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Enantioselective alkynylation of carbonyl compounds with trimethoxysilylalkynes catalyzed by lithium binaphtholate

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ABSTRACT

Enantioselective alkynylation of aldehydes and ketones was accomplished using trimethoxysilylalkynes as alkynylating reagents and lithium 3,3′-diphenylbinaphtholate as a catalyst. Optically active propargylic alcohols were obtained in good to high chemical yields and enantioselectivities. Alkynylation of acetylpyridines afforded biologically active pyridyl propargylic alcohols in good enantioselectivities.

1. Introduction

Optically active propargylic alcohols are important precursors for the synthesis of a wide range of biologically active compounds.[1] Secondary alcohols are generally prepared by the enantioselective reduction of ketones. However, secondary propargylic alcohols are not prepared in this way because some alkynyl ketones are prone to decomposition or isomerization even under mild conditions. Moreover, tertiary propargylic alcohols cannot, in principle, be prepared by the reduction. Therefore, the enantioselective alkynylation of carbonyl compounds is an alternative approach to the preparation of chiral propargylic alcohols.[2] The first enantioselective catalytic approach was reported by Soai, who used alkynylzinc as an alkynylating agent and an amino alcohol as a catalyst.[3] Since then, several cases of the enantioselective alkynylation of carbonyl compounds have been reported using various catalysts.[4–7]

Recently another access to the propargylic alcohols was reported by Scheidt, who found that alkoxides activated trialkoxysilylalkynes to react with ketones as well as aldehydes.[8,9] In their report, they postulate the formation of hypervalent silicate[10] from trialkoxysilylalkyne and alkoxide. We previously reported that lithium binaphtholate activated trimethoxysilyl enol ethers to form hypervalent silicate, which reacted with an aldehyde to afford an aldol adduct in high chemical and optical yields.[11] Here, we disclose the details of the enantioselective alkynylation of aldehydes and ketones using trimethoxysilylalkynes in the presence of lithium binaphtholates as catalyst.[12]

2. Results and discussion

2.1. Alkynylation of aldehydes

We first investigated the alkynylation of benzaldehyde (**1a**) with trimethoxy(phenylethynyl)silane (**2a**)[13] in THF using lithium binaphtholate[14] prepared from binaphthol (**4a**) and BuLi as the catalyst. The reaction proceeded smoothly to afforded the propargylic alcohol in high yield, but the enantioselectivity was quite low (Table 1, entry 1).[15] Screening of the binaphthol derivatives revealed that introduction of substituents at 3,3′-position of binaphthol increased the enantioselectivity. Among various 3,3′-substituted binaphthols tested, we found that the diphenyl derivative (**4h**) gave the most promising selectivity (entry 8).

With the appropriate catalyst precursor in hand, we investigated alkynylation of benzaldehyde (**1a**) with various trimethoxysilylalkynes. A wide variety of trimethoxysilylalkynes reacted with benzaldehyde to afford the adduct in high yields, however, the reactivity and enantioselectivity depended on the substituent on the opposite side of alkyne (Table 2). Cyclohexenyl (entry 3), benzyloxymethyl (entry 4), and silyloxymethyl (entry 5) derivatives gave lower selectivities, and the *n*-butyl derivative (entry 2) reacted quite slowly with low selectivity.

Because the best result was obtained using the phenyl derivative **2a**, we investigated the phenylethynylation of various aldehydes

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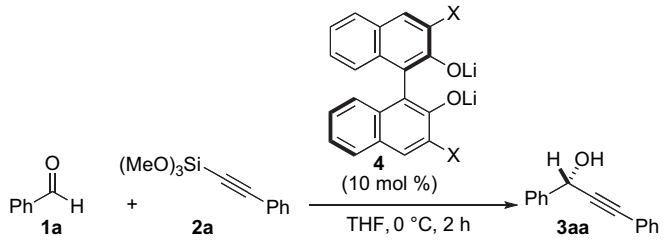
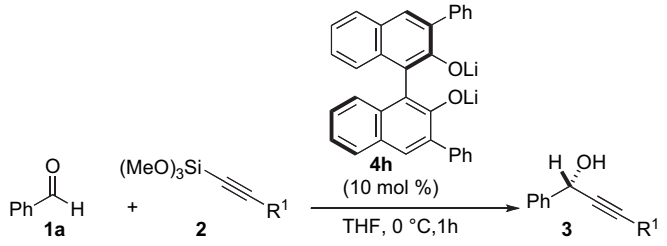
Table 1
Screening of binaphthol derivative in the phenylethynylation of benzaldehyde with trimethoxy(phenyethynyl)silane



Entry	X in binaphthol	Yield, %[a]	ee, %[b]
1	H (**4a**)	97	18
2	Cl (**4b**)	92	54
3	Br (**4c**)	97	52
4	I (**4d**)	90	52
5	COOMe (**4e**)	97	6
6	Me (**4f**)	98	50
7	$SiMe_3$ (**4g**)	98	41
8	Ph (**4h**)	98	58
9	3,5-$Me_2C_6H_3$ (**4i**)	98	34

[a] Isolated yield.
[b] Determined by HPLC.

Table 2
Alkynylation of benzaldehyde with various trimethoxysilylalkynes



Entry	R^1 in silylalkyne	Product	Yield, %[a]	ee, %[b]
1	Ph (**2a**)	**3aa**	98	58
2[c]	*n*-Bu (**2b**)	**3ab**	85	21
3	Cyclohexen-1-yl (**2c**)	**3ac**	89	46
4	$BnOCH_2$ (**2d**)	**3ad**	90	38
5	$(i\text{-Pr})_3SiOCH_2$ (**2e**)	**3ae**	94	41

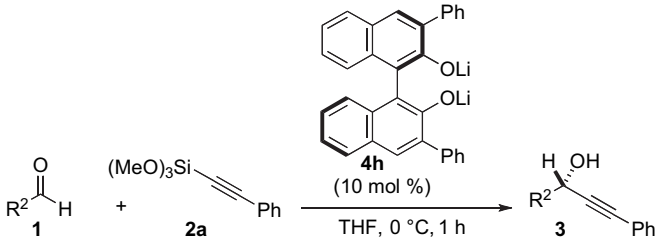
[a] Isolated yield.
[b] Determined by HPLC.
[c] 18 h.

with this derivative (Table 3). Naphthaldehydes **1b** and **1c** gave results similar to those of benzaldehyde (entries 2 and 3). Electron-deficient groups, such as trifluoromethyl, on benzene ring decreased the selectivity (entry 4), whereas electron-donating groups, such as methoxy or dimethylamino, tend to increase the selectivity (entries 5 and 6). In particular, dimethylaminobenzaldehyde **1f** gave the best enantioselectivity, 65%. The alkynylation proceeded smoothly with non-aromatic aldehydes, such as cinnamaldeyde **1g**, hydrocinnamaldehyde **1h**, or cyclohexylcarboxaldehyde **1i**, however, the observed selectivities were rather low (entries 7–9).

