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Synthesis of Allene Substituted Nipecotic Acids by Allenylation of Terminal Alkynes

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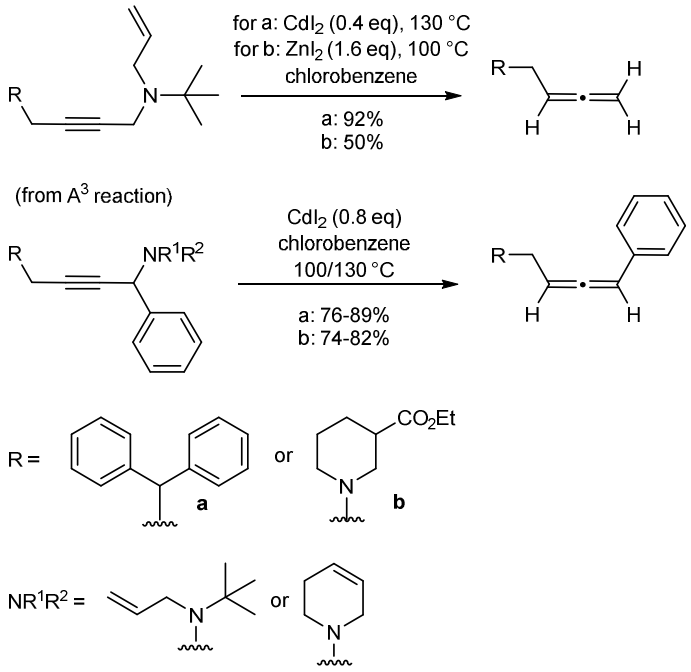
Dedicated to Prof. Dr. Herbert Mayr with warmest wishes on the occasion of his 70th birthday.



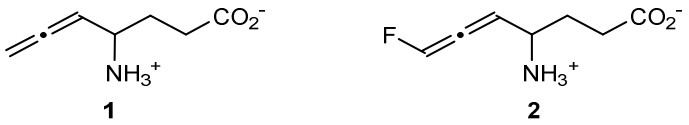
Abstract

The relative reactivities of several secondary amines serving as hydride donors in propargylic amines undergoing a [1,5]-hydride transfer reaction to yield the respective terminal and 1,3-disubstituted allenes were studied. For this study, a two-step procedure was employed. At first the synthesis of propargylic amines via the Cu^{I}-

catalyzed aldehyde-alkyne-amine reactions (A^3 coupling) was accomplished. The obtained propargylic amines were subsequently transformed to the desired allenes under CdI_2 or ZnI_2 catalysis. As a result, among the various secondary amines employed, differing in steric bulk, electronic nature and conformational properties, allyl(*tert*-butyl)amine was found to be the best hydride donor for the synthesis of terminal allenes. For the synthesis of 1,3-disubstituted allenes, the propyne derivatives containing either a allyl(*tert*-butyl)amine or a 1,2,3,6-tetrahydropyridine (THP) unit in propargylic position performed best. Finally, with the developed procedure, nipecotic acid derivatives containing an *N*-allenyl substituent could be synthesized with good yields using either ZnI_2 as catalyst for the preparation of 1-substituted or CdI_2 for the synthesis of 1,3-disubstitued allenes.

Introduction

Allenes are important and useful building blocks in organic synthesis. Many natural products, molecular materials and pharmaceuticals with an allene moiety are known.[1,2,3,4] For example, allenic derivatives of γ-aminobutyric acid (GABA) **1** and **2** have been synthesized as potential inhibitors of the pyridoxalphosphate-dependent enzyme GABA-aminotransferase (Scheme 1).[5,6]

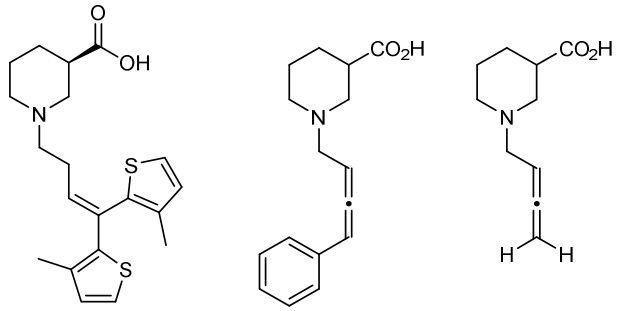


1 **2**

Scheme 1. Allenic derivatives of γ-aminobutyric acid

With GABA being the major inhibitory neurotransmitter in the mammalian central nervous system, a malfunction of its neurotransmission is involved in several diseases like epilepsy,[7] Alzheimer`s disease,[8] neuropathic pain,[9] and depression.[10]

mGAT1 is considered to be the most important GABA transporter subtype for the regulation of neurotransmitter levels in the synaptic cleft.[11] Lipophilic derivatives of the nipecotic acid are known to inhibit the uptake of mGAT1. One example of such a nipecotic acid based drug is Tiagabine (Gabitril®) (**3**), which is used as add-on therapy for epilepsy (Scheme 2, structure **3**).[12] It is known that nipecotic acid derivatives with a diaryl moiety attached via a spacer to the cyclic amino acid exhibit good inhibitory activities at mGAT1. Hence it appears promising to synthesize similar nipecotic acid derivatives, for example by implementation of an allene moiety in the spacer (Scheme 2, structure **4**), as new potential mGAT1 inhibitors. To be able to compare the inhibitory activity of nipecotic acid derivatives such as **4** with the nipecotic acid derivative containing solely an allenyl spacer, the parent compound **5** is of interest, too, as this would allow to analyze the contribution of the different subunits to the overall potencies of the final inhibitors.



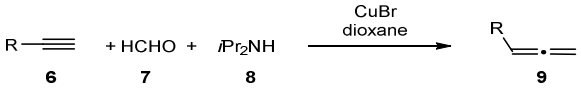
3 Tiagabine **4** **5**

*Scheme 2. Tiagabine (**3**), new nipecotic acid derivatives with allenyl spacer (**4**,**5**)*

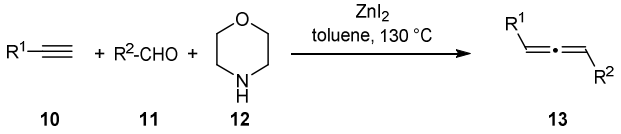
Efficient synthetic methods for the preparation of terminal and 1,3-disubstituted allenes are of high interest in organic chemistry. Until now, many synthetic methods have been developed to access allenes.[13,14] One of these methods is the so called

ATA reaction, the allenylation of terminal alkynes by their reaction with aldehydes or ketones and secondary amines in the presence of metal promoters like CuBr, CdI_2 and ZnI_2.[15,16,17,18] This method is based on the pioneering Crabbé homologation (Scheme 3), the generation of monosubstituted allenes **9** by a three-component reaction of terminal alkynes **6**, paraformaldehyde (**7**), and diisopropylamine (**8**) in the presence of substoichiometric amounts of CuBr.[18] Until now, several modifications of this reaction have been reported. For example, Ma and coworkers reported a one-pot synthesis of 1,3-disubstituted allenes **13** from terminal alkynes **10**, aldehydes **11**, and morpholine (**12**) in the presence of ZnI_2 at elevated temperature (Scheme 3).[17] Later on, several groups developed asymmetric versions of this kind of reaction by using either chiral ligands in combination with Lewis acids[19] or chiral secondary amines (**20**, **23**)[20,21,22,27-33] for the synthesis of chiral propargylic amines as intermediates. Che and coworkers for instance described a two-step procedure for the synthesis of axially chiral allenes **22**, including first a gold(III)salen complex catalyzed synthesis of chiral propargylic amines **21** from chiral amine **20** followed by a Au^{3+} or Ag^{+} mediated rearrangement providing chiral allenes **22** in high enantioselectivity (Scheme 3).[23,24] A one-step procedure to axially chiral 1,3-disubstituted allenes has been reported by Periasamy and coworkers[21,22] as well as by Ma and coworkers[20,27-33] (Scheme 3).

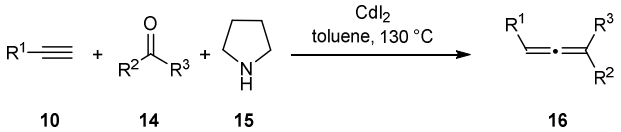
Crabbé homologation[18]



Ma and coworkers[15,16,17,25,26]

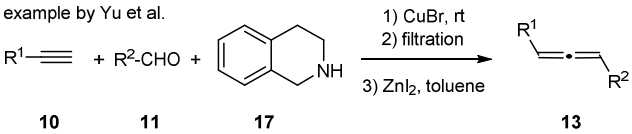


R^1 = alkyl, aryl; R^2 = alkyl, aryl



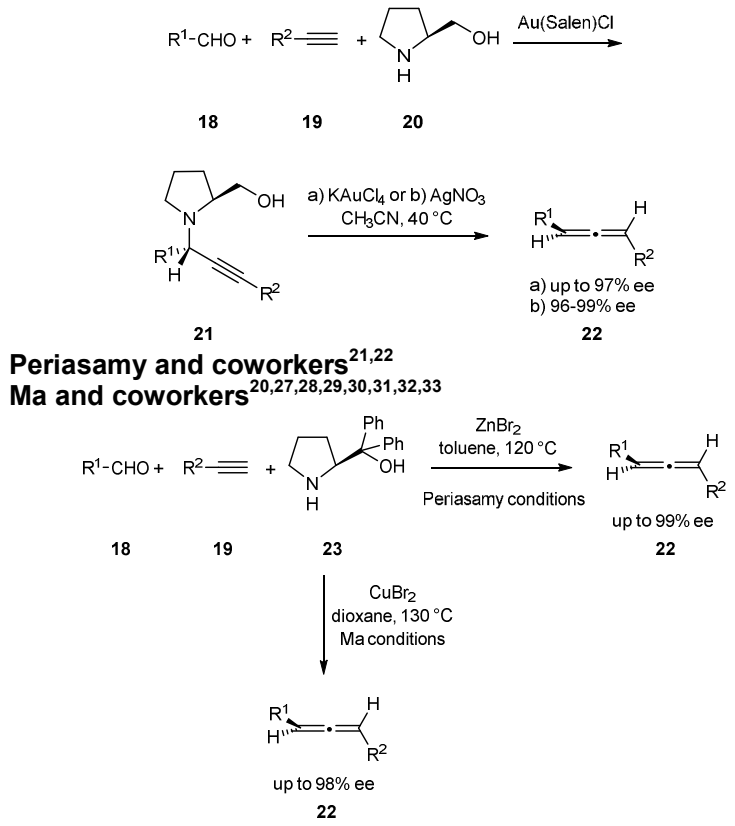
R^1, R^2 = alkyl, aryl; R^3 = alkyl, H

Yu and coworkers[34]/ Ma and coworkers[27]



R^1 = alkyl, aryl; R^2 = alkyl, aryl

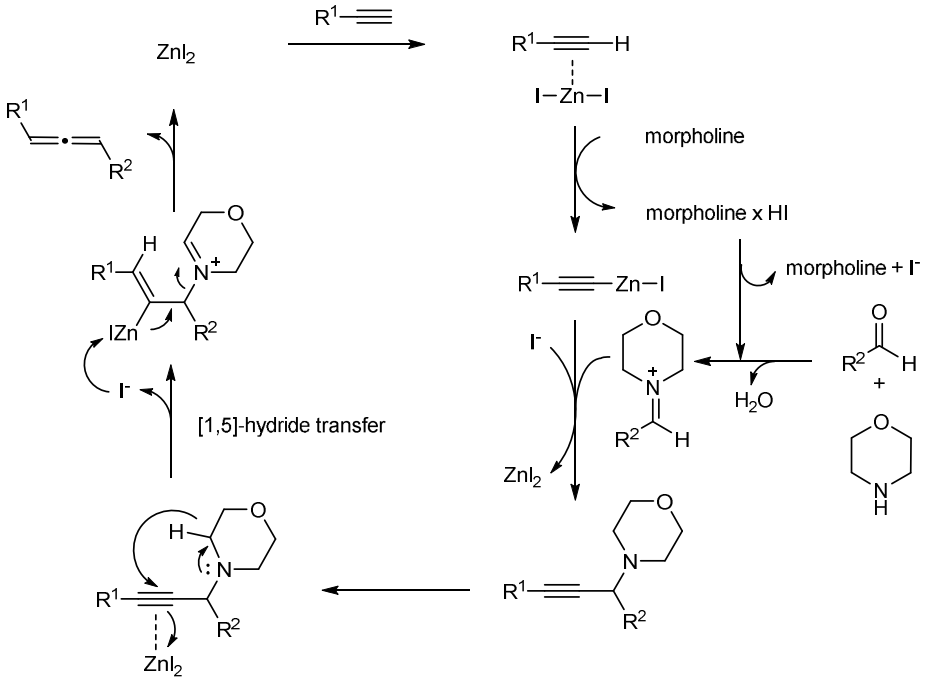
Che and coworkers[23,24]



Scheme 3. Previous works

According to the reaction mechanism proposed by Ma et al.[15] in the ATA reaction at first propargylic amines are formed which upon [1,5]-hydride transfer and subsequent elimination of the thus formed iminium subunit yield the final allenes (Scheme 4). Since it is reported that the generation of propargylic amines from terminal alkynes, aldehydes, and secondary amines can be performed at room temperature,[34,35] it is reasonable to assume that the [1,5]-hydride transfer process described by Ma[15] is the rate-determining step[34] in the allene synthesis. Accordingly, this is the step which requires elevated temperature to proceed (Scheme 4). To accelerate the [1,5]-hydride transfer reaction, Yu and coworkers[34] selected their amine on the criterion of the best hydride donating ability (Scheme 3), but despite their good results with tetrahydroisoquinoline (THIQ, **17**) as hydride donor for the synthesis of 1,3-disubstituted allenes **13**, they were not able to perform the formation of terminal allenes **9** with paraformaldehyde and THIQ in noticeable yields. Based on this

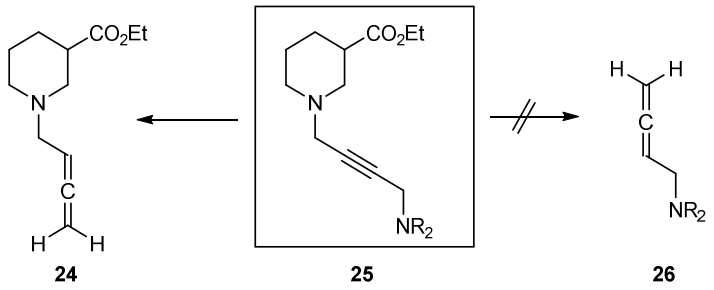
observation, we assumed that besides the known electronic influence of the hydride donor, there might be some additional factors that could have an important impact on the allene formation. Hence, we were interested in studying of how the nature of the hydride donor influences the formation of terminal and 1,3-disubstituted allenes. To this end, the ATA reaction should be performed in two steps, i.e. the synthesis of the propargylic amines and the rearrangement of the latter to the corresponding allene derivatives.



Scheme 4. Postulated mechanism for the ATA reaction by Ma and coworkers[17]

For the intended synthesis of allene substituted nipecotic acid derivatives such as **5** and related compounds by a [1,5]-hydride transfer process, alkyne derivatives such as **25** had to serve as starting materials. However, with two amino groups in propargylic position in **25** the [1,5]-hydride transfer process may deliver either the allenyl substituted amine **26** or the desired nipecotic acid derivative **24** depending on the propensity of the amino function NR_2 as compared to the nipecotic acid residue to

serve as hydride donor (Scheme 5). This study ought to identify amines with distinctly better capabilities in mediating the allene formation than a nipecotic acid residue to exclude the latter to participate in the [1,5]-hydride transfer process. With amino residues NR_2 suitable for this purpose nipecotic acid derivatives **24** (Scheme 5) and **53a**-**e** (Table 5) containing an allene moiety in the spacer should be synthesized.



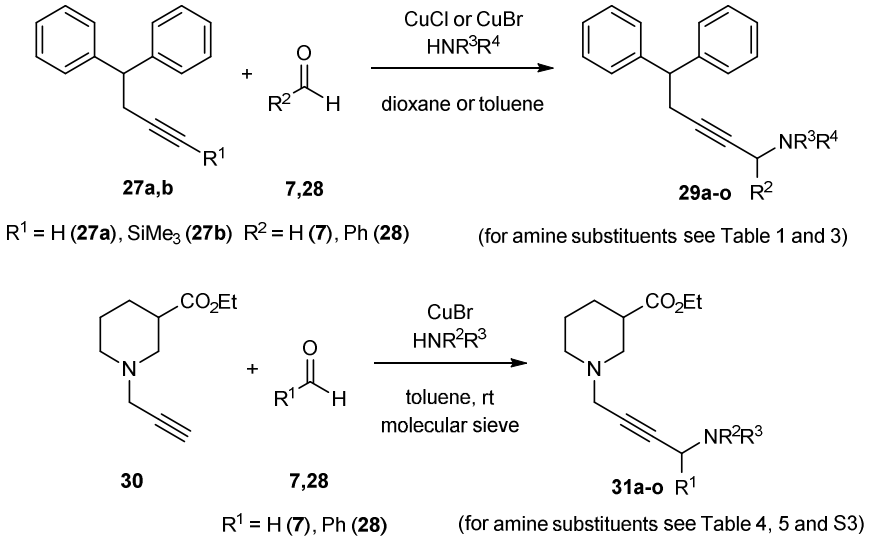
Scheme 5. Intramolecular competition reaction

Results and Discussion

Synthesis of propargylic amines

In order to be able to study the [1,5]-hydride transfer process separately from the formation of the propargylic amines, a two-step procedure was followed, i.e. at first the propargylic amines were synthesized and subsequently subjected to a rearrangement reaction to give the corresponding allenes. The propargylic amines **29a**-**o** and **31a**-**o** required for this study were synthesized by A^3 coupling from ~~terminal~~ alkynes **27a**, **27b**, and **30**, and a set of different secondary amines and aldehydes (Scheme 6, Table S1, for the use of ketones in this reaction see chapter 1 of SI).The propargylic amines **29a**-**o** derived from 4,4-diphenylbut-1-yne (**27a**,**b**) were intended to serve as test systems to study the [1,5]-hydride transfer process in the absence of a nipecotic acid residue. The substituents on the amino nitrogen were varied with respect to sterical demand, utilizing methyl, ally, *i*Pr and *t*-Bu residues,

and with respect to electronic properties, introducing residues like methyl, allyl and *i*Pr as the hydride donating part of the amine.



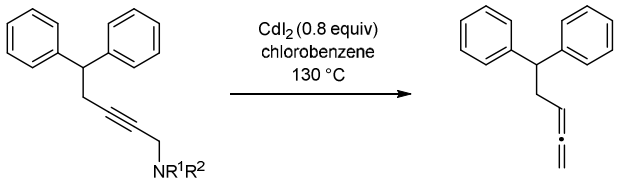
Scheme 6: Synthetic route to employed propargylic amines

Studies on the effect of hydride donors on the formation of terminal allene 32

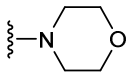
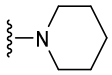
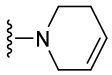
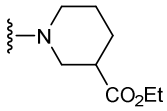
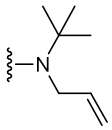
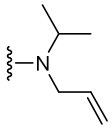
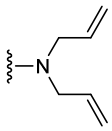
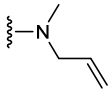
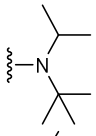
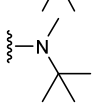
For the conversion of propargylic amines **29a**-**k** derived from formaldehyde as carbonyl component to terminal allene **32**, reaction conditions similar to a protocol established by Ma and coworkers were employed.[15] However, to improve the solubility of the reactants, chlorobenzene instead of toluene was used as solvent in the present experiments. Initial allene formation reactions were carried out with the propargylic amine **29a**, derived from the known hydride donor morpholine, also frequently used by Ma and coworkers[17] (Table 1, entry 1). This reaction and all other reactions listed in Table 1 were conducted by heating the respective propargylic amine (**29a**-**k**) with 0.8 equiv of CdI_2 in chlorobenzene at 130 °C, conditions under which all compounds were found to undergo a transformation reaction. In each case, the reaction was run until all starting material had been consumed or in the case of

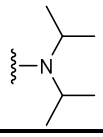
the less reactive hydride donors until no further transformation could be observed by TLC.

*Table 1. Influence of different hydride donors[36] on the formation of terminal allene **32**[a]*



29a-k **32**

entry	starting material	NR^1R^2	t [h]	yield [%]
1[c]	**29a**		3.75	2
2[c]	**29b**		3.75	3
3[b]	**29c**		2.00	29
4[c]	**29d**		4.50	6
5[b]	**29e**		2.00	88
6[b]	**29f**		2.00	65
7[c]	**29g**		3.50	24
8[c]	**29h**		3.00	18
9[c]	**29i**		4.00	21
10[b]	**29j**		3.25	66

11[b]	**29k**		1.25	82

[a] The reaction was conducted using propargylic amine (0.5 mmol) and CdI_2 (0.8 equiv) at 130 °C in 4.0 mL of anhyd chlorobenzene. [b] The reaction was stopped when all starting material was consumed (detection by TLC). [c] The reaction was stopped when no further transformation could be observed (detection by TLC).

