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Further investigations into imine-mediated formation of allylic nitro compounds

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ABSTRACT

Nitro alkanes are valuable starting materials for functionalisation via their corresponding anions as well as their transformation into other important groups such as ketones via the Nef reaction. Herein, we report a process development study for the construction of a series of cyclic allylic nitro compounds that features a greener solvent and a lower cost, more robust catalyst than previously reported. The process was developed to target the selective synthesis of an important fragrance intermediate, namely, α-dehydroherbac. Process scoping and optimisation involved solvent & catalyst screening along with a basic kinetic investigation to evaluate critical reaction parameters (concentration and reagents ratio). The final optimised conditions were further demonstrated via synthesis of a small collection of additional derivatives to demonstrate scope and utility.

1. Introduction

Allylic nitro compounds are a synthetically versatile class of structures capable of delivering a wide range of secondary products possessing important structural motifs. These include α,β-unsaturated ketones [1–3], allylic amines [4–13], allylic nitriles [14], unsaturated β-nitro alcohols [15–18], unsaturated β-amino alcohols [19], unsaturated α-nitro ketones [20], 2-nitro-1,3-dienes as well as further functionalised products [21].

The nitroaldol or Henry reaction is a widely used transformation for the construction of conjugated nitroalkanes [16,22]. In 1982, Barton et al. detailed the use of imine catalysis to promote nitroaldol reactions which yielded α,β-unsaturated nitro compounds useful in the synthesis of corticosteroid derivatives [23]. The same catalysed reaction was later explored in more detail by Tamura et al. which demonstrated *N,N*-dimethylethylenediamine (**2**) was successful at converting various ketones into useful allylic nitro compounds (Scheme 1) [24]. More recently, this methodology was also used for the synthesis of a small collection of symmetrical cycloalkene allylic nitro compounds by Hayashi to develop a metal-free Nef reaction with molecular oxygen [25]. Our interest in the cited methods rose from an opportunity to exploit this transformation for the synthesis of dehydroherbac (**5a**) [26], an important intermediate in the flavour and fragrance industry used to prepare Galbascone **6** [27]. It was anticipated that by coupling this methodology with a subsequent Nef reaction we would be able to deliver compound **5** in high selectivity towards the desired α-isomer **5a**.

To our knowledge, this strategy has received no attention with respect to its use in the selective preparation of asymmetric cycloalkenyl allylic nitro compounds since these initial discoveries in 1982/1986. We herein therefore report a detailed study that led us to an improved synthetic methodology for the preparation of primary and secondary allylic nitro compounds from ketones and nitroalkanes The primary focus of the development work was with an industrial view to utilising the chemistry at scale for the manufacture of fragrance ingredients [28].

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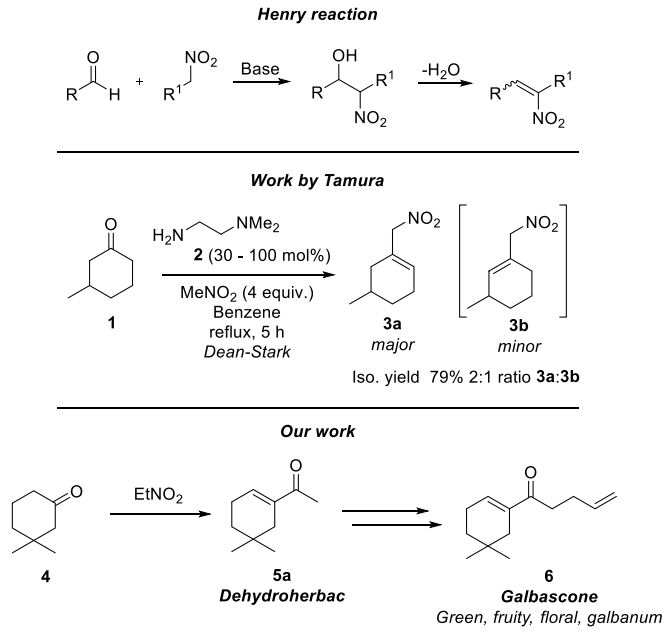
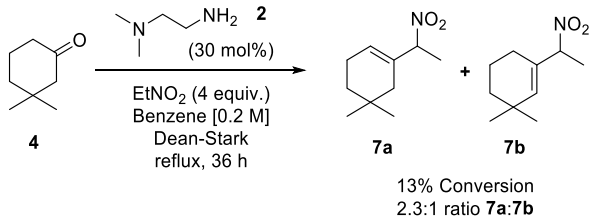


Scheme 1. The Henry reaction *vs* the formation of allylic nitro compounds via imine catalysis and the application in the synthesis of the industrial intermediate to Galbascone (**6**), dehydroherbac (**5a**).



Scheme 2. Reaction conditions for an initial of the irregular nitro-aldol reaction of **4**.

2. Results and discussion

2.1. Design and optimisation of the method

As an initial test reaction commercially available 3,3-dimethylcyclohexanone (**4**) was treated with four equivalents of nitroethane and 0.3 equivalents of *N,N*-dimethylethylendiamine (**2**) in benzene (0.2 M) under Dean-Stark reflux to remove water (Scheme 2). These conditions, initially reported by Tamura, gave a low 13% yield (quantified GC-MS) after 36 h (no additional reaction was seen beyond this point) and a modest selectivity towards the desired regioisomer (equitable to the reaction of the model compound **1**, Scheme 1).

Using a higher ratio of nitroethane (ten equivalents) immediately resulted in an improved result, furnishing 60% yield with a 3.6:1 selectivity in favour of the desired product **7a** but still requiring an extended 72 h of reaction. To our delight, increasing the concentration from 0.2 to 1.0 M further enhanced the efficiency of the reaction giving 96% yield and a matching selectivity after only 24 h (Fig. 1).

As the use of benzene is now heavily regulated within industrial settings, we opted to evaluate alternative solvents that would allow for efficient azeotropic removal of water (Fig. 2). After the initial screening of solvents, we found the reactions carried out in an apolar solvents, such as toluene, cyclohexane, and benzene tend to have slower reaction kinetics than those reactions performed in more polar solvents like ethyl acetate (AcOEt), 4-methyltetrahydropyran (4-Me-THP), and 2-methyltetrahydrofuran (2-Me-THF). This increase in the rate may be attributed to a capacity of these solvents to facilitate proton transfer and stabilise charged reaction intermediates (e.g., iminium).

Interestingly, monitoring the isomers composition via GC, we observed that the ratio between **7a** and **7b** changes over time in the various solvents. For all solvents, the desired isomer **7a** is initially favoured over isomer **7b**, however, as the reaction progresses it was shown to slowly change with a higher proportion of **7b** being noted. Ethyl acetate (Figs. 2 and 3) was found to be the optimal solvent, as it provides the best selectivity (ratio **7a**:**7b**, 5.4:1) and overall yield (87.5%) in a practical reaction time of 8 h (energy usage and prospective plant utilisation) whilst being suitable as a greener substitute solvent.

The generally observed regioselectivity encountered is consistent with Tamura's study (e.g. compound **1**, Scheme 1) and can be rationalised by considering the sterics involved in the deprotonation of the diamine adduct **9** (Scheme 3). The interaction of the gem-dimethyl unit on the ring and the *N,N*-dimethyl functionality of the catalyst generates a preference for deprotonation at the α-carbon (highlighted in green in Scheme 3) resulting from less steric interactions, thus giving the α-product **7a** preferentially.

The rate of the reaction was found to be highly dependent on the

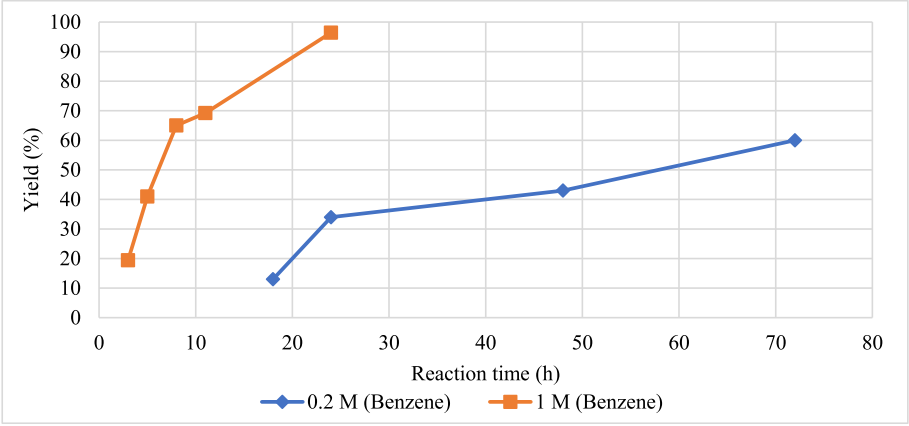


Fig. 1. Combined conversion to **7a** and **7b** for the irregular nitro-aldol reaction of substrate **4**. Experiments were performed at 25 mmol scale, yields were determined by calibrated GC-MS.

