Angewandte Chemie

DOI: 10.1002/anie.200803436

Asymmetric Catalysis

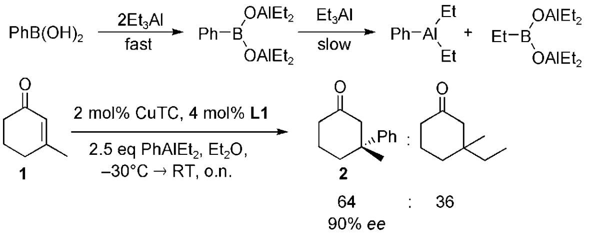
Copper-Catalyzed Asymmetric Conjugate Addition of Aryl Aluminum Reagents to Trisubstituted Enones: Construction of Aryl-Substituted Quaternary Centers**

*Christine Hawner, Kangying Li, Virginie Cirriez, and Alexandre Alexakis**

In the field of asymmetric conjugate addition (ACA) to enones, much effort has been directed towards the development of copper- and rhodium-catalyzed reactions of alkylmetal as well as aryl- and vinylboronic acid reagents.[1] While most reports deal with disubstituted substrates, the construction of enantioenriched all-carbon quaternary stereocenters is still a synthetic challenge.[2] Recently, a number of interesting reports concerning the copper-catalyzed version provided solutions to this problem. However, the use of the classical alkylzinc reagents requires special conditions, such as reactive substrates, for example, nitroalkenes[3] and doubly activated enones.[4] Less-reactive trisubstituted cyclic enones are only accessible with specialized N-heterocyclic carbene (NHC) ligands[5] or more reactive nucleophiles, such as, trialkylaluminum reagents. In combination with stronger coordinating solvents, their enhanced Lewis acidity has made trialkylaluminum reagents very successful in the ACA.[6] Grignard reagents are also useful owing to their wide scope of reaction, but the enantioselectivities are generally lower than with Al and Zn reagents.[7]

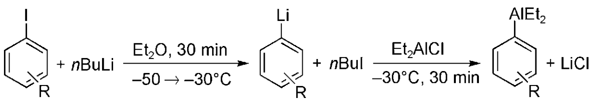
Although quaternary centers are ubiquitous motifs in natural and pharmaceutical products, only few reports deal with their formation through the ACA. Most examples are limited to the addition of phenyl and *p*-anisyl,[5,7] the aryl group is already present in the substrate[6c,d] or activated substrates[8] are required. To date, no general method has been developed to *introduce* a wide range of aromatic groups to trisubstituted enones. In our search for a solution to this problem, we turned our attention to aluminum reagents, as they had proven to be very successful in the introduction of alkyl substituents. However, aryl aluminum reagents are not commercially available. Similarly, the commercial availability of aryl zinc reagents is restricted to diphenyl zinc and other routes have been developed to obtain the desired compounds, such as transmetalation of arylboronic acids with diethyl zinc[9] or of aryl lithiums with zinc dichloride.[8b,10]

We therefore envisaged generating aryl alanes in similar ways. First, the phenyl transfer from phenylboronic acid to triethylaluminum was performed (Scheme 1). Three equivalents of triethylaluminum were necessary for the ACA to take place. We reasoned that in a first step, 2 equivalents of Et_3Al reacted with 1 equivalent of $PhB(OH)_2$, which was followed by the phenyl transfer from borane to the third equivalent of Et_3Al to form the phenyl alane. However, the ethyl transfer to the substrate 3-methylcyclohex-2-enone (**1**) lead to 36% of undesired byproduct.



Scheme 1. Transmetalation of phenylboronic acid to triethylaluminum. CuTC = copper thiophencarboxylate.

Therefore, we were looking for another option to generate aryl alanes and turned towards a sequence consisting of halogen–metal exchange between an aryl halide and *n*BuLi giving the corresponding aryl lithium compound which was then transmetalated with a dialkylaluminum chloride reagent to generate the desired dialkyl aryl aluminum species in situ (Scheme 2).[11] The diethylphenyl alane thus generated was used as nucleophile in the copper-catalyzed ACA of 3-methylcyclohex-2-enone.



Scheme 2. I/Li-exchange–Li/Al-transmetalation sequence.

