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Diastereoselective alkynylation of glucose-modified imines with terminal alkynes

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ABSTRACT

The copper(I)-catalyzed enantioselective alkynylation of aldimines incorporating a 2,3,4,6-tetrakis-*O*-pivaloyl-D-glucopyranosyl (Piv_4Glc) chiral auxiliary with terminal alkynes is reported. The present system provides a versatile tool for the construction of optically active propargylamine derivatives. Good yields and enantiomeric excess values were achieved with an array of imines and biologically active, propargylamine derivatives.

1. Introduction

Chiral propargylamine derivatives that are key structural fragments within biologically active materials have attracted broad interests, particularly in the areas of synthetic methodology, bioorganic and medicinal chemistry, and natural product synthesis.[1,2] Rasagiline, a novel second-generation propargylamine, is a selective and irreversible inhibitor of monoamine oxidase type B (MAO-B) used for the treatment of Parkinson's disease (PD)[3] and in preventing cell death. Rasagiline and other propargylamines can prevent the opening of permeability transition pore in insolated mitochondria, regulate the apoptotic machinery in mitochondria, and rescue or protect deteriorated neurons in neurodegenerativedisorders.[4,5] *N*-Propargylamine derivatives of nitroxyls (JSAKs) can also act as promising antioxidants and protectors of targets against ROS toxicity.[5,6] Propargylamine is also a new interesting medicinal agent building block, due to the rich chemistry to which the alkyne can be modified, the presence of a C≡C bond in the desired targets offers particularly an opportunity for further synthetic elaboration on the chiral nitrogen-containing compounds, which are the framework of a number of biologically active compounds and natural products. In addition, the reaction is atom economical as the nucleophile is generated directly.

As a consequence of the essential role played by these *N*-propargylamine derivatives in biological systems and their utility as synthetic building blocks, a range of useful methodologies for the synthesis of these compounds have been reported, such as the alkynylglycine skeleton was formed via the coupling of α-haloglycinates with an excess of reactive metal alkynilides[7] and of three-component one-pot;[8] particularly, catalyzed asymmetric alkynylation of imines.[9,10]

The enantioselective addition to C=N bonds provides a versatile method for the synthesis of chiral nitrogen-containing scaffolds in biologically active compounds and natural products.[2,10,11] Previously, we reported the enantioselective strecker reaction of aldimines incorporating a 2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosyl(Piv_4Glc) chiral auxiliary and achieved several α-amino acids and interesting medicinal agents.[12] Currently, we employ *N*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosyl) aldimine as a chiral template, and obtain desired propargylamines by the alkynylation of imines with terminal alkynes. In this process, a new bond is formed between an sp^3 carbon and an sp carbon.

2. Results and discussion

Continuing our work in *C*-glycoside synthesis,[12] we applied the alkynylation reaction to *N*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosyl)aldimine **1** prepared according to an already known procedure.[12c] The alkynylation was accomplished by mixing imines **1** with 2 equiv of phenylacetylene **2** in the presence of $CuOTf{\cdot}0.5C_6H_6$ (10% equiv). This led to the corresponding propargylamine **3** in 95% yield with a diastereomeric ratio of 96%.

We investigated $Cu(OTf)_2$ as a catalyst in the reaction, but the reaction was very slow and gave poor yields, resulting in low conversion after 32 h at room temperature (Table 1). We also examined other Lewis acids such as $SnCl_4$ and $ZnCl_2$, but the reactions were disordered due to the formation of unknown products.

Next, a series of imines **1** from glucosamine were tested as electrophilic species. The reaction was conducted in two different solvents: dichloromethane and toluene. The best results were obtained when aromatic imines containing an electron-withdrawing group were used in CH_2Cl_2 at room temperature (Table 1). The results indicate that the electron-withdrawing group of aldimines reduces the electron intensity of the carbon

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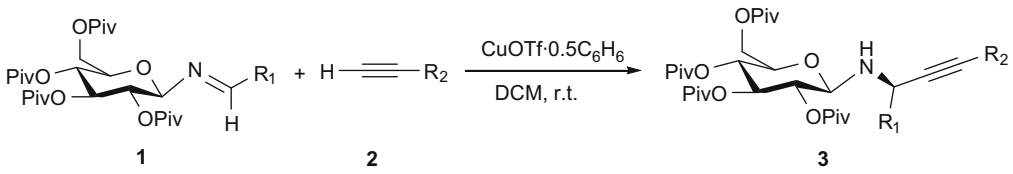
Table 1
Influence of different lewis acids and solvents on the alkynylation reaction[a]