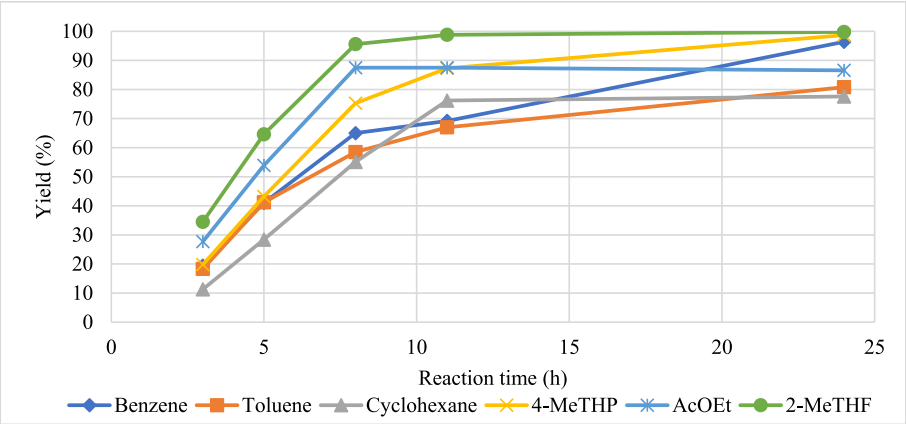


Fig. 2. Selected results for the combined conversion to **7a** and **7b** for the irregular nitro-aldol reaction of substrate **4**. Experiments were performed at 25 mmol scale, yields were determined by calibrated GC-MS.

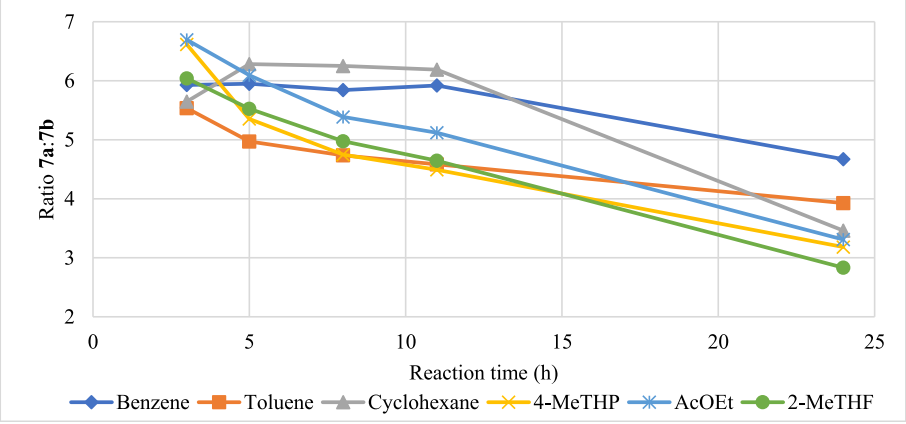
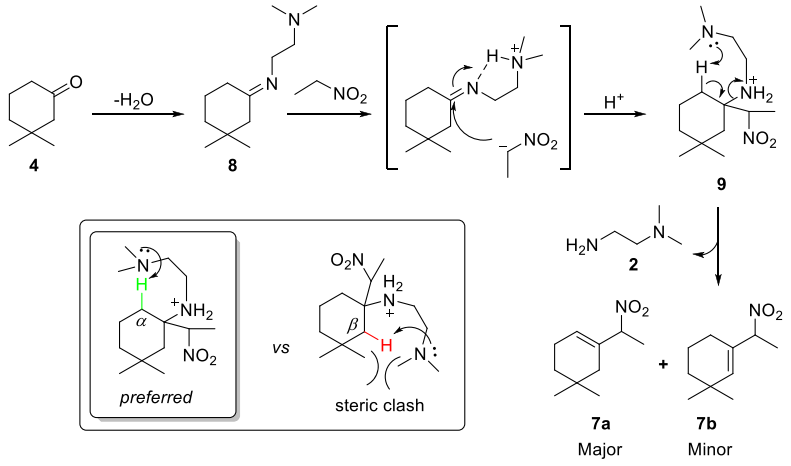


Fig. 3. Ratio **7a**:**7b** in respect to reaction time for the irregular nitro-aldol reaction of substrate **4**. Experiments were performed at 25 mmol scale, yields were determined by calibrated GC-MS.



Scheme 3. Mechanistic rationalisation for the observed selectivity.

efficient removal of water. In fact, excluding the Dean-Stark apparatus was highly detrimental to the reaction furnishing only 29% yield after 8 h and 48% after 24 h. Further supporting the need for water removal, molecular sieves proved effective generating 67% yield after 8 h and 80% after 24 h. However, calcium chloride, which has previously been shown to be an effective dehydrating and beneficial additive for iminium nitroaldol reactions [28,29],was not effective (acheiving only 48% after 24 h) giving an identical yield to the simple reflux set-up.

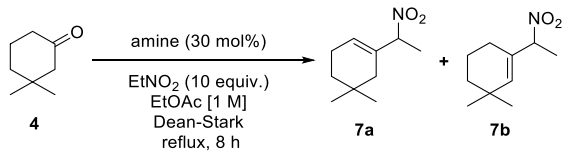
Based upon the working hypothesis of steric factors being

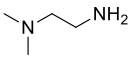
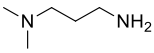
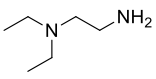
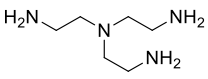
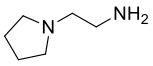
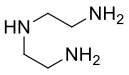
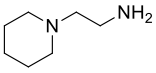
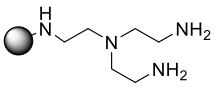
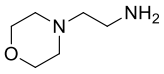
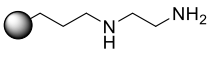
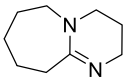
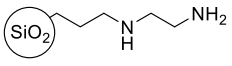
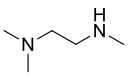
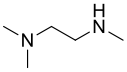
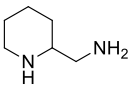
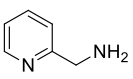
reasonable for the selectivity between **7a** to **7b** we attempted to gain enhancement of this ratio by evaluating an expanded series of alternative catalysts, compounds **10**–**25**. The reactions (50 mmol) were run at 1.0 M concentration in EtOAc with 10 equivalents of nitroethane and 30 mol% of the catalyst for 8 h under Dean-Stark conditions as a baseline (Table 1).

As shown in Table 1, the best results were obtained employing either *N,N*-diethylethylendiamine (**10**) or 1-(2-aminoethyl)pyrrolidine (**11**) along with the initial catalyst **2** (*Entries* 1-3). During the investigation, the loss of catalyst **2** was observed through the characteristic odour noted in the aqueous layer collected in the Dean-Stark (also indicated by additional volume). The catalyst evidenced boil-off (bp. 105 °C) would inevitably be associated with a decrease in the reaction kinetic over time. As this was not encountered to the same extent with catalysts **10** and **11** this may be related to their higher boiling points (146 and 170 °C, respectively). As anticipated, increasing the steric hindrance at the basic nitrogen moiety improved the selectivity of the reaction, especially when a cyclic system was utilised. Both the diethyl and pyrrolidine derivatives gave good yields and selectivity. The higher selectivity shown by catalyst **11** encouraged us to further explore the piperidine **12** and morpholine **13** rings but sadly these showed decreased selectivity and yield, suggesting an optimal fitting of the pyrrolidine unit.

To validate the proposed imine-based mechanism (Scheme 3), a set of control experiments were performed; a strong non-nucleophilic amine base, namely, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, **14** [30]) was tested to analyse if basic catalysis was

Table 1
Screening of alternative catalysts for the irregular nitro-aldol reaction of **4**.[a].



Entry	Base	b.p.[c]	Yield(%)[b] (7a:7b)	Entry	Base		Yield(%)[b] (7a:7b)
1		**2** 105 °C	87 (*5.4*)	11		**20**	5 (*4.1*)
2		**10** 146 °C	56 (*5.8*)	12		**21**	30 (*4.2*)
3		**11** 170 °C	81 (*8.5*)	13		**22**	29 (*2.5*)
4		**12** 186 °C	70 (*4.8*)	14		**23**	<1 –
5		**13** 224 °C	32 (*4.5*)	15		**24**	0 –
6		**14**	0 –	16		**25**	29 (3.5)
7	nPrNH$_2$ Et_3N	**15** **16**	0 –	17	Silica gel	**26**	0 –
8		**17**	6 (*3.1*)	18	Silica gel 	**26** **17**	8 –
9		**18**	42 (*3.4*)	19	PS-Immobilised DBU	**27**	0 –
10		**19**	0 –	20	PS-BEMP	**28**	0 –

[a] Reactions carried out on 50 mmol scale at 1.0 M, 8 h reaction; [b] Yield estimated by GC-MS; [c] Boiling points reported only for key molecules; BEMP = 2-tert-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine.

