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Tetrahedron 62 (2006) 410–421
Tetrahedron

The α-effect in iminium ion catalysis

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Received 19 May 2005; revised 4 July 2005; accepted 31 August 2005

Available online 23 September 2005

Abstract—The α-effect can be used as an effective means to promote iminium ion catalysed transformations, providing acyclic scaffolds to aid in catalyst design. A thorough investigation of the structure–activity relationship of the catalyst architecture reveals optimal substituents of a disubstituted carbamate and a secondary alkyl group around a hydrazine scaffold. Molecular modelling investigations provide a mechanistic rationale to the results observed.
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1. Introduction

The use of secondary amines to accelerate traditional organic transformations through LUMO-lowering has recently caught the imagination of the synthetic community. Although simple in both design and mechanistic rationale, the catalysts reported to be effective in these reactions are having a major impact on contemporary organic synthesis and the way in which chemists think about preparing molecules, offering practically simple ways to prepare complex targets. The scope and number of transformations are continuing to expand[1] and now include Diels–Alder cycloaddition,[2] [3+2] cycloadditions,[3] conjugate addition reactions of pyrroles,[4] indoles,[5] anilines,[6] nitro alkanes[7] and hydride,[8] Mukaiyama–Michael reactions,[9] cyclopropanations[10] and [4+3] cycloaddition reactions.[11]

We have recently become interested in the design and synthesis of novel catalyst architectures that will allow for the lowering of catalyst loading within these reactions.[12] Based on the original proposal by MacMillan that the rate determining step of these processes is iminium ion formation,[2b] we believed that increasing the nucleophilicity of secondary amine catalysts may well allow us to meet our original goals. To this end, we recently reported that the α-effect can be used as an effective platform with which to accelerate the iminium ion catalysed Diels–Alder reaction between a variety of dienes and dienophiles, providing novel acyclic structures for future catalyst design.[12] Herein, we provide a full report on our synthetic and theoretical investigations to gain a greater understanding of iminium ion formation and the factors controlling this fascinating and vibrant area of organocatalysis.

The most effective catalysts in both iminium ion and enamine catalysis share a common structure of a secondary amine embedded within a five-membered ring (Fig. 1).[13] We rationalized that this enhances the nucleophilicity of the secondary amine, allowing effective formation of iminium ions, and postulate that such an increase in nucleophilicity could also be achieved by exploiting the α-effect.

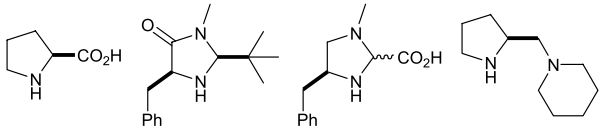

Figure 1. Effective secondary amine catalysts.

The α-effect is defined as a positive deviation of an α-nucleophile (a nucleophile bearing an unshared pair of electrons on an atom adjacent to the nucleophilic site) from a Brønsted-type plot of log K_{nuc} versus pK_a constructed for a series of normal related nucleophiles.[14] More generally, it is the influence of an atom bearing a lone pair of electrons on the reactivity at the adjacent site. The enhanced reactivity of α-nucleophiles was first reported in 1947, and the phenomenon was later given its name by Edwards and Pearson in 1962.[15] The origins of the observation are of some debate and several possible explanations have been offered. These include the ground state of the nucleophile

Keywords: α-Effect; Iminium ion catalysis; DFT calculations.
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0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.08.110

being destabilized by repulsion between the adjacent pairs of electrons,[16] stabilization of the transition state by the extra pair of electrons,[17] and the adjacent pair of electrons reducing solvation of the nucleophile.[18] It is notable that this phenomenon is generally believed to have several origins, and that the nature of the individual effects and the exact conditions under which they are operative have not been unambiguously identified. Nonetheless, the effect is genuine and has been invoked to explain chemical reactivity.[19] Within this paper we report our results on the use of the α-effect in the acceleration of the Diels–Alder reaction with acyclic secondary amine containing scaffolds from both a theoretical and practical basis.

2. Results and discussion

In order to establish if the α-effect provided an effective platform for iminium ion catalysis we conducted a series of experiments in order to compare the aminocatalytic activity of a pyrrolidine-type system, an acyclic secondary amine and an acyclic secondary amine with an α-heteroatom. We examined four commercially available acyclic secondary amines **1**–**4**, and compared their reactivity to proline methyl ester **5**, which has previously been reported to be effective in catalyzing the Diels–Alder reaction and allows direct comparison to the level of activity attainable with cyclic amine systems (Fig. 2). The results obtained are outlined in Table 1. We initially adopted standard reaction conditions

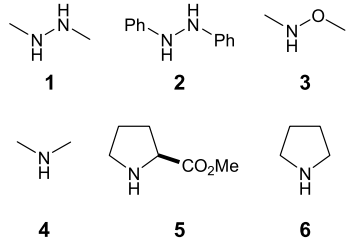
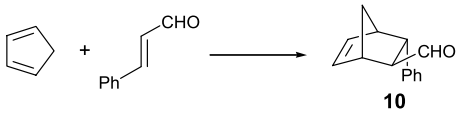


Figure 2. Commercially available amines.

