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Synthetic Methods

Development of a *syn*-Selective Mannich Reaction of Aldehydes with Propargylic Imines by Dual Catalysis: Asymmetric Synthesis of Functionalized Propargylic Amines

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Abstract: Direct coupling of enolizable aldehydes with *C*-alkynyl imines is realized affording the corresponding propargylic Mannich adducts of *syn* configuration, thus complementing previous methods that gave access to the *anti*-isomers. The combination of proline and a urea Brønsted base cocatalyst is key for the reactions to proceed under very mild conditions (3–10 mol% catalyst loading, dichloromethane as solvent, −20 °C, 1.2 molar equivalents of aldehyde) and with virtually total stereocontrol (*syn*/*anti* ratio up to 99:1; *ee* up to 99%). Some possibilities of further chemical elaboration of adducts are also briefly illustrated.

Introduction

In response to the growing importance played by chiral amines in the development of bioactive molecules, including α- and β-amino acids, considerable efforts have been made to construct chiral amines stereoselectively.[1] In this context, propargylic amines not only are present in a number of bioactive compounds,[2] but may also serve as versatile building blocks in synthesis[3] owing to the rich chemistry of both the amine and alkyne moieties. Among the methods for their preparation (Figure 1),[4] the addition of terminal alkynes to imines,[5] and the 1,2-addition of organometallic reagents to propargylic imines[6] are especially attractive because the C–C bond and stereocenter are generated concurrently. Although, these standard catalytic and asymmetric methods usually allow for the generation of a sole stereocenter, they offer almost no chance to introduce additional functionality.

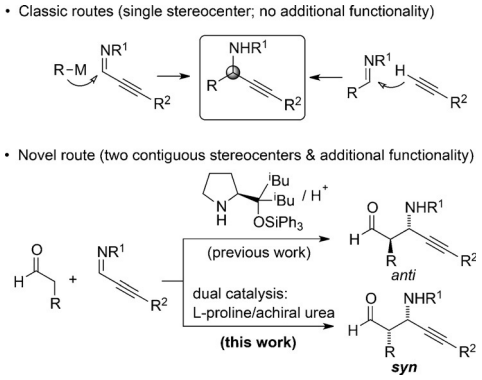

Figure 1. Direct catalytic asymmetric routes to propargylic amine synthesis.

Quite recently, we communicated a new asymmetric entry to propargylic amines based on an amine-catalyzed direct Mannich reaction of aldehydes with *C*-alkynyl imines.[7] The method not only proceeds under very mild reaction conditions, but also adducts (propargylic β-amino aldehydes or derived amino alcohols) with two contiguous stereogenic centers, and several sites amenable for further synthetic manipulation are afforded. Notably, simple reduction of the alkynyl to alkyl or alkenyl moieties established new routes to otherwise difficult to prepare Mannich adducts, such as those formally derived from highly enolizable imines or azadienes, respectively.[8,9] In our original report, reactions were promoted by a prolinol silyl ether catalyst and Mannich adducts with *anti*-relative configuration were obtained as major diastereomers.[7] In order to have full access to adducts with either stereoconfiguration, we set to find a route to the stereo-complementary *syn*-adducts. In this paper, we report the direct *syn*-selective and highly enantioselective Mannich reaction of aldehydes with alkynyl imines based on a dual proline achiral aminal/urea catalysis system.

Results and Discussion

Since the seminal reports from the groups of List[10] and Barbas[11] on proline-catalyzed enantioselective Mannich reactions, much work has been devoted to further develop this reaction for the stereoselective production of β-amino carbonyl compounds.[8] Whilst several classes of azomethine functions participate in this and related direct asymmetric Mannich reactions, to our knowledge *C*-alkynyl imines had essentially not

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been reported before our work on this subject.[12] We are aware of a single report on the catalytic asymmetric Mannich reaction involving alkynyl imines, in which Snapper, Hoveyda, and co-workers[13] described the reaction of silyl enol ethers (or silyl ketene acetals as acetate enolate equivalents) with *N*-2-methoxyphenyl alkynylidenamines using a chiral silver catalyst as the stereocontrol/activation agent.

At the outset of the present investigation, we hypothesized that proline and related bifunctional amine catalysts, known to promote Mannich reactions[8] through List–Houk-type transition states[10,14] similar to **A** (Figure 2), would lead to the corresponding *syn*-configured propargylic adducts. Such a pathway would be mechanistically complementary to **B**, previously proposed by us to explain the preferential formation of *anti*-adducts from reactions catalyzed by prolinol ethers.[7]

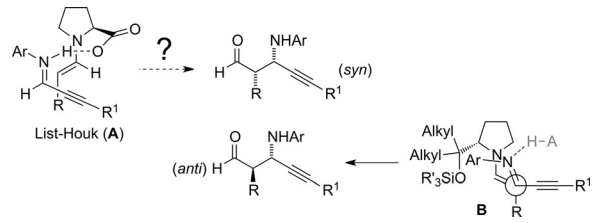
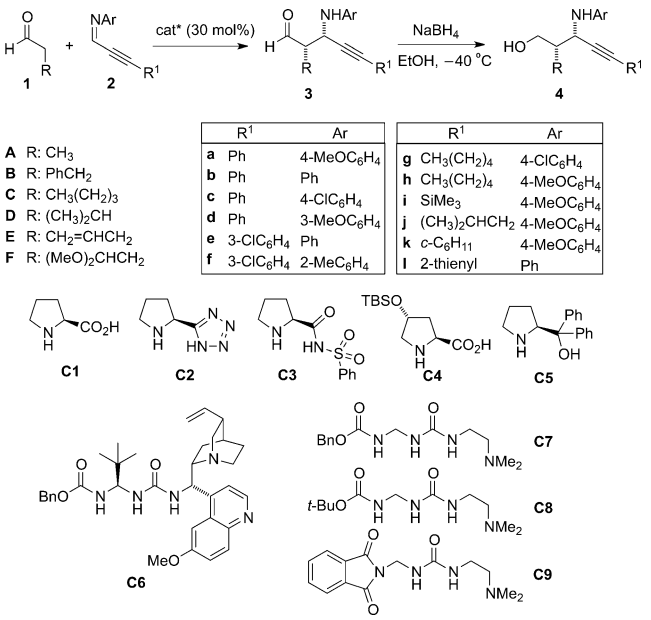


Figure 2. Proposed models for the *anti*- and *syn*-selective Mannich reactions involving propargylic imines.

In order to validate the above hypothesis, standard bifunctional pyrrolidines **C1**–**C5** were first evaluated using the coupling of propanal **1 A** with alkynyl imine **2 a** as the model reaction (Scheme 1). As the data in Table 1 show, among selected catalysts, **C1** (L-proline)[10,11] and **C4**[15] provided the best results in terms of chemical yield, but also both *syn*/*anti* ratios (up to 95:5) and enantioselectivity in DMF as solvent (entries 1 and 11). Catalysts **C2**[16] and **C3**[17] also promoted the reaction, although providing somewhat inferior yields and considerably lower diastereoselectivity (*syn*/*anti* 85:15 and 80:20, respectively; entries 9 and 10). The prolinol catalyst **C5**, which has been shown to be effective in several organocatalytic transformations,[18] did not promote the reaction (entry 12). Other solvents examined in the proline-catalyzed reaction did not improve the results (DMSO, THF) or led to no reaction at all (dioxane; entry 5). A common problem associated to the above catalytic conditions was the formation of variable amounts of the homoaldol side product that complicated the product isolation in certain instances. In addition to this problem, even for the best conditions (proline as catalyst in DMF at −40 °C, entry 3), the reaction required no less than 30 mol% of the catalyst, and lower catalyst loadings resulted in decreased chemical yield and stereoselectivity.



Scheme 1. Direct coupling of aldehydes with propargylic imines to form *syn*-configured propargylic aminoalcohols.

