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Asymmetric Catalysis

Rhodium-Catalyzed Asymmetric 1,4-Addition of Aryl Alanes to Trisubstituted Enones: Binap as an Effective Ligand in the Formation of Quaternary Stereocenters**

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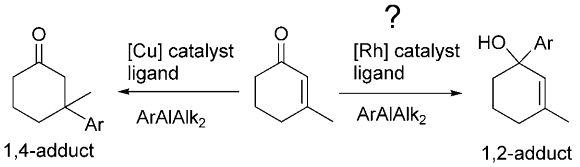
The creation of quaternary all-carbon- or heteroatom-substituted stereogenic centers is an important transformation in organic synthesis, and quaternary centers[1] are a common motif in natural products. Several groups, ourselves among them, have worked on this challenge and one way that has been found to access these centers is through copper-catalyzed conjugate addition reactions.[2] However, in such reactions, the introduction of aryl groups presents an additional challenge owing to the steric hindrance of the system.[2e–g,l] Special activation is required and aluminum organyls are strong Lewis acids that can coordinate to the enone and thus render the substrate more electrophilic; as such, they have been especially successful in the copper-catalyzed aryl-addition reaction.[3] Although rhodium in combination with boron reagents is the metal of choice when introducing aryl groups into α,β-unsaturated systems,[4] for a long time the addition to trisubstituted substrates was limited to very few activated substrates.[5] Only recently have a few articles appeared that report the rhodium-catalyzed formation of quaternary centers on enones,[6] of which one[6b] presents a single example with poor yield. In the more general studies,[6a,c] several parameters in the original protocol[7] needed to be changed:[7] boronic acids were replaced by tetraarylborates[6a] and boroxines,[6c] and chiral diene ligands were used because commercially available binap did not give any conversion. Furthermore, 2–4 equivalents of the nucleophile (bearing four aryl groups per equivalent in the case of tetraarylborates) were needed. These requirements left room for the development of more atom-economical reactions for the formation of benzylic quaternary centers that allow the use of more easily accessible ligands.

Enones are interesting starting materials as they contain several reactive sites that might be transformed regioselectively. 1,4-Addition to enones has been studied more than 1,2-addition,[8] but in 2007 an interesting article was published reporting the rhodium-catalyzed addition of Me_3Al and $PhAlMe_2$ to 2-cyclohexenone giving the 1,2-adduct as the main product in very high *ee*.[9] Therefore, we were interested in testing our previously reported methodology[3a] for the generation of aryl alanes[10] by application in the rhodium-catalyzed addition to 3-substituted 2-cyclohexenones, assuming that an additional substituent in the β position would result in a preference for 1,2-addition, and especially as rhodium-catalyzed conjugate addition to trisubstituted enones had not been reported at the time we started the project. As we had obtained very high enantioselectivities in copper-catalyzed 1,4-additions to the same substrates, we were hoping to be able to develop a complementary methodology that would give us selective 1,2-addition with rhodium and 1,4-addition with copper (Scheme 1).



Scheme 1. Enantioselective rhodium-catalyzed 1,4-addition to trisubstituted enones. Alk = alkyl, Ar = aryl.

In the first instance, we generated Me_2AlPh[11] through a transmetalation reaction from commercial PhLi and Me_2AlCl and, to our great surprise, we obtained the 1,4-adduct almost exclusively and in very high *ee* using [{Rh(cod)Cl}$_2$] (cod = 1,5-cyclooctadiene) and (*R*)-binap (**L1**; Scheme 2).

Intrigued by this inversion of the expected reactivity we decided to pursue this reaction further. Furthermore, the prospect of developing a method that would allow the use of commercially available binap instead of dienes that require multistep syntheses (although some dienes have been recently commercialized) seemed highly interesting to us.

We first generated the alane from the corresponding aryl iodide through an I/Li exchange with *n*BuLi, followed by transmetalation with Me_2AlCl, which would give us access to a wide range of nucleophiles (Scheme 3). It should be noted

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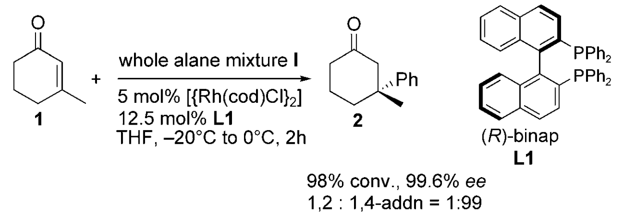
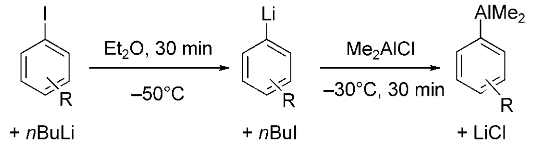
$$\begin{matrix}\text{PhLi (3 equiv)}\\ +\\ \text{Me}_2\text{AlCl (3 equiv)}\end{matrix} \xrightarrow{-30°\text{C, 30 min}} \text{PhAlMe}_2 + \text{LiCl (s)} \quad \textbf{(I)}$$