2.2. Alkynylation of ketones

Chiral tertiary alcohols represent important structural motifs in organic syntheses.[16] The enantioselective alkynylations of aldehydes have been widely investigated, however, few successful reports of the alkynylation of ketones exist due to their low reactivities.[17,18] As the reactivity of trialkoxysilylalkynes are sufficiently high to react with ketones,[8] we next started to investigate the alkynylation of ketones.

Table 3
Phenylethynylation of various aldehydes with trimethoxy(phenyethynyl)silane[a]



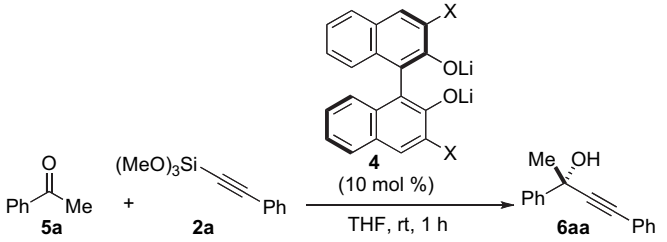
Entry	R^2 in aldehyde	Product	Yield, %[a]	ee, %[b,c]
1	Ph (**1a**)	**3aa**	98	58
2	1-Naphthyl (**1b**)	**3ba**	95	53
3	2-Naphthyl (**1c**)	**3ca**	98	49
4	4-$CF_3C_6H_4$ (**1d**)	**3da**	86	41
5	4-$MeOC_6H_4$ (**1e**)	**3ea**	86	60
6	4-$Me_2NC_6H_4$ (**1f**)	**3fa**	86	65
7	PhCH=CH (**1g**)	**3ga**	79	42
8	$PhCH_2CH_2$ (**1h**)	**3ha**	81	31
9	Cyclohexyl (**1i**)	**3ia**	84	45

[a] Silylalkyne 1.5 equiv, catalyst 10 mol %, 0 °C, 1 h. See Experimental.
[b] Isolated yield.
[c] Determined by HPLC. The absolute configurations were determined by comparison of the sign of optical rotation of the product, see Experimental.

First, we examined the phenylethynylation of acetophenone under the conditions we used for the alkynylation of aldehydes. The adduct was obtained in a high enantioselectivity but the chemical yield was moderate (Table 4, entry 1, 59% yield, 76% ee). Again, optimization of the reaction conditions and a search for chiral catalysts did not identify any catalysts that were better than 3,3′-diphenylbinaphthol. Reaction at 0 °C gave a better selectivity but a lower yield (entry 5). We then tested slow addition of the ketone to the mixture of catalyst and alkyne over 3 h to prevent self-aldol reaction of acetophenone and found that the chemical yield was significantly increased (entry 6). Increasing the number of equivalents of alkyne gave a better chemical yield with no reduction of enantioselectivity (entry 7).

The results obtained from the reaction of 1.5 equiv trimethoxy(phenylethynyl)silane **2a** are summarized in Table 5. Similar enantioselectivities and chemical yields were obtained using

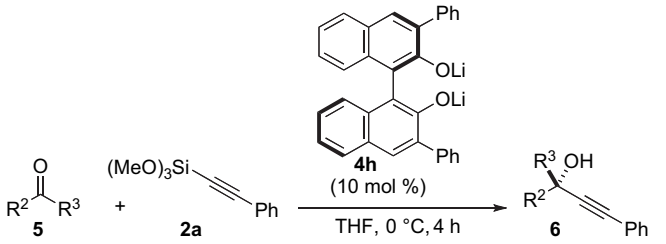
Table 4
Screening of the conditions of the phenylethynylation of acetophenone



Entry	X in BINOL	Yield, %[a]	ee, %[b]
1	Ph (**4h**)	59	76
2	H (**4a**)	24	10
3	Cl (**4b**)	36	22
4	Me (**4f**)	37	29
5[c]	Ph (**4h**)	51	82
6[c,d]	Ph (**4h**)	64	82
7[c,d,e]	Ph (**4h**)	81	82

[a] Isolated yield.
[b] Determined by HPLC.
[c] 0 °C.
[d] Slow addition of ketone over 3 h and an additional 1 h.
[e] alkyne, 3 equiv.

Table 5
Phenylethynylation of various ketones with trimethoxy(phenyethynyl)silane[a]

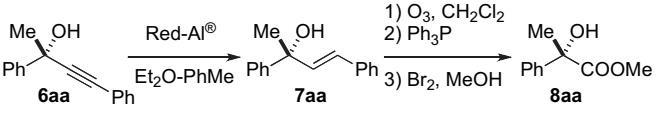


Entry	R^2, R^3 in ketone	Product	Yield, %[b]	ee, %[c]
1	Ph, Me (**5a**)	**6aa**	64	82
2	2-naphthyl, Me (**5b**)	**6ba**	60	76
3	4-MeC_6H_4, Me (**5c**)	**6ca**	57	81
4	4-$MeOC_6H_4$, Me (**5d**)	**6da**	61	81
5	4-$NO_2C_6H_4$, Me (**5e**)	**6ea**	71	72
6	4-FC_6H_4, Me (**5f**)	**6fa**	67	79
7	4-$CF_3C_6H_4$, Me (**5g**)	**6ga**	63	75
8	Ph, Et (**5h**)	**6ha**	77	61
9	Ph, *i*-Pr (**5i**)	**6ia**	65	8
10	$PhCH_2CH_2$, Me (**5j**)	**6ja**	92	41
11	Cyclohexyl, Me (**5k**)	**6ka**	74	52
12	*tert*-Bu, Me (**5l**)	**6la**	64	43

[a] Silylalkyne 1.5 equiv, catalyst 10 mol %, 0 °C, 4 h. See Experimental.
[b] Isolated yield.
[c] Determined by HPLC.

