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Intramolecular Kulinkovich–de Meijere reactions of various disubstituted alkenes bearing amide groups

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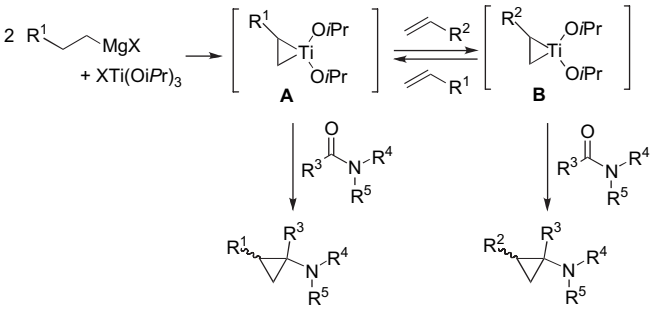
ABSTRACT

A range of amides fitted with (*E*) or (*Z*) disubstituted alkene groups were prepared and evaluated in intramolecular Kulinkovich–de Meijere reactions. The corresponding aminocyclopropanes were obtained with high diastereoselectivity. Good yields could be achieved with substrates bearing suitable substitutions at the olefin moieties.

1. Introduction

The reaction of tertiary carboxylic amides with titanium alkoxides of the form $XTi(O^iPr)_3$ (X=Me, Cl, O^iPr) and excess amounts of Grignard reagents (normally more than 2 equiv when X≠Me) is a powerful method for the preparation of aminocyclopropanes (Kulinkovich–de Meijere reaction).[1–4] In the presence of alkenes, the putative intermediate titanacyclopropane species **A** initially formed can undergo ligand exchange to give complex **B**, which leads to cyclopropane products resulting from alkene–amide coupling (Scheme 1).[5,6] This process is essentially limited to monosubstituted alkenes, even using cyclic Grignard reagents such as *cyclo*-pentylmagnesium chloride or *cyclo*-hexylmagnesium chloride, which have been shown to generally drive the equilibrium towards the formation of complex **B**.[7] Good yields have nonetheless been obtained from disubstituted alkenes in the special cases where they were part of conjugated polyene systems or geometrically constrained rings.[8–10]

A few years ago, we reported a study dealing with intramolecular Kulinkovich–de Meijere reactions starting from a few (*Z*) and (*E*) *N*-hex-3-enyl acetamides.[11] Although these reactions were poorly efficient because of competitive intermolecular reactions, they were found to be totally diastereoselective. A mechanistic hypothesis was formulated to account for the stereochemistry of the desired products, supported by a study published afterwards by Casey et al.[12]



Scheme 1. Kulinkovich–de Meijere reactions, without or with alkene ligand exchange.

In order to improve these intramolecular reactions, we decided to investigate the effect of an additional functional group on the substrate. Indeed, a suitable group might coordinate to the titanium intermediate complex **C** and direct the ligand exchange elementary step (Scheme 2). Our strategy for a rapid access to various substrates was to prepare them by cross-metathesis from the parent compound *N*-but-3-enyl-*N*-phenylacetamide **1a**.

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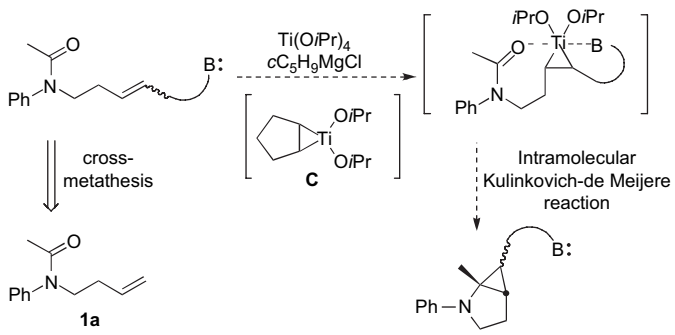


Scheme 2. Intramolecular Kulinkovich–de Meijere reaction with substrate-directed ligand exchange.

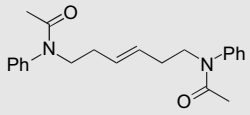
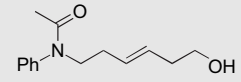
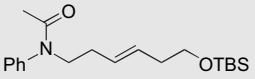
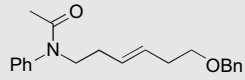
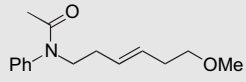
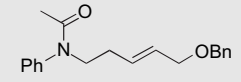
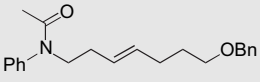
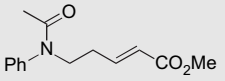
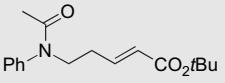
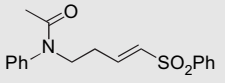
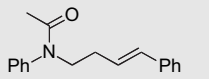
2. Results and discussion

Using Grubbs second generation catalyst, the cross-coupling metathesis of **1a** with various alkenes turned out to be of poor efficiency and feeble reproducibility due to double-bond migration and/or competition with homo-coupling processes. The use of a catalytic amount of 2,6-dichloro-1,4-benzoquinone (DQ), which inhibits double-bond migration,[13] gave satisfactory and reliable results in the preparation of **1b** as well as the cross-metathesis of **1a** with excess amounts of allyl alcohol, 3-buten-1-ol or 4-penten-1-ol, readily granting access to compounds **1c**–**h** (Table 1, entries 1–7).[14] We recently reported that a catalytic amount of a boron-based Lewis acid such as chlorocatecholborane could enhance the efficiency of cross-metathesis reactions involving nitrogen-containing alkenes.[15] Compounds **1i**–**l** were prepared in moderate to excellent yields using this method, with high diastereoselectivity in favour of the *E* isomers (Table 1, entries 8–11).

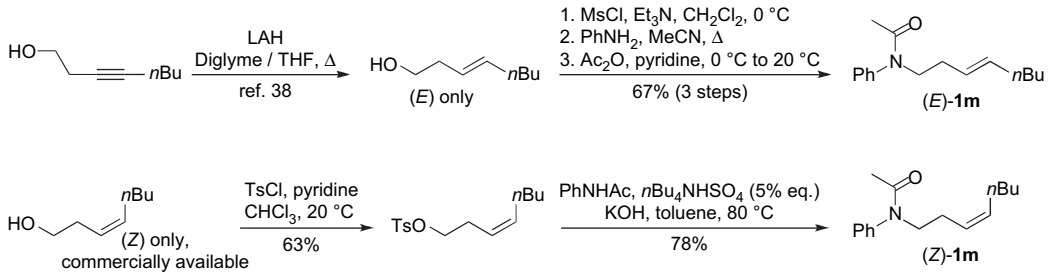
For comparison purposes, *n*-butyl derivatives (*E*)-**1m** and (*Z*)-**1m** were prepared in pure diastereoisomeric form following independent routes (Scheme 3). A range of pure (*Z*) alkenyl amides were also synthesised from alcohol (*Z*)-**1c**, obtained by standard cleavage of the *para*-methoxybenzyl (PMB) protected compound (*Z*)-**1n**.[16] This (*Z*) homoallylether, as well as the analogous benzyl derivative (*Z*)-**1e**, was prepared as a single diastereoisomer using the chemistry of Sato, namely via the intermediary of titanacyclopropene complexes generated from the corresponding alkynes (Scheme 4).[17,18]

With alkenyl amides **1b**–**q** in hand, they were submitted to the intramolecular Kulinkovich–de Meijere reaction conditions. The results are presented in Table 2, as well as that obtained from the reference compound **1a** (entry 1).[5,19] In agreement with our

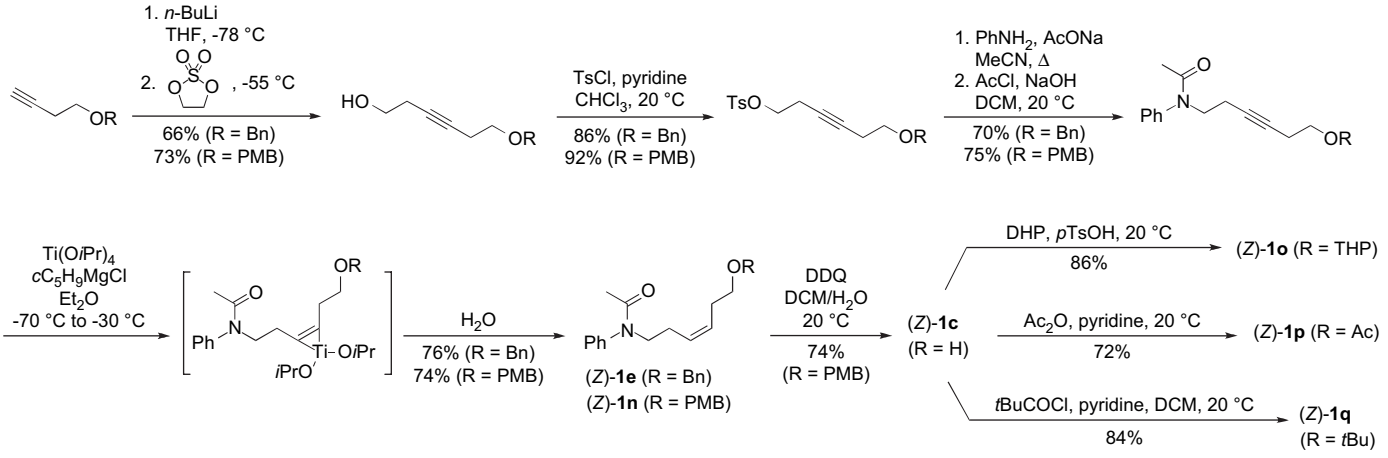
Table 1
Preparation of alkenyl amides **1b**–**l** by cross-metathesis using Grubbs second generation catalyst

Entry	Starting alkene(s)	Method[a]	Product		Yield % (*E*/*Z* ratio)
1	**1a**	A		**1b**	60 (85:15)
2	**1a** (1.0 equiv) and 3-buten-1-ol (4.0 equiv)	A		**1c**	71 (75:25)[b]
3	**1a** (1.0 equiv) and 3-buten-1-ol (4.0 equiv)	A		**1d**	66 (85:15)[c]
4	**1a** (1.0 equiv) and 3-buten-1-ol (4.0 equiv)	A		**1e**	59 (85:15)[c]
5	**1a** (1.0 equiv) and 3-buten-1-ol (4.0 equiv)	A		**1f**	60 (85:15)[c]
6	**1a** (1.0 equiv) and allyl alcohol (4.0 equiv)	A		**1g**	33 (89:11)[c]
7	**1a** (1.0 equiv) and 4-penten-1-ol (4.0 equiv)	A		**1h**	45 (80:20)[c]
8	**1a** (1.0 equiv) and methyl acrylate (1.0 equiv)	B		**1i**	91 (>98:2)
9	**1a** (1.0 equiv) and *tert*-butyl acrylate (1.0 equiv)	B		**1j**	72 (>98:2)
10	**1a** (1.0 equiv) and phenylvinylsulfone (1.0 equiv)	B		**1k**	44 (>98:2)
11	**1a** (1.0 equiv) and styrene (1.0 equiv)	B		**1l**	44 (>98:2)

[a] Method A: the cross-metathesis reaction was performed in the presence of a catalytic amount of DQ. Method B: reaction was performed in the presence of a catalytic amount of chlorocatecholborane (see Section 4 for details).
[b] Combined yield for the cross-metathesis reaction, protection of the alcohol function as a *tert*-butyldimethylsilyl ether **1d**, purification and deprotection under acidic conditions (see Ref. 14).
[c] Combined yield for the cross-metathesis reaction and protection of the alcohol function either as a *tert*-butyldimethylsilyl, a benzyl or a methyl ether (see Ref. 14).



Scheme 3. Synthesis of alkenes (*E*)-**1m** and (*Z*)-**1m**.



Scheme 4. Synthesis of (*Z*) alkenes **1c**, **1e** and **1n**–**1q**.

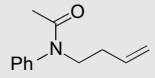
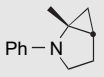
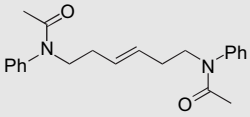
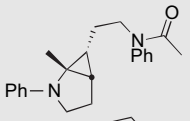
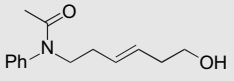
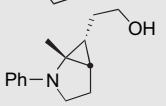
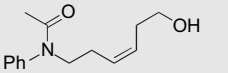
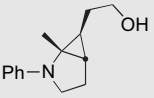
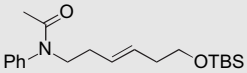
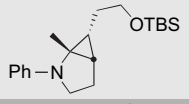
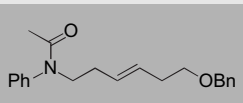
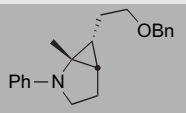
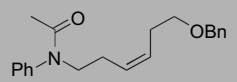
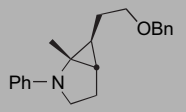
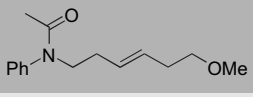
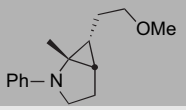
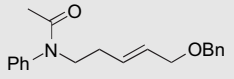
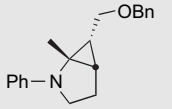
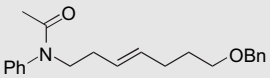
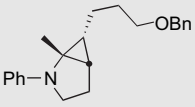
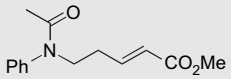
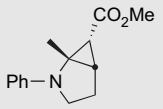
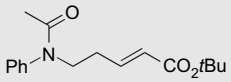
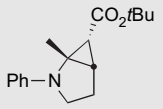
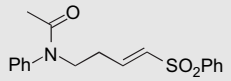
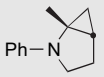
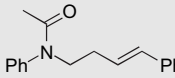
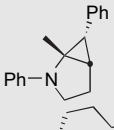
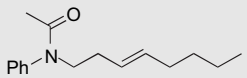
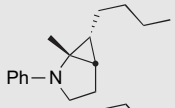
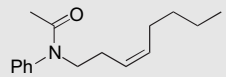
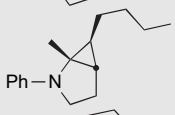
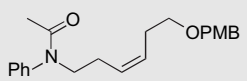
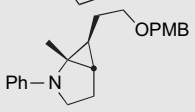
previous report,[11] all the diastereoisomerically pure compounds **1** used were converted into the corresponding aminocyclopropanes **2** with complete diastereoselectivity (entries 2, 4, 6, 8, 9, 17–21 and 24). Yet, when the starting materials were diastereoisomeric mixtures, the cis/trans ratios of the products **2** were usually found to be significantly lower than the original (*E*)/(*Z*) ratios of the alkene substrates (entries 3, 5, 7, 12, 23). However, this can be simply explained by a faster reaction of the (*Z*) diastereoisomers relative to the (*E*) diastereoisomers: the conversions were not complete and proportions of (*E*) diastereoisomers were higher in the recovered starting materials than at the beginning of the reactions.

The relative configurations of the asymmetric carbon atoms in the products **2** were established on the basis of the ^3J coupling constants between the vicinal protons born by the cyclopropane ring, whenever these could be measured accurately ($^3J_{cis} \approx 8.5$ Hz; $^3J_{trans} \approx 5.0$ Hz).[20] When signal overlap prevented the determination of these coupling constants, the signals of the endocyclic methylene protons geminal to the nitrogen atom were examined. The following reliable empirical rule was used: for the cis diastereoisomers, two triplets of doublets ($^3J \approx 10.0$ and 4.5 Hz in the 3.00–3.15 ppm region and $^3J \approx 10.0$ and 6.5 Hz in the 3.95–4.05 ppm region); for the trans diastereoisomers, a doublet of triplets ($^3J \approx 10.0$ and 8.5 Hz in the 2.85–2.90 ppm region) and a triplet of doublets ($^3J \approx 10.0$ and 3.5 Hz in the 3.90–3.95 ppm region). In the case of the isolated single diastereoisomer of compound **2b** prepared from (*E*)-**1b**, this empirical rule and the cyclopropane proton vicinal coupling constants were in agreement with the X-ray crystallographic structure obtained from single crystals. A cis relationship between the nitrogen-containing fused ring and the *N*,*N*-acetylphenylaminoethyl substituent was evidenced (Fig. 1). This, as well as all the other results, unequivocally supports our earlier proposal stating that the reaction gives cis products from (*E*) alkenes and trans products from (*Z*) alkenes in a diastereospecific fashion (Scheme 5).[11]

According to our initial hypothesis, compounds **1b**, **1d**, **1e**, **1f**, **1h**, **1n** and **1o** bearing functional groups susceptible to coordinate to the titanium atom and favour ligand exchange, all gave better results than the reference compounds (*E*)- and (*Z*)-**1m** (entries 2, 5–10, 12, 19 and 20 vs entries 17 and 18). The reaction of the free alcohol **1c** was also attempted, with an unsurprisingly poor result (entries 3 and 4). Quite remarkably, the aminocyclopropane product **2b** was obtained in 24% yield from **1b**, which is rather substantial given the opportunities for unwanted intermolecular side-reactions offered by both molecules under the reaction conditions. The silyl ether **1d** was converted into aminocyclopropane **2d** in 38% yield, which suggests that the *tert*-butyldimethylsilyloxy group could coordinate to the metal centre quite efficiently. This is surprising but after all not unconceivable given the small size of the titanium atom. Importantly, the reaction of amides **1e** and **1f** fitted with more suitable coordinating benzyloxy or methoxy groups furnished the corresponding products **2e** and **2f** in best yields (entries 7–10). The better coordinating ability of the less bulky methoxyethyl compound **1f** was evidenced, and the very satisfactory 78% yield observed for the formation of aminocyclopropane **2f** is comparatively close to the 90% yield achieved from the monosubstituted alkene **1a** (entry 1).

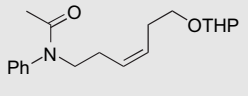
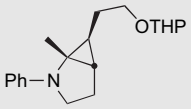
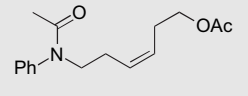
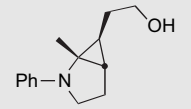
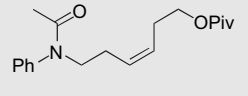
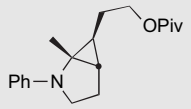
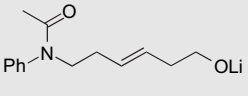
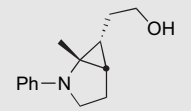
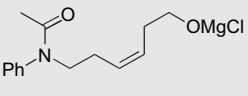
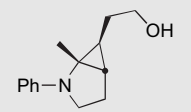
In contrast, the lithium or magnesium salts of alcohol **1c**, which could have been foreseen as excellent ligand exchange directing functions in the light of literature precedence,[21–25] led to the cyclopropylamine products only in poor yield and low conversion (entries 23 and 24). These results can be paralleled with a report published by Sato et al. 10 years ago, where alkoxides appeared to behave as more sterically demanding groups than the *tert*-butyldimethylsilyloxy group in the $Ti(O^iPr)_4/^iPrMgCl$-mediated cyclisation of enynes and allenynes.[26] Indeed, the same kind of effect seems to operate here (compare the results obtained with the alkoxides **1r** and **1s** with those obtained with the TBS compound **1d**).

Table 2
Intramolecular Kulinkovich–de Meijere reactions performed on alkenyl amides **1a**–**s**[a]

Entry	Alkenyl amide **1** (*E*/*Z* ratio)		Aminocyclopropane product[b]		Yield % (cis/trans ratio)[b]	Unreacted **1** % (*E*/*Z* ratio)
1		**1a**		**2a**	90[5,19]	0
2		**1b** (>98:2)[c]		**2b**	24 (>98:2)	8 (>98:2)
3		**1c** (75:25)		**2c**	9 (64:36)	89 (79:21)
4		**1c** (0:100)		**2c**	10 (<2:98)	62 (<2:98)
5		**1d** (85:15)		**2d**	38 (68:32)	17 (98:2)
6		**1d** (98:2)[d]		**2d**	24 (98:2)	34 (>98:2)
7		**1e** (85:15)		**2e**	**53** (79:21)	16 (87:13)
8		**1e** (0:100)		**2e**	**44** (<2:98)	14 (<2:98)
9		**1e** (0:100)		**2e**	**50** (<2:98)[e]	24 (<2:98)
10		**1f** (90:10)		**2f**	**78** (92:8)	18 (Not determined)
11		**1g** (89:11)		**2g**	Traces	4 (Not determined)
12		**1h** (80:20)		**2h**	24 (68:32)	25 (95:5)
13		**1i** (>98:2)		**2i**	0, See text	23 (>98:2)
14		**1j** (>98:2)		**2j**	0, See text	0
15		**1k** (>98:2)		**2a**	11	62 (>98:2)
16		**1l** (>98:2)		**2l**	0, See text	23 (>98:2)
17		**1m** (100:0)		**2m**	18 (>98:2)	41 (>98:2)
18		**1m** (0:100)		**2m**	12 (<2:98)	52 (<2:98)
19		**1n** (0:100)		**2n**	33 (<2:98)[e]	49 (<2:98)

(*continued on next page*)

Table 2 (*continued*)

Entry	Alkenyl amide **1** (*E*/*Z* ratio)	Aminocyclopropane product[b]	Yield % (cis/trans ratio)[b]	Unreacted **1** % (*E*/*Z* ratio)
20	 **1o** (0:100)	 **2o**	23 (<2:98)[e]	26 (<2:98)
21	 **1p** (0:100)	 **2c**	8 (<2:98)[e]	4 (<2:98)
22	 **1q** (0:100)	 **2q**	0[e]	27 (<2:98)
23	 **1r** (75:25)[f]	 **2c**	17 (66:34)	73 (80:20)
24	 **1s** (0:100)[g]	 **2c**	21 (<2:98)[e]	49 (<2:98)

[a] The Kulinkovich–de Meijere reactions were performed using 1.5 equiv of $Ti(O^iPr)_4$ and 4.0 equiv of *c*-C_5H_9MgCl, in diethyl ether unless otherwise stated.
[b] The major diastereoisomer of the product **2** is represented; cis and trans refer to the relative configurations of the nitrogen atom and the side chain on the cyclopropane ring.
[c] The pure (*E*) diastereoisomer of compound **1b**, obtained by chromatography and crystallisation, was used. The reaction was performed in THF because of the poor solubility of this compound in diethyl ether.
[d] A 98:2 mixture of (*E*) and (*Z*) diastereoisomers of alkenyl amide **1d** was obtained by purifying unreacted starting material from the crude product of the previous experiment run on a 85:15 mixture of (*E*) and (*Z*) diastereoisomers.
[e] The reaction was performed in toluene.
[f] Compound **1c** was treated with *n*-BuLi (1.0 equiv) prior to the addition of $Ti(O^iPr)_4$ (1.5 equiv) and *cyclo*-pentylmagnesium chloride (4.0 equiv).
[g] Compound (*Z*)-**1c** was treated with *cyclo*-pentylmagnesium chloride (1.0 equiv) prior to the addition of $Ti(O^iPr)_4$ (1.5 equiv) and *cyclo*-pentylmagnesium chloride (4.0 equiv).

