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Palladacycle-Catalyzed Highly Efficient Kinetic Resolution of 1-Hydroxy-2-aryl-1,2-dihydronaphthalenes via Dehydration Reaction

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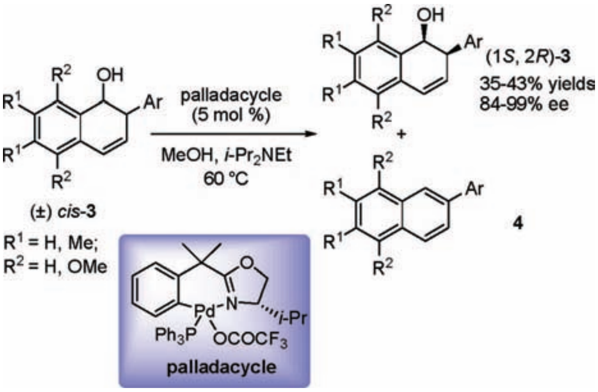
ABSTRACT



Palladacycles showed their high efficiency in the kinetic resolution of 1-hydroxy-2-aryl-1,2-dihydronaphthalenes via dehydration, providing optically active products in high yields and high ee with an *S* factor up to 26. The superiority of a benzylic-substituted palladacycle in asymmetric induction was also demonstrated.

Palladacycles as readily available, air- and moisture-tolerant, highly active catalysts have attracted more attention over the years.[1] Many different types of palladacycles have been synthesized and have shown their usefulness in a variety of reactions. However, in many cases, palladacycles serve as catalyst precursors only,[1d] and asymmetric catalysis has only been realized in a few examples,[2,3] even though chiral palladacycles were used.[4,5] A great challenge still remains regarding the applications of palladacycles as efficient catalysts in asymmetric catalysis.

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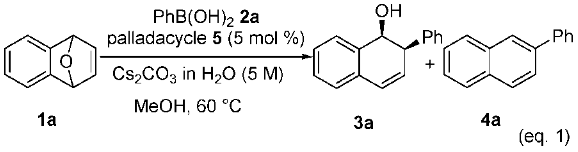
On the other hand, the kinetic resolution is a powerful tool in gaining optically active molecules from racemic starting materials.[6,7] Enormous advances, especially in the use of chiral transition-metal complexes as catalysts, have been made over the years. High efficiency regarding ee value and yield of one enantiomer as product has been realized in many reactions using a kinetic resolution strategy. Ring-opening reactions of epoxides[7a,b,r] and aziridines,[7c] epoxidation and dihydroxylation of alkenes,[7d−f] acylation,[7g] oxidative transfer hydrogenation,[7h] Baeyer−Villiger reaction,[7i] hydrogenation of alkenes and imines,[7j,k] ring-closing metathesis,[7l] Pd-catalyzed allylic alkylation,[7m,n] cyclopropanation using diazoesters,[7o] alcoholysis of anhydrides,[7p] 1,4-conjugated addition,[7q] and cycloaddition reaction[7r] are among the most general types of reactions used in kinetic resolution. However, few reports achieved kinetic resolution via dehydration reaction of alcohols though it is a very common type of reaction in organic synthesis.[8] Furthermore, there are no reports of using palladacycles as catalysts in kinetic resolution.

During our program aimed at the applications of palladacycles in organic synthesis, we have reported highly catalytic activity of chiral benzylic-substituted ligands,[5] and the catalytic effciency of related palladacycles has also been revealed in hydrophenylation and ring-opening reactions of oxa-bicyclic alkenes with $ArCH_2ZnBr$.[5d] In the latter case, the palladacycle should be the real catalyst,[5d] though the products were racemic. However, moderate ee for the ring-opening product was afforded when phenylboronic acid was the reagent using palladacycle **5** as catalyst.[5e] In addition, we also observed kinetic resolution phenomenon. In this paper, we report the kinetic resolution of 1-hydroxy-2-aryl-1,2-dihydronaphthalenes via dehydration catalyzed by palladacycle with high efficiency, providing the products in high ee.

First we investigated the reaction of oxabicyclic alkene **1a** with $PhB(OH)_2$ **2a** using palladacycle **5** as catalyst (eq 1). It was found that the ee value of the product varied depending on the reaction time. Ring-opening product **3a** was provided in 23% yield and in 33% ee when the reaction ran for 40 min. The yield increased to 98% while the ee value remained 33% if the reaction time was 1.5 h. However, the ee value increased to 41% but the yield decreased to 86% and naphthylene **4a** was separated in 12% yield if the reaction time was prolonged to 2 h. When the reaction ran for 3 h, **3a** was afforded in 52% yield and in 84% ee accompanied by 40% yield of **4a**. Ring-opening product **3a** in 97% ee was obtained if the reaction time was 4 h, but the yield was reduced to 45% while **4a** was provided in 48% yield. No **3a** was found, and only **4a** was separated in 90% yield if the reaction ran for 12 h.



