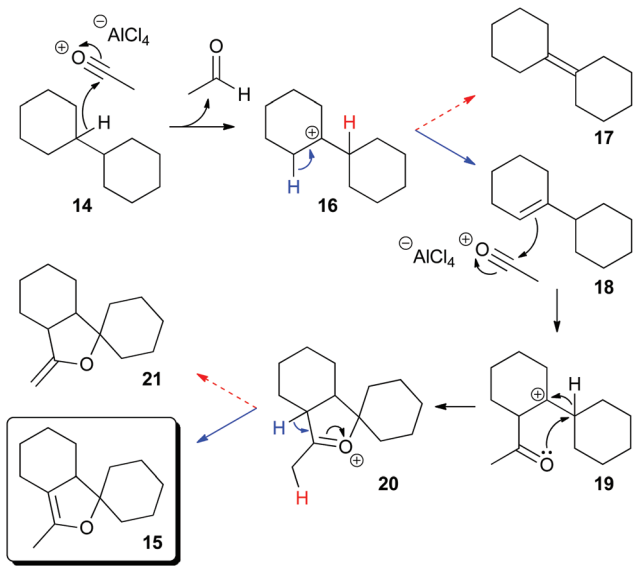


Scheme 4 C–H activation of bicyclohexyl.

^{13}C-NMR analysis of the crude reaction mixture after workup indicated the presence of a single product in addition to unreacted bicyclohexyl (Scheme 4).

Structural elucidation of **15** was by means of DEPT and 2D NMR experiments in conjunction with crystallographic studies on derivatives (*vide infra*). The observations that both sp^2 carbons and one sp^3 carbon in **15** were quaternary and that a methyl group was present (3H singlet in the ^{1}H spectrum) led to the proposal of the structure shown, on the basis of the mechanism given in Scheme 5. Abstraction of the tertiary hydride gives cation **16**, from which two isomeric alkenes are accessible. In contrast to the decalin case (where the tetrasubstituted alkene is formed), we propose that loss of a proton from **16** leads to trisubstituted alkene **18** as opposed to **17**. Regioselective reaction with a second acylium ion gives the second tertiary cation intermediate **19**. Attack of the oxygen and [1,2]-hydride shift, analogous with the decalin case, forms the spiro-centre and gives oxonium **20**. Of the two isomeric enol ethers available from deprotonation of **20**, it is **15** that is formed in preference to **21**. That neither cyclohexyl ring undergoes ring contraction is noteworthy, as $AlCl_3$-mediated formation of 2,2′-dimethylbicyclopentyl from bicyclohexyl (in the absence of acetyl chloride) has been reported.[17]

DFT modelling studies (M06/6-31G(d) basis set)[18] support the contention that in the bicyclohexyl case, formation of trisubstituted alkene **18** is favoured over tetrasubstituted alkene **17**.



Scheme 5 C–H activation of bicyclohexyl.

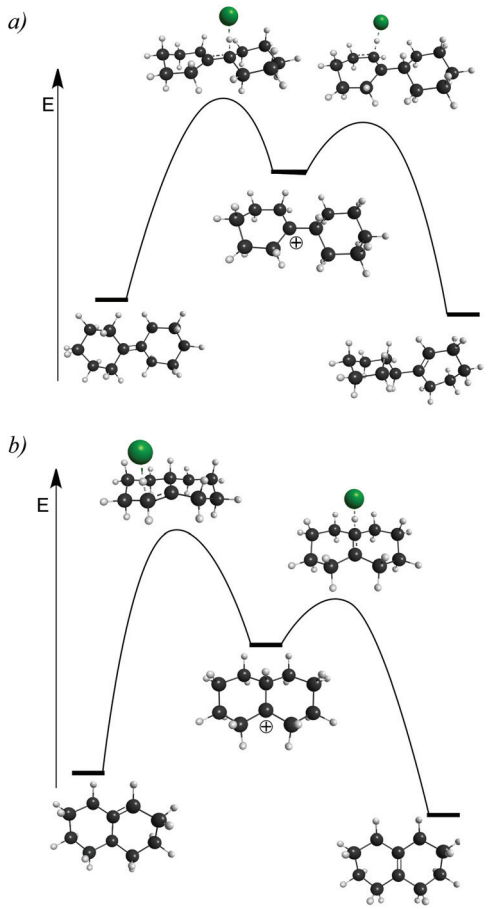
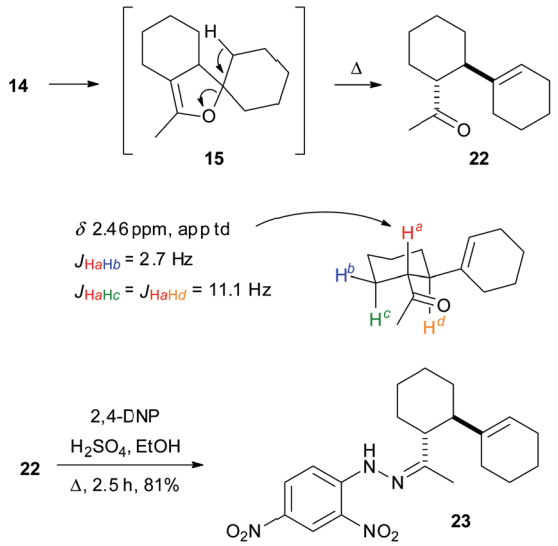