Table 1. Screening of the catalyst for the reaction of propanal (**1 A**) with imine **2 a**.[a]

Entry	Cat.	Cocat.	Solvent	*T* [°C]	*t* [h]	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1	**C1**	–	DMF	0	48	n.d.	87:13	86
2	**C1**	–	DMF	−20	48	63	92:8	98
3	**C1**	–	DMF	−40	48	60	95:5	98
4	**C1**	–	DMSO	−20	48	n.d.	65:35	n.d.
5	**C1**	–	Dioxane	RT	48	NR	–	–
6	**C1**	–	THF	0	48	80	80:20	99
7	**C1**	–	THF	−5	48	n.d.	85:15	n.d.
8	**C1**	–	THF	−20	48	NR	–	–
9	**C2**	–	DMF	−20	48	48	85:15	n.d.
10	**C3**	–	DMF	−20	48	52	80:20	n.d.
11	**C4**	–	DMF	−20	48	58	95:5	99
12	**C5**	–	DMF	−20	48	NR	–	–
13	**C1**	**C6**	THF	−20	48	73	99:1	99
14	**C1**	**C6**	MTBE	−20	48	53	70:30	99
15	**C1**	**C6**	DCM	−20	16	88	99:1	99
16[e]	**C1**	**C6**	DCM	−20	16	88	99:1	99
17	–	**C6**	DCM	RT	48	NR	–	–
18	**C1**	**C7**	DCM	−20	4	79	94:6	95
19	**C1**	**C8**	DCM	−20	4	80	98:2	98

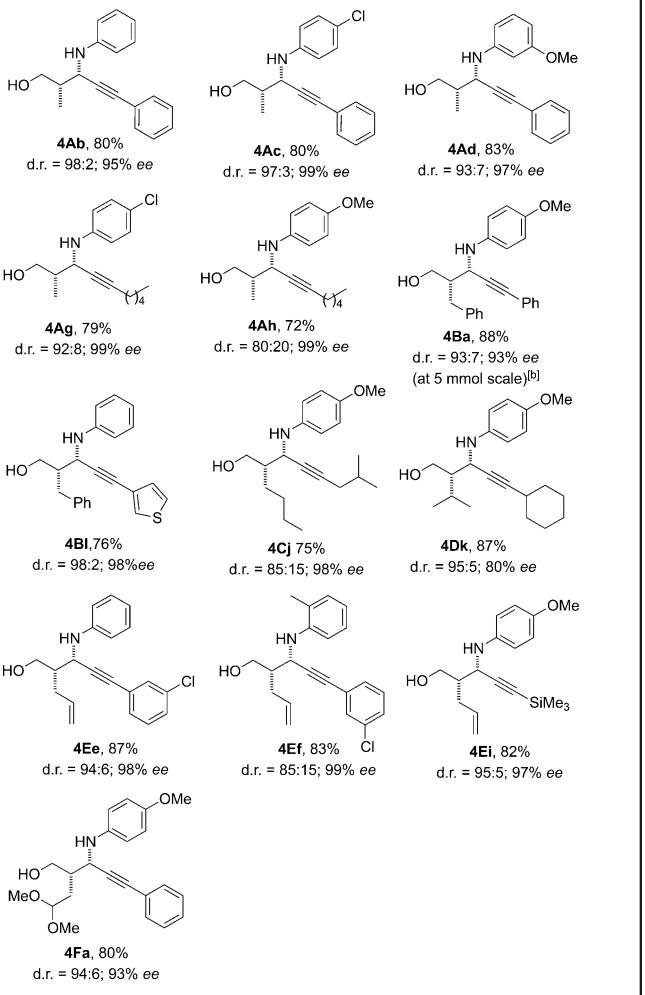
[a] Reactions conducted with; entries 1–12: **2 a** (0.5 mmol), **1 A** (3 mmol) and catalyst (30 mol%) in solvent (1.5 mL); entries 13–20: **2 a** (0.5 mmol), **1 A** (0.6 mmol), proline (10 mol%) and cocatalyst (10 mol%) in solvent (2.0 mL), otherwise stated. [b] Yield of isolated product **4Aa**. [c] Determined by ^{1}H NMR and chiral HPLC. [d] Determined by chiral HPLC of crude **4Aa** before purification. [e] Using 3 mol% of each catalyst. MTBE = methyl *tert*-butyl ether; DCM = dichloromethane.

We then decided to explore the influence of several cocatalysts with amphoteric H-bond donor/acceptor character (entries 13–19). These types of combinations involving a pyrrolidine catalyst and a Brønsted base/H-bond donor cocatalyst, both chiral,[19] have recently been reported to improve the reactivity and selectivity profiles of each individual catalyst component.[20] Indeed, we observed significant improvement for the proline-catalyzed Mannich reaction between **1 A** and **2 a** upon addition of cocatalyst **C6** (entries 13–16), recently introduced by us as new bifunctional Brønsted base/H-bond donor catalyst.[21] First advantage was that otherwise inefficient solvents, particularly relatively apolar dichoromethane, could now

be used successfully. Most significant, while keeping the enantioselectivity almost perfect and the chemical yield high, the *syn*/*anti* ratio could be improved up to 99:1 with catalyst loading as low as 3 mol% (entry 16). On the other hand, **C6** alone (entry 17) was unable to catalyze the reaction and unaltered starting materials were recovered after two days of stirring at room temperature. Next, we wondered whether an achiral bifunctional cocatalyst[22] could produce a similar improvement, since literature precedents in this matter were not fully supportive. Although the rate enhancement of a proline-catalyzed Mannich reaction of an activated *N*-Boc imine by action of achiral bifunctional cocatalyst is reported,[22a] previous studies indicated that such achiral additives did not improve the reaction stereoselectivity, particularly *syn*/*anti* selectivity.[19a] Gratifyingly, we observed that the reaction between propanal and propargylic imine **2** carried out in the presence of proline and cocatalysts **C7** or **C8** (10 mol% each) were complete after 4 hour at −20 °C, leading to *syn*-adduct in good diastereo- and enantioselectivity (entries 18 and 19). Results with proline/**C8** were slightly better (entry 19) and this combination was adopted for further exploration of this Mannich reaction. In addition, under these latter conditions the aldehyde donor could be employed in nearly equimolar amount with respect to the imine thus overcoming the formation of side products from the homoaldol reaction.

A pool of representative *C*-alkynyl imines was subjected to the selected conditions to produce the Mannich adducts **3**, for which diastereomeric ratios and enantiomeric excesses were determined after reduction to the propargylic amines **4**. In general *ee*'s were greater than 93% (Table 2) and essentially a single *syn* diastereomer is produced. It is important to note that whilst essentially similar results were obtained with cocatalyst **C7**, **C9** was less effective than both **C8** and **C7**. For example, the reaction of **1B** with **2a** catalyzed by combined proline/**C9** provided, after reduction of the intermediate aldehyde, compound **4Ba** in 80:20 *syn*/*anti* ratio and 75% *ee* for the major diastereomer. This distinct behavior of **C7** and **C8** as compared with **C9** seems to indicate that the third NH group, present in both **C7** and **C8** but absent in **C9**, plays a role during stereocontrol. On the other hand, a good correlation between the *E*/*Z* ratio of starting imine and the *syn*/*anti* ratio of formed adduct was observed, indicative of high stereospecificity. Thus, although the *syn*-isomer was essentially the only product formed starting from purely *E*-imines, the reactions employing imines **2f**, **2h**, and **2j** with *E*/*Z* compositions of 85:15, 80:20, and 85:15, respectively, afforded the corresponding products **4Ah**, **4Cj**, and **4Ef** as mixtures of diastereomers in the same ratios (see Table 2). Though it is difficult to establish the precise role played by each catalyst component in the above Mannich reactions during the key C–C bond forming event, we propose a modify List–Houk-type reaction model, in which the tertiary amine–urea cocatalyst further stabilizes the structure as tentatively depicted in Figure 3. Although alternative scenarios, including an enol-mediated pathway,[23] cannot be ruled out, our model imply the assembly of proline and the urea cocatalyst through H-bonding[22e] rather than purely electrostatic interaction (ion pair).[19a]

Table 2. Scope of the aldehyde and imine substrates.[a]



[a] Reactions conducted in CH_2Cl_2 (2 mL) at −20 °C using imine (0.5 mmol) and aldehyde (0.55 mmol) in the presence of **C1** (0.05 mmol) and **C8** (0.05 mmol); yields of aminoalcohol products after reduction with $NaBH_4$ at −40 °C→0 °C and chromatographic purification; both d.r. and *ee* of major diastereomer determined by HPLC of the crude material before purification. [b] Data using combined **C1** and **C9**: d.r. = 80:20, *ee* = 75%.

