J|A|C|S COMMUNICATIONS

Published on Web 07/15/2010

α-Selective Ni-Catalyzed Hydroalumination of Aryl- and Alkyl-Substituted Terminal Alkynes: Practical Syntheses of Internal Vinyl Aluminums, Halides, or Boronates

Fang Gao and Amir H. Hoveyda*

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467

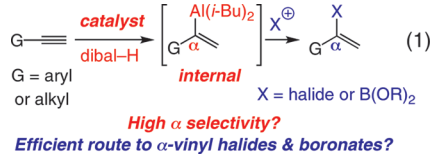
Received March 11, 2010; E-mail: amir.hoveyda@bc.edu

Abstract: A method for Ni-catalyzed hydroalumination of terminal alkynes, leading to the formation of α-vinylaluminum isomers efficiently (>98% conv in 2−12 h) and with high selectivity (95% to >98% α), is described. Catalytic α-selective hydroalumination reactions proceed in the presence of a reagent (diisobutylaluminum hydride; dibal-H) and 3.0 mol % metal complex ($Ni(dppp)Cl_2$) that are commercially available and inexpensive. Under the same conditions, but with $Ni(PPh_3)_2Cl_2$, hydroalumination becomes highly β-selective, and, unlike uncatalyzed transformations with dibal-H, generates little or no alkynylaluminum byproducts. All hydrometalation reactions are reliable, operationally simple, and practical and afford an assortment of vinylaluminums that are otherwise not easily accessible. The derived α-vinyl halides and boronates can be synthesized through direct treatment with the appropriate electrophiles [e.g., Br_2 and methoxy(pinacolato)boron, respectively]. Ni-catalyzed hydroaluminations can be performed with as little as 0.1 mol % catalyst and on gram scale with equally high efficiency and selectivity.

Herein, we demonstrate that commercially available and inexpensive Ni-based catalysts and diisobutylaluminum hydride (dibal-H) convert alkyl- or aryl-substituted alkynes to *internal* (or α-) vinylaluminums efficiently and with exceptional selectivity (95% to >98% α isomer). The catalytic protocol offers a one-pot, high yielding and selective method for conversion of terminal alkynes to α-vinyl halides[1] and boronates[2] — valuable entities otherwise prepared by less efficient routes that are intolerant of several functional groups.[3] Moreover, aryl-substituted terminal β-vinylaluminums, formed along with substantial amounts of byproducts in uncatalyzed hydroaluminations, can be accessed in high yield by the catalytic process.

Selective and practical methods for alkyne hydrometalations are of substantial value.[4] The resulting vinylmetals might be utilized to access vinyl halides and boronates, intermediates critical to catalytic cross-coupling, one of the most important classes of transformations in chemical synthesis.[5,6] Vinylaluminums are mildly nucleophilic reagents that can be used in catalytic C−C bond forming processes,[7] including those that are enantioselective.[8] *Alkyl*-substituted vinylaluminums can be prepared[9] by reaction of alkynes with dibal-H;[10] the corresponding processes with *aryl* alkynes, however, suffer from competitive alkyne deprotonation, affording significant amounts of alkynylaluminums.[11,12] Regardless of varying efficiencies, all existing terminal alkyne hydroaluminations favor β-substituted isomers strongly or, often, exclusively. In contrast, a procedure that directly delivers internal or α-substituted vinylaluminums (eq 1) reliably and selectively does not exist. We reasoned that the above shortcomings might be resolved by rendering alkyne hydroalumination catalytic (eq 1) and that α selectivity might be achievable through manipulation of a catalyst's structure and the energetics of the catalytic cycle.[13] An efficient catalytic hydroalumination might also facilitate metal hydride addition to such a degree that adventitious alkyne deprotonation is avoided.

