Catalytic enantioselective addition of terminal alkynes to aromatic aldehydes using zinc-hydroxyamide complexes†

Gonzalo Blay,[a] Luz Cardona,[a] Isabel Fernández,[a] Alícia Marco-Aleixandre,[a] M. Carmen Muñoz[b] and José R. Pedro*[a]

Received 12th June 2009, Accepted 17th July 2009
First published as an Advance Article on the web 17th August 2009
DOI: 10.1039/b911592g

A mandelamide ligand, derived from (*S*)-mandelic acid and (*S*)-phenylethanamine, catalyzes the addition of aryl-, alkyl- and silyl-alkynylzinc reagents to aromatic and heteroaromatic aldehydes with good yields and good to high enantioselectivities.

Introduction

The enantioselective alkynylation of aldehydes is one of the most convenient methods for the synthesis of chiral nonracemic secondary propargylic alcohols, as a new C-C bond is formed concomitantly with the creation of a stereogenic center in a single transformation.[1] These kinds of compounds serve as precursors for a variety of chiral materials since the heteroatom and alkyne are handles for further transformations. For this reason, propargylic alcohols have been used as intermediates in the efficient synthesis of many natural products and pharmaceuticals.[2]

A number of catalytic protocols for this enantioselective reaction have been developed in the last years. In most of them, bisalkynylzinc or alkylakynylzinc species are used as nucleophiles because these reagents feature a high functional group tolerance and a slow rate of addition to carbonyl groups in the absence of a Lewis basic ligand.[3] After the pioneering work by Carreira *et al.*[4] on the alkynylation of aldehydes with zinc acetylides generated *in situ* from terminal alkynes and $Zn(OTf)_2$ using ephedrine as chiral inductor, a number of *N*,*O* ligands have been employed as catalysts or pre-catalysts in these reactions. Examples include amino alcohols,[5] imino alcohols,[6] oxazolidines,[7] hydroxy sulfonamides[8] and hydroxy carboxyamides.[9] Furthermore, some catalysts based on the axially chiral 1,1′-bi-2-naphthol ligand and Ti(IV) have been developed.[10] Based on the same kinds of ligands, Shibasaki has described the asymmetric alkynylation of aldehydes promoted by the In(III)/BINOL complex and Cy_2NMe.[11]

The design of new chiral ligands to be used in catalytic enantioselective reactions is an area of permanent interest. Easy preparation by short pathways from readily available non expensive starting materials, modularity and structural variation, low molecular weight, availability in both enantiomeric forms and stability are desirable features in any ligand of practical use. According to these premises, our group has been developing hydroxy amide chiral ligands that are conveniently synthesized in simple, short sequences and from cheap, easily available chiral resources.[12] Recently we disclosed that simple (*S*)-mandelamides (Fig. 1) in combination with $Ti(O^iPr)_4$ could be used to effectively catalyze the addition of dialkylzinc reagents to aldehydes with moderate to good enantioselectivity.[13] In absence of $Ti(OiPr)_4$, these ligands also catalyze the addition of dimethylzinc to α-ketoesters,[14] and we have advanced the alkynylation of heteroaromatic aldehydes,[15] with good yields and enantioselectivities for both reactions.

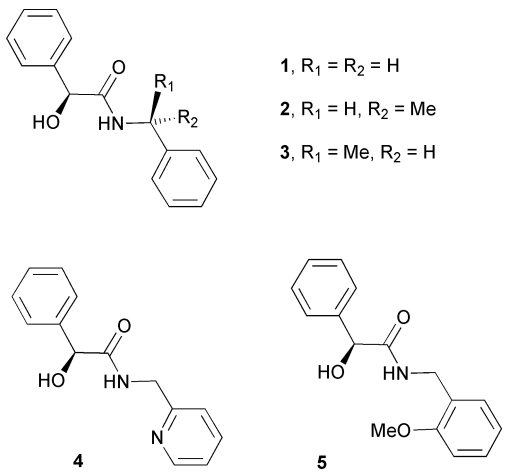


Fig. 1 Mandelamide ligands used in this study.

In this paper, we report the enantioselective addition of a variety of terminal alkynes to aromatic and heteroaromatic aldehydes using simple mandelamide ligands and dimethylzinc, with high yields and good to high enantioselectivities.

Results and discussion

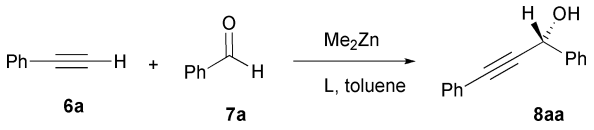
Addition of phenylacetylene

The reaction between benzaldehyde and phenylacetylene in the presence of Me_2Zn and mandelamides **1-5** in toluene was used for the optimization process (Scheme 1, Table 1). $Ti(OiPr)_4$ was not used to avoid addition of dimethlyzinc to the aldehyde.[13] The study of this reaction revealed the following results:[15]

a) Mandelamides (*S*)-**1** and (*S*,*S*)-**3** gave the best results in terms of enantioselectivity.

[a]*Departament de Química Orgànica, Facultat de Química, Universitat de València, Dr. Moliner 50, E-46100-Burjassot (València), Spain. E-mail: jose.r.pedro@uv.es; Fax: +34 963544328*
[b]*Departamento de Física Aplicada, Universidad Politécnica de Valencia, E-46071, València, Spain*

† Electronic supplementary information (ESI) available: NMR spectra and HPLC chromatograms for compounds **8be**, **8cd**, **8ce**, **8de**, **8ds**, **8dt**, **8du** and **9**. CCDC reference numbers 734711. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b911592g



Scheme 1 Addition of phenylacetylene to benzaldehyde.

Table 1 Alkynylation of benzaldehyde (**7a**) with phenylacetylene (**6a**) in the presence of dimethylzinc and mandelamides as chiral ligands[a]

Entry	L	*T*/°C	**8aa** Yield[b] (%)	Ee[c](%)
1	**1**	0	65	51
2	**2**	0	80	29
3	**3**	0	85	50
4	**4**	0	85	4
5	**5**	0	87	31
6	**1**	50	90	42
7	**3**	50	86	65
8	**1**	70	84	40
9	**3**	70	90	70
10[d]	**3**	70/0	81	3
11[e]	**3**	70/0	95	89
12[ef]	**3**	70/0	87	79
13[eg]	**3**	70/0	68	64
14[eh]	**3**	70/0	90	79

[a] All the reactions were carried out in toluene under nitrogen, **7a** (1 mmol), **L** (0.2 mmol), Me_2Zn (6 mmol), **6a** (7.2 mmol). [b] Isolated product after column chromatography. [c] Determined by HPLC on a Chiralcel OD-H column. [d] Reaction according Scheme 2, equation 2. [e] Reaction according Scheme 2, equation 1. [f] Me_2Zn (5 mmol). [g] Me_2Zn (4 mmol). [h] Et_2Zn (6 mmol)

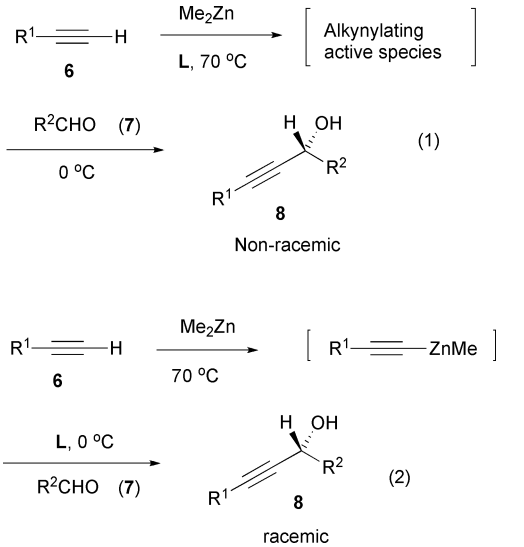
b) The enantioselectivity of the reaction was dependent on the temperature of reaction between the alkyne and dimethylzinc.

c) The enantioselectivity of the reaction was dependent on the order of addition of the mandelamide ligand.

