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Synthesis of 3,3-disubstituted α-tetralones by rhodium-catalysed reaction of 1-(2-haloaryl)cyclobutanols†

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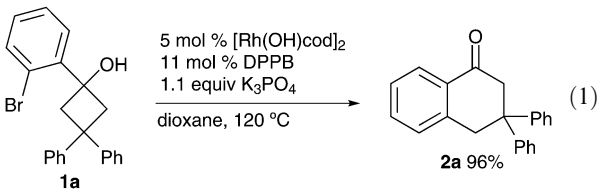
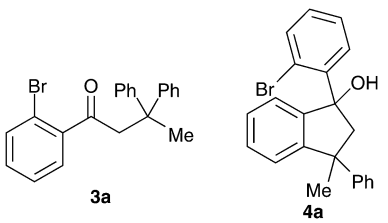
The rhodium-catalysed reaction of 1-(2-haloaryl)cyclobutanols afforded 3,3-disubstituted α-tetralones. The reaction was applied to the asymmetric synthesis of α-tetralones bearing a chiral quaternary carbon centre at the 3-position, which was otherwise difficult to execute.

Transition metal-catalysed reactions involving an elementary step to cleave a carbon–carbon single bond render it possible to reconstruct a main framework of organic molecules, providing unique synthetic transformations.[1] We and others have developed palladium-[2] and rhodium-catalysed[3] reactions of cyclobutanols,[4,5] in which intermediary metal cyclobutanolates produce a variety of compounds depending upon the transition metals and the substituents. For example, rhodium cyclobutanolates undergo ring opening by β-carbon elimination to generate (δ-ketoalkyl)rhodium(I) species, with which three pathways are known to ensue. When a 3,3-dialkyl-substituted cyclobutanol is employed as the starting substrate, the resulting alkylrhodium(I) intermediate undergoes a 1,3-rhodium shift to form a rhodium enolate, protonation of which furnishes an acyclic ketone.[3d] On the other hand, in the case that an aryl group is attached to the 3-position, a 1,4-rhodium shift occurs with the ring-opened (δ-ketoalkyl)-rhodium(I) species to furnish an arylrhodium(I) intermediate, which intramolecularly adds to the carbonyl group to afford indanols.[3b,c] When a cyclobutanol has an alkene or allene substituent at the 1-position, the alkylrhodium(I) intermediate undergoes 1,2-addition across the carbon–carbon double bond, leading to the formation of cyclohexanones or cyclohexenones.[3e] Herein is disclosed a rhodium-catalysed reaction of cyclobutanols bearing an *o*-bromoaryl moiety at the 1-position, which furnishes 3,3-disubstituted α-tetralones. Unlike the previous examples, the reaction mechanism involves a rhodium(I)/(III) oxidation/reduction process.

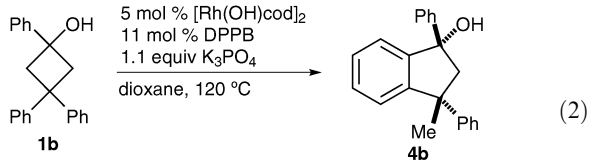
When a dioxane solution of 1-(2-bromophenyl)-3,3-diphenylcyclobutanol (**1a**) was heated at 120 °C in the presence of $[Rh(OH)cod]_2$ (5 mol%), DPPB (11 mol%) and K_3PO_4 (1.1 equiv.) for 15 h, α-tetralone **2a** was obtained in 96% isolated yield‡ (eqn (1)).[6] No formation of acyclic ketone **3a** and indanol **4a** was detected by GC-MS analysis of the reaction mixture, being suggestive that the intermediacy of the ring-opened (δ-ketoalkyl)rhodium species was unlikely.[3]



(1)



