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Catalytic Enantioselective Synthesis of α-Substituted Secondary Allylic Alcohols from Terminal Alkynes and Aldehydes via Vinylaluminum Reagents

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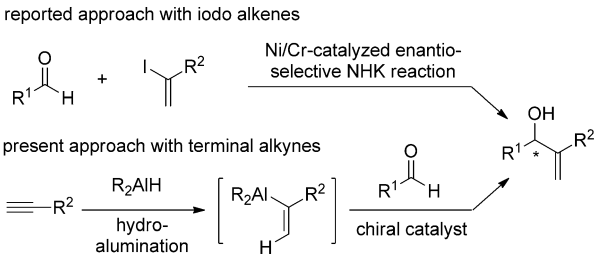
Enantioenriched chiral secondary allylic alcohols are among the most versatile chiral building blocks in asymmetric synthesis. Considerable attention has been focused on the catalytic enantioselective synthesis of these alcohols, especially through the stereocontrolled coupling of readily available starting components.[1,2] Although chiral allylic alcohols with various substitution patterns are in demand, advances in this area have mostly been focused towards the synthesis of β-substituted *E* allylic alcohols.[3,4] In contrast, very few methods have been developed for the synthesis of α-substituted allylic alcohols.[5,3f] Recently, Kishi and coworkers reported an efficient method for the enantioselective coupling of aldehydes with vinyl iodides through the Ni/Cr-catalyzed Nozaki–Hiyama–Kishi (NHK) reaction (Scheme 1).[5] The efficiency and robustness of this reaction for the synthesis of α-substituted allylic alcohols has been well-demonstrated by its application in natural-product syntheses.[6]



Scheme 1. Catalytic enantioselective synthesis of α-substituted secondary allylic alcohols.

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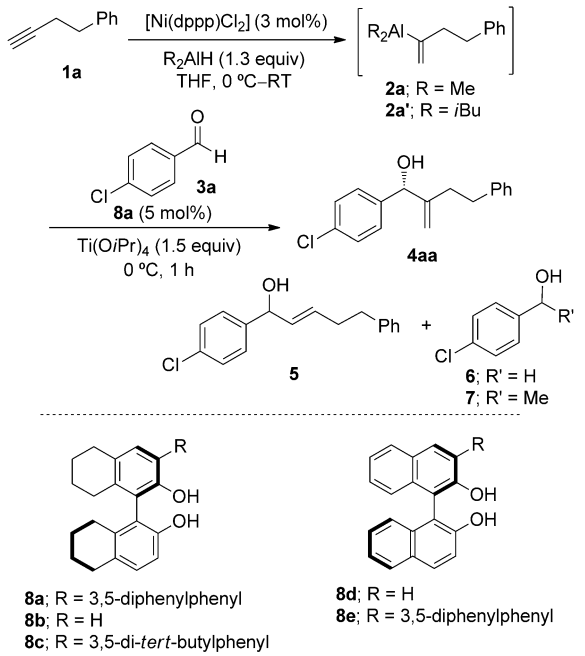
The Ni-catalyzed hydroalumination of terminal alkynes with *i*Bu_2AlH, providing α-substituted vinylaluminum reagents with high Markovnikov selectivity has been reported recently by Hoveyda et al.[7] It occurred to us that the enantioselective addition of the generated vinylaluminum reagents to aldehydes could provide an alternative route to allylic alcohols by using easily accessible alkynes as staring materials (Scheme 1). We now report a straightforward and efficient method for the catalytic enantioselective synthesis of α-substituted secondary allylic alcohols starting from terminal alkynes and aldehydes via vinylaluminum reagents.

We have recently reported the versatility of a chiral titanium catalyst derived from DPP-H_8-BINOL (DPP = 3,5-diphenylphenyl, BINOL = 1,1′-bi-2-naphthol) **8a** and excess titanium tetraisopropoxide for the enantioselective addition of a variety of organometallic reagents, such as Grignard,[8] organoboron,[9] alkylzinc,[10] and aryltitanium reagents,[11] to aldehydes. These results prompted us to apply the chiral titanium catalyst to the reaction of *p*-chlorobenzaldehyde **3a** with vinylaluminum reagent **2a′**, which are generated from 4-phenyl-1-butyne **1a** according to the protocol described by Hoveyda et al.[7] (Scheme 2).[12,13] Thus, treatment of **1a** (1.5 equiv) in hexane with *i*Bu_2AlH (1.5 equiv), in the presence of [Ni(dppp)Cl_2] (dppp = 1,3-bis(diphenylphosphino)-propane, 3 mol% with respect to **1a**), followed by the reaction of the resulting vinylaluminum reagent, **2a′**, with aldehyde **3a** in the presence of ligand **8a** (5 mol%) and titanium tetraisopropoxide (1.5 equiv), in THF at 0°C for 1 h, afforded allylic alcohol **4aa** in 18% yield and 77% enantiomeric excess (*ee*). The major product of this reaction was *p*-chlorobenzyl alcohol (**6**, 34%), suggesting that the formation of vinylaluminum reagent **2a′**, bearing isobutyl groups, resulted in a preferential hydride reduction of the aldehyde.[14]