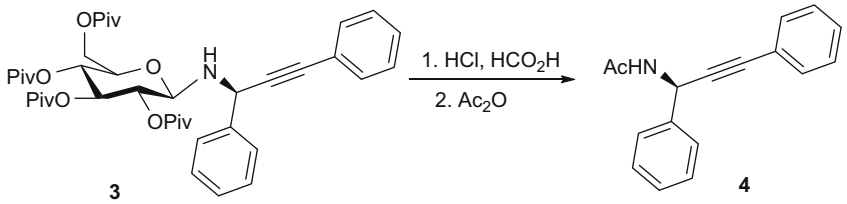
1 2 3

Entry	Catalyst	Solvent	R_1	R_2	Conditions	Compound	Yield[b] (%)	de[c] (%)
1	CuOTf·0.5C_6H_6	CH_2Cl_2	**1a** (Ph)	**2a** (Ph)	rt, 24 h	**3a**	90	90
2	CuOTf·0.5C_6H_6	CH_2Cl_2	**1b** (4-NO_2–C_6H_4)	**2a** (Ph)	rt, 24 h	**3b**	94	91
3	CuOTf·0.5C_6H_6	Toluene	**1b** (4-NO_2–C_6H_4)	**2a** (Ph)	rt, 24 h	**3b**	68	73
4	CuOTf·0.5C_6H_6	CH_2Cl_2	**1c** (4-Cl–C_6H_4)	**2a** (Ph)	rt, 24 h	**3c**	92	93
5	$Cu(OTf)_2$	CH_2Cl_2	**1c** (4-Cl–C_6H_4)	**2a** (Ph)	rt, 32 h	**3c**	62	81
6	$SnCl_4$	CH_2Cl_2	**1c** (4-Cl–C_6H_4)	**2a** (Ph)	rt, 32 h	—		
7	$ZnCl_2$	CH_2Cl_2	**1c** (4-Cl–C_6H_4)	**2a** (Ph)	rt, 32 h	—		
6	CuOTf·0.5C_6H_6	CH_2Cl_2	**1d** (3-NO_2–C_6H_4)	**2a** (Ph)	rt, 24 h	**3d**	95	96
7	CuOTf·0.5C_6H_6	CH_2Cl_2	**1e** (4-CF_3–C_6H_4)	**2a** (Ph)	rt, 24 h	**3e**	91	93
8	CuOTf·0.5C_6H_6	CH_2Cl_2	**1f** (4-CH_3–C_6H_4)	**2a** (Ph)	rt, 36 h	**3f**	84	92
9	CuOTf·0.5C_6H_6	CH_2Cl_2	**1c** (4-Cl–C_6H_4)	**2b** (*n*-butyl)	rt, 24 h	**3g**	72	78
10	CuOTf·0.5C_6H_6	CH_2Cl_2	**1c** (4-Cl–C_6H_4)	**2c** (TMS)	rt, 36 h	**3h**	37	28

[a] All reactions were performed in a 0.5 mmol scale of **1** using 2 equiv of phenylacetylene **2** in 3 mL solvent with 10 mol % of catalyst at room temperature.
[b] Isolated yield.
[c] The enantiomeric excess was determined by HPLC with a chiral stationary phase (Daicel Chiralpak AD).

atom of aldimines, which enhances the electrophilic ability. Subsequently, we investigated the addition of different terminal alkynes to imine. The reaction between imine **1c** and 1-hexyne **2b** afforded the corresponding propargylamine **3g** in 72% yield and 78% de. Unfortunately, the methodology did not work well with trimethylsilyl acetylene **2c**, which reacted with imine **1c** to give the corresponding propargylamine **3h** in 37% yield and 28% de (Table 1, entry 10).