Table 1. Catalysis of the Diels–Alder reaction with commercially available amines[a]



7 **8** **10** + *endo* isomer **9**

Entry	Catalyst	Time (h)	*endo*:*exo*[b]	Yield (%)
1	None	48	64:36	7
2[c]	NEt_3·HCl	48	63:37	7
3[c]	**4**·HCl	48	38:62	22
4[c]	**3**·HCl	48	34:66	65
5[c]	**3**·HCl	72	34:66	80
6[d]	**1**·HCl	72	68:32	48
7[d]	**2**·HCl	48	38:62	33
8[c]	**5**·HCl	48	29:71	85
9[c]	**6**·HCl	24	32:68	9

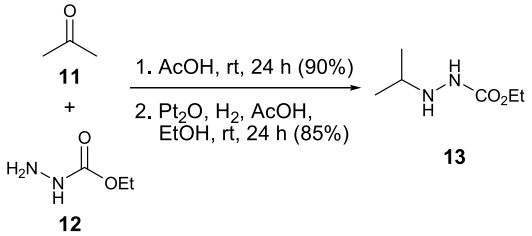
[a] Carried out in methanol/water 19:1 at room temperature with 10 mol% catalyst.
[b] Ratio determined by ^{1}H NMR of crude reaction mixture.
[c] Catalyst used as HCl salt.
[d] Catalyst used as bis-HCl salt.

of 10 mol% catalyst, in a methanol/water mixture 19:1 and examined the Diels–Alder reaction between *trans*-cinnamaldehyde **8** and cyclopentadiene **7**.

In the absence of any catalyst, or in the presence of only the protonic acid co-catalyst, the reaction proceeded to just 7% completion in 48 h with the *endo*-isomer predominating (Table 1, entries 1 and 2). Observations by MacMillan and others suggest that the *exo*-isomer of the product **10** predominates when iminium ion catalysis is occurring, as was observed with the proline methyl ester **5** (Table 1, entry 8). The use of *N*,*N*-dimethylamine hydrochloride as the catalyst afforded a 22% yield of adduct **8** with the *exo*-isomer predominating (Table 1, entry 3), suggesting that iminium ion catalysis was occurring, albeit sluggishly. Significantly, the use of *N*,*O*-dimethylhydroxylamine hydrochloride as the catalyst led to a significant increase in the yield observed for the reaction (Table 1, entry 4), which suggested that it would indeed be possible to accelerate these reactions by taking advantage of the α-effect. Extension of the reaction time further did allow for the increased formation of the Diels–Alder adduct to 80% (Table 1, entry 5). Changing to a nitrogen based α-heteroatom with the commercially available hydrazines—*N*,*N*′-dimethylhydrazine (Table 1, entry 6) and *N*,*N*′-diphenylhydrazine (Table 1, entry 7)—showed lower yield for the transformation but did show a marked increase from *N*,*N*-dimethylamine.

Having shown that the α-effect could be used to accelerate these iminium ion catalysed transformations, we then sought to further develop the catalyst structure to enhance the rate of the catalytic cycle to match or increase those displayed by cyclic secondary amines. In the search for further modification of the catalyst architecture we made the observation that pyrrolidine hydrochloride **6**·HCl was ineffective in catalysing the Diels–Alder reaction between cyclopentadiene and cinnamaldehyde (Table 1, entry 9) when compared to proline methyl ester hydrochloride **5**·HCl (Table 1, entry 8). This suggested that a carbonyl-group β- to the nucleophilic nitrogen was also involved within the iminium ion formation. We, therefore, targeted a series of catalysts that incorporated both the α-heteroatom and a carbonyl functionality in the β-position to discover if these had further effect on the reactivity of these secondary amines.

Our initial target was the ethyl carbazate derived system **13**, easily prepared in two-steps from commercially available starting materials via a condensation–reduction protocol in 77% overall yield (Scheme 1). Evaluation of the activity of **13**·HCl under standard conditions (10 mol% cat, MeOH/



Scheme 1. Synthesis of catalyst **13**.

H_2O 19:1, room temperature, 48 h) gave the Diels–Alder adducts in 93% isolated yield (*endo*:*exo* ratio 34:66). Thus, introduction of a carbonyl group β- to the reactive centre does indeed markedly increase catalytic activity, providing a new molecular scaffold for catalyst design and development.

Having established a positive effect on activity, we set about optimising our catalyst structure. We examined five variables within our system (Fig. 3) to provide further insight into the catalysts' structure–activity relationship (SAR), with the ultimate goal of designing a second generation catalyst capable of accelerating these reactions at lower catalyst loading and reaction times.

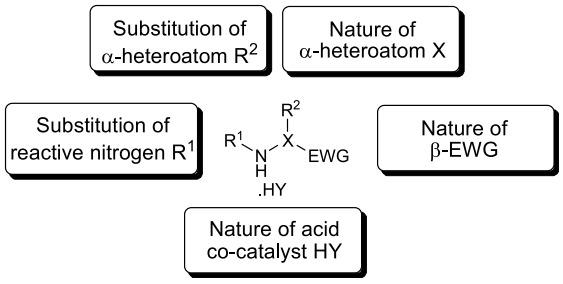


Figure 3. Variables altered for SAR of catalyst.

SAR studies on the catalyst architecture began by varying substitution of the reactive nitrogen centre R^1 with the amines **13**, **14** and **15** (Fig. 4) (see Section 5 for full details of catalyst synthesis). These compounds contained primary, secondary and tertiary substitution directly adjacent to the reactive nitrogen.

The results obtained for these catalysts are outlined in Table 2. The optimal substitution pattern proved to be a secondary centre directly attached to the nucleophilic

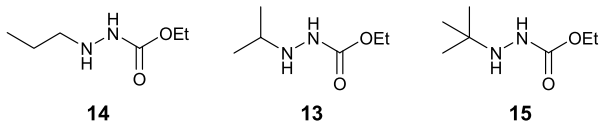


Figure 4. Substitution of reactive nitrogen R^1.

nitrogen (entry 2, **13**·HCl, 90%) with both primary (entry 1, **14**·HCl, 75%) and tertiary (entry 3, **15**·HCl, 32%) substitution providing significantly lower yields of product. Reducing the reaction time to just 6 h with **13**·HCl (entry 4) gave the product in 74% isolated yield, and performing the reaction in methanol led to a further dramatic increase in the amount of isolated product (entry 5, 90%).

