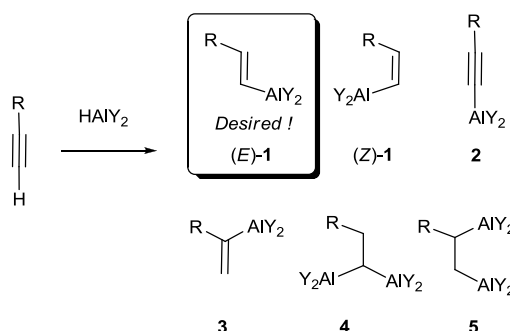


ZrCl₂(η -C₅Me₅)₂-AlHCl₂•(THF)₂: Efficient hydroalumination of terminal alkynes and cross-coupling of the derived alanes

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Stabilized AlHCl₂•(THF)₂ hydroaluminates RC≡CH with exceptional chemo-, regio- and stereoselectivity under efficient ZrCl₂(η -C₅Me₅)₂ catalysis (2-5 mol%). The resulting vinyl alanes undergo palladium cross-coupling with a wide range of sp² electrophiles (aryl, heteroaryl and vinyl halides/pseudohalides) in good to excellent yields.

Despite the intrinsic usefulness of Zweifel's HAlBu₂ⁱ (DIBAL-H), direct formation of α -vinylalanes **1** (Scheme 1, Y = Buⁱ) by this reagent using terminal acetylenes is not without issues:^{1,2} (i) Neat DIBAL-H is significantly pyrophoric. (ii) Direct thermal reaction of RC≡CH and DIBAL-H in heptane (Negishi's procedure³) is limited to R = alkyl as more electron withdrawing R groups lead to significant alkyne deprotonation (giving **2**) not hydroalumination. (iii) Attaining highly chemo- and regioselective terminal alkyne hydroalumination under such conditions can be challenging (i.e. formation of only (*E*)-**1** without any **2** or (*Z*)-**1**, or **3**). Sometimes relatively high terminal C(1) selectivity can be attained through the use of catalysts,⁴ or by use of RC≡TMS as a terminal alkyne surrogates.⁵ (iv) Alkyne over reduction (leading to **4-5**) and functional group intolerance are also known common issues. (v) The presence of bulky, potentially transferable, *i*-butyl groups in alanes **1** (R = Buⁱ) is also known to complicate or slow subsequent transmetalation to modern selective catalysts when using such vinylalanes as terminal C-nucleophiles in cascade approaches.



Scheme 1 Desired (*E*)-**1** and common by-products in hydroalumination of RC≡CH by HAlY₂ (Y = Buⁱ, Cl).

Because of the above limitations alternative hydrometalation strategies⁶ have been developed, often using B- and Zr-based reagents. Vinylboranes although easily prepared can be sensitive to hydrodeboration in subsequent couplings unless more expensive pinacol⁷ or MIDA-based⁸ reagents are used. Moreover, transmetalation or other activation of vinylboranes is typically required for such species. While stoichiometric use of the Schwartz reagent⁹ ZrHCl(η -C₅H₅)₂ with RC≡CH does offer clean access to vinyl zirconoceny species, analogous of (*E*)-**1**, this is at the cost of poor mass/atom economy.

In seeking a route to (*E*)-**1**, where Y is a small, non transferable group, we considered dichloroalane (HAlCl₂). Although there is no report of terminal alkyne hydroalumination¹⁰ with this reagent, its use is attractive as stabilized adducts¹¹ (including some formed directly from AlCl₃/Al powder and H₂ at large scales¹²) are already known. We could note that some of these can be

handled for short times in air (ca. 30 min.) and thought the decreased reactivity of such adducts might allow clean formation of (*E*)-**1** without the complications of Scheme 1. Preliminary studies revealed $\text{HAlCl}_2 \cdot (\text{THF})_2$ provided the desired reactivity in tests with 1-decyne (Table 1). The relative populations of **1-5** are most easily attained by integration of the singlets in the $^2\text{H}\{^1\text{H}\}$ decoupled NMR spectrum of the crude, D_2O quenched, reaction mixtures. This simple mechanistic technique does not seem to have been greatly used before to screen hydroaluminations (see Supporting Data for details).

