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Copper-Catalyzed Asymmetric 1,4-Addition of Alkenyl Alanes to *N*-Substituted-2-3-dehydro-4-piperidones

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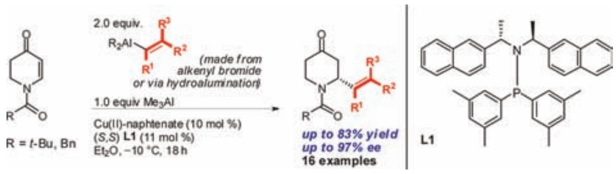
ABSTRACT



Readily available vinyl alanes are used in the Cu-catalyzed asymmetric conjugate addition reaction to *N*-substituted-2-3-dehydro-4-piperidones. The enhanced reactivity of recently developed and easily prepared phosphine amine ligands in combination with inexpensive Cu(II)naphtenate (CuNp) allows the introduction of a great variety of alkenyl, alkyl, and aryl aluminums in high enantioselectivity.

Since the pioneering work of Hayashi in 2004 related to the asymmetric conjugate addition (ACA) of arylzinc reagents to 2,3-dihydro-4-piperidones, these kinds of compounds have become benchmark substrates for ACA.[1] Various aryl and alkyl nucleophiles such as arylzinc,[1] arylboronic acids,[2] arylboroxines,[3] tetraarylborates,[4] aryl-[2-(hydroxymethyl)-phenyl]dimethylsilanes,[5] arylsiloxanes,[6] aryltitanium tri-isopropoxides, and alkylzinc[7] and alkylaluminum reagents[8] were successfully introduced affording highly enantioenriched products. However, all reported attempts to introduce the highly functionalizable vinyl group failed.[1,2b] This and the fact that the corresponding piperidone products represent valuable building blocks in the synthesis of pharmaceutically active piperidines caught our attention.[9] Over the past four years, we showed particular interest in the introduction of the alkenyl group to various Michael acceptors. This includes β-substituted cyclic enones, which upon addition of a carbon nucleophile form an all carbon quaternary stereogenic center.[10] Therefore, we reasoned that two recently developed reaction protocols might solve the longstanding challenge of alkenyl addition to 2,3-dihydro-4-piperidones such as **1a** (Scheme 1).[10e,f] Herein, we present an efficient set of protocols for catalytic ACA reactions for a wide range of alkenyl aluminum reagents with unactivated substrates **1a** and **1b**. The requisite aluminum-based reagents can be prepared efficiently via hydroalumination or

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(6) Gini, F.; Hessen, B.; Feringa, B. L.; Minnaard, A. J. *Chem. Commun.* **2007**, 710–712.
(7) Sebesta, R.; Pizzuti, M. G.; Boersma, A. J.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2005**, 1711–1713. (b) Endo, K.; Ogawa, M.; Shibata, T. *Angew. Chem.* **2010**, *122*, 2460–2463. *Angew Chem. Int. Ed.* **2010**, *49*, 2410–2413.
(8) Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Org. Biomol. Chem.* **2008**, 3464–3466.
(9) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953–2989 and references therein.
(10) (a) Alexakis, A.; Albrow, V.; Biswas, K.; d'Augustin, M.; Prietob, O.; Woodward, S. *Chem. Commun.* **2005**, 2843–2845. (b) Vuagnoux-d'Augustin, M.; Alexakis, A. *Chem.—Eur. J.* **2007**, *13*, 9647–9662. (c) Hawner, C.; Li, K.; Cirriez, V.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *120*, 8334–8337. *Angew. Chem., Int. Ed.* **2008**, *47*, 8211–8214. (d) Palais, L.; Alexakis, A. *Chem.—Eur. J.* **2009**, *15*, 10473–10485. (e) Müller, D.; Hawner, C.; Tissot, M.; Palais, L.; Alexakis, A. *Synlett* **2010**, 1694–1698. (f) Müller, D.; Tissot, M.; Alexakis, A. *Org. Lett.* **2011**, *13*, 3040–3043.

