Samarium(II) iodide-mediated intramolecular pinacol coupling reactions with cyclopropyl ketones†

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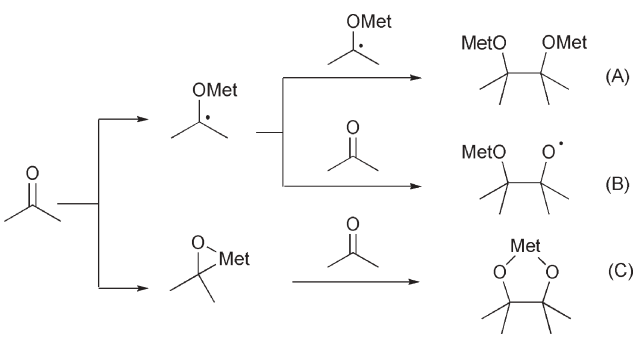
The first reported intramolecular pinacol coupling of cyclopropyl ketones has been achieved, demonstrating that cyclisation competes favourably with ring-opening of the cyclopropyl ketyl radical.

Samarium(II) iodide is one of the most widely used single electron transfer (SET) agents in organic synthesis. Since its introduction to the synthetic community by Kagan and co-workers,[1] this reagent has been utilised for a variety of transformations, including ketyl–olefin coupling, Barbier- and Reformatsky-type reactions amongst many others.[2] Despite detailed investigations, the mechanisms of many reactions mediated by SmI_2 remain ambiguous, although they have been shown to involve a variety of radical, anionic and organosamarium intermediates.[2,3] In this regard, cyclopropyl ketones have often been employed as mechanistic probes for SmI_2-promoted reactions of ketones, with ring-opening of the cyclopropane (or lack thereof) taken as evidence for (or against) the involvement of ketyl radical anions.[4] Several examples of synthetic strategies employing the SmI_2-mediated reductive ring-opening of cyclopropyl ketones have also been reported.[5]

One particularly common transformation mediated by SmI_2 is the pinacol coupling reaction of carbonyls to produce 1,2-diols.[6] The intramolecular reaction has been widely employed for the synthesis of carbocyclic systems,[2,7] and we have reported its use to access *N*-heterocyclic diols.[8] The typical mechanisms that have been proposed for low-valent metal-mediated pinacol reactions are shown in Scheme 1.[6,9] Initial formation of an anionic ketyl radical can be followed by either dimerisation (path A) to produce the diol, or by radical addition to another carbonyl group producing an oxyradical (path B) which is subsequently reduced to the corresponding anion. Alternatively, metal oxirane intermediates may be produced followed by anionic addition to the carbonyl (path C). Due to the fast rates for 5- and 6-*exo*-trig radical cyclisations onto a carbonyl group, pathway B is thought to be the dominant mechanism for reactions forming small rings.[7,9] However, there are no literature examples of intramolecular pinacol reactions employing cyclopropyl ketones to investigate the mechanism of this key transformation.‡ We have sought to address this and in this communication report the first examples of SmI_2-mediated pinacol coupling reactions of cyclopropyl ketones, showing that cyclisation to form a 5-membered ring can compete favourably with cyclopropyl ring-opening.

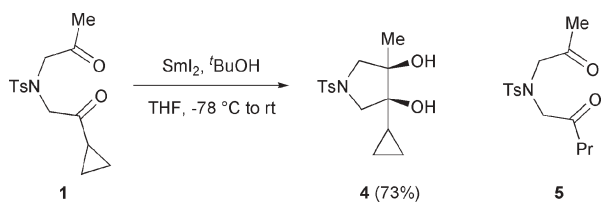


Scheme 1 Proposed mechanisms for pinacol coupling reactions.

The three key cyclopropyl ketones **1**–**3** employed in this study were produced using the route we have described previously.[8] The diketone **1**, was first submitted to our standard pinacol cyclisation conditions (SmI_2 (2.5 equiv.), ^{t}BuOH (3 equiv.), −78 °C to room temperature over 12 h). The only product from this reaction was the *cis*-diol **4**, isolated in 73% yield after column chromatography (Scheme 2). The yield and stereoselectivity (established from NOESY spectroscopy) seen in the formation of **4** is in agreement with our previous results for an analogue of **1** in which the cyclopropyl substituent is replaced by a methyl group.[8] Surprisingly, we saw no evidence (by ^{1}H and ^{13}C NMR spectroscopy or MS analysis of the crude reaction mixture) of the ring-opened product **5**, nor of any products that might conceivably arise from it by subsequent reductions, pinacol cyclisations or intramolecular aldol reactions.