Table 1 Hydroalumination of 1-decyne by $\text{HAlCl}_2 \cdot (\text{THF})_2$ (1.5 equiv.)^a

Run	Catalyst ^b	Conversion./% ^c	(<i>E</i>)- 1 :(<i>Z</i>)- 1 : 2 : 3 : 4 : 5 ^d
1	None	7	90 :0:0:0:0:10
2	Cp_2TiCl_2 (5 mol%)	77	53 :2:0:42:1:2
3	Cp_2ZrCl_2 (5 mol%)	up to 51	74 :0:15:5:5:0
4	$\text{Cp}^*_2\text{TiCl}_2$ (5 mol%)	>98	75 :3:0:6:14:3 ^e
5	$\text{Cp}^*_2\text{ZrCl}_2$ (5 mol%)	95	87 :0:1:2:7:3
6	$\text{Cp}^*_2\text{ZrCl}_2$ (2 mol%)	85	85 :0:0:2:11:2
7	$\text{Cp}^*_2\text{ZrCl}_2$ (1 mol%)	77	82 :0:0:2:15:2
8	$\text{Cp}^*_2\text{ZrCl}_2$ (0.5 mol%)	71	75 :0:0:3:18:3

^a Chemistry of Scheme 1 ($\text{R} = \text{C}_8\text{H}_{17}$, $\text{Y} = \text{Cl}$) using 1-decyne (1.0 mmol) in THF (1.4 mL) at 80 °C. ^b Cp is $\eta\text{-C}_5\text{H}_5$, Cp^* is $\eta\text{-C}_5\text{Me}_5$. ^c By ^1H NMR spectroscopy of the crude product. ^d By $^2\text{H}\{^1\text{H}\}$ NMR spectroscopy on D_2O quenched reaction mixture. ^e Minor additional uncharacterised components and d_0 -alkene also present.

The alane alone gave chemoselective hydroalumination but its rate was unacceptable (Run 1). Titanocene dichloride was active but poorly regioselective (Run 2). Simple zirconocene dichloride inhibited conversion provided poorer and variable conversions (Run 3). We speculated this was due to the formation of stable dichloroalane adducts, perhaps related to $\text{Cp}_2\text{Zr}(\mu\text{-H})(\mu\text{-H}_2\text{AlCl}_2)\text{ZrCp}_2$,¹³ and planned to disrupt this via use of sterically encumbered metallocenes.¹⁴ While $\text{Cp}^*_2\text{TiCl}_2$ has been employed in LiAlH_4 alkene hydroaluminations¹⁵ its use here had two negative features: firstly, with $\text{HAlCl}_2 \cdot (\text{THF})_2$ it gave unclean reactivity generating (*Z*)-**1**, **3-5** and hydrogen transfer products being; secondly, its literature preparation and cost are very uninviting.¹⁶ As far as we can determine, $\text{Cp}^*_2\text{ZrCl}_2$ has not been used in hydroalumination before. However, this pre-catalyst is highly potent for terminal alkyne HAlCl_2 addition (Runs 5-8), the only significant by-product being some **4**, which shows no reactivity towards electrophiles vs. (*E*)-**1** in subsequent catalysis.

A number of practical issues make the use of $\text{Cp}^*_2\text{ZrCl}_2\text{-HAlCl}_2 \cdot (\text{THF})_2$ rather attractive: (i) The alane (a non pyrophoric colourless crystalline solid) is easily prepared on at least 50 g scales (see Supporting Data) and it can be handled in air for up to 30 min with <5% decomposition. While this is not as robust as our air-stable AlMe_3 analogue DABAL- Me_3 , it does allow prompt weighing of gram quantities in the open laboratory.¹⁷ (ii) $\text{Cp}^*_2\text{ZrCl}_2$ is commercially available or alternatively easily prepared.¹⁸ (iii) Simple distillation of the alkyne allows low (2 mol%) catalyst loadings and short reaction times (down to 2 h) to be used. (iv) At 5 mol% the catalyst system is really rather robust and will often tolerate unpurified alkynes, variable reaction times (2-16 h) and alternative use of dioxane as a solvent.¹⁹ (v) Terminal alkynes with more acidic $\equiv\text{CH}$ bonds are also well tolerated (aryl- an ene-

ynes). (v) For more sterically encumbered alkynes (e.g. $\text{ArC}\equiv\text{CH}$, $\text{Bu}^t\text{C}\equiv\text{CH}$) $\text{Cp}^*_2\text{ZrCl}_2$ could be replaced by simple titanocene dichloride without appreciable formation of **3**. (vi) No transmetallation or solvent switch is needed allowing one-pot procedures. The applicability of these features was first demonstrated through simple cross-coupling of (*E*)- $\text{PhCH}=\text{CHAlCl}_2$ to PhBr (Table 2). Dichlorovinylalanes are rather rare, but synthetically useful, species mentioned only in passing in the literature.²⁰

