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Creation of Highly Congested Quaternary Centers via Cu-catalyzed Conjugate Addition of Alkenyl Alanates to *β*-Substituted Cyclic Enones

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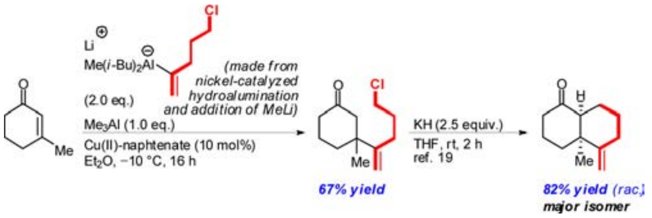
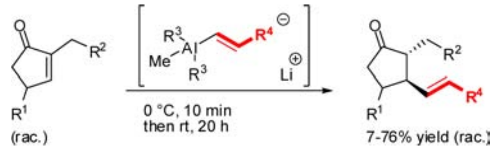
ABSTRACT



Easily prepared alkenylalanates proved to be excellent nucleophiles for the creation of highly congested quaternary centers via copper-catalyzed conjugate addition. In addition, functionalized *cis*-decaline systems can now be prepared in a simple two-step sequence involving Cu-catalyzed conjugate addition with functionalized alkenylalanates.

In the 1970s, Weiss and co-workers exploited lithium (*E*)-1-alkenylalanates for the synthesis of prostaglandines and congeners (Scheme 1).[1] They showed that lithium alkenylalanates undergo conjugate addition to cyclopentenones in the absence of a metal catalyst at room temperature to give the addition products in poor to good yields. Interestingly, only the alkenyl ligand on aluminum is specifically transferred in a 1,4-manner despite the presence of three alkyl ligands. The requisite alkenylalanates were easily prepared either by hydroalumination of alkynes and subsequent treatment with methyl lithium or by reaction of trimethylaluminium with the (*E*)-1-alkenyllithiums.

Scheme 1. Non-catalyzed Conjugate Addition of Alkenylalanates to Yield Prostaglandin Derivatives



With the exception of the MAD and MAT system, introduced by Yamamoto in 1987,[2] alkenylalanates were no longer used for 1,4-addition reactions because as Schwartz stated in 1980:[3] "..the use of these aluminum species for conjugate addition offers no advantage over the alkenylcuprate-based routes since both routes rely on the availability of the corresponding alkenyllithium reagent". During our work on the copper-catalyzed asymmetric conjugate addition using alkenylaluminums to *β*-substituted cyclic enones we were confronted with the problem that encumbered dimethylalkenylaluminums led to methyl instead of alkenyl-transfer (Scheme 2).[4] Moreover, sterically

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[1] (a) Weiss, M. J.; Bernady, K. F. *Tetrahedron Lett.* **1972**, *40*, 4083–4086. (f) Floyd, M. B.; Weiss, M. J. *Prostaglandins* **1973**, *3*, 921–924. (b) Bernady, K. F.; Poletto, J. F.; Weiss, M. J. *Tetrahedron Lett.* **1975**, *48*, 765–768. (c) Skotnicki, J. S.; Schaub, R. E.; Bernady, K. F.; Siuta, G. J.; Poletto, J. F.; Weiss, M. J. *J. Med. Chem.* **1977**, *20*, 1551–1557. (d) Bernady, K. F.; Floyd, M. B.; Poletto, J. F.; Weiss, A. H. *J. Org. Chem.* **1979**, *44*, 1438–1447. (e) Floyd, M. B.; Weiss, A. H. *J. Org. Chem.* **1979**, *44*, 71–75.

[2] Maruoka, K.; Nonoshita, K.; Yamamoto, H. *Tetrahedron Lett.* **1987**, *28*, 5723–5726.

