Indium-Mediated Reactions of Enamines in the Presence of Acid

Laurent Tussa, Chrystèle Lebreton, and Paul Mosset*

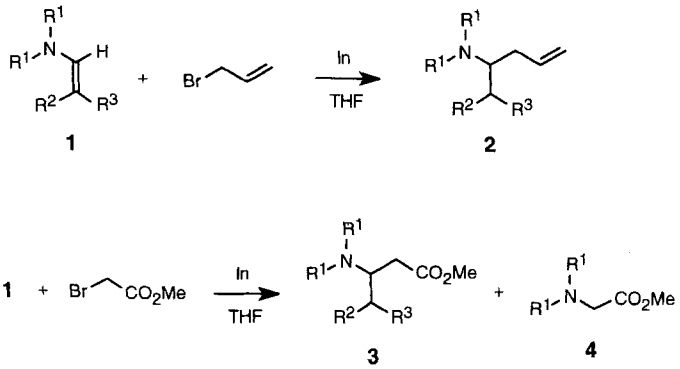
Abstract: The reaction of enamines with allyl bromide and metallic indium in THF to afford homoallylamines was greatly accelerated by the addition of one equivalent of a suitable carboxylic acid, such as acetic acid. It was established that the likely mechanism consists of a nucleophilic addition of an indium sesquihalide to the iminium salt formed by protonation of the enamine. Substituted allyl bromides also reacted with complete allylic transposition (γ-addition). In contrast to indium-mediated allylation of carbonyl compounds in which only two of the three allyl groups of the sesquihalide are involved, all three allyl groups are involved in the reaction with enamines. As a result only 2/3 equiv of indium are required. This allylation was also performed with zinc, tin, bismuth, and aluminum in the presence of a catalytic amount of $InCl_3$ instead of indium. However, these reactions invariably gave lower yields. The analogous reaction of methyl bromoacetate instead of allyl bromide was also studied. This "Reformatsky-type" process was also greatly accelerated by the addition of one equivalent of acetic acid. In this case, the yields remained moderate for both indium and zinc.

Keywords
allylations · enamines · iminium salts · indium · zinc

Introduction

Since 1988, the use of metallic indium has been the subject of increasing interest for C–C bond formation, particularly in reactions with carbonyl compounds.[1] Reactive halides (RX) such as allyl halides and α-halo esters react with indium to afford indium sesquihalides ($R_3In_2X_3$).[2] Subsequent nucleophilic addition to carbonyl compounds gives homoallylic alcohols[3, 4] or β-hydroxy esters.[4]

Recently, we described indium-mediated reactions of enamines **1** with allyl bromide or methyl bromoacetate yielding homoallylamines **2** and β-amino esters **3**, respectively (Scheme 1).[5] These reactions seemed surprising considering the nucleophilic character of enamines. The origin of the hydrogen atom incorporated in a β position to nitrogen was also unclear. The purpose of this paper is to present not only major improvements to these reactions, but also a likely mechanism.



Scheme 1. Indium-mediated reactions of enamines **1** with allyl bromide or methyl bromoacetate yielding homoallylamines **2** and β-amino esters **3** respectively.

Results and Discussion

From previous studies, the observed reactivity of enamines for the considered reactions seemed to parallel their basicity, since it increased with electron-donating substituents at nitrogen and at the β position. This behavior is compatible with an initial protonation of the enamine leading to an iminium salt. Glass acidity was suspected to be the proton source and also the origin of the incorporated hydrogen atom β to nitrogen. Moreover, better results were obtained when using a reaction flask prewashed with acid! However, these reactions still suffer from both long reaction times (ca. 20 h at room temperature) and often only moderate yields, probably due to slow or partial proton supply. Addition of one equivalent of isopropanol proved beneficial only for the allylation of highly reactive enamines. At this point, we surmised that addition of one equivalent of a suitable acid would lead to not only accelerated reactions, but also to improved yields—and this was indeed the case! Thus, when one equivalent of acetic acid was added to the enamine in anhydrous THF followed by indium (2/3 equiv) and allyl bromide (1.5 equiv), indium was consumed far more rapidly than in our previous experiments. After basic (Na_2CO_3) workup and

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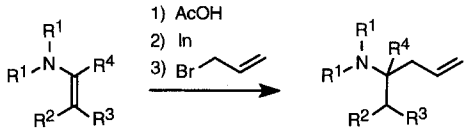
purification by chromatography on basic alumina, tertiary homoallylamines were isolated, often in good yields (Scheme 2, Table 1). From Table 1, it can be seen that the reaction appears to tolerate various patterns of substitution, including a phenyl group on the carbon β to nitrogen (a situation that previously led to poor reactivity; entries 2 and 6).



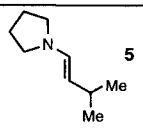
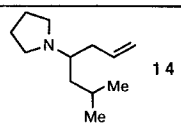
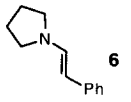
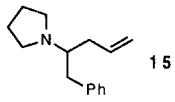
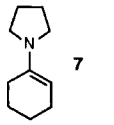
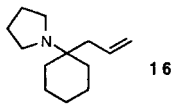
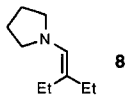
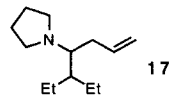
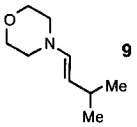
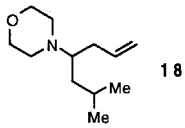
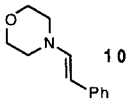
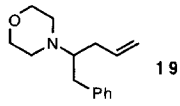
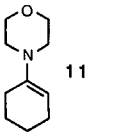
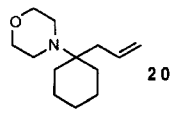
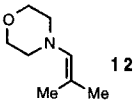
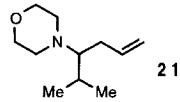
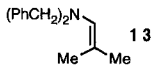
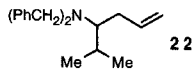
Scheme 2. Indium-mediated reactions of enamines with allyl bromide in the presence of acetic acid.

The influence of the acid added was studied for two enamines (Table 2). When acetic acid (pK_a 4.74) was replaced by a stronger organic acid—dichloroacetic acid (DCA, pK_a 1.30) or trifluoroacetic acid (TFA, pK_a 0.23)—then similar or moderately improved yields were obtained. It seems that this factor has little influence on the more reactive pyrrolidine-derived enamine (entries 1, 2, 3). However, the use of a stronger acid was beneficial for the less reactive morpholine-derived enamine (entries 4, 5, 6).

In order to confirm the origin of the incorporated hydrogen, deuterium labeling experiments were conducted with monodeuteriated acetic acid (AcOD) as the acid source. As expected, amines substituted by one deuterium atom at a position β to nitrogen were obtained. However, they only had a modest incorporation ratio of D (ca. 60%), probably due to some deuterium scrambling.[6]

Homoallylamines were assumed to be formed by nucleophilic addition of allylic indium sesquihalide $(allyl)_3In_2Br_3$ to the iminium ion. To test this hypothesis, the $(allyl)_3In_2Br_3$ was synthesized separately (THF, RT, 15 min) and then added to the iminium acetate obtained by adding one equivalent of acetic acid to the enamine. The resulting reaction was fast ($\leq$1 h) and it afforded identical homoallylamines. Yields were somewhat reduced owing to partial loss during transfers. Further support for this mechanism, from the nucleophilic additions of other organometallic reagents to iminium salts, has already been described in the literature. The R group of the organometallic reagent (RMgX, RLi) was also introduced at a position α to nitrogen.[7] Furthermore, Miginiac et al. reported the addition of zinc, magnesium, aluminum, and lithium organometallic reagents, where R is an allyl group, to an isolated iminium chlorohydrate; this reaction also led to tertiary homoallylamines.[8, 9]

Table 1. Synthesis of homoallylamines by the reaction of enamines with acetic acid, indium, and allyl bromide [a].

