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New Experimental Conditions for Tandem hydroalumination/Cu-Catalyzed Asymmetric Conjugate Additions to β-Substituted Cyclic Enones

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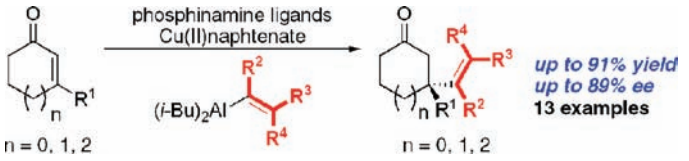
ABSTRACT



Readily available alkenylalanes, arising from hydroalumination of *unprotected* terminal alkynes, have been directly employed for the copper-catalyzed asymmetric conjugate addition (ACA) to β-substituted cyclic enones. The desired products, containing a quaternary stereogenic center, are generally obtained in good yields and enantioselectivities.

Since the discovery of the hydroalumination reaction of terminal alkynes by Wilke and Müller in 1960,[1] there have been only few reports of the use of such alkenylalanes in Cu-catalyzed conjugate addition reactions.[2] The use of these nucleophiles for catalytic asymmetric conjugate addition reactions is made difficult by the presence of up to 29% of Al-acetylides in vinylalanes.[3] These acetylides might act as competing ligands in the presence of a chiral copper complex and thus lead to undesired side reactions and decrease of enantioselectivities.[4] A solution to this problem was very recently reported by Hoveyda et al., who made use of Si-protected alkynes in order to circumvent the problem of Al-acetylide formation during the hydroalumination reaction.[5,6] The afforded Si-substituted vinylaluminums were used for NHC-Cu-catalyzed ACA to β-substituted cyclic enones yielding highly enantioenriched compounds. However, when nonprotected alkenylalanes were used, the enantioselectivity dropped significantly (30% ee).[5]

In order to avoid the presence of acetylides, we focused on the generation of vinylalanes from the corresponding vinyl halides.[7,8] This strategy proved to be particularly successful for conjugated alkenylalanes such as styrenylalanes but did have the drawback that for simple alkenyl substituents, such as hexenylalane, a longer and indirect synthesis of the mixed alane had to be effected, as shown in Scheme 1.

Therefore, we revisited the tandem hydroalumination-ACA reaction, keeping in mind that hydroaluminations

(1) Wilke, G.; Müller, H. *Justus Liebig Ann. Chem.* **1960**, *629*, 222–240.

(2) For two examples of racemic conjugate addition reactions, see: (a) Ireland, R. E.; Wipf, P. *J. Org. Chem.* **1990**, *55*, 1425–1426. (b) Wipf, P.; Smitrovich, J. H.; Moon, C. *J. Org. Chem.* **1992**, *57*, 3178–3186. For two examples of tandem hydroalumination–ACA reactions affording products in 50–73% ee, see:(c) Vuagnoux-d'Augustin, M.; Alexakis, A. *Chem.—Eur. J.* **2007**, *13*, 9647–9662. (d) Palais, L.; Alexakis, A. *Chem.—Eur. J.* **2009**, *15*, 10473–10485.

(3) Zweifel, G.; Miller, J. A. *Org. React.* **1984**, *32*, 375.

(4) For observations of the harmful effect of acetylides in ACA reactions, see: Corey, E. J.; Kwak, Y. *Org. Lett.* **2004**, *6*, 3385–3388.

(5) May, T. L.; Dabrowski, J. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 736–739.

(6) The use of Si-protected alkynes to circumvent Al-acetylide formation is a well-known strategy; see ref 3.

(7) For one example using (*E*)-1-iodohex-1-ene as a nucleophile precursor, see: (a) Hawner, C.; Li, K.; Cirriez, V.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8211–8214. For a more general disclosure affording product in up to 96% ee, see:(b) Müller, D.; Hawner, C.; Tissot, M.; Palais, L.; Alexakis, A. *Synlett* **2010**, 1694–1698.

(8) Generated Me_2Al-vinylalanes do have the advantage of being stronger Lewis acids than $(i\text{-}Bu)_2Al$-vinylalanes and therefore show higher reactivity.