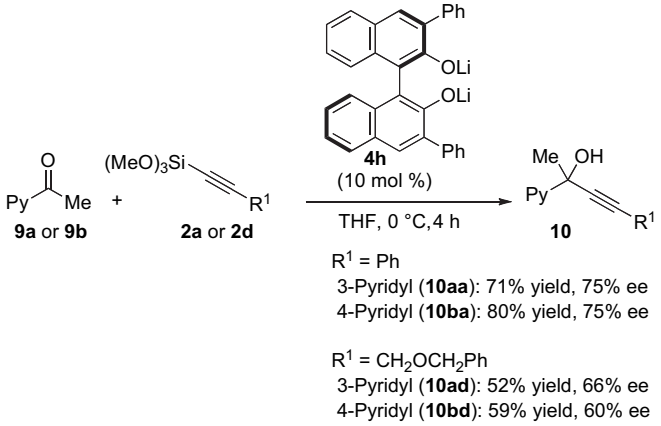
2-naphthaldehyde and 4′-substituted acetophenones (entries 1–7). Propiophenone **5h** gave a decreased selectivity (entry 8), and isobutyrophenone **5i** gave an almost racemic product (entry 9), which suggests the bulkiness of the aliphatic group has inferior effect on selectivity. Aliphatic ketones gave better chemical yields than acetophenone, but with lower selectivities (entries 10–12).

Because the magnitude of the optical rotation of **6aa** is small, some confusion exists in the literatures regarding the relationship between the sign of optical rotation and the molecule's absolute configuration.[19] To determine the absolute configuration of **6aa**, we first attempted the direct ozonolysis of propargylic alcohol to the corresponding acid, but only acetophenone was obtained. We next investigated ozonolysis after the reduction of the alkyne to the alkene. The obtained **6aa** was reduced using Red-Al® to olefin **7aa**[20], which was then transformed into methyl ester **8aa**[21] via ozonolysis (Scheme 1). The absolute configuration of the obtained ester was unambiguously determined to be *S* by the sign of optical rotation, which suggested that the original propargylic alcohol **6aa** had an *S*-configuration.



Scheme 1. Determination of the absolute configuration of **6aa**.

Pyridyl propargylic alcohols are important building blocks for the synthesis of biologically active compounds,[22] however, the successful enantioselective alkynylation of acetylpyridine has not been reported, because nitrogen atom in pyridine ring deactivates the chiral Lewis acid catalyst. Using a basic catalyst, our protocol may be applied to the alkynylation of basic substrate, such as acetylpyridines. We next investigated the addition of phenylethyne **2a** or benzyloxypropyne **2d** to 3-acetyl and 4-acetylpyridines (**9a** and **9b**). As expected, the reaction proceeded smoothly, and the corresponding alcohols **10** were obtained in good chemical and optical yields (Scheme 2). These results constitute the highest chemical yield and enantioselectivity reported to date for the alkynylation of acetylpyridines.[23]



Scheme 2. Alkynylation of acetylpyridines.

3. Conclusion

We demonstrated the first example of enantioselective alkynylation of carbonyl compounds using trialkoxysilylalkyne catalyzed by chiral lithium binaphtholate. The reactivity was sufficiently high that it could be applied to the catalytic alkynylation of ketones. Although the enantioselectivities were modest, these results demonstrate the synthetic utility of trimethoxysilylalkynes for the synthesis of optically active propargylic alcohols as building blocks for biologically active compounds.

4. Experimental

4.1. General

Optical rotations were obtained using a JASCO DIP-370 digital polarimeter. Infrared spectra were recorded using a JASCO FT/IR-5300. ^{1}H NMR and ^{13}C NMR spectra were recorded using JEOL JNM-ECX-400 (^{1}H, 400 MHz; ^{13}C, 100 MHz) spectrometer. Chemical shift values are expressed in parts per million relative to internal tetramethylsilane. Coupling constants (*J*) are reported in hertz (Hz). Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were obtained by electron impact with an ionization voltage of 70 eV using JEOL JMS-DX303 and JMS-BU20. HPLC was performed on JASCO PU-1580 with JASCO UV-1575 (λ=254 nm), and chiral separations were performed using Daicel chiralpak or chiralcel columns (φ 0.46×25 cm). Trimethoxy(phenylethynyl)silane (**2a**) was prepared by the literature method.[13] Binaphthol derivatives were prepared by the literature methods.[24]

4.2. Preparation of trimethoxysilylalkynes

*4.2.1. 1-Hexynyltrimethoxysilane (**2b**).* Hexyne (5.4 g, 66 mmol) was added to the solution of ethylmagnesium bromide (prepared from bromoethane 60 mmol and Mg 60 mmol) in ether (60 mL) and the mixture was refluxed for 2 h. After adding ether (100 mL) and $Si(OMe)_4$ (10 mL, 66 mmol) at 0 °C, the mixture was refluxed for another 2 h. After evaporation of the ether, the residue was extracted with ether and the resulting precipitate was filtered off. The filtrate was evaporated and distilled in vacuo to give **2b** as a colorless oil (7.9 g, 65%).

Bp 81–83 °C/5 mmHg. ^{1}H NMR ($CDCl_3$): δ 0.92 (t, 3H, *J*=7.3 Hz, CH_3), 1.44–1.58 (m, 4H, CH_2CH_2), 2.28 (t, 2H, *J*=7.1 Hz, C≡CCH_2), 3.59 (s, 9H, OCH_3). ^{13}C NMR ($CDCl_3$): δ 13.5, 19.2, 21.8, 30.2, 51.2, 74.3, 108.4. IR (neat): ν (cm^{-1}) 2960, 2943, 2843, 2185, 1458, 1194, 1190. LR-EIMS: 187 ($M^+-15(CH_3)$), 171 ($M^+-31(OCH_3)$), 121 (bp). HR-EIMS: calcd for $C_8H_{15}O_3Si$ 187.0791, found 187.0795.

*4.2.2. 1-Cyclohexenylethynyltrimethoxysilane (**2c**).* Bp 109–113 °C/3 mmHg. ^{1}H NMR ($CDCl_3$): δ 1.61–1.62 (m, 4H), 2.11–2.16 (m, 4H, CH_2), 3.60 (s, 9H, OCH_3), 6.32 (t, 1H, J=2.6 Hz, C=CH). ^{13}C NMR ($CDCl_3$): δ 21.2, 22.0, 25.7, 28.6, 50.8, 80.1, 107.4, 119.8, 138.8. IR (neat): ν (cm^{-1}) 2941, 2843, 2156, 1458, 1437, 1194, 1171, 1089. LR-EIMS: 226 (M^+, bp), 211, 195, 121. HR-EIMS: calcd for $C_{11}H_8O_3Si$ 226.1025, found 226.1015.

