Creation of Quaternary Stereogenic Centers via Copper-Catalyzed Asymmetric Conjugate Addition of Alkenyl Alanes to α,β-Unsaturated Cyclic Ketones

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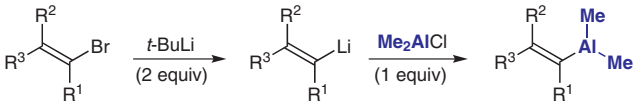
Abstract: SimplePhos ligands proved to be very powerful ligands in the generation of quaternary stereogenic centers by Michael addition of alkenyl-aluminum reagents to cyclic enones. Using commercially available and easily accessible alkenylbromides as alane precursors the present procedure offers a facile access to β-alkenyl-substituted cyclohexanones with high enantioselectivities up to 96%.

Key words: aluminum, alkenes, copper, Michael addition, asymmetric catalysis

The landmark discovery about the rhodium-catalyzed conjugate addition of organoboron reagents to electron-deficient olefins by Miyaura and co-workers[1] in 1997 gave rise to tremendous research efforts towards its asymmetric version.[2] Already in 1998 Hayashi showed that the use of a rhodium–BINAP complex achieved high enantioselectivities for the ACA of boronic acids to acyclic and cyclic enones.[3] In his report he also employed alkenyl boronic acids which afforded the corresponding products with high enantioselectivity. In contrast to the advances in this fast-growing field of rhodium-catalyzed ACA, the copper-catalyzed ACA employing alkenyl nucleophiles has been rather neglected and only few examples have been reported so far.[4]

In our continuing interest in the copper-catalyzed ACA we are focusing our attention towards the creation of quaternary centers via Michael addition.[4d,5] To this date no example has been published of the creation of quaternary stereogenic centers via the rhodium-catalyzed ACA with alkenyl nucleophiles and enones as substrates.[6] For copper-catalyzed ACA only some examples have been published so far; which include the drawback of using high catalyst loadings up to 30 mol%.[4c,d,f]

Mixed alanes as previously shown,[4d,7] combine strong nucleophilicity as well as electrophilic activation via complexation of the carbonyl moiety and thus allow the addition of various nucleophiles to tertiary substituted α,β-unsaturated ketones. From our previous investigations we knew that iodoolefins as precursors underwent this transformation with good enantioselectivity.[4d] However, this protocol was quite sensitive to the presence of in situ generated LiI, and so we decided to experiment with other nucleophile precursors, namely bromoolefins, of which many are commercially available or easily accessible synthetically.[8] Using a variant of the procedure published by Seebach,[9] we employed two equivalents of *t*-BuLi to perform the bromo–lithium exchange and then quenched the corresponding alkenyllithium with Me_2AlCl to generate the mixed alane species (Scheme 1). On the contrary the use of *n*-BuLi for the Br–Li exchange lead in the case of 2-bromopropene to acetylenic byproducts.[9]



Scheme 1 Generation of mixed alane species

It is well known, that in the case of mixed alane species the substituents with sp- and sp^2-carbon centers attached to the aluminum are faster transferred than substituents bearing sp^3-carbon centers.[10,13] Therefore the two alkyl substituents act usually as 'dummy substituents' meaning in most cases they transfer in small quantities or not at all.[4d] To investigate the 1,4 addition to β-substituted cyclic enones we chose 3-methylcyclohex-2-enone as a Michael acceptor and dimethyl(prop-1-en-2-yl)aluminum as nucleophile. From our experiences with the conjugate addition employing trialkylalanes and mixed arylalanes,[4c,d,f] we knew that CuTC as copper source, diethyl ether as solvent, and temperatures about –30 °C were good parameters to start with and screened under these conditions various ligands (Table 1, Figure 1, Scheme 2).