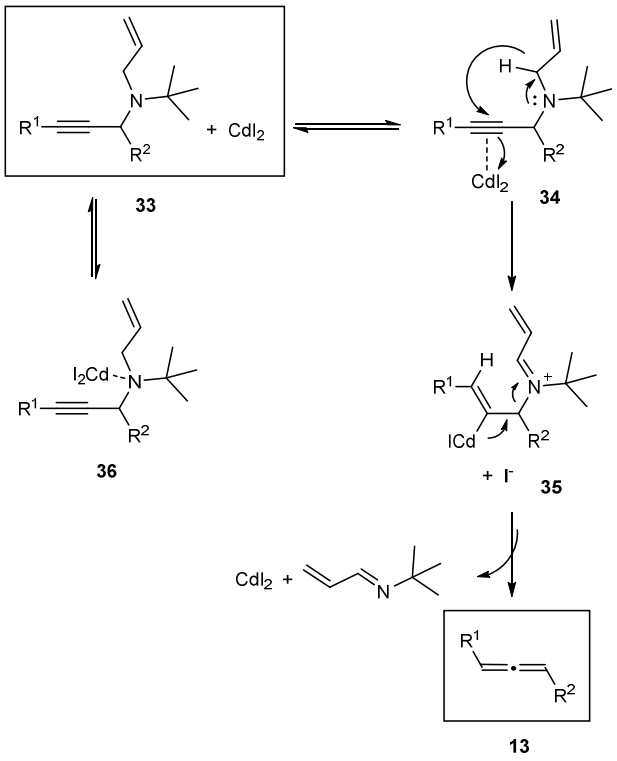
Electronic properties of hydride donors

In case of **29a** the yield of **32** was surprisingly low (2%, Table 1, entry 1). Utilizing piperidine as hydride donor afforded a similar low yield of allene **32** (3%, Table 1, entry 2), whereas the 1,2,3,6-tetrahydropyridine (THP) mediated allene conversion resulted in a significantly higher yield of 29% (Table 1, entry 3). Similar to THIQ, which according to Yu et al.[34] is especially well suited as hydride donor because of its electronic properties, also THP can be assumed to possess improved hydride donor capabilities. In addition to the ring structure, THP possesses two hydrogens in allylic position, adjacent to the amino group that should exhibit an increased propensity for the hydride shift reaction. This explains well the increased yield of allene **32** when utilizing the THP derivative **29c**.[34]

Steric properties of hydride donors

With the electronic properties having clearly a positive effect on the [1,5]-hydrogen transfer reaction, next allene formation reactions were studied, employing acyclic amines with an allyl group as hydride donating moiety for which the second amine substituent was varied with respect to the steric demand. With increasing steric demand of the second amine substituent, i.e. in the row from methyl to allyl to *i*Pr and *t*-Bu the yields for allene **32** increased from 18 to 88% (Table 1, entry 5-8). As indicated in Scheme 7 depicting the reaction mechanism for the formation of the allenes, the Lewis acid, CdI_2, will promote the [1,5]-hydride transfer reaction by

complexation of the alkyne moiety (**34**). This will initiate the hydride transfer to give the corresponding iminium ion **35**, which undergoes an elimination to give allene **13** as final product. Instead of complexing the triple bond, the Lewis acid may also complex the tertiary amino function present in the starting material (**36**). ^{1}H NMR spectra that have been obtained from mixtures of propargylic amine **29g** and ZnI_2 in chlorobenzene-d5 are in support of this assumption. In the presence of ZnI_2 signals arising from protons closest to the amino nitrogen experience a clear line broadening[37] and downfield shift as compared to those in the ^{1}H NMR spectrum of the pure amine **29g** (Figure S1). This may be best rationalized by the assumed complexation of the amino nitrogen of the propargylic amines by the Lewis acids (for more information see SI). Due to the electron withdrawing effect of the Lewis acid, when attached to the amino group, this species will not be able to undergo a [1,5]-hydride transfer reaction even if an additional molecule of Lewis acid was present at the triple bond. These three forms, the free starting material (**33**), the starting material complexing the CdI_2 via the triple bond (**34**) and the starting material complexing the CdI_2 via the amino function (**36**) will exist in an equilibrium (Scheme 7). The position of this equilibrium will depend on the steric demand of the amino subunit. With increasing steric demand the amino function will be less capable of complexing the Lewis acid CdI_2. Accordingly, the equilibrium will shift towards the reactive species with the triple bond attached to the Lewis acid, resulting in an increased reaction rate for the desired rearrangement reaction. In line with this hypothetic model, the yields of the final product steadily increase with the steric demand of the ”second” residue of the amino function in **29h**-**29e**.

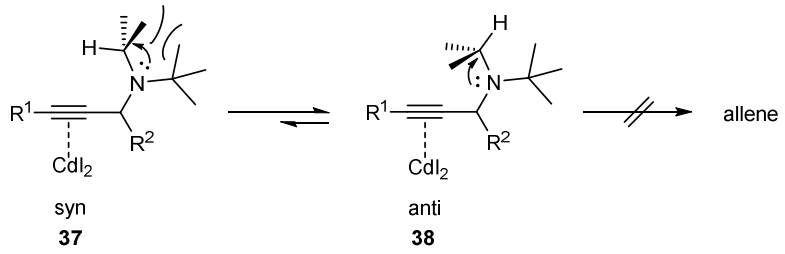


Scheme 7. Proposed mechanism for the allene formation

Conformational properties of hydride donors

The data listed for the rearrangement reaction of **29e**, **29i**, and **29j** also allow a comparison of the influence the nature of the hydride donating residue has on the outcome of the reaction. All of these compounds contain the same inert *t*-Bu group but vary with regard to the hydride donating N-substituent which is an allyl (**29e**), *i*Pr (**29i**), or methyl substituent (**29j**). Whereas the yield of the product decreases from 88% (Table 1, entry 5) to only 21% (Table 1, entry 9) when the allyl moiety is replaced by an *i*Pr residue, it raises to 66% (Table 1, entry 10) when a methyl group is present. With this trend not being in line with the electron donating ability of the varied residues (allyl, *i*Pr, methyl), the rearrangement must be governed by additional factors. For the [1,5]-hydride shift to occur the hydride donating residue must place the migrating hydride in a syn orientation to the alkyne acceptor. In case of the

isopropyl(*tert*-butyl)amino substituent in **29i**, the two major conformations given in Scheme 8 should exist in which the migrating hydride is either oriented syn (**37**) or anti (**38**) to the alkyne acceptor. Because of severe steric interactions between the methyl groups of the *i*Pr residue with the bulky *t*-Bu group, the syn orientation of the hydride should be strongly disfavored and as consequence thereof also the [1,5]-hydride shift reaction which nicely explains the low yield observed in this case.



Scheme 8. Isopropyl(tert-butyl)amine as hydride donor

Best performing hydride donor – a comparison

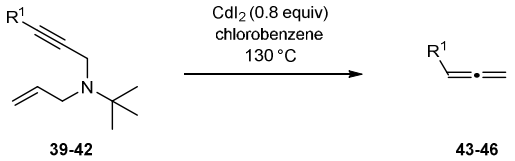
According to the results of the above described experiments the allyl group appears to possess the highest propensity to act as hydride donor, whereas the *t*-Bu residue is best suited as "second" N-substituent, that due to its steric demand hinders the formation of a complex between the amino function and the Lewis acid, that would hamper the desired rearrangement reaction. For comparison of the above described results with those of Crabbé and coworkers utilizing diisopropylamine as hydride donor (Scheme 3),[18] in addition transformation of the propargylic amine **29k** into allene **32** was studied (Table 1, entry 11). With the diisopropylamine residue in **29k** as hydride donor, terminal allene **32** could be obtained in a good yield of 82%. This is in line with the reasoning outlined above. For electronic reasons, the *i*Pr residues should exhibit favorable hydride donating abilities, whereas the steric demand of the two *i*Pr residues will lower the tendency of the amino nitrogen to form a complex with

the Lewis acid that would negatively affect the transfer reaction. Obviously, there is also a subtle control of the reactive conformation. Whereas a *t*-Bu residue as "second" substituent in combination with an *i*Pr as hydride donating moiety appears to disfavor the reactive conformation required for the hydride transfer reaction (Scheme 8), an *i*Pr instead of an *t*-Bu residue is obviously compatible with it. Besides, also the influence of the amount of CdI_2 on the formation of terminal allene **32** was studied employing propargylic amine **29e** that had led to the highest yield of the rearrangement product **32** (Table 1, entry 5). Applying 0.4, 0.8 and 1.2 equiv of CdI_2 under the same reaction conditions as for the reactions listed in Table 1, neither a trend nor a significant variation of the yield of allene **32** could be observed (Table S2, entry 1-3, 88-93% yield).

The scope of terminal alkynes

To demonstrate the applicability of the developed method for the synthesis of terminal allenes applying allyl(*tert*-butyl)amine as hydride donor, additionally alkynes **39**-**42** exhibiting different residues were included in this study (Table 2). All substrates (**39**-**42**) exhibiting either a pure alkyl residue, or a halogen, nitrile or ether function underwent transformation to the corresponding allene in excellent yields (83-97%, Table 2, entry 1-4).

Table 2. The scope of terminal alkynes



39-42 43-46

entry	R^1	t [h]	yield [%]
1	$CH_3(CH_2)_7$	3.00	94
2	$Cl(CH_2)_3$	3.00	83
3	$NC(CH_2)_3$	3.00	97
4	$PhCH_2OCH_2$	2.75	95

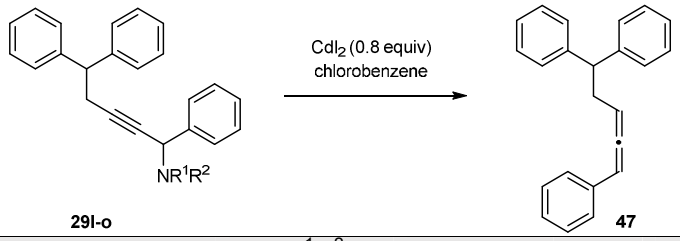
[a] The reaction was conducted using propargylic amine (0.5 mmol) and CdI_2 (0.8 equiv) at 130 °C in 4.0 mL of anhyd chlorobenzene. The reaction was stopped when all starting material was consumed (detection by TLC).

Studies on the effect of hydride donors on the formation of 1,3-disubstituted allene 47

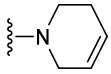
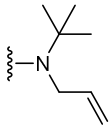
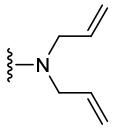
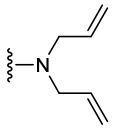
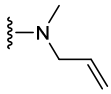
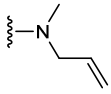
In additional experiments, the suitability of some of the above mentioned amino residues in [1,5]-hydride transfer reactions should be studied in which the substrate carries an additional substituent, i.e. a phenyl residue next to the amino group. For these experiments THP, allyl(methyl)amine, allyl(*tert*-butyl)amine, and diallylamine with different steric and electronic properties were selected as hydride donors. In contrast to the less substituted starting materials **29c**, **29g**, and **29h** exhibiting the same, sterically less demanding amino residues, i.e. THP, diallylamine and allyl(methyl)amine, that due to this feature had given low yields of the rearrangement product **32** (18-29%), the corresponding phenyl derivatives performed significantly better. In case of the THP derivative **29l**, the yield rose from 29% (for **29c** → **32**) to 89% (for **29l** → **47**). Thereby a temperature of only 100 °C (instead of 130 °C for **29c**) was sufficient to effect the desired transformation. For the diallylamine and allyl(methyl)amine derivatives, **29n** and **29o**, the yields for the rearrangement product **47** were likewise substantially higher, 75% for the transformation of **29n** to **47** (Table

3, entry 4) and 43% for the transformation of **29o** in **47** (Table 3, entry 6), compared to those of the less substituted propargylic amines (Table 1, entry 7, **29g** → **32**, 24%; Table 1, entry 8, **29h** → **32**, 18%). However, for this transformations again a reaction temperature of 130 °C was required, the yields at a temperature of 100 °C being in both cases with 10% of **47** much lower (Table 3, entry 3, 5). As with the formation of terminal allene **32** allyl(*tert*-butyl)amine performed well as hydride donor in the synthesis of 1,3-disubstituted allene **47** (**29m**, Table 3, entry 2) providing it in 76% yield, whereby the [1,5]-hydride transfer occurs already at a lower temperature of 100 °C. Diisopropylamine as well should be studied as a hydride donor in the formation of 1,3-disubsituted allene **47**. However, all attempts to synthesize the required propargylic amine, from the corresponding alkyne **27a**, benzaldehyde (**28**), and diisopropylamine failed, indicating that this amine is not suitable for this purpose which is most likely due to its high steric demand. Overall the transformations of the propargylic amines **29l**-**29o** to 1,3-disubstituted allene **47** appears to be less sensitive to the steric demand of R^1 and R^2 attached to the amino residue. This supports the assumption that complexation of the amino nitrogen by the Lewis acid, in competition with the complexation of the triple bond required for the induction of the rearrangement reaction, negatively affects the hydride donating ability of the respective alkyl amino subunit. With a phenyl residue in the direct neighborhood to the amino nitrogen contributing to the steric shielding of the latter, the steric encumbrance of the amino function provided by R^1 and R^2 becomes obviously less important for the reduction of the complexation of the amino nitrogen by the Lewis acid.

*Table 3. Influence of different hydride donors on the formation of 1,3-disubstituted allene **47**[a]*



29l-o **47**

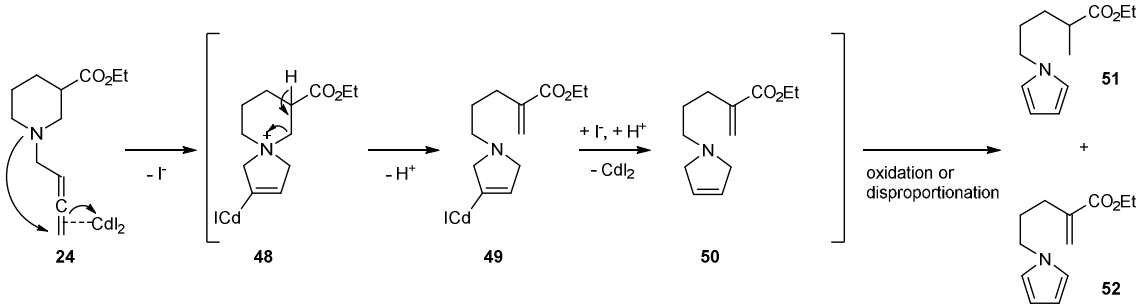
entry	starting material	NR^1R^2	temp [°C]	t [h]	yield [%]
1[b]	**29l**		100	3.25	89
2[b]	**29m**		100	4.25	76
3[c]	**29n**		100	6.00	10
4[b]	**29n**		130	4.50	75
5[c]	**29o**		100	5.00	10
6[c]	**29o**		130	4.00	43

[a] The reaction was conducted using propargylic amine (0.5 mmol) and CdI_2 (0.8 equiv) at 100/130 °C in 4.0 mL of anhyd chlorobenzene. [b] The reaction was stopped when all starting material was consumed (detection by TLC). [c] The reaction was stopped when no further transformation could be observed (detection by TLC).

Synthesis of allene substituted nipecotic acid ester 24

Based on the above described results, the formation of the nipecotic acid derived allene **24** was undertaken with the propargylic amine **31a** exhibiting an allyl(*tert*-butyl)amino residue as hydride donor, which had performed well in the [1,5]-hydride transfer reaction independent of the substitution in propargylic position adjacent to

the hydride donor. Using the same conditions as given in Table 1 for the preparation of **32**, i.e. treating **31a** in chlorobenzene with 0.8 equiv of CdI_2 at 130 °C for 2 h, no terminal allene **24**, but only side products **51** and **52** (Scheme 9) could be obtained (Table 4, entry 1). It appeared likely that the desired allene **24** might have had formed, but underwent subsequent transformation reactions to give the two side products **51** and **52**. This assumption was supported by literature data, according to which buta-2,3-dienyl amines are prone to rearrangement reactions giving rise to 2,5-dihydropyrroles, which may further easily undergo an oxidation reaction to give the corresponding pyrroles.[38,39] A reasonable reaction pathway for the formation of the pyrrole derivatives **51** and **52** from allene **24** is given in Scheme 9. As indicated in the first step the Lewis acid causes the aminobutadiene subunit to form the dihydropyrrole ring **48** as part of a spirocyclic ring system. The latter undergoes a retro Michael reaction to give the N-mono-substituted dihydropyrrole derivative **49** which after exchange of the metal substituent by a proton and either a subsequent oxidation or disproportionation yields pyrrole derivatives **51** and **52**.



Scheme 9: Proposed mechanism for the formation of side products 51 and 52 from allene 24.

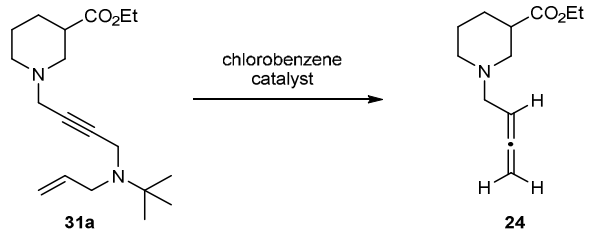
Optimization of the reaction conditions

This led us to vary the reaction conditions to possibly be able to isolate **24** under milder reaction conditions. Indeed, when the reaction temperature was lowered to

100 °C after 2 h minute amounts (< 4%) of allene **24** together with 5% of the side products **51** and **52** could be isolated (Table 4, entry 2). Lowering the temperature to 90 °C led to a slightly improved yield of 7% for **24** after 2 h (Table 4, entry 3) together with neglectable amounts of **51** and **52** (1%). However, when the reaction time was extended to 3.75 h, the desired product **24** was not detectable any longer, whereas the yield of the side products **51** and **52** had increased to 10% (Table 4, entry 4). Lowering the reaction temperature to 70 °C neither met any success leading only to **51** and **52** (11%), after an extended reaction time of 3 d required for a detectable conversion of small amounts of the starting material **31a** (Table 4, entry 5). With the subsequent reaction of allene **24** leading to the side products **51** and **52**, being quite fast as compared to the formation of **24**, further attempts to optimize the reaction with CdI_2 as catalyst were considered futile. Interestingly, with 0.8 equiv of ZnI_2 instead of CdI_2 at 90 °C after 7.75 h, 25% of allene **24** could be isolated whereas only 1% of the side products **51** and **52** had formed (Table 4, entry 8). The yield of **24** could be further increased to 37%, when the reaction was conducted at 100 °C, with no side products **51** and **52** being detectable (Table 4, entry 7). In this case the reaction had been stopped after 4.75 h, when still some starting material was left, but no further conversion could be observed by TLC. However, increasing the temperature to 130 °C was detrimental for the formation of the desired product: only the side products **51** and **52** (36%), but no allene **24** could be isolated (Table 4, entry 6). To support the assumption according to which the side products **51** and **52** are formed via allene **24**, additional experiments have been performed. When allene **24** was treated either with 0.8 equiv of ZnI_2 or 0.8 equiv of CdI_2 (in chlorobenzene) at a reaction temperature from 80-100 °C, TLC analysis of the reaction mixture revealed, that with CdI_2 as catalyst the formation of side products **51** and **52** started already at 80 °C, whereas with ZnI_2 side product formation started at a distinctly higher temperature, i.e. 100 °C.

Furthermore, up to 150 °C barely any of the side product **51** and **52** formed when neither of the catalyst was present. Obviously, CdI_2 appears to affect the transformation of **24** into the side products **51** and **52** already at lower temperature as compared to ZnI_2, whereas the [1,5]-hydride transfer reaction seems to be faster under ZnI_2 as compared to CdI_2 catalysis. Hence, ZnI_2 is the more appropriate Lewis acid for the synthesis of allene **24** from propargylic amine **31a**.

*Table 4. Optimization of reaction conditions for the synthesis of allene **24**[a]*



31a **24**

entry	catalyst	equiv	temp [°C]	t	yield [%]	side products **51/52** [%]
1	CdI_2	0.8	130	2.00 h	-	47
2	CdI_2	0.8	100	2.00 h	<4	5
3[b]	CdI_2	0.8	90	2.00 h	7	1
4	CdI_2	0.8	90	3.75 h	-	10
5[c]	CdI_2	0.8	70	3.00 d	-	11
6	ZnI_2	0.8	130	4.75 h	-	36
7	ZnI_2	0.8	100	4.75 h	37	-
8[d]	ZnI_2	0.8	90	7.75 h	25	1
9	**ZnI_2**	**1.6**	**100**	**4.00 h**	**50**	**-**
10	ZnI_2	0.4	100	4.50 h	29	-

[a] The reaction was conducted using propargylic amine (0.5 mmol) and catalyst in 4.0 mL of anhyd chlorobenzene. [b] About 15% of starting material could be covered. [c] Small amount of **24** could be observed after 6.50 h, after 3 d, all of **24** was transformed into **51/52** and starting material was still present. [d] About 20% of starting material could be covered.