Based upon the above results, we deduced that there should be a kinetic resolution process for **3a**. The fact that the reaction of racemic **3a** with 1.0 equiv of Cs_2CO_3 in the presence of 5 mol % of palladacycle **5** in MeOH provided optically active **3a** in 19% yield and in 11% ee accompanied by **4a** in 67% yield confirmed it. Control experiments revealed that strong bases only, such as KOH, Cs_2CO_3, K_2CO_3, and KF, caused dehydration of **3a** to give rise to **4a** in almost quantitative yields, while no reaction took place if palladacycle **5** or a weak base, such as Et_3N, pyridine, and *i*-Pr_2NEt, was used solely.

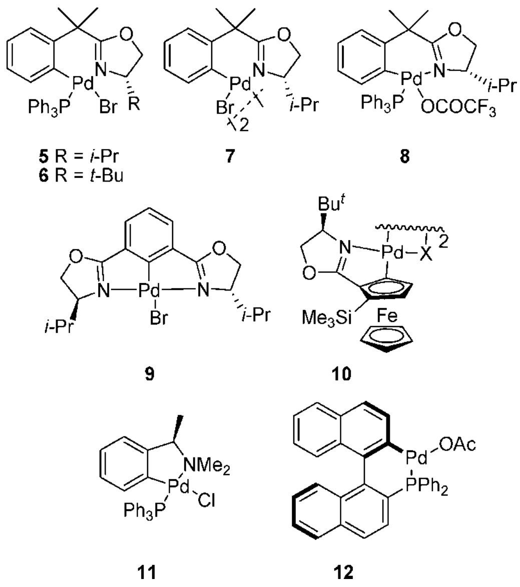


Figure 1. Structure of palladacycles.

Table 1. Optimization of Kinetic Resolution of 1,2-*cis*-**3a** Catalyzed by Palladacycles[a]

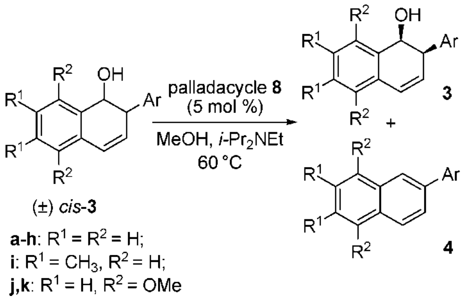
entry	palladacycle	base	product, **3a** yield (%)[b]	product, **3a** ee (%)[c]	**4a** yield (%)[b]
1	**5**	Et_3N	31	94	62
2	**6**	Et_3N	52	5	47
3[d]	**7**	Et_3N	18	99	70
4	**8**	Et_3N	37	94	56
5	**9**	Et_3N	90	0	4
6	**10**	Et_3N	40	88	55
7	**11**	Et_3N	46	14	54
8	**12**	Et_3N	38	5	58
9	**8**	*i*-Pr_2NEt	42	98	56
10	**8**	DABCO	26	98	72
11	**8**	pyridine	0		95

[a] Molar ratio of **3a**/base/palladacycle = 1.0:0.5:0.05, reaction time: 4 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Run for 10 h.

Investigations on the influence of palladacycles and base on the reaction (Table 1) showed that the structure of the palladacycle has a great impact on the efficiency of resolution. Among palladacycles we screened (Figure 1), benzylic-substituted palladacycles **5** and **8** demonstrated their superiority (entries 1 and 4), providing optically active **3a** in 31% yield with 94% ee accompanied by 62% yield of **4a** and 37% yield of **3a** with 94% ee and 56% of **4a**, respectively. However, palladacycle **6** with a tertiary butyl group as substituent on the oxazoline ring gave only 5% ee (entry 2), which reflects the relationship between the substituents at benzylic and oxazoline ring.[5b] Excellent ee was obtained using palladacycle dimer **7**, but the yield of **3a** was only 18% (entry 3). Lower ee was given using pincer complex **9** (entry 5) and palladacycle **11** derived from chiral benzylamine (entry 7). Dihydronaphthalene **3a** was recovered in 40% yield with 88% ee using Overman's palladacycle **10** (entry 6). The P-containing palladacycle **12** gave **3a** in 38% yield with only 5% ee (entry 8). The properties of the base also influence the reaction. A better result was afforded when *i*-Pr$_2$NEt was used as the base, providing **3a** in 42% yield with 98% ee (entry 9 vs entry 4). Stronger base DABCO gave a lower yield of **3a**, though with high ee (entry 10), and weak base pyridine did not allow the reaction to proceed (entry 11). A screen of common solvents showed that MeOH should be the choice.