The results of the ligand screening confirmed previous observations: An increase of the steric bulk on the BIPOL or aryl part and on the amine part promotes the enantioselectivity.[4f] This trend holds true for BIPOL (entries 3 vs. 4, Table 1), as well as for the SimplePhos ligands (entries 5 vs. 10, Table 1). To our delight SimplePhos ligands, a new class of ligands recently developed in our group,[4f,11] showed to be superior over all other classes of ligands we employed for the screening (Figure 1). SimplePhos ligand **L11** which was already successfully used for the copper-catalyzed ACA using trialkyl- and mixed aryl-alanes proved to be the most selective of its class.[4d,f] Interestingly, the electronic properties seem to play a major role in this transformation, the electron-poor ligand **L9** gave almost racemic mixtures whereas the phenyl-substituted ligand **L10** gave similar results as **L11**. For the majority of the optimization reactions we continued using the sim-

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Table 1 Screening of the Ligands[a]

Entry	Ligand	Conv. (%)[b]	Methyl/alkenyl transfer[b]	ee (%)[c]
1	**L1**	94	4:96	12 (*R*)
2	**L2**	85	11:87	5 (*S*)
3	**L3**	98	3/97	18 (*R*)
4	**L4**	100	4:96	32 (*R*)
5	**L5**	98	2:98	43 (*R*)
6	**L6**	100	3:97	49 (*R*)
7	**L7**	97	10:90	26 (*R*)
8	**L8**	98	3:97	19 (*R*)
9	**L9**	88	2:98	rac.
10	**L10**	100	2:98	59 (*R*)
11	**L11**	100	4:96	63 (*R*)
12	**L12**	2	n.d.	n.d.
13	(*R*)-BINAP	57	n.d.	13 (*R*)

[a] Reaction conditions as described in Scheme 2.
[b] Determined by GC-MS.
[c] Determined by chiral GC.

plest SimplePhos ligand **L5** due to its simple one-step synthesis.[4f] Gau and co-workers showed that the amount of alane used had a significant impact on the enantioselectivity in the addition of 2-thienylalane to 2′-acetophenone,[12] therefore we considered investigating the dependency of the enantioselectivity on the amount of alane used for the reaction (Table 2). To our surprise the amount of alane added had a huge influence on the enantioselectivity and caused significant changes up to 30% in difference.

Table 2 Study of the Effect of the Amount of Alane Added in the ACA as Described in Scheme 2[a,b]

Entry	Alane (equiv)	Conv. (%)[c]	Methyl/alkenyl transfer[c]	ee (%)[d]
1	3.0	100	3:97	49 (*R*)
2	2.8	100	3:97	52 (*R*)
3	2.3	100	6:94	62 (*R*)
4	2.0	100	5:95	66 (*R*)
5	1.7	100	9:91	68 (*R*)
6	1.4	100	20:80	73 (*R*)
7	1.2	100	25:75	78 (*R*)

[a] Reaction conditions as described in Scheme 2.
[b] Ligand **L5** was used for the optimization.
[c] Determined by GC-MS.
[d] Determined by chiral GC.

Even though less equivalents of alane afforded higher enantioselectivity it also led to an increase of undesired methyl transfer. We considered therefore the use of 2.0

