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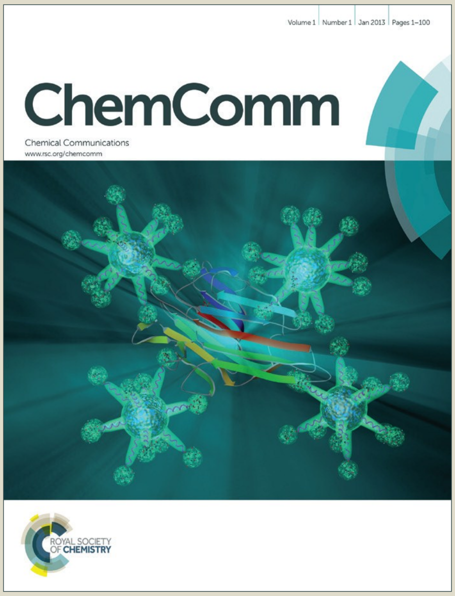

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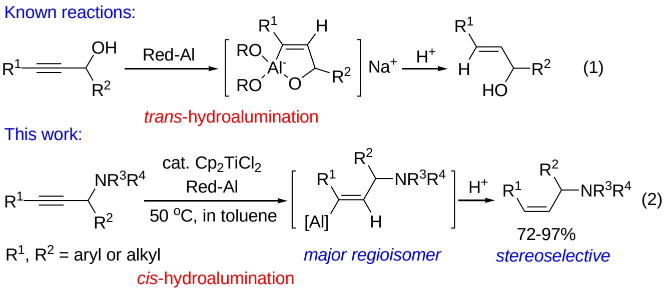
Cp_2TiCl_2-Catalyzed *cis*-Hydroalumination of Propargylic Amines with Red-Al: Stereoselective Synthesis of *Z*-Configured Allylic Amines

Renhong Sun, Jun Liu, Shuang Yang, Ming Chen, Ning Sun, Haoyi Chen, Xin Xie, Xu You, Shi Li and Yuanhong Liu*

A titanium-catalyzed *cis*-hydroalumination of propargylic amines with Red-Al is described, which provides an efficient way to *Z*-configured allylic amines in good to excellent yields with high stereoselectivity and good regioselectivity. The hydride-bridged Al/Ti bimetallic species may act as a real catalyst for this reaction.

Stereoselective synthesis of alkenes are highly important in organic synthesis since alkenes having a specific geometric configuration widely occur in natural products, and serve as useful building blocks for a large variety of transformation reactions. Although much progress has been achieved in this filed, most studies concentrated on the synthesis of thermodynamically more stable *E*-alkenes, while access to *Z*-alkenes are less established.[1] Hydroalumination of alkynes is a valuable and convenient protocol for the generation of alkenylaluminum intermediates, which in turn, are highly useful for the stereodefined construction of multi-substituted alkenes.[2-5] It has been demonstrated that various transition metals can catalyze the hydroalumination of alkynes, such as $NiCl_2$, $Ni(dppp)Cl_2$, $Cp^*{}_2ZrCl_2$ and Cp_2TiCl_2 etc.[4] Although hydroalumination of internal alkynes usually proceeded via *cis* addition of the Al-H bond to afford *Z*-alkenes as the kinetically favored products, however, in some cases, more stable *E*-alkenes were formed via isomerization.[3b-d, 3h, 4a, 4h,j] Among many variants, hydroalumination of propargylic alcohols is well utilized in organic synthesis.[5] For example, in the presence of $NaAlH_2(OCH_2CH_2OMe)_2$ (Red-Al), propargylic alcohols undergo *trans*-hydroalumination to produce *E*-allylic alcohols via deprotonation of OH group and formation of a cyclic vinyl alanate intermediate (Scheme 1, eq 1).[5e] Compared with propargylic alcohols, the hydroalumination of propargylic amines with Al-H reagents has far less been studied,[6] and there is no report for the *Z*-selective synthesis of allylic amines by hydroaluminations.[7] In this paper, we report our success in Cp_2TiCl_2-catalyzed regio- and stereoselective *cis*-hydroalumination of propargylic amines with Red-Al to *Z*-allylic amines (Scheme 1, eq 2). It should be noted that the reagent system of Cp_2TiCl_2/Red-Al has rarely been used for hydroalumination reactions.[8]



Scheme 1 Hydroalumination of propargylic substrates.

