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Dimethylzinc-Mediated, Enantioselective Synthesis of Propargylic Amines

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Abstract: A one-pot, enantioselective synthesis of *N*-aryl propargylic amines, using alkynylation reagents obtained from dimethylzinc and terminal acetylenes in combination with various aldehydes and *o*-methoxyaniline as starting materials, has been developed. Enantiopure β-amino alcohols derived from norephedrine were used as non-covalent chiral auxiliaries, both in stoichiometric or substoichiometric amount. After optimization, propargylic amines were obtained in good to high yields (up to 93%) and with moderate to high enantiomeric excesses (up to 97% *ee*). The possibility to recover the chiral auxiliary after the reaction was demonstrated.

Keywords: alkynes · amino alcohols · C–C bond formation · enantioselective synthesis · organozinc chemistry

Introduction

Methods for the efficient formation of carbon–carbon bonds are of great importance in organic chemistry, given the possibility that they offer to drastically increase molecular complexity in only one synthetic operation. To effect such transformations in an enantioselective manner, that is, controlling the absolute configuration of the products, is one of the main goals of contemporary organic synthesis.[1]

In recent years, the direct addition of acetylenes to carbon–heteroatom (usually oxygen or nitrogen) double bonds has attracted much attention as a convenient method for the generation of propargylic alcohols and amines, respectively. Such compounds have been often used as intermediates for the synthesis of complex natural molecules,[2,3] as well as other biologically active substances.[4]

Whereas the direct alkynylation of carbonyl compounds, both in a non-stereoselective and in an enantioselective manner, has been the subject of a large number of publications,[5,6] methods for the synthesis of propargylic amines by the direct addition of acetylenes are still rare.[5c–d,7]

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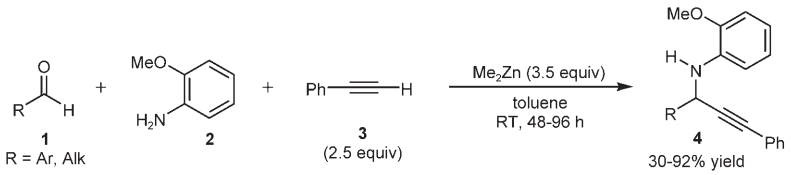
Most of the so far developed protocols for the enantioselective generation of propargyl amines involve the use of a chiral catalyst formed in situ by the combination of a copper(I) salt with a suitable chiral ligand. Knochel reported high levels of asymmetric induction using quinap as the ligand in the addition of alkynes to enamines,[8] subsequently developed in a three-component synthesis of propargylamines.[9,10] On the other hand, excellent results have been obtained in a similar reaction employing various Cu^{I}/pybox catalyst systems.[11,12] Furthermore, the use of chiral binaphthylamines and -imines as ligands has also been described.[13]

Alternative approaches to the enantioselective alkynylation of imines have been developed by Hoveyda and coworkers, who employed an amino acid derivative as a ligand in combination with $Zr(OiPr)_4 \cdot HOiPr$ as the chiral catalyst in the presence of a pre-formed alkynylzinc reagent,[14] and by Wu and Chong, who made use of binaphthol-modified alkynylboronates as chiral stoichiometric reagents for the addition to *N*-acetylimines.[15]

To date, only two reports concerning zinc-mediated enantioselective alkynylations of C=N electrophiles have appeared in the literature. In 2004, Jiang and Si described the application of an amino alcohol as a stoichiometric ligand for the $Zn(OTf)_2$-mediated addition of alkynes to an α-trifluoromethyl cyclic imine, which afforded products with extremely high enantiomeric excesses.[16] Two years later, another zinc-mediated enantioselective alkynylation was described by Inomata and co-workers, who employed alkynylzinc reagents, prepared in situ from terminal alkynes and dialkylzinc species, in combination with a small excess of di(*tert*-butyl)zinc tartrate for the addition to nitrones. Addi-

tion of product-like *N*-hydroxylamine to the reaction mixture provoked an increase in the enantiomeric excess of the products, and propargyl *N*-hydroxylamines with up to 95% *ee* could be prepared.[17,18] Recently, our research group reported that dimethylzinc is able to induce the addition of terminal acetylenes to carbonyl compounds in the *absence* of any ligand or activator,[19] leading to the formation of (racemic) propargylic alcohols.[20] The same methodology was subsequently extended to the conversion of *N*-activated imines and ultimately, a Me_2Zn-promoted one-pot synthesis of propargylic amines was developed, which made use of various aldehydes **1** and *o*-methoxyaniline as starting materials (Scheme 1).[21] Phenylacetylene (**3**) was the only alkyne used in that study leading to propargylic amines **4**.



Scheme 1. One-pot synthesis of propargylic amines using various aldehydes **1**, *o*-methoxyaniline (**2**), phenylacetylene (**3**) and dimethylzinc as starting materials.

In both the reactions involving carbonyl compounds and imines it was hypothesized that the substrate could act in a "ligand-like" fashion, coordinating dimethylzinc and thereby activating it for the acid/base reaction with the acetylene. On the other hand, dimethylzinc was also acting as a Lewis acid toward the imine substrate, enhancing its reactivity to the nucleophilic, in situ-formed mixed alkynylzinc reagent.

Given the absence of any chiral reagent in the reaction depicted in Scheme 1, the products were obtained in racemic form. It was anticipated that a chiral compound could act as a ligand for zinc and that this could possibly lead to the development of an enantioselective version of this transformation,[22] in analogy to the corresponding alkynylation of carbonyl compounds[5,6] and the asymmetric aza-Reformatsky reaction.[23] Chiral β-amino alcohols and related compounds were identified as the ligands of choice, due to their extensive application in the addition of organometallic reagents to carbon–heteroatom double bonds.[24]

Herein, we first report the extension of the dimethylzinc-mediated, one-pot synthesis of propargylic amines to the use of terminal alkynes other than phenylacetylene (**3**) and subsequently the development of an enantioselective version of this reaction, based on the use of enantiopure norephedrine-derived β-amino alcohols as ligands, employed both in equimolar or substoichiometric amount. To the best of our knowledge, although the corresponding processes involving aldehydes or ketones as substrates are well-known transformations, this is the first report concerning an enantioselective addition of alkynes to in situ-generated imines promoted by a dialkylzinc compound.

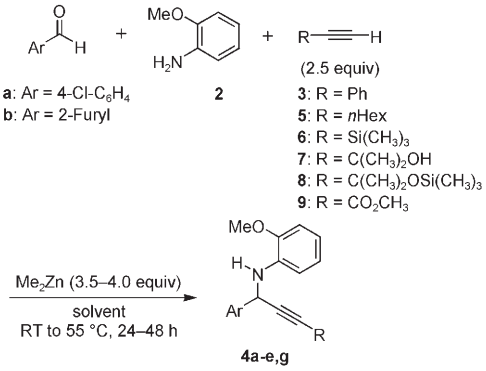
Results and Discussion

As mentioned above, the only alkyne used in the previously reported dimethylzinc-mediated one-pot synthesis of propargylic amines was phenylacetylene (**3**).[21] In order to increase the synthetic utility of the methodology, extension of this transformation to the use of other terminal alkynes was required. Therefore, the reaction of *p*-chlorobenzaldehyde (**1a**) and *o*-methoxyaniline (**2**) with some differently substituted acetylenes was examined. The results of these investigations are reported in Table 1.

Typically, the reaction between alkyne **3**, aromatic aldehydes and *o*-methoxyaniline was conducted in toluene at room temperature in the presence of an excess of dimethylzinc (Scheme 1 and Table 1, entry 1). Under these conditions, 1-octyne (**5**) could also be converted furnishing the corresponding propargylamine **4b** in moderate yield (entry 2). When trimethylsilylethine (**6**) was employed, no product was formed under standard conditions (entry 3).

As previously demonstrated,[21] the efficiency of the reaction with phenylacetylene could be improved by working under "concentrated conditions",[25] that is, employing as the only solvent the toluene

Table 1. One-pot synthesis of propargylic amines using aldehydes **1**, *o*-methoxyaniline (**2**) and various alkynes in combination with Me_2Zn.



Entry	R	Aldehyde	Product	*T* [°C]	Solvent	Yield (%)[a]
1[b]	Ph	**1a**	**4a**	25	toluene	76
2	*n*-Hex	**1a**	**4b**	25	toluene	42
3	$Si(CH_3)_3$	**1a**	**4c**	25	toluene	0
4	$Si(CH_3)_3$	**1a**	**4c**	55	–[c]	57
5	$C(CH_3)_2OH$	**1a**	**4d**	55	toluene	82
6	$C(CH_3)_2OSi(CH_3)_3$	**1a**	**4e**	55	toluene	55
7	CO_2CH_3	**1a**	**4f**	55	–[c]	0
8	Ph	**1b**	**4g**	25	CH_2Cl_2	50

[a] After flash column chromatography (see Experimental Section for details). [b] Taken from ref. [21] in order to allow comparison with the other data. [c] No additional solvent was used (see Results and Discussion for details).

already present in the commercial 2.0 M Me_2Zn solution used throughout the study. Application of these conditions to the addition of **6** was also fruitful here, and performing the reaction at 55 °C led to formation of the expected product in 57 % yield (entry 4).

Conversion of alkynes **7** and **8** could be conducted at 55 °C in the presence of toluene, furnishing propargylic amines **4d–e** in moderate to good yields (entries 5–6). Use of alkynes **7** and **8** is particularly interesting in view of the possibility to easily convert the products into terminal alkynes by employment of a basic reagent such as K_2CO_3,[26] if necessary after a desilylation step.

Unfortunately, electron-poor alkyne methyl propiolate (**9**) was not applicable to the reaction. Under concentrated conditions its employment did not lead to formation of the expected propargylamine, and the intermediate imine was the only product observed after the reaction (entry 7).

In addition to the experiments described above, the possibility to employ 2-furfuraldehyde (**1b**) as a substrate for the reaction with phenylacetylene (**3**) was examined. The one-pot synthesis of the corresponding propargylamine **4g** was conducted in dichloromethane at room temperature, and the product was obtained in moderate yield (entry 8). It should be mentioned here that the possibility of oxidatively convert the furan ring to carboxylic acid[27] could open an interesting new route to the synthesis of alkynyl α-amino acids.

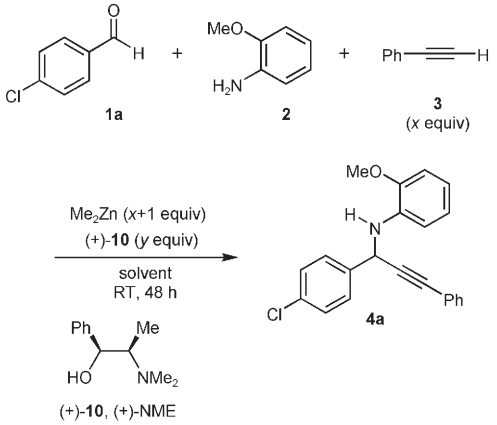
Having established that simple variations in the reaction conditions allowed the conversion of alkynes other than phenylacetylene (**3**) into the corresponding amines **4**, our attention was next turned to the development of a dimethylzinc-mediated enantioselective, one-pot synthesis of propargylic amines.

The addition of phenylacetylene (**3**) to the imine formed in situ from *p*-chlorobenzaldehyde (**1a**) and *o*-methoxyaniline (**2**) was chosen as the test reaction, and it was conducted under conditions identical to those of the reactions depicted in Scheme 1, the only modification being the employment of 1.0 equiv of (+)-*N*-methylephedrine [(+)-NME, (+)-**10**] as a chiral inductor. At the end of the reaction amine **4a** was obtained in 30 % yield and with 39 % *ee*.

With the aim to improve this result, a first series of experiments was conducted in which the solvent and the stoichiometry of the reaction were adjusted, always using amino alcohol (+)-**10** as the chiral auxiliary. The results are reported in Table 2.

Use of a substoichiometric quantity of amino alcohol **10** afforded amine **4a** in moderate yield and with much decreased *ee* (Table 2, entry 1 vs 2). To determine if the low yield in the experiment employing 1.0 equiv of (+)-**10** was related to problems in the formation of the intermediate imine from **1a** and **2**, these two compounds were first dissolved in toluene and stirred at 50 °C for 16 h in the presence of molecular sieves. The resulting solution was then filtered and the other components added. After 48 h stirring at room temperature, (+)-**4a** was isolated in 29 % yield and 41 % *ee* (entry 3). Since these values are almost identical to those obtained using the original protocol, an influence of the rate of the imine-formation step on the yield of the alkynylation reaction was excluded.

Table 2. Optimization of the one-pot asymmetric synthesis of propargylic amines with amino alcohol **10** as a chiral inducer.



Entry	Solvent	*x*	*y*	Yield (%)[a]	*ee* [%][b,c]
1	toluene	2.5	0.5	45	(+)17
2	toluene	2.5	1.0	30	(+)39
3[d]	toluene	2.5	1.0	29	(+)41
4	CH_2Cl_2	2.5	1.0	30	(+)53
5	CH_2Cl_2	3.0	1.0	56	(+)65
6	CH_2Cl_2	3.5	1.0	58	(+)63
7	CH_2Cl_2	4.0	1.0	50	(+)55

[a] After column chromatography. [b] Determined by HPLC using a chiral stationary phase (see Experimental Section for details). [c] The sign in parentheses corresponds to the sign of the optical rotation. [d] The imine formation step was conducted in the presence of MS 4 Å (see Results and Discussion for details).

A further increase in the amount of (+)-NME (to 1.5 equiv) was detrimental, since no product was formed under these conditions. The same outcome was observed by changing the solvent to *n*-hexane. In this case, the absence of reactivity is likely to be due to the limited solubility of *o*-methoxyaniline in this solvent, which probably prevented the imine formation to occur.[28]

On the other hand, the reaction conducted in dichloromethane furnished propargylic amine **4a** with the same yield as the reaction in toluene, but with a much improved enantiomeric excess (entry 4). This result was surprising, considering that toluene, or a mixture of toluene and *n*-hexane, is usually the solvent of choice for the addition of organozinc compounds to C=O or C=N electrophiles. As a consequence, all the reactions were subsequently performed in CH_2Cl_2.

The reactions conducted so far displayed generally low yields. With the aim to overcome this problem, the stoichiometry of the reaction was optimized. Therefore, various experiments were conducted in dichloromethane at room temperature, systematically varying the amount of dimethylzinc and phenylacetylene (**3**) (Table 2, entries 5–7).

Surprisingly, an increase in the quantity of alkyne **3** and Me_2Zn of only half an equivalent allowed improving the yield of the reaction, which was almost doubled. Furthermore, it had a positive effect also on the enantioselectivity,

product **4a** being now isolated with 65% *ee* (entry 5). While a further increase of 0.5 equiv did not change much of the reaction outcome, with the product having essentially the same *ee* as in the previous experiment (entry 6), use of 5.0 equiv of Me_2Zn provided a slightly inferior result both in terms of yield and enantioselectivity (entry 7).

With the promising result of Table 2, entry 5 in hand, the next step of the optimization was represented by the variation of the ligand structure.

In a first set of experiments, performed contemporarily to those presented in Table 2, compounds **11**–**19** having different structural features were employed as stoichiometric ligands for the test reaction, under the conditions of Table 2, entry 4. All molecules are either commercially available or accessible by known literature methods, and they already found application in other organozinc additions to carbon–heteroatom double bonds.