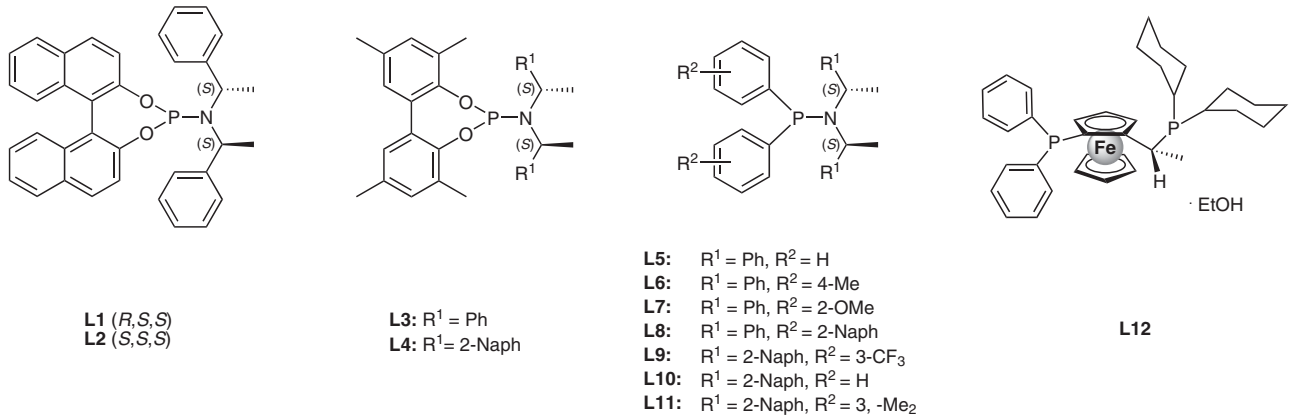
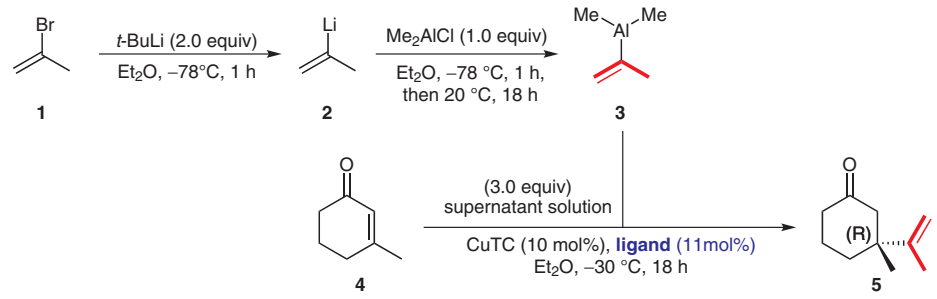


Figure 1 Screened ligands



Scheme 2 Standard reaction used for optimization

equivalents of alane as the best compromise between enantioselectivity and methyl transfer (entry 4, Table 2). Screening of various copper sources led in a couple of cases to a significant increase in enantioselectivity but also to an increase in methyl transfer (entries 3 and 4, Table 3). Therefore we decided to continue using CuTC as a copper source which afforded acceptable levels of enantioselectivities while reducing the amount of methyl transfer.

Table 3 Screening of Different Copper Sources[a,b]

Entry	CuX	Conv. (%)[c]	Methyl/alkenyl transfer[c]	ee (%)[d]
1	CuTC	100	5:95	66 (*R*)
2	CuCN	63	4:96	32 (*R*)
3	$Cu(OAC)_2 \cdot H_2O$	100	12:88	73 (*R*)
4	$CuCl_2$	73	11:89	70 (*R*)
5	$Cu(acac)_2$	100	21:79	66 (*R*)
6	$Cu(OTf)_2$	93	19:81	63 (*R*)
7	CuBr	97	5:95	59 (*R*)

[a] Reaction conditions as described in Scheme 2, except the use of 2.0 equiv of alane.
[b] Ligand **L5** was used for the optimization.
[c] Determined by GC-MS.
[d] Determined by chiral GC.

We also investigated the influence of the solvent on the reaction and found that THF led to almost racemic mixtures, CH_2Cl_2 to high methyl transfer and hexane to low conversion. Good results were only observed with methyl *tert*-butyl ether (MTBE) and diethyl ether (Table 4).

