

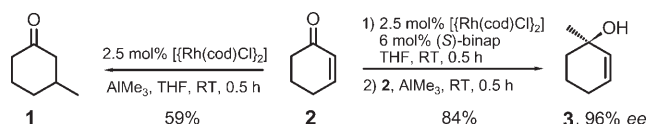
Rhodium-Catalyzed Enantioselective 1,2-Addition of Aluminum Organyl Compounds to Cyclic Enones

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Dedicated to Professor Armin de Meijere

Among carbon–carbon bond-forming processes the 1,2-addition of metal organyl compounds to carbonyl moieties is one of the major reactions in organic synthesis. In the last decade methods based on transition-metal catalysis have been developed that allow stereoselective reactions with a broad spectrum of aldehydes.^[1] However, ketones and especially enones still are problematic substrates for which only few catalyst systems are suitable.^[2] In contrast, asymmetric 1,4-additions of a variety of organometallic compounds to enones by copper, palladium, and rhodium catalysis are well-established.^[3] During our studies towards the total synthesis of the natural product spirodionin acid^[4] we envisaged such Rh-catalyzed enantioselective Michael additions to cyclic enones, yet employing aluminum organyl compounds, which—to the best of our knowledge—have hitherto not been used in combination with Rh catalysts.^[5]

Cyclohex-2-enone (**2**) was treated with $[\{\text{Rh}(\text{cod})\text{Cl}\}_2]$ (cod = cyclooctadiene) and an equimolar amount of AlMe_3 to give the desired 3-methylcyclohexanone (**1**, Scheme 1). To perform the transformation enantioselectively, in situ pre-



Scheme 1. Rhodium-catalyzed additions of AlMe_3 to **2** (yields determined by GC analysis).

pared $[\{\text{Rh}[(S)\text{-binap}]\text{Cl}\}_2]$ was used next; yet the use of this complex led to a dramatic change of the reaction course. Highly selective 1,2-addition was observed and 1-methylcyclohex-2-enol (**3**) was formed with 96% *ee*. Since this compound is a known aggregation pheromone of the Douglas-fir beetle, previously only available in multistep syntheses,^[6] the *R* configuration could be assigned to the product **3** based on the reported optical rotation.

The formation of **3** from **2** appears to be the first example of an enantioselective Rh-catalyzed 1,2-addition to an enone; thus, the reaction conditions were optimized.^[7,8] On lowering the temperature to 0°C or –20°C the enantioselectivity was only slightly increased to 98% *ee*, while the reaction was significantly retarded (Table 1, entries 1–3). Variation of the

Table 1: Variation of reaction temperature and Rh^I source.^[a]

Entry	Catalyst	<i>T</i> [°C]	<i>t</i> [h] ^[b]	Yield [%] ^[c]	<i>ee</i> [%] ^[d]
1	$[\{\text{Rh}(\text{cod})\text{Cl}\}_2]$	RT	0.5	84	96
2	$[\{\text{Rh}(\text{cod})\text{Cl}\}_2]$	0	3.8	85	97
3	$[\{\text{Rh}(\text{cod})\text{Cl}\}_2]$	–20	26	47 ^[e]	98
4	$[\text{Rh}(\text{cod})_2]\text{BF}_4$	0	5.0	81	99
5	$[\text{Rh}(\text{cod})\{\text{acac}\}]$	0	5.0	77	98
6	$[\{\text{Rh}(\text{cod})\text{OMe}\}_2]$	0	2.0	97	> 99
7	$[\{\text{Rh}(\text{cod})\text{OMe}\}_2]$	RT	0.5	78	97
8	$[\{\text{Rh}(\text{cod})\text{OMe}\}_2]^{\text{[f]}}$	RT	2.5	61	98
9	$[\{\text{Rh}(\text{cod})\text{OMe}\}_2]^{\text{[g]}}$	RT	1.5	4	n.d.

