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Catalytic Asymmetric Addition of Terminal Alkynes to Aldehydes Mediated by (1*R*,2*R*)-2-(Dimethylamino)-1,2-diphenylethanol

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Abstract: Catalytic asymmetric alkynylation of aldehydes with terminal alkynes was catalyzed by zinc triflate and (1*R*,2*R*)-2-(dimethylamino)-1,2-diphenylethanol in toluene to give the corresponding alcohols with high enantiomeric excess up to 98% in good yields.

Keywords: alcohols; aldehydes; alkynes; asymmetric catalysis; zinc

Introduction

The catalytic asymmetric alkylation of aldehydes with dialkylzinc reagents constitutes one of the significant historical milestones of modern asymmetric reactions.[1] Headed by Oguni and Noyori, tremendous efforts have been devoted to the development of efficient chiral sources.[2] Chiral amino alcohols have become the established sources for this purpose. The stereochemical pathway of the chiral amino alcohol-mediated asymmetric reaction has been well established by proposing a bimetallic complex of a chiral zinc alkoxide and a diorganozinc species, which also rationalizes the enhanced reactivity of the diorganozinc reagent. However, the drawback of this asymmetric alkylation exists in the relatively poor availability and necessity of careful handling of diorganozinc reagents, although many protocols for their preparation have been reported. Recent focus has been adjusted to the alkynylation of aldehydes with terminal alkynes, mostly because slightly acidic terminal alkynes are readily convertible *in situ* to zinc acetylides.[3] These brilliant asymmetric alkynylations of aldehydes and ketones have used the same type of chiral amino alcohols as depicted by **1** as a chiral source (Figure 1).[4] These amino alcohols have been proposed to form a bimetallic chelated complex **2**[2b,5] that gave the adducts with the observed absolute configurations.[6,7] However, one exception using a chiral amino alcohol **3**, instead of **1** has been reported where the adducts were obtained in high enantioselectivity even with ketones.[8] We are also interested in the amino alcohol of type **3** because of the expected relatively higher stability of the bimetallic complex **4**, where the steric repulsion shown in **2** would not exist. This expectation came from our previous studies on the external chiral ligand-controlled asymmetric reactions where 5-membered chelation plays a pivotal role.[9] We describe herein that a chiral amino alcohol **3a** (R = Ph) mediated the highly efficient catalytic asymmetric alkynylation of aldehydes with terminal alkynes giving adducts with up to 98% ee.

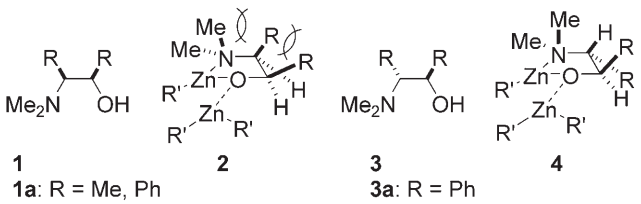
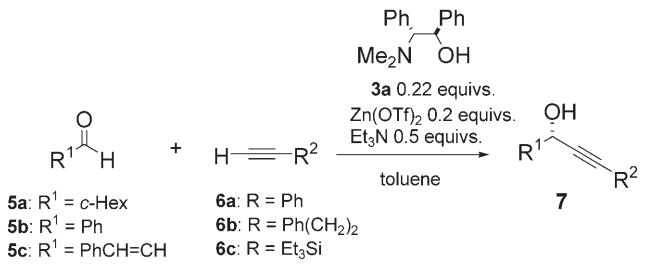


Figure 1. Chiral amino alcohols **1** and **3**, and their complexes **2** and **4** with organozinc species.

Results and Discussion

Asymmetric Alkynylation of Aldehydes

The alkynylation of cyclohexanecarbaldehyde (**5a**; R^1 = *c*-Hex) with phenylacetylene (**6a**; R^2 = Ph) was conducted in the presence of 0.22 equivs. of (1*R*,2*R*)-2-(dimethylamino)-1,2-diphenylethanol (**3a**; R = Ph), 0.2 equivs. of zinc triflate and 0.5 equivs. of triethylamine in toluene, that is, under the conditions developed by Carreira with use of the chiral amino alcohol **1a** (R = Me, Ph) (Scheme 1).[4g] The reaction proceeded quite smoothly



Scheme 1. Chiral amino alcohol **3a**-mediated catalytic asymmetric alkynylation of **5** with **6**.

