Kinetic resolution of donor-functionalised tertiary alcohols by Cu–H-catalysed stereoselective silylation using a strained silicon-stereogenic silane†

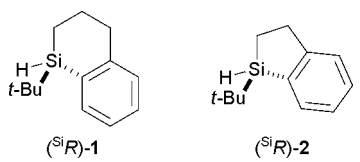
Betül Karatas, Sebastian Rendler, Roland Fröhlich‡ and Martin Oestreich*

Received 7th February 2008, Accepted 11th February 2008
First published as an Advance Article on the web 29th February 2008
DOI: 10.1039/b802186d

A series of propargylic tertiary alcohols decorated with an sp^2-hybridised nitrogen donor were kinetically resolved by reagent-controlled dehydrogenative Si–O coupling with a strained, highly reactive silicon-stereogenic cyclic silane.

Introduction

Non-enzymatic kinetic resolution[1,2] of alcohols by stereoselective silylation—as opposed to the related asymmetric acylation[3]—was disregarded entirely until it very recently became the focus of attention.[4] Initiated by a seminal contribution by Ishikawa *et al.*,[5] Hoveyda and Snapper *et al.* developed notable catalyst-controlled asymmetric silylation processes.[6] At the same time, we had devised a conceptually different, reagent-controlled silylation[7] by using privileged silicon-stereogenic silane (^{Si}R)-**1**[8,9] (Fig. 1) as a chiral resolving reagent. Our diastereoselective strategy is based on transition metal-catalysed dehydrogenative Si–O couplings, in which (^{Si}R)-**1** kinetically selects either of the enantiomeric transition metal–alkoxide complexes. The selectivity factors[2] *s* obtained in the Cu–H-catalysed etherification[10,11] of donor-functionalised secondary alcohols ($s \approx 10$)[7a] were substantially improved by employing a Rh(I)–carbene complex as catalyst ($s \approx 900$).[7b]



(^{Si}R)-**1** (^{Si}R)-**2**

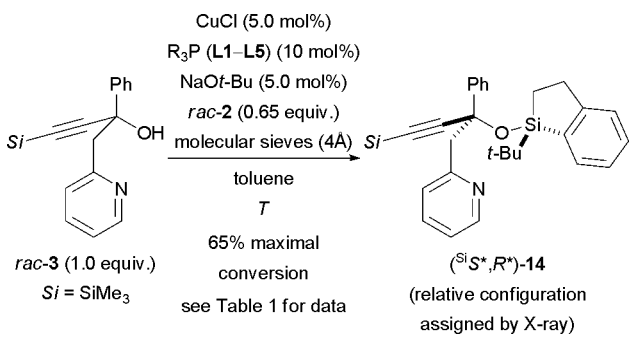
Fig. 1 Privileged silicon-stereogenic silanes.

We then entertained the idea to extend this technique to tertiary alcohols, for which a stereoselective silylation had not been reported so far. In fact, examples of their kinetic resolution are scarce, with only a handful enzymatic[12–14] (including catalytic antibodies[15]) as well as a single chemical method[16] known to date. In this paper, we report an unprecedented stereoselective silylation of (again donor-functionalised) tertiary alcohols through the use of the novel strained silicon-stereogenic silane (^{Si}R)-**2**[17] (Fig. 1).

Results and discussion

In our work on the kinetic resolution of secondary alcohols (*vide supra*),[7] the sterically encumbered tertiary silane (^{Si}R)-**1** was sufficiently reactive. Conversely, attempts to accomplish its dehydrogenative coupling with a tertiary alcohol failed without exception. We then reasoned that conversion might be, if at all, achieved by using a silane with enhanced Lewis acidity. The pivotal step in dehydrogenative Si–O couplings is likely to be a σ-bond metathesis of a transition metal–alkoxide and a Si–H bond,[11] which involves a Lewis acid–Lewis base interaction of silicon and oxygen. Aware of the concept of *strain-release Lewis acidity*,[18] we prepared (^{Si}R)-**2**,[17] which was accessed following a protocol similar to that for (^{Si}R)-**1**.[9] Gratifyingly, strained (^{Si}R)-**2** was significantly more reactive than (^{Si}R)-**1** in the Cu–H catalysis;[7a] no conversion was seen in the Rh(I)-catalysed process, which had emerged as so effective for secondary alcohols.[7b]

A brief screening of several 1-substituted (alkyl, aryl, alkenyl and alkynyl groups) 1-phenyl-2-(2-pyridinyl) ethanols quickly showed that merely a slender alkynyl substituent is tolerated at the tertiary carbon atom. Propargylic alcohol *rac*-**3** was chosen for optimisation of the reaction conditions (*rac*-**3** → *rac*-**14**, Scheme 1). As the success is reflected in the diastereoselectivity, *rac*-**2** was used for this.[7] Removal of any traces of water by molecular sieves greatly improved chemical yields. We had learned in our previous study that electron-rich monophosphines are markedly superior to electron-poor congeners in terms of reactivity.[7] This held true of this transformation as well (Table 1): poor σ-donor



Scheme 1 Optimisation of the reaction conditions and diastereoselectivity in the racemic series.

Organisch-Chemisches Institut, Westfälische Wilhelms-Universität, Corrensstrasse 40, D-48149, Münster, Germany. E-mail: martin.oestreich@uni-muenster.de; Fax: +49 (0)251 83-36501; Tel: +49 (0)251 83-33271

† Electronic supplementary information (ESI) available: Characterisation data of **14**–**24**, **26** and **28**, ^{1}H and ^{13}C NMR spectra of all new compounds as well as all four molecular structures; crystal structure data. See DOI: 10.1039/b802186d

‡ X-Ray crystal structure analysis.

Table 1 Assessment of phosphine ligands in Cu–H-catalysed Si–O coupling of *rac*-**2** (0.65 equiv.) and *rac*-**3** (1.0 equiv.). Diastereoselectivity as the pivotal parameter for the subsequent kinetic resolution

Entry	Ligand R_3P		T/°C	Conv.[a] (%)	dr of ($^{Si}S^*,R^*$)-**14**[b]
1	$(3,5\text{-}CF_3\text{-}C_6H_3)_3P$	**L1**	40	<5	53:47
2	Ph_3P	**L2**	20	60	88:12
3	$(3,5\text{-Xylyl})_3P$	**L3**	20	65	87:13
4	$(4\text{-}t\text{-Bu-}C_6H_4)_3P$	**L4**	20	65	92:8
5	$t\text{-BuPh}_2P$	**L5**	20	65	89:11

[a] Determined by ^{1}H NMR analysis and based on alcohol *rac*-**3** (65% corresponds to quantitative conversion using 0.65 equiv. of silane *rac*-**2**). [b] Diastereomeric ratio determined by GLC analysis using an SE-54 column.