Although the sole formation of **4** was unexpected, we could not rule out the possibility of selective reduction of the methyl ketone in **1**, followed by addition of the resulting ketyl radical anion onto the cyclopropyl ketone. To address this issue, we therefore examined the pinacol cyclisation of **2** where reduction of the cyclopropyl ketone is necessitated (Scheme 3). To our surprise, we again found no evidence for any ring-opened products in this reaction and the heterocyclic *cis*-diol **6** was isolated in 71% yield.[10]

The lack of any ring-opened products from **1** or **2** led us next to explore the reaction of ketone **3** (Scheme 4). Treatment of **3** with



Scheme 2

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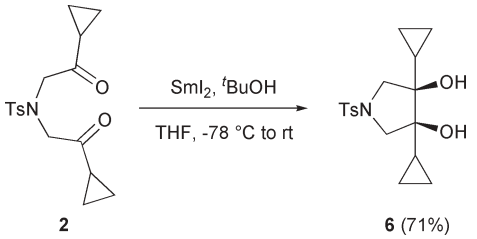
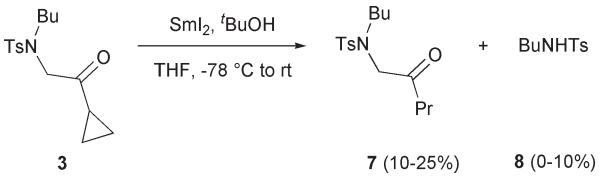
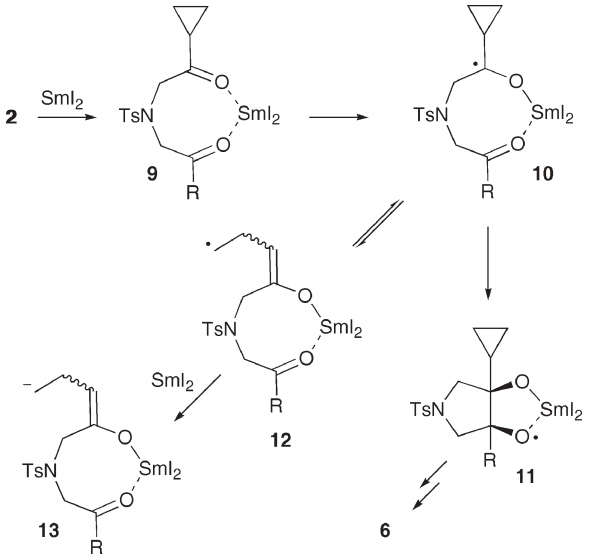


Scheme 3



Scheme 4



Scheme 5

SmI_2 (1.25 equiv.) and ^{t}BuOH (1.5 equiv.) resulted in a low yield (10%) of the ring-opened product **7**, together with appreciable amounts (60%) of recovered starting material. The yield of **7** could be increased to 25% by using excess reagents (SmI_2 3 equiv., ^{t}BuOH 4 equiv.) although a significant quantity of **3** was still re-isolated from this reaction, together with small amounts of **8**, which arises from reductive cleavage of the α-heteroatom from ketone **3** and/or **7**.[11] The poor conversion of **3** to **7** is at first glance surprising, although Skrydstrup and co-workers have recently reported similar low reactivity for the ring-opening of a cyclopropyl *N*-acyl oxazolidinone.[4b] Therefore, as a control experiment we exposed a 1 : 1 mixture of **2** and **3** to SmI_2–^{t}BuOH. Analysis of the crude reaction mixture using ^{1}H NMR spectroscopy confirmed our findings on the relative reactivity of the two substrates, with complete conversion of **2** → **6**, compared to *ca.* 10% conversion of **3** → **7**.