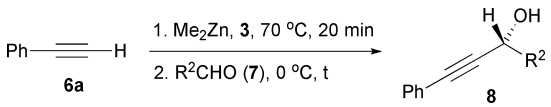
d) The enantioselectivity of the reaction was dependent on the number of equivalents of Me_2Zn

The optimal reaction conditions required pre-formation of the alkynylzinc reagent by heating the alkyne and Me_2Zn at 70 °C in the presence of the mandelamide ligand (until the formation of an abundant white precipitate), followed by addition of the aldehyde at 0 °C (Scheme 2, equation 1). Pre-formation of the alkynylzinc reagent in the absence of the ligand followed by the addition of ligand and aldehyde at 0 °C resulted in a racemic product (Scheme 2, equation 2). Although we do not have a clear explanation for this fact, we believe that the formation of the catalytic complex involves deprotonation of the mandelamide, which can be achieved by Me_2Zn at high temperature but not by the less basic pre-formed alkynylzinc reagent at 0 °C. The reduction in the number of equivalents of Me_2Zn (entries 12 and 13), as well as the use of Et_2Zn (entry 14) gave rise to a reduction in the enantioselectivity.

The optimized conditions were applied to a number of aromatic and aliphatic aldehydes (Scheme 3). The results are gathered in Table 2. In general, the reaction took place with high yields and enantiomeric excesses from good to high for most aromatic aldehydes (Table 2, entries 1–15). There is not a clear relationship between enantioselectivity and the electronic features of the substituents on the aromatic ring, although for *p*-halobenzaldehydes it can be observed an increase of the *ee* with the electronegativity of the halogen atom (entries 2–4). The presence of strong electron-



Scheme 2 Pre-formation of the alkynylzinc species and effect on the enantioseletivity of the reaction.



Scheme 3 Enantioselective addition of phenylacetylene to aldehydes.

withdrawing (NO_2) or electron-releasing (MeO) groups in *ortho* brought about a decrease in the enantioselectivity of the reaction. Remarkably, bulky naphthyl-aldehydes (entries 14 and 15) and, especially, heteroaromatic aldehydes bearing electron-rich five membered heterocycles provided the corresponding propargylic alcohols with high yields and enantioselectivities (entries 16–19). Aliphatic aldehydes reacted fast under the reaction conditions,

Table 2 Enantioselective addition of phenylacetylene (**6a**) to aldehydes according to Scheme 3[a]

Entry	7	R^2	*t* (h)	8	Yield[b] (%)	Ee[c](%)	Config.
1	**7a**	Ph	1	**8aa**	93	89	*R*
2	**7b**	4-BrC_6H_4	2	**8ab**	70	63	*R*
3	**7c**	4-ClC_6H_4	2	**8ac**	90	82	*R*
4	**7d**	4-FC_6H_4	1	**8ad**	96	88	*R*
5	**7e**	4-MeC_6H_4	1	**8ae**	70	79	*R*
6	**7f**	4-$MeOC_6H_4$	1.5	**8af**	80	76	*R*
7	**7g**	3-ClC_6H_4	2	**8ag**	91	76	*R*
8	**7h**	3-MeC_6H_4	2	**8ah**	90	80	*R*
9	**7i**	3-$MeOC_6H_4$	2	**8ai**	96	83	*R*
10	**7j**	2-ClC_6H_4	2	**8aj**	93	64	*R*
11	**7k**	2-$NO_2C_6H_4$	2.5	**8ak**	87	32	*R*
12	**7l**	2-MeC_6H_4	1.5	**8al**	90	81	*R*
13	**7m**	2-$MeOC_6H_4$	3.5	**8am**	89	59	*R*
14	**7p**	1-naphthyl	1	**8ap**	86	80	*R*
15	**7q**	2-naphthyl	1	**8aq**	91	89	*R*
16	**7r**	2-furyl	1	**8ar**	88	83	*S*
17	**7s**	3-furyl	1	**8as**	94	89	*S*
18	**7t**	2-thienyl	1.5	**8at**	91	90	*S*
19	**7u**	3-thienyl	2	**8au**	86	88	*S*
20	**7n**	$PhCH_2CH_2$	0.5	**8an**	99	34	*R*
21	**7o**	cyclohexyl	1	**8ao**	64	47	*R*

[a] All the reactions were carried out in toluene under nitrogen, **7** (1 mmol), **3** (0.2 mmol), Me_2Zn (6 mmol), **6a** (7.2 mmol). [b] Isolated product after column chromatography. [c] Determined by HPLC.

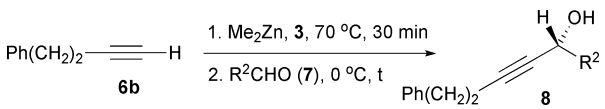
although with variable yields and low enantioselectivities (entries 20 and 21).

The absolute stereochemistry of the products was assigned by comparison of the optical rotation signs and HPLC retention times with values described in the literature for known compounds, and for the rest of the compounds it was assigned on the assumption of a uniform mechanistic pathway. According to this, the configuration of the stereogenic center was *R* in aromatic and aliphatic propargylic alcohols **8aa–8aq** and **8an–ao**, and *S* in heteroaromatic propargylic alcohols **8ar–8au**.[16]

Addition of aliphatic alkynes

Although a relatively large number of catalysts have been described for the alkynylation of aldehydes with phenylacetylene, the addition of other aliphatic alkynes has been less studied. For instance, only four examples of catalytic alkynylations of benzaldehyde with 4-phenyl-1-butyne (**6b**) have been reported so far.[4b,5h,6c,11]

We studied the addition of this alkyne to aldehydes under our catalytic conditions (Scheme 4). In this case, the pre-formation of the alkynylzinc reagent required a little bit longer time until the formation of the white precipitate (30 min). Several aromatic and heteroaromatic aldehydes were alkynylated with good yields and enantiomeric excesses (Table 3). Again the absolute configuration of the stereogenic center was assigned to be *R* in aromatic propargylic alcohols and *S* in heteroaromatic propargylic alcohols after comparison.



Scheme 4 Enantioselective addition of 4-phenyl-1-butyne to aldehydes.

Then, we studied the addition of the highly sterically hindered *tert*-butylacetylene (**6c**). This is a very challenging substrate on account of its bulkiness and lower reactivity. The addition of *t*-butylacetylene (**6c**) to benzaldehyde with an 80% yield and 53% *ee* reported by Jiang[5i] is the only successful example in the literature with aromatic aldehydes so far. Besides, Dahmen has reported the addition of **6c** to cyclohexanecarbaldehyde in the presence of a paracyclophane-based imino phenol with 52% yield and 82% *ee*,[5f] while Jiang reported 93% yield and 96% *ee* for the same reaction using an amino alcohol as ligand.[5h] In our conditions, the pre-formation of the alkynylzinc species required heating the alkyne and ligand **3** with dimethylzinc for 1 h until the apparition of the white precipitate (Scheme 5). In general the reaction required short times to completion (from 1 to 2.5 h) and the corresponding propargylic alcohols were obtained in very high yields and enantiomeric excesses from good to excellent, especially with heteroaromatic aldehydes (Table 4). These are the highest enantioselectivities described so far for the addition of *tert*-butylacetylene to aromatic aldehydes.

Table 3 Enantioselective addition of 4-phenyl-1-butyne (**6b**) to aldehydes according to Scheme 4[a]

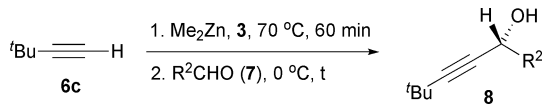
Entry	7	R^2	*t* (h)	8	Yield[b] (%)	Ee[c](%)	Config.
1	**7a**	Ph	3	**8ba**	96	88	*R*
2	**7d**	4-FC_6H_4	3	**8bd**	95	90	*R*
3	**7e**	4-MeC_6H_4	3	**8be**	94	87	*R*
4	**7r**	2-furyl	1.5	**8br**	96	90	*S*
5	**7s**	3-furyl	2.5	**8bs**	93	92	*S*
6	**7t**	2-thienyl	3.5	**8bt**	90	91	*S*
7	**7u**	3-thienyl	1.7	**8bu**	94	89	*S*

[a] All the reactions were carried out in toluene under nitrogen, **7** (1 mmol), **3** (0.2 mmol), Me_2Zn (6 mmol), **6b** (7.2 mmol). [b] Isolated product after column chromatography. [c] Determined by HPLC.