L1 formed an unreactive and unselective catalyst (entry 1) whereas moderately σ-donating **L2–5** combined good reactivity with reasonable diastereocontrol (entries 2–5). **L4** was routinely used from then on.

This protocol was subsequently applied to the kinetic resolution of a series of aryl-substituted propargylic alcohols *rac*-**3**-*rac*-**10** (Scheme 2 and Table 2, entries 1–8). Diastereoselectivity is dependent on conversion in the enantiomeric series (columns 10–12, Table 2), which is why we also provide the unbiased diastereomeric ratios and theoretical selectivity factors *s* from experiments in the racemic series (columns 7–9 and 17, Table 2). Diastereomeric ratios were generally within 90:10 (s = 19–45); there appears to be a minor influence of the electronic nature of the arene on its exact values: electron-withdrawing groups at the arene favour marginally higher numbers, *e.g.*, dr = 94:6 for R^2 = 4-chlorophenyl (entry 6) *versus* dr = 90:10 for R^2 = 4-anisyl (entry 4). The relative configuration of the racemic ethers **14–21** was assigned by X-ray crystal stucture analyses of **15**, **16** and **19**. In the enantiomeric series, the resolutions were performed either with (^{Si}R)-**2** or (^{Si}S)-**2** of 87–92% ee. The apparent selectivity factors, s', using the enantio*im*pure[20] resolving reagent range from 4.6–9.0,[2,19] which corresponds to enantiomeric excesses of 72–92% ee for the slow-reacting alcohols (*S*)-**3**, (*S*)-**5**, (*S*)-**8** and (*S*)-**9** as well as (*R*)-**4**, (*R*)-**6** and (*R*)-**7** at approximately 65% conversion. Absolute configurations were deduced from crystallographic analysis of (*S*)-**8** and the assigned relative configurations (*vide supra*).

In contrast, when replacing the aryl group by an alkyl substituent such as methyl (in *rac*-**11**), 2-propyl (in *rac*-**12**) or cyclohexyl (in *rac*-**13**), the diastereoselection completely collapsed (Table 2, entries 9–11). The steric bulk of the branched alkyl residues in *rac*-**12** and *rac*-**13** also retarded conversion, requiring extended reaction times.

Lastly, we exemplarily tested a 2-(6-picolinyl) and a 2-quinolinyl group as donors (Scheme 3). Among other hetarenes, these had proven successful in the recently developed Rh(I)-catalysed Si–O coupling.[7b] The selectivity factors for both *rac*-**25** → ($^{Si}S,R$)-**26** and *rac*-**27** → ($^{Si}S,R$)-**28** (Scheme 3) compared well with *rac*-**3** → ($^{Si}S,R$)-**14** (Table 2, entry 1). The chemical yield of (*S*)-**27** was lowered by competing *retro*-1,2-addition affording 2-methylquinoline.

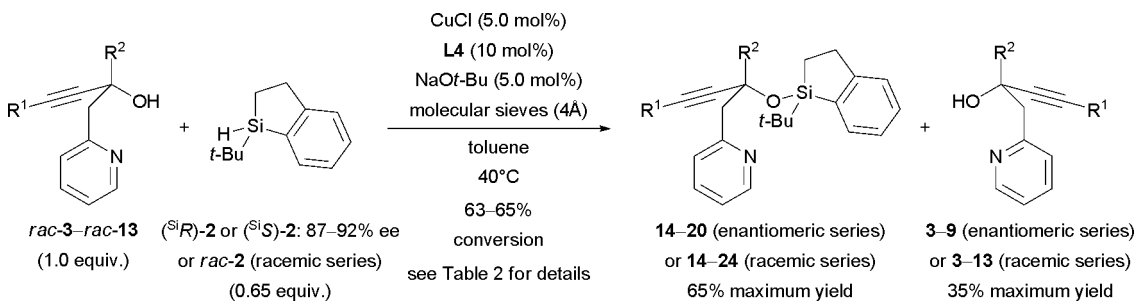
Conclusion

In summary, we have presented, for the first time, a kinetic resolution of tertiary (propargylic) alcohols, for which asymmetric syntheses are less prevalent,[21] by stereoselective silylation. The slow-reacting alcohols were isolated in 13–34% yield (at 65% conversion) with 72–94% ee; the fast-reacting alcohols might be liberated from the silyl ether in high chemical yield by chemoselective reductive cleavage of the Si–O bond.[22] These results bode well for the further development of chiral silanes as resolving reagents.

Experimental†

General procedure for the preparation of the donor-functionalised tertiary alcohols

In a flame-dried Schlenk flask, a solution of freshly destilled *i*-Pr_2NH (1.82 mL, 1.32 g, 13.0 mmol, 1.30 equiv.) in anhydrous THF (40 mL) was cooled to −78 °C followed by slow addition of *n*-BuLi (4.80 mL, 12.0 mmol, 1.20 equiv., 2.5 M solution in hexane).[23] The reaction mixture was then allowed to warm to room temperature and maintained at ambient temperature



Scheme 2 Kinetic resolution of 2-pyridinyl-substituted tertiary alcohols by diastereoselective alcohol silylation.