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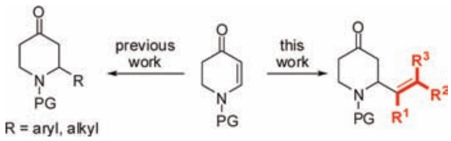
Scheme 1. Reported and This Work on the ACA to 2,3-Dihydro-4-piperidones

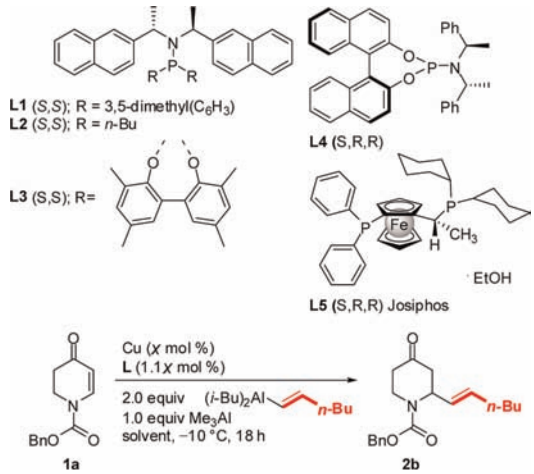


transmetalation reactions. Reactions, promoted in the presence of a chiral monodentate phosphine amine copper complex, afford the products with high enantioselectivity (up to 97%) whatever the nature of the nucleophile (aryl, alkenyl, and alkyl).

We began our investigations by examining the ability of highly efficient chiral copper complexes, previously reported in the literature in the context of Cu-catalyzed ACA with aluminum organyls, to promote the ACA of alkenyl aluminum reagents to 2−3-dehydydro-4-piperidones.[8,10b,10c,10d−10f,11] We selected **1a** as a representative substrate as it can be easily prepared in a simple one step procedure from commercially available 4-methoxypyridine.[12]

As shown in Table 1 (entries 1 and 2) the recently reported coactivation with $AlMe_3$ as a Lewis acid was absolutely critical for the outcome of the reaction.[10e] Only electron rich phosphine amine ligand **L2** was able to achieve almost full conversion without additional activation with $AlMe_3$ (entry 4). Interestingly, the presence of ethereal solvent for Me_3Al coactivation is absolutely vital as its absence results in mere methyl transfer (entry 5). The results depicted in Table 1 underline the very high reactivity of phosphine amine ligands in comparison to phosphoramidite, phospine, or ferrocene based ligands. Cu(II)naphtenate (CuNp), the most inexpensive organic copper salt, in combination with **L1** achieved the highest enantioselectivity (91%). Although the ligand loading of 11 mol % could not be further decreased without loss of enantioselectivity (Table 1, entry 3), this represents the lowest amount of ligand loading for the Cu-catalyzed ACA employing unprotected vinyl alanes made via hydroalumination.[13] Interestingly, no 1,2-addition product was formed which represented a common byproduct for the ACA of alkenyl alanes made via hydroalumination to β-substituted cyclic enones.[10b,f] We rationalize this observation by the fact that substrate **1a** does not contain a β-substituent and therefore no steric preference for the 1,2-addition is present. It is well-known that **1a** is less reactive in ACA reactions compared to simple cyclohexenones.[1,7a] However, we were surprised to see that its reactivity is

Table 1. Initial Examination of Various Chiral Cu-Complexes[a]



entry	L	Cu salt	solvent	conv[b] [%][b]	*ee*[c] [%]
1[d]	**L1**	CuNp[e];20	Et_2O	21	n.d.
2	**L1**	**CuNp[e];10**	$\mathbf{Et_2O}$	**100**	**91**
3	**L1**	CuNp[e];5	Et_2O	96	82
4[d]	**L2**	CuNp[e];10	toluene	94	71
5[e]	**L2**	CuNp[e];10	toluene	66[f]	n.d.
6	**L2**	CuNp[e];10	Et_2O	100	60
7	**L3**	CuTC; 10	Et_2O	78	26
8	**(*R*)-binap**	CuTC; 10	THF	62	27
9[g]	**L4**	$Cu(OTf)_2$; 10	Et_2O	31	n.d.
10	**L5**	CuTC; 10	Et_2O	n.d.[h]	n.d.