To initiate our search for an effective alkyne hydroalumination catalyst, we focused on Ni complexes, partly based on a report by Eisch regarding reactions of a small number of disubstituted alkynes



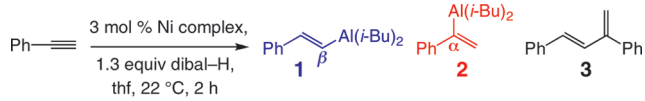
(1)

promoted by $Ni(acac)_2$.[14] The outcome of our screening studies, with phenylacetylene serving as the substrate, is summarized in Table 1. Reaction with $Ni(acac)_2$ and 1.3 equiv of dibal-H in tetrahydrofuran (thf) at 22 °C for 2 h leads to efficient hydrometalation (entry 1) but with a modest preference for the terminal vinylaluminum (68% **1** and 19% **2**) along with 13% of 1,3-diene **3**. Use of $NiCl_2 \cdot 6H_2O$ (entry 2) or Ni(0) complexes (entries 3−4) leads to similarly low selectivity and significant amounts of **3**. With 3 mol % $Ni(PPh_3)_2Cl_2$ (entry 5), hydroalumination proceeds with a strong preference for the terminal vinylaluminum (**1**:**2** = 93:7) and with <2% of the diene contaminant (^{1}H NMR analysis). More importantly, as depicted in entries 6−9 of Table 1, when Ni catalysts bear a bidentate phosphine ligand, hydrometalation occurs with total reversal of site selectivity. Vinylaluminum **2** is formed efficiently (>98% conv) and with >98% α selectivity when $Ni(dppp)Cl_2$ is used (entry 7).

In the absence of a catalyst, dibal-H reacts with phenylacetylene at 50 °C (hexanes or toluene)[15] to afford only ∼50% of the β-vinylaluminum (**1**) along with 25% styrene and 25% alkynylaluminum (due to deprotonation of alkyne by the vinylaluminum). In sharp contrast, alkyne deprotonation is not observed in any of the Ni-catalyzed reactions (<2%). Thus, in addition to allowing effective control of α or β selectivity, Ni complexes *enhance* hydrometalation *rates* to the extent that adventitious deprotonation is eliminated entirely.

Catalytic hydroaluminations can be performed with a considerable range of aryl alkynes (Table 2), affording α-vinylmetals efficiently

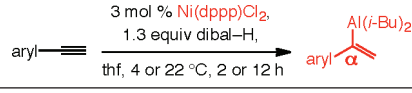
Table 1. Ni-Catalyzed Hydroalumination of Phenylacetylene[a]



entry	Ni complex	conv (%)[b]	**1**:**2**:**3** (%)[b]
1	$Ni(acac)_2$	97	68:19:13
2	$NiCl_2 \cdot 6H_2O$	95	45:35:20
3	$Ni(cod)_2$	>98	69:14:17
4	$Ni(PPh_3)_4$	>98	55:32:13
5	***$Ni(PPh_3)_2Cl_2$***	***>98***	***93:7:<2***
6	$Ni(dppe)Cl_2$	92	3:97:<2
7	***$Ni(dppp)Cl_2$***	***>98***	***<2:>98:<2***
8	$Ni(dppb)Cl_2$	76	8:92:<2
9	$Ni(dppf)Cl_2$	75	5:95:<2

[a] Reactions performed under N_2 atmosphere; <2% alkynyl aluminum product observed in all cases. [b] By analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures after quench with D_2O (0 °C, 30 min); see the Supporting Information for details.

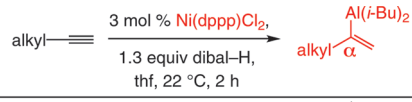
Table 2. α-Selective Ni-Catalyzed Hydroalumination of Arylacetylenes[a]

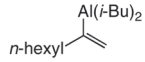
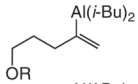
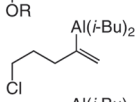
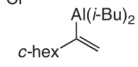
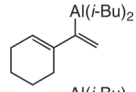
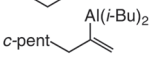


entry	aryl	temp (°C)	time (h)[b]	conv (%)[c]	α:β[c]
1	*o*-$OMeC_6H_4$	4	12	>98	98:2
2	*m*-$OMeC_6H_4$	22	2	>98	>98:2
3	*p*-$OMeC_6H_4$	4	12	>98	>98:2
4	*m*-$CF_3C_6H_4$	4	12	>98	95:5
5	*p*-$CF_3C_6H_4$	22	2	>98	97:3
6	*p*-FC_6H_4	22	2	>98	>98:2
7	*o*-ClC_6H_4	22	2	>98	>98:2
8	*o*-BrC_6H_4	22	2	>98	>98:2
9	*o*-MeC_6H_4	4	12	>98	>98:2
10	3-pyridyl	22	2	>98	>98:2
11	3-thienyl	22	2	>98	>98:2