Entry	Enamine	Homoallylamine	Time	% Yield
1	 **5**	 **14**	10 min	75
2	 **6**	 **15**	30 min	49
3	 **7**	 **16**	1 h	64 [b]
4	 **8**	 **17**	45 min	51 [c]
5	 **9**	 **18**	40 min	85
6	 **10**	 **19**	4 h	52
7	 **11**	 **20**	75 min	88 [d]
8	 **12**	 **21**	45 min	50 [e]
9	 **13**	 **22**	40 min	72

[a] Acetic acid (1 equiv) was added to a solution of enamine in THF; after 5 min, In powder (0.67 equiv) was added followed by allyl bromide (1.5 equiv). [b] If 1.2 equiv of acetic acid was used, then the reaction time was reduced to 10 min and the yield increased to 79%. [c] To prove that the incorporated H atom does not come from the solvent, this reaction was also performed in CCl_4; however, due to poor solubility of intermediates in this solvent, a yield of only 23% was obtained. [d] This reaction was also performed with presynthesized indium sesquihalide $(allyl)_3In_2Br_3$, which gave a 77% yield after 45 min. [e] With presynthesized $(allyl)_3In_2Br_3$, a 38% yield was obtained after 1 h.

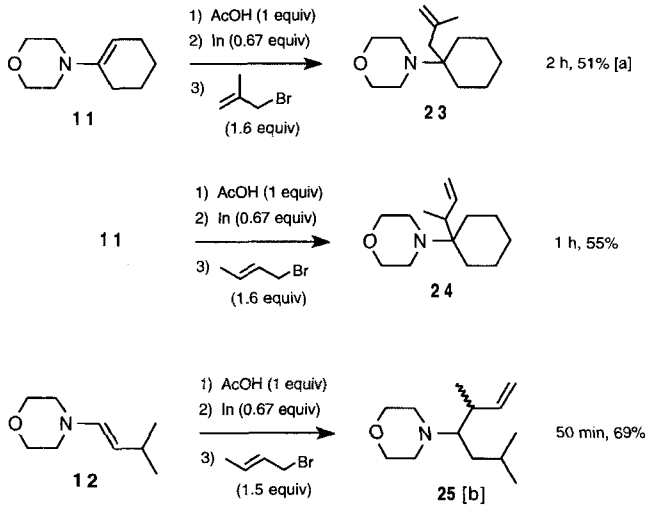
Abstract in French: *La réaction d'énamines avec le bromure d'allyle et l'indium métallique dans le THF pour conduire aux homoallylamines est fortement accélérée par addition d'un équivalent d'un acide carboxylique convenable tel que l'acide acétique. Il a été établi que le mécanisme probable consiste en une addition nucléophile d'un sesquihalogénure d'indium à un sel d'iminium formé par protonation de l'énamine. Les bromures allyliques substitués réagissent également avec transposition allylique complète (γ-addition). En contraste avec l'allylation des dérivés carbonylés au moyen de l'indium où seulement deux des trois groupes allyle sont mis en jeu, tous les trois groupes allyle sont impliqués dans la réaction avec les énamines réduisant ainsi la stœchiométrie de l'indium à 2/3 équivalent. Cette allylation a aussi été réalisée par le zinc, l'étain, le bismuth et l'aluminium en présence d'une quantité catalytique de $InCl_3$ à la place de l'indium mais invariablement avec des rendements inférieurs. La réaction analogue du bromoacétate de méthyle à la place du bromure d'allyle a également été étudiée. Cette réaction de "type Reformatsky" est aussi fortement accélérée par addition d'un équivalent d'acide acétique. Cependant dans ce cas, les rendements restent modestes que ce soit l'indium ou le zinc qui est utilisé.*

Table 2. Influence of carboxylic acid on the indium-mediated synthesis of homoallylamines [a].

Entry	Amine	Acid [b]	Time	% Yield
1	**17**	AcOH	45 min	51
2	**17**	DCA	1 h	47
3	**17**	TFA	1 h	54
4	**21**	AcOH	45 min	50
5	**21**	DCA	1 h	66
6	**21**	TFA	45 min	66

[a] The indicated carboxylic acid [b] (1 equiv) was added to a solution of enamine in THF (at 0 °C for DCA and TFA). After 5 min, In powder (0.67 equiv) was added at RT followed by allyl bromide (1.5 equiv). [b] DCA: dichloroacetic acid; TFA: trifluoroacetic acid.

Substituted allyl bromides, such as methallyl and crotyl bromides, also reacted similarly (Scheme 3). In the latter case, only complete allylic transposition was observed, as the result of γ-addition.[10] Thus, reaction of enamines **11** or **12**, indium, and acetic acid with crotyl bromide afforded amines **24** and **25**, respectively, in which the double bond had migrated to a terminal position. Amine **25** was obtained as a 2:1 mixture of diastereoisomers.



Scheme 3. Reaction of enamines **11** or **12**, indium, and acetic acid with crotyl bromide or $CH_2=C(CH_3)CH_2Br$. [a] With Zn (1.25 equiv) and $InCl_3$ (0.1 equiv) instead of In, a yield of 37% was obtained after 3 h. [b] Obtained as a 2:1 mixture of diastereomers.

One aspect that deserves attention is the fact that only 2/3 equiv of indium was used. Several yields were well above 67%, which implies that all three allylic groups of the indium sesquihalide are involved. This contrasts with the previously reported indium-mediated allylation and Reformatsky reactions of carbonyl compounds where only two of the three R groups of the indium sesquihalide were involved.

The efficiency of indium was also compared to that of two more electropositive metals—aluminum and zinc—and two less electropositive ones—tin and bismuth (Table 3). The same reaction proceeded with zinc, although in noticeably inferior yields, while aluminum proved to be inefficient. Metallic tin was also able to mediate the allylation affording comparable yields to zinc, but the reaction times were noticeably longer. Metallic bismuth was far less reactive. The effect of the further addition

Table 3. Comparison of the synthesis of homoallylamines mediated by indium vs. zinc or aluminum (with and without $InCl_3$).

