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Palladium-catalyzed kinetic resolution of *tert*-cyclobutanols via C–C bond cleavage

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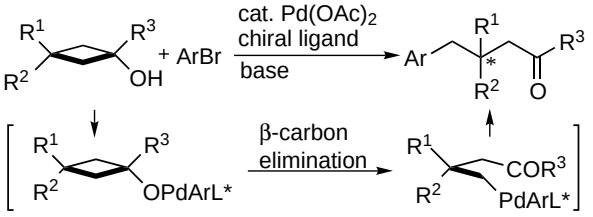
Abstract—Palladium-catalyzed kinetic resolution of *tert*-cyclobutanols with bromobenzene affords chiral ketones via C–C bond cleavage as well as chiral *tert*-cyclobutanols with moderate to good enantioselectivity.

Many useful and excellent methods for non-enzymatic kinetic resolution[1] of racemic alcohols, such as acylation,[2] epoxidation[3] and oxidation of a hydroxyl group,[4] has appeared in recent years.[5] Among them the metal-catalyzed oxidative kinetic resolution of secondary alcohols is one of the attractive techniques, the successful results of which being obtained using Ru(II) and Pd(II) complexes. For example, Noyori et al. reported the Ru(II)-catalyzed kinetic resolution of *sec*-alcohols by hydrogen transfer.[4b] Chiral Ru-porphyrin catalysis was studied by Gross et al.[4c] Our group also reported highly effective kinetic resolution of various *sec*-alcohols using chiral Ru(II) complex under hydrogen transfer conditions.[6] Quite recently, Pd(II)-catalyzed oxidative kinetic resolution of *sec*-alcohols using oxygen as a sole oxidant was reported by two groups, independently.[4g,h]

Recently, we have been studying the Pd(II)-catalyzed oxidative transformation of primary, secondary and tertiary alcohols.[7,8] We also reported Pd(0)-catalyzed arylation of *tert*-cyclobutanols with aryl bromide involving C–C bond cleavage[9] and its asymmetric version[10] (Scheme 1). During these studies we found that the kinetic resolution of racemic *tert*-cyclobutanols via the arylation involving C–C bond cleavage proceeded to give both chiral ketones and unreacted chiral alcohols. Enzymatic kinetic resolution of *rac*-benzoin via C–C bond cleavage was reported quite recently.[11] On the other hand, non-enzymatic kinetic resolution of alcohols via C–C bond cleavage has scarcely been reported, and also kinetic resolution of *tert*-alcohols has not yet been described in the literature so far.[4] We wish to report here the results of the Pd-catalyzed kinetic resolution of *tert*-cyclobutanols.



Scheme 1.

As chiral ferrocene-based ligand was disclosed to be effective for the enantioselective C–C bond cleavage of *tert*-cyclobutanols in our previous study,[10] we first examined the arylation of racemic alcohol **1a** (0.1 mmol) with bromobenzene (0.06 mmol) in toluene in the presence of a catalytic amount of $Pd(OAc)_2$, (*R*)-(*S*)-PPFA **I** {(*R*)-*N*,*N*-dimethyl-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]-ethylamine}, and Cs_2CO_3 (Eq. (1)). The results obtained under several conditions are listed in Table 1. As a result, **1a** was consumed in theoretical amount to give an arylated ketone **2a** in 52% yield with 34% ee and 40% of the alcohol **1a** was recovered with 49% ee (entry 1). The selectivity factor (k_{rel} values)[12] did not depend much on the concentration of the reaction mixture (entries 1–3). The increase of the amount of base (0.2 mmol) slightly increased the k_{rel} value (entry 4), while the reduction of the amount of the ligand **I** slightly decreased it (entry 5). Among analogous ligands **I**–**III**,[13] the best k_{rel} value (5.5) was obtained when the reaction was carried out using the ligand **III** at 50°C (entry 8).

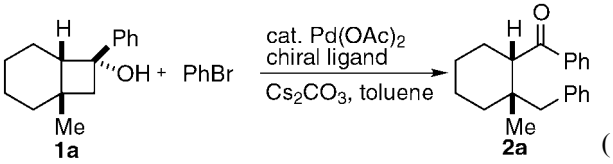


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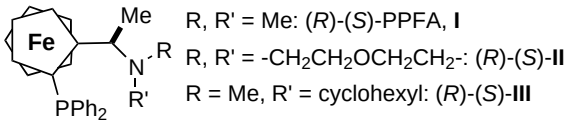
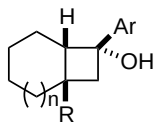
Table 1. Palladium-catalyzed kinetic resolution of *tert*-cyclobutanol **1a**[a]