Effect of different hydride donors on the formation of allene 24

The yields for converting propargylic amines **31c**-**f** (Table S3, entries 5-8), bearing different hydride donors, under optimized reaction conditions applying 0.8 equiv of ZnI_2 follow the same trends as in the test system (Table 1). Whereas diisopropylamine (Table S3, entry 3, **31b**) as well as allyl(*tert*-butyl)amine (Table S3, entry 1, **31a**) as hydride donors had afforded allene **24** in good yields, the starting materials with amino residues which are less hindered (Table S3, entry 5-7, THP **31c**, diallylamine **31d**, allyl(methyl)amine **31e**) or adopt a conformation less favorable for the [1,5]-hydride transfer reaction (Table S3, entry 8, isopropyl(*tert*-butyl)amine **31f**) afforded much lower yields of allene **24**. The generally lower yields compared to the test system **29** (Table 1) might be due to additional coordination of the catalyst to the nitrogen of the nipecotic acid subunit. But most notably, in none of the above described transformations of **31a**-**f**, an alternative allene product resulting from the nipecotic acid residue serving as a hydride donor could be detected. This agrees with former results according to which the nipecotic acid residue appeared to be among the least suited hydride donors tested (Table 1, entry 4, **29d → 32**, 6%).

Effect of amount of Lewis acid

Next, it was investigated how the amount of Lewis acid effects the outcome of the rearrangement reaction (Table 4). In contrast to the test system, where the yields of allene **32** were not influenced by the catalyst loading (Table S2), the use of 1.6 equiv instead of 0.8 equiv of ZnI_2 increased the yield for the transformation of **31a** into allene **24** from 37% (Table 4, entry 7) to 50% (Table 4, entry 9). In line with this result the yield of **24** decreased to 29% when only 0.4 equiv ZnI_2 were used (Table 4, entry 10). Alike the allyl(*tert*-butyl)amino derivative **31a** also **31b** (Table S3) containing the sterically demanding diisopropylamino residue gave upon treatment with 0.8 equiv of ZnI_2 a high yield of **24** (42%, Table S3, entry 3), which in contrast to the

transformation of **31a** in **24**, however, lowered to 12% when the amount of ZnI_2 was doubled (Table S3, entry 4). Hence, in case of the nipecotic acid derived propargylic amines, it depends on the hydride donor what influence the catalyst loading has on the yield of allene **24**.

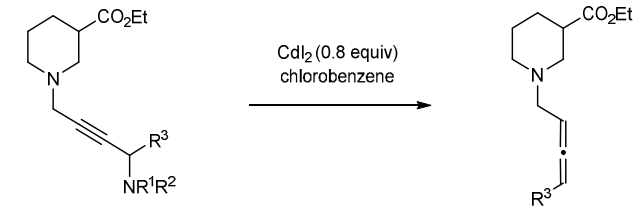
Synthesis of nipecotic acid ethyl esters with 1,3-disubstituted allene residues

Finally, the two-step procedure comprising preparation of the respective propargylic amine and subsequent rearrangement to an allene was also used for the preparation of the nipecotic acid derivatives ***rac*-(*R*$_a$,*R*)-53a-e** and ***rac*-(*R*$_a$,*S*)-53a-e** exhibiting an N-allene substituent with a terminal aryl or alkyl residue (Table 5) employing the propargylic amines **31g-o** as starting materials (mixture of racemic diastereomers, ~1:1; preparation see Scheme 6 and Table S1). Propargylic amines **31g** exhibiting an allyl(*tert*-butyl)amino residue and **31h** equipped with a THP moiety gave good yields of the allene derivative mixture ***rac*-(*R*$_a$,*R*)-53a**/***rac*-(*R*$_a$,*S*)-53a** (82% and 74%, respectively, Table 5, entry 1,2). This is in good line with the results obtained so far, the sterically demanding allyl(*tert*-butyl)amino moiety leading to good results independent of whether an additional residue in propargylic position adjacent to the amino function is present or not and the THP hydride donor only when, as in this case, a residue increasing the steric encumbrance of the amino nitrogen, like a phenyl group, is nearby. An attempt to improve the yield for the transformation of **31h** into ***rac*-(*R*$_a$,*R*)-53a**/***rac*-(*R*$_a$,*S*)-53a** by increasing the reaction temperature from 100 °C to 130 °C, led to the opposite, the yield being lower (Table 5, entry 3). This is likely to be assigned to an instability inferred by the nipecotic acid moiety.

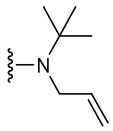
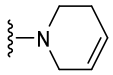
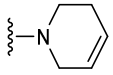
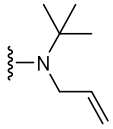
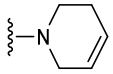
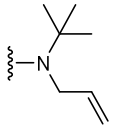
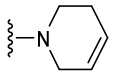
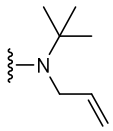
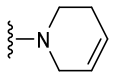
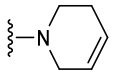
To explore the scope of aldehydes applicable in this method, furthermore propargylic amines **31i-o** derived from different aromatic (2-naphthaldehyde, biphenyl-2-carboxaldehyde) and aliphatic (butyraldehyde, isobutyraldehyde) aldehydes,

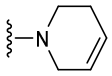
allyl(*tert*-butyl)amine and THP were employed as starting materials in this rearrangement reaction (Table 5, entry 4-11). Applying compounds with aryl residues, both hydride donors, allyl(*tert*-butyl)amine and THP, performed well, providing allenes **53b** and **53c** in yields of 63-86% (Table 5, entry 4-7). In case of the propargylic amines **31m** and **31n** with an alkyl residue present, i.e. an *n*-propyl substituent, the THP mediated allene formation (Table 5, entry 9) performed distinctly better than the allene formation based on propargylic amine **31m**, containing allyl(*tert*-butyl)amine as hydride donor (Table 5, entry 8). Compared to the THP-mediated allene formation, the allene formation mediated by allyl(*tert*-butyl)amine required longer reaction times. In a control experiment, the reaction time of THP containing propargylic amine **31n** has been extended from 1.5 h to 2.5 h. This led to a decrease in yield from 90% to 76% (Table 5, entry 9,10), which is likely to be due to product instability. Therefore, the longer reaction time required for the complete consumption of **31m** might explain the lower yield with allyl(*tert*-butyl)amine as hydride donor as compared to the excellent yield of the faster THP-mediated allene formation. The synthesis of allene **53e** exhibiting an isopropyl residue could only be performed with propargylic amine **31o** exhibiting THP as hydride donor (Table 5, entry 11), as attempts to synthesize the analogous propargylic amine based on isobutyraldehyde and allyl(*tert*-butyl)amine failed which is likely to be attributed to the high steric demand of these two components. Nonetheless, as indicated by these results THP and allyl(*tert*-butyl)amine are well suited hydride donors in [1,5]-hydride transfer reactions allowing a broad range of substituents in propargylic position next to the aforementioned amino groups.

*Table 5. Synthesis of 1,3-disubstituted allenes **53a-e**[a]*



rac-(*R,R*)/*rac*-(*R,S*) (~1:1) *rac*-(*R*$_a$,*R*)/*rac*-(*R*$_a$,*S*) (~1:1)

entry	starting material[b]	NR^1R^2	R^3	product	temp [°C]	t [h]	yield [%]
1	***rac*-(*R,S*)-31g** ***rac*-(*R,R*)-31g**		phenyl	***rac*-(*R*$_a$,*S*)-53a** ***rac*-(*R*$_a$,*R*)-53a**	100	3.75	82
2	***rac*-(*R,S*)-31h** ***rac*-(*R,R*)-31h**		phenyl	***rac*-(*R*$_a$,*S*)-53a** ***rac*-(*R*$_a$,*R*)-53a**	100	3.00	74
3	***rac*-(*R,S*)-31h** ***rac*-(*R,R*)-31h**		phenyl	***rac*-(*R*$_a$,*S*)-53a** ***rac*-(*R*$_a$,*R*)-53a**	130	1.25	51
4	***rac*-(*R,S*)-31i** ***rac*-(*R,R*)-31i**		2-naphthyl	***rac*-(*R*$_a$,*S*)-53b** ***rac*-(*R*$_a$,*R*)-53b**	100	2.75	76
5	***rac*-(*R,S*)-31j** ***rac*-(*R,R*)-31j**		2-naphthyl	***rac*-(*R*$_a$,*S*)-53b** ***rac*-(*R*$_a$,*R*)-53b**	100	1.50	75
6	***rac*-(*R,S*)-31k** ***rac*-(*R,R*)-31k**		2-biphenyl	***rac*-(*R*$_a$,*S*)-53c** ***rac*-(*R*$_a$,*R*)-53c**	100	4.00	63
7	***rac*-(*R,S*)-31l** ***rac*-(*R,R*)-31l**		2-biphenyl	***rac*-(*R*$_a$,*S*)-53c** ***rac*-(*R*$_a$,*R*)-53c**	100	1.75	86
8	***rac*-(*R,S*)-31m** ***rac*-(*R,R*)-31m**		*n*-propyl	***rac*-(*R*$_a$,*S*)-53d** ***rac*-(*R*$_a$,*R*)-53d**	100	2.50	51
9	***rac*-(*R,S*)-31n** ***rac*-(*R,R*)-31n**		*n*-propyl	***rac*-(*R*$_a$,*S*)-53d** ***rac*-(*R*$_a$,*R*)-53d**	100	1.50	90
10	***rac*-(*R,S*)-31n** ***rac*-(*R,R*)-31n**		*n*-propyl	***rac*-(*R*$_a$,*S*)-53d** ***rac*-(*R*$_a$,*R*)-53d**	100	2.50	76

11	***rac*-(*R,S*)-31o** ***rac*-(*R,R*)-31o**		isopropyl	***rac*-(R_a,*S*)-53e** ***rac*-(R_a,*R*)-53e**	100	1.50	84

[a] The reaction was conducted using propargylic amine (0.5 mmol) and CdI_2 (0.8 equiv) at 100 °C/130 °C in 4.0 mL of anhyd chlorobenzene. The reaction was stopped when all starting material was consumed (detection by TLC). [b] ≈ 1:1 mixture of both racemic diastereomers.

Conclusion

Studying the synthesis of terminal and 1,3-disubstituted allenes from propargylic amines via [1,5]-hydride transfer reactions under CdI_2 or ZnI_2 catalysis gave insight of how the electronic, steric and conformational properties of different secondary amines serving as hydride donors influence this reaction. Besides the known influence of the electronic properties of the amines, steric demand was found to play an important role regarding the synthesis of terminal allenes. By applying sterically demanding hydride donors like allyl(*tert*-butyl)amine, the reactivity limiting complexation of the hydride donor nitrogen by the Lewis acid is suppressed and the [1,5]-hydride transfer reaction can occur in significantly higher yields. With allyl(*tert*-butyl)amine an amine was found, which due to its electronic and steric characteristics is well suited for both, the synthesis of terminal and of 1,3-disubstituted allenes. With this herein reported method also terminal and 1,3-disubstituted allenes attached to a nipecotic acid building block were accessible in good yields.

Experimental

Unless otherwise noted, all reactions were performed in oven dried glassware under moisture-free conditions and argon- or nitrogen atmosphere. All commercial available reagents were used without further purification. Chlorobenzene was dried over $CaCl_2$, distilled under nitrogen atmosphere and stored over molecular sieves (4 Å) under nitrogen atmosphere prior to use. For chromatographic purposes only distilled solvents were used (EtOAc, PE 42-62 °C, DCM, MeOH). Flash column

chromatography was performed using silica gel (grading 0.035 - 0.070 mm). Thin layer chromatography (TLC) was carried out on precoated silica gel F_{254} glass plates. NMR spectra were measured at 298.1 K on 400 MHz (^{1}H NMR: 400 MHz, ^{13}C NMR: 101 MHz) and 500 MHz (^{1}H NMR: 500 MHz, ^{13}C NMR: 126 MHz) spectrometers. These NMR spectrometers were also used for DEPT, HMQC, HMBC and COSY experiments. The coupling constants were stated with an accuracy of 0.5 Hz. MestreNova was used for further analysis of the NMR data (s_{br} = broad singlet, hept = septet, Nip = nipecotic acid residue, dia = diastereomeric racemate, ^{13}C signals separated by a slash are illustrating the slightly different ppm values of the diastereomeric racemates). IR spectra were recorded with a FT-IR spectrometer and Spectrum v2.00 software was used for analysis. High-resolution mass spectrometry was performed with sector field mass spectrometer or LTQ FT Ultra mass spectrometer.

Synthesis of Alkynes:

*(4,4-Diphenylbut-1-yn-1-yl)trimethylsilane (**27b**).* To a Schlenk flask was added diphenylmethane (1.00 g, 5.94 mmol) in anhyd THF (20 mL). After cooling to 0 °C in an ice bath, a 1.6 M solution of *n*-BuLi in hexane (3.71 mL, 5.94 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h. Then 3-bromo-1-(trimethylsilyl)-1-propine (1.09 mL, 6.54 mmol) was added dropwise and the reaction was stirred at room temperature for 20 h. The completion of the reaction was monitored by TLC (PE/DCM = 9:1). The reaction mixture was quenched with 40 mL of phosphate buffer (pH 7) and extracted 6 times with Et_2O. The combined organic phases were then dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography (PE/DCM = 9:1) to afford **27b** (1.59 g, 96%) as colorless viscous oil: TLC: R_f = 0.33 (PE/DCM = 9:1); ^{1}H NMR (500 MHz,

$CDCl_3$) δ 0.04 (s, 9 H, Si(CH_3)$_3$), 2.91 (d, J = 7.6 Hz, 2 H, CHCH_2), 4.21 (t, J = 7.6 Hz, 1 H, CHCH$_2$), 7.16–7.25 (m, 2 H, ArH), 7.21–7.33 (m, 8 H, ArH); ^{13}C NMR (126 MHz, $CDCl_3$) δ -0.1, 26.9, 50.0, 86.9, 105.6, 126.4, 128.0, 128.3, 143.4; IR (neat) 3374, 3086, 3062, 3028, 2958, 2361, 2176, 1600, 1494, 1450, 1249, 1043, 842, 757, 697 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{22}Si$ 278.1491, found 278.1471.

*4,4-Diphenylbut-1-yne (**27a**).* This compound is literature known.[40] Because of already synthesized compound **27b**, a simple deprotection reaction[41] instead of the procedure described in literature was performed. Analytical data obtained agreed with published data. To a solution of TMS protected alkyne **27b** (3.31 g, 11.9 mmol) in THF (55 ml) was added 1 M TBAF solution in THF (1.50 eq, 5.17 mL, 17.9 mmol) and the mixture was stirred at rt overnight. After evaporation, the residue was filtered through a pad of silica gel (PE/DCM = 9:1) to afford **27a** as pale yellow crystals (1.80 g, 73%): mp = 72.1 °C (lit. 73.0-73.5 °C); TLC: R_f = 0.29 (PE/DCM = 9:1).

*Ethyl 1-(prop-2-yn-1-yl)piperidine-3-carboxylate (**30**).* Compound **30** was synthesized employing a synthesis route similar to a procedure described in literature.[42] Propargyl bromide solution (80 wt% in xylene, 1.00 equiv, 1.08 mL, 10.0 mmol) and ethyl nipecotate (1.20 equiv, 1.87 mL, 12.0 mmol) were dissolved in acetone (20 mL) and Na_2CO_3 (2.50 equiv, 2.65 g, 25.0 mmol) and NaI (0.50 equiv, 749 mg, 5.00 mmol) were added. The reaction mixture was refluxed for 72 h and the reaction was monitored by TLC. For quenching, DCM (50 mL) and water (50 mL) were added and the product was extracted five times with DCM. The combined organic phases were then dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography (PE/EtOAc = 8:2) to afford **30** as pale yellow oil (1.85 g, 95%): TLC: R_f = 0.60 (PE/EtOAc = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 3 H, OCH$_2$CH_3), 1.44 (qd, J = 11.7/3.9 Hz, 1 H, NCH$_2$CHCH_{ax}H$_{eq}$), 1.60

(m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.71–1.83 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.89–2.00 (m, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 2.22 (td, J = 11.0/3.1 Hz, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.26 (t, J = 2.4 Hz, 1 H, NCH_2CCH), 2.38 (t, J = 10.4 Hz, 1 H, $NCH_{ax}H_{eq}CHCH_2$), 2.59 (ddt, J = 11.0/10.4/3.9 Hz, 1 H, $NCH_2CH_{ax}CH_2$), 2.72–2.82 (m, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.96–3.05 (m, 1 H, $NCH_{ax}H_{eq}CHCH_2$), 3.32 (d, J = 2.4 Hz, or AB, J = 17.2 Hz, 2 H, NCH_2CCH), 4.14 (q, J = 7.1 Hz, 2 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.2, 24.5, 26.5, 41.9, 47.3, 52.2, 54.2, 60.4, 73.3, 78.7, 173.9; IR (neat) 3291, 2942, 2864, 2807, 1730, 1468, 1450, 1368, 1311, 1223, 1183, 1153, 1133, 1095, 1031, 1002, 900, 864, 791, 654 cm^{-1}; HRMS (ESI) m/z calcd for $C_{11}H_{18}NO_2$ $[M+H]^+$ 196.1338, found 196.1332.

Synthesis of Propargylic Amines:

General Procedure 1: To a Schlenk flask was added CuCl (1.5 equiv). Dioxane anhyd (12.0 mL/mmol) was then added, followed by TMS-protected alkyne (1.0 equiv), paraformaldehyde (1.2 equiv), amine (1.2 equiv) and $BF_3{\cdot}OEt_2$ (1.0 equiv). The reaction mixture was stirred at rt for 10 minutes and at 50 °C overnight. The completion of the reaction was monitored by TLC. After cooling to rt the reaction mixture was added to a 1:1 solution of saturated potassium sodium tartrate solution and saturated sodium hydrogen carbonate solution (44.0 mL/mmol) and extracted 5 times with EtOAc. The combined organic phases were then filtrated, dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography to afford the corresponding propargylic amine.

General Procedure 2: To a Schlenk flask was added CuBr (0.15 equiv) and molecular sieve (4Å). Toluene anhyd (5.00 mL/mmol) was then added, followed by the addition of the corresponding aldehyde (1.80 equiv), amine (1.40 equiv) and alkyne (1.00 equiv). The reaction mixture was stirred at rt overnight. The completion

of the reaction was monitored by TLC. The reaction mixture was then filtrated, washed with EtOAc and concentrated under vacuum. The crude product was purified by column chromatography to afford the corresponding propargylic amine. This procedure was performed according to a procedure described by Ma et al.[27,34]

*4-(5,5-Diphenylpent-2-yn-1-yl)morpholine (**29a**).* GP1 was followed using **27b** (200 mg, 0.720 mmol), CuCl (107 mg, 1.08 mmol), $BF_3{\cdot}OEt_2$ (213 mg, 0.720 mmol), morpholine (74.5 µl, 0.864 mmol) and paraformaldehyde (27.3 mg, 0.864 mmol). Purification by column chromatography (PE/EtOAc = 1:1, 1% NEt_3) afforded **29a** (162 mg, 74%) as yellow oil: TLC: R_f = 0.18 (PE/EtOAc = 1:1, 1% NEt_3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24–2.32 (m, 4 H, NCH_2CH$_2$OCH$_2$CH_2), 2.92 (dt, J = 7.8/2.2 Hz, 2 H, CHCH_2CCCH$_2$N), 3.10 (t, J = 2.2 Hz, 2 H, CHCH$_2$CCCH_2N), 3.59–3.67 (m, 4 H, NCH$_2$CH_2OCH_2CH$_2$), 4.21 (t, J = 7.8 Hz, 1 H, CHCH$_2$CCCH$_2$N), 7.15–7.22 (m, 2 H, ArH), 7.22–7.34 (m, 8 H, ArH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.7, 47.5, 50.4, 52.1, 66.8, 76.5, 84.0, 126.5, 127.9, 128.4, 143.4; IR (neat) 3357, 3060, 3026, 2957, 2922, 2852, 2809, 1599, 1494, 1451, 1346, 1330, 1313, 1288, 1115, 1004, 860, 737, 699 cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{24}NO^+$ $[M+H]^+$ 306.1858, found 306.1852.