*4.2.3. (3-Benzyloxy-1-propynyl)trimethoxysilane (**2d**).* Bp 149–151 °C/4 mmHg. ^{1}H NMR ($CDCl_3$): δ 3.62. (s, 9H, OCH_3), 4.23 (s, 2H, C≡CCH_2), 4.63 (s, 2H, $PhCH_2$), 7.26–7.37 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 50.9, 57.2, 71.3, 81.5, 101.7, 128.0, 128.1, 128.5, 137.1. IR (neat): ν (cm^{-1}) 3032, 2945, 2845, 2185, 1495, 1456, 1437, 1387, 1354, 1259, 1193, 1087, 1089. LR-EIMS: 265 (M^+-1), 251, 121 (bp). HR-EIMS: calcd for $C_{13}H_{17}O_4Si$ 265.0893, found 265.0896.

*4.2.4. (3-Triisopropylsilyoxy-1-propynyl)-trimethoxysilane (**2e**).* Bp 125–126 °C/2 mmHg. ^{1}H NMR ($CDCl_3$): δ 1.06–1.63 (m, 21H, $CHCH_3$), 3.59 (s, 9H OCH_3), 4.43 (s, 2H,). ^{13}C NMR ($CDCl_3$): δ 11.9, 17.8, 50.8, 52.2, 79.1, 104.7. IR (neat): ν (cm^{-1}) 3312, 2945, 2892, 2868, 2189, 2123, 1463, 1384, 1369, 1263, 1194, 1101. LR-EIMS: 289 ($M^+-C_3H_7$), 259 (bp). HR-EIMS: calcd for $C_{12}H_{25}O_4Si_2$ 289.1310, found 289.1301.

4.3. Enantioselective alkynylation of aldehydes

*4.3.1. (S)-1,3-Diphenyl-2-propyn-1-ol (**3aa**)*[4c]. A solution of *n*-BuLi (0.094 mmol) in hexane (0.2 M, 0.48 mL) was added to the solution of 3,3′-diphenylbinaphthol (21 mg, 0.047 mmol) in THF (3 mL) at 0 °C. Benzaldehyde (50 mg, 0.49 mmol) and alkyne (0.16 mL, 0.72 mmol) were successively added to the mixture, and the solution was stirred for 1 h at the same temperature. The reaction was quenched with KF/KH_2PO_4 solution (15% KF, 10% KH_2PO_4, 2 mL), and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated. Silica gel chromatography afforded the alcohol **3aa** as an oil (100 mg, 98%).

$[\alpha]_D^{22}$ −1.3 (*c* 0.9, $CHCl_3$), 58% ee. [lit.[4c]: $[\alpha]_D^{27}$ −2.4 (*c* 1.2, $CHCl_3$), 86% ee, *S*]. HPLC (Daicel chiralcel OD-H, hexane/IPA=9/1, 1.0 mL/min): t_R(min) 12.9 (minor), 21.1 (major). ^{1}H NMR ($CDCl_3$): δ 2.26 (d, 1H, J=6.2 Hz, OH), 5.70 (d, 1H, J=6.2 Hz, PhCH), 7.30–7.50 (m, 8H, Ph), 7.63 (d, 2H, J=6.8 Hz, Ph).

*4.3.2. (S)-1-Phenyl-2-heptyn-1-ol (**3ab**)*[4c]. $[\alpha]_D^{22}$ −3.9 (*c* 1.4, $CHCl_3$), 21% ee. [lit.[4c]: $[\alpha]_D^{25}$ −18.1 (*c* 1.3, $CHCl_3$), 75% ee, *S*]. HPLC (Daicel chiralcel OD-H, hexane/IPA=19/1, 1.0 mL/min): t_R(min) 8.2 (major), 12.5 (minor). ^{1}H NMR ($CDCl_3$): δ 0.92 (t, 3H, J=7.1 Hz, CH_3), 1.40–1.57 (m, 4H, CH_2), 2.06 (d, 1H, J=6.0 Hz, OH), 2.27–2.30 (m, 2H, CH_2), 5.46 (d, 1H, J=6.0 Hz, PhCH), 7.28–7.40 (m, 3H, Ph), 7.54–7.56 (m, 2H, Ph).

*4.3.3. (S)-3-Cyclohex-1-enyl-1-phenyl-2-propyn-1-ol (**3ac**)* [7d]. $[\alpha]_D^{22}$ −4.0 (*c* 1.2, $CHCl_3$), 46% ee. [lit.[7d]. $[\alpha]_D^{15}$ +6.7 (*c* 0.4, $CHCl_3$), 89% ee, *R*]. HPLC (Daicel chiralcel OD-H, hexane/IPA=19/1, 1.0 mL/min): t_R(min) 10.7 (major), 14.7 (minor). ^{1}H NMR ($CDCl_3$): δ 1.55–1.67 (m, 4H, CH_2), 2.09–2.15 (m, 5H, CH_2, and OH), 5.58 (d, 1H, J=6.4 Hz, C=CH), 6.17 (s, 1H, OCH), 7.31–7.40 (m, 3H, Ph), 7.54–7.57 (m, 2H, Ph).

*4.3.4. 4-Benzyloxy-1-phenyl-2-butyn-1-ol (**3ad**).* $[\alpha]_D^{22}$ −4.2 (*c* 1.1, $CHCl_3$), 38% ee. HPLC (Daicel chiralpak AD-H, hexane/IPA=9/1, 1.0 mL/min): t_R(min) 15.2 (major), 17.5 (minor). ^{1}H NMR ($CDCl_3$): δ 2.15 (d, 1H, J=6.0 Hz, OH), 4.28 (s, 2H, C≡CCH_2), 4.61 (s, 2H, $PhCH_2$), 5.54 (d, 1H, J=6.0 Hz, C≡CCH), 7.28–7.41 (m, 8H, Ph), 7.54–7.56 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$): δ 57.2, 64.1, 71.4, 82.1, 86.5, 126.4, 127.7, 128.0, 128.1, 128.3, 128.4, 137.0, 140.4. IR (neat): 3388, 3062, 3030, 2854, 1603, 1495, 1452, 1354, 1259, 1192, 1119, 1066 cm^{-1}. LR-EIMS: 251 (M^+-1). HR-EIMS: calcd for $C_{17}H_{15}O_2$ 251.1072, found 251.1067.

