A convenient, economical and scalable multi-gram synthesis of 1-vinylcyclopropyl 4-methylbenzenesulfonate

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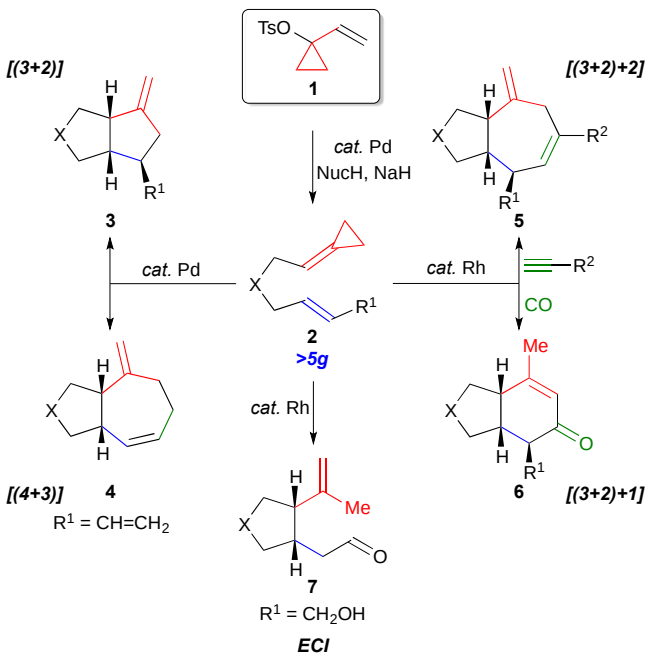
We describe a practical, economical, and scalable multi-gram synthesis of 1-vinylcyclopropyl 4-methylbenzenesulfonate. This intermediate is important for the rapid and economical synthesis of alkylidenecyclopropanes, which provides access to a variety of alicyclic systems *via* metal-catalysed higher-order carbocyclization and cycloisomerization reactions.

1-Vinylcyclopropyl 4-methylbenzenesulfonate (**1**) represents a particularly important synthetic intermediate for the construction of carbon- and heteroatom-tethered alkylidenecyclopropanes (ACPs) **2**.[1-3] ACPs provide versatile three-carbon synthons for a variety of metal-catalyzed cycloaddition reactions and as such are extremely important intermediates.[3] For example, this unit has featured in the palladium-catalyzed [(3+2)] and [(4+3)] carbocyclization reactions to afford **3** and **4**, respectively (Scheme 1).[3,4] More recently, we reported the rhodium-catalyzed [(3+2)+2] and [(3+2)+1] carbocyclizations of **2** with alkynes and carbon monoxide to afford **5** and **6**.[5,6] Furthermore, the ACP **2** (R^1 = CH_2OH) undergoes a facile ene-cycloisomerization reaction (ECI) to generate the five-membered ring **7**, thereby illustrating significant versatility of this motif.[7,8]

Since many ACPs are prepared directly from 1-vinylcyclopropyl-4-methylbenzenesulfonate **1** *via* a palladium-catalyzed Tsuji-Trost allylic alkylation with carbon and heteroatom nucleophiles, the ability to access suitable quantities of **1** in an affordable and efficient manner is important.[9,10] Preliminary studies centred on the synthesis of a variety of derivatives of ACP **2** from VCP **1**, highlighted a number of significant limitations with the preparation of this important intermediate (Scheme 2A). For example, VCP **1** can be prepared *via* protodesilylation of **8** followed by Grignard addition to the ketone and tosylation of the tertiary alcohol (Method A).[11] Alternatively, the oxidation and tosyl protection of **9**, followed by silyl deprotection and partial alkyne reduction provides the ACP **1** (Method B).[12] Nevertheless, the ability to prepare decagram quantities of **1** was hampered by, 1) the high cost of the precursors **8** and **9**,[13-15] 2) the difficult separation of **1** from unreacted *p*-toluenesulfonyl chloride (Method A), and 3) low temperature conditions (Method B), which in turn impacted our ability to develop new and exciting reactions involving ACPs. Despite the growing popularity of ACPs over the last decade, the limitations in the preparation of VCP **1** provided the impetus for the development of a practical and economical synthesis of this intermediate. Herein, we now report a scalable synthesis of VCP **1** from a cheap and readily available precursor, namely ethyl 3-chloropropionate **10**, using a 3-step synthetic sequence outlined in Scheme 2B.



Scheme 1 Synthetic utility of VCPs and ACPs (X = O, NTs, $C(CO_2Me)_2$).