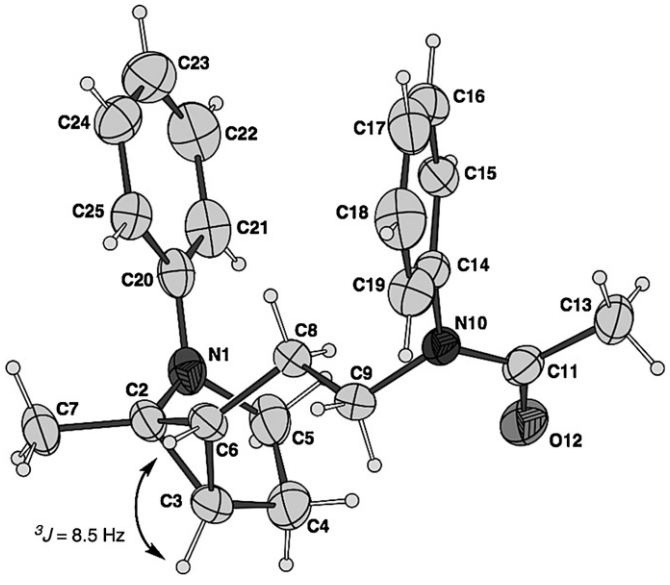
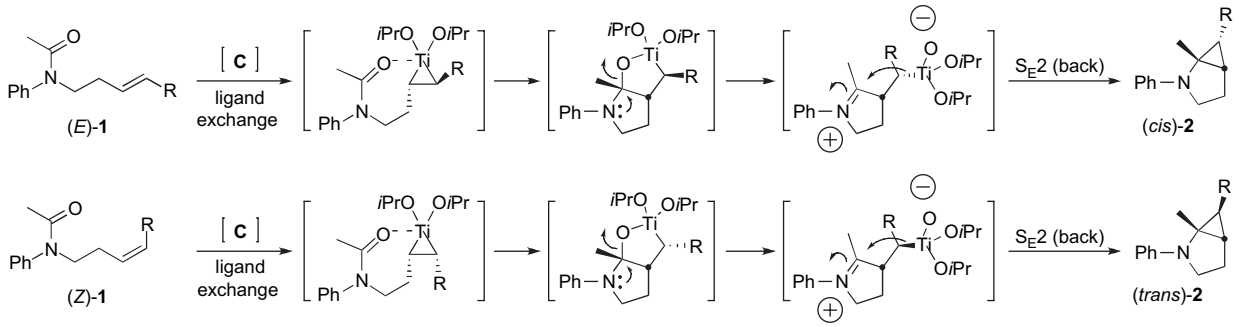


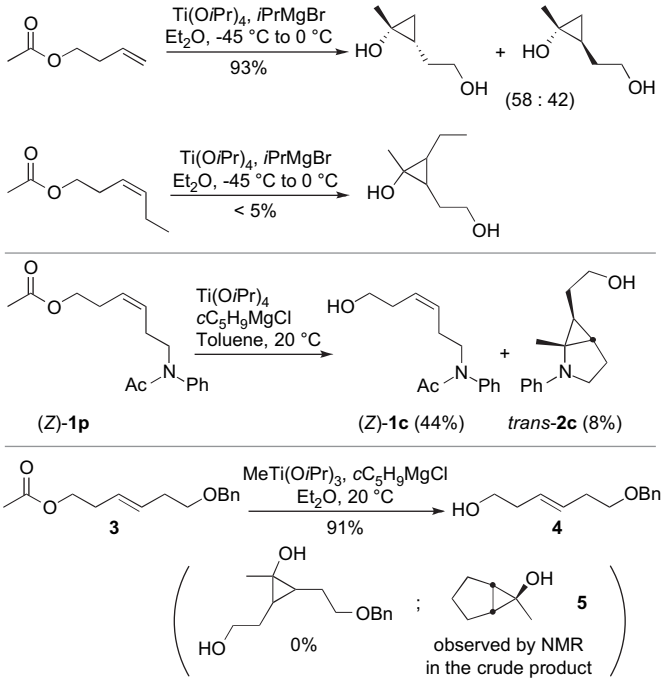
Figure 1. Ortep view of compound **2b**. Displacement ellipsoids are drawn at the 30% probability level.

In the case of the benzyloxy group, the influence of its distance to the olefin function was evaluated. The results established that the optimal spacer consisted of two methylene groups as in compound **1e**: the higher homologue **1h** was converted in significantly lower yield (24%, entry 12), while the reaction of allyl benzyl ether **1g** only afforded traces of the expected aminocyclopropane (entry 11). The intermediate titanium complex most probably underwent β-elimination of the benzyloxy group,[27] as extensive amounts of benzyl alcohol were detected in the crude reaction product. Both diastereoisomers of **1e** were converted into the corresponding diastereoisomeric aminocyclopropanes **2e** with essentially the same efficiency (entries 7 and 8). The reaction of (*Z*)-**1e** was found to be slightly better in toluene than in diethyl ether (entries 8 and 9), while the corresponding *para*-methoxybenzyl ether (*Z*)-**1n** and the THP acetal (*Z*)-**1o** proved to be less effective substrates (entries 19 and 20 vs entry 9).

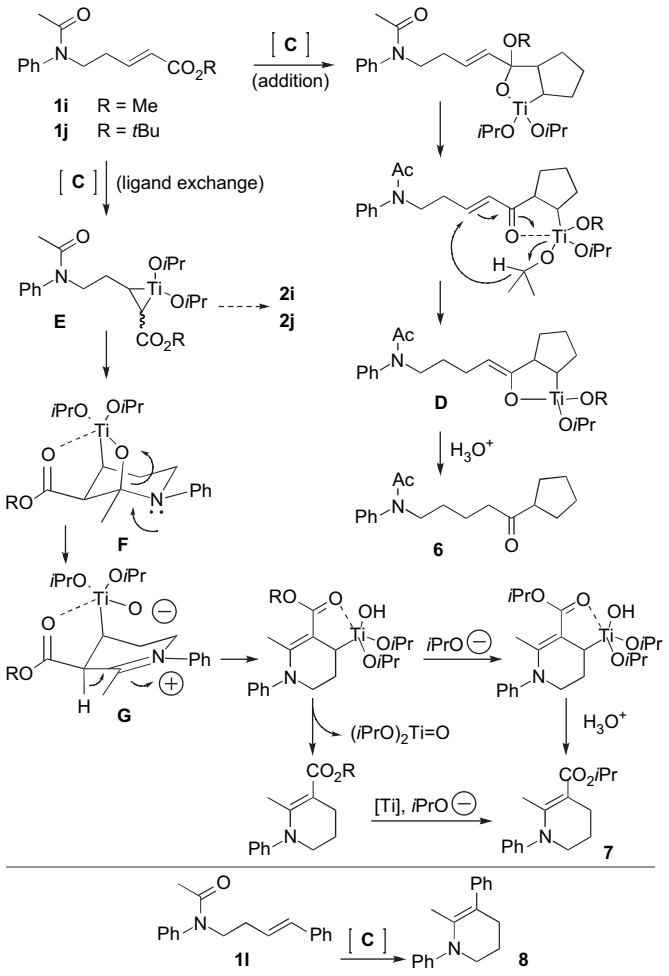
The case of esters (*Z*)-**1p** and (*Z*)-**1q** was especially interesting: it was hoped that in the event of a poorly efficient intramolecular Kulinkovich–de Meijere reaction, the roles of the amide and the ester functions could be reversed, i.e., the amide group could act as a ligand exchange directing group to favour an intramolecular Kulinkovich reaction at the ester function, delivering a cyclopropanol. This is normally a poorly efficient process when disubstituted alkenes are involved (Scheme 6, top).[28] When the reaction was attempted from the acetate ester (*Z*)-**1p**, the fastest process appeared to be an *intermolecular* Kulinkovich reaction, and therefore the main reaction product was de-acylated compound (*Z*)-**1c**. Aminocyclopropane *trans*-**2c** was also isolated in 8% yield, presumably resulting from a tandem intermolecular Kulinkovich reaction/intramolecular Kulinkovich–de Meijere reaction (Table 2, entry 21 and Scheme 6, middle). This is supported by the fact that the magnesium alkoxide (*Z*)-**1s** generated from (*Z*)-**1c** could give the same product (entry 24), although a tandem intramolecular Kulinkovich–de Meijere reaction/intermolecular Kulinkovich reaction could also be considered. Switching the acetyl group to a bulkier, less reactive pivaloyl derivative (*Z*)-**1q** did not improve the reaction (entry 22). As a control experiment, the Kulinkovich reaction of alkenyl ester **3**, bearing a 2-benzyloxyethyl group, was attempted and an exclusive *intermolecular* mechanistic pathway was observed, delivering alcohol **4** and cyclopropanol **5** (Scheme 6, bottom).



Scheme 5. The diastereospecific transformation of alkenyl amides **1** into bicyclic aminocyclopropanes **2**.



Scheme 6. Intramolecular Kulinkovich reactions starting from a monosubstituted and a disubstituted alkenyl ester (top).[28] Reaction of substrate (*Z*)-**1p** (middle) and alkenyl ester **3** (bottom).



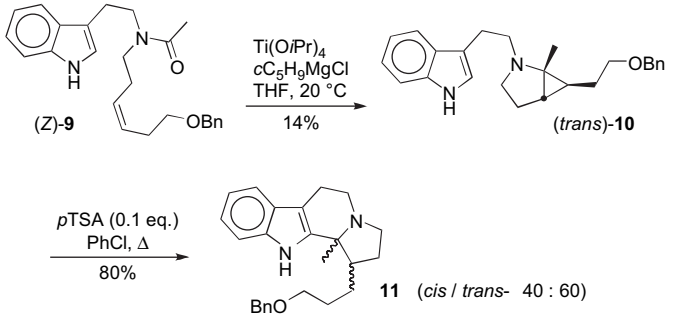
Scheme 7. Proposed mechanism for the formation of unexpected compounds **6** and **7**. Formation of compound **8**.

α,β-Unsaturated esters **1i** and **1j** led to complex mixtures of products. This is perhaps not surprising, since the expected donor–acceptor-substituted cyclopropane products **2i** and **2j** might be unstable.[29,30] However, ketone **6** and vinylogous carbamate **7** were isolated in low yield in both cases. The mechanism leading to these products is unclear: **2i** and **2j** are not likely intermediates, and the following tentative explanation may be proposed (Scheme 7). The initially generated bicyclic titanacyclopropane **C** might react in part with **1i** or **1j** according to an addition at the ester carbonyl group. After departure of the alkoxy leaving group, one could tentatively invoke a hydride transfer from an *iso*-propyloxy ligand of the titanium atom, which would result in the release of acetone and the formation of a stabilised titanium enolate **D** that would be hydrolysed to the ketone **6**. Alternatively, ligand exchange with **1i** or **1j** from complex **C** would deliver **E**. In contrast with the five-membered ring closure normally observed, formation of a six-membered ring **F** might then occur at least as a side-process. After carbon–oxygen bond cleavage giving the metallated iminium **G**, proton loss could be faster than aminocyclopropane ring formation, for which the required overlap of the π^* orbital of the iminium system and the small lobe of the σ C–Ti orbital would be geometrically difficult to achieve. Finally, transesterification to the corresponding *iso*-propyl ester, which is documented under these conditions,[31,32] would yield compound **7** after hydrolysis.

No expected aminocyclopropane could be isolated from the styrene-derivated alkenyl amide **1l** either, but careful analysis of the crude product revealed the presence of a major compound in about 30% yield. Its NMR data was consistent with cyclic enamine structure **8**, the latter could be formed according to a similar pathway as **7** (Scheme 7). Unsurprisingly, this molecule could not be isolated by flash column chromatography on silica gel. Interestingly, when the Kulinkovich–de Meijere reaction was attempted from the α,β-unsaturated sulfone **1k**, the only products isolated, apart from starting material (62%), were the aminocyclopropane **2a** (11%) and alkenyl amide **1a** (8%), both having lost

the sulfone moiety. A parallel can be made between this observation and recent results reported by the group of Ollivier involving oxygen-substituted alkenes,[32] and a similar mechanism could operate here.

An attempt to apply our method to the reaction of indole derivative (*Z*)-**9** bearing a suitable benzyloxyethyl group met little success with a 14% yield, showing that the observed improvement may be valid only for *N*-aryl substrates (Scheme 8). In spite of this disappointing result, we were able to successfully perform the thermal cyclisation of aminocyclopropane (*trans*)-**10** according to our previously described method,[33] for which no substrate with this degree of substitution had been tested so far.



Scheme 8. Cyclopropanation of (*Z*)-**9** followed by cyclisation to **11**.

3. Conclusion

In summary, alkenyl amides bearing a 2-alkyloxyethyl substitution at the carbon–carbon double bond are the best substrates among the range of (*Z*) and (*E*) disubstituted alkenes investigated for intramolecular Kulinkovich–de Meijere reactions. The corresponding aminocyclopropanes could indeed be obtained in satisfactory yields (up to 78%), which is a marked improvement over Kulinkovich–de Meijere reactions performed with ordinary disubstituted alkene substrates. Various transformations have been developed starting from this kind of bicyclic cyclopropylamines, which make them attractive intermediates for the construction of polycyclic nitrogen-containing molecules.[19,33,34] As an example of application, aminocylopropane *trans*-**2d** was recently oxidised electrochemically to afford a stable endoperoxide compound in one step, that displayed moderate but interesting activity against the chloroquine-resistant FcB1 strain of *Plasmodium falciparum*.[34] Finally, the present method appears to be essentially restricted to *N*-aryl alkenyl amide substrates and could not be extended to *N*-alkyl amides or alkenyl esters. We will devote further work to try and overcome this limitation.

4. Experimental

4.1. General

NMR spectra were recorded with AM 300, AVANCE 300 (^{1}H at 300 MHz, ^{13}C at 75.5 MHz) and AVANCE 500 (^{1}H at 500 MHz, ^{13}C at 125.8 MHz) Bruker spectrometers. Chemical shifts are given in parts per million, referenced to the peak of tetramethylsilane, defined at δ=0.00 (^{1}H NMR), or the solvent peak of $CDCl_3$, defined at δ=77.0 (^{13}C NMR). Flash column chromatography was performed on SDS Chromagel silica gel 60 (35–70 μm) or Merck neutral alumina gel 90 (activity I, II or II-III). In some cases, a few drops of triethylamine were added to the solvent/alumina gel mixture during the preparation of the column. All reactions were carried out under argon. The temperatures mentioned are the temperatures of the cold baths used. THF and diethyl ether were purified using a PureSolv solvent purification system (Innovative Technology Inc.). Chloroform was passed through a column containing a 10 cm high amount of silica gel of the type specified above. *cyclo*-Pentylmagnesium chloride 2 M solution in diethyl ether was purchased from Sigma–Aldrich or Fluka and titrated once a month according to a previously reported method.[18] The preparation of *N*-but-3-enyl-*N*-phenylacetamide **1a** has already been described elsewhere.[5,19]

4.2. Cross-metathesis of 1a with alkenes, method A

Typically, 2,6-dichloro-1,4-benzoquinone (10% equiv, 0.30 mmol, 53 mg) and Grubbs second generation catalyst (2.0% equiv, 60 μmol, 40 mg) were added to a solution of alkenyl amide **1a** (1.0 equiv, 3.0 mmol, 0.57 g) and requisite alkene (4.0 equiv, 12 mmol) in freshly distilled CH_2Cl_2 (15 mL). The mixture was heated at reflux for 7 days. After cooling, the reaction medium was concentrated under reduced pressure to afford the crude product.

*4.2.1. N,N′-(Hex-3-ene-1,6-diyl)bis(N-phenylethanamide) (**1b**)*

The general procedure for the cross-metathesis of **1a** (method A) was adapted to the synthesis of the homo-coupling product **1b** using **1a** (2.0 equiv, 0.81 mmol, 0.15 g), CH_2Cl_2 (4.0 mL), 2,6-dichloro-1,4-benzoquinone (10% equiv, 40 μmol, 7.2 mg) and Grubbs second generation catalyst (2.0% equiv, 8.1 μmol, 6.9 mg). The crude product was obtained as a green solid (0.17 g). The *E*/*Z* diastereoisomeric ratio of the expected alkenyl diamide **1b** was 85:15 as estimated by ^{13}C NMR spectroscopy. Purification by flash column chromatography (EtOAc/heptane, gradient from 30% to 100%, then MeOH/EtOAc 5%) yielded starting compound **1a** (56 mg, 0.30 mmol, 36%) and diamide **1b** (85 mg, 0.24 mmol, 60%). The (*E*) isomer of **1b** could be obtained in pure form by performing a crystallisation from EtOAc.

Note: in the absence of 2,6-dichloro-1,4-benzoquinone (DQ), the efficiency and rate of the preparation of the homo-coupling product **1b** proved to be strongly dependent on the batch of catalyst used, with isolated yields ranging from 0% to 85%.

*4.2.1.1. (E)-N,N′-(Hex-3-ene-1,6-diyl)bis(N-phenylethanamide) ((E)-**1b**).* Colourless crystals. Mp 171.3–172.4 °C. IR (neat): 2916, 1647, 1590, 1490, 1444, 1402, 1295, 1177 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.81 (s, 6H), 2.19 (dddd, *J*=8.0, 7.0, 3.5, 1.5 Hz, 4H), 3.71 (dd, *J*=8.0, 7.0 Hz, 4H), 5.39 (tt, *J*=3.5, 1.5 Hz, 2H), 7.15 (br d, *J*=7.5 Hz, 4H), 7.30–7.47 (m, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.7, 30.9, 48.3, 127.7, 128.1, 128.9, 129.5, 142.9, 170.1. MS (ES$^+$) *m*/*z* *373* (MNa^+). HRMS (ES$^+$) *m*/*z* calcd for $C_{22}H_{26}N_2NaO_2$ (MNa^+) 373.1892, found 373.1884.

*4.2.1.2. (Z)-N,N′-(Hex-3-ene-1,6-diyl)bis(N-phenylethanamide) ((Z)-**1b**).* ^{13}C NMR (75.5 MHz, $CDCl_3$), characteristic signal: δ 25.9 (allylic CH_2).

*4.2.2. N-(6-Hydroxyhex-3-enyl)-N-phenylethanamide (**1c**)*

A mixture of AcOH and H_2O (3:1, 5.3 mL) was added to a solution of **1d** (*E*/*Z*≈75:25, 1.0 equiv, 0.79 mmol, 0.27 g, see Section 4.2.3 for preparation) in THF (1.3 mL). After 16 h of stirring at 20 °C, the solvents were removed under reduced pressure (heptane was added to carry AcOH away) to yield a yellow oil (0.20 g). Purification by flash column chromatography (EtOAc/heptane, gradient from 30% to 100%) yielded pure alcohol **1c** (0.18 g, 0.77 mmol, 97%) in an *E*/*Z* ratio of 75:25 as evaluated by ^{1}H and ^{13}C NMR spectroscopies.

*4.2.2.1. N-(6-Hydroxyhex-3-enyl)-N-phenylethanamide (**1c**) (E/Z≈75:25).* Colourless oil. IR (neat): 3391, 1646, 1636, 1594, 1495, 1398, 1298, 1051, 702 cm^{-1}. MS (ES$^+$) *m*/*z* 234 (MH^+), 253, *256* (MNa^+), 257. HRMS (ES$^+$) *m*/*z* calcd for $C_{14}H_{19}NNaO_2$ (MNa^+) 256.1313, found 256.1304.

*4.2.2.2. (E)-N-(6-Hydroxyhex-3-enyl)-N-phenylethanamide ((E)-**1c**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.82 (s, 3H), 2.16–2.36 (m, 4H), 3.03 (br s, 1H), 3.61 (t, J=6.5 Hz, 2H), 3.76 (t, J=7.5 Hz, 2H), 5.46–5.52 (m, 2H), 7.14–7.21 (m, 2H), 7.30–7.48 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.5, 30.8, 35.7, 48.5, 61.6, 127.7, 127.9, 128.6, 129.3, 129.4, 142.7, 170.4. See Section 4.6.1 for the analytical data of (*Z*)-**1c**.

*4.2.3. N-(6-(tert-Butyldimethylsilyloxy)hex-3-enyl)-N-phenylethanamide (**1d**)*

The general procedure for the cross-metathesis of **1a** (method A) was applied to 3-buten-1-ol starting from 3.0 mmol of **1a**. Purification of the crude product (1.3 g) by flash column chromatography (EtOAc/heptane, gradient from 10% to 50%, then MeOH/EtOAc, gradient from 0% to 5%) yielded starting alkenyl amide **1a** (0.14 g, 0.72 mmol, 24%) and a mixture of the expected cross-product **1c**, hex-3-ene-1,6-diol[35,36] and diamide **1b** (0.68 g).

This mixture was dissolved in CH_2Cl_2 (5.0 mL) and added dropwise to a solution of *tert*-butyldimethylsilyl chloride (1.7 equiv, 5.0 mmol, 0.75 g) and imidazole (1.7 equiv, 5.0 mmol, 0.34 g) in CH_2Cl_2 (20 mL). After 18 h of stirring at 20 °C, Et_2O (15 mL) and H_2O (10 mL) were added. The organic layer was separated, washed with H_2O (10 mL) and brine (10 mL), then dried over Na_2SO_4, filtered and concentrated to afford a black oil (1.2 g). Purification by flash column chromatography (EtOAc/heptane, gradient from 10% to 50%, then MeOH/EtOAc 5%) yielded 1,6-di(*tert*-butyldimethylsilyloxy)hex-3-ene (*E*/*Z*≈56:44, 20 mg, 59 μmol), pure alkenyl amide **1d** (0.70 g, 2.0 mmol, 66%) in an *E*/*Z* ratio of 85:15 as evaluated by GC/MS and diamide **1b** (55 mg, 0.16 mmol, 10%).

4.2.3.1. 1,6-Di(tert-butyldimethylsilyloxy)hex-3-ene (E/Z≈79:21). Pale yellow oil. IR (neat): 2952, 2927, 2894, 1252, 1094, 831, 810, 772 cm^{-1}. MS (ES$^+$) *m*/*z* *367* (MNa^+), 368. HRMS (ES$^+$) *m*/*z* calcd for $C_{18}H_{40}NaO_2Si_2$ (MNa^+) 367.2465, found 367.2464.

4.2.3.2. (E)-1,6-Di(tert-butyldimethylsilyloxy)hex-3-ene. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.04 (s, 12H), 0.89 (s, 18H), 2.21 (tdd, J=7.0, 4.0, 1.5 Hz, 4H), 3.61 (t, J=7.0 Hz, 4H), 5.46 (tt, J=4.0, 1.5 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −5.3, 18.4, 26.0, 36.4, 63.2, 128.6.

4.2.3.3. (Z)-1,6-Di(tert-butyldimethylsilyloxy)hex-3-ene. ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals: δ 2.28 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$), characteristic signals: δ 31.2, 62.9, 127.6.