We optimized the experimental conditions using commercial PhLi for the transmetalation step generating $PhAlEt_2$. On the basis of work by Hoveyda et al,[8b] we decided to start our investigations with 9 equivalents of $PhAlEt_2$ at −30 °C and to use only the supernatant solution, as LiCl precipitated from the reaction mixture (Scheme 3).

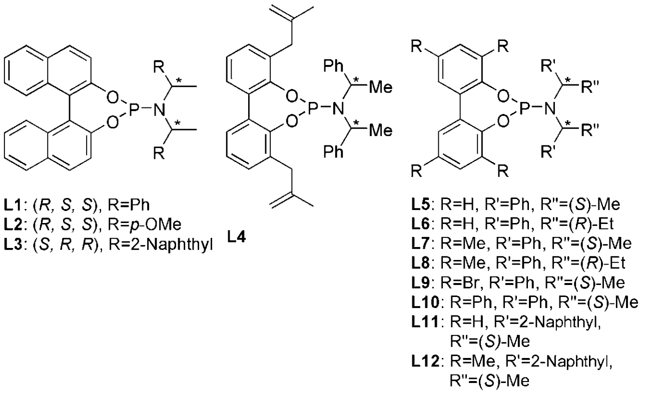
The reaction was very selective towards the aryl transfer and went to full conversion giving 97% *ee*. Et_2AlCl proved to be a better transmetalation agent than Me_2AlCl and $i\mathrm{Bu}_2AlCl$. From a large number of phosphoramidite ligands

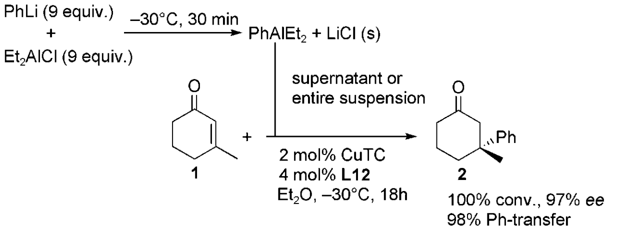
---

[*] C. Hawner, Dr. K. Li, V. Cirriez, Prof. Dr. A. Alexakis
Department of Organic Chemistry, University of Geneva
30 quai ernest Ansermet, 1211 Geneve 4 (Switzerland)
Fax: (+41) 223-793-215
E-mail: alexandre.alexakis@chiorg.unige.ch

[**] We thank the European Community (Marie Curie Early Stage Researcher Training, MEST-CT-2005-019780) for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200803436.





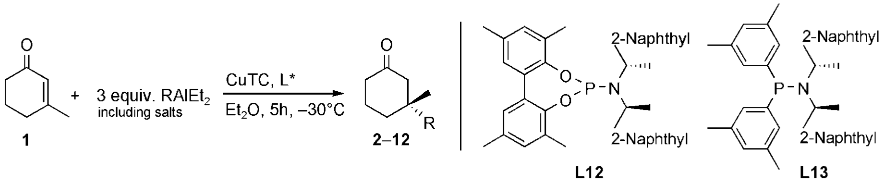
Scheme 3. Conjugate addition with $PhAlEt_2$ as the nucleophile.

(see Supporting Information for results) and eleven different copper salts, **L12** and CuTC were chosen (Scheme 3). Interestingly, the ligand had a significant influence on conversion and especially *ee* value, whereas almost all the copper salts gave the same results. The use of less than 9 equivalents of phenyl alane was detrimental for the conversion and both conversion and excess decreased when THF was used as solvent.

Since the separation of the supernatant from the resulting salts is not convenient, we added the whole suspension to the mixture of CuTC and **L12** in Et_2O to see if the salts influenced the reaction. This was not the case and exactly the same results were obtained as in the salt-free reactions.

We were interested in adding substituted aryl groups for which the lithiated precursor is not commercially available. Therefore, we conducted further optimization with in situ prepared PhLi, which was generated through I/Li-exchange from PhI. However, no conversion occurred. For the tandem hydroalumination–ACA reaction of vinyl alanes, 30 mol% of CuX and 30 mol% of ligand are necessary for the reaction to take place.[6d] Therefore, we increased the catalyst loading to 10 mol% using equimolar amounts of copper and ligand. At the same time, we added only 3 equivalents of alane. Under these conditions, the reaction lead to full conversion and the same *ee* values as obtained using the commercial PhLi.

Table 1: Screening of nucleophiles.