In order to ascertain whether the enhanced catalyst activity observed was due to the α-heteroatom, the β-carbonyl, or both, we prepared the glycine ethyl ester derived catalyst **16**.[20] The catalysts **17**·HCl[21] and **18**·HCl,[22] containing an oxygen α-heteroatom and a β-carbonyl, were also synthesised allowing us to compare the effects of carbon, nitrogen and oxygen in the α-position. With oxygen as the α-heteroatom the reactions were sluggish (Table 2, entries 8–10) providing the adducts **9** and **10** in <28% isolated yield after 6 h. Examination of a range of solvents and reaction conditions with these catalysts showed significantly lower conversions, confirming that methanol appears to be the most appropriate solvent for this class of transformation. The glycine ethyl ester derived catalyst **16**·HCl (Table 2, entries 6 and 7) showed that the α-heteroatom is essential for effective reactivity of our systems with the products only being isolated in up to 5% yield. This set of results, therefore, suggested that a synergistic effect of both the α-heteroatom and the β-carbonyl was responsible for the reactivity within the acyclic catalysts used (Fig. 5).

Curiosity into what lay behind the need for an electron

Table 2. Iminium ion catalysed SAR studies[a]

Entry	Catalyst	Solvent	Time (h)	*endo*:*exo*[b]	Yield (%)
1	**14**·HCl	MeOH[c]	24	35:65	75
2	**13**·HCl	MeOH[c]	24	37:63	90
3	**15**·HCl	MeOH[c]	24	35:65	32
4	**13**·HCl	MeOH[c]	6	34:66	74
5	**13**·HCl	MeOH	6	33:67	90
6	**16**·HCl	MeOH	6	35:65	5
7	**16**·HCl	MeOH[c]	6	34:66	3
8	**17**·HCl	MeOH	6	35:65	28
9	**17**·HCl	MeOH[c]	6	34:66	13
10	**18**·HCl	MeOH	6	50:50	12
11	**19**·HCl	MeOH	6	33:67	82
12	**20**·HCl	MeOH	6	33:67	86
13	**21**·HCl	MeOH	24	42:58	69
14	**19**·TFA	MeOH	24	33:67	81
15	**19**·$MeSO_3H$	MeOH	48	36:64	74
16	**19**·$PhCO_2H$	MeOH	48	47:53	10
17	**19**·HBr	MeOH	24	35:65	97
18	**19**·HI	MeOH	24	32:68	98
19	**19**·HPF_6	MeOH	24	30:70	98
20	**22**·HCl	MeOH	6	35:65	98
21	**23**·HCl	MeOH	6	35:65	89
22	**24**·HCl	MeOH	6	34:66	34
23	**24**·HCl	MeOH	24	35:65	70

[a] Diels–Alder reaction between cyclopentadiene and cinnamaldehyde at room temperature with 10 mol% catalyst.
[b] Ratio determined by ^1H NMR of crude reaction mixture.
[c] Water (5%) added by volume.

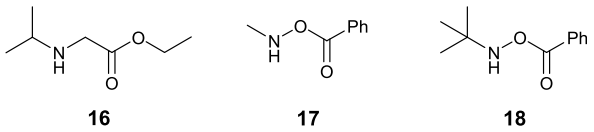


Figure 5. Alteration of α-heteroatom X.

withdrawing group on the α-heteroatom, led us to synthesize a further family of compounds varying the nature of this group (Fig. 6). The amides **19** and **20** and the sulfonamide **21** were prepared to measure their influence when compared to the carbamate derivative **13**.

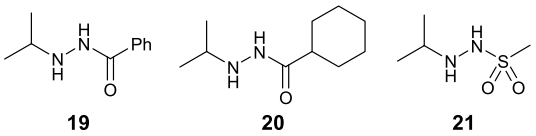


Figure 6. Modification of EWG.

Each of these hydrazine derivatives appeared to be effective catalysts, although they did not perform as well as the carbamate **13**·HCl. With the amides **19** and **20** the Diels–Alder adducts were isolated in 82 and 86% yields, respectively, (Table 2, entries 11 and 12) after just 6 h. Although the sulfonamide performed well when compared to the catalysts without an electron withdrawing group on the α-heteroatom, it still returned significantly less product when compared to the carbamates and amides, with an extended reaction time of 24 h needed in order to obtain a respectable yield (entry 13).

The next variable we addressed was the nature of acid co-catalyst HX. Our initial work revealed that as the pK_a of the acid co-catalyst decreased, the length of time necessary for the reaction to proceed increased (Table 2, entries 14–16). Interestingly, however, we found that with benzoic acid as the co-catalyst, the *endo*:*exo* ratio of the products was significantly different to the usual 2:1 ratio observed with most other reactions (entry 16). An interesting phenomenon of these iminium ion catalysed Diels–Alder reactions is that with α,β-unsaturated aldehydes the *exo*-isomer predominates, a complementary and potentially synthetically significant alternative to the Lewis acid catalysed process, which tends to give the *endo*-adduct preferentially. To check the effect of counter anion size on the geometry of the reaction products, we prepared the ·HBr and ·HI salts of **19**, and compared the diastereomeric ratio of the Diels–Alder adducts (Table 2, entries 17–19). However, in all cases the ratio of the *endo* and *exo* isomers was 2:1, even for the non-coordinating anion PF_6^-, that is, the ratio observed for most of the systems used within this investigation (Fig. 7).

Finally, the effect of the substituent on the α-heteroatom was examined by preparing the methyl substituted carbamate **22** and amide **23** as well as the more sterically encumbered *tert*-butyl carbamate **24**. As in the substitution of the reactive nitrogen, catalyst reactivity is sensitive to steric encumbrance around the α-heteroatom, the *tert*-butyl derivative requiring 24 h in order to reach 70% conversion for the reaction (Table 2, entries 22 and 23). However, we were delighted to discover that with a methyl substituent on the α-heteroatom, an increase in the amount of isolated product was observed. This was the case for both the carbamate (entry 20) and the amide (entry 21) derivatives leading to our most effective catalyst system observed to date.