Entry	Enamine	Homoallylamine	Conditions [a]	Time	% Yield
1	**8**	**17**	In	45 min	51
			Zn	4 h	30
			Zn + $InCl_3$	3.5 h	26 [b]
			Al	3 h	0 [c]
			Al + $InCl_3$	3.5 h	48
2	**9**	**18**	In	40 min	85
			Zn	30 min	47
			Al	2 h	0 [d]
			Al + $InCl_3$	3 h	0 [d]
			Sn	6 h	45 [e]
			Bi	23 h	48
3	**11**	**20**	In	75 min	88
			Zn	2 h	52
			Zn + $InCl_3$	4 h	51
			Al	2 h	0 [c]
			Al + $InCl_3$	2 h	75
			Sn	9 h	38 [f]
			Bi	48 h	34
4	**12**	**21**	In	45 min	50
			Zn	4 h	39
			Zn + $InCl_3$	1 h	35
			Al	3.5 h	0 [c]
			Al + $InCl_3$	2 h	- [g]
			Sn	7 h	43 [h]
			Bi	32 h	25

[a] Acetic acid (1 equiv) was added to a solution of enamine in THF. After 5 min, the metal was added, followed by allyl bromide (1.5 equiv); the following quantities of metal/catalyst were used: In: In powder (0.67 equiv); Zn: Zn powder (1.25 equiv); Zn + $InCl_3$: Zn powder (1.25 equiv) and $InCl_3$ (0.1 equiv); Al: Al powder (1 equiv); Al + $InCl_3$: Al powder (1 equiv) and $InCl_3$ (0.1 equiv); Sn: Sn powder (1.2 equiv); Bi: Bi powder (1 equiv). [b] 20% yield after 1 h. [c] No reaction. [d] Starting enamine was recovered along with minor amounts of by-products in which **18** was not detected. [e] Tin consumption was 49% [f] Tin consumption was 70%. [g] Several products; the homoallylamine is a minor component. [h] Tin consumption was 64%.

of a catalytic amount (0.1 equiv) of $InCl_3$ was also studied. It was found that metallic indium was regenerated at the expense of the more electropositive Al or Zn. A similar catalytic procedure has already been reported for the allylation of carbonyl compounds.[11, 12] Little change was observed on additon of catalytic amounts of indium to the zinc system; however, good results were observed in some cases for the aluminum system. Additionally, the metal (Al or Zn) that gave the best results in the catalytic procedure varied from reaction to reaction. However, the yields obtained were always inferior to those from the use of indium alone. Furthermore, reactions appeared to be slower and their progress was less convenient to follow because the disappearance of the metal was less easily visualized.

Previously, we reported that a "Reformatsky-type" reaction is similarly observed when an enamine is stirred with indium and methyl bromoacetate in THF.[5] The products formed are β-amino esters **3** and significant amounts of **4** as by-product (Scheme 1). As for the allylation reactions, these experiments were repeated with addition of acetic acid (1 equiv) to the enamine in THF followed by indium (2/3 equiv) and methyl bro-

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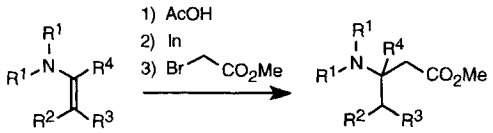
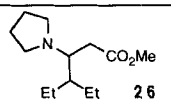
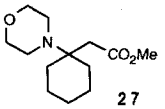
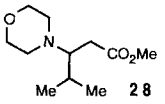
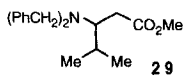
moacetate (1.4 equiv). Compared to our previous results, the addition of acetic acid also greatly accelerated the reactions. Furthermore, no or very little by-product **4** was formed, but unfortunately yields remained moderate (Scheme 4, Table 4).



Scheme 4. Indium-mediated reactions of enamines with methyl bromoacetate in the presence of acetic acid.

Table 4. Synthesis of β-amino esters by the reaction of enamines with acetic acid, indium or zinc (with and without $InCl_3$), and methyl bromoacetate.

Entry	Enamine	β-Amino ester	Conditions [a]	Time	% Yield
1	**8**	 **26**	In	45 min	35
			Zn	1 h	- [b]
			Zn + $InCl_3$	1 h	29
2	**11**	 **27**	In	1 h	26
			Zn	1.5 h	41
			Zn + $InCl_3$	2.5 h	32
3	**12**	 **28**	In	4 h	36
			Zn	4 h	17
			Zn + $InCl_3$	1 h	14
4	**13**	 **29**	In	2 h	23
			Zn	2 h	1 [c]
			Zn + $InCl_3$	2 h	3 [c]

[a] Acetic acid (1 equiv) was added to a solution of enamine in THF. After 5 min, the metal was added, followed by methyl bromoacetate (1.4 equiv); the following quantities of metal/catalyst were used: In: In powder (0.67 equiv); Zn: Zn powder (1.25 equiv); Zn + $InCl_3$: Zn powder (1.25 equiv) and $InCl_3$ (0.1 equiv). [b] By-products were formed. [c] Corrected yield of **29**, taking into account the fact that a ca. 2:1 mixture of by-product **4** ($R^1 = CH_2Ph$) and **29** was obtained.

Similarly to our results on the allylation reactions, it is reasonable to postulate that β-amino esters are formed by nucleophilic addition of indium sesquihalide $(MeO_2CCH_2)_3In_2Br_3$ to the iminium salt. The use of zinc instead of indium also afforded β-amino esters, but the yields were highly dependent on the starting enamine. For instance, enamine **8** failed to give **26** (entry 1), while enamine **11** gave **27** in better yield than with indium. The addition of a catalytic amount of $InCl_3$ afforded a comparable result to that obtained with indium in the case of the pyrrolidine-derived enamine **8**, while it seemed detrimental in the case of morpholine-derived enamines. The reactivity of a dibenzylamine-derived enamine **13** was also studied, because benzyl groups can easily be cleaved. Unfortunately, this gave the worst results: low to very low yields and even formation of by-product **4** when zinc was used. So far, attempts to improve these "Reformatsky-type" reactions, for example, by changing the temperature, the stoichiometry, or the nature of the acid, or by using the more reactive ethyl iodoacetate instead of methyl bromoacetate, have not met with much success. A possible explanation of the moderate yields may be a partial consumption of the β-amino ester by quaternarization with the unreacted haloacetate. To minimize this problem, the indium sesquihalide was also pre-synthesized in the case of ethyl iodoacetate (35 min at RT in THF). Subsequent addition of the enamine followed by acetic acid afforded the expected β-amino ester. Unfortunately, the yields were not improved.

Conclusion

Compared to our previous results, we found that the addition of an equimolar amount of acetic acid to an enamine greatly improved subsequent indium-mediated reactions with allyl halides or methyl bromoacetate. Additionally, a likely mechanism was proposed, which involves a nucleophilic addition of an indium sesquihalide to an iminium salt. Furthermore, in contrast to the reactions of other electrophiles (carbonyl compounds, etc.), all three (and not just two) R groups of $R_3In_2Br_3$ are involved in reactions with iminium salts; the required indium stoichiometry is thus reduced from 1 to 2/3 equiv. Allylations were also performed with some other metal systems instead of indium, but these all gave inferior yields. The experimental procedure used for the described reactions is straightforward and does not require the handling of reactive organometallic reagents. The "Reformatsky-type" reactions still need to be improved, and extension might be possible to other reactive halides.[13]

Experimental Section

Melting points above 60 °C were determined with a Kofler bench. IR spectra were recorded on a Nicolet 205 FT-IR spectrometer. NMR spectra were measured using dilute solutions on a Bruker ARX 400 spectrometer. Chemical shifts were recorded as δ downfield from the internal standard (TMS). Thin layer chromatography (TLC) was carried out on aluminum sheets precoated with silica gel $60F_{254}$ (E. Merck). The plates were inspected by UV light followed by development with iodine vapor. Elemental analyses were performed by ENSCR on an Eager 200 CHN elemental analyzer. Mass spectra (MS) were recorded on a Finnigan INCOS 500 spectrometer. High resolution mass spectra (HRMS) were obtained under electronic impact at 70 eV from a Varian MAT 311 spectrometer at the Centre Régional de Mesures Physiques de l'Ouest. Picrates were obtained by the addition of an equimolar amount of picric acid to the purified amine, followed by isopropanol (10–30 mL mmol^{-1}), the mixture was heated until dissolution was complete, then slowly cooled in a Dewar overnight, the crystals were collected, then washed with cold isopropanol (≈ −15 °C).