at room temperature (rt) for 2 h to give the alcohol (*S*)-**7aa**[10] in 96% isolated yield (Table 1, entry 1). The enantiomeric excess (ee) was determined to be 96% by chiral stationary phase HPLC. This result encouraged us to continue our examination on other alkynes and aldehydes, because the yield and enantioselectivity are higher than those (94% yield, 86% ee) obtained by using chiral amino alcohol **1a** (R = Me, Ph).[4g] Thus, the reaction of **5a** with phenylethylacetylene (**6b**; $R^2 = PhCH_2CH_2$) at room temperature for 5 h gave **7ab** with 93% ee quantitatively (entry 2). The reaction with triethylsilylacetylene (**6c**; $R^2 = Et_3Si$) at 50 °C for 6 h gave **7ac** with 98% ee in 79% yield (entry 3). These results apparently indicate that the chiral amino alcohol **3a** is superior or equal to **1a** in yield and enantioselectivity.

The reaction of benzaldehyde (**5b**; $R^1 = Ph$) with **6a** required relatively harsh conditions, at 50 °C for 24 h, to give **7ba** with 93% ee in 51% yield, along with recovery of **5c** in 45% yield (entry 4).[11] With use of 0.6 equivs. of **3a**, 0.55 equivs. of zinc triflate and 0.6 equivs. of triethylamine the reaction proceeded at room temperature for 12 h to give **7ba** with 94% ee in 80% yield (entry 5). The reaction with **6b** at room temperature for 12 h gave **7bb** with 96% ee in 73% yield (entry 6). The reaction of **5b** with **6c** at 100 °C for 12 h gave **7bc** with 90% ee in 30% yield along with concomitant formation of its ketone and benzyl alcohol each in 19% yield (entry 7).

Cinnamaldehyde (**5c**; $R^1 = PhCH{=}CH$) was also an applicable substrate under the conditions of 0.6 equivs. of **3a**, 0.55 equivs. of zinc triflate and 0.6 equivs. of triethylamine at room temperature for 12 h to give **7ca** with 98% ee in 75% yield (entry 8). The reaction of **5c** with **6b** at room temperature for 12 h gave **7cb** with 98% ee in 47% yield, along with recovery of **5c** in 43% yield (entry 9).

Stereochemical Pathway

The chiral amino alcohol **3a**-mediated alkynylation of **5a** ($R^1 = c$-Hex) with **6a** ($R^2 = Ph$) produced (*S*)-**7aa**. The absolute configuration of the newly created chiral center is predictable based on the model **8** (Figure 2). The carbonyl oxygen atom of the aldehyde coordinates to the zinc of the bimetallic complex, and an alkynyl group attacks the carbonyl carbon of the aldehyde as shown to produce the alcohol (*S*)-**7aa** with the same absolute configuration.

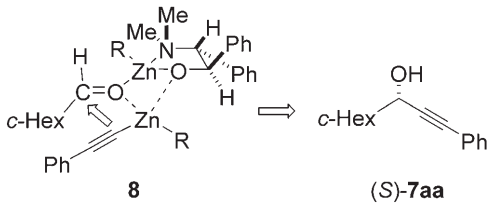


Figure 2. Model **8** predicting the stereochemistry of (*S*)-**7**.

Conclusion

Based on the expectation that a chiral amino alcohol **3** should form a relatively more rigid 5-membered chelate with organozinc reagent than **1** where two contiguous substituents are *cis*, the highly efficient alkynylation of aldehydes with terminal alkynes was developed by using **3a** as a chiral amino alcohol. The enantioselectivity, mediated by **3a**, reached up to 98% and was thus higher than those observed by using **1a**.

Table 1. Catalytic asymmetric alkynylation of aldehydes **5** with **6** by the mediation of **3a**.

Entry	R^1	R^2	Temperature [°C]	Time [h]	Yield [%]	ee [%]
1	*c*-Hex	Ph	rt	1	96	96
2	*c*-Hex	$Ph(CH_2)_2$	rt	5	99	93
3	*c*-Hex	Et_3Si	50	6	79	98
4	Ph	Ph	50	24	51	93
5[a]	Ph	Ph	rt	12	80	94
6[a]	Ph	$Ph(CH_2)_2$	rt	12	73	96
7	Ph	Et_3Si	100	12	30	90
8[a]	PhCH=CH	Ph	rt	12	75	98
9[a]	PhCH=CH	$Ph(CH_2)_2$	rt	12	47	98

[a] 0.6 equivs. of amino alcohol **3a**, 0.55 equivs. of $Zn(OTf)_2$, and 0.6 equivs. of Et_3N were used.