*4.3.5. 1-Phenyl-4-triisopropylsilanyloxy-2-butyn-1-ol (**3ae**).* $[\alpha]_D^{22}$ −5.3 (*c* 1.1, $CHCl_3$), 41% ee. HPLC (Daicel chiralcel OD-H, hexane/IPA=19/1, 1.0 mL/min): t_R(min) 12.4 (minor), 14.3 (major). ^{1}H NMR ($CDCl_3$): δ 1.02–1.17 (m, 21H, $CHCH_3$), 2.16 (d, 1H, J=5.8 Hz, OH), 5.51 (d, 1H, J=5.8 Hz, PhCH), 7.32–7.39 (m, 3H, Ph), 7.53–7.55 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$): δ 12.0, 17.9, 52.0, 64.6, 84.2, 85.5, 126.6, 128.3, 128.5, 140.5. IR (neat): ν (cm^{-1}) 3367, 3088, 3064, 3032, 2943, 2891, 2866, 2725, 2715, 1603, 1495, 1468, 1464, 1369, 1327, 1261, 1192, 1130, 1090, 1068, 1014. LR-FABMS: (NBA+NaI) 341 (M^+). HR-FABMS: (NBA+NaI) calcd for $C_{19}H_{30}O_2Si$ 341.1913, found 341.1926.

*4.3.6. (R)-1-(1-Naphthyl)-3-phenyl-2-propyn-1-ol (**3ba**)*[4d]. $[\alpha]_D^{25}$ +16.8 (*c* 1.0, $CHCl_3$), 53% ee. [lit.[4d]: $[\alpha]_D^{25}$ +29.1 (*c* 0.52 $CHCl_3$), 94% ee, *R*]. HPLC (Daicel chiralcel OD-H, hexane/IPA=6/1, 1.0 mL/min): t_R(min) 11.1 (minor), 19.5 (major). ^{1}H NMR ($CDCl_3$): δ 2.38 (d, 1H, J=6.0 Hz, OH), 6.37 (d, 1H, J=6.0 Hz, OCH), 7.32–7.33(m, 3H, Ar–H), 7.47–7.62 (m, 5H, Ar–H), 7.86–7.95 (m, 3H, Ar–H), 8.39 (d, 1H, J=8.2 Hz, Ar–H).

*4.3.7. (S)-1-(2-Naphthyl)-3-phenyl-2-propyn-1-ol (**3ca**)*[4c]. $[\alpha]_D^{22}$ +5.9 (*c* 1.0, $CHCl_3$), 49% ee. [lit.[4c]: $[\alpha]_D^{25}$ +8.8 (*c* 0.69 $CHCl_3$), 92% ee, *S*]. HPLC (Daicel chiralcel OD-H, hexane/IPA=6/1, 1.0 mL/min): t_R(min) 10.9 (minor), 27.8 (major). ^{1}H NMR ($CDCl_3$): δ 2.36 (d, 1H, J=6.4 Hz, OH), 5.87 (d, 1H, J=6.4 Hz, ArCH), 7.30–7.35(m, 3H, Ar–H), 7.49–7.52 (m, 4H, Ar–H), 7.72–7.75 (m, 1H, Ar–H), 7.85–7.91 (m, 3H, Ar–H), 8.06 (s, 1H, Ar–H).

*4.3.8. (S)-3-Phenyl-1-(4-trifluoromethylphenyl)-2-propyn-1-ol (**3da**)*[4c]. $[\alpha]_D^{22}$ −3.0 (*c* 1.2, $CHCl_3$), 41% ee. [lit.[4c]: $[\alpha]_D^{27}$ −6.9 (*c* 1.4, $CHCl_3$), 87% ee, *S*] HPLC (Daicel chiralcel OD-H, hexane/IPA=6/1, 1.0 mL/min): t_R(min) 5.7 (minor), 23.0 (major). ^{1}H NMR ($CDCl_3$): δ 2.38 (d, 1H, J=6.0 Hz, OH), 5.76 (d, 1H, J=6.0 Hz, ArCH), 7.32–7.35 (m, 3H, Ar–H), 7.46–7.48 (m, 2H, Ar–H), 7.66–7.70 (m, 2H, Ar–H), 7.74–7.76 (m, 2H, Ar–H).

*4.3.9. (S)-1-(4-Methoxyphenyl)-3-phenyl-2-propyn-1-ol (**3ea**)*[4c]. $[\alpha]_D^{22}$ −4.2 (*c* 1.1, $CHCl_3$), 60% ee. [lit.[4c]: $[\alpha]_D^{27}$ −4.2 (*c* 1.7, $CHCl_3$), 80% ee, *S*]. HPLC (Daicel chiralcel OD-H, hexane/IPA=6/1, 1.0 mL/min): t_R(min) 11.0 (minor), 18.4 (major). ^{1}H NMR ($CDCl_3$): δ 2.21 (d, 1H, J=6.2 Hz, OH), 3.83 (s, 3H, CH_3) 5.65 (d, 1H, J=6.2 Hz, ArCH), 6.92–6.94 (m, 2H, Ar–H), 7.32–7.33 (m, 3H, Ar–H), 7.46–7.48 (m, 2H, Ar–H), 7.54–7.56 (m, 2H, Ar–H).

*4.3.10. 1-(4-Dimethylamino)-3-phenyl-2-propyn-1-ol (**3fa**)*[9a]. $[\alpha]_D^{22}$ −7.5 (*c* 1.2, $CHCl_3$). HPLC (Daicel chiralcel OD-H, hexane/IPA=6/1, 1.0 mL/min): t_R (min) 10.0 (minor), 18.8 (major). ^{1}H NMR ($CDCl_3$): δ 2.15 (br, 1H, OH), 3.00 (s, 6H, CH_3) 5.61 (s, 1H, ArCH), 6.73–6.76 (m, 2H, Ar–H), 7.31–7.32 (m, 3H, Ar–H), 7.47–7.50 (m, 4H, Ar–H).

*4.3.11. (S)-1,5-Diphenyl-1-penten-4-yn-3-ol (**3ga**)*[4c]. $[\alpha]_D^{22}$ −1.6 (*c* 1.1, $CHCl_3$), 42% ee. [lit.[4c]: $[\alpha]_D^{27}$ −7.3 (*c* 0.5, $CHCl_3$), 61% ee, *S*]. HPLC (Daicel chiralcel OD-H, hexane/IPA=9/1, 1.0 mL/min): t_R (min) 12.6 (minor), 32.6 (major). ^{1}H NMR ($CDCl_3$): δ 2.07 (d, 1H, J=6.2 Hz, OH), 5.29 (dd, 1H, J=6.2, 9.0 Hz, OCH), 6.39 (dd, 1H, J=9.0, 16 Hz, C=CH), 6.85 (d, 1H, J=16 Hz, PhCH), 7.27–7.49 (m 10H, Ar–H).