The absolute configurations of propargylamines **3**were determined by transforming compound **3** into known acetamide **4** (Scheme 1). The major isomer **3** from the nucleophilic addition reaction was treated with dried HCl in HCOOH for 10 h, followed by N-acetylation (Ac_2O, *i*-Pr_2NEt, CH_2Cl_2, 2 h) to give acetamine **4** in 78% yield (Scheme 1). The acetamide **4** showed an optical rotation of $[\alpha]_D^{20} = +11.6$ (*c* 0.054, $CHCl_3$), which allowed us to assign the (*R*)-configuration to the stereogenic center. The (*R*)-enantiomer has been described to have a specific rotation of $[\alpha]_D^{22} = +36.1$ (*c* 0.82, $CHCl_3$).[13] This result is consistent with our previous work,[12b,c] the Piv_4Glc group plays a significant role in controlling the diastereoselective addition of phenylacetylene **2** to imine **1**. On the basis of the presented results, we proposed the key transition state shown in (Fig. 1). Herein, Cu^I is coordinated to both the N-atom of the imine and O-atoms of glucopyranose cycle and carbonyl group of the 2-*O*-pivaloyl group. This complexation decreased the



3 4

Scheme 1.

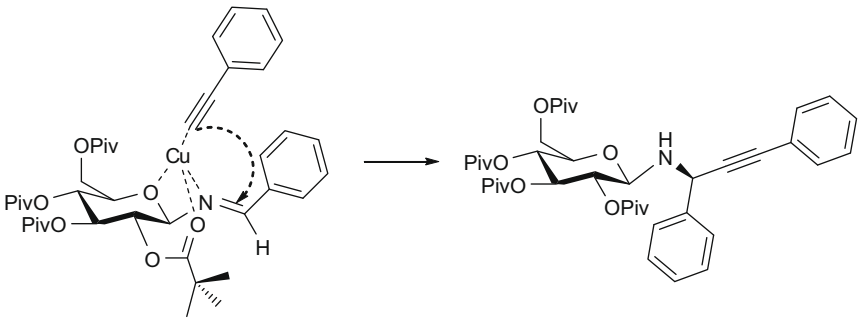


Figure 1. Proposed models for the diastereoselective addition of terminal alkyne **3**.

electron density at the C-atom of the C=N moiety and led to an attack of the terminal alkyne.

3. Conclusions

In conclusion, the diastereoselective addition of phenylacetylene to *N*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosyl)aldimines under Cu^{I} catalysis was proven to occur cleanly in good yields (84–95%) and diastereoselectivities (89–96%). This has opened up access to various chiral propargylamines.

4. Experimental

4.1. General

N-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-glucopyranosyl)aldimines **1a–f** were prepared as previously described.[12c] Other reagents were commercially obtained at highest commercial quality and were used without further purification. Dichloromethane and toluene were freshly distilled from CaH_2 under nitrogen prior to use. All non-aqueous reactions were carried out under anhydrous conditions within a nitrogen atmosphere. Column chromatography was performed on silica gel grade 60 (230–400 mesh). Analytical TLC: Silica Gel 60, F254 plates from Merck, which were visualised by UV and phosphomolybdic acid staining. Melting points were recorded on *X4-Data* microscopic melting-point apparatus; uncorrected. Optical rotation values were measured on a PerkinElmer P241 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX-400 spectrometer and all measurements were performed with tetramethylsilane as an internal standard; δ in ppm, *J* in hertz. Mass spectra were acquired on Bruker Esquire 3000 plus spectrometer; in *m*/*z*.

4.2. General procedure for the synthesis of propargylamines 3

Imines **1** (0.5 mmol) and CuOTf·0.5C_6H_6 (0.025 g, 0.05 mmol) were added to a dried 5-mL reaction flask containing a magnetic stirring bar. Freshly distilled and well-degassed CH_2Cl_2 (3 mL) was added, and the mixture was stirred at room temperature for 1 h. Phenylacetylene (0.102 g, 1.0 mmol) was sequentially added under vigorous stirring. The resulting solution was stirred at room temperature until TLC showed the completion of the reaction. The resulting mixture was then filtered through a short plug of silica gel and purified by column chromatography on silica gel neutralized with triethylamine to afford the desired alkynylation product **3** as a light yellow oil.

