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

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Abstract

Methods 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), are 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$_3$)$_2$Cl$_2$, hydroalumination becomes highly β-selective, and, unlike uncatalyzed transformations with dibal–H, generates little or no alkynylaluminum byproducts. All hydrometallation 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.
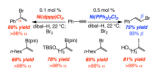
Herein, we disclose that commercially available and inexpensive Ni-based catalysts and diisobutylaluminum hydride (dibal–H) convert alkyl- or aryl-substituted alkynes to *internal* (or α-) vinylaluminums efficiently and with exceptional selectivity (95% to >98% α isomer). The catalytic protocol offers 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 hydrometallations 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

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Supporting Information Available: Experimental procedures and spectral, analytical data for all products (PDF). This material is available on the web: http://www.pubs.acs.org

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.
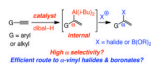
(1)

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 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 two hours leads to efficient hydrometallation (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) lead 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, hydrometallation 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).

It must be noted that, 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* hydrometallation *rates* to the extent that adventitious deprotonation is entirely obviated.

Catalytic hydroaluminations can be performed with a considerable range of aryl alkynes (Table 2), affording α-vinylmetals efficiently and selectively. Transformations are performed at 4–22 °C and require ≤12 hours. 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 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$_3$)$_2$Cl$_2$, proceeding with high β-selectivity (85.5% to >98%) and with minimal alkyne deprotonation; complete data is 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.

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 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] 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.

Ni-catalyzed hydroalumination and vinyl halide synthesis is amenable to scale up and requires 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]

(2)

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]

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$_2$Cl$_2$,[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 CuCl, KOAc, LiCl or a phosphine), and only 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 afford 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 hydroaluminations26 and applications to other classes of alkynes as well as hydride sources are in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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13. For selectivity reversal in Ni-catalyzed H–P and H–S addition to terminal alkynes, see: Han L-B, Zhang C, Yazawa H, Shimada S. J. Am. Chem. Soc. 2004; 126:5080. [PubMed: 15099086]

14. Eisch JJ, Foxton MW. J. Organomet. Chem. 1968; 12:33.

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$_3$)$_2$Cl$_2$) are complete in 2 h at 22 °C. For data regarding this class of catalytic hydroaluminations, see the Supporting Information.

17. (a) Ref 1a. Moran WJ, Morken JP. Org. Lett. 2006; 8:2413. [PubMed: 16706539]

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19. In a similar manner, the β-vinyl bromide derived from vinylaluminum **1** is obtained in 75% yield from a reaction performed on 10 mmol of phenylacetylene with 0.5 mol % Ni(PPh$_3$)$_2$Cl$_2$.

20. Synthesis of α-vinylboronates by an NHC–Cu-catalyzed hydroboration of a propargyl ether and a propargyl amide was recently reported to proceed with ~90% α selectivity: Lee Y, Jang H, Hoveyda AH. J. Am. Chem. Soc. 2009; 131:18234. [PubMed: 19968273]