viable as indicated by certain related literature [31,32] (*Entry 6*). A simple primary amine namely, propylamine (**15**) and a tertiary amine (triethylamine, **16**) were also screened in combination to assess the need for the ethylenediamine moiety (*Entry 7*). However, no reaction was detected from any of these test reactions. Next, the secondary amine equivalents **17** and **18** were tested to assess whether the reaction could also proceed through an iminium-type mechanism, although reaction was noted, these catalysts resulted in very only poor conversions (*Entry 8&9*). The pyridine derivative **19** also proved unsuccessful, suggesting that the lone pair of the tertiary nitrogen base plays a key role in the reaction (pyridine conjugate acid pK_a ~5 *vs* triethylamine conjugate acid pK_a ~11 in H_2O) (*Entry 10*). The internal chain extended derivative **20** had a drastic impact resulting in only a 5% yield indicating that geometry (idealised 7-membered deprotonation transition state) is an important factor for deprotonation by the tertiary nitrogen base (*Entry 11*). Polymer-supported catalysts were investigated such as the trisamine **23**, however, the results were poor. The lower yields obtained from other homogenous trisamine derivatives (**21** and **22**) suggested a supported catalyst more similar to **2** should be considered (*Entries 12–14*). As such, a polymer-supported ethylendiamine **24** was examined but the outcome was also unsatisfying (*Entry 15*). Inspired by the work of Kobayashi et al. on heterogeneous catalysis for reaction condensations in flow, we decided to investigate 3-(ethylendiamino)propyl-functionalised silica gel (**25**) as the catalyst [28,29]. To our delight, the reaction partially formed the product, albeit in a low **7a**:**7b** (3.5:1) ratio (*Entry 16*). The activity of the latter may be explained by a higher surface area compared to the polymer-bound catalyst and therefore better accessibility of the ethylendiamine moiety. A further possible explanation may be the bi-functionality of the silica support also acting as a source of acid promoting the catalysis. However, no reaction was detected when only silica gel was used (*Entry 17*), or when silica and ethylene diamine were combined (*Entry 18*). The use of other additives, in combination, such as 1-benzyl-3-phenylurea and *p*-toluenesulfonic acid on the homogenous reaction appeared to have no effect on either the yield or rate of the reaction, suggesting the higher activity of the silica gel catalyst may be fully associated with accessibility to the active sites.

To evaluate the selectivity (isomer ratio of **7a** and **7b**) and efficiency over longer reaction times (24 h) we decided to monitor transformations involving three of the most active homogeneous catalyst (**2**, **10** and **11**) and the most active heterogeneous material (**25**) (Figs. 4 and 5). The heterogeneous catalyst takes longer to reach its peak conversion compared to the homogenous catalysts due to a diffusion-dependent reaction rate (and possibly a higher steric environment). For catalyst **25** the selectivity does not change significantly throughout the reaction period (3:1 at 3 h *vs* 2.8:1 after 24 h) suggesting the steric environment around the active site does not induce much preference toward any specific

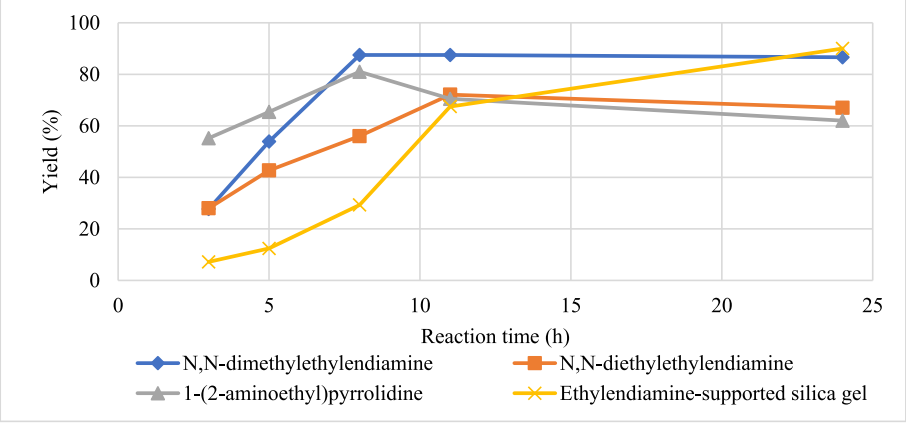


Fig. 4. Conversion to **7a** and **7b** in relation with the reaction time and the nature of the catalyst for the irregular nitro-aldol reaction of compound **4**. Experiments were performed at 25 mmol scale, yields were determined by calibrated GC-MS.

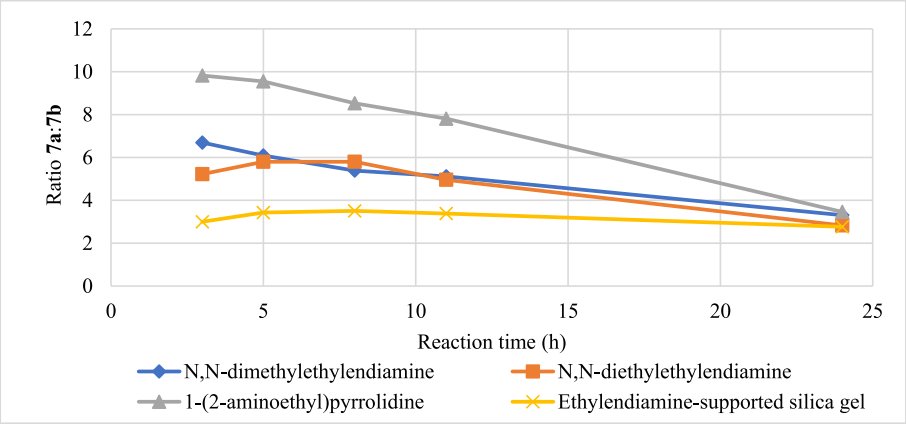


Fig. 5. Ratio **7a**:**7b** in relation with the reaction time and the nature of the catalyst for the irregular nitro-aldol reaction of compound **4**. Experiments were performed at 25 mmol scale, yields were determined by calibrated GC-MS.

deprotonation. By contrast catalysts **10** and **11** displayed the highest selectivity (~9:1 for **7a**) after 5 h, albeit at low conversions (40–65%). After 8 h, catalyst **11** achieved a much higher conversion with conserved selectivity (8.5 *vs* 9.5 originally). The selectivity of catalyst **10** instead showed a rapid decline to 5.8 and ultimately under-performing the initial catalyst **2** regarding yields 87% *vs* 56% yield after 8 h.

As already observed during the initial solvent screen, the ratio of **7a**:**7b** was seen to fall to a lower value over 24 h. This was initially assumed to be due to α-to β-isomer interconversion, however, when catalysts **10** and **11** were investigated in detail, the overall calibrated conversion to **7** (sum of **7a**+**7b**) was seen to decreases as the reaction proceeds, which would suggest a decomposition pathway is occurring. In fact, when an enhanced isomer mixture containing a 14:1 ratio, **7a**:**7b** (obtained by column chromatography of a 5.4:1 **7a**:**7b** mixture), was subjected to the reaction conditions, a rapid decrease in the isomer **7a** was observed (Fig. 6). By contrast the content of isomer **7b** decreased only slightly over the same time. The experiment was also repeated on a 5.4:1 mixture of **7a**:**7b** with the same behaviour being noted but with a slower rate of decomposition (Fig. 7).

These experiments suggest that the observed deterioration in the **7a**:**7b** ratio under the reaction conditions is due to preferential decomposition of the **7a** isomer. We propose a plausible explanation as outlined in Scheme 4. As previously described in Scheme 3, the deprotonation of the diamine adduct **9** plays a central role in the selectivity of the final material, which could be either of the two isomers **7a** and **7b** or the alternative α,β-unsaturated nitro compound **29**. The formation of the latter is in equilibrium as the amino catalyst could still re-insert into the double bond and regenerate the adduct **9**. The nitro compound **30** could also easily interconvert into **7a** and **7b** also via an amino-catalysed prototropic process. As observed from experimental data, the thermodynamic product of reaction seems to be the isomer **7b**, which less likely interconverts into **27** due to steric arguments. On the other hands, the less steric hindered α proton on **7a** could more certainly involved into the prototropic process, converting in **29** and therefore yielding the isomer **7b**. As the steric geometry impediment on the catalyst increases, its ability to re-insert into **30** falls, therefore behaving more as a base and facilitating the prototropic process from the isomer **7a** to **27**. The accumulation of the unsaturated nitro compound **30** along with the basic conditions of the reaction could then trigger side reactions with either the products **7** or other active intermediates causing decomposition/browning.

Despite the fact that the optimum selectivity was obtained with the pyrrolidine derivative **11**, the diethyl derivative **10** was strategically selected moving forward due to its more attractive price (£150 *diethyl* **10** *vs* £195 *dimethyl* **2** *vs* £1420 *pyrrolidine* **11**, Apollo Scientific prices for 1 kg accessed 1st July 2022). Doubling the catalyst loading of **10** (from 30 mol%) resulted in a slight increase in

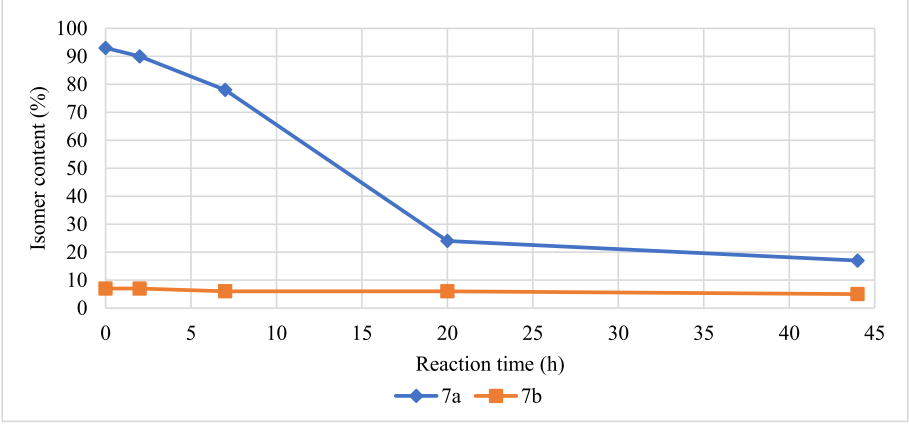


Fig. 6. Content of a 14:1 **7a**:**7b** isomer mixture *vs* time under the reaction conditions. The experiment was conducted on a 1 mmol scale, using 1,3,5-trimethoxybenzene as an internal standard as monitored by ^{1}H NMR.