General procedure: Anhydrous THF (1.6 mL) and enamine[14] (0.7 mmol) were introduced under N_2 into a flame-dried two-necked reaction flask equipped with a condenser connected to an oil bubbler. Acetic acid (40 μL, 0.7 mmol) was added with stirring. When dichloroacetic or trifluoroacetic acid was added instead, the THF solution of enamine was previously cooled to 0 °C, and 5 min after the acid addition, the ice bath was removed and the resulting mixture was allowed to warm to RT for 10 min. Five minutes after addition of acetic acid, one of the following powdered metals was added: In powder[15] (54 mg, 0.47 mmol, 0.67 equiv), Zn powder[15] (57.2 mg, 0.875 mmol, 1.25 equiv), Al powder[15] (19 mg, 0.7 mmol, 1 equiv), Sn powder[15] (100 mg, 0.84 mmol, 1.2 equiv), or Bi powder[15] (146.3 mg, 0.7 mmol, 1 equiv); in some cases a catalytic amount of $InCl_3$[15] (15.5 mg, 0.07 mmol, 0.1 equiv) was also added. Finally, allyl bromide (91 μL, 1.05 mmol, 1.5 equiv) or methyl bromoacetate (91 μL, 0.96 mmol, 1.4 equiv) was added. The resulting mixture was stirred at RT for the indicated time. After addition of saturated aqueous Na_2CO_3 (5–6 mL), the mixture was extracted with ether (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4 or $MgSO_4$). In the reactions with tin, the white precipitate was removed by filtration over basic alumina (0.7 g). Concentration in vacuo afforded an oily

residue, which was purified by flash-chromatography on basic alumina (2–3 g) using gradient elution from petroleum ether to ether/petroleum ether (1:9 to 3:7, depending on the polarities of the amines). All amines were obtained as colorless oils, except **23** and **27** which were white crystals.

2-Methyl-4-pyrrolidinohept-6-ene (14): $R_f \approx 0.02$ (ethyl acetate/petroleum ether 3:7, lengthened spot); IR (neat, KBr): $\tilde{\nu}$ = 3076, 2956, 2870, 2791, 1639 (C=C), 1466, 1384, 1366, 997, 908 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.88 (ddt, J = 17.1, 10.1, 7.1 Hz, 1H, H–C6), 5.07 (ddt, J = 17.0, 2.1, 1.5 Hz, 1H, H–C7), 5.04 (ddt, J = 10.1, 2.1, 1.1 Hz, 1H, H–C7), 2.62 (very broad t, J = 6.5 Hz, 4H, 2 CH_2–N), 2.45 (broad tdd, J = 6.5, 6.2, 4.2 Hz, 1H, H–C4), 2.33 (dddt, J = 14.4, 6.9, 4.2, 1.4 Hz, 1H, H–C5), 2.23 (pseudo dddt, J = 14.4, 7.3, 6.3, 1.1 Hz, 1H, H–C5), 1.77 (m, 4H, 2 CH_2CH_2–N), 1.67 (d septet, J = 7.4, 6.6 Hz, 1H, H–C2, e.g. $CH(CH_3)_2$), 1.41–1.32 (m, 2H, H–C3), 0.89 (d, J = 6.6 Hz, 3H, CH_3), 0.88 (d, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.01 (C6 e.g. CH=CH_2), 116.43 (C7), 60.51 (C4), 50.49 (2 CH_2–N), 40.83 (C3), 35.99 (C5), 25.30 (C2 e.g. $CH(CH_3)_2$), 23.59 (CH_3), 23.44 (2 CH_2CH_2–N), 22.36 (CH_3).

Picrate salt: yellow crystals (*i*PrOH), m.p. 110 °C; $C_{18}H_{26}N_4O_7$ (410.4): calcd C 52.68, H 6.39, N 13.65; found C 53.02, H 6.50, N 13.84.

2-Pyrrolidino-1-phenylpent-4-ene (15): IR (neat, KBr): $\tilde{\nu}$ = 3073, 3064, 3027, 2965, 2930, 2785, 1639 (C=C), 1604 (aromatic C=C), 1495, 1454, 1137, 910, 745, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.25 (m, 2H), 7.22–7.17 (m, 3H), 5.90 (ddt, J = 17.0, 10.3, 7.0 Hz, 1H, H–C4), 5.06 (ddt, J = 10.3, 2.2, 1.2 Hz, 1H, H–C5), 5.03 (ddt, J = 17.0, 2.2, 1.5 Hz, 1H, H–C5), 2.99 (m, 1H, H–C1 e.g. CH_2–Ph), 2.76–2.61 (m, 6H, 2 CH_2–N, 1H of CH_2–Ph e.g. H–C1, and H–C2), 2.29–2.12 (m, 2H, H–C3), 1.85–1.74 (m, 4H, 2 CH_2CH_2–N); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.28 (C_{ipso}), 135.50 (C4 e.g. CH=CH_2), 129.40 (2 C_{ortho}), 128.24 (2 C_{meta}), 125.87 (C_{para}), 116.82 (C5), 64.92 (C2), 51.17 (2 CH_2–N), 37.65 (C3), 35.52 (C1 e.g. CH_2Ph), 23.51 (2 CH_2CH_2–N).

Picrate salt: yellow crystals (*i*PrOH), m.p. 108 °C; $C_{21}H_{24}N_4O_7$ (444.4): calcd C 56.75, H 5.44, N 12.61; found C 57.05, H 5.51, N 12.69.

1-Allyl-1-pyrrolidinocyclohexane (16): IR (neat, KBr): $\tilde{\nu}$ = 3074, 2931, 2852, 2798, 1637 (C=C), 1463, 1446, 1163, 1081, 1019, 996, 907 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.94–5.81 (m, 1H, CH=), 5.06–4.97 (m, 2H, =CH_2), 2.68 (broad, 4H, 2 CH_2–N), 2.20 (broad d, J = 7.4 Hz, 2H, CH_2CH=), 1.71 (broad apparent p, J = 3.0 Hz, 4H, 2 CH_2CH_2–N), 1.66–1.51 (m, 5H, H_{eq}), 1.49–1.30 (m, 5H, H_{ax}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.21 (CH=), 116.34 (=CH_2), 56.43 (C–N_{quat}), 44.05 (2 CH_2–N), 36.91 (CH_2–CH=), 33.20 (2 CH_2 α to C_{quat}), 26.13 (CH_2 γ to C_{quat}), 24.36 (2 CH_2CH_2–N), 21.76 (2 CH_2 β to C_{quat}); MS (CI, NH_3): 168 (100) $[M+H]^+$.

Picrate salt: long and thin yellow needles (*i*PrOH), m.p. 114.5 °C; $C_{19}H_{26}N_4O_7$ (422.4): calcd C 54.02, H 6.20, N 13.26; found C 54.43, H 6.33, N 13.39.