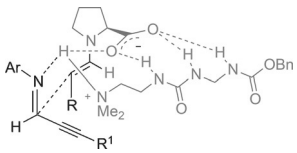
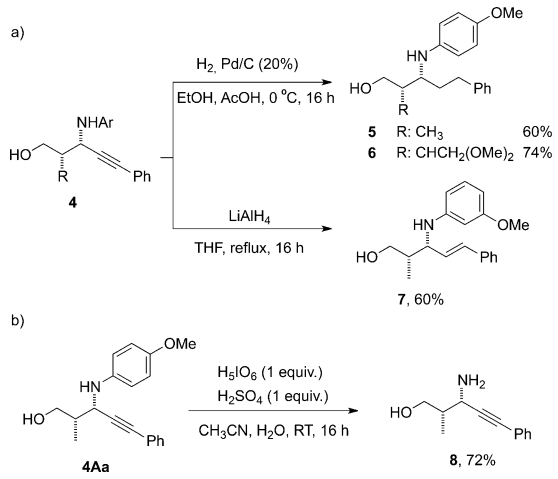


Figure 3. Proposed model for the *syn*-selective Mannich reactions involving dual catalysis.

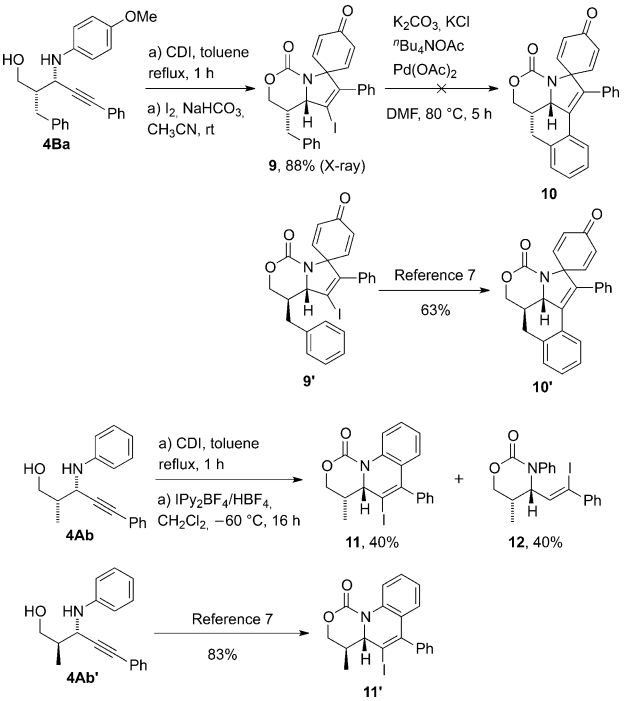
Another attractive aspect of this investigation is that controlled hydrogenation of the alkyne moiety in adducts **4** (Scheme 2) leads in a straightforward manner to products formally derived from challenging Mannich reactions. Thus, β-amino alcohols **5** and **6** are formal Mannich products involving imines derived from enolizable aldehydes, whereas **7** would imply α,β-unsaturated imines. These imine substrates are prob-



Scheme 2. Elaboration of adducts through: a) partial/total hydrogenation of alkyne; b) deprotection of *p*-methoxyphenyl amine.

lematic due to the competitive α-deprotonation[24] and conjugate addition processes,[25] and alternative synthetic routes to adducts like **5**–**7** are highly demanding. On the other hand, exposure of **4Aa** to oxidative *N*-dearylation according to the method reported by Rutjes[26] provided aminoalcohol **8** in 72% yield.

In addition to the observations noted above, the stereochemical and structural attributes of the resulting propargylamine adducts may also be translated into their derived products, taking advantage of the suitability of the alkynyl moiety to participate in several intramolecular cyclization processes[27] (Scheme 3). However, notable differences were observed in the reactivity patterns of adducts **4** as compared with the behavior



Scheme 3. Divergences in intramolecular cyclizations of *syn*/*anti*-isomers.

of the corresponding *anti* congeners (vide infra). For example, applying Larock's *ipso*-halocyclization[28] to adduct **4Ba**, spirocycle **9** was produced in good yield. Incidentally, an X-ray analysis[29] of this crystalline product served to determine its absolute configuration and consequently of the precursor Mannich adduct **4Ba**, and also confirmed the relative *syn* stereochemistry of the above Mannich reactions. However, although the analog of configuration *anti* (**9′**) has been demonstrated to participate effectively in an intramolecular Heck reaction leading to **10′**,[7] treatment of **9** under the standard Heck conditions afforded unreacted starting material exclusively. Failure of **9** in such a cyclization reaction may be ascribed to unfavorable steric effects, as indicated in the stereoviews of Figure 4. In another example of divergent reactivity when comparing the *syn* versus *anti* propargylic amine adducts, the electrophilic carbocyclization of **4Ab** under Barluenga's conditions[30] led to an almost equimolar mixture of the corresponding cyclization product **11** and the hydroiodation product **12**, whereas the corresponding *anti*-adduct **4Ab'** afforded tricycle **11'** in a clean transformation.[7]

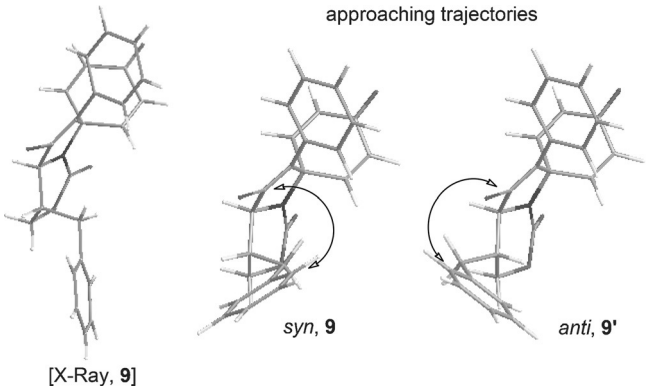


Figure 4. Crystal structure of **9** and stereoviews of the approaching trajectories for intramolecular cyclizations of stereoisomers **9** and **9′**.

Conclusion

The first direct reaction of aldehydes with *C*-alkynyl imines to afford the corresponding Mannich adducts of *syn*-relative configuration has been described. This reaction, using proline as the only catalyst, proceeds with reasonably good yield and stereoselectivity (*syn*/*anti* ratio up to 95:5) in DMF as solvent, even though no less than 30 mol% catalyst is required and variable amounts of homoaldol side product are also formed. However, by using proline in combination with a simple achiral aminal/urea-based cocatalyst, not only conditions are more benign (equimolar amount of reagents, CH_2Cl_2 as solvent, RT, loading of each cocatalyst 10 mol%), but also the *syn*-isomers are obtained as almost exclusive products (*syn*/*anti* up to 99:1, 99% *ee*). This dual activation catalytic reaction is general for a range of *C*-alkynyl imines and a simple reduction of the alkynyl moiety in adducts gives access to otherwise elusive Mannich products, such as those formally derived from enolizable or α,β-unsaturated imines.