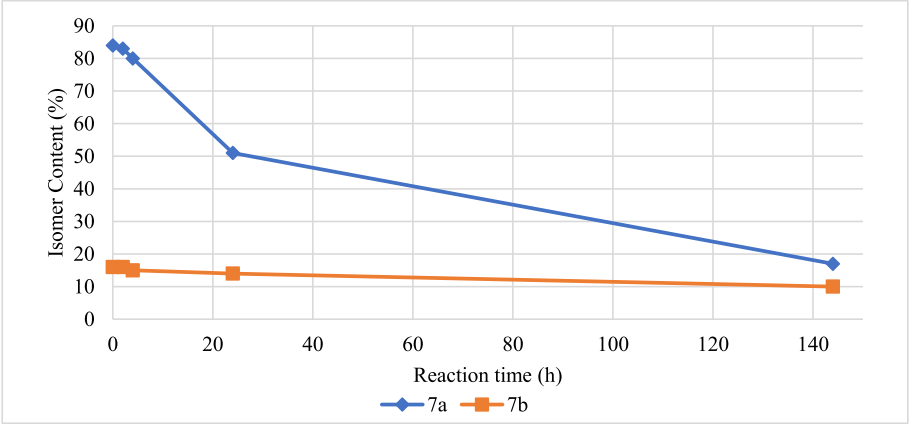
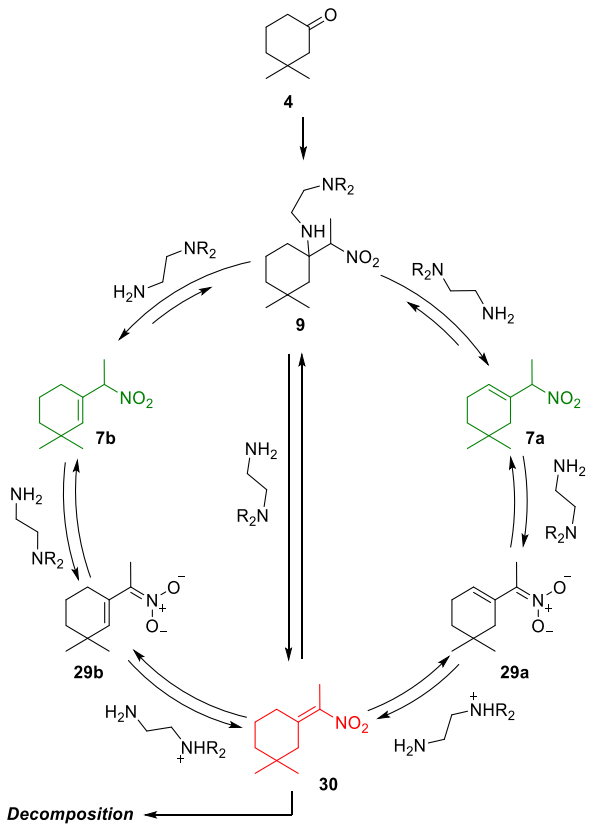


Fig. 7. Content of a 5.4:1 **7a**:**7b** isomer mixture *vs.* time. The experiment was conducted on a 1 mmol scale, using 1,3,5-trimethoxybenzene as an internal standard as monitored by ^{1}H NMR.



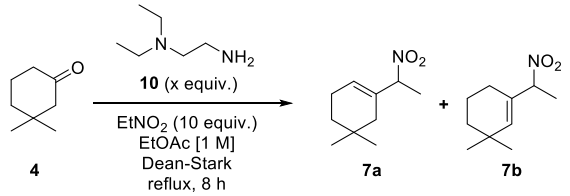
Scheme 4. Postulated mechanism for isomer interconversion and decomposition of product **7a**.

the observed yield, although this was also associated with reduced selectivity (Table 2). Further raising the catalyst loading was found to be detrimental to both the yield and selectivity. Presumably, the selectivity is decreased due to an enhanced rate of decomposition of isomer **7a** with a higher catalyst loading; see discussion above. Alternatively, decreasing the catalyst loading as expected directly impacted conversion in a non-desirable way.

We next explored the potential of decreasing the stoichiometry of the highly flammable and potentially explosive nitroethane, an aspect of concern for industrial scale usage based on safety and cost. Unfortunately, a reduction in the nitroethane equivalents resulted in a steep decrease in the rate of reaction (Fig. 8). This was noted to also be associated with a decline in the bulk reaction temperature caused by a proportional increase in the volatile solvent component (EtOAc); and resulting in a notable poorer water removal. In an attempt to mitigate this, we raised the concentration of the reaction from 1.0 to 2.5 M which increased the progression of the reaction (76% yield after 24 h compared to 24%), however, the final selectivity (**7a**:**7b**) of this transformation was only 3.4:1 (Fig. 9). It is worth noting that the highest conversion for catalyst **10** under the standard conditions (10 equivalents) was reached at 11 h (70%) with a selectivity **7a**:**7b** of 5.0:1. As such the revised 2.5 M concentrated reaction performs comparably, giving a slightly lower yield of 62% but with a higher 5.8:1 **7a**:**7b** ratio.

The optimised process was then scaled up (to 1 mol scale) using the conditions earlier identified (30 mol% diethyl catalyst **10**, 2.5 equiv. $EtNO_2$, 2.5 M in EtOAc) with the product isolated by distillation. It was found that an acid wash prior to distillation was benifical to avoid co-distillation of multiple, but trace, unidentified side products. Following distillation, the product was isolated in 75% (137.4 g) and good selectivity 5.7:1. Interestingly, a viscous polymeric residue was left behind (28.4 g) which could not be identified but would account for the decomposition identified in Scheme 4.

Table 2
Variation of base stoichiometry on observed yield and selectivity.



Entry[a]	Loading (mol%)	Yield (%)[b]	Ratio 7a:7b
1	5	29	2.0 : 1
2	15	45	4.9 : 1
3	30	56	5.8 : 1
4	60	66	4.4 : 1
5	100	41	3.0 : 1

[a] Reactions carried out on 50 mmol scale at 1.0 M.
[b] Yield determined by quantified GC-MS analysis.

2.2. The Nef transformation

With an optimised process capable of generating multi-gram quantities of **7**, investigations into the subsequent Nef reaction, to furnish **5**, were evaluated. Since the discovery of the Nef reaction in 1894 [2], a variety of alternative conditions to the classical base-acid treatment have been reported [1]. Interesting examples include the use of oxone [30], organic bases such as DABCO [25] and DBU [35] and biocatalytic methods[[36],37]. A range of such conditions were screened for the Nef reaction of **7**, however, none provided better yields than the classical reaction conditions (nitronate salt formation with NaOH, followed by treatment with either H_2SO_4/HCl). Following a brief DoE optimisation exercise the best conditions were identified as those shown in Table 3, entry 3. In all cases, retention of the staring material isomeric ratio was observed.

To validate this process and check for consistency at larger scale two duplicate reactions of 0.5 mol scale (91.5 g) were conducted. After vacuum distillation improved isolated yields of 79 and 81% were achieved, for which the higher yields are attributed to the easier distillation at scale.

2.3. Application on different substrates

The optimal conditions developed for the synthesis of compound **7** were next applied to a range of other cyclic substrates **28**–**35** (Table 4). The nitroaldol reaction was first investigated with nitroethane (*Entries 1–6*). Increasing the ring size generally led to a drop in yields with cycloheptanone **28** giving the nitro olefin **29** in 61% isolated yield whilst cyclooctanone **30** gave **31** in only 39% (*Entries 2&3*). The reaction of 3,5,5-trimethylcyclohexanone **32** displayed the same preference towards product **7** derived from deprotonation at the less sterically hindered position (*Entry 4*), however, with a lower selectivity (1.9:1, **33a**:**33b**) and a lower yield of 25%. The reaction of nitroethane with dihydrocarvone **34**, a substrate possessing α-methyl functionality, gave only traces of the product (GC-MS) even after 48 h suggesting that α-susbtituted ketone systems are not compatible (*Entry 5*). The reaction with menthone **35**, possessing α-isopropyl functionality led to no reaction with nitroethane, futher reinforcing this hypothesis (*Entry 6*).

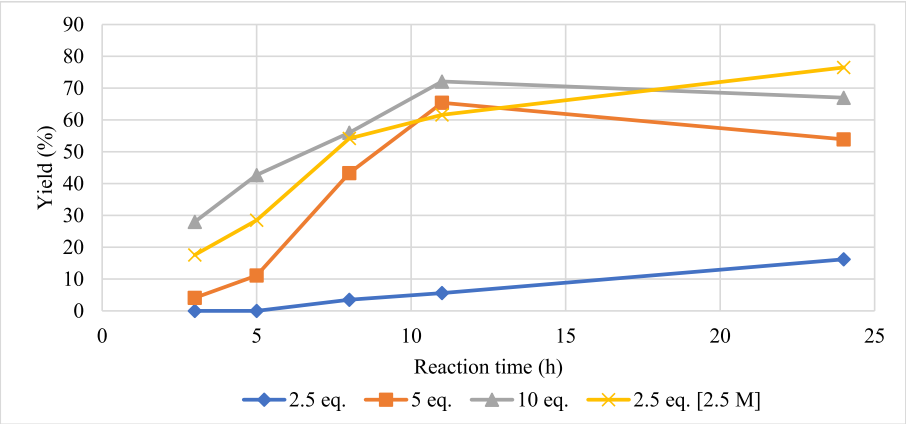


Fig. 8. Conversion of **7a** and **7b** in relation with the reaction time and the equivalents of the nitroethane employed for the irregular nitro-aldol reaction of **4**. The experiments were carried out on a 25 mmol scale. The experiment at 2.5 M was performed on 62.5 mmol. Yields were determined by calibrated GC-MS.

