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Base-Free Conditions for Rhodium-Catalyzed Asymmetric Arylation To Produce Stereochemically Labile α-Aryl Ketones

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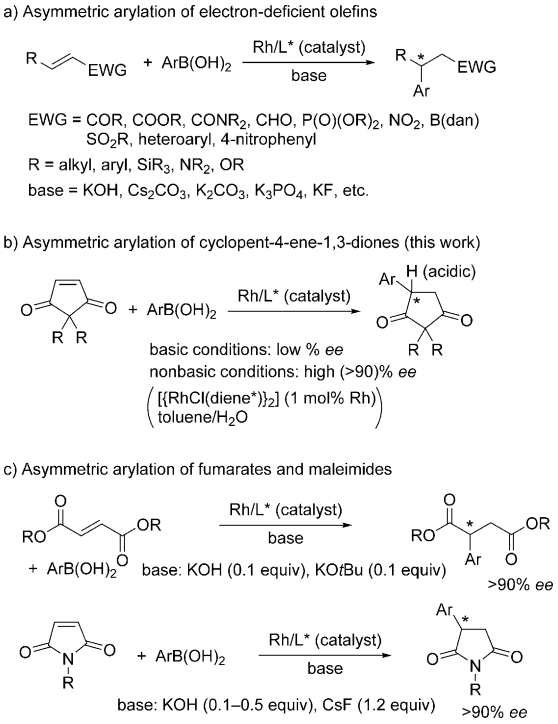
Abstract: *The asymmetric arylation of 2,2-dialkyl cyclopent-4-ene-1,3-diones with aryl boronic acids was found to be efficiently catalyzed by a chiral diene–rhodium μ-chloro dimer, [{RhCl((R)-diene*)}$_2$], in the absence of bases in toluene/H_2O to give 2,2-dialkyl 4-aryl cyclopentane-1,3-diones in high yields with high enantioselectivity. Such compounds can not be obtained with high enantiomeric purity under the standard basic conditions used for rhodium-catalyzed asymmetric arylation because the α-aryl ketone products undergo racemization under the basic conditions.*

Asymmetric conjugate arylation of electron-deficient olefins is one of the most efficient methods of constructing stereogenic carbon centers at the benzylic position,[1] and the rhodium-catalyzed asymmetric arylation is currently attracting considerable attention owing to its high enantioselectivity and high reliability as well as the advantages of using organoboron reagents as nucleophiles.[2] The olefinic substrates used for the rhodium-catalyzed asymmetric arylation have the general structure RCH=CH(EWG), in which EWG stands for an electron-withdrawing group (Scheme 1a). The substituent R, which is connected to the stereogenic carbon center of the products, is an alkyl or aryl group in most cases;[2] heteroatom substitution, whereby R is a silyl,[3] amino,[4] or alkoxy[5] group, has also been reported. Rhodium-catalyzed conjugate arylation has generally been performed under basic conditions, typically with KOH (0.1–1.0 equiv) as a base, which has been proposed to generate a hydroxo–rhodium species and/or a reactive borate species.[2] Although cyclopent-4-ene-1,3-diones have recently been studied as substrates for asymmetric desymmetrization,[6] to the best of our knowledge, their rhodium-catalyzed asymmetric arylation has not been reported, probably owing to the stereochemical instability of the arylation products containing stereogenic carbon centers substituted with aryl and carbonyl groups. Because of the acidic hydrogen atom, racemization of the 4-arylated products readily takes place under the basic conditions used for rhodium-catalyzed asymmetric arylation (see below). Herein we report that the asymmetric arylation of cyclopent-4-ene-1,3-diones with high enantioselectivity (mostly ≥98% *ee*) is possible with a chiral diene–rhodium μ-chloro dimer catalyst, [{RhCl((*R*)-diene*)}$_2$], under non-basic conditions (Scheme 1b). As related substrates giving products with a stereogenic center at the α-position to a carbonyl group, fumarates[7] and maleimides[8] have been reported to be applicable to the rhodium-catalyzed arylation under standard basic conditions (Scheme 1c). Products with high *ee* values are obtained without difficulty because the ester and imide products are more stable against racemization under basic conditions.



Scheme 1. Rhodium-catalyzed asymmetric arylation of electron-deficient olefins. dan = 1,8-naphthalenediaminato.

