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Palladium-catalysed asymmetric arylation of *tert*-cyclobutanols *via* enantioselective C–C bond cleavage

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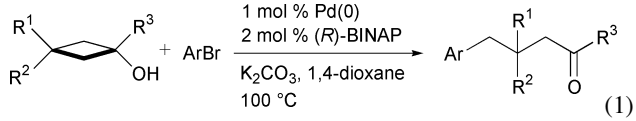
Received (in Cambridge, UK) 29th August 2001, Accepted 12th November 2001
First published as an Advance Article on the web 4th December 2001

Palladium-catalysed arylation of *tert*-cyclobutanols with aryl bromide involving enantioselective C–C bond cleavage affords chiral ketones with moderate to good enantioselectivity.

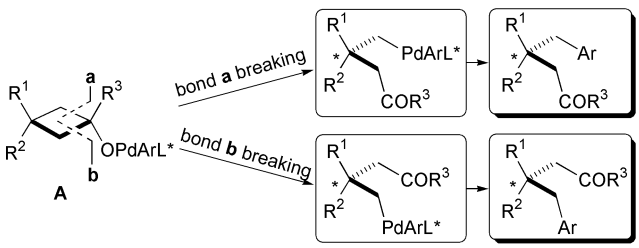
Transition metal-catalysed asymmetric reactions have been used as modern and powerful methods for the synthesis of optically active compounds, mainly by a carbon–hydrogen, a carbon–heteroatom, and a carbon–carbon bond formation to create a new chiral centre on carbon.[1] In sharp contrast, although a metal-catalysed selective C–C bond cleavage reaction has been found in recent years,[2] the example of the enantioselective C–C bond cleavage reaction has been scarcely reported to the best of our knowledge.[3] We have recently disclosed a Pd(0)-catalysed arylation of *tert*-cyclobutanols involving β-carbon elimination from an intermediate arylpalladium(II)-alcoholate to afford arylated ketones [eqn. (1)].[4]



(1)

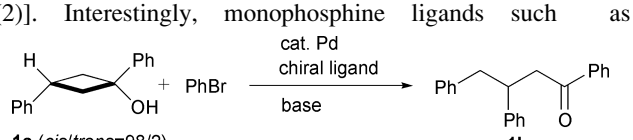
This ring cleavage reaction has a potential to produce chiral ketones if the enantioselective carbon–carbon bond cleavage *via* palladium(II)-alcoholate of 3-substituted-cyclobutanols **A** (bond **a** or **b**) would occur as shown in Scheme 1.

In our preliminary communication of this novel reaction, the produced ketones were racemic in spite of the use of (*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) as a chiral phosphine ligand. In the search for a successful asymmetric arylation involving an enantioselective C–C bond cleavage using several chiral phosphine ligands, we found that some monophosphine ligands work effectively to give the chiral ketones in high yields with moderate to good enantiomeric excess. We wish to report here the effective asymmetric arylation of 3-substituted *tert*-cyclobutanols.



Scheme 1

First, the arylation of *tert*-cyclobutanol **1a** was carried out using some commercially available chiral bisphosphine ligands, such as (*R*)-Tol-BINAP, (*R*)-(*S*)-BPPFA, (+)-Me-DUPHOS and (+)-DIOP, in place of BINAP. Only slight stereoselectivity was observed (~2% ee), but the product yields were quite low [eqn. (2)]. Interestingly, monophosphine ligands such as (*R*)-MeO-MOP and (*S*)-H-MOP[5] were found to give the product ketone **1b** in good yields with up to *ca.* 30% ee (the results are not shown). However, the improvement of the optical yields could not be attained using such ligands during the optimisation of the reaction conditions. Next, we examined a commercially available ligand (*R*)-*N*,*N*-dimethyl-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine [(*R*)-(*S*)-PPFA, **I**] and we found that it showed a better selectivity. Treatment of **1a** (*cis*/*trans* = 98/2) with 1.2 equiv. of PhOTf (phenyl trifluoromethanesulfonate) in the presence of 5 mol% $Pd(OAc)_2$, 20 mol% ligand **I** and 1.2 equiv. of Cs_2CO_3 as a base in THF at 90 °C afforded **1b** in 42% yield with 59% ee (Table 1, entry 1). In this reaction, the ratio of the isomeric alcohols greatly affected the ee value of the product ketone. For example, when the arylation of **1a** (*cis*/*trans* = 80/20) with PhOTf was carried out under the same conditions as entry 1 in Table 1, the ee value of **1b** decreased to 36%. Then, we attempted to optimise the reaction conditions by changing the solvent, the reaction temperature, the base and the arylating agent using **1a** (*cis*/*trans* = 98/2). When the reaction was carried out in toluene, an improvement in product yield was observed, although the optical yield slightly decreased (entry 3).



