Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 64 (2008) 3457–3463
Tetrahedron
www.elsevier.com/locate/tet

Carbon–carbon bond formation via a tandem cationic 2-aza-Cope rearrangement–Lewis acid promoted Petasis reaction

Sara Stas, Kourosch Abbaspour Tehrani*, Georges Laus

Faculty of Sciences, Department of Applied Biological Sciences and Engineering, Laboratory for Organic Chemistry, Vrije Universiteit Brussel, Pleinlaan 2, B-1050 Brussels, Belgium

Received 11 January 2008; received in revised form 7 February 2008; accepted 7 February 2008
Available online 9 February 2008

Abstract

Potassium alkynyltrifluoroborates and potassium (2-phenyl)vinyltrifluoroborates react with *N*-3-butenyl-(2,2-dichloro-1-propylidene)amine in the presence of $BF_3 \cdot Et_2O$ as a Lewis acid to synthesize rearranged Mannich products. The reaction starts with a cationic 2-aza-Cope rearrangement of the imine, followed by the Lewis acid promoted borono-Mannich-type reaction on the rearranged imine to result in a new class of functionalized *N*-homoallylamines.

Keywords: Boron; Imine; 2-Aza-Cope; Tandem reaction; Petasis

1. Introduction

The aza-Cope rearrangement is a well known synthetic route for the formation of new carbon–carbon bonds under mild reaction conditions.[1–11] Depending on the nitrogen-position (*n*) in the substrate, the rearrangement is identified as *n*-aza-Cope rearrangement. 3-Aza-Cope rearrangements have been extensively described in literature and occur within *N*-allylic enamines with a geminally disubstituted enamine system.[1] The 2-aza-Cope rearrangement has been mainly reported as taking place with iminium salts and, in that case, it is referred to as cationic 2-aza-Cope or azonia-[3,3]-sigmatropic rearrangement (Scheme 1).[2–11]

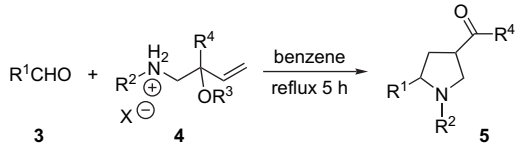
Scheme 1. Reversible cationic aza-Cope rearrangement.

The most attractive feature of this rearrangement is the reorganization occurring under remarkably mild conditions, typically at rt. The main drawback of the method is the reversibility of the process. To be synthetically useful, the cationic 2-aza-Cope rearrangement should be irreversible in a certain direction. Therefore, many applications are carried out in benzo-heterocyclic systems where the rearrangement is driven by aryl conjugation of the product iminium ion (R^3=aryl in Scheme 1).[3] Another strategy to direct the rearrangement is to combine the cationic aza-Cope rearrangement with a subsequent reaction, which drives this equilibrated sigmatropic process towards a final product.[4] Three different tandem reactions have been described in the literature with the cationic aza-Cope process as the first reaction taking place. The second step can be an iminium ion hydrolysis in which one of the iminium isomers is more reactive to water than the more substituted iminium group.[4,5] In some isolated examples this has been effected via an iminium ion reduction.[6] A nucleophile induced ene–iminium cyclization is another possibility to drive the equilibrium towards the desired product.[7] The most intensively documented tandem process is the aza-Cope–Mannich cyclization.[8] This last tandem process, first introduced by Overman, is only possible with iminium salts containing a 2-oxygenated homoallylamine moiety. This

* Corresponding author. Tel.: +32 (0)26293292; fax: +32 (0)26293304.
E-mail address: kourosch.abbaspour.tehrani@vub.ac.be (K. Abbaspour Tehrani).

0040-4020/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.02.025

method allows a variety of polysubstituted pyrrolidines like 3-acylpyrrolidines **5** to be obtained in excellent yields from aldehydes **3** and 2-oxygenated homoallylic amines **4** (Scheme 2). The tandem aza-Cope rearrangement–Mannich reaction was employed as the key step in the total synthesis of several complex natural products like tricyclic amines[9] and different alkaloids[10] such as asparagamine A,[10a] strychnine,[10b] pancracine,[10c] melsocine,[8c] Amaryllidaceae alkaloids[10d] and many others.[11]



Scheme 2. Tandem aza-Cope rearrangement–Mannich cyclization.

To the best of our knowledge, tandem aza-Cope–Mannich reactions were only described to create aza-heterocycles, but were never used to synthesize acyclic amines.

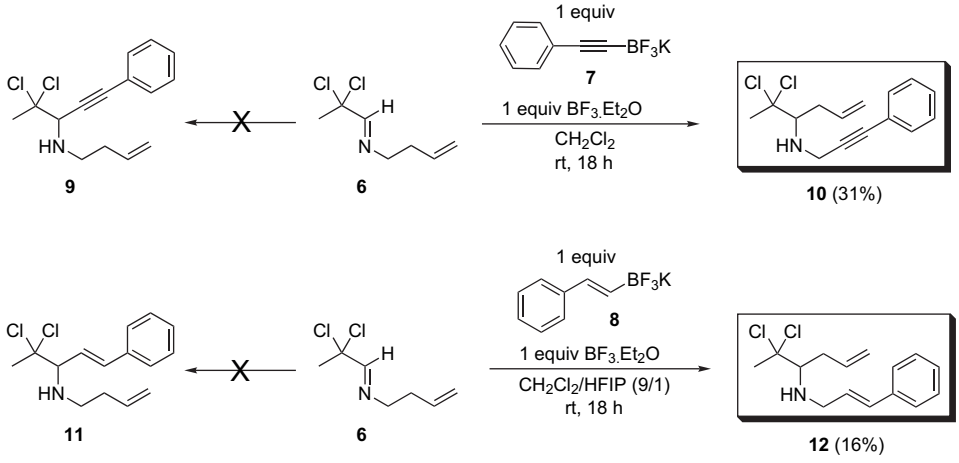
Recently we developed a new modified Petasis reaction with α,α-dichlorinated aldimines as carbonyl equivalents, and organodifluoroboranes, synthesized in situ from organotrifluoroborates and $BF_3\cdot Et_2O$, as nucleophilic compounds.[12] Despite the extensive use of tandem cationic aza-Cope rearrangements–Mannich reaction, there have been no reports using a (modified) Petasis reaction as second step. In the present paper, we describe the extension of this Lewis acid promoted Mannich-type reaction to the use of *N*-3-butenyl-(2,2-dichloro-1-propylidene)amine as the imine-component.

