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Kinetic Resolution of Chiral Cyclohex-2-enones by Rhodium(I)/binap-Catalyzed 1,2- and 1,4-Additions

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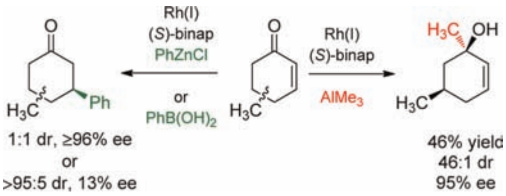
ABSTRACT



The feasibility of kinetic resolutions of racemic monosubstituted cyclohex-2-enones by Rh/binap-catalyzed reactions was investigated. 1,2-Addition of $AlMe_3$ to the 5-substituted derivatives furnished allylic alcohols in the matched case, while the less reactive enantiomers were either left over or transformed into *trans*-3,5-disubstituted cyclohexanones in parallel or sequential 1,4-additions. Altogether, these represent regiodivergent reactions on racemic mixtures. In contrast, 1,4-addition of aryl groups led to inferior results since either catalyst or substrate control dominated.

Enantioselective additions of carbon nucleophiles to cyclic enones, particularly cyclohex-2-enones, are highly important transformations in organic synthesis. For 1,4-additions, Cu-catalyzed processes are well established,[1] yet the Rh-catalyzed 1,4-addition of aryl groups, the Hayashi–Miyaura reaction, has also been developed into a powerful tool.[2] While boron organyls are the principal reagents in this transformation, other metal organyls, e.g. zinc reagents, can be used as well.[2c,e] Recently, we reported on the first Rh/binap-catalyzed addition of aluminum organyls,[3] which surprisingly occurs in a highly selective 1,2-manner and thus yields valuable enantiopure tertiary allylic alcohols.[4]

In the case of 1,4-addition, most studies were performed on cyclohex-2-enone itself or on 3-substituted derivatives.[5] In contrast, little is known about reactions with chiral cyclohex-2-enones, even though such compounds are the rule rather than the exception when it comes to the preparation of synthetic targets. Additionally, the correlation of substrate control and catalyst control is interesting for mechanistic and synthetic reasons; it can open the door to kinetic resolutions of racemic starting materials, if both modes of control are comparably strong.[6] To the best of our knowledge, 4-substituted chiral cyclohex-2-enones were never investigated under Rh-catalysis but show significant substrate control in Cu-catalyzed 1,4-additions,[7]

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[1] For reviews, see: (a) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796–2823. (b) Jerphagnon, T.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2009**, *38*, 1039–1075. (c) Ji, J.-X.; Chan, A. S. C. Catalytic Asymmetric Conjugate Addition. In *Catalytic Asymmetric Synthesis*, 3rd ed.; Ojima, I., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2010; pp 439–495.

[2] (a) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169–196. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829–2844. (c) Shintani, R.; Tokunaga, N.; Doi, H.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 6240–6241. (d) Yoshida, K.; Hayashi, T. Rhodium(I)-Catalyzed Asymmetric Addition of Organometallic Reagents to Electron-Deficient Olefins. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; WILEY-VCH Verlag GmbH & Co. KGaA: Weinheim, 2005; pp 55–77. (e) Hargrave, J. D.; Allen, J. C.; Frost, C. G. *Chem.—Asian J.* **2010**, *5*, 386–396. (f) Edwards, H. J.; Hargrave, J. D.; Penrose, S. D.; Frost, C. G. *Chem. Soc. Rev.* **2010**, *39*, 2093–2105.

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[7] (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015–6018. (b) Lopez-Pelegrin, J. A.; Janda, K. D. *Chem.—Eur. J.* **2000**, *6*, 1917–1922. (c) William, A. D.; Kobayashi, Y. *Org. Lett.* **2001**, *3*, 2017–2020. (d) Naasz, R.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 927–930.