Table 2 Kinetic resolution of pyridinyl-functionalised tertiary alcohols by Cu–H-catalysed dehydrogenative Si–O coupling

Entry	Racemic alcohol	R^1	R^2	Silane		Silyl ether (racemic series)[a]			Silyl ether (enantiomeric series)			Recovered alcohol				
				No.	ee[b] (%)	No.	Yield[c] (%)	dr[d]	No.	Yield[c] (%)	dr[d]	No.	Yield[c] (%)	ee[b] (%)	s^e	s^f
1	*rac*-**3**	$SiMe_3$	Ph	(^{Si}R)-**2**	92	($^{Si}S^*,R^*$)-**14**	51	92:8	($^{Si}S,R$)-**14**	58	76:24	(*S*)-**3**	34	88	7.6	30
2	*rac*-**4**	$SiMe_3$	4-Tolyl	(^{Si}S)-**2**	90	($^{Si}R^*,S^*$)-**15**[g]	61	92:8	($^{Si}R,S$)-**15**	58	78:22	(*R*)-**4**	34	84	6.6	30
3	*rac*-**5**	$SiMe_3$	2-Anisyl	(^{Si}R)-**2**	87	($^{Si}S^*,R^*$)-**16**[g]	59	89:11	($^{Si}S,R$)-**16**	64	81:19	(*S*)-**5**	32	72	4.6	19
4	*rac*-**6**	$SiMe_3$	4-Anisyl	(^{Si}S)-**2**	90	($^{Si}R^*,S^*$)-**17**	54	90:10	($^{Si}R,S$)-**17**	56	78:22	(*R*)-**6**	34	84	6.6	22
5	*rac*-**7**	$SiMe_3$	4-Fluorophenyl	(^{Si}S)-**2**	90	($^{Si}R^*,S^*$)-**18**	59	92:8	($^{Si}R,S$)-**18**	55	81:19	(*R*)-**7**	32	86	7.0	30
6	*rac*-**8**	$SiMe_3$	4-Chlorophenyl	(^{Si}R)-**2**	92	($^{Si}S^*,R^*$)-**19**[g]	58	94:6	($^{Si}S,R$)-**19**	59	79:21	(*S*)-**8**[h]	24	92	9.0	45
7	*rac*-**9**	Ph	Ph	(^{Si}R)-**2**	92	($^{Si}S^*,R^*$)-**20**	61	90:10	($^{Si}S,R$)-**20**	62	72:28	(*S*)-**9**	25	92	9.0	22
8	*rac*-**10**	Ph	4-Anisyl	*rac*-**2**	—	($^{Si}R^*,S^*$)-**21**	64	90:10	—	—	—	—	—	—	—	22
9	*rac*-**11**	$SiMe_3$	Me	*rac*-**2**	—	($^{Si}R^*,R^*$)-**22**	61	59:41	—	—	—	—	—	—	—	1.7
10	*rac*-**12**	$SiMe_3$	2-Pr	*rac*-**2**	—	($^{Si}R^*,S^*$)-**23**	47	51:49	—	—	—	—	—	—	—	1.1
11	*rac*-**13**	Ph	Cy	*rac*-**2**	—	($^{Si}R^*,S^*$)-**24**	51	56:44	—	—	—	—	—	—	—	1.4

[a] Diastereomeric ratio in the racemic series is not biased by conversion. [b] Determined by HPLC analysis using Daicel Chiralcel columns providing baseline separation of enantiomers. [c] Yield (based on starting racemic alcohol) of analytically pure silyl ether and recovered alcohol, respectively isolated by flash chromatography on silica gel. [d] Determined by ^{1}H NMR analysis prior to purification by integration of the baseline-separated resonance signals of the diastereomers. [e] Apparent selectivity factor based on enantio*im*pure silane[20] calculated from $s = \ln[(1 - \text{conv.}) \times (1 - \text{ee})]/\ln[(1 - \text{conv.}) \times (1 + \text{ee})]$. [19,20] [f] Theoretical selectivity factor based on enantiopure silane calculated from $s = \ln[(1 - 0.5) \times (1 - \text{de}_{rac})]/\ln[(1 - 0.5) \times (1 + \text{de}_{rac})]$; de_{rac} in the racemic series corresponds to ee of the recovered alcohol in the enantiomeric series at exactly 50% conversion (provided that both follow identical kinetics). [g] Relative configuration secured by X-ray crystal structure analysis.† [h] Absolute configuration secured by X-ray crystal structure analysis.†

for 30 minutes. After recooling to −78 °C, a solution of the respective methyl substituted *N*-hetarene (10.0 mmol, 1.00 equiv.) in anhydrous THF (10 mL) was added in one portion and stirred at this temperature for further 30 minutes. Subsequently, the appropriate ketone[24] (12.0 mmol, 1.20 equiv.) was added dropwise to the deeply coloured mixture. After 30 minutes at −78 °C, the reaction mixture was quenched with H_2O (10 mL) and diluted with *tert*-butyl methyl ether (10 mL). The pH was adjusted to 7–8 by adding aqueous HCl (2 M), and the organic phase was separated. Extraction of the aqueous phase with dichloromethane (3 × 25 mL) and washing of the combined organic extracts with brine (20 mL) was followed by drying of the organic phases over Na_2SO_4. The solvents were evaporated under reduced pressure affording the desired alcohol as a crystalline solid or colourless oil.

Representative procedure for the Cu–H-catalysed Si–O coupling

A Schlenk tube was charged with molecular sieves (4 Å), CuCl (2.0 mg, 20 μmol, 5.0 mol%), tris(4-*tert*-butyl)phosphine (17.2 mg, 40.0 μmol, 10.0 mol%) and degassed toluene (1.5 mL) followed by addition of solid NaO*t*-Bu (1.9 mg, 20 μmol, 5.0 mol%). At room temperature, the pre-catalyst was then successively treated with a solution of alcohol *rac*-**3** (118.2 mg, 400.0 μmol) in toluene (2.0 mL) and a solution of silane (^{Si}R)-**2** (49.5 mg, 260 μmol, 0.65 equiv., 92% ee) in toluene (0.5 mL). The reaction mixture was maintained at 40 °C until GC analysis of an aliquot indicated complete conversion (after approximately 24 h) of (^{Si}R)-**2** into ($^{Si}S,R$)-**14** (dr = 76:24). The crude mixture was transferred to a round-bottomed flask and silica gel was added; the solvent was evaporated under reduced pressure. Purification by flash chromatography on silica gel (cyclohexane–*tert*-butyl methyl ether = 95:5 → 75:25) gave ($^{Si}S,R$)-**14** (110.0 mg, 58%, dr = 76:24) as well as enantioenriched alcohol (*S*)-**3** (34.6 mg, 34%, 88% ee) as colourless oils.