Table 4 Enantioselective addition of *tert*-butylacetylene (**6c**) to aldehydes according to Scheme 5[a]

Entry	7	R^2	*t* (h)	8	Yield[b] (%)	Ee[c](%)	Config.
1	**7a**	Ph	3	**8ca**	93	67	*R*
2	**7d**	4-FC_6H_4	3	**8cd**	91	65	*R*
3	**7e**	4-MeC_6H_4	3	**8ce**	93	66	*R*
4	**7r**	2-furyl	1.5	**8cr**	79	85	*S*
5	**7s**	3-furyl	2.5	**8cs**	98	90	*S*
6	**7t**	2-thienyl	3.5	**8ct**	95	90	*S*
7	**7u**	3-thienyl	1.7	**8cu**	90	77	*S*

[a] All the reactions were carried out in toluene under nitrogen, **7** (1 mmol), **3** (0.2 mmol), Me_2Zn (6 mmol), **6c** (7.2 mmol). [b] Isolated product after column chromatography. [c] Determined by HPLC.



Scheme 5 Enantioselective addition of *tert*-butylacetylene to aldehydes.

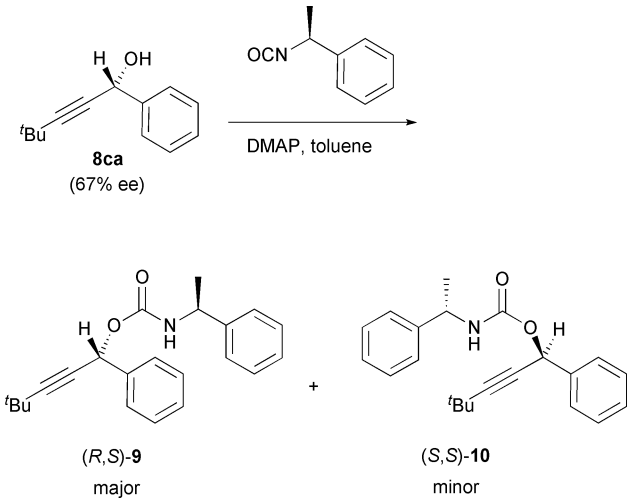
In this case, an assignment of the absolute stereochemistry of the products with literature data was not possible. To determine the absolute stereochemistry of compound **8ca** (67% *ee*) we prepared a carbamate derivative. Upon reaction with (*S*)-phenylethyl isocyanate, a mixture of two diastereomeric carbamates was obtained (Scheme 6).[17] The major diastereomer (*R,S*)-**9** could be separated by crystallization and its relative stereochemistry was determined by X-ray analysis‡ of the crystals. Knowing the absolute stereochemistry at C9 was *S* from the method of synthesis, the *R* absolute stereochemistry at the propargylic carbon C2 then follows (Fig. 2). This result shows that *tert*-butylacetylene follows the same stereochemical pathway as phenylacetylene and 4-phenyl-1-butyne.

Addition of trimethylsilylacetylene

Finally we studied the addition of trimethylsilylacetylene (**6d**) to aldehydes. This alkyne is a synthetic equivalent of acetylene and allows obtaining terminal propargylic alcohols after removal of the trimethylsilyl group. A few examples on the enantioselective addition of trimethylsilylacetylene to some aromatic[5b,f,g,j,8f,10l] and aliphatic[4c,5g,h] aldehydes has been described.

The addition of **6d** was carried out by following the described procedure. Formation of the white precipitate required heating

‡ **Crystal data:** $C_{22}H_{25}NO_2$, $M = 335.43$, monoclinic, $a = 9.9740(3)$, $b = 8.8110(3)$, $c = 12.1490(5)$ Å, $\beta = 108.2480(10)$, $V = 1013.97(6)$, $Z = 2$, 8581 reflections measured, 4178 reflections independent ($R_{int} = 0.0957$, $R = 0.0683$, $R_{all} = 0.1258$), Flack parameter = –1(2). CCDC 734711 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.



Scheme 6 Synthesis of carbamate derivatives of compound **8ca**.

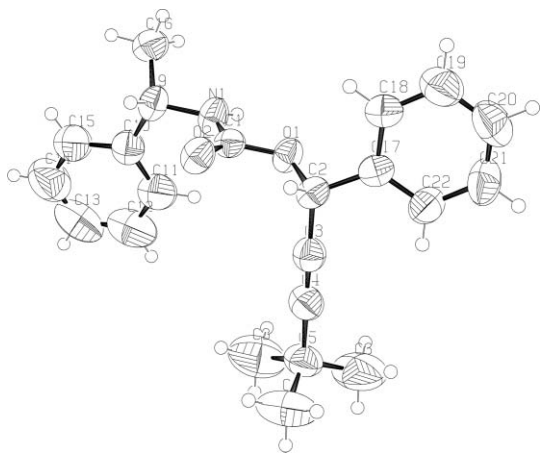
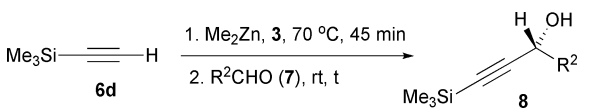


Fig. 2 ORTEP diagram for (*R,S*)-**9** with ellipsoids drawn at 40% probability.

with Me_2Zn at 70 °C for 45 min. The resulting alkynylzinc reagent was less reactive and the reaction with the aldehydes was carried out at rt (Scheme 7). Yields between 67–90% were obtained with all tested aldehydes (Table 5). Again, heterocyclic aldehydes gave higher enantiomeric excesses, from 80 to 90% *ee* (entries 4–7), than benzaldehyde derivatives (entries 1–3), which provided the expected products with *ee* in the range of 50%.



Scheme 7 Enantioselective addition of trimethylsilylacetylene to aldehydes.

Conclusions

In conclusion, simple mandelamides and dimethylzinc catalyze the enantioselective addition of terminal alkynes to aromatic and heteroaromatic aldehydes affording high yields and enantioselectivities of the corresponding propargylic alcohols. Terminal alkynes substituted with aromatic, aliphatic or trimethylsiyl groups can be used as nucleophilic partners in the reaction. An advantage of our catalytic system is that mandelamide ligands are easily prepared in a one step procedure, and a modular design of the catalyst is possible by varying the starting hydroxy acid and amine; also, both enantiomers of the catalyst are available from the corresponding mandelic acid and α-methylbenzylamine enantiomers. Furthermore, the reaction times are short and, unlike most other described procedures, the use of additional Lewis acid such as $Ti(O^iPr)_4$ is not required.

Table 5 Enantioselective addition of trimethylsilylacetylene (**6d**) to aldehydes according to Scheme 7[a]

Entry	7	R^2	*t* (h)	8	Yield[b](%)	Ee[c](%)	Config.
1	**7a**	Ph	23	**8da**	67	52	*R*
2	**7d**	4-FC_6H_4	23	**8dd**	79	57	*R*
3	**7e**	4-MeC_6H_4	23	**8de**	72	51	*R*
4	**7r**	2-furyl	2	**8dr**	87	78	*S*
5	**7s**	3-furyl	6.5	**8ds**	84	74	*S*
6	**7t**	2-thienyl	21	**8dt**	81	72	*S*
7	**7u**	3-thienyl	7	**8du**	90	69	*S*

[a] All the reactions were carried out in toluene under nitrogen, **7** (1 mmol), **3** (0.2 mmol), Me_2Zn (6 mmol), **6d** (7.2 mmol). [b] Isolated product after column chromatography. [c] Determined by HPLC.