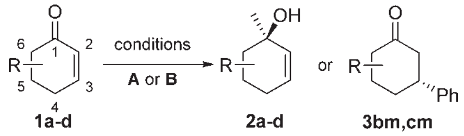
10.1021/ol300387f

thus allowing for a moderately effective kinetic resolution.[7d] Rh-catalyzed 1,4-additions to racemic 5-TMS- or 5-phenylcyclohex-2-enone proceeded with high enantioselectivity but low diastereoselectivity, thus revealing the predominance of catalyst control.[8] Substrate control, however, can prevail under Cu-catalysis resulting in only one diastereomer, but with low ee.[8c] With a different Cu-catalyst, however, Feringa et al. achieved very impressive kinetic resolutions of various 5-substituted derivatives.[7d] Finally, 6-substituted cyclohex-2-enones exerted very low substrate control in both Cu- and Rh-catalyzed 1,4-additions, and mixtures of diastereomers were obtained which, via their enolates, could be epimerized into enantiopure *trans*-2,5-disubstituted cyclohexanones.[9,10] Herein, we report on kinetic resolutions of 4- and 5-substituted cyclohex-2-enones by Rh/binap-catalyzed 1,2-addition of $AlMe_3$ or 1,4-addition of boron and zinc organyls.

First, addition reactions to geminal dimethylated cyclohex-2-enones were studied to determine whether substituents in the respective positions would interfere with the catalyst. As already reported,[4] 1,2-addition of $AlMe_3$ to the 4,4-dimethylated **1b** occurred in the same high yield as in the case of the unsubstituted **1a** (Table 1, entries 1, 2). The 5,5-dimethylated **1c** furnished only a moderate yield, while the 6,6-disubstituted **1d** showed again a very high reactivity (entries 3, 4). In contrast, **1b** did not undergo a 1,4-addition of $PhB(OH)_2$ but slowly decomposed, while **1c** smoothly reacted to cyclohexanone **3cm** (entries 5, 6).

These results led to the hypothesis that the 1,2-addition is most promising for kinetic resolutions of 5-substituted cyclohex-2-enones whereas the 1,4-addition might be suitable for those with substituents in the 4-position. Therefore, racemic 5-methylcyclohex-2-enone (**1e**) was reacted with $AlMe_3$ (1.2 equiv) and GC analysis revealed the formation of the 1,2-adduct *cis*-(*R*,*R*)-**2e** in 50% yield with 79% ee, together with the 1,4-adduct (*S*,*S*)-**4e** (15% yield, 96% ee) and traces of *trans*-**2e** (Table 2, entry 1). Enantiopure (*R*)-**1e** was then treated with the Rh-catalysts containing (*S*)- and (*R*)-binap, respectively, and the former turned out to be the matched pair furnishing only *cis*-**2e** in an excellent yield (entry 2). In the case of the mismatched pair, however, both diastereomers of the 1,2-adduct **2e** were obtained in 9% combined yield and, additionally, the 1,4-adduct (*R*,*R*)-**4e** was formed as a single diastereomer in 16% yield, most likely the consequence of a *trans*-selectivity under substrate control (entry 3).[11] Obviously, steric interactions hampered the regular coordination of (*R*)-**1e** to the (*R*)-catalyst, but some sort of unspecific activation must have occurred. These results elucidate that, under the conditions of entry 1, (*S*)-**1e** is transformed unspecifically leading to the moderate 79% ee in the formation of *cis*-**2e**. Finally, *rac*-**1e** was treated with the racemic catalyst, which furnished almost exclusively *cis*-**2e** (entry 4). Thus, the inherent 1,2-selectivity of the Rh-catalyzed $AlMe_3$ addition is maintained and combined with strong substrate control, leading to a highly selective approach of the methyl group from the face opposite to the substituent in the 5-position.

Table 1. Addition to Geminal Dimethylated Cyclohex-2-enones



entry	cyclohex-2-enone	cond.[a]	temp (°C)	time (h)	product, yield (%)[b]	ee (%)[c]
1	R = H (**1a**)[d]	**A**	0	2	**2a**, 84 (97)	98
2	4,4-dimethyl (**1b**)[d]	**A**	60	3.5	**2b**, 86	99
3	5,5-dimethyl (**1c**)[d]	**A**	rt	2.5	**2c**, 31	99
4	6,6-dimethyl (**1d**)	**A**[e]	0	2.5	**2d**, 89 (99)	99
5	4,4-dimethyl (**1b**)	**B**	60	22	**3bm**, 0[f]	-
6	5,5-dimethyl (**1c**)	**B**	40	3	**3cm**, 82	>99

[a] **A**: $[Rh(cod)OMe]_2$ (2.5 mol %), (*S*)-binap (6.0 mol %), THF, rt, 15 min, then enone, $AlMe_3$ (1.0 equiv), temp, time. **B**: $[Rh(cod)OH]_2$ (1.5 mol %), (*R*)-binap (3.6 mol %), dioxane/H_2O (10:1), rt, 1 h, then enone, $PhB(OH)_2$ (2.5 equiv), temp, time. [b] Yield of isolated product, GC yield in parentheses. [c] Determined by chiral GC. [d] See ref 4. [e] $[Rh(cod)Cl]_2$ and 1.2 equiv of $AlMe_3$ were used. [f] Slow decomposition.