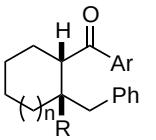
Entry	Ligand (mmol)	Cs_2CO_3 (mmol)	Toluene (mL)	Temp. (°C)	Time (h)	Product **2a**		Recovered alcohol **1a**		k_{rel}
						Yield (%)[b]	Ee (%)[c]	Yield (%)[b]	ee (%)[c]	
1	**I** (0.02)	0.1	0.5	80	36	52	34	40	49	3.1
2	**I** (0.02)	0.1	1.0	80	36	48	35	43	42	2.8
3	**I** (0.02)	0.1	1.5	80	52	42	31	48	38	2.9
4	**I** (0.02)	0.2	1.0	80	33	50	43	40	52	3.3
5	**I** (0.01)	0.2	1.0	80	36	52	35	34	42	2.2
6	**II** (0.02)	0.2	1.0	80	36	60	28	26	54	2.3
7	**III** (0.02)	0.2	1.0	80	39	59	37	31	70	3.7
8[d]	**III** (0.02)	0.2	0.5	50	48	54	47	43	65	5.5

[a] Reaction conditions: alcohol **1a** (0.1 mmol), $Pd(OAc)_2$ (0.005 mmol), PhBr (0.06 mmol).
[b] GLC yield based on **1a**.
[c] Determined by HPLC. Absolute configuration of a rich enantiomer was not determined.
[d] PhBr (0.055 mmol) was used.





1: n = 1, R = Me
3: n = 1, R = H
5: n = 2, R = H



2: n = 1, R = Me
4: n = 1, R = H
6: n = 2, R = H

Table 2 shows the results of the kinetic resolution of some racemic *tert*-cyclobutanols. The *tert*-cyclobutanols **1** bearing different aryl substituents also served as substrates, significant substituent effects of which being not observed (entries 1–5). In the case of the alcohol **3** (entries 6–9), which has H atoms at angular positions, total material balance was not kept well because of the formation of dehydrogenated ring-opening ketone (a phenyl group is not introduced),[7g] which may be formed by β-hydrogen elimination from the intermediate alkylpalladium species produced via β-carbon elimination of an alkoxypalladium species. In addition, we confirmed that **3** gradually decomposed even in the absence of bromobenzene under similar conditions to produce the same dehydrogenated product together with a small amount of unidentified products.[14] Even in such a case, the recovered alcohol was found to be optically active (after 23 h, 55% recovery, 20% ee). The reduction of the amount of base improved the balance of the total yield (entry 7). When the reaction was carried out using bromobenzene (0.2 mmol), the improvement of both total yield and k_{rel} value was observed, although competitive side reaction could not be completely avoided (entry 8). The resolution of **3**

Table 2. Palladium-catalyzed kinetic resolution of *tert*-cyclobutanols **1a**–**1e**, **3** and **5**[a]

Entry	Alcohol (0.2 mmol)	Ar	Product ketone	Temp. (°C)	Time (h)	Product ketone		Recovered alcohol		k_{rel}
						Yield (%)[b]	ee (%)	Yield (%)[b]	ee (%)	
1	**1**	**a**: Ph	**2a**	50	24	48	56	46	59	5.3
2	**1**	**b**: 4-ClC_6H_4	**2b**	50	35	45	60	54	46	4.9
3	**1**	**c**: 4-MeC_6H_4	**2c**	50	36	36	67	63	28	3.7
4	**1**	**d**: 4-$MeOC_6H_4$	**2d**	50	36	27	68	72	26	6.5
5	**1**	**e**: 2-naphthyl	**2e**	50	35	39	67	61	40	6.4
6	**3**	Ph	**4**	50	24	45	50	25	82	3.9
7[c]	**3**	Ph	**4**	50	28	47	64	38	62	4.0
8[d]	**3**	Ph	**4**	50	15	58	51	31	92	7.1
9[d]	**3**	Ph	**4**	Rt	65	35	77	61	37	5.3
10	**5**	Ph	**6**	50	48	55	68	43	84	11.4

[a] Reaction conditions: alcohol (0.2 mmol), $Pd(OAc)_2$ (0.01 mmol), ligand **III** (0.04 mmol), PhBr (0.11 mmol), Cs_2CO_3 (0.4 mmol), toluene (1 mL) under N_2.
[b] Isolated yield based on the alcohol employed.
[c] Cs_2CO_3 (0.11 mmol) was used.
[d] PhBr (0.2 mmol) was used.

could be performed even at room temperature (ca. 28°C) after 65 h (entry 9). The best k_{rel} value was obtained using the alcohol **5** as a substrate, which reached 11.4.

In summary, we have demonstrated the palladium-catalyzed kinetic resolution of *tert*-cyclobutanols via C–C bond cleavage. This resolution can produce the chiral ketones and alcohols, in which the ketones include a quaternary chiral carbon center. Our efforts to improve the selectivity and to expand the scope of this resolution are now in progress.

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