Table 1 summarizes the results obtained for the rhodium-catalyzed asymmetric addition of $PhB(OH)_2$ (**2a**) to 2,2-diethylcyclopent-4-ene-1,3-dione (**1a**). In the first set of experiments, a rhodium complex coordinated with (*R*)-diene*,[9,10] which is readily accessible from (−)-α-phellandrene and is one of the most enantioselective chiral diene ligands for the asymmetric conjugate arylation, was used as a catalyst. The reaction in the presence of KOH (20 mol%) in dioxane/H_2O (10:1) at 50 °C, which are commonly used reaction conditions for the addition to maleimides and other electron-deficient olefins,[2,8] proceeded well to give the

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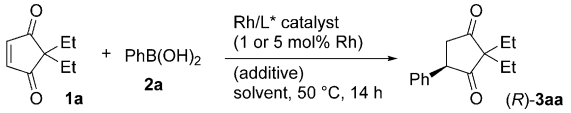
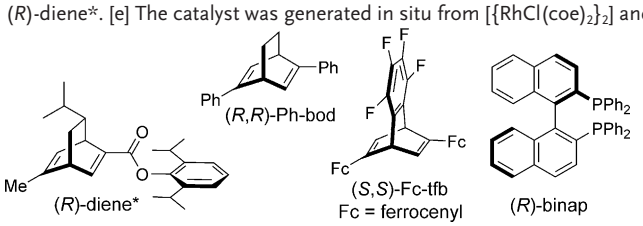
Table 1: Rhodium-catalyzed asymmetric addition of $PhB(OH)_2$ (**2a**) to 2,2-diethylcyclopent-4-ene-1,3-dione (**1a**).[a]



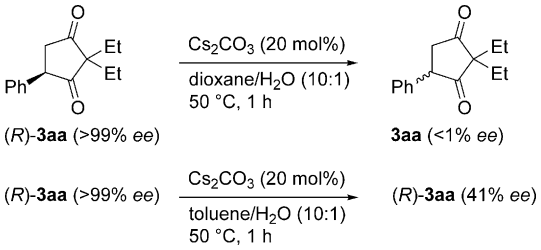
Entry	Rh catalyst (mol% Rh)	Additive	Solvent [mL]	Yield [%][b]	*ee* [%][c]
1	$[\{RhCl((R)\text{-diene*})\}_2]$ (5)	KOH (20 mol%)	dioxane/H_2O (1.0/0.1)	93	<1
2	$[\{RhCl((R)\text{-diene*})\}_2]$ (5)	Cs_2CO_3 (20 mol%)	dioxane/H_2O (1.0/0.1)	96	<1
3	$[\{Rh(OH)((R)\text{-diene*})\}_2]$ (5)[d]	–	dioxane/H_2O (1.0/0.1)	93	35
4	$[\{RhCl((R)\text{-diene*})\}_2]$ (5)	–	dioxane/H_2O (1.0/0.1)	14	91
5	$[\{RhCl((R)\text{-diene*})\}_2]$ (5)	–	toluene/H_2O (1.0/0.1)	85	>99
6	$[\{RhCl((R)\text{-diene*})\}_2]$ (1)	–	toluene/H_2O (1.0/0.1)	65	>99
7	$[\{RhCl((R)\text{-diene*})\}_2]$ (1)	–	toluene/H_2O (1.0/0.5)	91	>99
8	$[\{RhCl((R,R)\text{-Ph-bod})\}_2]$ (1)	–	toluene/H_2O (1.0/0.5)	70	99
9	$[\{RhCl((S,S)\text{-Fc-tfb})\}_2]$ (1)	–	toluene/H_2O (1.0/0.5)	38	94
10	$[\{RhCl((R)\text{-binap})\}_2]$ (1)[e]	–	toluene/H_2O (1.0/0.5)	9	96
11	$[\{RhCl((R)\text{-diene*})\}_2]$ (1)	KOH (4 mol%)	toluene/H_2O (1.0/0.5)	91	54
12	$[\{RhCl((R)\text{-diene*})\}_2]$ (1)	Cs_2CO_3 (20 mol%)	toluene/H_2O (1.0/0.5)	93	83

[a] Reaction conditions: **1a** (0.15 mmol), **2a** (0.30 mmol), Rh catalyst (1 or 5 mol% Rh), 50°C, 14 h. [b] Yield of **3aa** isolated by GPC. [c] The *ee* value was determined by HPLC analysis on a chiral-stationary-phase column. The absolute configuration (*R*) was determined by X-ray crystal-structure analysis of the related compound **3cb** (see Table 2). [d] The catalyst was generated in situ from $[\{Rh(OH)(coe)_2\}_2]$ and (*R*)-diene*. [e] The catalyst was generated in situ from $[\{RhCl(coe)_2\}_2]$ and (*R*)-binap. coe = cyclooctene.