Experimental

General experimental

Glassware was oven-dried overnight at 120 °C. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040–0.063 mm. Specific optical rotations were recorded on a Perkin-Elmer 241 polarimeter using sodium light (D line 589 nm), values are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded in a Nicolet Avatar 320 FT-IR spectrometer. NMR spectra were recorded on Bruker Advance spectrometers in the deuterated solvents as stated, using residual non-deuterated solvent as internal standard and $CFCl_3$ as internal standard for ^{19}F NMR. *J* values are given in Hz. The carbon type was determined by DEPT experiments. Mass spectra were recorded on a Fisons Instruments VG Autospec GC 8000 series. Mass spectra (EI) were run at 70 eV. Mass spectra (FAB) were carried out at 30 kV in a MNBA matrix. Chiral HPLC analyses were performed in an Agilent 1100 series instrument equipped with a refraction index detector using chiral stationary columns from Daicel. Retention times are given in min. All alkynes and aldehydes were commercially available and used as purchased without further purification. Toluene was distilled from CaH_2 and stored on 4 Å molecular sieves. Mandelamides were prepared according to procedures described in the literature.[13,15]

General Procedure for the catalytic asymmetric alkynylation of aldehydes

A 2 M solution of Me_2Zn in toluene (3 mL, 6 mmol) was added to a solution of alkyne **6** (7.2 mmol) in dry toluene (5 mL), under argon at room temperature. After 15 min, a solution of ligand **3** (83 mg, 0.2 mmol) in dry toluene (2 mL) was added and, after 15 min at room temperature, the solution was heated at 70 °C until the

formation of an abundant white precipitate in the solution (20 min for alkyne **6a**, 30 min for alkyne **6b**, 60 min for alkyne **6c** and 45 min for alkyne **6d**). Then, the reaction mixture was cooled to 0 °C and aldehyde **7** (1 mmol) was added. After the reaction was complete (TLC), 1M HCl (20 mL) was added (CAUTION! Gas evolution) and the reaction extracted with diethyl ether (3 × 15 mL). The organic layer was washed with brine, dried, concentrated and chromatographed on silica gel to give compound **8**.

(*R*)-1,3-Diphenyl-2-propyn-1-ol (8aa)[4a,10j,15]

Ee was determined by HPLC (Chiralcel OD-H), hexane:*i*-PrOH 90:10, 1 mL/min, major enantiomer (*R*) t_r = 13.1 min, minor enantiomer (*S*) t_r = 21.7 min, to be 89%; $[\alpha]_D^{25}$ +6.7 (*c* 0.54 in $CHCl_3$).

(*R*)-1-(4-Bromophenyl)-3-phenyl-2-propyn-1-ol (8ab)[8b]

Ee was determined by HPLC (Chiralcel OD-H, hexane:*i*-PrOH 90:10, 1 mL/min), major enantiomer (*R*) t_r = 10.1 min, minor enantiomer (*S*) t_r = 33.3 min, to be 62% *ee*; $[\alpha]_D^{25}$ +8.8 (*c* 0.54 in $CHCl_3$).

(*R*)-1-(4-Chlorophenyl)-3-phenyl-2-propyn-1-ol (8ac)[8b]

Ee was determined by HPLC (Chiralcel OD-H, hexane:*i*-PrOH 90:10, 1 mL/min), major enantiomer (*R*) t_r = 9.6 min, minor enantiomer (*S*) t_r = 27.2 min, to be 82%; $[\alpha]_D^{25}$ +6.2 (*c* 0.53 in $CHCl_3$).

(*R*)-1-(4-Fluorophenyl)-3-phenyl-2-propyn-1-ol (8ad)[8b]

Ee was determined by HPLC (Chiralcel OD-H, hexane:*i*-PrOH 90:10, 1 mL/min), major enantiomer (*R*) t_r = 9.5 min, minor enantiomer (*S*) t_r = 27.4 min, to be 88%; $[\alpha]_D^{25}$ +5.2 (*c* 0.51 in $CHCl_3$).

(*R*)-1-(4-Methylphenyl)-3-phenyl-2-propyn-1-ol (8ae)[7c]

Ee was determined by HPLC (Chiralcel OD-H, hexane:*i*-PrOH 90:10, 1 mL/min), major enantiomer (*R*) t_r = 9,9 min, minor enantiomer (*S*) t_r = 20.6 min, to be 79%; $[\alpha]_D^{25}$ +2.8 (*c* 0.47 in $CHCl_3$).

(*R*)-1-(4-Methoxylphenyl)-3-phenyl-2-propyn-1-ol (8af)[8b]

Ee was determined by HPLC (Chiralcel OD-H, hexane:*i*-PrOH 90:10, 1 mL/min), major enantiomer (*R*) t_r = 15.0 min, minor enantiomer (*S*) t_r = 31.1 min, to be 76%; $[\alpha]_D^{25}$ +24.1 (*c* 0.31 in $CHCl_3$).

(*R*)-1-(3-Chlorophenyl)-3-phenyl-2-propyn-1-ol (8ag)[6b]

Ee was determined by HPLC (Chiralcel OD-H, hexane:*i*-PrOH 90:10, 1 mL/min), major enantiomer (*R*) t_r = 9.8 min, minor enantiomer (*S*) t_r = 30.1 min, to be 76%; $[\alpha]_D^{25}$ +12.6 (*c* 0.54 in $CHCl_3$).

(*R*)-1-(3-Methylphenyl)-3-phenyl-2-propyn-1-ol (8ah)[6b]

Ee was determined by HPLC (Chiralcel OD-H, hexane:*i*-PrOH 90:10, 1 mL/min), major enantiomer (*R*) t_r = 11.5 min, minor enantiomer (*S*) t_r = 23.5 min, to be 80%; $[\alpha]_D^{25}$ +3.1 (*c* 0.54 in $CHCl_3$).

(*R*)-1-(3-Methoxhyphenyl)-3-phenyl-2-propyn-1-ol (8ai)[6b]

Ee was determined by HPLC (Chiralcel OD-H, hexane:*i*-PrOH 90:10, 1 mL/min), major enantiomer (*R*) t_r = 18.0 min, minor enantiomer (*S*) t_r =26.7 min, to be 83%; $[\alpha]_D^{25}$ +5.4 (*c* 0.51 in $CHCl_3$).

(*R*)-1-(2-Chlorophenyl)-3-phenyl-2-propyn-1-ol (8aj)[7c]

Ee was determined by HPLC (Chiralcel OD-H, hexane:*i*-PrOH 90:10, 1 mL/min), major enantiomer (*R*) t_r = 10.5 min, minor enantiomer (*S*) t_r = 11.5 min, to be 64%; $[\alpha]_D^{25}$ −37.9 (*c* 0.51 in $CHCl_3$).

(*R*)-1-(2-Nitrophenyl)-3-phenyl-2-propyn-1-ol (8ak)[5g]

Ee was determined by HPLC (Chiralcel OD-H, hexane:*i*-PrOH 90:10, 1 mL/min), major enantiomer (*R*) t_r = 14.6 min, minor enantiomer (*S*) t_r = 17.0 min, to be 32%; $[\alpha]_D^{25}$ −12.4 (*c* 0.53 in $CHCl_3$).

(*R*)-1-(2-Methylphenyl)-3-phenyl-2-propyn-1-ol (8al)[10h]

Ee was determined by HPLC (Chiralcel OD-H, hexane:*i*-PrOH 90:10, 1 mL/min), major enantiomer (*R*) t_r = 9.9 min, minor enantiomer (*S*) t_r = 22.2 min, to be 81%; $[\alpha]_D^{25}$ −12.4 (*c* 0.53 in $CHCl_3$).

(*R*)-1-(2-Methoxyphenyl)-3-phenyl-2-propyn-1-ol (8am)[8b]

Ee was determined by HPLC (Chiralcel OD-H, hexane:*i*-PrOH 90:10, 1 mL/min), major enantiomer (*R*) t_r = 16.1 min, minor enantiomer (*S*) t_r =18.1 min, to be 59%; $[\alpha]_D^{25}$ −5.8 (*c* 0.55 in $CHCl_3$).