The structures of compounds **11**–**19** are shown in Figure 1 (top), while the enantiomeric excesses of the products of the reactions in which they were used as ligands are presented in a graph [Figure 1, bottom; where the result obtained with (+)-**10** is also shown for comparison].

As can be seen from Figure 1, almost all of the screened compounds provided the product with low enantiomeric excess. The only inducers, which were able to promote the formation of **4a** with more than 50% *ee* were, together with (+)-NME **10**, tertiary amino alcohols (1*R*,2*S*)-1,2-diphenyl-2-pyrrolidinylethan-1-ol (**18**) and (+)-di-*n*-butylnorephedrine [(+)-DBNE, (+)-**19**],[29] which furnished the best result (65% *ee*).

The poor result obtained with ferrocene (S,R_p)-**17**, a compound introduced by us in 1997,[30] was unexpected, considering that (S,R_p)-**17** is one of the most selective catalysts for the asymmetric arylzinc addition to aldehydes.[31] The outcome of the reaction performed in the presence of amino alcohol (1*S*,2*S*)-**16**, which produced **4a** with only 21% *ee*, was even more surprising, since this compound had already been employed by Jiang to carry out highly enantioselective alkynylation processes, using aldehydes,[32] α-keto esters,[33] and even, as already mentioned, an activated imine[16] as substrates. In the present case, the lack of selectivity of the reaction could be due to the increased steric bulk around the nitrogen atom in comparison with the other substrates previously converted using (1*S*,2*S*)-**16**.

Compounds (+)-**10** and (+)-**19** are both derived from norephedrine,[34] and the only difference between them is the different length of the alkyl groups bound to the nitrogen atom (methyl in **10** and *n*-butyl in **19**). Since a notable increase in the enantioselectivity (from 53 to 65% *ee*, see Figure 1) was observed as an effect of this small structural variation, we next prepared a series of other norephedrine derivatives and tested them as chiral inducers in the test reaction, with the aim to further improve the enantioselectivity of the process.

The preparation of tertiary amino alcohols (1*R*,2*S*)-**22a**–**k** required a simple double alkylation of (1*R*,2*S*)-norephedrine [(1*R*,2*S*)-**20**] either with 2.0 equiv of an alkyl bromide or

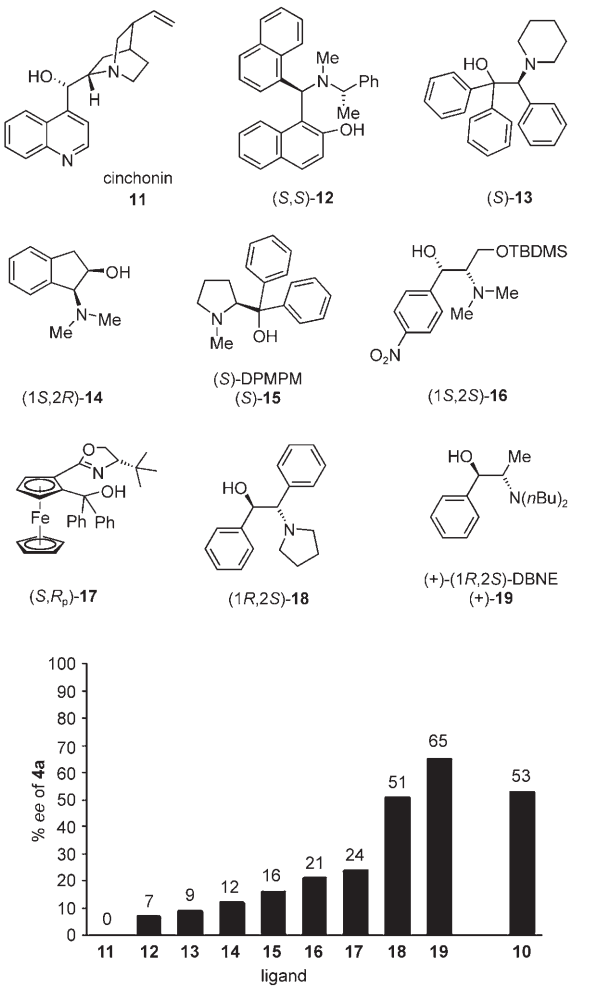
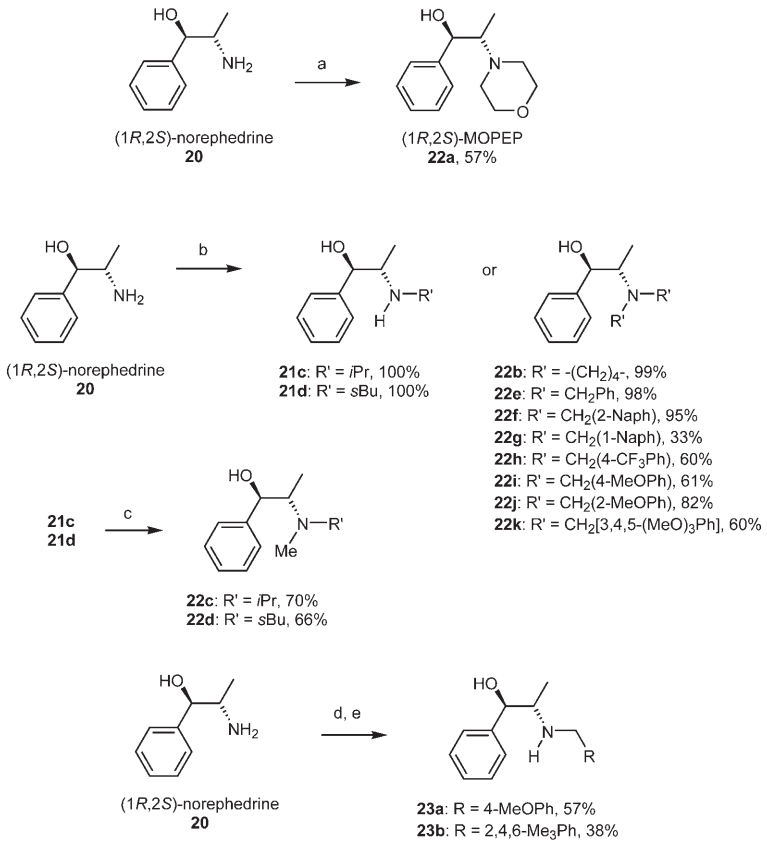


Figure 1. Dependence of the enantiomeric excess of **4a** on the structure of the chiral inducer shown at the top.

iodide, or 1.0 equiv of a dibromide in the case of compounds featuring a cyclic amine moiety (Scheme 2). When isopropyliodide or 2-methylpropyliodide were used in the transformation, only the mono-alkylated products were obtained, probably as a consequence of the increased steric hindrance of these halides. In this case the resulting secondary amines (1*R*,2*S*)-**21a**,**b** were subjected to an Eschweiler–Clarke methylation to yield compounds (1*R*,2*S*)-**22a**,**b** with two different substituents on the nitrogen (Scheme 2). In addition, secondary amino alcohols (1*R*,2*S*)-**23a**,**b** were also prepared by means of a reductive amination reaction between (1*R*,2*S*)-**20** and two different aldehydes. The preparation of compounds (1*R*,2*S*)-**22a**–**k** and (1*R*,2*S*)-**23a**,**b** is depicted in Scheme 2.

It should be pointed out that whereas (1*R*,2*S*)-**22a**–**e** and (1*R*,2*S*)-**23a**,**b** are known compounds, some of which have already been used as ligands in enantioselective catalysis, amino alcohols (1*R*,2*S*)-**22f**–**k** have not been reported yet, as indicated by a literature search conducted using the CAS SciFinder software.



Scheme 2. a) Di(2-bromoethyl) ether (1.1 equiv), Et_3N (3.0 equiv), DMSO, reflux, 72 h; b) R′X (2.0 equiv), K_2CO_3 (5.0–10.0 equiv), MeCN, reflux, 18–34 h; c) HCO_2H (5.0 equiv), HCHO (3.0 equiv), H_2O, reflux, 18 h; d) RCHO (1.0 equiv), toluene, reflux, 10 h; e) $NaBH_4$ (3 equiv), MeOH, reflux, 0.5 h.

The results obtained in the reaction of *p*-chlorobenzaldehyde (**1a**), *o*-methoxyaniline (**2**), and phenylacetylene (**3**) in the presence of amino alcohols **22** and **23** are reported in Table 3 (the result already reported in Table 2, entry 5 is reproduced in entry 1 to facilitate the comparison with the others).

When (+)-(1*R*,2*S*)-DBNE [(1*R*,2*S*)-**19**] was used under optimized conditions, **4a** was obtained in synthetically useful yield, but no improvement in its enantiomeric excess was observed (Table 3, entry 2), in contrast to what was found with (+)-NME (see Table 2, entry 4 vs 5). Application of compounds bearing a cyclic amine moiety, (1*R*,2*S*)-**22a**[35] and (1*R*,2*S*)-**22b**,[29] provided the product with reduced enantiomeric excess in comparison with (+)-DBNE (entries 3–4). Compounds (1*R*,2*S*)-**22c**,**d**,[36,37] with two different substituents on the nitrogen atom, furnished results very similar to that obtained with (+)-NME (entries 5–6 vs entry 1), with the bulkier (1*R*,2*S*)-**22c** being slightly superior to (1*R*,2*S*)-**22d**. These results suggest that only one bulky substituent on the nitrogen atom is not sufficient to induce a significant increase in the enantioselectivity of the reaction in comparison with the alkynylation performed with a ligand bearing two small, or unbranched, alkyl substituents on nitrogen.

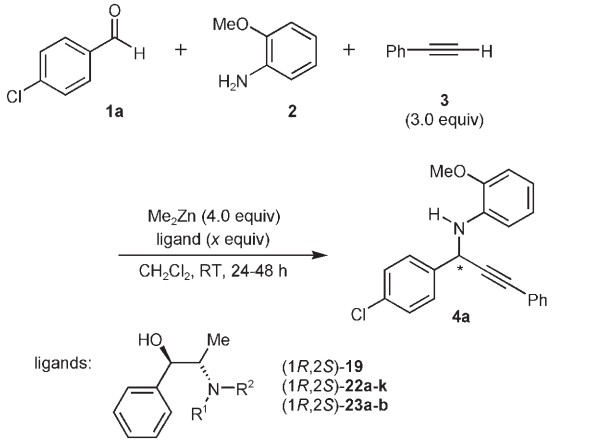
A major improvement in the enantiomeric excess of amine **4a** was observed when amino alcohol (1*R*,2*S*)-**22e**,[38] bearing two benzyl groups, was used (entry 7). Once again, a variation of the substituents on the nitrogen atom had a rather large effect on the enantioselectivity of the reaction. This result was surprising, considering that a highly enantioselective addition of alkyl- or arylzinc organometallics employing (1*R*,2*S*)-**22e** as a ligand has never been reported, and therefore the latter is generally considered to be a less effective chiral promoter than, for example, NME (**10**) or DBNE (**19**). As can be seen from the data presented in Table 3, the enantiomeric excess of (−)-**4a** could be further increased to 91% *ee* after a single recrystallization from *n*-hexane.

In the previous reaction amino alcohol (1*R*,2*S*)-**22e** was used in a stoichiometric amount (1.0 equiv). We anticipated that the possibility to recover and reuse the ligand would considerably increase the synthetic value of our methodology. Accordingly, after chromatographic purification of (−)-**4a** using a mixture of *n*-pentane and diethyl ether as the eluent (see Experimental Section for details), an attempt was made to recover (1*R*,2*S*)-**22e** from the column, simply by eluting with pure diethyl ether. As a result, the amino alcohol could be re-isolated in about 85% (compared to initial quantity).[39] After addition of the remaining 0.15 equiv to reconstitute its initial amount, (1*R*,2*S*)-**22e** was reused in the same reaction, giving (−)-**4a** with slightly decreased yield but with substantially the same enantiomeric excess (entry 8). When the reaction using (1*R*,2*S*)-**22e** was performed at 8°C instead than at RT, the result was practically identical (entry 9), although in this case a longer reaction time (96 h) was needed.

Since compound (1*R*,2*S*)-**22e**, bearing two benzyl groups on the nitrogen atom, gave a result superior to those obtained with all the other ligands tested so far, some other dibenzylic norephedrine derivatives, prepared as shown in Scheme 2, were applied in the test reaction. Steric and electronic properties of the aromatic rings were systematically changed to assess their influence on the selectivity.

Compound (1*R*,2*S*)-**22f**, with two 2-naphthylmethyl groups, provided the product in good yield with 80% *ee* (entry 10), a result similar to that obtained with (1*R*,2*S*)-**22e**. To our surprise, when the more hindered (1*R*,2*S*)-**22g**, bearing 1-naphthylmethyl groups, was employed, a signifi-

Table 3. Application of various amino alcohols as chiral inducers in the one-pot asymmetric synthesis of propargylic amines.



Entry	Ligand	Equiv amino alcohol	Yield (%)[a]	*ee* [%][b–d]
1	(1*S*,2*R*)-**10**	1.0	56	(+)65
2	(1*R*,2*S*)-**19**	1.0	76	(−)63
3	(1*R*,2*S*)-**22a**	1.0	71	(−)30
4	(1*R*,2*S*)-**22b**	1.0	40	(−)43
5	(1*R*,2*S*)-**22c**	1.0	55	(−)64
6	(1*R*,2*S*)-**22d**	1.0	56	(−)52
7	(1*R*,2*S*)-**22e**	1.0	83	(−)82 (91)
8[e]	(1*R*,2*S*)-**22e**	1.0	73	(−)83
9[f]	(1*R*,2*S*)-**22e**	1.0	84	(−)82
10	(1*R*,2*S*)-**22f**	1.0	80	(−)80
11	(1*R*,2*S*)-**22g**	1.0	48	(−)43
12	(1*R*,2*S*)-**22h**	1.0	85	(−)58
13[g]	(1*R*,2*S*)-**22i**	1.0	83	(−)87 (93)
14	(1*R*,2*S*)-**22j**	1.0	60	(−)26
15	(1*R*,2*S*)-**22k**	1.0	84	(−)77
16	(1*R*,2*S*)-**22i**	0.4	85	(−)80
17	(1*R*,2*S*)-**23a**	0.4	72	(−)23
18	(1*R*,2*S*)-**23b**	0.4	84	(−)6

[a] After column chromatography (see Experimental Section for details). [b] Determined by HPLC using a chiral stationary phase (see Experimental Section for details). [c] The sign in parentheses corresponds to the sign of the optical rotation. [d] Values in parentheses indicate the enantiomeric excess after recrystallization from *n*-hexane. [e] The reaction was performed using the amino alcohol recycled from the reaction in entry 7. [f] The reaction was performed at 8°C for 96 h. [g] The amino alcohol was recovered at the end of the reaction.

cant decrease in both yield and enantiomeric excess of (−)-**4a** was observed (entry 11).

In the case of compound (1*R*,2*S*)-**22h**, having two electron-poor aryl rings as an effect of the trifluoromethyl substituents present in *para*-position, the yield of propargyl amine was again high, but its enantiomeric excess was only moderate (entry 12). We reasoned that electron-withdrawing substituents on the aromatic rings could contribute to reduce the electron density on the nitrogen atom, leading to a weaker chelate complex with the metal, thus decreasing the enantioselectivity of the reaction.