*1-(5,5-Diphenylpent-2-yn-1-yl)piperidine (**29b**).* GP1 was followed using **27b** (267 mg, 0.958 mmol), CuCl (142 mg, 1.44 mmol), $BF_3{\cdot}OEt_2$ (283 mg, 0.958 mmol), piperidine (115 µl, 1.15 mmol) and paraformaldehyde (36.3 mg, 1.15 mmol). Purification by column chromatography (PE/EtOAc = 1:1, 1% NEt_3) afforded **29b** (263 mg, 91%) as yellow oil: TLC: R_f = 0.15 (PE/EtOAc = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (s_{br}, 2 H, NCH$_2$CH$_2$CH_2CH$_2$CH$_2$), 1.49 (p, J = 5.7 Hz, 4 H, NCH$_2$CH_2CH$_2$CH_2CH$_2$), 2.22 (s_{br}, 4 H, NCH_2CH$_2$CH$_2$CH$_2$CH_2), 2.92 (dt, J = 7.8/2.2 Hz, 2 H, NCH$_2$CCCH_2), 3.11 (t, J = 2.2 Hz, 2 H, NCH_2CCCH$_2$), 4.21 (t, J = 7.8 Hz, 1 H, CHCH$_2$), 7.13–7.26 (m, 2 H, ArH), 7.21–7.33 (m, 8 H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 23.8, 25.7, 25.9, 47.9,

50.5, 52.9, 77.2, 83.3, 126.4, 128.0, 128.3, 143.6; IR (neat) 3085, 3060, 3026, 2932, 2852, 2796, 2753, 1945, 1878, 1800, 1748, 1600, 1494, 1466, 1451, 1384, 1367, 1340, 1325, 1308, 1298, 1275, 1251, 1187, 1155, 1116, 1104, 1081, 1037, 993, 958, 908, 858, 781, 738, 699, 613 cm^{-1}; HRMS (ESI) m/z calcd for $C_{22}H_{26}N^+$ $[M+H]^+$ 304.2065, found 304.2060.

*1-(5,5-Diphenylpent-2-yn-1-yl)-1,2,3,6-tetrahydropyridine (**29c**).* GP1 was followed using **27b** (557 mg, 2.00 mmol), CuCl (297 mg, 3.00 mmol), $BF_3{\cdot}OEt_2$ (591 mg, 2.00 mmol), 1,2,3,6-tetrahydropyridine (223 µl, 2.40 mmol) and paraformaldehyde (75.9 mg, 2.40 mmol). Purification by column chromatography (PE/EtOAc = 1:1, 1% NEt_3) afforded **29c** (439 mg, 73%) as yellow oil: TLC: R_f = 0.37 (PE/EtOAc = 1:1, 1% NEt_3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04–2.14 (m, 2 H, $NCH_2CHCHC\mathit{H_2}CH_2$), 2.37 (t, J = 5.7 Hz, 2 H, $NCH_2CHCHCH_2C\mathit{H_2}$), 2.78–2.86 (m, 2 H, $NC\mathit{H_2}CHCHCH_2CH_2$), 2.92 (dt, J = 7.8/2.2 Hz, 2 H, $CHC\mathit{H_2}CCCH_2N$), 3.23 (t, J = 2.2 Hz, 2 H, $CHCH_2CCC\mathit{H_2}N$), 4.20 (t, J = 7.8 Hz, 1 H, $C\mathit{H}CH_2CCCH_2N$), 5.53–5.72 (m, 2 H, $NCH_2C\mathit{H}C\mathit{H}CH_2CH_2$), 7.13–7.21 (m, 2 H, ArH), 7.21–7.33 (m, 8 H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.7, 26.2, 46.9, 48.4, 50.4, 50.7, 76.9, 83.5, 124.6, 125.2, 126.4, 127.9, 128.4, 143.5; IR (neat) 3028, 2909, 2799, 1948, 1874, 1802, 1713, 1599, 1494, 1450, 1430, 1327, 1195, 1128, 1113, 1031, 1004, 970, 803, 738, 699 cm^{-1}; HRMS (ESI) m/z calcd for $C_{22}H_{24}N^+$ $[M+H]^+$ 302.1909, found 302.1905.

*N,N-diallyl-5,5-diphenylpent-2-yn-1-amine (**29g**).* GP1 was followed using **27b** (200 mg, 0.720 mmol), CuCl (107 mg, 1.08 mmol), $BF_3{\cdot}OEt_2$ (213 mg, 0.720 mmol), diallylamine (107 µl, 0.864 mmol) and paraformaldehyde (27.3 mg, 0.864 mmol). Purification by column chromatography (PE/EtOAc = 9:1, 1% NEt_3) afforded **29g** (170 mg, 75%) as pale yellow oil: TLC: R_f = 0.21 (PE/EtOAc = 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.85 (dt, J = 6.6/1.3 Hz, 4 H, $N(C\mathit{H_2}CHCH_2)_2$), 2.94 (dt, J = 7.8/2.1 Hz, 2 H,

CHC*H*$_2$CCCH$_2$N), 3.23 (t, *J* = 2.1 Hz, 2 H, CHCH$_2$CCC*H*$_2$N), 4.21 (t, *J* = 7.8 Hz, 1 H, C*H*CH$_2$CCCH$_2$N), 5.02–5.10 (m, 4 H, N(CH$_2$CHC*H*$_2$)$_2$), 5.66–5.78 (m, 2 H, N(CH$_2$C*H*CH$_2$)$_2$), 7.15–7.23 (m, 2 H, ArH), 7.23–7.32 (m, 8 H, ArH); ^{13}C NMR (126 MHz, CDCl$_3$) *δ* 25.7, 41.6, 50.6, 56.1, 76.1, 83.7, 117.8, 126.5, 127.9, 128.4, 135.5, 143.5; IR (neat) 3377, 3062, 3027, 2919, 2815, 1642, 1494, 1450, 1327, 1110, 921, 738, 698 cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{26}N^+$ $[M+H]^+$ 316.2065, found 316.2061.

*N-allyl-N-methyl-5,5-diphenylpent-2-yn-1-amine (**29h**).* GP1 was followed using **27b** (557 mg, 2.00 mmol), CuCl (297 mg, 3.00 mmol), BF$_3$·OEt$_2$ (591 mg, 2.00 mmol), allyl(methyl)amine (235 µl, 2.40 mmol) and paraformaldehyde (75.9 mg, 2.40 mmol). Purification by column chromatography (PE/EtOAc = 6:4, 1% NEt$_3$) afforded **29h** (498 mg, 86%) as pale yellow oil: TLC: R_f = 0.61 (PE/EtOAc = 6:4); ^{1}H NMR (400 MHz, CDCl$_3$) *δ* 2.07 (s, 3 H, N*Me*), 2.79 (dt, *J* = 6.6/1.3 Hz, 2 H, NMeC*H*$_2$CHCH$_2$), 2.93 (dt, *J* = 7.8/2.2 Hz, 2 H, CHC*H*$_2$CCCH$_2$N-), 3.18 (t, *J* = 2.2 Hz, 2 H, CHCH$_2$CCC*H*$_2$N), 4.21 (t, *J* = 7.8 Hz, 1 H, C*H*CH$_2$CCCH$_2$N), 5.00–5.11 (m, 2 H, NMeCH$_2$CHC*H*$_2$), 5.73 (ddt, *J* = 17.1/10.6/6.6 Hz, 1 H, NMeCH$_2$C*H*CH$_2$), 7.13–7.22 (m, 2 H, ArH), 7.22–7.34 (m, 8 H, ArH); ^{13}C NMR (101 MHz, CDCl$_3$) *δ* 25.7, 41.3, 45.4, 50.5, 58.6, 76.4, 83.7, 117.7, 126.4, 127.9, 128.4, 135.5, 143.5; IR (neat) 3027, 2913, 2788, 2359, 1945, 1600, 1494, 1450, 1327, 1192, 1128, 1082, 1031, 996, 922, 836, 789, 737, 699 cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{24}N^+$ $[M+H]^+$ 290.1909, found 290.1904.

*N,N-diisopropyl-5,5-diphenylpent-2-yn-1-amine (**29k**).* GP1 was followed using **27b** (382 mg, 1.37 mmol), CuCl (203 mg, 2.06 mmol), BF$_3$·OEt$_2$ (405 mg, 1.37 mmol), diisopropylamine (231 µl, 1.64 mmol) and paraformaldehyde (52.0 mg, 1.64 mmol). Purification by column chromatography (PE/EtOAc = 1:1, 1% NEt$_3$) afforded **29k** (269 mg, 61%) as pale yellow oil: TLC: R_f = 0.26 (PE/EtOAc = 1:1, 1% NEt$_3$); ^{1}H NMR

(500 MHz, $CDCl_3$) δ 0.94 (d, J = 6.5 Hz, 12 H, $N(CH(CH_3)_2)_2$), 2.89 (dt, J = 7.8/2.2 Hz, 2 H, $CHCH_2CCCH_2N$), 2.95 (h, J = 6.5 Hz, 2 H, $N(CH(CH_3)_2)_2$), 3.28 (t, J = 2.2 Hz, 2 H, $CHCH_2CCCH_2N$), 4.18 (t, J = 7.8 Hz, 1 H, $CHCH_2CCCH_2N$), 7.14–7.21 (m, 2 H, ArH), 7.21–7.33 (m, 8 H, ArH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.4, 25.9, 34.1, 47.9, 50.4, 80.5, 81.7, 126.4, 127.9, 128.3, 143.7; IR (neat) 3086, 3062, 3027, 2966, 2928, 2873, 2613, 1945, 1875, 1802, 1600, 1494, 1451, 1380, 1362, 1326, 1202, 1176, 1117, 1081, 1032, 749, 737, 698 cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{30}N^+$ $[M+H]^+$ 320.2378, found 320.2376.

*Ethyl 1-(5,5-diphenylpent-2-yn-1-yl)piperidine-3-carboxylate (**29d**).* GP2 was followed using **27a** (206 mg, 1.00 mmol), CuBr (21.5 mg, 0.150 mmol), ethyl nipecotate (0.23 ml, 1.4 mmol) and paraformaldehyde (56.9 mg, 1.80 mmol). Purification by column chromatography (PE/EtOAc = 1:1) afforded **29d** (333 mg, 89%) as pale yellow oil: TLC: R_f = 0.33 (PE/EtOAc = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.20–1.36 (m, 1 H, $NCH_2CHCH_{eq}H_{ax}CH_2CH_2$), 1.40–1.55 (m, 1 H, $NCH_2CHCH_2CH_{eq}H_{ax}CH_2$), 1.56–1.67 (m, 1 H, $NCH_2CHCH_2CH_{eq}H_{ax}CH_2$), 1.80–1.91 (m, 2 H, $NCH_2CHCH_{eq}H_{ax}CH_2CH_{eq}H_{ax}$), 2.11 (t, J = 10.7 Hz, 1 H, $NCH_{eq}H_{ax}CHCH_2CH_2CH_2$), 2.42–2.55 (m, 2 H, $NCH_2CHCH_2CH_2CH_{eq}H_{ax}$), 2.81 (dd, J = 11.1/3.6 Hz, 1 H, $NCH_{eq}H_{ax}CHCH_2CH_2CH_2$), 2.92 (dt, J = 7.8/2.2 Hz, 2 H, $CHCH_2CCCH_2N$), 3.17 (dt, J = 3.1/2.2 Hz, 2 H, $CHCH_2CCCH_2N$), 4.09–4.17 (m, 2 H, OCH_2CH_3), 4.21 (t, J = 7.8 Hz, 1 H, $CHCH_2CCCH_2N$), 7.10–7.23 (m, 2 H, ArH), 7.20–7.35 (m, 8 H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.2, 24.5, 25.7, 26.4, 41.9, 47.6, 50.4, 51.8, 54.0, 60.3, 76.6, 83.8, 126.4, 127.9, 128.4, 143.5, 174.0; IR (neat) 3086, 3061, 3027, 2937, 2854, 2806, 1947, 1882, 1730, 1600, 1494, 1467, 1451, 1367, 1316, 1223, 1181, 1153, 1132, 1090, 1031, 1000, 979, 956, 906, 868, 790, 750, 700, 608 cm^{-1}; HRMS (ESI) m/z calcd for $C_{25}H_{30}NO_2^+$ $[M+H]^+$ 376.2277, found 376.2271.

*N-allyl-N-(tert-butyl)-5,5-diphenylpent-2-yn-1-amine (**29e**).* GP2 was followed using **27a** (598 mg, 2.90 mmol), CuBr (62.4 mg, 0.435 mmol), allyl(*tert*-butyl)amine (0.61 ml, 4.06 mmol) and paraformaldehyde (165 mg, 5.22 mmol). Purification by column chromatography (PE/EtOAc = 6:4) afforded **29e** (877 mg, 91%) as pale yellow oil: TLC: R_f = 0.82 (PE/EtOAc = 6:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (s, 9 H, *t-Bu*), 2.90 (dt, *J* = 7.7/2.1 Hz, 2 H, NCH_2CCCH_2), 3.04 (d, *J* = 6.5 Hz, 2 H, NCH_2CHCH_2), 3.35 (t, *J* = 2.1 Hz, 2 H, NCH_2CCCH_2), 4.19 (t, *J* = 7.7 Hz, 1 H, NCH_2CCCH_2CH), 4.97–5.06 (m, 2 H, NCH_2CHCH_2), 5.70 (ddt, *J* = 16.7/10.1/6.5 Hz, 1 H, NCH_2CHCH_2), 7.15–7.24 (m, 2 H, ArH), 7.20–7.32 (m, 8 H, ArH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.8, 27.6, 36.3, 49.7, 50.4, 54.7, 79.8, 82.4, 116.7, 126.4, 127.9, 128.4, 137.4, 143.6; IR (neat) 3063, 3027, 2971, 2913, 1944, 1800, 1728, 1640, 1600, 1494, 1451, 1432, 1416, 1389, 1362, 1334, 1307, 1270, 1217, 1203, 1128, 1081, 1032, 1018, 994, 941, 917, 860, 826, 783, 748, 737, 699, 645, 617 cm^{-1}; HRMS (ESI) m/z calcd for $C_{24}H_{30}N^+$ $[M+H]^+$ 332.2378, found 332.2376.

*N-allyl-N-isopropyl-5,5-diphenylpent-2-yn-1-amine (**29f**).* GP2 was followed using **27a** (237 mg, 1.15 mmol), CuBr (24.7 mg, 0.172 mmol), allyl(isopropyl)amine (160 mg, 1.61 mmol) and paraformaldehyde (65.4 mg, 2.07 mmol). Purification by column chromatography (PE/EtOAc = 1:1) afforded **29f** (185 mg, 51%) as pale yellow oil: TLC: R_f = 0.58 (PE/EtOAc = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, *J* = 6.5 Hz, 6 H, $NCH(CH_3)_2$), 2.66 (hept, *J* = 6.5 Hz, 1 H, $NCH(CH_3)_2$), 2.91 (dt, *J* = 7.8/2.2 Hz, 2 H, $CHCH_2CCCH_2N$), 2.94 (dt, *J* = 6.6/1.3 Hz, 2 H, NCH_2CHCH_2), 3.25 (t, *J* = 2.2 Hz, 2 H, $CHCH_2CCCH_2N$), 4.20 (t, *J* = 7.8 Hz, 1 H, $CHCH_2CCCH_2N$), 4.99–5.10 (m, 2 H, NCH_2CHCH_2), 5.73 (ddt, *J* = 16.9/10.2/6.6 Hz, 1 H, NCH_2CHCH_2), 7.12–7.22 (m, 2 H, ArH), 7.22–7.34 (m, 8 H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 19.8, 25.8, 38.9, 50.5, 50.6, 52.6, 77.8, 82.8, 117.2, 126.4, 127.9, 128.4, 136.5, 143.6; IR (neat) 3062,

3027, 2964, 2927, 2811, 1944, 1733, 1641, 1600, 1494, 1450, 1382, 1362, 1325, 1253, 1171, 1140, 1115, 1081, 1032, 995, 949, 918, 876, 780, 737, 698 cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{28}N^+$ $[M+H]^+$ 318.2222, found 318.2218.

*N-(tert-butyl)-N-isopropyl-5,5-diphenylpent-2-yn-1-amine (**29i**).* GP2 was followed using **27a** (297 mg, 1.44 mmol), CuBr (31.0 mg, 0.216 mmol), isopropyl(*tert*-butyl)amine (0.32 mL, 2.02 mmol) and paraformaldehyde (81.9 mg, 2.59 mmol). Purification by column chromatography (PE/EtOAc = 9:1) afforded **29i** (363 mg, 76%) as white solid: TLC: R_f = 0.23 (PE/EtOAc = 9:1); mp = 47.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (d, J = 6.6 Hz, 6 H, NCH(CH_3)$_2$), 1.04 (s, 9 H, N*t-Bu*), 2.88 (dt, J = 7.7/2.1 Hz, 2 H, NCH_2CCCH_2), 3.20 (hept, J = 6.6 Hz, 1 H, NC*H*(CH_3)$_2$), 3.31 (t, J = 2.1 Hz, 2 H, NCH_2CCCH_2), 4.17 (t, J = 7.7 Hz, 1 H, C*H*CH_2), 7.13–7.20 (m, 2 H, ArH), 7.21–7.30 (m, 8 H, ArH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.4, 25.9, 28.4, 31.7, 46.6, 50.4, 55.1, 80.0, 84.1, 126.3, 127.9, 128.3, 143.8; IR (neat) 3062, 3027, 2970, 2926, 1600, 1558, 1540, 1494, 1451, 1388, 1362, 1338, 1306, 1253, 1218, 1170, 1113, 1081, 1051, 1032, 923, 788, 737, 698 cm^{-1}; HRMS (ESI) m/z calcd for $C_{24}H_{32}N^+$ $[M+H]^+$ 334.2535, found 334.2533.

*N-(tert-butyl)-N-methyl-5,5-diphenylpent-2-yn-1-amine (**29j**).* GP2 was followed using **27a** (297 mg, 1.44 mmol), CuBr (31.0 mg, 0.216 mmol), methyl(*tert*-butyl)amine (0.25 mL, 2.02 mmol) and paraformaldehyde (81.9 mg, 2.59 mmol). Purification by column chromatography (PE/EtOAc = 1:1) afforded **29j** (423 mg, 96%) as pale yellow oil: TLC: R_f = 0.26 (PE/EtOAc = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (s, 9 H, N*t-Bu*), 2.17 (s, 3 H, N*Me*), 2.90 (dt, J = 7.7/2.1 Hz, 2 H, $CHCH_2$), 3.21 (t, J = 2.1 Hz, 2 H, NCH_2CCCH_2), 4.20 (t, J = 7.7 Hz, 1 H, C*H*CH_2), 7.14–7.21 (m, 2 H, ArH), 7.21–7.31 (m, 8 H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.9, 26.3, 34.9, 40.6, 50.3, 54.1, 79.7, 82.3, 126.4, 127.9, 128.3, 143.7; IR (neat) 3086, 3061, 3027, 2971, 2785, 1945,

1801, 1600, 1494, 1451, 1387, 1361, 1262, 1218, 1120, 1081, 1000, 947, 823, 750, 737, 698 cm^{-1}; HRMS (ESI) m/z calcd for $C_{22}H_{28}N^+$ $[M+H]^+$ 306.2222, found 306.2219.

*N-allyl-N-(tert-butyl)undec-2-yn-1-amine (**39**).* GP2 was followed using 1-decyne (0.36 mL, 2.0 mmol), CuBr (43 mg, 0.30 mmol), allyl(*tert*-butyl)amine (0.43 mL, 2.8 mmol) and paraformaldehyde (114 mg, 3.60 mmol). Purification by column chromatography (PE/EtOAc = 9:1) afforded **39** (477 mg, 90%) as colorless oil: TLC: R_f = 0.56 (PE/EtOAc = 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3 H, CH_2CH_3), 1.17 (s, 9 H, $NC(CH_3)_3$), 1.21–1.34 (m, 8 H, $(CH_2)_4$), 1.34–1.43 (m, 2 H, $CH_2CH_2CH_2CC$), 1.43–1.54 (m, 2 H, $CH_2CH_2CH_2CC$), 2.16 (tt, J = 7.0/2.2 Hz, 2 H, $CH_2CH_2CH_2CC$), 3.28 (d, J = 6.6 Hz, 2 H, NCH_2CHCH_2), 3.46 (t, J = 2.2 Hz, 2 H, NCH_2CC), 5.09 (ddt, J = 10.0/2.3/1.2 Hz, 1 H, $NCH_2CHCH_{trans}H_{cis}$), 5.23 (dq, J = 16.9/1.6 Hz, 1 H, $NCH_2CHCH_{trans}H_{cis}$), 5.83 (ddt, J = 16.9/10.0/6.6 Hz, 1 H, NCH_2CHCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.1, 18.8, 22.7, 27.7, 28.9, 28.9, 29.1, 29.3, 31.9, 36.6, 50.0, 54.9, 78.0, 84.4, 116.6, 137.6; IR (neat) ṽ 2959, 2928, 2856, 1745, 1641, 1465, 1432, 1389, 1362, 1332, 1270, 1216, 1203, 1129, 1073, 1018, 993, 940, 915, 825 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{34}N^+$ $[M+H]^+$ 264.2691, found 264.2686.