(*R*)-1,5-Diphenyl-2-pentyn-3-ol (8an)[5d]

Ee was determined by HPLC (Chiralcel OD-H, hexane:*i*-PrOH 90:10, 1 mL/min), major enantiomer (*R*) t_r = 15.6 min, minor enantiomer (*S*) t_r = 28.9 min, to be 34%; $[\alpha]_D^{25}$ −22.3 (*c* 0.53 in $CHCl_3$).

(*R*)-1-Cyclohexyl-3-phenyl-2-propyn-1-ol (8ao)[18]

Ee was determined by HPLC (Chiralcel OD-H, hexane:*i*-PrOH 90:10, 1 mL/min), major enantiomer (*R*) t_r = 6.2 min, minor enantiomer (*S*) t_r = 12.8 min, to be 49%; $[\alpha]_D^{25}$ −4.0 (*c* 0.54 in $CHCl_3$).

(*R*)-3-Phenyl-1-(naphth-1-yl)-2-propyn-1-ol (8ap)[10h]

Ee was determined by HPLC (Chiralpack AD-H, hexane:*i*-PrOH 90:10, 1 mL/min), major enantiomer (*R*) t_r = 22.9 min, minor enantiomer (*S*) t_r = 17.1 min, to be 80%; $[\alpha]_D^{25}$ −19.8 (*c* 0.48 in $CHCl_3$).

(*R*)-3-Phenyl-1-(naphth-2-yl)-2-propyn-1-ol (8aq)[5g]

Ee was determined by HPLC (Chiralpack AD-H, hexane:*i*-PrOH 90:10, 1 mL/min), major enantiomer (*R*) t_r = 22.9 min, minor

enantiomer (*S*) t_r = 17.1 min, to be 80%; $[\alpha]_D^{25}$ −19.8 (*c* 0.48 in $CHCl_3$).

(*S*)-1-(Furan-2-yl)-3-phenyl-2-propyn-1-ol (8ar)[10j,15]

Ee was determined by HPLC (Chiralcel OD-H), hexane:*i*-PrOH 90:10, 1 mL/min, major enantiomer t_r = 10.3 min, minor enantiomer t_r = 21.1 min, to be 83%; $[\alpha]_D^{25}$ +34.0 (*c* 0.58 in $CHCl_3$).

(*S*)-1-(Furan-3-yl)-3-phenyl-2-propyn-1-ol (8as)[11,15]

Ee was determined by HPLC (Chiralcel OD-H), hexane:*i*-PrOH 90:10, 1 mL/min, major enantiomer t_r = 9.6 min, minor enantiomer t_r = 24.7 min, to be 89%; $[\alpha]_D^{25}$ +3.0 (*c* 0.53 in $CHCl_3$).

(*S*)-3-Phenyl-1-(thiophen-2-yl)-2-propyn-1-ol (8at)[15]

Ee was determined by HPLC (Chiralcel OD-H), hexane:*i*-PrOH 90:10, 1 mL/min, major enantiomer t_r = 11.2 min, minor enantiomer t_r = 23.2 min, to be 90%; $[\alpha]_D^{25}$ +20 (*c* 0.53 in $CHCl_3$).

(*S*)-3-Phenyl-1-(thiophen-3-yl)-2-propyn-1-ol (8au)[11,15]

Ee was determined by HPLC (Chiralcel OD-H), hexane:*i*-PrOH 90:10, 1 mL/min, major enantiomer t_r = 11.5 min, minor enantiomer t_r = 30.8 min, to be 88%; $[\alpha]_D^{25}$ +20 (*c* 0.53 in $CHCl_3$).

(*R*)-1,5-Diphenyl-2-pentyn-1-ol (8ba)[11,15]

Ee was determined by HPLC (Chiralcel OD-H, hexane:*i*-PrOH 90:10, 1 mL/min), major enantiomer (*R*) t_r = 15.7 min, minor enantiomer (*S*) t_r = 27.4 min, to be 88%; $[\alpha]_D^{25}$ +13.0 (*c* 0.52 in $CHCl_3$).

(*R*)-1-(4-Fluorophenyl)-5-phenyl-2-pentyn-1-ol (8bd)[11]

Ee was determined by HPLC (Chiralcel OD-H, hexane:*i*-PrOH 90:10, 1 mL/min), major enantiomer (*R*) t_r = 12.3 min, minor enantiomer (*S*) t_r = 34.8 min, to be 90%; $[\alpha]_D^{25}$ +17.6 (*c* 0.54 in $CHCl_3$).

(*R*)-1-(4-Methylphenyl)-5-phenyl-2-pentyn-1-ol (8be)

Ee was determined by HPLC (Chiralcel OD-H, hexane:*i*-PrOH 90:10, 1 mL/min), major enantiomer (*R*) t_r = 11.4 min, minor enantiomer (*S*) t_r = 22.2 min, to be 87%; $[\alpha]_D^{25}$ +16.3 (*c* 0.56 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3373, 2970, 2222, 1225, 1013, 814 and 762; δ_H(300 MHz; $CDCl_3$) 7.28 (d, *J* 7.8, 2H), 7.25–7.10 (m, 5H), 7.08 (d, *J* 7.8, 2H), 5.31 (s, 1H), 2.78 (t, *J* 7.5, 2H), 2.49 (td, *J* 7.5 and 1.8, 2H), 2.28 (s, 3H) and 2.00 (br s, 1H); δ_C (75 MHz; $CDCl_3$) 140.5 (C), 138.2 (C), 138.0 (C), 129.2 (2CH), 128.5 (2CH), 128.4 (2CH), 126.6 (2CH), 126.3 (CH), 86.5 (C), 80.9 (C), 64.6 (CH), 34.9 (CH_2), 21.1 (CH_3) and 21.0 (CH_2); *m*/*z* (EI) 250.1353 (M^+, 27%, $C_{18}H_{18}O$ requires 250.1358), 235 (17), 217 (5), 119 (33) and 91 (100).

(*S*)-1-(Furan-2-yl)-5-phenyl-2-pentyn-1-ol (8br)[15]

Ee was determined by HPLC (Chiralcel OD-H), hexane:*i*-PrOH 90:10, 1 mL/min, major enantiomer t_r = 13.9 min, minor enantiomer t_r = 21.7 min, to be 90%; $[\alpha]_D^{25}$ +14.2 (*c* 0.54 in $CHCl_3$).

(*S*)-1-(Furan-3-yl)-5-phenyl-2-pentyn-1-ol (8bs)[15]

Ee was determined by HPLC (Chiralcel OD-H), hexane:*i*-PrOH 90:10, 1 mL/min, major enantiomer t_r = 11.9 min, minor enantiomer t_r = 22.6 min, to be 92%; $[\alpha]_D^{25}$ +12.3 (*c* 0.52 in $CHCl_3$).

(*S*)-5-Phenyl-1-(thiophen-2-yl)-2-pentyn-1-ol (3bt)[15]

Ee was determined by HPLC (Chiralcel OD-H), hexane:*i*-PrOH 90:10, 1 mL/min, major enantiomer t_r = 14.7 min, minor enantiomer t_r = 30.6 min, to be 91%; $[\alpha]_D^{25}$ +27.5 (*c* 0.57 in $CHCl_3$).

(*S*)-5-Phenyl-1-(thiophen-3-yl)-2-pentyn-1-ol (3bu)[15]

Ee was determined by HPLC (Chiralcel OD-H), hexane:*i*-PrOH 90:10, 1 mL/min, major enantiomer t_r = 14.7 min, minor enantiomer t_r = 29.9 min, to be 89%; $[\alpha]_D^{25}$ +15.4 (*c* 0.51 in $CHCl_3$).

(*R*)-4,4-Dimethyl-1-phenyl-2-pentyn-1-ol (3ca)[15]

Ee was determined by HPLC (Chiralcel OD-H), hexane:*i*-PrOH 90:10, 1 mL/min, major enantiomer t_r = 5.8 min, minor enantiomer t_r = 4.7 min, to be 67%; $[\alpha]_D^{25}$ +18.8 (*c* 0.51 in $CHCl_3$).