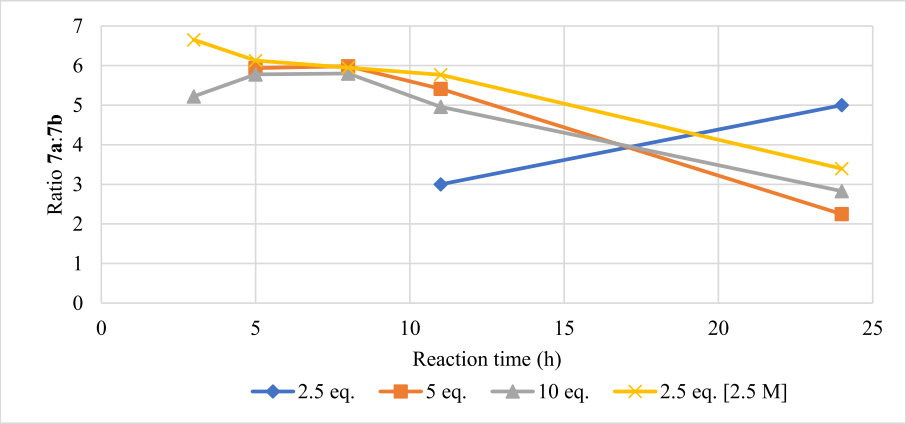
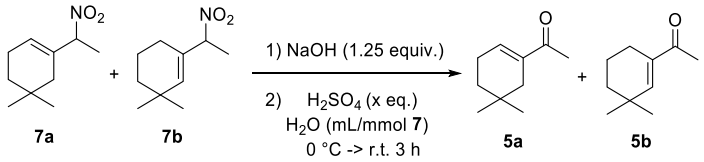


Fig. 9. Ratio **7a**:**7b** in relation with the reaction time and the equivalents of the nitroethane employed for the irregular nitro-aldol reaction of **4**. The experiments were carried out on a 25 mmol scale. The experiment at 2.5 M was performed on 62.5 mmol.

Table 3
Selected examples conditions for the Nef reaction of isomers **7**.



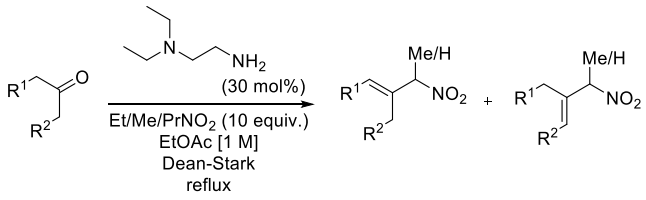
Entry[a]	H_2SO_4 (equiv.)	H_2O (ml/mmol 7)	Yield (%)[b]
1	3	1	62
2	3	1	63
3	2	0.5	65

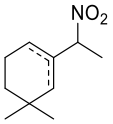
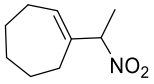
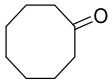
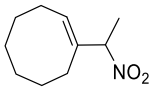
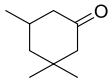
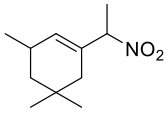
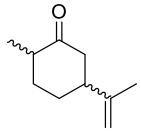
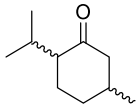
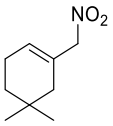
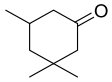
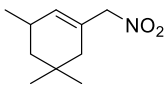
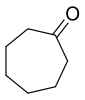
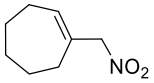
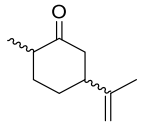
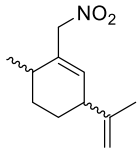
[a] Experiments were carried out on a 82 mmol scale.
[b] The product was isolated via vacuum distillation. Ratio of product was consistent with starting material ratio of 5.7:1.

Upon reaction with nitromethane, however, dihydrocarvone **34** delivered the nitro olefins **39** in 89% isolated yield (3.3:1, **39a**:**39b**), again with selectivity directed towards the less sterically hindered position **39a** (*Entry 10*). Treatment of menthone **35** with nitromethane gave only traces of the products (GC-MS), (*Entry 11*).

The reaction of nitromethane with 3,3-dimethylcyclohexanone (**4**), 3,5,5-trimethylcyclohexanone (**35**), and cycloheptanone (**31**) also progressed smoothly delivering the nitroolefins **39**, **40**, and **41** in respectively 94% (3.0:1, **39a**:**39b**), 65% (3.0:1, **40a**:**40b**), and 75% isolated yield (*Entries 7–9*). Upon reaction of **4** and **31** with 1-nitropropane (*Entries 12&13*), no product formation was observed suggesting that the reaction is limited to nitroethane and

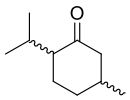
Table 4
Nitro olefins prepared using the developed methodology.



Entry[a]	Ketone		RNO_2	Product		Yield (%)[b]
1[c]		**4**	$EtNO_2$		**7**[d]	78% (5.4:1)
2		**31**	$EtNO_2$		**32**	61%
3		**33**	$EtNO_2$		**34**	39%
4		**35**	$EtNO_2$		**36**[e]	25% (1.9:1)
5		**37**	$EtNO_2$	traces of product observed by GC-MS		–
6		**38**	$EtNO_2$	no reaction		–
7		**4**	$MeNO_2$		**39**[f]	94% (2.2:1)
8		**35**	$MeNO_2$		**40**[g]	65% (1:1)
9		**31**	$MeNO_2$		**41**	75%
10		**34**	$MeNO_2$		**42**[h]	89% (3.3:1)

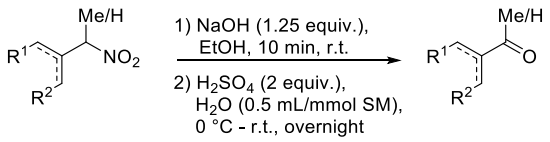
(*continued on next page*)

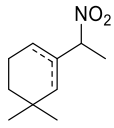
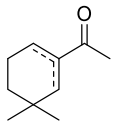
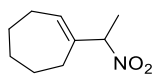
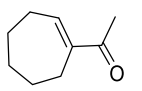
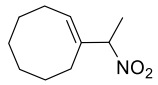
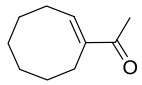
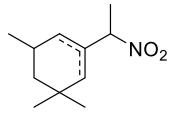
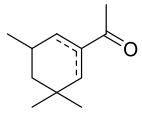
Table 4 (*continued*)

Entry[a]	Ketone		RNO_2	Product	Yield (%)[b]
11		**38**	$MeNO_2$	traces of product observed by GC-MS	–
12		**4**	*n*-$PrNO_2$	no reaction	–
13		**31**	*n*-$PrNO_2$	no reaction	–
14		**31**	*i*-$PrNO_2$	no reaction	–

[a] Reactions conducted on 50 mmol scale unless stated otherwise.
[b] Isolated yield.
[c] Reaction carried out on 0.50 mol scale.
[d] Starting material regioisomeric ratio **7a**:**7b** = 5.4:1.
[e] Starting material regioisomeric ratio was **36a**:**36b** 1.9:1.
[f] Starting material regioisomeric ratio was **39a**:**39b** 2.2:1.
[g] Starting material regioisomeric ratio was **40a**:**40b** 1:1.
[h] Starting material regioisomeric ratio was **42a**:**42b** 3.3:1.

Table 5
Nef reaction of nitro olefins **7**, **32**–**36**.



Entry[a]	Nitro olefin		Product		Yield (%)[b]
1		**7**		**5**	65% (5.8:1)
2		**32**		**43**	42%
3		**34**		**44**	47%
4		**36**		**45**	54% (1.9:1)

[a] Reactions conducted on 6–82 mmol scale.
[b] Isolated yield.

nitromethane. The same-behavior was exhibited for the reaction with 2-nitropropane (*Entry 14*). This is consistent with many reported lietaure conditions in which more substituted nitroalkanes have proven challenging to add into cyclic ketones, invariably this is identified as being due to steric factors.

The corresponding Nef reactions of the secondary nitro olefins **7**, **32**–**36** all furnished the corresponding ketones in moderate yields with again retention of the original isomer ratios (Table 5). In the case of the primary nitro olefins **39**–**42**, starting material was mostly recovered under these conditions. We note no optimisation of the conditions for these substates was undetaken.