The following experiments were carried out in order to provide information for mechanistic interpretation of the reaction pathway (eqn (2)). When the same reaction conditions were applied to cyclobutanol **1b** lacking a bromo group on the phenyl ring, indanol **4b** was the sole product obtained (84% yield).[3b,c] The reaction of **1b** in the presence of bromobenzene also yielded indanol **4b** in 83% yield without participation of bromobenzene. This result stands in marked contrast to that obtained with a palladium(0) catalyst; bromobenzene participates in the palladium-catalysed reaction of cyclobutanol **1b** to form a δ-arylated ketone.[2d] The contrasting results indicate that rhodium(I) is far less reactive towards bromobenzene than palladium(0).[7] Overall, the presence of the bromo group within the cyclobutanol skeleton dictated the reaction pathway to a new direction, *i.e.*, to the formation of α-tetralones.



(2)

in the absence of PhBr 84% dr = > 20:1
in the presence of PhBr (1.2 equiv) 83% dr = > 20:1

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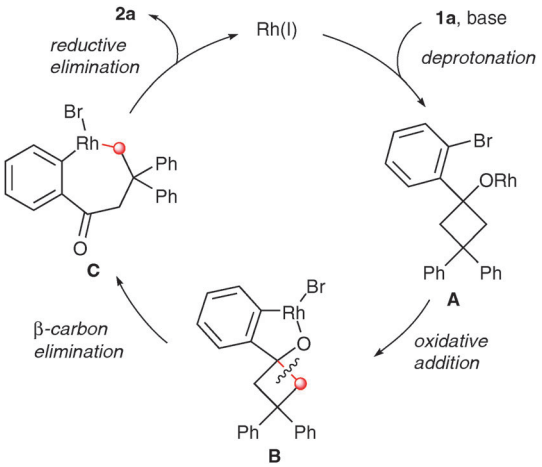
† Electronic supplementary information (ESI) available: Experimental procedures and characterisation data for new compounds. See DOI: 10.1039/c2cc16907j



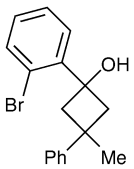
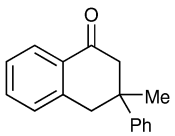
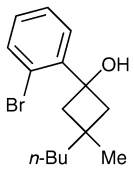
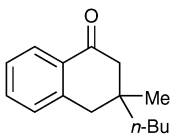
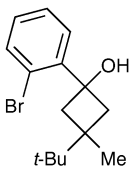
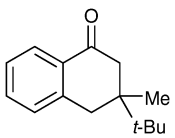
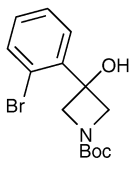
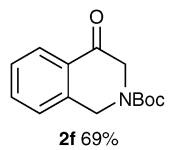
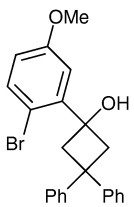
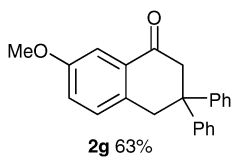
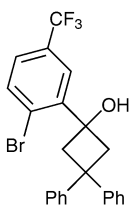
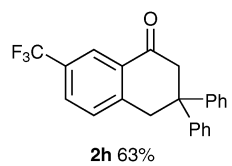
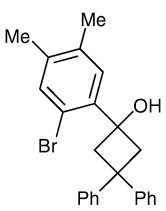
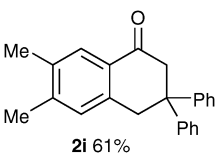
Scheme 1 A possible mechanism.

On the basis of these results, we propose a possible mechanism for the formation of **2a** from **1a** as depicted in Scheme 1. Cyclobutanol **1a** initially reacts with a rhodium(I) complex in the presence of a base to generate rhodium(I) cyclobutanolate **A**. The rhodium(I) centre is geometrically constrained in proximity to the bromoaryl group, and thus, an oxidative addition process is facilitated to give five-membered rhodacycle(III) **B**.[8] Then, the four-membered carbocycle is opened by β-carbon elimination to afford seven-membered rhodacycle(III) **C**.[9] Finally, reductive elimination provides α-tetralone **2a** with regeneration of the rhodium(I) catalyst.