If this hypothesis were correct, a ligand featuring electron rich aromatic rings should provide a better result. Indeed, this proved to be the case, as (1*R*,2*S*)-**22i**, with *p*-methoxy-substituted phenyl rings, furnished product (−)-**4a** in 83% yield with 87% *ee* (entry 13). Once again, a single recrystallization from *n*-hexane allowed increasing the enantiomeric excess to 93% *ee*. As described above for (1*R*,2*S*)-**22e**, amino alcohol (1*R*,2*S*)-**22i** could also be recovered after the reaction. Elution with pure diethyl ether provided this time about 90% of the ligand compared with its initial amount.

Aiming to further improve the selectivity of the one-pot alkynylation reaction, compound (1*R*,2*S*)-**22j**, regioisomer of (1*R*,2*S*)-**22i**, was also tested as a chiral inducer. Surprisingly, however, the enantiomeric excess of (−)-**4a** was only 26% (entry 14). A possible explanation of this result involves additional coordination of the metal by the *ortho*-methoxy groups in (1*R*,2*S*)-**22j**, with consequent modification of the transition state geometry of the alkynyl transfer step.

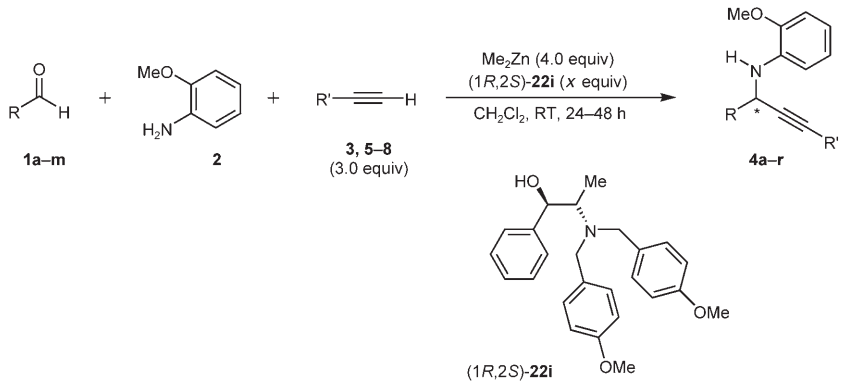
A further increase in electron density was unfruitful, as demonstrated by the application of compound (1*R*,2*S*)-**22k**. The product could be obtained in high yield, and the enantiomeric excess was again near to the 80% value, but still lower than that obtained with (1*R*,2*S*)-**22i** (entry 15).

As already reported in Table 2, when the test reaction was performed using (+)-NME as the ligand in toluene, a strong reduction in the enantiomeric excess of the product was observed upon employment of a substoichiometric quantity of the chiral inducer (Table 2, entry 1 vs 2). In the course of the optimization process, however, not only a much more efficient inducer than (+)-**10** had been identified with (1*R*,2*S*)-**22i**, but also the stoichiometry and the solvent of the reaction were changed. We therefore wanted to determine if less than 1.0 equiv of (1*R*,2*S*)-**22i** could be used in the process without affecting the enantioselectivity of the alkynylation reaction. Gratifyingly, we observed that use of 0.4 equiv of the ligand under otherwise identical conditions afforded (−)-**4a** with roughly the same yield as in the stoichiometric reaction, and still with reasonable 80% *ee* (entry 16 vs entry 13).

Finally, to determine if a tertiary amine moiety was really necessary to induce the formation of propargylamine (−)-**4a** with good enantioselectivity, the two known secondary amino alcohols (1*R*,2*S*)-**23a**,**b** were applied as chiral inducers in the test reaction.[40,41] As can be seen from entries 17 and 18, in the presence of these two chiral promoters the product was obtained in good to high yield, but the enantiomeric excess was only moderate in the best case. This seems to indicate that two substituents on the nitrogen atom are required to achieve a high degree of selectivity in the alkynylation reaction.

With compound (1*R*,2*S*)-**22i** in hand, an amino alcohol had been identified which was able to promote the formation of the propargylic amine in synthetically useful yield and with good enantiomeric excess. To test the applicability of (1*R*,2*S*)-**22i** to other substrates and the possibility to use alkynes different than phenylacetylene (**3**) in the transformation, the scope of the enantioselective dimethylzinc-mediated one-pot synthesis of propargylic amines was subsequently examined. The results obtained in those experiments are listed in Table 4 (the results in Table 3, entry 13

Table 4. One-pot asymmetric synthesis of various propargylic amines using aldehydes **1**, *o*-methoxyaniline (**2**) and various alkynes in combination with amino alcohol (1*R*,2*S*)-**22i** and Me_2Zn.



Entry	R	R′	*x*	Product[a]	Yield (%)[b]	*ee* [%][c,d]
1	4-ClPh (**1a**)	Ph	0.4	**4a**	85	80
2	4-ClPh (**1a**)	Ph	1.0	**4a**	83	87 (93)
3	Ph (**1c**)	Ph	0.4	(*S*)-**4h**	67	87
4	4-MePh (**1d**)	Ph	0.4	**4i**	66	83
5	2-MePh (**1e**)	Ph	0.4	**4j**	83	79
6	4-MeOPh (**1f**)	Ph	0.4	**4k**	74	81
7	4-MeOPh (**1f**)	Ph	1.0	**4k**	52	87 (92)
8	3-MeOPh (**1g**)	Ph	0.4	**4l**	90	84
9	3-MeOPh (**1g**)	Ph	1.0	**4l**	81	88
10	2-MeOPh (**1h**)	Ph	0.4	**4m**	84	97
11	2-MeOPh (**1h**)	Ph	1.0	**4m**	75	97
12	2-BrPh (**1i**)	Ph	0.4	**4n**	89	81
13	2-Naph (**1j**)	Ph	0.4	**4o**	78	81 (91)
14	1-Naph (**1k**)	Ph	0.4	**4p**	62	86
15	2-(5-Br)-thienyl (**1l**)	Ph	0.4	**4q**	89	68
16	*c*-Hex (**1m**)	Ph	0.4	**4r**	93	85
17	4-ClPh (**1a**)	*n*-Hex	0.4	**4b**	64[e]	53
18	4-ClPh (**1a**)	*n*-Hex	1.0	**4b**	65[e]	73
19	4-ClPh (**1a**)	TMS	0.4	(*S*)-**4c**	24	35
20[f]	4-ClPh (**1a**)	TMS	0.4	(*S*)-**4c**	75	24
21[f]	4-ClPh (**1a**)	$C(CH_3)_2OH$	0.4	**4d**	30	13
22	4-ClPh (**1a**)	$C(CH_3)_2OTMS$	0.4	**4e**	26	49
23[f]	4-ClPh (**1a**)	$C(CH_3)_2OTMS$	0.4	**4e**	62	34

[a] In all cases products with a negative sign of the optical rotation were obtained. [b] After column chromatography (see Experimental Section for details). [c] determined by HPLC using a chiral stationary phase (see Experimental Section for details). [d] Values in parentheses indicate the enantiomeric excess after recrystallization from *n*-hexane. [e] Reaction time was 72 h. [f] The reaction was conducted in toluene at 55 °C for 24 h.

and 16 are repeated in Table 4, entry 1–2 to facilitate the comparison with the others).

When benzaldehyde (**1c**) was used as the starting material, the corresponding product (−)-**4h** having *S* configuration[14] was obtained in moderate yield with 87% *ee* (Table 4, entry 3). Considering the similarities in the structures of all the substrates and assuming a similar mode of action of the chiral promoter in every case, the same absolute configuration can be tentatively assigned also to the other propargylamines prepared in the present study. The sign of optical rotation was negative in every case.

p-Methylbenzaldehyde (**1d**) gave rise to propargylic amine (−)-**4i** in 66% yield with 83% *ee*, while compound (−)-**4j**, stemming from *o*-methylbenzaldehyde (**1e**), was isolated in higher yield, but with a lower enantiomeric excess of 79% (entries 4–5).

Propargylamines (−)-**4k** and (−)-**4l** derived from *p*- and *m*-anisaldehyde (**1f** and **1g**), respectively, could be prepared in good to high yields with 81–84% *ee* (entries 6 and 8). Interestingly, when a stoichiometric amount of (1*R*,2*S*)-**22i** was employed for their synthesis, they were obtained with slightly higher enantiomeric excesses (which in the case of the *p*-MeO compound could be further increased by recrystallization), but the yields were lower (entries 7 and 9). To our surprise, when the regioisomer of aldehydes **1f** and **1g**, *o*-anisaldehyde (**1h**), was used as the substrate, propagylamine (−)-**4m** was obtained in good yield with an excellent enantiomeric excess (97% *ee*, entry 10). In this case employment of a stoichiometric quantity of chiral inducer did not improve the enantioselectivity of the reaction, but once again the yield of the product was reduced (entry 11).

The observed increase in the enantioselectivity of the process in the case of aldehyde **1h** could be due to an additional coordination by the oxygen atom in the *ortho*-position of the substrate. When a very bulky and non-coordinating group such as a bromine atom was placed in the *ortho*-position, a product with a much lower enantiomeric excess (81%) was obtained (entry 12). It should be noted that enantioenriched amines such as (−)-**4a** and (−)-**4n** could find applications as building blocks for the synthesis of more complex molecules, for example by means of cross-coupling reactions involving the reactive carbon–halogen bond.

The reaction involving 2-naphthaldehyde (**1i**) furnished, once again, the corresponding product in good yield with 81% *ee*. This value could be improved to 91% *ee* by means of a single recrystallization from *n*-hexane (entry 13). In contrast to what was previously observed for the reactions in entries 3–4, the more hindered 1-naphthaldehyde (**1j**) gave a more selective reaction in this case, with propargylic amine (−)-**4p** being obtained with 86% *ee* (entry 14).

The present protocol for the enantioselective one-pot synthesis of propargylamines can also be applied to other

classes of aldehydes as substrates, as exemplified by the reactions reported in entries 15–16. When an heteroaromatic substrate such as 5-bromo-thiophen-2-carbaldehyde (**1l**) was used as the starting material, the corresponding product (−)-**4q** was isolated in high yield but with a much lower enantiomeric excess (68%, entry 15).[42] Although in this case the enantioselectivity of the alkynylation reaction was only moderate, the possibility of further using enantioenriched amine (−)-**4q** as a substrate for metal-catalyzed cross-coupling reactions should be again mentioned.

α-Branched aliphatic aldehydes are also viable substrates of the reaction, as demonstrated by the result shown in entry 16. When subjected to the reaction conditions, cyclohexanecarbaldehyde (**1m**) gave rise to the corresponding *N*-OMP-propargylamine (−)-**4r** in excellent yield and with good enantiomeric excess (85%). The capacity to convert imines derived from aromatic and aliphatic aldehydes with comparable levels of selectivity is a remarkable feature of the present alkynylation protocol.

In order to test the possibility of using alkynes different than phenylacetylene (**3**) for the preparation of enantioenriched propargylic amines, a series of experiments was conducted employing *p*-chlorobenzaldehyde (**1a**) in combination with acetylenes **5**–**8**, always in the presence of chiral amino alcohol (1*R*,2*S*)-**22i** (entries 17–23).

Use of 1-octyne (**5**) together with 0.4 equiv of (1*R*,2*S*)-**22i** led to the formation of propargylamine (−)-**4b** in good yield but with only 53% *ee* (entry 17). Interestingly, when the amino alcohol was used in stoichiometric amount, the enantiomeric excess of the product could be substantially increased to 73% *ee* (entry 18). If compared to the reactions employing aldehyde **1a** in combination with phenylacetylene (**3**) with the same stoichiometry (Table 4, entries 1 and 2), these results indicate that 1.0 equiv of chiral inducer is required to attain a similar level of enantioselectivity when moving from alkyne **3** to **5**.

The result obtained with trimethylsilylethyne (**6**) was disappointing, the corresponding propargylic amine (−)-**4b** being isolated in low yield and enantioselectivity (entry 19). Performing the reaction in toluene at 55°C instead of CH_2Cl_2 at room temperature helped to increase the yield, but the enantioselectivity was reduced even further under these conditions (entry 20). A similar behavior was exhibited also by the reactions using alkynes **7**–**8**. In both cases an acceptable yield of the product could be obtained only by working at 55°C, while the enantiomeric excesses remained low in every case, not exceeding 49% *ee* (entries 21–23).

Conclusion

In the present work our studies on the dimethylzinc-mediated, one-pot synthesis of propargylamines have been described. Firstly, it was demonstrated that, by means of simple modifications of the original procedure, the scope of this reaction could be extended to include alkynes other than phenylacetylene (**3**). While use of trimethylsilylethyne (**6**) and various alkyl-substituted alkynes provided the corresponding products in moderate to good yield, the present methodology finds a limitation in the impossibility to use electron-poor acetylenes such as methyl propiolate (**9**). The scarce nucleophilicity of the corresponding mixed zinc acetylenide, possibly due to an equilibrium with the corresponding O−Zn allene, can be assumed to be responsible for the observed lack of reactivity.

Subsequently, an asymmetric version of the one-pot synthesis of propargylic amines was developed, which makes use of a (1*R*,2*S*)-norephedrine derivative as a chiral inducer, employed in equimolar or substoichiometric amount (40 mol%). After a considerable optimization effort, which involved improvement of various parameters such as solvent, stoichiometry of the reaction and ligand structure, various amines stemming from aromatic, heteroaromatic and aliphatic α-branched aldehydes, in combination with *o*-methoxyaniline (**2**) and phenylacetylene (**3**), could be prepared in moderate to high yields with enantiomeric excesses ranging from 68 to 97% *ee*. In some cases, the enantiomeric purity of the products could be increased by means of a single recrystallization from *n*-hexane. When alkynes other than **3** were employed in the reaction, however, much lower enantiomeric excesses were generally observed, ranging from 13 to 53% *ee*. In the case of 1-octyne (**5**) the selectivity of the reaction could be substantially improved to 73% *ee* by use of a stoichiometric quantity of the chiral promoter (1*R*, 2*S*)-**22i**.

We are currently trying to identify new and more efficient chiral auxiliaries, with the aim of broadening the reaction scope, improving its enantioselectivity and reducing the required amount of catalyst. We also plan to initiate efforts directed to the elucidation of the reaction mechanism. The results of these investigations will be reported in due course.