*N-allyl-N-(tert-butyl)-6-chlorohex-2-yn-1-amine (**40**).* GP2 was followed using 5-chloro-1-pentyne (0.22 mL, 2.0 mmol), CuBr (43 mg, 0.30 mmol), allyl(*tert*-butyl)amine (0.43 mL, 2.8 mmol) and paraformaldehyde (114 mg, 3.60 mmol). Purification by column chromatography (PE/EtOAc = 9:1) afforded **40** (443 mg, 97%) as colorless oil: TLC: R_f = 0.34 (PE/EtOAc = 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 9 H, $NC(CH_3)_3$), 1.94 (p, J = 6.6 Hz, 2 H, $ClCH_2CH_2CH_2$), 2.37 (tt, J = 6.6/2.2 Hz, 2 H, $ClCH_2CH_2CH_2$), 3.27 (dt, J = 6.5/1.3 Hz, 2 H, NCH_2CHCH_2), 3.45 (t, J = 2.2 Hz,

2 H, NCH_2CC), 3.66 (t, *J* = 6.6 Hz, 2 H, ClCH_2CH_2CH_2), 5.10 (ddt, *J* = 10.0/2.3/1.3 Hz, 1 H, NCH_2CHCH$_{trans}$$H_{cis}$), 5.23 (dq, *J* = 16.9/1.3 Hz, 1 H, NCH_2CHCH_{trans}H$_{cis}$), 5.82 (ddt, *J* = 16.9/10.0/6.5 Hz, 1 H, NCH_2CHCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 16.3, 27.7, 31.5, 36.5, 43.8, 50.1, 54.9, 79.3, 82.1, 116.6, 137.5; IR (neat) ṽ 2972, 1716, 1642, 1433, 1416, 1390, 1362, 1333, 1290, 1270, 1218, 1203, 1128, 1073, 1019, 994, 940, 918, 859 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{23}ClN^+$ $[M+H]^+$ 228.1519, found 228.1515.

*7-(Allyl(tert-butyl)amino)hept-5-ynenitrile (**41**).* GP2 was followed using hex-5-ynenitrile (0.22 mL, 2.0 mmol), CuBr (43 mg, 0.30 mmol), allyl(*tert*-butyl)amine (0.43 mL, 2.8 mmol) and paraformaldehyde (114 mg, 3.60 mmol). Purification by column chromatography (PE/EtOAc = 7:3) afforded **41** (408 mg, 94%) as pale yellow oil: TLC: R_f = 0.31 (PE/EtOAc = 7:3); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 1.16 (s, 9 H, NC(CH_3)$_3$), 1.85 (p, *J* = 7.0 Hz, 2 H, NCCH$_2$CH_2CH$_2$), 2.37 (tt, *J* = 7.0/2.2 Hz, 2 H, NCCH$_2$CH$_2$CH_2), 2.49 (t, *J* = 7.0 Hz, 2 H, NCCH_2CH$_2$CH$_2$), 3.27 (dt, *J* = 6.4/1.3 Hz, 2 H, NCH_2CHCH$_2$), 3.45 (t, *J* = 2.2 Hz, 2 H, NCH_2CC), 5.10 (ddt, *J* = 10.0/2.2/1.2 Hz, 1 H, NCH$_2$CHCH$_{trans}$$H_{cis}$), 5.22 (dq, *J* = 16.9/1.6 Hz, 1 H, NCH$_2$CHCH_{trans}H$_{cis}$), 5.82 (ddt, *J* = 16.9/10.0/6.4 Hz, 1 H, NCH$_2$CHCH$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 16.2, 18.0, 24.7, 27.6, 36.5, 50.2, 54.9, 80.4, 81.1, 116.7, 119.2, 137.4; IR (neat) ṽ 2972, 1640, 1454, 1431, 1390, 1363, 1333, 1311, 1269, 1216, 1203, 1128, 1110, 1074, 1019, 994, 939, 918 cm^{-1}; HRMS (ESI) m/z calcd for $C_{14}H_{23}N^+$ $[M+H]^+$ 219.1861, found 219.1857.

*N-allyl-4-(benzyloxy)-N-(tert-butyl)but-2-yn-1-amine (**42**).* GP2 was followed using [(prop-2-yn-1-yloxy)methyl]benzene (0.29 mL, 2.0 mmol), CuBr (43 mg, 0.30 mmol), allyl(*tert*-butyl)amine (0.43 mL, 2.8 mmol) and paraformaldehyde (114 mg, 3.60 mmol). Purification by column chromatography (PE/EtOAc = 8:2) afforded **42** (478

mg, 88%) as colorless oil: TLC: R_f = 0.57 (PE/EtOAc = 7:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (s, 9 H, NC(CH_3)$_3$), 3.31 (d, J = 6.5 Hz, 2 H, NCH_2CHCH$_2$), 3.55 (t, J = 1.9 Hz, 2 H, NCH_2CC), 4.19 (t, J = 1.9 Hz, 2 H, OCH_2CC), 4.60 (s, 2 H, ArCH_2), 5.11 (ddt, J = 10.0/2.3/1.2 Hz, 1 H, NCH$_2$CHCH$_{trans}H_{cis}$), 5.25 (dq, J = 16.9/1.6 Hz, 1 H, NCH$_2$CHCH_{trans}H$_{cis}$), 5.83 (ddt, J = 16.9/10.0/6.5 Hz, 1 H, NCH$_2$CHCH$_2$), 7.23–7.43 (m, 5 H, ArH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.7, 36.6, 50.2, 54.9, 57.7, 71.4, 79.8, 85.2, 116.8, 127.8, 128.1, 128.4, 137.3, 137.6; IR (neat) ṽ 3065, 3030, 2972, 2500, 1809, 1641, 1496, 1454, 1428, 1416, 1389, 1362, 1332, 1268, 1203, 1101, 1070, 1026, 994, 940, 918, 735, 697 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{26}NO^+$ $[M+H]^+$ 272.2014, found 272.2009.

*Ethyl 1-{4-[allyl(tert-butyl)amino]but-2-yn-1-yl}piperidine-3-carboxylate (**31a**).* GP2 was followed using **30** (586 mg, 3.00 mmol), CuBr (64.6 mg, 0.450 mmol), allyl(*tert*-butyl)amine (0.63 mL, 4.20 mmol) and paraformaldehyde (171 mg, 5.40 mmol). Purification by column chromatography (PE/EtOAc = 1:1) afforded **31a** (898 mg, 93%) as pale yellow oil: TLC: R_f = 0.27 (PE/EtOAc = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (s, 9 H, N*t*-Bu), 1.25 (t, J = 7.1 Hz, 3 H, OCH$_2$CH_3), 1.42 (qd, J ≈ 11.7/3.9 Hz, 1 H, NCH$_2$CHCH_{ax}H$_{eq}$), 1.52–1.68 (m, 1 H, NCH$_2$CH_{ax}H$_{eq}$CH$_2$CH), 1.76 (dp, J ≈ 13.2/3.9 Hz, 1 H, NCH$_2$CH$_{ax}H_{eq}$CH$_2$CH), 1.89–2.06 (m, 1 H, NCH$_2$CHCH$_{ax}H_{eq}$), 2.19 (td, J ≈ 11.1/3.9 Hz, 1 H, NCH_{ax}H$_{eq}$CH$_2$CH$_2$CH), 2.34 (t, J ≈ 10.5 Hz, 1 H, NCH_{ax}H$_{eq}$CHCH$_2$), 2.58 (ddt, J ≈ 11.7/10.5/3.9 Hz, 1 H, NCH$_2$CH_{ax}CH$_2$), 2.73–2.83 (m, 1 H, NCH$_{ax}H_{eq}$CH$_2$CH$_2$CH), 2.99–3.08 (m, 1 H, NCH$_{ax}H_{eq}$CHCH$_2$), 3.29 (dt, J = 6.5/1.3 Hz, 2 H, NCH_2CH=CH$_2$), 3.32 (t, J = 2.0 Hz, 2 H, NCH$_2$CCCH_2Nip), 3.51 (t, J = 2.0 Hz, 2 H, NCH_2CCCH$_2$Nip), 4.13 (q, J = 7.1 Hz, 2 H, OCH_2CH$_3$), 5.10 (ddt, J = 10.0/2.2/1.3 Hz, 1 H, NCH$_2$CH=CH$_{trans}H_{cis}$), 5.24 (ddt, J = 17.1/2.2/1.3 Hz, 1 H, NCH$_2$CH=CH_{trans}H$_{cis}$), 5.81 (ddt, J = 17.1/10.0/6.5 Hz, 1 H, NCH$_2$CH=CH$_2$); ^{13}C NMR

(101 MHz, $CDCl_3$) δ 14.2, 24.6, 26.6, 27.7, 36.5, 42.0, 47.8, 50.1, 52.4, 54.3, 54.9, 60.3, 78.8, 83.5, 116.7, 137.5, 174.0; IR (neat) 3076, 2973, 2805, 1733, 1641, 1467, 1451, 1390, 1364, 1322, 1270, 1217, 1203, 1181, 1152, 1133, 1095, 1046, 1031, 995, 940, 916, 866 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{33}N_2O_2^+$ $[M+H]^+$ 321.2542, found 321.2540.

*Ethyl 1-[4-(diisopropylamino)but-2-yn-1-yl]piperidine-3-carboxylate (**31b**).* GP2 was followed using **30** (391 mg, 2.00 mmol), CuBr (43.0 mg, 0.300 mmol), diisopropylamine (0.39 mL, 2.80 mmol) and paraformaldehyde (114 mg, 3.60 mmol). Purification by column chromatography (DCM/MeOH = 9:1) afforded **31b** (586 mg, 95%) as yellow oil: TLC: R_f = 0.37 (DCM/MeOH = 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, J = 6.6 Hz, 12 H, $N(CH(CH_3)_2)_2$)), 1.25 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.41 (qd, $J \approx$ 11.8/3.7 Hz, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 1.52–1.68 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.76 (dp, $J \approx$ 13.3/3.4 Hz, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.89–2.00 (m, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 2.18 (td, J = 11.1/3.0 Hz, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.33 (t, $J \approx$ 10.6 Hz, 1 H, $NCH_{ax}H_{eq}CHCH_2$), 2.58 (ddt, $J \approx$ 11.8/10.6/3.8 Hz, 1 H, $NCH_2CH_{ax}CH_2$), 2.73–2.82 (m, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.98–3.07 (m, 1 H, $NCH_{ax}H_{eq}CHCH_2$), 3.24 (hept, J = 6.6 Hz, 2 H, $N(CH(CH_3)_2)_2$), 3.31 (t, J = 2.0 Hz, 2 H, NCH_2CCCH_2N(diisopropyl)), 3.48 (t, J = 2.0 Hz, 2 H, NCH_2CCCH_2N(diisopropyl)), 4.13 (q, J = 7.1 Hz, 2 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.2, 20.5, 24.6, 26.6, 34.3, 42.0, 47.8, 48.7, 52.4, 54.4, 60.3, 78.5, 83.7, 174.0; IR (neat) 3420, 2966, 2939, 2872, 2804, 1733, 1466, 1381, 1363, 1321, 1179, 1153, 1134, 1095, 1031, 867 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{33}N_2O_2^+$ $[M+H]^+$ 309.2542, found 309.2539.

*Ethyl 1-{4-[3,6-dihydropyridin-1(2H)-yl]but-2-yn-1-yl}piperidine-3-carboxylate (**31c**).* GP2 was followed using **30** (391 mg, 2.00 mmol), CuBr (43.0 mg, 0.300 mmol),

1,2,3,6-terahydropyridine (0.26 mL, 2.80 mmol) and paraformaldehyde (114 mg, 3.60 mmol). Purification by column chromatography (DCM/MeOH = 9:1) afforded **31c** (540 mg, 93%) as yellow oil: TLC: R_f = 0.40 (DCM/MeOH = 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.42 (qd, J = 11.5/3.9 Hz, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 1.54–1.66 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.76 (dp, J = 13.3/3.9 Hz, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.91–1.98 (m, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 2.13–2.25 (m, 3 H, $NCH_2CHCHCH_2CH_2$ and $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.33 (t, J ≈ 10.5 Hz, 1 H, $NCH_{ax}H_{eq}CHCH_2$), 2.58 (ddt, J ≈ 11.5/10.5/3.9 Hz, 1 H, $NCH_2CH_{ax}CH_2$), 2.65 (t, J = 5.7 Hz, 2 H, $NCH_2CHCHCH_2CH_2$), 2.75–2.83 (m, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.98–3.06 (m, 1 H, $NCH_{ax}H_{eq}CHCH_2$), 3.06–3.12 (m, 2 H, $NCH_2CHCHCH_2CH_2$), 3.31–3.36 (m, 2 H, NCH_2CCCH_2Nip), 3.42 (t, J = 2.0 Hz, 2 H, NCH_2CCCH_2Nip), 4.07–4.20 (m, 2 H, OCH_2CH_3), 5.63–5.72 (m, 1 H, $NCH_2CHCHCH_2CH_2$), 5.72–5.82 (m, 1 H, $NCH_2CHCHCH_2CH_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.2, 24.6, 26.2, 26.6, 41.9, 47.0, 47.7, 48.9, 51.1, 52.5, 54.4, 60.4, 79.7, 80.2, 124.8, 125.1, 174.0; IR (neat) 3373, 3033, 2939, 2908, 2801, 1731, 1465, 1448, 1323, 1223, 1182, 1153, 1134, 1094, 1031, 1004, 867, 803, 654 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{27}N_2O_2^+$ $[M+H]^+$ 291.2073, found 291.2068.

*Ethyl 1-[4-(diallylamino)but-2-yn-1-yl]piperidine-3-carboxylate (**31d**).* GP2 was followed using **30** (391 mg, 2.00 mmol), CuBr (43.0 mg, 0.300 mmol), diallylamine (0.35 mL, 2.80 mmol) and paraformaldehyde (114 mg, 3.60 mmol). Purification by column chromatography (PE/EtOAc = 1:1) afforded **31d** (546 mg, 90%) as colorless oil: TLC: R_f = 0.21 (PE/EtOAc = 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.43 (qd, J = 12.4/4.2 Hz, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 1.55–1.67 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.77 (dp, J ≈ 13.4/3.7 Hz, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.92–2.03 (m, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 2.21 (td, J = 11.2/3.1 Hz, 1 H,

NCH_{ax}H$_{eq}$CH$_2$CH$_2$CH), 2.37 (t, J = 10.5 Hz, 1 H, NCH_{ax}H$_{eq}$CHCH$_2$), 2.59 (tt, J ≈ 11.5/3.9 Hz, 1 H, NCH$_2$CH_{ax}CH$_2$), 2.75–2.83 (m, 1 H, NCH$_{ax}$$H_{eq}CH_2CH_2$CH), 3.00–3.07 (m, 1 H, NCH$_{ax}$$H_{eq}$CHCH$_2$), 3.13 (dt, J ≈ 6.5/1.2 Hz, 4 H, N(CH_2CHCH$_2$)$_2$), 3.36 (t, J = 2.0 Hz, 2 H, NCH_2CCCH$_2$N(diallyl)), 3.40 (t, J = 2.0 Hz, 2 H, NCH$_2$CCCH_2N(diallyl)), 4.09–4.18 (m, 2 H, OCH_2CH$_3$), 5.15 (ddt, J ≈ 10.1/1.8/1.2 Hz, 2 H, N(CH$_2$CHCH$_{trans}$$H_{cis}$)$_2$), 5.24 (dq, J ≈ 17.0/1.8 Hz, 2 H, N(CH$_2$CHCH_{trans}H$_{cis}$)$_2$), 5.84 (ddt, J ≈ 17.0/10.1/6.5 Hz, 2 H, N(CH$_2$CHCH$_{trans}$H$_{cis}$)$_2$); ^{13}C NMR (126 MHz, CDCl$_3$) δ 14.2, 24.6, 26.6, 41.7, 42.0, 47.7, 52.4, 54.3, 56.5, 60.3, 79.8, 118.0, 135.4, 174.0; IR (neat) 3077, 2978, 2939, 2812, 1732, 1643, 1467, 1449, 1429, 1367, 1322, 1255, 1222, 1181, 1153, 1133, 1095, 1031, 996, 921, 850, 792 cm^{-1}; HRMS (ESI) m/z calcd for C$_{18}$H$_{29}$N$_2$O$_2^+$ [M+H]$^+$ 305.2229, found 305.2226.

*Ethyl 1-{4-[allyl(methyl)amino]but-2-yn-1-yl}piperidine-3-carboxylate (**31e**).* GP2 was followed using **30** (391 mg, 2.00 mmol), CuBr (43.0 mg, 0.300 mmol), allyl(methyl)amine (0.27 mL, 2.80 mmol) and paraformaldehyde (114 mg, 3.60 mmol). Purification by column chromatography (DCM/MeOH = 9:1) afforded **31e** (525 mg, 94%) as pale yellow oil: TLC: R_f = 0.68 (DCM/MeOH = 18:2); ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.25 (t, J = 7.1 Hz, 3 H, OCH$_2$CH_3), 1.43 (qd, J ≈ 11.5/4.0 Hz, 1 H, NCH$_2$CHCH_{ax}H$_{eq}$), 1.54–1.67 (m, 1 H, NCH$_2$CH_{ax}H$_{eq}$CH$_2$CH), 1.77 (dp, J ≈ 13.3/4.0 Hz, 1 H, NCH$_2$CH$_{ax}$$H_{eq}CH_2$CH-), 1.88–2.02 (m, 1 H, NCH$_2$CHCH$_{ax}$$H_{eq}$), 2.20 (td, J ≈ 11.2/4.0 Hz, 1 H, NCH_{ax}H$_{eq}$CH$_2$CH$_2$CH), 2.31 (s, 3 H, -N*Me*), 2.36 (t, J ≈ 10.7 Hz, 1 H, NCH_{ax}H$_{eq}$CHCH$_2$), 2.59 (ddt, J ≈ 11.5/10.7/3.9 Hz, 1 H, NCH$_2$CH_{ax}CH$_2$), 2.75–2.83 (m, 1 H, NCH$_{ax}$$H_{eq}CH_2CH_2$CH), 2.99–3.07 (m, 1 H, NCH$_{ax}$$H_{eq}$CHCH$_2$), 3.06 (dt, J ≈ 6.6/1.2 Hz, 2 H, NCH_2CH=CH$_2$), 3.32–3.38 (m, 4 H, NCH_2CCCH_2), 4.09–4.18 (m, 2 H, OCH_2CH$_3$), 5.15 (ddt, J ≈ 10.1/1.8/1.2 Hz, 1 H, NCH$_2$CH=CH$_{trans}$$H_{cis}$), 5.22 (dq, J ≈ 17.0/1.8 Hz, 1 H, NCH$_2$CH=CH_{trans}H$_{cis}$), 5.84 (ddt, J ≈ 17.0/10.1/6.6 Hz, 1 H,

$NCH_2CH{=}CH_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.2, 24.6, 26.6, 41.7, 41.9, 45.5, 47.7, 52.4, 54.3, 59.1, 60.4, 79.9, 80.0, 118.0, 135.4, 174.0; IR (neat) 3404, 2941, 2793, 1732, 1644, 1558, 1450, 1321, 1222, 1181, 1153, 1133, 1095, 1031, 997, 922 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{27}N_2O_2^+$ $[M+H]^+$ 279.2073, found 279.2068.

*Ethyl 1-{4-[tert-butyl(isopropyl)amino]but-2-yn-1-yl}piperidine-3-carboxylate (**31f**).* GP2 was followed using **30** (391 mg, 2.00 mmol), CuBr (43.0 mg, 0.300 mmol), isopropyl(*tert*-butyl)amine (0.44 mL, 2.80 mmol) and paraformaldehyde (114 mg, 3.60 mmol). Purification by column chromatography (DCM/MeOH = 9:1) afforded **31f** (596 mg, 93%) as colorless oil: TLC: R_f = 0.40 (DCM/MeOH = 9:1); ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, J = 6.6 Hz, 6 H, $NCH(CH_3)_2$), 1.22 (s, 9 H, N*t*-Bu), 1.25 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.41 (qd, J = 12.2/4.5 Hz, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 1.52–1.68 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.75 (dp, J ≈ 13.2/3.8 Hz, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.89–2.00 (m, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 2.18 (td, J = 11.3/3.0 Hz, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.33 (t, J = 10.7 Hz, 1 H, $NCH_{ax}H_{eq}CHCH_2$), 2.58 (tt, J ≈ 11.5/3.9 Hz, 1 H, $NCH_2CH_{ax}CH_2$), 2.73–2.83 (m, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.99–3.07 (m, 1 H, $NCH_{ax}H_{eq}CHCH_2$), 3.30 (t, J = 1.9 Hz, 2 H, $NipCH_2CCCH_2$), 3.37 (hept, J = 6.6 Hz, 1 H, $NCH(CH_3)_2$), 3.46–3.53 (m, 2 H, $NipCH_2CCCH_2$), 4.13 (q, J = 7.1 Hz, 2 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.2, 22.5, 24.6, 26.6, 28.5, 31.9, 42.0, 47.0, 47.9, 52.5, 54.4, 55.7, 60.3, 77.3, 87.6, 174.0; IR (neat) 2971, 2940, 2869, 2802, 1734, 1465, 1389, 1362, 1309, 1253, 1218, 1173, 1152, 1134, 1114, 1095, 1047, 1031, 862, 794 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{35}N_2O_2^+$ $[M+H]^+$ 323.2699, found 323.2696.