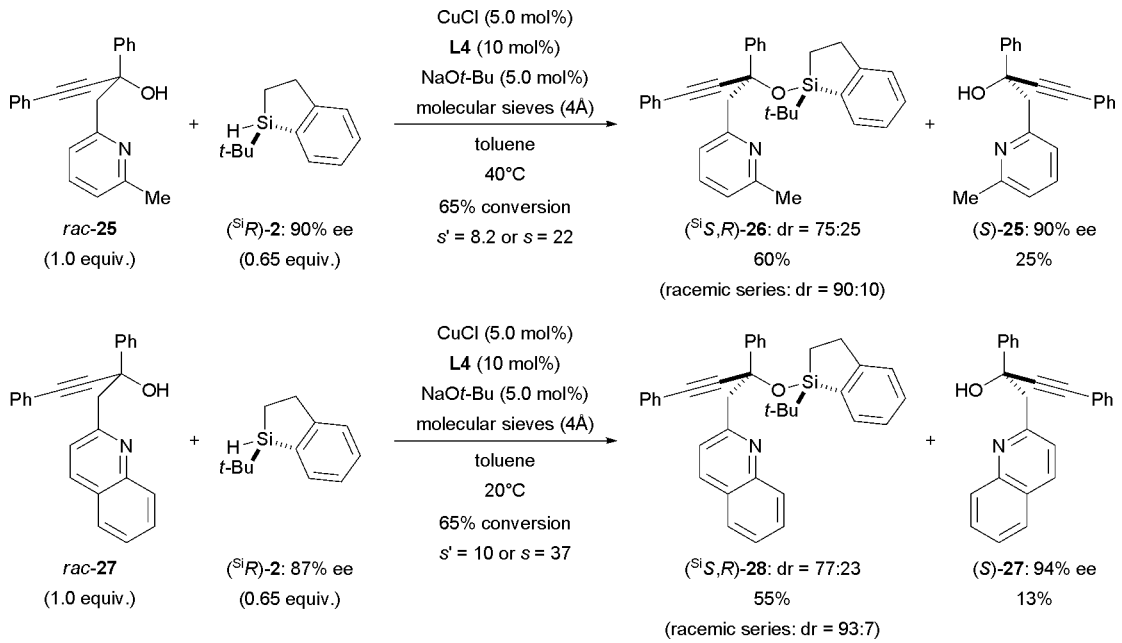
2-Phenyl-1-pyridin-2-yl-4-(trimethylsilanyl)but-3-yn-2-ol (3)

Analytical data for *rac*-**3**: Yield: 88%. R_f = 0.58 (cyclohexane–*tert*-butyl methyl ether = 1 : 1). M.p. 92 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.03 (s, 9H), 3.18 (d, J = 14.2 Hz, 1H), 3.32 (d, J = 14.2 Hz, 1H), 7.13 (d, J = 7.7 Hz, 1H), 7.22 (ddd, J = 7.7, 5.0, 0.6 Hz, 1H), 7.25–7.39 (m, 3H), 7.65 (ddd, $J = J$ = 7.7 Hz, J = 1.8 Hz, 1H), 7.72–7.76 (m, 2H), 8.53 (ddd, J = 5.0, 1.8, 0.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.03, 51.6, 73.2, 90.0, 108.0, 122.2, 124.8, 125.7, 127.7, 128.3, 137.1, 144.2, 148.2, 158.7. IR (film) 3255 (br, O–H), 2168 (w, C≡C) cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{21}NOSi$ ($M + Na^+$): 318.1285; found: 318.1289. Anal. calcd for $C_{18}H_{21}NOSi$ (295.46): C, 73.17; H, 7.16; N, 4.74; found: C, 73.08; H, 7.24; N, 4.69.

Analytical data for (*S*)-**3** (88% ee, Entry 1, Table 2): Yield: 34%. $[\alpha]^{20}_D$ = +32.6, $[\alpha]^{20}_{578}$ = +34.8, $[\alpha]^{20}_{546}$ = +42.4, $[\alpha]^{20}_{436}$ = +102.1 (c 0.450, $CHCl_3$). HPLC (Daicel Chiralcel IB column, column temperature 20 °C, solvent *n*-heptane–isopropanol = 90 : 10, flow rate 0.80 mL min^{-1}, λ = 230 nm): t_R = 5.94 min for (*R*)-**3**, t_R = 6.86 min for (*S*)-**3**.

1-Pyridin-2-yl-2-(4-tolyl)-4-(trimethylsilanyl)but-3-yn-2-ol (4)

Analytical data for *rac*-**4**: Yield: 94%. R_f = 0.58 (cyclohexane–*tert*-butyl methyl ether = 1 : 1). M.p. 61 °C. ^{1}H NMR (300 MHz,



Scheme 3 Variation of the donor: 2-(6-picolinyl) and 2-quinolinyl substitution.

$CDCl_3$): δ 0.02 (s, 9H), 2.34 (s, 3H), 3.16 (d, J = 14.2 Hz, 1H), 3.31 (d, J = 14.2 Hz, 1H), 7.11–7.22 (m, 4H), 7.60–7.66 (m, 3H), 8.51 (ddd, J = 5.0, 1.8, 0.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −0.1, 21.2, 51.6, 73.0, 89.7, 108.2, 122.1, 124.8, 125.5, 128.9, 137.0, 137.2, 141.4, 148.2, 158.8. IR (film) 3271 (br, O–H), 2168 (w, C≡C) cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{23}NOSi$ (M + H$^+$): 310.1622; found: 310.1620. Anal. calcd for $C_{19}H_{23}NOSi$ (309.48): C, 73.74; H, 7.49; N, 4.53; found: C, 73.70; H, 7.52; N, 4.45.

Analytical data for (*R*)-**4** (84% ee, Entry 2, Table 2): Yield: 34%. $[\alpha]^{20}_D$ = −26.4, $[\alpha]^{20}_{578}$ = −28.4, $[\alpha]^{20}_{546}$ = −33.8, $[\alpha]^{20}_{436}$ = −81.5 (*c* 0.580, $CHCl_3$). HPLC (Daicel Chiralcel IA column, column temperature 20 °C, solvent *n*-heptane–isopropanol = 98 : 2, flow rate 0.80 mL min^{-1}, λ = 230 nm): t_R = 14.27 min for (*S*)-**4**, t_R = 15.80 min for (*R*)-**4**.