Experimental Section

General remarks: Air-sensitive manipulations were carried out under an inert atmosphere of argon using standard Schlenk techniques. The glassware employed for those manipulations was either oven- or flame-dried and then cooled under a stream of argon. Toluene was distilled from sodium/benzophenone, CH_2Cl_2 from calcium hydride prior to use. Ethyl acetate, diethyl ether, petroleoum ether (PE; b.p. 40–70°C) and *n*-pentane for flash column chromatography[43] were distilled and *n*-hexane was dried over activated molecular sieves before use. DMSO and acetonitrile were reagent-grade and were used as received. Benzaldehyde, 2-furfuraldehyde and 1-naphthaldehyde were distilled prior to use, whereas all the other aldehydes were used as received from commercial sources. ^1H and ^{13}C NMR spectra were recorded either on a Varian Gemini 300 spectrometer (300 and 75 MHz, respectively) or on a Varian Inova 400 spectrometer (400 and 100 MHz, respectively). IR spectra were measured on a Perkin-Elmer PE 1760 FT instrument as KBr pellets or neat (in the case of liquid compounds). Only characteristic absorption bands are reported; absorptions are given in wavenumbers (cm^{-1}). MS spectra were recorded on a Varian MAT 212 or on a Finnigan MAT 95 spectrometer with EI ionization, at a 70 eV ionization potential. High resolution mass spectra (HRMS) were recorded on a Finnigan MAT 95 spectrometer. Optical rotation measurements were conducted at room temperature with a Perkin-Elmer PE 241 polarimeter at a wavelength of 589 nm (D-line of a Na-vapor lamp). HPLC measurements were performed at room

temperature with a Merck-Hitachi HPLC apparatus (L-7400 UV-detector, L-7100 pump and D-7000 integrator) using columns with chiral stationary phase purchased from Chiral Technologies Ltd. (formerly Daicel Chemical Industries Ltd.). Elemental analyses were obtained using a Heraeus CHN-O-Rapid instrument. Melting points were measured in open capillaries with a Büchi B-540 apparatus and are uncorrected. Compounds (1*R*,2*S*)-**23a**,**b** were prepared according to literature procedures.[40,41]

(1*R*,2*S*)-2-(Morpholin-4-yl)-1-phenyl-1-propanol [(1*R*,2*S*)-22a]: A solution of 2,2′-dibromodiethyl ether (90%, 1.62 g, 0.88 mL, 7.0 mmol, 1.2 equiv) in DMSO (5.0 mL) was added dropwise to a mixture of (1*R*,2*S*)-norephedrine (**20**, 0.907 g, 6.0 mmol) and Et_3N (1.78 g, 2.5 mL, 17.5 mmol, 2.9 equiv) in DMSO (6.0 mL). The reaction mixture was heated at reflux and stirred for 72 h, then poured into 0.25 M aq NaOH (60 mL) and extracted with Et_2O (3×25 mL). The combined organic phases were dried on $MgSO_4$. Evaporation of the solvent yielded the crude product. Purification by recrystallization from *n*-hexane afforded pure (1*R*,2*S*)-**22a** (0.744 g, 3.4 mmol, 57%) as light yellow needles. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.76 (d, J = 6.9 Hz, 3H), 2.46–2.64 (m, 5H), 3.48 (br s, 1H), 3.66 (t, J = 4.7 Hz, 4H), 4.85 (d, J = 3.9 Hz, 1H), 7.14–7.20 (m, 1H), 7.22–7.29 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.0, 51.0, 64.9, 67.5, 71.8, 125.9, 126.9, 128.0, 141.7. All other data were in agreement with those reported in the literature.[34]

General procedure 1 (GP 1): Double alkylation of (1*R*,2*S*)-norephedrine (20)

The appropriate alkyl halide (5.0 mmol, 1.0 equiv in the case of 1,4-dibromobutane, and 10.0 mmol, 2.0 equiv in the case of the other alkyl halides) and K_2CO_3 (3.46–6.92 g, 25.0–50.0 mmol, 5.0–10.0 equiv) were added to a solution of (1*R*,2*S*)-norephedrine (**20**, 0.756 g, 5.0 mmol) in CH_3CN (30 mL). The heterogeneous mixture was heated to reflux and stirred for 24 h. After the reaction was complete according to TLC, the mixture was cooled to RT and the solid K_2CO_3 was removed by filtration and washed with ethyl acetate (20 mL). The combined filtrates were concentrated in vacuo to give the crude product. If necessary, the residue was purified by flash column chromatography affording the double alkylated norephedrines (**22e–k**).

When isopropyl iodide and 2-methylpropyl iodide were used, only the corresponding monoalkylated products (**21c**,**d**) were obtained, which were used for the following methylation reaction without further purification.

(1*R*,2*S*)-1-Phenyl-2-(pyrrolidin-1-yl)-1-propanol [(1*R*,2*S*)-22b]: Prepared according to GP 1 starting from (1*R*,2*S*)-**20** (0.756 g, 5.0 mmol) and 1,4-dibromobutane (1.08 g, 5.0 mmol, 1.0 equiv). Purification by flash column chromatography (PE/ethyl acetate/Et_3N 4:1:0.1) afforded pure (1*R*,2*S*)-**22b** (1.02 g, 4.9 mmol, 99%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.72 (d, J = 6.6 Hz, 3H), 1.69–1.79 (m, 4H), 2.41 (dq, J = 6.6, 3.3 Hz, 1H), 2.52–2.62 (m, 2H), 2.66–2.76 (m, 2H), 3.55 (br s, 1H), 4.94 (d, J = 3.0 Hz, 1H), 7.13–7.20 (m, 1H), 7.23–7.30 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.2, 23.6, 51.9, 65.4, 72.7, 125.8, 126.7, 127.9, 141.7. All other data were in agreement with those reported in the literature.[28]

(1*R*,2*S*)-*N*,*N*-Dibenzylnorephedrine [(1*R*,2*S*)-22e]: Prepared according to GP 1 starting from (1*R*,2*S*)-**20** (0.756 g, 5.0 mmol) and benzylbromide (1.71 g, 10.0 mmol, 2.0 equiv). Pure (1*R*,2*S*)-**22e** (1.62 g, 4.9 mmol, 98%) was immediately obtained as a colorless oil, and could be used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (d, J = 6.6 Hz, 3H), 2.56 (br s, 1H), 3.10 (qu, J = 6.7 Hz, 1H), 3.60 (AB system, 4H), 4.75 (d, J = 6.0 Hz, 1H), 7.17–7.32 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.3, 54.7, 58.5, 75.7, 126.7, 126.9, 127.3, 128.0, 128.2, 128.7, 139.8, 143.1. All other analytical data were in agreement with those reported in the literature.[37]

(1*R*,2*S*)-*N*,*N*-Di(2-naphthyl)norephedrine [(1*R*,2*S*)-22f]: Prepared according to GP 1 starting from (1*R*,2*S*)-**20** (0.756 g, 5.0 mmol) and 2-bromomethylnaphthalene (2.21 g, 10.0 mmol, 2.0 equiv). Pure (1*R*,2*S*)-**22f** (2.05 g, 4.75 mmol, 95%) was immediately obtained as a yellow solid, and could be used without further purification. M.p. 50–51 °C; $[\alpha]_D^{20}$ = −121.6 (c = 1.01, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (d, J = 6.7 Hz, 3H), 2.33 (br s, 1H), 3.09 (qu, J = 6.7 Hz, 1H), 3.68 (AB system, 4H), 4.68 (d, J = 6.7 Hz, 1H), 7.06–7.12 (m, 2H), 7.14–7.26 (m, 5H), 7.30–7.42 (m, 4H), 7.53 (s, 2H), 7.62–7.75 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.2, 54.7, 58.4, 76.1, 125.5, 125.9, 127.0, 127.1, 127.40, 127.44, 127.7, 127.7, 127.9, 128.1, 132.8, 133.3, 137.4, 143.2; IR (KBr): $\tilde{\nu}$ = 3424, 3053, 2926, 2805, 1506, 1365, 1153, 1127 cm^{-1}; MS (EI, 70 eV): m/z: 324 $[M-C_7H_7O]^+$, 281, 182, 141 $[C_{11}H_9]^+$, 115, 77; HRMS (EI): m/z: calcd for $C_{24}H_{22}N$: 324.1752; found: 324.1753 $[M-C_7H_7O]^+$.

(1*R*,2*S*)-*N*,*N*-Di(1-naphthyl)norephedrine [(1*R*,2*S*)-22g]: Prepared according to GP 1 starting from (1*R*,2*S*)-**20** (0.510 g, 3.4 mmol) and 1-chloromethylnaphthalene (0.883 g, 5.0 mmol, 1.5 equiv). Purification by flash column chromatography (Et_2O/*n*-pentane/Et_3N 1:1:0.1) afforded pure (1*R*,2*S*)-**22g** (0.360 g, 0.84 mmol, 33%) as a yellow oil. $[\alpha]_D^{20}$ = +32.7 (c = 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (d, J = 6.6 Hz, 3H), 2.18 (br s, 1H), 3.19 (dt, J = 6.6, 12.5 Hz, 1H), 4.18 (AB system, 4H), 4.93 (d, J = 5.5 Hz, 1H), 6.96–7.02 (m, 2H), 7.11–7.25 (m, 5H), 7.32–7.48 (m, 6H), 7.73 (d, J = 8.0 Hz, 2H), 7.81 (d, J = 8.1 Hz, 2H), 7.90 (d, J = 8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.0, 53.3, 59.1, 76.2, 124.7, 125.0, 125.3, 125.4, 126.5, 127.1, 127.6, 127.7, 128.0, 128.2, 132.3, 133.7, 135.0, 143.1; IR (neat): $\tilde{\nu}$ = 3558, 3419, 2936, 2836, 2716, 1679, 1595, 1459, 1381, 1242, 1032 cm^{-1}; MS (CI, CH_4, 70 eV): m/z: 445 $[M+CH_4]^+$, 431 $[M]^+$, 414, 392, 374, 284, 254, 241, 164, 121, 107 $[C_7H_7O]^+$, 91, 79; HRMS (EI): m/z: calcd for $C_{31}H_{27}N$: 413.2144; found: 413.2144 $[M-H_2O]^+$.

(1*R*,2*S*)-*N*,*N*-Di[(4-trifluoromethylphenyl)methyl]norephedrine [(1*R*,2*S*)-22h]: Prepared according to GP 1 starting from (1*R*,2*S*)-**20** (0.756 g, 5.0 mmol) and 1-bromomethyl-4-trifluoromethylbenzene (2.39 g, 10.0 mmol, 2.0 equiv). Purification by flash column chromatography (PE/ethyl acetate/Et_3N 8:1:0.05) afforded pure (1*R*,2*S*)-**22h** (1.40 g, 2.99 mmol, 60%) as a colorless oil. $[\alpha]_D^{20}$ = −32.4 (c = 0.80, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (d, J = 6.7 Hz, 3H), 1.99 (br s, 1H), 2.89 (qu, J = 6.7 Hz, 1H), 3.57 (AB system, 4H), 4.68 (d, J = 6.7 Hz, 1H), 7.02–7.08 (m, 2H), 7.10–7.17 (m, 4H), 7.19–7.28 (m, 3H), 7.37–7.44 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.0, 54.2, 59.1, 76.3, 125.1, 125.2, 126.8, 127.8, 128.3, 128.8, 129.1, 129.5, 143.3, 143.8; IR (neat): $\tilde{\nu}$ = 3402, 2968, 2930, 1920, 1727, 1619, 1326, 1125, 1067 cm^{-1}; MS (EI, 70 eV): m/z: 448 $[M-F]^+$, 360 $[M-C_7H_7O]^+$, 200, 159 $[C_8H_6F_3]^+$, 109, 77; HRMS (EI): m/z: calcd for $C_{18}H_{23}NF_6$: 360.1187; found: 360.1187 $[M-C_7H_7O]^+$.

(1*R*,2*S*)-*N*,*N*-Di[(4-methoxyphenyl)methyl]norephedrine [(1*R*,2*R*)-22i]: Prepared according to GP 1 starting from (1*R*,2*S*)-**20** (0.756 g, 5.0 mmol) and 1-bromomethyl-4-methoxybenzene (2.01 g, 10.0 mmol, 2.0 equiv). Purification by flash column chromatography (PE/ethyl acetate/Et_3N 6:1:0.05) afforded pure (1*R*,2*S*)-**22i** (1.20 g, 3.07 mmol, 61%) as a colorless oil. $[\alpha]_D^{20}$ = −64.7 (c = 1.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (d, J = 6.6 Hz, 3H), 2.70 (br s, 1H), 3.10 (qu, J = 6.7 Hz, 1H), 3.48 (AB system, 4H), 3.79 (s, 6H), 4.70 (d, J = 6.3 Hz, 1H), 6.77–6.83 (m, 4H), 7.05–7.11 (m, 4H), 7.17–7.23 (m, 2H), 7.24–7.33 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.4, 53.8, 55.3, 58.1, 75.6, 113.6, 126.8, 127.2, 128.0, 129.7, 131.8, 143.1, 158.5; IR (neat): $\tilde{\nu}$ = 3447, 2933, 2833, 2248, 2060, 1883, 1610, 1510, 1457, 1246, 1173, 1034 cm^{-1}; MS (EI, 70 eV): m/z: 285, 284 $[M-C_7H_7O]^+$, 162, 122, 121 $[C_8H_9O]^+$, 77; HRMS (EI): m/z: calcd for $C_{18}H_{22}NO_2$: 284.1650; found: 284.1650 $[M-C_7H_7O]^+$.

(1*R*,2*S*)-*N*,*N*-Di[(2-methoxyphenyl)methyl]norephedrine [(1*R*,2*R*)-22j]: Prepared according to GP 1 starting from (1*R*,2*S*)-**20** (0.513 g, 3.4 mmol) and 1-chloromethyl-2-methoxybenzene (0.906 g, 5.8 mmol, 1.7 equiv). Purification by flash column chromatography (Et_2O/*n*-pentane/Et_3N 1:1:0.1) afforded pure (1*R*,2*S*)-**22j** (0.930 g, 2.4 mmol, 82%) as a pale yellow oil. $[\alpha]_D^{20}$ = −21.0 (c = 0.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (d, J = 6.9 Hz, 3H), 3.11 (dt, J = 5.0, 6.9 Hz, 1H), 3.70 (AB system, 4H), 3.82 (s, 6H), 3.90 (br s, 1H), 4.75 (d, J = 5.0 Hz, 1H), 6.81–6.92 (m, 4H), 7.16–7.30 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.8, 49.8, 55.3, 59.8, 75.8, 110.2, 120.3, 126.3, 126.7, 127.7, 127.7, 128.0, 130.3, 142.7, 157.6; IR (neat): $\tilde{\nu}$ = 3562, 3038, 2959, 2872, 1947, 1817, 1592, 1503, 1452, 1366, 1238, 1156 cm^{-1}; MS (CI, CH_4, 70 eV): m/z: 392 $[M+1]^+$, 374 $[M-OH]^+$, 284 $[M-C_7H_7O]^+$, 121, 107 $[C_7H_7O]^+$, 91, 79; HRMS (EI): m/z: calcd for $C_{18}H_{22}NO_2$: 284.1650; found: 284.1651 $[M-C_7H_7O]^+$.

(1*R*,2*S*)-*N*,*N*-Di[(3,4,5-trimethoxyphenyl)methyl]norephedrine [(1*R*,2*R*)-22k]: Prepared according to GP 1 starting from (1*R*,2*S*)-**20** (0.756 g, 5.0 mmol) and 1-bromomethyl-3,4,5-trimethoxybenzene[43] (2.61 g, 10.0 mmol, 2.0 equiv). Purification by flash column chromatography (PE/

ethyl acetate/Et_3N 5:1:0.1) afforded pure (1*R*,2*S*)-**22k** (1.52 g, 2.98 mmol, 60%) as a yellow oil. $[\alpha]_D^{20} = -27.2$ ($c = 0.89$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.27$ (d, $J = 6.4$ Hz, 3H), 2.23 (br s, 1H), 3.15 (qu, $J = 6.8$ Hz, 1H), 3.51 (AB system, 4H), 3.75 (s, 12H), 3.82 (s, 6H), 4.68 (d, $J = 7.6$ Hz, 1H), 6.36 (s, 4H), 7.14–7.20 (m, 2H), 7.24–7.32 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 9.1$, 54.8, 56.0, 58.2, 60.8, 76.6, 105.5, 127.2, 127.5, 128.1, 135.5, 136.8, 143.6, 153.0; IR (neat): $\tilde{\nu} = 3479$, 2936, 2832, 1593, 1504, 1460, 1377, 1233, 1126 cm^{-1}; MS (EI, 70 eV): *m*/*z*: 404 $[M-C_7H_7O]^+$, 222, 181 $[C_9H_{16}O_3]^+$, 148, 106, 77; HRMS (EI): *m*/*z*: calcd for $C_{22}H_{30}NO_6$: 404.2073; found: 404.2073 $[M-C_7H_7O]$.