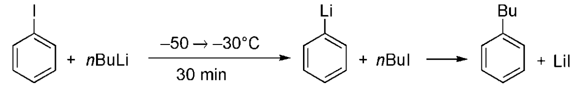


Entry	R	CuTC [mol%]	L [mol%]	L*	Product	Yield [%]	*ee* [%]
1	Ph	5	5	**L12**	**2**	n.d.[c]	97
2	Ph	10	11	**L12**	**2**	75	96.5
3	Ph	10	11	**L13**	**2**	n.d.[c]	94
4	*m*-MeC_6H_4	5	5.5	**L12**	**3**	0	
5	*m*-MeC_6H_4	10	11	**L12**	**3**	87	96.8
6	*m*-MeC_6H_4	5	10	**L12**	**3**	n.d.[c]	97.8
7	*p*-MeC_6H_4	10	11	**L12**	**4**	82	96.3
8[d]	*o*-MeC_6H_4	10	11	**L13**	**5**	82	84.6
9	*m*-$OMeC_6H_4$	10	11	**L12**	**6**	66	98
10	*p*-$OMeC_6H_4$	10	11	**L12**	**7**	81	95
11	*p*-$OMeC_6H_4$	5	5.5	**L12**	**7**	0	
12	*p*-$OMeC_6H_4$	5	10	**L12**	**7**	n.d.[c]	97.2
13[a]	2-naphthyl	10	11	**L12**	**8**	59	98.6
14	*m*-$CF_3C_6H_4$	10	11	**L12**	**9**	73	94.9
15	*p*-$CF_3C_6H_4$	10	11	**L12**	**10**	74	98.4
16	*m*-BrC_6H_4	10	11	**L12**	**11**	76	97.7
17[b]	Bu-CH=CH	10	10	**L12**	**12**	93	82

[a] 2-Bromonaphthalene served as aryl halide. [b] The reaction was stirred for 19 h at −30 °C, conversion was 80%. [c] n.d. = not determined. [d] The reaction was stirred for 21 h at −10 °C.

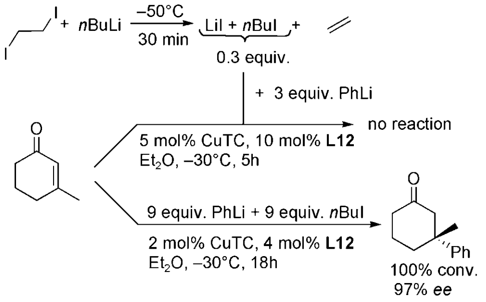
To investigate the scope of the reaction, we decided to use a variety of different aryl groups and a vinyl alane in this transformation (Table 1). As SimplePhos ligands give higher yields and *ee* values than phosphoramidite ligands in the addition of $AlMe_3$ to 3-phenylcyclohex-2-enone,[6c] we tested this new kind of ligand under the optimized reaction conditions. This study showed that a wide range of electron-donating and electron-withdrawing groups, which can be substituted in *para*- or *meta*-position are successful in this reaction giving full conversion and very high *ee* values. Only the *o*-substituted aryl groups required special conditions. Whereas ligand **L12** led to only moderate conversion and low *ee* values, the use of SimplePhos **L13** improved the results. Overnight reaction at 10 °C achieved full conversion and 84.6% *ee* (Table 1, entry 8). Aryl bromides could also be used for the generation of the corresponding alane, as shown by 2-bromonaphthalene (Table 1, entry 13). Although a catalyst loading below 5 mol% was ineffective, 5 mol% of copper salt and ligand were sufficient for the addition of a simple phenyl group (Table 1, entry 1), but double this amount proved to be necessary for substituted aryl groups. In some cases, a 5:10 mol% ratio of CuTC:**L12** was successful (Table 1, entries 6 and 12). The absolute configuration of the phenyl adduct was determined to be *R*, and by extension we ascribe this configuration to the other aryl substituents as well. Our methodology can be extended to vinyl alanes by starting from the corresponding iodide (Table 1, entry 17). The desired adduct, which also had the *R*-configuration, could be obtained with higher *ee* value and lower catalyst loading than previously reported for the tandem hydroalumination–A.C.A.[6d]

To understand why a higher catalyst loading was necessary when the in situ prepared PhLi was used instead of the commercial one, we studied the influence of *n*BuI and LiI in the ACA. The commercial PhLi is free of these two reagents. However, 1 equivalent of *n*BuI is formed during the I/Li-exchange step, and LiI, which is soluble in Et$_2$O, can be generated through the attack of PhLi on *n*BuI, even though this reaction is very slow at low temperature (Scheme 4).[12]



Scheme 4. Generation of LiI during the I/Li-exchange.

