Department of
Pure and Applied Chemistry

Examination for the degree of MChem

MChem Chemistry

CH553 Chemistry Specialisation Paper A

Advanced And Modern Methods In Organic Synthesis (CH509)

Friday 15th December 2023 **Start: 14:00** **Duration:1 h 40 min**

You must answer **BOTH** questions.

Answer **TWO** questions in total.

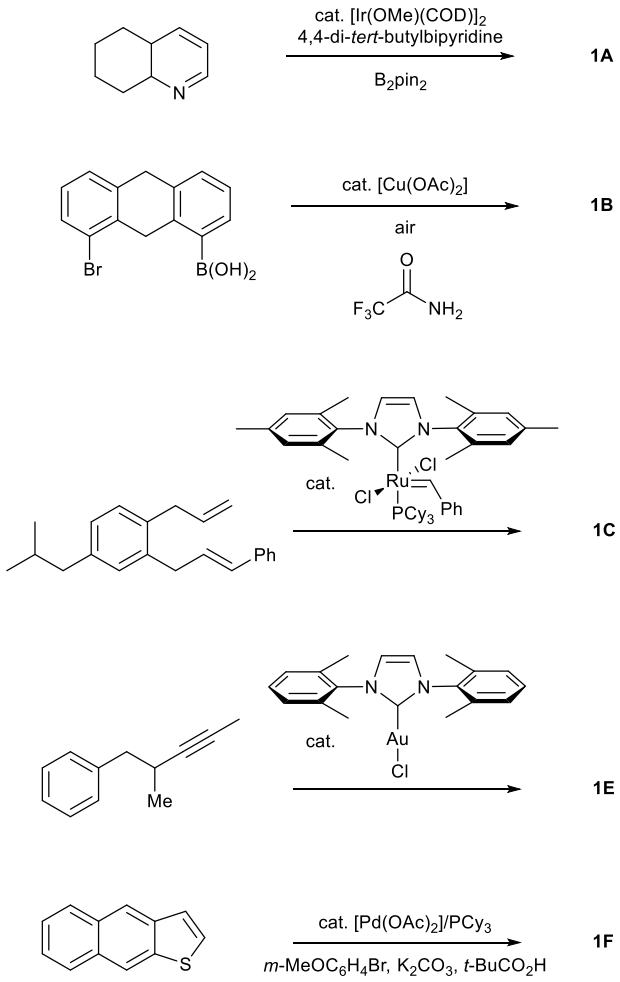
A Periodic Table is included on the final page.

Advanced And Modern Methods In Organic Synthesis Part 1 (CH509)

1. Please **READ THE INSTRUCTIONS** for each part carefully as there is an element of choice in some parts.

   Answer **BOTH** parts (a) and (b) fully, and **TWO** sub-parts from (c), and **ONE** sub-part from (d).

   (a) Draw the products **1A** – **1F** that are formed in the following reactions as the major organic product(s). You do **NOT** need to provide reaction mechanisms.

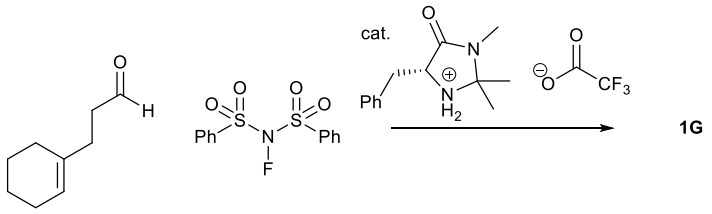


[1 x 6]

Question 1 continues on page 4

Question 1 continued…

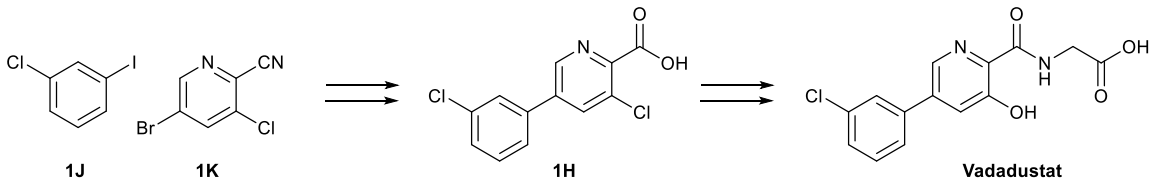
(b) Draw the product **1G** that is formed in the following reaction and describe, using an appropriate sketch of the key bond-forming and stereochemistry-determining step, why **1G** is the major product of the reaction.



