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Dicarbonylchloro(pentabenzylcyclopentadienyl)ruthenium as Racemization Catalyst in the Dynamic Kinetic Resolution of Secondary Alcohols

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Dicarbonylchloro(pentabenzylcyclopentadienyl)ruthenium has been prepared and its structure confirmed by X-ray analysis. This complex shows excellent catalytic activity and modest stability against air in racemization reactions of secondary alcohols. In *Candida antarctica* lipase B (CAL-B) catalyzed dynamic kinetic resolution (DKR) of 1-phenyl- and 1-(furan-2-yl)ethanol compounds, the new complex shows improved performance as an alcohol racemization catalyst in comparison with its well-known pentaphenylcyclopentadienyl analogue, hitherto considered as the leading catalyst candidate.

Introduction

Dynamic kinetic resolution (DKR) of racemic *sec*-alcohols by combination of enzymes with transition-metal catalysts, originally developed by Williams[1] and Bäckvall,[2] is a useful method for the production of chiral building blocks.[3] In such processes, in-situ racemization of the slower reacting enantiomer by a metal catalyst enables theoretical yields of 100%, not reachable in traditional kinetic resolutions (KR), which by theory stop at the maximum yield of 50%. Various metal complexes are known to racemize alcohols, the key issues of catalytic activity, stability and compatibility with enzymes being met, however, by only a few systems.[4] Hitherto, the most successful catalyst design has been based on half-sandwich ruthenium complexes, e.g., **1**–**3** (Figure 1), of which the (pentaphenylcyclopentadienyl)ruthenium complex **1** is often claimed as the currently best candidate.[5] Both catalyst **1** and its amino-substituted analogue **2**[6] can be successfully utilized in DKR at ambient temperature, whereas the initially employed Shvo's catalyst **3** requires higher temperatures for generating the active monoruthenium species.[2,7] Nevertheless, complexes such as **1** and **2** can be considered as being far from optimal, in terms of cost and ease of preparation, air and moisture stability, activity, compatibility with polar solvents and substrate scope. Furthermore, the preparation of ligand precursors for **1** and **2**, even starting from the commercially available tetraphenylcyclopentadienone, is not straightforward, involving the use of air-sensitive Grignard reagents, lithium-based reducing agents and dry solvents.

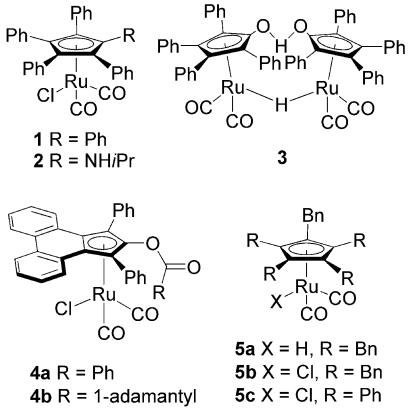

Figure 1. Half-sandwich ruthenium complexes **1**–**5**.

Results and Discussion

We have recently prepared a number of half-sandwich, indenyl-based Ru complexes containing fused aromatic ring substituents and initially screened their efficiencies as racemization catalysts for (*S*)-1-phenylethanol.[8] In this series of complexes, enhanced racemization performance (albeit clearly inferior to that of **1**) was observed with the benzoyloxy-substituted catalyst **4a**, containing a pendant aromatic phenyl ring, when compared with its 1-adamantyl-substituted analogue **4b** (Figure 1). This led us to investigate further the pendant aromatic substituent effects in

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Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

