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Amino thiols versus amino alcohols in the asymmetric alkynylzinc addition to aldehydes

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ABSTRACT

A series of modular amino thiol and amino alcohol ligands have been synthesized in enantiopure form from common enantiopure precursors. Their structures have been optimized for performance in the asymmetric alkynylzinc addition to aldehydes, and a direct comparison of the effect of the S and O coordinating atoms on the catalytic outcome of these ligands has been performed. Amino thiols have shown to be superior as ligands for this type of chemistry.

1. Introduction

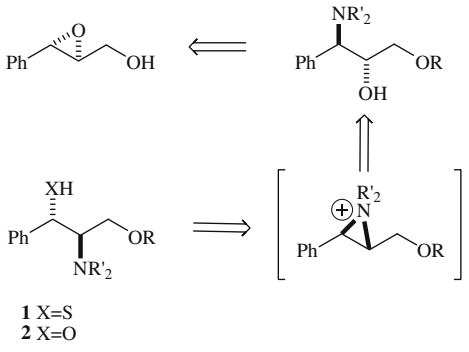
The use of chiral amino thiol ligands in asymmetric organozinc additions to aldehydes has been developed in view of the excellent results obtained with these ligands in conversion and stereoselectivity. This was attributed to a beneficial effect of the coordinating sulfur atom in enhancing the reactivity of the dialkylzinc compounds, since sulfur has a greater affinity for Zn than oxygen. Moreover, aminothiolate–zinc complexes are considered better Lewis acids than aminoalcoholate–zinc complexes, which enhance the reactivity of the aldehyde.[1]

Although some amino thiol ligands exhibit a clearly superior performance than amino alcohols in carbonyl additions, to the best of our knowledge only one direct comparison of structurally identical ligands has been carried out in the asymmetric diethylzinc addition to aldehydes. Kang et al. showed that amino thiols enhanced reaction rate, enantioselectivity, and asymmetric amplification, and discussed their results in terms of changes in the reaction mechanism. In particular, it was suggested that besides increasing the amount of free monomeric catalyst, aminothiolate–zinc dimers could behave as efficient catalysts as well.[2]

The asymmetric alkynylation of aldehydes using amino thiols has scarcely been studied.[3] In fact, only one example has been described in the literature, with limited success.[4] A related asymmetric vinylation using amino thiols as chiral ligands has also been reported.[5] Herein we report on the successful use of amino thiol ligands in the asymmetric alkynylation of aldehydes (up to quantitative yield, up to 90% ee). Comparison with the otherwise identical amino alcohols allowed us to establish that *S*-containing ligands are superior for this particular application.

2. Results and discussion

We based our approach on the preparation of modular ligands (amino alcohols and amino thiols) arising from a common amino alcohol intermediate. In turn, these compounds can be readily prepared from enantiopure (*S,S*)-phenylglycidol using a well-established O-alkylation-ring opening sequence developed by our group (Scheme 1).[6,7]



Scheme 1. Strategy for the preparation of amino thiols and amino alcohols.

Besides the electronic characteristics arising from the thiol/hydroxyl groups, the steric effects of the ligands must also be modulated in order to fine-tune catalytic activity and enantioselectivity.[8] The dialkylamino and *O*-alkyl groups were selected for this purpose. With respect to the amino substituent, a piperidino group was chosen due to its proven effectivity in related ligands for asymmetric diethylzinc additions.[6,7] A dimethylamino group was also used to minimize steric interactions. With respect to the alkoxy group, two extreme *O*-alkyl groups (methyl and trityl) were

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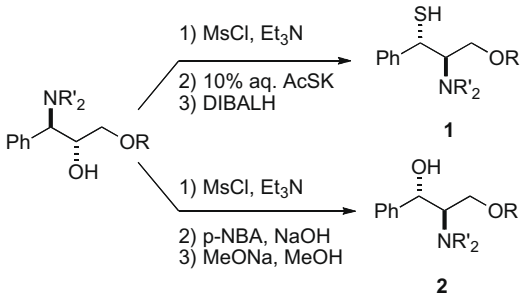
also introduced into the structure to control the steric hindrance of that part of the ligand.[8]

Once the amino alcohol intermediates had been prepared in enantiopure form from phenylglycidol, they were treated with methanesulfonyl chloride and triethylamine in dichloromethane to form an aziridinium cation, which was not isolated but treated in situ with S or O nucleophiles, in this case, potassium thioacetate or sodium *p*-nitrobenzoate. The ring opening of this aziridinium intermediate took place stereospecifically with complete regioselectivity. It should be pointed out that the products are in fact regioisomers of the starting amino alcohols. The reduction or hydrolysis of these compounds yielded the corresponding amino thiols and amino alcohols, in good to excellent overall yields (Scheme 2). We had prepared ligand **1aa** before by means of this sequence, and it proved to be an extremely active and enantioselective amino thiol for diethylzinc additions to aldehydes.[9]



Ligand	R	NR'$_2$	Overall yield/%
1aa	CPh_3	piperidino	89
1ab	CPh_3	NMe_2	62
1ba	CH_3	piperidino	Quant.
1bb	CH_3	NMe_2	49
2aa	CPh_3	piperidino	61
2ab	CPh_3	NMe_2	54
2bb	CH_3	NMe_2	57

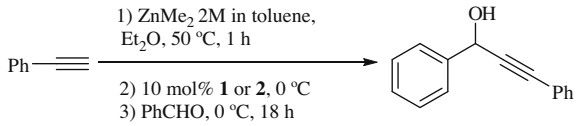
Scheme 2. Synthesis of amino thiols **1** and amino alcohols **2**.