*N,N-diallyl-1,5,5-triphenylpent-2-yn-1-amine (**29n**).* GP2 was followed using **27a** (413 mg, 2.00 mmol), CuBr (43.0 mg, 0.300 mmol), diallylamine (0.35 mL, 2.80 mmol) and benzaldehyde (0.37 mL, 3.60 mmol). Purification by column chromatography

(PE/EtOAc = 19:1) afforded **29n** (728 mg, 93%) as white solid: mp = 44.0 °C; TLC: R_f = 0.54 (PE/EtOAc = 19:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.62 (ddt, J = 14.1/8.2/1.0 Hz, 2 H, N(CH_2CHCH_2)$_2$), 2.97 (ddt, J = 14.1/4.2/1.9 Hz, 2 H, N(CH_2CHCH_2)$_2$), 3.08 (dd, J = 7.8/2.1 Hz, 2 H, NCHCCCH_2), 4.29 (t, J = 7.8 Hz, 1 H, NCHCCCH$_2$CH), 4.71 (t, J = 2.1 Hz, 1 H, NCHCCCH$_2$CH), 5.00–5.07 (m, 2 H, N(CH$_2$CHCH_{cis}H$_{trans}$)$_2$), 5.07–5.15 (m, 2 H, N(CH$_2$CHCH$_{cis}$$H_{trans}$)$_2$), 5.71 (dddd, J = 17.1/10.1/8.2/4.2 Hz, 2 H, N(CH$_2$CHCH$_2$)$_2$), 7.14–7.26 (m, 5 H, ArH), 7.27–7.34 (m, 8 H, ArH), 7.34–7.41 (m, 2 H, ArH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.8, 50.8, 53.1, 55.9, 77.3, 86.1, 117.0, 126.5, 127.0, 127.8, 128.0, 128.2, 128.5, 136.8, 139.6, 143.5; IR (neat) 3062, 3027, 2923, 2817, 1946, 1726, 1641, 1600, 1493, 1449, 1417, 1351, 1328, 1274, 1122, 1081, 1030, 995, 971, 918, 874, 841, 814, 782, 736, 698 cm^{-1}; HRMS (ESI) m/z calcd for $C_{29}H_{30}N^+$ $[M+H]^+$ 392.2378, found 392.2376.

*N-allyl-N-methyl-1,5,5-triphenylpent-2-yn-1-amine (**29o**).* GP2 was followed using **27a** (349 mg, 1.69 mmol), CuBr (36.4 mg, 0.254 mmol), allyl(methyl)amine (0.23 mL, 2.37 mmol) and benzaldehyde (0.31 mL, 3.04 mmol). Purification by column chromatography (PE/EtOAc = 19:1) afforded **29o** (407 mg, 66%) as colorless resin: TLC: R_f = 0.18 (PE/EtOAc = 19:1); ^{1}H NMR (400 MHz) δ 1.92 (s, 3 H, NMe), 2.79 (ddt, J = 13.4/7.5/1.1 Hz, 1 H, NCH$_a$$H_b$CHCH$_2$), 2.88 (ddt, J = 13.4/5.5/1.6 Hz, 1 H, NCH_aH$_b$CHCH$_2$), 3.07 (dd, J = 7.8/2.1 Hz, 2 H, NCHCCCH_2CH), 4.29 (t, J = 7.8 Hz, 1 H, NCHCCCH$_2$CH), 4.60 (t, J = 2.1 Hz, 1 H, NCHCCCH$_2$CH), 5.01–5.16 (m, 2 H, NCH$_2$CHCH_2), 5.78 (dddd, J = 17.4, 10.1, 7.5, 5.5 Hz, 1H, NCH$_2$CHCH$_2$), 7.15–7.27 (m, 5 H, ArH), 7.27–7.39 (m, 10 H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.8, 37.4, 50.7, 57.4, 59.1, 76.9, 86.6, 117.3, 126.5, 127.1, 127.9, 128.0, 128.4, 128.5, 136.4, 139.1, 143.5; IR (neat) 3061, 3027, 2977, 2913, 2876, 2845, 2814, 2788, 1947, 1802, 1642, 1600, 1493, 1449, 1349, 1324, 1272, 1195, 1155, 1127, 1081, 1019,

995, 962, 919, 874, 840, 782, 736, 698 cm^{-1}; HRMS (ESI) m/z calcd for $C_{27}H_{28}N^+$ $[M+H]^+$ 366.2222, found 366.2219.

*rac-[Ethyl (R)-1-{4-[3,6-dihydropyridin-1(2H)-yl]-4-phenylbut-2-yn-1-yl}(S)-piperidine-3-carboxylate] (**rac-(R,S)-31h**) and rac-[ethyl (R)-1-{4-[3,6-dihydropyridin-1(2H)-yl]-4-phenylbut-2-yn-1-yl}(R)-piperidine-3-carboxylate] (**rac-(R,R)-31h**).* GP2 was followed using **30** (293 mg, 1.50 mmol), CuBr (32.3 mg, 0.225 mmol), 1,2,3,6-tetrahydropyridine (0.20 mL, 2.10 mmol) and benzaldehyde (0.27 mL, 2.70 mmol). Purification by column chromatography (PE/EtOAc = 1:1) afforded **31h** as mixture of both diastereomeric racemates (341 mg, 62%) as yellow oil: TLC: R_f = 0.45 (PE/EtOAc = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.44 (qd, J = 11.6/4.0 Hz, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 1.53–1.70 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.73–1.84 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.89–1.99 (m, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 2.06–2.22 (m, 2 H, $NCH_2CHCHCH_2CH_2$), 2.27 (td, J = 11.0/3.1 Hz, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.44 (t, J = 10.6 Hz, 1 H, $NCH_{ax}H_{eq}CHCH_2$), 2.54–2.70 (m, 3 H, $NCH_2CH_{ax}CH_2$ and $NCH_2CHCHCH_2CH_2$), 2.77–2.86 (m, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 3.01–3.15 (m, 3 H, $NCH_{ax}H_{eq}CHCH_2$ and $NCH_2CHCHCH_2CH_2$), 3.45–3.51 (m, 2 H, $NCHPhCCCH_2N$), 4.08–4.18 (m, 2 H, OCH_2CH_3), 4.74 (s_{br}, 1 H, $NCHPhCCCH_2N$), 5.66 (m, 1 H, $NCH_2CHCHCH_2CH_2$), 5.72 (m, 1 H, $NCH_2CHCHCH_2CH_2$), 7.22–7.30 (m, 1H, ArH), 7.30–7.38 (m, 2H, ArH), 7.56–7.63 (m, 2 H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.2, 24.6, 26.5, 41.9, 46.3, 47.8, 49.0, 52.4, 54.4, 60.3, 61.2, 81.1, 82.4, 125.0, 125.6, 127.5, 128.1, 128.5, 138.4, 174.0; IR (neat) 3031, 2939, 2807, 1731, 1466, 1449, 1319, 1268, 1223, 1181, 1152, 1132, 1095, 1029, 999, 973, 950, 727, 697, 654, 626 cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{31}N_2O_2^+$ $[M+H]^+$ 367.2386, found 367.2386; stereochemistry has not been assigned.

*1-(1,5,5-triphenylpent-2-yn-1-yl)-1,2,3,6-tetrahydropyridine (**29l**).* To a Schlenk flask was added CuBr (66 mg, 0.460 mmol). Then dioxane anhyd (12.0 mL/mmol) was added, followed by benzaldehyde (0.24 mL, 2.40 mmol), 1,2,3,6-tetrahydropyridine (0.22 mL, 2.40 mmol), **27b** (557 mg, 2.00 mmol) and $BF_3{\cdot}OEt_2$ (591 mg, 2.00 mmol). The reaction mixture was stirred for 10 min at rt and at 50 °C for 25 hours. The completion of the reaction was monitored by TLC. After cooling to rt the reaction mixture was added to a 1:1 solution of saturated potassium sodium tartrate solution and saturated sodium hydrogen carbonate solution (44.0 mL/mmol) and extracted 5 times with EtOAc. The combined organic phases were then filtrated, dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography (PE/EtOAc = 9:1) to afford **29l** (203 mg, 27%) as colorless crystals: mp = 94.6 °C; TLC: R_f = 0.66 (PE/EtOAc = 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.95–2.14 (m, 2 H, $NCH_2CHCHC\mathit{H}_2CH_2$), 2.29–2.43 (m, 2 H, $NCH_2CHCHCH_2C\mathit{H}_2$), 2.75–2.92 (m, 2 H, $NC\mathit{H}_2CHCHCH_2CH_2$), 3.05 (dd, J = 7.8/2.1 Hz, 2 H, $CHC\mathit{H}_2CC$), 4.27 (t, J = 7.8 Hz, 1 H, $C\mathit{H}CH_2CC$), 4.54 (t, J = 2.1 Hz, 1 H, $NC\mathit{H}CC$), 5.57 (m, 1 H, $NCH_2C\mathit{H}CHCH_2CH_2$), 5.66 (m, 1 H, $NCH_2CHC\mathit{H}CH_2CH_2$), 7.15–7.26 (m, 5 H, ArH), 7.26–7.37 (m, 10 H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.9, 26.5, 45.8, 48.6, 50.7, 61.0, 77.7, 86.3, 124.7, 125.7, 126.5, 127.2, 127.9, 128.0, 128.4, 128.5, 138.5, 143.5; IR (neat) 3417, 3060, 3028, 2910, 2811, 1949, 1600, 1493, 1449, 1028, 727, 697 cm^{-1}; HRMS (ESI) m/z calcd for $C_{28}H_{28}N^+$ $[M+H]^+$ 378.2222, found 378.2222; synthesis based on the procedure of Ma et al.[27,34]

*N-allyl-N-(tert-butyl)-1,5,5-triphenylpent-2-yn-1-amine (**29m**).* To a Schlenk flask was added CuBr (43.0 mg, 0.300 mmol). Toluene anhyd (5.00 mL/mmol) was then added, followed by benzaldehyde (0.37 mL, 3.60 mmol), allyl(*tert*-butyl)amine (0.42 mL, 2.80 mmol), **27b** (557 mg, 2.00 mmol) and $BF_3{\cdot}OEt_2$ (591 mg, 2.00 mmol). The reaction

mixture was stirred at rt for 27 hours. The completion of the reaction was monitored by TLC. The reaction mixture was then filtrated over a short pad of silica gel and eluted with DCM. The crude product was purified by MPLC (PE, 5% EtOAc) on silica gel to afford **29m** as colorless resin (270 mg, 33%): TLC: R_f = 0.68 (PE/EtOAc = 19:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (s, 9 H, N*t-Bu*), 2.97–3.03 (m, 2 H, NCH_2CHCH_2), 3.05 (dd, J = 7.8/2.0 Hz, 2 H, NCHCCCH_2), 4.28 (t, J = 7.8 Hz, 1 H, CHCH_2CC), 4.57 (dq, J ≈ 10.1/1.8 Hz, 1 H, NCH_2CHCH_{cis}H$_{trans}$), 4.69 (dq, J = 17.2/1.8 Hz, 1 H, NCH_2CHCH$_{cis}$$H_{trans}$), 4.87 ($s_{br}$, 1 H, NC$H$CC), 5.38 (ddt, J = 17.2/10.1/5.9 Hz, 1 H, NCH_2CHCH_2), 7.10–7.25 (m, 5 H, ArH), 7.25–7.38 (m, 10 H, ArH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.0, 28.6, 48.5, 50.7, 53.0, 56.2, 81.4, 85.5, 112.6, 126.6, 126.6, 127.6, 128.1, 128.3, 128.6, 141.6, 142.1, 143.7; IR (neat) 3061, 3027, 2971, 2911, 1946, 1877, 1804, 1637, 1600, 1493, 1449, 1390, 1363, 1203, 910, 733, 697 cm^{-1}; HRMS (ESI) m/z calcd for $C_{30}H_{34}N^+$ $[M+H]^+$ 408.2691, found 408.2695; synthesis based on the procedure of Ma et al.[27,34]

*rac-[Ethyl (R)-1-{4-[allyl(tert-butyl)amino]-4-phenylbut-2-yn-1-yl}(S)-piperidine-3-carboxylate] (**rac-(R,S)-31g**) and rac-[ethyl (R)-1-{4-[allyl(tert-butyl)amino]-4-phenylbut-2-yn-1-yl}(R)-piperidine-3-carboxylate] (**rac-(R,R)-31g**)*. To a Schlenk flask was added CuBr (21.5 mg, 0.150 mmol). Toluene anhyd (5.0 mL/mmol) was then added, followed by benzaldehyde (0.18 mL, 1.80 mmol), allyl(*tert*-butyl)amine (0.21 mL, 1.40 mmol), $BF_3{\cdot}OEt_2$ (296 mg, 1.00 mmol) and **30** (195 mg, 1.00 mmol). The reaction mixture was stirred at 50 °C for 20 hours. The completion of the reaction was monitored by TLC. After cooling to rt, the reaction mixture was filtrated, washed with EtOAc and concentrated under vacuum. The crude product was then purified by column chromatography (PE/EtOAc = 1:1) to afford **31g** as mixture of both diastereomeric racemates (118 mg, 30%) as yellow oil: TLC: R_f = 0.69 (PE/EtOAc =

1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.25 (s, 9 H, N*t-Bu*), 1.37–1.53 (m, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 1.55–1.71 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.73–1.85 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.91–2.00 (m, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 2.29 (tt, J = 11.1/3.3 Hz, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.40–2.51 (m, 1 H, $NCH_{ax}H_{eq}CHCH_2$), 2.55–2.68 (m, 1 H, $NCH_2CH_{ax}CH_2$), 2.79–2.89 (m, 1 H, -$NCH_{ax}H_{eq}CH_2CH_2CH$), 3.05–3.14 (m, 1 H, -$NCH_{ax}H_{eq}CHCH_2$-), 3.26–3.33 (m, 2 H, $NCH_2CH{=}CH_{trans}H_{cis}$), 3.41–3.54 (m, 2 H, $NCHCCCH_2N$), 4.14 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.63 (dq, J = 10.2/1.8 Hz, 1 H, $NCH_2CH{=}CH_{trans}H_{cis}$), 4.79 (dq, J = 17.3/1.8 Hz, 1 H, $NCH_2CH{=}CH_{trans}H_{cis}$), 5.08 ($s_{br}$, 1 H, $NCHCCCH_2N$), 5.41–5.56 (m, 1 H, $NCH_2CH{=}CH_2$), 7.16–7.25 (m, 1 H, ArH), 7.25–7.33 (m, 2 H, ArH), 7.55–7.70 (m, 2 H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.2, 24.6, 26.6, 28.7, 42.0, 47.9, 48.8, 52.5, 53.1, 54.4, 56.3, 60.3, 82.0, 85.0, 112.9, 126.8, 127.6, 128.2, 141.3, 141.8, 174.0; IR (neat) 3061, 2973, 2941, 2802, 1947, 1732, 1637, 1600, 1491, 1467, 1449, 1415, 1391, 1365, 1322, 1255, 1217, 1203, 1181, 1152, 1133, 1096, 1068, 1046, 1030, 994, 911, 750, 731, 696 cm^{-1}; HRMS (ESI) m/z calcd for $C_{25}H_{37}N_2O_2^+$ $[M+H]^+$ 397.2855, found 397.2857; synthesis procedure based on a procedure published by Ma et al.,[27,34] stereochemistry has not been assigned.

*rac-[Ethyl (R)-1-{4-[allyl(tert-butyl)amino]-4-(naphthalen-2-yl)but-2-yn-1-yl}(R)-piperidine-3-carboxylate] (**rac-(R,R)-31i**) and rac-[ethyl (R)-1-{4-[allyl(tert-butyl)amino]-4-(naphthalen-2-yl)but-2-yn-1-yl}(S)-piperidine-3-carboxylate] (**rac-(R,S)-31i**).* GP2 was followed applying CuBr (129 mg, 0.900 mmol, 0.3 equiv), toluene abs. (12 mL), 2-naphthaldehyde (843 mg, 5.40 mmol), allyl(*tert*-butyl)amine (0.63 mL, 4.2 mmol), $BF_3{\cdot}OEt_2$ (0.66 mL, 3.0 mmol, instead of molecular sieve) and **30** (586 mg, 3.00 mmol) at 50 °C overnight. The crude product was purified by column chromatography (PE/EtOAc = 8:2) to afford **31i** as mixture of both

diastereomeric racemates as pale yellow resin (278 mg, 21%): TLC: R_f = 0.21 (PE/EtOAc = 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.30 (s, 9 H, $NC(CH_3)_3$), 1.41–1.54 (m, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 1.60–1.73 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.81 (dq, J = 14.8/3.6 Hz, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.92–2.05 (m, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 2.29–2.41 (m, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.47–2.58 (m, 1 H, $NCH_{ax}H_{eq}CHCH_2$), 2.60–2.71 (m, 1 H, $NCH_2CH_{ax}CH_2$), 2.84–2.95 (m, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 3.16 (d_{br}, J = 10.7 Hz, 1 H, $NCH_{ax}H_{eq}CHCH_2$), 3.27–3.40 (m, 2 H, $NCH_2CH=CH_2$), 3.55 (s, 2 H, $NCHCCCH_2N$), 4.14 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.56 (dq, J = 10.2/1.7 Hz, 1 H, $NCH_2CH=CH_{trans}H_{cis}$), 4.77 (dq, J = 17.2/1.7 Hz, 1 H, $NCH_2CH=CH_{trans}H_{cis}$), 5.22 (s, 1 H, $NCHCCCH_2N$), 5.36–5.52 (m, 1 H, $NCH_2CH=CH_2$), 7.40–7.49 (m, 2 H, ArH), 7.69–7.87 (m, 4 H, ArH), 8.09 (s, 1 H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.4, 24.8, 26.8, 28.9, 42.1, 48.1, 48.8, 52.6/52.7, 53.4, 54.5/54.6, 56.6, 60.5, 82.4, 85.1, 113.1, 125.7, 125.9, 126.6, 127.3, 127.6, 128.2, 132.8, 133.2, 139.3, 141.4, 174.1; IR (neat) ṽ 3057, 2972, 2940, 2869, 2805, 1731, 1634, 1602, 1506, 1467, 1451, 1416, 1391, 1364, 1325, 1275, 1239, 1217, 1201, 1182, 1152, 1133, 1095, 1031, 995, 910, 860, 814, 788, 735 cm^{-1}; HRMS (ESI) m/z calcd for $C_{29}H_{39}N_2O_2^+$ $[M+H]^+$ 447.3012, found 447.3005; stereochemistry has not been assigned.