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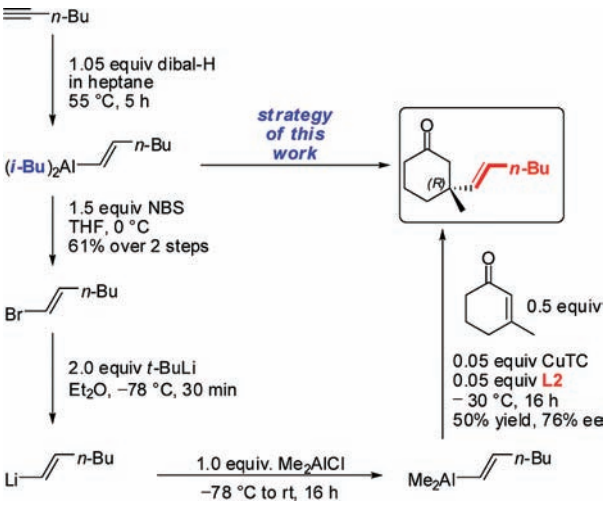
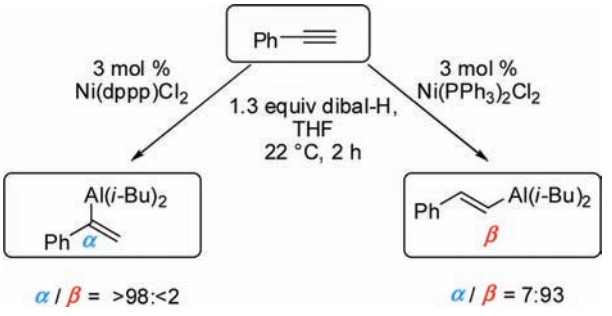
Scheme 1. Direct Use of the $(i\text{Bu})_2$Al-vinyl Nucleophile



had to be done in a way as to keep the Al-acetylide formation as low as possible. For alkynes bearing secondary or tertiary alkyl substituents, low amounts of the Al-acetylide formation are usually observed, and the generated alane can be used without precautions.[9] We were aware that for primary alkyl-substituted alkynes depending on the chain length of the alkyl group significant amounts of the acetylide are formed.[10] Previous studies showed that lower amounts of alkenylaluminums led to higher enantioselectivities, which is probably due to the fact that the alane did contain substances which had a deleterious effect on the active complex.[11] Therefore, our initial strategy was to keep the amount of alane as low as possible but also to employ strong donor ligands which tightly bind to copper and therefore are less prone to substitution by a nonchiral acetylide ligand.

Scheme 2. Selective Generation of α- and β-Alkenylalanes[12]



Hoveyda and co-workers recently reported the nickel-catalyzed hydroalumination of conjugated alkynes with high levels of α- or β-selectivity and even more important with very low levels (<2%) of Al-acetylide formation (Scheme 2).[12,13]

(9) For formation of <2% of Al-acetylide, see ref 3.

(10) 6% of Al-acetylide formation for the hydroalumination of hexyne; see ref 3.

Having validated the concerns for the hydroalumination reactions for different substrates such as primary, secondary, and tertiary alkyl-substituted alkynes as well as for conjugated alkynes, we started optimizing the reaction conditions. From our experience in the field of ACA reactions with alkenylalanes, we knew that phosphoramidite ligands, and especially electron-rich phosphinamine ligands, afforded such reactions with good to excellent enantioselectivities.[2c,d,7a,7b] Therefore, we envisaged screening ligands which can be easily prepared on a multigram scale and a second-generation SimplePhos ligand **L3a** bearing an alkyl instead of an aryl group, thus rendering it even more electron rich (Figure 1).[14,15]

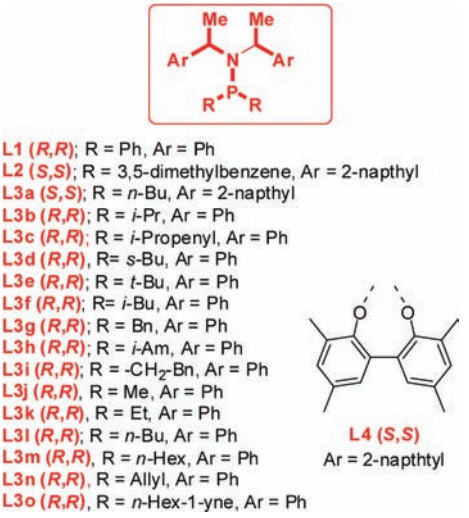


Figure 1. Phosphinamine and phosphoramidite ligand library.