*4.2.3.4. N-(6-(tert-Butyldimethylsilyloxy)hex-3-enyl)-N-phenylethanamide (**1d**) (E/Z≈85:15).* Yellow oil. IR (neat): 2953, 2927, 2855, 1661, 1596, 1495, 1390, 1360, 1093, 969, 833, 811, 773, 699 cm^{-1}. MS (ES$^+$) *m*/*z* 348 (MH^+), *370* (MNa^+), 371. Anal. Calcd for $C_{20}H_{33}NO_2Si$: C 69.11, H 9.57. Found: C 69.08, H 9.39.

*4.2.3.5. (E)-N-(6-(tert-Butyldimethylsilyloxy)hex-3-enyl)-N-phenylethanamide ((E)-**1d**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.02 (s, 6H), 0.87 (s, 9H), 1.80 (s, 3H), 2.12–2.31 (m, 4H), 3.57 (t, J=7.0 Hz, 2H), 3.72 (t, J=7.5 Hz, 2H), 5.32–5.52 (m, 2H), 7.15 (dd, J=7.0, 1.5 Hz, 2H), 7.35 (tt, J=7.0, 1.5 Hz, 1H), 7.40 (t, J=7.0 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −5.3, 18.3, 22.8, 25.9, 31.1, 36.2, 48.7, 63.1, 127.8, 128.2, 128.6, 129.0, 129.6, 143.1, 170.1.

*4.2.3.6. (Z)-N-(6-(tert-Butyldimethylsilyloxy)hex-3-enyl)-N-phenylethanamide ((Z)-**1d**).* ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals: δ 0.86 (s, 9H), 1.81 (s, 3H), 3.56 (t, J=7.0 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$), characteristic signals: δ 48.5, 62.7.

*4.2.4. N-(6-(Benzyloxy)hex-3-enyl)-N-phenylethanamide (**1e**)*

The general procedure for the cross-metathesis of **1a** (method A) was applied to 3-buten-1-ol starting from 4.0 mmol of **1a**. Purification of the crude product by flash column chromatography (EtOAc/heptane, gradient from 10% to 50%, then MeOH/EtOAc, gradient from 0% to 5%) yielded a 35:65 mixture of the expected cross-product **1c** and hex-3-ene-1,6-diol (1.7 g).

Sodium hydride (60% in oil, 4.6 equiv, 19 mmol, 0.75 g) was added portionwise at 0 °C to a solution of the preceding mixture in THF (26 mL), followed by tetra-*n*-butylammonium iodide (6.6% equiv, 0.27 mmol, 98 mg) and benzyl bromide (6.5 equiv, 26 mmol, 3.1 mL). After 18 h of stirring at 20 °C, Et_2O (35 mL) and 1 N HCl aq solution (30 mL) were added. The organic layer was separated, and the aqueous phase was extracted with Et_2O (30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford a brown oil (4.1 g). Benzylation proved to be incomplete, probably because of aging of the NaH used, and purification by flash column chromatography (EtOAc/heptane, gradient from 10% to 60%, then MeOH/EtOAc, gradient from 0% to 5%) yielded a 80:20 mixture of the expected benzylated cross-product **1e** and alcohol **4** (0.96 g, see Section 4.8.1 for analytical data), as well as alkenyl alcohol **1c** (83 mg, 0.36 mmol, 9%).

In order to obtain pure **1e**, the preceding mixture of **1e** and 6-(benzyloxy)hex-3-en-1-ol was dissolved in CH_2Cl_2 (0.50 mL) and added dropwise to a solution of *tert*-butyldimethylsilyl chloride (0.50 mmol, 76 mg) and imidazole (0.50 mmol, 34 mg) in CH_2Cl_2 (2.0 mL). After 2 h 30 min of stirring at 20 °C, Et_2O (10 mL) and H_2O (10 mL) were added. The organic layer was separated, washed with H_2O (2×5.0 mL), then dried over Na_2SO_4, filtered and concentrated to afford a yellow oil (0.92 g). Purification by flash column chromatography (EtOAc/heptane, gradient from 10% to 100%) yielded pure (6-(benzyloxy)hex-3-enyloxy)(*tert*-butyl)dimethylsilane (0.16 g, 0.49 mmol) and alkenyl amide **1e** (0.77 g, 2.4 mmol, 59%) both in an *E*/*Z* ratio of ≈85:15 as estimated by ^{13}C NMR spectroscopy.

4.2.4.1. (6-(Benzyloxy)hex-3-enyloxy)(tert-butyl)dimethylsilane (E/Z≈85:15). Colourless oil. IR (neat): 2952, 2925, 2854, 1253, 1096, 968, 833, 811, 773, 732, 695 cm^{-1}. MS (ES$^+$) *m*/*z* *343* (MNa^+), 344, 382. Anal. Calcd for $C_{19}H_{32}O_2Si$: C 71.19, H 10.06. Found: C 71.05, H 10.19.

4.2.4.2. (E)-(6-(Benzyloxy)hex-3-enyloxy)(tert-butyl)dimethylsilane. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.89 (s, 9H), 2.22 (tdd, J=7.0, 3.5, 1.5 Hz, 2H), 2.32 (tdd, J=7.0, 3.5, 1.5 Hz, 2H), 3.48 (t, J=7.0 Hz, 2H), 3.61 (t, J=7.0 Hz, 2H), 4.50 (s, 2H), 5.50 (tt, J=3.5, 1.5 Hz, 2H), 7.22–7.37 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −5.3, 18.3, 25.9, 33.2, 36.4, 63.2, 70.1, 72.9, 127.5, 127.6, 128.3, 128.5, 128.7, 138.5.

4.2.4.3. (Z)-(6-(Benzyloxy)hex-3-enyloxy)(tert-butyl)dimethylsilane. ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals: δ 2.39 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$), characteristic signals: δ 62.8, 69.9.

*4.2.4.4. N-(6-(Benzyloxy)hex-3-enyl)-N-phenylethanamide (**1e**) (E/Z≈85:15).* IR (neat): 2928, 2853, 1656, 1651, 1639, 1634, 1594, 1494, 1393, 1362, 1097, 1074, 735, 697 cm^{-1}. MS (ES$^+$) *m*/*z* *346* (MNa^+). HRMS (ES$^+$) *m*/*z* calcd for $C_{21}H_{25}NNaO_2$ (MNa^+) 346.1783, found 346.1779.

*4.2.4.5. (E)-N-(6-(Benzyloxy)hex-3-enyl)-N-phenylethanamide ((E)-**1e**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80 (s, 3H), 2.23 (dt, J=8.0, 7.0 Hz, 2H), 2.29 (td, J=7.0, 6.0 Hz, 2H), 3.46 (t, J=7.0 Hz, 2H), 3.73 (t, J=7.0 Hz, 2H), 4.49 (s, 2H), 5.36–5.58 (m, 2H), 7.11–7.43 (m, 10H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.7, 31.0, 33.0, 48.6, 70.0, 72.8, 127.4, 127.6, 127.8, 128.2, 128.3, 128.6, 128.8, 129.6, 138.4, 143.0, 170.2. See Section 4.5.1 for the analytical data of (*Z*)-**1e**.

*4.2.5. N-(6-Methoxyhex-3-enyl)-N-phenylethanamide (**1f**)*

The general procedure for the cross-metathesis of **1a** (method A) was applied to 3-buten-1-ol starting from 3.9 mmol of **1a**.

Purification of the crude product (1.8 g) by flash column chromatography (EtOAc/heptane, gradient from 10% to 50%, then MeOH/EtOAc, gradient from 0% to 5%) yielded a 28:72 mixture of the expected cross-product **1c** and hex-3-ene-1,6-diol (1.4 g).

Sodium hydride (60% in oil, 4.7 equiv, 12 mmol, 0.47 g) was added portionwise to a solution of the preceding mixture (0.92 g) in THF (10 mL) at 0 °C, followed by methyl iodide (4.7 equiv, 12 mmol, 0.73 mL). After 16 h 30 min of stirring at 20 °C, Et_2O (30 mL) and 0.3 N HCl aq solution (30 mL) were added. The organic layer was separated, and the aqueous phase was extracted with Et_2O (2×30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford a brown oil (0.93 g). Purification by flash column chromatography (EtOAc/heptane, gradient from 10% to 50%) yielded pure alkenyl amide **1f** (0.38 g, 1.5 mmol, 60%) in an *E*/*Z* ratio of 85:15 as evaluated by GC/MS.

*4.2.5.1. N-(6-Methoxyhex-3-enyl)-N-phenylethanamide (**1f**) (E/Z≈ 85:15).* Yellow oil. IR (neat): 2926, 2866, 1657, 1651, 1595, 1495, 1393, 1296, 1113, 967, 700 cm^{-1}. MS (ES^+) *m*/*z 270* (MNa^+), 271. HRMS (ES^+) *m*/*z* calcd for $C_{15}H_{21}NNaO_2$ (MNa^+) 270.1410, found 270.1465.

*4.2.5.2. (E)-N-(6-Methoxyhex-3-enyl)-N-phenylethanamide ((E)-**1f**).* ^1H NMR (300 MHz, $CDCl_3$): δ 1.81 (s, 3H), 2.17–2.34 (m, 4H), 3.32 (s, 3H), 3.37 (t, *J*=6.5 Hz, 2H), 3.74 (t, *J*=7.5 Hz, 2H), 5.41–5.48 (m, 2H), 7.13–7.20 (m, 2H), 7.30–7.47 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.7, 31.0, 32.8, 48.5, 58.4, 72.3, 127.7, 128.1, 128.6, 128.7, 129.5, 143.0, 170.1.

*4.2.5.3. (Z)-N-(6-Methoxyhex-3-enyl)-N-phenylethanamide ((Z)-**1f**).* ^1H NMR (300 MHz, $CDCl_3$), characteristic signals: δ 1.83 (s, 3H), 3.30 (s, 3H), 3.35 (t, *J*=6.5 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$), characteristic signals: δ 25.9, 27.8, 72.1.

*4.2.6. N-(5-(Benzyloxy)pent-3-enyl)-N-phenylethanamide (**1g**)*

The general procedure for the cross-metathesis of **1a** (method A) was applied to allyl alcohol starting from 0.95 mmol of **1a**. Purification of the crude product by flash column chromatography (EtOAc/heptane, gradient from 10% to 50%, then MeOH/EtOAc, gradient from 0% to 5%) yielded starting alkenyl amide **1a** (0.10 g, 0.53 mmol, 56%) and a mixture of the expected *N*-(5-hydroxypent-3-enyl)-*N*-phenylethanamide and but-2-ene-1,4-diol (0.18 g).

Sodium hydride (60% in oil, 3.0 equiv, 2.8 mmol, 0.11 g) was added portionwise to a solution of the preceding mixture in THF (2.5 mL) at 0 °C, followed by tetra-*n*-butylammonium iodide (2.7% equiv, 26 μmol, 9.6 mg) and benzyl bromide (3.0 equiv, 2.8 mmol, 0.33 mL). After 2 h of stirring at 20 °C, Et_2O (10 mL) and 0.3 N HCl aq solution (10 mL) were added. The organic layer was separated, and the aqueous phase was extracted with Et_2O (10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford a yellow oil (0.56 g). Purification by flash column chromatography (EtOAc/heptane, gradient from 10% to 40%) yielded pure 1,4-di(benzyloxy)but-2,3-ene (*E*/*Z*≈97:3, 0.21 g, 0.80 mmol)[37] and pure alkenyl amide **1g** (97 mg, 0.31 mmol, 33%) with an *E*/*Z* ratio of 89:11 as estimated by ^{13}C NMR spectroscopy.

*4.2.6.1. N-(5-(Benzyloxy)pent-3-enyl)-N-phenylethanamide (**1g**) (E/Z≈89:11).* Yellow oil. IR (neat): 2928, 2852, 1652, 1594, 1494, 1392, 1295, 1093, 1070, 1026, 970, 736, 697 cm^{-1}. MS (ES^+) *m*/*z* 202, 310 (MH^+), *332* (MNa^+), 333, 460. HRMS (ES^+) *m*/*z* calcd for $C_{20}H_{23}NNaO_2$ (MNa^+) 332.1626, found 332.1609.

*4.2.6.2. (E)-N-(5-(Benzyloxy)pent-3-enyl)-N-phenylethanamide ((E)-**1g**).* ^1H NMR (300 MHz, $CDCl_3$): δ 1.81 (s, 3H), 2.29 (m, 2H), 3.78 (t, *J*=7.5 Hz, 2H), 3.95 (dd, *J*=4.5, 1.0 Hz, 2H), 4.47 (s, 2H), 5.56–5.74 (m, 2H), 7.07–7.62 (m, 10H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.6, 30.6, 48.2, 70.4, 71.7, 127.4, 127.5, 127.7, 128.0, 128.2, 128.4, 129.5, 130.6, 138.2, 142.8, 170.1.

*4.2.6.3. (Z)-N-(5-(Benzyloxy)pent-3-enyl)-N-phenylethanamide ((Z)-**1g**).* ^{13}C NMR (75.5 MHz, $CDCl_3$), characteristic signals: δ 26.1, 65.6, 72.0.

*4.2.7. N-(7-(Benzyloxy)hept-3-enyl)-N-phenylethanamide (**1h**)*

The general procedure for the cross-metathesis of **1a** (method A) was applied to 4-penten-1-ol starting from 1.2 mmol of **1a**. Purification of the crude product by flash column chromatography (EtOAc/heptane, gradient from 10% to 50%, then MeOH/EtOAc, gradient from 0% to 5%) yielded starting alkenyl amide **1a** (0.11 g, 0.59 mmol, 50%) and a 28:72 mixture of the expected *N*-(7-hydroxyhept-5-enyl)-*N*-phenylethanamide and oct-4-ene-1,8-diol (0.41 g).

Sodium hydride (60% in oil, 4.0 equiv, 4.8 mmol, 0.19 g) was added portionwise to a solution of the preceding mixture in THF (4.4 mL) at 0 °C, followed by tetra-*n*-butylammonium iodide (3.7% equiv, 44 μmol, 16 mg) and benzyl bromide (4.0 equiv, 4.8 mmol, 0.58 mL). After 5 h of stirring at 20 °C, Et_2O (10 mL) and 0.3 N HCl aq solution (10 mL) were added. The organic layer was separated, and the aqueous phase was extracted with Et_2O (10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford a green oil (1.1 g). Purification by flash column chromatography (EtOAc/heptane 20%) yielded pure alkenyl amide **1h** (0.18 g, 0.54 mmol, 45%) with an *E*/*Z* ratio of 80:20 as estimated by GC/MS.

*4.2.7.1. N-(7-(Benzyloxy)hept-3-enyl)-N-phenylethanamide (**1h**) (E/Z≈80:20).* Yellow oil. IR (neat): 2931, 2853, 1656, 1595, 1494, 1392, 1296, 1099, 1074, 968, 735, 697 cm^{-1}. MS (ES^+) *m*/*z* 346, *360* (MNa^+). HRMS (ES^+) *m*/*z* calcd for $C_{22}H_{27}NNaO_2$ (MNa^+) 360.1939, found 360.1955.

*4.2.7.2. (E)-N-(7-(Benzyloxy)hept-3-enyl)-N-phenylethanamide ((E)-**1h**).* ^1H NMR (300 MHz, $CDCl_3$): δ 1.65 (tt, *J*=7.5, 6.5 Hz, 2H), 1.81 (s, 3H), 2.06 (br td, *J*=7.5, 6.5 Hz, 2H), 2.20 (tdd, *J*=7.5, 6.5, 1.5 Hz, 2H), 3.45 (t, *J*=6.5 Hz, 2H), 3.71 (t, *J*=7.5 Hz, 2H), 4.48 (s, 2H), 5.39 (AB part of an ABX_2Y_2 system, δ_A=5.34 ppm, δ_B=5.44 ppm, J_{AB}=15.5 Hz, J_{AX}=6.5 Hz, J_{AY}=1.5 Hz, J_{BX}=1.0 Hz, J_{BY}=6.5 Hz, 2H), 7.11–7.21 (m, 2H), 7.22–7.48 (m, 8H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.7, 29.0, 29.3, 30.9, 48.6, 69.6, 72.7, 126.9, 127.4, 127.5, 127.7, 128.1, 128.2, 129.5, 131.9, 138.5, 143.0, 170.0.

*4.2.7.3. (Z)-N-(7-(Benzyloxy)hept-3-enyl)-N-phenylethanamide ((Z)-**1h**).* ^1H NMR (300 MHz, $CDCl_3$), characteristic signals: δ 3.39 (t, *J*=6.5 Hz, 2H), 3.78 (t, *J*=7.5 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$), characteristic signals: δ 48.4, 69.8.

4.3. Cross-metathesis of 1a with alkenes, method B

Typically, the reaction was performed in a 25 mL Schlenk flask equipped with a condenser. A solution of alkenyl amide **1a** (1.0 equiv, 1.0 mmol, 0.19 g), requisite alkene (1.0 equiv, 1.0 mmol) and *B*-chlorocatecholborane (10% equiv, 0.10 mmol, 15 mg) in toluene (5.0 mL) was degassed once. Grubbs second generation catalyst (5.0% equiv, 50 μmol, 42 mg) was added and the reaction mixture was then heated at 80 °C for 12 h. After cooling, methanol was added and after 30 min, the solvents were removed in vacuo.

*4.3.1. (E)-Methyl 5-(N-phenylethanamido)pent-2-enoate ((E)-**1i**)*

The general procedure for the cross-metathesis of **1a** (method B) was applied to methyl acrylate (1.0 equiv, 1.0 mmol, 90 μL). Purification of the crude product by flash column chromatography (Et_2O/petroleum ether, 80%) yielded pure (*E*)-**1i** (0.22 g, 0.91 mmol, 91%) as a pale green oil. IR (neat): 2948, 1723, 1658, 1593, 1495,

1439, 1397, 1278, 1208, 1169, 1034 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.83 (s, 3H), 2.46 (tdd, J=7.5, 7.0, 1.5 Hz, 2H), 3.71 (s, 3H), 3.86 (t, J=7.5 Hz, 2H), 5.86 (dt, J=15.5, 1.5 Hz, 1H), 6.89 (dt, J=15.5, 7.0 Hz, 1H), 7.18 (d, J=7.0 Hz, 2H), 7.33–7.49 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.4, 30.3, 47.1, 51.1, 122.4, 127.8, 127.8, 129.6, 142.4, 145.3, 166.3, 170.0. MS (ES^+) *m/z 270* (MNa^+).

4.3.2. (*E*)-*tert*-Butyl 5-(*N*-phenylethanamido)pent-2-enoate ((*E*)-**1j**)

The general procedure for the cross-metathesis of **1a** (method B) was applied to *tert*-butyl acrylate (1.0 equiv, 3.0 mmol, 0.44 mL). Purification of the crude product by flash column chromatography (Et_2O/petroleum ether, 80%) yielded pure (*E*)-**1j** (0.62 g, 2.1 mmol, 72%) as a viscous colourless oil. IR (neat): 2976, 2932, 1709, 1652, 1595, 1494, 1392, 1366, 1290, 1150, 976 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.46 (s, 9H), 1.83 (s, 3H), 2.44 (tdd, J=7.5, 7.0, 1.5 Hz, 2H), 3.83 (t, J=7.5 Hz, 2H), 5.76 (dt, J=15.5, 1.5 Hz, 1H), 6.75 (dt, J=15.5, 7.0 Hz, 1H), 7.16 (br d, J=7.0 Hz, 2H), 7.31–7.47 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.6,28.0, 30.3, 47.6, 80.0, 124.7, 127.9, 128.0, 129.7, 142.7, 143.7, 165.4, 170.1. MS (ES^+) *m/z* 174, 256, *312* (MNa^+), 313. HRMS (ES^+) *m/z* calcd for $C_{17}H_{23}NNaO_3$ (MNa^+) 312.1576, found 312.1552.

4.3.3. (*E*)-*N*-Phenyl-*N*-(4-(phenylsulfonyl)but-3-enyl)ethanamide ((*E*)-**1k**)

The general procedure for the cross-metathesis of **1a** (method B) was applied to phenyl vinyl sulfone (1.0 equiv, 1.0 mmol, 0.17 g). Purification of the crude product by flash column chromatography (Et_2O/petroleum ether, 80%) yielded pure (*E*)-**1k** (0.14 g, 0.44 mmol, 44%). Colourless oil. IR (neat): 3056, 2935, 1654, 1592, 1494, 1444, 1397, 1311, 1146, 1085, 824 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.78 (s, 3H), 2.49 (qd, J=7.0, 1.5 Hz, 2H), 3.85 (t, J=7.0 Hz, 2H), 6.38 (dt, J=15.0, 1.5 Hz, 1H), 6.90 (dt, J=15.0, 7.0 Hz, 1H), 7.08 (br d, J=7.5 Hz, 2H), 7.31–7.46 (m, 3H), 7.50–7.66 (m, 3H), 7.87 (br d, J=7.0 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.5, 29.7, 46.6, 127.5, 127.7, 128.0, 129.1, 129.7, 131.9, 133.2, 140.2, 142.2, 143.1, 170.2. MS (ES^+) *m/z* 349, *352* (MNa^+), 353, 365.

4.3.4. (*E*)-*N*-Phenyl-*N*-(4-phenylbut-3-enyl)ethanamide ((*E*)-**1l**)

The general procedure for the cross-metathesis of **1a** (method B) was applied to styrene (1.0 equiv, 4.0 mmol, 0.46 mL). Purification of the crude product by flash column chromatography (Et_2O/petroleum ether, 60%) yielded pure (*E*)-**1l** (0.47 g, 1.8 mmol, 44%). Pale yellow oil. IR (neat): 2930, 1651, 1594, 1493, 1392, 1297, 964, 741, 693 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.82 (s, 3H), 2.45 (tdd, J=7.5, 7.0, 1.5 Hz, 2H), 3.85 (t, J=7.5 Hz, 2H), 6.12 (dt, J=16.0, 7.0 Hz, 1H), 6.40 (dt, J=16.0, 1.5 Hz, 1H), 7.13–7.45 (m, 10H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.7, 31.4, 48.4, 125.9, 127.0, 127.7, 127.7, 128.1, 128.3, 129.5, 131.7, 137.3, 142.9, 170.1. MS (ES^+) *m/z* 266 (MH^+), *288* (MNa^+), 289. HRMS (ES^+) *m/z* calcd for $C_{18}H_{19}NNaO$ (MNa^+) 288.1364, found 288.1362.