We then turned our attention to the use of Me_2AlH, instead of *i*Bu_2AlH, with the expectation that the vinylaluminum reagent **2a**, bearing methyl groups, would not be able to reduce the aldehyde. The aluminum hydride reagent, in hexane, was prepared in quantitative yield by the reaction of Me_2AlCl with NaH by following the reported procedure with some modification.[15,16] Me_2AlH exhibited similar efficiency and regioselectivity to that of *i*Bu_2AlH for the hydroalumination of alkyne **1a**. Treatment of **1a** with Me_2AlH (1.7 equiv), in the presence of [Ni(dppp)Cl_2] (3 mol%), in THF/hexane (0°C–room temperature), followed by quenching the reaction mixture with D_2O, gave a 11:1 mixture of



Scheme 2. Enantioselective preparation of allylic alcohol **4aa** from alkyne **1a** and aldehyde **3a**.

$PhCH_2CH_2CD{=}CH_2$ and $PhCH_2CH_2CH{=}C(D)H$ in 82% yield.

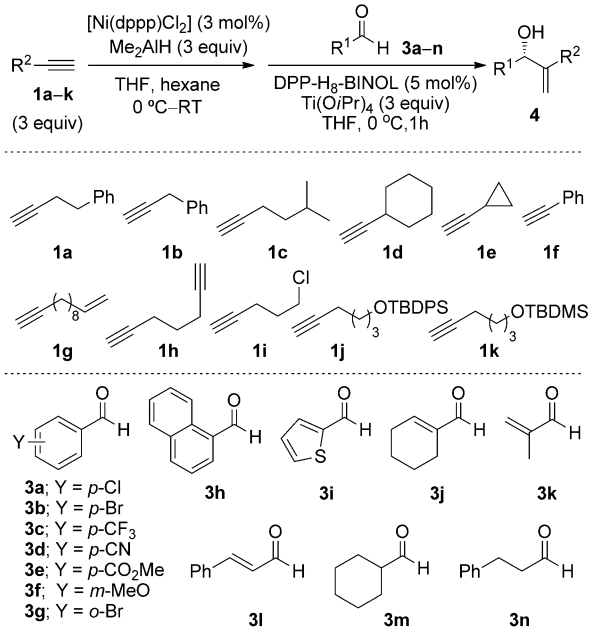
When vinylaluminum reagent **2a**, generated from **1a** (1.5 equiv), was employed in the subsequent reaction with aldehyde **3a**, in the presence of ligand **8a** (5 mol%) and titanium tetraisopropoxide (1.5 equiv), **4aa** was obtained as a major product in 50% yield and 92% *ee* (Table 1, entry 1). In this reaction, methyl adduct **7** (10%) and regioisomeric alkenyl adduct **5** (<2%) were obtained as by-products, but no reduction product, **6**, was detected. To improve the yield of **4aa**, the molar ratio of **1a**/Me_2AlH/titanium tetraisopropoxide was optimized (Table 1, entries 2–5). A yield of 75% and an *ee* value of 93% were obtained when 3 equivalents of each reagent were used (Table 1, entry 5). Under these conditions, reactions were also carried out with BINOL derivatives **8b–e** as ligands. H_8-BINOL **8b** exhibited a relatively high selectivity of 84% *ee* (Table 1, entry 7). A high *ee* value of 93% was observed for 3,5-di-(*tert*-butyl)phenyl derivative **8c** (Table 1, entry 8). On the other hand, the enantioselectivity of the reaction when BINOL **8d** or DPP-BINOL **8e** were used was inferior to that obtained when octahydro derivatives **8b** and **8a** were used (Table 1, entries 9 and 10). α-Substituted vinylaluminum reagent **2a**, in the absence of titanium tetraisopropoxide and ligand **8a**, was much less reactive towards the aldehyde (Table 1, entry 11); however, **2a** did undergo carbonyl addition in the absence of ligand **8a** when titanium tetraisopropoxide was present (Table 1, entry 12). Notably, the activity of the titanium catalyst, derived from **8a**, is high enough to overwhelm the background racemic reaction between reagent **2a** and titanium tetraisoproxide.[17] Reducing the catalyst loading to 2 mol% unfortunately resulted in lower selectivity (82% *ee*, Table 1, entry 6).