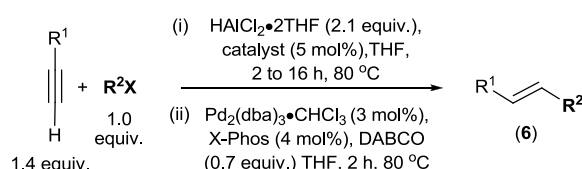
Table 2 Optimisation of the hydroalumination/cross-coupling procedure^a

Run	Hydroalumination Catalyst ^b	Additive ^c	Yield/% ^d
1	Cp_2TiCl_2 (5 mol%)	None	75
2	Cp_2TiCl_2 (5 mol%)	DABCO	94 ^e
3	$\text{Cp}^*_2\text{ZrCl}_2$ (5 mol%)	None	81
4	$\text{Cp}^*_2\text{ZrCl}_2$ (5 mol%)	DABCO	94 ^e

^a Chemistry of Scheme 1 ($\text{R} = \text{Ph}$, $\text{Y} = \text{Cl}$) using phenylacetylene (2.00 mmol) in THF (4 mL) at 80 °C. ^b Cp is $\text{h-C}_5\text{H}_5$, Cp^* is $\text{h-C}_5\text{Me}_5$. ^c 0.7 equiv. based on phenylacetylene. ^d By GC (FactorFour column) tridecane internal standard. ^e Isolated yield.

Conditions similar to our related DABAL- Me_3 coupling proved effective.²¹ In particular, addition of DABCO to form the DABAL-(vinyl) Cl_2 reagent *in situ* led to a maximised yield of the desired (*E*)-product. Satisfyingly, the presence of neither the zirconium catalyst nor small amounts of **4** ($\text{Y} = \text{Cl}$) inhibit the coupling and no other co-promoter was needed. Extending this procedure raises three key questions: firstly, how general is the cross-coupling procedure with respect to the alkyne and electrophile? Secondly, is Pd-catalysed cross-coupling limited to the proprietary X-phos ligand? Finally, how does this procedure ‘measure up’ against established DIBAL-H based processes? The generality of the two-stage process is demonstrated in Table 3. The required vinyl alanes were attained from precursor alkynes using $\text{Cp}^*_2\text{ZrCl}_2$ (5 mol%) with reaction times of 2-16 h; for hindered alkynes Cp_2TiCl_2 (5 mol%, 2 h) was sometimes used. In reaction of $\text{HO}(\text{CH}_2)_3\text{C}\equiv\text{CH}$ extra equivalents of $\text{HAICl}_2\cdot(\text{THF})_2$ was used together with InCl_3 co-catalysis.²² Similar approaches were used for pyridyl and quinoyl bromides.