With the whole set of ligands in hand, we proceeded to test them in the asymmetric alkynylzinc addition to aldehydes. The alkynylzinc compounds were generated by mixing the acetylene with $ZnMe_2$,[10] following Soai's original procedure.[11] This method has found widespread application because there is no necessity to use other metal sources to generate the active catalyst. Typically, amino alcohols, imino alcohols, or salen-type ligands have been employed as chirality sources.[12] Herein, we chose phenylacetylene, dimethylzinc, and benzaldehyde as reagents, and diethyl ether as solvent. After the generation of methyl(phenylethynyl)zinc at 50 °C, the asymmetric addition was carried out at 0 °C, using a 10 mol % of ligand. The results are summarized in Table 1.

It can bee seen that amino thiols were superior ligands for this reaction, leading in all cases except for **1bb** to higher yields. Enantioselectivities were also much higher when thiol ligands were employed (compare entries 1–5, 2–6, and 4–7, Table 1). Thus, it can be seen that structurally identical ligands show higher activities and enhanced stereoselectivities when a thiol moiety is present instead of a hydroxyl group. Regarding the optimal structure of the ligand, it is also clear from Table 1 that both a piperidino ring and a bulky trityl group are key to achieving high ee's in the reaction. Yields seem to be less dependent on the ligand structure, but more dependent on the electronic nature of the ligand. Thus, amino thiols generate the propargyl alcohol with ca. 90% conversion whereas this type of amino alcohol furnishes the product in 60–70% conversion.

Next, the reaction conditions were studied using the optimal ligand **1aa** in the same reaction (Table 2). The effects of solvent, concentration, and temperature on the reaction outcome were analyzed.

Table 1
Screening of ligands **1–2**



Entry	Ligand	Conv.[a] (%)	ee[b] (%)
1	**1aa**	93	87
2	**1ab**	90	71
3	**1ba**	92	73
4	**1bb**	36	67
5	**2aa**	71	31
6	**2ab**	66	29
7	**2bb**	61	10

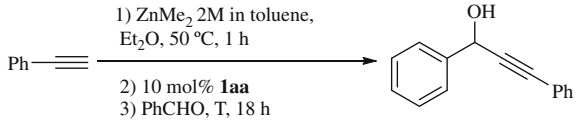
[a] Determined by ^{1}H NMR on the crude product.
[b] Determined by HPLC in a Chiralcel OD column.

Changes in the concentration did not improve the results. Performing the reaction under more concentrated conditions furnished the propargyl alcohol in quantitative yield, but at the expense of enantioselectivity (entry 2). On the other hand, dilution only made the reaction slower, and the product was isolated with identical ee (entry 3). Reactions performed in toluene or dichloromethane increased the conversion too, but again with diminished ee's, especially in the case of CH_2Cl_2 (entries 4 and 5). The enantioselectivity did not noticeably change at different temperatures, but reactions were much slower below 0 °C (entries 1 and 6 vs entries 7 and 8). In conclusion, diethyl ether turns out to be the solvent of choice, whereas a temperature between 0 and 25 °C is required in order to achieve reasonable reaction rates.

Finally the scope of this catalytic system was checked under the conditions selected above (Table 3).

The optimal catalyst **1aa** furnishes the propargyl alcohols in high yields and ee's for benzaldehyde and naphthaldehyde, and arylacetylenes with electron-withdrawing groups (entries 1–6 and 12). Other aromatic aldehydes also react gently under these conditions albeit with somewhat lower enantioselectivity (entries 7, 13, 14, and 15). On the other hand, *p*-anisaldehyde reaches 90% ee although with a poorer yield of only 29% (entry 11). A particular case is 2,6-dimethoxybenzaldehyde (entry 16) where the low yield and ee can be attributed to the steric hindrance around the carbonyl group. These results suggest important electronic effects on both the conversion and stereoselectivity of the reaction. The addition of alkynes

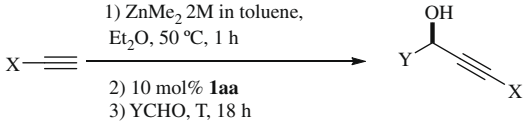
Table 2
Optimization of the alkynyl addition with ligand **1aa**



Entry	Solvent	*T* (°C)	Conv.[a] (%)	ee[b] (%)
1	Et_2O	0	93	87
2[c]	Et_2O	0	100	79
3[d]	Et_2O	0	82	87
4	Toluene	0	100	81
5	CH_2Cl_2	0	98	51
6	Et_2O	25	91	89
7	Et_2O	−10	78	86
8	Et_2O	−20	54	86

[a] Determined by ^{1}H NMR on the crude product.
[b] Determined by HPLC in a Chiralcel OD column.
[c] Concentration was 10 times higher than in entry 1.
[d] Diluted twice with respect to entry 1.

