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An Efficient CuCN-Catalyzed Synthesis of Optically Active 2,3-Allenols from Optically Active 1-Substituted 4-Chloro-2-butyn-1-ols

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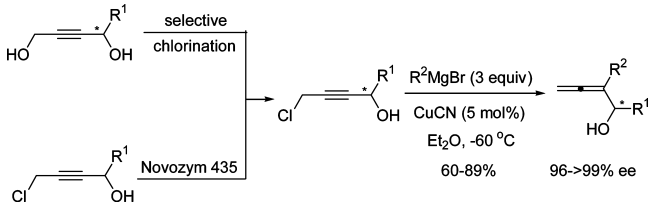

The sequential treatment of optically active terminal propargylic alcohols with *n*-BuLi/$(HCHO)_n$ and regioselective chlorination afforded the corresponding optically active 4-chloro-2-butyn-1-ols. With R^1 being a methyl or an ethyl group, an alternative for the synthesis of the corresponding optically active propargylic alcohols is the Novozym 435-catalyzed kinetic resolution of these racemic 4-chloro-2-butyn-1-ols. The subsequent reaction of these optically active 4-chloro-2-butyn-1-ols with the corresponding Grignard reagents under the catalysis of 5 mol % of CuCN afforded the optically active secondary 2,3-allenols in good yields with up to >99% ee.

Allenes are a class of compounds with two orthogonal π-bonds and have proven to be useful intermediates in organic synthesis.[1,2] Of particular interest is 2,3-allenols, which can be used for the synthesis of 2,5-dihydrofurans,[3] 2(5*H*)-furanones,[4] vinylic epoxides,[5] β-halo-β,γ-alkenals,[3l,6] β-halo-β,γ-alkenones,[3l,7] 2-halo-1,3(*Z*)-dienes,[8] and allylic alcohols.[9] Thus, it is highly desirable to develop efficient methodologies for the synthesis of optically active 2,3-allenols with high ee value. Usually, optically active 2,3-allenols are prepared by the enantioselective reduction of 1,2-allenyl ketones,[10] the reaction of optically active propargylic/allenic metallic reagents with carbonyl groups,[11] Crabbé reaction of optically active terminal propargylic alcohols,[12] the cross-coupling reaction with optically active alkynyl oxiranes[13] and the kinetic resolution of racemic 2,3-allenols.[14] However, there are still some difficulties: some of the reagents or catalysts for these known methods are not easily available or the enantioselectivities are not satisfactory and the kinetic resolution of racemic 2,3-allenols is restricted to one or two carbon 1,2-allenyl carbinols.[14] In our previous report, we disclosed a synthesis of optically active 2,3-allenols from the reaction of easily available propargylic methyl ethers with Grignard reagents in moderate yield with up to 99% ee, but in some cases the yield is not satisfactory, and the 1-substituent group is limited to an aryl group.[15] Herein, we wish to report a more efficient and general synthesis of optically active 2,3-allenols from optically active 1-substituted 4-chloro-2-butyn-1-ols of high ee value in moderate to high yields by using CuCN as the catalyst.

Synthesis of the Starting Materials. The racemic starting materials **3a**−**e** can be prepared by treating propargylic chloride with *n*-BuLi and subsequent reaction with the corresponding aldehydes[16] (Scheme 1).

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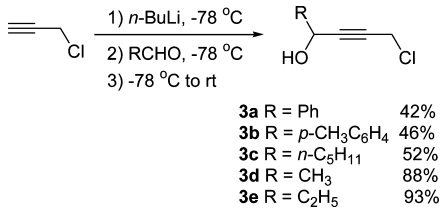
SCHEME 1



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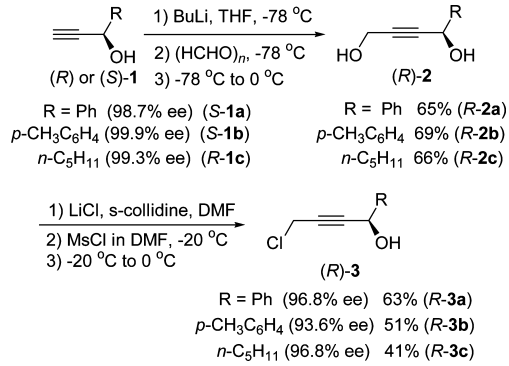