Fig. 1 (a) Energy profile for formation of bicyclohexylidene **17** (left) and 1-cyclohexylcyclohexene **18** (right) from cation **16**. (b) Energy profile for formation of $\Delta^{1,9}$-octalin (left) and $\Delta^{9,10}$-octalin **7** (right) from cation **12**.

The transition state for formation of **18** *via* deprotonation of cation **16** by a chloride anion was calculated to be lower in energy by 10.8 kJ mol^{-1} than the corresponding transition state for formation of **17** (Fig. 1a). Alkene **18** is also the thermodynamic product, lower in energy than **17** by 2.4 kJ mol^{-1}. In contrast, the situation is reversed for decalin, wherein the transition state for formation of $\Delta^{9,10}$-octalin **7** from cation **12** was found to be lower in energy by 31.6 kJ mol^{-1} than the corresponding transition state for formation of its trisubstituted alkene isomer, $\Delta^{1,9}$-octalin (Fig. 1b); $\Delta^{9,10}$-octalin **7** was also calculated to be lower in energy than $\Delta^{1,9}$-octalin by 6.7 kJ mol^{-1}. This quantitation of $\Delta\Delta G^{\ddagger}$ for the divergent elimination pathways from cations **12** and **16** supports the mechanistic proposals in Schemes 3 and 5; only few experimental data on directly comparable eliminations have been reported previously.[19,20]

Complete separation of **15** from unreacted bicyclohexyl **14** proved problematic – complete removal of bicyclohexyl (b.pt. 227 °C/1 atm) under vacuum distillation required elevated temperatures which induced rearrangement of **15**. The rearrangement product was identified as **22**, with the relative configuration being assigned on the basis of Karplus



Scheme 6 Rearrangement of **15** to **22**.

analysis[21] of the $^{3}J_{HH}$ coupling constants for the ketone α-methine (Scheme 6). The identity of **22** was further confirmed by formation of a 2,4-dinitrophenylhydrazone derivative **23** and its X-ray crystallographic analysis (Fig. 2).

Separation of enol ether **15** from unreacted bicyclohexyl **14** was also attempted by chromatography. In the event, **15** proved hygroscopic, undergoing quantitative incorporation of adventitious moisture upon contact with silica to give hydrate **24** (Scheme 7). This hydrate was amenable to X-ray crystallographic analysis, which confirmed the relative stereochemistry as shown in Fig. 3.

Encouraged by the ease and selectivity with which **15** may be transformed into functionalised products, we sought to examine the analogous reaction of other bicycloalkyls. Bicyclopentyl **25**[22] was subjected to Baddeley's conditions with the expectation of obtaining a product analogous to **15**. In fact, **25**

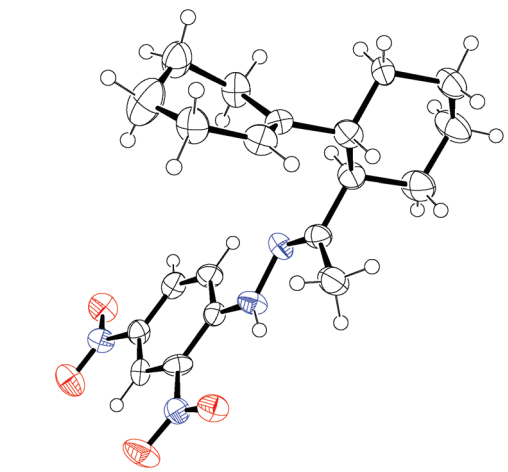
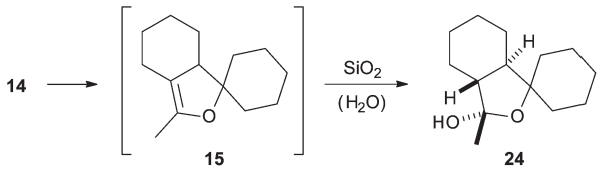