2-(2-Methoxyphenyl)-1-pyridin-2-yl-4-(trimethylsilanyl)but-3-yn-2-ol (5)

Analytical data for *rac*-**5**: Yield: 85%. R_f = 0.32 (cyclohexane–*tert*-butyl methyl ether = 1 : 1). M.p. 89 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 9H), 3.52 (d, J = 13.8 Hz, 1H), 3.61 (d, J = 13.8 Hz, 1H), 3.91 (s, 3H), 6.91–6.95 (m, 2H), 7.13–7.18 (m, 2H), 7.25 (m, 1H), 7.58 (ddd, J = J = 7.6 Hz, J = 1.8 Hz, 1H), 7.72 (dd, J = 8.0, 1.8 Hz, 1H), 8.47 (ddd, J = 5.0, 1.8, 0.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −0.2, 47.4, 55.7, 71.3, 87.6, 107.8, 112.0, 120.6, 121.7, 124.8, 127.0, 128.7, 131.6, 136.4, 147.8, 156.4, 158.5. IR (film) 3254 (br, O–H), 2170 (w, C≡C) cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{23}NO_2Si$ (M + H$^+$): 326.1571; found: 326.1569. Anal. calcd for $C_{19}H_{23}NO_2Si$ (325.48): C, 70.11; H, 7.12; N, 4.30; found: C, 69.51; H, 7.23; N, 4.07.

Analytical data for (*S*)-**5** (72% ee, Entry 3, Table 2): Yield: 32%. $[\alpha]^{20}_D$ = +97.4, $[\alpha]^{20}_{578}$ = +103.2, $[\alpha]^{20}_{546}$ = +121.2, $[\alpha]^{20}_{436}$ = +257.5 (*c* 0.740, $CHCl_3$). HPLC (Daicel Chiralcel IA column, column temperature 20 °C, solvent *n*-heptane–isopropanol = 98 : 2, flow rate 0.80 mL min^{-1}, λ = 230 nm): t_R = 14.05 min for (*R*)-**5**, t_R = 15.27 min for (*S*)-**5**.

2-(4-Methoxyphenyl)-1-pyridin-2-yl-4-(trimethylsilanyl)but-3-yn-2-ol (6)

Analytical data for *rac*-**6**: Yield: 85%. R_f = 0.42 (cyclohexane–*tert*-butyl methyl ether = 1 : 1). M.p. 77 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.02 (s, 9H), 3.14 (d, J = 14.2 Hz, 1H), 3.30 (d, J = 14.2 Hz, 1H), 3.81 (s, 3H), 6.88–6.91 (m, 2H), 7.13 (d, J = 7.4 Hz, 1H), 7.22 (dd, J = 7.4, 4.9 Hz, 1H), 7.62–7.67 (m, 3H), 8.53 (ddd, J = 4.9, 1.6, 0.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 0.0, 51.7, 55.5, 72.9, 86.9, 108.3, 113.6, 122.1, 124.8, 127.0, 136.6, 137.0, 148.4, 159.0, 159.2. IR (film) 3253 (br, O–H), 2167 (w, C≡C) cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{23}NO_2Si$ (M + Na$^+$): 348.1390; found: 348.1396. Anal. calcd for $C_{19}H_{23}NO_2Si$ (325.48): C, 70.11; H, 7.12; N, 4.30; found: C, 69.79; H, 7.23; N, 4.29.

Analytical data for (*R*)-**6** (84% ee, Entry 4, Table 2): Yield: 34%. $[\alpha]^{20}_D$ = −22.6, $[\alpha]^{20}_{578}$ = −24.2, $[\alpha]^{20}_{546}$ = −29.0, $[\alpha]^{20}_{436}$ = −67.8, $[\alpha]^{20}_{365}$ = −164 (*c* 0.545, $CHCl_3$). HPLC (Daicel Chiralcel IA column, column temperature 20 °C, solvent *n*-heptane–isopropanol = 95 : 5, flow rate 0.80 mL min^{-1}, λ = 230 nm): t_R = 13.83 min for (*S*)-**6**, t_R = 15.47 min for (*R*)-**6**.

2-(4-Fluorophenyl)-1-pyridin-2-yl-4-(trimethylsilanyl)but-3-yn-2-ol (7)

Analytical data for *rac*-**7**: Yield: 93%. R_f = 0.52 (cyclohexane–*tert*-butyl methyl ether = 1 : 1). M.p. 59 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.03 (s, 9H), 3.16 (d, J = 14.4 Hz, 1H), 3.30 (d, J = 14.4 Hz, 1H), 7.01–7.07 (m, 2H), 7.14 (d, J = 7.6 Hz, 1H), 7.25 (m, 1H), 7.65–7.73 (m, 3H), 8.53 (ddd, J = 4.9, 2.0, 0.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 0.1, 51.5, 72.8, 90.3, 107.8, 115.0 (d, J_{C-F} = 21.3 Hz), 122.3, 124.9, 127.5 (d, J_{C-F} = 8.1 Hz), 137.2, 140.1 (d, J_{C-F} = 2.9 Hz), 148.2, 158.5, 162.4 (d, J_{C-F} = 243.9 Hz). IR (film) 3264 (br, O–H), 2169 (w, C≡C) cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{20}FNOSi$ (M + Na$^+$): 336.1190; found: 336.1206. Anal. calcd for $C_{18}H_{20}FNOSi$ (313.45): C, 68.97; H, 6.43; N, 4.47; found: C, 68.80; H, 6.49; N, 4.34.

Analytical data for (*R*)-**7** (86% ee, Entry 5, Table 2): Yield: 32%. $[\alpha]^{20}_{D} = -21.1$, $[\alpha]^{20}_{578} = -22.6$, $[\alpha]^{20}_{546} = -27.2$, $[\alpha]^{20}_{436} = -68.0$, $[\alpha]^{20}_{365} = -177$ (*c* 0.715, $CHCl_3$). HPLC (Daicel Chiralcel IA column, column temperature 20 °C, solvent *n*-heptane–isopropanol = 98 : 2, flow rate 0.80 mL min^{-1}, $\lambda = 230$ nm): $t_R = 11.96$ min for (*S*)-**7**, $t_R = 12.81$ min for (*R*)-**7**.

2-(4-Chlorophenyl)-1-pyridin-2-yl-4-(trimethylsilanyl)but-3-yn-2-ol (8)

Analytical data for *rac*-**8**: Yield: 91%. $R_f = 0.55$ (cyclohexane–*tert*-butyl methyl ether = 1 : 1). M.p. 86 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.03 (s, 9H), 3.16 (d, $J = 14.2$ Hz, 1H), 3.28 (d, $J = 14.2$ Hz, 1H), 7.13 (d, $J = 7.6$ Hz, 1H), 7.23 (ddd, $J = 7.6$, 4.9, 0.8 Hz, 1H), 7.31–7.34 (m, 2H), 7.64–7.68 (m, 3H), 8.52 (ddd, $J = 4.9$, 1.9, 0.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −0.3, 51.1, 72.5, 90.1, 107.4, 122.1, 124.6, 127.0, 128.1, 133.2, 137.0, 142.7, 148.0, 158.2. IR (film) 3254 (br, O–H), 2169 (w, C≡C) cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{20}ClNOSi$ ($M + Na^+$): 352.0895; found: 352.0899. Anal. calcd for $C_{18}H_{20}ClNOSi$ (329.90): C, 65.53; H, 6.11; N, 4.25; found: C, 65.58; H, 6.27; N, 4.19.