[a] 2.5 mol% of dimeric or 5 mol% of monomeric Rh precatalyst, 6 mol% (*S*)-binap, THF, 0.5 h, RT, then **2**, AlMe_3 (1.0 equiv). [b] Time until full consumption of **2**. [c] Yield of **3** determined by GC. [d] Determined by chiral GC. [e] 49% conversion. [f] 0.5 mol% precatalyst and 1 mol% binap. [g] 0.05 mol% precatalyst and 0.1 mol% binap. n.d. = not determined.

precatalyst led to similar results when starting from complexes with noncoordinating or bidentate counterions (Table 1, entries 4 and 5), yet significant improvements were achieved when using $[\{\text{Rh}(\text{cod})\text{OMe}\}_2]$, thus increasing the yield to 97% with 99% *ee* (entry 6). In a second set of experiments the catalyst loading was reduced, which still gave good results with 1 mol%, but almost no conversion with 0.1 mol% (Table 1, entries 7–9).

Furthermore, the influence of the solvent was examined, revealing that THF is the best choice. With other ethers the yield decreased in the order 1,2-dimethoxyethane > dioxane > Et_2O ; hydrocarbons such as toluene proved unsuitable owing to significant background reactivity.^[9] To gain insight into the sudden change of the reaction course, various mono- and bidentate phosphine ligands were tested (PPh_3 , $\text{P}n\text{Bu}_3$, dppe, dppb, diop),^[10] yet none of them led to the formation of the 1,4-adduct **1** or the 1,2-adduct **3** in more than 10% yield. Furthermore, no conversion occurred in the presence of binap when omitting the Rh precatalyst, thus proving catalysis by a Rh–binap species.

Only one methyl group of AlMe_3 is transferred under these conditions, as use of less than one equivalent of the alane resulted in an incomplete conversion (Table 2, entry 1).

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Table 2: Variation of the methylaluminum reagent in the synthesis of **3**.^[a]

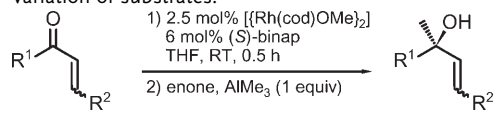
Entry	Reagent	Equiv	<i>t</i> [h]	Yield [%] ^[b]
1	AlMe ₃	0.33	4	33 ^[c]
2	AlMe ₂ Cl	1.0	2	60
3	AlMe ₂ OMe	1.0	1	47 ^[d]
4	AlMeCl ₂	1.0	3	0
5	DABCO-2 AlMe ₃	1.0	1.75 ^[e]	98

[a] 2.5 mol% [{Rh(cod)OMe}₂], 6 mol% (*S*)-binap, THF, 0.5 h, RT, then **2**, alane, RT. [b] Yield of **3** determined by GC. [c] 74 % conversion. [d] 50 % conversion. [e] Performed at 0 °C.

Dimethylaluminum chloride and methoxide could be employed in this transformation, but these compounds gave inferior results, while the respective dichloride led to decomposition (Table 2, entries 2–4). In contrast, the quite air-stable and easily usable Lewis acid/base pair obtained from 1,4-diazabicyclo[2.2.2]octane (DABCO) and two equivalents of AlMe₃^[11] gave an excellent yield of **3** and thus could be used instead of the pure, pyrophoric AlMe₃ (Table 2, entry 5).

Under the optimized conditions the transformation of **2** furnished the natural product **3** in 84 % yield of isolated product with an excellent *ee* value of 98 % (Table 3, entry 1).

Table 3: Variation of substrates.^[12]

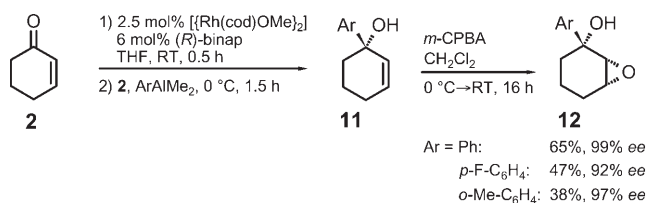
				
Entry	Enone	<i>T</i> [°C], <i>t</i> [h]	Yield [%] ^[a]	<i>ee</i> [%] ^[b]
1	cyclohex-2-enone (2)	0, 2	84	98
2	4 : R ⁴ =Me R ⁵ =H	60, 3.5	86	99
3	5 : R ⁴ =H R ⁵ =Me	RT, 2.5	31	99
4	cyclohept-2-enone (6)	0→RT, 3	74	98
5	cyclopent-2-enone (7)	0→RT, 2	10	n.d.
6	8	RT, 1	28 ^[c]	> 95
7	9	RT, 3.5	49	7
8	propiophenone (10)	66, 8	14 ^[d]	54

[a] Yield of isolated product. [b] Determined by chiral GC. [c] 50 % conversion. [d] Determined by GC analysis, 14 % conversion. n.d. = not determined.