Other cyclobutanols bearing an *o*-haloaryl group at the 1-position were subjected to the rhodium-catalysed reaction conditions (Table 1). Cyclobutanols having alkyl and aryl substituents at the 3-position participated in the reaction to give α-tetralones in good yields (entries 1–3). On the other hand, cyclobutanols with the 3-position being unsubstituted provided a complex mixture, probably due to the concurrence of β-hydride elimination with intermediate **C**. The azetidin-3-ol could be employed instead of cyclobutanols to furnish isoquinolinone **2f** in 69% yield (entry 4). Both electron-donating and -withdrawing groups were admitted on the aryl ring (entries 5–7). An iodo counterpart of **1c** underwent the reaction at 100 °C to form **2c** in 72% yield, indicating that aryl iodides were more reactive than aryl bromides. In contrast, the reaction of the chloro analogue of **1a** was much slower. The product **2a** was obtained in 42% yield with the unreacted starting compound remaining even after 48 h. The reaction of the cyclobutanol bearing an *o*-bromobenzyl group gave a complex mixture. These results revealed the importance of the geometrical constraint as well as the reactivity toward oxidative addition of the haloaryl moiety.

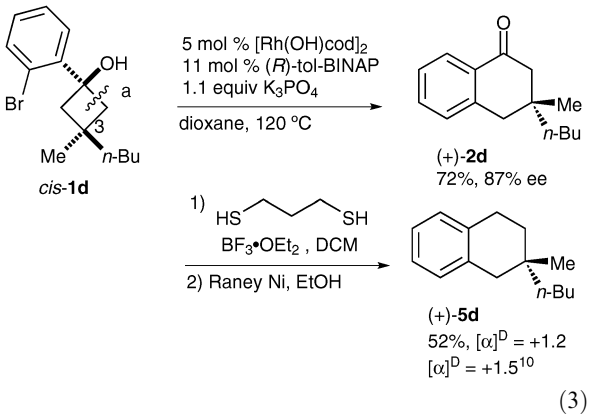
Next, we examined the asymmetric induction by using various chiral ligands to find that tol-BINAP exhibited a fairly good enantioselectivity. When *cis*-**1d** was treated with a Rh(I)/(*R*)-tol-BINAP catalyst in dioxane, (+)-**2d** was obtained in 72% yield with 87% ee (eqn (3)). On the other hand, the other diastereomer *trans*-**1d** afforded the opposite enantiomer (−)-**2d** in 69% yield with 81% ee (eqn (4)). Both enantiomers were derivatised to the corresponding tetralins and their absolute configurations were determined by the measurement

Table 1 Scope of the rhodium-catalysed reaction of 1-(2-bromoaryl)-cyclobutanols[a]

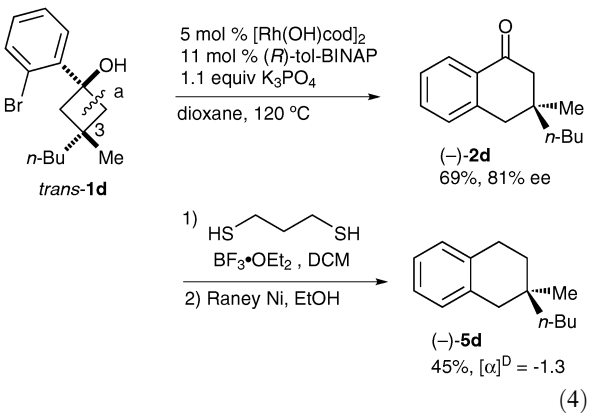
Entry	1	2[b]
1[c,d]	 **1c**	 **2c** 79%
2[c]	 **1d**	 **2d** 75%
3[c]	 **1e**	 **2e** 82%
4[d]	 **1f**	 **2f** 69%
5[e]	 **1g**	 **2g** 63%
6[d]	 **1h**	 **2h** 63%
7[f,g]	 **1i**	 **2i** 61%