Analytical data for (*S*)-**8** (92% ee, Entry 6, Table 2): Yield: 24%. $[\alpha]^{20}_{D} = +13.5$, $[\alpha]^{20}_{578} = +14.7$, $[\alpha]^{20}_{546} = +17.9$, $[\alpha]^{20}_{436} = +43.9$ (*c* 1.11, $CHCl_3$). HPLC (Daicel Chiralcel IA column, column temperature 20 °C, solvent *n*-heptane–isopropanol = 98 : 2, flow rate 0.80 mL min^{-1}, $\lambda = 230$ nm): $t_R = 12.57$ min for (*S*)-**8**, $t_R = 14.11$ min for (*R*)-**8**.

2,4-Diphenyl-1-pyridin-2-ylbut-3-yn-2-ol (9)

Analytical data for *rac*-**9**: Yield: 88%. $R_f = 0.42$ (cyclohexane–*tert*-butyl methyl ether = 1 : 1). M.p. 97 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.34 (d, $J = 14.4$ Hz, 1H), 3.45 (d, $J = 14.4$ Hz, 1H), 7.21–7.36 (m, 8H), 7.40–7.46 (m, 2H), 7.52 (br s, 1H), 7.70 (ddd, $J = J = 7.7$ Hz, $J = 1.8$ Hz, 1H), 7.82–7.86 (m, 2H), 8.59 (ddd, $J = 4.9$, 1.8, 0.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.5, 73.3, 85.5, 92.0, 122.3, 123.0, 124.7, 125.7, 127.7, 128.3, 128.3, 128.4, 131.8, 137.2, 144.7, 148.5, 158.9. IR (film) 3254 (br, O–H), 2229 (w, C≡C) cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{17}NO$ ($M + H^+$): 300.1383; found: 300.1380. Anal. calcd for $C_{21}H_{17}NO$ (299.37): C, 84.25; H, 5.72; N, 4.68; found: C, 84.11; H, 5.79; N, 4.58.

Analytical data for (*S*)-**9** (92% ee, Entry 7, Table 2): Yield: 25%. $[\alpha]^{20}_{D} = +40.8$, $[\alpha]^{20}_{578} = +43.2$, $[\alpha]^{20}_{546} = +51.5$, $[\alpha]^{20}_{436} = +116$ (*c* 0.820, $CHCl_3$). HPLC (Daicel Chiralcel IB column, column temperature 20 °C, solvent *n*-heptane–isopropanol = 90 : 10, flow rate 0.80 mL min^{-1}, $\lambda = 230$ nm): $t_R = 10.04$ min for (*R*)-**9**, $t_R = 11.00$ min for (*S*)-**9**.

2-(4-Methoxyphenyl)-4-phenyl-1-pyridin-2-ylbut-3-yn-2-ol (10)

Analytical data for *rac*-**10**: Yield: 92%. $R_f = 0.30$ (cyclohexane–*tert*-butyl methyl ether = 1 : 1). M.p. 101–102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.28 (d, $J = 14.4$ Hz, 1H), 3.40 (d, $J = 14.4$ Hz, 1H), 3.81 (s, 3H), 6.90–6.94 (m, 2H), 7.18–7.25 (m, 7H), 7.40 (br s, 1H), 7.66 (ddd, $J = J = 7.7$ Hz, $J = 1.7$ Hz, 1H), 7.70–7.74 (m, 2H), 8.55 (ddd, $J = 4.8$, 1.7, 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.6, 55.5, 72.9, 85.4, 92.1, 113.7, 122.2, 123.0, 124.7, 127.0, 128.2, 128.3, 131.8, 137.0, 137.2, 148.5, 159.0, 159.2. IR (film) 3254 (br, O–H), 2230 (w, C≡C) cm^{-1}. HRMS (ESI) calcd for $C_{22}H_{19}NO_2$ ($M + H^+$): 330.1489; found: 330.1487. Anal. calcd for $C_{22}H_{19}NO_2$ (329.40): C, 80.22; H, 5.81; N, 4.25; found: C, 79.99; H, 5.90; N, 4.19.

2-Methyl-1-pyridin-2-yl-4-(trimethylsilanyl)but-3-yn-2-ol (11)

Analytical data for *rac*-**11**: Yield: 82%. $R_f = 0.30$ (cyclohexane–*tert*-butyl methyl ether = 1 : 1). Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.00 (s, 9H), 1.57 (s, 3H), 3.06 (d, $J = 14.1$ Hz, 1H), 3.13 (d, $J = 14.1$ Hz, 1H), 6.36 (br s, 1H), 7.20 (d, $J = 7.6$ Hz, 1H), 7.21 (m, 1H), 7.66 (ddd, $J = J = 7.6$ Hz, $J = 1.8$ Hz, 1H), 8.49 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.2, 29.7, 48.9, 67.9, 86.7, 109.6, 121.8, 124.5, 136.7, 148.1, 158.8. IR (film) = 3323 (br, O–H), 2167 (w, C≡C) cm^{-1}. HRMS (ESI) calcd for $C_{13}H_{19}NOSi$ ($M + Na^+$): 256.1128; found: 256.1121.

4-Methyl-3-pyridin-2-ylmethyl-1-(trimethylsilanyl)pent-1-yn-3-ol (12)

Analytical data for *rac*-**12**: Yield: 76%. $R_f = 0.58$ (cyclohexane–*tert*-butyl methyl ether = 1:1). Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.08 (s, 9H), 1.04 (d, $J = 6.8$ Hz, 3H), 1.00 (d, $J = 6.8$ Hz, 3H), 1.80 (qq, $J = J = 6.8$ Hz, 1H), 2.97 (s, 2H), 7.10 (d, $J = 7.7$ Hz, 1H), 7.11 (m, 1H), 7.57 (ddd, $J = J = 7.7$ Hz, $J = 1.9$ Hz, 1H), 8.39 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 0.04, 17.3, 17.9, 37.7, 44.8, 74.8, 88.8, 107.7, 121.8, 124.7, 136.8, 148.1, 159.4. IR (film) 3318 (br, O–H), 2165 (m, C≡C) cm^{-1}. HRMS (ESI) calcd for $C_{15}H_{23}NOSi$ ($M + H^+$): 262.1622; found: 262.1628. Anal. calcd for $C_{15}H_{23}NOSi$ (261.44): C, 68.91; H, 8.87; N, 5.36; found: C, 68.50; H, 8.87; N, 5.72.