Under the conditions for a kinetic resolution with 0.5 equiv of $AlMe_3$, *rac*-**1e** reacted extraordinarily well furnishing almost exclusively the expected *cis*-(*R*,*R*)-**2e** in 46% yield with 95% ee together with unreacted (*S*)-**1e** in 32% yield with 97% ee (entry 5). Similar results were obtained at a lower temperature, with the air-stable Lewis acid–base pair DABCO·$2AlMe_3$ (DABCO = 1,4-diazabicyclo[2.2.2]-octane)[12] or with the bulkier 5-isopropylcyclohexenone **1f** (entries 6–8). Compared to the known kinetic resolution of 5-substituted cyclohex-2-enones by Cu-catalyzed 1,4-additions,[7d] this procedure furnishes synthetically interesting allylic alcohols in high yield and optical purity while the amount of recovered starting material is lower due to unspecific side reactions.

Besides the possibility of a kinetic resolution, the Rh-catalyzed addition of $AlMe_3$ to **1e** is an unprecedented example of a regiodivergent reaction on a racemic mixture (regiodivergent RRM)[6] due to the formation of the

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(8) Rh-catalysis: (a) Chen, Q.; Kuriyama, M.; Soeta, T.; Hao, X.; Yamada, K.-i.; Tomioka, K. *Org. Lett.* **2005**, *7*, 4439–4441. (b) Tomioka, K. *Pure Appl. Chem.* **2006**, *78*, 2029–2034. Cu-catalysis: (c) Soeta, T.; Selim, K.; Kuriyama, M.; Tomioka, K. *Tetrahedron* **2007**, *63*, 6573–6576.

(9) Rh-catalysis: (a) Mediavilla Urbaneja, L.; Krause, N. *Tetrahedron: Asymmetry* **2006**, *17*, 494–496. (b) Chen, Q.; Soeta, T.; Kuriyama, M.; Yamada, K.-i.; Tomioka, K. *Adv. Synth. Catal.* **2006**, *348*, 2604–2608. Cu-catalysis: (c) Mediavilla Urbaneja, L.; Alexakis, A.; Krause, N. *Tetrahedron Lett.* **2002**, *43*, 7887–7890. (d) Selim, K.; Soeta, T.; Yamada, K.-i.; Tomioka, K. *Chem.—Asian J.* **2008**, *3*, 342–350.

(10) For Cu-catalyzed asymmetric 1,4-additions to other chiral cyclohex-2-enones, see: (a) Imbos, R.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron* **2001**, *57*, 2485–2489. (b) Jagt, R. B. C.; Imbos, R.; Naasz, R.; Minnaard, A. J.; Feringa, B. L. *Isr. J. Chem.* **2001**, *41*, 221–230. For 1,4-additions to chiral cyclic substrates catalyzed by achiral Rh-complexes, see ref 2f and (c) Ramnauth, J.; Poulin, O.; Bratovanov, S. S.; Rakhit, S.; Maddaford, S. P. *Org. Lett.* **2001**, *3*, 2571–2573.

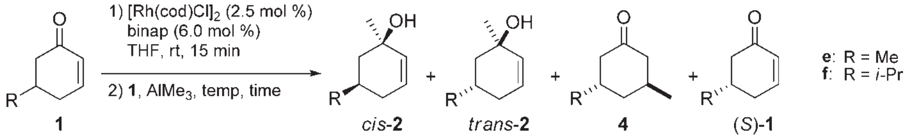
(11) For a discussion on the origin of *trans*-selectivity in cuprate additions, see: Corey, E. J.; Hannon, F. J. *Tetrahedron Lett.* **1990**, *31*, 1393–1396.

(12) Biswas, K.; Prieto, O.; Goldsmith, P. J.; Woodward, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 2232–2234.

(13) For asymmetric 1,2-additions of mixed aluminum-zinc organyls to aldehydes, see: Shannon, J.; Bernier, D.; Rawson, D.; Woodward, S. *Chem. Commun.* **2007**, 3945–3947.

(14) See Supporting Information for details.