Fig. 2 Solid state structure of **23**. Ellipsoids are represented at 50% probability. H atoms are shown as spheres of arbitrary radius. Only one of two molecules in the unit cell is shown for clarity.



Scheme 7 Hydration of **15** upon chromatography.

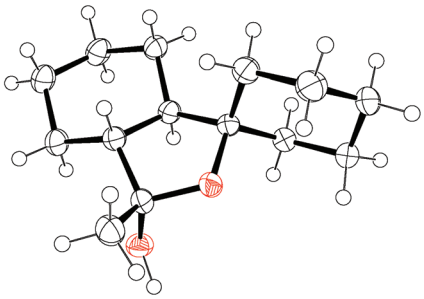
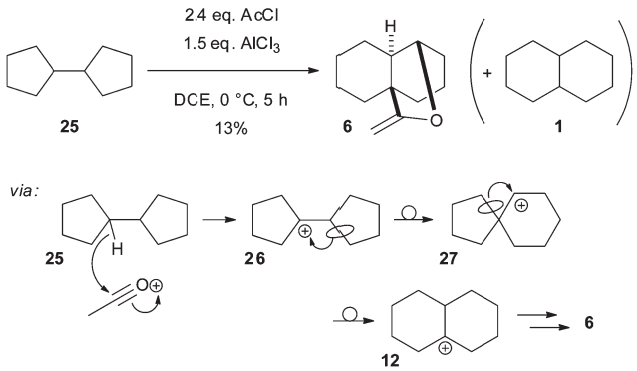


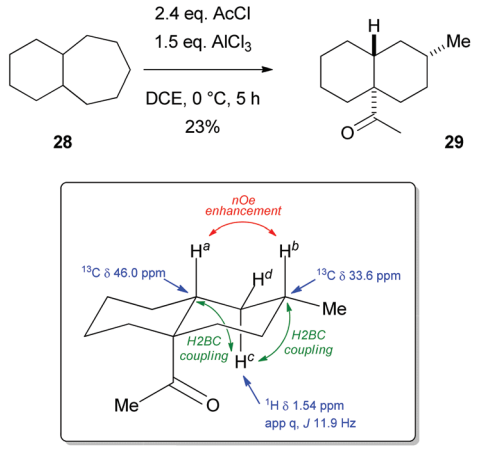
Fig. 3 Solid state structure of **24**. Ellipsoids are represented at 50% probability. H atoms are shown as spheres of arbitrary radius. Only one of two molecules in the unit cell is shown for clarity.



Scheme 8 C–H activation of **25** and its transformation into **6** by skeletal rearrangement.

instead furnished the same product **6** originally observed by Baddeley (Scheme 8). In addition, both *cis*- and *trans*-decalin were recovered. We rationalise the formation of **6** by a skeletal rearrangement of bicyclopentyl cation **26** occurring to give decalin cation **12** prior to any loss of a proton (formation of **6** then proceeds as per the decalin case). The observed formation of decalin itself in the reaction of **25** is also suggestive of this sequence of events. It should also be noted that $AlCl_3$-mediated isomerisation of bicyclopentyl to decalin (in the absence of acetyl chloride) is in fact a known process.[23]

We next examined substrates that shared the bicyclo[*m.n.*0]-alkane skeleton of decalin. Hydrindane, the ring contracted bicyclo[4.3.0]nonane analogue of decalin, has been reported[6n] to undergo the Baddeley reaction, albeit less cleanly, furnishing ring contracted analogues of **6**. Thus, we instead examined the reactivity of bicyclo[5.4.0]undecane **28**.[24] Upon exposure to Baddeley's conditions, **28** gave a mixture of an acylated species

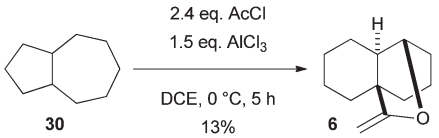


Scheme 9 Baddeley reaction of bicyclo[5.4.0]undecane **28**.