General procedure 2 (GP 2): **Methylation of monoalkylnorephedrines (1*R*,2*S*)-21c–d**

A round-bottom flask was charged with compound (1*R*,2*S*)-**21c** or (1*R*,2*S*)-**21d** (5.0 mmol). Formic acid (90% solution in H_2O, 0.75 mL, 25.0 mmol, 5.0 equiv) and formaldehyde (37% solution in H_2O, 0.82 mL, 15.0 mmol, 3.0 equiv) were added in sequence at RT, and the resulting mixture was heated to reflux and stirred for 18 h. The solution was allowed to cool to RT, and 1.0 M aq NaOH was added until pH > 8. The aqueous layer was then extracted with CH_2Cl_2 (3×25 mL). The organic layer was washed with satd. aq NaCl (50 mL) and dried over Na_2SO_4. Removal of the solvent in vacuo afforded crude (1*R*,2*S*)-**22c**,**d**, which were then purified by flash column chromatography.

(1*R*,2*S*)-*N*-Isopropyl-*N*-methylnorephedrine [(1*R*,2*S*)-22c]: (1*R*,2*S*)-Norephedrine (**20**, 0.756 g, 5.0 mmol) was treated with 2-iodopropane (1.70 g, 10.0 mmol, 2.0 equiv) according to GP 1 to furnish the monoalkylated product (1*R*,2*S*)-**21c** in quantitative yield. This compound was subsequently methylated according to GP 2. Purification by flash column chromatography (PE/ethyl acetate/Et_3N 5:1:0.1) afforded pure (1*R*,2*S*)-**22c** (0.720 g, 3.5 mmol, 69%) as a light yellow oil. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.84$ (d, $J = 6.9$ Hz, 3H), 1.04 (d, $J = 6.4$ Hz, 3H), 1.08 (d, $J = 6.7$ Hz, 3H), 2.18 (s, 3H), 2.92 (dq, $J = 6.9$, 4.3 Hz, 1H), 3.12 (sept, $J = 6.5$ Hz, 1H), 4.11 (br s, 1H), 4.80 (d, $J = 4.3$ Hz, 1H), 7.21–7.29 (m, 1H), 7.31–7.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.8$, 18.3, 19.0, 31.6, 51.1, 60.9, 72.5, 126.1, 126.7, 127.9, 142.3. All the other analytical data were in agreement with those reported in the literature.[35]

(1*R*,2*S*)-*N*-Isobutyl-*N*-methylnorephedrine [(1*R*,2*S*)-22d]: (1*R*,2*S*)-Norephedrine (**20**, 0.756 g, 5.0 mmol) was treated with 1-iodo-2-methylpropane (1.84 g, 10.0 mmol, 2.0 equiv) according to GP 1 to furnish the monoalkylated product (1*R*,2*S*)-**21d** in quantitative yield. This compound was subsequently methylated according to GP 2. Purification by flash column chromatography (PE/ethyl acetate/Et_3N 2:1:0.05) afforded pure (1*R*,2*S*)-**22d** (0.730 g, 3.3 mmol, 66%) as a light yellow oil. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.80$ (t, $J = 6.6$ Hz, 6H), 0.82 (d, $J = 6.6$ Hz, 3H), 1.69 (sept, $J = 6.6$ Hz, 1H), 2.10 (s, 3H), 2.09–2.22 (m, 2H), 2.68 (dq, $J = 6.8$, 4.7 Hz, 1H), 3.68 (br s, 1H), 4.71 (d, $J = 4.4$ Hz, 1H), 7.12–7.19 (m, 1H), 7.22–7.28 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 10.3$, 20.7, 20.9, 26.6, 38.8, 63.9, 64.4, 73.2, 126.1, 126.7, 127.9, 142.3. All the other analytical data were in agreement with those reported in the literature.[36]

General procedure 3 (GP 3): **One-pot synthesis of propargylic imines 4a–e,g**

Method A (standard conditions): In an oven-dried Schlenk flask under an inert atmosphere of argon were placed *p*-chlorobenzaldehyde (**1a**, 0.056 g, 0.4 mmol) or 2-furfuraldehyde (**1b**, 0.038 g, 0.4 mmol) and *o*-methoxyaniline (**2**, 0.049 g, 0.4 mmol, 1.0 equiv), followed by anhydrous toluene (4.0 mL). After 30 min stirring, a 2.0 M solution of dimethylzinc in toluene (0.7 mL, 1.4 mmol, 3.5 equiv) was added. The reaction mixture was then stirred for another 30 min, before adding the appropriate alkyne (**3** or **5**–**8**, 1.0 mmol, 2.5 equiv). The resulting solution was stirred at the appropriate temperature for 48 h. The reaction mixture was then diluted with diethyl ether (5.0 mL), and quenched with water (10 mL). The resulting heterogeneous mixture was filtered over Celite. The aqueous phase was separated and washed with diethyl ether (2×5.0 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the crude product, which was purified by flash column chromatography.

Method B (concentrated conditions): In an oven-dried Schlenk flask under an inert atmosphere of argon were placed *p*-chlorobenzaldehyde (**1a**, 0.056 g, 0.4 mmol) and *o*-methoxyaniline (**2**, 0.049 g, 0.4 mmol, 1.0 equiv). A 2.0 M solution of dimethylzinc in toluene (0.7 mL, 1.4 mmol, 3.5 equiv) was immediately added. The reaction mixture was stirred for 30 min, before adding the appropriate alkyne (**5** or **9**, 1.0 mmol, 2.5 equiv). The resulting solution was stirred at room temperature or at 55 °C for 48 h. From hereon the protocol followed the procedure reported above for Method A.

General Procedure 4 (GP 4): **Enantioselective synthesis of propargylic amines 4a–r under optimized conditions**

In an oven-dried Schlenk flask under an inert atmosphere of argon were placed the appropriate aldehyde (**1a–m**, 0.4 mmol) and *o*-methoxyaniline (**2**, 0.049 g, 0.4 mmol, 1.0 equiv), followed by anhydrous CH_2Cl_2 (2.5 mL). After 30 min of stirring, a 2.0 M solution of dimethylzinc in toluene (0.8 mL, 1.6 mmol, 4.0 equiv) was added. The reaction mixture was stirred for 30 min, and amino alcohol (1*R*,2*S*)-**22i** (0.063–0.157 g, 0.16–0.4 mmol, 0.4–1.0 equiv) dissolved in CH_2Cl_2 (1 mL), was added. The resulting solution was stirred for additional 30 min, before adding the appropriate alkyne (**3** or **5**–**8**, 1.2 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature for 48 h. Subsequently, it was diluted with diethyl ether (5.0 mL) and quenched with water (10 mL). The resulting heterogeneous mixture was filtered over Celite. The aqueous phase was separated and washed with diethyl ether (2×5.0 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the crude product, which was purified by flash column chromatography.

***N*-(2-Methoxyphenyl)-3-amino-3-(4-chlorophenyl)-1-phenylprop-1-yne (4a)**: The preparation of racemic amine **4a** according to GP 3A has already been reported in ref. [21].

Nonracemic amine **4a** was prepared according to GP 4 starting from *p*-chlorobenzaldehyde (**1a**, 0.056 g, 0.4 mmol), *o*-methoxyaniline (**2**, 0.049 g, 0.4 mmol, 1.0 equiv) and phenylacetylene (**3**, 0.123 g, 1.2 mmol, 3.0 equiv). Purification by flash column chromatography (*n*-pentane/diethyl ether 30:1) afforded pure (−)-**4a** (0.115 g, 0.33 mmol, 83%) as a light yellow oil that solidified upon standing. $[\alpha]_D^{20} = -84.9$ ($c = 0.70$, $CHCl_3$); HPLC (Chiralcel OD-H, 254 nm, heptane/*i*PrOH 95:5, flow rate = 0.6 mL min^{-1}): t_r (+, minor) = 9.2 min, t_r (−, major) = 11.0 min; *ee* = 87%; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.83$ (s, 3H), 4.81 (br s, 1H), 5.43 (s, 1H), 6.78–6.85 (m, 4H), 7.26–7.33 (m, 3H), 7.36 (d, $J = 8.1$ Hz, 2H), 7.42–7.45 (m, 2H), 7.62 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 49.8$, 55.4, 85.1, 88.1, 109.5, 111.6, 117.9, 121.0, 122.6, 128.2, 128.4, 128.6, 128.8, 131.7, 133.7, 136.1, 138.5, 147.1; MS (EI, 70 eV): *m*/*z*: 350–348 $[M+1]^+$, 349–347 $[M]^+$, 236 $[M-C_6H_4Cl]^+$, 227–225, 189, 77; elemental analysis calcd (%) for $C_{22}H_{18}NOCl$ (347.84): C 75.97, H 5.22, N 4.03; found: C 76.18, H 5.35, N 3.95.

***N*-(2-Methoxyphenyl)-1-amino-1-(4-chlorophenyl)non-1-yne (4b)**: Racemic amine **4b** was prepared according to GP 3A starting from *p*-chlorobenzaldehyde (**1a**, 0.056 g, 0.4 mmol), *o*-methoxyaniline (**2**, 0.049 g, 0.4 mmol, 1.0 equiv) and 1-octyne (**5**, 0.110 g, 1.0 mmol, 2.5 equiv). Purification by flash column chromatography (*n*-pentane/diethyl ether 65:1) afforded pure *rac*-**4b** (0.055 g, 0.17 mmol, 42%) as a colorless oil.

Nonracemic amine **4b** was prepared according to GP 4 starting from *p*-chlorobenzaldehyde (**1a**, 0.056 g, 0.4 mmol), *o*-methoxyaniline (**2**, 0.049 g, 0.4 mmol, 1.0 equiv) and 1-octyne (**5**, 0.132 g, 1.2 mmol, 3.0 equiv). Purification by flash column chromatography (*n*-pentane/diethyl ether 65:1) afforded pure **4b** (0.091 g, 0.26 mmol, 65%) as a colorless oil. $[\alpha]_D^{20} = -46.6$ ($c = 0.86$, $CHCl_3$); HPLC (Chiralcel OD-H, 254 nm, heptane/*i*PrOH 95:5, flow rate = 0.6 mL min^{-1}): t_r (−, major) = 7.5 min, t_r (+, minor) = 9.7 min; *ee* = 73%; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.80$ (t, $J = 6.9$ Hz, 3H), 1.11–1.31 (m, 6H), 1.36–1.45 (m, 2H), 2.12 (dt, $J = 7.1$, 2.0 Hz, 2H), 3.75 (s, 3H), 4.57 (br s, 1H), 5.13 (s, 1H), 6.57–6.66 (m, 2H), 6.68–6.78 (m, 2H), 7.22–7.28 (m, 2H), 7.41–7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.0$, 17.7, 21.5, 27.4, 27.5, 30.2, 48.2, 54.3, 77.9, 84.7, 108.3, 110.4, 116.5, 119.8, 127.4, 127.5, 132.2, 135.1, 138.0, 145.8; IR (neat): $\tilde{\nu} = 3418$, 2930, 2857, 1600, 1511, 1456, 1242, 1224, 1029 cm^{-1}; MS (EI, 70 eV): *m*/*z*: 357–355 $[M]^+$, 272–270 $[M-C_6H_{11}]^+$, 244 $[M-C_6H_4Cl]^+$, 235–233 $[M-C_7H_8O]^+$, 153–151, 127–125, 95; elemental analysis calcd (%) for $C_{22}H_{26}NOCl$ (355.90): C 74.24, H 7.36, N 3.94; found: C 74.49, H 7.10, N 4.32.

***N*-(2-Methoxyphenyl)-3-amino-3-(4-chlorophenyl)-1-trimethylsilylprop-1-yne (4c)**:[14] Racemic amine **4c** was prepared according to GP 3B starting from *p*-chlorobenzaldehyde (**1a**, 0.056 g, 0.4 mmol), *o*-methoxyaniline (**2**, 0.049 g, 0.4 mmol, 1.0 equiv) and trimethylsilylacetylene (**6**, 0.118 g, 1.2 mmol, 3.0 equiv). Purification by flash column chromatography (*n*-pentane/diethyl ether 30:1) afforded pure *rac*-**4c** (0.078 g, 0.23 mmol, 57%) as a light yellow oil.

Nonracemic amine **4c** was prepared according to GP 4 starting from *p*-chlorobenzaldehyde (**1a**, 0.056 g, 0.4 mmol), *o*-methoxyaniline (**2**, 0.049 g, 0.4 mmol, 1.0 equiv) and trimethylsilylacetylene (**6**, 0.118 g, 1.2 mmol, 3.0 equiv), using toluene as a solvent at 55 °C for 24 h. Purification by flash column chromatography (*n*-pentane/diethyl ether 30:1) afforded pure **4c** (0.103 g, 0.30 mmol, 75%) as a light yellow oil. $[\alpha]_D^{20} = -15.7$ ($c = 1.1$, $CHCl_3$); HPLC (Chiralcel OD, 254 nm, heptane/*i*PrOH 99:1, flow rate = 0.8 mL min^{-1}): t_r (*R*, minor) = 7.5 min, t_r (*S*, major) = 9.6 min; *ee* = 24%; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.00$ (s, 9H), 3.69 (s, 3H), 4.50 (s, 1H), 5.09 (d, $J = 0.5$ Hz, 1H), 6.57–6.65 (m, 4H), 7.11–7.19 (m, 2H), 7.32–7.40 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 0.0$, 50.0, 55.5, 90.0, 104.5, 109.7, 111.8, 118.0, 121.1, 128.7, 128.9, 133.7, 136.2, 138.5, 147.3. All the other analytical data were in agreement with those reported in the literature.[14]

***N*-(2-Methoxyphenyl)-1-amino-1-(4-chlorophenyl)-5-hydroxy-5-methylpent-2-yne (4d)**: Racemic amine **4d** was prepared according to GP 3A starting from *p*-chlorobenzaldehyde (**1a**, 0.056 g, 0.4 mmol), *o*-methoxyaniline (**2**, 0.049 g, 0.4 mmol, 1.0 equiv) and 3-hydroxy-3-methylbut-1-yne (**7**, 0.105 g, 1.2 mmol, 3.0 equiv). Purification by flash column chromatography (*n*-pentane/diethyl ether 2:1) afforded pure *rac*-**4d** (0.109 g, 0.33 mmol, 82%) as a light yellow oil.