Experimental Section

Synthesis of propargylic imines 2: Imines **2a–l** were prepared as previously described:[7] A mixture of aldehyde (5 mmol), the corresponding amine (5 mmol), and $MgSO_4$ (2 g, 400 mg mmol^{-1}) in dry CH_2Cl_2 (25 mL) was stirred at room temperature for 16 h. The mixture was filtered through a pad of celite and concentrated. The resulting yellow solid was disaggregated with hexanes and filtered. The imines thus obtained were pure enough to carry out the Mannich reaction without further purification.

General procedure for the preparation of catalysts C7–C9: To a cooled solution of the corresponding N-protected amino acid (5 mmol, 1 equiv), in dry THF (20 mL) were added isobutyl chloroformate (1 equiv, 0.65 mL), 5 mmol), and *N*-methylmorpholine (1 equiv, 0.6 mL, 5 mmol), and the mixture was stirred at −20 °C for 20 min. Then, a suspension of NaN_3 (1.5 equiv, 0.48 g in 5 mL of H_2O, 7.5 mmol) was added and the reaction mixture was stirred at the same temperature. After 30 min, the organic layer was separated, evaporated, and the residue was dissolved in CH_2Cl_2 (30 mL) and washed with water (15 mL). The organic phase was dried over $MgSO_4$, and concentrated under vacuum to give a yellow oil, which was dissolved in dry CH_2Cl_2 (10 mL). The resulting solution was heated at 40 °C under nitrogen for 1–2 h. The reaction was monitored by IR analysis until disappearance of the azide band (2140 cm^{-1}). After completion, the corresponding amine was added (0.7 equiv, 3.5 mmol) and the reaction mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel to afford the desired catalysts.

Benzyl ((3-(2-(dimethylamino)ethyl)ureido)methyl)carbamate C7: The title compound was prepared from Cbz-glycine (5 mmol) and *N*,*N*-dimethylethane-1,2-diamine (3.5 mmol) according to the general procedure. Colorless oil, yield: 791 mg, 2.7 mmol, 62%. ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 7.42–7.34 (m, 5H), 5.16 (d, *J* = 6.0 Hz, 2H), 3.91 (d, *J* = 5.6 Hz, 2H), 3.44–3.27 (m, 2H), 2.43 (m, *J* = 6.1 Hz, 2H), 2.31–2.20 ppm (s, 6H). ^{13}C NMR (300 MHz, $CDCl_3$) δ = 169.1, 156.8, 135.7, 128.6, 128.3, 128.3, 67.3, 58.0, 53.6, 45.5, 45.3 ppm.

***tert*-Butyl ((3-(2-(dimethylamino)ethyl)ureido)methyl)carbamate C8**: The title compound was prepared from (*tert*-butoxycarbonyl)-glycine (5 mmol) and *N*,*N*-dimethylethane-1,2-diamine (3.5 mmol) according to the general procedure. White solid, yield: 600 mg, 2.31, mmol, 66%. M.p. 104–106 °C; ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 5.61 (s, 1H), 5.12 (s, 1H), 4.49 (s, 2H), 3.27 (q, *J* = 5.4 Hz, 2H), 2.44 (t, *J* = 5.8 Hz, 2H), 2.26 (s, 6H), 1.47 ppm (s, 9H). ^{13}C NMR (300 MHz, $CDCl_3$) δ = 158.9, 156.9, 79.9, 59.4, 47.5, 45.6, 38.4, 28.7 ppm.

1-(2-(Dimethylamino)ethyl)-3-((1,3-dioxoisoindolin-2-yl)methyl)urea C9: The title compound was prepared from 2-(1,3-dioxoisoindolin-2-yl)acetic acid (5 mmol) and *N*,*N*-dimethylethane-1,2-diamine (3.5 mmol) according to the general procedure. White solid, yield: 527 mg, 1.82, mmol, 52%. M.p. 138–140 °C; ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 7.99–7.83 (m, 2H), 7.76 (dd, *J* = 5.5, 3.0 Hz, 2H), 4.38 (s, 2H), 3.44–3.32 (m, 2H), 2.53–2.42 (m, 2H), 2.27 ppm (s, 6H). ^{13}C NMR (300 MHz, $CDCl_3$) δ = 168.0, 166.2, 134.5, 132.4, 123.9, 57.7, 45.3, 40.9, 37.1 ppm.

General procedure for the Mannich reaction: To a solution of the corresponding propargylic imine **2** (0.5 mmol, 1 equiv), L-proline **C1** (5.8 mg, 0.05 mmol, 10 mol%), and cocatalyst **C6** or **C8** (0.05 mmol, 10 mol%) in DCM (2 mL) at −20 °C was added aldehyde **1** (0.6 mmol, 1.2 equiv). The resulting solution was stirred at −20 °C for 4 h. Then, EtOH (1 mL) and $NaBH_4$ (4.5 mmol, 8 equiv) were successively added at −40 °C and after allowing the mixture to reach 0 °C, it was stirred at this temperature until the reaction completion (typically 30–60 min). The reaction mixture was quenched with an aqueous NH_4Cl solution (saturated, 4 mL) and allowed to reach room temperature. After extraction with DCM (3× 6 mL), the combined organic phases were washed with brine (4× 10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The product was purified by flash column chromatography on silica gel (eluent: mixtures of hexane/ethyl acetate).

(2*S*,3*S*)-3-((4-Methoxyphenyl)amino)-2-methyl-5-phenylpent-4-yn-1-ol (4Aa): Prepared according to the general procedure starting from propanal **1A** (40 μL, 0.55 mmol) and 4-methoxy-*N*-(3-phenylprop-2-ynylidene) aniline (**2a**; 118 mg, 0.5 mmol). Yellow oil, yield: 129.9 mg, 88% yield. $[\alpha]_D^{22} = -132.3$ (*c* = 1, 98% *ee*, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.36 (dd, *J* = 6.8, 3.0 Hz, 2H), 7.28 (d, *J* = 2.3 Hz, 4H), 6.80 (d, *J* = 3.1 Hz, 4H), 4.37 (d, *J* = 4.1 Hz, 1H), 3.94 (dd, *J* = 10.9, 7.7 Hz, 1H), 3.80 (dd, *J* = 10.9, 4.1 Hz, 1H), 3.76 (s, 3H), 2.33–2.17 (m, 1H), 1.15 ppm (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 140.8, 131.8, 128.3, 116.8, 114.8, 88.4, 84.7, 66.2, 55.8, 52.5, 39.6, 13.7 ppm; HRMS (ESI): *m/z* calcd for $C_{19}H_{22}NO_2$ 296.1651; found: 296.1665.The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 97/3, flow rate = 0.6 mL min^{-1}, retention times: 84.6 min (major) and 94.8 min (minor)).

(2*S*,3*S*)-2-Methyl-5-phenyl-3-(phenylamino)pent-4-yn-1-ol (4Ab): Prepared according to the general procedure starting from propanal **1A** (40 μL, 0.55 mmol) and *N*-(3-*p*henylprop-2-ynylidene) aniline (**2b**; 118 mg, 0.5 mmol). Yellow oil, yield: 106.1 mg, 80%. $[\alpha]_D^{22} = -146.9$ (*c* = 1, 95% *ee*, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.37 (dd, *J* = 6.6, 3.2 Hz, 2H), 7.31–7.18 (m, 5H), 6.82–6.75 (m, 3H), 4.47 (d, *J* = 4.1 Hz, 1H), 3.96 (dd, *J* = 10.9, 7.9 Hz, 1H), 3.80 (dd, *J* = 10.8, 4.3 Hz, 1H), 2.34–2.22 (m, 1H), 1.15 ppm (d, *J* = 7.0 Hz, 3H);^{13}C NMR ($CDCl_3$, 75 MHz) δ = 146.9, 131.8, 129.3, 128.3, 118.7, 114.5, 88.2, 84.5, 66.0, 50.7, 39.7, 13.9 ppm; HRMS (ESI): *m/z* calcd for $C_{18}H_{20}NO$ 266.1552; found: 266.1545. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 95/5, flow rate = 1 mL min^{-1}, retention times: 13.0 min (minor) and 14.5 min (major)).