4.4. Synthesis of amides (*E*)-1m and (*Z*)-1m

4.4.1. (*E*)-*N*-(Oct-3-enyl)-*N*-phenylethanamide ((*E*)-**1m**)

Methanesulfonyl chloride (1.1 equiv, 3.8 mmol, 0.29 mL) was added dropwise to a solution of (*E*)-3-octen-1-ol[38] (1.0 equiv, 3.4 mmol, 0.44 g) and triethylamine (1.1 equiv, 3.8 mmol, 0.53 mL) in CH_2Cl_2 (14 mL) at 0 °C. After 45 min of stirring at 20 °C, the reaction mixture was diluted with CH_2Cl_2 (20 mL), and then washed with saturated $NaHCO_3$ aq solution (2×10 mL) and H_2O (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford fairly pure (*E*)-oct-3-enyl methanesulfonate (0.64 g, 3.1 mmol, 90%) as a yellow oil that was used in the next step without further purification. IR (neat): 2957, 2926, 2857, 1466, 1350, 1170, 1091, 1055, 952, 913, 838, 795, 729 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, J=7.0 Hz, 3H), 1.27–1.38 (m, 4H), 2.01 (qd, J=6.5, 1.0 Hz, 2H), 2.44 (qd, J=6.5, 1.0 Hz, 2H), 3.00 (s, 3H), 4.21 (t, J=6.5 Hz, 2H), 5.47 (AB part of an ABX_2Y_2 system, δ_A=5.36 ppm, δ_B=5.58 ppm, J_{AB}=15.5 Hz, J_{AX}=6.5 Hz, J_{AY}=1.0 Hz, J_{BX}=1.0 Hz, J_{BY}=6.5 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.8, 22.1, 31.3, 32.2, 32.4, 37.4, 69.6, 123.3, 134.9. MS (ES^+) *m/z 229* (MNa^+). HRMS (ES^+) *m/z* calcd for $C_9H_{18}NaO_3S$ (MNa^+) 229.0874, found 229.0893.

(*E*)-Oct-3-enyl methanesulfonate (1.0 equiv, 3.1 mmol, 0.64 g) was added to a solution of aniline (3.0 equiv, 9.4 mmol, 0.85 mL) in acetonitrile (3.0 mL). After 38 h of stirring at reflux, the mixture was cooled and concentrated under reduced pressure. Et_2O (50 mL) and 1 N NaOH aq solution (20 mL) were added. The organic layer was separated, and the aqueous phase extracted with Et_2O (25 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford an orange oil (1.2 g). This oil was dissolved in pyridine (7.5 mL), and acetic anhydride (4.0 equiv, 12 mmol, 1.2 mL) was added dropwise at 0 °C. After 3 h of stirring at 20 °C, the mixture was diluted with CH_2Cl_2 (50 mL) and then washed successively with organic layer was separated, washed with 1 N NaOH aq solution (50 mL), H_2O (50 mL), 1 N HCl aq solution (2×50 mL) and H_2O (50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to afford a red oil (1.6 g). Purification by flash column chromatography (EtOAc/heptane, gradient from 10% to 20%) yielded pure (*E*)-**1m** (0.56 g, 2.3 mmol, 74%) as a yellow oil. IR (neat): 2955, 2924, 2854, 1859, 1595, 1494, 1450, 1436, 1392, 1361, 1295, 968, 771, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, J=7.0 Hz, 3H), 1.21–1.37 (m, 4H), 1.82 (s, 3H), 1.96 (qd, J=6.5, 1.5 Hz, 2H), 2.21 (tdd, J=7.5, 6.5, 1.0 Hz, 2H), 3.74 (t, J=7.5 Hz, 2H), 5.39 (AB part of an ABX_2Y_2 system, δ_A=5.34 ppm, δ_B=5.44 ppm, J_{AB}=15.5 Hz, J_{AX}=6.5 Hz, J_{AY}=1.0 Hz, J_{BX}=1.5 Hz, J_{BY}=6.5 Hz, 2H), 7.17 (m, 2H), 7.30–7.48 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.6, 21.8, 22.5, 30.8, 31.2, 31.9, 48.5, 126.1, 127.5, 127.9, 129.3, 132.5, 142.8, 169.7. MS (ES^+) *m/z* 246 (MH^+), *268* (MNa^+), 269, 513 ($2MNa^+$), 514. HRMS (ES^+) *m/z* calcd for $C_{16}H_{23}NNaO$ (MNa^+) 246.1858, found 246.1861.

4.4.2. (*Z*)-*N*-(Oct-3-enyl)-*N*-phenylethanamide ((*Z*)-**1m**)

para-Toluenesulfonyl chloride (1.3 equiv, 65 mmol, 12 g portionwise) was added portionwise to a solution of (*Z*)-oct-3-en-1-ol (1.0 equiv, 50 mmol, 7.7 mL) and pyridine (1.5 equiv, 75 mmol, 6.1 mL) in $CHCl_3$ (25 mL) at 0 °C. After 18 h of stirring at 20 °C, the reaction mixture was diluted with Et_2O (0.10 L) and then washed successively with 1 N HCl aq solution (0.10 L), saturated $NaHCO_3$ aq solution (0.10 L) and H_2O (50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford a colourless oil (11 g). Purification by flash column chromatography (EtOAc/heptane, gradient from 0% to 5%) yielded pure (*Z*)-oct-3-enyl 4-methylbenzenesulfonate (8.9 g, 32 mmol, 63%) as a colourless oil. IR (neat): 2957, 2927, 2865, 1360, 1180, 961, 910, 815, 661 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, J=6.5 Hz, 3H), 1.22–1.34 (m, 4H), 1.96 (q, J=6.5 Hz, 2H), 2.39 (q, J=7.0 Hz, 2H), 2.44 (s, 3H), 4.00 (t, J=7.0 Hz, 2H), 5.22 (m, 1H), 5.47 (m, 1H), 7.34 (d, J=8.5 Hz, 2H), 7.78 (d, J=8.5 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.8, 21.5, 22.1, 26.8, 26.9, 31.4, 69.7, 122.5, 127.7, 129.7, 133.0, 133.7, 144.6. MS (ES^+) *m/z* 195, 227, *305* (MNa^+). Anal. Calcd for $C_{15}H_{22}O_3S$: C 63.80, H 7.85. Found: C 63.67, H 7.98.

Potassium hydroxide (powdered, 2.0 equiv, 30 mmol, 2.0 g) and tetra-*n*-butylammonium hydrogen sulfate (5% equiv, 0.75 mmol, 0.25 g) were added successively to a suspension of *N*-phenylacetamide (1.1 equiv, 17 mmol, 2.2 g) in toluene (45 mL). The mixture was stirred at 20 °C for 3 h, then heated to 80 °C. (*Z*)-Oct-3-enyl 4-methylbenzenesulfonate (1.0 equiv, 15 mmol, 4.2 g) was added and the reaction medium was stirred for 6 h at 80 °C. After cooling, the mixture was diluted with Et_2O (50 mL) and 1 N HCl aq solution (50 mL). The organic layer was separated, and the aqueous

phase extracted with Et_2O (2×50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford a yellow oil (3.8 g). Purification by flash column chromatography (EtOAc/heptane, gradient from 0% to 30%) yielded pure (*Z*)-**1m** (2.9 g, 12 mmol, 78%) as a yellow oil. IR (neat): 2956, 2928, 2858, 1662, 1595, 1495, 1394, 1298 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, *J*=6.5 Hz, 3H), 1.22–1.35 (m, 4H), 1.83 (s, 3H), 1.97 (q, *J*=7.0 Hz, 2H), 2.28 (q, *J*=7.5 Hz, 2H), 3.72 (t, *J*=7.5 Hz, 2H), 5.23–5.52 (m, 2H), 7.18 (br d, *J*=7.5 Hz, 2H), 7.31–7.47 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.8, 22.1, 22.7, 25.7, 26.9, 31.6, 48.6, 125.5, 127.7, 128.1, 129.5, 132.2, 143.0, 170.1. MS (ES^+) *m/z 268* (MNa^+).

4.5. Synthesis of amides (*Z*)-1e and (*Z*)-1n

*4.5.1. (Z)-N-(6-(Benzyloxy)hex-3-enyl)-N-phenylethanamide ((Z)-**1e**)*

n-Butyllithium (1.2 M in hexanes, 1.0 equiv, 9.0 mmol, 7.4 mL) was added dropwise to a solution of 4-benzyloxybut-1-yne[39] (1.0 equiv, 9.0 mmol 1.4 g) in THF (30 mL) at −78 °C. The purple solution was allowed to warm to −50 °C in 35 min and 1,3,2-dioxathiolane-2,2-dioxide[40,41] (1.0 equiv, 9.0 mmol, 1.1 g) was added. The mixture, which turned yellow, was stirred for 2 h at that temperature and the cold bath was then removed. Saturated NH_4Cl aq solution (40 mL) and Et_2O (20 mL) were added. The organic layer was separated and the aqueous phase was extracted with Et_2O (2×40 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a yellow oil (1.8 g). Purification by flash column chromatography (EtOAc/heptane, gradient from 10% to 20%) yielded pure 6-(benzyloxy)hex-3-yn-1-ol (1.2 g, 6.0 mmol, 66%) as a colourless oil. IR (neat): 3392, 2865, 1454, 1362, 1095, 1043, 735, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.39 (tt, *J*=6.5, 2.5 Hz, 2H), 2.47 (tt, *J*=7.0, 2.5 Hz, 2H), 2.54 (br s, 1H, OH), 3.55 (t, *J*=7.0 Hz, 2H), 3.63 (t, *J*=6.5 Hz, 2H), 4.53 (s, 2H); 7.23–7.38 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.0, 23.0, 61.0, 68.5, 72.8, 77.8, 78.8, 127.6, 127.6, 128.3, 137.8. MS (ES^+) *m/z* 209, *227* (MNa^+), 228. HRMS (ES^+) *m/z* calcd for $C_{13}H_{16}NaO_2$ (MNa^+) 227.1048, found 227.1078. Anal. Calcd for $C_{13}H_{16}O_2$: C 76.44, H 7.90. Found: C 76.13, H 7.97.

para-Toluenesulfonyl chloride (1.2 equiv, 7.2 mmol, 1.4 g) was added portionwise at 0 °C to a solution of 6-(benzyloxy)hex-3-yn-1-ol (1.0 equiv, 6.0 mmol, 1.2 g) and pyridine (1.5 equiv, 9.0 mmol, 0.73 mL) in $CHCl_3$ (6 mL). After 24 h of stirring at 20 °C, the reaction mixture was diluted with Et_2O (30 mL), and then washed successively with 0.3 N HCl aq solution (30 mL), saturated $NaHCO_3$ aq solution (30 mL) and H_2O (30 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford a yellowish oil (2.2 g). Purification by flash column chromatography (EtOAc/heptane, gradient from 5% to 20%) yielded pure 6-(benzyloxy)hex-3-ynyl 4-methylbenzenesulfonate (1.8 g, 5.1 mmol, 86%) as a colourless oil. IR (neat): 2359, 1359, 1188, 1174, 1096, 970, 899, 814, 738, 698, 661 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.40 (tt, *J*=7.0, 2.5 Hz, 2H), 2.43 (s, 3H), 2.51 (tt, *J*=7.0, 2.5 Hz, 2H), 3.50 (t, *J*=7.0 Hz, 2H), 4.05 (t, *J*=7.0 Hz, 2H), 4.52 (s, 2H), 7.23–7.38 (m, 7H), 7.79 (d, *J*=8.5 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.6, 19.9, 21.5, 68.0, 68.3, 72.8, 75.1, 79.4, 127.5, 127.5, 127.8, 128.3, 129.7, 132.8, 138.0, 144.7. MS (ES^+) *m/z 381* (MNa^+), 382. Anal. Calcd for $C_{20}H_{22}O_4S$: C 67.01, H 6.19. Found: C 66.91, H 6.36.

6-(Benzyloxy)hex-3-ynyl 4-methylbenzenesulfonate (1.0 equiv, 3.6 mmol, 1.3 g) was added to a mixture of aniline (3.0 equiv, 11 mmol, 1.0 mL) and sodium acetate (1.0 equiv, 3.6 mmol, 0.50 g) in acetonitrile (5.0 mL) at reflux. After 46 h of stirring at reflux, the reaction medium was cooled and diluted with CH_2Cl_2 (30 mL), then washed with 1 N HCl aq solution (2×30 mL) to remove the excess amount of aniline (the protonated alkylated aniline remained in the organic layer). The organic phase was then washed with 1 N NaOH aq solution (30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to afford a viscous dark brown oil (1.0 g). This oil was dissolved in CH_2Cl_2 (20 mL). Acetyl chloride (1.5 equiv, 5.4 mmol, 0.37 mL) was added at 0 °C, followed by 1 N NaOH aq solution (20 mL). After 20 min of vigorous stirring, the organic layer was separated, washed with 1 N HCl aq solution (20 mL) and H_2O (20 mL), then dried over sodium sulfate, filtered and concentrated under reduced pressure to afford a viscous dark brown oil (1.1 g). Purification by flash column chromatography (EtOAc/heptane, gradient from 10% to 30%) yielded pure *N*-(6-(benzyloxy)hex-3-ynyl)-*N*-phenylethanamide (0.82 g, 2.5 mmol, 70%) as a colourless oil. IR (neat): 2912, 2860, 1657, 1595, 1494, 1391, 1362, 1299, 1097, 737, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.82 (s, 3H), 2.36–2.46 (m, 4H), 3.51 (t, *J*=7.0 Hz, 2H), 3.82 (t, *J*=7.0 Hz, 2H), 4.52 (s, 2H), 7.16–7.23 (m, 2H), 7.23–7.43 (m, 8H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.7, 19.7, 22.3, 47.8, 68.3, 72.4, 77.9, 78.1, 127.2, 127.2, 127.5, 127.7, 127.9, 129.2, 137.8, 142.6, 169.7. MS (ES^+) *m/z 344* (MNa^+), 345. HRMS (ES^+) *m/z* calcd for $C_{21}H_{23}NNaO_2$ (MNa^+) 344.1626, found 344.1592.

Titanium(IV) *iso*-propoxide (2.0 equiv, 2.0 mmol, 0.59 mL) was added at −70 °C to a suspension of *N*-(6-(benzyloxy)hex-3-ynyl)-*N*-phenylethanamide (1.0 equiv, 1.0 mmol, 0.32 g) in Et_2O (20 mL), followed by *cyclo*-pentylmagnesium chloride (1.8 M in Et_2O, 4.0 equiv, 4.0 mmol, 2.2 mL) dropwise. The resulting yellow mixture was allowed to warm to −30 °C in 5 min and maintained at that temperature for 15 min, by which time it had become orange. The reaction medium was then hydrolysed at −30 °C with 0.3 N HCl aq solution (40 mL) and allowed to warm to 20 °C. The mixture was diluted with Et_2O (30 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O (2×30 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford an orange oil (0.37 g). Purification of the crude product by two successive flash column chromatographies (silica gel, EtOAc/heptane, gradient from 10% to 20%, then neutral alumina gel, same solvent system) yielded starting alkyne (36 mg, 0.11 mmol, 11%) and pure (*Z*)-**1e** (0.25 g, 0.76 mmol, 76%) as a colourless oil. IR (neat): 2856, 1651, 1595, 1494, 1392, 1360, 1296, 1093, 1026, 735, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.82 (s, 3H), 2.24–2.36 (m, 4H), 3.44 (t, *J*=7.0 Hz, 2H), 3.73 (t, *J*=7.5 Hz, 2H), 4.48 (s, 2H), 5.36–5.55 (m, 2H), 7.15 (br d, *J*=7.5 Hz, 2H), 7.23–7.44 (m, 8H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.7, 25.9, 27.9, 48.5, 69.7, 72.7, 127.4, 127.5, 127.7, 127.7, 128.0, 128.0, 128.2, 129.5, 138.4, 143.0, 170.1. MS (ES^+) *m/z* 309, *346* (MNa^+), 347. HRMS (ES^+) *m/z* calcd for $C_{21}H_{25}NNaO_2$ (MNa^+) 346.1783, found 346.1797.

*4.5.2. (Z)-N-(6-(4-Methoxybenzyloxy)hex-3-enyl)-N-phenylethanamide ((Z)-**1n**)*

n-Butyllithium (1.2 M in hexanes, 1.0 equiv, 25 mmol, 21 mL) was added dropwise over 30 min to a solution of 1-((but-3-ynyloxy)methyl)-4-methoxybenzene[42] (1.0 equiv, 25 mmol, 4.8 g) in THF (50 mL) at −70 °C. The solution was stirred for 30 min at −70 °C (black colour), and 1,3,2-dioxathiolane-2,2-dioxide[40,41] (1.0 equiv, 25 mmol, 3.2 g) was added. The mixture was stirred for 30 min at −70 °C, and then allowed to warm to −50 °C over 2 h. The cold bath was removed, and a mixture of H_2O (0.50 mL) and concentrated H_2SO_4 (0.40 mL) was added. The reaction medium was stirred for 1 h (hydrolysis was monitored by TLC analysis). NaOH aq solution (1 N, 50 mL) was then added. The organic layer was separated and the aqueous phase was extracted with Et_2O (2×0.20 L). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a brown oil (5.4 g). Purification by flash column chromatography (EtOAc/heptane, gradient from 10% to 30%) yielded pure 6-(4-methoxybenzyloxy)-hex-3-yn-1-ol (4.3 g, 18 mmol, 73%) as a viscous colourless oil. IR (neat): 3401, 2864, 1612, 1512, 1244, 1173, 1089, 1032, 820 cm^{-1}. ^1H

NMR (300 MHz, $CDCl_3$): δ 2.38 (tt, J=6.5, 2.5 Hz, 2H), 2.45 (tt, J=7.0, 2.5 Hz, 2H), 2.73 (br s, 1H, OH), 3.52 (t, J=7.0 Hz, 2H), 3.63 (t, J=6.5 Hz, 2H), 3.78 (s, 3H), 4.46 (s, 2H), 7.06 (AA′BB′ system,[43] δ_A=6.87 ppm, δ_B=7.25 ppm, K=5.0 Hz, L=8.0 Hz, N=8.5 Hz (M could not be measured accurately), 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.9, 22.9, 55.0, 60.9, 68.1, 72.3, 77.8, 78.7, 113.6, 129.2, 129.9, 159.1. MS (ES^+) *m/z 257* (MNa^+). HRMS (ES^+) m/z calcd for $C_{14}H_{18}NaO_3$ (MNa^+) 257.1154, found 257.1142.

para-Toluenesulfonyl chloride (1.05 equiv, 18 mmol, 3.4 g) was added portionwise at 0 °C to a solution of 6-(4-methoxybenzyloxy)hex-3-yn-1-ol (1.0 equiv, 17 mmol, 4.0 g) in pyridine (4.0 equiv, 68 mmol, 5.5 mL). After 1.5 h of stirring at 20 °C and 15 h of standing at 0 °C (fridge), the reaction mixture was diluted with Et_2O (70 mL), and then washed successively with 1 N HCl aq solution (70 mL), saturated $NaHCO_3$ aq solution (70 mL) and H_2O (70 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford 6-(4-methoxybenzyloxy)hex-3-ynyl 4-methylbenzenesulfonate (6.1 g, 16 mmol, 92%) as a colourless oil that was used in the next step without further purification. IR (neat): 2861, 1511, 1358, 1245, 1188, 1173, 1094, 969, 898, 813, 757 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.38 (tt, J=7.0, 2.5 Hz, 2H), 2.42 (s, 3H), 2.50 (tt, J=7.0, 2.5 Hz, 2H), 3.47 (t, J=7.0 Hz, 2H), 3.78 (s, 3H), 4.05 (t, J=7.0 Hz, 2H), 4.44 (s, 2H), 7.05 (AA′BB′ system,[43] δ_A=6.87 ppm, δ_B=7.24 ppm, K=5.0 Hz, L=8.0 Hz, N=8.5 Hz (M could not be measured accurately), 4H), 7.55 (AA′BB′ system,[43] δ_A=7.32 ppm, δ_B=7.78 ppm, K=3.5 Hz, L=7.5 Hz, N=8.5 Hz (M could not be measured accurately), 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.6, 19.9, 21.5, 55.1, 68.0, 68.0, 72.4, 75.0, 79.4, 113.7, 127.8, 129.2, 129.7, 130.0, 132.8, 144.7, 159.1. MS (ES^+) *m/z 411* (MNa^+), 412. HRMS (ES^+) m/z calcd for $C_{21}H_{24}NaO_5S$ (MNa^+) 411.1242, found 411.1222.

6-(4-Methoxybenzyloxy)hex-3-ynyl 4-methylbenzenesulfonate (1.0 equiv, 14 mmol, 5.5 g) was added to a mixture of aniline (3.0 equiv, 43 mmol, 4.0 mL) and sodium acetate (1.0 equiv, 14 mmol, 2.0 g) in acetonitrile (20 mL). After 20 h of stirring at reflux, the mixture was cooled, diluted with CH_2Cl_2 (50 mL) and washed successively with 1 N HCl aq solution (60 mL), 1 N NaOH aq solution (60 mL) and H_2O (60 mL). It was then dried over sodium sulfate, filtered and concentrated under reduced pressure to afford a viscous brown oil (4.4 g). This oil was dissolved in CH_2Cl_2 (50 mL). Acetyl chloride (1.5 equiv, 21 mmol, 1.5 mL) was added at 0 °C, followed by 1 N NaOH aq solution (45 mL). After 5 min of vigorous shaking, the organic layer was separated, washed with 1 N HCl aq solution (50 mL) and H_2O (50 mL), then dried over sodium sulfate, filtered and concentrated under reduced pressure to afford a viscous yellow oil (4.6 g). Purification by flash column chromatography (EtOAc/heptane, gradient from 10% to 30%) yielded pure *N*-(6-(4-methoxybenzyloxy)hex-3-ynyl)-*N*-phenylethanamide (3.7 g, 11 mmol, 75%) as a viscous colourless oil. IR (neat): 2910, 2859, 1656, 1651, 1495, 1392, 1300, 1244, 1091, 1031 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.82 (s, 3H), 2.35–2.45 (m, 4H), 3.48 (t, J=7.0 Hz, 2H), 3.79 (s, 3H), 3.82 (t, J=7.0 Hz, 2H), 4.45 (s, 2H), 7.06 (AA′BB′ system,[43] δ_A=6.87 ppm, δ_B=7.25 ppm, K=5.0 Hz, L=8.0 Hz, N=8.5 Hz (M could not be measured accurately), 4H), 7.19 (br d, J=7.5 Hz, 2H), 7.29–7.43 (m, 3H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 17.8, 19.8, 22.4, 47.9, 54.9, 68.1, 72.2, 78.0, 78.2, 113.5, 127.7, 127.9, 129.0, 129.4, 130.0, 142.6, 158.9, 169.9. MS (ES^+) *m/z 374* (MNa^+), 375. HRMS (ES^+) m/z calcd for $C_{22}H_{25}NNaO_3$ (MNa^+) 374.1732, found 374.1717.