Table 2. Rhodium-Catalyzed Addition of $AlMe_3$ to 5-Substituted Cyclohex-2-enones



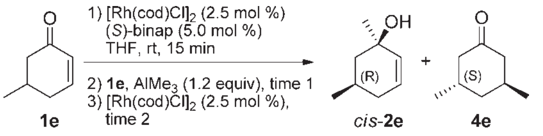
entry	1	binap	$AlMe_3$ (equiv)	temp (°C)	time (h)	*cis*-2 yield (%)[a]	*cis*-2 ee (%)[b]	*trans*-2 yield (%)[a]	4 yield (%)[a]	(*S*)-1 yield (%)[a]	(*S*)-1 ee (%)[b]
1	*rac*-**1e**	(*S*)	1.2	rt	1	50	79 (*R*,*R*)	3	15 (*S*,*S*)[c]	-	-
2	(*R*)-**1e**	(*S*)	1.2	rt	1	92 (87)	>99 (*R*,*R*)	-	-	-	-
3	(*R*)-**1e**	(*R*)	1.2	rt	2	5	>99 (*R*,*R*)	4	16 (*R*,*R*)	-	-
4	*rac*-**1e**	*rac*	1.2	rt	0.5	87	0	-	1 (*rac*)	-	-
5	*rac*-**1e**	(*S*)	0.5	0	4	46	95 (*R*,*R*)	1	4 (*S*,*S*)	32	97
6	*rac*-**1e**	(*S*)	0.5	−10	21	46	92 (*R*,*R*)	1	3 (*S*,*S*)	25	93
7	*rac*-**1e**	(*S*)	-[d]	0	2	52	96 (*R*,*R*)	<1	2 (*S*,*S*)	39	93
8	*rac*-**1f**	(*S*)	0.5	0	6	52 (46)	96 (*R*,*R*)	6	5 (*S*,*S*)	25	96

[a] GC yield, isolated yield in parentheses. [b] Determined by chiral GC. [c] 96% ee. [d] 0.5 equiv of DABCO·$2AlMe_3$ was used.

1,2-adduct *cis*-**2e** from (*R*)-**1e** and the 1,4-adduct **4e** from (*S*)-**1e** (entry 1). Because the attempted optimization of the yield of (*S*,*S*)-**4e** met with little success we envisaged a transformation which may be called "sequential regiodivergent RRM": The kinetic resolution of **1e** by a 1,2-addition to the (*R*)-enantiomer followed by a 1,4-addition to the less reactive (*S*)-enantiomer in the same reaction vessel.

As the achiral complex $[Rh(cod)Cl]_2$ (cod = cyclooctadiene) catalyzes the racemic 1,4-addition of $AlMe_3$ to cyclohex-2-enone,[4] experiments were performed in which in situ formed $[Rh(binap)Cl]_2$ for the 1,2-addition and an excess of $AlMe_3$ were present from the beginning; additional $[Rh(cod)Cl]_2$ was added after a time delay (time 1, Table 3). A delay of 15 min was obviously too long as (*S*)-**1e** had already partially reacted in an unspecific manner (concluded from the low ee of *cis*-**2e** and the low yield of (*S*,*S*)-**4e**, entry 1). Addition of $[Rh(cod)Cl]_2$ after only 5 min furnished **4e** in higher yield with a low ee, indicating incomplete conversion of (*R*)-**1e** at this time (entry 2). The best results were obtained with a time delay of 10 min at rt leading to a 75% combined yield of 1,2- and 1,4-adduct, both with >90% ee (entry 3).

Table 3. Kinetic Resolution of **1e** Followed by 1,4-Addition of Remaining (*S*)-**1e**

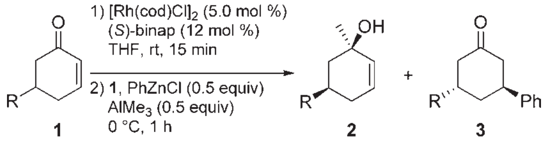


entry	time 1 (min)	time 2 (min)	yield *cis*-**2e** (%)[a]	ee *cis*-**2e** (%)[b]	yield **4e** (%)[a]	ee **4e** (%)[b]
1	15	60	49	86	22	96
2	5	5	34	95	29	51
3	10	20	49	92	26	91
4[c]	180	60	45	94	25	88

[a] GC yield. [b] Determined by chiral GC. [c] Reaction carried out at 0 °C.