[a] Reactions under N_2 atmosphere. [b] Reaction times correspond to hydroalumination portion of the process (not including D_2O quench). [c] By analysis of 400 MHz ^1H NMR spectra of unpurified mixtures (after D_2O); <2% alkynylaluminum observed.

Table 3. α-Selective Ni-Catalyzed Hydroalumination of Alkylacetylenes[a]



entry	product		conv (%)[b]	α:β[c]
1			>98	>98:2
2		R = H	>98	97:3
3		R = OTBS	>98	>98:2
4			>98	>98:2
5			>98	>98:2
6			>98[d]	98:2
7			>98	96.5:3.5

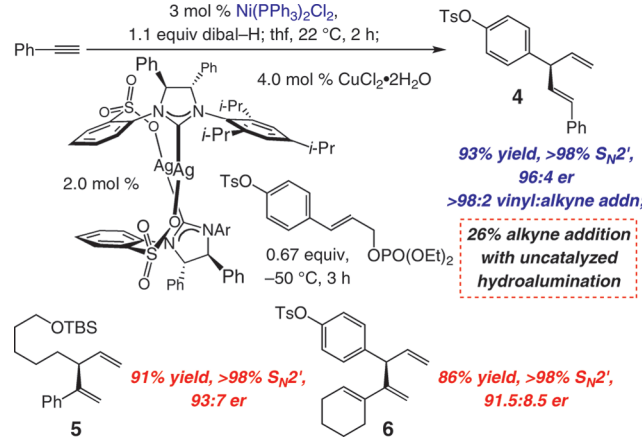
[a–c] See Table 2; 2.3 equiv of dibal-H in entry 2; 3 h for entry 4. [d] Performed at 4 °C for 12 h; ~5% alkyne deprotonation observed.

and selectively. Transformations are performed at 4−22 °C and require ≤12 h. Alkynes bearing electron-donating (entries 1−3) or electron-withdrawing units (entries 4−8) or sterically congested aryl acetylenes (entries 7−9) are suitable substrates. N- or S-containing heterocyclic substrates readily undergo hydroalumination with high selectivity (entries 10−11). Two additional points are noteworthy: (1) None of the transformations with $Ni(dppp)Cl_2$ generate the alkynylaluminum side product, which is obtained in significantly larger amounts in the *absence* of the catalyst (see above). (2) Reactions can be performed with commercial grade thf and Ni salts that are used as received (see below for an example).

α-Selective catalytic hydroaluminations of alkyl-substituted alkynes proceed readily and with high selectivity as well (Table 3);[16] only in one case (entry 6), ~5% alkyne deprotonation is observed (<2% otherwise). Alkynes bearing a linear (entries 1−4), α- (entries 5−6), or β-branched (entry 7) alkyl unit can be used.

The same range of substrates shown in Table 2 undergo hydroalumination readily in the presence of $Ni(PPh_3)_2Cl_2$, proceeding with high β-selectivity (85.5% to >98%) and with minimal alkyne deprotonation; complete data are available in the Supporting Information. Only alkyl-substituted β-vinylaluminums, which can be accessed by (uncatalyzed) reaction of dibal-H with a terminal alkyne, have so far been utilized in metal-catalyzed enantioselective C−C bond formation.[8] Efficient access to a wider range of α- and β-vinylaluminums would substantially expand the utility of such reagents. Cu-catalyzed enantioselective alkylations in Scheme 1 demonstrate this point. An aryl-substituted β-vinylaluminum, obtained through the above Ni-catalyzed process, can be used to synthesize 1,4-diene **4** with high efficiency and in 96:4 er. In contrast, when the vinylmetal prepared by uncatalyzed hydroalumination is utilized, 26% of the undesired *alkyne* (vs vinyl) addition product is generated. Furthermore, synthesis of enantiomerically enriched 1,4-dienes **5** and **6** is rendered feasible because the requisite α-vinylaluminums can now be easily prepared.