Table 3
Substrate scope in the alkynyl addition with ligand **1aa**



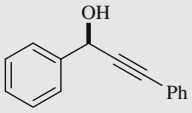
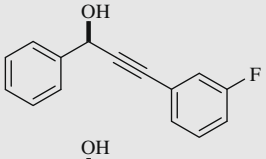
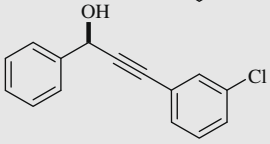
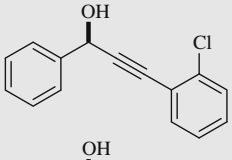
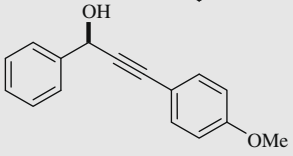
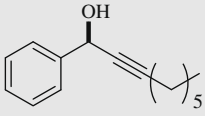
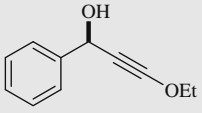
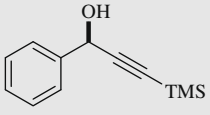
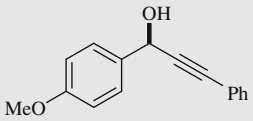
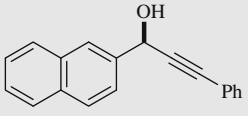
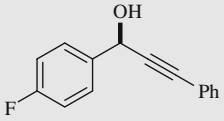
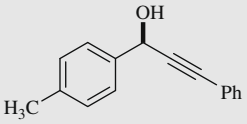
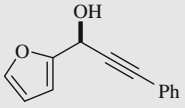
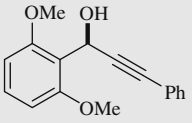
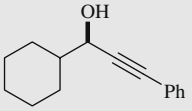
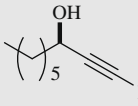
Entry	Product[a]	Conv.[b] (%)	ee[c] (%)
1		93	87
2		95	83
3		100	84
4		98	86
5		85	66
6		64	54
7		93	27
8		52	26
9		29	90
10		64	85
11		75	77

Table 3 (*continued*)

Entry	Product[a]	Conv.[b] (%)	ee[c] (%)
12		72	71
13		70	67
14		30	9
15		93	43
16		100	46

[a] Absolute configuration determined by comparison of the specific rotation or chiral HPLC traces with the literature.
[b] Conversion determined by ^{1}H NMR of the crude product. In some cases, pure product was isolated by flash chromatography and yield matched with conversion.
[c] Ee determined by chiral HPLC analysis.

other than arylacetylenes resulted in moderate ee's (entries 8–10). Finally, the use of aliphatic aldehydes such as cyclohexanecarbaldehyde and hexanal (entries 17 and 18) furnished the corresponding propargyl alcohols in high yield but moderate enantioselectivity. The reaction was found to yield the (*R*)-enantiomer for some propargyl alcohols, by comparison of their specific rotation or chiral HPLC retention times with previously reported data.[12,13] The same configuration is assumed for the remainder of the products.

A simple model can be built to explain these results (Fig. 1). The aminothiolate–methylzinc complex can coordinate both the alkynylzinc and the aldehyde, in a similar fashion as the well-known amino alcohols for the asymmetric addition of diethylzinc to aldehydes. The aldehyde must then adopt the positioning depicted in Figure 1 (with the phenyl group *anti* to the aminothiolate–zinc complex) to minimize steric repulsion. In this manner, alkynyl transfer can take place to afford carbonyls with the observed sense of enantiocontrol.

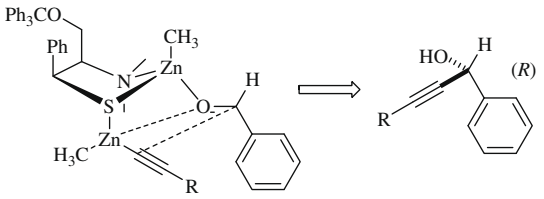


Figure 1. Stereoselectivity model.

3. Conclusions

In conclusion, we have shown how amino thiols behave as improved ligands with respect to structurally identical amino alcohols in the asymmetric alkynylation of aldehydes using

organozinc reagents. Much better yields and stereoselectivities can be reached by simply changing the hydroxyl group by a thiol, although the ee is very dependent on the ligand structure too. Amino thiols are particularly promising for the addition of arylacetylenes to aromatic aldehydes with good yields and ee's.