DKR and to prepare a pentabenzylcyclopentadienyl analogue of **1**, namely the dicarbonylchlororuthenium complex **5b** (Figure 1), the hydride analogue **5a** of which has been described earlier in the context of alcohol dihydroxylation.[9] In comparison to C_5Ph_5H, the high-yield preparation of C_5Bn_5H is both seemingly simple and cost-efficient, *even on a large scale*, consisting of the reaction of dicyclopentadiene with sodium benzylate in BnOH.[10] The molecular structure of **5b**, determined in the present study (Figure 2), shows the expected η^5-bonding of the ruthenium atom also found in the closely analogous half-sandwich pentabenzylcyclopentadienyl complexes $C_5Bn_5M(CO)_3OTf$ (M = Mo, W)[11] and $C_5Bn_5Co(CO)_2$,[12] being in all essential structural features also similar to complex **1**.[5]

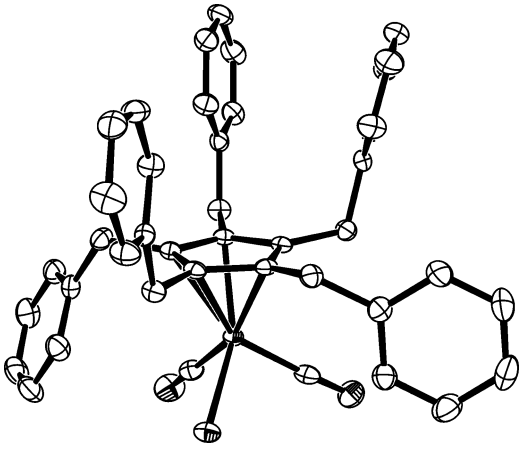
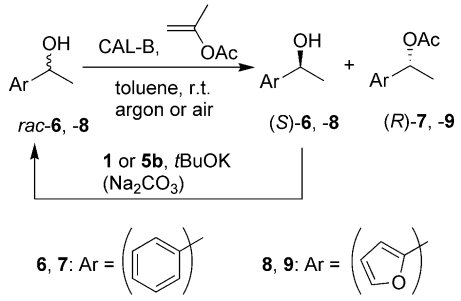


Figure 2. X-ray structure of **5b**. Hydrogen atoms are omitted for clarity. Ellipsoids are drawn at 50% probability level.

Complex **5b** was first evaluated as a catalyst for racemization of (*S*)-1-phenylethanol [(*S*)-**6**] (Scheme 1) and the results compared with those obtained with **1** under identical conditions. Under argon with 0.2 mol-% catalyst loading, both catalysts **5b** and **1** show similar initial reaction rates. However, at 50% *ee* level, the activity of **1** decays by decomposition, whereas **5b** remains effective (Figure 3). At 1 mol-% concentration under argon, both **5b** and **1** result in complete racemization within minutes, displaying activities too high to be measured accurately. In air, at 1 mol-% concentration, complex **5b** shows a considerably better activity than catalyst **1** providing, after 1 min, higher conversion than **1** after 5 min (Figure 4).

For further investigating the effect of benzyl substituents in racemization catalysts, the monobenzyl-substituted analogue of **1**, complex **5c**, was prepared by reaction of deprotonated C_5Ph_4BnH with $[Ru(CO)_3Cl_2]_2$. The monobenzyl-substituted ligand precursor was prepared in a manner similar to that utilized earlier for the C_5Ph_5H analogue.[5] Also the structure of **5c** was confirmed by X-ray analysis (Figure 5)[13] to have essential features analogous to those of **1**[5] and **5b**. The racemization activity of **5c** in air is similar to that of **1** (Figure 4) indicating that, for improved performance, the cooperative action of several pendant substituents, as in **5b**, would be required for gaining benefits in catalyst activity and stability.



Scheme 1. DKR of *rac*-**6** and *rac*-**8** with **1** and **5b**.

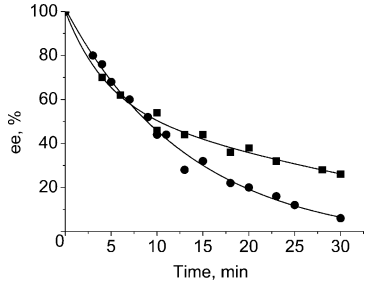


Figure 3. Racemization of (*S*)-**6** by complexes **1** (■) and **5b** (●) (0.2 mol-%) under argon.