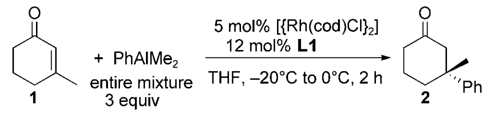
Scheme 2. Enantioselective rhodium-catalyzed 1,4-addition to trisubstituted enones.



Scheme 3. Generation of aryl alanes from aryl iodides.

that one equivalent of *n*BuI is generated as a by-product in this sequence. We then proceeded in testing the mixture in the 1,4-addition to 3-methyl-2-cyclohexenone (Table 1).

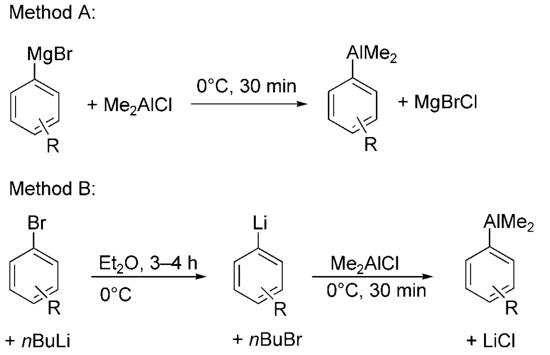
Table 1: Phenyl iodide as aryl source in the asymmetric conjugate addition reaction.



Entry	Aryl source	Additive	Conv. [%][a]	*ee* [%]
1	PhLi	none	98	99.6
2	PhI	none	29	98.5
3	PhLi	*n*BuI	1	n.d.
4	PhLi	*n*BuBr	100	99.4

[a] Conversion was determined by ^{1}H NMR analysis.

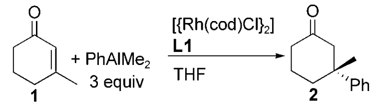
This table clearly shows that *n*BuI interferes in the reaction, as 98% conversion was achieved starting from commercial PhLi (Table 1, entry 1), but only 29% conversion was observed when the aryl alane was derived from PhI (Table 1, entry 2). To confirm this assumption, we added 1 equivalent of *n*BuI to commercial PhLi and generated the alane from this mixture. Indeed, the conversion was severely impaired, which means that *n*BuI is detrimental to this reaction (Table 1, entry 3). It is possible that oxidative addition of *n*BuI takes place at rhodium, leading to β-hydride elimination on the butyl group and subsequent formation of a catalytically ineffective Rh/hydride complex. However, this phenomenon was not observed for the *n*BuBr, as full conversion still took place in its presence (Table 1, entry 4). Aryl iodides are thus not good aryl sources under these conditions and we thus envisaged two alternative methodologies to access aryl alanes: In the first one (method A; Scheme 4), the alane was obtained from the corresponding aryl Grignard reagent through transmetalation with Me_2AlCl, and in the second (method B), a Br/Li exchange was performed on an aryl bromide with *n*BuLi, followed by transmetalation with Me_2AlCl.



Scheme 4. Methods for the generation of the alane nucleophile.

We used method A to optimize our reaction conditions. Changing the aryl source from aryl iodides to Grignard reagents did not improve the conversion, as a similar result was obtained as for phenyl iodide (Table 2, entry 1). However, we observed an important improvement when the addition of the magnesium salts was avoided (Table 2, entry 2). It seems like the latter are also detrimental for the reaction. Therefore, we tested dioxane as the solvent, as it is known to precipitate magnesium salts, and it is a popular solvent[4] for rhodium-catalyzed conjugate addition reactions. The reaction temperature needed to be increased owing to the melting point of dioxane. Under tetrahydrofuran-free conditions, full conversion took place even at reduced catalyst loading, but almost no enantiomeric excess was achieved (Table 2, entry 3). It is thought that the active catalyst does not form in dioxane, so that free [{Rh(cod)Cl}$_2$] promoted this reaction for the most part. Therefore, we had to find a way to supply enough tetrahydrofuran to allow the formation of the

Table 2: Optimization of reaction conditions using method A.