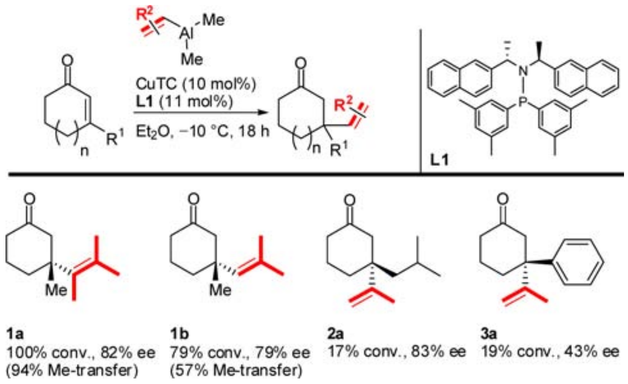
[3] Schwartz, J.; Loots, M. J.; Kosugi, H. *J. Am. Chem. Soc.* **1980**, *402*, 1333–1340.

[4] (a) Müller, D.; Hawner, C.; Tissot, M.; Palais, L.; Alexakis, A. *Synlett* **2010**, 1694–1698. (b) Müller, D.; Tissot, M.; Alexakis, A. *Org. Lett.* **2011**, *13*, 3040–3043. (c) Müller, D.; Alexakis, A. *Org. Lett.* **2012**, *14*, 1842–1845.

10.1021/ol400378v

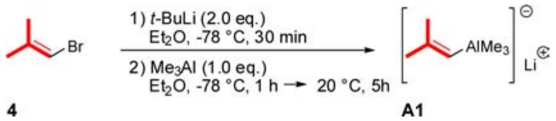
congested substrates gave low conversion and afforded only traces of the desired product. In both cases, we were unable to isolate and characterize the desired products and hence focused on the racemic syntheses of these β-disubstituted cyclic enones.

Scheme 2. Formation of Highly Encumbered Quaternary Stereogenic Centers: A Challenging 1,4-Addition



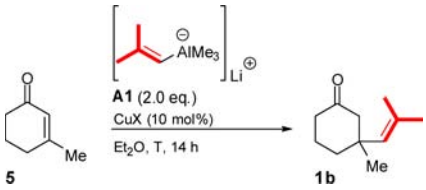
Only a few conjugate additions of alkenylcuprate reagents to sterically congested β-substituted enones were reported in the literature and most of them use unhindered vinyl-cuprate reagents made from commercially available vinylmagnesium bromide.[5] Protocols using other alkenyl cuprates often note the occurrence of low conversion,[6] isomerization of configuration during the preparation of the alkenyl Grignard reagent,[7] the requirement of a Lewis acid for efficient 1,4-addition[8] and the use of stoichiometric amounts of toxic CuCN[9] or malodorous $P(n\text{-}Bu)_3$.[10] Hence, we were considering alternative nucleophiles for the construction of highly congested quaternary centers via Cu-catalyzed conjugate addition reactions. A first indication that alkenyl alanates might be appropriate nucleophiles came from the observation that alkenylalanes generated from the corresponding alkenyl bromides via Br−Li exchange and reaction with Me_2AlCl reacted better when a slight excess of *t*-BuLi was used. Therefore, we decided to synthesize alkenyl alanates by the reaction of alkenyllithiums with Me_3Al and to employ them *in situ* for the Cu-catalyzed conjugate addition (Scheme 3 and Table 1). Many alkenylbromides, such as **4**, are commercially available or can be easily prepared.[11]