Table 4 Investigation of Various Ratios of MTBE and Et_2O on the Enantioselectivity[a,b]

Entry	Solvent[c]	Solvent[d]	Conv. (%)[e]	Methyl/alkenyl transfer[e]	ee (%)[f]
1	Et_2O	Et_2O	100	3:97	89 (*R*)
2	Et_2O	Et_2O[g]	96	6:94	93 (*R*)
3	Et_2O	Et_2O[h]	100	23:67	93 (*R*)
4	Et_2O	MTBE	91	3:97	95 (*R*)
5	MTBE	Et_2O	100	6:94	93 (*R*)
6	MTBE	MTBE	58	5:95	96 (*R*)

[a] Reaction conditions as described in Scheme 2, except the use of 2.0 equiv of alane.
[b] Ligand **L11** was employed.
[c] Solvent used for the generation of the alane.
[d] Solvent used for the complex formation (CuTC and ligand).
[e] Determined by GC-MS.
[f] The ee was determined by chiral GC.
[g] 15mol% of ligand used.
[h] $Cu(OAc)_2 \cdot H_2O$ was used as copper source.

Diethyl ether as a solvent for complex formation seems to be necessary for good conversions (entries 1 and 5, Table 4), whereas MTBE favored high enantioselectivites (entries 5 and 6, Table 4). To ensure complete conversion and at the same time to increase the enantioselectivity we prepared the complex in diethyl ether and the alane in MTBE which afforded the same levels of enantioselectivity as observed when employing 15 mol% of the ligand (entry 2). For all the above results the reactions were performed on a typical scale of 10.8 mmol, in order to ensure the consistency of the alane we prepared. To exclude a dependency of the reaction outcome on the amount of alane prepared we synthesized several propenyl-alane solutions in diethyl ether in a 1.8–4.5 mmol scale and observed no major difference in enantioselectivity by using these solutions. We also investigated the stability of the propenyl-alane stock solutions and observed that storing the solution at room temperature over one month afforded comparable levels of enantioselectivity and conversion. This finding shows that alkenylalanes possess the same levels of stability as previously observed for arylalanes.[7] Before testing the optimized conditions for different substrates we wanted to check if the addition of lithium salts and variations in the *t*-BuLi/Me_2AlCl ratio would have an influence on the reaction (Table 5).

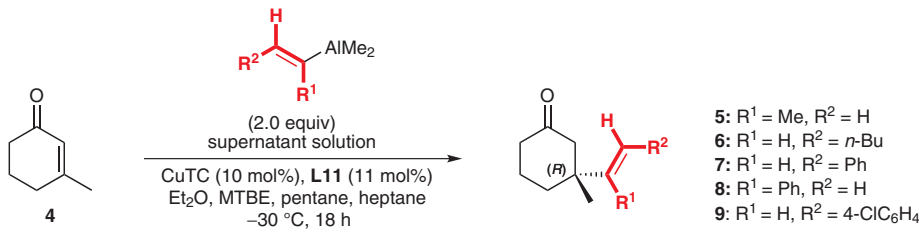
Table 5 Influence of Lithium Salts and Variation of the *t*-BuLi/Me_2AlCl Ratio on the Reaction Outcome[a,b]

Entry	Ratio *t*-BuLi/Me_2AlCl	Conv. (%)[c]	Methyl/alkenyl transfer[b]	ee (%)[d]
1	2.0:1.0	100	6:94	93 (*R*)
2[e]	2.0:1.0	100	4:96	83 (*R*)
3	1.8:1.0	91	30:70	83 (*R*)
4	2.0:0.9	100	4:96	77 (*R*)

[a] Reaction conditions as described in Scheme 2, except the use of 2.0 equiv of alane and complex formation in MTBE.
[b] Ligand **L11** was employed.
[c] Determined by GC-MS.
[d] Determined by chiral GC.
[e] Addition of salts.