Titanium(IV) *iso*-propoxide (2.0 equiv, 8.0 mmol, 2.4 mL) was added at −70 °C to a solution of *N*-(6-(4-methoxybenzyloxy)hex-3-ynyl)-*N*-phenylethanamide (1.0 equiv, 4.0 mmol, 1.4 g) in Et_2O (80 mL), followed by *cyclo*-pentylmagnesium chloride (2.0 M in Et_2O, 4.0 equiv, 16 mmol, 7.8 mL) dropwise over 20 min. The resulting yellow mixture was allowed to warm to −30 °C in 5 min and maintained at that temperature for 45 min, by which time it had become brown. The reaction medium was then hydrolysed at −30 °C with 0.3 N HCl aq solution (0.10 L), and allowed to warm to 20 °C. The organic layer was separated and the aqueous phase was extracted with Et_2O (2×0.10 L). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford a viscous yellow oil (1.5 g). Purification of the crude product by two successive flash column chromatographies (neutral alumina gel, EtOAc/heptane, gradient from 10% to 30%) yielded starting alkyne (0.19 g, 0.55 mmol, 14%) and (*Z*)-**1n** (1.0 g, 3.0 mmol, 74%, contaminated with traces of starting alkyne) as a viscous colourless oil. IR (neat): 2933, 2855, 1651, 1512, 1495, 1392, 1300, 1245, 1089, 1032, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.81 (s, 3H), 2.23–2.35 (m, 4H), 3.42 (t, J=7.0 Hz, 2H), 3.73 (t, J=7.5 Hz, 2H), 3.79 (s, 3H), 4.41 (s, 2H), 5.34–5.55 (m, 2H), 7.05 (AA′BB′ system,[43] δ_A=6.86 ppm, δ_B=7.23 ppm, K=5.0 Hz, L=8.0 Hz, N=8.5 Hz (M could not be measured accurately), 4H), 7.15 (br d, J=7.5 Hz, 2H), 7.28–7.44 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.7, 25.9, 27.9, 48.4, 55.1, 69.3, 72.4, 113.6, 127.7, 127.7, 128.0, 128.0, 129.1 and 129.5, 130.5, 143.0, 159.0, 170.1. MS (ES^+) *m/z 376* (MNa^+), 377. Anal. Calcd for $C_{22}H_{27}NO_3$: C 74.76, H 7.70. Found: C 74.74, H 7.84.

4.6. Synthesis of amides (*Z*)-1c, (*Z*)-1o, (*Z*)-1p and (*Z*)-1q

*4.6.1. (Z)-N-(6-Hydroxyhex-3-enyl)-N-phenylethanamide ((Z)-**1c**)*

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (1.0 equiv, 3.0 mmol, 0.69 g) was added to a solution of PMB ether (*Z*)-**1n** (contaminated with about 4% of *N*-(6-(4-methoxybenzyloxy)hex-3-ynyl)-*N*-phenylethanamide) (1.0 equiv, 3.0 mmol, 1.1 g) in a mixture of CH_2Cl_2 (30 mL) and H_2O (2.0 mL). After 2.5 h of stirring at 20 °C, a precipitate had formed and the red mixture was filtered. The solution was diluted with Et_2O (70 mL), washed with saturated $NaHCO_3$ aq solution (100 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to afford a viscous yellow-orange oil (1.0 g). Purification by flash column chromatography (EtOAc/heptane, gradient from 20% to 100%) yielded pure alcohol (*Z*)-**1c** (0.52 g, 2.2 mmol, 74%) as a colourless oil. IR (neat): 3394, 2928, 2873, 1633, 1594, 1495, 1396, 1296, 1047, 1024, 729, 699 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.83 (s, 3H), 2.20 (br s, 1H, OH), 2.26–2.38 (m, 4H), 3.64 (t, J=6.5 Hz, 2H), 3.73 (t, J=7.5 Hz, 2H), 5.43–5.57 (m, 2H), 7.18 (br d, J=7.5 Hz, 2H), 7.32–7.48 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.7, 25.8, 30.9, 49.0, 61.9, 127.9, 128.0, 128.2, 128.6, 129.7, 143.0, 170.5. MS (ES^+) m/z 253, 254, *256* (MNa^+), 257. Anal. Calcd for $C_{14}H_{19}NO_2$: C 72.07, H 8.21. Found: C 72.01, H 8.43.

*4.6.2. (Z)-N-Phenyl-N-(6-(tetrahydro-2H-pyran-2-yloxy)hex-3-enyl)ethanamide ((Z)-**1o**)*

para-Toluenesulfonic acid (1.0% equiv, 8.0 μmol, 1.4 mg) was added to a mixture of alcohol (*Z*)-**1d** (1.0 equiv, 0.80 mmol, 0.19 g) and dihydropyrane (1.1 equiv, .88 mmol, 83 μL). After 4 h of stirring at 20 °C, the mixture was diluted with diethyl ether (20 mL) and washed with saturated Na_2CO_3 aq solution (20 mL). The aqueous layer was extracted with diethyl ether (2×20 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford a colourless oil (0.26 g). Purification by flash column chromatography (EtOAc/heptane, gradient from 10% to 50%) yielded pure homoallylic ether (*Z*)-**1o** (0.22 g, 0.69 mmol, 86%) as a colourless oil. IR (neat): 2939, 2868, 1657, 1595, 1495, 1391, 1120, 1073, 1028, 982, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43–1.90 (m, 6H), 1.83 (s, 3H), 2.24–2.35 (m, 4H), 3.37 (dt, J=9.5, 7.0 Hz, 1H), 3.48 (m, 1H), 3.71 (dt, J=9.5, 7.0 Hz, 1H), 3.74 (t, J=7.5 Hz, 2H), 3.84 (ddd, J=11.0, 7.5, 3.5 Hz, 1H), 4.56 (dd, J=4.0, 3.0 Hz, 1H), 5.36–5.55 (m, 2H), 7.17 (br d, J=7.5 Hz, 2H), 7.31–7.47 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.4, 22.7, 25.3, 25.9, 27.9, 30.5, 48.4, 62.1, 66.7, 98.6, 127.6, 127.7, 128.1, 128.1, 129.5, 142.9, 170.1. MS (ES^+) *m/z 340* (MNa^+), 341. HRMS (ES^+) m/z calcd for $C_{19}H_{27}NNaO_3$ (MNa^+) 340.1889, found 340.1899.

*4.6.3. (Z)-6-(N-Phenylethanamido)hex-3-enyl ethanoate ((Z)-**1p**)*

Acetic anhydride (2.0 equiv, 1.8 mmol, 0.17 mL) was added to a solution of alcohol (*Z*)-**1c** (1.0 equiv, 0.90 mmol, 0.21 g) in pyridine (6.0 equiv, 5.4 mmol, 0.44 mL). The mixture was stirred for 16 h at 20 °C, then diluted with Et_2O (20 mL) and washed with 0.3 N HCl aq solution (2×20 mL) followed by H_2O (20 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to afford a viscous brown oil (0.22 g). Purification by flash column chromatography (EtOAc/heptane, gradient from 10% to 40%) yielded pure acetate (*Z*)-**1p** (0.18 g, 0.65 mmol, 72%) as a colourless oil. IR (neat): 2934, 1733, 1651, 1595, 1495, 1391, 1362, 1234, 1032, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.83 (s, 3H), 2.02 (s, 3H), 2.26–2.39 (m, 4H), 3.74 (t, *J*=7.5 Hz, 2H), 4.04 (t, *J*=7.0 Hz, 2H), 5.36–5.55 (m, 2H), 7.18 (br d, *J*=7.0 Hz, 2H), 7.31–7.49 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.7, 22.6, 25.7, 26.7, 48.4, 63.5, 126.7, 127.7, 127.9, 128.6, 129.5, 142.8, 170.1, 170.8. MS (ES^+) *m*/*z* 243, 287, 296, *298* (MNa^+), 299. Anal. Calcd for $C_{16}H_{21}NO_3$: C 69.79, H 7.69. Found: C 70.01, H 7.82.

*4.6.4. (Z)-6-(N-Phenylethanamido)hex-3-enyl 2,2-dimethylpropanoate ((Z)-**1q**)*

Pyridine (1.2 equiv, 0.31 mmol, 25 μL) and trimethylacetyl chloride (1.2 equiv, 0.31 mmol, 39 μL) were added successively to a solution of alcohol (*Z*)-**1d** (1.0 equiv, 0.26 mmol, 60 mg) in CH_2Cl_2 (0.20 mL) at 0 °C. The mixture was allowed to warm to 20 °C and stirred at that temperature for 18 h, then diluted with CH_2Cl_2 (15 mL). The solution was washed with 0.3 N HCl aq solution (2×15 mL) and H_2O (15 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to afford a viscous brown oil (87 mg). Purification by flash column chromatography (EtOAc/heptane, gradient from 10% to 30%) yielded pure acetate (*Z*)-**1q** (69 mg, 0.22 mmol, 84%) as a colourless oil. IR (neat): 2360, 2340, 1724, 1657, 1596, 1495, 1394, 1284, 1151, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.17 (s, 9H), 1.83 (s, 3H), 2.24–2.38 (m, 4H), 3.74 (t, *J*=7.5 Hz, 2H), 4.03 (t, *J*=7.0 Hz, 2H), 5.37–5.52 (m, 2H), 7.17 (br d, *J*=7.5 Hz, 2H), 7.30–7.48 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.7, 25.9, 26.9, 27.1, 38.6, 48.5, 63.5, 127.0, 127.8, 128.0, 128.4, 129.6, 143.0, 170.2, 178.4. MS (ES^+) *m*/*z* 243, 329, *340* (MNa^+), 341. HRMS (ES^+) *m*/*z* calcd for $C_{19}H_{27}NNaO_3$ (MNa^+) 340.1889, found 340.1868.

4.7. Intramolecular Kulinkovich–de Meijere reactions

Typically, titanium(IV) *iso*-propoxide (1.5 equiv, 1.5 mmol, 0.44 mL) was added to a solution of the substrate under study (1.0 equiv, 1.0 mmol) in Et_2O (20 mL), followed by *cyclo*-pentylmagnesium chloride (2.0 M in Et_2O, 4.0 equiv, 4.0 mmol, 2.0 mL) dropwise at 20 °C. After 20 min of stirring, water (15 mL) was added to the dark solution, which was exposed to air, and stirring was continued until decolouration. Et_2O (50 mL) and H_2O (50 mL) were then added. The organic layer was separated, and the aqueous phase was extracted with Et_2O (50 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The crude product was analysed by NMR spectroscopy, and then purified by flash column chromatography (neutral alumina gel, activity II).

*4.7.1. Reaction of alkenyl diamide (E)-**1b***

The general procedure for the intramolecular Kulinkovich–de Meijere reactions was applied to alkenyl amide (*E*)-**1b** (1.0 equiv, 0.75 mmol, 0.26 g) in THF, under more diluted conditions (30 mL of THF), to afford the crude product (0.42 g) as a brown oil. Analysis of this crude product by ^1H NMR spectroscopy revealed a complex mixture of compounds. ^{13}C NMR spectroscopy confirmed the presence of the expected *cis* aminocyclopropane *cis*-**2b**, while the corresponding trans diastereoisomer was not detected (no peak between 51 ppm and 54 ppm). Purification by two successive flash column chromatographies (neutral alumina gel, activity II-III, EtOAc/heptane, gradient from 0% to 100%, then EtOAc/heptane, gradient from 0% to 20%) and by several preparative TLCs yielded *N*-(2-((1*R**,5*S**,6*R**)-1-methyl-2-phenyl-2-azabicyclo[3.1.0]hexan-6-yl)ethyl)aniline (7.3 mg, 25 μmol, 3%), (*E*)-*N*-(6-((1-cyclopentylethyl)(phenyl)amino)hex-3-enyl)-*N*-phenylethanamide (2.7 mg, 6.6 μmol, 1%), (*E*)-*N*-(6-((6-methylbicyclo[3.1.0]hexan-6-yl)(phenyl)amino)hex-3-enyl)-*N*-phenylethanamide (2.9 mg, 7.2 μmol, 1%), pure (*cis*)-**2b** (60 mg, 0.18 mmol, 24%), (*E*)-*N*-phenyl-*N*-(6-(phenylamino)hex-3-enyl)ethanamide (18 mg, 58 μmol, 8%) and starting (*E*)-**1b** (22 mg, 64 μmol, 8%).

4.7.1.1. N-(2-((1S,5S*,6R*)-1-Methyl-2-phenyl-2-azabicyclo[3.1.0]hexan-6-yl)ethyl)-N-phenylethanamide (cis-**2b**).* Crystals suitable for X-ray diffraction studies (26 mg) were obtained by recrystallising (*cis*)-**2b** from heptane containing a few drops of CH_2Cl_2. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 682237. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk). Colourless crystals. Mp 102.1–103.2 °C. IR (neat): 3401, 2930, 1656, 1597, 1497, 1396, 1363, 1070, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.07 (td, *J*=8.5, 5.5 Hz, 1H), 1.19 (dddd, *J*=13.5, 9.5, 8.5, 5.5 Hz, 1H), 1.41 (ddd, *J*=8.5, 7.5, 1.5 Hz, 1H), 1.47 (s, 3H), 1.52 (ddt, *J*=13.5, 10.0, 5.5 Hz, 1H), 1.77 (s, 3H), 1.82 (dddd, *J*=13.0, 10.0, 6.5, 1.5 Hz, 1H), 2.24 (dddd, *J*=13.0, 10.0, 7.5, 4.5 Hz, 1H), 3.02 (td, *J*=10.0, 4.5 Hz, 1H), 3.57 (ddd, *J*=13.0, 10.0, 5.5 Hz, 1H), 3.85 (ddd, *J*=13.0, 10.0, 5.5 Hz, 1H), 3.97 (td, *J*=10.0, 6.5 Hz, 1H), 6.57 (br d, *J*=8.5 Hz, 2H), 6.63 (tt, *J*=7.5, 1.0 Hz, 1H), 7.00 (m, 2H), 7.13 (br dd, *J*=8.5, 7.5 Hz, 2H), 7.26–7.36 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.3, 22.2, 22.4, 22.8, 28.5, 31.1, 46.5, 49.2, 55.9, 113.8, 115.8, 127.6, 127.8, 128.6, 129.5, 143.1, 147.9, 170.1. MS (ES^+) *m*/*z* 335 (MH^+), *357* (MNa^+).

4.7.1.2. N-(2-((1R,5S*,6R*)-1-Methyl-2-phenyl-2-azabicyclo[3.1.0]hexan-6-yl)ethyl)aniline.* ^1H NMR (300 MHz, $CDCl_3$): δ 1.14–1.34 (m, 2H), 1.48 (ddd, *J*=8.5, 7.5, 1.5 Hz, 1H), 1.54 (s, 3H), 1.63 (m, 1H), 1.87 (dddd, *J*=13.5, 10.0, 6.0, 1.5 Hz, 1H), 2.33 (dddd, *J*=13.5, 10.0, 7.5, 4.5 Hz, 1H), 3.16 (td, *J*=10.0, 4.5 Hz, 1H), 3.16 (m, 2H), 3.63, (br s, 1H, NH), 4.05 (td, *J*=10.0, 6.0 Hz, 1H), 6.50 (br d, *J*=8.5 Hz, 2H), 6.60–6.74 (m, 4H), 7.12 (br dd, *J*=8.5, 7.5 Hz, 2H), 7.20 (br dd, *J*=8.5, 7.5 Hz, 2H).

4.7.1.3. (E)-N-(6-((1-Cyclopentylethyl)(phenyl)amino)hex-3-enyl)-N-phenylethanamide. Colourless oil. IR (neat): 3407, 2929, 1661, 1596, 1498, 1394, 1296, 1159, 1032 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.12 (d, *J*=6.5 Hz, 3H), 1.10–1.35 (m, 3H), 1.43–1.83, (m, 5H), 1.83 (s, 3H), 2.05 (dquint, *J*=10.0, 8.0 Hz 1H), 2.09–2.32 (m, 4H), 3.13 (AB part of an ABXY system, δ_A=3.10 ppm, δ_B=3.17 ppm, J_{AB}=15.0 Hz, J_{AX}=10.0 Hz, J_{AY}=5.5 Hz, J_{BX}=5.5 Hz, J_{BY}=10.5 Hz, 2H), 3.53 (dq, *J*=10.0 and 6.5 Hz, 1H), 3.74 (t, *J*=7.5 Hz, 2H), 5.44 (AB part of an ABX_2Y_2 system, δ_A=5.42 ppm, δ_B=5.47 ppm, J_{AB}=15.5 Hz, J_{AX}=6.0 Hz, J_{AY}=0.0 Hz, J_{BX}=0.0 Hz, J_{BY}=6.0 Hz, 2H), 6.64 (t, *J*=7.5 Hz, 2H), 6.72 (d, *J*=8.5 Hz, 2H), 7.13–7.22 (m, 3H), 7.35 (t, *J*=7.0 Hz, 1H), 7.42 (t, *J*=7.5 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.2, 22.8, 25.2, 25.8, 30.7, 30.9, 31.2, 31.2, 43.7, 45.1, 48.8, 59.6, 113.5, 115.8, 127.8, 128.2, 128.3, 129.0, 129.6, 129.8, 143.2, 149.0, 170.2. MS (ES^+) *m*/*z* 309, 405 (MH^+), *427* (MNa^+). HRMS (ES^+) *m*/*z* calcd for $C_{27}H_{37}N_2O$ (MH^+) 405.2906, found 405.2941; calcd for $C_{27}H_{36}N_2NaO$ (MNa^+) 427.2725, found 427.2741.

4.7.1.4. (E)-N-(6-((6-Methylbicyclo[3.1.0]hexan-6-yl)(phenyl)amino)-hex-3-enyl)-N-phenylethanamide. Colourless oil. IR (neat): 2925, 2864, 1661, 1597, 1497, 1393, 1295, 1168, 749, 698 cm^{-1}. ^1H NMR

(400 MHz, $CDCl_3$): δ 1.10 (s, 3H), 1.47 (m, 1H), 1.60 (m, 2H); 1.73 (m, 2H), 1.83 (s, 3H), 1.84 (m, 1H), 1.99 (m, 2H), 2.19–2.33 (m, 4H), 3.25 (m, 2H), 3.75 (t, J=7.5 Hz, 2H), 5.45 (AB part of an ABX_2Y_2 system, δ_A=5.44 ppm, δ_B=5.47 ppm, J_{AB}=15.5 Hz, J_{AX}=5.5 Hz, J_{AY}=0.0 Hz, J_{BX}=0.0 Hz, J_{BY}=5.5 Hz, 2H), 6.59–6.75 (m, 3H), 7.12–7.24 (m, 4H), 7.35 (m, 1H), 7.42 (m, 2H). MS (ES^+) *m/z* 403 (MH^+), *425* (MNa^+), 426.

4.7.1.5. (E)-N-Phenyl-N-(6-(phenylamino)hex-3-enyl)ethanamide Yellow oil. IR (neat): 3364, 2924, 2853, 1650, 1599, 1500, 1398, 1298, 970 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.82 (s, 3H), 2.16–2.37 (m, 4H), 3.12 (t, J=6.5 Hz, 2H), 3.55–3.85 (br s, 1H, NH), 3.76 (t, J=7.5 Hz, 2H), 5.49 (AB part of an ABX_2Y_2 system, δ_A=5.47 ppm, δ_B=5.51 ppm, J_{AB}=15.5 Hz, J_{AX}=5.5 Hz, J_{AY}=0.0 Hz, J_{BX}=0.0 Hz, J_{BY}=5.5 Hz, 2H), 6.61 (dd, J=8.0, 1.0 Hz, 2H), 6.68 (tt, J=7.5 and 1.0 Hz, 1H), 7.10–7.21 (m, 4H), 7.30–7.46 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.8, 31.1, 32.4, 43.1, 48.6, 112.8, 117.2, 127.9, 128.2, 129.2, 129.4, 129.5, 129.7, 143.0, 148.3, 170.3. MS (ES^+) *m/z* 174, 204, 216, *309* (MH^+), 310. HRMS (ES^+) *m/z* calcd for $C_{20}H_{25}N_2O$ (MH^+) 309.1967, found 309.1975.

*4.7.2. Reaction of alkenyl amide **1c** (E/Z≈75:25)*

The general procedure for the intramolecular Kulinkovich–de Meijere reactions was applied to alkenyl amide **1c** (*E*/*Z*≈75:25, 1.0 equiv, 0.48 mmol, 0.11 g), under more diluted conditions (16 mL of Et_2O), to afford the crude product (99 mg) as a yellow oil. Analysis by ^1H NMR spectroscopy revealed the presence of the expected aminocyclopropane **2c** in an estimated yield of about 9% (cis/trans≈64:36, see Sections 4.7.21.1 and 4.7.22.1 for analytical data). The crude reaction product also contained starting material **1c** (89%, *E*/*Z*≈79:21 evaluated by ^{13}C NMR by measuring the relative heights of the peaks corresponding to the CH_2 groups adjacent to the nitrogen atom).

*4.7.3. Reaction of alkenyl amide (Z)-**1c***

The general procedure for the intramolecular Kulinkovich–de Meijere reactions was applied to alkenyl amide (*Z*)-**1c** (1.0 equiv, 0.26 mmol, 62 mg) with a larger amount of *cyclo*-pentylmagnesium chloride (5.0 equiv) and under more diluted conditions (11 mL of Et_2O), to afford the crude product (58 mg) as a viscous brown oil. Analysis of this crude product by ^1H NMR spectroscopy revealed the presence of the expected *trans* aminocyclopropane *trans*-**2c** in an estimated yield of about 10% (see Section 4.7.22.1 for analytical data). The cis diastereoisomer was not detected. The crude reaction product also contained a mixture of compounds retaining the carbon–carbon double bond (86%), including starting material (*Z*)-**1c** (75%). Purification by flash column chromatography (EtOAc/heptane, gradient from 30% to 100%) yielded pure starting (*Z*)-**1c** (38 mg, 0.16 mmol, 62%).

*4.7.4. Reaction of alkenyl amide **1d** (E/Z≈85:15)*

The general procedure for the intramolecular Kulinkovich–de Meijere reactions was applied to alkenyl amide **1d** (*E*/*Z*≈85:15, 1.0 equiv, 2.0 mmol, 0.70 g), under more diluted conditions (68 mL of Et_2O), to afford the crude product (0.68 g) as a yellow oil. Analysis by ^1H NMR spectroscopy revealed the presence of the expected aminocyclopropane **2d** in an estimated yield of 38% (cis/trans≈68:32). The crude product also contained a mixture of compounds retaining the carbon–carbon double bond (44%), including starting material **1d** (18%). Purification by flash column chromatography (neutral alumina gel, activity II, EtOAc/heptane, gradient from 0% to 30%) yielded pure (*cis*)-**2d** (98 mg, 0.30 mmol, 15%) and starting **1d** (*E*/*Z*≈98:2 as measured by GC/MS, 0.12 g, 0.34 mmol, 17%).