Scheme 3. Generation of Mixed Alkenylalanate **A1**



Not surprisingly, when the reaction was performed under the conditions reported by Weiss (No metal catalyst, room temperature) the desired product **1b** was observed (Table 1 entry 1). However, GC-MS analysis showed about 19% of side products, which could not be characterized. When we carried out the reaction at −10 °C in the presence of 10 mol % of Cu(II)naphthenate or $CuBr\cdot SMe_2$, clean reaction occurred and **1b** was observed as a single product (entries 2−3). It is worthy to mention that this represents the first metal-catalyzed conjugate addition employing alkenyl alanates.[12] Why alkenyl alanates react in such a clean manner, in Cu-catalyzed conjugate addition, might be rationalized by the fact that after every transmetalation of an alkenyl group to copper, one molecule of Lewis acidic trialkylaluminum is released which then activates the substrate by complexation to the carbonyl oxygen. Hence, alkenylalanates are not only highly nucleophilic reagents, comparable to Grignard reagents, but are also a source of catalytic amounts of trialkylaluminum reagent which acts as a strong Lewis acid. The double activating ability of alkenyalanates also explains why conjugate additions with alanates do not require additional Lewis acids such as BF_3 or TMS-Cl.

Table 1. Optimization of Reaction Conditions[a]



entry	Cu-salt	*T* (°C)	conv[b] [%]
1		+20	92
2	**Cu(II)naphthenate**	**−10**	**>98**
3	$CuBr.Me_2S$	−10	>98
4[c]	Cu(II)naphthenate	−10	>98
5[d]	Cu(II)naphthenate	−10	30
6[e]	Cu(II)naphthenate	−10	95
7[f]	Cu(II)naphthenate	−10	>98

[a] Reactions performed under Ar atmosphere on a 0.30 mmol scale. [b] Determined by GC-MS. [c] Reaction performed with 1.5 equiv of Li-Alanate **A1**. [d] Reaction time was 2 h. [e] Reaction performed in THF. [f] Preformation of chiral complex with **L1** (11 mol %); product was obtained as a racemic mixture.

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(5) (a) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135–631.

(6) Barnes, D. M.; Bhagavatula, L.; DeMattei, J.; Gupta, A.; Hill, D. R.; Manna, S.; McLaughlin, M. A.; Nichols, P.; Premchandran, R.; Rasmussen, M. W.; Tian, Z. P.; Wittenberger, S. J. *Tetrahedron: Asymmetry* **2003**, *14*, 3541–3551.

(7) Mechin, B.; Naulet, N. *J. Organomet. Chem.* **1972**, *39*, 229–236.

(8) (a) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahdron Lett.* **1986**, *27*, 4025–4028. (b) Piers, E.; Yeung, B. W. A. *J. Org. Chem.* **1984**, *49*, 4567–4569.

(9) Representative examples: (a) Lipshutz, B. H.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 7440–7441. (b) Delaloge, F.; Prunet, J.; Pancrazi, A.; Lallemand, J. *Tetrahdron Lett.* **1997**, *38*, 237–240. (c) Aradjo, M. A.; Barrientos-Astigarraga, R. E.; Ellensohn, R. M.; Comasseto, J. V. *Tetrahdron Lett.* **1999**, *40*, 5115–5118.

(10) Suzuki, M.; Suzuki, T.; Kawagishi, T.; Noyori, R. *Tetrahdron Lett.* **1980**, *21*, 1247–1250.

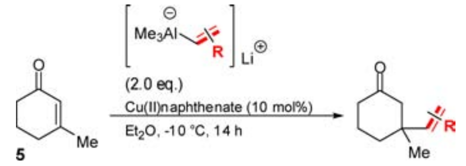
(11) For some examples for the synthesis of various alkenyl bromides see: (a) Al Dulaymi, J. R.; Baird, M. S.; Simpson, M. J.; Nyman, S. *Tetrahedron* **1996**, *52*, 12509–12520. (b) Abbas, S.; Hayes, C. J.; Worden, S. *Tetrahedron Lett.* **2000**, *41*, 3215–3219. (c) Wolfe, J. P.; Yang, Q.; Hay, M. B.; Ney, J. E. *Adv. Synth. Catal.* **2005**, *347*, 1614–1620.