[2,2]

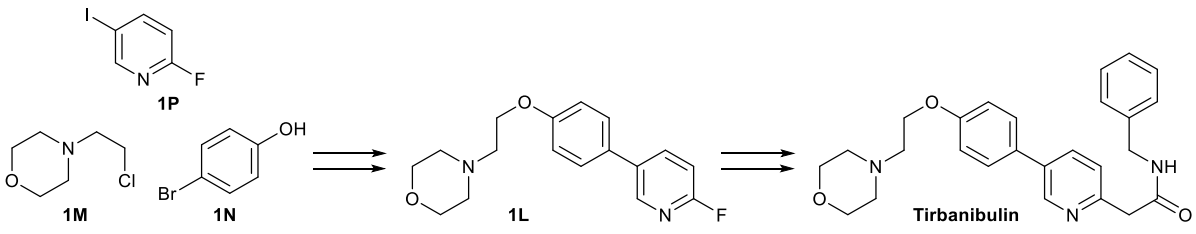
(c) Answer **TWO** of the following three sub-parts (i) – (iii). In each case you must propose a multi-step synthetic route, indicating all catalysts and reagents required at each step; you can assume that all required catalysts and reagents, and any simple substrates, are available. A retrosynthetic analysis is not required, but you may find this a useful way to approach each question. Each route should comprise approximately three steps.

(i) Vadadustat is a treatment for anaemia associated with chronic kidney disease. Propose a synthetic route to intermediate **1H** from starting materials **1J** and **1K**.



[5]

(ii) Tirbanibulin is a treatment for actinic keratosis. Propose a synthetic route to intermediate **1L** from starting materials **1M**, **1N**, and **1P**.

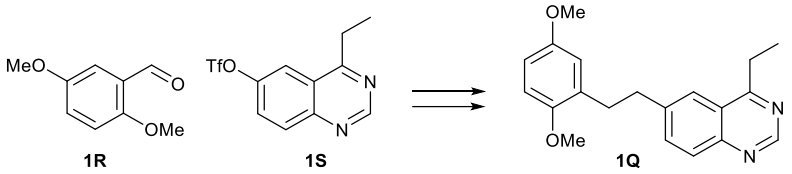


[5]

Question 1 continues on page 5

Question 1 continued…

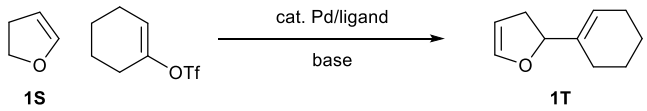
(iii) Compound **1P** has potential applications in the treatment of hyperproliferative skin conditions. Propose a synthetic route to **1Q** from starting materials **1R** and **1S**.



[5]

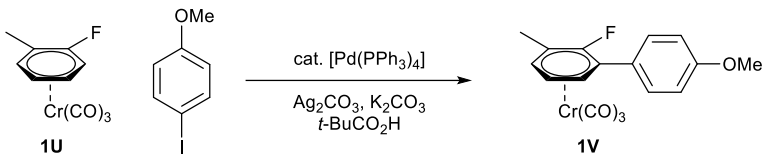
(d) Answer **ONE** of the following sub-parts: (i) **OR** (ii).

(i) Cross-coupling reactions on some substrates can lead to migration of the alkene from its original position, such as in the reaction of **1S** to form **1T**. Suggest a mechanism for this alkene migration. (Hint: consider what steps might take place at the end of the catalytic cycle).



[5]

(ii) In some C-H activation reactions, silver-centred bases are used. It has been suggested that the silver salts may not be simply acting as bases, because transmetalation from silver to metals such as palladium is known to be feasible. Propose a catalytic cycle for the reaction of **1U** to **1V** in the scheme below. (Hint: start from a silver carboxylate complex).