The facial selectivities of the Rh-catalyzed 1,2- and 1,4-addition to cylohex-2-enone are reversed: while (*S*)-binap directs the 1,2-addition of $AlMe_3$ to the *si* face, the 1,4-addition of aryl groups occurs on the opposite face.[2,4] Thus, we envisaged another special type of divergent RRM, a parallel kinetic resolution (PKR)[6] with the same chiral precatalyst but two different organometallic reagents. Catalyzed by Rh/(*S*)-binap, the 1,2-addition of $AlMe_3$ to (*R*)-**1e** is the matched pair (cf. Table 2, entry 5). We expected that the 1,4-addition of PhZnCl to (*S*)-**1e** to form *trans*-(3*S*,5*S*)-3-methyl-5-phenylcyclohexanone **3em** should be the matched pair in the conjugate addition because it would fit with the usual *trans*-selectivity of substrate control. Although both addition reactions must proceed via entirely different mechanisms, and thus different catalytic species, it was indeed possible to perform them in parallel (Scheme 1).[13] Both, product (*R*,*R*)-**2e** from the 1,2-addition of $AlMe_3$ and product **3em** from the 1,4-addition of PhZnCl were formed in 33% yield with ee's ≥95%; however, the latter was formed as a *trans*/*cis* mixture with a 4:1 dr. Using the bulkier substrate **1f** the diastereoselectivity was only slightly increased.

Scheme 1. Parallel Rh-Catalyzed 1,2-Addition of $AlMe_3$ and 1,4-Addition of PhZnCl[a]



	2	3
e[b] (R = Me)	33% 95% ee	33%, 4:1 dr 99%/99% ee
f (R = *i*-Pr)	27% >99% ee	48%, 5:1 dr 98%/>99% ee

[a] Yields determined by GC. [b] Additionally 19% of (*S*)-**1e** with 96% ee.

These results are highly interesting from a conceptual and mechanistic point of view, but not completely

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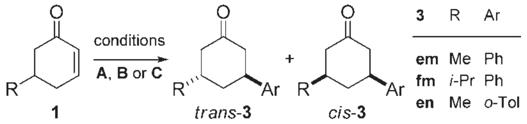
(15) *cis*-Selective 1,4-additions of cuprates to enantiopure 5-alkoxycyclohex-2-enones have been described: Hareau, G. P. J.; Koiwa, M.; Hikichi, S.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 3640–3650 and references therein.

satisfying due to the moderate dr in the formation of the 1,4-adducts. To analyze the substrate control, PhZnCl or $PhB(OH)_2$ were added to enone **1e** furnishing 1:1 mixtures of *cis*- and *trans*-**3em** in excellent optical purities (Table 4, entries 1, 2). From GC analyses of the reaction progress, the ratio of rate constants k_{fast}/k_{slow} (the *s*-factor)[6] was calculated as 5.8−6.1 with PhZnCl and 1.3−1.5 with $PhB(OH)_2$.[14] These low selectivities could not be increased using the bulkier enone **1f** or the bulkier (*o*-Tol)ZnCl (entries 3, 4). In the absence of any catalyst control, i.e. with *rac*-binap, formation of the *trans*-diastereomers was favored with selectivities from 4:1 to 12:1 (entries 5−8). Thus, the strong catalyst control of the Hayashi−Miyaura reaction outpaces the significant substrate control of such enones.[8a,b] This contrasts sharply with not only the corresponding Cu-catalyzed 1,4-additions[7d,8c] but also the $[Rh(cod)Cl]_2$-catalyzed 1,4-addition of $AlMe_3$ which led to pure *trans*-product **4** (cf. Table 3). Although this is a problem for the PKR described above (Scheme 1), it enables the diastereoselective formation of *cis*-3,5-disubstituted cyclohexanones from enantiopure 5-substituted cyclohex-2-enones: The transformation of (*R*)-**1e** catalyzed by the (*S*)-catalyst furnished almost pure *cis*-**3em** (entry 9) and is, to the best of our knowledge, the first *cis*-selective 1,4-addition to a 5-substituted cyclohex-2-enone which is not based on precoordination of the reagent to a heteroatomic substituent.[15]