*4.3.12. (S)-1,5-Diphenyl-1-pentyn-3-ol (**3ha**)*[4c]. $[\alpha]_D^{22}$ +18.3 (*c* 1.4, $CHCl_3$), 31% ee. [lit.[4c] $[\alpha]_D^{27}$ +28.4 (*c* 1.1, $CHCl_3$), 49% ee, *S*]. HPLC (Daicel chiralcel OD-H, hexane/IPA=9/1, 1.0 mL/min): t_R (min) 14.8 (minor), 26.2 (major). ^{1}H NMR ($CDCl_3$): δ 1.89 (d, 1H, J=5.5 Hz, OH), 2.11–2.15 (m, 2H, CH_2), 2.83–2.93 (2H, m, CH_2), 4.55–4.65 (1H, m, OCH), 7.20–7.36 (m, 8H, Ar–H), 7.43–7.46 (m, 2H, Ar–H).

*4.3.13. (S)-1-Cyclohexyl-3-phenyl-2-propyn-1-ol (**3ia**)*[6c]. $[\alpha]_D^{20}$ +4.1 (*c* 1.2, $CHCl_3$), 45% ee. [lit.[6c] $[\alpha]_D^{26}$ −9.2 (*c* 1.0, $CHCl_3$), 96% ee, *R*]. HPLC (Daicel chiralcel OD-H, hexane/IPA=9/1, 1.0 mL/min): t_R (min) 5.8 (minor), 11.6 (major). ^{1}H NMR ($CDCl_3$): δ 1.06–1.31 (m, 5H, CH_2),

1.65–1.95 (m, 7H, OH and C_6H_{11}), 4.38 (t, 1H, J=6.0 Hz, OCH), 7.30–7.32 (m, 3H, Ar–H), 7.43–7.45 (m, 2H, Ar–H).

4.4. Enantioselective alkynylation of ketones

*4.4.1. (S)-2,4-Diphenyl-but-3-yn-2-ol (**6aa**)*[17k]. *n*-BuLi (0.16 M in hexane, 0.58 mL, 0.094 mmol) was added to a solution of (*R*)-3,3′-diphenylbinaphthol (21 mg, 0.047 mmol) in THF (3 mL) at 0 °C under an Ar atmosphere. Trimethoxy(phenylethynyl)silane (156 mg, 0.71 mmol) was added to the mixture in one portion, and then a solution of acetophenone (56 mg, 0.47 mmol) in THF (0.5 mL) was added over 3 h at the same temperature. After stirring for another 1 h, the reaction was quenched with tetrabutylammonium fluoride (1.0 M in THF, 4 mL). The mixture was stirred for 0.5 h and extracted with EtOAc. The organic layer was washed with water and brine successively. Drying over sodium sulfate, and concentration under reduced pressure and separation by silica gel column chromatography afforded the alcohol (85 mg, 81%) as a colorless oil. Enantiomeric excess was determined by chiral HPLC. See the next section for the determination of the absolute configuration.

$[\alpha]_D^{16}$ −6.6 (*c* 1.0, $CHCl_3$), 82% ee. HPLC (Daicel chiralcel OD-H, hexane/IPA=19/1, 1.0 mL/min): t_R (min) 8.6 (minor), 10.5 (major). ^{1}H NMR ($CDCl_3$): δ 1.87 (s, 3H, CH_3), 2.46 (s, 1H, OH), 7.30–7.50 (m, 8H, Ar–H), 7.73–7.75 (m, 2H, Ar–H).

*4.4.2. 2-(2-Naphthyl)-4-phenyl-but-3-yn-2-ol (**6ba**)*[17l]. $[\alpha]_D^{20}$ +17.4 (*c* 0.44, $CHCl_3$), 76% ee. HPLC (Daicel chiralcel OD-H, hexane/IPA=9/1, 1.0 mL/min): t_R (min) 8.6 (minor), 11.4 (major). ^{1}H NMR ($CDCl_3$): δ 1.95 (s, 3H, CH_3), 2.59 (s, 1H, OH), 7.34–7.35 (m, 3H, Ar–H), 7.48–7.52 (m, 4H, Ar–H), 7.80–7.88 (m, 4H, Ar–H), 8.19 (s, 1H, Ar–H).

*4.4.3. 2-(4-Methylphenyl)-4-phenyl-but-3-yn-2-ol (**6ca**)*[17l]. $[\alpha]_D^{18}$ −5.4 (*c* 0.56, $CHCl_3$), 81% ee. HPLC (Daicel chiralcel OD-H, hexane/IPA=19/1, 1.0 mL/min): t_R (min) (minor), 11.6 (major). ^{1}H NMR ($CDCl_3$): δ 1.86 (s, 3H, CH_3), 2.37 (s, 3H, Ar–CH_3), 2.41 (s, 1H, OH), 7.19 (d, 2H, J=8.2 Hz), 7.32–7.33 (m, 3H, Ar–H), 7.47–7.49 (m, 2H, Ar–H), 7.62 (d, 2H, J=8.2 Hz).

*4.4.4. (S)-2-(4-Methoxyphenyl)-4-phenyl-but-3-yn-2-ol (**6da**)*[17l]. $[\alpha]_D^{19}$ −8.0 (*c* 0.44, $CHCl_3$), 81% ee. [lit.[17l] $[\alpha]_D^{25}$ +10.2 (*c* 0.4, $CHCl_3$), 68% ee, *R*]. HPLC (Daicel chiralcel OD-H, hexane/IPA=19/1, 1.0 mL/min): t_R (min) 12.7 (minor), 21.3 (major). ^{1}H NMR ($CDCl_3$): δ 1.86 (s, 3H, CH_3), 2.42 (s, 1H, OH), 3.82 (s, 3H, OCH_3), 6.90–6.93 (m, 2H), 7.32–7.35 (m, 3H, Ar–H), 7.47–7.49 (m, 2H, Ar–H), 7.64–7.67 (m, 2H, Ar–H).

*4.4.5. 2-(4-Nitrophenyl)-4-phenyl-but-3-yn-2-ol (**6ea**)*[17d]. $[\alpha]_D^{17}$ −1.9 (*c* 1.0, $CHCl_3$), 72% ee. HPLC (Daicel chiralcel OD-H, hexane/IPA=19/1, 1.0 mL/min): t_R (min) 21.1 (minor), 26.3 (major). ^{1}H NMR ($CDCl_3$): δ 1.88 (s, 3H, CH_3), 2.57 (s, 1H, OH), 7.34–7.36 (m, 3H, Ar–H), 7.46–7.49 (m, 2H, Ar–H), 7.90 (d, J=9.2 Hz, 2H, Ar–H), 8.25 (m, 2H, Ar–H).