Under the optimized conditions (Table 1, entry 5), the scope of the catalytic enantioselective alkenylation was studied for a range of aldehydes by using aluminum reagent **2a** (Scheme 3). The reaction of *para*- and *meta*-substituted benzaldehyde derivatives (**3a** and **3c–f**) afforded the corresponding alkenylation products **4** in good yields and high selectivities (91–93% *ee*, Table 2, entries 1–5). On the other hand, only moderate enantioselectivity was observed for *ortho*-substituted derivative **3g** (Table 2, entry 6). High selectivities (88–91% *ee*) were also observed for the reaction of heteroaromatic aldehyde **3i** and α,β-unsaturated aldehydes **3j** and **3k** (Table 2, entries 7–9). The reaction of aliphatic aldehyde **3m**, however, resulted in a moderate selec-

Table 1. Optimization of reaction conditions for hydroalumination and enantioselective alkenylation leading to **4aa**.[a]

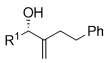
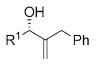
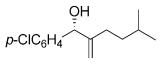
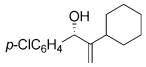
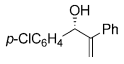
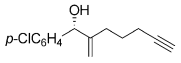
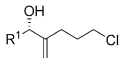
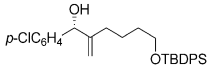
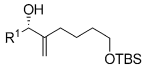
Entry	**1a** [equiv]	Me_2AlH [equiv]	$Ti(OiPr)_4$ [equiv]	Ligand	Yield [%]	*ee* [%]	**7** yield [%]
1	1.5	2.6	1.5	**8a**	50	92	10
2	2	2.6	2	**8a**	63	92	8
3	2.5	2.6	2.5	**8a**	67	91	10
4	2.5	2.6	3	**8a**	61	90	15
5	3	3	3	**8a**	75	93	4
6[b]	3	3	3	**8a**	74	82	6
7	3	3	3	**8b**	74	84	4
8	3	3	3	**8c**	68	93	10
9	3	3	3	**8d**	74	65	3
10	3	3	3	**8e**	75	80	4
11	1.5	2.6	0	–	trace	–	trace
12	3	3	3	–	50	–	11

[a] Unless otherwise noted, reactions were carried out with 5 mol% of ligand **8**. [b] 2 Mol% of **8a** was employed as a ligand.



Scheme 3. Catalytic enantioselective synthesis of α-substituted secondary allylic alcohols from terminal alkynes **1** and aldehydes **3**.

Table 2. Catalytic enantioselective synthesis of 1,1-disubstituted allylic alcohols **5** from aldehyde **2** and alkynes **3**.

Entry	Allylic alcohol		Yield[a] [%]	*ee*[b] [%]
1		**4aa**; $R^1 = p$-ClC_6H_4	75	93[c]
2		**4ac**; $R^1 = p$-$CF_3C_6H_4$	77	91
3		**4ad**; $R^1 = p$-CNC_6H_4	61	91
4		**4ae**; $R^1 = p$-$CO_2MeC_6H_4$	65	91
5		**4af**; $R^1 = m$-$MeOC_6H_4$	74	92
6		**4ag**; $R^1 = o$-BrC_6H_4	73	68
7		**4ai**; R^1 = 2-thienyl	69	91
8		**4aj**; R^1 = 1-cyclohexenyl	74	88
9		**4ak**; $R^1 = CH_2=C(Me)$	39	88
10		**4am**; R^1 = Cy	62	68
11		**4ba**; $R^1 = p$-ClC_6H_4	69	91
12		**4bb**; $R^1 = p$-BrC_6H_4	70	92
13		**4ca**	62	91
14		**4da**	33	90
15		**4ea**; $R^1 = p$-ClC_6H_4	63	94
16		**4en**; $R^1 = PhCH_2CH_2$	68	71
17		**4fa**	50	77
18		**4ga**; $R^1 = p$-ClC_6H_4	62	91
19		**4gh**; R^1 = 1-naphthyl	78	92
20		**4ha**	58	95
21		**4ia**; $R^1 = p$-ClC_6H_4	72	92
22		**4il**; R^1 = PhCH=CH	51	84
23		**4ja**	70	93
24		**4ka**; $R^1 = p$-ClC_6H_4	60	93
25		**4kd**; $R^1 = p$-CNC_6H_4	60	93