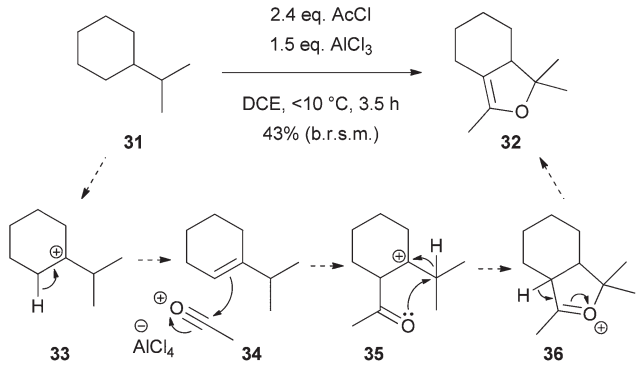
29 and various enol ether products, of which only **29** proved to be isolable in pure form. Unambiguous assignment of **29** required extensive characterisation by NMR spectroscopic means at high frequency, to minimise overlap of resonances. The structure was assigned as follows. The presence of a ketone as the sole sp^2 carbon in the ^{13}C spectrum and a clear 3H singlet (δ 2.02 ppm) in the ^1H spectrum implied a structure analogous with **2** (*i.e.* a monoacylated species having only 3 double bond equivalents in total, confirmed by mass spectrometry). Secondly, the existence of a quaternary sp^3 carbon environment (present in the ^{13}C spectrum but absent in the HSQC spectrum) implies the acyl group is located on a ring junction. Thirdly, a characteristic 3H doublet (δ 0.82 ppm, J 6.3 Hz) in the ^1H spectrum was indicative of the presence of a methyl group adjacent to a methine, which we ascribe to a (precedented) ring contraction of the seven-membered ring.[6l] Establishing which ring position bears the methyl group was more complex. An H2BC spectrum was acquired,[25] in which both tertiary carbon environments (the carbons bearing H^a and H^b, see Scheme 9) showed clear coupling to H^c. As the H2BC experiment only shows 2-bond H–C correlations, this served to establish unambiguously which ring carbon bears the methyl group. The gross structure of **29** having been assigned, the final elucidation of relative stereochemistry was by means of a NOESY spectrum. Specifically, a clear through-space coupling between H^a and H^b was observed, indicating that they are 1,3-diaxially disposed and finally confirming the structure of **29**.

We also examined the reactivity of bicyclo[5.3.0]decane **30**,[26] isomeric with decalin. As per our other C_{10} substrate, **25**, the sole product was once again Baddeley's original enol ether **6** (Scheme 10).

For each of the substrates described above, all the methines are equivalent. In contrast, isopropylcyclohexane **31** (available from reduction of cumene or α-methylstyrene) has two inequivalent sites of possible hydride abstraction. Whilst this increases the number of possible products that may be formed from **31** under Baddeley conditions, we nevertheless



Scheme 10 C–H activation of **30** and its transformation into **6** by skeletal rearrangement.



Scheme 11 C–H activation of isopropylhexane **31**.

undertook to explore its C–H activation chemistry as it is commercially available and inexpensive.[27] Application of the standard conditions gave a reaction mixture in which a single product predominated. NMR spectroscopic data indicated both sp^2 carbons to be quaternary and as such **32** was assigned the structure shown, analogous with the product derived from reaction of bicyclohexyl[28] (Scheme 11). This functionalisation of **31** in the cyclohexane 2-position is regiocomplimentary to the functionalisation of **31** with $GaCl_3$ which reportedly exhibits a preference for the 3- and 4-positions.[29] Unreacted **31** could be removed by cold trap vacuum distillation at room temperature, but attempted distillation of **32** itself resulted in decomposition to an intractable mixture.

Conclusions

We have demonstrated the applicability of Baddeley's "aliphatic Friedel–Crafts" procedure to a range of saturated hydrocarbon substrates. A variety of novel oxygenated structures have been produced, identified and, in the case of bicyclohexyl, have been further elaborated. A mechanistic explanation has been proposed that rationalises Baddeley's original results and also the formation of the products described here. We anticipate that the products described here will serve as useful building blocks in a variety of synthetic contexts.

