Platinum Catalysed Ring Opening Isomerisation of Piperidine Cyclopropanes

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Introduction

Cyclic enamines bearing an electron withdrawing protecting group on nitrogen,[1] such as ene-sulfonamide **1a**, have been shown to be useful precursors to oxygenated piperidines by hydroboration-oxidation,[2] epoxidation-ring opening[3] and by dihydroxylation.[4] This chemistry has been used in this laboratory for the stereoselective synthesis of pseudoconhydrine,[5] azimic acid,[6] and 5-hydroxysedamine.[7] We were attracted to the idea of using these ene-sulfonamides for carbon-carbon bond formation. This has previously been achieved by halogenation-cross coupling[8] and by C-H bond activation[9] using palladium catalysis. Harrity has shown that ene-sulfonamides may be cyclopropanated and the resulting cyclopropanes undergo ring opening on treatment with halogens.[10]

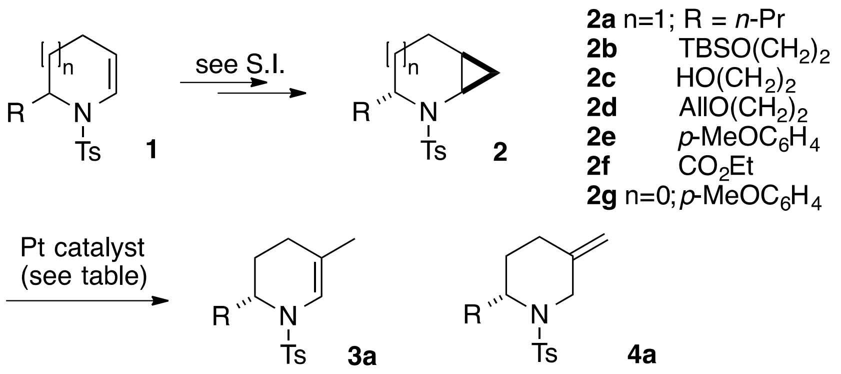
Results and Discussion

We determined to further explore the scope of the cyclopropane chemistry. Cyclopropane **2a** which was obtained by Furukawa cyclopropanation of ene-sulfonamide **1a** (Scheme 1), was already available to us from our synthesis of pseudoconhydrine.[5] Cyclopropanation proceeded in this case with complete diastereoselectivity. The product was presumed to have *trans*-stereochemistry, as indicated by Harrity.[10] Additional cyclopropanes with a variety of synthetic relevant side chains were prepared by cyclopropanation of the corresponding ene-sulfonamides or by simple transformations of other cyclopropanes.[11] All cyclopropanation reactions except one gave a single isomer, presumed to be the *trans* isomer. In the case of **2e**, X-ray crystallography confirmed this stereochemical assignment.[12] Cyclopropanation of **1f** gave the corresponding cyclopropane **2f** as a 1:1 mixture of isomers. A cyclopropane **2g** fused to a five membered ring was also prepared. The structure of this compound was also confirmed by X-ray crystallography.[12]

Ring opening was initially attempted using Brønsted acids in the hope of obtaining a methyl substituent, a process already demonstrated by Boeckman in the tetrahydropyran series.[13,14] Treatment of cyclopropane **2a** with either tosic acid or trifluoroacetic acid in hot methanol resulted in no reaction and recovery of starting material. We, therefore, resorted to transition metal chemistry to effect ring opening in a C-C bond activation process.[15] Tipper reported in 1955[16] that cyclopropane reacts with platinum(II) chloride to give a complex subsequently shown to contain a platinacyclobutane.[17,18] Several groups have shown that, when the cyclopropane is substituted with an alcohol or ether group, the platinacyclobutane is unstable and undergoes ring opening.[19] The chemistry has also been applied to sugar derived cyclopropanes, but not, to our knowledge, to nitrogen heterocycles. The behavior of the cyclopropanes **2a**-**g** on treatment with platinum catalysts was then studied.

Treatment of cyclopropane **2a** with Zeise's dimer in dichloromethane at room temperature resulted in no reaction, although some conversion could be observed in toluene (Table 1, entry 1). On the other hand, in refluxing toluene (entry 2), complete conversion to an almost inseparable mixture of *exo*- and *endo*-cyclic olefins, **3a** and **4a**, was observed with a ratio of 0.24:1 in favour of the less stable *exo*-isomer **4a** (Scheme 2).[20] Interestingly, in refluxing *m*-xylene, the ratio was enhanced to 0.18:1 (entry 3). Switching to a more electrophilic platinum(II) triflate complex, $(EtCN)_4Pt(OTf)_2$, prepared by the method of Kukushkin,[21] resulted in exclusive formation of the *endo*-cyclic isomer **3a** (entry 2). To the best of our knowledge, this is the first use of this complex as a catalyst in an organic transformation.