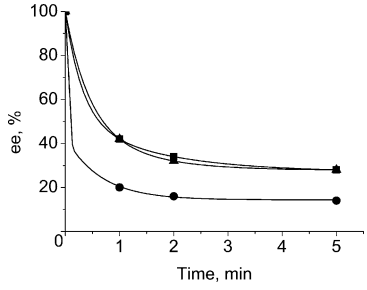


Figure 4. Racemization of (*S*)-**6** by complexes **1** (■), **5b** (●) and **5c** (▲) (1 mol-%) in air.

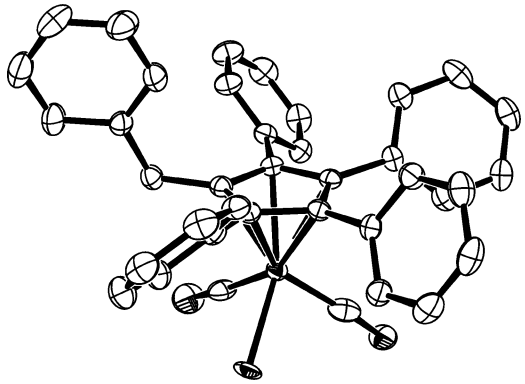


Figure 5. X-ray structure of **5c**. Hydrogen atoms are omitted for clarity. Ellipsoids are drawn at 50% probability level.

Encouraged by the racemization results obtained with **5b**, we next investigated this catalyst vs. **1** in combination with *Candida antarctica* lipase B (Novozym® 435, CAL-B on lipophilic PMA carrier) for the dynamic kinetic resolution of

rac-**6** and *rac*-**8** (Scheme 1). The substrates were selected on the basis that their DKR has been thoroughly studied earlier by Bäckvall.[5] The conventional kinetic resolution of *rac*-**6** and *rac*-**8** in dry toluene in the presence of CAL-B (3 mg mL^{-1}) and isopropenyl acetate (1.5 equiv.) is fast and highly enantioselective (enantiomer ratio $E >> 200$) to afford the enantiopure resolution products (*S*)-**6** and (*R*)-**7**, and (*S*)-**8** and (*R*)-**9**, respectively, at 50% conversion (Table 1). In addition to fast enantioselective acylation, (*S*)-**6** and (*S*)-**8** were totally racemized within 2 min by using **5b** (1 mol-% loading) in toluene under argon. Accordingly, *rac*-**6** and *rac*-**8** should be well suited as model substrates for DKR in the present study. The DKR results obtained with catalysts **5b** and **1** are collected in Table 2.

Table 1. KR of *rac*-**6** and *rac*-**8** with isopropenyl acetate (1.5 equiv.) and CAL-B (3 mg mL^{-1}) in toluene (1 mL) at 23 °C.

Entry	Substrate ([M])	Time [h]	Conversion [%]	*ee*[(*S*)-**6**/(*S*)-**8**] (%)	*ee*[(*R*)-**7**/(*R*)-**9**] (%)
1	**6** (0.2)	3	50	>99	>99
2	**6** (0.5)	4	50	98	>99
3	**8** (0.2)	1	50	98	98
4	**8** (0.5)	1.5	50	98	99

Table 2. DKR of *rac*-**6** and *rac*-**8** with isopropenyl acetate (1.5 equiv.) and CAL-B preparation (3 mg mL^{-1}) in toluene (1 mL) in the presence of **1** and **5b**, *t*BuOK and Na_2CO_3 at 23 °C. Conditions: 0.5 M substrate, 4 mol-% of **1** or **5b** and 5 mol-% of *t*BuOK; 0.2 M substrate, 10 mol-% of **1** or **5b** and 12.5 mol-% of *t*BuOK.