Experimental Section

All melting points are uncorrected. IR spectra were expressed in cm^{-1}. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$. Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Column chromatography was carried out on silica gel. The absolute configuration of the product alcohols **7** was determined by comparison of specific rotations and retention times on HPLC with those reported, except for **7bc** whose absolute configuration was tentatively assigned by analogy. Zinc triflate, aldehydes and alkynes were purchased and purified by the standard methods prior to use. Chiral amino alcohol **3a** was prepared according to the reported procedure.[12]

Typical Procedure for the Amino Alcohol 3a-Mediated Catalytic Asymmetric Addition of Alkynes to Aldehydes;(*S*)-1-Cyclohexyl-3-phenylprop-2-yn-1-ol (7aa;R^1 = *c*-Hex, R^2 = Ph; Table 1, entry 1)

Under an argon atmosphere, to a mixture of $Zn(OTf)_2$ (73 mg, 0.20 mmol) and amino alcohol **3a** (53 mg, 0.22 mmol) in toluene (1.0 mL) was added triethylamine (70 μL, 0.5 mmol) and the mixture was stirred for 2 h at room temperature. Ethynylbenzene (**6a**; 0.13 mL, 1.2 mmol) was added and the solution was stirred for additional 0.5 h. To the solution was added cyclohexanecarbaldehyde (**5a**; 0.11 mL, 1.0 mmol) in one portion. The reaction mixture was stirred at room temperature for 2 h. The mixture was quenched with saturated ammonium chloride at room temperature and extracted with ethyl acetate. The organic extracts were washed with brine, dried over sodium sulfate, and then concentrated to give a pale yellow oil (290 mg). Column chromatography (hexane/EtOAc, 20/1) gave **7aa**[13] as a colorless oil; yield: 206 mg (96% yield); R_f (hexane/EtOAc, 9/1): 0.14; $[\alpha]_D^{26}$: +10.9 (*c* 1.1, $CHCl_3$) for 96% ee (HPLC, Daicel Chiralcel OD-H, hexane/2-PrOH, 9/1, 1.0 mL/min, 254 nm, minor 5.0 min and major 10.4 min).

(*S*)-1-Cyclohexyl-5-phenylpent-2-yn-1-ol [7ab; R^1 = *c*-Hex, R^2 = $Ph(CH_2)_2$;[13] Entry 2]

A colorless oil (yield: 240 mg, 99%) was obtained by column chromatography (hexane/EtOAc, 15/1); R_f (hexane/EtOAc, 10/1): 0.25; $[\alpha]_D^{28}$: +1.5 (*c* 1.0, $CHCl_3$) for 93% ee (HPLC, Daicel Chiralcel OD-H, hexane/2-PrOH, 9/1, 1.0 mL/min, 254 nm, minor 9.7 min and major 13.2 min).

(*S*)-1-Cyclohexyl-3-(triethylsilyl)prop-2-yn-1-ol (7ac; R^1 = *c*-Hex, R^2 = Et_3Si;[4g] Entry 3)

The reaction was run at 50 °C. A colorless oil (yield: 198 mg, 79%) was obtained by column chromatography (hexane/EtOAc, 30/1); R_f (hexane/EtOAc, 9/1): 0.27; $[\alpha]_D^{27}$: +5.2 (*c* 1.1, $CHCl_3$) for 98% ee. The ee was determined after conversion to 3,5-dinitrobenzoate (HPLC, Daicel Chiralcel OD-H, hexane/2-PrOH, 100/6, 0.3 mL/min, 254 nm, minor 35.6 min and major 38.1 min).

(*S*)-1,3-Diphenylprop-2-yn-1-ol (7ba; R^1 = Ph, R^2 = Ph;[13] Entry 5)

0.55 equivs. of $Zn(OTf)_2$ (200 mg, 0.55 mmol), 0.6 equivs. of amino alcohol **3a** (145 mg, 0.60 mmol), and 0.6 equivs. of triethylamine (84 μL, 0.60 mmol) were used. A colorless oil (yield: 167 mg, 80%) was obtained by column chromatography (hexane/EtOAc, 8/1); R_f (hexane/EtOAc, 9/1): 0.11; $[\alpha]_D^{25}$: −1.6 (*c* 0.88, $CHCl_3$) for 94% ee (HPLC, Daicel Chiralcel OD-H, hexane/2-PrOH, 9/1, 1.0 mL/min, 254 nm, minor 10.9 min and major 19.8 min).