(*R*)-4,4-Dimethyl-1-(4-fluorophenyl)-2-pentyn-1-ol (8cd)

Ee was determined by HPLC (Chiralcel OD-H, hexane:*i*-PrOH 90:10, 1 mL/min), major enantiomer (*R*) t_r = 5.0 min, minor enantiomer (*S*) t_r = 4.6 min, to be 65%; $[\alpha]_D^{25}$ +20.3 (*c* 0.57 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3358, 2970, 2231, 1606, 1508, 1262, 1157, 1067, 985, 860, 836 and 771; δ_H(300 MHz; $CDCl_3$) 7.51 (dd, *J* 8.4 and 5.4, 2H), 7.05 (t, *J* 8.4, 2H), 5.42 (s, 1H), 2.14 (br s, 1H), 1.26 (s, 9H); δ_C(75 MHz; $CDCl_3$) 162.5 (C, $J_{C\text{-}F}$ (d) 244.4), 137.1 (C, $J_{C\text{-}F}$ (d) 2.8), 128.5 (2CH, $J_{C\text{-}F}$ (d) 7.8), 115.3 (2CH, $J_{C\text{-}F}$ (d) 21.1), 96.1 (C), 78.2 (C), 64.0 (CH), 30.9 ($3CH_3$), 27.5 (C); *m*/*z* (EI) 206.1115 (M^+, 100%, $C_{13}H_{15}FO$ requires 206.1107), 123 (42) and 69 (36).

(*R*)-4,4-Dimethyl-1-(4-methylphenyl)-2-pentyn-1-ol (8ce)

Ee was determined by HPLC (Chiralpack AD-H, hexane:*i*-PrOH 90:10, 1 mL/min), major enantiomer (*R*) t_r = 5.9 min, minor enantiomer (*S*) t_r = 5.2 min, to be 66%; $[\alpha]_D^{25}$ +20.1 (*c* 0.56 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3374, 2969, 2231, 1512, 1363, 1262, 1066, 982, 817 and 759; δ_H(300 MHz; $CDCl_3$) 7.43 (d, *J* 8.4, 2H), 7.18 (d, *J* 8.4, 2H), 5.41 (s, 1H), 2.36 (s, 3H), 2.08 (br s, 1H) and 1.27 (s, 9H); δ_C(75 MHz; $CDCl_3$) 138.5 (C), 137.9 (C), 129.1 (2CH), 126.7 (2CH), 95.5 (C), 78.5 (C), 64.5 (CH), 30.9 ($3CH_3$), 27.5 (C) and 21.1 (CH_3); *m*/*z* (EI) 202.1539 (M^+, 91%, $C_{14}H_{18}O$ requires 202.1358), 187 (100), 172 (27) and 145 (58).

(*S*)-1-(Furan-2-yl)-4,4-dimethyl-2-pentyn-1-ol (8cr)[15]

Ee was determined by HPLC (Chiralcel OD-H, hexane:*i*-PrOH 90:10, 1 mL/min), major enantiomer (*S*) t_r = 5.6 min, minor enantiomer (*R*) t_r = 5.3 min, to be 85%; $[\alpha]_D^{25}$ +16.8 (*c* 0.53 in $CHCl_3$).

(*S*)-1-(Furan-3-yl)-4,4-dimethyl-2-pentyn-1-ol (8cs)[15]

Ee was determined by HPLC (Chiralcel OD-H, hexane:*i*-PrOH 90:10, 0.5 mL/min), major enantiomer (*S*) t_r = 9.5 min, minor

enantiomer (*R*) t_r = 9.1 min, to be 90%; $[\alpha]_D^{25}$ +16.2 (*c* 0.56 in $CHCl_3$).

(*S*)-4,4-Dimethyl-1-(tiophen-2-yl)-2-pentyn-1-ol (8ct)[15]

Ee was determined by HPLC (Chiralcel OD-H, hexane:*i*-PrOH 90:10, 1 mL/min), major enantiomer (*S*) t_r = 5.7 min, minor enantiomer (*R*) t_r = 5.1 min, to be 90%; $[\alpha]_D^{25}$ +38.4 (*c* 0.51 in $CHCl_3$).

(*S*)-4,4-Dimethyl-1-(tiophen-3-yl)-2-pentyn-1-ol (8cu)[15]

Ee was determined by HPLC (Chiralcel OD-H, hexane:*i*-PrOH 90:10, 1 mL/min), major enantiomer (*S*) t_r = 5.5 min, minor enantiomer (*R*) t_r = 5.0 min, to be 77%; $[\alpha]_D^{25}$ +17.7 (*c* 0.57 in $CHCl_3$).

(*R*)-3-(Trimethylsilyl)-1-phenyl-2-propyn-1-ol (8da)[6b,10l]

Ee was determined by HPLC (Chiralpack AD-H, hexane:*i*-PrOH 95:5, 1 mL/min), major enantiomer (*R*) t_r = 7.4 min, minor enantiomer (*S*) t_r = 6.5, to be 52%;$[\alpha]_D^{25}$ +11.2 (*c* 0.58, $CHCl_3$).

(*R*)-1-Fluorophenyl-3-(trimethylsilyl)-2-propyn-1-ol (8dd)[10l]

Ee determined by HPLC (Chiralpack AD-H, hexane:*i*-PrOH 95:5, 1 mL/min), major enantiomer (*R*) t_r = 6.8 min, minor enantiomer (*S*) t_r = 6.1 min, to be 57%; $[\alpha]_D^{25}$ +13.7 (*c* 0.54 in $CHCl_3$).

(*R*)-1-Methylphenyl-3-(trimethylsilyl)-2-propyn-1-ol (8de)

Ee determined by HPLC (Chiralpack AD-H, hexane:*i*-PrOH 95:5, 1 mL/min), major enantiomer (*R*) t_r = 8.2 min, minor enantiomer (*S*) t_r = 6.7 min, to be 51%; $[\alpha]_D^{25}$ +13.3 (*c* 0.52 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3375, 2960, 2899, 2173, 1513, 1411, 1250, 1043, 983, 843 and 761; δ_H(300 MHz; $CDCl_3$) 7.43 (d, *J* 8.4, 2H), 7.19 (d, *J* 8.4, 2H), 5.42 (s, 1H), 2.36 (s, 3H), 2.15 (br s, 1H) and 0.20 (s, 9H); δ_C(75 MHz; $CDCl_3$) 138.2 (C), 137.5 (C), 129.3 (2CH), 126.7 (2CH), 105.1 (C), 91.3 (C), 64.8 (CH), 21.2 (CH3) and –0.2 ($3CH_3$); MS (EI) 218.1130 (M^+, 100%, $C_{13}H_{18}OSi$ requires 218.1127), 203 (86) and 175 (43).

(*S*)-1-(Furan-2-yl)-3-(trimethylsilyl)-2-propyn-1-ol (8dr)[5g]

Ee determined by HPLC (Chiralpack AD-H, hexane:*i*-PrOH 95:5, 0.5 mL/min), major enantiomer (*S*) t_r = 13.2 min, minor enantiomer (*R*) t_r = 12.8 min, to be 74%; $[\alpha]_D^{25}$ +16.2 (*c* 0.52 in $CHCl_3$).

(*S*)-1-(Furan-3-yl)-3-(trimethylsilyl)-2-propyn-1-ol (8ds)

Ee determined by HPLC (Chiralpack AD-H, hexane:*i*-PrOH 93:7, 1 mL/min), major enantiomer (*S*) t_r = 5.9 min, minor enantiomer (*R*) t_r = 5.4 min, to be 73%; $[\alpha]_D^{25}$ +11.3 (*c* 0.59 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3363, 2960, 2173, 1503, 1410, 1251, 1160, 1204, 943, 845 and 760; δ_H(300 MHz; $CDCl_3$) 7.52 (m, 1H), 7.40 (t, *J* 1.6, 1H), 6.50 (m, 1H), 5.38 (s, 1H), 2.12 (br s, 1H), 0.20 (s, 9H); δ_C(75 MHz; $CDCl_3$) 143.6 (CH), 140.3 (CH), 126.1 (C), 109.2 (CH), 104.4 (C), 90.0 (C), 57.7 (CH) and –0.2 ($3CH_3$); MS (EI) 194.0773 (M^+, 100%, $C_{10}H_{14}O_2Si$ requires 194.0763), 179 (58), 161 (30), 104 (86) and 73 (54).