(2*S*,3*S*)-3-((4-Chlorophenyl)amino)-2-methyl-5-phenylpent-4-yn-1-ol (4Ac): Prepared according to the general procedure starting from propanal **1A** (40 μL, 0.55 mmol) and (*E*)-4-chloro-*N*-(3-phenylprop-2-yn-1-ylidene)aniline (**2c**; 119.8 mg, 0.5 mmol). Yellow oil, yield: 119.6 mg, 80%. $[\alpha]_D^{22} = -239.6$ (*c* = 1, 99% *ee*, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.45–7.04 (m, 7H), 6.70 (d, *J* = 8.9 Hz, 2H), 4.41 (d, *J* = 4.1 Hz, 1H), 4.00–3.92 (m, 1H), 3.80 (dd, *J* = 10.8, 4.2 Hz, 1H), 2.28 (ddd, *J* = 11.3, 8.3, 4.2 Hz, 1H), 1.13 ppm (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 145.6, 131.8, 129.0, 128.3, 123.1, 122.8, 115.5, 87.7, 84.6, 65.8, 50.8, 39.5, 14.0 ppm; HRMS (ESI): *m/z* calcd for $C_{18}H_{19}NOCl$ 300.1155; found: 300.1168. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 97/3, flow rate = 0.6 mL min^{-1}, retention times: 53.8 min (minor) and 58.1 min (major)).

(2*S*,3*S*)-3-((3-Methoxyphenyl)amino)-2-methyl-5-phenylpent-4-yn-1-ol (4Ad): Prepared according to the general procedure starting from propanal **1A**) (40 μL, 0.55 mmol) and (*E*)-3-methoxy-*N*-(3-phenylprop-2-yn-1-ylidene)aniline (**2d**; 117.9 mg, 0.5 mmol). Yellow oil, yield: 122.4 mg, 83%. $[\alpha]_D^{22} = -246.9$ (*c* = 1, 97% *ee*, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.38 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.33–7.25 (m, 3H), 7.16–7.07 (m, 2H), 6.43–6.32 (m, 3H), 4.45 (s, 1H), 3.99–3.90 (m, 1H), 3.78 (s, 3H), 3.77 (s, 1H), 2.33–2.22 (m, 1H), 1.14 ppm (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 160.8, 148.3, 131.8, 130.0, 128.3, 107.3, 103.9, 100.3, 88.1, 84.4, 65.8, 55.2, 50.6, 39.7, 13.9 ppm; HRMS (ESI): *m/z* calcd for $C_{19}H_{21}NO_2$ 296.1655;

found: 296.1651. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 90/10, flow rate = 0.5 mL min^{-1}, retention times: 10.7 min (minor) and 14.2 min (major)).

(2*S*,3*S*)-3-((4-Chlorophenyl)amino)-2-methyldec-4-yn-1-ol (4Ag): Prepared according to the general procedure starting from propanal **1A** (40 μL, 0.55 mmol) and (*E*)-4-chloro-*N*-(oct-2-yn-1-ylidene)aniline (**2g**; 116.8 mg, 0.5 mmol). Yellow oil, yield: 121.2 mg, 79%. $[\alpha]_D^{22} = -101.5$ ($c = 1$, 99% *ee*, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) $\delta = 7.18–7.08$ (m, 2H), 6.71–6.59 (m, 2H), 4.12 (dd, $J = 4.6$, 2.5 Hz, 2H), 3.87 (dd, $J = 10.8$, 8.1 Hz, 1H), 3.72 (dd, $J = 10.8$, 4.1 Hz, 1H), 2.15 (td, $J = 7.0$, 2.1 Hz, 3H), 1.35–1.20 (m, 5H), 1.05 (dd, $J = 6.9$, 2.8 Hz, 3H), 0.92–0.81 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.7, 128.9, 122.8, 115.4, 85.1, 78.2, 65.8, 50.5, 39.4, 31.0, 28.5, 22.1, 18.6, 14.0 ppm; HRMS (ESI): *m/z* calcd for $C_{17}H_{24}NOCl$ 294.8316; found: 294.1633. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 98:2, flow rate = 1 mL min^{-1}, retention times: 10.3 min (minor) and 14.9 min (major)).

(2*S*,3*S*)-3-((4-Methoxyphenyl)amino)-2-methyldec-4-yn-1-ol (4Ah): Prepared according to the general procedure starting from propanal **1A** (40 μL, 0.55 mmol) and (*E*)-4-methoxy-*N*-(oct-2-yn-1-ylidene)aniline (**2h**; 114.6 mg, 0.5 mmol). Yellow oil, yield: 109.1 mg, 72%. $[\alpha]_D^{22} = -62.8$ ($c = 1$, 99% *ee*, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) $\delta = 6.87–6.62$ (m, 4H), 4.16–4.07 (m, 1H), 3.90–3.83 (m, 1H), 3.75 (d, $J = 2.8$ Hz, 3H), 3.71 (d, $J = 4.0$ Hz, 1H), 2.18–2.07 (m, 2H), 1.45 (s, 2H), 1.34–1.22 (m, 4H), 1.06 (d, $J = 7.0$ Hz, 2H), 0.98–0.83 ppm (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) $\delta = 153.2$, 141.0, 116.7, 114.7, 85.2, 78.9, 66.2, 55.7, 52.2, 39.4, 31.0, 28.5, 22.2, 18.7, 14.0, 13.7 ppm; HRMS (ESI): *m/z* calcd for $C_{18}H_{28}NO_2$ 290.2120; found: 290.2115. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC hexane/isopropanol 90:10, flow rate = 0.5 mL min^{-1}, retention times: 20.1 min (minor) and 24.3 min (major)).

(2*S*,3*S*)-2-Benzyl-3-((4-methoxyphenyl)amino)-5-phenylpent-4-yn-1-ol (4Ba): Prepared according to the general procedure starting from hydrocinnamaldehyde **1B** (73 μL, 0.55 mmol) and (*E*)-4-methoxy-*N*-(3-phenylprop-2-ynylidene) aniline (**2a**; 118 mg, 0.5 mmol). Yellow oil, yield: 163.1 mg, 88%. $[\alpha]_D^{22} = -29.4$ ($c = 1$, 99% *ee*, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) $\delta = 7.45–7.17$ (m, 10H), 6.78 (d, $J = 9.1$ Hz, 2H), 6.66 (d, $J = 9.1$ Hz, 2H), 4.38 (d, $J = 3.8$ Hz, 1H), 4.01 (dd, $J = 11.0$, 7.6 Hz, 1H), 3.93–3.84 (m, 1H), 3.75 (s, 3H), 2.96–2.67 ppm (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) $\delta = 153.1$, 140.6, 139.6, 131.7, 129.1, 128.5, 128.2, 126.3, 116.4, 114.7, 87.9, 85.2, 63.9, 55.6, 50.7, 46.1, 34.7 ppm; HRMS (ESI): *m/z* calcd for $C_{25}H_{26}NO_2$ 372.1964; found: 372.1971. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA hexane/isopropanol/ethanol 95:2:3, flow rate = 1 mL min^{-1}, retention times: 26.0 min (major) and 38.3 min (minor).