Entry	Substrate ([M])	Catalyst	Time [h]	Yield[d] [%]	*ee*[(*R*)-**7**/(*R*)-**9**] [%]
1	**6** (0.2)	**1**[a]	3/24	55/71	>99/>99
2	**6** (0.5)	**1**[a]	3/24	48/84	>99/>99
3	**6** (0.5)	**1** (air)[a]	24	54	99
4	**6** (0.5)	**1**[b]	3/7/24	51/59/88	>99/>99/>99
5	**6** (0.2)	**5b**[a]	3/7/24	79/84/72	>99/>99/99
6	**6** (0.5)	**5b**[a]	3/24	56/84	>99/>99
7	**6** (0.5)	**5b** (air)[a]	24	53	>99
8	**6** (0.2)	**5b**[b]	4/16/24	71/80/73	98/98/97
9	**6** (0.5)	**5b**[b]	3/7/24	69/85/94	>99/>99/>99
10	**6** (0.5)	**5b**[c]	3/7/24	63/71/89	99/99/99
11	**8** (0.5)	**1**[b]	3/7/24	50/62/89	98/96/94
12	**8** (0.2)	**5b**[b]	3/7/24	69/81/50	98/97/94
13	**8** (0.5)	**5b**[b]	3/7/24	64/81/90	98/98/97

[a] 0.5 mmol Na_2CO_3. [b] 1.5 mmol Na_2CO_3. [c] *t*BuOK (1 M)/THF (5 mol-%). [d] By chiral GC.

It is well known that, even under dry reaction conditions, the residual water in enzyme preparation always results in some hydrolysis of the activated acyl donors (here isopropenyl acetate).[14,15] Whereas in conventional KR this usually can be considered as a harmless side reaction, in DKR the Ru catalyst present may be unstable towards the acid formed. Enzymatic hydrolysis of the acylated alcohol products (*R*)-**7** and (*R*)-**9** may also take place to some extent, especially at high conversions.

Due to the instability of ruthenium catalysts in the presence of acids, an effective racemization of (*S*)-**6** and (*S*)-**8** in DKR requires that the acetic acid released is neutralized in situ. Accordingly, higher amounts of Na_2CO_3 were observed to afford somewhat higher conversions (Table 2, Entries 2 vs. 4 and 6 vs. 9). Under optimized DKR conditions for *rac*-**6** and *rac*-**8** using 4 mol-% Ru loading, **5b** is more stable than **1**, showing considerably higher activity. In 24 h, both catalysts finally led to 90–95% formation of the acetates (*R*)-**7** and (*R*)-**9**, respectively. By performing the DKR on a preparative scale with 2.49 mmol of *rac*-**6**, 2.11 mmol (85%, *ee* = 99%) of (*R*)-**7** was separated by column chromatography, in accordance with the 98% yield in the reaction mixture. During the DKR, the corresponding ketones are produced from the alcohols **6** and **8** in minimal amounts (2–4%) only.

The present study indicates that argon is essential for successful DKR with both **1** and **5b** as racemization catalysts. In air, the yields of enantiopure (*R*)-**7** remain at the level of conventional kinetic resolution (Entries 3 and 7).

Conclusions

We have demonstrated that complex **5b** shows high stability in comparison with the well-known and widely used Bäckvall catalyst **1**, allowing highly effective DKR of the secondary alcohols *rac*-**6** and *rac*-**8**. Further studies on the substrate scope are currently in progress. The two secondary alcohols investigated in the present study were transformed into their corresponding (*R*)-acetates in *ee* ≥ 97% at 90–95% yield. The enhanced stability of the pentabenzylcyclopentadienyl complex **5b** as compared to its pentaphenylcyclopentadienyl analogue **1** may be related to the better shielding of the metal center towards hydrolysis, thus hindering catalyst decomposition. Finally, the ease of preparation of **5b** and its promising performance may prove it as a viable substitute for **1** as a racemization catalyst for future DKR applications.