*rac-[Ethyl (R)-1-{4-[3,6-dihydropyridin-1(2H)-yl]-4-(naphthalen-2-yl)but-2-yn-1-yl}(R)-piperidine-3-carboxylate] (**rac-(R,R)-31j**) and rac-[ethyl (R)-1-{4-[3,6-dihydropyridin-1(2H)-yl]-4-(naphthalen-2-yl)but-2-yn-1-yl}(S)-piperidine-3-carboxylate] (**rac-(R,S)-31j**).* GP2 was followed applying CuBr (43 mg, 0.30 mmol), toluene abs. (8 mL), 2-naphthaldehyde (562 mg, 3.60 mmol), 1,2,3,4-tetrahydropyridine (0.26 mL, 2.8 mmol) and **30** (391 mg, 2.00 mmol). The crude product was purified by column chromatography (PE/EtOAc = 7:3) to afford **31j** as mixture of both diastereomeric

racemates as pale yellow resin (695 mg, 83%): TLC: R_f = 0.13 (PE/EtOAc = 7:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (t, J = 7.1 Hz, 1.5 H, OCH_2CH_3, dia 1 or dia 2), 1.23 (t, J = 7.1 Hz, 1.5 H, OCH_2CH_3, dia 1 or dia 2), 1.47 (qd, J = 11.8/3.5 Hz, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 1.59–1.68 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.76–1.83 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.96 (dq, J = 12.8/4.1 Hz, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 2.08–2.22 (m, 2 H, $NCH_2CH_2CHCHCH_2$), 2.31 (td, J = 11.0/3.1 Hz, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.49 (t, J = 10.6 Hz, 0.5 H, $NCH_{ax}H_{eq}CHCH_2$, dia 1 or dia 2), 2.50 (t, J = 10.6 Hz, 0.5 H, $NCH_{ax}H_{eq}CHCH_2$, dia 1 or dia 2), 2.58–2.73 (m, 3 H, $NCH_2CH_{ax}CH_2$ and $NCH_2CH_2CHCHCH_2$), 2.81–2.89 (m, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 3.03–3.20 (m, 3 H, $NCH_{ax}H_{eq}CHCH_2$ and $NCH_2CH_2CHCHCH_2$), 3.48–3.57 (m, 2 H, $NCHCCCH_2N$), 4.10–4.17 (m, 2 H, OCH_2CH_3), 4.88 (t, J = 1.3 Hz, 1 H, $NCHCCCH_2N$), 5.60–5.79 (m, 2 H, $NCH_2CH_2CHCHCH_2$), 7.41–7.51 (m, 2 H, ArH), 7.72 (dd, J = 8.5/1.7 Hz, 1 H, ArH), 7.77–7.90 (m, 3 H, ArH), 8.06 (s, 1 H, ArH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.2, 24.6, 26.6, 26.6, 42.0, 46.3/46.4, 47.8, 49.3/49.3, 52.5, 54.5/54.5, 60.3, 61.4, 81.2/81.2, 82.8/82.8, 125.1, 125.7, 125.9, 126.0, 126.6, 127.3, 127.6, 127.8, 128.1, 133.0, 133.1, 136.2, 174.0; IR (neat) ṽ 3029, 2937, 2805, 1729, 1601, 1507, 1465, 1449, 1366, 1349, 1316, 1223, 1181, 1152, 1130, 1095, 1028, 999, 975, 955, 902, 860, 824, 795, 781, 761, 736 cm^{-1}; HRMS (ESI) m/z calcd for $C_{27}H_{33}N_2O_2^+$ $[M+H]^+$ 417.2542, found 417.2538; stereochemistry has not been assigned.

*rac-[Ethyl (R)-1-{4-([1,1'-biphenyl]-2-yl)-4-[allyl(tert-butyl)amino]but-2-yn-1-yl}(R)-piperidine-3-carboxylate] (**rac-(R,R)-31k**) and rac-[ethyl (R)-1-{4-([1,1'-biphenyl]-2-yl)-4-[allyl(tert-butyl)amino]but-2-yn-1-yl}(S)-piperidine-3-carboxylate] (**rac-(R,S)-31k**).* GP2 was followed applying CuBr (86 mg, 0.60 mmol), dioxane abs. (8.0 mL), [1,1'-biphenyl]-2-carbaldehyde (0.58 mL, 3.6 mmol), allyl(*tert*-butyl)amine (0.42 mL, 2.8 mmol) and **30** (391 mg, 2.00 mmol). After stirring for 1 h at rt, the mixture was heated

to 50 °C, $BF_3{\cdot}OEt_2$ (0.51 mL, 2.00 mmol) was added and the reaction mixture stirred at 50 °C overnight. The crude product was purified by flash column chromatography (PE/EtOAc = 7:3) to afford **31k** as mixture of both diastereomeric racemates as pale yellow resin (200 mg, 21%): TLC: R_f = 0.32 (PE/EtOAc = 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74 (s, 9 H, *t*-Bu),1.25 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3, dia 1 and dia 2), 1.44 (qd, *J* = 11.9/4.3 Hz, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 1.54–1.69 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.73–1.84 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.90–2.02 (m, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 2.25 (ddt, *J* = 11.2/7.9/4.1 Hz, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.42 (t, *J* = 10.7 Hz, 1 H, $NCH_{ax}H_{eq}CHCH_2$), 2.55–2.66 (m, 1 H, $NCH_2CH_{ax}CH_2$), 2.82 (d_{br}, *J* = 11.4 Hz, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 3.01–3.21 (m, 2 H, $NCH_{ax}H_{eq}CHCH_2$ and $NCH_2CH{=}CH_2$), 3.33 (ddt, *J* = 17.2/5.5/1.8 Hz, 1 H, $NCH_2CH{=}CH_2$), 3.37–3.49 (m, 2 H, $NCHCCCH_2N$), 4.14 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 4.51 (dq, *J* = 10.1/1.7 Hz, 1 H, $NCH_2CH{=}CH_{trans}H_{cis}$), 4.60 (dq, *J* = 17.3/1.7 Hz, 1 H, $NCH_2CH{=}CH_{trans}H_{cis}$), 5.06–5.18 (m, 1 H, $NCH_2CH{=}CH_2$), 5.21 (t, *J* = 2.2 Hz, 1 H, $NCHCCCH_2N$), 7.07–7.13 (m, 1 H, ArH), 7.22–7.44 (m, 7 H, ArH), 7.81 (dt, *J* = 7.3/2.1 Hz, 1 H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.2, 24.6, 26.6, 27.4, 42.0, 47.1, 48.0, 50.5, 52.5/52.6, 54.5, 56.2, 60.3, 81.8, 86.0, 112.1, 126.7, 126.8, 126.9, 127.7, 129.3, 129.4, 129.7, 130.1, 138.4, 140.8, 141.9, 142.9, 174.0; IR (neat) $\tilde{\nu}$ 2956, 1732, 1475, 1439, 1390, 1364, 1309, 1281, 1252, 1214, 1199, 1182, 1152, 1133, 1095, 1071, 1031, 912, 753, 701 cm^{-1}; HRMS (ESI) m/z calcd for $C_{31}H_{41}N_2O_2^+$ $[M+H]^+$ 473.3168, found 473.3166; stereochemistry has not been assigned.

*rac-[Ethyl (R)-1-{4-([1,1'-biphenyl]-2-yl)-4-[3,6-dihydropyridin-1(2H)-yl]but-2-yn-1-yl}(R)-piperidine-3-carboxylate] (**rac-(R,R)-31l**) and rac-[ethyl (R)-1-{4-([1,1'-biphenyl]-2-yl)-4-[3,6-dihydropyridin-1(2H)-yl]but-2-yn-1-yl}(S)-piperidine-3-carboxylate] (**rac-(R,S)-31l**).* GP2 was followed applying CuBr (21.5 mg, 0.15 mmol),

toluene abs. (5.00 mL), [1,1'-biphenyl]-2-carbaldehyde (0.29 mL, 1.8 mmol), 1,2,3,4-tetrahydropyridine (0.13 mL, 1.4 mmol) and **30** (195 mg, 1.00 mmol). The crude product was purified by column chromatography (PE/EtOAc = 8:2) to afford **31l** as mixture of both diastereomeric racemates as colorless resin (373 mg, 84%): TLC: R_f = 0.23 (PE/EtOAc = 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3 H, OCH_2CH_3, dia 1 and dia 2), 1.42 (qd, J = 11.3/3.5 Hz, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 1.51–1.66 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.75 (dp, J = 13.1/3.8 Hz, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.87–1.97 (m, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 1.96–2.17 (m, 2 H, $NCH_2CH{=}CHCH_2CH_2$), 2.22 (td, J = 11.0/3.0 Hz, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.34–2.49 (m, 2 H, $NCH_{ax}H_{eq}CHCH_2$ and $NCH_2CH{=}CHCH_2CH_2$), 2.52–2.68 (m, 2 H, $NCH_2CH_{ax}CH_2$ and $NCH_2CH{=}CHCH_2CH_2$), 2.76 (d_{br}, J = 11.3 Hz, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.85–3.08 (m, 3 H, $NCH_{ax}H_{eq}CHCH_2$ and $NCH_2CH{=}CHCH_2CH_2$), 3.34–3.48 (m, 2 H, $NCHCCCH_2N$), 4.12 (q, J = 7.1 Hz, 2 H, OCH_2CH_3, dia 1 and dia 2), 4.52 (t, J = 1.9 Hz, 1 H, $NCHCCCH_2N$), 5.55–5.72 (m, 2 H, $NCH_2CH{=}CHCH_2CH_2$), 7.22–7.29 (m, 1 H, ArH), 7.29–7.42 (m, 5 H, ArH), 7.46–7.56 (m, 2 H, ArH), 7.72–7.81 (m, 1 H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.2, 24.5, 26.5/26.5, 41.9, 46.4, 47.7, 48.2, 52.4/52.4, 54.3, 58.1, 60.3, 81.7/81.7, 82.3/82.3, 124.8, 125.6, 126.8, 127.0, 127.4, 127.7, 129.2, 129.7, 130.3, 136.5, 141.1, 142.6, 174.0; IR (neat) ṽ 3057, 3030, 2938, 2909, 2864, 2804, 1731, 1477, 1466, 1449, 1367, 1347, 1315, 1279, 1252, 1222, 1181, 1152, 1132, 1095, 1047, 1029, 1009, 998, 973, 948, 774, 750, 702, 654 628, 617 cm^{-1}; HRMS (ESI) m/z calcd for $C_{29}H_{35}N_2O_2^+$ $[M+H]^+$ 443.2699, found 443.2702; stereochemistry has not been assigned.

*rac-[Ethyl (R)-1-{4-[allyl(tert-butyl)amino]hept-2-yn-1-yl}(R)-piperidine-3-carboxylate] (**rac-(R,R)-31m**) and rac-[ethyl (R)-1-{4-[allyl(tert-butyl)amino]hept-2-yn-1-yl}(S)-*

*piperidine-3-carboxylate] (**rac-(R,S)-31m**).* GP2 was followed applying CuBr (86 mg, 0.60 mmol, 0.30 equiv), dioxane abs. (8 mL), butyraldehyde (0.33 mL, 3.6 mmol), allyl(*tert*-butyl)amine (0.42 mL, 2.8 mmol) and **30** (391 mg, 2.00 mmol) at rt for 2 h. Then $BF_3 \cdot OEt_2$ (0.44 mL, 2.0 mmol) was added and the reaction mixture was heated to 50 °C for 3 h and was stirred at rt overnight. The crude product was purified by column chromatography (PE/EtOAc = 8:2) to afford **31m** as mixture of both diastereomeric racemates as yellow oil (235 mg, 32%): TLC: R_f = 0.31 (PE/EtOAc = 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.1 Hz, 3 H, $NCHCH_2CH_2CH_3$), 1.11 (s, 9 H, $N(CH_3)_3$), 1.25 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.35–1.52 (m, 5 H, $NCH_2CHCH_{ax}H_{eq}$ and $NCHCH_2CH_2CH_3$), 1.55–1.67 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.72–1.81 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.90–2.00 (m, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 2.19 (tt, J = 11.2/2.9 Hz, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.34 (t, J = 10.5 Hz, 1 H, $NCH_{ax}H_{eq}CHCH_2$), 2.54–2.64 (m, 1 H, $NCH_2CH_{ax}CH_2$), 2.77 (dt_{br}, J = 11.2/3.5 Hz, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.99–3.07 (m, 1 H, $NCH_{ax}H_{eq}CHCH_2$), 3.22–3.40 (m, 4 H, $NCHCCCH_2N$ and $NCH_2CH{=}CH_2$), 3.72 (t, J = 6.1 Hz, 1 H, $NCHCCCH_2N$), 4.14 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.92 (dd, J = 10.2/2.1 Hz, 1 H, $NCH_2CH{=}CH_{trans}H_{cis}$), 5.13 (dq, J = 16.4/2.1 Hz, 1 H, $NCH_2CH{=}CH_{trans}H_{cis}$), 5.87 (ddt, J = 16.4/10.2/5.3 Hz, 1 H, $NCH_2CH{=}CH_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 13.9, 14.4, 19.9, 24.7, 26.7, 28.3, 39.6, 42.1, 47.9, 48.1, 49.8, 52.5/52.5, 54.4/54.4, 56.0, 60.5, 78.6, 88.2, 112.9, 142.6, 174.2; IR (neat) $\tilde{\nu}$ 2958, 2871, 2804, 1734, 1643, 1467, 1453, 1391, 1365, 1309, 1242, 1218, 1202, 1182, 1152, 1133, 1094, 1031, 995, 910 cm^{-1}; HRMS (ESI) m/z calcd for $C_{22}H_{39}N_2O_2^+$ $[M+H]^+$ 363.3012, found 363.3005; stereochemistry has not been assigned.

*rac-[Ethyl (R)-1-{4-[3,6-dihydropyridin-1(2H)-yl]hept-2-yn-1-yl}(R)-piperidine-3-carboxylate] (**rac-(R,R)-31n**) and rac-[ethyl (R)-1-{4-[3,6-dihydropyridin-1(2H)-yl]hept-*

*2-yn-1-yl}(S)-piperidine-3-carboxylate] (**rac-(R,S)-31n**).* GP2 was followed using CuBr (32.3 mg, mmol, 0.225 equiv), toluene abs. (6 mL), butyraldehyde (0.25 mL, 2.7 mmol), 1,2,3,4-tetrahydropyridine (0.20 mL, 2.1 mmol) and **30** (293 mg, 1.50 mmol). The crude product was purified by column chromatography (PE/EtOAc = 8:2) to afford **31n** as mixture of both diastereomeric racemates as yellow oil (385 mg, 77%): TLC: R_f = 0.17 (PE/EtOAc = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, J = 7.3 Hz, 3 H, $NCHCH_2CH_2CH_3$), 1.25 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 1.35–1.72 (m, 6 H, $NCHCH_2CH_2CH_3$, $NCH_2CHCH_{ax}H_{eq}$, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.72–1.82 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.89–2.00 (m, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 2.09–2.30 (m, 3 H, $NCH_2CH{=}CHCH_2CH_2$ and $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.35 (t, J = 10.7 Hz, 1 H, $NCH_{ax}H_{eq}CHCH_2$), 2.48–2.65 (m, 2 H, $NCH_2CH_{ax}CH_2$ and $NCH_2CH{=}CHCH_2CH_2$), 2.69–2.86 (m, 2 H, $NCH_2CH{=}CHCH_2CH_2$ and $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.94–3.11 (m, 2 H, $NCH_{ax}H_{eq}CHCH_2$ and $NCH_2CH{=}CHCH_2CH_2$), 3.11–3.24 (m, 1 H, $NCH_2CH{=}CHCH_2CH_2$), 3.30–3.41 (m, 2 H, $NCHCCCH_2N$), 3.45 (t_{br}, J = 7.5 Hz, 1 H, $NCHCCCH_2N$), 4.13 (q, J = 7.0 Hz, 2 H, OCH_2CH_3), 5.62–5.82 (m, 2 H, $NCH_2CH{=}CHCH_2CH_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 13.8, 14.2, 20.0, 24.6, 26.5, 26.6, 35.7, 41.9, 46.6, 47.7, 48.5, 52.4/52.4, 54.3/54.3, 57.2, 60.3, 79.9, 83.0, 125.0, 125.5, 174.0; IR (neat) ṽ 3031, 2956, 2937, 2870, 2804, 1732, 1465, 1449, 1366, 1321, 1222, 1180, 1151, 1133, 1093, 1046, 1030 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{33}N_2O_2^+$ $[M+H]^+$ 333.2542, found 333.2534; stereochemistry has not been assigned.

*rac-[Ethyl (R)-1-{4-[3,6-dihydropyridin-1(2H)-yl]-5-methylhex-2-yn-1-yl}(R)-piperidine-3-carboxylate] (**rac-(R,R)-31o**) and rac-[ethyl (R)-1-{4-[3,6-dihydropyridin-1(2H)-yl]-5-methylhex-2-yn-1-yl}(S)-piperidine-3-carboxylate] (**rac-(R,S)-31o**).* GP2 was followed applying CuBr (43 mg, 0.30 mmol), toluene abs. (8 mL), isobutyraldehyde (0.33 mL,

3.6 mmol), 1,2,3,4-tetrahydropyridine (0.26 mL, 2.8 mmol) and **30** (391 mg, 2.00 mmol). The crude product was purified by column chromatography (PE/EtOAc = 7:3) to afford **31o** as mixture of both diastereomeric racemates as colorless resin (651 mg, 98%): TLC: R_f = 0.26 (PE/EtOAc = 7:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (d, J = 6.6 Hz, 3 H, NCH(CH_3)$_2$), 1.06 (d, J = 6.6 Hz, 3 H, NCH(CH_3)$_2$), 1.25 (t, J = 7.1 Hz, 3 H, OCH$_2$CH_3), 1.42 (dq, J = 12.0/3.5 Hz, 1 H, NCH$_2$CHCH_{ax}H$_{eq}$), 1.55–1.65 (m, 1 H, NCH$_2$CH_{ax}H$_{eq}$CH$_2$CH), 1.73–1.80 (m, 1 H, NCH$_2$CH$_{ax}$$H_{eq}CH_2$CH), 1.86 (dp, J = 9.8/6.6 Hz, 1 H, NCH(CH$_3$)$_2$), 1.90–1.98 (m, 1 H, NCH$_2$CHCH$_{ax}$$H_{eq}$), 2.13–2.25 (m, 3 H, NCH$_2$CH=CHCH_2CH$_2$ and NCH_{ax}H$_{eq}$CH$_2$CH$_2$CH), 2.37 (t, J = 10.7 Hz, 1 H, NCH_{ax}H$_{eq}$CHCH$_2$), 2.45 (dt, J = 11.3/5.7 Hz, 1 H, NCH$_2$CH=CHCH$_2$CH_2), 2.59 (tt, J = 10.7/3.9 Hz, 1 H, NCH$_2$CH_{ax}CH$_2$), 2.72 (dt, J = 11.3/5.7 Hz, 1 H, NCH$_2$CH=CHCH$_2$CH_2), 2.75–2.83 (m, 1 H, NCH$_{ax}$$H_{eq}CH_2CH_2$CH), 2.94 (dt, J = 9.8/1.9 Hz, 1 H, NCHCCCH$_2$), 2.96–3.08 (m, 2 H, NCH$_{ax}$$H_{eq}$CHCH$_2$ and NCH_2CH=CHCH$_2$CH$_2$), 3.09–3.17 (m, 1 H, NCH_2CH=CHCH$_2$CH$_2$), 3.34–3.43 (m, 2 H, NCHCCCH_2N), 4.13 (qd, J = 7.1/1.0 Hz, 2 H, OCH_2CH$_3$), 5.62–5.78 (m, 2 H, NCH$_2$CH=CHCH$_2$CH$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.3, 20.0, 20.8, 24.7, 26.7, 26.7, 30.6, 42.1, 46.4, 47.8, 49.3, 52.5, 54.4/54.4, 60.5, 64.6, 80.2, 82.8, 125.1, 126.0, 174.2; IR (neat) ṽ 3032, 2955, 2868, 2806, 1732, 1637, 1466, 1450, 1381, 1366, 1321, 1260, 1222, 1181, 1152, 1133, 1095, 1031, 1001, 976, 956 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{33}N_2O_2^+$ $[M+H]^+$ 333.2542, found 333.2534; stereochemistry has not been assigned.

Synthesis of Allenes:

General Procedure 3: To a Schlenk tube CdI_2 (0.8 equiv) was added under argon atm. The CdI_2 was then heated with a heat gun under vacuum until the pale yellow solid turned to darker yellow. Chlorobenzene anhyd (8.0 mL/mmol) was added,

followed by the propargylic amine (1.0 equiv). The reaction mixture was stirred at 100/130 °C until all starting material was consumed (detection via TLC). After cooling to rt the crude product was purified by column chromatography to afford the corresponding allene.

*Penta-3,4-diene-1,1-diyldibenzene (**32**).* GP3 was followed applying CdI_2 (146 mg, 0.399 mmol), chlorobenzene anhyd (4.0 mL) and **29e** (166 mg, 0.500 mmol) at 130 °C for 2.00 h. The crude product was purified by column chromatography (PE/EtOAc = 9:1) to afford allene **32** (97.0 mg, 88%) as colorless resin: TLC: R_f = 0.83 (PE/EtOAc = 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76 (ddt, J = 7.9/7.1/2.9 Hz, 2 H, $CHCH_2CHCCH_2$), 4.04 (t, J = 7.9 Hz, 1 H, $CHCH_2CHCCH_2$), 4.56 (dt, J = 6.8/2.9 Hz, 2 H, $CHCH_2CHCCH_2$), 5.00 (p, J = 6.8 Hz, 1 H, $CHCH_2CHCCH_2$), 7.12–7.19 (m, 2 H, ArH), 7.19–7.30 (m, 8 H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 34.6, 51.2, 74.7, 88.2, 126.2, 128.0, 128.4, 144.2, 209.1; IR (neat) 3085, 3061, 3026, 2915, 1954, 1599, 1494, 1450, 1082, 1030, 845, 784, 751, 738, 699 cm^{-1}; HRMS (DEP/EI) m/z calcd for $C_{17}H_{16}$ 220.1252, found 220.1250.