2. Results and discussion

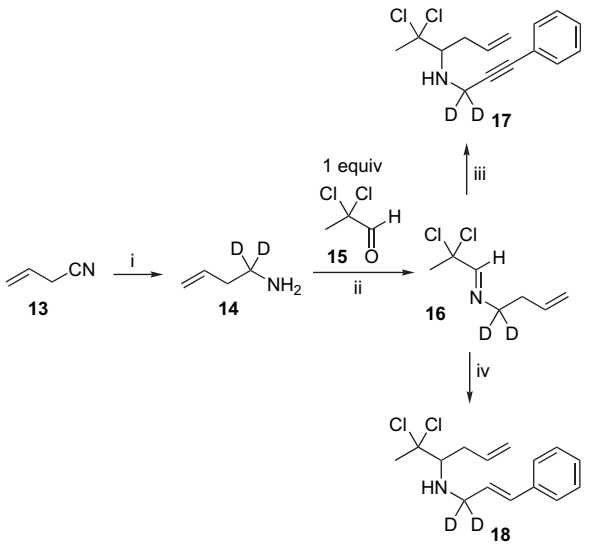
N-3-Butenyl-(2,2-dichloro-1-propylidene)amine (**6**) was synthesized in 66% yield by stirring 2,2-dichloropropanal and 3-butenylamine[13] in CH_2Cl_2 in the presence of anhydrous $MgSO_4$ as desiccant. Imine **6** was subsequently used without any further purification in a one-pot Mannich reaction (Scheme 3) with potassium phenylethynyltrifluoroborate (**7**) or potassium (2-phenyl)vinyltrifluoroborate (**8**), in the presence of $BF_3\cdot Et_2O$. Unreacted starting material, reaction product and side products (phenylacetylene or styrene) could be obtained from the crude reaction mixtures by preparative HPLC. ^{1}H NMR-analysis of the products indicated the absence of a typical singlet or a doublet in the 3.4–4 ppm region, and suggested the formation of other compounds than the expected Mannich bases **9** or **11**. Complete spectral investigation of these compounds by means of both 1-D (^{1}H NMR, ^{13}C NMR) and 2-D (HMBC and HMQC) allowed us to assign the structures of the rearranged homoallylamines **10** and **12** to the above obtained Mannich products. Because of the rather low yields of the homoallylamines **10** (31%) and **12** (16%), an alternate purification by flash chromatography (silica gel) was attempted. This, however, resulted in even lower isolated yields of 25% for **10** and 11% for **12**.[14]

These results are in accordance with a tandem cationic aza-Cope rearrangement–Lewis acid promoted Mannich process as reaction mechanism. In order to confirm this reaction mechanism, deuterium labelled *N*-3-butenyl-(2,2-dichloro-1-propylidene)amine (**16**) was synthesized. First 1,1-dideuteriobut-3-enylamine (**14**) was prepared by reduction of allylcyanide (**13**) with trideuterioalane.[13a] The rather low isolated yield of 19% can be explained by the high water solubility of **14**. In a next step, **14** was used in reaction with 2,2-dichloropropanal (**15**) to prepare the corresponding deuterated imine **16** with a yield of 37%. It was gratifying to observe that the reaction of the dideuterated imine **16** with potassium phenylethynyltrifluoroborate (**7**) or potassium (2-phenyl)vinyltrifluoroborate in the presence of $BF_3\cdot Et_2O$ led, respectively, to the dideuterated rearranged Mannich products **17** and **18**. ^{1}H NMR spectral analysis clearly revealed the position of both deuterium atoms on the methylene carbon next to the nitrogen atom (Scheme 4).

Scheme 5 shows the mechanistic details of this tandem aza-Cope rearrangement–modified Petasis reaction. In the three-component reaction mixture of deuterated imine **16**, organotrifluoroborate and $BF_3\cdot Et_2O$, first the formation of the very electrophilic difluoroborane[15,12] takes place, which coordinates with the imine to form iminium species **19**. Next, a cationic 2-aza-Cope rearrangement of the iminium salt, similar to the aza-Cope rearrangements described in literature,[2] occurs



Scheme 3. Lewis acid promoted Mannich-type reaction with *N*-3-butenyl-(2,2-dichloro-1-propylidene)amine results in rearranged Mannich products.

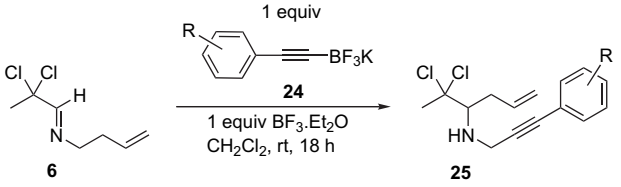


Scheme 4. Deuterium labelling strategy. Reagents and conditions: (i) $AlCl_3$ (1 equiv), $LiAlD_4$ (1 equiv), Et_2O, 0 °C, 1.5 h (19%); (ii) anhydrous $MgSO_4$ (3 equiv), CH_2Cl_2, reflux, 2 h (37%); (iii) **7** (1 equiv), $BF_3{\cdot}Et_2O$ (1 equiv), CH_2Cl_2, rt, 18 h (17%); (iv) **8** (1 equiv), $BF_3{\cdot}Et_2O$ (1 equiv), CH_2Cl_2/HFIP (9/1), rt, 18 h (7%).

through a cyclic transition state **20**, giving rise to a new iminium ion **21**, which is less sterically hindered than the starting sigmatropic isomer **19**. Therefore a Mannich reaction preferably takes place with **21** as imine-component: the R-group is transferred to the electrophilic deuteriomethylene group and after aqueous work-up the intermediate aminodifluoroborane[12] **22** is converted to the rearranged Mannich product **23**. In the literature the equilibrium is shifted to the sigmatropic isomer, which experiences either aryl conjugation[3] with an arylgroup in α-position of the iminium ion or mesomeric stabilization[8] in the presence of an allylic alkoxy group. The rather low yields, observed in our reaction, may be explained by the absence of any of these stabilizing factors. The only driving force here being the final Lewis acid modified Petasis reaction on less sterically hindered iminium isomer **21**. In this context it is worth mentioning that no trace of the product of a modified Petasis reaction was ever observed from starting imine **16**. This process is the first example of a tandem aza-Cope–borono-Mannich reaction leading to aliphatic amines.