(2*S*,3*S*)-2-Benzyl-3-((4-methoxyphenyl)amino)-5-(thiophen-3-yl)pent-4-yn-1-ol (4Bl): Prepared according to the general procedure starting from hydrocinnamaldehyde **1B** (73 μL, 0.55 mmol) and (*E*)-4-methoxy-*N*-(3-(thiophen-3-yl)prop-2-yn-1-ylidene)aniline (**2l**, 105.6 mg, 0.5 mmol). Yellow oil, yield: 131.8 mg, 76% yield. $[\alpha]_D^{22} = -2.9$ ($c = 1$, 98% *ee*, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) $\delta =$ 7.33–7.01 (m, 11H), 6.67 (t, $J = 7.8$ Hz, 1H), 6.39 (d, $J = 9.5$ Hz, 2H), 3.72–3.64 (m, 2H), 3.55 (d, $J = 5.5$ Hz, 1H), 2.91–2.76 (m, 1H), 2.75–2.53 (m, 3H), 2.16 (d, $J = 11.9$ Hz, 1H), 2.07–1.79 ppm (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) $\delta = 147.8$, 141.9, 140.2, 129.6, 129.2, 128.7, 128.6, 126.7, 126.1, 126.0, 117.6, 113.6, 63.7, 62.5, 53.5, 45.2, 34.3, 33.8, 33.8, 33.1, 32.2, 31.0, 29.8 ppm; HRMS (ESI): *m/z* calcd for $C_{22}H_{21}NOS$ 347.4760; found: 347.0307. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 95:5, flow rate = 1 mL min^{-1}, retention times: 17.5 min (minor) and 19.8 min (major)).

(2*S*,3*S*)-2-Butyl-3-((4-methoxyphenyl)amino)-7-methyloct-4-yn-1-ol (4Cj): Prepared according to the general procedure starting from hexanal **1C** (66 μL, 0.55 mmol) and (*E*)-4-methoxy-*N*-(5-methylhex-2-ynylidene)aniline (**2j**; 108 mg, 0.5 mmol). White solid, yield: 118.8 mg, 75%. m.p. 75–78 °C; $[\alpha]_D^{22} = -170.8$ ($c = 1$, 99% *ee*, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) $\delta = 6.87–6.61$ (m, 4H), 4.19 (s, 1H), 3.92 (dd, $J = 11.0$, 7.6 Hz, 1H), 3.81 (d, $J = 3.5$ Hz, 1H), 3.76 (s, 3H), 2.06 (dd, $J = 6.4$, 2.0 Hz, 2H), 1.75 (dt, $J = 13.2$, 6.6 Hz, 1H), 1.45–1.23 (m, 8H), 0.92 ppm (d, $J = 6.5$ Hz, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) $\delta = 153.3$, 141.0, 116.7, 114.7, 84.1, 79.67, 64.7, 55.8, 51.6, 44.2, 29.7, 28.1, 27.9, 23.0, 21.99, 14.0 ppm; HRMS (ESI): *m/z* calcd for $C_{20}H_{32}NO_2$ 318.2433; found: 318.2419. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 98:2, flow rate = 0.5 mL min^{-1}, retention times: 48.7 min (minor) and 68.4 min (major)).

(2*S*,3*S*)-5-Cyclohexyl-2-isopropyl-3-((4-methoxyphenyl)amino)-pent-4-yn-1-ol (4Dk): Prepared according to the general procedure starting from isovaleraldehyde **1D** (59 μL, 0.55 mmol) and (*E*)-*N*-(3-cyclohexylprop- 2-ynylidene)-4-methoxyaniline (**2k**; 121 mg, 0.5 mmol). Yellow oil, yield: 143.5 mg, 87%. $[\alpha]_D^{22} = -60.8$ ($c = 1$, 78% *ee*, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) $\delta = 6.82–6.77$ (m, 2H), 6.74–6.69 (m, 2H), 4.28–4.24 (m, 1H), 3.99 (dd, $J = 11.3$, 8.0 Hz, 1H), 3.88 (dd, $J = 11.3$, 3.3 Hz, 1H), 3.75 (d, $J = 1.9$ Hz, 3H), 1.78–1.68 (m, 3H), 1.52–1.23 (m, 10H), 1.05 (d, $J = 6.7$ Hz, 4H), 1.00 ppm (d, $J = 6.7$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) $\delta = 153.1$, 140.9, 116.5, 114.7, 90.1, 79.1, 63.0, 55.8, 50.2, 49.7, 32.7, 29.0, 27.6, 25.9, 24.7, 21.2, 20.4 ppm; HRMS (ESI): *m/z* calcd for $C_{21}H_{32}NO_2$ 330.2433; found: 330.2444. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak AS-H, hexane/isopropanol 95:5, flow rate = 1 mL min^{-1}, retention times: 10.7 min (major) and 16.4 min (minor)).

(*S*)-2-((*S*)-3-(3-Chlorophenyl)-1-(phenylamino)prop-2-yn-1-yl)pent-4-en-1-ol (4Ee): Prepared according to the general procedure starting from 4- pentenal **1E** (55 μL, 0.55 mmol) and (*E*)-*N*-(3-(3-chlorophenyl)prop-2-yn-1-ylidene)aniline (**2e**; 119.8 mg, 0.5 mmol). Yellow oil, yield: 141.3 mg, 87% ; $[\alpha]_D^{22} = -158.4$ ($c = 1$, 99% *ee*, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) $\delta = 7.38–7.10$ (m, 4H), 6.84–6.61 (m, 2H), 5.82 (dd, $J = 17.2$, 7.0 Hz, 1H), 5.23–4.93 (m, 2H), 4.55 (d, $J = 3.6$ Hz, 1H), 4.05–3.84 (m, 1H), 3.71 (d, $J = 5.9$ Hz, 1H), 3.63 (s, 1H), 2.38–2.07 (m, 4H), 1.74–1.58 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) $\delta = 138.2$, 136.9, 135.8, 131.6, 129.9, 129.5, 129.4, 129.3, 128.5, 118.7, 117.5, 116.7, 115.2, 114.3, 113.6, 89.1, 83.4, 64.1, 63.8, 54.5, 49.3, 44.0, 42.9, 33.2, 31.9, 31.2, 30.9 ppm; HRMS (ESI): *m/z* calcd for $C_{20}H_{21}ClNO$ 3326.1312 found: 326.1321. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane/isopropanol 98:2, flow rate = 0.5 mL min^{-1}, retention times: 31.0 min (minor) and 36.6 min (major)).

(*S*)-2-((*S*)-3-(3-Chlorophenyl)-1-(o-tolylamino)prop-2-yn-1-yl)pent-4-en-1-ol (4Ef): Prepared according to the general procedure starting from 4-pentenal **1E** (55 μL, 0.55 mmol) and (*E*)-*N*-(3-(3-chlorophenyl)prop-2-yn-1-ylidene)-2-methylaniline (**2f**; 126.8 mg, 0.5 mmol). Yellow oil, yield: 140.6 mg, 83%; $[\alpha]_D^{22} = -125.8$ ($c = 1$, 99% *ee*, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) $\delta = 7.42–7.03$ (m, 4H), 6.89–6.63 (m, 2H), 5.97–5.75 (m, 1H), 5.34–4.96 (m, 2H), 4.57 (d, $J = 3.1$ Hz, 1H), 4.05 (s, 1H), 3.91 (d, $J = 3.2$ Hz, 1H), 3.71 (d, $J = 6.0$ Hz, 1H), 2.37–2.22 (m, 2H), 2.15 ppm (d, $J = 10.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) $\delta = 144.8$, 138.2, 136.9, 135.8, 131.6, 130.4, 130.2, 129.9, 129.5, 128.5, 127.2, 127.0, 123.3, 118.1, 117.5, 116.9, 116.7, 115.2, 111.4, 110.4, 89.3, 83.3, 64.3, 63.8, 54.0, 49.2, 44.0, 42.7,

33.4, 32.9, 32.1, 31.1, 30.9, 17.7 ppm; HRMS (ESI): *m/z* calcd for $C_{21}H_{23}ClNO$ 340.1468; found: 340.1478. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane/isopropanol 98:2, flow rate = 0.5 mL min^{-1}, retention times: 54.1 min (minor) and 69.1 min (major)).