Experimental Section

General Remarks and Crystallography: All manipulations with air- and moisture-sensitive compounds were performed under argon by using standard Schlenk techniques. Solvents were purchased from standard vendors and dried by standard procedures (THF, toluene: redistilled from Na/benzophenone ketyl; DCM: redistilled from calcium hydride). NMR spectra were recorded with a Bruker Avance 600 MHz spectrometer. Unresolved signals are denoted as "ur". Chiral GC analysis was performed with a gas chromatograph equipped with a Varian capillary column CP7502 (racemization) or on a Chromapack CP-Chirasil-Dex CB column (DKR). (*S*)-1-Phenylethanol was obtained by enzymatic kinetic resolution of the racemate and purified by column chromatography. Commercially available (*S*)-1-phenylethanol (Aldrich, 97%) gives unreproducible results. Likewise, potassium *tert*-butoxide, required for activation of the racemization catalyst, should be freshly sublimated in order to obtain reproducible results. Racemic 1-phenylethanol was obtained from Fluka, tetraphenylcyclopentadienone and 1-(2-furyl)-ethanol were obtained from Aldrich. CAL-B was purchased from Novozymes. Pentabenzylcyclopentadiene was prepared by a method described in the literature.[10] CCDC-713844 (**5b**) and -713845 (**5c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Dicarbonylchloro(pentabenzylcyclopentadienyl)ruthenium (5b): Complex **5b** was prepared by two routes: Deprotonation of pentabenzylcyclopentadiene with *n*BuLi followed by reaction with $[Ru(CO)_3Cl_2]_2$ provided low yields only (for details, see Supporting Information). Much better results were obtained by a one-pot chlorination of the corresponding hydride **5a**, prepared in a manner similar to the synthesis of dicarbonylchloro(pentaphenylcyclopentadienyl)ruthenium (**1**). Thus, a mixture of C_5Bn_5H (310 mg, 0.6 mmol), $Ru_3(CO)_{12}$ (128 mg, 0.2 mol), decane (6 mL) and toluene (3 mL) were heated at 160 °C in a closed vessel for 72 h. The vessel was cooled to room temp., opened, chloroform (1 mL) was added and the heating continued at 150 °C for 2 h. After cooling to room temp., the mixture was concentrated in vacuo and the residue purified by column chromatography to provide 225 mg (53%) of **5b** as a yellow microcrystalline solid. ^{1}H NMR (600.13 MHz, $CDCl_3$, 25 °C): δ = 3.57 (s, 10 H, CH_2), 6.88 (ur, 10 H, *m*-H), 7.12–7.13 (m, 15 H, *o*- and *p*-H) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 30.72 (CH_2), 105.26 (Cp ring), 126.72 (*o*-C), 128.47 (*p*-C), 128.57 (*m*-C), 137.93 (*i*-C), 197.10 (C=O) ppm. MS: exact mass calcd. for $C_{42}H_{35}{}^{102}Ru^{35}ClO_2$(+Na) 731.1267, found 731.1271; exact mass calcd. for $C_{42}H_{35}{}^{102}Ru^{35}ClO_2$(+K) 747.1006, found 747.0970; exact mass calcd. for $C_{42}H_{35}{}^{102}Ru^{35}ClO_2$(+Na/CO) 703.1318, found 703.1310; exact mass calcd. for $C_{42}H_{35}{}^{102}Ru^{35}ClO_2$(–Cl) 673.1681, found 673.1643.