The substrates, **2b** and **2d**, having either the TBS or allyl protecting groups proved unstable under both sets of conditions and led to no identifiable products (entries 5 and 7). On the other hand, the corresponding free alcohol **2c** gave exclusively the *endo*-product **3f** under both sets of conditions (entry 6). The ester substrate **2f** behaved in the same way, giving the *endo*-isomer **3f** regardless of the catalyst used (entry 9). The behavior of the *p*-methoxyphenyl substrate **2e** mirrored that of the *n*-propyl substrate **2a**. With the platinum triflate catalyst, the only product was the *endo*-isomer **3e**, while the use of Zeise's dimer gave a mixture of the two isomers, **3e** and **4e** (entry 8). The corresponding pyrrolidine substrate **2g** decomposed when $(EtCN)_4Pt(OTf)_2$ was used, but remained unreacted when Zeise's dimer was employed (entry 10).



Scheme 1. Cyclopropanation and Ring opening isomerisation.

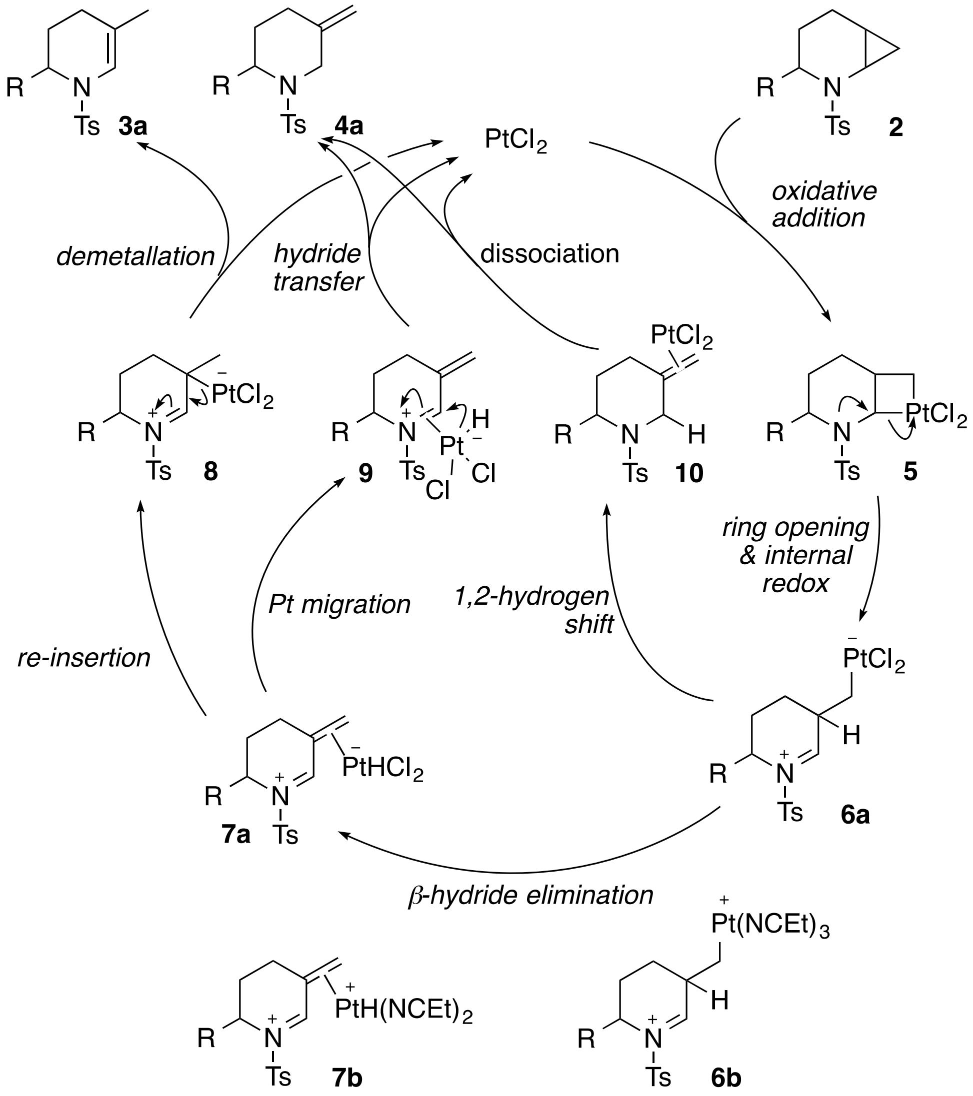
Table 1. Ring opening isomerisation reactions