[a] Isolated yield. [b] Determined by HPLC analysis by using a chiral column. [c] The absolute configuration was determined by the method described by Mosher et al.[18] TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl.

tivity of 68% *ee* (Table 2, entry 10). Notably, the reaction tolerated aldehydes that possessed potentially reactive cyano and ester substituents (Table 2, entries 3 and 4).

To further investigate the scope for vinylaluminum reagents **2**, reactions were carried out with vinylaluminum reagents prepared in situ from terminal alkynes **1a–k** by the Ni-catalyzed hydroalumination reaction with Me_2AlH. Aluminium reagents generated from 3-phenylprop-1-yne **1b** and 5-methylhex-1-yne **1c** exhibited high enantioselectivity and good reactivity towards aromatic aldehydes (Table 2, entries 11–13). The size of the α-substituent of the vinylaluminum reagents affected the reactivity, but not the enantioselectivity of the reactions. Hence, the reaction of **3a** with the cyclohexyl-substituted reagent, generated from **1d**, resulted in a low yield of corresponding product **4da** (90% *ee*, Table 2, entry 14), whereas the reaction of **3a** with a reagent bearing a less sterically demanding cyclopropyl group, generated from **1e**, afforded corresponding product **4ea** (94% *ee*) in good yield (Table 2, entry 15). Moderate enantioselectivity was observed in the reaction of **3a** with a reagent derived from phenylacetylene (**1f**, Table 2, entry 17). Under the optimized conditions, enyne **1g**, as well as diyne **1h**, was successfully employed as an alkyne component, as exemplified in the highly enantioselective formation of dienyl carbinols **4ga** and **4gh** (Table 2, entries 18 and 19) and en-ynyl carbinol **4ha** (Table 2, entry 20). Notably, this reaction tolerates alkynes with chloride and silyloxy substituents (Table 2, entries 21–25). The corresponding functionalized allylic alcohols (**4ia**, **4il**, **4ja**, **4ka**, and **4kd**) were obtained with high enantioselectivities (84–93% *ee*) and in good yields.

In summary, we have developed a general one-pot method for the highly enantioselective synthesis of α-substituted allylic alcohols starting from readily available terminal alkynes and aldehydes and proceeding via vinylaluminum reagents. The use of Me_2AlH is essential in the Ni-catalyzed hydroalumination step to generate vinylaluminum reagents that cannot reduce the aldehyde starting material. High enantioselectivities were achieved at a low catalyst loading (5 mol%) in the subsequent addition reaction. The present study shows the applicability of the DPP-H_8-BINOL derived titanium catalyst for the enantioselective carbonyl addition of organoaluminum reagents and demonstrates the versatilty of this catalytic system.

Experimental Section

General procedure for catalytic enantioselective synthesis of α-substituted secondary allylic alcohols: A hexane solution of Me_2AlH (1.1 M, 1.4 mL, 1.5 mmol) was added to a stirred solution of [Ni(dppp)Cl_2] (24 mg, 0.045 mmol) in THF (1.4 mL) at room temperature. After 5 min, the reaction mixture was cooled to 0 °C. After dropwise addition of alkyne **1** (1.5 mmol), the resulting black solution was stirred for 1 h at 0 °C and then at room temperature for 3 h. THF (6 mL), titanium tetraisopropoxide (0.44 mL, 1.5 mmol), DPP-H_8-BINOL **8a** (13 mg, 0.025 mmol), and aldehyde **3** (0.5 mmol), in this order, was

added to the resulting solution of vinylaluminum reagent **2** at 0°C. After being stirred for 1 h at 0°C, the reaction mixture was poured into a two-phase mixture of ethyl acetate (10 mL) and aqueous 1 N HCl (30 mL) and extracted three times with ethyl acetate. The combined organic layers were washed successively with aqueous 5% $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/toluene or ethyl acetate/hexane, to give allylic alcohols **4**. The *ee* values of **4** were determined by HPLC analysis by using a chiral column.

Acknowledgements

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Keywords: allylic alcohols · asymmetric catalysis · asymmetric synthesis · hydrometalation · titanium

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