4. Experimental

4.1. General procedures

Reactions were performed in flame-dried flasks sealed under an argon atmosphere. Liquids were transferred into septum-capped flasks via syringe or cannula. Anhydrous solvents were obtained from a solvent purification system and were used as collected. Chemicals were purchased from Aldrich or Acros. Aldehydes were distilled prior to use, and all other reagents were used as received. MS spectra were recorded with a Waters LCT Premier HPLC-TOF spectrometer that may be operated in ESI or APCI modes, or with a Waters GCT GC-TOF spectrometer with CI or EI options. Optical rotations were measured with a JASCO P-1030 polarimeter at 589 nm using 100 × 3.5 mm or 10 × 10 mm cells. NMR spectra were recorded with a Bruker Avance 400 Ultrashield spectrometer, which records ^{1}H NMR spectra at 400 MHz with TMS as the internal standard, and ^{13}C NMR spectra at 100 MHz with $CDCl_3$ as the reference. Coupling constants J are in hertz and chemical shifts δ in parts per million. IR spectra were measured with a Bruker Tensor 27 FTIR with an ATR cell. HPLC analyses were performed in an Agilent 110 Series apparatus equipped with UV–vis detector and autosampler. Chiral analyses were carried out using a Chiralcel OD-H column, with hexane/isopropanol mixtures as eluent.

4.1.1. Synthesis of (*S*)-(1*S*,2*R*)-1-phenyl-2-(piperidin-1-yl)-3-(trityloxy)propyl ethanethioate Ac-1aa

(1*R*,2*R*)-1-Phenyl-1-(piperidin-1-yl)-3-(trityloxy)propan-2-ol (1.3 g, 2.72 mmol) was weighed in a flame-dried round-bottomed flask under argon, and dissolved in anhydrous dichloromethane (20 mL. The solution was cooled to 0 °C. Then triethylamine (1.26 mL 8.99 mmol) and methanesulfonyl chloride (0.34 mL 4.36 mmol) were added. After 2 h at 0 °C, a 10% aqueous thioacetate solution was added (1.21 g AcSK, 10.59 mmol). The mixture was left reacting overnight, while reaching room temperature slowly. Then it was quenched with water and extracted with dichloromethane (×3). The organic layers were washed with a 1% aqueous hydrochloric acid solution (50 mL and a bicarbonate solution (50 mL, dried with anhydrous sodium sulfate, and evaporated under vacuum. The product was isolated in pure form and used without further purification. Quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (s, 6H), 2.18 (s, 3H), 2.25–2.34 (m, 2H), 2.38–2.47 (m, 2H), 3.09–3.17 (m, 1H), 3.18–3.24 (m, 1H), 3.35 (dd, J^1 = 6.6 Hz, J^2 = 9.7 Hz, 1H), 4.8 (d, J = 7.5 Hz, 1H), 7.14–7.32 (m, 15H), 7.46–7.50 (m, 5H) ppm. DEPTQ NMR (100 MHz, $CDCl_3$): δ 24.7 (CH_2), 26.6 (CH_2), 30.4 (CH_3), 48.8 (CH), 51.4 (CH_2), 61.1 (CH_2), 68.5 (CH), 126.9 (CH), 127.7 (CH), 128.5 (CH), 128.9 (CH), 144.0 (C) ppm; IR 3058, 3026, 2925, 1687, 1490, 1445, 1055, 769, 740, 704 cm^{-1}; $[\alpha]_D^{20} = +8.2$ (c 0.81, $CDCl_3$).

4.1.2. Synthesis of (1*S*,2*R*)-1-phenyl-2-(piperidin-yl)-3-(trityloxy)propane-1-thiol 1aa

In a flame-dried, round-bottomed flask, **Ac-1aa** was weighed (147 mg, 0.27 mmol) and dissolved in anhydrous diethyl ether (2.5 mL under argon. The solution was cooled to −78 °C and 1 M DIBALH in hexane (0.58 mL 0.58 mmol) was added dropwise. The reaction mixture was allowed to warm up to rt, and stirred for a further 5 h. Then it was cooled again at −78 °C, and methanol (2.5 mL was added dropwise. When the solution reached room temperature the solvent was evaporated under vacuum. The crude was purified by flash chromatography (SiO_2–2.5% Et_3N, and a gradient of hexane/AcOEt 0:100). Yield = 89%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 6H), 2.32 (m, 4H), 3.07 (dd, J^1 = 5.6 Hz, J^2 = 12.3 Hz, 1H), 3.31 (dd, J^1 = 5.4 Hz, J^2 = 9.8 Hz, 1H), 3.39 (dd, J^1 = 5.8 Hz, J^2 = 9.8 Hz, 1H), 4.22 (d, J = 6.8 Hz, 1H), 7.20–7.32 (m, 15H), 7.46–7.50 (m, 5H) ppm; DEPTQ NMR (100 MHz, $CDCl_3$): δ 24.6 (CH_2), 26.7 (CH_2), 44.3 (CH), 51.8 (CH_2), 61.1 (CH_2), 70.6 (CH), 126.6 (CH), 127.0 (CH), 127.7 (CH), 127.8 (CH), 128.1 (CH), 128.8 (CH), 129.3 (CH), 142.60 (C), 144.0 (C) ppm; IR 3057, 3024, 2931, 2848, 2799, 1596, 1489, 1444, 1061, 767, 743, 703 cm^{-1}; $[\alpha]_D^{20} = +52.7$ (c 2.1, $CDCl_3$); HRMS (ESI+ve) calcd for $C_{33}H_{35}NSO{\cdot}H+$ 494.2518, found 494.2531.