Nonracemic amine **4d** was prepared according to GP 4 starting from *p*-chlorobenzaldehyde (**1a**, 0.056 g, 0.4 mmol), *o*-methoxyaniline (**2**, 0.049 g, 0.4 mmol, 1.0 equiv) and 3-hydroxy-3-methylbut-1-yne (**7**, 0.105 g, 1.2 mmol, 3.0 equiv), using toluene as a solvent at 55 °C for 24 h. Purification by flash column chromatography (*n*-pentane/diethyl ether 2:1) afforded pure **4d** (0.039 g, 0.12 mmol, 30%) as a light yellow oil. HPLC (Chiralcel OD-H, 254 nm, heptane/*i*PrOH 97:3, flow rate = 0.8 mL min^{-1}): t_r (+, minor) = 30.1 min, t_r (−, major) = 43.0 min; *ee* = 13%; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.50$ (s, 6H), 1.94 (br s, 1H), 3.84 (s, 3H), 4.39 (br s, 1H), 5.27 (s, 1H), 6.73–6.81 (m, 4H), 7.31–7.39 (m, 2H), 7.47–7.55 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 31.4$, 31.5, 49.2, 55.5, 65.2, 81.0, 89.9, 109.6, 111.7, 118.0, 120.9, 128.5, 128.8, 133.6, 136.0, 138.3, 147.1; IR (neat): $\tilde{\nu} = 3409$, 3058, 2842, 1906, 1599, 1458, 1236, 1166, 1024 cm^{-1}; ; MS (EI, 70 eV): *m*/*z*: 330–328 $[M]^+$, 270–268 $[M-C_3H_7O]^+$, 207–205 $[M-C_7H_8NO]^+$, 171, 128, 112, 94, 76; elemental analysis calcd (%) for $C_{19}H_{20}NO_2Cl$ (329.82): C 69.19, H 6.11, N 4.25; found: C 68.88, H 6.61, N 4.75.

***N*-(2-Methoxyphenyl)-1-amino-1-(4-chlorophenyl)-5-methyl-5-trimethylsilyloxypent-2-yne (4e)**: Racemic amine **4e** was prepared according to GP 3A starting from *p*-chlorobenzaldehyde (**1a**, 0.056 g, 0.4 mmol), *o*-methoxyaniline (**2**, 0.049 g, 0.4 mmol, 1.0 equiv) and 3-methyl-3-trimethylsilyloxybut-1-yne (**8**, 0.189 g, 1.2 mmol, 3.0 equiv). Purification by flash column chromatography (*n*-pentane/diethyl ether 30:1) afforded pure *rac*-**4e** (0.088 g, 0.22 mmol, 55%) as a light yellow oil.

Nonracemic amine **4e** was prepared according to GP 4 starting from *p*-chlorobenzaldehyde (**1a**, 0.056 g, 0.4 mmol), *o*-methoxyaniline (**2**, 0.049 g, 0.4 mmol, 1.0 equiv) and 3-methyl-3-trimethylsilyloxybut-1-yne (**8**, 0.189 g, 1.2 mmol, 3.0 equiv). Purification by flash column chromatography (*n*-pentane/diethyl ether 30:1) afforded pure **4e** (0.042 g, 0.10 mmol, 26%) as a light yellow oil. $[\alpha]_D^{20} = -27.4$ ($c = 1.0$, $CHCl_3$); HPLC (Chiralcel OD, 254 nm, heptane/*i*PrOH 99:1, flow rate = 0.8 mL min^{-1}): t_r (+, minor) = 5.9 min, t_r (−, major) = 7.2 min; *ee* = 49%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.09$ (s, 9H), 1.47 (s, 6H), 3.85 (s, 3H), 4.69 (s, 1H), 5.28 (s, 1H), 6.72–6.80 (m, 4H), 7.31–7.39 (m, 2H), 7.47–7.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 1.9$, 33.1, 33.2, 49.4, 55.5, 66.5, 81.6, 90.2, 109.5, 111.7, 117.9, 121.0, 127.2, 128.5, 128.7, 133.5, 136.1, 138.4, 147.1; IR (neat): $\tilde{\nu} = 3422$, 2963, 2353, 1652, 1512, 1460, 1242, 1166, 1032 cm^{-1}; MS (EI, 70 eV): *m*/*z*: 403–401 $[M]^+$, 280–278 $[M-C_7H_8NO]^+$, 243, 188, 153, 131, 92, 73; elemental analysis calcd (%) for $C_{22}H_{28}NO_2ClSi$ (402.00): C 65.73, H 7.02, N 3.48; found: C 66.20, H 6.92, N 3.85.

***N*-(2-Methoxyphenyl)-3-amino-3-(2-furyl)-1-phenylprop-1-yne (4g)**: Prepared according to GP 3A starting from 2-furylaldehyde (**1b**, 0.038 g, 0.4 mmol), *o*-methoxyaniline (0.049 g, 0.4 mmol, 1.0 equiv) and phenylacetylene (0.123 g, 1.2 mmol, 3.0 equiv), using dichloromethane as the solvent. Purification by flash column chromatography (*n*-pentane/diethyl ether 10:1) afforded pure **4g** (0.060 g, 0.20 mmol, 50%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.86$ (s, 3H), 4.85 (br s, 1H), 5.60 (s, 1H), 6.38 (dd, $J = 3.3$, 1.9 Hz, 1H), 6.53 (dq, $J = 3.3$, 0.8 Hz, 1H), 6.74–6.84 (m, 2H), 6.87–6.94 (m, 2H), 7.26–7.34 (m, 3H), 7.39–7.46 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 44.7$, 55.5, 83.8, 86.4, 107.6, 109.7, 110.4, 111.9, 118.2, 121.0, 122.6, 128.2, 128.4, 131.8, 135.8, 142.6, 147.4, 152.0; IR (neat): $\tilde{\nu} = 3392$, 3049, 2930, 2847, 1724, 1597, 1506, 1453, 1243, 1126, 1020 cm^{-1}; MS (EI, 70 eV): *m*/*z*: 303 $[M]^+$, 272 $[M-CH_3O]^+$, 181 $[M-C_7H_8NO]^+$, 152, 127, 105, 92, 77; elemental analysis calcd (%) for $C_{20}H_{17}NO_2$ (303.35): C 79.19, H 5.65, N 4.62; found: C 79.16, H 5.69, N 4.59.

(*S*)-*N*-(2-Methoxyphenyl)-3-amino-1,3-diphenylprop-1-yne [(*S*)-4h]:[14] Prepared according to GP 4 starting from benzaldehyde (**1c**, 0.042 g, 0.4 mmol), *o*-methoxyaniline (0.049 g, 0.4 mmol, 1.0 equiv) and phenylacetylene (0.123 g, 1.2 mmol, 3.0 equiv). Purification by flash column chromatography (*n*-pentane/diethyl ether 25:1) afforded pure (*S*)-**4h** (0.081 g, 0.26 mmol, 67%) as a yellow oil. $[\alpha]_D^{20} = -78.4$ ($c = 1.01$, $CHCl_3$); HPLC (Chiralcel OD-H, 254 nm, heptane/*i*PrOH 95:5, flow rate = 0.6 mL min^{-1}): t_r (*R*, minor) = 8.4 min, t_r (*S*, major) = 12.0 min; *ee* = 87%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.83$ (s, 3H), 4.78 (s, 1H), 5.50 (s, 1H), 6.71–6.91 (m, 4H), 7.23–7.44 (m, 8H), 7.64–7.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 50.4$, 55.5, 84.9, 88.7, 109.6, 111.7, 117.7, 121.1, 122.9, 127.4, 128.0, 128.16, 128.20, 128.7, 131.8, 136.4, 139.9, 147.1; IR (neat): $\tilde{\nu} = 3418$, 3062, 2934, 2834, 1600, 1510, 1243, 1223 cm^{-1}; MS (EI, 70 eV): *m*/*z*: 313 $[M]^+$, 282 $[M-CH_3O]^+$, 236, 225, 191 $[M-C_7H_8NO]^+$; HRMS (EI): *m*/*z*: calcd for $C_{22}H_{19}NO$: 313.1467; found: 313.1466.

(−)-*N*-(2-Methoxyphenyl)-3-amino-3-(4-methylphenyl)-1-phenylprop-1-yne (4i): Prepared according to GP 4 starting from *p*-methylbenzaldehyde (**1d**, 0.048 g, 0.4 mmol), *o*-methoxyaniline (0.049 g, 0.4 mmol, 1.0 equiv) and phenylacetylene (0.123 g, 1.2 mmol, 3.0 equiv). Purification by flash column chromatography (*n*-pentane/diethyl ether 25:1) afforded pure (−)-**4i** (0.098 g, 0.29 mmol, 74%) as a yellow oil. $[\alpha]_D^{20} = -72.6$ ($c = 1.01$, $CHCl_3$); HPLC (Chiralcel OD-H, 254 nm, heptane/*i*PrOH 95:5, flow rate = 0.6 mL min^{-1}): t_r (+, minor) = 8.1 min, t_r (−, major) = 10.0 min; *ee* = 83%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.29$ (s, 3H), 3.75 (s, 3H), 4.66 (br s, 1H), 5.38 (s, 1H), 6.63–6.74 (m, 2H), 6.76–6.84 (m, 2H), 7.10–7.23 (m, 5H), 7.30–7.36 (m, 2H), 7.44–7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.3$, 50.2, 55.5, 84.7, 89.0, 109.6, 111.6, 117.6, 121.1, 123.0, 127.3, 128.2, 128.2, 129.4, 131.8, 136.5, 137.0, 137.7, 147.1; IR (neat): $\tilde{\nu} = 3422$, 3054, 2933, 1600, 1512, 1455, 1427, 1340, 1244, 1123, 1028 cm^{-1}; MS (EI, 70 eV): *m*/*z*: 327 $[M]^+$, 295, 236 $[M-C_7H_7O]^+$, 205 $[M-C_7H_8NO]^+$, 189, 178, 91, 77; HRMS (EI): *m*/*z*: calcd for $C_{23}H_{21}NO$: 327.1622; found: 327.1623.

(−)-*N*-(2-Methoxyphenyl)-3-amino-3-(2-methylphenyl)-1-phenylprop-1-yne (4j): Prepared according to GP 4 starting from *o*-methylbenzaldehyde (**1e**, 0.048 g, 0.4 mmol), *o*-methoxyaniline (0.049 g, 0.4 mmol, 1.0 equiv) and phenylacetylene (0.123 g, 1.2 mmol, 3.0 equiv). Purification by flash column chromatography (*n*-pentane/diethyl ether 20:1) afforded pure (−)-**4j** (0.104 g, 0.32 mmol, 82%) as a light yellow oil. $[\alpha]_D^{20} = -87.0$ ($c = 0.83$, $CHCl_3$); HPLC (Chiralcel OD-H, 254 nm, heptane/*i*PrOH 98:2, flow rate = 0.6 mL min^{-1}): t_r (+, minor) = 8.0 min, t_r (−, major) = 10.0 min; *ee* = 79%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.38$ (s, 3H), 3.74 (s, 3H), 4.56 (br s, 1H), 5.49 (s, 1H), 6.62–6.68 (m, 1H), 6.69–6.76 (m, 2H), 6.78–6.83 (m, 1H), 7.12–7.22 (m, 6H), 7.30–7.36 (m, 2H), 7.68–7.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.0$, 47.9, 55.4, 84.4, 88.5, 109.4, 111.2, 117.4, 121.1, 122.9, 126.3, 127.2, 127.9, 128.1, 128.1, 130.7, 131.7, 136.1, 136.5, 137.5, 147.0; IR (neat): $\tilde{\nu} = 3419$, 3059, 2938, 1599, 1509, 1456, 1236, 1124, 1032 cm^{-1}; MS (EI, 70 eV): *m*/*z*: 327 $[M]^+$, 296, 236 $[M-C_7H_7O]^+$, 205 $[M-C_7H_8NO]^+$, 190, 178, 127, 123, 77; elemental analysis calcd (%) for $C_{23}H_{21}NO$ (327.42): C 84.37, H 6.46, N 4.28; found: C 84.26, H 6.35, N 4.32.

(−)-*N*-(2-Methoxyphenyl)-3-amino-3-(4-methoxyphenyl)-1-phenylprop-1-yne (4k): Prepared according to GP 4 starting from *p*-methoxybenzalde-

hyde (**1f**, 0.054 g, 0.4 mmol), *o*-methoxyaniline (0.049 g, 0.4 mmol, 1.0 equiv) and phenylacetylene (0.123 g, 1.2 mmol, 3.0 equiv). Purification by flash column chromatography (*n*-pentane/diethyl ether 10:1) afforded pure (−)-**4k** (0.071 g, 0.21 mmol, 52%) as a yellow oil that solidified upon standing. $[\alpha]_D^{20} = -89.1$ ($c = 0.60$, $CHCl_3$); HPLC (Chiralcel OD-H, 254 nm, heptane/*i*PrOH 98:2, flow rate = 0.6 mL min^{-1}): t_r (−, major) = 13.6 min, t_r (+, minor) = 15.5 min; *ee* = 87%; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.85$ (s, 3H), 3.86 (s, 3H), 4.74 (d, $J = 5.5$ Hz, 1H), 5.47 (d, $J = 5.5$ Hz, 1H), 6.73–6.85 (m, 2H), 6.88–7.00 (m, 4H), 7.27–7.35 (m, 3H), 7.40–7.48 (m, 2H), 7.57–7.66 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 49.8$, 55.36, 55.41, 84.6, 89.0, 109.6, 111.7, 114.1, 117.6, 121.1, 123.0, 128.2, 128.2, 128.6, 131.8, 132.1, 136.5, 147.2, 159.4; IR (KBr): $\tilde{\nu} = 3426$, 2944, 1601, 1508, 1451, 1243, 1220, 1169 cm^{-1}; MS (EI, 70 eV): *m*/*z*: 343 $[M]^+$, 236, 221 $[M-C_7H_8NO]^+$, 206, 178, 152, 92, 77; elemental analysis calcd (%) for $C_{23}H_{21}NO$ (343.42): C 80.44, H 6.16, N 4.08; found: C 80.43, H 6.00, N 4.16.

(−)-*N*-(2-Methoxyphenyl)-3-amino-3-(3-methoxyphenyl)-1-phenylprop-1-yne (4l): Prepared according to GP 4 starting from *m*-methoxybenzaldehyde (**1g**, 0.054 g, 0.4 mmol), *o*-methoxyaniline (0.049 g, 0.4 mmol, 1.0 equiv) and phenylacetylene (0.123 g, 1.2 mmol, 3.0 equiv). Purification by flash column chromatography (*n*-pentane/diethyl ether 15:1) afforded pure (−)-**4l** (0.111 g, 0.32 mmol, 81%) as a yellow oil. $[\alpha]_D^{20} = -75.2$ ($c = 0.94$, $CHCl_3$); HPLC (Chiralcel OD-H, 254 nm, heptane/*i*PrOH 95:5, flow rate = 0.6 mL min^{-1}): t_r (+, minor) = 10.6 min, t_r (−, major) = 14.0 min; *ee* = 88%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.84$ (s, 3H), 3.85 (s, 3H), 4.79 (br s, 1H), 5.48 (s, 1H), 6.73–6.78 (m, 1H), 6.80–6.93 (m, 5H), 7.23–7.37 (m, 6H), 7.39–7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 50.5$, 55.4, 55.5, 84.8, 88.7, 109.6, 111.6, 113.0, 113.5, 117.7, 119.7, 121.1, 122.9, 128.17, 128.21, 129.7, 131.8, 136.4, 141.5, 147.1, 159.9; IR (neat): $\tilde{\nu} = 3418$, 3060, 2937, 1600, 1511, 1490, 1456, 1432, 1249, 1124, 1032 cm^{-1}; MS (EI, 70 eV): *m*/*z*: 343 $[M]^+$, 312, 236 $[M-C_7H_7O]^+$, 221 $[M-C_7H_8NO]^+$, 178, 120, 77; HRMS (EI): *m*/*z*: calcd for $C_{23}H_{21}NO_2$: 343.1572; found: 343.1572.