3. Conclusion

In summary, a novel method for the synthesis of α-dehydroherbac **5a** has been described which gives high selectivity towards the desired double bond isomer **5a** in good yield and in a readily scaled process. Our continued development of this iminium-amine catalysed methodology additionally inspired several improvements over previously reported conditions in that a greener solvent (EtOAc *vs* benzene) could be used along with a lower cost catalyst (**10** *vs* **2**). We have also shown that steric influences in the catalyst alkylation have a significant impact on the selectivity and as such there is scope for further refinement based upon the catalyst and substate pairing. The scope of the methodology developed was more widely demonstrated and the reaction was shown to be effective for the synthesis of cyclic allylic nitro compounds from cyclic ketones and both nitromethane and nitroethane.

4. Materials and methods

Unless otherwise stated, all solvents were purchased from Fisher Scientific and used without further purification. Substrates and their precursors and reagents were purchased from Alfa Aesar or Sigma Aldrich and used as received. ^{1}H NMR spectra were recorded on either Bruker Avance-400, Varian VNMRS-600 or Varian VNMRS-700 instruments and are reported relative to residual solvent: $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra were recorded on the same instruments and are reported relative to $CHCl_3$ (δ 77.16 ppm). Data for ^{1}H NMR are reported as follows: chemical shift (δ/ppm) (multiplicity, coupling constant (Hz), integration).

Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br. s = broad singlet, app. = apparent. Data for ^{13}C NMR are reported in terms of chemical shift (δ_C/ppm). DEPT-135, COSY, HSQC, HMBC and NOESY experiments were used in structural assignments. IR spectra were obtained using a PerkinElmer Spectrum Two UATR Two FT-IR Spectrometer (neat, ATR sampling) with the intensities of the characteristic signals being reported as weak (w, <20% of tallest signal), medium (m, 21–70% of tallest signal) or strong (s, >71% of tallest signal). Low and high resolution mass spectrometry was performed using the indicated techniques. Gas chromatography mass spectrometry (GC-MS) was performed on a Shimadzu QP2010-Ultra equipped with an Rxi-5Sil MS column in EI mode. Atmospheric solids analysis probe mass spectrometry (ASAP-MS) was performed using a Waters LCT Premier XE. For accurate mass measurements the deviation from the calculated formula is reported in ppm.

SiO_2 column chromatography was performed using Sigma Aldrich silica gel (grade 9385, pore size 60A) and standard manual column apparatus. For TLC, Sigma Aldrich glass-backed plates were used and visualisation was performed using UV-irradiation or a $KMnO_4$ stain. Organic solutions were concentrated under reduced pressure using a Buchi rotary evaporator and hi-vacuum was achieved using an Edwards RV5 pump and Schlenk line. Kugelrohr distillation was performed using a Buchi Glass Oven B-3585 and vacuum distillation was performed using a Buchi V-700 vacuum pump equipped with a V-850 vacuum controller attached to a standard distillation pig setup.

4.1. 3,3-Dimethylcyclohexanone **4**

Prepared via selective hydrogenation of dimedone according to the literature.[33, 34, 35] ^1H NMR (400 MHz, $CDCl_3$) δ 2.31–2.25 (m, 2H), 2.16 (t, J = 0.8 Hz, 2H), 1.94–1.85 (m, 2H), 1.62–1.57 (m, 2H), 0.99 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.3, 55.0, 40.9, 38.0, 36.1, 28.6, 22.5 ppm; FT-IR ν_{max} 503 (w), 1076 (w), 1225 (m), 1291 (w), 1368 (w), 1455 (w), 1708 (s), 2954 (m, br); GC-MS R_t 2.60 min, *m/z* 126 $[M]^+$, 111 $[M\text{-}Me]^+$.

General Procedure for the Amine-Catalysed Irregular Nitro-Aldol reaction exemplified by the reaction of 3,3-dimethylcyclohexanone.

A mixture of 3,3-dimethylcyclohexanone (40.0 g, 0.305 mol), *N*,*N*-diethylethylenediamine (4.3 mL, 10 mol%), EtOAc (30 mL) and nitroethane (214 mL, 10 equiv.) was stirred in a round-bottom flask equipped with Dean-Stark trap (pre-filled with EtOAc) and reflux condenser and heated at reflux. After 3 h, a second portion of *N*,*N*-diethylethylenediamine (4.3 mL, 10 mol%) was added and a third portion (4.3 mL, 10 mol%) was added after a further 3 h. After a total of 22 h the reaction was cooled to r.t. and the nitroethane and EtOAc were removed under reduced pressure. The mixture was diluted with EtOAc (100 mL) and amine residues were removed by washing with 1 M HCl (2 × 100 mL). The remaining solution was concentrated *in vacuo* to give the crude product which was purified according to the methods indicated below.

4.2. 5,5-Dimethyl-1-(1-nitroethyl)cyclohex-1-ene **7a** and 3,3-dimethyl-1-(1-nitroethyl)cyclohex-1-ene **7b**

Obtained by reaction of nitroethane with 3,3-dimethyl cyclohexanone as a pale yellow liquid isolated by vacuum distillation (b.p. 105–110 °C/10 mbar) as a pale-yellow oil (0.305 mol scale, 43.3 g, 78%, **7a**:**7b** = 5.7:1). For **7a**: ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (m, 1H), 5.00 (q, J = 7.6 Hz, 1H), 2.14 (m, 2H), 1.88–1.71 (qq, J = 18.9, 2.0 Hz, 2H), 1.62 (d, J = 6.8 Hz, 3H), 1.39–1.33 (m, 2H), 0.93 (s, 3H), 0.91 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.0, 128.4, 88.3, 37.8, 34.4, 28.8, 28.3, 27.4, 23.2, 16.9 ppm; FT-IR ν_{max} 663 (w), 860 (w), 1364 (w), 1384 (m), 1449 (w), 1545 (s), 2918 (w); GC-MS R_t 3.71 min, *m/z* 137 $[M - NO_2]^+$; ASAP-HRMS *m/z* found $[M+H]^+$ 184.1344, $C_{10}H_{18}NO_2$ requires 184.1338 (Δ = 3.3 ppm). For **7b**: ^1H NMR (600 MHz, $CDCl_3$) δ 5.59 (s, 1H), 4.92 (q, J = 7.0 Hz, 1H), 2.02–1.87 (m, 2H), 1.67–1.62 (m, 2H), 1.62 (d, J = 6.8 Hz, 3H), 1.45–1.35 (m, 2H), 0.98 (s, 3H), 0.97 (s, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 139.5, 130.8, 88.3, 36.5, 32.0, 29.6, 29.2, 24.3, 19.4, 17.0 ppm; FT-IR ν_{max} 663 (w), 860 (w), 1364 (w), 1384 (m), 1449 (w), 1545 (s), 2918 (w); GC-MS R_t 3.61 min, *m/z* 137 $[M - NO_2]^+$; ASAP-HRMS *m/z* found $[M+H]^+$ 184.1344, $C_{10}H_{18}NO_2$ requires 184.1338 (Δ = 3.3 ppm).

4.3. 1-(1-Nitroethyl)cyclohept-1-ene [24] **32**

Obtained by reaction of nitroethane with cycloheptanone as a yellow liquid (50.0 mmol scale, 5.17 g, 61%), isolated by SiO_2 column chromatography (hexane:EtOAc, 95:5), R_f (8:2, hexane:EtOAc) 0.7. ^1H NMR (400 MHz, $CDCl_3$) δ 6.05 (t, J = 6.5 Hz, 1H), 4.99 (q, J = 6.9 Hz, 1H), 2.25–2.18 (m, 4H), 1.81–1.74 (m, 2H), 1.62 (d, J = 6.8 Hz, 3H), 1.59–1.44 (m, 4H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4, 134.8, 89.5, 32.3, 28.4, 28.3, 26.6, 26.2, 17.3 ppm; FT-IR ν_{max} 861 (m), 1354 (m), 1384 (m), 1447 (m), 1544 (s), 2850 (w), 2921 (m); GC-MS R_t 3.63 min, *m/z* 123 $[M - NO_2]^+$.

4.4. 1-(1-Nitroethyl)cyclooct-1-ene [24] **34**

Obtained by reaction of nitroethane with cyclooctanone as a pale yellow liquid (50.0 mmol scale, 3.60 g, 39%), isolated by SiO_2 column chromatography (hexane:EtOAc, 95:5), R_f (9:1, hexane:EtOAc) 0.5. ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (t, J = 8.2 Hz, 1H), 5.05 (q, J = 6.8 Hz, 1H), 2.33–2.26 (m, 2H), 2.24–2.16 (m, 2H), 1.65 (d, J = 6.8 Hz, 3H), 1.60–1.42 (m, 8H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.6, 132.7, 88.5, 29.4, 29.0, 26.3, 26.3, 26.2, 26.1, 17.6 ppm; FT-IR ν_{max} 758 (w), 860 (w), 1359 (w), 1383 (w), 1449 (w), 1469 (w), 1545 (s), 2852 (w), 2926 (m); GC-MS R_t 4.05 min, *m/z* 137 $[M - NO_2]^+$.

4.5. 3,5,5-Trimethyl-1-(1-nitroethyl)cyclohex-1-ene/3,3,5-trimethyl-1-(1-nitroethyl)cyclohex-1-ene **36a** & **36b**

Obtained by reaction of nitroethane with cyclooctanone as a pale yellow liquid (50.0 mmol scale, 2.51 g, 25%), isolated by SiO_2 column chromatography (hexane:EtOAc, 95:5), R_f (9:1, hexane:EtOAc) 0.4. Obtained as a mixture of *endo* double bond isomers along with the two corresponding *exo* isomers. NMR spectra of the mixture was not resolved; FT-IR ν_{max} 1362 (m), 1384 (m), 1456 (m), 1520 (s), 1548 (s), 2907 (m), 2952 (m); GC-MS R_t 3.74 + 3.69 min, *m/z* 151 $[M - NO_2]^+$; ASAP-HRMS *m/z* found $[M+H]^+$ 198.1483, $C_{11}H_{20}NO_2$ requires 198.1494 (Δ = 5.6 ppm).