Scheme 1. Applications of Ni-Catalyzed Hydroaluminations[a]

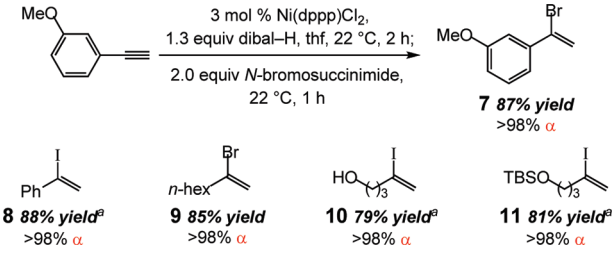


[a] Synthesis of **5** and **6** at −15 °C. Ar = 2,4,6-(*i*-Pr)$_3$-C_6H_2.

Ni-catalyzed vinylaluminum synthesis is more efficient than other alternatives, which involve initial synthesis of a vinyl halide, followed by metal−halogen exchange (*n*-BuLi) and treatment with an aluminum chloride. In addition to being a lengthier route, the latter two-vessel protocol requires α-vinyl halides prepared from terminal alkynes by hydroiodation (HI)[1c,d] or halo-boration (BBr_3)/proto-deboration with 15−20 equiv of HOAc),[17] which constitute strongly acidic conditions (specific examples below).

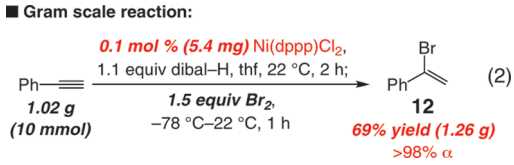
Ni-catalyzed hydroalumination does more than obviate the need for intermediacy of vinyl halides and the attendant harsh conditions leading to vinylaluminums; it provides an efficient route for the synthesis of this valuable class of halogenated building blocks. Treatment of the α-vinylaluminums with *N*-bromo- or *N*-iodosuccinimide furnishes vinyl bromides or iodides in >98% α-selectivity and 79−88% yield after chromatography (Scheme 2). Synthesis of α-vinylbromide **7** or iodide **11** would not be feasible through the BBr_3/HOAc[1a] and hydroiodation[1c,d,18] (concomitant removal of methyl or silyl ether). Vinyl halide synthesis through Ni-catalyzed hydroalumination is a practical process. Iodide **8** is obtained in 83% yield and >98% α selectivity with commercial grade thf and Ni catalyst (not purified); similarly, the alkyl-substituted iodide formed by catalytic hydroalumination of 1-octyne and treatment with *N*-iodosuccinimide is obtained in 89% yield and 96% α selectivity.

Scheme 2. Conversion of Terminal Alkynes to α-Vinyl Halides[a]



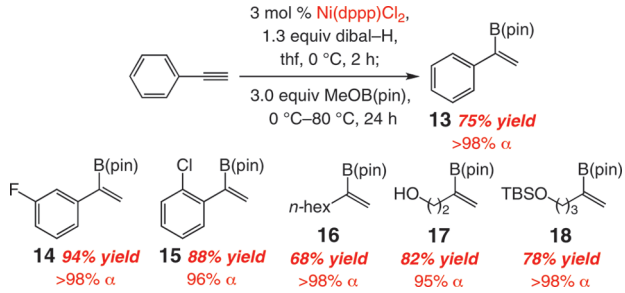
[a] Reaction with *N*-iodosuccinimide under otherwise identical conditions. See the Supporting Information for experimental details.