3-Ethyl-4-pyrrolidinohept-6-ene (17): $R_f \approx 0.05$ (ethyl acetate/petroleum ether 3:7, lengthened spot); IR (neat, NaCl): $\tilde{\nu}$ = 3076, 2963, 2932, 2875, 2787, 1639 (C=C), 1460, 908 cm^{-1}; ^1H NMR and ^{13}C NMR in $CDCl_3$: see ref. [5]; HRMS (70 eV, EI) $C_{13}H_{25}N$: $[M]^+$ calcd 195.1987, found 195.1996 and $C_{10}H_{20}N$: $[M - {}^{\cdot}CH_2CH{=}CH_2]^+$ calcd 154.1595, found 154.1596; m/z (%): 195 (0.9) $[M]^+$, 154 (66.4) $[M - {}^{\cdot}CH_2CH{=}CH_2]^+$, 124 (100) $[M - {}^{\cdot}CHEt_2]^+$.

Picrate salt: yellow crystals (*i*PrOH), m.p. 121 °C; $C_{19}H_{28}N_4O_7$ (424.5): calcd C 53.77, H 6.65, N 13.20, found C 53.91, H 6.76, N 13.25.

2-Methyl-4-morpholinohept-6-ene (18): R_f = 0.56 (ethyl acetate/petroleum ether 3:7); IR (neat, KBr): $\tilde{\nu}$ = 3076, 2956, 2926, 2853, 2812, 1639 (C=C), 1467, 1452, 1155, 1119, 995, 910 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.80 (dddd, J = 17.0, 10.2, 7.7, 6.6 Hz, 1H, H–C6), 5.02 (ddt, J = 17.0, 2.0, 1.5 Hz, 1H, H–C7), 4.99 (ddt, J = 10.2, 2.0, 1.2 Hz, 1H, H–C7), 3.71–3.62 (m, 4H, 2 CH_2–O), 2.59 (pseudo dddd, J = 11.3, 5.4, 3.9, 1.0 Hz, 2H, CH_2–N), 2.50 (dddd, J = 8.1, 7.7, 6.0, 5.4 Hz, 1H, H–C4), 2.46 (pseudo dddd, J = 11.3, 5.3, 3.8, 1.1 Hz, 2H, CH_2–N), 2.33 (dddt, J = 13.8, 6.7, 5.4, 1.5 Hz, 1H, H–C5), 1.95 (dtt, J = 14.0, 7.7, 1.2 Hz, 1H, H–C5), 1.73 (dqqd, J = 8.0, 6.7, 6.6, 6.0 Hz, 1H, H–C2 e.g. $CHMe_2$), 1.36 (ddd, J = 14.0, 8.1, 6.0 Hz, 1H, H–C3), 1.11 (ddd, J = 14.0, 8.0, 6.0 Hz, 1H, H–C3), 0.88 (d, J = 6.7 Hz, 3H, Me), 0.86 (d, J = 6.6 Hz, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.37 (C6), 115.76 (C7), 67.60 (2 CH_2–O), 61.85 (C4), 48.73 (2 CH_2–N), 39.25 (C3), 34.08 (C5), 24.88 (C2), 23.11 (CH_3), 22.39 (CH_3); MS (CI, NH_3): m/z (%): 198 (100) $[M+H]^+$; HRMS (70 eV, EI) $C_9H_{18}NO$: $[M - {}^{\cdot}CH_2CH{=}CH_2]^+$ calcd 156.1388, found 156.1386; m/z (%): 156 (100) $[M - {}^{\cdot}CH_2CH{=}CH_2]^+$, 140 (11.9) $[M - {}^{\cdot}iBu]^+$, 114 (9.5), 41 (14.9), 18 (12.1). The picrate did not crystallize and remained oily.

2-Morpholino-1-phenylpent-4-ene (19): R_f = 0.41 (ether/petroleum ether 1:1); IR (neat, KBr): $\tilde{\nu}$ = 3074, 3063, 3027, 2955, 2928, 2854, 2811, 1639 (C=C), 1603 (aromatic C=C), 1495, 1454, 1117, 910, 855, 742, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.24 (m, 2 H_{meta} aromatic), 7.22–7.15 (m, 3 $H_{ortho+para}$ aromatic), 5.88–5.75 (m, 1H, H–C4), 5.03–4.95 (m, 2H, H–C5), 3.72–3.62 (m, 4H, 2 CH_2–O), 2.90 (dd, J = 13.5, 5.9 Hz, 1H, H–C1 e.g. CH_2–Ph), 2.74 (dddd, J = 7.7, 7.1, 6.8, 5.9 Hz [broad apparent p, J = 6.8 Hz], 1H, H–C2), 2.67–2.57 (m [mainly broad apparent t, J = 4.5 Hz], 4H, 2 CH_2–N), 2.50 (dd, J = 13.5, 7.7 Hz, 1H, H–C1), 2.28 (dtt, J = 14.5, 7.0, 1.4 Hz, 1H, H–C3), 2.08 (dddt, J = 14.5, 7.4, 6.2, 1.3 Hz, 1H, H–C3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.62 (C_{ipso}), 136.83 (C4), 129.23 (2 C_{ortho}), 128.20 (2 C_{meta}), 125.81 (C_{para}), 115.93 (C5), 67.43 (2 CH_2–O), 66.35 (C2), 48.99 (2 CH_2–N), 35.70 (C1), 34.31 (C3); MS (CI, NH_3): m/z (%): 232 (100) $[M+H]^+$; HRMS (70 eV, EI) $C_{15}H_{21}NO$: $[M]^+$ calcd 231.1623, found 231.1612 and $C_{12}H_{16}NO$: $[M - {}^{\cdot}CH_2CH{=}CH_2]^+$ calcd 190.1232, found 190.1237; m/z (%): 231 (0.25) $[M]^+$, 190 (48.5) $[M - {}^{\cdot}CH_2CH{=}CH_2]^+$, 140 (100) $[M - {}^{\cdot}CH_2Ph]^+$. The picrate did not crystallize and remained oily.

1-Allyl-1-morpholinocyclohexane (20): Colorless oil which crystallized in freezer yielding white crystals melting at 3 °C; R_f = 0.41 (ether/petroleum ether 3:7); IR (neat, KBr): $\tilde{\nu}$ = 3074, 2934, 2851, 2810, 1637 (C=C), 1455, 1268, 1155, 1121, 983, 909, 856 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.82 (ddt, J = 15.8, 11.2, 7.4 Hz, 1H, CH=), 5.00 (dt, J = 15.8, 1.3 Hz, 1H, =CH_2), 5.00–4.96 (m, 1H, =CH_2), 3.70–3.64 (m, 4H, 2 CH_2–O), 2.60–2.54 (m, 4H, 2 CH_2–N), 2.12 (dt, J = 7.5, 1.2 Hz, 2H, CH_2CH=), 1.71–1.51 (m, 5H, H_{eq}), 1.39–1.17 (m, 5H, H_{ax}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.75 (CH=), 116.77 (=CH_2), 68.12 (2 CH_2–O), 57.17 (C–N_{quat}), 44.93 (2 CH_2–N), 38.17 (CH_2–CH=), 32.29 (2 CH_2 α to C_{quat}), 26.25 (CH_2 γ to C_{quat}), 21.01 (2 CH_2 β to C_{quat}).