phenylation product, 4-phenylcyclopentane-1,3-dione **3aa**, in 93% yield (Table 1, entry 1). However, unfortunately, **3aa** isolated by gel permeation chromatography (GPC) was racemic. Product **3aa** and some other 4-aryl cyclopentane-1,3-diones described herein should not be subjected to silica-gel chromatography because a considerable extent of racemization occurs on exposure to silica gel. Racemic **3aa** was also produced with Cs_2CO_3 in place of KOH (Table 1, entry 2). Less basic conditions with $[\{Rh(OH)((R)\text{-diene*})\}_2]$ as the catalyst without an additional base gave enantiomerically enriched **3aa**, although with only 35% *ee* (entry 3). We found that **3aa** was obtained with a high *ee* value of 91%, albeit in low (14%) yield, with $[\{RhCl((R)\text{-diene*})\}_2]$ as the catalyst in the absence of a base[11] (entry 4). It may be concluded that the low *ee* value of the product obtained under basic conditions is due to the racemization of **3aa**, originally formed with high enantioselectivity in the catalytic asymmetric hydrophenylation. We studied solvent effects on the catalytic activity and racemization, and found that a biphasic solvent system consisting of toluene and H_2O[12,13] greatly improved the catalytic activity and maintained the high original *ee* value of product. Thus, the reaction with $[\{RhCl((R)\text{-diene*})\}_2]$ (5 mol% Rh) in toluene/H_2O (10:1) gave the product **3aa** in 85% yield with >99% *ee* (Table 1, entry 5). The amount of catalyst was successfully reduced to 1 mol% by adding more water to the reaction system (entries 6 and 7). The best solvent system with 1 mol% of the Rh catalyst was a mixture of toluene and H_2O in a ratio of 10:5; under these conditions, **3aa** was obtained in 91% yield with >99% *ee* (Table 1, entry 7). Under the same conditions, the rhodium complexes with (*R*,*R*)-Ph-bod[14] and (*S*,*S*)-Fc-tfb[15] also catalyzed the phenylation reaction, but the yields were lower (entries 8 and 9). With (*R*)-binap,[16] the reaction was very slow (entry 10). Even in the toluene/H_2O (10:5) solvent system, the use of bases caused the racemization of **3aa**, although the racemization was much slower than in dioxane/H_2O (entries 11 and 12).

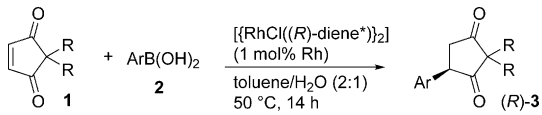
The product (*R*)-**3aa** (>99% *ee*) was treated with Cs_2CO_3 in dioxane/H_2O and toluene/H_2O under conditions similar to those for the rhodium-catalyzed asymmetric phenylation (Scheme 2). As expected, complete racemization was observed within 1 h in dioxane/H_2O. In toluene/H_2O, the racemization was much slower. The slow racemization in this biphasic system may be ascribed to the low concentration of the inorganic base in the toluene phase, which contains most of the organic product **3aa**.



Scheme 2. Racemization of **3aa** under basic conditions.

Under the optimal conditions found for the asymmetric phenylation of **1a** (Table 1, entry 7), reactions of two other cyclopent-4-ene-1,3-dione substrates and several aryl boronic acids were performed (Table 2). In reactions of **1a**, the enantiomeric purity of the products was very high (>99% *ee*) for all aryl boronic acids substituted with electron-withdrawing groups, which would promote the racemization, as well as those with electron-donating groups (Table 2, entries 2–6). The enantioselectivity in the reactions of 2,2-diphenyl substrate **1b** and spiro compound **1c** was lower than that for **1a**, but the products were still formed with over 90% *ee* (entries 7 and 8).