At the beginning, we focused on the reactivity of tertiary propargylic amine **1a** (Table 1). In the absence of any catalyst, reaction of **1a** with 1.0 equiv of Red-Al in toluene or THF at room temperature afforded chalcone **3a** in 53% and 81% yields, respectively after hydrolysis[9] (entries 1-2). **3a** might be formed via formation of an allenic amine intermediate under basic conditions followed by hydrolysis.[10] To our surprise, addition of a catalytic amount of Cp_2TiCl_2 (5 mol%) before adding Al-reagent to the reaction mixture dramatically changed the reaction pathway, in which *Z*-allylic amine **2a** was provided in quantitative yields and excellent stereoselectivity (*Z*/*E* = 100:1 or as single *Z*-isomer) at 50 °C or 80 °C in toluene, whereas **3a** was completely suppressed (entries 6-7). The results indicated that the transient "Ti-H" or "Al-H" species produced by the

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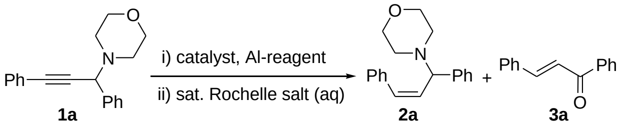
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032 (P. R. China). E-mail: yhliu@sioc.ac.cn

Electronic Supplementary Information (ESI) available: Experimental details, NMR spectra of all compounds, X-ray crystallography of **7a** and **11**. CIF files for CCDC-1040902 (**7a**), 1040903 (**11**). See DOI: 10.1039/c000000x/

reaction of Cp2TiCl2 with Red-Al played an important role in this reaction (vide infra). Switching the solvent from toluene to THF led to the decreased yield of **2a** (entry 8). Reducing the amount of Red-Al to 0.5 equiv slightly decreased the yield of **2a** to 94% with a longer reaction time (entry 9). The combination of 5 mol% of Cp2TiCl2 and DIBAL-H furnished **2a** in only 36% yield at 80 °C (entry 10). It was noted that other metal catalysts such as Cp2ZrCl2, Cp*2ZrCl2, Ti(O^{i}Pr)4 failed to give the satisfactory results (entries 11-13).

Table 1. Optimization of the reaction conditions.