The substrate scope of the reaction was evaluated using optimized conditions (Table 2). Using palladacycle **8** as catalyst and *i*-Pr$_2$NEt as base in MeOH at 60 °C, *all-cis*-2-aryl-1,2-dihydronaphthalen-1-ols **3** were suitable substrates to provide optically active **3** with the yields ranging from 35 to 43% and with high ee value ranging from 84−99%. The reactions showed high efficiency, and the *S* factor was between 9 and 26.[9] Reaction of **3** with phenyl and naphthyl substituents afforded enantiomeric enriched products **3** with higher *S* values (entries 1 and 7). The presence of a substituent at the meta and para positions of the phenyl ring, whatever its electronic property, has no great influence on the *S* value. All reactions of **3** with 3- and 4-substituted phenyl ring gave optically active **3** with similar *S* values (entries 2−5). However, dihydronaphthalene **3f** with a substituent at the ortho position of 2-aryl gave optically active product **3f** with a slightly higher *S* value (entry 6). Substituents on the dihydronaphthalene ring did not affect the efficiency of the reaction. Substituted **3i−k** afforded corresponding products with high *S* values (entries 9−11). It is worth noting that dihydronaphthalene **3h** with PhCH═CH as substituent was also a suitable substrate, giving product with a lower *S* value (entry 8). The absolute configuration of **3a** was determined as (1*S*,2*R*) by comparing its optical rotation and HPLC trace with that reported by Lautens.[10]

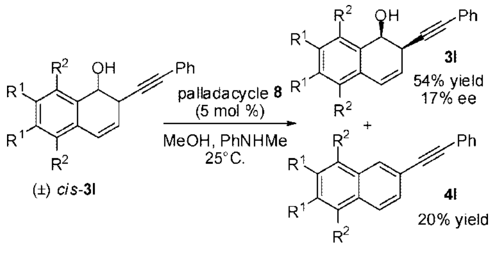
Table 2. Kinetic Resolution of Various Substrates[a]



entry	3,Ar	product, 3 yield %[b]	product, 3 ee %[c]	product, 3 S[f]	4 yield %[b]
1	**a**, Ph	42	98	26	56
2	**b**, 3-ClC$_6$H$_4$	38	91	15	59
3[d]	**c**, 3-MeOC$_6$H$_4$	41	86	12	56
4	**d**, 4-MeOC$_6$H$_4$	35	99	16	58
5	**e**, 4-CF$_3$C$_6$H$_4$	43	86	13	55
6[e]	**f**, 2-MeC$_6$H$_4$	38	99	20	58
7[e]	**g**, 1-naphthyl	40	99	24	55
8	**h**, PhCH=CH	40	84	9	58
9[d]	**i**, phenyl	41	92	14	57
10	**j**, phenyl	38	97	16	60
11	**k**, 4-MeOC$_6$H$_4$	38	99	20	47

[a] Reaction conditions: **3**/^{i}Pr$_2$NEt/**8** = 1.0:0.5:0.05. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Et$_3$N as base. [e] Run for 10 h. [f] Calculated by the equation: $\ln[(1 - C)(1 - \mathrm{ee})]/\ln[(1 - C)(1 + \mathrm{ee})]$.[6a]

The reaction of phenylethynyl-substituted dihydronaphthalene **3l** also provided optically active **3l** in 54% yield by using palladecycle **8** as catalyst and PhNHMe as base. Though the ee value was only 17%, it represents the first example of asymmetric synthesis of phenylacetyl-substituted dihydronaphthalene (eq 2).[11] Again, the choice of base is important, and the reaction provided a complex mixture if stronger base Et$_3$N or *i*-Pr$_2$NEt was used.



(eq 2)

No dehydration product was detected when racemic *trans*-**3a**[12] was treated under the optimized conditions, which suggests that the dehydration might proceed via an E2 elimination mechanism.[13]

In conclusion, highly efficient kinetic resolution via dehydration using chiral palladacycles was realized, which represents an alternative method for kinetic resolution and

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demonstrates the superiority of benzylic substituted palladacycle **8** in asymmetric induction. These results also provide a useful index for designing new catalyst systems. Investigations on the detailed mechanism and applications of palladacycles in asymmetric catalysis as well as the kinetic resolution via dehydration are in progress.

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Supporting Information Available: General procedure for palladacycle-catalyzed kinetic resolution of **3** and spectra data for **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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