(*S*)-1,5-Diphenylpent-2-yn-1-ol [7bb; R^1 = Ph, R^2 = $Rh(CH_2)_2$;[13] Entry 6]

0.55 equivs. of $Zn(OTf)_2$ (200 mg, 0.55 mmol), 0.6 equivs. of amino alcohol **3a** (145 mg, 0.60 mmol), and 0.6 equivs. of triethylamine (84 μL, 0.60 mmol) were used. A colorless oil was obtained by column chromatography (hexane/EtOAc, 9/1); yield: 173 mg (73%); R_f (hexane/EtOAc, 6/1): 0.06; $[\alpha]_D^{29}$: −15.1 (*c* 1.0, $CHCl_3$) for 96% ee (HPLC, Daicel Chiralcel OD-H, hexane/2-PrOH, 9/1, 1.0 mL/min, 254 nm, minor 16.0 min and major 26.9 min). The starting **5b** was recovered in 12% yield.

(*S*)-3-(Triethylsilyl)-1-phenylprop-2-yn-1-ol (7bc; R^1 = Ph, R^2 = Et_3Si; Entry 7)

The reaction was run at 100 °C. A colorless was obtained oil by column chromatography (hexane/EtOAc, 30/1); yield: 74 mg (30%); R_f (hexane/EtOAc, 9/1): 0.23; $[\alpha]_D^{25}$: −22.2 (*c* 0.76, $CHCl_3$) for 90% ee (HPLC, Daicel Chiralcel OD-H, hexane/2-PrOH, 100/6, 0.6 mL/min, 254 nm, major 17.7 min and minor 24.9 min); ^1H NMR: δ = 0.64 (6H, q, *J* = 7.8 Hz), 1.01 (9H, t, *J* = 7.8 Hz), 2.14 (1H, d, *J* = 6.4 Hz), 5.48 (1H, d, *J* = 6.4 Hz), 7.33 (1H, t, *J* = 7.2 Hz), 7.38 (2H, dd, *J* = 7.0, 7.2 Hz), 7.57 (2H, d, *J* = 7.0 Hz); ^{13}C NMR: δ = 4.2, 7.4, 65.1, 89.2, 106.2, 126.8, 128.4, 128.6, 140.5; IR (neat): ν = 3348, 1454, 1415, 1385, 1042, 983, 729; EI-MS: *m/z* = 246 (M^+), 175, 147, 115, 99; anal. calcd. for $C_{15}H_{22}OSi$: C 73.11, H 9.00; found: C 73.20, H 8.90.

(*S*)-(*E*)-1,5-Diphenylpent-1-en-4-yn-3-ol (7ca; R^1 = PhCH=CH, R^2 = Ph;[14] Entry 8)

0.55 equivs. of $Zn(OTf)_2$ (200 mg, 0.55 mmol), 0.6 equivs. of amino alcohol **3a** (145 mg, 0.60 mmol), and 0.6 equivs. of triethylamine (84 μL, 0.60 mmol) were used. Colorless needles were obtained by column chromatography (hexane/EtOAc, 9/1); yield: 176 mg (75%); mp 88–89 °C; R_f (hexane/EtOAc, 9/1): 0.08; $[\alpha]_D^{25}$: −4.9 (*c* 1.0, $CHCl_3$) for 98% ee (HPLC, Daicel Chiralcel OD-H, hexane/2-PrOH, 9/1, 1.0 mL/min, 254 nm, minor 22.7 min and major 66.3 min).

(*S*)-(*E*)-1,7-Diphenylhept-1-en-4-yn-3-ol [7cb; R^1 = PhCH=CH, R^2 = $Ph(CH_2)_2$;[13] Entry 9]

0.55 equivs. of $Zn(OTf)_2$ (200 mg, 0.55 mmol), 0.6 equivs. of amino alcohol **3a** (145 mg, 0.60 mmol), and 0.6 equivs. of tri-

ethylamine (84 μL, 0.60 mmol) were used. Column chromatography (hexane/EtOAc, 9/1) gave **7cb** as colorless needles; yield: 123 mg (47%); mp 67–68 °C; R_f (hexane/EtOAc, 6/1): 0.06; $[\alpha]_D^{23}$: −11.7 (*c* 1.1, $CHCl_3$) for 98% ee (HPLC, Daicel Chiralcel OD-H, hexane/2-PrOH, 85/15, 1.0 mL/min, 254 nm, major 26.5 min and minor 34.8 min). The starting **5c** was recovered in 43% yield.

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[10] The first "**a**" and second "**a**" for **7aa** come from **5a** and **6a**.

[11] Carreira has reported that aromatic aldehydes gave adducts in lower yields due to concomitant Cannizzaro reaction. In contrast we did not observe the production of such byproducts, see Ref.[4g]

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