(2)

Table 1 Palladium-catalysed asymmetric arylation of 1,3-diphenyl-1-cyclobutanol **1a**[a]

Entry	Ligand	PhX	Solvent (mL)	Temp. (°C)	Time (h)	GLC yield (%)[b]	ee (%)
1	**I**	PhOTf	THF (1.0)	90	24	42	59
2	**I**	PhOTf	1,4-dioxane (1.0)	90	24	12	52
3	**I**	PhOTf	toluene (1.0)	90	24	70	48
4	**I**	PhOTf	toluene (0.5)	70	72	24	57
5	**I**	PhBr	toluene (0.5)	70	72	71[c]	59
6	**I**	PhBr	toluene (0.5)	80	48	70[c]	58
7[d]	**I**	PhBr	toluene (0.5)	80	48	11	57
8	**II**	PhBr	toluene (0.5)	80	48	98[c]	49
9	**III**	PhBr	toluene (0.5)	80	48	93[c]	74

[a] *Reaction conditions*: **1a** (0.10 mmol), $Pd(OAc)_2$ (0.005 mmol), ligand (0.02 mmol), PhX (0.12 mmol), Cs_2CO_3 (0.12 mmol), under N_2. **1a** was completely consumed in entries 8 and 9. [b] Based on **1a** employed. [c] Isolated yield. [d] K_2CO_3 was used as a base.

DOI: 10.1039/b107736h

Bromobenzene as arylating agent gave **1b** in both higher selectivity and yield (entries 4–6). The use of K_2CO_3 instead of Cs_2CO_3, on the other hand, seriously diminished the product yield (entry 7). Next, other chiral ligands **II** and **III** were synthesised[6] and applied to this arylation. The use of **III** resulted in higher selectivity than the use of **I** or **II**, and thus, **1b** was obtained in 93% yield with 74% ee (entry 9).

The results of the asymmetric arylation of several monocyclic *tert*-cyclobutanols leading to chiral γ-arylated ketones under the optimised conditions described above are listed in Table 2.† Using bromobenzene as arylating agent under the conditions composed of $Pd(OAc)_2$, ligand **III**,‡ and Cs_2CO_3 in toluene, the substrate alcohols were completely consumed within 24 h, and 3-substituted cyclobutanols **1a**, **2a**, and **3a** gave the corresponding γ-arylated ketones **1b**, **2b**, and **3b** in high yields with moderate to good enantioselectivity, respectively (entries 1, 5 and 6). The lower reaction temperature (60 °C) did not affect the ee value (entry 2). The arylation of **1a** with *p*-bromochlorobenzene or *p*-bromotoluene also occurred smoothly to give **1c** and **1d** in high yields with good ee value (entries 3 and 4). Similarly, the reaction of **3a** with 2-bromonaphthalene afforded **3c** in high yield (entry 7). It should be noted that this arylation could also be applied to the 1-alkyl-substituted cyclobutanol **4a**, and the corresponding dialkylketone **4b** was obtained in high yield with moderate enantioselectivity (entry 8). 3-Disubstituted cyclobutanols gave the corresponding ketones having quaternary carbon centres.[7] Treatment of cyclobutanol **5a**[8] under the same conditions for 47 h afforded

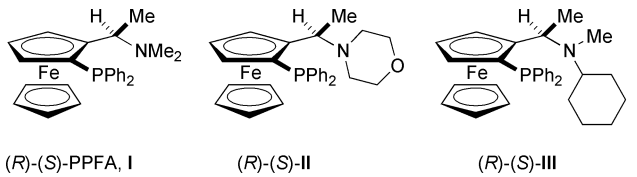
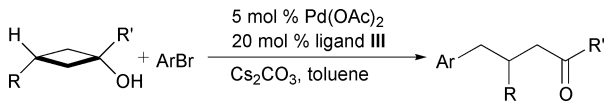
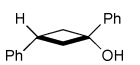
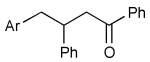
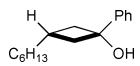
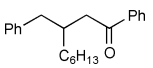
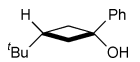
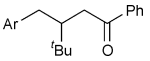
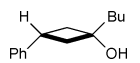
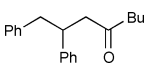


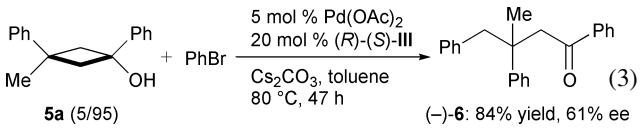
Table 2 Palladium-catalysed asymmetric arylation of *tert*-cyclobutanols[a]