4.6. 5,5-Dimethyl-1-(nitromethyl)cyclohex-1-ene **39a** and 3,3-dimethyl-1-(nitromethyl)cyclohex-1-ene **39b**

Obtained by reaction of nitromethane with 3,3-dimethylcyclohexanone as a pale yellow liquid (55.0 mmol scale, 8.80 g, 94%), isolated by SiO_2 column chromatography (hexane:EtOAc, 98:2) as a mixture of double bond isomers (3.0:1, **39a**:**39b**), R_f (9:1, hexane:EtOAc). For **39a**: 0.7. ^1H NMR (700 MHz, $CDCl_3$) δ 5.91–5.88 (m, 1H), 4.79 (s, 2H), 2.16–2.12 (m, 2H), 1.84 (s, 2H), 1.34 (t, J = 6.4 Hz, 2H), 0.92 (s, 6H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ 132.0, 127.4, 82.7, 40.3, 34.2, 29.0, 27.9, 23.3 ppm; FT-IR ν_{max} 665 (w), 1367 (m), 1428 (w), 1550 (s), 2920 (w, br); GC-MS R_t 3.42 min, *m/z* 123 $[M - NO_2]^+$; ASAP-HRMS *m/z* found $[M+H]^+$ 170.1186, $C_9H_{16}NO_2$ requires 170.1181 (Δ = 2.9 ppm). For **39b**: 0.7.

^{1}H NMR (700 MHz, $CDCl_3$) δ 5.64–5.61 (m, 1H), 4.77 (s, 2H), 2.01 (t, J = 6.3 Hz, 2H), 1.70–1.65 (m, 2H), 1.43–1.40 (m, 2H), 1.00 (s, 6H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ 143.0, 126.2, 82.8, 36.2, 32.3, 29.3, 26.6, 19.3 ppm; FT-IR ν_{max} 665 (w), 1367 (m), 1428 (w), 1550 (s), 2920 (w, br); GC-MS R_t 3.37 min, *m/z* 123 $[M - NO_2]^+$; ASAP-HRMS *m/z* found $[M+H]^+$ 170.1186, $C_9H_{16}NO_2$ requires 170.1181 (Δ = 2.9 ppm).

4.7. 3,5,5-Trimethyl-1-(nitromethyl)cyclohex-1-ene **40a** and 3,3,5-trimethyl-1-(nitromethyl)cyclohex-1-ene **40b**

Obtained by reaction of nitromethane with 5-methyl-3,3-dimethylcyclohexanone as a clourless liquid (102.7 mmol scale, 18.8 g, 65%, **40a**:**40b**, 1:1), isolated by a vacuum distillation (b.p. 54–57 °C/0.6 mbar). Signal not reported are those that were overlapping. For **40a**: ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.73 (tt, J = 2.3, 1.2 Hz, 1H), 4.80 (d, J = 1.1 Hz, 2H), 2.34–2.26 (m, 1H), 1.91 (dt, J = 16.6, 3.4 Hz, 1H), 1.73 (dt, J = 17.0, 2.3 Hz, 1H), 1.49–1.45 (m, 2H), 1.02 (d, J = 7.8 Hz, 5H), 1.00 (s, 3H), 0.87 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 137.96, 126.86, 82.81, 44.13, 40.43, 31.66, 30.17, 28.97, 25.20, 21.07. FT-IR ν_{max} (mixture) 643 (m), 1199 (w), 1371 (m), 1428 (w), 1457 (w), 1550 (s), 2869 (w), 2907 (w), 2955 (w); GC-MS R_t 3.69 min, *m/z* 137.2 $[M - NO_2]^+$; ASAP-HRMS *m/z* found $[M+H]^+$ 184.1334, $C_{10}H_{18}NO_2$ requires 184.1338 (Δ = −2.2 ppm). For **40b**: Signal not reported are those that were overlapping. ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.62 (dt, J = 2.4, 1.3 Hz, 1H), 4.78 (dd, J = 2.3, 1.2 Hz, 2H), 2.10–2.03 (m, 1H), 1.85–1.76 (m, 1H), 1.64 (ddd, J = 17.0, 11.0, 2.5 Hz, 1H), 1.45 (ddd, J = 5.8, 2.2, 1.1 Hz, 1H), 1.02 (s, 3H), 0.98 (s, 3H), 0.97 (d, J = 6.5 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 142.92, 126.06, 82.71, 45.42, 35.50, 33.71, 30.77, 28.64, 26.04, 22.03. FT-IR ν_{max} (mixture) 643 (m), 1199 (w), 1371 (m), 1428 (w), 1457 (w), 1550 (s), 2869 (w), 2907 (w), 2955 (w); GC-MS R_t 3.62 min, *m/z* 137.2 $[M - NO_2]^+$; ASAP-HRMS *m/z* found $[M+H]^+$ 184.1334, $C_{10}H_{18}NO_2$ requires 184.1338 (Δ = −2.2 ppm).

4.8. 1-(Nitromethyl)cyclohept-1-ene [24] **41**

Obtained by reaction of nitromethane with cycloheptanone as a yellow liquid (50.0 mmol scale, 5.83 g, 75%), isolated by SiO_2 column chromatography (hexane:EtOAc, 95:5), R_f (8:2, hexane:EtOAc) 0.6. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (t, J = 6.4 Hz, 1H), 4.84 (d, J = 0.8 Hz, 2H), 2.34–2.16 (m, 4H), 1.84–1.73 (m, 2H), 1.65–1.50 (m, 4H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.4, 134.4, 84.4, 31.9, 31.3, 28.6, 26.3, 26.2 ppm; FT-IR ν_{max} 643 (m), 848 (w), 1306 (w), 1370 (m), 1447 (w), 1547 (s), 2851 (w), 2923 (m); GC-MS R_t 3.50 min, *m/z* 109 $[M - NO_2]^+$.

4.9. 6-Methyl-1-(nitromethyl)-3-(prop-1-en-2-yl)cyclohex-1-ene **42a** and 1-methyl-2-(nitromethyl)-4-(prop-1-en-2-yl)cyclohex-1-ene **42b**

Obtained by reaction of nitromethane with dihydrocarvone as a pale yellow liquid (50.0 mmol scale, 8.65 g, 89%), purified by SiO_2 column chromatography (hexane:EtOAc, 95:5) as a mixture of diastereoisomers **42a** along with the double bond isomer, **42b** (**42a**:**42b** = 3.3:1.0), R_f (8:2, hexane:EtOAc). For **42a**: 0.6. ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.80 (s, 1H), 5.04–4.98 (m, 1H), 4.80 (m, 1H), 4.79–4.74 (m, 1H), 4.69 (m, 1H), 2.85–2.77 (m, 1H), 2.33–2.27 (m, 1H), 1.89–1.67 (m, 2 × 1H), 1.74–1.71 (m, 3H), 1.59–1.42 (m, 1 + 0.5H), 1.32 (m, 0.5H), 1.06 (dd, J = 7.1, 3.7 Hz, 3H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ (147.6 + 147.5), (136.8 + 136.3), (133.6 + 133.4), (111.5 + 111.2), (80.6 + 80.4), (43.7 + 43.3), (30.5 + 30.0), (29.5 + 28.8), (25.0 + 23.5), (21.1 + 21.0), (19.0 + 18.9) ppm. FT-IR ν_{max} 892 (m), 1372 (m), 1428 (w), 1549 (s), 1644 (w), 2936 (w); GC-MS R_t 3.94 + 3.96 min, *m/z* 149 $[M - NO_2]^+$; ASAP-HRMS *m/z* found $[M+H]^+$ 196.1326, $C_{11}H_{18}NO_2$ requires 196.1338 (Δ = 6.1 ppm). For **42b**: 0.6. ^{1}H NMR (700 MHz, $CDCl_3$) δ 4.98–4.89 (dd, J = 41.8, 6.0 Hz, 2H), 4.73 (m, 1H), 4.70–4.69 (m, 1H), 2.22–2.02 (m, 5H), 1.81 (m, 1H), 1.78 (s, 3H), 1.73 (s, 3H), 1.46–1.42 (m, 1H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ 148.8, 138.5, 120.4, 109.1, 78.0, 41.1, 34.0, 32.5, 27.3, 20.7, 19.2 ppm; FT-IR ν_{max} 892 (m), 1372 (m), 1428 (w), 1549 (s), 1644 (w), 2936 (w); GC-MS R_t 4.09 min, *m/z* 149 $[M - NO_2]^+$; ASAP-HRMS *m/z* found $[M+H]^+$ 196.1326, $C_{11}H_{18}NO_2$ requires 196.1338 (Δ = 6.1 ppm).