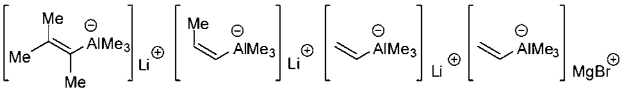
Further optimizations of the reaction conditions showed that decreasing the amount of alkenyl Alanate **1b** from 2.0 to 1.5 equivalents still afforded full conversion (entry 4). Nevertheless, we continued to use 2.0 equivalents as for other substrates such as **9** the conversion was low using less than 2.0 equivalents (Table 3, entry 4). For the formation of product **1b** we noted that the conversion was only 30% after 2 h, which shows that the reaction proceeds relatively slowly (entry 7). No stereocontrol was observed in the presence of a chiral copper complex, which typically afforded high enantioselectivities for the conjugate addition with alanes (entry 7).[13] Next, we envisaged the conjugate addition of a number of various bulky alkenyl alanates whose dimethylalkenyl aluminum congeners afforded high levels of undesired Me-transfer (Table 2; compare to Scheme 2). The exceptional preference for the alkenyl-transfer in alkenylalanates is best illustrated for the conjugate addition of highly encumbered Alanate **A2** (entry 1), which cleanly affords the desired product in good isolated yields and without occurrence of Me-transfer. The feasibility and practicality of the procedure needs to be emphasized. For instance (*Z*)-bromopropene was transformed by bromine–lithium exchange into the corresponding (*Z*)-alkenyllithium with retention of configuration. Subsequent treatment of the alkenyllithium with a commercial solution of Me_3Al in hexanes afforded Alanate **A2**, which is configurationally stable at room temperature. Then the suspension of the Alanate and lithium salts was cooled to −10 °C and a hydrocarbon solution of Cu(II)-naphthenate was added followed by addition of the neat enone. Hence, all the required reagents are commercially available solutions and no predrying of copper-salts or the formation of a cyanocuprate reagent as the case for "traditional" cuprate chemistry is required.

Though conjugate additions with vinylcuprate reagent to afford congested quaternary centers are well-known, the high synthetic value of the $CH{=}CH_2$ unit was reason enough to test if lithium vinyl Alanate prepared from inexpensive vinyl bromide would cleanly undergo 1,4-addition. Indeed, the reaction worked perfectly well and afforded the product in high yield (entry 4). In contrast, when vinyl Grignard reagent was used for the preparation of Alanate **A5** the yield was very low (entry 5). We reason that magnesium salts or the presence of THF, which stems from the Grignard reagent, might be the origin of the sluggish reaction.[14]

On the basis of the previous results with sterically encumbered alkenyl nucleophiles we were confident that alkenyl alanates would also efficiently undergo conjugate addition to sterically congested enones bearing alkyl or aryl-substituents in the *β*-position (Table 3).

Table 2. Cu-catalyzed Conjugate Addition with Various Alkenyl Alanates[a]



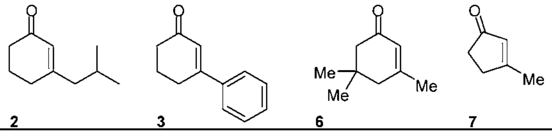


A2 **A3** **A4** **A5**

Entry	Alanate	conv[b] [%][b]	yield[c] [%]
1[d]	**A1**	100	60 (**1b**)
2	**A2**	100	66 (**1a**)
3	**A3**	100	81 (**1c**)
4[d]	**A4**	100	83 (**1d**)
5	**A5**	30	15 (**1d**)

[a] Reactions performed under Ar atmosphere on a 0.9 mmol scale. [b] Estimated by GC-MS. [c] Isolated yield. [d] Performed on a 2.0 mmol scale.

Table 3. Copper-catalyzed Conjugate Addition of Alkenylalanate **A6** to *β*-Substituted Cyclic Enones[a]



2 **3** **6** **7**

Entry	Substrate	conv[b] [%][b]	yield
1	**2**	100	65 (**2a**)
2[d]	**3**	100	44 (**3a**)
3	**6**	100	77 (**6a**)
4[d]	**7**	85	30 (**7a**)

[a] Reactions performed under Ar atmosphere on a 0.90 mmol scale. [b] Estimated by GC-MS. [c] Isolated yield. [d] Reaction carried out on 0.45 mmol; 11% of 1,2-addition; estimated by GC-MS.