(*S*)-2-((*S*)-1-((4-Methoxyphenyl)amino)-3-(trimethylsilyl)prop-2-yn-1-yl)pent-4-en-1-ol (4Ei): Prepared according to the general procedure starting from 4-pentenal **1E** (55 μL, 0.55 mmol) and (*E*)-4-methoxy-*N*-(3-(trimethylsilyl)prop-2-ynylidene)aniline (**2i**; 116 mg, 0.5 mmol). Yellow oil, yield: 129.2 mg, 82%; $[\alpha]_D^{22} = -81.8$ (*c* = 1, 97% *ee*, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 6.86–6.60 (m, 4H), 5.92–5.75 (m, 1H), 5.18–4.95 (m, 2H), 4.15 (dd, *J* = 19.5, 5.6 Hz, 1H), 3.91 (dd, *J* = 11.1, 7.4 Hz, 1H), 3.82 (d, *J* = 3.7 Hz, 1H), 3.76 (s, 3H), 2.34–2.12 (m, 3H), 1.68 (d, *J* = 14.6 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 1H), 0.13 ppm (d, *J* = 5.8 Hz, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 153.4, 140.7, 136.0, 117.3, 116.8, 115.0, 114.7, 104.8, 90.0, 64.1, 55.8, 51.4, 43.8, 33.0 ppm; HRMS (ESI): *m/z* calcd for $C_{18}H_{28}NO_2Si$ 318.1884; found: 318.1889. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 95/5, flow rate = 1 mL min^{-1}, retention times: 13.5 min (minor) and 18 min (major)).

(2*S*,3*S*)-2-(2,2-Dimethoxyethyl)-3-((4-methoxyphenyl)amino)-5-phenylpent-4-yn-1-ol (4Fa): Prepared according to the general procedure starting from 4,4-dimethoxybutanal (**1F**; 72.6 mg, 0.55 mmol) and (*E*)-4-methoxy-*N*-(3-phenylprop-2-ynylidene) aniline (**2a**; 118 mg, 0.5 mmol). Yellow oil, yield: 147 mg, 80%. $[\alpha]_D^{22} = -102.2$ (*c* = 0.82, 93% *ee*, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.38–7.26 (m, 5H), 6.82–6.75 (m, 3H), 4.60 (t, *J* = 5.6 Hz, 1H), 4.43 (d, *J* = 4.7 Hz, 1H), 3.99 (dd, *J* = 11.2, 6.5 Hz, 1H), 3.88 (dd, *J* = 11.2, 4.2 Hz, 1H), 3.76 (s, 3H), 3.38 (d, *J* = 3.0 Hz, 6H), 3.36–3.32 (m, 2H), 2.06–2.03 (m, 1H), 2.02–1.97 (m, 1H), 1.89–1.78 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 153.4, 140.8, 131.8, 128.3, 116.7, 114.8, 103.4, 88.3, 84.9, 64.6, 55.8, 53.5, 52.8, 51.7, 40.9, 31.3 ppm; HRMS (ESI): *m/z* calcd for $C_{22}H_{29}NO_4$ [*M*+H], 270.2018; found, 270.2030. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 80/20, flow rate = 0.5 mL min^{-1}, retention times: 19.5 min (minor) and 24.3 min (major)).

(2*S*,3*R*)-3-((4-Methoxyphenyl)amino)-2-methyl-5-phenylpentan-1-ol (5): To a solution of (2*S*,3*S*)-3-((4-methoxyphenyl)amino)-2-methyl-5-phenylpent-4-yn-1-ol (**4Ba**; 111.8 mg, 0.38 mmol) in ethanol (1.1 mL) was added acetic acid (21.2 μL, 0.38 mmol) and 20% wt of Pd/C (22.4 mg) at room temperature. The reaction mixture was stirred at 0 °C under H_2 atmosphere (1 atm) overnight, then filtered through celite and concentrated under vacuum. The crude material was purified by flash column chromatography on silica gel (eluent hexane/ethyl acetate 80/20) to give the title compound **5** as colorless oil. Yield: 63.1 mg (60%). $[\alpha]_D^{22} = -20.2$ (*c* = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.32–7.09 (m, 5H), 6.76 (d, *J* = 9.0 Hz, 2H), 6.59 (d, *J* = 8.9 Hz, 2H), 3.75 (s, 3H), 3.66 (d, *J* = 5.8 Hz, 2H), 2.68 (d, *J* = 7.8 Hz, 3H), 2.08–1.95 (m, 1H), 1.82 (q, *J* = 7.9, 7.3 Hz, 2H), 0.95 ppm (d, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 152.5, 142.1, 141.9, 128.4, 126.0, 115.6, 115.0, 66.7, 57.0, 55.9, 37.6, 34.5, 33.2, 11.3 ppm; HRMS (ESI): *m/z* calcd for $C_{19}H_{26}NO_2$ 300.1964; found: 300.1981.

(2*S*,3*R*)-2-(2,2-Dimethoxyethyl)-3-((4-methoxyphenyl)amino)-5-phenylpentan-1-ol (6): To a solution of (2*S*,3*S*)-2-(2,2-dimethoxyethyl)-3-((4-methoxyphenyl)amino)-5-phenylpent-4-yn-1-ol (**4Ah**; 55.8 mg, 0.15 mmol) in ethanol (0.5 mL) was added acetic acid (9 μL, 0.15 mmol) and 20% wt of Pd/C (12 mg) at room temperature. The reaction mixture was stirred at 0 °C under H_2 atmosphere (1 atm) overnight, then filtered through celite and concentrated under vacuum. The crude material was purified by flash column chromatography on silica gel (eluent hexane/ethyl acetate 80/20) to give the title compound **6** as brown oil. Yield: 41 mg (74%). $[\alpha]_D^{22} = -5.9$ (*c* = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.36–7.14 (m, 6H), 6.80 (d, *J* = 9.0 Hz, 2H), 6.62 (d, *J* = 9.0 Hz, 2H), 4.45 (d, *J* = 5.4 Hz, 1H), 3.79 (d, *J* = 2.2 Hz, 3H), 3.39–3.34 (m, 6H), 2.70 (s, 4H), 1.70 ppm (d, *J* = 5.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 152.5, 141.8, 128.5, 126.0, 115.5, 115.0, 103.8, 64.6, 57.1, 55.9, 53.0, 38.6, 33.7, 33.0, 30.5 ppm; HRMS (ESI): *m/z* calcd for $C_{22}H_{32}NO_4$ 374.2331; found: 374.2336.

(2*S*,3*R*,*E*)-3-((3-Methoxyphenyl)amino)-2-methyl-5-phenylpent-4-en-1-ol (7): $LiAlH_4$ (45.6 mg, 1.2 mmol) was added to a solution of (2*S*,3*S*)-3-((3-methoxyphenyl)amino)-2-methyl-5-phenylpent-4-yn-1-ol (**4Ba**; 93.1 mg, 0.3 mmol) in THF (3 mL) at room temperature. The reaction mixture was immediately heated to reflux and stirred overnight. The mixture was cooled to room temperature, diluted with AcOEt (10 mL) and filtered through celite. The solution was washed with an aqueous solution of saturated NH_4Cl (10 mL), and the organic layer dried with $MgSO_4$ and concentrated under vacuum. The title compound **7** was obtained as yellow oil. Yield: 54 mg (60%). $[\alpha]_D^{22} = -104.9$ (*c* = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.49–7.04 (m, 5H), 6.45–6.13 (m, 3H), 4.22 (s, OH), 4.20–4.11 (m, 1H), 3.83–3.72 (m, 3H), 1.30 (t, *J* = 7.1 Hz, 1H), 1.18 (d, *J* = 7.0 Hz, 1H), 1.01 ppm (dd, *J* = 24.4, 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 160.89, 149.11, 136.98, 131.46, 130.05, 129.54, 128.62, 127.54, 126.49, 106.85, 102.80, 99.74, 65.89, 58.34, 55.18, 40.19, 12.86 ppm; HRMS (ESI): *m/z* calcd for $C_{19}H_{24}NO_2$ 298.1807; found: 298.1809.