4.7.4.1. (1S,5S*,6R*)-6-(2-(tert-Butyldimethylsilyloxy)ethyl)-1-methyl-2-phenyl-2-azabicyclo[3.1.0]hexane (cis-**2d**).* Yellow oil. IR (neat): 3024, 2952, 2926, 2854, 1598, 1501, 1360, 1250, 1093, 832, 810 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ −0.01 (s, 6H), 0.86 (s, 9H), 1.08–1.31 (m, 2H), 1.43 (ddd, J=8.0, 7.5, 1.0 Hz, 1H), 1.47–1.72 (m, 1H), 1.50 (s, 3H), 1.88 (dddd, J=13.0, 10.0, 6.0, 1.0 Hz, 1H), 2.30 (dddd, J=13.0, 10.0, 7.5, 4.5 Hz, 1H), 3.15 (td, J=10.0, 4.5 Hz, 1H), 3.59–3.68 (m, 2H), 4.04 (td, J=10.0, 6.0 Hz, 1H), 6.63 (d, J=8.0 Hz, 2H), 6.64 (t, J=8.0 Hz, 1H), 7.17 (t, J=8.0 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −5.3, 14.1, 18.4, 26.0, 27.6, 28.5, 30.7, 31.9, 46.4, 55.9, 63.3, 113.9, 115.8, 128.7, 148.0. MS (ES^+) *m/z 332* (MH^+), 354 (MNa^+). HRMS (ES^+) *m/z* calcd for $C_{20}H_{34}NOSi$ (MH^+) 332.2410, found 332.2403.

4.7.4.2. (1S,5S*,6S*)-6-(2-(tert-Butyldimethylsilyloxy)ethyl)-1-methyl-2-phenyl-2-azabicyclo[3.1.0]hexane (trans-**2d**).* ^1H NMR (300 MHz, $CDCl_3$), characteristic signals: δ 1.04 (t, J=5.5 Hz, 1H), 1.52 (s, 3H), 2.87 (dt, J=9.5, 8.5 Hz, 1H), 3.94 (td, J=9.5, 3.0 Hz, 1H).

*4.7.5. Reaction of alkenyl amide (E)-**1d***

The general procedure for the intramolecular Kulinkovich–de Meijere reactions was applied to alkenyl amide **1d** (recovered from the preceding experiment, *E*/*Z*=98:2, 1.0 equiv, 0.35 mmol, 0.12 g) to afford the crude product (0.11 g) as a yellow oil. Analysis by ^1H NMR spectroscopy revealed the presence of the expected aminocyclopropane **2d** in an estimated yield of about 24% (cis/trans≈98:2). The crude reaction product also contained a mixture of compounds retaining the carbon–carbon double bond (52%), including starting material (*E*)-**1d** (34%).

*4.7.6. Reaction of alkenyl amide **1e** (E/Z≈85:15)*

The general procedure for the intramolecular Kulinkovich–de Meijere reactions was applied to alkenyl amide **1e** (*E*/*Z*≈85:15, 1.0 equiv, 2.3 mmol, 0.75 g), under more diluted conditions (78 mL of Et_2O), to afford the crude product (0.74 g) as a yellow oil. Analysis by ^1H NMR spectroscopy revealed the presence of the expected aminocyclopropane **2e** in an estimated yield of about 53% (cis/trans≈79:21). The crude reaction product also contained a mixture of compounds retaining the carbon–carbon double bond (31%), including starting material **1e** (16%). Purification by flash column chromatography (neutral alumina gel, activity II, EtOAc/heptane, gradient from 0% to 30%) yielded pure (*cis*)-**2e** (39 mg, 0.13 mmol, 5%), an unpure 80:20 mixture of (*cis*) and (*trans*)-**2e** (0.47 g), *N*-(6-(benzyloxy)hex-3-enyl)aniline (67 mg, 0.23 mmol, 10%) and starting **1e** (*E*/*Z*≈87:13 as measured by GC/MS, 0.12 g, 0.36 mmol, 16%). A sample of pure (*trans*)-**2e** could be obtained by performing a further flash column chromatography.

4.7.6.1. (1S,5S*,6R*)-6-(2-(Benzyloxy)ethyl)-1-methyl-2-phenyl-2-azabicyclo[3.1.0]hexane (cis-**2e**).* Colourless oil. IR (neat): 3026, 2930, 2858, 1599, 1502, 1484, 1453, 1361, 1325, 1112 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.09–1.30 (m, 2H), 1.43 (ddd, J=8.0, 7.5, 1.5 Hz, 1H), 1.50 (s, 3H), 1.62 (m, 1H), 1.85 (dddd, J=13.0, 9.5, 6.0, 1.5 Hz, 1H), 2.28 (dddd, J=13.0, 10.0, 7.5, 4.5 Hz, 1H), 3.14 (ddd, J=10.0, 9.5, 4.5 Hz, 1H), 3.42–3.56 (m, 2H), 4.03 (td, J=10.0, 6.0 Hz, 1H), 4.46 (s, 2H), 6.61 (d, J=8.5 Hz, 2H), 6.63 (t, J=7.5 Hz, 1H), 7.14 (dd, J=8.5, 7.5 Hz, 2H), 7.25–7.38 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.3, 22.4, 24.6, 28.4, 30.8, 46.4, 55.8, 70.2, 72.8, 113.9, 115.8, 127.4, 127.5, 128.3, 128.6, 138.6, 147.9. MS (ES^+) *m/z 308* (MH^+), 330 (MNa^+). Anal. Calcd for $C_{21}H_{25}NO$: C 82.04, H 8.20. Found: C 81.81, H 8.26. See Section 4.7.7 for the analytical data of (*trans*)-**2e**.

4.7.6.2. (E)-N-(6-(Benzyloxy)hex-3-enyl)aniline. Colourless oil. IR (neat): 2925, 2854, 1603, 1506, 1319, 1101, 747, 694 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.32 (q, J=6.5 Hz, 2H), 2.36 (q, J=6.5 Hz, 2H), 3.13 (t, J=6.5 Hz, 2H), 3.50 (t, J=6.5 Hz, 2H), 3.65 (br s, 1H, NH), 4.52 (s, 2H), 5.44–5.64 (m, 2H), 6.38 (br d, J=8.5 Hz, 2H), 6.69 (br t, J=7.5 Hz, 1H), 7.16 (br dd, J=8.5, 7.5 Hz, 2H), 7.25–7.40 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 32.5, 33.1, 43.2, 69.9, 72.9, 112.9, 117.3,

127.5, 127.6, 128.4, 129.1, 129.2, 129.5, 138.4, 148.3. MS (ES^+) *m/z 304* (MNa^+). HRMS (ES^+) *m/z* calcd for $C_{19}H_{23}NNaO$ (MNa^+) 304.1677, found 304.1648.

*4.7.7. Reaction of alkenyl amide (Z)-**1e***

The general procedure for the intramolecular Kulinkovich–de Meijere reactions was applied to alkenyl amide (*Z*)-**1e** (1.0 equiv, 0.20 mmol, 65 mg), under more diluted conditions (8.0 mL of Et_2O), to afford the crude product (64 mg). Analysis of this crude product by ^1H NMR spectroscopy revealed the presence of the expected *trans* aminocyclopropane *trans*-**2e** in an estimated yield of about 44%. The cis diastereoisomer was not detected. The crude reaction product also contained a mixture of compounds retaining the carbon–carbon double bond (38%), including starting material (*Z*)-**1e** (14%) and the corresponding deacetylated compound (*Z*)-*N*-(6-(benzyloxy)hex-3-enyl)aniline (14%).

The general procedure for the intramolecular Kulinkovich–de Meijere reactions was also applied to alkenyl amide (*Z*)-**1e** (1.0 equiv, 0.49 mmol, 0.16 g) in toluene, under more diluted conditions (20 mL of toluene), to afford the crude product (0.17 g) as a brown oil. Analysis of this crude product by ^1H NMR spectroscopy revealed the presence of the expected *trans* aminocyclopropane *trans*-**2e** in an estimated yield of about 50%. The cis diastereoisomer was not detected. The crude reaction product also contained a mixture of compounds retaining the carbon–carbon double bond (38%), including starting material (*Z*)-**1e** (24%) and the corresponding deacetylated compound (*Z*)-*N*-(6-(benzyloxy)hex-3-enyl)aniline (9%). Purification of the crude product by two successive flash column chromatographies (neutral alumina gel, activity I, EtOAc/heptane, gradient from 0% to 30%, then silica gel, EtOAc/heptane, gradient from 0% to 5%) yielded pure starting (*Z*)-**1e** (38 mg, 0.12 mmol, 24%) and pure (*trans*)-**2e** (68 mg, 0.22 mmol, 45%). Further purification of some collected fractions by preparative TLC delivered pure (*Z*)-*N*-(6-(benzyloxy)hex-3-enyl)aniline (12 mg, 42 μmol, 9%) and pure (*Z*)-*N*-(6-(benzyloxy)hex-3-enyl)-*N*-(1-cyclopentylethyl)aniline (3.2 mg, 8.4 μmol, 2%).

4.7.7.1. (1S,5S*,6S*)-6-(2-(Benzyloxy)ethyl)-1-methyl-2-phenyl-2-azabicyclo[3.1.0]hexane (trans-**2e**).* Colourless oil. IR (neat): 2927, 2857, 1599, 1497, 1453, 1358, 1105, 748, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (td, *J*=7.0, 5.0 Hz, 1H), 1.03 (dd, *J*=6.0, 5.0 Hz, 1H), 1.49 (s, 3H), 1.65 (dq, *J*=14.0, 7.0 Hz, 1H), 1.80 (dq, *J*=14.0, 7.0 Hz, 1H), 1.94 (ddd, *J*=12.5, 8.5, 3.0 Hz, 1H), 2.29 (dddd, *J*=12.5, 9.5, 8.5, 6.0 Hz, 1H), 2.86 (dt, *J*=10.0, 8.5 Hz, 1H), 3.60 (t, *J*=7.0 Hz, 2H), 3.93 (td, *J*=10.0, 3.0 Hz, 1H), 4.54 (s, 2H), 6.74 (tt, *J*=7.5, 1.0 Hz, 1H), 6.79 (br d, *J*=8.5 Hz, 2H), 7.18 (br dd, *J*=8.5, 7.5 Hz, 2H), 7.23–7.38 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.2, 26.5, 27.2, 30.3, 30.8, 46.5, 53.1, 70.2, 73.0, 116.4, 117.6, 127.5, 127.5, 128.3, 128.7, 138.5, 149.7. MS (ES^+) *m/z* 304, *308* (MH^+), 362 ($MNaMeOH^+$).

4.7.7.2. (Z)-N-(6-(Benzyloxy)hex-3-enyl)aniline. Colourless oil. IR (neat): 2925, 2854, 1601, 1504, 1453, 1318, 1095, 1028, 746, 692 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.39 (dt, *J*=7.0, 6.5 Hz, 2H), 2.40 (q, *J*=7.0 Hz, 2H), 3.16 (t, *J*=7.0 Hz, 2H), 3.49 (t, *J*=6.5 Hz, 2H), 4.53 (s, 2H), 5.44–5.64 (m, 2H), 6.59 (br d, *J*=8.5 Hz, 2H), 6.69 (tt, *J*=7.5, 1.0 Hz, 1H), 7.16 (br dd, *J*=8.5, 7.5 Hz, 2H), 7.24–7.38 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 27.2, 28.1, 43.9, 69.7, 72.9, 113.3, 117.8, 127.6, 127.6, 128.3, 128.4, 128.9, 129.2, 138.4, 147.7. MS (ES^+) *m/z* 243, *282* (MH^+), 283, 304 (MNa^+), 305. HRMS (ES^+) *m/z* calcd for $C_{19}H_{23}NNaO$ (MNa^+) 304.1677, found 304.1715.

4.7.7.3. (Z)-N-(6-(Benzyloxy)hex-3-enyl)-N-(1-cyclopentylethyl)-aniline. Colourless oil. IR (neat): 2950, 2861, 1595, 1499, 1453, 1357, 1097, 1028, 743, 694 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.13 (d, *J*=6.5 Hz, 3H), 1.14–1.29 (m, 3H), 1.45–1.61 (m, 3H), 1.61–1.72 (m, 1H), 1.77 (m, 1H), 2.05 (dquint, *J*=10.0, 8.0 Hz 1H), 2.26 (m, 1H), 2.31–2.44 (m, 3H), 3.16 (AB part of an ABXY system, δ_A=3.12 ppm, δ_B=3.20 ppm, J_{AB}=14.5 Hz, J_{AX}=10.0 Hz, J_{AY}=6.0 Hz, J_{BX}=5.5 Hz, J_{BY}=10.5 Hz, 2H), 3.47 (t, *J*=7.0 Hz, 2H), 3.54 (dq, *J*=10.0, 6.5 Hz, 1H), 4.51 (s, 2H), 5.44–5.56 (m, 2H), 6.65 (t, *J*=7.5 Hz, 1H), 6.76 (br d, *J*=8.5 Hz, 2H), 7.19 (br dd, *J*=8.5, 7.5 Hz, 2H), 7.25–7.40 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 17.3, 25.2, 25.7, 26.3, 28.1, 30.8, 31.2, 43.4, 45.2, 59.9, 69.9, 72.9, 113.8, 116.0, 127.4, 127.5, 127.6, 128.3, 128.6, 129.0, 138.5, 149.0. MS (ES^+) *m/z* 282, *378* (MH^+), 400 (MNa^+). HRMS (ES^+) *m/z* calcd for $C_{26}H_{36}NO$ (MH^+) 378.2797, found 378.2802; calcd for $C_{26}H_{35}NNaO$ (MNa^+) 400.2616, found 400.2633.

*4.7.8. Reaction of alkenyl amide **1f** (E/Z≈90:10)*

The general procedure for the intramolecular Kulinkovich–de Meijere reactions was applied to alkenyl amide **1f** (*E*/*Z*≈90:10, 1.0 equiv, 0.15 mmol, 36 mg) to afford the crude product (34 mg) as a yellow oil. Analysis by ^1H NMR spectroscopy revealed the presence of the expected aminocyclopropane **2f** in an estimated yield of 78% (cis/trans≈92:8). The crude reaction product also contained a mixture of compounds retaining the carbon–carbon double bond (23%), including starting material **1f** (18%). Purification by flash column chromatography (neutral alumina gel, activity II, EtOAc/heptane, gradient from 0% to 100%) yielded pure (*cis*)-**2f** (24 mg, 0.10 mmol, 69%). Note: the starting material used was a different batch from the one described in Section 4.2.5, hence the slightly different *E*/*Z* ratio (90:10 vs 85:15).

4.7.8.1. (1S,5S*,6R*)-6-(2-Methoxyethyl)-1-methyl-2-phenyl-2-azabicyclo[3.1.0]hexane (cis-**2f**).* Colourless oil. IR (neat): 2926, 2864, 2824, 1598, 1501, 1483, 1459, 1380, 1360, 1323, 1249, 1182, 1140, 1114, 1069, 992, 745, 694 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.16–1.25 (m, 2H), 1.45 (td, *J*=7.5, 1.0 Hz, 1H), 1.51 (s, 3H), 1.53–1.66 (m, 1H), 1.87 (dddd, *J*=13.5, 10.0, 6.5, 1.0 Hz, 1H), 2.30 (dddd, *J*=13.5, 10.0, 7.5, 4.5 Hz, 1H), 3.15 (td, *J*=10.0, 4.5 Hz, 1H), 3.30 (s, 3H), 3.31–3.47 (m, 2H), 4.04 (td, *J*=10.0, 6.5 Hz, 1H), 6.63 (d, *J*=8.0 Hz, 2H), 6.64 (t, *J*=7.5 Hz, 1H), 7.17 (dd, *J*=8.0, 7.5 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.3, 22.5, 24.4, 28.5, 30.7, 46.5, 55.9, 58.6, 72.7, 113.9, 115.9, 128.7, 148.0. MS (ES^+) *m/z* 200, *232* (MH^+), 233, 300. HRMS (ES^+) *m/z* calcd for $C_{15}H_{22}NO$ (MH^+) 232.1701, found 232.1706.

4.7.8.2. (1S,5S*,6S*)-6-(2-Methoxyethyl)-1-methyl-2-phenyl-2-azabicyclo[3.1.0]hexane (trans-**2f**).* ^1H NMR (300 MHz, $CDCl_3$), characteristic signals: δ 2.87 (dt, *J*=9.5, 8.5 Hz, 1H), 3.94 (td, *J*=9.5, 3.0 Hz, 1H).

*4.7.9. Reaction of alkenyl amide **1g** (E/Z≈89:11)*

The general procedure for the intramolecular Kulinkovich–de Meijere reactions was applied to alkenyl amide **1g** (*E*/*Z*≈89:11, 1.0 equiv, 0.31 mmol, 96 mg) to afford the crude product (84 mg) as a yellow oil. Analysis by ^1H NMR spectroscopy revealed the presence of the expected aminocyclopropane **2g** (traces), starting material **1g** (4%) and extensive amounts of benzyl alcohol (70%).

4.7.9.1. (1S,5S*,6R*)-6-(Benzyloxymethyl)-1-methyl-2-phenyl-2-azabicyclo[3.1.0]hexane (cis-**2g**).* ^1H NMR (500 MHz, $CDCl_3$), characteristic signals: δ 3.15 (td, *J*=10.0, 4.5 Hz, 1H), 4.05 (td, *J*=10.0, 6.5 Hz, 1H).

4.7.9.2. (1S,5S*,6S*)-6-(Benzyloxymethyl)-1-methyl-2-phenyl-2-azabicyclo[3.1.0]hexane (trans-**2g**).* ^1H NMR (500 MHz, $CDCl_3$), characteristic signals: δ 2.86 (dt, *J*=10.0, 8.5 Hz, 1H), 3.93 (td, *J*=10.0, 3.5 Hz, 1H).

*4.7.10. Reaction of alkenyl amide **1h** (E/Z≈80:20)*

The general procedure for the intramolecular Kulinkovich–de Meijere reactions was applied to alkenyl amide **1h** (*E*/*Z*≈80:20, 1.0 equiv, 0.56 mmol, 0.19 g) to afford the crude product (0.15 g) as

a yellow oil. Analysis by ^{1}H NMR spectroscopy revealed the presence of the expected aminocyclopropane **2h** in an estimated yield of about 24% (cis/trans≈68:32). The crude reaction product also contained a mixture of compounds retaining the carbon–carbon double bond (66%), including starting material **1h** (35%). Purification by flash column chromatography (neutral alumina gel, activity II, EtOAc/heptane, gradient from 0% to 100%) yielded pure alkenyl amide **1h** (*E*/*Z*≈95:5 as measured by GC/MS, 48 mg, 0.14 mmol, 25%). Neither (*cis*)-**2h** nor (*trans*)-**2h** was isolated in a pure form.

4.7.10.1. (1R,5S*,6R*)-6-(3-(Benzyloxy)propyl)-1-methyl-2-phenyl-2-azabicyclo[3.1.0]hexane (cis-**2h**).* ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals: δ 3.13 (tdd, *J*=10.0, 4.5, 1.0 Hz, 1H), 4.01 (tdd, *J*=10.0, 6.5, 1.0 Hz, 1H).

4.7.10.2. (1R,5S*,6S*)-6-(3-(Benzyloxy)propyl)-1-methyl-2-phenyl-2-azabicyclo[3.1.0]hexane (trans-**2h**).* ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals: δ 2.85 (dtd, *J*=10.0, 8.5, 2.5 Hz, 1H), 3.91 (tdd, *J*=10.0, 3.5, 1.5 Hz, 1H).

*4.7.11. Reaction of alkenyl amide (E)-**1i***

The general procedure for the intramolecular Kulinkovich–de Meijere reactions was applied to alkenyl amide (*E*)-**1i** (1.0 equiv, 0.82 mmol, 0.20 g), under more diluted conditions (33 mL of Et_2O), to afford 0.24 g of crude product. Purification by flash column chromatography (neutral alumina gel, activity II-III, EtOAc/heptane, gradient from 5% to 100%) yielded pure vinylogous carbamate **7** (17 mg, 66 μmol, 8%), ketone **6** (20 mg, 69 μmol, 8%) and starting amide (*E*)-**1i** (46 mg, 0.19 mmol, 23%).

*4.7.11.1. N-(5-Cyclopentyl-5-oxopentyl)-N-phenylethanamide (**6**)* Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46–1.85 (m, 12H), 1.82 (s, 3H), 2.46 (t, *J*=7.0 Hz, 2H), 2.83 (quint, *J*=8.0 Hz, 1H), 3.69 (t, *J*=7.0 Hz, 2H), 7.16 (dd, *J*=8.0, 1.5 Hz, 2H), 7.30–7.47 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.8, 22.8, 26.0, 27.3, 28.9, 41.1, 48.6, 51.4, 127.7, 127.9, 129.5, 142.9, 170.1, 212.8.

*4.7.11.2. Isopropyl 2-methyl-1-phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (**7**).* Colourless oil. IR (neat): 1679, 1562, 1491, 1235, 1197, 1095, 1053 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (d, *J*=6.0 Hz, 6H), 1.86 (tt, *J*=6.5, 5.5 Hz, 2H), 2.13 (t, *J*=1.0 Hz, 3H), 2.47 (t, *J*=6.5 Hz, 2H), 3.49 (tq, *J*=5.5, 1.0 Hz, 2H), 5.05 (sept, *J*=6.0 Hz, 1H), 7.06 (dd, *J*=7.5, 1.5 Hz, 2H), 7.19 (tt, *J*=7.5, 1.5 Hz, 1H), 7.34 (t, *J*=7.5 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.1, 21.8, 22.3, 24.1, 52.7, 65.8, 99.3, 125.6, 127.0, 129.2, 147.0, 152.8, 168.8. MS (ES$^+$) *m*/*z* 218, 256, 260 (MH^+), *270*, 282 (MNa^+), 314 ($MNaMeOH^+$).

*4.7.12. Reaction of alkenyl amide (E)-**1j***

The general procedure for the intramolecular Kulinkovich–de Meijere reactions was applied to alkenyl amide (*E*)-**1j** (1.0 equiv, 0.80 mmol, 0.23 g), under more diluted conditions (32 mL of Et_2O), to afford the crude product (0.18 g) as a brown viscous oil. Analysis by ^{1}H NMR spectroscopy showed the complete consumption of the starting material and revealed the presence of vinylogous carbamate **7** (about 24% yield). Analysis by ^{13}C NMR spectroscopy allowed to estimate the amount of ketone **6** (about 9% yield). Purification of the crude product by flash column chromatography (neutral alumina gel, activity II-III, EtOAc/heptane, gradient from 0% to 50%) yielded pure vinylogous carbamate **7** (25 mg, 96 μmol, 12%) and impure ketone **6** (29 mg) that we were not able to isolate in completely pure form.

*4.7.13. Reaction of alkenyl amide (E)-**1k***

The general procedure for the intramolecular Kulinkovich–de Meijere reactions was applied to alkenyl amide (*E*)-**1k** (1.0 equiv, 0.78 mmol, 0.26 g), under more diluted conditions (35 mL of Et_2O), to afford 0.27 g of crude product. Purification by flash column chromatography (neutral alumina gel, activity II-III, EtOAc/heptane, gradient from 0% to 50%) yielded pure aminocyclopropane **2a**[5,19] (15 mg, 85 μmol, 11%), alkenyl amide **1a** (11 mg, 61 μmol, 8%) and extensively isomerised starting material **1k** (0.16 g, 0.49 mmol, 62%). Indeed, this latter product consisted of 61% of (*E*)-**1k** and 39% of a mixture of (*E*) and (*Z*)-*N*-phenyl-*N*-(4-(phenylsulfonyl)but-2-enyl)ethanamide. In retrospect, analysis of the ^{1}H NMR spectrum of the crude product showed that the observed isomerisation had occurred at the stage of the chromatographic purification.