Picrate salt: yellow crystals (*i*PrOH/acetone 2:1), m.p. 155 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 10.57 (broad, 1H, NH^+), 8.91 (s, 2H aromatic), 5.91 (ddt, J = 17.0, 10.1, 7.3 Hz, 1H, CH=), 5.34 (ddt, J = 17.0, 1.4, 1.4 Hz, 1H, =CH_2), 5.32 (ddt, J = 10.1, 1.4, 1.2 Hz, 1H, =CH_2), 4.00 (pseudo d, 4H, J = 9.3 Hz, 2 CH_2–O), 3.63 (broad d, J = 11.5 Hz, 2H, CH_2–N), 3.22 (very broad p, J = 8.7 Hz, 2H, CH_2–N), 2.69 (dt, J = 7.3, 1.4 Hz, 2H, CH_2CH=), 2.05 (very broad d, J = 12.4 Hz, 2H), 1.92–1.79 (m, 4H), 1.70 (broad dt, J = 12.5, 3.2 Hz, 1H), 1.40 (qt, J = 13.5, 3.6 Hz, 2H), 1.13 (qt, J = 13.2, 3.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.32 (C–O_{ipso}), 141.77 (2 C–$(NO_2)_{ipso}$), 131.16 (CH=), 128.30 (C–$(NO_2)_{ipso}$), 126.72 (2 $CH_{aromatic}$), 120.92 (=CH_2), 69.34 (C–N_{quat}), 64.39 (2 CH_2–O), 46.93 (2 CH_2–N), 34.13 (CH_2–CH=), 31.07 (2 CH_2 α to C_{quat}), 24.39 (CH_2 γ to C_{quat}), 22.39 (2 CH_2 β to C_{quat}); $C_{19}H_{26}N_4O_8$ (438.4): calcd C 52.05, H 5.98, N 12.78 found C 52.17, H 6.06, N 12.82.

2-Methyl-3-morpholinohex-5-ene (21): R_f = 0.55 (ether/petroleum ether 1:1); IR (neat, KBr): $\tilde{\nu}$ = 3076, 2957, 2852, 2810, 1638 (C=C), 1468, 1450, 1290, 1257, 1119, 1011, 994, 909, 857 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.89 (ddt, J = 17.1, 10.1, 6.9 Hz, 1H, H–C5), 5.04 (ddt, J = 17.1, 2.0, 1.5 Hz, 1H, H–C6), 4.97 (ddt, J = 10.1, 2.0, 1.2 Hz, 1H, H–C6), 3.69–3.60 (m, 4H, 2 CH_2–O), 2.65 (pseudo dddd, J = 11.4, 5.3, 3.9, 1.0 Hz, 2H, CH_2–N), 2.53 (pseudo dddd, J = 11.4, 5.3, 3.9, 1.0 Hz, 2H, CH_2–N), 2.36–2.25 (m, 1H, H–C4), 2.21–2.11 (m, 2H, H–C3,4), 1.80 (dqq, J = 7.0, 6.7, 6.7 Hz, 1H, H–C2), 0.94 (d, J = 6.7 Hz, 3H, Me), 0.91 (d, J = 6.7 Hz, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.72 (C5 e.g. CH=CH_2), 115.26 (C6), 70.27 (C3), 67.66 (2 CH_2–O), 50.05 (2 CH_2–N), 31.94 (C4), 29.88 (C2), 20.80 (Me), 20.05 (Me).

Picrate salt: yellow crystals (*i*PrOH), m.p. 123–124 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 10.71 (broad, 1H, NH^+), 8.92 (s, 2H aromatic), 5.80 (dddd, J = 17.1, 10.2, 7.1, 6.5 Hz, 1H, H–C5), 5.27 (dtd, J = 17.1, 1.6, 1.1 Hz, 1H, H–C6), 5.22 (dtd, J = 10.2, 1.4, 1.1 Hz, 1H, H–C6), 4.27–3.90 (m, 4H, 2 CH_2–O), 3.67–3.42 (broad, 2H, CH_2–N), 3.29–3.03 (broad, 2H, CH_2–N), 3.20 (td, J = 5.7, 3.5 Hz, 1H, H–C3), 2.65 (dddt, J = 16.1, 7.2, 6.1, 1.3 Hz, 1H, H–C4), 2.55 (dddt, J = 16.1, 6.4, 5.6, 1.6 Hz, 1H, H–C4), 2.33 (qdd, J = 7.0, 6.7, 3.5 Hz, 1H, H–C2), 1.05 (d, J = 7.0 Hz, 3H, Me), 1.04 (d, J = 6.7 Hz, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.50 (C–O_{ipso}),

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141.61 (2 C–$(NO_2)_{ipso}$), 134.07 (C5), 128.57 (C–$(NO_2)_{ipso}$), 126.80 (2 $CH_{aromatic}$), 119.25 (C6), 72.27 (C3), 63.78 (2 CH_2–O), 51.23 (CH_2–N), 50.12 (CH_2–N), 29.58 (C4), 28.07 (C2), 21.67 (Me), 17.20 (Me); $C_{17}H_{24}N_4O_8$ (412.4): calcd C 49.51, H 5.87, N 13.59; found C 49.32, H 5.98, N 13.66.

3-Dibenzylamino-2-methylhex-5-ene (22): Colorless oil which crystallized on storage in freezer yielding white crystals melting at 14–15 °C; IR (neat, KBr): $\tilde{\nu}$ = 3063, 3027, 2956, 2929, 2799, 1638 (olefinic C=C), 1602 (aromatic C=C), 1494, 1454, 1028, 906, 745, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37 (pseudo dm, $J \approx 7.5$ Hz, 4H, aromatic H_{ortho}), 7.29 (pseudo tt, $J \approx 7.5$, 1.5 Hz, 4H, aromatic H_{meta}), 7.21 (ddt, J = 8.1, 6.4, 1.3 Hz, 2H, aromatic H_{para}), 5.86 (ddt, J = 17.1, 10.1, 7.0 Hz, 1H, H–C5), 5.06 (ddt, J = 17.1, 2.0, 1.6 Hz, 1H, H–C6), 4.99 (ddt, J = 10.1, 2.0, 1.3 Hz, 1H, H–C6), 3.75 (d, J = 13.7 Hz, 2H, CH_2Ph), 3.54 (d, J = 13.7 Hz, 2H, CH_2Ph), 2.47 (dddt, J = 14.5, 7.1, 5.8, 1.4 Hz, 1H, H–C4), 2.36 (dt, J = 7.5, 5.8 Hz, 1H, H–C3), 2.19 (dddt, J = 14.5, 7.0, 5.8, 1.4 Hz, 1H, H–C4), 1.90 (d septet, J = 7.5, 6.7 Hz, 1H, H–C2), 0.97 (d, J = 6.7 Hz, 3H, CH_3), 0.85 (d, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.51 (2 C_{ipso}), 138.94 (C5 e.g. CH=CH_2), 128.94 (4 C_{ortho}), 128.05 (4 C_{meta}), 126.64 (2 C_{para}), 115.24 (C6), 62.88 (C3), 54.33 (2 CH_2Ph), 31.68 (C4), 30.17 (C2 e.g. $CH(CH_3)_2$), 21.25 (CH_3), 20.63 (CH_3).

Picrate salt: thin yellow needles (*i*PrOH), m.p. 138 °C; $C_{27}H_{30}N_4O_7$ (522.6): calcd C 62.06, H 5.79, N 10.72; found C 62.19, H 5.80, N 10.70.