Table 3 Scope of the hydroalumination/cross-coupling procedure^a

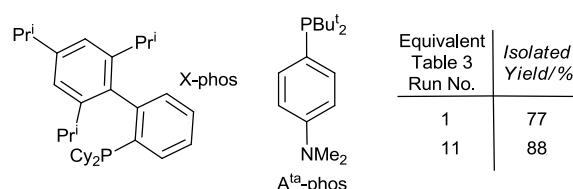


Run	Catalyst ^b	R ¹	R ²	X	Yield/% ^c
1	Zr	C ₆ H ₁₃	Ph	Br	98
2	Zr	C ₈ H ₁₇	Ph	Br	96
3	Zr	Bu ⁱ	Ph	Br	88
4	Ti	Bu ^t	Ph	Br	93 ^d
5	Zr	Ph	Ph	I	98
6	Zr	Ph	Ph	OTf	86 ^e
7	Zr	Ph	Ph	Cl	41
8	Zr	BnO(CH ₂) ₃	Ph	Br	75
9	Zr	HO(CH ₂) ₃	Ph	Br	61 ^f
10	Ti	Bu ^t	3,5-Me ₂ Ph	Br	86
11	Zr	C ₆ H ₁₃	3,5-Me ₂ Ph	Br	95
12	Zr	Ph	3,5-Me ₂ Ph	Br	96
13	Ti	Bu ^t	1-naphthyl	Br	71
14	Zr	C ₆ H ₁₃	1-naphthyl	Br	57
15	Zr	C ₆ H ₁₃	2-naphthyl	Br	91
16	Ti	Bu ^t	3-MeOPh	Br	71
17	Ti	Bu ^t	4-CF ₃ Ph	Br	71
18	Zr	C ₆ H ₁₃	4-CF ₃ Ph	Br	94
19	Zr	C ₆ H ₁₃	3-(NO ₂)Ph	Br	55
20	Zr	C ₆ H ₁₃	4-(CO ₂ Me)Ph	Br	85
21	Zr	C ₆ H ₁₃	4-MePh	Br	87
22	Ti	Bu ^t	2-MePh	Br	81
23	Zr	C ₆ H ₁₃	2-MePh	Br	92
24	Ti	Bu ^t	3-MePh	Br	65
25	Zr	C ₆ H ₁₃	3-MePh	Br	95
26	Zr	C ₆ H ₁₃	mesityl	Br	99
27	Zr	C ₆ H ₁₃	4-(CN)Ph	Br	95
28	Zr	C ₆ H ₁₃	3-(CN)Ph	Br	94
29	Zr	C ₆ H ₁₃	(E)-CH=CHPh	Br	63
30	Zr		Ph	Br	68
31	Zr	C ₆ H ₁₃	3-pyridyl	Br	63 ^f
32	Zr	C ₆ H ₁₃	6-quinoyl	Br	94 ^g
33	Zr	C ₆ H ₁₃	2-thiophenyl	Br	72
34	Zr	C ₆ H ₁₃	3-thiophenyl	Br	90
35	Zr	C ₆ H ₁₃	2-furyl	Br	78
36	Zr	C ₆ H ₁₃		Br	77

^a R²X (2.0 mmol) in THF (4 mL) for hydroalumination; cross-coupling components added in additional THF (4 mL). ^b Zr is Cp*₂ZrCl₂; Ti is Cp₂TiCl₂. ^c Isolated yields. ^d 41% yield was attained with the Zr catalyst. ^e Use of the Ti catalyst led to a mixture of C(1) and C(2) products. ^f Additional HAlCl₂ used (1.1 equiv.) in hydroalumination. ^g Additional HAlCl₂ used (1.1 equiv.) in hydroalumination and InCl₃ co-catalysis (14-21 mol%) in cross-coupling.

While >20 combinations in Table 3 gave 80-99% yields, the following substrates were noted to have issues: (i) Although ethers and alcohol functional groups in the alkyne were tolerated attempts to use alkynes containing ester or cyano functions led to their reduction or catalyst inactivation respectively. (ii) Esters were tolerated in the coupling partner but nitro groups were partially attacked. In coupling of pyridyl-type heterocycles additional excesses of alane and InCl₃ co-catalysis were required to attain acceptable yields. Finally, if unpurified alkynes were used significant

amounts of d_0 -alkene were occasionally detected at long reaction times due to hydrogen transfer. However, this did not affect the overall efficiency of the process as excesses of (*E*)-**1** are still present. To answer the question of the efficacy of the process described here against literature precedent direct comparison against standard DIBAL-H based hydroalumination conditions was made using a common Pd-coupling catalyst (see Supporting Data). In each case investigated the dichloroalane route was quicker and higher yielding. In other trials we could also replace X-phos with the non-proprietary, and industrially used A[†]-phos²³ ligand, with some success (Scheme 2).



Scheme 2 Comparison of proprietary and non proprietary ligands.

Overall, a non pyrophoric alane (that can be handled briefly in air) providing >40:1 reactive (*E*)-C(1)-organoalanes from low loadings of commercial catalysts with minimal by-products constitutes useful methodology. It has wide range, high potential for use on large scales, compares well to current systems and can be expected to find use in both cross-coupling and other subsequent metal-catalysed processes using such vinyl alanes as nucleophiles. The latter are currently being actively investigated by us.

Notes and references

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