(*S*)-3-Trimethylsilyl-1-(tiophen-2-yl)-2-propyn-1-ol (8dt)

Ee determined by HPLC (Chiralpack AD-H, hexane:*i*-PrOH 95:5, 0,5 mL/min), major enantiomer (*S*) t_r = 14.8 min, minor enantiomer (*R*) t_r = 13.0 min, to be 63%; $[\alpha]_D^{25}$ +28.7 (*c* 0.57 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3394, 2960, 2899, 2174, 1410, 1251, 1041, 844, 794 and 761; δ_H(300 MHz; $CDCl_3$) 7.30 (dd, *J* 5.0, 0.9, 1H), 7.18 (unresolved dt, *J* 3.5, 1H), 6.98 (dd, *J* 5.0 and 3.5, 1H), 5.64 (s, 1H), 2.40 (br s, 1H) and 0.22 (s, 9H); δ_C(75 MHz; $CDCl_3$) 144.3 (C), 126.7 (CH), 126.2 (CH), 125.7 (CH), 104.0 (C), 91.2 (C), 60.6 (CH) and –0.3 ($3CH_3$); *m*/*z* (EI) 210.0532 (M^+, 100%, $C_{10}H_{14}OSiS$ requires 210.0535), 195 (9), 167 (97) and 120 (91).

(*S*)-3-Trimethylsilyl-1-(tiophen-3-yl)-2-propyn-1-ol (8du)

Ee determined by HPLC (Chiralpack AD-H, hexane:*i*-PrOH 95:5, 1 mL/min), major enantiomer (*S*) t_r = 8.0 min, minor enantiomer (*R*) t_r = 6.8 min, to be 69%; $[\alpha]_D^{25}$ +13.9 (*c* 0.56 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3363, 3105, 2959, 2173, 1419, 1251, 1041, 844, 794 and 761; δ_H(300 MHz; $CDCl_3$) 7.40 (m, 1H), 7.32 (dd, *J* 5.1 and 3.0, 1H), 7.18 (dd, *J* 5.1 and 1.2, 1H), 5.48 (s, 1H), 2.25 (br s, 1H), 0.21 (s, 9H); δ_C(75 MHz; $CDCl_3$) 141.7 (C), 126.5 (CH), 126.4 (CH), 122.8 (CH), 104.7 (C), 90.7 (C), 60.9 (CH) and –0.2 ($3CH_3$); *m*/*z* (EI) 210.0535 (M^+, 100%, $C_{10}H_{14}OSiS$ requires 210.0535), 195 (3), 167 (36), 120 (13).

Synthesis of carbamates 9 and 10

A solution of (*R*)-4,4-dimethyl-1-phenyl-2-pentyn-1-ol (**8ca**, 83.4 mg, 0.44 mmol, Table 5, entry 1, 67% ee), (*S*)-phenylethyl isocyante (113 μL, 0.72 mmol) and a catalytic amount of 4-dimethylaminopyridine (DMAP) in toluene (1.7 mL) was stirred at 80 °C under nitrogen atmosphere for 24 h. The solvent was removed under reduced pressure and the concentrated was dissolved in dichloromethane and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography eluting with hexane-EtOAc gave a mixture of two diastereomeric carbamates (121.5 mg, 85%). The major diastereomer (43 mg) could be obtained pure after crystallization from toluene (0.4 mL). A second crystallization allowed to obtain suitable crystals for X-ray analysis.

Major diastereomer (*R,S*)-**9**: mp128–129 °C (toluene), $[\alpha]_D^{25}$ –13.2 (*c* 0.55 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3038, 2969, 2241, 1690, 1541, 1224, 1053, 914, 698; δ_H(300 MHz; $CDCl_3$) 7.54 (unresolved d, 2H), 7.40–7.20 (m, 8H), 6.42 (s, 1H), 5.03 (br d, *J* 6.6, 1H), 4.84 (qd, J 7.2 and 6.6), 1.44 (d, *J* 7.2, 3H) and 1.23 (s, 9H); δ_C(75 MHz; $CDCl_3$) 154.5 (C), 143.4 (C), 138.2 (C), 128.6 (CH), 128.5 (CH), 128.4 (CH), 127.7 (CH), 127.3 (CH), 125.9 (CH), 96.2 (C), 75.4 (C), 66.6 (CH), 50.8 (CH), 30.7 (CH_3), 27.5 (CH_3) and 22.4 (C); δ_H(300 MHz; dmso-d_6) 7.98 (d, *J* 8.1, 1H), 7.50–7.20 (m, 10H), 6.28 (s, 1H), 4.63 (dq, *J* 8.1 and 6.9, 1H), 1.29 (d, *J* 6.9, 3H) and 1.17 (s, 9H); δ_C(75 MHz; dmso-d_6) δ 154.2 (C), 144.8 (C), 138.3 (C), 128.5 (CH), 128.2 (CH), 127.2 (CH), 126.6 (CH), 125.7 (CH), 95.3 (C), 76.3 (C), 64.9 (CH), 50.1 (CH), 30.4 (CH_3), 27.0 (CH_3) and 22.6 (C); *m*/*z* (FAB) 335.1889 (M^+, 0.5%, $C_{22}H_{25}NO_2$ requires 335.1885) and 171 (100).

Minor diastereomer (*S,S*)-**10**, significative peaks taken from the diastereomeric mixture: δ_H(300 MHz; dmso-d_6) 7.98 (d, *J* 8.1,

1H), 7.50–7.20 (m, 10H), 6.30 (s, 1H), 4.67 (dq, $J = 8.1$ and 6.9, 1H), 1.33 (d, $J = 6.9$, 3H), 1.21 (s, 9H).

Acknowledgements

Financial support from the Ministerio de Ciencia e Innovación and FEDER (CTQ 2006–14199/BQU) is gratefully acknowledged.

Notes and references

1 For reviews see: (*a*) B. M. Trost and A. Weiss, *Adv. Synth. Catal.*, 2009, **351**, 963–983; (*b*) L. Pu, *Tetrahedron*, 2003, **59**, 9873–9886; (*c*) P. G. Cozzi, R. Hilgraf and N. Zimmerman, *Eur. J. Org. Chem.*, 2004, 4095–4105.

2 For some representative examples, see: (*a*) A. Armstrong and D. P. G. Emmerson, *Org. Lett.*, 2009, **11**, 1547–1550; (*b*) M. A. Boone, F. E. McDonald, J. Lichter, S. Lutz, R. Cao and K. I. Hardcastle, *Org. Lett.*, 2009, **11**, 851–854; (*c*) S. Chandrasekhar, B. V. D. Vijaykumar and T. V. Pratap, *Tetrahedron: Asymmetry*, 2008, **19**, 746–750; (*d*) Y. Hayashi, H. Yamaguchi, M. Toyoshima, K. Okado, T. Toyo and M. Shoji, *Org. Lett.*, 2008, **10**, 1405–1408; (*e*) J. Li, S. Park, R. L. Miller and D. Lee, *Org. Lett.*, 2009, **11**, 571–574; (*f*) T. Nagamitsu, D. Takano, M. Seki, S. Arima, M. Ohtawa, K. Shiomi, Y. Harigaya and S. Ōmura, *Tetrahedron*, 2008, **64**, 8117–8127; (*g*) P. A. Roethle and D. Trauner, *Org. Lett.*, 2006, **8**, 345; (*h*) B. M. Trost, T. J. J. Mueller and J. Martinez, *J. Am. Chem. Soc.*, 1995, **117**, 1888–1899.