First, we optimized the conditions for the most challenging nucleophile, namely hexenylalane, which is known to contain 6% of deleterious Al acetylide (Table 1).[10]

For all the studied reactions and especially in the absence of ligand (entry 6), significant amounts of the 1,2-addition−dehydration products were observed.[16] As expected, conversion and the preference for 1,4-addition was significantly improved with the strong donor ligand **L3a**, whereas weaker donor ligands such as **L1** and **L4** gave rise to large amounts of 1,2-addition (entries 1−4). Surprisingly, ligand **L2**, though affording high enantioselectivity (entry 2), led only to poor 1,4:1,2

(11) For instance, such a substance might be LiCl, which was shown to decrease enantioselectivities; see ref 7b.

(12) Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10961–10963.

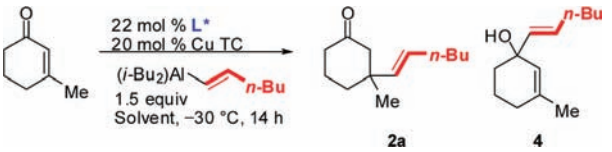
(13) In the absence of a Ni catalyst usually high levels of Al-acetylide formation (>20%) is observed; see ref 12.

(14) See the Supporting Information for details.

(15) For the synthesis of SimplePhos Ligands, see: (a) Palais, L.; Mikhel, I. S.; Bournaud, C.; Micouin, L.; Falciola, C. A.; Vuagnoux-d Augustin, M.; Rosset, S.; Bernardinelli, G.; Alexakis, A. *Angew Chem. Int. Ed.* **2007**, *46*, 7462–7465. (b) Reference 2d. (c) Bournaud, C.; Falciola, C.; Lecourt, T.; Rosset, S.; Alexakis, A.; Micouin, L. *Org. Lett.* **2006**, *8*, 3581–3584.

(16) This has been observed previously; see ref 2c.

Table 1. Optimization of Reaction Conditions[a]



entry	L*	solvent	conv[b] (%)	**2a**:**4**[c]	ee (**2a**)[d] (%)
1	**L1**	Et_2O	100	65:35	51 (*S*)
2	**L2**	Et_2O	98	51:49	83 (*R*)
3	**L3a**	Et_2O	100	85:15	76 (*R*)
4	**L4**	Et_2O	98	53:47	77 (*R*)
5[e]	**L3a**	Et_2O	100	87:13	77 (*R*)
6		Et_2O	75	25:75	
7	**L3a**	THF	80	92:8	66 (*R*)
8	**L3a**	EtOAc	98	94:6	75 (*R*)
9	**L3a**	DCM	88	42:58	74 (*R*)
10	**L3a**	toluene	97	84:16	84 (*R*)
11	**L2**	toluene	96	24:77	83 (*R*)
12	**L3a**	hexane	100	52:48	73 (*R*)
13[e]	**L3a**	toluene	72	93: 7	83 (*R*)
14[f]	**L3a**	**toluene**	**97**	**91:9**	**82 (*R*)**
15[g]	**L3a**	toluene	100	82:18	83 (*R*)
16[h]	**L3a**	toluene	96	32:68	79 (*R*)
17[i]	**L3a**	toluene	100	54:46	81 (*R*)

[a] Reaction performed under Ar atmosphere on a 0.3 mmol scale. [b] Determined by GC/MS. [c] Determination of the corresponding elimination products by GC/MS. [d] Determined by chiral GC analysis. [e] Reaction performed with 1.2 equiv of alkenylalane. [f] Reaction performed with 13 mol % of Cu(II)naphthenate instead of CuTC. [g] Addition of 20 mol % of hex-1-yne. [h] Addition of 20 mol % of hex-1-ynyldiisobutylaluminum. [i] Reaction carried out with 11 mol % of **L3a** and 7 mol % of Cu(II)napththenate on a 2.0 mmol scale.

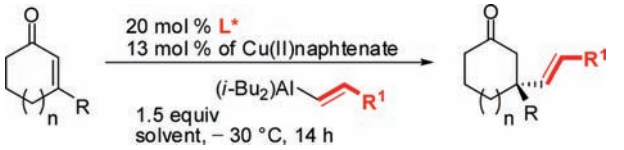
ratios, implying that not only electronic factors influence the regioselectivity.