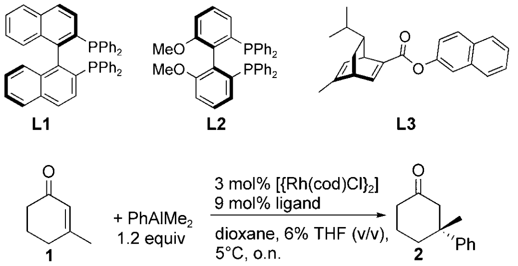
Entry	*T* [°C]	*t* [h]	Equiv alane	Mg salts	Rh cat./**L1** [mol%]	Conv. [%][a]	*ee* [%]
1	−20 to 10	3	3.0	yes	5:12.5	29	99.6
2	−20 to 10	3	3.0	no	5:12.5	57	98.5
3[b]	5	o.n.	3.0	no	3:9	96	7
4[c]	5	o.n.	1.2	no	3:9	99	98

[a] Conversion was determined by ^{1}H NMR analysis. [b] Dioxane was used as the solvent. [b] Dioxane containing 6% THF (v/v) was used as the solvent. o.n. = overnight.

active catalyst, but no more than necessary, to minimize its degradation. Therefore, we used dioxane as a solvent that contained 6% (v/v) tetrahydrofuran. It seemed like this amount of tetrahydrofuran was enough to promote the coordination of binap to rhodium since 98% *ee* was obtained with almost full conversion when only 1.2 equivalents of alane was used with 3 mol% rhodium dimer (Table 2, entry 4).

With the optimized conditions in hand, we performed a ligand screening (Table 3). (*R*)-Binap gave the best conversion (Table 3, entry 1), but good results were also achieved with (*S*)-OMe-biphep (**L2**), especially in terms of enantioselectivity (Table 3, entry 2). The results with diene **L3** were disappointing. Good conversion was achieved when the active catalyst was generated in situ, but the enantiomeric excess was low (Table 3, entry 3). When the active catalyst was preformed, higher conversion was achieved, but the enantioselectivity remained low (Table 3, entry 4).

Table 3: Ligand screening using method A for alane generation.

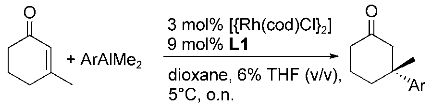


Entry	Ligand	Conv. [%][a]	*ee* [%]
1	**L1**	99	98
2	**L2**	96	99[b]
3	**L3**	86	11
4[c]	**L3**	95	17

[a] Conversion was determined by ^{1}H NMR analysis. [b] The opposite enantiomer was obtained. [c] The Rh/diene catalyst was preformed and used as the isolated compound.

Therefore, we decided to continue our investigations with binap under these new conditions screening different nucleophiles. It should be pointed out that for 3-ethyl cyclohexenone, under the same reaction conditions, Me_3Al gave only the 1,4 adduct, albeit with 17% conversion and 45% *ee*. We then tested different aryl nucleophiles (Table 4). Method B was also tested under the optimized conditions. Aryl groups with different electron-donating and electron-withdrawing substituents were added in good yields and nearly perfect enantioselectivities. Method B was also successful, as the same results were obtained for the addition of a phenyl group (Table 4, entry 2). It was then also applied for the addition of the electron-withdrawing trifluoromethyl-substituted aryl group. Our brief study showed that increasing the number of equivalents of alane did not lead to improved conversion (Table 4, entry 6 vs. entry 7) and that the whole mixture could be used without detrimental effect (Table 4, entry 7 vs. entry 8). This makes the use of method B very convenient as no separation of salts and supernatant is necessary. Furthermore, in the case of method B, the use tetrahydrofuran as the sole solvent led to a complex mixture of products, which underlines the importance of working in dioxane (Table 4, entry 9).

Table 4: Screening of different nucleophiles.

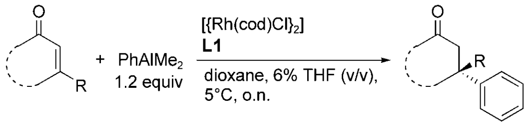


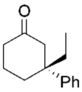
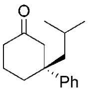
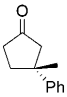
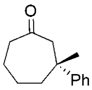
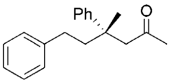
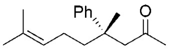
Entry	Ar	Method	Equiv alane	Prod.	Conv. [%][a]	Yield [%]	*ee* [%]
1	C_6H_5	A	1.2	**2**	99	71	98
2	C_6H_5	B	1.5	**2**	99	n.d.	99
3	m-MeC_6H_4	A	1.2	**3**	99	73	98
4	p-MeC_6H_4	A	1.2	**4**	93	50	96
5	m-OMeC_6H_4	A	1.0	**5**	99	75	98
5	p-OMeC_6H_4	A	1.2	**6**	99	57	95
6	m-$CF_3C_6H_4$	B	1.2	**7**	98	61	99
7	m-$CF_3C_6H_4$	B	1.5	**7**	93	n.d.	99
8[b]	m-$CF_3C_6H_4$	B	1.5	**7**	96	n.d.	>99
9[b,c]	m-$CF_3C_6H_4$	B	1.5	**7**	–[d]	n.d.	n.d.