[a] Reactions performed under an Ar atmosphere on a 0.30 mmol scale. [b] Determined by GC-MS. [c] Determined by chiral Supercritical Fluid Chromatography. [d] No $AlMe_3$ added. [e] Solution of Cu(II)naphtenate (CuNp) in pentane. [f] Only methyl transfer observed. [g] 20 mol % of ligand used. [h] Complex reaction mixture.

even lower compared to 3-methylcyclohex-2-enone when exposed to our standard protocol.[14]

With the optimized reaction conditions in hand we envisaged the introduction of a great variety of alkenyl groups. The simplest way to generate an alkenylalane is hydroalumination of a terminal alkyne (Table 2, entry 1). Usually such reactions proceed cleanly by *syn*-addition of H−Al(*i*-Bu)$_2$ to the triple bond and only small amounts of Al-acetylides are formed.[15] A directing group such as *tert*-butoxy in close proximity to the alkyne changes the mechanism, and *anti*-addition is observed instead (Table 2, entry 2).[16] Conjugation of the triple bond with an aromatic system, double or triple bonds, or an electron-withdrawing substituent greatly increases the acidity of the acetylenic hydrogen. This allows the formation of significant amounts of metalation, instead of a hydroalumination product; e.g.

(11) (a) d'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem.* **2005**, *117*, 1400–1402. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376–1378. (b) Vuagnoux-d'Augustin, M.; Kehrli, S.; Alexakis, A. *Synlett* **2007**, *13*, 2057–2060. (c) Tissot, M.; Müller, D.; Belot, S.; Alexakis, A. *Org. Lett.* **2010**, *12*, 2770–2773. (d) Gremaud, L.; Alexakis, A. *Angew. Chem.* **2012**, *124*, 818–821. *Angew. Chem., Int. Ed.* **2012**, *51*, 794–797.

(12) See Supporting Information for details.

(13) Previous reports employed between 22−30 mol % of ligand (cf. ref 10b, 10f).

(14) Without activation with $AlMe_3$, **L1** gave 98% conversion of the addition of (*E*)-hex-1-enyldiisobutylaluminum to 3-methylcyclohex-2-enone at −30 °C whereas the addition of the same reagent to substrate **1a** at −10 °C gave only 21% conversion under the same conditions.

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

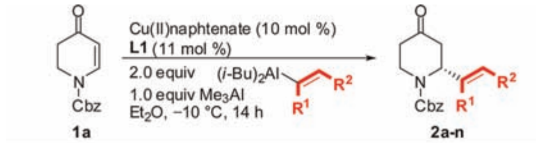
(16) Alexakis, A.; Duffault, J. M. *Tetrahedron Lett.* **1988**, *29*, 6243–6246.

Table 2. Representative Protocols for the Generation of Various Alkenyl Alanes

entry/ protocol		reaction	
1[a]	n-Bu—≡	1.0 equiv dibal-H, hexanes, 50 °C, 2 h	n-Bu⁄⁀Al(i-Bu)2
2[b]	tBuO⁄≡	1.0 equiv dibal-H, hexanes, 50 °C, 2 h	tBuO⁄⁀ Al(i-Bu)2
3[c]	Ph—≡	Ni(dppp)Cl2 (3 mol %), 1.3 equiv dibal-H, THF, 22 °C, 2 h	Ph(Al(i-Bu)2)C=CH2
4[d]	Ph—≡	Ni(PPh3)2Cl2 (3 mol %), 1.3 equiv dibal-H, THF, 22 °C, 2 h	Ph⁄⁀Al(i-Bu)2
5[e]	Ph⁄⁀Br	1) tBuLi (2.0 equiv) Et2O, −78°C, 30 min; 2) Me2AlCl (1.0 equiv) Et2O, −78 °C, 1 h, then 20 °C, 5 h	Ph⁄⁀AlMe2