The addition of salts proved to be detrimental for the enantioselectivity (Table 5, entry 2). The investigation of the *t*-BuLi/Me_2AlCl showed that ensuring a precise ratio of *t*-BuLi and Me_2AlCl was critical to achieve good conversions and enantioselectivities.[13] Any excess of either *t*-BuLi or Me_2AlCl led to a loss of enantioselectivity (entries 3 and 4) and in the case of an excess of Me_2AlCl also to low conversion and high methyl transfer (entry 3). Therefore we used only fresh solutions of *t*-BuLi and Me_2AlCl to ensure that the used concentration was as close to the indicated concentrations as possible. With the optimized conditions in hand we applied this methodology to various nucleophiles and substrates and carried out the reactions on a 1.5 mmol scale instead of a 0.3 mmol scale, as used for the optimization reactions, in order to

Table 6 Screening of Alkenylalanes[15]



Entry	Product	Conv. (%)[a]	Methyl/alkenyl transfer[a]	Yield (%)[b]	$[\alpha]_D^{20}$	ee (%)[c]
1	5	100	4:96	85	–62.5	91 (*R*)
2	6	94	2:98	50	–39.2	76 (*R*)
3	7	97	0:100	64	–70.8	91 (*R*)
4	8	94	11:89	27	–35.6	94 (*R*)
5	9	97	1:99	71	–92.1	96 (*R*)

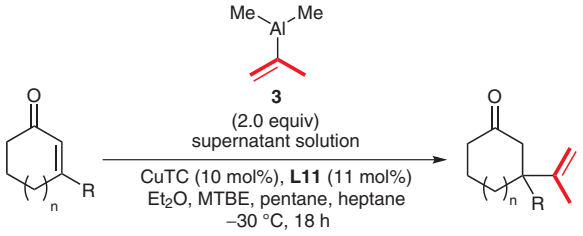
[a] Determined by GC-MS.
[b] Isolated yield.
[c] The ee was determined by chiral GC and chiral SFC.

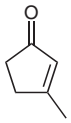
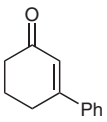
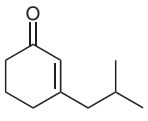
prove its synthetic use (Table 6). For methcyclohexenone **4** all the tested nucleophiles gave good to excellent levels of enantioselectivity. The difference in enantioselectivity for product **5** (entry 1, Table 5 vs. entry 1, Table 6) is probably due to a slightly different ratio in the *t*-BuLi/Me_2AlCl ratio. Due to the sensitivity of the reaction towards the purity of the alkenyl alane slight variations on enantioselectivity are inevitable. In the case of product **6**, *n*-hexenylbromide as nucleophile precursor contained 9% of an impurity which we could not remove by common purification methods. Whether this impurity is responsible for the drop in enantioselectivity is not clear yet. Product **8** has been isolated in poor yield due to the fact that commercially available α-bromostyrene contains approximately 4% of the trans-β-bromostyrene which was much faster transferred and thus led to a 8:92 ratio of **7**/**8**.[14] Nevertheless we succeeded in separating compound **8** from **7** and the methyl adduct by column chromatography. This shows that, especially in the case of secondary bromoalkenes as nuclophile precursors, it is absolutely vital to avoid β-bromoalkene impurities which might lead to a large amount of undesired and difficult to separate side product.

It should also be noted that encumbered nucleophiles led to higher levels of methyl transfer whereas in the case of unhindered nucleophiles, such as the nucleophiles leading to products **6**, **7**, and **9** almost no methyl transfer was observed. The absolute configuration of compound **6** has been determined by comparison of its optical rotation with previously reported data,[4d] whereas for compounds **5**, **7**–**9** we suppose that the ligand directs the attack towards the same facial side, as demonstrated for SimplePhos ligands before.[4f]

Having explored different kinds nucleophiles, we wanted to explore the reaction scope by choosing more challenging substrates such as **10**–**12**. Unfortunately, in all cases a drop of conversion and enantioselectivity was observed. The difficulties encountered when using cyclopentenones as substrates for the copper-catalyzed ACA have been reported several times in the literature.[4d,e,5] We believe that the reason for the drop in reactivity is the diminished orbital overlap between the π-orbitals of the C=O bond and

Table 7 Screening of Substrates



Entry	Substrate	Conv. (%)[a]	Methyl/alkenyl transfer[a]	ee (%)[b]
1	 **10**	49	n.d.	48
2	 **11**	19	0:100	43
3	 **12**	17	n.d.	83