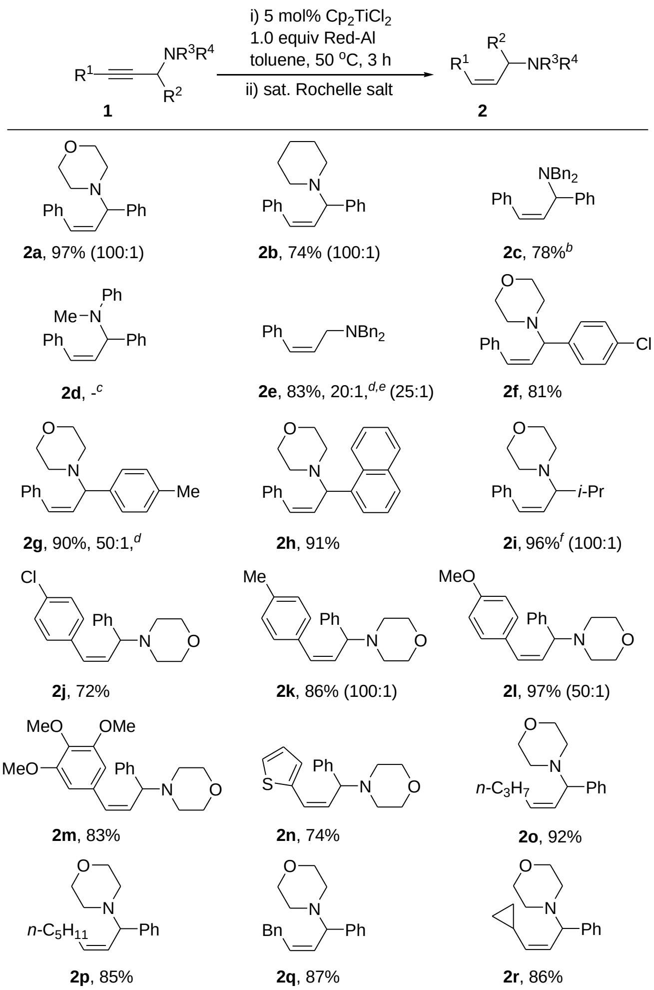
1a **2a** **3a**

entry	Al-reagent (equiv)	catalyst (5 mol%)	solvent	temp (°C)	time (h)	yield of **2a** (%)[a,b]	yield of **3a** (%)[a]
1	Red-Al (1.0)	-	toluene	rt	3	0	53
2	Red-Al (1.0)	-	THF	rt	1	0	81[c]
3	DIBAL-H (1.0)	-	toluene	rt	6	0	0
4	DIBAL-H (1.0)	-	toluene	80	6	20 (13:1)	0
5	Red-Al (1.0)	Cp_2TiCl_2	toluene	rt	6	21 (14:1)	31
6	Red-Al (1.0)	Cp_2TiCl_2	toluene	50	3	99 (100:1)[d]	0
7	Red-Al (1.0)	Cp_2TiCl_2	toluene	80	3	100 (only *Z*)	0
8	Red-Al (1.0)	Cp_2TiCl_2	THF	50	3	61 (20:1)	2
9	Red-Al (0.5)	Cp_2TiCl_2	toluene	50	8	94 (100:1)	1
10	DIBAL-H (1.0)	Cp_2TiCl_2	toluene	80	6	36 (-[e])	0
11	Red-Al (1.0)	Cp_2ZrCl_2	toluene	50	7	3	36
12	Red-Al (1.0)	$Cp^*{}_2ZrCl_2$	toluene	50	7	4	61
13	Red-Al (1.0)	Ti(O^{i}Pr)$_4$	toluene	50	3	-[f]	27

[a] ^{1}H NMR yields using CH_2Br_2 as the internal standard. All reactions were carried out by adding the reactants in this order: **1a** (0.3 mmol), solvent (5 mL), catalyst, Al-reagent. [b] *Z*/*E* ratio is shown in parentheses. [c] Isolated yield was 80% after the reaction was quenched by water. [d] Isolated yield was 97%. [e] Not determined. [f] 2% *of E*-**2a** was formed.

With the optimized reaction conditions in hand, the substrate scope of this reaction was further explored (Table 2). It was found that the reaction was applied to a wide variety of propargylic amines, and in all cases, the corresponding allylic amines were obtained as single *Z*-alkene isomers or with high stereoselectivity. The scope of *N*-substituents R^3 and R^4 in **1** was first examined. When the morpholine group in **1a** was replaced by piperidine or *N,N*-dibenzyl groups, the corresponding allylic amines **2b** and **2c** were produced smoothly in 74% and 78% yields, respectively. However, employing a *N*-methyl-*N*-phenyl substituted propargylic amine could not afford the desired **2d**, instead, a complex reaction mixture resulted. The effect of substituent (R^2) at the propargylic position was investigated next. Substrate **1e** bearing two hydrogen substituents at the propargylic position was compatible, furnishing **2e** in 83% yield. In this case, an over-reduction product of *N*,*N*-dibenzyl-3-phenylpropan-1-amine was also observed, indicating a small amount of dialuminates might be formed during the reaction. Aryl or alkyl groups were all suitable for R^2 substituents, providing **2f**-**i** in 81-96% yields. The substituent effect on alkyne terminus (R^1) was then examined. For aryl-substituted alkynes, the functionalities of -Cl, -Me, -MeO and 3,4,5-(MeO)$_3$ groups on the aromatic rings were tolerated well, leading to the corresponding products **2j**-**m** in good to high yields. A thienyl-group was also well compatible to afford **2n** in 74% yield. The reactions with alkyl-substituted alkynes such as n-propyl, n-pentyl, benzyl or cyclopropyl substituted ones were also satisfactory, leading to **2o**-**r** in 85-92% yields. Allylic amines are important building blocks for the synthesis of heterocycles and bioactive substances,[11] our method provided a convenient route to stereodefined allylic amines.

Table 2. Substrate scope of Cp_2TiCl_2-catalyzed hydroalumination reactions.[a]

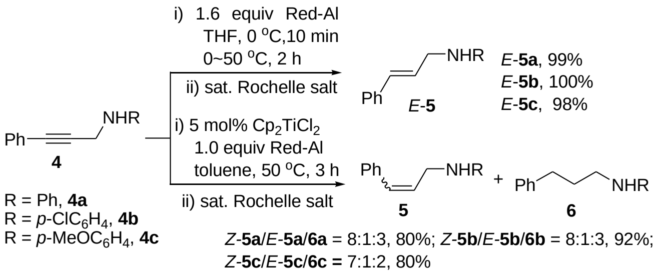


2a, 97% (100:1)
2b, 74% (100:1)
2c, 78%[b]
2d, -[c]
2e, 83%, 20:1,[d,e] (25:1)
2f, 81%
2g, 90%, 50:1,[d]
2h, 91%
2i, 96%[f] (100:1)
2j, 72%
2k, 86% (100:1)
2l, 97% (50:1)
2m, 83%
2n, 74%
2o, 92%
2p, 85%
2q, 87%
2r, 86%

[a] Isolated yield of pure *Z*-isomer. *Z*/*E* ratio of the crude products is shown in the parenthese. [b] Containing a small amount of byproduct. [c] Complicated reaction mixtute was observed. [d] *Z*/*E* ratio of isolated products. [e] Containing 13% of *N*,*N*-dibenzyl-3-phenylpropan-1-amine. [f] 80 °C.