Table 4. 1,4-Addition of ArZnCl and $PhB(OH)_2$ to Enones **1e,f**

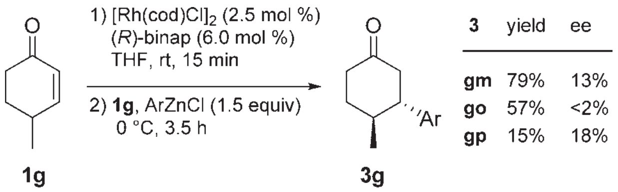


entry	cond.[a]	**1**	binap	yield **3** (%)[b]	*trans*/*cis*[c]	ee *trans* (%)[d]	ee *cis* (%)[d]
1	**A**	*rac*-**1e**	(*S*)	87	1:1	96	>99
2	**B**	*rac*-**1e**	(*R*)	82	1:1	97	>99
3	**A**[e]	*rac*-**1f**	(*R*)	79	1.1:1	97	>99
4	**C**	*rac*-**1e**	(*S*)	74[f]	1.2:1	94	>99
5	**A**	*rac*-**1e**	*rac*	79	7:1	-	-
6	**B**	*rac*-**1e**	*rac*	84	4:1	-	-
7	**A**[e]	*rac*-**1f**	*rac*	79	8:1	-	-
8	**C**	*rac*-**1e**	*rac*	73[f]	12:1	-	-
9	**B**	(*R*)-**1e**	(*S*)	85	1:25	>99	>99

[a] **A**: (1) $[Rh(cod)Cl]_2$ (1.5 mol %), binap (3.6 mol %), THF, rt, 15 min; (2) **1**, PhZnCl (1.5 equiv), 0 °C, 30 min. **B**: (1) $[Rh(cod)OH]_2$ (1.5 mol %), binap (3.1 mol %), dioxane/H_2O (10:1), rt, 1 h; (2) **1e**, $PhB(OH)_2$ (2.5 equiv), 35 °C, 4 h. **C**: (1) $[Rh(cod)Cl]_2$ (1.5 mol %), binap (3.6 mol %), THF, rt, 15 min; (2) **1e**, (*o*-Tol)ZnCl (1.5 equiv), 0 °C, 1.5 h. [b] Isolated yield of inseparable mixtures of *trans*- and *cis*-**3**. [c] Determined by ^1H NMR of the crude product. [d] Determined by chiral HPLC. [e] Reaction time 1.5 h. [f] Diastereomers separable by chromatography.

Drawn from the 1,4-additions to the geminal disubstituted cyclohexenones a much stronger substrate control was expected in the case of 4-substituted cyclohexenones (cf. Table 1, entries 5, 6). Yet, when **1g** was treated with $PhB(OH)_2$ and $[Rh(binap)OH]_2$, no conversion occurred and a change in color from red to yellow indicated decomposition of the catalyst. Transformation with the more reactive PhZnCl, however, was possible and furnished only the *trans*-diastereomer **3gm** in a good yield but with very low ee (Scheme 2). Inferior results were achieved when varying the aryl group, and time-resolved GC analysis of the reaction with 0.5 equiv of PhZnCl revealed a maximum ee of 74% for **3gm** at 13% conversion and a maximum ee of 15% for **1g** at 21% conversion.[14] The substrate control of **1g** thus almost completely overrides catalyst control, making kinetic resolutions hardly possible.

Scheme 2. 1,4-Addition of Various Aryl Groups to Enone **1g**



m: Ar = Ph. – **o**: Ar = *p*-FC_6H_4. – **p**: Ar = *p*-$MeOC_6H_4$.

In summary, it can be stated that the ratio of rate constants k_{fast}/k_{slow} is very low in Rh/binap-catalyzed 1,4-additions of aryl groups to chiral cyclohex-2-enones because catalyst control is too strong in the case of a 5- or 6-substitution[8,9] and substrate control is too strong in the case of a 4-substitution. The 1,2-addition of $AlMe_3$, however, allows for a kinetic resolution of 5-substituted derivatives, and interesting regiodivergent reactions can be accomplished either as sequential reactions of the same metal organyl with two different catalysts or as parallel reactions of two different metal organyls with the same catalyst. This special behavior of 5-substituted cyclohexenones in 1,2- and 1,4-additions and the opposite facial selectivity strongly suggest two entirely disparate reaction mechanisms. Contrary to the conjugate addition, the methyl group might be delivered directly from the alane and not via transmetalation to rhodium.

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Supporting Information Available. Experimental procedures and data from the characterization of compounds, determination of *s*-factors for 1,4-additions to **1e**, attempted kinetic resolution of **1g** by 1,4-addition of ArZnCl, and ORTEP drawing of *cis*-**3em**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.