Remarkably, alkenylalanate **A6** cleanly afforded the desired addition-products in good yields for all encumbered cyclohexenone substrates (entries 1–3). Only phenyl-substituted substrate **3** gave lower yields, which are due to the smaller scale (0.45 mmol) and 11% of 1,2-addition product. We were delighted that even isophorone **6**, a notoriously unreactive Michael acceptor gave full conversion with encumbered Alanate **A6**. Cyclopentenone substrate **7** was causing troubles in alane chemistry as the presence of only a small excess of Me_2AlCl for the generation of the requisite dimethyl-2-propenylaluminum led to complete

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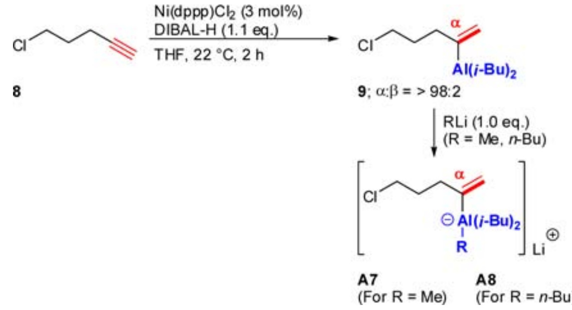
(12) Copper and nickel catalyzed conjugate additions using $LiAlMe_4$ was reported by Ashby: Ashby, E. C.; Heinsohn, G. *J. Org. Chem.* **1974**, *39*, 3297–3299.

(13) For an overview of Cu-catalyzed asymmetric conjugate additions with alkenylaluminums see: Müller, D.; Alexakis, A. *Chem. Commun.* **2012**, *48*, 12037–12049.

(14) It is well-known that THF coordinates the Lewis acids such as Li^+ or AlR_3 and hence slows down conjugate addition reactions.

Scheme 4. Generation of Mixed alkenyl Alanates **A7** and **A8**

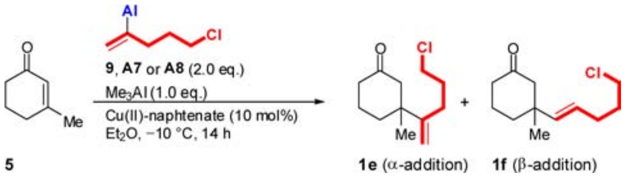


degradation of the substrate, which was probably due to Lewis acid induced aldol-condensation reactions. In contrast strongly basic Alanate reagent **A6** favored the clean formation of addition-product **7a**. However, volatility of product **7a** and incomplete conversion led to low isolated yield.

Finally, we were interested if the developed methodology would also allow for efficient 1,4-addition of highly congested alkenyl alanates generated by Ni-catalyzed hydroalumination and treatment of alane with MeLi or *n*-BuLi as shown in Scheme 4. Alanates **A7** and **A8**, as well as alane **9**, were tested for the Cu-catalyzed conjugate addition to enone **5** (Table 4). Before investigating the Cu-catalyzed conjugate addition with alkenylalanates **A7** and **A8** (Table 4, entries 3−6) we were interested if alane **9** would also be able to undergo clean 1,4-addition (entries 1−2). Moreover, we evaluated the noncatalyzed conjugate addition of Alanate **A8** applying conditions described by Weiss and co-workers (Entry 7).[1]