Although no traces of *n*BuPh were detectable by GC-MS below −15 °C, we wondered if even small, undetectable amounts of LiI could disrupt the reaction. Therefore, we added *n*BuI and LiI to the commercial PhLi to study the influence of these two reagents on the reaction (Scheme 5).



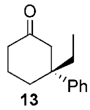
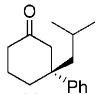
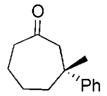
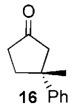
Scheme 5. Study of the role of LiI and *n*BuI in the ACA.

While *n*BuI did not influence the reaction at all, the presence of LiI prevented any conversion from taking place. Consequently, careful temperature control during the I/Li exchange is necessary to restrain the formation of LiI.

We were also interested in understanding if LiI interacted with the ligand or any other reagent of the transformation. However, when LiI was added to a solution of **L12** in Et$_2$O and a small amount of C_6D_6, no change in the shift of the ^{31}P NMR signal could be detected. We therefore suppose that LiI interacts at a different point of the reaction.

Finally we tested differently substituted cyclohexenones as well as enones with different ring sizes (Table 2). After optimization of the reaction conditions, the phenyl alane could also add to other substrates giving excellent *ee* values in all cases except with 3-methylcyclopent-2-enone (Table 2, entry 4), where only 77.5 % *ee* was obtained. This result is, however, still the highest excess ever reported for the Michael addition to this substrate. However, the reaction conditions and the ligand had to be adapted to the more challenging substrates. We found that higher temperature and longer reaction times were needed to give satisfactory degrees of conversion. Unfortunately, these conditions lead to an increase of ethyl transfer with the exception of the *i*Bu-substituted cyclohexenone, where no ethyl adduct was detected. However, in all cases the product could be isolated in good yields. Furthermore, the more reactive SimplePhos ligand **L13** gave better conversion and slightly higher *ee* values for products **14–16** than the equivalent phosphoramidite ligand.

Table 2: Screening of substrates.[a]

Entry	Product	Ligand	Conversion [%][b]	Yield [%]	*ee* [%]
1[c]	 **13**	**L12**	94	77	95
2	 **14**	**L13**	91	58	98.6
3[d]	 **15**	**L13**	99	62	96.5
4[e]	 **16**	**L13**	100	67	77.5

[a] Reaction conditions: 10 mol % CuTC, 11 mol % ligand, Et$_2$O, overnight, −10 °C. [b] Determined by GC-MS. [c] 13 % ethyl transfer determined by GC-MS. [d] 3 % ethyl transfer determined by GC-MS. [e] 7 % ethyl transfer determined by GC-MS.

In summary, we have developed the first copper-catalyzed ACA, which allows the addition of a wide range of aryl alanes to 3-methylcyclohex-2-enone with excellent conversion and *ee* values leading to the formation of chiral aryl-substituted quaternary centers. Furthermore, we have shown that this reaction is general to a variety of substrates carrying different β-substituents or having different ring sizes. The desired alane can easily be generated from the corresponding aryl iodide or bromide through an I/Li-exchange–Li/Al-transmetalation sequence and no separation of the resulting insoluble LiCl is necessary, which makes this method highly convenient. Even vinyl alanes can be generated in this way and used in the ACA successfully.

Experimental Section

Typical procedure: The aryl iodide (1.05 mmol) was dissolved in Et$_2$O (0,5 mL) under inert atmosphere and cooled to −55 °C before the addition of *n*BuLi (3.15 mmol, 656 µL, 1.6 M in hexanes). The mixture was stirred for 30 min at −55 °C. Then, Et$_2$AlCl (1.05 mmol, 1.05 mL, 1 M in hexanes) was added dropwise and stirred for 30 min between −50 and −20 °C. In a separate flask, the copper salt (10 mol %), the ligand (11 mol %), and Et$_2$O (1.5 mL) were stirred thoroughly at room temperature for 30 min. The flask was cooled to −30 °C and the alane suspension including the salts was added to the copper/ligand mixture. After 5 min, the substrate (0.35 mmol) was introduced. After 5 h at −30 °C the reaction was quenched with 10 % HCl (20 mL). Et$_2$O was added (20 mL) and the layers were separated. The aqueous phase was extracted one more time with Et_2O (20 mL). The combined organic phases were extracted once with NaOH (1M, 20 mL) and once with H_2O (20 mL). The organic layers were combined and dried over $MgSO_4$. The solution was then collected by filtration over silica, and concentrated in vacuo. The crude was purified by flash chromatography on a silica column with a mixture of pentane/Et_2O (9:1) as eluent.