entry	starting cyclopropane, R	conditions	Zeise's dimer		$(EtCN)_4Pt(OTf)_2$	
			endo: *exo* (3:4) ratio	yield	*endo*: *exo* (3:4) ratio	yield
1	2a, *n*-Pr	tol 48h RT	1:0.22	incomplete	-	-
2	2a, *n*-Pr	tol reflux	0.24:1	ND	1:0	3a 81%
3	2a, *n*-Pr	xyl reflux	0.18:1	ND	-	-
4	2a, *n*-Pr	MeOH reflux	1:0	3a 83%	-	-
5	2b, CH_2CH_2OTBS	tol reflux	-	dec	-	dec
6	2c, CH_2CH_2OH	tol reflux	1:0	3c	1:0	3c 56%
7	2d, $CH_2CH_2Oallyl$	tol reflux	-	dec	-	dec
8	2e, *p*-$MeOC_6H_4$	tol reflux	55:45	3e, 4e ND	1:0	3e 50%
9	2f, CO_2Et[a]	tol reflux	1:0	3f 71%	1:0	3f
10	2g, *p*-$MeOC_6H_4$	tol reflux	-	NR	-	dec

a) Mixture of isomers

No reaction was observed using palladium(II) salts, $Pd(OAc)_2$, $(MeCN)_2PdCl_2$ and $Pd(O_2CCF_3)_2$, or with platinum(II) iodide. The failure of this last complex to react is likely to be due to poor solubility. Gold(III) chloride was similarly ineffective, but use of triphenylphosphinegold(I) chloride in combination with silver triflate in refluxing toluene gave the *endo*-cyclic isomer 3a in 76% yield.

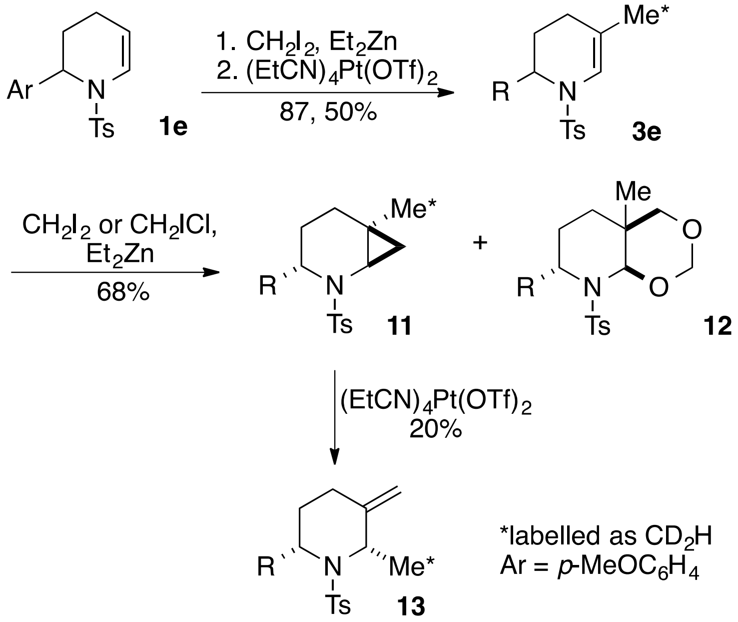
A mechanism may be proposed by adapting that put forward by Madsen (Scheme 2).[19c,d] Regioselective oxidative addition of platinum(II) to the cyclopropane **2** gives a platinacyclobutane **5** which undergoes ring opening to give a η^1-complex **6a** containing an iminium ion. We presume that the cyclopropane bond in question is activated by the nitrogen lone pair. β-Hydride elimination then yields a η^2-complex **7a** which may undergo re-insertion followed by demetallation to yield the *endo*-cyclic isomer **3**, or platinum migration from the alkene to the iminium ion, followed by hydride transfer to yield the *exo*-cyclic isomer **4**. It may be suggested that the increase in the proportion of the *exo*-cyclic isomer **4** on increasing the temperature could be due to accelerating an otherwise slow migration and conversion of **7a** to **9**. It may be further suggested that the cationic intermediate **7b** resulting from use of $(EtCN)_4Pt(OTf)_2$ shuts down the migration pathway, hence giving complete selectivity for the *endo*-cyclic isomer **3**. This would be because a cationic platinum centre would not migrate towards an iminium cation. Alternatively, it may be proposed, that the *exo*-cyclic isomer **4** arises from a 1,2-shift of hydride from the β-position to the iminium ion **6a**, driven by the anionic platinum (see below). It may be further proposed that the less electron rich intermediate **6b** derived from $(EtCN)_4Pt(OTf)_2$ is unable to provide the driving force for this 1,2-migration, hence the complete selectivity for the *endo*-isomer **3**. Our present results cannot distinguish between these pathways.