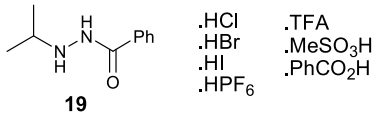


Figure 7. Nature of the acid co-catalyst HX.

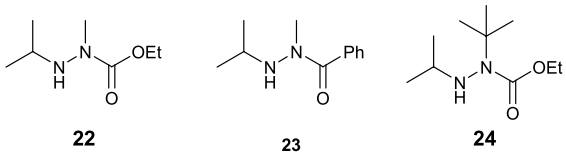


Figure 8. Substitution of α-heteroatom R^2.

3. Theoretical calculations

Along with experimental work, theoretical calculations were carried out on the formation of iminium ions in order to provide a basis for further catalyst design as well as aid in interpretation of our synthetic results. We aimed to establish a mechanism for the formation of the active species, and hence to understand the effect of functional groups surrounding the reactive nitrogen centre on reactivity, ultimately with the aim of developing a predictive scale for amine reactivity (Fig. 8).

Initially, we constructed a realistic model of the reaction conditions used in the practical work above, namely an ensemble including the hydrochloride salt of dimethylamine, acrolein as a model electrophile, and a single explicit water molecule, all enclosed within a spherical dielectric approximation of methanol solvation. Optimization of this

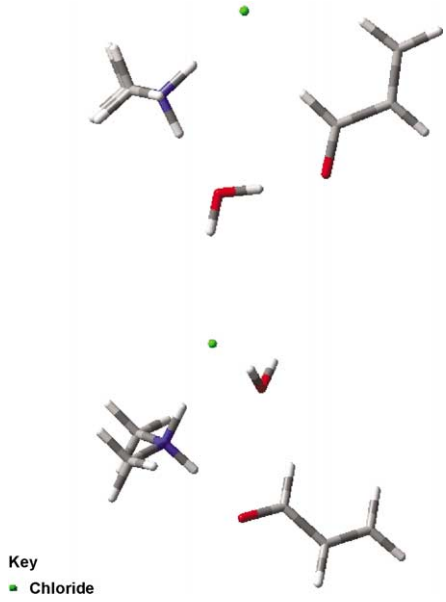


Figure 9. Two optimized reaction geometries.

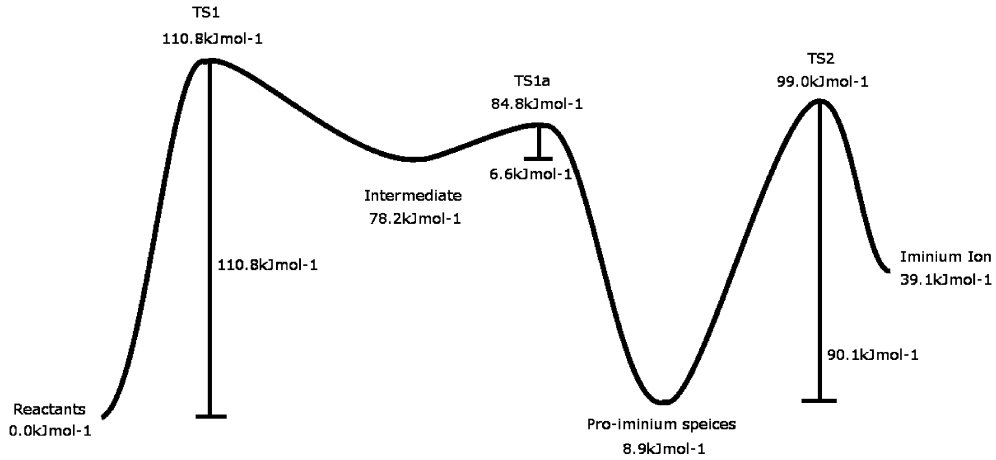
Figure 10. (a) Optimised geometry of 'pro-iminium' and (b) iminium ion products.

reaction mixture from varying starting points revealed a number of stable conformations of very similar energy, and with negligible barriers to inter-conversion of each. Figure 9 shows two such starting conformations, which differ in energy by just 2.9 kJ mol^{-1}. Addition of further explicit water molecules to this ensemble led to the chloride occupying a comparable position as shown in Figure 9, that is forming a close contact with the protonated amine (Cl$\cdots$H = 1.9–2.1 Å), with minor changes in other geometrical details.

A second stable structure is found, ca. 10 kJ mol^{-1} higher in energy than the reactant complex, in which the N–C bond has formed and a proton transferred from amine to carbonyl (see Fig. 10a). Here again, the chloride ion is closely associated with the protonated amine centre, with the water hydrogen bonded to both Cl^- and OH. The N–C bond length in this 'pro-iminium ion' species is 1.56 Å, that is, somewhat longer than a typical N–C single bond (cf. 1.46 Å in dimethylamine). A third low energy minimum, corresponding to the iminium ion product after elimination of water from the pro-iminium species, was located ca. 40 kJ mol^{-1} above the reactants. This product contains the expected N=C double bond, as evidenced by the planar disposition of groups about N, and the N=C length of 1.31 Å (Fig. 10b).

Transition states connecting these minima were located using the QST3 approach in G03, specifying reactant and product structures along with a guess of a transition state obtained from relaxed potential energy surface (PES) scans. A transition state linking the reactant and pro-iminium product (denoted TS1) was located in this manner, with a single imaginary frequency of 139.9*i* cm^{-1}. TS1 is 110 kJ mol^{-1} higher in energy than the reactant complex, a sizeable barrier due largely to transfer of a proton from the amine to chloride, accompanied by small re-orientation of acrolein and water. A second transition state, TS2, accompanies the elimination of water from this initial product, again essentially a proton transfer from amine to oxygen, mediated by the presence of chloride. TS2, with imaginary frequency 405.6*i* cm^{-1}, is ca. 90 kJ mol^{-1} above the pro-iminium species. Thus, the barrier associated with initial formation of the N–C bond is rather higher in energy than subsequent elimination of water to the final product.