*4.7.14. Reaction of alkenyl amide (E)-**1l***

The general procedure for the intramolecular Kulinkovich–de Meijere reactions was applied to alkenyl amide (*E*)-**1l** (0.96 mmol, 0.26 g) to afford the crude product (0.25 g) as a bright yellow oil. Analysis of this crude product by ^{1}H and ^{13}C NMR spectroscopy revealed the presence of starting material in an estimated yield of about 20%. The ^{1}H and ^{13}C NMR signals of the major product (about 30% yield) were found not to be consistent with the expected aminocyclopropane structure, but rather with that of cyclic enamine **8**. Moreover, attempted purification by flash column chromatography (EtOAc/heptane, gradient from 0% to 100%) yielded starting material only (59 mg, 0.22 mmol, 23%), and the major product could not be isolated. Nonetheless, we believe the following characteristic NMR data, extracted from the NMR spectra of the crude product, can be associated with enamine structure **5**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.74 (s, 3H), 3.79 (t, *J*=5.0 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.7, 22.7, 53.2, 147.8.

*4.7.15. Reaction of alkenyl amide (E)-**1m***

The general procedure for the intramolecular Kulinkovich–de Meijere reactions was applied to alkenyl amide (*E*)-**1m** (1.0 equiv, 0.20 mmol, 50 mg) to afford the crude product (44 mg) as a yellow oil. Analysis of this crude product by ^{1}H NMR spectroscopy revealed the presence of the expected *cis* aminocyclopropane *cis*-**2m** in an estimated yield of about 18%. The trans diastereoisomer was not detected. The crude reaction product also contained a mixture of compounds retaining the carbon–carbon double bond (70%), including starting material (*E*)-**1m** (41%).

4.7.15.1. (1R,5S*,6R*)-6-Ethyl-1-methyl-2-phenyl-2-azabicyclo[3.1.0]-hexane (cis-**2m**).* ^{1}H NMR (500 MHz, $CDCl_3$), characteristic signals: δ 0.82 (t, *J*=7.0 Hz, 3H), 1.49 (s, 3H), 3.14 (td, *J*=10.0, 4.5 Hz, 1H), 4.03 (td, *J*=10.0, 6.5 Hz, 1H).

*4.7.16. Reaction of alkenyl amide (Z)-**1m***

The general procedure for the intramolecular Kulinkovich–de Meijere reactions was applied to alkenyl amide (*Z*)-**1m** (1.0 equiv, 0.20 mmol, 50 mg) to afford the crude product (58 mg) as a yellow oil. Analysis of this crude product by ^{1}H NMR spectroscopy revealed the presence of the expected *trans* aminocyclopropane *trans*-**2m** in an estimated yield of about 12%. The cis diastereoisomer was not detected. The crude reaction product also contained a mixture of compounds retaining the carbon–carbon double bond (65%), including starting material (*Z*)-**1m** (52%).

4.7.16.1. (1R,5S*,6S*)-6-Ethyl-1-methyl-2-phenyl-2-azabicyclo[3.1.0]-hexane (trans-**2m**).* ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals: δ 1.47 (s, 3H), 2.87 (dt, *J*=10.0, 8.5 Hz, 1H), 3.93 (td, *J*=10.0, 3.5 Hz, 1H).

*4.7.17. Reaction of alkenyl amide (Z)-**1n***

The general procedure for the intramolecular Kulinkovich–de Meijere reactions was applied to alkenyl amide (*Z*)-**1o** (1.0 equiv, 0.70 mmol, 0.25 g) in toluene, under more diluted conditions (28 mL of toluene), to afford the crude product (0.24 g) as a viscous

yellow oil. Analysis by ^{1}H NMR spectroscopy revealed the presence of the expected *trans* aminocyclopropane *trans*-**2n** in an estimated yield of about 29%. The cis diastereoisomer was not detected. The crude reaction product also contained a mixture of compounds retaining the carbon–carbon double bond (57%), including starting material (*Z*)-**1n** (53%). Purification of the crude product by two successive flash column chromatographies (neutral alumina gel, activity II-III, EtOAc/heptane, gradient from 0% to 20%, then EtOAc/heptane, gradient from 0% to 5%) yielded pure (*trans*)-**2n** (77 mg, 0.23 mmol, 33%), pure (*Z*)-*N*-(6-(4-methoxybenzyloxy)hex-3-enyl)aniline (11 mg, 36 μmol, 5%) and pure starting (*Z*)-**1n** (0.12 g, 0.34 mmol, 49%). Further purification of some collected fractions by preparative TLC delivered (*Z*)-*N*-(1-cyclopentylethyl)-*N*-(6-(4-methoxybenzyloxy)hex-3-enyl)aniline (6.6 mg, 16 μmol, 2%).

4.7.17.1. (1S,5S*,6S*)-6-(2-(4-Methoxybenzyloxy)ethyl)-1-methyl-2-phenyl-2-azabicyclo[3.1.0]hexane (trans-**2n**).* Colourless oil. IR (neat): 2931, 2856, 1599, 1511, 1495, 1245, 1092, 1033, 818, 751, 730, 696 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (td, *J*=7.0, 4.5 Hz, 1H), 1.02 (dd, *J*=6.0, 5.0 Hz, 1H), 1.48 (s, 3H), 1.71 (AB part of an ABX_2Y system, δ_A=1.64 ppm, δ_B=1.78 ppm, J_{AB}=14.0 Hz, J_{AX}=7.0 Hz, J_{AY}=7.0 Hz, J_{BX}=7.0 Hz, J_{BY}=7.0 Hz, 2H), 1.94 (ddd, *J*=12.5, 9.0, 3.0 Hz, 1H), 2.29 (dddd, *J*=12.5, 9.5, 8.5, 6.0 Hz, 1H), 2.86 (ddd, *J*=9.5, 9.0, 8.5 Hz, 1H), 3.57 (m, 2H), 3.79 (s, 3H), 3.93 (td, *J*=9.5, 3.0 Hz, 1H), 4.48 (s, 2H), 6.74 (tt, *J*=7.5, 1.0 Hz, 1H), 6.79 (dd, *J*=8.5, 1.0 Hz, 2H), 7.06 (AA′BB′ system,[43] δ_A=6.87 ppm, δ_B=7.26 ppm, *K*=5.0 Hz, *L*=8.0 Hz, *N*=8.5 Hz (*M* could not be measured accurately), 4H), 7.19 (dd, *J*=8.5, 7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 15.3, 26.6, 27.2, 30.3, 30.8, 46.6, 53.2, 55.3, 70.0, 72.7, 113.8, 116.4, 117.6, 128.7, 129.2, 130.6, 149.7, 159.1. MS (ES$^+$) *m*/*z* 338 (MH$^+$), *360* (MNa$^+$). Anal. Calcd for $C_{22}H_{27}NO_2$: C 78.30, H 8.06. Found: C 77.99, H 8.09.

4.7.17.2. (Z)-N-(6-(4-Methoxybenzyloxy)hex-3-enyl)aniline. Colourless oil. IR (neat): 2961, 1737, 1651, 1512, 1455, 1245, 909, 727, 695 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.37 (q, *J*=6.5 Hz, 2H), 2.39 (q, *J*=6.5 Hz, 2H), 3.15 (t, *J*=6.5 Hz, 2H), 3.46 (t, *J*=6.5 Hz, 2H), 3.80 (s, 3H), 4.46 (s, 2H), 5.44–5.62 (m, 2H), 6.57 (dd, *J*=8.5, 1.0 Hz, 2H), 6.68 (tt, *J*=7.5, 1.0 Hz, 1H), 7.07 (AA′BB′ system,[43] δ_A=6.87 ppm, δ_B=7.26 ppm, *K*=5.0 Hz, *L*=8.0 Hz, *N*=8.5 Hz (*M* could not be measured accurately), 4H), 7.15 (dd, *J*=8.5, 7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 27.3, 28.1, 43.4, 55.2, 69.4, 72.6, 112.8 and 113.8, 117.2, 128.4, 128.7, 129.2, 129.2, 130.5, 148.3, 159.2.

4.7.17.3. (Z)-N-(1-Cyclopentylethyl)-N-(6-(4-methoxybenzyloxy)hex-3-enyl)aniline. Colourless oil. IR (neat): 2933, 2854, 1601, 1510, 1245, 1090, 1033, 748, 692 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.13 (d, *J*=6.5 Hz, 3H), 1.10–1.29 (m, 3H), 1.44–1.58 (m, 2H), 1.60–1.70 (m, 2H), 1.77 (m, 1H), 2.05 (dquint, *J*=10.0, 8.0 Hz, 1H), 2.25 (m, 1H), 2.30–2.41 (m, 3H), 3.16 (AB part of an ABXY system, δ_A=3.12 ppm, δ_B=3.19 ppm, J_{AB}=14.5 Hz, J_{AX}=10.0 Hz, J_{AY}=6.0 Hz, J_{BX}=5.5 Hz, J_{BY}=10.5 Hz, 2H), 3.44 (t, *J*=7.0 Hz, 2H), 3.54 (dq, *J*=10.0, 6.5 Hz, 1H), 3.80 (s, 3H), 4.44 (s, 2H), 5.44–5.54 (m, 2H), 6.65 (t, *J*=7.5 Hz, 1H), 6.76 (d, *J*=8.5 Hz, 2H), 7.06 (AA′BB′ system,[43] δ_A=6.87 ppm, δ_B=7.25 ppm, *K*=5.0 Hz, *L*=8.0 Hz, *N*=8.5 Hz (*M* could not be measured accurately), 4H), 7.19 (dd, *J*=8.5, 7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 17.3, 25.3, 25.8, 26.3 and 28.2, 30.8, 31.2, 43.4, 45.2, 55.3, 59.9, 69.6, 72.5, 113.8, 113.8, 116.0, 127.4, 128.6, 129.1, 129.2, 130.6, 149.1, 159.1. MS (ES$^+$) *m*/*z* 408 (MH$^+$), *430* (MNa$^+$), 431. HRMS (ES$^+$) *m*/*z* calcd for $C_{27}H_{38}NO_2$ (MH$^+$) 408.2903, found 408.2936; calcd for $C_{27}H_{37}NNaO_2$ (MNa$^+$) 430.2722, found 430.2721.

*4.7.18. Reaction of alkenyl amide (Z)-**1o***

The general procedure for the intramolecular Kulinkovich–de Meijere reactions was applied to alkenyl amide (*Z*)-**1o** (1.0 equiv, 0.50 mmol, 0.16 g) in toluene, under more diluted conditions (20 mL of toluene), to afford the crude product (0.16 g) as an oil. Analysis by ^{1}H NMR spectroscopy revealed the presence of the expected *trans* aminocyclopropane *trans*-**2o** in an estimated yield of about 34%. The cis diastereoisomer was not detected. The crude reaction product also contained a mixture of compounds retaining the carbon–carbon double bond (48%). Purification of the crude product by two successive flash column chromatographies (neutral alumina gel, activity I, EtOAc/heptane, gradient from 0% to 100%, then silica gel, EtOAc/heptane, gradient from 0% to 10%) yielded pure (*trans*)-**2o** (35 mg, 0.12 mmol, 23%), (*Z*)-*N*-(1-cyclopentylethyl)-*N*-(6-(tetrahydro-2*H*-pyran-2-yloxy)hex-3-enyl)aniline (7.7 mg, 21 μmol, 4%), pure (*Z*)-*N*-(6-(tetrahydro-2*H*-pyran-2-yloxy)hex-3-enyl)aniline (12 mg, 43 μmol, 9%) and pure starting (*Z*)-**1o** (42 mg, 0.13 mmol, 26%).

4.7.18.1. (1S,5S*,6S*)-1-Methyl-2-phenyl-6-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-2-azabicyclo[3.1.0]hexane (trans-**2o**).* Colourless oil. Mixture of two diastereoisomers (*55*:45). IR (neat): 2925, 2867, 1600, 1496, 1119, 1076, 1060, 1031, 750, 695 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (m, 1H), 1.05 (dd, *J*=6.0, 5.0 Hz, 1H), *1.49* and 1.50 (2×s, 3H), 1.50–1.90 (m, 8H), 1.96 (ddd, *J*=12.5, 8.5, 3.5 Hz, 1H), 2.31 (dddd, *J*=12.5, 9.5, 8.5, 6.0 Hz, 1H), 2.88 (dt, *J*=9.5, 8.5 Hz, 1H), 3.45–3.58 (m, 2H), 3.82–3.93 (m, 2H), 3.94 (ddd, *J*=10.0, 9.5, 3.5 Hz, 1H), *4.63* and 4.64 (2×t, *J*=4.5 Hz, 1H), 6.71–6.88 (m, 3H), *7.21* and 7.22 (2×dd, *J*=8.5, 7.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 15.2 and *15.3*, 19.6 and *19.7*, 25.5, 25.5, 26.6, 30.3, 30.7, 30.8, 53.3, 62.3 and *62.4*, 63.7, *67.2* and 67.3, 98.9 and 99.0, 116.5, 117.7, 128.8, 149.7. MS (ES$^+$) *m*/*z* 298, *302* (MH$^+$), 303, 324 (MNa$^+$). HRMS (ES$^+$) *m*/*z* calcd for $C_{19}H_{28}NO_2$ (MH$^+$) 302.2120, found 302.2094.

4.7.18.2. (Z)-N-(1-Cyclopentylethyl)-N-(6-(tetrahydro-2H-pyran-2-yloxy)hex-3-enyl)aniline. Colourless oil. Mixture of two diastereoisomers. IR (neat): 2943, 2867, 1596, 1500, 1136, 1120, 1075, 1030, 985, 744, 692 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (d, *J*=6.5 Hz, 3H), 1.42–1.90 (m, 14H), 2.07 (dquint, *J*=10.0, 8.0 Hz, 1H), 2.18–2.45 (m, 4H), 3.17 (AB part of an ABXY system, δ_A=3.13 ppm, δ_B=3.20 ppm, J_{AB}=15.0 Hz, J_{AX}=10.0 Hz, J_{AY}=6.0 Hz, J_{BX}=5.5 Hz, J_{BY}=10.5 Hz, 2H), 3.40 (dt, *J*=9.5, 7.0 Hz, 1H), 3.48 (m, 1H), 3.55 (dq, *J*=10.0, 6.5 Hz, 1H), 3.74 (dt, *J*=9.5, 7.0 Hz, 1H), 3.86 (ddd, *J*=11.0, 8.0, 3.5 Hz, 1H), 4.59 (dd, *J*=4.0, 2.5 Hz, 1H), 5.41–5.59 (m, 2H), 6.65 (t, *J*=7.5 Hz, 1H), 6.77 (d, *J*=8.5 Hz, 2H), 7.20 (dd, *J*=8.5, 7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 17.3, 19.6, 25.3, 25.5, 25.8, 26.3, 28.2, 30.7, 30.8, 31.2, 43.5, 45.2, 59.8, 62.3, 67.0, 98.8, 113.8, 116.0, 127.6, 128.5, 129.1, 149.1. MS (ES$^+$) *m*/*z* 372 (MH$^+$), 392, *394* (MNa$^+$), 395. HRMS (ES$^+$) *m*/*z* calcd for $C_{24}H_{38}NO_2$ (MH$^+$) 372.2903, found 372.2892.

4.7.18.3. (Z)-N-(6-(Tetrahydro-2H-pyran-2-yloxy)hex-3-enyl)aniline. Colourless oil. IR (neat): 2939, 2866, 1601, 1503, 1136, 1119, 1074, 1028, 905, 868, 746, 731, 691 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45–1.89 (m, 6H), 2.37 (q, *J*=6.5 Hz, 2H), 2.40 (q, *J*=7.0 Hz, 2H), 3.16 (t, *J*=6.5 Hz, 2H), 3.42 (dt, *J*=9.5, 7.0 Hz, 1H), 3.50 (m, 1H), 3.76 (dt, *J*=9.5, 7.0 Hz, 1H), 3.87 (ddd, *J*=11.0, 8.0, 3.0 Hz, 1H), 4.59 (dd, *J*=4.0, 3.5 Hz, 1H), 5.46–5.62 (m, 2H), 6.61 (d, *J*=8.5 Hz, 2H), 6.69 (t, *J*=7.5, 1H), 7.17 (dd, *J*=8.5, 7.5 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.6, 25.5, 27.4, 28.1, 30.7, 43.5, 62.4, 66.9, 98.8, 112.9, 117.3, 128.3, 128.7, 129.2, 148.3. MS (ES$^+$) *m*/*z* ES$^+$ *m*/*z* 276 (MH$^+$), *298* (MNa$^+$). HRMS (ES$^+$) *m*/*z* calcd for $C_{17}H_{26}NO_2$ (MH$^+$) 276.1964, found 276.1961; calcd for $C_{17}H_{25}NNaO_2$ (MNa$^+$) 298.1783, found 298.1793.

*4.7.19. Reaction of alkenyl amide (Z)-**1p***

The general procedure for the intramolecular Kulinkovich–de Meijere reactions was applied to alkenyl amide (*Z*)-**1p** (1.0 equiv, 0.60 mmol, 0.17 g) in toluene, under more diluted conditions (24 mL of toluene), to afford the crude product (0.18 g) as a viscous brown oil. Analysis of this crude product by ^{1}H NMR spectroscopy revealed the presence of the starting material and the

corresponding deacetylated compound (*Z*)-**1c** in an estimated yield of about 16% and 44%, respectively. Aminocyclopropane *trans*-**2c** (11%) was detected as well (see Section 4.7.22.1 for analytical data), while the cis diastereoisomer was not observed. Purification of the crude product by flash column chromatography (EtOAc/heptane, gradient from 20% to 100%) yielded pure (*trans*)-**2c** (10 mg, 48 μmol, 8%), starting (*Z*)-**1p** (6.6 mg, 24 μmol, 4%) and pure (*Z*)-**1c** (61 mg, 0.26 mmol, 44%).

*4.7.20. Reaction of alkenyl amide (Z)-**1q***

The general procedure for the intramolecular Kulinkovich–de Meijere reactions was applied to alkenyl amide (*Z*)-**1q** (1.0 equiv, 0.20 mmol, 64 mg) in toluene, under more diluted conditions (8.0 mL of toluene), to afford the crude product (61 mg) as a viscous brown oil. Analysis by ^{1}H NMR spectroscopy revealed the presence of the starting material and the corresponding alcohol (*Z*)-**1c** in an estimated yield of about 35% and 12%, respectively. Traces of aminocyclopropane *trans*-**2c** were detected as well (see Section 4.7.22.1 for analytical data), while the cis diastereoisomer was not observed at all. Purification of the crude product by flash column chromatography (neutral alumina gel, activity II, EtOAc/heptane, gradient from 10% to 100%) yielded pure starting (*Z*)-**1q** (17 mg, 54 μmol, 27%).

*4.7.21. Reaction of alkenyl amide **1r** (E/Z≈75:25)*

n-Butyllithium (1.2 M in hexanes, 1.1 equiv, 0.85 mmol, 0.73 mL) was added at −78 °C to a solution of alkenyl amide **1c** (*E*/*Z*≈75:25, 1.0 equiv, 0.77 mmol, 0.18 g) in diethyl ether (15 mL). The reaction mixture was allowed to warm to 20 °C, and then the general procedure for the intramolecular Kulinkovich–de Meijere reactions was applied to afford the crude product (0.19 g) as a yellow oil. Analysis by ^{1}H NMR spectroscopy revealed the presence of the expected aminocyclopropane **2c** in an estimated yield of about 17% (cis/trans≈66:34; see Sections 4.7.21.1 and 4.7.22.1 for analytical data). The crude reaction product also contained a mixture of compounds retaining the carbon–carbon double bond (79%), including starting material **1c** (73%, *E*/*Z*≈80:20 as estimated by ^{1}H and ^{13}C NMR spectroscopies). Purification by flash column chromatography (neutral alumina gel, activity II, EtOAc/heptane, gradient from 0% to 30%) yielded pure **2c** (cis/trans≈75:25 as estimated by ^{1}H NMR spectroscopy, 21 mg, 96 μmol, 12%).

4.7.21.1. 2-((1S,5S*,6R*)-1-Methyl-2-phenyl-2-azabicyclo[3.1.0]hexan-6-yl)ethanol (cis-**2c**).* ^{1}H NMR (500 MHz, $CDCl_3$), characteristic signals: δ 1.53 (s, 3H), 1.88 (dddd, *J*=13.5, 10.0, 6.0, 1.0 Hz, 1H), 2.32 (dddd, *J*=13.5, 10.0, 7.5, 4.5 Hz, 1H), 3.15 (td, *J*=10.0, 5.0 Hz, 1H), 3.59–3.76 (m, 2H), 4.04 (td, *J*=10.0, 6.5 Hz, 1H), 6.60–6.74 (m, 3H), 7.13–7.32 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$), characteristic signals: δ 20.4, 22.6, 27.6, 28.5, 30.4, 55.9, 63.0, 113.8, 116.0, 128.8.

*4.7.22. Reaction of alkenyl amide (Z)-**1s***

The general procedure for the intramolecular Kulinkovich–de Meijere reactions was applied to alkenyl amide (*Z*)-**1s** generated by treating a solution of (*Z*)-**1c** (1.0 equiv, 0.54 mmol, 0.13 g) in toluene (20 mL) with *cyclo*-pentylmagnesium chloride (1.0 equiv) at 0 °C, prior to the addition of titanium(IV) *iso*-propoxide (1.5 equiv) and *cyclo*-pentylmagnesium chloride (4.0 equiv) at 20 °C. The crude product (0.12 g) was obtained as a viscous greenish oil. Analysis by ^{1}H spectroscopy revealed the presence of the expected *trans* aminocyclopropane *trans*-**2c** in an estimated yield of about 21%. The cis diastereoisomer was not detected. The crude reaction product also contained a mixture of compounds retaining the carbon–carbon double bond (65%), including (*Z*)-**1c** (60%). Purification of the crude product by flash column chromatography (neutral alumina gel, activity II-III, EtOAc/heptane, gradient from 10% to 100%) yielded pure (*trans*)-**2c** (25 mg, 0.12 mmol, 21%) and (*Z*)-**1c** (62 mg, 0.27 mmol, 49%).

Note: this reaction was also performed in Et_2O, with a lower yield of 12% for (*trans*)-**2c** as estimated by ^{1}H NMR spectroscopy of the crude product.