[a] Determined by GC-MS.
[b] The ee was determined by chiral GC.

the C=C bond due to a smaller interior angle of the cyclopentenone scaffold. This would lead to a higher LUMO at the β-position and thus lower the reactivity. A conjugating group such as phenyl will probably also lead to a deactivation of the β-position of the conjugated system by decreasing the positive partial charge via π-donation. This would explain the drop in conversion for substrate **11**. Substrate **12** shows that the reaction is much more sensitive to bulky substrates than to sterically demanding nucleophiles such as **8**. The level of enantioselectivity, however, did only drop slightly (entry 3, Table 7).

In summary, we have described an efficient copper-catalyzed 1,4-addition of vinyl alanes to cyclic enones. Reactions are promoted by SimplePhos ligands which afford the desired β-alkenylcycloalkanones in up to 96% enantioselectivity. The present methodology allows ACA reactions to create quaternary stereogenic centers employing commercially available or easily accessible alkenylbromides.

Challenging substrates, such as **10–12** evidently need more powerful ligands for better enantioselectivity and conversion. The development of such ligands and application of the methodology towards the synthesis of natural products are among the objectives being pursued in our laboratories.

Acknowledgment

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(15) **General Procedure for the Cu-Catalyzed ACA Employing Alkenylalanes Exemplified for Product 5**
To a solution of 2-propenylbromide (480 μL, 653 mg, 5.4 mmol, 1.0 equiv) in MTBE (6.0 mL) was added under inert atmosphere a fresh solution of *t*-BuLi (6.75 mL, 10.8 mmol, 1.6 M in pentane, 2.0 equiv) at –78 °C. The reaction was stirred for 30 min at this temperature. Then a fresh solution of Me_2AlCl (6.0 mL, 5.4 mmol, 0.9 M in heptane, 1.0 equiv) was added, and the reaction mixture was stirred for another 2 h maintaining the temperature at –78 °C. Now the cooling bath was removed, and the reaction vessel was immediately submerged in a water bath. The alane was stirred over night at r.t., and 1 h before use of the solution for catalysis stirring was stopped to ensure precipitation of the salts. Then, 10.5 mL corresponding to 2.0 equiv of the supernatant solution of alane was taken out with a syringe and slowly added to the metal complex. In a separate flask, CuTc (28.5 mg, 0.15 mmol, 10 mol%), ligand **L11** (93.5 mg, 0.17 mmol, 11 mol%), and Et_2O (5.0 mL) were thoroughly stirred at r.t. for 1 h. Then the flask was cooled to –30 °C, and the corresponding alane (10.5 mL, 3.0 mmol, 2.0 equiv) was added. After 15 min of stirring 3-methyl-2-cyclohexenone **4** (170 μL, 165 mg, 1.50 mmol, 1 equiv) was added, and the reaction mixture was stirred for 18 h at this temperature. Then the reaction mixture was quenched at –30 °C with MeOH (1.0 mL) and let warm to r.t. An aqueous solution of HCl (10%, 15 mL) was added, followed by Et_2O (50 mL). Extraction of the aqueous phase with Et_2O (2 × 50 mL) and addition of NaOCl solution (10%, 4 mL) to the combined organic solvents afforded a pale yellow suspension which after extensive shaking turned into a blue suspension.[16] After removal of the aqueous phase the organic phase was dried over Na_2SO_4, and the solvent was removed in vacuo. The remaining crude oil was purified by flash chromatography (SiO_2; pentane–Et_2O = 7:1), and the pure compound **5** was afforded as a colorless oil with a pleasant eucalyptus like fragrance (194 mg, 1.27 mmol, 85%, R_f = 0.23 in pentane–Et_2O = 9:1). The analytical data were in accord with the ones reported in the literature.[17] Chiral separation: Chirasil DEX-CB, 60-0-1-115-0-20-170, 50 cm/s, t_{R1} = 44.80 min, t_{R2} = 47.35 min.
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