(−)-*N*-(2-Methoxyphenyl)-3-amino-3-(2-methoxyphenyl)-1-phenylprop-1-yne (4m): Prepared according to GP 4 starting from *o*-methoxybenzaldehyde (**1h**, 0.054 g, 0.4 mmol), *o*-methoxyaniline (0.049 g, 0.4 mmol, 1.0 equiv) and phenylacetylene (0.123 g, 1.2 mmol, 3.0 equiv). Purification by flash column chromatography (*n*-pentane/diethyl ether 25:1) afforded pure (−)-**4m** (0.115 g, 0.34 mmol, 84%) as a yellow oil. $[\alpha]_D^{20} = -52.7$ ($c = 0.63$, $CHCl_3$); HPLC (Chiralcel OD, 254 nm, heptane/*i*PrOH 99.5:0.5, flow rate = 0.6 mL min^{-1}): t_r (−, major) = 27.6 min, t_r (+, minor) = 35.0 min; *ee* = 97%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.74$ (s, 3H), 3.80 (s, 3H), 4.73 (br s, 1H), 5.76 (d, $J = 4.4$ Hz, 1H), 6.60–6.66 (m, 1H), 6.68–6.72 (m, 1H), 6.75–6.82 (m, 2H), 6.85 (dd, $J = 8.2$, 0.9 Hz, 1H), 6.92 (dt, $J = 7.4$, 0.9 Hz, 1H), 7.15–7.26 (m, 3H), 7.29–7.35 (m, 2H), 7.62 (dd, $J = 7.5$, 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 44.7$, 55.5, 55.8, 83.5, 89.4, 109.5, 111.0, 111.7, 117.4, 120.9, 121.1, 123.2, 128.0, 128.1, 128.2, 128.4, 129.2, 131.8, 136.6, 147.2, 159.6; IR (neat): $\tilde{\nu} = 3421$, 2934, 1599, 1510, 1458, 1246, 1125, 1028 cm^{-1}; MS (EI, 70 eV): *m*/*z*: 343 $[M]^+$, 312, 236 $[M-C_7H_7O]^+$, 221 $[M-C_7H_8NO]^+$, 189, 178, 115, 65; elemental analysis calcd (%) for $C_{23}H_{21}NO$ (343.42): C 80.44, H 6.16, N 4.08; found: C 80.73, H 6.54, N 4.06.

(−)-*N*-(2-Methoxyphenyl)-3-amino-3-(2-bromophenyl)-1-phenylprop-1-yne (4n): Prepared according to GP 4 starting from *o*-bromobenzaldehyde (**1i**, 0.074 g, 0.4 mmol), *o*-methoxyaniline (0.049 g, 0.4 mmol, 1.0 equiv) and phenylacetylene (0.123 g, 1.2 mmol, 3.0 equiv). Purification by flash column chromatography (*n*-pentane/diethyl ether 20:1) afforded pure (−)-**4n** (0.140 g, 0.36 mmol, 89%) as a yellow oil. $[\alpha]_D^{20} = -47.2$ ($c = 1.0$, $CHCl_3$); HPLC (Chiralcel OD-H, 254 nm, heptane/*i*PrOH 95:5, flow rate = 0.6 mL min^{-1}): t_r (+, minor) = 8.8 min, t_r (−, major) = 10.0 min; *ee* = 81%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.78$ (s, 3H), 4.78 (br s, 1H), 5.71 (s, 1H), 6.57–6.81 (m, 4H), 7.07–7.40 (m, 5H), 7.50–7.56 (m, 2H), 7.70–7.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 50.4$, 55.5, 84.7, 87.8, 109.6, 111.5, 117.9, 121.2, 122.7, 123.6, 128.0, 128.2, 128.4, 128.9, 129.5, 131.8, 133.2, 136.1, 139.0, 147.1; IR (neat): $\tilde{\nu} = 3417$, 3060, 2933, 2835, 1599, 1511, 1455, 1345, 1244, 1127, 1028 cm^{-1}; MS (EI, 70 eV): *m*/*z*: 393–391 $[M]^+$, 362–360, 271–269 $[M-C_7H_8NO]^+$, 236 $[M-C_6H_4Br]^+$, 189; HRMS (EI): *m*/*z*: calcd for $C_{22}H_{18}NOBr$: 391.0572; found: 391.0572.

(−)-*N*-(2-Methoxyphenyl)-3-amino-3-(2-naphthyl)-1-phenylprop-1-yne (4o): Prepared according to GP 4 starting from 2-naphthaldehyde (**1j**, 0.062 g, 0.4 mmol), *o*-methoxyaniline (0.049 g, 0.4 mmol, 1.0 equiv) and phenylacetylene (0.123 g, 1.2 mmol, 3.0 equiv). Purification by flash column chromatography (*n*-pentane/diethyl ether 18:1) afforded pure (−)-**4o** (0.113 g, 0.31 mmol, 78%) as a yellow oil that solidified upon standing. $[\alpha]_D^{20} = -69.9$ ($c = 0.85$, $CHCl_3$); HPLC (Chiralcel OD-H, 254 nm, heptane/*i*PrOH 95:5, flow rate = 0.6 mL min^{-1}): t_r (+, minor) = 11.4 min, t_r (−, major) = 16.1 min; *ee* = 81%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.76$ (s, 3H), 4.80 (br s, 1H), 5.58 (s, 1H), 6.63–6.82 (m, 4H), 7.17–7.24 (m, 3H), 7.32–7.44 (m, 4H), 7.67 (dd, $J = 8.7$, 1.7 Hz, 1H), 7.74–7.83 (m, 3H), 8.05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 50.7$, 55.5, 85.2, 88.7, 109.6, 111.7, 117.8, 121.1, 122.9, 125.4, 126.1, 126.2, 127.7, 128.15, 128.21, 128.3, 128.6, 131.8, 133.1, 133.4, 136.5, 137.3, 147.2; IR (neat): $\tilde{\nu} = 3391$, 2936, 2854, 1598, 1505, 1455, 1235, 1123, 1026 cm^{-1}; MS (EI, 70 eV): *m*/*z*: 363 $[M]^+$, 241 $[M-C_7H_8NO]^+$, 226, 139, 115, 77; elemental analysis calcd (%) for $C_{26}H_{21}NO$ (363.45): C 85.92, H 5.82, N 3.85; found: C 86.14, H 5.99, N 3.92.

(−)-*N*-(2-Methoxyphenyl)-3-amino-3-(1-naphthyl)-1-phenylprop-1-yne (4p): Prepared according to GP 4 starting from 1-naphthaldehyde (**1k**, 0.062 g, 0.4 mmol), *o*-methoxyaniline (0.049 g, 0.4 mmol, 1.0 equiv) and phenylacetylene (0.123 g, 1.2 mmol, 3.0 equiv). Purification by flash column chromatography (*n*-pentane/diethyl ether 13:1) afforded pure (−)-**4p** (0.090 g, 0.25 mmol, 62%) as a yellow oil. $[\alpha]_D^{20} = -48.7$ ($c = 0.96$, $CHCl_3$); HPLC (Chiralcel OD-H, 254 nm, heptane/*i*PrOH 98:2, flow rate = 0.6 mL min^{-1}): t_r (+, minor) = 13.0 min, t_r (−, major) = 14.9 min; *ee* = 86%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.70$ (s, 3H), 4.78 (br s, 1H), 6.04 (s, 1H), 6.65–6.75 (m, 2H), 6.77–6.88 (m, 2H), 7.16–7.22 (m, 3H), 7.30–7.37 (m, 3H), 7.39–7.48 (m, 2H), 7.77 (d, $J = 8.5$ Hz, 1H), 7.80–7.85 (m, 1H), 7.93 (d, $J = 6.9$ Hz, 1H), 8.10–8.16 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 48.1$, 55.5, 85.3, 88.6, 109.6, 111.3, 117.6, 121.2, 123.0, 123.7, 125.4, 125.5, 125.8, 126.5, 128.18, 128.21, 128.8, 129.0, 130.9, 131.8, 134.1, 134.6, 136.5, 147.1; IR (neat): $\tilde{\nu} = 3417$, 3055, 2937, 2838, 1598, 1509, 1453, 1232, 1125, 1030 cm^{-1}; MS (EI, 70 eV): *m*/*z*: 363 $[M]^+$, 241 $[M-C_7H_8NO]^+$, 226, 115, 92, 65; elemental analysis calcd (%) for $C_{26}H_{21}NO$ (363.45): C 85.92, H 5.82, N 3.85; found: C 85.64, H 5.88, N 3.82.

(−)-*N*-(2-Methoxyphenyl)-3-amino-3-[2-(5-bromo)thienyl]-1-phenylprop-1-yne (4q): Prepared according to GP 4 starting from 5-bromo-2-thienylaldehyde (**1l**, 0.077 g, 0.4 mmol), *o*-methoxyaniline (0.049 g, 0.4 mmol, 1.0 equiv) and phenylacetylene (0.123 g, 1.2 mmol, 3.0 equiv). Purification by flash column chromatography (*n*-pentane/diethyl ether 3:1) afforded pure (−)-**4q** (0.142 g, 0.36 mmol, 89%) as a yellow oil. $[\alpha]_D^{20} = -62.5$ ($c = 0.52$, $CHCl_3$); HPLC (Chiralcel OD-H, 254 nm, heptane/*i*PrOH 95:5, flow rate = 0.6 mL min^{-1}): t_r (+, minor) = 9.5 min, t_r (−, major) = 11.6 min; *ee* = 68%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.86$ (s, 3H), 4.87 (d, $J = 7.6$ Hz, 1H), 5.68 (d, $J = 7.4$ Hz, 1H), 6.80–6.88 (m, 4H), 6.95 (d, $J = 3.8$ Hz, 1H), 7.05 (dd, $J = 3.8$, 1.2 Hz, 1H), 7.26–7.34 (m, 4H), 7.41–7.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 46.5$, 55.6, 84.7, 87.4, 109.8, 112.1, 118.5, 121.0, 122.3, 125.5, 128.21, 128.23, 128.5, 129.5, 131.7, 135.5, 145.7, 147.3; IR (neat): $\tilde{\nu} = 3402$, 3059, 2936, 2838, 2237, 1729, 1599, 1508, 1448, 1338, 1241, 1124, 1030 cm^{-1}; MS (EI, 70 eV): *m*/*z*: 399–397 $[M]^+$, 320–318, 277–275 $[M-C_7H_8NO]^+$, 196–194, 151, 138, 107, 91, 65; elemental analysis calcd (%) for $C_{20}H_{16}NOBrS$ (398.31): C 60.31, H 4.05, N 3.52; found: C 60.97, H 4.37, N 3.40.

(−)-*N*-(2-Methoxyphenyl)-3-amino-3-(cyclohexyl)-1-phenylprop-1-yne (4r): Prepared according to GP 4 starting from cyclohexanecarbaldehyde (**1m**, 0.045 g, 0.4 mmol), *o*-methoxyaniline (0.049 g, 0.4 mmol, 1.0 equiv) and phenylacetylene (0.123 g, 1.2 mmol, 3.0 equiv). Purification by flash column chromatography (*n*-pentane/diethyl ether 3:1) afforded pure (−)-**4r** (0.119 g, 0.37 mmol, 93%) as a yellow oil. $[\alpha]_D^{20} = -105.7$ ($c = 0.70$, $CHCl_3$); HPLC (2 × Chiralcel OD-H, 254 nm, heptane/*i*PrOH 99.5:0.5, flow rate = 0.3 mL min^{-1}): t_r (+, minor) = 48.2 min, t_r (−, major) = 52.2 min; *ee* = 85%; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.05$–1.35 (m, 5H), 1.60–1.74 (m, 4H), 1.79–1.93 (m, 2H), 3.78 (s, 3H), 4.11 (d, $J = 5.7$ Hz, 1H), 4.41 (br s, 1H), 6.59–6.67 (m, 1H), 6.69–6.78 (m, 2H), 6.79–6.86 (m, 1H), 7.15–7.22 (m, 3H), 7.28–7.34 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 26.1$, 26.2, 26.5, 28.8, 30.2, 42.4, 51.5, 55.5, 83.6, 89.3, 109.6, 111.2,

117.0, 121.2, 128.2, 128.3, 131.8, 132.1, 136.9, 147.2; IR (neat): $\tilde{\nu}$ = 3425, 2926, 2852, 1600, 1513, 1453, 1245, 1222, 1124, 1029 cm^{-1}; MS (EI, 70 eV): *m/z*: 319 $[M]^+$, 236 $[M-C_6H_{11}]^+$, 134, 115, 91, 77; elemental analysis calcd (%) for $C_{22}H_{25}NO$ (319.44): C 82.72, H 7.89, N 4.38; found: C 82.79, H 8.15, N 4.26.

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[1] a) *Stereocontrolled Organic Synthesis* (Ed.: B. M. Trost), Blackwell Scientific Publications, London, **1994**; b) R. S. Atkinson, *Stereoselective Synthesis*, Wiley, Chichester, **1995**; c) *Advanced Asymmetric Synthesis* (Ed.: G. R. Stephenson), Chapman and Hall, London, **1996**; d) G.-Q. Lin, Y.-M. Li, A. S. C. Chan, *Principles and Applications of Asymmetric Synthesis*, Wiley, Chichester, **2001**.

[2] Examples of application of propargylic alcohols to the synthesis of natural compounds: vitamins E and K: a) N. Cohen, R. J. Lopresti, C. Neukom, G. Saucy, *J. Org. Chem.* **1980**, *45*, 582; alkaloids: b) L. E. Overman, K. L. Bell, *J. Am. Chem. Soc.* **1981**, *103*, 1851; palytoxin: c) J. Leder, H. Fujioka, Y. Kishi, *Tetrahedron Lett.* **1983**, *24*, 1463; cystochalasin: d) G. Stork, E. J. Nakamura, *J. Am. Chem. Soc.* **1983**, *105*, 5510; e) S. H. Cheon, W. J. Christ, L. D. Hawkins, H. Jin, Y. Kishi, *Tetrahedron Lett.* **1986**, *27*, 4759; sterepolide: f) B. M. Trost, P. A. Hipskind, J. Y. L. Chung, C. Chan, *Angew. Chem.* **1989**, *101*, 1559; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1502; chlorotricholide: g) W. R. Roush, R. J. Sciotti, *J. Am. Chem. Soc.* **1994**, *116*, 6457; methylenolactocin: h) G. Zhu, X. Lu, *J. Org. Chem.* **1995**, *60*, 1087; for a recent application towards the synthesis of polyketide members of the cytostatine family, see: i) J. A. Marshall, M. P. Borbeau, *Org. Lett.* **2003**, *5*, 3197.