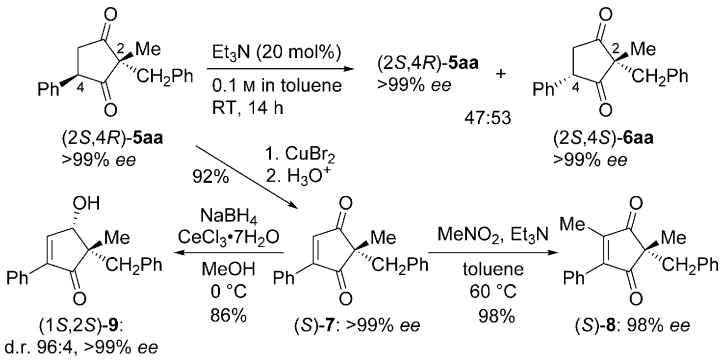
Table 2: Asymmetric arylation of 2,2-disubstituted cyclopent-4-ene-1,3-diones **1** with $ArB(OH)_2$ (**2**) catalyzed by $[\{RhCl((R)\text{-diene*})\}_2]$.[a]



Entry	R, R in **1**	Ar in **2**	**3**	Yield [%][b]	*ee* [%][c]
1	Et, Et (**1a**)	Ph (**2a**)	**3aa**	91	>99
2	Et, Et (**1a**)	4-MeC_6H_4 (**2b**)	**3ab**	98	>99
3	Et, Et (**1a**)	4-$MeOC_6H_4$ (**2c**)	**3ac**	94	>99
4	Et, Et (**1a**)	4-BrC_6H_4 (**2d**)	**3ad**	92	>99
5	Et, Et (**1a**)	4-$CF_3C_6H_4$ (**2e**)	**3ae**	92	>99
6	Et, Et (**1a**)	1-naphthyl (**2f**)	**3af**	93	>99
7	Ph, Ph (**1b**)	4-MeC_6H_4 (**2b**)	**3bb**	88	96
8	$(CH_2)_4$ (**1c**)	4-MeC_6H_4 (**2b**)	**3cb**	96	93

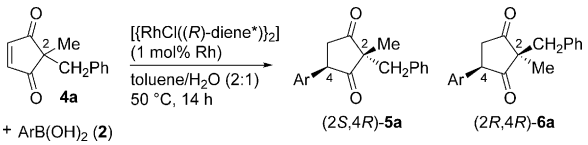
[a] Reaction conditions: **1** (0.15 mmol), **2** (0.30 mmol), $[\{RhCl((R)\text{-diene*})\}_2]$ (1 mol% Rh), toluene (1.0 mL), H_2O (0.5 mL). [b] Yield of **3** isolated by GPC. [c] The *ee* value was determined by HPLC analysis on chiral-stationary-phase columns. The absolute configuration (*R*) was determined by X-ray crystal-structure analysis of **3cb**.

The present catalytic system was applied to the asymmetric arylation of cyclopent-4-ene-1,3-diones with two different substituents at the 2-position to generate two stereogenic centers at the 2- and 4-positions (Table 3). The reaction of **4a**, in which the two substituents are methyl and benzyl, with $PhB(OH)_2$ (**2a**) in the presence of $[\{RhCl((R)\text{-diene*})\}_2]$ in a toluene/H_2O biphasic solvent system gave the diastereomeric phenylation products (2*S*,4*R*)-**5aa** and (2*R*,4*R*)-**6aa** in a ratio of 94:6 with ≥99 and 74% *ee*, respectively, in high yield (Table 3, entry 1).[17] The absolute configuration (2*S*) of **5aa** was determined by oxidation to the olefinic compound (*S*)-**7**[18] whose configuration was determined by X-ray crystal-structure analysis[19] (Scheme 3). The minor product **6aa** had the same configuration at the 4-position and the opposite configuration at the 2-position. The epimerization of (2*S*,4*R*)-**5aa** with Et_3N (Scheme 3), for which the equilibrated ratio of the diastereoisomers was around 1:1, gave (2*S*,4*S*)-**6aa**, which is the enantiomer of (2*R*,4*R*)-**6aa** formed as a minor diastereoisomer in the asymmetric reaction under the conditions in entry 1 of Table 3. The observed decrease in the **5aa**/**6aa** ratio and the concurrent decrease in their *ee* value under basic conditions (Table 3, entries 2 and 3) are well accounted for by epimerization at the 4-position of the diastereoisomers with opposite absolute configurations at the 2-position.



Scheme 3. Epimerization and transformation of (2*S*,4*R*)-**5aa**.