2-Cyclohexyl-4-phenyl-1-pyridin-2-ylbut-3-yn-2-ol (13)

Analytical data for *rac*-**13**: Yield: 89%. $R_f = 0.51$ (cyclohexane–*tert*-butyl methyl ether = 1 : 1). M.p. 98–99 °C. ^{1}H NMR (400 MHz, C_6D_6): δ 1.29 (m, 3H), 1.60 (m, 3H), 1.83 (m, 3H), 2.21 (d, $J = 12.7$ Hz, 1H), 2.54 (d, $J = 13.0$ Hz, 1H), 2.99 (d, $J = 14.1$ Hz, 1H), 3.13 (d, $J = 14.1$ Hz, 1H), 6.52 (dd, $J = 7.5$, 4.9 Hz, 1H), 6.76 (d, $J = 7.5$ Hz, 1H), 6.87–6.90 (m, 3H), 6.99 (ddd, $J = J = 7.5$ Hz, $J = 1.8$ Hz, 1H), 7.09 (s, 1H), 7.18–7.22 (m, 2H), 8.09 (ddd, $J = 4.9$, 1.8, 0.8 Hz, 1H). ^{13}C NMR (100 MHz, C_6D_6): δ 27.3, 28.1, 28.8, 45.8, 49.1, 74.8, 85.4, 93.7, 122.0, 124.3, 125.0, 128.3, 128.7, 132.2, 136.8, 148.8, 160.6. IR (film) = 3301 (br, O–H), 2226 (w, C≡C) cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{23}NO$ ($M + H^+$): 306.1852; found: 306.1845. Anal. calcd for $C_{21}H_{23}NO$ (305.42): C, 82.59; H, 7.59; N, 4.59; found: C, 82.38; H, 7.68; N, 4.56.

1-(6-Methylpyridin-2-yl)-2,4-diphenylbut-3-yn-2-ol (25)

Analytical data for *rac*-**25**: Yield: 96%. $R_f = 0.61$ (cyclohexane–*tert*-butyl methyl ether = 1 : 1). M.p. 72–73 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.58 (s, 3H), 3.26 (d, $J = 14.3$ Hz, 1H), 3.34 (d, $J = 14.3$ Hz, 1H), 6.99 (d, $J = 7.7$ Hz, 1H), 7.08 (d, $J = 7.7$ Hz, 1H), 7.22–7.25 (m, 5H), 7.30 (dd, $J = J = 7.6$ Hz, 1H), 7.40 (dd, $J = J = 7.6$ Hz, 2H), 7.55 (dd, $J = J = 7.7$ Hz, 1H), 7.82 (d, $J = 7.6$ Hz, 2H), 7.86 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.5, 51.4, 73.2, 85.4, 92.1, 121.6, 121.9, 123.1, 125.7, 127.7, 128.2, 128.3, 128.4, 131.8, 137.4, 144.9, 157.4, 158.2. IR (film) 3242 (br, O–H), 2228 (w, C≡C) cm^{-1}. HRMS (ESI) calcd for $C_{22}H_{19}NO$ ($M + H^+$): 314.1539; found: 314.1534. Anal. calcd

for $C_{22}H_{19}NO$ (313.40): C, 84.31; H, 6.11; N, 4.47; found: C, 84.04; H, 6.35; N, 4.22.

Analytical data for (*S*)-**25** (90% ee, Scheme 3): Yield: 25%. $[\alpha]^{20}_{D} = +97.4$, $[\alpha]^{20}_{578} = +103.2$, $[\alpha]^{20}_{546} = +121.2$, $[\alpha]^{20}_{436} = +257.5$ (*c* 0.740, $CHCl_3$). HPLC (Daicel Chiralcel IB column, column temperature 20 °C, solvent *n*-heptane–isopropanol = 90 : 10, flow rate 0.80 mL min^{-1}, $\lambda = 230$ nm): $t_R = 7.83$ min for (*R*)-**25**, $t_R = 10.61$ min for (*S*)-**25**.

2,4-Diphenyl-1-quinolin-2-ylbut-3-yn-2-ol (27)

Analytical data for *rac*-**27**: Yield: 90%. $R_f = 0.62$ (cyclohexane–*tert*-butyl methyl ether = 1 : 1). M.p. 107 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.52 (d, $J = 14.4$ Hz, 1H), 3.58 (d, $J = 14.4$ Hz, 1H), 7.18–7.22 (m, 5H), 7.30–7.34 (m, 2H), 7.39–7.44 (m, 2H), 7.54 (m, 1H), 7.74 (m, 1H), 7.76 (br s, 1H), 7.81–7.88 (m, 3H), 8.12 (d, $J = 8.4$ Hz, 1H), 8.15 (d, $J = 8.4$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.1, 73.2, 85.4, 92.1, 122.9, 123.0, 125.8, 126.6, 127.2, 127.8, 128.2, 128.3, 128.4, 129.0, 130.2, 131.8, 137.2, 144.8, 147.0, 159.6. IR (film) = 3232 (br, O–H), 2228 (w, C≡C) cm^{-1}. HRMS (ESI) calcd for $C_{25}H_{19}NO$ ($M + H^+$): 350.1539; found: 350.1542. Anal. calcd for $C_{25}H_{19}NO$ (349.43): C, 85.93; H, 5.48; N, 4.01; found: C, 85.86; H, 5.45; N, 3.84.

Analytical data for (*S*)-**27** (94% ee, Scheme 3): Yield: 13%. $[\alpha]^{20}_{D} = +173$, $[\alpha]^{20}_{578} = +183$, $[\alpha]^{20}_{546} = +216$ (*c* 0.535, $CHCl_3$). HPLC (Daicel Chiralcel IB column, column temperature 20 °C, solvent *n*-heptane–isopropanol = 98 : 2, flow rate 0.80 mL min^{-1}, $\lambda = 230$ nm): $t_R = 20.61$ min for (*S*)-**27**, $t_R = 23.23$ min for (*R*)-**27**.