Deprotection of *p*-*N*-methoxyphenylamine 4Aa: To a solution of aminoalcohol **4Ab** (60 mg, 0.2 mmol) in MeCN/H_2O (5 mL, 1:1) was added H_5IO_6 (45 mg, 0.2 mmol, 1 equiv) and 2 M H_2SO_4 (0.1 mL). The mixture was stirred for 16 h at room temperature and washed with CH_2Cl_2 (3×100 mL). The resulting aqueous phase was subsequently basified to pH 10.5 by slow addition of 20% KOH at 0 °C, and the resulting mixture was extracted with EtOAc (4×100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The essentially pure amine **8** was obtained as yellow oil (27 mg, 72% yield). $[\alpha]_D^{22} = -13.6$ (*c* = 0.2, 98% *ee*, CH_2Cl_2) ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 7.55–7.23 (m, 5H), 4.14 (d, *J* = 3.7 Hz, 1H), 3.93 (dd, *J* = 11.0, 7.3 Hz, 1H), 3.79 (dd, *J* = 11.0, 3.4 Hz, 1H), 2.07 (tq, *J* = 7.0, 3.5 Hz, 1H), 1.10 ppm (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 131.5, 128.3, 122.8, 89.7, 84.3, 67.1, 66.9, 48.8, 39.6, 12.5 ppm.

Carbocyclizations to products 9, 11 and 12

Synthesis of 9: To a solution of (2*S*,3*S*)-2-benzyl-3-((4-methoxyphenyl)amino)-5-phenylpent-4-yn-1-ol (**4Ba**; 3 mmol, 1 g) in toluene (3 mL) at room temperature was added 1,1-carbonyldimidazole (1.4 g, 9 mmol). The mixture was immediately heated to reflux and stirred for 1 h, then cooled to room temperature and quenched with 1 M HCl. The mixture was extracted with EtOAc (3×10 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum to give the N,O-diprotected product. This crude material was dissolved in CH_3CN (30 mL), and I_2 (2.3 g, 9 mmol) and $NaHCO_3$ (529.3 mg, 60.3 mmol) were added and the reaction mixture was stirred at room temperature until completion (5 h). Then, the reaction mixture was diluted with diethyl ether (25 mL) and washed with saturated aqueous $Na_2S_2O_3$ (20 mL). The organic layer was separated, and the aqueous layer was extracted with another 25 mL of diethyl ether. The combined organic layers were dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure, and the resulting product was purified by silica gel column chromatography (eluent EtOAc/hexane, 20:80) to

afford the title compound **9** as yellow solid that was crystallized from a mixture of CH_2Cl_2/Et_2O. Yield: 448 mg (88%). m.p. 199–201 °C; $[\alpha]_D^{22} = -59.9$ ($c = 0.94$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) $\delta = 7.41–7.28$ (m, 9H), 7.06 (ddd, $J = 6.5$, 3.4, 2.2 Hz, 2H), 6.87 (dd, $J = 10.0$, 3.1 Hz, 2H), 6.73 (dd, $J = 10.1$, 3.1 Hz, 1H), 6.25 (ddd, $J = 23.6$, 10.0, 1.9 Hz, 2H), 5.02 (d, $J = 2.4$ Hz, 1H), 4.29 (d, $J = 2.1$ Hz, 2H), 3.81 (s, 1H), 2.57 ppm (d, $J = 8.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) $\delta = 184.3$, 149.2, 146.7, 146.4, 144.4, 137.7, 132.2, 130.6, 130.3, 129.4, 129.4, 129.2, 129.0, 128.4, 127.1, 114.6, 95.8, 70.4, 68.9, 55.5, 36.7, 29.5 ppm, HRMS (ESI): m/z calcd for $C_{25}H_{21}NO_3I$ 510.0566; found: 510.0543.

Synthesis of 11/12: To a solution (2*S*,3*S*)-2-methyl-5-phenyl-3-(phenylamino)pent-4-yn-1-ol (**4Ab**; 666 mg, 2.5 mmol) in toluene (2.5 mL) at room temperature was added 1,1-carbonyldimidazole (1.2 g, 7.8 mmol). The mixture was immediately heated to reflux and stirred for 1 h, then cooled to room temperature and quenched with 1 M HCl. The mixture was extracted with EtOAc (3× 10 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum to give the N,O-diprotected product, which was used in the next step without further purification. IPy_2BF_4 (929.8 mg, 2.5 mmol, 1 equiv) was stirred in dichloromethane (12.5 mL) at room temperature under nitrogen atmosphere for 5 min until a homogeneous solution was obtained. The solution was then cooled to −40 °C and HBF_4 (54% in Et_2O, 0.6 mL, 1 equiv) was added. After stirring the mixture for additional 10 min, it was cooled to −60 °C and previously prepared N,O-diprotected product was added. The mixture was stirred at the same temperature for 16 h and then poured into crushed ice/water. Sodium thiosulfate (5% aqueous solution, 10 mL) was added, and the product was extracted with dichloromethane (3 ×10 mL). The combined organic layers were washed with water and dried over Na_2SO_4. After removing the volatiles under reduced pressure, the crude was subjected to silica gel column chromatography (eluent hexane then hexane/ethyl acetate) to give 5-iodo-4-methyl-6-phenyl-4,4*a*-dihydro-1*H*,3*H*-[1,3]oxazino[3,4-*a*]quinolin-1-one (**11**) as yellow oil. Yield: 417.3 mg (40%). $[\alpha]_D^{22} = -89.5$ ($c = 0.94$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) $\delta = 7.59–7.23$ (m, 14H), 4.59 (dd, $J = 4.7$, 1.8 Hz, 1H), 4.28 (ddd, $J = 10.9$, 4.3, 1.9 Hz, 1H), 4.17–4.01 (m, 1H), 2.78–2.62 (m, 1H), 1.19 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) $\delta = 131.7$, 130.7, 130.2, 129.3, 129.0, 128.9, 128.6, 128.5, 128.2, 127.8, 127.5, 127.1, 69.8, 56.9, 31.6, 12.7 ppm; HRMS (ESI): m/z calcd for $C_{19}H_{16}NO_2I$ 418.2465; found: 292.1347 [M−I]; and (4*S*,5*S*)-4-((*Z*)-2-iodo-2-phenylvinyl)-5-methyl-3-phenyl-1,3-oxazinan-2-one (**12**) as yellow oil. Yield: 419.3 mg (40%); $[\alpha]_D^{22} = -40.50$ ($c = 0.8$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) $\delta = 8.14$ (s, 1H), 7.51–7.27 (m, 8H), 7.07 (s, 1H), 6.52 (dd, $J = 9.3$, 2.5 Hz, 2H), 4.61 (dd, $J = 6.0$, 2.7 Hz, 2H), 4.41 (d, $J = 5.1$ Hz, 1H), 2.51 (dt, $J = 11.6$, 6.1 Hz, 1H), 1.29 ppm (d, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) $\delta = 146.0$, 137.9, 136.9, 135.6, 131.6, 130.7, 128.5, 128.3, 117.0, 116.2, 79.8, 69.5, 48.8, 37.1, 13.9 ppm; HRMS (ESI): m/z calcd for $C_{19}H_{18}NO_2I$ 420.2625; found: 295.3660 [M−I].

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