Because of the high modularity of alkyl-substituted phospinamines, we synthesized a small library of such ligands and screened them for the reaction depicted in Table 1.[14] α-Branched alkyl groups (**L3b**, **L3c**, **L3d**, **L3e**) were impossible to synthesize, which we believe is due to the high steric demand. β-Branched alkyl substituents (**L3f**, **L3g**) only afforded messy reactions and low enantioselectivities. Only γ-branched ligands (**L3h**, **L3i**) afforded reasonable levels of enantioselectivity and clean reactions; however, they did not surpass the selectivities achieved by their *n*-Bu counterpart. For the linear alkyl substituents the following trend was observed: **L3o** < **L3j** < **L3k** < **L3n** < **3m** < **3l**. Hence, the initially used ligand **L3a** was the most selective ligand of its kind for this reaction.

Final optimizations and control experiments were carried out (entries 7−17, Table 1).[14] Several points regarding these reactions are noteworthy: (1) Donor solvents such as THF and EtOAc favor the 1,4-addition, whereas noncoordinating solvents such as hexane and DCM lead to high levels of 1,2-addition. (2) EtOAc can be used for such reactions, implying the high functional group tolerance of such alkenylalanes. (3) Lowering the amount of alane does slightly favor the 1,4-adduct (entries 5 and 13). (4) Only 13 mol % of Cu(II) naphthenate as the most inexpensive organic copper salt afforded the same selectivities as CuTC (copper thiophene 2-carboxylate). Given that this Cu salt can be used as a stock solution, we favored this Cu source over CuTC.[14] (5) Free alkyne (entry 15) did not have a major effect on the regioselectivity of the reaction, whereas upon addition of 20 mol % of the corresponding acetylide the 1,2-addition becomes the predominant reaction pathway (entry 16). Surprisingly, the presence of Al-acetylide did not have a great influence on the enantioselectivity.

With the optimized reaction conditions in hand (entry 14), we focused on enlarging the nucleophile scope. Two methods were developed (methods A and B) because it was found that **L2** worked equally efficient as **L3a** when nucleophiles other than hexenylalane were used.[17] Moreover, we found that for substrates other than 3-methylcyclohex-2-enone the established reaction conditions were inefficient (low conversions). We knew that such transformations were possible with Me_2Al-vinyl species and managed to solve this problem by activation of the substrate with 1 equiv of Me_3Al.[18,19]

Table 2. Cu-Catalyzed ACA of Unprotected Alkenylalanes to β-Substituted Cyclic Enones[a]



entry	substrate (R; method)[b]	*n*	reagent (R^1)	1,4:1,2[c]	yield[d] (%)	ee[e] (%)
1[f]	Me; A	0	*n*-Bu	82:18	44 (**1a**)	34
2	Me; A	1	*n*-Bu	91:9	72 (**2a**)	83
3	Me; A	1	$(CH)_2$ (c-C_5H_9)	85:15	49 (**2b**)	75
4	Me; B	1	Bn	95:5	61 (**2c**)	82
5	Me; A	1	Cy	94:6	91 (**2d**)	79
6	Me; B	1	*t*-Bu	95:5	79 (**2e**)	85
7[f]	Et; A	1	*n*-Bu	92:8	65 (**2f**)	55
8[f]	*i*-Bu; B	1	*n*-Bu	63:37	41 (**2g**)	89
9[f]	Me; A	2	*n*-Bu	93:7	57 (**3a**)	79

[a] Reactions performed under argon on a 0.6 mmol scale. [b] Method A: **L3a**, toluene. Method B: **L2**, Et_2O. [c] Determined by GC/MS. [d] Yield of isolated 1,4-adduct. [e] Determined by chiral GC. [f] Activation with 1.0 equiv of Me_3Al, Et_2O, −20 °C.

As the data in Table 2 indicate, a relatively large scope of alkyl-substituted alkenes undergo ACA efficiently with good levels of enantioselectivity. Furthermore, we were able to achieve high levels of enantioselectivity for

(17) Concerning the selectivities of **L2** and **L3a**, most of the reactions showed differences in enantioselectivities of < 15%. However, **L3a** gives higher enantioselectivities for 5- and 7-membered substrates, whereas **L2** affords particularly high enantioselectivities for sterically demanding substrates or nucleophiles.