*Undeca-1,2-diene (**43**).* GP3 was followed applying CdI_2 (146 mg, 0.399 mmol), chlorobenzene anhyd (4.0 mL) and **39** (132 mg, 0.500 mmol) at 130 °C for 3 h. The crude product was purified by column chromatography (PE, 5% EtOAc) to afford **43** (71.4 mg, 94%) as colorless oil: TLC: R_f = 0.73 (PE, 5% EtOAc); the analytical and spectroscopic data are consistent with those reported in literature.[43]

*6-Chlorohexa-1,2-diene (**44**).* GP3 was followed applying CdI_2 (146 mg, 0.399 mmol), chlorobenzene anhyd (4.0 mL) and **40** (114 mg, 0.500 mmol) at 130 °C for 3 h. The crude product was purified by column chromatography (PE) to afford **44** (48.2 mg, 83%) as colorless oil: TLC: R_f = 0.53 (PE, 4% EtOAc); analytical and spectroscopic data are consistent with those reported in literature.[44]

*Hepta-5,6-dienenitrile (**45**).* GP3 was followed applying CdI_2 (146 mg, 0.399 mmol), chlorobenzene anhyd (4.0 mL) and **41** (109 mg, 0.500 mmol) at 130 °C for 3 h. The crude product was purified by column chromatography (DCM) to afford **45** (52 mg, 97%) as colorless oil: TLC: R_f = 0.55 (DCM); analytical and spectroscopic data are consistent with those reported in literature.[45]

*[(Buta-2,3-dien-1-yloxy)methyl]benzene (**46**).* GP3 was followed applying CdI_2 (146 mg, 0.399 mmol), chlorobenzene anhyd (4.0 mL) and **42** (136 mg, 0.500 mmol) at 130 °C for 2.75 h. The crude product was purified by column chromatography (DCM) to afford **46** (76 mg, 95%) as colorless oil: TLC: R_f = 0.63 (DCM); analytical and spectroscopic data are consistent with those previously reported in literature.[46]

*Penta-3,4-diene-1,1,5-triyltribenzene (**47**).* GP3 was followed applying CdI_2 (146 mg, 0.399 mmol), chlorobenzene anhyd (4.0 mL) and **29m** (204 mg, 0.500 mmol) at 100 °C for 4.25 hours. The crude reaction mixture was purified by column chromatography (PE/DCM = 1:1) to afford allene **47** (113 mg, 76%) as colorless resin: TLC: R_f = 0.65 (PE, 5% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.83–2.97 (m, 2 H, CHC*H*$_2$CHCCH), 4.12 (t, *J* = 7.8 Hz, 1 H, C*H*CH$_2$CHCCH), 5.49 (q, *J* = 6.7 Hz, 1 H, CHCH$_2$C*H*CCH), 6.03 (dt, *J* = 6.7/2.8 Hz, 1 H, CHCH$_2$CHCC*H*), 6.91–7.03 (m, 2 H, ArH), 7.10–7.37 (m, 13 H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 35.3, 51.2, 93.3, 94.75, 126.24, 126.28, 126.6, 126.7, 127.9, 128.1, 128.4, 128.5, 128.5, 134.5, 144.2, 205.8; IR (neat) 3083, 3060, 3027, 2908, 1949, 1598, 1494, 1450, 1265, 1176, 1072, 1028, 912, 875, 790, 772, 741, 699, 629 cm^{-1}; HRMS (DEP/EI) m/z calcd for $C_{23}H_{20}$ 296.1565, found 296.1558.

*Ethyl 1-(buta-2,3-dien-1-yl)piperidine-3-carboxylate (**24**).* To a Schlenk tube ZnI_2 (255 mg, 0.799 mmol) was added. The ZnI_2 was then heated with a heat gun under vacuum until the pale yellow solid turned to darker yellow. Chlorobenzene anhyd (4.0

mL) was added, followed by **31a** (160 mg, 0.499 mmol). The reaction mixture was stirred at 100 °C for 4.00 h. After cooling to rt, the reaction mixture was directly purified by column chromatography (PE/EtOAc = 1:1) to afford allene **24** (52.6 mg, 50%) as pale yellow oil: TLC: R_f = 0.39 (PE/EtOAc = 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.43 (qd, J = 11.9/4.1 Hz, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 1.52–1.65 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.74 (dp, J = 13.4/3.6 Hz, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.91–1.99 (m, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 2.04 (td, J = 11.2/2.9 Hz, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.19 (t, J = 10.9 Hz, 1 H, $NCH_{ax}H_{eq}CHCH_2$), 2.56 (tt, J = 10.9/3.9 Hz, 1 H, $NCH_2CH_{ax}CH_2$), 2.82 (dt_{br}, J = 11.2/4.1 Hz, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.99–3.06 (m, 1 H, $NCH_{ax}H_{eq}CHCH_2$), 3.06 (dtd, J = 7.2/2.5/1.3 Hz, 2 H, NCH_2CHCCH_2), 4.13 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.71 (dt, J = 6.6/2.5 Hz, 2 H, NCH_2CHCCH_2), 5.16 (p, $J \approx$ 7.0 Hz, 1 H, NCH_2CHCCH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.2, 24.6, 27.0, 41.9, 53.2, 54.9, 57.7, 60.3, 74.8, 86.5, 174.2, 209.4; IR (neat) 3345, 2940, 2803, 1956, 1731, 1630, 1467, 1452, 1367, 1309, 1277, 1253, 1218, 1180, 1152, 1134, 1094, 1030, 844, 793 cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_{20}NO_2^+$ $[M+H]^+$ 210.1494, found 210.1488.

*rac-[Ethyl (R_a)-1-(4-phenylbuta-2,3-dien-1-yl)(S)-piperidine-3-carboxylate] (**rac-(R_a,S)-53a**) and rac-[ethyl (R_a)-1-(4-phenylbuta-2,3-dien-1-yl)(R)-piperidine-3-carboxylate] (**rac-(R_a,R)-53a**).* GP3 was followed applying CdI_2 (146 mg, 0.399 mmol), chlorobenzene anhyd (4.0 mL) and **31g** (198 mg, 0.499 mmol) at 100 °C for 3.75 h. The crude reaction mixture was purified by column chromatography (PE/EtOAc = 1:1) to afford allene **53a** as mixture of both diastereomeric racemates (117 mg, 82%) as pale yellow oil: TLC: R_f = 0.44 (PE/EtOAc = 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 1.5 H, OCH_2CH_3, dia 1 or dia 2), 1.26 (t, J = 7.1 Hz, 1.5 H, OCH_2CH_3, dia 1 or dia 2), 1.39–1.52 (m, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 1.53–

1.68 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.71–1.82 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.92–2.01 (m, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 2.07–2.17 (m, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.27 (t, *J* = 10.3 Hz, 0.5 H, $NCH_{ax}H_{eq}CHCH_2$, dia 1), 2.29 (t, *J* = 10.3 Hz, 0.5 H, $NCH_{ax}H_{eq}CHCH_2$, dia 2), 2.53–2.65 (m, 1 H, $NCH_2CH_{ax}CH_2$), 2.82–2.92 (m, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 3.04–3.10 (m, 0.5 H, $NCH_{ax}H_{eq}CHCH_2$, dia 2), 3.10–3.16 (m, 0.5 H, $NCH_{ax}H_{eq}CHCH_2$, dia 1), 3.16–3.26 (m, 2 H, NCH_2CHCCH), 4.09–4.18 (m, 2 H, OCH_2CH_3), 5.59 (q, *J* = 7.0 Hz, 0.5 H, NCH_2CHCCH, dia 1 or dia 2), 5.61 (q, *J* = 7.0 Hz, 0.5 H, NCH_2CHCCH, dia 1 or dia 2), 6.14–6.21 (m, 1 H, NCH_2CHCCH), 7.15–7.24 (m, 1 H, ArH), 7.25–7.37 (m, 4 H, ArH); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 14.2/14.3, 24.6/24.7, 26.8/26.9, 41.9/42.0, 53.2/53.2, 54.9/55.0, 57.8, 60.3, 91.3/91.4, 94.6/94.7, 126.8, 126.9, 128.6, 134.3, 174.1/174.1, 206.1/206.1; IR (neat) 3406, 2940, 2798, 1949, 1730, 1597, 1495, 1459, 1366, 1311, 1218, 1181, 1152, 1134, 1094, 1029, 911, 875, 774, 719, 691 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{24}NO_2^+$ $[M+H]^+$ 286.1807, found 286.1801; stereochemistry has not been assigned.

*rac-{Ethyl (R_a)-1-[4-(naphthalen-2-yl)buta-2,3-dien-1-yl](R)-piperidine-3-carboxylate} (**rac-(R_a,R)-53b**) and rac-{ethyl (R_a)1-[4-(naphthalen-2-yl)buta-2,3-dien-1-yl](S)-piperidine-3-carboxylate} (**rac-(R_a,S)-53b**).* GP3 was followed applying CdI_2 (146 mg, 0.399 mmol), chlorobenzene abs. (4 mL) and **31i** (223 mg, 0.500 mmol) at 100 °C for 2.75 h and the crude product was purified by column chromatography (PE/EtOAc = 7:3) to afford **53b** as mixture of both diastereomeric racemates (128 mg, 76%) as pale yellow resin: TLC: R_f = 0.16 (PE/EtOAc = 7:3); ^1H NMR (400 MHz, CD_2Cl_2) *δ* 1.13 (t, *J* = 7.1 Hz, 1.5 H, OCH_2CH_3, dia 2), 1.15 (t, *J* = 7.1 Hz, 1.5 H, OCH_2CH_3, dia 1), 1.31–1.43 (m, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 1.43–1.57 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.60–1.72 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.83 (dt, *J* = 12.9/4.3 Hz, 1 H,

$NCH_2CHCH_{ax}H_{eq}$), 2.01–2.13 (m, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.21 (t, *J* = 10.7 Hz, 0.5 H, $NCH_{ax}H_{eq}CHCH_2$, dia 1), 2.24 (t, *J* = 10.7 Hz, 0.5 H, $NCH_{ax}H_{eq}CHCH_2$, dia 2), 2.41–2.54 (m, 1 H, $NCH_2CH_{ax}CH_2$), 2.68–2.83 (m, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.91–2.99 (m, 0.5 H, $NCH_{ax}H_{eq}CHCH_2$, dia 2), 2.99–3.07 (m, 0.5 H, $NCH_{ax}H_{eq}CHCH_2$, dia 1), 3.12 (dd, *J* = 7.2/2.4 Hz, 2 H, NCH_2CHCCH), 4.00 (qd, J = 7.1/0.6 Hz, 1 H, OCH_2CH_3, dia 2), 4.03 (q, J = 7.1 Hz, 1 H, OCH_2CH_3, dia 1), 5.59 (q, *J* = 6.8 Hz, 1 H, NCH_2CHCCH), 6.28 (dt, *J* = 6.3/2.4 Hz, 1 H, NCH_2CHCCH), 7.30–7.46 (m, 3 H, ArH), 7.58 (s, 1 H, ArH), 7.65–7.79 (m, 3 H, ArH); ^{13}C NMR (101 MHz, CD_2Cl_2) *δ* 14.6/14.6, 25.3, 27.4, 42.6/42.6, 53.8/53.8, 55.6, 58.3/58.3, 60.7/60.8, 92.6/92.6, 95.3/95.3, 125.2, 126.0, 126.2, 126.8, 128.2, 128.2, 128.7, 132.7, 133.2, 134.3, 174.5, 207.0/207.0; IR (neat) ṽ 3054, 2940, 2796, 1946, 1730, 1628, 1598, 1558, 1540, 1508, 1466, 1450, 1366, 1351, 1308, 1271, 1216, 1180, 1152, 1134, 1094, 1030, 949, 893, 857, 819, 752, 732 cm^{-1}; HRMS (ESI) m/z calcd for $C_{22}H_{26}NO_2^+$ $[M+H]^+$ 336.1964, found 336.1958; stereochemistry has not been assigned.

*rac-[Ethyl (R_a)-1-{4-[(1,1'-biphenyl)-2-yl]buta-2,3-dien-1-yl}(R)-piperidine-3-carboxylate] (**rac-(R_a,R)-53c**) and rac-[ethyl (R_a)-1-{4-[(1,1'-biphenyl)-2-yl]buta-2,3-dien-1-yl}(S)-piperidine-3-carboxylate] (**rac-(R_a,S)-53c**).* GP3 was followed applying CdI_2 (146 mg, 0.399 mmol), chlorobenzene abs. (4.00 mL) and **31l** (221 mg, 0.500 mmol) at 100 °C for 1.75 h and the crude product purified by column chromatography (PE/EtOAc = 7:3) to afford **53c** as mixture of both diastereomeric racemates (156 mg, 86%) as pale yellow resin: TLC: R_f = 0.39 (PE/EtOAc = 7:3); ^1H NMR (500 MHz, $CDCl_3$) *δ* 1.23 (t, *J* = 7.1 Hz, 1.5 H, OCH_2CH_3, dia 1 or dia 2), 1.25 (t, *J* = 7.1 Hz, 1.5 H, OCH_2CH_3, dia 1 or dia 2), 1.44 (qd, *J* = 11.8/3.8 Hz, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 1.52–1.65 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.70–1.81 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.87–2.02 (m, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 2.02–2.14 (m, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.25 (t, *J*

= 10.7 Hz, 1 H, NC$H_{ax}$$H_{eq}CHCH_2$), 2.52–2.63 (m, 1 H, NC$H_2CH_{ax}CH_2$), 2.79–2.89 (m, 1 H, NC$H_{ax}$$H_{eq}CH_2CH_2$CH), 3.08–3.01 (m, 0.5 H, NC$H_{ax}$$H_{eq}CHCH_2$, dia 1 or dia 2), 3.08–3.22 (m, 2.5 H, NCH_2CHCCHPh and NC$H_{ax}$$H_{eq}CHCH_2$, dia 1 or dia 2), 4.12 (q, *J* = 7.1 Hz, 1 H, OCH_2CH_3, dia 1), 4.14 (q, *J* = 7.1 Hz, 1 H, OCH_2CH_3, dia 2), 5.49–5.58 (m, 1 H, NCH_2C*H*CCH), 6.19–6.26 (m, 1 H, NCH_2CHCC*H*), 7.21–7.46 (m, 8 H, ArH), 7.50–7.56 (m, 1 H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 14.2/14.2, 24.6/24.6, 26.9/26.9, 42.0/42.0, 53.1/53.2, 55.0/55.0, 57.8/57.8, 60.3, 91.0/91.0, 92.8/92.8, 126.7, 127.1, 127.4/127.4, 127.5, 128.2, 129.7, 130.2, 131.7, 140.3/140.3, 140.8/140.8, 174.1/174.1, 206.5/206.6; IR (neat) ṽ 3428, 3057, 3024, 2939, 2855, 2796, 1947, 1730, 1596, 1480, 1466, 1450, 1435, 1366, 1342, 1309, 1217, 1181, 1151, 1133, 1095, 1047, 1030, 1008, 881, 770, 746, 702 cm^{-1}; HRMS (ESI) m/z calcd for $C_{24}H_{28}NO_2^+$ $[M+H]^+$ 362.2120, found 362.2118; stereochemistry has not been assigned.

*rac-[Ethyl (R_a)-1-(hepta-2,3-dien-1-yl)(R)-piperidine-3-carboxylate] (**rac-(R_a,R)-53d**) and rac-[ethyl (R_a)-1-(hepta-2,3-dien-1-yl)(S)-piperidine-3-carboxylate] (**rac-(R_a,S)-53d**).* GP3 was followed applying CdI_2 (146 mg, 0.399 mmol), chlorobenzene abs. (4 mL) and **31n** (166 mg, 0.500 mmol) at 100 °C for 1.5 h and the crude product was purified by column chromatography (PE/EtOAc = 7:3) to afford **53d** as mixture of both diastereomeric racemates (113 mg, 90%) as colorless oil: TLC: R_f = 0.25 (PE/EtOAc = 7:3); ^{1}H NMR (500 MHz, CD_2Cl_2) *δ* 0.84 (t, *J* = 7.4 Hz, 3 H, $CH_2CH_2CH_3$), 1.15 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 1.28–1.39 (m, 3 H, $CH_2CH_2CH_3$ and $NCH_2CHCH_{ax}H_{eq}$), 1.45 (dddt, *J* = 13.0/11.6/10.7/3.9 Hz, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.58–1.66 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.77–1.84 (m, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 1.86–1.98 (m, 3 H, $CH_2CH_2CH_3$ and , $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.05 (t, *J* = 10.6 Hz, 0.5 H, $NCH_{ax}H_{eq}CHCH_2$, dia 1), 2.09 (t, *J* = 10.6 Hz, 0.5 H, $NCH_{ax}H_{eq}CHCH_2$, dia 2), 2.42

(ddtd, *J* = 11.0/10.1/3.9/1.0 Hz, 1 H, $NCH_2CH_{ax}CH_2$), 2.63–2.72 (m, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.84–2.96 (m, 3 H, NCH_2CHCCH and $NCH_{ax}H_{eq}CHCH_2$), 4.01 (qd, *J* = 7.1/0.8 Hz, 2 H, OCH_2CH_3), 4.92–5.10 (m, 2 H, NCH_2CHCCH); ^{13}C NMR (126 MHz, CD_2Cl_2) *δ* 14.0, 14.6, 22.9/23.0, 25.2/25.2, 27.5/27.5, 31.4/31.4, 42.6/42.6, 53.7/53.8, 55.5/55.6, 58.9/59.0, 60.7, 88.1/88.1, 91.2/91.2, 174.6/174.6, 205.6/205.7; IR (neat) ṽ 2957, 2935, 2871, 2797, 1962, 1733, 1466, 1454, 1367, 1335, 1309, 1274, 1218, 1181, 1152, 1134, 1095, 1047, 1031, 995, 960, 877, 863, 795 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{26}NO_2^+$ $[M+H]^+$ 252.1964, found 252.1957; stereochemistry has not been assigned.

*rac-[Ethyl (R_a)-1-(5-methylhexa-2,3-dien-1-yl)(R)-piperidine-3-carboxylate] (**rac-(R_a,R)-53e**) and rac-[ethyl (R_a)-1-(5-methylhexa-2,3-dien-1-yl)(S)-piperidine-3-carboxylate] (**rac-(R_a,S)-53e**).* GP3 was followed applying CdI_2 (146 mg, 0.399 mmol), chlorobenzene abs. (4 mL) and **31o** (166 mg, 0.500 mmol) at 100 °C for 1.5 h. The crude product was purified by column chromatography (PE/EtOAc = 7:3) to afford **53e** as mixture of both diastereomeric racemates (105 mg, 84%) as colorless oil: TLC: R_f = 0.24 (PE/EtOAc = 7:3); ^1H NMR (400 MHz, CD_2Cl_2) *δ* 1.01 (dd, *J* = 6.8/0.7 Hz, 6 H, $CH(CH_3)_2$), 1.22 (t, *J* = 7.1 Hz, 1.8 H, OCH_2CH_3, dia 1), 1.23 (t, *J* = 7.1 Hz, 1.2 H, OCH_2CH_3, dia 2), 1.34–1.47 (m, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 1.47–1.59 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.66–1.75 (m, 1 H, $NCH_2CH_{ax}H_{eq}CH_2CH$), 1.84–1.95 (m, 1 H, $NCH_2CHCH_{ax}H_{eq}$), 2.03 (td, *J* = 11.1/3.0 Hz, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.12 (t, *J* = 10.7 Hz, 0.6 H, $NCH_{ax}H_{eq}CHCH_2$, dia 1), 2.19 (t, *J* = 10.7 Hz, 0.4 H, $NCH_{ax}H_{eq}CHCH_2$, dia 2), 2.22–2.37 (m, 1 H, $NCH(CH_3)_2$), 2.45–2.55 (m, 1 H, $NCH_2CH_{ax}CH_2$), 2.71–2.81 (m, 1 H, $NCH_{ax}H_{eq}CH_2CH_2CH$), 2.90–3.09 (m, 3 H, NCH_2CHCCH and $NCH_{ax}H_{eq}CHCH_2$), 4.09 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 5.06–5.20 (m, 2 H, NCH_2CHCCH); ^{13}C NMR (101 MHz, CD_2Cl_2) *δ* 14.6, 22.9, 25.2/25.2,

27.5/27.5, 28.5/28.6, 42.5/42.6, 53.9, 55.6/55.7, 59.1/59.2, 60.7, 89.6/89.6, 98.9/99.0, 174.6/174.6, 203.9/204.0; IR (neat) ṽ 2959, 2868, 2796, 1960, 1733, 1620, 1466, 1453, 1366, 1344, 1303, 1217, 1181, 1152, 1134, 1095, 1031, 995, 874 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{26}NO_2^+$ $[M+H]^+$ 252.1964, found 252.1957; stereochemistry has not been assigned.

Supporting Information: Overview of the procedures applied for the propargylic amine synthesis, additional data for the influence of the catalyst loading on the allene formation, amine reactivity study with nipecotic acid derived propargylic amines, ^1H NMR experiment to investigate ZnI_2 coordination to **29g** and copies of the ^1H and ^{13}C NMR spectra.

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