Acknowledgements

The research was supported by the Deutsche Forschungsgemeinschaft (Oe 249/4–1), the Fonds der Chemischen Industrie (predoctoral fellowship to S.R., 2005–2007) and the Aventis Foundation (Karl Winnacker fellowship to M.O., 2006–2008). The authors thank Oliver Plefka for elaborating the resolution of the strained silane[17] and Eduard Hartmann for skilful technical assistance in the substrate identification.

References and notes

1 E. Vedejs and M. Jure, *Angew. Chem., Int. Ed.*, 2005, **44**, 3974–4001.
2 H. B. Kagan and J. C. Fiaud, in *Topics in Stereochemistry*, ed. E. L. Eliel and S. H. Wilen, Wiley, New York, 1988, vol. 18, pp. 249–330.
3 E. J. Jarvo and S. J. Miller, in *Comprehensive Asymmetric Catalysis-Supplement 1*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer, Berlin, 2004, pp. 189–206.
4 S. Rendler and M. Oestreich, *Angew. Chem., Int. Ed.*, 2008, **47**, 248–250.
5 T. Isobe, K. Fukuda, Y. Araki and T. Ishikawa, *Chem. Commun.*, 2001, 243–244.
6 (*a*) Y. Zhao, J. Rodrigo, A. H. Hoveyda and M. L. Snapper, *Nature*, 2006, **443**, 67–70; (*b*) Y. Zhao, A. W. Mitra, A. H. Hoveyda and M. L. Snapper, *Angew. Chem., Int. Ed.*, 2007, **46**, 8471–8474.
7 (*a*) S. Rendler, G. Auer and M. Oestreich, *Angew. Chem., Int. Ed.*, 2005, **44**, 7620–7624; (*b*) H. F. T. Klare and M. Oestreich, *Angew. Chem., Int. Ed.*, 2007, **46**, 9335–9338.
8 (*a*) M. Oestreich, *Chem.–Eur. J.*, 2006, **12**, 30–37; (*b*) S. Rendler and M. Oestreich, *Beilstein J. Org. Chem.*, 2007, **3**, 9; (*c*) M. Oestreich, *Synlett*, 2007, 1629–1643.
9 S. Rendler, G. Auer, M. Keller and M. Oestreich, *Adv. Synth. Catal.*, 2006, **348**, 1171–1182.
10 C. Lorenz and U. Schubert, *Chem. Ber.*, 1995, **128**, 1267–1269.
11 S. Rendler and M. Oestreich, *Angew. Chem., Int. Ed.*, 2007, **46**, 498–504.
12 (*a*) D. O'Hagan and N. A. Zaidi, *J. Chem. Soc., Perkin Trans. 1*, 1992, 947–949; (*b*) D. O'Hagan and N. A. Zaidi, *Tetrahedron: Asymmetry*, 1994, **5**, 1111–1118.
13 I. Brackenridge, R. McCague, S. M. Roberts and N. J. Turner, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1093–1094.
14 (*a*) S. Hari Krishna, M. Persson and U. T. Bornscheuer, *Tetrahedron: Asymmetry*, 2002, **13**, 2693–2696; (*b*) B. Heinze, R. Kourist, L. Fransson, K. Hult and U. T. Bornscheuer, *Protein Eng. Des. Sel.*, 2007, **20**, 125–131; (*c*) R. Kourist, S. Bartsch and U. T. Bornscheuer, *Adv. Synth. Catal.*, 2007, **349**, 1393–1398.
15 B. List, D. Shabat, G. Zhong, J. M. Turner, A. Li, T. Bui, J. Anderson, R. A. Lerner and C. F. Barbas III, *J. Am. Chem. Soc.*, 1999, **121**, 7283–7291.
16 (*a*) E. R. Jarvo, C. A. Evans, G. T. Copeland and S. J. Miller, *J. Org. Chem.*, 2001, **66**, 5522–5527; (*b*) M. C. Angione and S. J. Miller, *Tetrahedron*, 2006, **62**, 5254–5261.
17 O. Plefka, *Diplomarbeit*, Albert-Ludwigs-Universität, Freiburg (Germany), 2006.
18 (*a*) S. E. Denmark, R. T. Jacobs, G. Dai-Ho and S. Wilson, *Organometallics*, 1990, **9**, 3015–3019; (*b*) A. G. Myers, S. E. Kephart and H. Chen, *J. Am. Chem. Soc.*, 1992, **114**, 7922–7923; (*c*) S. E. Denmark, B. D. Griedel and D. M. Coe, *J. Org. Chem.*, 1993, **58**, 988–990; (*d*) K. Matsumoto, K. Oshima and K. Utimoto, *J. Org. Chem.*, 1994, **59**, 7152–7155; (*e*) X. Zhang, K. N. Houk and J. L. Leighton, *Angew. Chem., Int. Ed.*, 2005, **44**, 938–941.
19 J. M. Goodman, A.-K. Köhler and S. C. M. Alderton, *Tetrahedron Lett.*, 1999, **40**, 8715–8718.
20 T. O. Luukas, C. Girard, D. R. Fenwick and H. B. Kagan, *J. Am. Chem. Soc.*, 1999, **121**, 9299–9306.
21 D. J. Ramón and M. Yus, *Angew. Chem., Int. Ed.*, 2004, **43**, 284–287.
22 Standard reaction conditions:[7a,9] Dibal (1.0 equiv.), CH_2Cl_2, 0 °C. It is important to avoid prolonged reaction times, as partial reduction of the alkyne is then seen.
23 (*a*) A. Ohsawa, T. Uezu and H. Igeta, *Chem. Pharm. Bull.*, 1979, **27**, 916–922; (*b*) A. Ohsawa, T. Uezu and H. Igeta, *Chem. Pharm. Bull.*, 1978, **26**, 2428–2434.
24 (*a*) R. Suzuki, H. Tsukuda, N. Watanabe, Y. Kuwatani and I. Ueda, *Tetrahedron*, 1998, **54**, 2477–2496; (*b*) L. Maurette, C. Tedeschi, E. Sermot, M. Soleilhavoup, F. Hussain, B. Donnadieu and R. Chauvin, *Tetrahedron*, 2004, **60**, 10077–10098; (*c*) K. A. Parker and M. W. Ledeboer, *J. Org. Chem.*, 1996, **61**, 3214–3217.