[a] Contains 6% of metalation and 4% of bis-hydroalumination product.[15] [b] Directing groups such as O*t*Bu afford purely the *syn* hydroalumination product.[16] [c] The β-hydroalumination product and the metalation product are formed in <2%.[17] [d] 7% of the α-hydroalumination product is formed; the metalation product is formed in <2%.[17] [e] Control of the exact ratio of *t*BuLi to Me_2AlCl is of great importance, as an excess of either *t*BuLi or Me_2AlCl can lead to a decrease in enantioselectivity.[10e]

Table 3. Cu-Phosphine Amine Catalyzed ACA of Vinylaluminums to Michael Acceptor **1a**[a]



entry	generation of alane[b]	reagent R[1]	reagent R[2]	yield[c] [%]	ee[d] [%]
1	1	H	*n*-Pr	57 (**2a**)	89
2	1	H	*n*-Bu	50 (**2b**)	91
3[e]	1	H	*n*-C_5H_{11}	63 (**2c**)	90
4	1	H	Cy	54 (**2d**)	86
5	1	H	*t*-Bu	60 (**2e**)	84
6[e,f,g]	1	H	(chloroalkyl, drawn) Cl	77 (**2f**)	96
7	1	H	(chloroalkyl, drawn) Cl	59 (**2g**)	95
8	4	H	Ph	37 (**2h**)	97
9	5	H	Ph	80 (**2h**)	97
10	4	H	*p*-FC_6H_4	35 (**2i**)	95
11	5	H	*p*-FC_6H_4	75 (**2i**)	96
12[e]	4	H	*p*-$MeOC_6H_4$	31 (**2j**)	53
13[e,g]	5	H	*p*-$MeOC_6H_4$	37 (**2j**)	91
14[h]	4	H	Ph	10 (**2h**)	0
15	3	*n*-Bu	H	52 (**2k**)	86
16	3	Ph	H	65 (**2l**)	80
17	5	Me	H	83 (**2m**)	90

[a] Reactions performed under Ar atmosphere on a 0.30 mmol scale; conversion = 100% determined by GC-MS or TLC. [b] The number indicated refers to the protocol of alane generation (Table 2) which was used. [c] Yields of isolated vinyl addition products. [d] Determined by chiral Supercritical Fluid Chromatography. [e] 22 mol % of **L1** and 20 mol % of Cu(II)naphtenate (CuNp) were used. [f] 3 equiv of alane added. [g] Addition of 0.2 mL of THF. [h] No Cu(II)naphtenate (CuNp) added, conversion < 100%.

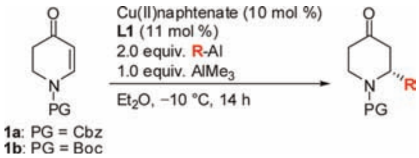
29% of Al-acetylide is obtained for the hydroalumination of phenylacetylene.[15] Therefore, Hoveyda et al. developed a protocol for the Ni-catalyzed hydroalumination which suppresses this side reaction and even allows, by choice of ligand, a selective α or β hydroalumination (Table 2, entries 3–4).[17] In contrast, we reported the synthesis of conjugated alkenyl alanes from the corresponding bromides by a lithium–bromine exchange with *t*BuLi, followed by transmetalation with Me_2AlCl (Table 2, entry 5).[10e] This approach is advantageous for the synthesis of conjugated β-alkenyl alanes because compared to the Ni-catalyzed hydroalumination the obtained alanes do not suffer from contamination by α-alkenyl alanes.