(18) Unpublished results.

(19) From the work of Wipf, we already knew that activation with TMS-Cl and BF_3 did not accelerate such reactions; see ref 2b.

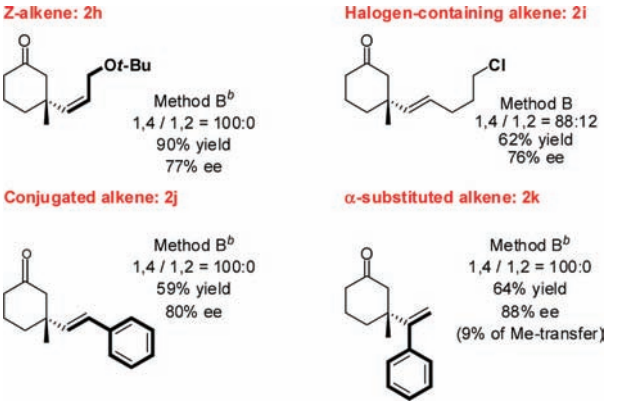
sterically hindered substrates and cycloheptenone (entries 8 and 9).[20] Not surprisingly, cyclopentenone adduct **1a** was obtained with low levels of enantioselectivities (entry 1).[21] These findings imply that the developed methodology is somewhat complementary to Hoveyda's recent work on Si-substituted vinyl alanes.[5]

In order to further extend the nucleophile scope, we thought about introduction of *Z*-alkenes (**2h**), halogen-containing alkenes (**2i**), conjugated alkenes (**2j**), and α-substituted alkenes (**2k**). *Z*-Alkenes are easily accessible via hydroalumination of propargylic ethers,[22] whereas for the α-substituted alkene and the conjugated alkene we envisaged employing Ni-catalyzed hydroalumination as recently explored by Hoveyda and co-workers (Scheme 2).[12]

We were delighted to see that all of these challenging nucleophiles did undergo ACA to 3-methylcyclohex-2-enone with good levels of enantioselectivity (Scheme 3). Several points for Scheme 3 are noteworthy: (1) For all of the depicted adducts there is no precedence for the addition of such nucleophiles in tandem hydroalumination–ACA reactions.[23] (2) Despite the presence of THF and nickel salts, good enantioselectivities were obtained for both the α- and the *β*-styrenyl adducts. (3) Surprisingly, the α- and *β*-styrenyl compounds gave no rise to 1,2-addition. (4) In the case of the *β*-styrenyl adduct, we observed no addition of the α-styrenylalane, which is in accord with previous observations.[24]

In conclusion, we have shown that nonprotected in situ generated alanes can be employed directly for the Cu-catalyzed ACA. Challenges in such reactions, namely the presence of Al-acetylides, have been met making use of several strategies. Moreover, a library of second-generation SimplePhos ligands has been synthesized, and a simple protocol is provided for the synthesis of **L2** and **L3a** on a multigram scale which we hope will stimulate the use of such ligands in asymmetric transformations.

Scheme 3. Further Extension of the Nucleophile Scope[a]



[a] Reaction conditions as indicated for Table 2.
[b] Activation with 1.0 equiv of Me_3Al, −20 °C.

Acknowledgment. 2cWe thank the Swiss National Research Foundation (Grant No. 200020-126663) and COST action D40 (SER Contract No. C07.0097) for financial support as well as BASF for the generous gift of chiral amines.

Supporting Information Available. Experimental procedures, NMR spectra, and chiral separations for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) Cycloheptenones prooved to be inefficient in catalysis with Si-protected alkenyl alanes; see ref 5.
(21) **L2** and **L4** afforded inferior enantioselectivities for the addition of trialkylaluminum to *β*-substituted cyclopentenones compared to the cyclohexenone counterparts; see refs 2c and 2d.
(22) Alexakis, A.; Duffault, J. M. *Tetrahedron Lett.* **1988**, *29*, 6243–6246.
(23) For the *β*-styrenyl adduct there has been only precedence for Si-protected alkenyl alanes; see ref 5.
(24) As previously observed, *β*-styrenylalane adds much faster than the α-styrenylalane, see ref 7b.