Received: July 16, 2008

Keywords: asymmetric catalysis · copper · enones · Michael addition · quaternary stereocenters

---

[1] For reviews on asymmetric conjugate additions, see: a) A. Alexakis, C. Benhaim, *Eur. J. Org. Chem.* **2002**, 3221–3226; b) N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, 171–196; c) T. Hayashi, *Acc. Chem. Res.* **2000**, *33*, 354–362.

[2] a) C. Jiang, B. M. Trost, *Synthesis* **2006**, 369–396; b) A. Baro, J. Christoffers, *Adv. Synth. Catal.* **2005**, *347*, 1473–1482.

[3] J. Wu, D. M. Mampreian, A. H. Hoveyda, *J. Am. Chem. Soc.* **2005**, *127*, 4584–4585.

[4] A. W. Hird, A. H. Hoveyda, *J. Am. Chem. Soc.* **2005**, *127*, 14988–14989.

[5] K. Lee, K. Brown, A. W. Hird, A. H. Hoveyda, *J. Am. Chem. Soc.* **2006**, *128*, 7182–7184.

[6] a) M. d'Augustin, L. Palais, A. Alexakis, *Angew. Chem.* **2005**, *117*, 1400–1402; *Angew. Chem. Int. Ed.* **2005**, *44*, 1376–1378; b) N. Fuchs, M. d'Augustin, M. Humam, A. Alexakis, R. Taras, S. Gladiali, *Tetrahedron: Asymmetry* **2005**, *16*, 3143–3146; c) L. Palais, I. S. Mikhel, C. Bournaud, L. Micouin, C. A. Falciola, M. Vuagnoux-d'Augustin, S. Rosset, G. Bernardinelli, A. Alexakis, *Angew. Chem.* **2007**, *119*, 7606–7609; *Angew. Chem. Int. Ed.* **2007**, *46*, 7462–7465; d) M. Vuagnoux-d'Augustin, A. Alexakis, *Chem. Eur. J.* **2007**, *13*, 9647–9662; e) M. Vuagnoux-d'Augustin, S. Kehrli, A. Alexakis, *Synlett* **2007**, 2057–2060.

[7] a) D. Martin, S. Kehrli, M. d'Augustin, H. Clavier, M. Mauduit, A. Alexakis, *J. Am. Chem. Soc.* **2006**, *128*, 8416–8417; b) Y. Matsumoto, K. Yamada, K. Tomioka, *J. Org. Chem.* **2008**, *73*, 4578–4581.

[8] a) A. J. Wilsily, E. Fillion, *J. Am. Chem. Soc.* **2006**, *128*, 2774–2775; b) M. K. Brown, T. L. May, C. A. Baxter, A. H. Hoveyda, *Angew. Chem.* **2007**, *119*, 1115–1118; *Angew. Chem. Int. Ed.* **2007**, *46*, 1097–1100; c) A. Wilsily, E. Fillion, *Org. Lett.* **2008**, *10*, 2801–2804.

[9] J. Rudolph, C. Bolm, *J. Am. Chem. Soc.* **2002**, *124*, 14850–14851.

[10] a) D. Peña, F. López, S. R. Harutyunyan, A. J. Minnaard, B. L. Feringa, *Chem. Commun.* **2004**, 1836–1837; b) J. G. Kim, P. J. Walsh, *Angew. Chem.* **2006**, *118*, 4281–4284; *Angew. Chem. Int. Ed.* **2006**, *45*, 4175–4178.

[11] M. Oishi, in *Science of Synthesis*, *Vol. 7* (Ed.: H. Yamamoto), Thieme, Stuttgart, **2004**, p. 261.

[12] G. Cahiez, D. Bernard, J. F. Normant, *Synthesis* **1976**, 245–248.