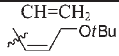
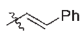
Under optimized conditions alkyl substituted β-vinyl aluminums (Table 3, entries 1–7) undergo ACA with good yields and high enantioselectivity (84–96% ee). This is particularly interesting given that Cu-catalyzed ACA using dialkylzinc reagents gave only low yields and enantioselectivity when employing longer alkyl chains such as *n*Bu.[7a] Moreover, the length of the alkyl chain did not have an influence on the outcome of the reaction (entries 1–3). This also holds true for functionalized alkynes (entries 6–7) which are very useful for further transformations (*vide infra*). Although the increased steric bulk of the alkyl substituent led to a decrease in enantioselectivity, high levels of stereoinduction are still maintained (entries 4–5). To compare the influence of the preparation of the alkenyl aluminums, products **2h–j** were made from alanes prepared according to protocols 4 and 5 (Table 2). Both alanes usually gave the same levels of enantioselectivity (Table 3, entries 8–13, with the exception of **2j**), and in all cases yields were greatly improved when the alane was prepared according to protocol 5 (Table 2). We rationalize this observation by the fact that the Ni-catalyzed hydroalumination affords alkenyl alanes which are less pure (cf. footnote *d*, Table 2) than alanes made from vinyl bromide by a lithium–bromine exchange, transmetalation sequence. To exclude the possibility that the ACA reaction in the presence of nickel salts is catalyzed by a chiral nickel complex, generated through ligand transfer from copper to nickel, we performed the reaction in the absence of copper salt. Since nickel was reported to catalyze 1,4-addition reactions with alanes it came to no surprise that the reaction still proceeded, although less efficiently (Table 3, entry 14).[18] The fact that in the absence of copper salt no enantioselectivity was observed emphasizes the efficiency of the chiral copper catalyst which in the presence of this racemic background reaction was still able to afford products with high optical purity (97% ee for **2h**). In contrast to the Ni-catalyzed β-hydroalumination the α-hydroalumination proceeds cleanly (cf. footnote *d*, Table 2) and the products **2k** and **2l** were cleanly formed in high optical purity. It is noteworthy that product **2k** represents

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

(18) First reports of nickel catalyzed conjugate addition; using alkyl aluminums: (a) Jeffery, A. E.; Meisters, A.; Mole, T. *Aust. J. Chem.* **1974**, *27*, 2569–2576. (b) Aryl aluminums: Westermann, J.; Imbery, U.; Nguyen, A. T.; Nickisch, K. *Eur. J. Inorg. Chem.* **1998**, 295–298. (c) Alkyne aluminums: Hansen, R. T.; Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* **1978**, *100*, 2244–2245.

Table 4. Extension of the Methodology[a]



entry	generation of alane[b]	PG	R	Yield[c] (%)	ee[d] (%)
1	5[e]	Cbz	$CH{=}CH_2$	37 (**2n**)	63
2[f]	2	Cbz		45 (**2o**)	49
3	4	Boc		44 (**2p**)	95
4	5	Boc		50 (**2p**)	97
5	5[g]	Cbz	Ph	65 (**2q**)	92
6	c.a.[h]	Cbz	Me	64 (**2r**)	97
7[f]	c.a.[i]	Cbz	Et	46 (**2s**)	97

[a] Reactions performed under Ar atmosphere on a 0.30 mmol scale; conversion = 100% determined by GC-MS and TLC. [b] The number indicated refers to the protocol of alane generation (Table 2) which was used. [c] Yields of isolated and vinyl addition products. [d] Determined by chiral Supercritical Fluid Chromatography. [e] Vinylalane prepared from vinylmagnesium bromide (see Supporting Information for details). [f] 22 mol % of **L1** and 20 mol % of Kubas salt $[Cu(CH_3CN)_4]BF_4$ were used; 3 equiv of alane added; Et_2O replaced by THF. [g] Aryl alane prepared from aryl bromide (see Supporting Information for details). [h] Commercially available, only addition of 2.0 equiv of Me_3Al. [i] Commercially available, only addition of 2.0 equiv of Et_3Al.