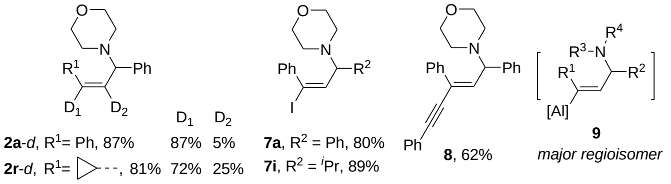
The secondary propargylic amines were also evaluated. In the absence of Ti-catalyst, *E*-allylic amines **5a**-**c** were obtained as single isomers in quantitative yields (Scheme 2). In these cases, the reactions might also proceed via cyclic vinyl alanate intermediate analogous to that in the reduction of propargylic alcohols with Red-Al. In the presence of Ti-catalyst, *Z*-allylic amines were obtained as the major isomers with the *Z*/*E* ratio ranging from 7:1 to 8:1.

To clearify the regiochemistry of hydroalumination reactions, deuterium incorporation experiments were performed by quenching the reaction mixture derived from **1a** or **1r** with D_2O (Scheme 3). The

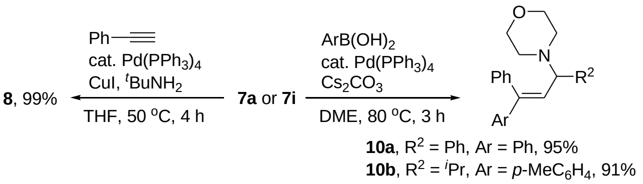


Scheme 2 Hydroalumination of secondary propargylic amines.

deuterated products were formed with high overall deuterium incorporation. ^{1}H NMR analysis indicated that deuterium labeled predominantly at the carbon α to the R^1 substituent. Aryl-substituted alkyne showed better regioselectivity than cyclopropyl-substituted one. Iodinolysis of the reaction mixture derived from **1a** and **1i** by NIS afforded alkenyl iodide **7a**[12] and **7i** in good yields, in which iodine attached at the carbon α to the phenyl group. In addition, treatment of the reaction mixture derived from **1a** with alkynyl bromide in the presence of 1.1 equiv of CuCN afforded alkynylated product **8** in 62% yield. According to these results, the vinylaluminum intermediate **9** was proposed as the major regioisomer via *cis* addition of Al-H species. The obtained alkenyl iodides can be employed as useful building blocks for further reactions. For example, coupling of **7a** or **7i** with phenylacetylene or ArB(OH)$_2$ in the presence of palladium catalyst afforded **8** and **10** in high yields (Scheme 4).

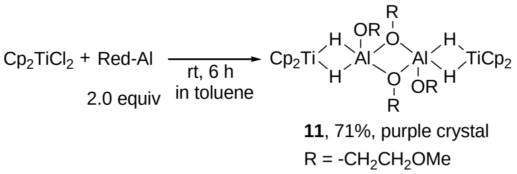


Scheme 3 Transformations of vinylaluminum intermediate.



Scheme 4 Transformations of compounds **7.**

So far there is no detailed mechanistic study for Ti-catalyzed hydroalumination of alkenes or alkynes. Recently, Szymoniak et al. reported a Cp2TiCl2-catalyzed hydroalumination of pentafulvenes with DIBAL-H, and the bimetallic complexes of [Ti(μ-H)(μ-Cl)Al] or [Ti(μ-H)2Al] was proposed as the catalytically active hydride species for these reactions.[13] However, the structures of these metal complexes were not identified. To understand the reaction mechanism, we tried to isolate the possible metal hydride intermediates. Treatment of Cp2TiCl2 with Red-Al in a ratio of 1:2 in toluene resulted in a color change from red to purple accompanying H2 evolution,[14] and a dimmer (**11**) of hydride-bridged bimetallic complex Cp2Ti(μ-H)2Al(OCH2CH2OCH3)2 was isolated in 71% yield from the solution (Scheme 5). The NMR data of trivalent titanium complex **11** was not available due to its paramagnetism. The structure of **11** was unambiguously determined by X-ray crystallography.[12] In the structure, both titanium and aluminum adopt a distorted tetrahedral geometry, and the lengths of Ti-H[15a] and Al-H[15b-c] bonds are within the reported range.[15] Complex **11** showed similar catalytic activity as that of the Cp2TiCl2 for hydroalumination of **1a** under the standard reaction conditions to afford *Z*-**2a** in 98% yield. The results indicated that bimetallic complex **11** or its monomer might act as the active species in hydroalumination reactions.