4.2.1. *N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-glucopyranosyl)-1,3-diphenylprop-2-ynylamine 3a

Yield (0.450 mmol, 0.317 g, 90%). $[\alpha]_D^{20} = +30.55$ (*c* 0.036, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 7.59 (d, *J* = 6.8, 2H), 7.46–7.26 (m, 8H), 5.48 (t, *J* = 12.0, 1H), 5.22 (t, *J* = 9.2, 1H), 5.07 (m, 1H), 4.92 (d, *J* = 13.2, 1H), 4.77 (s, 1H), 4.63 (d, *J* = 9.2, 1H), 4.26–4.05 (m, 1H), 3.85 (d, *J* = 8.8, 1H) , 2.05 (br, 1H), 1.07–1.35 (m, 36H). ^{13}C NMR (100 MHz, $CDCl_3$): 178.1, 177.4, 177.0, 176.5, 139.4, 131.7, 128.7, 128.5, 128.4, 128.3, 127.6, 127.4, 122.8, 87.8, 81.5, 77.0, 73.1, 72.6, 68.3, 67.0, 62.3, 50.1, 38.8, 38.7, 38.5, 27.2, 27.1, 27.0. HR-MS: calcd for $[C_{41}H_{55}NO_9+Na]^+$ 728. 3775, found: 728.3779.

4.2.2. *N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-glucopyranosyl)-1-(4-nitrophenyl)-3-phenylprop-2-ynylamine 3b

Yield (0.470 mmol, 0.353 g, 94%). $[\alpha]_D^{20} = +32.4$ (*c* 0.032, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 8.40 (d, *J* = 8.4, 1H), 8.20 (d, *J* = 8.4, 1H), 8.08 (d, *J* = 8.8, 1H), 7.67 (d, *J* = 8.8, 2H), 7.44–7.27 (m, 4H), 5.45 (m, 1H), 5.27 (t, *J* = 6.8, 1H), 5.22 (d, *J* = 12.0, 1H), 5.12 (dd, *J* = 9.6, 3.6, 1H), 4.92 (d, *J* = 9.2, 1H), 4.65 (d, *J* = 9.2, 1H), 4.23 (t, *J* = 9.2, 1H), 3.93 (t, *J* = 8.0, 1H), 2.52 (s, 1H), 1.30–1.11 (m, 36H). ^{13}C NMR (100 MHz, $CDCl_3$): 177.9, 177.4, 177.0, 176.8, 148.4, 147.4, 128.6, 128.5, 128.3, 128.2, 127.7, 124.1, 86.3, 81.7, 76.9, 73.0, 72.4, 70.7, 67.4, 61.1, 55.9, 38.8, 38.7, 38.5, 27.3, 27.1, 27.0. HR-MS: calcd for $[C_{41}H_{54}N_2O_{11}+Na]^+$ 773.3625, found: 773.3629.

4.2.3. *N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-glucopyranosyl)-1-(4-chlorophenyl)-3-phenylprop-2-ynylamine 3c

Yield (0.460 mmol, 0.340 g, 92%). $[\alpha]_D^{20} = +36.6$ (*c* 0.023, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 7.52(d, *J* = 8.0, 1H), 7.41–7.36 (m, 2H), 7.33–7.30 (m, 6H), 5.34 (t, *J* = 9.6, 1H), 5.23 (dd, *J* = 12.4, 8.0, 1H), 5.10 (t, *J* = 9.2, 1H), 4.94–4.86 (m, 1H), 4.78–4.76 (d, *J* = 8.0, 1H), 4.61–4.59 (d, *J* = 8.0, 1H), 4.45–4.40 (t, *J* = 9.6, 1H), 4.14 (s, 1H), 2.19 (s, 1H), 1.28–1.02 (m, 36H). ^{13}C NMR (100 MHz, $CDCl_3$): 177.8, 177.3, 176.8, 176.4, 139.7, 133.5, 130.0, 129.4, 128.6, 128.4, 128.3, 128.2, 124.7, 86.2, 81.8, 76.1, 73.2, 72.4, 70.6, 65.8, 62.2, 51.7, 38.8, 38.7, 38.5, 27.2, 27.1, 27.0. HR-MS: calcd for $[C_{41}H_{54}ClNO_9+Na]^+$ 762.3385, found: 762.3381.