[3] Examples of application of propargylic amines to the synthesis of natural compounds: synthesis of dynemicines: a) J. A. Porco, Jr., F. J. Schoenen, T. J. Stout, J. Clardy, S. L. Schreiber, *J. Am. Chem. Soc.* **1990**, *112*, 7410; b) K. C. Nicolaou, C.-K. Hwang, A. L. Smith, S. V. Wendeborn, *J. Am. Chem. Soc.* **1990**, *112*, 7416; c) T. Yoon, M. D. Shair, S. J. Danishefsky, G. K. Shulte, *J. Org. Chem.* **1994**, *59*, 3752; formal total synthesis of (+)-conessine: d) B. Jiang, M. Xu, *Angew. Chem.* **2004**, *116*, 2597; *Angew. Chem. Int. Ed.* **2004**, *43*, 2543; synthesis of (+)-saxitoxin: e) J. J. Fleming, J. Du Bois, *J. Am. Chem. Soc.* **2006**, *128*, 3926.

[4] See, for example: synthesis of β-lactams: a) M. Shibasaki, Y. Ishida, G. Iwasaki, T. Iimori, *J. Org. Chem.* **1987**, *52*, 3488; b) N. Miyachi, F. Kanda, M. Shibasaki, *J. Org. Chem.* **1989**, *54*, 3551; synthesis of inhibitors of the serotonine and norepinephrine transporter: c) A. Hoepping, K. M. Johnson, C. George, J. Flippen-Anderson, A. P. Kozikowski, *J. Med. Chem.* **2000**, *43*, 2064; synthesis of plant protectives (herbicides and fungicides): d) C. Swithenbank, P. J. McNulty, K. L. Viste, *J. Agric. Food Chem.* **1971**, *19*, 417.

[5] For reviews on the alkynylation of carbonyl compounds, see: a) D. E. Frantz, R. Fässler, C. S. Tomooka, E. M. Carreira, *Acc. Chem. Res.* **2000**, *33*, 373; b) L. Pu, *Tetrahedron* **2003**, *59*, 9873; c) P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.* **2004**, 4095; d) P. Aschwanden, E. M. Carreira in *Acetylene Chemistry: Chemistry, Biology and Material Science* (Eds.: F. Diederich, P. J. Stang, R. R. Tykwinski), Wiley-VCH, Weinheim, **2004**, p. 269.

[6] Recent examples of enantioselective alkynylation of aldehydes: a) T. Fang, D.-M. Du, S.-F. Lu, J. Xu, *Org. Lett.* **2005**, *7*, 2081; b) C. C. Watts, P. Thoniyot, L. C. Hirayama, T. Romano, B. Singaram, *Tetrahedron: Asymmetry* **2005**, *16*, 1829; c) J. E. D. Kirkham, T. D. L. Courtney, V. Lee, J. E. Baldwin, *Tetrahedron* **2005**, *61*, 7219; d) M. G. Pizzuti, S. Superchi, *Tetrahedron: Asymmetry* **2005**, *16*, 2263; e) R. Takita, K. Yakura, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 13760; f) B. M. Trost, A. H. Weiss, A. Jacobi von Wangelin, *J. Am. Chem. Soc.* **2006**, *128*, 8; g) G. Gao, Q. Wang, X.-Q. Yu, R.-G. Xie, L. Pu, *Angew. Chem.* **2006**, *118*, 128; *Angew. Chem. Int. Ed.* **2006**, *45*, 122; h) D. P. G. Emmerson, W. P. Hems, B. G. Davis, *Org. Lett.* **2006**, *8*, 207; i) Z. Xu, L. Lin, J. Xu, W. Yan, R. Wang, *Adv. Synth. Catal.* **2006**, *348*, 506; j) J. Ekström, A. B. Zaitsev, H. Adolfsson, *Synlett* **2006**, 884; k) A. R. Rajaram, L. Pu, *Org. Lett.* **2006**, *8*, 2019; l) G. Blay, I. Fernandez, A. Marco-Aleixandre, J. R. Pedro, *J. Org. Chem.* **2006**, *71*, 6674; m) C. Wolf, S. Liu, *J. Am. Chem. Soc.* **2006**, *128*, 10996; recent examples of enantioselective alkynylation of ketones: n) L. Liu, R. Wang, Y.-F. Kang, C. Chen, Z.-Q. Xu, Y.-F. Zhou, M. Ni, H.-Q. Cai, M.-Z. Gong, *J. Org. Chem.* **2005**, *70*, 1084; o) Y.-F. Kang, L. Liu, R. Wang, Y.-F. Zhou, W.-J. Yan, *Adv. Synth. Catal.* **2005**, *347*, 243; p) C. Chen, L. Hong, Z.-Q. Xu, L. Liu, R. Wang, *Org. Lett.* **2006**, *8*, 2277; q) G. Lu, X. Li, Y.-M. Li, F. Y. Kwang, A. S. C. Chan, *Adv. Synth. Catal.* **2006**, *348*, 1926.

[7] For a review, see: L. Zani, C. Bolm, *Chem. Commun.* **2006**, 4263.

[8] a) C. Koradin, K. Polborn, P. Knochel, *Angew. Chem.* **2002**, *114*, 2651; *Angew. Chem. Int. Ed.* **2002**, *41*, 2535; b) C. Koradin, N. Gommermann, K. Polborn, P. Knochel, *Chem. Eur. J.* **2003**, *9*, 2797.

[9] a) N. Gommermann, C. Koradin, K. Polborn, P. Knochel, *Angew. Chem.* **2003**, *115*, 5941; *Angew. Chem. Int. Ed.* **2003**, *42*, 5763; b) N. Gommermann, P. Knochel, *Chem. Commun.* **2004**, 2324; c) H. Dube, N. Gommermann, P. Knochel, *Synthesis* **2004**, 2015; d) N. Gommermann, P. Knochel, *Tetrahedron* **2005**, *61*, 11418; e) N. Gommermann, A. Gherig, P. Knochel, *Synlett* **2005**, 2796; f) N. Gommermann, P. Knochel, *Synlett* **2005**, 2799; g) N. Gommermann, P. Knochel, *Chem. Eur. J.* **2006**, *12*, 4380; application to the asymmetric synthesis of the natural product homolaudanosine: h) A. M. Taylor, S. L. Schreiber, *Org. Lett.* **2006**, *8*, 143.

[10] Recently a variation of the same protocol, based on the use of new, axially chiral pinap ligands, has been reported: a) T. F. Knöpfel, P. Aschwanden, T. Ichikawa, T. Watanabe, E. M. Carreira, *Angew. Chem.* **2004**, *116*, 6097; *Angew. Chem. Int. Ed.* **2004**, *43*, 5971; b) P. Aschwanden, C. R. J. Stephenson, E. M. Carreira, *Org. Lett.* **2006**, *8*, 2437.

[11] a) C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2002**, *124*, 5638; b) C. Wei, J. T. Mague, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5749; c) A. Bisai, V. K. Singh, *Org. Lett.* **2006**, *8*, 2405; use of polymer-bound Cu^I/pybox complexes: d) A. Weissberg, B. Halak, M. Portnoy, *J. Org. Chem.* **2005**, *70*, 4556; for a review, see: e) C. Wei, Z. Li, C.-J. Li, *Synlett* **2004**, 1472.

[12] Asymmetric addition of alkynes to an α-imino ester: J.-X. Ji, J. Wu, A. S. C. Chan, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 11196.

[13] a) M. Benaglia, D. Negri, G. Dell'Anna, *Tetrahedron Lett.* **2004**, *45*, 8705; b) S. Orlandi, F. Colombo, M. Benaglia, *Synthesis* **2005**, 1689; c) F. Colombo, M. Benaglia, S. Orlandi, F. Usuelli, G. Celentano, *J. Org. Chem.* **2006**, *71*, 2064.

[14] J. F. Traverse, A. H. Hoveyda, M. L. Snapper, *Org. Lett.* **2003**, *5*, 3273.

[15] a) T. R. Wu, J. M. Chong, *Org. Lett.* **2006**, *8*, 15; for a similar procedure employing a chiral *B*-alkynyl borabicyclononane as a reagent see: b) A. Z. Gonzalez, E. Canales, J. A. Soderquist, *Org. Lett.* **2006**, *8*, 3331.

[16] B. Jiang, Y.-G. Si, *Angew. Chem.* **2004**, *116*, 218; *Angew. Chem. Int. Ed.* **2004**, *43*, 216.

[17] W. Wei, M. Kobayashi, Y. Ukaji, K. Inomata, *Chem. Lett.* **2006**, *35*, 176.

[18] For diastereoselective approaches to the synthesis of propargylic amines based on the in situ generation of alkynylzinc nucleophiles catalyzed by Zn^{II} salts, see: a) D. E. Frantz, R. Fässler, E. M. Carreira, *Angew. Chem.* **2002**, *114*, 3180; *Angew. Chem. Int. Ed.* **2002**, *41*, 3054; b) D. Topic, P. Aschwanden, R. Fässler, E. M. Carreira, *Org. Lett.* **2005**, *7*, 5329; c) B. Jiang, Y.-G. Si, *Tetrahedron Lett.* **2003**, *44*, 6767.

[19] This was a surprising result, considering that a mixture of only dimethylzinc and phenylacetylene was previously reported to be unreac-

tive toward aldehydes. See: Z. Li, V. Upadhyay, A. E. DeCamp, L. DiMichele, P. J. Reider, *Synthesis* **1999**, 1453.
[20] P. G. Cozzi, J. Rudolph, C. Bolm, P.-O. Norrby, C. Tomasini, *J. Org. Chem.* **2005**, *70*, 5733.
[21] L. Zani, S. Alesi, P. G. Cozzi, C. Bolm, *J. Org. Chem.* **2006**, *71*, 1558.
[22] P. G. Cozzi, *personal communication to the authors.*
[23] P. G. Cozzi, E. Rivalta, *Angew. Chem.* **2005**, *117*, 3666; *Angew. Chem. Int. Ed.* **2005**, *44*, 3600; P. G. Cozzi, *Adv. Synth. Catal.* **2006**, *348*, 2075.
[24] Reviews: a) K. Soai, T. Shibata in *Comprehensive Asymmetric Catalysis, Vol. 2* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, p. 911; b) L. Pu, H.-B. Yu, *Chem. Rev.* **2001**, *101*, 757; c) D. Enders, U. Reinhold, *Tetrahedron: Asymmetry* **1997**, *8*, 1895; d) S. E. Denmark, O. J.-C. Nicaise in *Comprehensive Asymmetric Catalysis, Vol. 2* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, p. 923; e) R. Bloch, *Chem. Rev.* **1998**, *98*, 1407; f) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069; g) F. Schmidt, R. T. Stemmler, J. Rudolph, C. Bolm, *Chem. Soc. Rev.* **2006**, *35*, 454.
[25] Walsh demonstrated that the efficiency and selectivity of the enantioselective alkylzinc addition to ketones could be substantially improved under "concentrated" or solvent-free conditions, see: S.-J. Jeon, H. Li, P. J. Walsh, *J. Am. Chem. Soc.* **2005**, *127*, 16416.
[26] For an example employing propargylic alcohols as substrates, see: D. Boyall, F. López, H. Sasaki, D. Frantz, E. M. Carreira, *Org. Lett.* **2000**, *2*, 4233.
[27] a) A. S. Demir, *Pure Appl. Chem.* **1997**, *69*, 105; b) G. Alvaro, G. Martelli, D. Savoia, A. Zoffoli, *Synthesis* **1998**, 1773; c) G. Borg, M. Chino, J. A. Ellman, *Tetrahedron Lett.* **2001**, *42*, 1433; d) A. S. Demir, Ö. Sesenoglu, D. Ülkü, C. Arici, *Helv. Chim. Acta* **2003**, *86*, 91.
[28] THF had already been found to be inapplicable for the ligand-free reaction, see Supporting Information for ref. [21].
[29] First application in catalysis: K. Soai, S. Yokoyama, T. Hayasaka, *J. Org. Chem.* **1991**, *56*, 4264.
[30] C. Bolm, K. Muñiz-Fernández, A. Seger, G. Raabe, *Synlett* **1997**, 1051.
[31] See, for example: C. Bolm, N. Hermanns, J. P. Hildebrand, K. Muñiz, *Angew. Chem.* **2000**, *112*, 3607; *Angew. Chem. Int. Ed.* **2000**, *39*, 3465.
[32] a) B. Jiang, Z. Chen, W. Xiong, *Chem. Commun.* **2002**, 1524; b) Z. Chen, W. Xiong, B. Jiang, *Chem. Commun.* **2002**, 2098.
[33] B. Jiang, Z. Chen, X. Tang, *Org. Lett.* **2002**, *4*, 3451.
[34] It should be pointed out that the optical rotation of the compounds sold by Aldrich as (+)-**10** and (+)-**19** was measured in two different solvents. In fact, the absolute configuration of their stereocenters is opposite. Accordingly, the sense of asymmetric induction in the reactions promoted by (+)-(1*S*,2*R*)-**10** was opposite to that of the reaction promoted by (+)-(1*R*,2*S*)-**19**.
[35] K. Soai, T. Hatanaka, T. Miyazawa, *J. Chem. Soc. Chem. Commun.* **1992**, 1097.
[36] a) P. A. Chaloner, S. A. R. Perera, *Tetrahedron Lett.* **1987**, *28*, 3013; b) P. A. Chaloner, E. Langadianou, *Tetrahedron Lett.* **1990**, *31*, 5185; c) P. A. Chaloner, E. Langadianou, S. A. R. Perera, *J. Chem. Soc. Perkin Trans. 1* **1991**, 2731.
[37] S. Terashima, N. Tanno, K. Koga, *Tetrahedron Lett.* **1980**, *21*, 2753.
[38] a) M. T. Reetz, M. W. Drewes, A. Schmitz, *Angew. Chem.* **1987**, *99*, 1186; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1141; b) R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, V. Molteni, L. Raimondi, *Tetrahedron* **1995**, *51*, 8941.
[39] The NMR spectrum of the fraction resulting from flash column chromatography was identical to that of clean (1*R*,2*S*)-**22e** obtained from the alkylation reaction depicted in Scheme 2.
[40] (1*R*,2*S*)-**23a** has already been employed as a ligand in enantioselective catalysis. For an application in the enantioselective deconjugation of α,β-unsaturated esters, see: a) O. Piva, F. Henin, J. Muzart, J.-P. Pete, *Tetrahedron Lett.* **1987**, *28*, 4825; for an application in the Ru-catalyzed asymmetric transfer hydrogenation, see: b) K. Everaere, J.-F. Carpentier, A. Mortreux, M. Bulliard, *Tetrahedron: Asymmetry* **1999**, *10*, 4083.
[41] (1*R*,2*S*)-**23b** has been used as an intermediate for the preparation of a chiral auxiliary to be used in diastereoselective aldol reactions, see: M. Kurosu, M. Lorca, *J. Org. Chem.* **2001**, *66*, 1205.
[42] When 2-furfuraldehyde (**1b**) was used as the substrate in combination with phenylacetylene (**3**) the corresponding product was initially obtained in good yield with high enantiomeric excess (96% *ee*). Unfortunately, problems were encountered in reproducing this result, which therefore could not be confirmed. We are currently conducting additional investigations in order to elucidate this peculiar behavior.
[43] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.
[44] J. D. Olszewski, M. Marshalla, M. Sabat, R. J. Sundberg, *J. Org. Chem.* **1994**, *59*, 4285.

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