4.1.3. Synthesis of (*S*)-(1*S*,2*R*)-2-(dimethylamino)-1-phenyl-3-(trityloxy)propyl ethanethioate Ac-1ab

The procedure was analogous to that used for **Ac-1aa**. Yield = 88%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.15 (s, 3H), 2.17 (s, 6H), 3.14–3.20 (m, 1H), 3.30–3.31 (m, 2H), 4.82 (d, J = 7.7 Hz, 1H), 7.17–7.29 (m, 16H), 7.43–7.47 (m, 4H) ppm; DEPTQ NMR (100 MHz, $CDCl_3$): δ 30.5 (CH_3), 42.4 (CH_3), 48.8 (CH), 60.8 (CH_2), 67.7 (CH), 127.0 (CH), 127.0 (CH), 127.8 (CH), 128.2 (CH), 128.4 (CH), 128.6 (CH), 128.9 (CH), 140.9 (C), 143.9 (C), 194.3 (C) ppm; IR 3057, 3026, 2929, 2870, 2778, 2360, 1686, 1597, 1490, 1447, 1068, 762, 745, 696 cm^{-1}; $[\alpha]_D^{20} = +101.3$ (c 0.046, $CDCl_3$); HRMS (ESI+ve) calcd for $C_{32}H_{33}NO_2S{\cdot}Na+$ 518.2130, found 518.2106.

4.1.4. Synthesis of (1*S*,2*R*)-2-(dimethylamino)-1-phenyl-3-(trityloxy)propane-1-thiol 1ab

The procedure was analogous to the one described for **1aa**. Yield = 70%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.09 (s, 6H), 2.98–3.03 (m, 1H), 3.29 (dd, J^1 = 5.6 Hz, J^1 = 10.0 Hz, 1H), 3.39 (dd, J^1 = 4.2 Hz, J^1 = 10.0 Hz, 1H), 4.18 (d, J = 7.4 Hz, 1H), 7.13–7.22 (m, 16H), 7.35–7.38 (m, 4H) ppm; DEPTQ NMR (100 MHz, $CDCl_3$): δ 42.7(CH_3), 44.5 (CH), 60.7 (CH_2), 69.6 (CH), 126.9 (CH), 126.9 (CH), 127.1 (CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 128.2 (CH), 128.9 (CH), 129.4 (CH), 142.7 (C), 143.9 (C), 147.2 (C) ppm; IR 3056, 3024, 2928, 2869, 2826, 2777, 1736, 1596, 1490, 1447, 1238, 1064, 985, 760, 745, 695 cm^{-1}; $[\alpha]_D^{20} = +35.8$ (c 0.45, $CDCl_3$); HRMS (ESI+ve) calcd for $C_{30}H_{31}NOS{\cdot}H+$ 454.2205, found 454.2223.

4.1.5. Synthesis of (*S*)-(1*S*,2*R*)-3-methoxy-1-phenyl-2-(piperidin-1-yl)propyl ethanethioate Ac-1ba

The procedure was analogous to the one described for **Ac-1aa**. Quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (s, 6H), 2.28 (s, 3H), 2.37–2.46 (m, 2H), 2.50–2.58 (m, 2H), 3.08 (m, 1H), 3.33 (s, 3H), 3.51 (dd, J^1 = 5.2 Hz, J^2 = 10.0 Hz, 1H), 3.55 (dd, J = 6.7 Hz, J = 10.0 Hz, 1H), 4.80 (m, J = 7.3 Hz, 5H), 7.18–7.33 (m, 5H) ppm; DEPTQ NMR (100 MHz, $CDCl_3$): δ 24.6 (CH_2), 26.6 (CH_2), 30.5 (CH_3), 48.6 (CH), 51.4 (CH_2), 58.7 (CH_3), 67.8 (CH), 70.7 (CH_2), 126.8 (CH), 127.9 (CH), 128.5 (CH), 141.4 (C), 194.8 (C) ppm; IR 3348, 2927, 2850, 2805, 1687, 1451, 1104, 960, 699 cm^{-1}; $[\alpha]_D^{20} = +86.8$ (c 0.050, $CDCl_3$); HRMS (ESI+ve) calcd for $C_{17}H_{25}NO_2S{\cdot}H+$ 308.1684, found 308.1682.