Since the yield obtained in the tandem process with potassium (2-phenyl)vinyltrifluoroborate is lower compared to potassium phenylethynyltrifluoroborate, and because the previously reported Lewis acid promoted Mannich-type reaction[12] also resulted in better yields when alkynyltrifluoroborates were used, the scope of this reaction with regard to different alkynyltrifluoroborates was investigated. The reaction between *N*-3-butenyl-(2,2-dichloro-1-propylidene)-

Table 1
Cationic aza-Cope–modified Petasis reaction with arylethynyltrifluoroborates



R (**24**)	Yield **25**[a] (%)
H (**7**)	31 (**10**)
3-OMe (**24a**)	27 (**25a**)
4-Et (**24b**)	17 (**25b**)

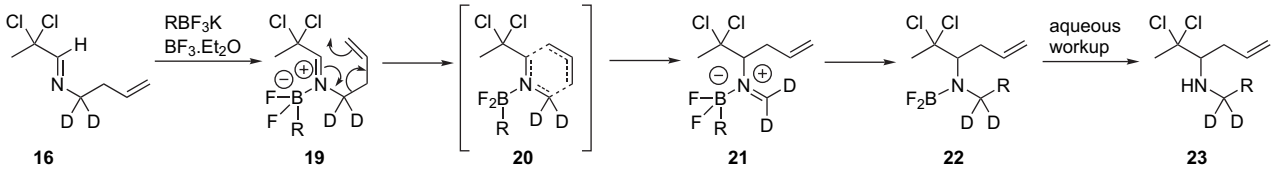
[a] Yield after preparative HPLC.

amine (**6**), potassium arylethynyltrifluoroborates **24** with electron-donating substituents and $BF_3{\cdot}Et_2O$ also resulted in moderate isolated yields of the rearranged Mannich products **25** (Table 1).

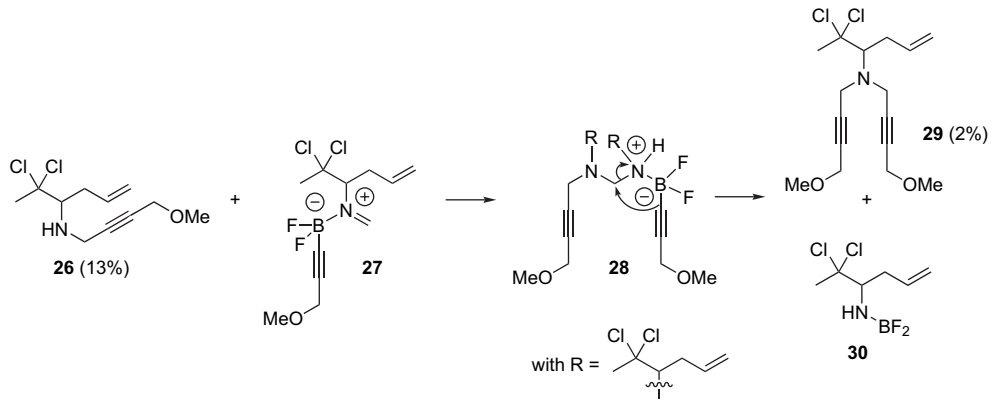
The sigmatropic rearrangement–Mannich reaction tandem process was also evaluated with aliphatic alkynyltrifluoroborates like potassium (3-methoxy-1-propynyl)trifluoroborate (Scheme 6). During flash chromatography of the reaction mixture two products were isolated. Besides the expected rearranged Mannich product **26** (13% yield) also a minor side product was obtained, which could be identified as a tertiary amine **29** with two 4-methoxy-2-butynyl nitrogen substituents (2% yield). It is assumed that this side product is formed by an addition of the rearranged Mannich product **26** to the least sterical hindered sigmatropic isomer **27**, formed during the cationic 2-aza-Cope rearrangement. Intramolecular transfer of the 3-methoxypropargyl group in the intermediate aminal **28** to the aminal-carbon finally results in the tertiary amine **29**. The side product **30**, formed according to the proposed mechanism, has never been observed, probably because of its volatility. The reason why this extra product is formed here, and not in the other aza-Cope–Mannich reactions, remains unclear.

3. Conclusion

In summary, a tandem cationic 2-aza-Cope rearrangement–Lewis acid promoted borono-Mannich reaction of *N*-3-butenyl-(2,2-dichloro-1-propylidene)amine with organotrifluoroborates was developed. This hitherto unreported type of aza-Cope rearrangement in combination with a modified Petasis reaction provides a new route to a new class of geminally dichlorinated secondary homoallylamines. This novel variation of the modified Petasis reaction occurs through



Scheme 5. Reaction mechanism of the tandem cationic 2-aza-Cope rearrangement–Lewis acid promoted borono-Mannich reaction.



Scheme 6. Tandem 2-aza-Cope rearrangement–Lewis acid promoted Mannich reaction with potassium (3-methoxy-1-propynyl)trifluoroborate.

a tandem process in which first a 2-azonia-[3,3]-sigmatropic rearrangement of the iminium salt, formed between imine and organodifluoroborane, takes place, followed by the Lewis acid promoted Mannich reaction.

4. Experimental

4.1. General

GC–MS analyses were performed using an Interscience, GC 8000 series gas chromatograph with an EC™-5 column (length: 30 m, internal diameter: 0.32 mm, film thickness: 0.25 μm). Products are injected in a split injector (250 °C); the inert carrier gas is helium. The mass spectrometer is a Fisons Instruments MD 800 using electron impact (70 eV) as ionization method. HRMS was measured with a VGQuattro II mass spectrometer. High resolution ^{1}H NMR (250 MHz) and ^{13}C NMR (62.9 MHz) spectra were recorded in $CDCl_3$ on a Bruker Avance DRX 250 spectrometer. Chemical shifts are reported in parts per million downfield from TMS. ^{13}C NMR assignments were made using DEPT, HMQC and HMBC spectra. Infrared spectra were recorded with an Avatar 370 FT-IR apparatus (Thermo Nicolet). Unless otherwise stated, the IR-spectra were recorded using the attenuated total reflection technology. Flash chromatography was performed using Merck silica (diameter 40–63 μm). TLC-analysis was performed on glass backed plates (Merck) coated with 0.2 mm silica with UV-indicator 60_{F254}. Preparative HPLC was performed using a Gilson HPLC (332 PUMP) and a Gilson UV-detector (UV/VIS-156) with a reversed phase Discovery BIO wide pore C_{18} column (length: 25 cm, internal diameter: 21.2 mm, particle size: 10 μm) using a MeCN/H_2O gradient containing 0.1% TFA. Potassium (2-phenylvinyl)trifluoroborate,[16a] potassium phenylethynyltrifluoroborate,[16b] potassium (3-methoxyphenyl)ethynyltrifluoroborate,[12] potassium (4-ethylphenyl)ethynyltrifluoroborate[12] and potassium (3-methoxy-1-propynyl)trifluoroborate[16c] were prepared according to literature procedures. 2,2-Dichloropropanal was prepared by halogenation of propanal with chlorine gas.[17] Deuterated and non-deuterated 3-butenylamine were synthesized according to literature procedures.[13a,b] We are also grateful to EBURON ORGANICS for a generous gift of 3-butenylamine (purity of 90% in NMR).