In order to check whether these transition states do indeed link the expected reactants and products, we perturbed each TS both forwards and backwards along the imaginary eigenvalue, then carried out geometry optimisation. This process resulted in previously located minima from TS2, as shown in Scheme 2. Perturbing backwards from TS1 gave the reactant complex as expected, but forward from TS1 resulted in a new minimum structure, confirmed as such via harmonic frequency calculation, just 32.6 kJ mol^{-1} below TS1. This 'intermediate' structure differs from the TS only by relative rotation of the various moieties, with both acrolein and HCl rotated towards their orientation in the pro-iminium product.



Scheme 2. Reaction profile of dimethylamine hydrochloride and acrolein.

A third transition state, TS1a, separates this intermediate from the pro-iminium structure, with a barrier of just 7 kJ mol^{-1}, that is, essentially negligible when compared to the barriers associated with TS1 and TS2. The structure of this transition state is interesting, as it appears the water molecule mediates proton transfer from H–Cl to oxygen, acting as a 'proton shuttle'. Thus, it appears that only this step requires the presence of an explicit water molecule, and hence explains the frequent requirement for trace water in the reaction mixture.

In order to test this choice of theoretical method, we re-calculated this potential energy surface (PES) using both a larger basis set, 6-311++G (2d,p), and a density functional, mPW1PW91, reported to give improved barriers for model organic reactions.[26] In both cases, neither structures nor relative energies of stationary points differed significantly from those reported above. The larger basis set reduced barriers at TS1 and TS2 by 6.8 and 0.8 kJ mol^{-1}, respectively, while the alternative functional increased these by 4.8 and 2.0 kJ mol^{-1}, respectively.

Therefore, we have confidence in our B3LYP/6-31+G(d) calculations that indicate a three-step, rather than a two-step mechanism for formation of an iminium ion from dimethylamine hydrochloride and acrolein, albeit with one energetically unimportant step, as shown in Scheme 2. There is, therefore, considerable scope for electronic and/or steric effects, through modification of the amine, to alter the kinetics of iminium ion formation.

Applying the same methods to two α-nucleophiles, namely *N*,*N*′-dimethylhydrazine **1** and *N*,*O*-dimethylhydroxyl amine **3**, yields a broadly similar PES to that shown in Scheme 2 in each case (Fig. 11). Both reaction paths show a clear effect of the α-heteroatom, reducing the barriers at TS1 and TS2 by between 5 and 35 kJ mol^{-1}. Specific effects are apparent in these results: the *N*-heteroatom reduces the second barrier by substantially more than the first, while the opposite is true for the *O*-heteroatom. Thus, there appears to be a subtle interplay of effects at work here, consistent with the generally accepted view that the α-effect is a complex one. Subsequent theoretical studies will attempt to explain these results in terms of the electronic structure of the relevant minima and transition states.

These results are directly relevant to those in Table 1, and are, therefore, consistent with the rather small increase in catalytic activity seen for *N*,*N*′-dimethylhydrazine and the rather larger effect found with *N*,*O*-dimethyl-hydroxyl-amine. The reaction pathway proposed here is also consistent with the effect of counter anion noted in Table 2: a key step in iminium ion formation is transfer of a proton from *N* to *O*, mediated by the counter anion. Acids of increasing pK_a should be progressively worse at mediating such a step, and, therefore, lead to lower catalytic activity.

A further interesting observation linking both synthetic and theoretical investigations is the addition of water to some reaction mixtures, which is only required for catalysts lacking a β-carbonyl. This suggests the possiblity that the carbonyl group is intimately involved with iminium ion formation, acting as a proton shuttle in an analogous manner to the water molecule in the calculations presented. Introduction of the β-carbonyl may, therefore, provide an intramolecular route for this, and hence may explain why this functionality removes the need for water in the reaction medium.

4. Conclusion

In summary, through a combination of both synthetic and theoretical studies we have shown that the α-effect is an effective platform for iminium ion catalysis. The synthetic studies have shown an arrangement of a tertiary centre on the reactive nitrogen together with a methyl substituent and an ethyl carbamate on the α-heteroatom leads to a highly effective catalyst architecture. DFT calculations have revealed a realistic mechanistic pathway for iminium ion formation and have shown that transition state energies can be significantly perturbed through the incorporation of an α-heteroatom. Of particular note is the fact that both a counter-anion and a proton-shuttle (water) are necessary for this process to occur. A possible reason for the counter-intuitive need for an electron-withdrawing-group on the

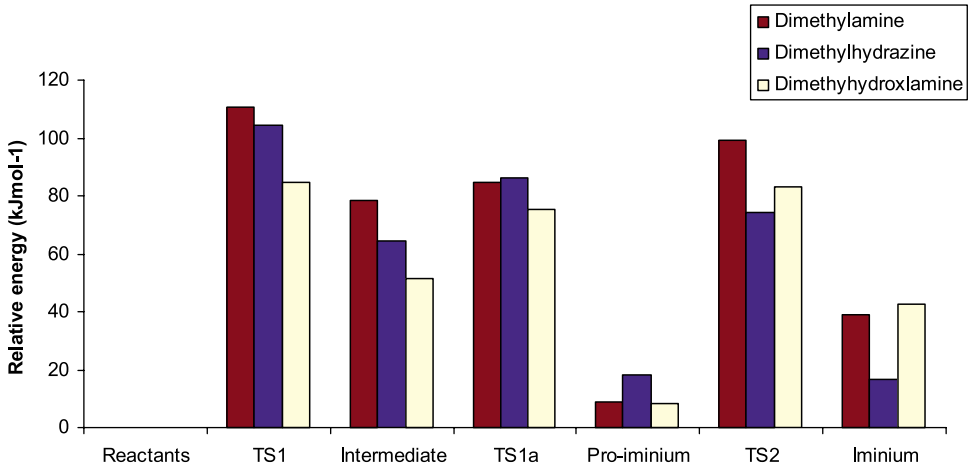


Figure 11. Comparison of reaction path of three amines.