*4.4.6. (S)-2-(4-Fluorophenyl)-4-phenyl-but-3-yn-2-ol (**6fa**)*[17l]. $[\alpha]_D^{22}$ −8.5 (*c* 0.53, $CHCl_3$), 79% ee. [lit.[17l] $[\alpha]_D^{25}$ +5.0 (*c* 0.4, $CHCl_3$), 54% ee, *R*]. HPLC (Daicel chiralcel OD-H, hexane/IPA=19/1, 1.0 mL/min): t_R (min) 8.2 (minor), 10.2 (major). ^{1}H NMR ($CDCl_3$): δ 1.86 (s, 3H, CH_3), 2.46 (s, 1H, OH), 7.04–7.08 (m, 2H, Ar–H), 7.31–7.35 (m, 3H, Ar–H), 7.47–7.49 (m, 2H, Ar–H), 7.68–7.71 (m, 2H, Ar–H).

*4.4.7. 2-(4-Trifluoromethylphenyl)-4-phenyl-but-3-yn-2-ol (**6ga**)*[17k]. $[\alpha]_D^{24}$ −6.1 (*c* 1.6, $CHCl_3$), 75% ee. HPLC (Daicel chiralcel OD-H, hexane/IPA=19/1, 1.0 mL/min): t_R (min) 8.3 (minor), 10.1 (major). ^{1}H NMR ($CDCl_3$): δ 1.87 (s, 3H, CH_3), 2.53 (s, 1H, OH), 7.32–7.36 (m, 3H, Ar–H), 7.47–7.49 (m, 2H, Ar–H), 7.65 (d, 2H, J=8.2 Hz), 7.84 (d, 2H, J=8.2 Hz).

*4.4.8. 1,3-Diphenyl-pent-1-yn-3-ol (**6ha**)*[17k]. $[\alpha]_D^{23}$ −6.7 (*c* 1.0, $CHCl_3$), 61% ee. HPLC (Daicel chiralcel OD-H, hexane/IPA=29/1, 1.0 mL/min): t_R (min) 9.4 (minor), 11.0 (major). ^{1}H NMR ($CDCl_3$): δ 1.03 (t, 3H, J=7.3 Hz, $-CH_2CH_3$), 1.95–2.11 (m, 2H, $-CH_2CH_3$), 2.45 (s, 1H, OH), 7.30–7.40 (m, 6H Ar–H), 7.48–7.51 (m, 2H, Ar–H), 7.68–7.77 (m, 2H, Ar–H).

*4.4.9. 4-Methyl-1,3-diphenyl-pent-1-yn-3-ol (**6ia**)*[25]. $[\alpha]_D^{20}$ −1.0 (*c* 0.81, $CHCl_3$), 8% ee. HPLC (Daicel chiralcel AD-H, hexane/IPA=19/1, 1.0 mL/min): t_R (min) 10.5 (major), 15.9 (minor). ^{1}H NMR ($CDCl_3$): δ 0.89 (d, 3H, J=6.8 Hz), 1.14(d, 3H, J=6.8 Hz), 2.14–2.23 (m, 1H), 2.41 (s, 1H, OH), 7.28–7.39 (m, 6H, Ar–H), 7.49–7.51 (m, 2H, Ar–H), 7.67–7.69 (m, 2H, Ar–H).

*4.4.10. 3-Methyl-1,5-diphenyl-pent-1-yn-3-ol (**6ja**)*[17d]. $[\alpha]_D^{16}$ +6.0 (*c* 1.0, $CHCl_3$), 41% ee. HPLC (Daicel chiralcel OD-H, hexane/IPA=19/1, 1.0 mL/min): t_R (min) 11.4 (minor), 16.2 (major). ^{1}H NMR ($CDCl_3$): δ 1.63 (s, 3H, CH_3), 2.01–2.10 (m, 2H), 2.91–2.95 (m, 2H), 7.18–7.22 (m, 8H, Ar–H), 7.43–7.46 (m, 2H, Ar–H).

*4.4.11. 2-Cyclohexyl-4-phenyl-but-3-yn-2-ol (**6ka**)*[17g]. $[\alpha]_D^{17}$ +2.7 (*c* 1.0, $CHCl_3$), 52% ee. HPLC (Daicel chiralcel OD-H, hexane/IPA=19/1, 1.0 mL/min): t_R (min) 5.7 (minor), 7.9 (major). ^{1}H NMR ($CDCl_3$): δ 1.14–1.30 (m, 5H), 1.51–1.52 (m, 1H), 1.54 (s, 3H, CH_3), 1.68–1.71 (m, 1H), 1.82–1.84 (m, 2H), 1.91–1.95 (m, 1H), 2.02–2.05 (m, 1H), 7.30–7.31 (m, 3H, Ar–H), 7.41–7.44 (m, 2H, Ar–H).

*4.4.12. 3,4,4-Trimethyl-1-phenyl-pent-1-yn-3-ol (**6la**)*[17d]. $[\alpha]_D^{21}$ +2.2 (*c* 2.2, $CHCl_3$), 43% ee. HPLC (Daicel chiralcel OD-H, hexane/IPA=19/1, 1.0 mL/min): t_R (min) 5.5 (minor), 8.2 (major). ^{1}H NMR ($CDCl_3$): δ 1.12 (s, 9H, CCH_3), 1.54 (s, 3H, CH_3), 1.94 (s, 1H, OH), 7.29–7.31 (m, 3H, Ar–H), 7.41–7.43 (m, 2H, Ar–H).

4.5. Determination of the absolute configuration of chiral propargylic alcohol 6

*4.5.1. (S)-2-Hydroxy-2-phenylpropanoic acid methyl ester (**8aa**)*[21]. A solution of Red-Al® in toluene (65%, 0.54 mL) was added to a solution of alcohol **6aa** ($[\alpha]_D^{16}$ −6.6 (*c* 1.0, $CHCl_3$), 82% ee, 116 mg) in ether (20 mL) at 0 °C and the mixture was stirred at room temperature for 4 h. The reaction was quenched by dropwise addition of MeOH (5 mL) at 0 °C. The mixture was dilute with EtOAc and washed with a saturated solution of Rochelle's salt. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield a yellow oil, which was purified by column chromatography (eluent: Hex/EtOAc=8/1) to afford alkene **7aa** (105 mg, 90% yield) as a colorless oil.