Dicarbonylchloro(tetraphenylbenzylcyclopentadienyl)ruthenium (5c): *n*BuLi (0.21 mL of a 1.6 M solution in hexane) was added to a solution of C_5Ph_4BnH (153 mg, 0.33 mmol) (for preparation, see Supporting Information) in THF (2 mL) at –60 °C. The mixture was stirred for 20 min followed by warming to room temp. Next, a solution of $[Ru(CO)_3Cl_2]_2$ (102 mg, 0.2 mmol) in THF (1 mL) was added. The mixture was stirred at room temp. for 2 h, concentrated, and purified by column chromatography (hexane/DCM, 3:1→1:1) to provide 42 mg (20%) of **5c** as a yellow crystalline solid. ^{1}H NMR (600.13 MHz, $CDCl_3$, 25 °C): δ = 3.66 (s, 2 H, CH_2), 6.60 (d, ^3J = 7.7 Hz, 2 H, *o*-Bn) 7.00 (d, ^3J = 7.7 Hz, 4 H, *o*-Ph), 7.04–7.10 (m, 7 H, *m*-Ph, *m*-Bn, *p*-Bn), 7.15 (ur, 2 H, *p*-Ph), 7.22–7.28 (m, 6 H, *m*-Ph, *p*-Ph), 7.30 (d, ^3J = 7.7 Hz, 4 H, *o*-Ph) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 31.25 (CH_2), 102.30, 106.59, 117.21, 126.40 (*p*-Bn), 127.79 (*o*-Ph), 128.24 (*m*-Bn), 128.36 (*m*-Ph), 128.51 (*p*-Ph), 128.54 (*p*-Ph), 128.59 (*o*-Bn), 129.39, 129.75, 131.97 (*m*-Ph), 132.53 (*o*-Ph), 137.92, 196.98 (C=O) ppm. MS: exact mass calcd. for $C_{38}H_{27}{}^{102}Ru^{35}ClO_2$(+K) 691.0380, found 691.0369.

Procedure for the Racemization of (*S*)-1-Phenylethanol: A solution of *t*BuOK in THF (1 mL of 0.012 M, 12 μmol, 3 mol-%) was added to a solution of **1** or **5b** (4 μmol, 1 mol-%) in toluene (2 mL). The reaction mixture was stirred for 3 min, followed by addition of (*S*)-1-phenylethanol (56 mg, 0.4 mmol) (Scheme S2, see Supporting Information). Samples from the reaction mixture were acylated with propionic anhydride in pyridine in the presence of DMAP. Derivatization stops the racemization reaction and enhances the resolution of peaks in the GC.

Kinetic Resolution (KR) of *rac*-6 and *rac*-8: In a typical procedure, the racemic substrate (0.2 M or 0.5 M) in dry toluene (1 mL) and the CAL-B preparation (3 mg) were added in a vial. The addition of isopropenyl acetate (0.3 M or 0.75 M) initialized the acylation. The reactions were monitored by taking samples at intervals, filtering and analyzing them by GC after derivatization with propionic anhydride in the presence of pyridine and DMAP (1%).

Dynamic Kinetic Resolution (DKR) of *rac*-6 and *rac*-8: In a typical procedure, dry toluene (0.6 mL) was added to a mixture of *t*BuOK (12.5 or 5 mol-%), Ru-catalyst **5b** or **1** (10 or 4 mol-%), CAL-B (3 mg) and anhydrous Na_2CO_3 (0.5 or 1.5 mmol) under argon in a Schlenk tube. The racemic substrate (0.201 mmol or 0.498 mmol) in toluene (0.2 mL) was added with a syringe after 6 min; 4 min later, isopropenyl acetate (0.30 mmol or 0.75 mmol) in toluene (0.2 mL) was added to initialize the acylation. The reactions were monitored by taking samples at intervals, filtering and analyzing them by GC after derivatization with propionic anhydride in the presence of pyridine and DMAP (1%). Dodecane or undecane was used as a standard for quantitative analyses.

Supporting Information (see footnote on the first page of this article): Additional experimental details, NMR spectra and selected crystallographic data for complexes **5b** and **5c**.

Acknowledgments

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[13] The molecular structure of **5c** shows a disorder, in which the Cl ligand and one of the two CO ligands have two orientations in a 1:1 ratio. In Figure 5, only one orientation of the disordered ligands is shown. For a more detailed illustration, see Supporting Information.
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