α-heteroatom may lie in the mechanism of formation of the iminium ion. Further studies are now underway to explain the need for a β-carbonyl within our catalyst structure and to incorporate these fundamental findings within a chiral catalyst for use in iminium ion catalysed transformations.

5. Experimental

5.1. General

All ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on a Bruker DPX-400, Bruker Avance 500 or Bruker DPX-250 spectrometer, with ^{13}C spectra being recorded at 100, 125 or 62.5 MHz. Mass spectra were obtained using a Fisons VG platform II spectrometer. High resolution mass spectra were obtained by the EPSRC mass spectrometry service, Swansea. Melting points were determined on a Khofler Hot Stage Micro Melting Point Apparatus and are uncorrected. Infrared spectra were recorded in the range 4000–600 cm^{-1} using a Perkin–Elmer 1600 series spectrophotometer as thin films or as nujol mulls. Thin-layer chromatography (TLC) was performed on Merck 5554 60F silica gel coated aluminium plates and detection was effected with a solution of 10% ceric sulfate in 10% sulfuric acid, followed by heating the plates. Purification of compounds was achieved by medium pressure chromatography using Merck 9385 60 silica gel.

All DFT calculations were carried out using the Gaussian03 package.[23] Initial optimisations and transition state searches were carried out at the B3LYP/6-31+G(d,p) level,[24,25] within an Onsager solvent shell of methanol. Subsequent calculations to test these methods employed the larger 6-311++G(2d,p) basis set, as well as the mPW1PW91 functional,[26] and an alternative PCM model of methanol solvation.[27] All minima and transition states were characterised as such via harmonic frequency calculation and examination of any resulting imaginary eigenvalues.

5.1.1. *N′*-Isopropylidenehydrazinecarboxylic acid ethyl ester. Ethyl carbazate (2.20 g, 21.1 mmol) was stirred in an excess of acetone (10 mL), containing acetic acid (30 μL, 0.5 mmol), for 24 h at ambient temperature. Water (20 mL) was added and the reaction mixture extracted with dichloromethane (3×20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and reduced in vacuo to afford the title compound (2.75 g, 90%) as a colourless solid; mp 72–73 °C [lit.[28] mp 75–76 °C]; ν_{max} (nujol)/cm^{-1} 3236, 1730, 1649, 1530, 1239; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (1H, s, N*H*) 4.06 (2H, q, J=6.4 Hz, OCH_2CH$_3$) 1.83 (3H, s, N=CCH_3) 1.71 (3H, s, N=CCH_3) 1.11 (3H, t, J=6.4 Hz, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4 (C) 151.0 (C) 61.6 (CH_2) 25.4 (CH_3) 16.3 (CH_3) 14.5 (CH_3); *m/z* (EI) $[M]^+$144 (19%), 98 (93), 44 (100), 41 (69); HRMS (EI) (found 144.0898 $[M]^+$; $C_6H_{12}N_2O_2$ requires 144.0899).

5.1.2. *N′*-Isopropylhydrazinecarboxylic acid ethyl ester 13. Platinum oxide (17 mg, 73 μmol) was placed in nitrogen flushed flask with ethanol (3.4 mL) and acetic acid (1.7 mL). *N′-iso*propylidene-hydrazinecarboxylic acid ethyl ester (0.50 g, 3.5 mmol) was added, the flask was charged with hydrogen stirred for 24 h at ambient temperature. The reaction mixture was filtered over Celite® and the filtrate was neutralised with saturated sodium bicarbonate solution (25 mL). The volatiles were removed under reduced pressure and the aqueous phase was extracted with diethyl ether (5×10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced in vacuo to give the title compound **13** (0.43 g, 85%) as a colourless viscous liquid; ν_{max} (film)/cm^{-1} 3314, 1701, 1529, 1266; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (1H, s, N*H*) 4.13 (2H, q, J=6.9 Hz, OCH_2CH$_3$) 3.15 (1H, sept, J=6.6 Hz, NC*H*(CH$_3$)$_2$) 1.24 (3H, t, J=6.9 Hz, OCH$_2$CH_3) 1.01 (6H, d, J=6.6 Hz, NCH(CH_3)$_2$) δ_C (100 MHz, $CDCl_3$) 158.0 (C) 61.7 (CH_2) 51.2 (CH) 20.9 (CH_3) 15.0 (CH_3); *m/z* (EI) $[M]^+$147 (21%), 131 (100), 103 (64), 85 (91), 42 (74); HRMS (EI) (found 146.1053 $[M]^+$; $C_6H_{14}N_2O_2$ requires 146.1055).

Treatment with dry ethereal HCl gave the corresponding salt **13**·HCl as a colourless solid; mp 85–87 °C; ν_{max} (nujol)/cm^{-1} 3397, 2922, 2853, 1732, 1538, 1462, 1377, 1263, 1022; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.89 (2H, br s, NH_2) 9.58 (1H, br s, N*H*) 4.22 (2H, q, J=7.1 Hz, OCH_2CH$_3$) 3.82 (1H, sept, J=6.6 Hz, NC*H*(CH$_3$)$_2$) 1.39 (6H, d, J=6.6 Hz, NCH(CH_3)$_2$) 1.24 (3H, t, J=7.1 Hz, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7 (C) 62.4 (CH_2) 55.1 (CH) 17.5 (CH_3) 14.3 (CH_3); *m/z* (APcI) $[M+H–HCl]^+$147 (100%); HRMS (ES) (found 147.1127 $[M+H–HCl]^+$; $C_6H_{14}N_2O_2$ requires 147.1128).