Table 3: Asymmetric arylation of 2-benzyl-2-methylcyclopent-4-ene-1,3-dione (**4a**) with $ArB(OH)_2$ (**2**) catalyzed by $[\{RhCl((R)\text{-diene*})\}_2]$.[a]

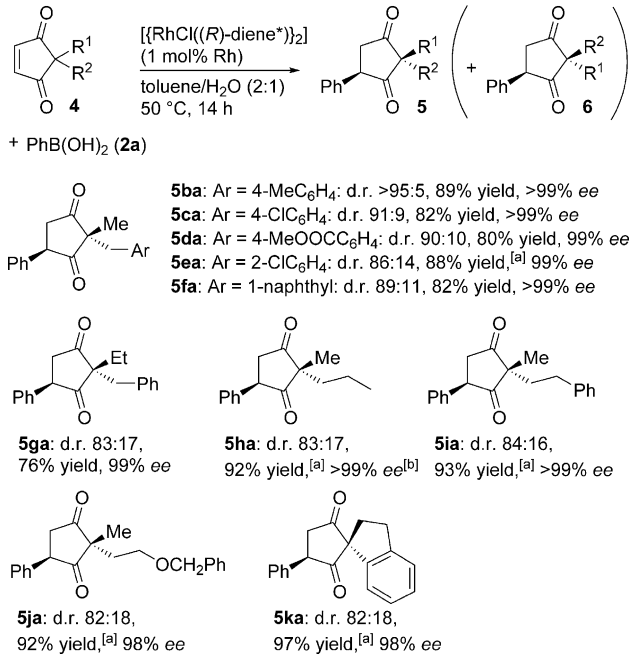


Entry	Ar in **2**	**5a**/**6a**	Yield [%][b]	*ee* [%][c]
1	Ph (**2a**)	94:6	87 (**5aa**)	>99[d]
2[e]	Ph (**2a**)	78:22	92[f] (**5aa**)	97[d]
3[g]	Ph (**2a**)	54:46	88[f] (**5aa**)	94[d]
4	4-MeC_6H_4 (**2b**)	94:6	89 (**5ab**)	>99
5	3-MeC_6H_4 (**2g**)	95:5	92 (**5ag**)	>99
6[h]	2-MeC_6H_4 (**2h**)	95:5	94 (**5ah**)	>99
7	4-$MeOC_6H_4$ (**2c**)	93:7	89 (**5ac**)	>99
8	3-$MeOC_6H_4$ (**2i**)	95:5	89 (**5ai**)	>99
9	4-$PhOC_6H_4$ (**2j**)	>95:5	89 (**5aj**)	>99
10	4-BrC_6H_4 (**2d**)	95:5	92 (**5ad**)	>99
11	4-$CF_3C_6H_4$ (**2e**)	94:6	91 (**5ae**)	>99
12	3-ClC_6H_4 (**2k**)	93:7	79 (**5ak**)	>99
13	3,5-$Me_2C_6H_3$ (**2l**)	93:7	90 (**5al**)	>99
14	3,4-$(OCH_2O)C_6H_3$ (**2m**)	94:6	86 (**5am**)	>99
15	1-naphthyl (**2f**)	94:6	92 (**5af**)	>99
16	2-naphthyl (**2n**)	90:10	84 (**5an**)	>99
17[h]	3-thienyl (**2o**)	95:5	87 (**5ao**)	>99

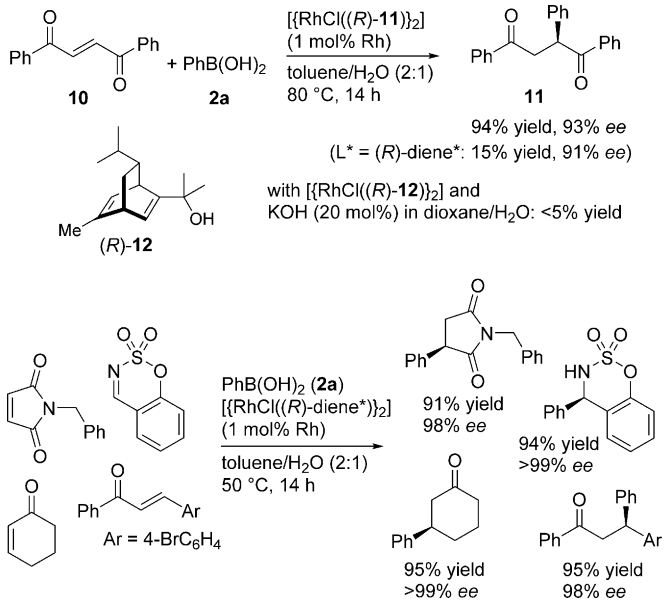
[a] Reaction conditions: **4a** (0.15 mmol), **2** (0.30 mmol), and $[RhCl((R)\text{-diene*})]_2$ (1 mol% Rh) in toluene (1.0 mL) and H_2O (0.5 mL). [b] Yield of isolated **5a**. [c] The *ee* values of **5a** were determined by HPLC analysis on chiral-stationary-phase columns. The absolute configuration of **5aa** was determined to be 2*S*,4*R* by X-ray crystal-structure analysis of (*S*)-**7** (see Scheme 3). [d] The ee values of **6aa** are 74% *ee* (2*R*,4*R*), 62% *ee* (2*S*,4*S*), and 90% *ee* (2*S*,4*S*) in entries 1, 2, and 3, respectively. [e] The catalyst was $[\{Rh(OH)((R)\text{-diene*})\}_2]$ (5 mol% Rh) generated in situ from $[\{Rh(OH)(coe)_2\}_2]$ and (*R*)-diene*. [f] Yield of a mixture of **5aa** and **6aa**. [g] The reaction was carried out with $[\{RhCl((R)\text{-diene*})\}_2]$ (5 mol% Rh) and KOH (20 mol%) in dioxane (1.0 mL) and H_2O (0.1 mL). [h] The reactions was carried out with $ArB(OH)_2$ (0.45 mmol) and $[\{RhCl((R)\text{-diene*})\}_2]$ (2 mol% Rh).