[a] Conversion was determined by ^{1}H NMR analysis. [b] The whole mixture was added, including the LiCl salts. [c] THF was used as solvent. [d] A complex mixture was observed.

Finally, we investigated the substrate scope. Table 5 shows that a wide range of linear and cyclic substrates can be used in this transformation. Excellent enantioselectivities were obtained in all cases, even for the linear substrates. The olefin geometry of the enone influenced the absolute configuration of the product as *E* and *Z* substrates gave opposite

Table 5: Screening of different substrates.



Entry		Product	Rh cat./**L1** [mol%]	Conv. [%]	Yield [%]	*ee* [%]
1	**8**		3:9	96	66	99
2	**9**		5:12.5	71	35	99
3	**10**		3:9	100	46	>99
4	**11**		5:12.5	86	56	95
5[a]	**12**		5:12.5	91	55	93
6	**13**		5:12.5	100	52	>95

[a] The product was synthesized from (*E*)-4-methyl-6-phenylhex-3-en-2-one. The corresponding *Z* substrate gave the opposite enantiomer in 88% *ee*.

enantiomers (Table 5, entry 5). Remarkably, even the challenging five-membered-ring substrate displayed excellent reactivity, and near-perfect selectivity was achieved (Table 4, entry 3). The reduced yield could be explained by the sensitivity of the product towards column purification.

From mechanistic aspects, it is clear that the reaction proceeds through the formation of an rhodium/aryl species, and the enone is activated by the Lewis acidity of the aluminum reagent.[6,12]

In summary, we have shown that aryl alanes are excellent nucleophiles for the rhodium-catalyzed conjugate addition reaction. Whilst elevated temperatures are usually required with boron nucleophiles, only 1.2 to 1.5 equivalents of alane afforded the same transformation overnight at 5°C. Most importantly, commercially available binap promoted the reaction. An important electronic effect of the alkyl substituent in the 4-position of trisubstituted enones was discovered which directs the nucleophilic attack to the 4-position despite additional steric bulk. A range of electron-donating and electron-withdrawing substituents were tolerated on the aromatic ring and the desired alanes were generated from both the corresponding lithium or Grignard precursors. Finally, a wide range of cyclic and acyclic substrates led to excellent enantioselectivities in this transformation.

Experimental Section

Method A: At 0°C, Me$_2$AlCl (1 equiv) was added to the aryl magnesium bromide (1 equiv in THF) and reacted for 30 min at 0°C. The salts were allowed to precipitate over 10–20 min at 0°C and the supernatant was used.

Method B: The aryl bromide (0.525 mmol) was dissolved in anhydrous Et$_2$O (0.5 mL) at RT. Then the flask was cooled to 0°C and *n*BuLi (0.33 mL, 0.525 mmol, 1.6 M in heptane) was added. The reaction mixture was stirred for 3 to 4 h at 0°C before the addition of Me$_2$AlCl (0.525 mL, 0.525 mmol, 1 M in hexanes) at 0°C. A precipitate of LiCl then appeared and the reaction mixture was stirred for 30 min at 0°C.

Conjugate addition reaction: THF (0.1 mL) was added to [{Rh(cod)Cl}$_2$] (3 mol%) and ligand (9 mol%), and the mixture was stirred for 2 min at RT. Then, dioxane (1.6 mL) was added and the mixture was stirred for 30–50 min. The mixture was cooled to 5°C and the organoalane was added to the catalyst mixture, followed by the substrate. The reaction was stirred overnight at 5°C before quenching with 10% HCl. The aqueous layer was extracted with EtOAc (2 × 20 mL) and the combined organic phases were washed with brine before drying over MgSO$_4$, filtration through silica, and evaporation of the solvents. The crude mixture was purified by column chromatography on silica gel using Et$_2$O/pentane as an eluent.

Some yields may be improved by scaling up the reactions to 2 mmol; for example, see Table 4, entry 1.

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Keywords: aryl alanes · asymmetric catalysis · Michael addition · quaternary stereocenters · rhodium

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[11] Et$_2$AlPh did not give any conversion, probably owing to β-hydride elimination.

[12] Preliminary ^{31}P NMR experiments show the characteristic signals for the Ph-Rh-binap complex[4b] upon mixing PhMgBr and the Rh-binap-Cl complex, but not with ArAlMe$_2$; further investigations are underway.