Scheme 2. Proposed mechanisms for ring opening isomerisation.

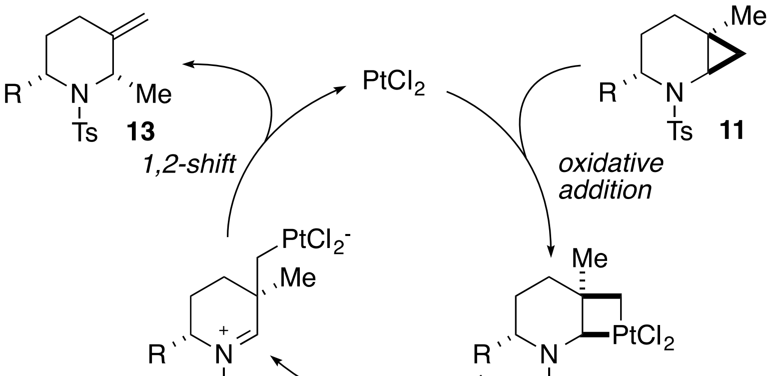
Given that an iminium ion is proposed as an intermediate, we attempted to trap this with an added nucleophile as achieved by Madsen in the tetrahydropyran series.[17b,c] No such adduct could be isolated upon addition of methanol, benzyl alcohol, acetic acid or allyl trimethylsilane. Further, no evidence for intramolecular trapping of the iminium ion was observed for the substrate **2c** containing a free alcohol group. Instead, addition of methanol caused complete selectivity for the *endo*-cyclic isomer **3a** (entry 4). We suggest that the use of a more polar solvent stabilises the more charge separated species **1a**, removing the driving force for migration. The failure to trap the iminium ion, however, suggests that its lifetime is short and intermolecular processes cannot compete with the intramolecular platinum mediated processes.

Given the β-hydride elimination step in the proposed mechanism, we felt that it would be of interest to study the corresponding reaction in which the proton in question was replaced by a methyl group, thus blocking this step. Thus, ene-sulfonamide **3e** was subjected to Furukawa cyclopropanation (Scheme 3). While the expected trisubstituted *trans*-cyclopropane **11** was obtained, the reaction was sluggish and the yield poor. A surprising by-product was obtained which was identified by both spectroscopic methods and X-ray crystallography as the dioxolane **12**.[12] It is notable that this material was obtained as a single diastereoisomer. The formation of this compound can be attributed to the formation of formaldehyde *in situ* by oxidation of the intermediate zinc carbenoid by adventitious oxygen. This formaldehyde then participates in a Prins reaction with ene-sulfonamide **3e**, catalysed by the Lewis acidic zinc salts.[22] To our knowledge, this is only the second example of a formaldehyde Prins reaction of a nitrogen substituted alkene.[23] In contrast, cyclopropanation using chloroiodomethane in place of diiodomethane, which is believed to lead to a more reactive carbenoid,[24] selectively gave the cyclopropane **11** in useful yield. Subjecting cyclopropane **11** to the reaction conditions using Zeise's dimer gave the *exo*-cyclic alkene **13**. A NOESY experiment confirmed the *cis*-diaxial-relationship between the two substituents α- to nitrogen. This was subsequently confirmed by X-ray crystallography.[12] To confirm the origin of the α-methyl group in the product, the experiment was repeated with the β-methyl group of cyclopropane **21** having a double deuterium label. This material was obtained by using CD_2I_2 in the cyclopropanation of ene-sulfonamide **1e**, leading to **2e** and thence **11** possessing a CD_2 moiety. The deuterium was found to be in the α-methyl group of piperidine **13**, confirming that a 1,2-shift of this methyl group occurs. We propose that oxidative addition to cyclopropane **11** and opening of platinacyclobutane **14** occur as for the non-methylated substrate (Scheme 4), but this is then followed by a 1,2-shift of the methyl group, which may be considered as a platinum driven Wagner-Meerwein rearrangement (Scheme 9), giving piperidine **13**. While the isolated yield of piperidine **13** was modest (20%), this represents a new mode of reactivity in this system.