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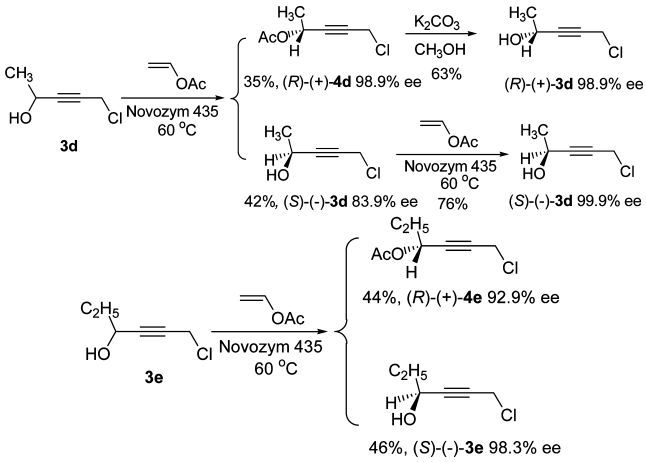
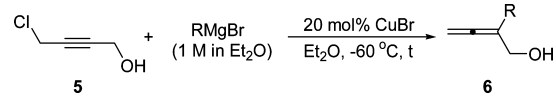


It is known that optically active terminal propargylic alcohols **1** can be easily prepared from racemic propargylic alcohols **1** through Novozym 435-catalyzed kinetic resolution[17] with R being an Ar group or an alkyl group beyond C_5 unit connected to the hydroxylated carbon atom. By treating the optically active propargylic alcohols **1a**−**c** with *n*-BuLi and the subsequent reaction with $(HCHO)_n$, optically active 1-substituted 2-butyn-1,4-diols **2a**−**c** may be formed. Subsequent selective chlorination of the primary hydroxyl group afforded the optically active 1-substituted 4-chloro-2-butyn-1-ols **3a**−**c** (Scheme 2).

For the substrates with R being a methyl or an ethyl group, we tried the kinetic resolution of racemic 1-substituted 4-chloro-2-butyn-1-ols **3d** or **3e** to afford the required optically active 1-substituted 4-chloro-2-butyn-1-ols **3d** and **3e** in high enantiopurity[17] (Scheme 3).

At first we tried the reaction of 4-chloro-2-butyn-1-ol **5** with *n*-C_4H_9MgBr in Et_2O without any catalyst but only a trace amount of product was afforded. However, when 20 mol % of CuBr was used, luckily, 2-butyl-2,3-butadienol was formed in 79% yield (entry 1, Table 1). With these results in hand, we studied the scope of this reaction with some typical results being summarized in Table 1.

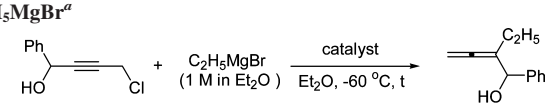
TABLE 1. CuBr-Catalyzed Reaction of 4-Chloro-2-butyn-1-ol 5 with Alkyl or Phenyl Grignard Reagents



5 6

entry	R	*t* (h)	yield (%)
1	*n*-C_4H_9	4.7	79 (**6a**)
2	*n*-C_7H_{15}	3.0	59 (**6b**)
3	*n*-$C_{10}H_{21}$	3.3	63 (**6c**)
4	Ph	5.4	46 (**6d**)

TABLE 2. Cu(I)-Catalyzed Reaction of Racemic 3a with C_2H_5MgBr[a]



3a 7a

entry	C_2H_5MgBr (equiv)	catalyst (mol %)	*t* (h)	yield of **7a** (%)	recovery of **3a** (%)
1	4		16	0	84
2	4	CuCl (20)	16	38	8
3	4	CuBr (20)	16	54	8
4	4	CuI (20)	16	24	43
5	4	CuCN (20)	16	75	2
6	3	CuCN (10)	19	74	5
7	3	CuCN (5)	12.5	71 (63)	2
8	3	CuCN (2)	19	55	26
9[b]	3	CuCN (5)	12	61	13
10[c]	3	CuCN (5)	3.5	46	6
11[d]	3	CuCN (5)	3.5	21	0

[a] NMR yields determined by using 1,3,5-trimethyl benzene as the internal standard. The isolated yield is given in parentheses; [b] Reaction temperature: −50 °C; [c] Reaction temperature: −40 °C; [d] Reaction temperature: rt.

Then the racemic 4-chloro-1-phenyl-2-butyn-1-ol **3a** was used as the model substrate to optimize the conditions for the reaction with C_2H_5MgBr to prepare secondary 2,3-allenols in ether (Table 2). First, different Cu(I) salts were screened as the catalyst with 4.0 equiv of C_2H_5MgBr in ether (entries 2−5, Table 2); it turned out that CuCN was found to be the best catalyst affording the product **7a** in 75% NMR yield with 2% of the reactant being recovered (entry 5, Table 2). Then the effect of the amount of the catalyst on the reaction was studied (entries 6−8, Table 2): 5 mol % was found to be the best catalyst affording the product **7a** in 71% NMR yield (63% isolated yield) with a trace amount of reactant **3a** being recovered (2%); the effect of reaction temperature was also screened (entries 9−11, Table 2). When the reaction was conducted at rt, it was not clean: 2-ethyl-1-phenyl-2-hexen-1-ol was formed in 18% NMR yield based on the analysis of the ^1H NMR spectra of the crude product. This compound was formed by the carbometalation of the 2,3-allenol **7a** with EtMgBr (entry 11, Table 2).[9] Finally, the best results were obtained when the reaction was conducted at −60 °C with 5 mol % of CuCN as the catalyst, using 3.0 equiv of Grignard reagent to afford the target product **7a** in 71% NMR yield (entry 7, Table 2).