4.7.22.1. 2-((1S,5S*,6S*)-1-Methyl-2-phenyl-2-azabicyclo[3.1.0]hexan-6-yl)ethanol (trans-**2c**).* Viscous colourless oil. IR (neat): 3354, 2929, 2867, 1599, 1494, 1355, 1312, 1034, 750, 695 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (td, *J*=7.0, 5.0 Hz, 1H), 1.06 (dd, *J*=6.0, 5.0 Hz, 1H), 1.50 (s, 3H), 1.68 (AB part of an ABX_2Y system, δ_A=1.60 ppm, δ_B=1.76 ppm, J_{AB}=14.0 Hz, J_{AX}=7.0 Hz, J_{AY}=7.0 Hz, J_{BX}=7.0 Hz, J_{BY}=7.0 Hz, 2H), 1.97 (ddd, *J*=12.5, 9.0, 3.0 Hz, 1H), 2.31 (dddd, *J*=12.5, 10.0, 8.0, 6.0 Hz, 1H), 2.87 (ddd, *J*=9.5, 9.0, 8.0 Hz, 1H), 3.77 (t, *J*=7.0 Hz, 2H), 3.94 (ddd, *J*=10.0, 9.5, 3.0 Hz, 1H), 6.72–6.83 (m, 3H), 7.23 (dd, *J*=8.5, 7.5 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.3, 26.5, 26.5, 30.9, 33.1, 46.3, 53.1, 62.7, 116.3, 117.7, 128.8, 149.7. MS (ES^+) *m*/*z* *218* (MH^+), 240 (MNa^+), 261, 272 ($MNaMeOH^+$), 305. HRMS (ES^+) *m*/*z* calcd for $C_{14}H_{20}NO$ (MH^+) 218.1545, found 218.1543. Anal. Calcd for $C_{14}H_{19}NO$: C 77.38, H 8.81. Found: C 77.03, H 8.91.

4.8. Synthesis and reaction of alkenyl ester 3

*4.8.1. 6-(Benzyloxy)hex-3-enyl ethanoate (**3**)*

A mixture of AcOH and H_2O (3:1, 2.0 mL) was added to a solution of (6-(benzyloxy)hex-3-enyloxy)(*tert*-butyl)dimethylsilane (*E*/*Z*≈85:15, 1.0 equiv, 0.30 mmol, 95 mg, see Section 4.2.4 for preparation) in THF (1.0 mL). After 17 h of stirring at 20 °C, the solvents were removed under reduced pressure (heptane was added to carry AcOH away) to yield alcohol **4** (64 mg, *E*/*Z*≈85:15 estimated by ^{13}C NMR spectroscopy) as colourless crystals that were used in the next step without further purification.

Acetic anhydride (1.2 equiv, 0.36 mmol, 34 μL) was added to a solution of the preceding crystals (64.0 mg) in pyridine (1.0 mL) at 0 °C. After 7 h of stirring at 20 °C, most of the pyridine was removed under reduced pressure. Purification by flash column chromatography (EtOAc/heptane, gradient from 10% to 50%) yielded pure ester **3** (70 mg, 0.28 mmol, 94%) as an 85:15 mixture of *E* and *Z* diastereoisomers (measured by ^{13}C and ^{1}H NMR spectroscopies).

*4.8.1.1. 6-(Benzyloxy)hex-3-enyl ethanoate (**3**) (E/Z≈85:15).* Colourless oil. IR (neat): 2923, 2854, 1736, 1453, 1362, 1233, 1099, 1028, 969, 735, 696 cm^{-1}. MS (ES^+) *m*/*z* *271* (MNa^+). HRMS (ES^+) *m*/*z* calcd for $C_{15}H_{20}NaO_3$ (MNa^+) 271.1310, found 271.1303.

*4.8.1.2. (E)-6-(Benzyloxy)hex-3-enyl ethanoate ((E)-**3**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.02 (s, 3H), 2.33 (td, *J*=6.5, 6.0 Hz, 4H), 3.48 (t, *J*=6.5 Hz, 2H), 4.07 (t, *J*=6.5 Hz, 2H), 4.51 (s, 2H), 5.51 (AB part of an ABX_2Y_2 system, δ_A=5.47 ppm, δ_B=5.55 ppm, J_{AB}=15.5 Hz, J_{AX}=6.0 Hz, J_{AY}=0 Hz, J_{BX}=0 Hz, J_{BY}=6.0 Hz, 2H), 7.21–7.42 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.9, 31.9, 33.0, 63.9, 69.8, 72.8, 127.2, 127.5, 127.5, 128.3, 129.5, 138.4, 171.0.

*4.8.1.3. (Z)-6-(Benzyloxy)hex-3-enyl ethanoate ((Z)-**3**).* ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals: δ 2.39 (m, 4H), 4.06 (t, *J*=6.5 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$), characteristic signals: δ 26.8, 28.0, 63.7, 69.6.

*4.8.1.4. (E)-6-(Benzyloxy)hex-3-en-1-ol ((E)-**4**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.76 (br s, 1H), 2.27 (qd, *J*=6.0, 1.0 Hz, 2H), 2.35 (qd, *J*=6.5, 1.0 Hz, 2H), 3.49 (t, *J*=6.5 Hz, 2H), 3.61 (t, *J*=6.0 Hz, 2H), 4.51 (s, 2H), 5.52 (AB part of an ABX_2Y_2 system, δ_A=5.48 ppm, δ_B=5.56 ppm, J_{AB}=15.5 Hz, J_{AX}=6.5 Hz, J_{AY}=1.0 Hz, J_{BX}=1.0 Hz, J_{BY}=6.0 Hz, 2H), 7.19–7.43 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 33.0, 36.0, 61.8, 69.8, 72.8, 127.5, 127.6, 128.1, 128.3, 130.0, 138.3.

*4.8.1.5. (Z)-6-(Benzyloxy)hex-3-en-1-ol ((Z)-**4**).* ^{13}C NMR (75.5 MHz, $CDCl_3$), characteristic signals: δ 28.0, 30.7, 61.9, 69.4.

*4.8.2. Reaction of **3***

Methyltri*iso*-propoxytitane[44,45] (1.5 equiv, 0.40 mmol, 95 μL) was added at 20 °C to a solution of ester **6** (*E*/*Z*≈85:15, 1.0 equiv, 0.26 mmol, 65 mg) in Et_2O (5.0 mL), followed by *cyclo*-pentylmagnesium chloride (1.6 M in Et_2O, 2.5 equiv, 0.66 mmol, 0.41 mL) dropwise. After 20 min of stirring, water (15 mL) was added to the brown solution, which was exposed to air, and stirring was continued until decolouration. Et_2O (15 mL) and H_2O (15 mL) were then added. The organic layer was separated, and the aqueous phase was extracted with Et_2O (15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford a colourless oil (61 mg). Analysis by ^{1}H and ^{13}C NMR spectroscopies revealed the presence of alcohol **4** (91% yield as estimated by integration of the corresponding signals in the ^{1}H NMR spectrum), as well as cyclopropanol **5**.

4.8.2.1. (1R,5S*,6R*)-6-Methylbicyclo[3.1.0]hexan-6-ol (**5**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.45 (dd, *J*=4.5, 2.0 Hz, 2H), 1.56–1.97 (m, 7H). ^{13}C NMR (75.5 MHz, $CDCl_3$), characteristic signals: δ 16.1, 25.7, 26.2, 32.0.

4.9. Preparation of tetrahydrocarboline 11

*4.9.1. (Z)-N-(2-(1H-Indol-3-yl)ethyl)-N-(6-(benzyloxy)hex-3-enyl)-ethanamide ((Z)-**9**)*

Tryptamine (2.0 equiv, 12 mmol, 2.0 g) was added to a solution of 6-(benzyloxy)hex-3-ynyl 4-methylbenzenesulfonate (1.0 equiv, 6.0 mmol, 2.2 g, see compound (*Z*)-**1d** for the preparation of this tosylate) in acetonitrile (15 mL), and the mixture was heated at reflux for 3 h. After cooling, the solvent was removed under reduced pressure, then CH_2Cl_2 (40 mL) and 1 N NaOH aq solution (40 mL) were added. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2×40 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford a viscous brown oil (4.0 g). Purification by flash column chromatography (EtOAc/heptane, gradient from 20% to 100%) yielded pure *N*-(2-(1*H*-indol-3-yl)ethyl)-6-(benzyloxy)hex-3-yn-1-amine (1.5 g, 4.4 mmol, 73%) as a viscous yellow oil. IR (neat): 2912, 2847, 1454, 1358, 1338, 1095, 1028, 1009, 736, 696 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60 (br s, 1H, NH), 2.27–2.40 (m, 4H), 2.74 (t, *J*=6.5 Hz, 2H), 2.95 (br s, 4H), 3.45 (t, *J*=7.0 Hz, 2H), 4.48 (s, 2H), 6.91 (d, *J*=2.5 Hz, 1H), 7.04–7.18 (m, 2H), 7.22–7.35 (m, 6H), 7.59 (d, *J*=7.5 Hz, 1H), 8.55 (br s, 1H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.7, 19.9, 25.6, 48.0, 49.2, 68.6, 72.7, 78.1, 78.9, 111.1, 113.4, 118.7, 118.9, 121.7, 122.0, 127.3, 127.6, 127.6, 128.3, 136.3, 138.0. MS (ES$^+$) *m*/*z* 144, *347* (MH$^+$), 348, 369 (MNa$^+$). HRMS (ES$^+$) *m*/*z* calcd for $C_{23}H_{27}N_2O$ (MH$^+$) 347.2123, found 347.2100.

Acetyl chloride (1.5 equiv, 6.6 mmol, 0.45 mL) was added to a solution of *N*-(2-(1*H*-indol-3-yl)ethyl)-6-(benzyloxy)hex-3-yn-1-amine (1.0 equiv, 4.4 mmol, 1.5 g) in CH_2Cl_2 (15 mL) at 0 °C. The resulting solution was poured in a separating funnel, and 1 N NaOH aq solution (15 mL) was added. The reaction mixture was vigorously shaken for 5 min. The organic layer was separated, washed with 1 N HCl aq solution (20 mL) and H_2O (20 mL), then dried over sodium sulfate, filtered and concentrated under reduced pressure to afford *N*-(2-(1*H*-indol-3-yl)ethyl)-*N*-(6-(benzyloxy)hex-3-ynyl)-ethanamide as a viscous yellow oil (1.7 g, 4.4 mmol, 99%) that was used in the next step without further purification. IR (neat): 3264, 2916, 2861, 1621, 1454, 1419, 1360, 1097, 1009, 737, 697 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, *56*:44 mixture of two rotamers): δ *1.86* and 2.14 (2×s, 3H), 2.28–2.50 (m, 4H), *2.95* (t, *J*=7.0 Hz, 1.12H), 3.00 (t, *J*=8.0 Hz, 0.88H), 3.29 (t, *J*=7.0 Hz, 0.88H), 3.42–3.67 (m, 5.12H), *4.47* and 4.48 (2×s, 2H), *6.88* and 6.91 (2×d, *J*=2.0 Hz, 1H), 7.04–7.20 (m, 2H), 7.22–7.36 (m, 6H), *7.53* and 7.64 (2×d, *J*=7.5 Hz, 1H), 8.69 and *8.85* (2×br s, 1H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$, *56*:44 mixture of two rotamers): δ *17.9* and 19.0, 19.9 and *20.0*, *21.1* and 21.6, 23.4 and *24.6*, *45.2* and 48.0, 46.9 and *50.1*, 68.3 and *68.5*, *72.7* and 72.7, *77.3*, 78.2, *78.7*, 79.3, 111.1 and *111.4*, *111.4* and 112.7, *117.9* and 118.5, 119.0 and *119.2*, 121.6 and *121.8*, 122.0 and *122.3*, *126.9* and 127.3, *127.5* and 127.5, *127.5* and 127.5, 128.2 and *128.2*, 136.2 and *136.2*, 137.9 and *137.9*, 170.5 and *170.7*. MS (ES$^+$) *m*/*z* 347, 389 (MH$^+$), *411* (MNa$^+$), 412. HRMS (ES$^+$) *m*/*z* calcd for $C_{25}H_{28}N_2NaO_2$ (MNa$^+$) 411.2048, found 411.2056.

The preparation of (*Z*)-**9** was first attempted by forming and hydrolysing a titanacyclopropene complex,[17,18] however, with incomplete conversion possibly due to solubility problems: titanium(IV) *iso*-propoxide (2.0 equiv, 8.0 mmol, 2.4 mL) was added at −70 °C to a suspension of *N*-(2-(1*H*-indol-3-yl)ethyl)-*N*-(6-(benzyloxy)hex-3-ynyl)ethanamide (1.0 equiv, 4.0 mmol, 1.5 g) in Et_2O (80 mL), followed by *cyclo*-pentylmagnesium chloride (1.9 M in Et_2O, 4.0 equiv, 16 mmol, 8.2 mL), dropwise. The resulting yellow mixture was allowed to warm to −30 °C in 5 min and maintained at that temperature for 45 min, by which time it had become brown. The reaction medium was then hydrolysed at −30 °C with 0.3 N HCl aq solution (0.10 L), and allowed to warm to 20 °C. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2×0.15 L). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford a viscous green oil (1.5 g). Analysis of the crude product using ^{1}H and ^{13}C NMR spectroscopy revealed that it essentially contained a 52:48 mixture of starting alkyne and wanted alkene (*Z*)-**9**.

The mixture thus obtained was then submitted to a catalytic hydrogenation reaction mediated by palladium on barium sulfate:[46] To a mixture of 5% palladium on barium sulfate (10% equiv, 0.19 mmol, 0.40 g) and quinoline (10% equiv, 0.19 mmol, 22 μL) in EtOAc (15 mL) was added a solution of 1.4 g of the preceding 52:48 mixture of *N*-(2-(1*H*-indol-3-yl)ethyl)-*N*-(6-(benzyloxy)hex-3-ynyl)ethanamide (1 equiv, 1.9 mmol) and alkene (*Z*)-**9** (1.7 mmol) in EtOAc (5.0 mL). The flask was flushed three times with argon, and then three times with hydrogen. After 6 h of stirring at 20 °C, 63 mL (2.6 mmol) of H_2 was absorbed. The black mixture was filtered, and the solid rinsed with EtOAc several times. The solvent was removed under reduced pressure to afford a viscous brown oil (1.4 g). Analysis of the crude product using ^{1}H and ^{13}C NMR spectroscopy revealed that it stilled contained about 18% of starting alkyne. The procedure was thus repeated on this crude product (65 μL of 5% Pd/$BaSO_4$, 65 μL of quinoline, 22 mL of H_2) to afford a viscous brown oil (1.4 g). Purification by flash column chromatography (EtOAc/heptane, gradient from 30% to 100%) yielded pure (*Z*)-**9** (1.3 g, 3.3 mmol, 83% overall yield for the Ti-mediated and the Pd-catalysed hydrogenation reactions) as a viscous yellow oil. IR (neat): 3265, 2927, 2854, 1615, 1454, 1421, 1096, 736, 696 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, *53*:47 mixture of two rotamers): δ 1.90 and *2.10* (2×s, 3H), 2.26 and *2.31* (2×q, *J*=7.5 Hz, 2H), *2.35* and 2.37 (2×q, *J*=6.5 Hz, 2H), 2.98 and *3.02* (2×t, *J*=7.5 Hz, 2H), 3.17 and *3.53* (2×t, *J*=7.5 Hz, 2H), 3.45 and *3.47* (2×t, *J*=6.5 Hz, 2H), *3.39* and 3.62 (t, *J*=7.5 Hz, 2H), *4.49* and 4.50 (2×s, 2H), 5.34–5.56 (m, 2H), 6.96 and *7.01* (2×d, *J*=2.0 Hz, 1H), 7.08–7.24 (m, 2H), 7.24–7.39 (m, 6H), *7.55* and 7.67 (2×d, *J*=8,0 Hz, 1H), *8.06* and 8.15 (2×br s, 1H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$, *53*:47 mixture of two rotamers): δ *20.9* and 21.3, 23.2 and *24.3*, *25.6* and 26.5, *27.6* and 27.6, *45.2* and 48.5, 46.8 and *49.3*, 69.1 and *69.4*, *72.4* and 72.5, 110.9 and *111.1*, *111.3* and 112.2, *117.6* and 118.2, 118.6 and *118.8*, 121.2 and *121.4*, 121.9 and *122.3*, *126.4* and 126.7, *127.1* and 127.5, *127.2* and 127.2, *127.2* and 127.2, *127.8* and 128.6, *127.9* and 127.9, *136.1* and 136.1, 137.9 and *138.0*, 170.1 and *170.4*. MS (ES$^+$) *m*/*z* *413* (MNa$^+$), 414. HRMS (ES$^+$) *m*/*z* calcd for $C_{25}H_{30}N_2NaO_2$ (MNa$^+$) 413.2205, found 413.2191.

4.9.2. 3-(2-((1S,5S*,6S*)-6-(2-(Benzyloxy)ethyl)-1-methyl-2-azabicyclo[3.1.0]hexan-2-yl)ethyl)-1H-indole ((trans)-**10**)*

Titanium(IV) *iso*-propoxide (1.5 equiv, 1.5 mmol, 0.44 mL) was added at 20 °C to a solution of alkenyl amide (*Z*)-**9** (1.0 equiv, 1.0 mmol, 0.39 g) in THF (40 mL), followed by *cyclo*-pentylmagnesium chloride (1.9 M in Et_2O, 4.0 equiv, 4.0 mmol, 2.1 mL) dropwise. After 20 min of stirring, water (0.10 L) and Et_2O (60 mL) were added to the dark mixture. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3×0.10 L). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford a viscous brown oil (0.38 g). Purification of the crude product by two successive flash column chromatographies (neutral alumina gel, activity II, EtOAc/heptane, gradient from 30% to 100%, then MeOH/EtOAc, gradient from 1% to 5%) yielded pure starting alkenyl amide (*Z*)-**9** (0.19 g, 0.49 mmol, 49%) and pure aminocyclopropane (*trans*)-**10** (52 mg, 0.14 mmol, 14%) as colourless crystals. Mp 124.5–125.0 °C. IR (neat): 2920, 2864, 1450, 1231, 1084, 1071, 734, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, *J*=4.0 Hz, 1H), 1.02 (td, *J*=7.0, 4.0 Hz, 1H), 1.37 (s, 3H), 1.46–1.65 (m, 2H), 1.85 (m, 1H), 1.96–2.12 (m, 2H), 2.39 (ddd, *J*=11.5, 9.0, 7.0 Hz, 1H), 2.87–2.99 (m, 2H), 3.15 (ddd, *J*=11.5, 9.5, 7.5 Hz, 1H), 3.25 (m, 1H), 3.45 (t, *J*=7.0 Hz, 2H), 4.48 (s, 2H), 6.97 (d, *J*=2.0 Hz, 1H), 7.06–7.21 (m, 2H), 7.21–7.35 (m, 6H), 7.61 (d, *J*=7.5 Hz, 1H), 8.35 (br s, 1H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.0, 15.4, 25.0, 26.4, 28.2, 29.5, 49.6, 50.1, 52.6, 70.4, 72.9, 111.1, 114.6, 118.8, 119.1, 121.5, 121.8, 127.4, 127.5, 127.5, 128.3, 136.2, 138.5. MS (ES^+) *m*/*z* 244, *375* (MH^+), 376. HRMS (ES^+) *m*/*z* calcd for $C_{25}H_{31}N_2O$ (MH^+) 375.2436, found 375.2439.

*4.9.3. Tetrahydrocarboline (**11**)*

A solution of aminocyclopropane (*trans*)-**10** (1.0 equiv, 0.11 mmol, 41 mg) in chlorobenzene (2 mL) was heated at reflux for 8 h. The reaction being incomplete according to TLC analysis, *para*-toluenesulfonic acid (10% equiv, 11 μmol, 1.9 mg) was added and the mixture was stirred at reflux for a further 24 h under a static atmosphere of Ar. After cooling, the solvent was removed under reduced pressure to afford a viscous black oil (44 mg). Analysis of this crude product by ^{13}C NMR spectroscopy revealed a ≈40:60 ratio for the cis and trans diastereoisomers, defined according to the relative configurations of the methyl and 2-benzyloxyethyl groups, and assigned by comparison with diastereoisomers of a similar carboline.[33] Purification by flash column chromatography (NH_4OH saturated aq solution/EtOAc gradient from 0% to 5%) yielded pure *cis*-**11** (9.2 mg, 25 μmol, 22%), a 47:53 mixture of cis and trans diastereoisomers of **11** (14 mg, 37 μmol, 34%), and pure *trans*-**11** (10 mg, 27 μmol, 24%). *Less polar cis-**11***: brown oil. IR (neat): 3295, 2924, 2854, 1453, 1095, 907, 727, 697 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.41 (s, 3H), 1.47–1.64 (m, 3H), 1.82 (m, 1H), 1.86–2.00 (m, 2H), 2.14 (m, 1H), 2.57 (m, *J*=16.0 Hz, 1H), 2.87 (td, *J*=9.5, 6.0 Hz, 1H), 2.92 (ddd, *J*=16.0, 11.0, 5.5 Hz, 1H), 3.02 (m, 1H), 3.16–3.33 (m, 2H), 3.51–3.59 (m, 2H), 4.54 (AB system, δ_A=4.53 ppm, δ_B=4.55 ppm, J_{AB}=12.0 Hz, 2H), 7.08 (t, *J*=7.5 Hz, 1H), 7.12 (t, *J*=7.5 Hz, 1H), 7.23 (d, *J*=7.5 Hz, 1H), 7.28–7.39 (m, 5H), 7.47 (d, *J*=7.5 Hz, 1H), 7.77 (br s, 1H, NH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 16.6, 22.6, 28.4, 28.5, 30.3, 43.4, 47.3, 48.5, 61.0, 70.0, 73.0, 106.0, 110.7, 118.2, 119.4, 121.5, 127.0, 127.7, 127.7, 128.5, 135.8, 135.8, 138.4. MS (ES^+) *m*/*z* *375* (MH^+), 376. HRMS (ES^+) *m*/*z* calcd for $C_{25}H_{31}N_2O$ (MH^+) 375.2436, found 375.2446. *More polar trans-**11***: brown oil. IR (neat): 3313, 2927, 2860, 1668, 1620, 1453, 1093, 907, 726, 697 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.23 (m, 1H), 1.50 (m, 1H), 1.68–1.83 (m, 2H), 1.93–2.02 (m, 2H), 2.01 (s, 3H), 2.10 (m, 1H), 2.51 (dd, *J*=15.5, 3.5 Hz, 1H), 2.99–3.23 (m, 5H), 3.51 (m, 1H), 3.59 (m, 1H), 4.56 (s, 2H), 7.05–7.14 (m, 2H), 7.19 (m, 1H), 7.28–7.38 (m, 5H), 7.48 (d, *J*=7.5 Hz, 1H), 7.93 (br s, 1H, NH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 16.0, 27.4, 27.9, 29.0, 29.0, 42.4, 46.9, 50.0, 63.2, 70.1, 73.1, 109.7, 110.7, 118.0, 119.1, 121.6, 126.9, 127.7, 127.8, 128.5, 135.8, 136.0, 138.4. MS (ES^+) *m*/*z* 375 (MH^+), 376. HRMS (ES^+) *m*/*z* calcd for $C_{25}H_{31}N_2O$ (MH^+) 375.2436, found 375.2441.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.06.067.

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