4.2.4. *N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-glucopyranosyl)-1-(3-nitrophenyl)-3-phenylprop-2-ynylamine 3d

Yield (0.475 mmol, 0.356 g, 95%). $[\alpha]_D^{20} = +16.9$ (*c* 0.043, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 8.70 (s, 2H), 8.50–8.47 (m, 2H), 8.24 (d, *J* = 7.6, 2H), 7.78 (t, *J* = 7.6, 2H), 7.29 (s, 1H), 5.30 (t, *J* = 9.6, 1H), 5.05 (t, *J* = 9.6, 1H), 4.80 (t, *J* = 10.0, 1H), 4.24 (t, *J* = 8.4, 1H), 4.15 (d, *J* = 3.6, 1H), 4.07 (d, *J* = 2.8, 2H), 3.67–3.63 (m, 1H), 3.01 (t, *J* = 8.0, 1H), 1.24–1.09 (m, 36H). ^{13}C NMR (100 MHz, $CDCl_3$): 178.0, 177.4, 177.1, 176.9, 149.2, 142.1, 135.5, 130.1, 128.5, 128.4, 128.3, 125.3, 124.3, 122.2, 86.5, 82.2, 77.0, 73.0, 72.6, 70.3, 65.4, 62.1, 55.8, 38.8, 38.6, 38.5, 27.3, 27.2, 27.0. HR-MS: calcd for $[C_{41}H_{54}N_2O_{11}+Na]^+$ 773.3625, found: 773.3630.

4.2.5. *N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-glucopyranosyl)-1-(4-trifluoromethyl)penyl-3-phenylprop-2-ynylamine 3e

Yield (0.455 mmol, 0.352 g, 91%). $[\alpha]_D^{20} = +31.4$ (*c* 0.027, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 7.73 (dd, *J* = 13.6, 8.4, 1H), 7.62 (s, 2H), 7.53 (t, *J* = 7.6, 1H), 7.45–7.29 (m, 5H), 5.53–5.41 (m, 1H), 5.37 (d, *J* = 4.0, 1H), 5.30–5.24 (m, 1H), 5.19 (t, *J* = 6.8, 1H), 5.11 (q, *J* = 8.0, 1H), 4.96 (t, *J* = 8.8, 1H), 4.28–4.05 (m 2H), 3.58 (q, *J* = 4.4, 1H), 1.27–1.12 (m, 36H). ^{13}C NMR (100 MHz, $CDCl_3$): 177.9, 177.5, 177.1, 176.7, 146.2, 129.5, 128.5, 128.4, 128.3, 128.1, 128.0, 125.7, 125.2, 123.0, 87.1, 81.2, 76.0, 73.3, 71.7, 70.2, 65.7, 62.5, 51.1, 38.8, 38.7, 38.5, 27.3, 27.1, 27.0. HR-MS: calcd for $[C_{42}H_{54}F_3NO_9+Na]^+$ 796.3648, found: 796.3652.

4.2.6. *N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-glucopyranosyl)-1-(4-methylphenyl)-3-phenylprop-2-ynylamine 3f

Yield (0.420 mmol, 0.302 g, 84%). $[\alpha]_D^{20} = +17.2$ (*c* 0.073, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 7.29–7.26 (d, *J* = 2.8, 1H), 7.22–7.20 (d, *J* = 6.8, 1H), 7.13–7.08 (m, 4H), 6.64 (d, *J* = 8.0, 2H), 6.45 (d, *J* = 7.6, 1H), 5.57 (t, *J* = 8.8, 1H), 5.34 (t, *J* = 7.6, 1H), 5.14 (d, *J* = 9.6, 1H), 4.85 (t, *J* = 9.6, 1H), 4.42 (t, *J* = 9.6, 1H), 4.34 (q, *J* = 8.4, 1H), 4.20–4.15 (m, 1H), 3.79–3.75 (t, *J* = 5.2, 1H), 2.46 (s, 3H), 1.19–1.14 (m, 36H). ^{13}C NMR (100 MHz, $CDCl_3$): 177.7, 177.4, 177.1, 176.5, 138.6, 137.4, 129.0, 128.7, 128.5, 128.3, 128.2, 123.5, 86.0, 80.5, 76.1, 73.0, 72.2, 70.1, 65.7, 62.4, 52.3, 38.8, 38.6, 38.5, 27.2, 27.1, 27.0. 23.8. HR-MS: calcd for $[C_{42}H_{57}NO_9+Na]^+$ 742.3931, found: 742.3934.