4.1.6. Synthesis of (1*S*,2*R*)-3-methoxy-1-phenyl-2-(piperidin-1-yl)propane-1-thiol 1ba

The procedure was analogous to the one described for **1aa**. Quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (s, 6H), 2.29 (m, 2H), 2.42 (m, 2H), 2.90 (m, ^{1}H), 3.25 (s, 3H), 3.47 (dd, J^1 = 4.6 Hz, J^2 = 9.9 Hz, 1H), 3.58 (dd, J^1 = 5.9 Hz, J^2 = 10.0 Hz, 1H), 4.11 (d, J = 7.5 Hz, 1H), 7.07–7.12 (m, 1H), 7.15–7.19 (m, 2H), 7.21–7.25 (m, 2H) ppm; DEPTQ NMR (100 MHz, $CDCl_3$): δ 24.7 (CH_2), 26.5 (CH_2), 51.3 (CH_2), 56.0 (CH), 58.7 (CH_3), 66.5 (CH), 71.0 (CH2), 126.6 (CH), 127.5 (CH), 129.3 (CH), 140.8 (C) ppm; IR 3059, 3026, 2927, 2803, 1702. 1597, 1452, 1309, 1271, 1202, 1166, 745, 698 cm^{-1}; $[\alpha]_D^{20} = +179.7$ (c 0.27, $CDCl_3$);

HRMS (ESI+ve) calcd for $C_{15}H_{23}NOS{\cdot}H+$ 266.1579, found 266.1569.

4.1.7. Synthesis of (*S*)-(1*S*,2*R*)-2-(dimethylamino)-3-methoxy-1-phenylpropyl ethanethioate Ac-1bb

The procedure was analogous to the one described for **Ac-1aa**. Yield = 98%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29 (s, 3H), 2.30 (s, 6H), 3.04 (dd, J^1 = 5.8 Hz, J^2 = 11.2 Hz, 1H), 3.32 (s, 3H), 3.50 (m, 2H), 4.90 (d, J = 6.8 Hz, 1H), 7.20–7.36 (m, 5H) ppm; DEPTQ NMR (100 MHz, CDCl3): δ 30.5 (CH_3), 42.2 (CH_3), 47.7 (CH), 58.8 (CH_3), 67.3 (CH), 70.0 (CH_2), 127.1 (CH), 128.3 (CH), 128.3 (CH) ppm; IR 3060, 3027, 2922, 2871, 2827, 2780, 1686, 1451, 1353, 1278, 1187, 1115, 953, 767, 728, 697 cm^{-1}; $[\alpha]_D^{20} = +226.3$ (*c* 0.053, $CDCl_3$); HRMS (ESI+ve) calcd for $C_{14}H_{21}NO_2S.Na+$ 290.1191, found 290.1178.

4.1.8. Synthesis of (1*S*,2*R*)-2-(dimethylamino)-3-methoxy-1-phenylpropane-1-thiol 1bb

The procedure was analogous to the one described for **1aa**. Yield = 50%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16 (s, 6H), 2.93–2.97 (m, 1H), 3.24 (s, 3H), 3.56 (dd, J^1 = 3.6 Hz, J^2 = 10.2 Hz, 1H), 3.60 (dd, J^1 = 5.8 Hz, J^2 = 10.2 Hz, 1H), 4.19 (d, J = 7.9 Hz, 1H), 7.14–7.29 (m, 5H) ppm. DEPTQ NMR (100 MHz, $CDCl_3$): δ 41.8 (CH_3), 55.2 (CH), 58.7 (CH_3), 65.6(CH), 70.2(CH_2), 127.0 (CH), 128.0 (CH), 129.2 (CH), 140.7 (C) ppm; IR 2922, 1453, 1377, 1279, 1120, 697 cm^{-1}; $[\alpha]_D^{20} = +97.7$ (*c* 3.4, $CDCl_3$); HRMS (ESI+ve) calcd for $C_{12}H_{19}NSO.H+$ 226.1266, found 226.1270.

4.1.9. Synthesis of (1*S*,2*R*)-1-phenyl-2-(piperidin-1-yl)-3-(trityloxy)propyl 4-nitrobenzoate PNB-2aa

In a flame-dried flask, (1*R*,2*R*)-1-phenyl-1-(piperidin-1-yl)-3-(trityloxy)propan-2-ol (1.3 g, 2.72 mmol) was dissolved in anhydrous dichloromethane (30 mL under argon. At 0 °C triethylamine (1.26 mL 8.99 mmol) and methanesulfonyl chloride (0.34 mL 4.36 mmol) were added and the mixture was stirred at that temperature. After 2 h, *p*-nitrobenzoic acid (4.0 g, 15.25 mmol) and NaOH (0.61 g, 15.25 mmol) dissolved in water (90 mL were added. After 20 min, the ice bath was removed and the mixture was allowed to react overnight at room temperature. The reaction mixture was quenched with water and extracted with dichloromethane (50 mL× 3). The combined organic layers were washed with hydrochloric acid (0.04 % v/v in water) and saturated aqueous solution of $NaHCO_3$, and dried over anhydrous sodium sulfate. The solvent was removed under vacuum. The crude product was purified by flash chromatography on triethylamine pretreated silica gel (2.5% v/v), with hexane and ethyl acetate mixtures as eluent. 61% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ1.38–1.50 (m, 6H), 2.56–2.64 (m, 2H), 2.69–2.76 (m, 2H), 3.43 (m, 1H), 3.56 (dd, J^1 = 3.9 Hz, J^2 = 9.8 Hz, 1H), 3.63 (dd, J^1 = 6.5 Hz, J^2 = 9.8 Hz, 1H), 6.26 (d, J = 7.0 Hz, 1H), 7.25–7.46 (m, 14H), 7.53–7.57 (m, 6H), 8.08–8.11 (m, 2H), 8.25–8.28 (m, 2H) ppm; IR 3027, 2971, 2933, 2801, 1721, 1603, 1527, 1490, 1445, 1316, 1271, 1109, 905, 698 cm^{-1}; HRMS (ESI+ve) calcd for $C_{40}H_{38}N_2O_5.H+$ 627.2859, found 627.2885.