With the optimized reaction condition in hand (entry 7, Table 2), the scope of the CuCN-catalyzed reaction of 1-substituted 4-chloro-2-butyn-1-ols **3** with Grignard reagents was studied (Table 3). It can be concluded that the reaction can be used to

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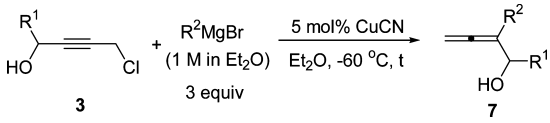
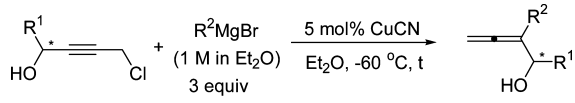
TABLE 3. CuCN-Catalyzed Reaction of Racemic 1-Substituted 4-Chloro-2-butyn-1-ols 3 with Alkyl Grignard Reagents



entry	R^1	R^2	t (h)	yield of **7** (%)
1	Ph (**3a**)	C_2H_5	12.5	63 (**7a**)
2	Ph (**3a**)	i-C_3H_7	10	92 (**7b**)
3	Ph (**3a**)	n-C_4H_9	18	61 (**7c**)
4	Ph (**3a**)	n-C_5H_{11}	17	76 (**7d**)
5	p-$CH_3C_6H_4$ (**3b**)	C_2H_5	11	53 (**7e**)
6	p-$CH_3C_6H_4$ (**3b**)	n-C_4H_9	18	63 (**7f**)
7	p-$CH_3C_6H_4$ (**3b**)	n-C_5H_{11}	17	71 (**7g**)
8	p-$CH_3C_6H_4$ (**3b**)	n-C_7H_{15}[a]	17	79 (**7h**)
9	n-C_5H_{11} (**3c**)	C_2H_5	11	61 (**7i**)
10	n-C_5H_{11} (**3c**)	n-C_4H_9	5	69 (**7j**)
11	n-C_5H_{11} (**3c**)	n-C_5H_{11}	17	67 (**7k**)
12	n-C_5H_{11} (**3c**)	n-C_7H_{15}[a]	17	63 (**7l**)
13	CH_3 (**3d**)	n-C_4H_9	17	70 (**7m**)
14	CH_3 (**3d**)	n-C_7H_{15}[a]	17	98 (**7n**)
15	C_2H_5 (**3e**)	n-C_4H_9	11	71 (**7o**)
16	C_2H_5 (**3e**)	n-C_5H_{11}	13	74 (**7p**)

[a] Grigard reagent (4 equiv) was used.

TABLE 4. CuCN-Catalyzed Reaction of Optically Active 1-Substituted 4-Chloro-2-butyn-1-ols 3 with Grignard Reagents



	3				**7**	
entry	R^1	ee (%)	R^2	t (h)	yield (%)	ee (%)
1	Ph (*R*-**3a**)	97.7	C_2H_5	13	67 (*R*-**7a**)	97.7
2	Ph (*R*-**3a**)	97.7	i-C_3H_7	10	89 (*R*-**7b**)	97.2
3	Ph (*R*-**3a**)	96.8	n-C_4H_9	13	60 (*R*-**7c**)	96.2
4	n-C_5H_{11} (*R*-**3c**)	96.8	n-C_4H_9	5	73 (*R*-**7j**)	—[a]
5	CH_3 (*S*-**3d**)	99.9	n-C_4H_9	11	69 (*S*-**7m**)	99.9
6	CH_3 (*R*-**3d**)	98.9	n-C_4H_9	11	69 (*R*-**7m**)	99.0
7	CH_3 (*S*-**3d**)	99.9	n-C_7H_{15}	9	79 (*S*-**7n**)	99.9
8	C_2H_5 (*S*-**3e**)	98.3	n-C_4H_9	11	70 (*S*-**7o**)	98.1
9	C_2H_5 (*S*-**3e**)	98.3	n-C_5H_{11}	7	79 (*S*-**7p**)	98.2