4.1.1. Synthesis of 1,1-dideuteriobut-3-enylamine (**14**)

This compound was prepared analogous to the procedure for the preparation of 3-butenylamine.[13a]

Yield: 832 mg (scale 60 mmol, yield 19%), colourless liquid.

^{1}H NMR (250 MHz, $CDCl_3$): δ 5.81–5.73 (1H, m, $CH_2CH{=}CH_2$), 5.15–5.05 (2H, m, $CH_2CH{=}CH_2$), 2.19 (2H, d, J=6.2 Hz, CD_2CH_2).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ 136.2 ($CH_2CH{=}CH_2$), 116.6 ($CH_2CH{=}CH_2$), 40.5 (CD_2, quintet, J=21.1 Hz), 37.9 (CD_2CH_2).

IR (ATR, cm^{-1}): ν_{max} 3074, 2924, 2843, 2610, 1619, 1391, 1367, 1004, 975, 829, 700, 661.

4.2. Synthesis of N-3-butenyl-(2,2-dichloro-1-propylidene)-amine (**6**); general procedure

To a stirred solution of 2,2-dichloropropanal (**15**) (50 mmol, 6.35 g) in CH_2Cl_2 (50 mL) was added $MgSO_4{\cdot}3H_2O$ (150 mmol, 26.16 g) as desiccant, followed by 3-butenylamine (47.5 mmol, 3.38 g). The solution was stirred under reflux for 2 h. Afterwards, the solution was filtered and concentrated under reduced pressure. Yield: 5.91 g (66%), colourless liquid.

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.76 (1H, s, HCN), 5.85–5.69 (1H, m, $CH_2CH{=}CH_2$), 5.17–5.03 (2H, m, $CH_2CH{=}CH_2$), 3.57 (2H, t, J=6.9 Hz, NCH_2), 2.39 (2H, q, J=6.9 Hz, $CH_2CH{=}CH_2$), 2.26 (3H, s, CH_3).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ 160.6 (CN), 135.3 ($CH_2CH{=}CH_2$), 116.8 ($CH_2CH{=}CH_2$), 84.5 (CCl_2), 58.6 (NCH_2), 34.1 ($CH_2CH{=}CH_2$), 32.6 (CH_3).

IR (ATR, cm^{-1}): ν 1667 (C=N), 1437, 1380 ($HC{=}CH_2$).

MS (70 eV, *m/z* (%)): 183 ($[M+4]^+$, 0.6), 181 ($[M+2]^+$, 1.6), 179 (M^+, 1.3), 140 (52), 138 (58), 111 (17), 110 (15), 109 (15), 105 (14), 104 (16), 102 (50), 97 (19), 82 (83), 79 (19), 78 (18), 76 (72), 68 (28), 67 (25), 63 (16), 61 (29), 54 (100), 51 (38).

*4.2.1. N-(2,2-Dichloro-1-propylidene)-(1,1-dideuterio-3-butenyl)amine (**16**)*

Compound **16** was prepared in an analogous manner.

Yield: 670 mg (scale 10 mmol, yield 37%), light-yellow oil.

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.76 (1H, s, HCN), 5.79–5.69 (1H, m, CH_2CH=CH_2), 5.13–5.03 (2H, m, CH_2CH=CH_2), 2.51 (2H, d, J=6.8 Hz, CH_2CH=CH_2), 2.27 (3H, s, CH_3).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ 159.8 (CN), 134.5 (CH_2CH=CH_2), 118.4 (CH_2CH=CH_2), 83.7 (CCl_2), 31.8 (CH_2CH=CH_2), 30.6 (CH_3), quintet of CD_2 is not visible.

IR (ATR, cm^{-1}): ν 1641, 1620 (C=N), 1378, 1353 (C=C).

MS (70 eV, *m/z* (%)): 185 ([M+4]$^+$, 3), 183 ([M+2]$^+$, 9), 181 (M$^+$, 11), 146 (99), 140 (98), 109 (98), 103 (100), 99 (51), 97 (54), 83 (99), 75 (99), 68 (100), 61 (99), 52 (99).

4.3. Synthesis of the dichlorinated homoallylamines; general procedure

To a stirred solution of **6** (0.5 mmol, 89 mg) in CH_2Cl_2 (4 mL) was added the potassium alkynyltrifluoroborate (1 equiv, 0.5 mmol) in one portion, followed by $BF_3\cdot Et_2O$ (1 equiv, 0.5 mmol, 71 mg). The reaction mixture was stirred for 18 h at rt and poured into aqueous NaOH (4 mL, 0.5 M). After isolation of the organic layer, the aqueous phase was washed with CH_2Cl_2 (4×5 mL). The organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure.

The reaction with potassium (2-phenylvinyl)trifluoroborates was carried out in the same way but with CH_2Cl_2/HFIP (9/1) as solvent mixture. Unless otherwise stated, all these reactions were purified by preparative HPLC.

*4.3.1. N-(5,5-Dichloro-1-hexene-4-yl)-(3-phenyl-2-propynyl)-amine (**10**)*

Yield: 44 mg (31%), dark-yellow oil.