Scheme 5 Isolation of the metal-hydride intermediate.

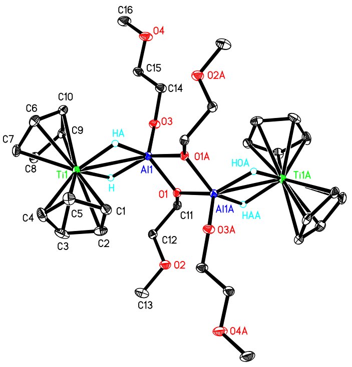
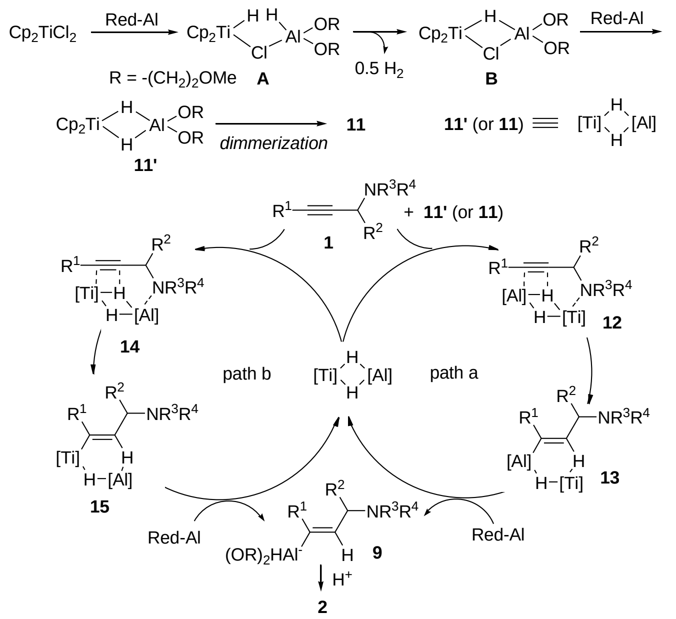


Figure 1 Crystal structure of complex **11**. Hydrogen atoms are omitted for clarity. The thermal ellipsoids correspond to 30% probability. Selected bond lengths [Å] and angles [deg]: Ti1···Al1 2.7619(6), Ti1-H 1.767(19), Ti1-HA 1.776(18), Al1-H 1.705(19), Al1-HA 1.745(19), Al1-O(1) 1.8521(13), Al1-O3 1.7224(13), Al1-Ti1-H 36.5(6), H-Al1-HA 76.6(9), H-Ti1-HA 74.3(9).

Based on the above results, a plausible reaction mechanism leading to the major regioisomer is presented in Scheme 6. Initially, the reaction of Cp_2TiCl_2 with first equivalent of Red-Al affords **A** by chloride-hydride exchange reaction, which converts to **B** via elimination of hydrogen.[16] **B** reacts with the second equivalent of Red-Al to give the bimetallic complex **11'** or it's dimmer **11**. To account for the regioselectivity observed in above reactions, we suggest that the bimetallic species **11'** or **11** might act as a cooperative catalyst. Thus in path a, the titanium may coordinate with the amino group in **12**, which serves as a temporary tether to make the aluminum metal closer to the alkyne terminus bearing a R^1 group. Subsequent *cis*-hydroalumination followed by reaction with Red-Al affords vinyl aluminate **9** and regenerate the catalyst. Hydrolysis of **9** leads to the *Z*-allylic amine **2**. In path b, the bimetallic species may also act as a hydrotitanation agent to give the vinyltitanocene **15** via **14**, which undergoes transmetalation with Red-Al to generate **9**. It is also possible that both of the reaction pathways may operate in the reaction process.



Scheme 6 Possible reaction mechanism for the formation of the major regioisomer.

In summary, we have developed a Cp_2TiCl_2-catalyzed *cis*-hydroalumination of propargylic amines with Red-Al. The reaction provides an efficient way to *Z*-configured allylic amines in good to excellent yields with high stereoselectivity and good regioselectivity. The hydride-bridged Al/Ti bimetallic species could be isolated and characterized by X-ray crystallography through the reaction of Cp_2TiCl_2 with Red-Al, which may act as a real catalyst for this reaction. Further investigations on the detailed reaction mechanism and application of this chemistry are in progress.

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