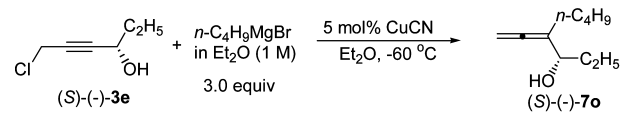
[a] Unable to determine.

prepare differently substituted 2,3-allenols in moderate to good yields. It should be noted that when R^2 is a secondary alkyl group, i.e., an isopropyl group, the reaction afforded the 1-phenyl-2-(isopropyl)-2,3-butdienol **7b** in 92% yield (entry 2, Table 3). It should be noted that no reaction was observed when 4-hydroxy-4-aryl-2-butynyl methyl ethers were treated with secondary alkyl Grignard reagent in our previous report.[15] R^1 not only can be an aryl group (entries 1−8, Table 3), but also an alkyl group (entries 9−16, Table 3). It should also be pointed out that when n-$C_7H_{15}MgBr$ was used, 4 equiv of Grignard reagent were necessary to have a complete consumption of the substrates **3** (entries 8, 12, and 14, Table 3).

Under the optimized conditions, the reaction of optically active 1-substituted 4-chloro-2-butyn-1-ols **3** with Grignard reagents shows no obvious racemization (Table 4).

The reaction of (*S*)-6-chloro-4-hexyn-3-ol (*S*)-**3e** afforded (*S*)-4-butylhexa-4,5-dien-3-ol (*S*)-**7o** in almost the same yield (71%) when 10.0 mmol of (*S*)-**3e** was used as compared to a 0.5 mmol scale reaction (70%) (Scheme 4).

SCHEME 4



65.1 mg, 0.50 mmol, 98.3% ee
1.3244 g, 10.0 mmol, 98.3% ee

53.3 mg, 70%, 98.1% ee
1.1002 g, 71%, 98.1% ee

In conclusion, we have developed an efficient CuCN-catalyzed synthesis of optically active 2,3-allenols from optically active 1-substituted 4-chloro-2-butyn-1-ols with up to >99% ee. Due to the easy availability of the starting materials[17] and the synthetic potential of the products,[3j,k,m] this method may be useful in organic synthesis. Further studies in this area are currently under investigation in our laboratory.

Experimental Section

^1H NMR and ^{13}C NMR were recorded on instruments operated at 300 and 75 MHz, respectively. Deuteriochloroform ($CDCl_3$) was used as solvent in all NMR experiments. Chemical shifts (δ) are given in parts per million (ppm). Infrared spectra were recorded on a FT-IR spectrometer. Mass spectra were carried out in EI or ESI mode. HRMS spectra were carried out in EI and ESI mode. The enantiomeric excess values (ee) were determined by HPLC or GC analysis with chiral columns. Flash column chromatography was performed on silica gel (10−40 μ).

Synthesis of (*R*)-(−)-2-Ethyl-1-phenyl-2,3-butadien-1-ol ((*R*)-(−)-7a): Typical Procedure. To a dried Schlenk vessel were added anhydrous Et_2O (2.1 mL), CuCN (1.4 mg, 0.016 mmol), and (*R*)-(+)-4-chloro-1-phenyl-2-butyn-1-ol ((*R*)-(+)-**3a**) (54.4 mg, 0.30 mmol, 97.7% ee) at room temperature. A solution of C_2H_5MgBr in Et_2O (0.9 mL, 1 M in Et_2O, 0.9 mmol) was then added dropwise to the resulting mixture at −60 °C under nitrogen in 5 min. After the addition was over, the reaction mixture was stirred for 13 h as monitored by TLC, quenched with saturated ammonium chloride solution (1 mL), extracted with ether (10 mL × 3), washed with brine (10 mL), and dried over anhydrous sodium sulfate. Evaporation and column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10/1) afforded (*R*)-(−)-**7a**[15] (34.9 mg, 67%) with 97.7% ee as determined by HPLC analysis (Chiralcel OD-H, *n*-hexane/*i*-PrOH = 90/10, 0.8 mL/min, λ = 230 nm, t_R = 7.6 min (major), 7.0 min (minor)): $[\alpha]^{20}_D$ −137.8 (*c* 1.13, $CHCl_3$); oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.24 (m, 5 H), 5.14−5.07 (m, 1 H), 5.07−4.97 (m, 2 H), 2.32 (d, J = 4.5 Hz, 1 H), 1.93−1.71 (m, 2 H), 0.97 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.8, 142.1, 128.3, 127.7, 126.6, 109.9, 80.2, 74.1, 20.9, 11.9.

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Supporting Information Available: Detailed experimental procedures and analytical data for all new products not listed in the text and ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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