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.47–7.38 (2H, m, $CH_{arom.ortho}$), 7.33–7.25 (3H, m, $CH_{arom.meta+para}$), 6.06–5.89 (1H, m, CH_2CH=CH_2), 5.25–5.13 (2H, m, CH_2CH=CH_2), 3.83 (2H, s, $NHCH_2$), 3.21 (1H, d×d, J=9.3, 3.2 Hz, CHNH), 2.97–2.86 and 2.31–2.22 (2×1H, 2×m, CH_2CH=CH_2), 2.20 (3H, s, CH_3).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ 135.1 (CH_2CH=CH_2), 131.5 ($C_{arom.ortho}$), 128.3 ($C_{arom.meta}$), 128.1 ($C_{arom.para}$), 123.0 ($C_{arom.quat.}$), 118.4 (CH_2CH=CH_2), 94.9 (CCl_2), 87.4, 83.9 (C≡$CC_{arom.}$), 67.7 (CHNH), 39.5 ($NHCH_2$), 36.9 (CH_2CH=CH_2), 34.2 (CH_3).

IR (ATR, cm^{-1}): ν 3363 (NH), 1640, 1598 (C=C aromate), 1489, 1441 (HC=CH).

MS (70 eV, *m/z* (%)): 285 ([M+4]$^+$, 0.4), 283 ([M+2]$^+$, 2), 281 (M$^+$, 3), 242 (36), 240 (37), 204 (13), 185 (21), 184 (50), 167 (12), 115 (100), 113 (10), 102 (16), 89 (31), 82 (11), 77 (13), 65 (16), 63 (21).

HRMS (ESI): *m/z* calcd for $C_{15}H_{17}NCl_2$+H: 282.0816; found: 282.0843.

*4.3.2. N-(5,5-Dichloro-1-hexene-4-yl)-(3-phenyl-2-propenyl)-amine (**12**)*

Yield: 23 mg (16%), dark-yellow oil.

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.39–7.19 (5H, m, aromate), 6.50 (1H, d, J=15.9 Hz, $CHCH$=$C_{arom.quat.}$), 6.22 (1H, d×t, J=15.9, 6.4 Hz, CH=$CHC_{arom.quat.}$), 5.99–5.82 (1H, m, CH_2CH=CH_2), 5.22–5.15 (2H, m, CH_2CH=CH_2), 3.56 (2H, d×d, J=6.4, 1.3 Hz, $NHCH_2$), 2.98–2.93 (1H, m, CHNH), 2.90–2.85 and 2.32–2.23 (2×1H, 2×m, CH_2CH=CH_2), 2.19 (3H, s, CH_3).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ 136.9 ($C_{arom.quat.}$), 135.3 ($CHCHC_{arom.quat.}$), 131.5 ($CHCHC_{arom.quat.}$), 128.6 ($C_{arom.ortho}$), 128.2 (CH_2CH=CH_2), 127.5 ($C_{arom.para}$), 126.3 ($C_{arom.meta}$), 118.0 (CH_2CH=CH_2), 95.3 (CCl_2), 68.5 (CHNH), 52.2 ($NHCH_2$), 37.2 (CH_2CH=CH_2), 34.5 (CH_3).

IR (ATR, cm^{-1}): ν 1494, 1447 (C=C aromate), 1370 (HC=CH).

MS (70 eV, *m/z* (%)): 287 ([M+4]$^+$, trace), 285 ([M+2]$^+$, trace), 283 (M$^+$, trace), 214 (11), 213 (80), 132 (11), 118 (9), 117 (100), 115 (78), 108 (9), 102 (8), 94 (18), 91 (44), 89 (9), 77 (13), 65 (12), 63 (8), 53 (17), 51 (13).

HRMS (ESI): *m/z* calcd for $C_{15}H_{19}NCl_2$+H: 284.0973; found: 284.0894.

*4.3.3. N-(5,5-Dichloro-1-hexene-4-yl)-(1,1-dideuterio-3-phenyl-2-propynyl)amine (**17**)*

Yield: 24 mg (17%), yellow oil.

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.38–7.31 (2H, m, $CH_{arom.ortho}$), 7.26–7.21 (3H, m, $CH_{arom.meta+para}$), 5.99–5.82 (1H, m, CH_2CH=CH_2), 5.17–5.06 (2H, m, CH_2CH=CH_2), 3.13 (1H, d×d, J=9.4, 3.2 Hz, CHNH), 2.89–2.79 and 2.23–2.15 (2×1H, 2×m, CH_2CH=CH_2), 2.12 (3H, s, CH_3).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ 134.1 (CH_2CH=CH_2), 130.5 ($C_{arom.ortho}$), 127.3 ($C_{arom.meta}$), 127.1 ($C_{arom.para}$), 122.0 ($C_{arom.quat.}$), 117.3 (CH_2CH=CH_2), 94.0 (CCl_2), 86.4 (C≡$CC_{arom.quat.}$), 82.8 (C≡$CC_{arom.quat.}$), 66.6 (CHNH), 38.3–37.2 (CD_2, m), 35.9 (CH_2CH=CH_2), 33.1 (CH_3).

IR (ATR, cm^{-1}): ν 3356 (NH), 2079 (C≡C), 1640, 1598, 1489, 1442 (C=C aromate), 1372, 1337, 1269 (HC=CH, CH=CH_2).

MS (70 eV, *m/z* (%)): 283 (M$^+$, 0.2), 279 (M$^+$–(2×D), 0.4), 186 (100), 176 (37), 175 (39), 155 (65), 153 (37), 145 (36), 141 (51), 139 (53), 128 (36), 117 (35), 115 (86), 114 (63), 99 (62), 97 (87), 77 (35), 63 (46), 61 (40), 57 (60).

HRMS (ESI): *m/z* calcd for $C_{15}H_{15}D_2NCl_2$+H: 284.0932; found: 284.0901.

*4.3.4. N-(5,5-Dichloro-1-hexene-4-yl)-(1,1-dideuterio-3-phenyl-2-propenyl)amine (**18**)*

Yield: 10 mg (7%), yellow oil.