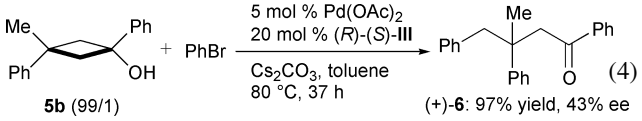


Entry	Substrate (*cis*/*trans*)	Ar	Product and isolated yield (%)		ee (%)[b]
1		Ph		99	77
2[c]	**1a** (98/2)	Ph	**1b**	83	78
3		*p*-ClC_6H_4	**1c**	90	73
4		*p*-MeC_6H_4	**1d**	91	75
5		Ph		99	64
	2a (96/4)		**2b**		
6		Ph		99	53
	3a (97/3)		**3b**		
7		2-naphthyl	**3c**	92	60
8[d]		Ph		86	60
	4a (99/1)		**4b**		

[a] Reaction conditions: alcohol (0.2 mmol), $Pd(OAc)_2$ (0.01 mmol), (*R*)-(*S*)-**III** (0.04 mmol), aryl bromide (0.24 mmol), Cs_2CO_3 (0.24 mmol), toluene (1 mL), 80 °C, 24 h under N_2. [b] Determined by HPLC. [c] 60 °C, 48 h. [d] 42 h.

(−)-**6**[9] with 61% ee, while the isomer **5b**[8] gave (+)-**6**[9] with 43% ee when reacted for 37 h [eqns. (3) and (4)]. These results





suggest that the enantioselective C–C bond cleavage preferentially occurs at the C–C bond in the same direction in ligand **III**-ligated palladium(II)-alcoholates, irrespective of the substituents at the 3-position on the cyclobutane ring, although details are not yet known.

In summary, we have described the novel asymmetric arylation of *tert*-cyclobutanols involving C–C bond cleavage, in which the possibility of enantioselective C–C bond cleavage was demonstrated using some chiral ligands. Our study for finding a more efficient stereocontrolled catalytic system for this reaction is now in progress.

Notes and references

† *Experimental*: A mixture of $Pd(OAc)_2$ (0.01 mmol), (*R*)-(*S*)-**III** (0.04 mmol), Cs_2CO_3 (0.24 mmol) and toluene (0.5 mL) in a 10 mL two-necked flask was stirred at rt under N_2. After 0.5 h, aryl bromide (0.24 mmol) and alcohol (0.20 mmol) in toluene (0.5 mL) were added and the mixture was stirred at 80 °C until the reaction had reached completion by monitoring with TLC analysis. The reaction mixture was cooled to rt and then filtered through a pad of Florisil. The filtrate was concentrated under vacuum to give an oil, which was subjected to column chromatography on SiO_2 with EtOAc–hexane (2 : 98) as eluent. The enantiomeric excess was determined by HPLC using Daicel Chiralcel® AD and OD columns (4.6 × 250 mm, 3% propan-2-ol–hexane) at 25 °C.

‡ *Analytical data for ligand* **III**: Ligand **III** is a new compound synthesised from (*R*)-(*S*)-PPFOAc and *N*-methylcyclohexylamine according to the reported procedure, ref 6. Yellow solid; mp 159.2–160.0 °C; $[\alpha]_D^{25}$ = −286.9 (*c* = 0.5, $CHCl_3$); IR (KBr) 2956, 2939, 2774, 1446, 1433, 818, 749, 739, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.49–1.58 (m, 10H), 1.29 (d, *J* = 6.3 Hz, 3H), 1.65 (s, 3H), 2.15–2.30 (m, 1H), 3.70 (s, 1H), 3.73–4.26 (m, 4H), 3.94 (s, 5H), 7.01–7.70 (m, 10H). ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 31.3. Anal. Calcd. for $C_{31}H_{36}FeNP$: C, 73.09; H, 7.12; N, 2.75; Found: C, 73.02; H, 7.07; N, 2.82%.

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8 Alcohols **5a** and **5b** were separated by high performance preparative liquid chromatography. However, the exact stereochemistry (*cis* or *trans*) is not yet clear. The stereochemistry presented here was presumed from the ^1H-NMR of an analogous alcohol.
9 Specific rotation of **6**; (−)-**6**: $[\alpha]_D^{25}$ = −10.2 (*c* = 0.5, in $CHCl_3$); (+)-**6**; $[\alpha]_D^{25}$ = +4.2 (c = 0.5, in $CHCl_3$).