Experimental

General

Reactions which required the use of anhydrous, inert atmosphere techniques were carried out under an atmosphere of nitrogen. Solvents were dried and degassed by passing

through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. Petrol refers to petroleum ether, bp 40–60 °C. TLCs were performed using aluminium-backed plates precoated with Alugram®SIL G/UV and visualized by UV light (254 nm) and/or $KMnO_4$ followed by gentle warming. Flash column chromatography was carried out using Davisil LC 60 Å silica gel (35–70 micron) purchased from Fisher Scientific. IR spectra were recorded on a Perkin-Elmer 1600 FT IR spectrometer with absorbances quoted as ν in cm^{-1}. NMR spectra were run in $CDCl_3$ (unless otherwise specified) on Bruker Avance 250, 300, 400 or 500 MHz instruments at 298 K. Mass spectra were recorded with a micrOTOF electrospray time-of-flight (ESI-TOF) mass spectrometer (Bruker Daltonik). Aluminium trichloride (98%, #206911), acetyl chloride (98%, #11,418-9) and 1,2-dichloroethane (99.8%, anhydrous, #284505) were purchased from Sigma-Aldrich. Caution was taken when using large quantities of possibly carcinogenic chlorinated solvents; reaction workup, product isolation and purification was performed in a fume hood with appropriate personal protective equipment employed.

3′-Methyl-5′,6′,7′,7a′-tetrahydro-4′*H*-spiro(cyclohexane-1,1′-isobenzofuran) 15. AcCl (28.3 g, 0.361 mol, 2.4 eq.) was added over 15 min to a suspension of $AlCl_3$ (30.0 g, 0.223 mol, 1.5 eq.) in CH_2ClCH_2Cl (70 mL) and stirred for 20 min. The resulting yellow solution was then cooled to 0 °C. Over 20 min, bicyclohexyl (25.0 g, 0.150 mol, 1.0 eq.) was added, and the reaction mixture stirred for a further 3 h. The resulting orange solution was gradually added to a vigorously stirred slurry of ice-water (500 mL); a cherry-red colour was observed. The reaction mixture was transferred to a separating funnel and extracted with CH_2Cl_2. Organic extracts were combined and washed with ice-water (2 × 250 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure on a rotary evaporator to give crude product. Bicyclohexyl (19.9 g, 80%) was recovered by fractional distillation (64–66 °C, 1.6–1.7 torr), and the orange residue identified as 3′-methyl-5′,6′,7′,7a′-tetrahydro-4′*H*-spiro(cyclohexane-1,1′-isobenzofuran) **15** (2.19 g, 33% based on recovered starting material) and bicyclohexyl mixture as an oil. δ_H (250 MHz) 2.33–0.80 (19H, m [including 1.67 (3H, s, $-CH_3$)]) ppm; δ_C (75 MHz) 141.7 (=*C*-(CH_3)–O, 4°), 108.4 (C=*C*–C, 4°), 84.4 (–C–O, 4°), 53.6, 38.3, 31.8, 27.8, 26.8, 26.7, 25.5, 24.2, 22.6, 22.5, 11.0 ($-CH_3$) ppm; ν_{max} (film) 2924, 2852, 1447, 1353, 1265, 1221, 1180, 1143, 1088, 1034, 953, 928, 890, 839, 815, 737 cm^{-1}; HRMS (ESI+) *m*/*z* calcd for $(C_{14}H_{22}O + H)^+$ 207.1743; found 207.1710.

***trans*-Methyl 2-(cyclohex-1-enyl)cyclohexyl ketone 22.** The above procedure for formation of **15** was carried out using AcCl (226 g), $AlCl_3$ (240 g) and bicyclohexyl (200 g). Purification of the crude by vacuum distillation (64–66 °C, 1.6–1.7 torr) led to recovery of bicyclohexyl (101 g, 50%); an increase in temperature (104–108 °C, 1.5 torr) led to the isolation of *trans*-methyl 2-(cyclohex-1-enyl)cyclohexyl ketone **22** (9.38 g, 7.6% based on recovered starting material). δ_H (300 MHz) 5.34–5.31 (1H, m,=C*H*R), 2.46 (1H, app td, *J* 11.1, 2.7 Hz, C(O)–C*H*<), 2.18–0.72 (20H, m [including 1.99 (3H, s, $-CH_3$)]) ppm; δ_C (75 MHz) 212.4 (C=O), 139.9, 121.8, 55.1, 48.1, 31.5, 29.2, 28.5, 26.0, 25.8, 25.4, 25.0, 22.9, 22.4 ppm; ν_{max} 2923, 2854, 1705, 1447, 1355, 1244, 1220, 1161, 920, 882 cm^{-1}; HRMS (ESI+) *m*/*z* calcd for $(C_{14}H_{22}O + H)^+$ 207.1743; found 207.1765.