1-(2-Methylprop-2-en-1-yl)-1-morpholinocyclohexane (23): White crystals, m.p. 35–36 °C; R_f = 0.62 (ether/petroleum ether 1:1); IR (Nujol, KBr): $\tilde{\nu}$ = 3073, 1640 (C=C), 1455, 1268, 1122, 983, 889 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.84 (dq, J = 2.6, 1.4 Hz, 1H, CH_2 =), 4.65 (dq, J = 2.6, 0.9 Hz, 1H, =CH_2), 3.72–3.65 (m, 4H, 2 CH_2–O), 2.56–2.52 (m, 4H, 2 CH_2–N), 2.04 (d, J = 0.7 Hz, 2H, CH_2CH=), 1.78 (dd, J = 1.4, 0.9 Hz, 3H, Me), 1.71–1.55 (m, 5 H_{eq}), 1.40–1.28 (m, 4 H_{ax}), 1.25–1.10 (m, 1 H_{ax}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.47 (C=), 114.32 (=CH_2), 68.06 (2 CH_2–O), 57.91 (C–N_{quat}), 44.47 (2 CH_2–N), 40.53 (CH_2–C=), 32.35 (2 CH_2 α to C_{quat}), 26.16 (CH_2 γ to C_{quat}), 25.74 (Me), 20.91 (2 CH_2 β to C_{quat}); $C_{14}H_{25}NO$ (223.4): calcd C 75.28, H 11.28, N 6.27; found: C 74.90, H 11.54, N 5.98.

1-(1-Methylprop-2-en-1-yl)-1-morpholinocyclohexane (24): R_f = 0.64 (ether/petroleum ether 1:1); IR (neat, KBr): $\tilde{\nu}$ = 3072, 2939, 2850, 1636 (C=C), 1455, 1268, 1120, 984, 910, 853 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.85 (ddd, J = 17.0, 10.2, 9.0 Hz, 1H, CH=), 4.95 (ddd, J = 17.0, 2.0, 0.9 Hz, 1H, CH_2=), 4.93 (dd, J = 10.2, 2.0 Hz, 1H, =CH_2), 3.62 (apparent t, J = 4.5 Hz, 4H, 2 CH_2–O), 2.83–2.71 (m, 4H, 2 CH_2–N), 2.38 (dq, J = 9.0, 7.0 Hz, 1H, CH–Me), 1.81–1.49 (m, 5 H_{eq}), 1.42–1.09 (m, 5 H_{ax}), 0.97 (d, J = 7.0 Hz, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.62 (CH=), 113.93 (=CH_2), 68.60 (2 CH_2–O), 58.97 (C–N_{quat}), 46.32 (2 CH_2–N), 45.82 (CH–Me), 31.13 (CH_2 α to C_{quat}), 30.10 (CH_2 α to C_{quat}), 26.68 (CH_2 γ to C_{quat}), 21.35 (CH_2 β to C_{quat}), 21.27 (CH_2 β to C_{quat}), 16.81 (Me).

Picrate salt: yellow crystals (*i*PrOH), m.p. 163–164 °C; $C_{20}H_{28}N_4O_8$ (452.5): calcd C 53.09, H 6.24, N 12.38; found C 53.58, H 6.32, N 12.49.

2,5-Dimethyl-4-morpholinohept-6-ene (25): R_f = 0.56 (ether/petroleum ether 1:1); Obtained as a 2:1 mixture of diastereoisomers; IR (neat, KBr): $\tilde{\nu}$ = 3076, 2956, 2868, 2852, 2810, 1639 (C=C), 1467, 1452, 1119, 1001, 910 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.84 (ddd, J = 17.1, 10.5, 7.3 Hz, 0.33H, H–C6 of minor), 5.73 (ddd, J = 17.1, 10.2, 8.4 Hz, 0.67H, H–C6 of major), 4.98 (ddd, J = 17.1, 2.0, 1.0 Hz, 0.67H, H–C7 of major), 4.95 (ddd, J = 17.1, 1.9, 1.2 Hz, 0.33H, H–C7 of minor), 4.934 (ddd, J = 10.5, 1.9, 0.9 Hz, 0.33H, H–C7 of minor), 4.926 (ddd, J = 10.2, 2.0, 0.5 Hz, 0.67H, H–C7 of major), 3.70–3.58 (m, 4H, 2 CH_2–O), 2.65–2.55 (m, 4H, 2 CH_2–N), 2.41–2.30 (m, 1.33H, H–C5 e.g. CH–Me of both isomers and H–C4 of minor), 2.25 (ddd, J = 7.8, 7.0, 4.6 Hz, 0.67H, H–C4 of major), 1.76–1.59 (m, 1H, H–C2 of both), 1.42 (ddd, J = 14.1, 8.1, 5.9 Hz, 0.33H, H–C3 of minor), 1.40 (ddd, J = 14.2, 8.0, 5.6 Hz, 0.67H, H–C3 of major), 1.073 (ddd, J = 14.2, 8.3, 4.6 Hz, 0.67H, H–C3 of major), 1.069 (ddd, J = 14.1, 8.1, 5.0 Hz, 0.33H, H–C3 of minor), 1.03 (d, J = 6.8 Hz, 2H, CH–CH_3 of major), 1.00 (d, J = 6.5 Hz, 1H, CH–CH_3 of minor), 0.89 (d, J = 6.6 Hz, 1H, Me of minor), 0.88 (d, J = 6.6 Hz, 2H, Me of major), 0.87 (d, J = 6.5 Hz, 1H, Me of minor), 0.84 (d, J = 6.5 Hz, 2H, Me of major); ^{13}C NMR (100 MHz, $CDCl_3$): δ = major: 143.10 (C6), 113.76 (C7), 67.79 (2 CH_2–O), 66.35 (C4), 49.58 (2 CH_2–N), 40.82 (C5), 37.07 (C3), 25.88 (C2), 23.37 (CH_3), 22.09 (CH_3), 19.23 (CH–CH_3); minor: 143.65 (C6), 112.85 (C7), 67.76 (2 CH_2–O), 66.28 (C4), 50.12 (2 CH_2–N), 39.95 (C5), 36.82 (C3), 25.77 (C2), 23.30 (CH_3), 22.34 (CH_3), 17.29 (CH–CH_3).

Picrate salt: bright yellow scales (*i*PrOH), m.p. 147 °C; $C_{19}H_{28}N_4O_8$ (440.5): calcd C 51.81, H 6.41, N 12.72; found: C 51.91, H 6.53, N 12.81.

Methyl 4-ethyl-3-pyrrolidinohexanoate (26): R_f = 0.20 (5% MeOH–CH_2Cl_2); IR (neat, KBr): $\tilde{\nu}$ = 2961, 2933, 2875, 2795, 1740 (C=O), 1461, 1436, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.67 (s, 3H, CO_2CH_3), 2.92 (ddd, J = 6.0, 4.8, 4.3 Hz, 1H, H–C3), 2.58–2.45 (m, 4H, 2 CH_2–N), 2.38 (dd, J = 16.1, 6.0 Hz, 1H, H–C2), 2.37 (dd, J = 16.1, 4.8 Hz, 1H, H–C2), 1.75–1.69 (m, 4H, 2 CH_2CH_2–N), 1.51–1.38 (m, 3H, H–C4 and CH_2CH_3), 1.27–1.13 (m, 2H, CH_2CH_3), 0.92 (t, J = 7.3 Hz, 3H, CH_3), 0.89 (t, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.44 (C1 e.g. CO), 61.52 (C3), 51.67 (OCH_3), 50.96 (2 CH_2–N), 44.37 (C4 e.g. $CH(CH_3)_2$), 34.12 (C2), 23.36 (2 CH_2CH_2–N), 23.15 (CH_2CH_3), 21.67 (CH_2CH_3), 12.25 (CH_3), 12.14 (CH_3).