5.1.3. *N′*-*t*Butylhydrazinecarboxylic acid ethyl ester 15. *tert*-Butylhydrazine hydrochloride (5.00 g, 40.1 mmol, 1 equiv) was cooled to 0 °C in a suspension of dichloromethane (50 mL) and aqueous sodium bicarbonate solution (50 mL). Ethyl chloroformate (4.35 g, 3.84 mmol, 40.1 mmol, 1.0 equiv) was added drop wise to the suspension and stirring was continued at 0 °C for 30 min and at ambient temperature overnight. The organic layer was separated and the aqueous layer extracted with dichloromethane (2×20 mL). The combined organics were dried (Na_2SO_4) and the volatiles removed in vacuo to give a colourless oil. Purification by flash column chromatography eluting with ether/light petroleum 1:1 afforded the title compound **15** (662 mg, 10%) as a colourless oil; ν_{max} (liquid film)/cm^{-1} 3302, 2973, 1713, 1538, 1475, 1445, 1388, 1364, 1335, 1269, 1214, 1150, 1062, 1030; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (1H, br s, N*H*) 4.10 (2H, q, J=6.8 Hz, OCH_2CH$_3$) 1.20 (3H, t, J=6.8 Hz, OCH$_2$CH_3) 1.02 (9H, s, NC(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1 (C) 61.4 (CH_2) 54.9 (C) 27.0 (CH_3) 14.6 (CH_3); *m/z* (APcI) $[M+H]^+$161 (100%); HRMS (ES) (found 161.1285 $[M+H]^+$; $C_7H_{16}N_2O_2$ requires 161.1285).

Treatment with dry ethereal HCl gave the corresponding salt **15**·HCl as a colourless solid; mp 157–158 °C; ν_{max} (nujol)/cm^{-1} 3238, 2924, 2684, 2326, 1714, 1531, 1463, 1376, 1275, 1176; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.77 (2H, br s, NH_2) 9.38 (1H, s, N*H*) 4.23 (2H, q, J=6.9 Hz, OCH_2CH$_3$) 1.41 (9H, s, NC(CH_3)$_3$) 1.26 (3H, t, J=6.9 Hz, OCH$_2$CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3 (C) 63.9 (CH_2) 63.3 (C) 24.8 (CH_3) 14.3 (CH_3); *m/z* (APcI) $[M+H–HCl]^+$161

(100%); HRMS (ES) (found 161.1284 $[M+H–HCl]^+$; $C_7H_{16}N_2O_2$ requires 161.1285).

5.1.4. *N*-Isopropylglycine ethyl ester 16. A solution of isopropyl amine (13.6 g, 230 mmol, 19.6 mL, 2.3 equiv) in toluene (100 mL) was treated with ethyl bromoacetate (16.7 g, 100 mmol, 11.1 mL, 1.0 equiv) at ambient temperature. The solution was refluxed for 2 h and subsequently stirred at room temperature for 16 h during which time a crystalline precipitate was formed. The solution was made alkaline with sodium hydroxide (50% solution, 20 mL) dissolving the precipitate. The organic layer was separated and washed with water, brine, and dried ($MgSO_4$). The volatiles were removed in vacuo and the product purified by distillation (5 mbar, 73–75 °C) [lit.[29] bp 30 °C at 2.00 Torr] to give the title compound **16** (12.3 g, 85%) as a clear colourless liquid; ν_{max} (film)/cm^{-1} 3335, 2966, 1740, 1466, 1379, 1347, 1098, 1028; ^1H NMR (400 MHz, $CDCl_3$) δ 4.12 (2H, q, $J=7.2$ Hz, OCH_2CH_3) 3.34 (2H, s, $NHCH_2CO$) 2.73 (1H, sept, $J=6.3$ Hz, $CH(CH_3)_2$) 1.52 (1H, br s, NH) 1.21 (3H, t, $J=7.2$ Hz, OCH_2CH_3) 0.99 (6H, d, $J=6.3$ Hz, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7 (C) 60.8 (CH_2) 48.7 (CH_2) 48.3 (CH_2) 22.7 (CH_3) 14.2 (CH_3); *m/z* (APcI) $[M+H]^+$146 (100%); HRMS (ES) (found 146.1177 $[M+H]^+$; $C_7H_{15}N_1O_2$ requires 146.1176).

Treatment with dry ethereal HCl gave the corresponding salt **16**·HCl as a colourless solid; mp 111–112 °C; ν_{max} (nujol)/cm^{-1} 3330, 2926, 2853, 2705, 2455, 1757, 1590, 1463, 1377; ^1H NMR (400 MHz, $CDCl_3$) δ 9.77 (2H, br s, NH_2) 4.21 (2H, q, $J=7.1$ Hz, OCH_2CH_3) 3.76 (2H, s, NCH_2COO) 3.56 (1H, m, $NCH(CH_3)_2$) 1.44 (6H, d, $J=6.7$ Hz, $NCH(CH_3)_2$) 1.24 (3H, t, $J=7.1$ Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0 (C) 62.5 (CH_2) 50.8 (CH) 44.2 (CH_2) 18.9 (CH_3) 14.0 (CH_3); *m/z* (APcI) $[M+H–HCl]^+$146 (100%); HRMS (ES) (found 146.1177 $[M+H–HCl]^+$; $C_7H_{15}N_1O_2$ requires 146.1176).