***trans*-Methyl 2-(cyclohex-1-enyl)cyclohexyl 2-(2,4-dinitrophenyl)hydrazone 23.** Ketone **22** (1.70 g, 8.24 mmol, 1.0 eq.) was dissolved in ethanol (20 mL) and the solution stirred. (2,4-Dinitrophenyl)hydrazine (2.50 g, 12.4 mmol, 1.5 eq.) was added, resulting in a red/orange mixture. H_2SO_4 (conc, 0.40 g, 4.12 mmol, 0.5 eq.) was added over 10 min, then the solution was heated to reflux for 2.5 h. Additional (2,4-dinitrophenyl)-hydrazine (0.80 g, 4.12 mmol, 0.5 eq.) was added and reflux continued until reaction complete; orange precipitate observed in red solution. The precipitate was filtered and air-dried overnight. Pure product was obtained by dissolving the precipitate in 95 : 5 petrol : EtOAc and removing 2,4-DNP (red crystals) by vacuum filtration. The filtrate was then concentrated under reduced pressure to give the product **23** as yellow crystals (2.56 g, 81%); a portion was re-crystallised from hot ethanol to form crystals for X-ray analysis. m.p. 121–122 °C; δ_H (250 MHz) 10.96 (1H, s, –NH), 9.12 (1H, d, *J* 2.5 Hz, aryl CH), 8.29 (1H, dd, *J* 9.5, 2.5 Hz, aryl CH), 7.93 (1H, d, *J* 9.5 Hz, aryl CH), 5.36 (1H, s,=C*H*R), 2.54, (1H, td, *J* 11.0, 2.8 Hz), 2.21–1.22 (20H, m [including 1.93 (3H, s, $-CH_3$)]) ppm; δ_C (75 MHz) 161.6, 145.2, 140.2, 137.5, 129.9, 128.9, 123.6, 122.3, 116.3, 50.2, 49.7, 31.6, 30.5, 26.2, 25.6, 25.5, 24.6, 22.9, 22.6, 13.1 ppm; ν_{max} 3636, 2981, 1619, 1518, 1139, 1074, 955 cm^{-1}; TOF-MS (ESI+) *m*/*z* calcd for $(C_{20}H_{26}N_4O_4 + Na)^+$ 409.1852; found 409.1868.

(3′*S,3a′*R**,7a′*R**)-3′-Methylhexahydro-3′*H*-spiro(cyclohexane-1,1′-isobenzofuran)-3′-ol 24.** A mixture of 3′-methyl-5′,6′,7′,7a′-tetrahydro-4′*H*-spiro(cyclohexane-1,1′-isobenzofuran) **15** and bicyclohexyl **14** was subjected to column chromatography (2.5 : 97.5 EtOAc : pet). (3′*S**,3a′*R**,7a′*R**)-3′-Methylhexahydro-3′*H*-spiro(cyclohexane-1,1′-isobenzofuran)-3′-ol **24** was identified as a white crystalline solid. m.p. 46–47 °C; R_f 0.35 (2.5 : 97.5 EtOAc : petrol); δ_H (500 MHz, C_6D_6) 2.10 (1H, s, –O*H*), 1.98–1.88 (1H, m), 1.88–1.80 (1H, m), 1.80–1.66 (5H, m), 1.63–1.57 (1H, m), 1.57–1.38 (8H, m) 1.35 (3H, s, CH_3), 1.31–1.19 (2H, m), 1.14–1.03 (1H, m) ppm; δ_C (500 MHz, C_6D_6) 105.9, 83.7, 45.8, 44.2, 38.8, 34.3, 29.1, 26.3, 25.2, 24.1, 24.0, 23.9, 23.9, 23.0 ppm; ν_{max} 3389, 2928, 2850, 1444, 1404, 1374, 1197, 1171, 1160, 1151, 1092, 1074, 946, 890, 875 cm^{-1}; HRMS (ESI+) *m*/*z* calcd for $(C_{14}H_{24}O_2 + Na)^+$ 247.1669; found 247.1691.