Picrate salt: yellow crystals (*i*PrOH), m.p. 165–166 °C; $C_{19}H_{28}N_4O_9$ (456.5): calcd C, 50.00; H, 6.18; N, 12.27. Found: C, 50.11; H, 6.24; N, 12.06.

Methyl (1-morpholinocyclohex-1-yl)acetate (27): White crystals; m.p. 49.5–50.5 °C; R_f = 0.51 (ether/petroleum ether 3:1); IR (nujol, KBr): $\tilde{\nu}$ = 1738 (C=O), 1456, 1441, 1317, 1267, 1229, 1139, 1120, 985 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.70–3.65 (m, 4H, 2 CH_2–O), 3.65 (s, 3H, CO_2Me), 2.58–2.48 (m, 4H, 2 CH_2–N), 2.33 (s, 2H, CH_2CO_2Me), 1.93–1.70 (m, 3H), 1.70–1.51 (m, 3H), 1.48–1.31 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.18 (CO_2Me), 67.90 (2 CH_2–O), 57.73 (C–N_{quat}), 51.41 (OMe), 44.80 (2 CH_2–N), 38.64 (CH_2CO_2Me), 33.00 (2 CH_2 α to C_{quat}), 25.93 (CH_2 γ to C_{quat}), 20.98 (2 CH_2 β to C_{quat}); $C_{13}H_{23}NO_3$ (241.3): calcd C 64.70, H 9.61, N 5.80; found C 64.95, H 9.76, N 5.58.

Methyl 4-methyl-3-morpholinopentanoate (28): R_f = 0.49 (ether/petroleum ether 3:1); IR (neat, KBr): $\tilde{\nu}$ = 2961, 2854, 2814, 1742 (C=O), 1259, 1118, 1015, 859 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.68 (s, 3H, OMe), 3.68–3.59 (m, 4H, 2 CH_2–O), 2.68 (ddd, J = 8.2, 7.0, 5.8 Hz, 1H, H–C3), 2.59–2.48 (m, 4H, 2 CH_2–N), 2.50 (dd, J = 15.2, 7.0 Hz, 1H, H–C2), 2.29 (dd, J = 15.2, 5.7 Hz, 1H, H–C2), 1.77 (dqq, J = 8.2, 6.7, 6.6 Hz, 1H, H–C4), 0.98 (d, J = 6.7 Hz, 3H, Me), 0.87 (d, J = 6.6 Hz, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.11 (C1), 67.59 (2 CH_2–O), 67.54 (C3), 51.65 (OMe), 49.35 (2 CH_2–N), 33.03 (C2), 30.32 (C4), 20.97 (Me), 19.74 (Me). Picrate salt: yellow crystals (*i*PrOH), m.p. 163–164 °C; $C_{17}H_{24}N_4O_{10}$ (444.4): calcd C 45.95, H 5.44, N, 12.61; found C 46.06, H 5.53, N 12.69.

Methyl 3-dibenzylamino-4-methylpentanoate (29): R_f = 0.57 (ether/petroleum ether 1:1); IR (neat, KBr): $\tilde{\nu}$ 3086, 3062, 3028, 2953, 2801, 1737 (C=O), 1494, 1454, 1194, 1028, 980, 748, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35 (pseudo dm, $J \approx 7$ Hz, 4H, aromatic H_{ortho}), 7.29 (pseudo tm, $J \approx 7.5$ Hz, 4H, aromatic H_{meta}), 7.22 (ddt, J = 8.2, 6.2, 1.4 Hz, 2H, aromatic H_{para}), 3.72 (d, J = 13.6 Hz, 2H, CH_2Ph), 3.64 (s, 3H, CO_2Me), 3.41 (d, J = 13.6 Hz, 2H, CH_2Ph), 2.85 (ddd, J = 8.4, 6.8, 5.3 Hz, 1H, H–C3), 2.68 (dd, J = 14.8, 5.3 Hz, 1H, H–C2), 2.30 (dd, J = 14.8, 6.8 Hz, 1H, H–C2), 1.88 (d septet, J = 8.4, 6.7 Hz, 1H, H–C4), 0.98 (d, J = 6.7 Hz, 3H, CH_3), 0.81 (d, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.13 (CO e.g. C1), 139.84 (2 C_{ipso}), 129.06 (4 C_{ortho}), 128.07 (4 C_{meta}), 126.82 (2 C_{para}), 61.36 (C3), 54.09 (2 CH_2Ph), 51.59 (OCH_3), 32.63 (C2), 30.81 (C4), 21.24 (CH_3), 19.82 (CH_3); HRMS (70 eV, EI) $C_{21}H_{27}NO_2$: $[M]^+$ calcd 325.2042, found 325.2036 and $C_{18}H_{20}NO_2$: $[M - {}^iPr]^+$ calcd 282.1494, found 282.1485; m/z (%): 325 (0.1) $[M]^+$, 282 (22.0) $[M - {}^iPr]^+$, 91 (100) $[PhCH_2N]^+$. The picrate did not crystallize and remained oily.

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[12] The use of indium trichloride was also reported for transmetalation reactions with allylstannanes [17] and tin [18].

[13] In subsequent exploratory experiments, propargyl bromide was also shown to react with enamines in the presence of acetic acid and indium or zinc. With indium, an approximately 1:1 mixture of isomeric α-allenyl and homopropargyl tertiary amines was obtained. With zinc, the same compounds were isolated in an approximately 9:1 ratio in favor of the acetylenic amine.

[14] Enamines **5**, **8**, and **12** were prepared in 58–60, 62, and 73% yield respectively by addition of 4 Å activated molecular sieves (beads, 100 mg mmol^{-1} of substrates) to a mixture of aldehyde and secondary amine in equimolar amounts, reaction 24 h at 3 °C or 4 h at 20 °C, removal of molecular sieves, and two successive distillations (glass wool was used to prevent extensive foaming). Enamines **6** and **9** were obtained by using 3 equiv of anhydrous $CaSO_4$ in anhydrous ether (0.5 mL mmol^{-1} amine) to condense the aldehyde (1.25 equiv) with the amine. Enamine **6** crystallized in the cold and was used as such, since it decomposed on distillation. Crystalline enamine **10** was similarly prepared, but 1 equiv of CaH_2 was used to complete the reaction. Enamine **7** was purchased from Lancaster. Enamine **11** was obtained by an azeotropic method [16] and is also commercially available. Enamine **13** was obtained by condensing excess isobutyraldehyde (2 + 2.5 equiv) with dibenzylamine by means of 4 Å activated molecular sieves (200 mg mmol^{-1} of amine) for 2 d at RT.

[15] Commercial indium powder from Aldrich (99.99%, stabilized with 1% MgO), zinc powder from BDH, aluminum powder from Janssen (99%, 200 mesh), tin powder from Prolabo (carbon free, for metallurgical analyses, article no. 23713), bismuth powder from Aldrich (99.5%, 100 mesh), and indium(III) chloride from Aldrich (98%) were used.

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