Ni-catalyzed hydroalumination and vinyl halide synthesis are amenable to scale up and require low catalyst loadings. As an example, with only 0.1 mol % Ni(dppp)Cl_2 and with inexpensive Br_2 as the halide source, α-vinyl bromide **12** is obtained in 69% yield after purification (eq 2; <2% β).[19]



α-Vinylboronates can be readily accessed through Ni-catalyzed alkyne hydroalumination (Scheme 3). Direct subjection of vinylaluminums with commercially available and inexpensive methoxy(pinacolato)borane delivers the desired products in >98% α selectivity and 68−94% yield after purification.[20]

Scheme 3. One-Pot Synthesis of α-Vinyl Boronates[a]



[a] Yields refer to purified α-vinylboronates; see the Supporting Information for experimental details. B(pin) = pinacolatoboron.

Several issues that underline the unique attributes of the α-vinyl boronate synthesis method described herein merit specific mention: (1) Hydroborations of terminal alkynes with pinacolborane, which require rigorously dried CH_2Cl_2,[21] or Rh-, Ir-,[22] and Zr-catalyzed[23] variants, furnish β-vinyl boronates exclusively or as the major isomer (<10% α).[24] (2) Alkyl-substituted α-vinyl boronates can be accessed through hydroborations that require stoichiometric amounts of a Cu complex (1.1 equiv of CuCl, KOAc, LiCl, or a phosphine) and only in up to 91% selectivity (typically 9−71%).[25] (3) α-Vinylboronates can be synthesized from α-vinylbromides by metal/halogen exchange (*n*-BuLi) and subjection to *i*-propoxypinacolborane.[17b] Cross-coupling of vinyl halides with $B_2(pin)_2$, promoted by the more costly Pd salts, also affords α-vinylboronates.[2] In addition to being two-vessel protocols (vs one-pot in Scheme 3), the latter processes require vinyl halides prepared by severely acidic procedures, rendering several vinyl halides inaccessible (see above). The present approach furnishes the vinylmetal directly. Finally, a vinylboronate that bears an aryl halide (e.g., **15**, Scheme 3) cannot be selectively prepared by the aforementioned metal/halogen exchange/boronate trap or Pd-catalyzed cross-coupling of the corresponding vinyl halide.

Investigations regarding the basis of selectivity reversal in Ni-catalyzed hydroaluminations[26] and applications to other classes of alkynes as well as hydride sources are in progress.

Acknowledgment. Financial support was provided by the NIH (GM-47480). Mass spectrometry facilities at Boston College are supported by the NSF (DBI-0619576).

Supporting Information Available: Experimental procedures and spectral, analytical data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) There is <2% reaction when phenylacetylene is treated with dibal-H in thf (at 22 °C, in 2 h).
(16) In the absence of a catalyst, *alkyl*-substituted substrates react relatively efficiently (in contrast to aryl alkynes) with dibal-H to afford β-vinylaluminums (>98% selectivity). Such uncatalyzed reactions proceed to ∼80% conversion after 6 h at 22 °C and must be heated to 55 °C (2 h) to achieve ∼90% conv. The Ni-catalyzed processes (Ni$(PPh_3)_2Cl_2$) are complete in 2 h at 22 °C. For data regarding this class of catalytic hydroaluminations, see the Supporting Information.
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(26) Initial studies indicate that Ni(0) complexes are involved (vs Ni(II)). Subjection of phenylacetylene to the conditions shown in Table 1, but with 3 mol % Ni(dppp)Cl_2 and 6 mol % MeMgI (to generate Ni(0)(dppp) complex in situ), affords **2** with 97% α selectivity (>98% conv). It is plausible that reactions proceed via an Al−Ni hydride [$(i\text{-Bu})_2$Al-Ni-H]; addition of Ni−H across the alkyne and subsequent alkenyl-Al reductive elimination regenerates the Ni(0) complex. See: (a) Eisch, J. J.; Sexsmith, S. R.; Fichter, K. C. *J. Organomet. Chem.* **1990**, *382*, 273. (b) Eisch, J. J.; Ma, X.; Singh, M.; Wilke, G. *J. Organomet. Chem.* **1997**, *527*, 301.

JA104896B