1-((2*R,4a*S**,8a*R**)-2-Methyldecahydronaphthalen-4a-yl)-ethanone 29.** AcCl (11.6 g, 0.236 mol, 2.4 eq.) was added over 5 min to a suspension of $AlCl_3$ (19.7 g, 0.148 mol, 1.5 eq.) in CH_2ClCH_2Cl (60 mL), with stirring. The resulting pale yellow solution was cooled to 0 °C and bicyclo[5.4.0]undecane, **28**, (15.0 g, 0.099 mol, 1.0 eq.) was added over 20 min. The reaction mixture was left to stir at 0 °C for 5 h. The deeper yellow solution was slowly poured into a stirred ice-water slurry, turning orange and back to yellow. The organic layer was extracted with CH_2Cl_2 (3 × 100 mL), washed with brine and dried over $MgSO_4$, then filtered. The filtrate was concentrated under reduced pressure. Crude product purified by vacuum

distillation (2.1–2.3 Torr, 76–90 °C) gave a mixture of enol ethers and 1-((2*R**,4a*S**,8a*R**)-2-methyldecahydronaphthalen-4a-yl)ethanone **29** (9.55 g) as the major product. This was purified further by column chromatography (100% pentane to 1 : 99 EtOAc : pentane) to give **29** as a single isomer (R_f 0.22 in 1 : 99 EtOAc : pentane) as a colourless oil (4.46 g, 23%). δ_H (400 MHz) 2.02 (3H, s, COC*H*$_3$), 2.01–1.96 (2H, m), 1.91–1.80 (1H, m), 1.75–1.68 (1H, m), 1.59–1.49 (3H, m [including 1.54, 1H, app q, *J* 11.9 Hz, H^c]), 1.48–1.36 (1H, m, H^b), 1.32–1.04 (7H, m [including 1.25–1.22, 1H, m, H^a]), 0.84 (3H, d, *J* 6.3 Hz, CHC*H*$_3$), 0.81–0.70 (1H, m) ppm; δ_C (100 MHz) 213.3 (C=O), 53.0 (4° *C*–C=O), 46.0 (3° H*C*–C–C=O), 37.9, 37.9, 37.8, 33.6 (*C*H–CH$_3$), 32.0, 29.0, 26.9, 26.0 (CO*C*H$_3$), 23.5, 22.4 (CH–*C*H$_3$) ppm; ν_{max} 2922, 2856, 1700, 1453, 1352, 1299, 1209, 1184, 1164, 1135, 1113, 940, 914 cm^{-1}; HRMS (ESI+) *m*/*z* calcd for $(C_{13}H_{22}O + Na)^+$ 217.1563; found 217.1564.

1,1,3-Trimethyl-1,4,5,6,7,7a-hexahydroisobenzofuran 32. AcCl (300 g, 3.82 mol, 2.4 eq.) was added over 20 min to a suspension of $AlCl_3$ (319 g, 2.39 mol, 1.5 eq.) in CH_2ClCH_2Cl (500 mL) and stirred for 20 min. The resulting yellow solution was cooled to 0 °C. Over 90 min isopropylcyclohexane **31** (200 g, 1.59 mol, 1.0 eq.) was added, and the reaction mixture stirred for a further 3.5 h. The resulting orange solution was gradually added to a vigorously stirred slurry of ice-water (500 mL); a cherry-red colour was observed, then orange. The reaction mixture was divided into 5 portions; each one in turn was transferred to a separating funnel and extracted with 1,2-dichloroethane (2 × 100 mL). Organic extracts were combined and washed with ice-water (2 × 100 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give the crude product. Distillation was performed at room temperature under reduced pressure – unreacted isopropylcyclohexane was collected in a cold trap, as a mixture with a byproduct identified as 1-chloroethylacetate. The residue was shown by NMR to contain 1,1,3-trimethyl-1,4,5,6,7,7a-hexahydroisobenzofuran **32** as the major product. δ_H (250 MHz) 2.33–0.69 (18H, m) ppm; δ_C (75 MHz) 141.6 (=C(Me)–O, 4°), 108.2 (–C–O, 4°), 83.3 (C=*C*–C, 4°), 53.6, 29.6, 28.5, 26.6, 25.7, 24.2, 22.9, 11.2 ppm; TOF-MS (ESI+) *m*/*z* calcd for $(C_{11}H_{18}O + H)^+$ 167.1436; found 167.1440.

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