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.32–7.13 (5H, m, aromate), 6.44 (1H, d, J=15.9 Hz, $CHCH$=$C_{arom.quat.}$), 6.15 (1H, d, J=15.9 Hz, CH=$CHC_{arom.quat.}$), 5.92–5.76 (1H, m, CH_2CH=CH_2), 5.17–5.08 (2H, m, CH_2CH=CH_2), 2.94–2.84 (1H, m, CHNH), 2.83–2.78 and 2.28–2.17 (2×1H, 2×m, CH_2CH=CH_2), 2.13 (3H, s, CH_3).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ 135.8 ($C_{arom.quat.}$), 134.1 (CH_2CH=CH_2), 131.5–130.8 ($CHCHC_{arom.quat.}$, m due to coupling with D), 127.6 ($C_{arom.meta}$), 126.6 ($C_{arom.para}$+$CHCHC_{arom.quat.}$), 125.3 ($C_{arom.ortho}$), 117.2 (CH_2CH=CH_2),

93.8 (CCl_2), 67.4 (CHNH), 50.5–50.1 (CD_2, m), 35.9 ($CH_2CH{=}CH_2$), 33.4 (CH_3).

IR (ATR, cm^{-1}): ν 1491, 1452, 1413 (C=C aromate), 1258 (HC=CH, $CH{=}CH_2$).

MS (70 eV, *m/z* (%)): 281 ($M^+-(2\times D)$, 1), 218 (31), 216 (96), 214 (100), 178 (45), 106 (39), 99 (40), 97 (54), 89 (38), 80 (38), 79 (57), 77 (50), 75 (38), 65 (40), 63 (49), 61 (49), 54 (38), 51 (40).

HRMS (ESI): *m/z* calcd for $C_{15}H_{17}D_2NCl_2$+H: 286.1088; found: 286.1037.

*4.3.5. N-(5,5-Dichloro-1-hexene-4-yl)-[3-(3-methoxyphenyl)-2-propynyl]amine (**25a**)*

Yield: 42 mg (27%), yellow oil.

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.15 (1H, d×d, J=7.9, 7.9 Hz, $C_{arom.quat.}CH_{arom.}CH_{arom.}CH_{arom.}C_{arom.quat.}$), 6.94 (1H, d×d×d, J=7.6, 1.1, 1.1 Hz, $C{\equiv}CC_{arom.quat.}CH_{arom.}$), 6.88 (1H, d×d≈t, J=1.8 Hz, $C_{arom.quat.}CH_{arom.}C_{arom.quat.}$), 6.80 (1H, d×d×d, J=8.2, 2.4, 1.0 Hz, $CH_{arom.}C_{arom.quat.}OMe$), 5.99–5.82 (1H, m, $CH_2CH{=}CH_2$), 5.17–5.07 (2H, m, $CH_2CH{=}CH_2$), 3.74 (2H, s, $NHCH_2$), 3.73 (3H, s, OMe), 3.12 (1H, d×d, J=9.4, 3.2 Hz, $CHCCl_2$), 2.89–2.79 and 2.23–2.16 (2×1H, 2×m, $CH_2CH{=}CH_2$), 2.12 (3H, s, CH_3), 1.55 (1H, s, NH).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ 159.3 ($C_{arom.quat.}OMe$), 134.1 ($CH_2CH{=}CH_2$), 128.4 ($MeOC_{arom.quat.}CH_{arom.}CH_{arom.}$), 123.0 ($C{\equiv}CC_{arom.quat.}$), 123.0 ($C{\equiv}CC_{arom.quat.}CH_{arom.}$), 117.3 ($CH_2CH{=}CH_2$), 115.5 ($MeOC_{arom.quat.}CH_{arom.}$), 113.6 ($C_{arom.quat.}CH_{arom.}C_{arom.quat.}$), 94.0 ($CCl_2$), 86.3 ($C{\equiv}C$-$C_{arom.quat.}$), 82.7 ($C{\equiv}CC_{arom.quat.}$), 66.7 (CHNH), 54.2 (MeO), 38.5 ($NHCH_2$), 36.0 ($CH_2CH{=}CH_2$), 33.1 (CH_3CCl_2).

IR (ATR, cm^{-1}): ν 3361 (NH), 1575, 1597 (C=C aromate), 1488, 1480, 1464, 1430 (HC=CH_2).

MS (70 eV, *m/z* (%)): 315 ($[M+4]^+$, trace), 313 ($[M+2]^+$, 0.2), 311 (M^+, 0.2), 214 (11), 146 (10), 145 (100), 130 (15), 115 (31), 102 (50), 99 (12), 97 (18), 91 (14), 89 (18), 77 (14), 76 (17), 75 (14), 65 (11), 63 (33), 62 (11), 61 (12), 54 (16), 53 (14), 51 (11).

HRMS (ESI): *m/z* calcd for $C_{16}H_{19}NOCl_2$+H: 312.0922; found: 312.0886.

*4.3.6. N-(5,5-Dichloro-1-hexene-4-yl)-[3-(4-ethylphenyl)-2-propynyl]amine (**25b**)*

Yield: 27 mg (17%), yellow oil.

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.26 (2H, d, J=8.1 Hz, $C{\equiv}CC_{arom.quat.}(CH_{arom.})_2$), 7.07 (2H, d, J=8.1 Hz, $CH_3CH_2C_{arom.quat.}(CH_{arom.})_2$), 5.99–5.70 (1H, m, $CH_2CH{=}CH_2$), 5.16–5.04 (2H, m, $CH_2CH{=}CH_2$), 3.73 (2H, s, $NHCH_2$), 3.13 (1H, d×d, J=9.3, 3.2 Hz, $CHCCl_2$), 2.89–2.78 and 2.23–2.14 (2×1H, 2×m, $CH_2CH{=}CH_2$), 2.54 (2H, q, J=7.6 Hz, CH_2CH_3), 2.12 (3H, s, CH_3), 1.57 (1H, s, NH), 1.15 (3H, t, J=7.6 Hz, CH_2CH_3).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ 143.5 ($C_{arom.quat.}Et$), 134.1 ($CH_2CH{=}CH_2$), 130.5 ($C{\equiv}CC_{arom.quat.}(C_{arom.})_2$), 126.8 ($CH_3CH_2C_{arom.quat.}(C_{arom.})_2$), 119.2 ($C{\equiv}CC_{arom.quat.}$), 117.3 ($CH_2CH{=}CH_2$), 94.0 ($CCl_2$), 85.7 ($C{\equiv}CC_{arom.quat.}$), 83.0 ($C{\equiv}CC_{arom.quat.}$), 66.6 ($CHCCl_2$), 38.5 ($NHCH_2$), 36.0 ($CH_2CH{=}CH_2$), 33.2 ($CH_3CCl_2$), 27.7 ($CH_2CH_3$), 14.3 ($CH_2CH_3$).