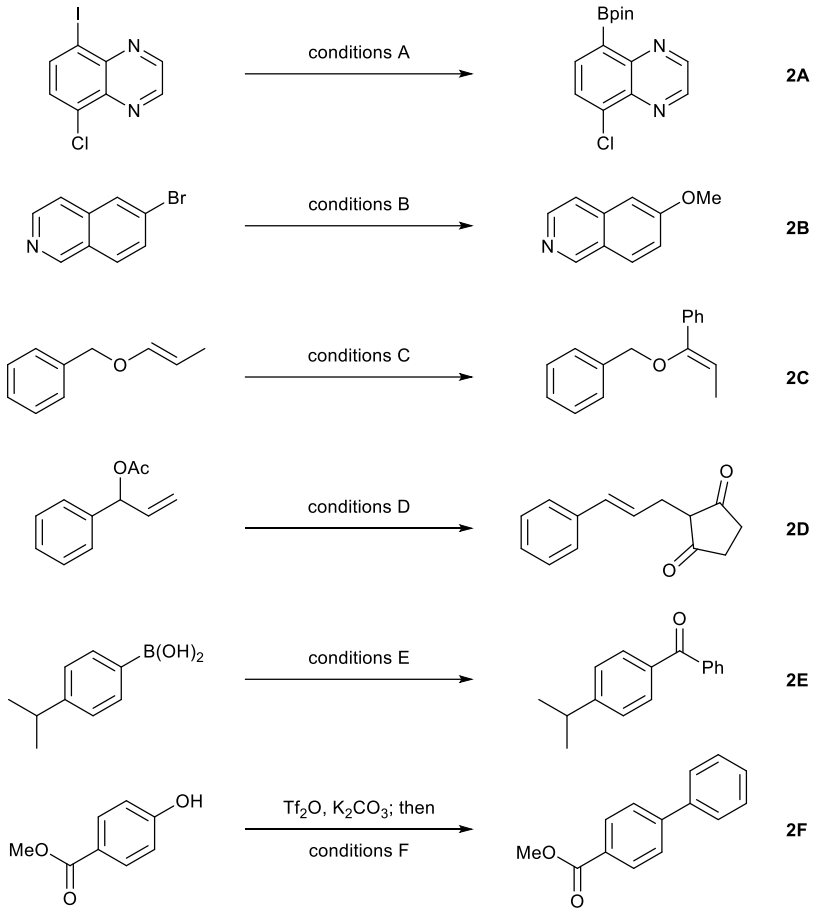


[5]

2. Please **READ THE INSTRUCTIONS** for each part carefully as there is an element of choice in some parts.

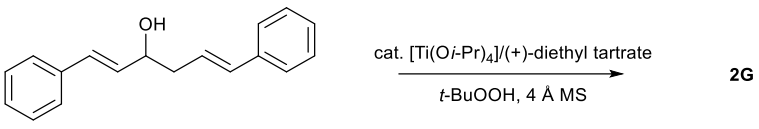
Answer **BOTH** parts (a) and (b) fully, and **TWO** sub-parts from (c).

(a) Write down suitable reaction conditions for the synthesis of products **2A** – **2F**, starting from the indicated starting material in each case. These conditions may include catalysts and/or additional reagents.



[1 x 6]

(b) Sketch a mnemonic that can be used to predict *stereoselectivity* in the titanium-catalysed asymmetric epoxidation of alkenes. Use this mnemonic to work out the structure of product **2G**, and explain why the reaction is also *regioselective* in this example.



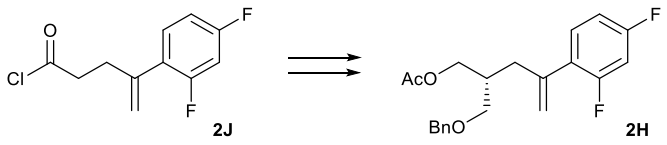
[2,1,2]

Question 2 continues on page 7

Question 2 continued…

(c) Answer **TWO** of the following three sub-parts (i) – (iii). In each case you must propose a **STEREOSELECTIVE** multi-step synthetic route, indicating all catalysts and reagents required at each step; you can assume that all required catalysts and reagents, and any simple substrates, are available. A retrosynthetic analysis is not required, but you may find this a useful way to approach each question. In each case, the synthetic route will comprise approximately four steps.

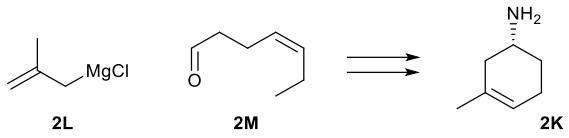
(i) Compound **2H** is an intermediate *en route* to potential antifungal agents. Propose a stereoselective synthetic route to compound **2H** from starting material **2J**.



2J **2H**

[7]

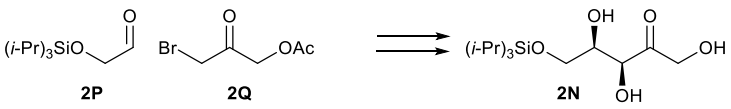
(ii) Compound **2K** is an intermediate *en route* to (−)-aphanorphine, which is of interest for its potential biological activity. Propose a stereoselective synthetic route to compound **2K** from starting materials **2L** and **2M**.



2L **2M** **2K**

[7]

(iii) Compound **2N** is an intermediate *en route* to the sugar D-xylulose. Propose a stereoselective synthetic route to **2N** from starting materials **2P** and **2Q**.