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§Electronic supplementary information (ESI) available. Representative procedures, spectral data and copies of spectra. See DOI:

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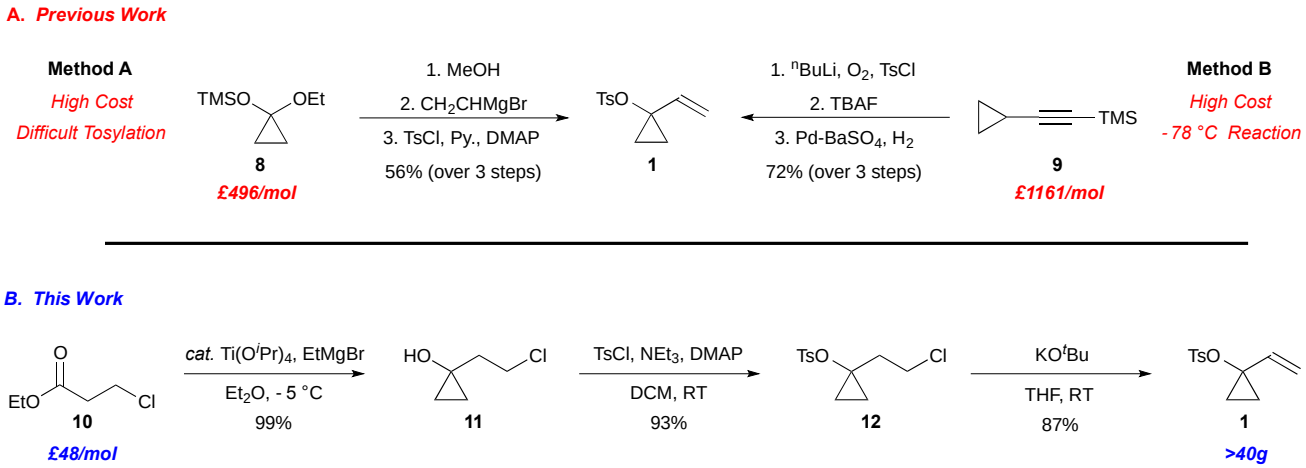

Scheme 2 A comparison of the methods utilized for the preparation of 1-vinylcyclopropyl-4-methylbenzenesulfonate **1**.

The synthesis of **1** commenced with the known Kulinkovich cyclopropanation of the ethyl ester **10** using catalytic titanium(IV) isopropoxide and ethylmagnesium bromide to afford the cyclopropanol **11** in 99% yield (Scheme 2B).[16,17] Tosylation of the tertiary cyclopropyl alcohol using *p*-toluenesulfonyl chloride and triethylamine with catalytic 4-dimethylaminopyridine (DMAP) furnished intermediate **12** in 93% yield. The tosylation of the tertiary alcohol proceeds smoothly in this case, which contrast to the aforementioned strategy wherein the tosylation of the tertiary *allylic* alcohol is more problematic (Scheme 1A; Method A). The sequence was then completed with an E2 elimination of the primary alkyl chloride with potassium *tert*-butoxide to furnish the desired VCP **1** in 87% yield (80% overall yield for 3 steps).[18,19] Gratifyingly, the synthesis can be performed on 30 g scale and all reactions are performed between –5 ℃ and room temperature. Hence, this operationally simple protocol provides a convenient and scalable sequence for the construction of VCP **1**, which is likely to prove useful to others to facilitate additional studies in this exciting area of research.

Procedures[20]

*1-(2-Chloroethyl)cyclopropanol (**11**)*: To a flame-dried 2L three-necked round-bottomed flask, equipped with a magnetic stirrer bar, thermometer and a pressure equalizing dropping funnel was added ethyl 3-chloropropanoate **10** (30.0 g, 220 mmol), anhydrous diethyl ether (700 mL) and titanium isopropoxide (13.01 mL, 43.9 mmol). The system was purged with a continuous flow of argon and the reaction mixture was cooled with stirring to −5 ℃ using a salt-ice bath. The addition funnel was charged with ethylmagnesium bromide (146 mL, 439 mmol; 3M in diethyl ether), which was added dropwise to the stirred reaction mixture at a rate to maintain the internal reaction temperature below +5 ℃ (*ca.* 30 minutes). After the addition was complete, the salt-ice bath was removed and the reaction mixture was warmed to room temperature and stirred for *ca.* 2 hours (t.l.c. control). The reaction was quenched by addition of a 1M aqueous hydrochloric chloride solution (300 mL) over 20 minutes using an ice bath was used to maintain the reaction temperature between 20-25 ℃. The mixture was then poured into a 3L separatory funnel, diluted with deionized water (500 mL) and partitioned with diethyl ether (2 x 500 mL). The organic phases were combined, washed with saturated aqueous sodium bicarbonate solution (500 mL), saturated aqueous NaCl solution (200 mL), dried (anhyd. $MgSO_4$), filtered and concentrated *in vacuo* to provide 1-(2-chloroethyl)cyclopropanol **11** as a colorless oil (26.45 g, 219 mmol, 99%), which was used without further purification.