IR (ATR, cm^{-1}): ν 3356 (NH), 1509, 1437 (C=C aromate), 1372, 1329 (HC=CH_2).

MS (70 eV, *m/z* (%)): 313 ($[M+4]^+$, 0.1), 311 ($[M+2]^+$, 0.6), 309 (M^+, 1), 270 (10), 268 (15), 213 (10), 212 (55), 144 (32), 143 (100), 141 (15), 129 (9), 128 (60), 127 (18), 115 (27), 102 (9), 99 (6), 91 (5), 89 (5), 77 (7), 65 (5), 63 (8).

HRMS (ESI): *m/z* calcd for $C_{17}H_{21}NCl_2$+H: 310.1129; found: 310.1086.

*4.3.7. N-(5,5-Dichloro-1-hexene-4-yl)-(4-methoxy-2-butynyl)amine (**26**)*

Yield: 16 mg (13% after flash chromatography with CH_2Cl_2/EtOH (99/1), R_f=0.25), light-yellow oil.

^{1}H NMR (250 MHz, $CDCl_3$): δ 6.01–5.84 (1H, m, $CH_2CH{=}CH_2$), 5.22–5.14 (2H, m, $CH_2CH{=}CH_2$), 4.11 (2H, t, J=1.9 Hz, CH_2OMe), 3.65 (2H, t, J=1.9 Hz, $NHCH_2$), 3.38 (3H, s, OMe), 3.10 (1H, d×d, J=9.3, 3.2 Hz, $CHCCl_2$), 2.93–2.82 and 2.27–2.20 (2×1H, 2×m, $CH_2CH{=}CH_2$), 2.16 (3H, s, CCl_2CH_3).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ 134.0 ($CH_2CH{=}CH_2$), 117.3 ($CH_2CH{=}CH_2$), 93.9 (CCl_2), 83.5 ($C{\equiv}CCH_2OMe$), 78.4 ($C{\equiv}CCH_2OMe$), 66.7 ($CHCCl_2$), 59.0 ($NHCH_2$), 56.6 (OMe), 37.9 (CH_2OMe), 35.9 (CH_3CCl_2), 33.1 ($CH_2CH{=}CH_2$).

IR (ATR, cm^{-1}): ν 3657 (NH), 1641 (C≡C), 1376, 1356 (HC=CH_2).

MS (70 eV, *m/z* (%)): 254 ($[M+5]^+$, 0.1), 252 ($[M+3]^+$, 0.3), 250 ($[M+1]^+$, 0.5), 210 (83), 208 (92), 172 (21), 153 (25), 152 (100), 107 (27), 106 (28), 104 (20), 94 (22), 93 (24), 92 (26), 91 (54), 80 (41), 79 (28), 77 (72), 70 (21), 68 (50), 65 (23), 55 (54), 53 (74), 52 (36), 51 (32).

HRMS (ESI): *m/z* calcd for $C_{11}H_{17}NOCl_2$+H: 250.0765; found: 250.0885.

*4.3.8. N-(5,5-Dichloro-1-hexene-4-yl)[bis(4-methoxy-2-butynyl)]amine (**29**)*

Yield: 4 mg (2% after flash chromatography with CH_2Cl_2/EtOH (99/1), R_f=0.32), yellow oil.

^{1}H NMR (250 MHz, $CDCl_3$): δ 6.05–5.89 (1H, m, $CH_2CH{=}CH_2$), 5.30–5.05 (2H, m, $CH_2CH{=}CH_2$), 4.11 (2×2H, t, J=1.8 Hz, 2×CH_2OMe), 3.80 (2H, t, J=1.8 Hz, $NHCH_2$), 3.78 (2H, t, J=1.8 Hz, $NHCH_2$), 3.45 (1H, d×d, J=9.6, 3.4 Hz, $CHCCl_2$), 3.38 (2×3H, s, 2×OMe), 2.94–2.83 and 2.73–2.60 (2×1H, 2×m, $CH_2CH{=}CH_2$), 2.21 (3H, s, CCl_2CH_3).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ 136.3 ($CH_2CH{=}CH_2$), 117.0 ($CH_2CH{=}CH_2$), 94.9 (CCl_2), 83.3 (2×$C{\equiv}CCH_2OMe$), 80.1 (2×$C{\equiv}CCH_2OMe$), 71.7 ($CHCCl_2$), 60.0 (2×$NHCH_2$), 57.6 (2×OMe), 40.8 (2×CH_2OMe), 35.8 (CH_3CCl_2), 32.1 ($CH_2CH{=}CH_2$).

IR (ATR, cm^{-1}): ν 3283 (NH), 2418 (C≡C), 1452, 1432 (C=C aromate), 1367 (HC=CH_2).

MS (ESI^+): 336/334/332 ($[M+5]^+$/$[M+3]^+$/$[M+1]^+$=8/38/54), 234 ($[M-97]^+$).

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{23}NO_2Cl_2$+H: 331.1106; found: 331.1125.

Acknowledgements

S.S. is a research assistant of the Fund for Scientific Research-Flanders (Belgium). We would like to thank EBURON ORGANICS for a generous gift of 3-butenylamine.