[a] Reaction conditions: 1.0 equiv. cyclobutanol **1**, 5 mol% $[Rh(OH)cod]_2$, 11 mol% DPPB, 1.1 equiv. K_3PO_4, dioxane (0.2 M), 120 °C, 24 h unless otherwise noted. [b] Isolated yields. [c] A diastereomer mixture of **1** was used. [d] 11 mol% of BINAP was employed instead of DPPB. [e] DMSO was employed instead of dioxane. [f] The reaction was conducted at 0.1 M, 150 °C. [g] Heated for 63 h.

of their optical rotations.[10] The absolute stereochemistry established that the (*R*)-tol-BINAP ligand favoured the cleavage of the bond a located on the right in the drawings of eqn (3) and (4), irrespective of the stereochemical arrangement at the 3-position.



(3)



(4)

In conclusion, we have developed a rhodium-catalysed reaction of 3,3-disubstituted 1-(2-haloaryl)cyclobutanols, which provides 3,3-disubstituted α-tetralones having a quaternary carbon centre in an enantiomerically enriched form. We failed to find such chiral α-tetralones by structural search on electronic databases, which was probably owing to the paucity of an appropriate synthetic method. Asymmetric conjugate addition of carbon nucleophiles to α,β-unsaturated carbonyl compounds is an authentic method for introducing a chiral centre at the position β to a carbonyl group. However, α-tetralones bearing a chiral quaternary carbon at the 3-position are inaccessible *via* conjugate addition to dehydrotetralone because 1-naphthol is the more stable tautomer of dehydrotetralone and unreactive as the conjugate acceptor. Therefore, the rhodium-catalysed reaction we have developed would serve as a useful synthetic method for such chiral α-tetralone derivatives.

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Notes and references

‡ General procedure: A mixture containing $[Rh(OH)(cod)]_2$ (2.3 mg, 5.0 μmol, 5.0 mol%), DPPB (4.7 mg, 11 μmol, 11 mol%), K_3PO_4 (23.3 mg, 0.11 mmol) and **1a** (37.9 mg, 0.10 mmol) in 1,4-dioxane (0.50 ml) was stirred at 120 °C for 15 h. After being cooled to room temperature, the reaction mixture was diluted with H_2O and extracted with AcOEt (three times). The combined organic phase was washed with H_2O and brine, dried over $MgSO_4$ and evaporated. The residue was purified by preparative thin-layer chromatography on silica gel (hexane : AcOEt = 10 : 1) to afford **2a** (28.7 mg, 0.096 mmol, 96%).

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6 The results with other ligands at 100 °C for 13 h: PPh_3 (<10%), P(*t*-Bu)$_3$ (<10%), IPr (0%), DPPP (23%), BINAP (30%), DPPB (53%).

7 Although the use of palladium complexes was also examined in the reaction of **1a** under various reaction conditions, tetralone **2a** was produced in less than 30% yield together with unidentified byproducts.

8 For rhodium-catalysed cross-coupling reactions which would involve a Rh(I)–Rh(III) redox process, see: (*a*) R. C. Larock, K. Narayanan and S. S. Hershberger, *J. Org. Chem.*, 1983, **48**, 4377; (*b*) P. A. Evans and D. Uraguchi, *J. Am. Chem. Soc.*, 2003, **125**, 7158; (*c*) K. Ueura, T. Satoh and M. Miura, *Org. Lett.*, 2005, **7**, 2229; (*d*) H. Yasui, K. Mizutani, H. Yorimitsu and K. Oshima, *Tetrahedron*, 2006, **62**, 1410; (*e*) M. L. Kantam, S. Roy, M. Roy, B. Sreedhar, B. M. Choudary and R. L. De, *J. Mol. Catal. A: Chem.*, 2007, **273**, 26; (*f*) L. Zhang and J. Wu, *Adv. Synth. Catal.*, 2008, **350**, 2409; (*g*) J.-Y. Yu and R. Kuwano, *Angew. Chem., Int. Ed.*, 2009, **48**, 7217.

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