4.2.7. *N*-(2,3,4,6-Tetra-O-pivaloyl-β-D-glucopyranosyl)-1-(4-chlorophenyl)-hept-2-ynylamine 3g

Yield (0.390 mmol, 0.281 g, 78%). $[\alpha]_D^{20} = +11.9$ (*c* 0.056, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.4, 2H), 7.10 (d, *J* = 8.4, 2H), 5.34 (t, *J* = 9.6, 1H), 5.22 (dd, *J* = 12.0, 8.0, 1H), 5.11 (t, *J* = 9.2,

1H), 4.93–4.85 (m, 1H), 4.78–4.77 (d, J = 8.0, 1H), 4.61–4.58 (d, J = 8.0, 1H), 4.45–4.41 (t, J = 9.6, 1H), 4.14 (s, 1H), 2.28 (tt, J = 7.2, 2.4, 2H), 2.19 (s, 1H), 1.45–1.38 (m, 2H), 1.36–1.30 (m, 2H), 1.27–1.01 (m, 36H), 0.86 (t, J = 7.6, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 177.8, 177.4, 176.8, 176.3, 139.4, 133.2, 129.9, 129.4, 128.6, 83.4, 81.7, 74.6, 73.3, 72.4, 70.6, 65.7, 62.2, 51.7, 38.8, 38.7, 38.5, 31.0, 27.2, 27.1, 27.0, 22.1, 18.6, 13.5. HR-MS: calcd for $[C_{39}H_{58}ClNO_9+Na]^+$ 742.3698, found: 742.3695.

4.2.8. *N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-glucopyranosyl)-1-(4-chlorophenyl)-3-(trimethylsilyl)-prop-2-ynylamine 3h

Yield (0.185 mmol, 0.136 g, 37%). $[\alpha]_D^{20} = +9.4$ (c 0.039, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 7.40 (d, J = 8.4, 2H), 7.08 (d, J = 8.4, 2H), 5.33 (t, J = 9.6, 1H), 5.23 (dd, J = 12.4, 8.4, 1H), 5.10 (t, J = 9.2, 1H), 4.94–4.85 (m, 1H), 4.79–4.76 (d, J = 8.0, 1H), 4.63–4.59 (d, J = 8.0, 1H), 4.45–4.41 (t, J = 9.6, 1H), 4.14 (s, 1H), 2.20 (s, 1H), 1.27–1.02 (m, 36H), 0.06 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): 177.8, 177.3, 176.8, 176.4, 139.7, 133.1, 129.6, 129.2, 128.8, 100.5, 91.5, 81.7, 73.2, 72.4, 70.6, 65.8, 62.3, 51.7, 38.8, 38.7, 38.5, 27.3, 27.1, 27.0, 0.8. HR-MS: calcd for $[C_{38}H_{58}ClNO_9Si+Na]^+$ 758.3467, found: 758.3471.

4.3. Synthesis of *N*-[(*R*)-1.3-diphenylprop-2-ynyl)acetamide 4[12c,13]

Anhydrous HCl gas was bubbled through a soln. of **3a** (0.212 g, 0.3 mmol) in formic acid (4 mL) for 10 h at rt. The soln was concentrated in vacuo and the residue was dissolved in 2 mL of dichloromethane. To this solution stirred at 0 °C were added successively diisopropylethylamine (105 μL, 0.6 mmol, 2 equiv) and acetic anhydride (90 μL, 0.9 mmol, 3 equiv). After 30 min at 0 °C and 2 h at room temperature, the resulting solution was extracted with water, and the organic layer was dried over magnesium sulfate. The solvent was removed under reduced pressure, and the product was used in the next step without purification: white solid (0.234 mmol, 0.059 g, 78%); mp: 173–174 °C; $[\alpha]_D^{22} = +11.6$ (c 0.054, $CHCl_3$); $[\alpha]_D^{22} = +36.1$ (c 0.82, $CHCl_3$).[13] ^{1}H NMR (400 MHz, $CDCl_3$): 2.11 (s, 3H), 6.28 (s, 2H), 7.35 (m, 6H), 7.43 (m, 2H), 7.60(d, J = 9.2, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 23.8, 45.0, 84.6, 87.3, 122.7, 127.4, 128.2, 128.4, 128.6, 128.7, 128.9, 132.4, 139.2, 169.0.

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