To evaluate the scope of the catalytic system, various substitution patterns of model substrate **2** were screened. No 1,2-adduct was formed when starting from 2- or 3-methylcyclohex-2-enone. Geminal methyl groups at C-4 or C-5 of the six-membered ring are tolerated, yet the reactivity of these substrates is significantly lower, thus requiring higher reaction temperatures to give the 1,2-addition products in high (from **4**) or moderate (from **5**) yields with excellent enantioselectivity (Table 3, entries 2 and 3). Furthermore,

cycloheptenone (**6**) can be transformed into the respective allyl alcohol in good yield while maintaining the high enantioselectivity (Table 3, entry 4). On the contrary, cyclic five-membered enones are problematic substrates since their 1,2-adducts are very prone to dehydration and thus formation of volatile dienes. With cyclopentenone (**7**), only a 10 % yield was achieved, and this yield was only slightly increased to 28 % by using the geminal-dimethylated cyclopentenone **8** (Table 3, entries 5 and 6). This result is also a consequence of the formation of oligomeric compounds as verified by GC–MS analyses. Presumably, small amounts of aluminum enolates arise from catalyzed or uncatalyzed 1,4-addition reactions and then undergo oligomerizing Michael additions with additional amounts of starting material.^[5a,d] Moreover, the catalytic system proved to be less suitable for the transformation of acyclic enones (**9**, entry 7) and aryl ketones (**10**, entry 8).

Besides methylation, this method can also be used for 1,2-arylations.^[13] The employment of mixed arylalanes, prepared in situ from AlMe₂Cl and the respective Grignard reagents, gave access to 1-arylcyclohex-2-enols **11** with only trace amounts of methylated **3** (Scheme 2). Owing to their instability, the crude allyl alcohols **11** were immediately oxidized to give diastereomerically pure epoxides **12** in fair yields with high enantioselectivity.^[12]



Scheme 2. 1,2-Arylation of cyclohex-2-enone (**2**) with subsequent epoxidation (yields refer to amounts of isolated products over the two steps). *m*-CPBA = *m*-chloroperbenzoic acid.

Regarding the mechanism of these transformations, an initial transmetalation of the organic residue from aluminum to rhodium seems likely, which is supported by the observed higher reactivity of [{Rh(cod)OMe}₂] as precatalyst compared to [{Rh(cod)Cl}₂]. A similar transmetalation was proven to be the first step in the Rh-catalyzed 1,4-addition of arylboronic acids.^[3d] However, the reaction clearly would not just continue by 1,2-addition of an assumed Rh–Me species to the enone, as no adduct **3** was obtained when adding enone **2** to a prestirred mixture of [{Rh(cod)OMe}₂], binap, and AlMe₃ in a 0.5:1:1 ratio.

In summary, we have developed the first highly enantioselective 1,2-additions to cyclic enones that lack substituents in the α -position. This transformation was achieved by combining the readily accessible rhodium/binap catalyst system with economically attractive alanes. The thus formed enantiomerically highly enriched allyl alcohols are interesting intermediates for versatile synthetic applications. Work is now in progress to precisely elucidate the mechanism of this reaction, which should provide the key for further enlarge-

ment of the scope regarding both the carbonyl compounds and the alanes.

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- [12] See the Supporting Information for experimental procedures, determination of the *ee* values, and analytical data of the new compounds.
- [13] Other trialkyl aluminum reagents turned out to be unsuitable; no conversion occurred with $\text{Al}i\text{Bu}_3$ while the use of AlEt_3 mainly afforded cyclohexanone.