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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*-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 JJ, Sexsmith SR, Fichter KC. J. Organomet. Chem. 1990; 382:273. (b) Eisch JJ, Ma X, Singh M, Wilke G. J. Organomet. Chem. 1997; 527:301.
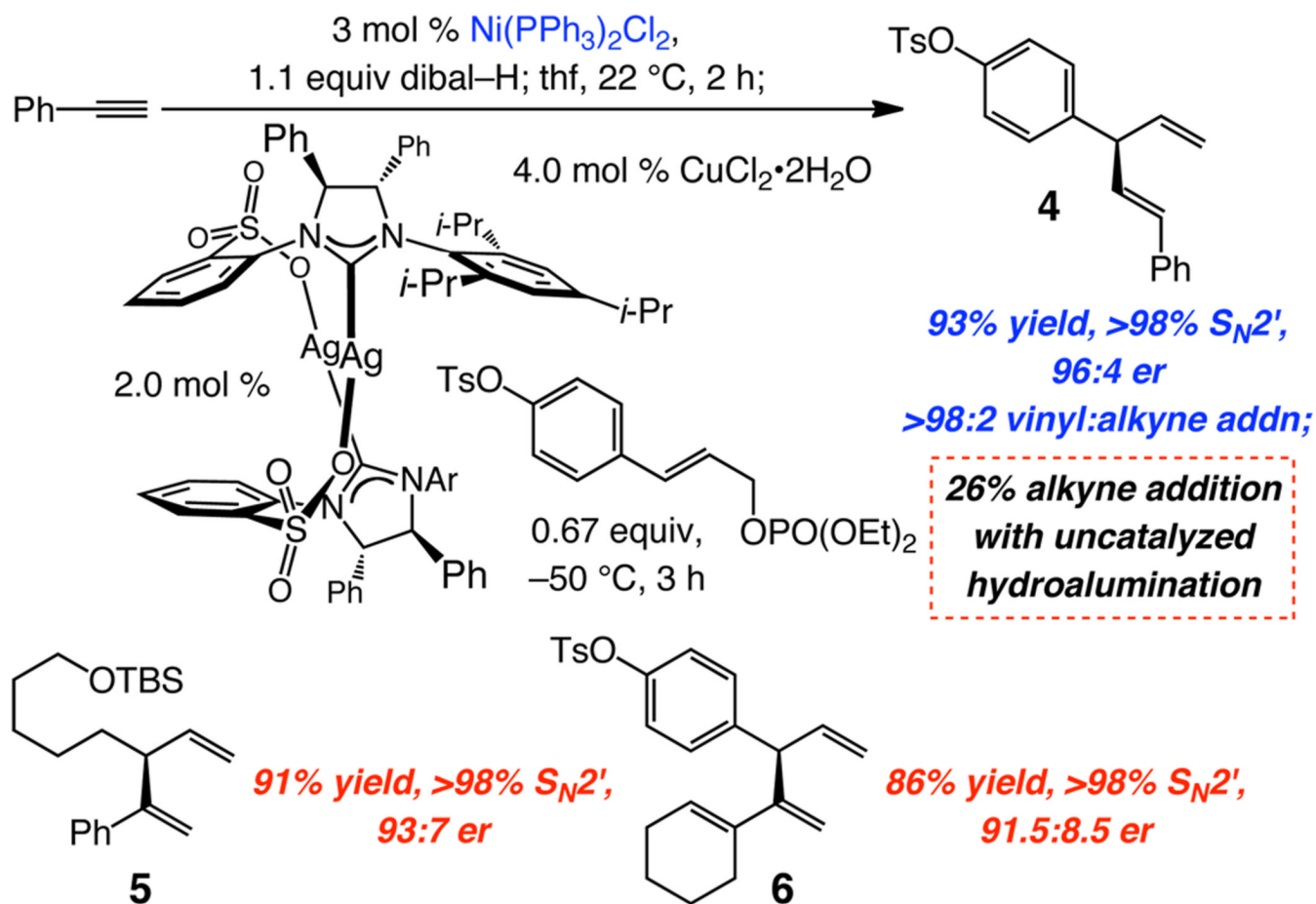
Scheme 1.
Applications of Ni-Catalyzed Hydroaluminations[a]
[a] Synthesis of **5** and **6** at –15 °C. Ar = 2,4,6-(*i*-Pr)$_3$-C$_6$H$_2$.
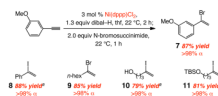
Scheme 2.
Conversion of Terminal Alkynes to α-Vinyl Halides

[a] Reaction with N-iodosuccinimide under otherwise identical conditions. See the Supporting Information for experimental details.
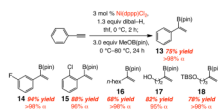
Scheme 3.
One Pot Synthesis of α-Vinyl Boronates[a]
[a] Yields refer to purified α-vinylboronates; see the Supporting Information for experimental details. B(pin) = pinacolatoboron.