References and notes

1. (a) Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847–1882; (b) Nakamura, H.; Yamamoto, Y. *Handbook of Organopalladium Chemistry for Organic Synthesis*; John Wiley & Sons: New York, NY, 2002; Vol. 2, pp 2919–2934; (c) Gomes, M. J. S.; Sharma, L.; Prabhakar, S.; Lobo, A. M.; Gloria, P. M. C. *Chem. Commun.* **2002**, 746–747; (d) McComsey, D. F.; Maryanoff, B. E. *J. Org. Chem.* **2000**, *65*, 4938–4943; (e) Yadav, J. S.; Reddy, B. V. S.; Rasheed, M. A.; Kumar, H. M. S. *Synlett* **2000**, 487–488.
2. (a) Overman, L. E.; Kakimoto, M.-a. *J. Am. Chem. Soc.* **1979**, *101*, 1310–1312; (b) Aron, Z. D.; Overman, L. E. *Org. Lett.* **2005**, *7*, 913–916; (c) Sugiura, M.; Mori, C.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 11038–11039; (d) Merino, P.; Tejero, T.; Mannucci, V. *Tetrahedron Lett.* **2007**, *48*, 3385–3388; (e) Doedens, R. J.; Meier, G. P.; Overman, L. E. *J. Org. Chem.* **1988**, *53*, 685–690.
3. (a) Knabe, J.; Höltje, H.-D. *Tetrahedron Lett.* **1969**, *10*, 2107–2108; (b) Marschall, J. A.; Babler, J. H. *J. Org. Chem.* **1969**, *34*, 4186–4188; (c) Grob, C. A.; Kunz, W.; Marbet, P. R. *Tetrahedron Lett.* **1975**, *16*, 2613–2616.
4. (a) Agami, C.; Couty, F.; Poursoulis, M. *Synlett* **1992**, 847–848; (b) Agami, C.; Couty, F.; Lin, J.; Mikaeloff, A.; Poursoulis, M. *Tetrahedron* **1993**, *49*, 7239–7250; (c) Agami, C.; Couty, F.; Lin, J.; Mikaeloff, A. *Synlett* **1993**, 349–350.
5. (a) Castelhano, A. L.; Krantz, A. *J. Am. Chem. Soc.* **1984**, *106*, 1877–1879; (b) Cook, G. R.; Stille, J. R. *J. Org. Chem.* **1991**, *56*, 5578–5583; (c) Bennett, D. J.; Hamilton, N. M. *Tetrahedron Lett.* **2000**, *41*, 7961–7964; (d) Cooke, A.; Bennett, J.; McDaid, E. *Tetrahedron Lett.* **2002**, *43*, 903–905.
6. (a) Esch, P. M.; Boska, I. M.; Hiemstra, H.; de Boer, R. F.; Speckamp, W. N. *Tetrahedron* **1991**, *47*, 4039–4062; (b) Rutjes, F. P. J. T.; Veerman, J. J. N.; Meester, W. J. N.; Hiemstra, H.; Schoemaker, H. E. *Eur. J. Org. Chem.* **1999**, 1127–1135.
7. (a) Meyers, A. I.; Miller, D. B.; White, F. H. *J. Am. Chem. Soc.* **1988**, *110*, 4778–4787; (b) Mooiwer, H. H.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1991**, *47*, 3451–3462; (c) Hays, S. J.; Malone, T. C.; Johnson, G. J. *J. Org. Chem.* **1991**, *56*, 4084–4086; (d) Gelas-Mialhe, Y.; Gramain, J. C.; Louvet, A.; Remuson, R. *Tetrahedron Lett.* **1992**, *33*, 73–76.
8. (a) Overman, L. E.; Kakimoto, M.-a.; Okazaki, M. E.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6622–6629; (b) Jacobsen, E. J.; Levin, J.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4329–4336; (c) Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 2598–2610; (d) Johnson, B. F.; Marrero, E. L.; Turley, W. A.; Lindsay, H. A. *Synlett* **2007**, 893–896; (e) Overman, L. E.; Okazaki, M. E.; Jacobsen, E. J. *J. Org. Chem.* **1985**, *50*, 2403–2405; (f) Overman, L. E.; Jacobsen, E. J.; Doedens, R. J. *J. Org. Chem.* **1983**, *48*, 3393–3400.
9. (a) Brummond, K. M.; Hong, S.-p. *J. Org. Chem.* **2005**, *70*, 907–916; (b) Brummond, K. M.; Lu, J. *Org. Lett.* **2001**, *3*, 1347–1349; (c) Earley, W. G.; Jacobsen, J. E.; Madin, A.; Meier, G. P.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 18046–18053.
10. (a) Brueggemann, M.; McDonald, A. I.; Overman, L. E.; Rosen, M. D.; Schwink, L.; Scott, J. P. *J. Am. Chem. Soc.* **2003**, *12*, 15284–15285; (b) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776–5788; (c) Overman, L. E.; Shim, J. *J. Org. Chem.* **1993**, *58*, 4662–4672; (d) Overman, L. E.; Wild, H. *Tetrahedron Lett.* **1989**, *30*, 647–650; See also references cited within these articles.
11. (a) Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241–11250; (b) Angle, S. R.; Fevig, J. M.; Knight, S. D.; Marquis, R. W., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 3966–3976; (c) Fevig, J. M.; Marquis, R. W., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5085–5086; (d) Overman, L. E.; Sworin, M.; Bass, L. S.; Clardy, J. *Tetrahedron* **1981**, *37*, 4041–4045.
12. Stas, S.; Abbaspour Tehrani, K. *Tetrahedron* **2007**, *63*, 8921–8931.
13. (a) Borst, M. L. G.; van der Riet, N.; Lemmens, R. H.; de Kanter, F. J. J.; Schakel, M.; Ehlers, A. W.; Mills, A. M.; Lutz, M.; Spek, A. L.; Lammertsma, K. *Chem.—Eur. J.* **2005**, 3631–3642; (b) Jacobson, M. A.; Williard, P. G. *J. Org. Chem.* **2002**, *67*, 3915–3918; (c) Miller, M. L.; Ray, P. S. *Tetrahedron* **1996**, *52*, 5739–5744; (d) Abd El Samii, Z. K. M.; Al Ashmawy, M. I.; Mellor, J. M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2517–2522.
14. Unpublished results. The reason for the loss in yield of the Mannich products during flash chromatography is due to their instability on silica. We noticed that under influence of SiO_2 1,2-dehydrochlorination occurs, leading to α-chloro-imines.
15. (a) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020–3027; (b) Vedejs, E.; Fields, S. C.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1993**, *115*, 11612–11613; (c) Vedejs, E.; Fields, S. C.; Hayashi, R.; Hitchcock, S. R.; Powell, D. R.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 2460–2470; (d) Billard, T.; Langlois, B. R. *J. Org. Chem.* **2002**, *67*, 997–1000.
16. (a) Molander, G. A.; Bernardi, C. R. *J. Org. Chem.* **2002**, *67*, 8424–8429; (b) Molander, G. A.; Katona, B. W.; Machrouhi, F. *J. Org. Chem.* **2002**, *67*, 8416–8423; (c) Stefani, H. A.; Cella, R.; Dörr, F. A.; Pereira, C. M. P.; Zeni, G.; Gomes, M. *Tetrahedron Lett.* **2005**, *46*, 563–567.
17. Bellesia, F.; De Buyck, L.; Ghelfi, F.; Pagnoni, U. M.; Parsons, A. F.; Pinetti, A. *Synthesis* **2003**, 2173–2178.