On the basis of the successful SmI_2-mediated pinacol cyclisation of diketone **2** (and to a lesser extent **1**), we can make the following observations as to the mechanism of the reaction. The lack of any ring-opened products seemingly points to reaction path (C) (Scheme 1) which avoids the formation of ketyl radicals. However, whilst metal oxirane species have been observed with transition metals such as vanadium or niobium,[12] the direct formation of these species by Sm(II) has not been reported and so this pathway is unlikely.§ A plausible reaction pathway (based on path (B) in Scheme 1) is presented in Scheme 5.¶ In this proposal, initial co-ordination of the oxophilic Sm(II) to both ketone groups gives **9** and facilitates inner-sphere[13] single electron transfer generating **10**. This would explain the comparatively low reactivity of **3** to SET as formation of an analogous chelated complex is not possible. The ketyl radical anion **10** subsequently undergoes 5-*exo*-trig cyclisation producing **11** which eventually leads to the product **6**. Ring-opening products would potentially arise from the sequence **10** → **12** → **13**. The lack of ring-opened products in the reaction of **2** may be explained by slow reduction of **12** under the reaction conditions, allowing ring-opening to be reversible. However, whilst there is no data available on the reversibility of ring-opening for alkyl cyclopropyl ketyl radicals, a consideration of estimated rate constants for the processes involved has led Guibé and co-workers[4a] to suggest that reversible ring-opening is unlikely at 0.1 M concentrations of SmI_2.‖ Therefore, the most likely explanation is that **10** undergoes 5-*exo*-trig cyclisation at a *faster rate* than cyclopropyl ring opening. The rate constant for ring opening of the methyl cyclopropyl ketyl radical has been shown to have a lower limit of 10^7 s^{-1} at 25 °C.[14] Whilst data is not available for the 5-*exo*-trig cyclisation of ketyl radicals onto carbonyls, the rate for the corresponding cyclisation of a primary radical onto an aldehyde is 8.7×10^5 s^{-1} (at 80 °C).[15] The fact that 5-*exo*-trig cyclisation of **10** competes so successfully with ring-opening is no doubt due to the nucleophilic nature of the ketyl radical anion together with chelation by Sm^{3+}, which increases the electrophilicity of the remaining carbonyl and lowers the entropic barrier to the cyclisation.

In summary, we have shown for the first time that cyclopropyl ketones can be successfully employed in intramolecular SmI_2-mediated pinacol coupling reactions. The fact that no ring-opened products are observed in these reactions suggests that the rate of 5-*exo*-trig cyclisation of a ketyl radical anion onto a ketone is faster than cyclopropyl ring-opening. In addition, our results point to the crucial role played by samarium chelation in increasing the rate of the pinacol cyclisation as well as in reduction of the carbonyl group by inner-sphere SET.[16]

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Notes and references

‡ There are a limited number of reports of successful intermolecular pinacol coupling reactions of cyclopropyl ketones without ring-opening. The reactions have been mediated by low-valent Ti reagents, Bu_3SnH–AIBN, or electro- and photochemical methods. However, two cases involved an aryl-substituted cyclopropyl ketone,[17] and aryl cyclopropyl ketyl anions have been shown to undergo slow and reversible ring-opening.[18] Two further examples involved the dimerisation of dicyclopropyl ketone[19] and cyclopropyl 1,2-diketones,[20] and the ketyl anions of both systems are apparently stable.[21] In the final example with acetylcyclopropane,[22] the authors suggest vicinal association of the ketones to polymeric low-valent titanium species and concerted electron transfer, thereby avoiding the formation of discrete ketyl radicals.

§ A Sm(II)-species has been shown to undergo reaction with benzophenone to give a disamarium(III) benzophenone-dianion complex.[23]

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¶ The intermediates shown in Scheme 5 may undergo protonation by ^{t}BuOH, although this is presumably discouraged by the chelate effect. We also cannot rule out reduction of radical **10** to the corresponding anion followed by anionic cyclisation, although this is unlikely in the presence of a proton donor.

‖ The rate constant for the reduction of **12** may be approximated to 7×10^6 s^{-1} at 25 °C, whilst the rate constant for cyclisation for the free 3-butenyl radical is 0.8×10^4 s^{-1}—for a detailed discussion see ref. 4*a*.

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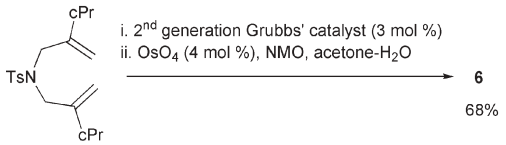

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