*labelled as CD_2H
Ar = *p*-$MeOC_6H_4$

Scheme 3. Cyclopropanation and ring opening isomerisation with a substituted alkene.



Ar = *p*-$MeOC_6H_4$

Scheme 4. Proposed mechanism of the ring opening isomerisation with a substituted alkene.

Conclusion

Platinum catalysed ring-opening isomerisation of piperidinyl cyclopropanes can give either the *endo*- or *exo*-cyclic products. The ratio depends on substitution pattern, solvent, temperature and catalyst. This is, in particular, a useful route to more highly substituted ene-sulfonamides. When the β-hydride elimination pathway is blocked, a novel platinum driven Wagner-Meerwein shift is observed. The chemistry should prove useful for the stereoselective synthesis of piperidine alkaloids.

Experimental Section

Ethyl 5-methyl-1-tosyl-1,2,3,4-tetrahydropyridine-2-carboxylate (**3f**): A solution of cyclopropane **2f** (150 mg, 0.46 mmol) and Zeise's dimer (27.3 mg, 0.046 mmol) in anhydrous toluene (4.5 mL) was heated at reflux under nitrogen for 15 h. The mixture was cooled and concentrated. The residue was purified by column chromatography on silica gel using hexane:EtOAc 90:10. **3f** was obtained as a colourless oil which slowly crystallized, 107 mg (0.33 mmol), yield: 71%.

^{1}H NMR δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.45 (s, 1H), 4.64 (dd, *J* = 4.4, 3.4 Hz, 1H), 4.12 (q, *J* = 8.0 Hz, 1H), 2.42 (s, 3H), 2.16 (dddd, *J* = 13.5, 5.9, 2.8, 1.9 Hz, 1H), 1.92 – 1.79 (m, 1H), 1.77 – 1.73 (m, 1H), 1.73 – 1.68 (m, 1H), 1.64 (s, 3H), 1.49 – 1.38 (m, 1H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 143.8, 136.4, 129.9, 127.3, 118.3, 116.7, 61.7, 54.4, 23.7, 23.4, 21.8, 21.0, 14.3; FTIR (nujol, cm^{-1}) υ_{max} 1749, 1168; MS (ESI+) *m/z* 324 (M + H$^+$, 86), 346 (M + Na$^+$, 100); HRMS calcd for $C_{16}H_{22}NO_4S$ (M + H$^+$) 324.1270; found: 324.1275.

2-(5-methyl-1-tosyl-1,2,3,4-tetrahydropyridin-2-yl)ethan-1-ol (**3c**): A solution of cyclopropane **2c** (75 mg, 0.25 mmol) and $(EtCN)_4Pt(OTF)_2$ (18 mg, 0.025 mmol) in anhydrous toluene (2.2 mL) was heated at reflux under nitrogen for 14 h. The mixture was cooled and concentrated. The residue was purified by column chromatography on silica gel using a gradient of hexane: EtOAc 85:15 to 80:20. **3c** was obtained as a colourless oil, 42 mg (0.14 mmol), yield: 56%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 6.36 (s, 1H), 4.22 – 3.98 (m, 1H), 3.88 (t, *J* = 11.4 Hz, 1H), 3.71 – 3.60 (3, 1H), 3.00 – 2.89 (m, 1H), 2.41 (s, 3H), 1.97 – 1.67 (m, 1H), 1.67 – 1.51 (m, 5H), 1.49 – 1.26 (m, 2H), 0.97 – 0.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 135.5, 129.9 (2C), 127.1 (2C), 119.6, 117.5, 58.4, 48.4, 34.0, 23.8, 23.0, 21.7, 21.0; FTIR (neat, cm^{-1}) υ_{max} 3417, 1635, 1448, 1161; MS (ESI+) *m/z* 296 (M + H$^+$, 100), 318 (M + Na$^+$, 94); HRMS calcd for $C_{15}H_{22}NO_3S$ (M + H$^+$) 296.1320; found: 296.1321.

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[20] The expected lower thermodynamic stability of the *exo*-isomer was confirmed by exposure of the mixture to rhodium(III) chloride in hot ethanol which resulted in formation of a mixture of *endo*-cyclic olefins. It may be noted that minimal isomerisation of the *exo*- to the *endo*-isomer could be observed during work-up and purification.

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