To our surprise alane **9** did not even afford traces of the desired product **1e** (entries 1−2).[15] Even in the presence of one equivalent of Me_3Al only a complex reaction mixture was observed by GC-MS; the observed unidentified products are probably resulting from 1,2-addition and elimination of the tertiary alcohol under acid workup.[16] To our delight use of alanates **A7** and **A8** afforded desired product **1e** with good conversion, albeit accompanied by about 7−9% of unidentified side-products (entries 3−4). Addition of one equivalent of Me_3Al (entries 5−6) helped to increase the conversion and to lower the amounts of noncharacterized side-products to < 3%. Intriguingly, we also detected small amounts (8−12%) the β-addition product **1f**. This is rather puzzling as in the absence of catalyst this side product was observed in only 2% of **1f** (entry 7).[17] The origin of the conjugate addition of the β-alkenyl nucleophile is unclear.[18] Nevertheless, the ease of the synthesis of **1e** in good yield from alkyne **8** is remarkable (entry 7). Piers in his previous work described the synthesis of **1e** by hydrostannation of alkyne **8**, followed by a Sn−Li exchange and transmetalation to copper to form the required cuprate reagent for the 1,4-addition.[19,20]

Table 4. Use of Sterically Congested Alkenylalanates Made via Ni-catalyzed Hydroalumination[a]



entry	Al-reagent	1e:1f[b]	conv.[c] [%]	yield[d][%]
1	**9**	n.d.[e]	100	n.i.[f,g]
2[h]	**9**	n.d.[e]	100	n.i.[f,g]
3	**A7**	n.d.[e]	96	n.i.[f]
4	**A8**	n.d.[e]	97	n.i.[f]
5[h]	**A7**	**91:9**	**100**	**67**
6[h]	**A8**	87:13	100	56
7[h]	**A8**[i]	98:2	96	24[j]

[a] Reactions performed under Ar atmosphere on a 0.90 mmol scale. [b] Determined by ^{1}H NMR of the purified product; in accordance with estimated GC-MS value of crude product. [c] Estimated by GC-MS [d] Isolated yield; unseparable mixture of **1e** and **1f**. [e] Not determined. [f] Not isolated. [g] Complex reaction mixture. [h] Co-activation with Me_3Al (1.0 equiv). [i] Reaction without copper, according to Weiss procedure. [j] Product contains 6% of unidentified side-product; Crude product contained 30% of unidentified side-products.

In conclusion, we developed an efficient and practical protocol for the conjugate addition of alkenyl alanates to form highly congested quaternary centers. The synthetic utility of this methodology was demonstrated by the conjugate addition of functionalized alkenyl Alanate **A7** to afford **1e** in good overall yield. The development of an asymmetric version for the Cu-catalyzed conjugate addition employing alkenyl-alanates is among the objectives being pursued in our laboratories.

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Supporting Information Available. Analytical data and NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(15) Observed by GC-MS; lack of signal at the corresponding retention time.

(16) Addition of Me_3Al leads to stronger Lewis acid activation compared to $(i\text{-Bu}_2)$Al(alkenyl). This concept of coactivation was successfully introduced for the Cu-catalyzed conjugate addition with sterically unhindered alkenylalauminums; see ref 4b.

(17) Hoveyda reported that the β-hydroalumination product was afforded in < 2%: Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10961–10963.

(18) From our previous work we know that β-alkenylaluminums react faster than α-alkenyaluminums. Hence, under non-catalyzed conditions one would expect 9−13% of β-alkenyl addition product which is not the case. Observations concerning isomerization of alkenyl nucleophiles were also made for Rh-catalyzed 1,4-additions: Corey, E. J.; Lalic, G. *Tetrahedron Lett*. **2008**, *49*, 4894–4896.

(19) (a) Piers, E.; Yeung, B. W. A. *J. Org. Chem.* **1984**, *49*, 4567–4569. (b) Piers, E.; Yeung, B. W. A.; Fleming, F. F. *Can. J. Chem.* **1993**, *71*, 280–286. **1e** was isolated in 55% yield.

(20) The corresponding lithium reagent is only semistable, as it decomposes quickly to methylenecyclobutane at temperatures higher than −63 °C; see ref 19.