4.1.10. Synthesis of (1*S*,2*R*)-1-phenyl-2-(piperidin-1-yl)-3-(trityloxy)propan-1-ol 2aa

In a flame-dried round-bottomed flask flushed with nitrogen, sodium methoxide (0.75 g, 13.19 mmol) was dissolved in 150 mL of methanol and transferred *via cannula* to another flask containing **PNB-2aa** (1.38 g, 2.20 mmol) in 15 mL of dichloromethane, at rt. After 30 minutes, the reaction mixture was treated with brine and the product was extracted with dichloromethane (x3). The combined organic layers were dried with anhydrous sodium sulfate and concentrated under vacuum, affording an orange oil. The crude product was purified by flash chromatography on triethylamine pre-treated silica gel (2.5% v/v), eluting with hexane:AcOEt mixtures of increasing polarity. Quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (m, 3H), 1.43 (m, 3H), 2.34 (m, 4H), 3.02 (dd, J^1 = 6.1 Hz, J^2 = 11.7 Hz, 1H), 3.16 (dd, J^1 = 6.7 Hz, J^2 = 9.8 Hz, 1H), 3.26 (dd, J^1 = 6.2 Hz, J^2 = 9.8 Hz, 1H), 4.88 (d, J = 5.3 Hz, 1H), 7.23–7.44 (m, 15H) ppm; DEPTQ NMR (100 MHz, $CDCl_3$): δ 24.4 (CH_2), 26.7 (CH_2), 52.5 (CH_2), 69.0 (CH), 71.1 (CH), 126.0 (CH), 127.1 (CH), 127.8 (CH), 128.6 (CH), 143.8 (C) ppm; IR 3375, 3057, 3026, 2929, 1597, 1490, 1447, 1060, 1031, 745, 697 cm^{-1}; $[\alpha]_D^{20} = +3.1$ (*c* 0.84, $CDCl_3$); HRMS (ESI+ve) calcd for $C_{33}H_{35}NO_2.H+$ 478.2757, found 478.2746.

4.1.11. Synthesis of (1*S*,2*R*)-2-(dimethylamino)-1-phenyl-3-(trityloxy)propyl 4-nitrobenzoate PNB-2ab

The procedure was analogous to the one described for **PNB-2aa**. Yield = 55%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30 (s, 3H), 3.37 (m, 1H), 3.42–3.48 (m, 1H), 3.49–3.55 (m, 1H), 6.17 (d, J = 6.6 Hz, 1H), 7.16–7.33 (m, 15H), 7.34–7.40 (m, 5H), 7.97 (m, 2H), 8.16 (m, 2H) ppm; DEPTQ NMR (100 MHz, $CDCl_3$): δ 42.3 (CH_3), 60.1 (CH_2), 68.0 (CH), 76.1 (CH), 123.5 (CH), 126.8 (CH), 127.1 (CH), 127.8 (CH), 128.1 (CH), 128.5 (CH), 128.7 (CH), 128.8 (CH), 130.8 (CH), 135.5 (C), 139.1 (C), 143.9 (C), 150.5 (C), 163.5 (C) ppm; IR 3057, 3031, 2934, 2830, 2782, 2324, 1724, 1604, 1525, 1490, 1269, 1100, 762, 697 cm^{-1}; $[\alpha]_D^{20} = +1.51$ (c = 0.057, $CHCl_3$); HRMS (ESI+ve) calcd for $C_{37}H_{34}N_2O_5.Na+$ 609.2352, found 609.2365.

4.1.12. Synthesis of (1*S*,2*R*)-2-(dimethylamino)-1-phenyl-3-(trityloxy)propan-1-ol 2ab

The procedure was analogous to the one described for **2aa**. Yield = 98%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.24 (s, 6H), 2.97 (dd, J^1 = 5.4 Hz, J^2 = 10.7 Hz, 1H), 3.20 (dd, J^1 = 5.9 Hz, J^2 = 10.2 Hz, 1H), 3.29 (dd, J^1 = 5.3 Hz, J^2 = 10.3 Hz, 1H), 4.95 (d, J = 4.7 Hz,1H), 7.20–7.28 (m, 14H), 7.36–7.39 (m, 6H) ppm; DEPTQ NMR (100 MHz, CDCl3): δ 43.4(CH_3), 60.4 (CH_2), 68.9 (CH), 72.0 (CH), 126.1 (CH), 127.1 (CH), 127.8 (CH), 128.6 (CH), 143.6 (C) ppm; IR 3057, 3024, 2932, 2873, 2827, 2781, 2361, 1596, 1489, 1447, 1057, 1031, 745, 696 cm^{-1}; $[\alpha]_D^{20} = +35.8$ (*c* 0.45, $CHCl_3$); HRMS (ESI+ve) calcd for $C_{30}H_{31}NO_2.H+$ 438.2453, found 438.2433.