Compound **7aa**: $[\alpha]_D^{22}$ −12.7 (*c* 2.5, $CHCl_3$), 81% ee. [lit.[20]: $[\alpha]_D^{20}$ +12.8 (*c* 0.63, $CHCl_3$), 91% ee, *S*]. HPLC (Daicel chiralcel OD-H, hexane/IPA=9/1, 1.0 mL/min): t_R (min) 9.1 (major), 12.0 (minor). ^{1}H NMR ($CDCl_3$): δ 1.80 (s, 3H, CH_3), 6.50 (d, 1H, J=16.0 Hz, CH=CH), 6.64 (d, 1H, J=16.0 Hz, CH=CH), 7.22–7.39 (m, 8H, Ar–H), 7.51–7.53 (m, 2H, Ar–H).

Ozone was bubbled into a solution of the alkene **7aa** (105.3 mg, 0.47 mmol) in dichloromethane (20 mL) at −78 °C until a blue color persisted. Oxygen was then passed through the solution and triphenylphosphine (123 mg, 0.47 mmol) was added to the mixture at the same temperature. The resulting mixture was stirred for 1 h at room temperature and concentrated under reduced pressure to yield a colorless oil, which was purified by silica gel column chromatography (eluent: Hex/EtOAc=6/1) to afford the corresponding aldehyde (53.8 mg, 76% yield) as a colorless oil.

Sodium bicarbonate (1.0 g, 12 mmol) was added to a solution of the above aldehyde in MeOH/water (9:1, 1.4 mL). To the mixture was added bromine (0.14 mL, 2.7 mmol) over 30 min with vigorous stirring at room temperature. After stirring for 2 h, excess bromine was decomposed using solid $Na_2S_2O_3$. The mixture was filtered, and the filtrate was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The obtained crude product was purified by column chromatography (eluent: Hex/CH_2Cl_2=3:2, 1:1, 1:3) to give the ester **8aa** (41.3 mg, 54% yield, 81% ee) as a colorless oil.

$[\alpha]_D^{21}$ +51 (*c* 1.3, $CHCl_3$), 81% ee. [lit.[21] $[\alpha]_D^{24}$ +55 (*c* 1.3, $CHCl_3$), 81% ee, *S*]. HPLC (Daicel chiralcel OD-H, hexane/IPA=49/1, 0.5 mL/min): t_R (min) 20.6 (major), 22.6 (minor). ^1H NMR ($CDCl_3$): δ 1.78 (s, 3H, CH_3), 3.75 (s, 1H, OH), 3.78 (s, 3H, OCH_3), 7.28–7.38 (m, 3H, Ar–H), 7.54–7.55 (m, 3H, Ar–H).

4.6. Enantioselective alkynylation of acetylpyridines

*4.6.1. 4-Phenyl-2-(pyridin-3-yl)-but-3-yn-2-ol (**10aa**)*[17k]. $[\alpha]_D^{24}$ −0.9 (*c* 1.0, $CHCl_3$), 75% ee. HPLC (Daicel chiralcel OD-H, hexane/IPA=9/1, 1.0 mL/min): t_R (min) 9.5 (minor), 12.2 (major). ^1H NMR ($CDCl_3$): δ 1.89 (s, 3H, CH_3), 7.27–7.35 (m, 4H), 7.46–7.51 (m, 2H, Ar–H), 8.01–8.03 (m, 1H, Ar–H), 8.54–8.56 (m, 1H, Ar–H), 8.99 (s, 1H, Ar–H).

*4.6.2. 4-Phenyl-2-(pyridin-4-yl)-but-3-yn-2-ol (**10ba**)*[22b]. $[\alpha]_D^{23}$ +1.6 (*c* 1.0, $CHCl_3$), 75% ee. HPLC (Daicel chiralcel OD-H, hexane/IPA=4/1, 1.0 mL/min): t_R (min) 7.3 (minor), 11.1 (major). ^1H NMR ($CDCl_3$): δ 1.84 (s, 3H, CH_3), 7.33–7.35 (m, 3H, Ar–H), 7.45–7.47 (m, 2H, Ar–H), 7.62 (d, 2H, *J*=6.0 Hz), 8.59 (s, 2H, Ar–H).

*4.6.3. 5-Benzyloxy-2-(pyridin-3-yl)-pent-3-yn-2-ol (**10ad**).* $[\alpha]_D^{20}$ +0.9 (*c* 1.1, $CHCl_3$), 66% ee. HPLC (Daicel chiralcel OD-H, hexane/IPA=9/1, 1.0 mL/min): t_R (min) 29.8 (minor), 37.2 (major). ^1H NMR ($CDCl_3$): δ 1.85 (s, 3H, CH_3), 4.27 (s, 2H), 4.59 (s, 2H), 7.26–7.34 (m, 6H, Ar–H), 7.93–7.95 (m, 1H, Ar–H), 8.50–8.54 (m, 1H, Ar–H), 8.90 (s, 1H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 33.3, 57.3, 68.2, 71.8, 81.4, 89.0, 123.1, 128.0, 128.1, 128.5, 132.9, 137.2, 141.1, 146.8, 148.7. IR (neat): ν (cm^{-1}) 3139, 2854, 1658, 1477, 1351, 1174, 1091, 1025, 740, 698. LR-FABMS 268: ($(M+H)^+$, bp), 149, 91, 55. HR-FABMS: calcd for $C_{17}H_{18}NO_2$ ($(M+H)^+$) 268.1338, found 268.1337.

*4.6.4. 5-Benzyloxy-2-(pyridin-4-yl)-pent-3-yn-2-ol (**10bd**).* $[\alpha]_D^{20}$ +1.8 (*c* 1.0, $CHCl_3$), 60% ee. HPLC (Daicel chiralpak AD-H, hexane/IPA=9/1, 1.0 mL/min): t_R (min) 9.2 (major), 10.8 (minor). ^1H NMR ($CDCl_3$): δ 1.74 (s, 3H, CH_3), 4.24 (s, 2H), 4.57 (s, 2H), 7.27–7.35 (m, 5H, Ar–H), 7.52 (d, 2H, *J*=6.0 Hz), 8.48 (d, 2H, *J*=6.0 Hz). ^{13}C NMR ($CDCl_3$): δ 33.0, 57.3, 68.5, 71.8, 81.0, 89.0, 120.1, 127.9, 128.0, 128.4, 137.1, 149.2, 155.1. IR (neat): ν (cm^{-1}) 3087, 2854, 1600, 1457, 1390, 1180, 1074, 825, 740, 698. LR-FABMS: 268 ($(M+H)^+$, bp), 149, 81, 57. HR-FABMS: calcd for $C_{17}H_{18}NO_2$ ($(M+H)^+$) 268.1338, found 268.1337.

Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.07.080.

References and notes

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