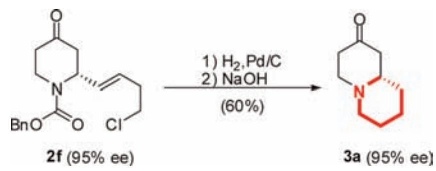
the first example of an ACA employing an alkyl substituted α-alkenyl alane made via Ni-catalyzed hydroalumination; the same reaction failed for 3-methylcyclohex-2-enone as the substrate.[19] Addition of isopropenylalane to substrate **1a** afforded product **2m** in high yield and enantioselectivity.

The simple vinyl group is certainly one of the most valuable substituents as it can undergo a wide range of further transformations such as the cross-metathesis reaction.[20] This motivated us to investigate the use of vinyl alane prepared in situ from inexpensive and commercially available vinyl magnesium bromide. Although yield and enantiomeric excess were moderate (Table 4, entry 1), **2n** represents the first example of a vinyl aluminum reagent employed for metal catalyzed ACA. The preparation of **2o** presented a challenge as standard conditions afforded the product (25%) as a mixture with the Me-transfer (23%) and *i*-Bu-transfer products (52%). Replacement of Et_2O by THF suppressed methyl as well as *i*-Bu transfer to < 5%, but the enantioselectivity was very low (14% ee).[21] Change of the copper salt to Kubas salt $[Cu(CH_3CN)_4]BF_4$ increased the enantioselectivity of the reaction (49%) while maintaining low levels of methyl and *i*-Bu transfer.[22] To check if the experimental conditions were also applicable for other substrates than **1a** we submitted substrate **1b** containing a Boc group instead of a Cbz group to the ACA reaction. We were pleased to see that the high enantioselectivity of 97% which was previously achieved for substrate **1a** (Table 3, entry 9) was maintained. The yield and enantioselectivity were slightly higher when hydroalumination protocol 5 was used instead of 4 (Table 4, entries 3−4). Having introduced a large variety of vinyl nucleophiles to substrate **1a** and **1b** we were interested if the methodology was general and would also allow for the introduction of alkyl and aryl nucleophiles. To our delight nonoptimized reaction conditions afforded products **2q**, **2r**, and **2s** in high enantioselectivities (> 90%) and good yields. The absolute configuration of addition products containing an alkenyl group was assigned *R* in analogy with the general bottom face attack observed for products **2q**, **2r**, and **2s**.[12]

In order to show the high synthetic potential of the developed methodology we submitted chlorine containing product **2f** to standard hydrogenation conditions. In one pot we carried out deprotection of the Cbz group, hydrogenation of the double bond, and an intramolecular S_N2 reaction (Scheme 2).[23]

(19) Müller, D.; Alexakis, A. *Unpublished results.*
(20) For an extensive article concerning cross metathesis reactions, see: Chatterjee, C.; Choi, T.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.
(21) The addition of THF was necessary also for the products **2f** and **2j**: for **2f**, to suppress about 20% of methyl and *i*-Bu transfer and, for **2j**, to ensure total conversion.
(22) We reported the use of Kubas salt $[Cu(CH_3CN)_4]BF_4$ in the context of ACA employing vinyl alanes before; cf. ref 10b.
(23) Under similar conditions product **2g** did not cyclize.

Scheme 2. One Pot Synthesis of Bicyclic Amine **3a**



In conclusion, we showed that the recently developed class of chiral phosphine amines,[11a] prepared in one or two steps from commercially available amines, achieved far superior results compared to all other ligands tested.[11a,10d,10f] In addition, we were able to use alkenyl alanes generated by hydroalumination from *unprotected* alkynes or by a simple lithium−bromine exchange, transmetalation sequence from vinyl bromides. The developed methodology proved to be particularly efficient for the ACA of aluminum organyls to unactivated substrates, and further applications toward other challenging substrates are among the objectives being pursued in our laboratories.

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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.

The authors declare the following competing financial interest(s): The authors declare no competing financial interest.