4.1.13. Synthesis of (1*S*,2*R*)-2-(dimethylamino)-3-methoxy-1-phenylpropyl 4-nitrobenzoate PNB-2bb

The procedure was analogous to the one described for **PNB-2aa**. Yield = 69%. ^{1}H NMR (400Mhz, $CDCl_3$): δ 2.40 (s, 3H), 3.22–3.26 (m, 1H), 3.30 (s, 3H), 3.66 (dd, J^1 = 3.6 Hz, J^2 = 10.2 Hz 1H), 3.77 (dd, J^1 = 7.3 Hz, J^2 = 10.2 Hz, 1H), 6.29 (d, J = 5.5 Hz, 1H), 7.26–7.31 (m, 1H), 7.33–7.40 (m, 4H), 8.24–8.26 (m, 2H), 8.30–8.32 (m, 2H) ppm; DEPTQ NMR (100 MHz, $CDCl_3$): δ 41.8 (CH_3), 59.0 (CH_3), 67.7 (CH), 68.7 (CH_2), 74.8 (CH), 123.7 (CH), 126.4 (CH), 128.0 (CH), 128.5 (CH), 130.8 (CH), 135.6 (C), 139.0 (C), 150.7 (C), 163.5 (C) ppm; IR 3032, 2871, 2829, 2783, 1723, 1606, 1525, 1454, 1344, 1268, 1100, 1014, 974, 872, 719, 699 cm^{-1}; $[\alpha]_D^{20} = -53.8$ (*c* 0.05, $CHCl_3$); HRMS (ESI+ve) calcd for $C_{19}H_{22}N_2O_5.Na+$ 381.1426, found 381.1429.

4.1.14. Synthesis of (1*S*,2*R*)-2-(dimethylamino)-3-methoxy-1-phenylpropan-1-ol 2bb

The procedure was analogous to the one described for **2aa**. Yield = 82%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 6H), 2.68 (dd, J^1 = 4.6 Hz, J^2 = 9.7 Hz, 1H), 3.28 (s, 3H), 3.40 (dd, J^1 = 5.3 Hz, J^2 = 10.1 Hz, 1H), 3.47 (dd, J^1 = 4.2 Hz, J^2 = 10.2 Hz, 1H), 5.01 (d, J = 4.5 Hz, 1H), 7.25–7.26 (m, 1H), 7.34–7.36 (m, 4H) ppm; DEPTQ NMR (100 MHz, $CDCl_3$): δ 43.2 (CH_3), 58.9 (CH_3), 68.5 (CH), 69.8 (CH_2), 72.5 (CH), 125.9 (CH), 127.0 (CH), 128.1 (CH) ppm; IR 3058, 2983, 2919, 2892, 2870, 2834, 2808, 2780, 1446, 1317, 1259, 1242, 1203, 1109, 1079, 1058, 951, 777, 684 cm^{-1};

$[\alpha]_D^{20} = +16.7$ (c 0.55, $CDCl_3$); HRMS (ESI+ve) calcd for $C_{12}H_{19}NO_2$.H+ 210.1503, found 210.1494.

4.1.15. Typical procedure for the asymmetric alkynylation of aldehydes: synthesis of (*R*)-1,3-diphenylprop-2-yn-1-ol

Dimethylzinc (4 mmol, 2 mL of 2 M solution in toluene) was added to a freshly distilled phenylacetylene (4 mmol, 0.44 mL solution in diethyl ether (12 mL, and the reaction mixture was stirred at 50 °C for 1 h. Then, the resulting solution was cooled to 0 °C, and the ligand (0.049 mmol) was added and stirred at 0 °C for 1 h. Finally, freshly distilled benzaldehyde (1 mmol) was added and the solution reacted for 4 h at 0 °C. The reaction mixture was then cautiously quenched with aq satd NH_4Cl (5 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. The residue obtained after evaporation of the solvent was purified by flash chromatography. ^1H NMR (400 MHz, $CDCl_3$): δ 2.31 (s, 1H), 5.61 (s, 1H), 7.21–7.32 (m, 6H), 7.4 (m, 2H), 7.50 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 65.1 (CH), 86.6 (C), 88.7 (C), 122.4 (CH), 126.7 (CH), 128.3 (CH), 128.4 (CH), 128.6 (CH), 128.6 (CH), 140.9 (C) ppm; IR 3350, 3059, 3028, 2928, 2197, 1697, 1597, 1313, 1033, 960, 912, 821, 756, 692 cm^{-1}; HPLC: Daicel CHIRALCEL-OD. Hexane/*i*-PrOH 90:10, 1.0 mL/min, λ = 254 nm, $t_R(R)$ = 12.0 min (major), $t_R(S)$ = 17.9 min; HRMS (ESI+ve) calcd for $C_{15}H_{12}O{\cdot}Na+$, 231.08, found 231.0868.

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