The corresponding arylation products **5ab**–**ao** were obtained from **4a** with high enantioselectivity (>99% *ee*) and diastereoselectivity (≥90:10) with various types of aryl boronic acids, including those with electron-withdrawing and electron-donating groups at *ortho*, *meta*, and *para* positions (Table 3, entries 4–17). Other diketones **4b**–**f** substituted with methyl and benzylic groups, **4g**–**j** with other alkyl groups, and the spiro compound **4k** were all found to be appropriate substrates for the asymmetric phenylation reaction. The corresponding products were obtained with high enantioselectivity (≥98% *ee*; Scheme 4).

Another substrate whose asymmetric arylation was made possible by the present conditions is 1,2-dibenzoylethene (**10**; Scheme 5). Under basic conditions with KOH (20 mol%) in dioxane/H_2O, the phenylation product **11** was not obtained because the decomposition of **10**[20] is faster than the asymmetric arylation. The reaction with $[\{RhCl((R)\text{-diene*})\}_2]$ (1 mol% Rh) as a catalyst in toluene/H_2O



Scheme 4. Asymmetric arylation of 2,2-disubstituted cyclopent-4-ene-1,3-diones **4** with $PhB(OH)_2$ (**2a**) catalyzed by $[\{RhCl((R)\text{-diene*})\}_2]$. Reaction conditions: **4** (0.15 mmol), **2a** (0.30 mmol), $[\{RhCl((R)\text{-diene*})\}_2]$ (1 mol% Rh), toluene (1.0 mL), H_2O (0.5 mL). Yields are for the main diastereoisomer **5** (isolated product). The *ee* values were determined by HPLC analysis on chiral-stationary-phase columns. The absolute configuration was estimated by stereochemical similarity to the reaction giving **5aa**. [a] Yield of a mixture of diastereoisomers **5** and **6**. [b] The *ee* value of the minor diastereoisomer **6ha** was 99%.



Scheme 5. Asymmetric phenylation of other substrates.

at 80 °C gave **11** with 91% *ee*, albeit in low (15%) yield. For this particular substrate, the diene ligand (*R*)-**12**[9c] improved the yield of **11** to 94%.

The present reaction conditions are also applicable to other substrates often employed in rhodium-catalyzed asymmetric arylation reactions.[2] Maleimide, cyclic and acyclic enones, and a cyclic sulfonylimine were all converted into the corresponding phenylation products with high enantioselectivity under the conditions used for cyclopent-4-ene-1,3-diones (Scheme 5).

In summary, the asymmetric hydroarylation was found to be efficiently catalyzed by a chiral diene-rhodium μ-chloro dimer without a base in toluene/H_2O. This reaction system is particularly useful for the asymmetric synthesis of stereochemically labile α-aryl ketones.

Acknowledgements

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Keywords: α-aryl ketones · asymmetric arylation · chiral diene ligands · racemization · rhodium

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[18] The olefinic compound (*S*)-**7** was further converted into (*S*)-**8** and (1*S*,2*S*)-**9** with high selectivity to demonstrate its synthetic utility.

[19] The X-ray crystal structures of (*R*)-**3cb** (CCDC 1453040) and (*S*)-**7** (CCDC 1453039) 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.

[20] Under basic conditions with KOH in dioxane/H_2O, **9** undergoes oligomerization/polymerization, which is probably initiated by the conjugate addition of hydroxide.

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