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$_2$•6H$_2$O	95	45:35:20
3	Ni(cod)$_2$	>98	69:14:17
4	Ni(PPh$_3$)$_4$	>98	55:32:13
5	*Ni(PPh$_3$)$_2$Cl$_2$*	*>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$_2$ atm; <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$_2$O (0 °C, 30 min); see the Supporting Information for details.

Table 2

α-Selective Ni-Catalyzed Hydroalumination of Arylacetylenes[a]

aryl—≡≡ $\xrightarrow[\text{thf, 4 or 22 °C, 2 or 12 h}]{\begin{array}{c}\text{3 mol % Ni(dppp)Cl}_2,\\\text{1.3 equiv dibal–H,}\end{array}}$ aryl $\overset{\text{Al(}i\text{-Bu)}_2}{\underset{\alpha}{\diagup}}$

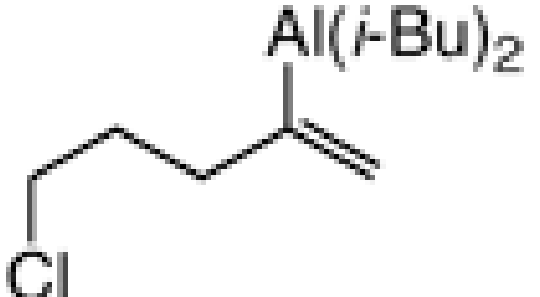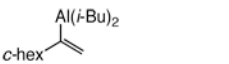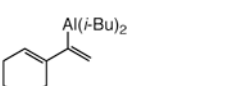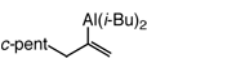| entry	aryl	temp (°C)	time (h)[b]	conv (%)[c]	α:β[c]
1	o-OMeC$_6$H$_4$	4	12	>98	98:2
2	m-OMeC$_6$H$_4$	22	2	>98	>98:2
3	p-OMeC$_6$H$_4$	4	12	>98	>98:2
4	m-CF$_3$C$_6$H$_4$	4	12	>98	95:5
5	p-CF$_3$C$_6$H$_4$	22	2	>98	97:3
6	p-FC$_6$H$_4$	22	2	>98	>98:2
7	o-ClC$_6$H$_4$	22	2	>98	>98:2
8	o-BrC$_6$H$_4$	22	2	>98	>98:2
9	o-MeC$_6$H$_4$	4	12	>98	>98:2
10	3-pyridyl	22	2	>98	>98:2
11	3-pyridyl	22	2	>98	>98:2
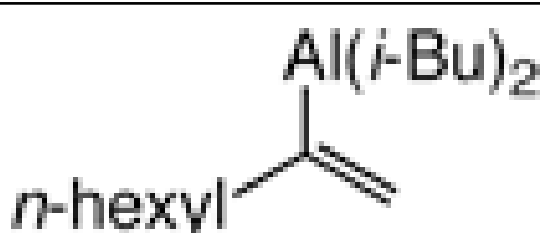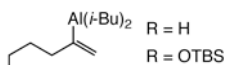
[a] Reactions under N$_2$ atm.

[b] Reaction times correspond to hydroalumination portion of the process (not including D$_2$O quench).

[c] By analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures (after D$_2$O); <2% alkynylaluminum observed.

Table 3

α-Selective Ni-Catalyzed Hydroalumination of Alkylacetylenes[a]
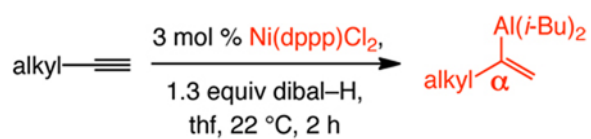
entry	product	conv (%)[b]	α:β[c]
1		>98	>98:2
2	R = H	>98	97:3
3	R = OTBS	>98	>98:2
4		>98	>98:2
5		>98	>98:2
6		>98[d]	98:2
7		>98	96.5:3.5

[a–c] See Table 2; 2.3 equiv dibal–H in entry 2; 3 h for entry 4.

[d] Performed at 4 °C for 12 h; ~5% alkyne deprotonation observed.