4.10. General Procedure for the Nef reaction of nitro olefins

The nitro olefin (82.0 mmol) was dissolved in EtOH (140 mL) and NaOH (4.10 g, 1.25 equiv.) was added, the mixture was stirred at r.t. for 30 min after which time the nitronate salt had precipitated. The suspension was cooled to 0 °C and a solution of H_2SO_4 (8.75 mL, 2 equiv.) in H_2O (41 mL) was added. After 1 h of stirring at 0 °C the reaction was allowed to warm to r.t. and stirred for a further 2 h. The EtOH was then removed under reduced pressure and the residue was neutralised with aqueous NaOH. The product was then extracted with DCM (3 × 60 mL) and the combined organic layers were concentrated under reduced pressure. Pure product was obtained according to the indicated method.

4.11. 1-(5,5-Dimethylcyclohex-1-en-1-yl)ethanone **5a** and 1-(3,3-dimethylcyclohex-1-en-1-yl)ethanone **5b**

Obtained from **7** (82.0 mmol scale, 8.11 g, 65%, **5a**:**5b** = 5.4:1), isolated by vacuum distillation (b.p. 85–95 °C/9 mbar). For **5a**: ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.87 (m, 1H), 2.28 (m(obscured), 2H), 2.28 (s, 3H), 2.01 (q, J = 2.2 Hz, 2H), 1.34 (t, J = 6.4 Hz, 2H), 0.90 (s, 6H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ 199.5, 139.7, 138.7, 36.4, 34.2, 28.5, 28.0, 25.3, 24.1 ppm; GC-MS R_t 3.32 min, *m/z* 152 $[M]^+$, 109 $[M - Ac]^+$; ASAP-HRMS *m/z* found $[M+H]^+$ 153.1281, $C_{10}H_{17}O$ requires 153.1279 (Δ = 1.3 ppm). For **5b**: ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.53 (t, J = 1.7 Hz, 1H), 2.27 (s, 3H), 2.15 (td, J = 6.3, 1.7 Hz, 2H), 1.61 (m, 2H), 1.43 (m, 2H), 1.06 (s, 6H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ 199.9, 149.7, 137.3, 36.3, 32.7, 29.1, 25.2, 23.1, 19.1 ppm; GC-MS R_t 3.24 min, *m/z* 152 $[M]^+$, 109 $[M - Ac]^+$; ASAP-HRMS *m/z* found $[M+H]^+$ 153.1281, $C_{10}H_{17}O$ requires 153.1279 (Δ = 1.3 ppm).

4.12. 1-(Cyclohept-1-en-1-yl)ethanone [36] **43**

Obtained from **32** as a colourless liquid (10.0 mmol scale, 584 mg, 42%), isolated by SiO_2 column chromatography (hexane:EtOAc, 95:5), R_f (8:2, hexane:EtOAc) 0.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (t, J = 6.7 Hz, 1H), 2.50–2.45 (m, 2H), 2.37–2.30 (m, 2H), 2.28 (s, 3H), 1.80–1.73 (m, 2H), 1.58–1.51 (m, 2H), 1.47–1.40 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.1, 146.5, 145.5, 32.2, 29.1, 26.1, 25.8, 25.3, 25.2 ppm; FT-IR ν_{max} 857 (m), 985 (m), 1198 (m), 1252 (m), 1280 (m), 1350 (m), 1449 (m), 1662 (s), 2850 (m), 2919 (m); GC-MS R_t 3.18 min, *m/z* 138 $[M]^+$, 95 $[M - Ac]^+$.

4.13. 1-(Cyclooct-1-en-1-yl)ethanone [37] **44**

Obtained from **34** as a colourless liquid (5.80 mmol scale, 417 mg, 47%), isolated by SiO_2 column chromatography (hexane:EtOAc, 95:5), R_f (8:2, hexane:EtOAc) 0.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (t, J = 8.3 Hz, 1H), 2.49–2.44 (m, 2H), 2.39–2.33 (m, 2H), 2.33 (s, 3H), 1.69–1.62 (m, 2H), 1.59–1.41 (m, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.1, 143.5, 143.1, 29.2, 29.1, 27.5, 26.5, 26.1, 25.4, 23.4 ppm; FT-IR ν_{max} 755 (m), 1199 (m), 1284 (m), 1350 (w), 1383 (w), 1653 (m), 1662 (s), 2852 (m), 2922 (m); GC-MS R_t 3.58 min, *m/z* 152 $[M]^+$.

4.14. 1-(3,5,5-Trimethylcyclohex-1-en-1-yl)ethanone **45a** and 1-(3,3,5-trimethylcyclohex-1-en-1-yl)ethanone **45b**

Obtained from **36** as a colourless liquid (9.29 mmol scale, 695 mg, 54%, **45a**:**45b** = 1.9:1), isolated by SiO_2 column chromatography (hexane:EtOAc, 95:5), R_f (8:2, hexane:EtOAc). For **45a**: 0.6. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.66 (m, 1H), 2.44–2.38 (m, 1H), 2.29 (s, 3H), 2.19–2.13 (m, 1H), 1.84–1.78 (m, 1H), 1.50–1.45 (m, 1H), 1.09 (d, J = 7.2 Hz, 3H), 1.00 (s, 3H), 0.97–0.92 (m, 1H), 0.80 (s, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.8, 144.9, 137.8, 43.9, 36.5, 31.7, 29.5, 29.5, 25.4, 25.1, 20.7 ppm; FT-IR ν_{max} (mixture) 755 (m), 1248 (m), 1364 (w), 1456 (w), 1635 (m), 1665 (s), 2870 (w), 2954 (m); GC-MS R_t 3.34 min, *m/z* 166 $[M]^+$; ASAP-HRMS *m/z* found $[M+H]^+$ 167.1425, $C_{11}H_{19}O$ requires 167.1436 (Δ = 6.6 ppm). For **45b**: 0.6. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.52 (m, 1H), 2.50–2.44 (m, 1H), 2.27 (s, 3H), 1.71–1.63 (m, 1H), 1.56–1.51 (m, 1H), 1.51–1.48 (m, 1H), 1.07 (s, 3H), 1.05 (s, 3H), 1.02 (m, 1H), 0.99 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.8, 149.5, 137.0, 45.3, 34.1, 31.8, 30.4, 28.4, 25.6, 25.3, 22.0 ppm; FT-IR ν_{max} (mixture) 755 (m), 1248 (m), 1364 (w), 1456 (w), 1635 (m), 1665 (s), 2870 (w), 2954 (m); GC-MS R_t 3.13 min, *m/z* 166 $[M]^+$; ASAP-HRMS *m/z* found $[M+H]^+$ 167.1425, $C_{11}H_{19}O$ requires 167.1436 (Δ = 6.6 ppm).

4.15. General Procedure for the synthesis of **7** from the intermediate enamine **8**

To a solution of ketone **4** (3.46 mL, 25 mmol, 1 equiv.) in toluene (18 mL) placed on a 25 mL one-necked round bottom flask equipped with a Dean-Stark apparatus, *N,N*-diethylethylendiamine (3.51 mL, 25 mmol, 1 equiv.) was added in one portion. The reaction mixture was heated under reflux for 24 h or until complete disappearance of the starting material in GC-MS (EI). The mixture was then allowed to cool at room temperature and concentrated under vacuum. The mixture was then employed for the second step. The mixture was then diluted with toluene (17 mL) and nitroethane (1.96 mL, 27.5 mmol, 1.1 equiv.) was added in one portion to the mixture. The mixture was monitored via GC-MS for 24 h at room temperature and 48 h under reflux.

4.16. 2-((3,3-dimethylcyclohexylidene)amino)-N,N-diethylethan-1-amine **8**

Obtained as a yellow liquid. Characterised as a mixture roughly 2:2:1 of **8**:**10**:**2**. Two isomers were detected, however we were unable to identify their absolute configuration. Major isomer: ^{1}H NMR (599 MHz, $CDCl_3$) δ 3.41–3.34 (m, 2H), 2.70–2.63 (m, 2H), 2.61–2.54 (m, 4H), 2.22–2.16 (m, 2H), 2.09 (s, 2H), 1.75–1.68 (m, 2H), 1.47–1.41 (m, 2H), 1.05–1.01 (m, 6H), 0.91 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.28, 54.08, 49.09, 47.65, 42.20, 39.51, 34.96, 28.65, 23.57, 11.88. Minor isomer: ^{1}H NMR (599 MHz, $CDCl_3$) δ 3.46–3.41 (m, 2H), 2.70–2.64 (m, 2H), 2.60–2.54 (m, 4H), 2.22–2.17 (m, 2H), 2.05 (s, 2H), 1.67–1.60 (m, 2H), 1.47–1.42 (m, 2H), 1.05–1.01 (m, 6H), 0.90 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.93, 54.03, 52.84, 49.03, 47.57, 39.11, 34.65, 28.46, 28.15, 22.68, 11.93. FT-IR ν_{max} (mixture) 729 (w), 1068 (m), 1367 (m), 1384 (m), 1459 (m), 1662 (m), 1711 (m), 2811 (m), 2869 (m), 2930 (s), 2961 (s); GC-MS R_t 4.14 min, *m/z* 224 $[M]^+$; ASAP-HRMS *m/z* found $[M+H]^+$ 225.2325, $C_{14}H_{29}N_2$ requires 225.2331 (Δ = −2.7 ppm).

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Guido Gambacorta and James S. Sharley reports financial support was provided by International Flavours & Fragrances Inc. Ian R. Baxendale has patent #P201531856 issued to International Flavours & Fragrances Inc. Ian R. Baxendale has patent #USP201762483014 issued to International Flavours & Fragrances Inc.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2022.133058.

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