2P **2Q** **2N**

[7]

END OF PAPER

DJN

Periodic Table of the Elements

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1 **H** Hydrogen 1.008																	2 **He** Helium 4.003
3 **Li** Lithium 6.941	4 **Be** Beryllium 9.012											5 **B** Boron 10.811	6 **C** Carbon 12.011	7 **N** Nitrogen 14.007	8 **O** Oxygen 15.999	9 **F** Fluorine 18.998	10 **Ne** Neon 20.180
11 **Na** Sodium 22.990	12 **Mg** Magnesium 24.305											13 **Al** Aluminum 26.982	14 **Si** Silicon 28.086	15 **P** Phosphorus 30.974	16 **S** Sulfur 32.066	17 **Cl** Chlorine 35.453	18 **Ar** Argon 39.948
19 **K** Potassium 39.098	20 **Ca** Calcium 40.078	21 **Sc** Scandium 44.956	22 **Ti** Titanium 47.88	23 **V** Vanadium 50.942	24 **Cr** Chromium 51.996	25 **Mn** Manganese 54.938	26 **Fe** Iron 55.933	27 **Co** Cobalt 58.933	28 **Ni** Nickel 58.693	29 **Cu** Copper 63.546	30 **Zn** Zinc 65.39	31 **Ga** Gallium 69.732	32 **Ge** Germanium 72.61	33 **As** Arsenic 74.922	34 **Se** Selenium 78.09	35 **Br** Bromine 79.904	36 **Kr** Krypton 84.80
37 **Rb** Rubidium 84.468	38 **Sr** Strontium 87.62	39 **Y** Yttrium 88.906	40 **Zr** Zirconium 91.224	41 **Nb** Niobium 92.906	42 **Mo** Molibdenum 95.94	43 **Tc** Technetium 98.907	44 **Ru** Ruthenium 101.07	45 **Rh** Rhodium 102.906	46 **Pd** Palladium 106.42	47 **Ag** Silver 107.868	48 **Cd** Cadmium 112.411	49 **In** Indium 114.818	50 **Sn** Tin 118.71	51 **Sb** Antimony 121.760	52 **Te** Tellurium 127.6	53 **I** Iodine 126.904	54 **Xe** Xenon 131.29
55 **Cs** Cesium 132.905	56 **Ba** Barium 137.327	57-71 Lanthanides	72 **Hf** Hafnium 178.49	73 **Ta** Tantalum 180.948	74 **W** Tungsten 183.85	75 **Re** Rhenium 186.207	76 **Os** Osmium 190.23	77 **Ir** Iridium 192.22	78 **Pt** Platinum 195.08	79 **Au** Gold 196.967	80 **Hg** Mercury 200.59	81 **Tl** Thallium 204.383	82 **Pb** Lead 207.2	83 **Bi** Bismuth 208.980	84 **Po** Polonium [208.982]	85 **At** Astatine 209.987	86 **Rn** Radon 222.018
87 **Fr** Francium 223.020	88 **Ra** Radium 226.025	89-103 Actinides	104 **Rf** Rutherfordium [261]	105 **Db** Dubnium [262]	106 **Sg** Seaborgium [266]	107 **Bh** Bohrium [264]	108 **Hs** Hassium [269]	109 **Mt** Meitnerium [268]	110 **Ds** Darmstadtium [269]	111 **Rg** Roentgenium [272]	112 **Cn** Copernicium [277]	113 **Uut** Ununtrium unknown	114 **Fl** Flerovium [289]	115 **Uup** Ununpentium unknown	116 **Lv** Livermorium [298]	117 **Uus** Ununseptium unknown	118 **Uuo** Ununoctium unknown

57 **La** Lanthanum 138.906	58 **Ce** Cerium 140.115	59 **Pr** Praseodymium 140.908	60 **Nd** Neodymium 144.24	61 **Pm** Promethium 144.913	62 **Sm** Samarium 150.36	63 **Eu** Europium 151.966	64 **Gd** Gadolinium 157.25	65 **Tb** Terbium 158.925	66 **Dy** Dysprosium 162.50	67 **Ho** Holmium 164.930	68 **Er** Erbium 167.26	69 **Tm** Thulium 168.934	70 **Yb** Ytterbium 173.04	71 **Lu** Lutetium 174.967
89 **Ac** Actinium 227.028	90 **Th** Thorium 232.038	91 **Pa** Protactinium 231.036	92 **U** Uranium 238.029	93 **Np** Neptunium 237.048	94 **Pu** Plutonium 244.064	95 **Am** Americium 243.061	96 **Cm** Curium 247.070	97 **Bk** Berkelium 247.070	98 **Cf** Californium 251.080	99 **Es** Einsteinium [254]	100 **Fm** Fermium 257.095	101 **Md** Mendelevium 258.1	102 **No** Nobelium 259.101	103 **Lr** Lawrencium [262]