3 B. Marx, E. Henry-Basch and P. Freon, *C. R. Acad. Sci. Ser. C*, 1967, **264**, 527–530.

4 (*a*) D. E. Frantz, R. Fassler and E. M. Carreira, *J. Am. Chem. Soc.*, 2000, **122**, 1806–1807; (*b*) N. K. Anand and E. M. Carreira, *J. Am. Chem. Soc.*, 2001, **123**, 9687–9688; (*c*) D. Boyall, D. E. Frantz and E. M. Carreira, *Org. Lett.*, 2002, **4**, 2605–2606; (*d*) D. Boyall, F. Lopez, H. Sasaki, D. E. Frantz and E. M. Carreira, *Org. Lett.*, 2000, **2**, 4233–4236; (*e*) E. El-Sayed, N. K. Anand and E. M. Carreira, *Org. Lett.*, 2001, **3**, 3017–3020.

5 (*a*) J. Zhong, S. Hou, Q. Bian, M. Yin, R. Na, B. Zheng, Z. Li, S. Liu and M. Wang, *Chem.–Eur. J.*, 2009, **15**, 3069–3071; (*b*) Z. Xu, N. Wu, Z. Ding, T. Wang, J. Mao and Y. Zhang, *Tetrahedron Lett.*, 2009, **50**, 926–929; (*c*) Z. Xu, J. Mao and Y. Zhang, *Catal. Commun.*, 2008, **10**, 113–117; (*d*) D. P. G. Emmerson, W. P. Hems and B. G. Davis, *Org. Lett.*, 2006, **8**, 207–210; (*e*) Z. C. C. Watts, P. Thoniyot, L. C. Hirayama, T. Romano and B. Singaram, *Tetrahedron: Asymmetry*, 2005, **16**, 1829–1835; (*f*) M. Yamashita, K. Yamadam and K. Omioka, *Adv. Synth. Catal.*, 2005, **347**, 1649–1652; (*g*) B. M. Trost, A. H. Weiss and A. J. von Wangelin, *J. Am. Chem. Soc.*, 2006, **128**, 8–9; (*h*) B. Jiang, Z. Chen and W. Xiong, *Chem. Commun.*, 2002, 1524–1525; (*i*) B. Jiang and Y. Feng, *Tetrahedron Lett.*, 2002, **43**, 2975–2977; (*j*) S. Liebehentschel, J. Cvengros and A. Jacobi von Wangelin, *Synlett*, 2007, 2574–2578.

6 (*a*) M. Omote, Y. Eto, A. Tarui, K. Sato and A. Ando, *Tetrahedron: Asymmetry*, 2009, **20**, 602–604; (*b*) M. Li, X.-Z Zhu, K. Yuan, B.-X. Cao and X.-L. Hou, *Tetrahedron: Asymmetry*, 2004, **15**, 219–222; (*c*) S. Dahmen, *Org. Lett.*, 2004, **6**, 2113–2116.

7 (*a*) Z. Xu, J. Mao and Y. Zhang, *Org. Biomol. Chem.*, 2008, **6**, 1288–1292; (*b*) Y. Kang, R Wang, L. Liu, C. Da, W. Yan and Z. Xu, *Tetrahedron Lett.*, 2005, **46**, 863–865; (*c*) A. L. Braga, H. R. Appelt, C. C. Silveria, L. A. Wessjohann and P. H. Schneider, *Tetrahedron*, 2002, **58**, 10413–10416.

8 (*a*) Z. Xu, R. Wang, J. Xu, C.-S. Da, W.-J. Yan and C. Chen, *Angew. Chem., Int. Ed.*, 2003, **42**, 5747–5749; (*b*) Z. Xu, C. Chen, J. Xu, M. Miao, W. Yan and R. Wang, *Org. Lett.*, 2004, **6**, 1193–1195; (*c*) M. Ni, R. Wang, Z. Han, B. Mao, C.-S Da, L. Liu and C. Chen, *Adv. Synth. Catal.*, 2005, **347**, 1659–1665; (*d*) Xu, L. Lin, J. Xu, W. Yan and R. Wanga, *Adv. Synth. Catal.*, 2006, **348**, 506–514; (*e*) V. J. Forrat, O. Prieto, D. J. Ramon and M. Yus, *Chem.–Eur. J.*, 2006, **12**, 4431–4445; (*f*) L. Qiu, Q. Wang, L. Lin, X. Liu, X. Jiang, Q. Zhao, G. Hu and R. Wang, *Chirality*, 2009, **21**, 316–323.

9 (*a*) Y. Li, Y. Tang, X. Hui, L. Huang and P. Xu, *Tetrahedron*, 2009, **65**, 3611–3614; (*b*) T. Fang, D. Du, S. Lu and J. Xu, *Org. Lett.*, 2005, **7**, 2081–2084.

10 (*a*) X. Li, G. Lu, X. Jia, Y. Wu and A. S. C. Chan, *Chirality*, 2007, **19**, 638–641; (*b*) G. Lu, X. Li, W. L. Chan and A. S. C. Chan, *Chem. Commun.*, 2002, 172–173; (*c*) G. Lu, X. Li, G. Chen, W. L. Chan and A. S. C. Chan, *Tetrahedron: Asymmetry*, 2003, **14**, 449–452; (*d*) J. Ruan, G. Lu, L. Xu, Y. Li and A. S. C. Chan, *Adv. Synth. Catal.*, 2008, **350**, 76–84; (*e*) G. Gao, D. Moore, R. Xie and L. Pu, *Org. Lett.*, 2002, **4**, 4143–4146; (*f*) G. Gao, R. Xie and L. Pu, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5417–5420; (*g*) M. Xu and L. Pu, *Org. Lett.*, 2002, **4**, 4555–4557; (*h*) D. Moore and L. Pu, *Org. Lett.*, 2002, **4**, 1855–1857; (*i*) D. Moore, W.-S. Huang, M.-H. Xu and L. Pu, *Tetrahedron Lett.*, 2002, **43**, 8831–8834; (*j*) Z.-B. Li and L. Pu, *Org. Lett.*, 2004, **6**, 1065–1068; (*k*) G. Gao, Q. Wang, X.-Q. Yu, R.-G. Xie and L. Pu, *Angew. Chem., Int. Ed.*, 2006, **45**, 122–125; (*l*) F. Yang, P. Xi, L. Yang, J. Lan, R. Xie and J. You, *J. Org. Chem.*, 2007, **72**, 5457–5460.

11 R. Takita, K. Yakura, T. Ohshima and M. Shibasaki, *J. Am. Chem. Soc.*, 2005, **127**, 13760–13761.

12 G. Blay, I. Fernández, A. Marco-Aleixandre and J.R. Pedro, *Tetrahedron: Asymmetry*, 2005, **16**, 1207–1213.

13 (*a*) G. Blay, I. Fernández, V. Hernández-Olmos, A. Marco-Aleixandre and J. R. Pedro, *J. Mol. Catal. A: Chem.*, 2007, **276**, 235–243; (*b*) G. Blay, I. Fernández, V. Hernández-Olmos, A. Marco-Aleixandre and J. R. Pedro, *Tetrahedron: Asymmetry*, 2005, **16**, 1953–1958.

14 (*a*) G. Blay, I. Fernández, A. Marco-Aleixandre and J. R. Pedro, *Synthesis*, 2007, 3754–3757; (*b*) G. Blay, I. Fernández, A. Marco-Aleixandre and J. R. Pedro, *Org. Lett.*, 2006, **8**, 1287–1290.

15 G. Blay, I. Fernández, A. Marco-Aleixandre and J. R. Pedro, *J. Org. Chem.*, 2006, **71**, 6674–6677.

16 This different configuration is due to a change in the priority order when applying the Cahn–Ingold–Prelog rules, not to a change in the stereochemical pathway of the reaction.

17 J. T. Njardarson, C. Gaul, D. Shan, X.-Y. Huang and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2004, **126**, 1038–1040.

18 M. Ishizaki and O. Hoshino, *Tetrahedron: Asymmetry*, 1994, **5**, 1901–1904.