*1-(2-Chloroethyl)cyclopropyl 4-methylbenzenesulfonate (**12**)*: To a flame-dried 2L two-necked round-bottomed flask, equipped with a magnetic stirrer bar, was added 1-(2-chloroethyl)cyclopropanol **11** (26.45 g, 219 mmol) and anhydrous dichloromethane (700 mL) under an atmosphere of argon. Triethylamine (36.6 mL, 263 mmol) was slowly added to the stirred reaction mixture followed by 4-dimethylaminopyridine (26.7 g, 219 mmol) in one portion. The reaction mixture was stirred at room temperature for *ca.* 30 minutes before *p*-toluenesulfonyl chloride (55.4 g, 285 mmol) was added and the resulting mixture stirred for

ca. 16 hours at room temperature. The reaction mixture was concentrated *in vacuo* to a volume of approximately 50-100 mL, quenched with deionized water (500 mL) and transferred to a a 3L separatory funnel. The aqueous phase was partitioned with diethyl ether (500 mL), diluted with saturated aqueous ammonium chloride (350 mL) and further partitioned with diethyl ether (2 x 350 mL). The combined organic phases were washed with deionized water (250 mL), dried (anhyd. $MgSO_4$), filtered and concentrated *in vacuo* (35 ℃, 1 torr) to afford the crude product. The crude material was dry-packed onto silica gel and purified *via* flash chromatography (SiO_2, eluting with 5-15% diethyl ether/petroleum ethers) to afford 1-(2-chloroethyl)cyclopropyl 4-methylbenzenesulfonate **12** (56.50 g, 206 mmol, 93%) as a pale green oil.

*1-Vinylcyclopropyl 4-methylbenzenesulfonate (**1**):* To a flame-dried 2L one-necked round-bottom flask, equipped with a magnetic stirrer bar was added 1-(2-chloroethyl)cyclopropyl 4-methylbenzenesulfonate **12** (56.5 g, 206 mmol) and anhydrous tetrahydrofuran (700 mL) under an atmosphere of argon. Potassium *tert*-butoxide (35.7 g, 308 mmol) was added at room temperature in one portion to the stirred solution, and the resulting suspension was stirred for an additional *ca.* 2 hours (monitored by NMR). The reaction mixture was concentrated *in vacuo* to a volume of approximately 500 mL, diluted with deionized water (300 mL), transferred into a 2L separatory funnel and partitioned with diethyl ether (350 mL). The aqueous layer was diluted with saturated aqueous ammonium chloride solution (200 mL) and further partitioned with diethyl ether (2 x 300 mL). The combined organic phases were washed with deionized water (300 mL), saturated aqueous NaCl solution (200 mL), dried (anhyd. $MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product. The crude material was dry-packed onto silica gel and purified *via* flash chromatography (SiO_2, eluting with 5-10% diethyl ether/petroleum ethers) to afford **1** (42.40 g, 178 mmol, 87%) as a pale yellow oil: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 5.89 (dd, J = 17.2, 10.8 Hz, 1H), 5.10 (d, J = 17.2 Hz, 1H), 5.01 (d, J = 11.1 Hz, 1H), 2.45 (s, 3H), 1.36 (d, A of AB, J_{AB} = 6.3 Hz, 1H), 1.35 (d, B of AB, J_{AB} = 6.1 Hz, 1H), 0.92 (dd, A of ABM, J_{AB} = 5.6 Hz, J_{AM} = 1.0 Hz, 1H), 0.91 (dd, B of ABM, J_{AB} = 6.0 Hz, J_{BM} = 0.8 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 144.84 (e), 136.62 (o), 135.01 (e), 129.83 (o), 127.94 (o), 113.52 (e), 65.47 (e), 21.73 (o), 14.04 (e); **IR** (Neat) 3003 (w), 1644 (w), 1596 (w), 1349 (vs), 1294 (m), 1165 (vs), 1089 (s), 1032 (s), 949 (vs), 906 (vs), 819 (vs) cm^{-1}; **HRMS** (ESI, $[M+H]^+$) calculated for $C_{12}H_{15}O_3S$ 239.0736, found 239.0729.

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20 See Electronic Supplementary Information (ESI) for full details of experimental procedures, structural analyses and reagent specifications.