5.1.5. Benzoic acid isopropylidene hydrazide. Benzoic hydrazide (5.00 g, 36.7 mmol) was stirred in an excess of acetone (22 mL, 0.3 mmol), containing acetic acid (40 μL, 0.7 mmol), for 48 h at ambient temperature. Water (30 mL) was added and the reaction mixture was extracted with dichloromethane (3×30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and reduced in vacuo to afford the title compound (5.57 g, 86%) as a colourless solid; mp 141–143 °C [lit.[30] mp 142–143 °C]; ν_{max} (nujol)/cm^{-1} 3221, 1655, 1578, 1578, 1531, 1490, 718, 668; ^1H NMR (400 MHz, $CDCl_3$) δ 8.70 (1H, s, NH) 7.79 (2H, d, $J=7.1$ Hz, ArH) 7.52 (1H, t, $J=7.1$ Hz, ArH) 7.44 (2H, dd, $J=7.1$, 7.1 Hz, ArH) 2.15 (3H, s, CH_3) 1.97 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6 (C) 156.9 (C) 134.1 (C) 132.1 (CH) 129.0 (CH) 127.6 (CH) 26.0 (CH_3) 17.3 (CH_3); *m/z* (EI) $[M]^+$176 (8%), 161 (50), 105 (100), 77 (31); HRMS (EI) (found 176.0950 $[M]^+$; $C_{10}H_{12}N_2O$ requires 176.0950).

5.1.6. Benzoic acid *N*′-Isopropylhydrazide 19. Platinum oxide (68 mg, 0.3 mmol) was placed in a nitrogen flushed flask with ethanol (12 mL) and acetic acid (6 mL). Benzoic acid isopropylidene hydrazide (2.50 g, 14.2 mmol) was added, the flask was charged with hydrogen and stirred for 48 h at ambient temperature. The reaction mixture was filtered over Celite® and the filtrate was neutralised with saturated sodium bicarbonate solution (180 mL). The volatiles were removed under reduced pressure and the aqueous phase was extracted with diethyl ether (5×50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced in vacuo to give the title compound **19** (2.18 g, 86%) as a colourless powder; mp 110–112 °C [lit.[31] mp 115–117 °C]; ν_{max} (nujol)/cm^{-1} 3289, 1640, 1537, 725, 693; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (1H, s, NH) 7.69 (2H, d, $J=7.7$ Hz, ArH) 7.46 (1H, t, $J=7.7$ Hz, ArH) 7.38 (2H, dd, $J=7.7$, 7.7 Hz, ArH) 4.81 (1H, s, NH) 3.18 (1H, sept, $J=6.2$ Hz, $NCH(CH_3)_2$) 1.05 (6H, d, $J=6.2$ Hz, $NCH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5 (C) 132.9 (C) 131.9 (CH) 128.7 (CH) 126.9 (CH) 51.4 (CH) 20.9 (CH_3); *m/z* (EI) $[M]^+$173 (3%), 163 (9), 122 (13), 105 (100), 77 (34); HRMS (EI) (found 178.1105 $[M]^+$; $C_{10}H_{14}N_2O$ requires 178.1106).

Treatment with dry ethereal HCl gave the corresponding salt **19**·HCl as a colourless solid; mp 215–218 °C; ν_{max} (nujol film)/cm^{-1} 3408, 2923, 2853, 2645, 1678, 1600, 1549, 1527, 1463, 1377; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (2H, d, $J=7.5$ Hz, ArH) 7.45 (1H, t, $J=7.4$ Hz, ArH) 7.31 (2H, dd, $J=7.5$, 7.4 Hz, ArH) 3.94 (1H, sept, $J=6.6$ Hz, $NCH(CH_3)_2$) 1.41 (6H, d, $J=6.6$ Hz, $NCH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8 (C) 133.5 (C) 128.7 (CH) 128.6 (CH) 128.5 (CH) 56.0 (CH) 18.0 (CH_3); *m/z* (ApcI) $[M+H–HCl]^+$179 (100%).

5.1.7. Cyclohexanecarboxylic acid *N*′-Isopropylhydrazide 20. Platinum oxide (108 mg, 0.48 mmol) was placed in a nitrogen flushed flask with ethanol (50 mL) and acetic acid (25 mL). Benzoic acid isopropylidene hydrazide (4.20 g, 23.8 mmol) was added, the flask was charged with hydrogen and stirred for 96 h at ambient temperature. The reaction mixture was filtered over Celite® and the filtrate was neutralised with saturated sodium bicarbonate solution (450 mL), which caused the product to precipitate and the suspension was extracted with diethyl ether (5×100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced in vacuo to give the title compound **20** (2.31 g, 53%) as a colourless powder; mp 120–124 °C [lit.[32] mp 122–123 °C]; ν_{max} (nujol)/cm^{-1} 3397, 2926, 1708, 1549, 1525, 1462, 1377, 1336, 1173, 1110; ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (1H, br s, NH) 4.61 (1H, m, NH) 3.08 (1H, m, $NCH(CH_3)_2$) 2.06 (1H, m, Cy) 1.80 (4H, m, Cy) 1.68 (1H, m, Cy) 1.46 (2H, m, Cy) 1.25 (3H, m, Cy) 1.03 (6H, d, $J=6.4$ Hz, $NCH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9 (C) 51.5 (CH_2) 44.2 (CH_2) 38.2 (CH) 29.8 (CH) 26.0 (CH_3) 21.1 (CH_2); *m/z* (APcI) $[M+H]^+$185 (95%) 143 (100); HRMS (ES) (found 185.1645 $[M+H]^+$; $C_{10}H_{21}N_2O$ requires 185.1648).

Treatment with dry ethereal HCl gave the corresponding salt **20**·HCl as a colourless solid; mp 193–194 °C; ν_{max} (nujol)/cm^{-1} 3330, 2923, 1707, 1548, 1525, 1461, 1377, 1336, 1259, 1192, 1174, 1111; ^1H NMR (400 MHz, $CDCl_3$) δ 5.30 (1H, s, NH) 3.81 (1H, sept, $J=6.6$ Hz, $NCH(CH_3)_2$) 2.60–2.50 (1H, m, O=CCH) 1.89–1.20 (10H, m, Cy) 1.43 (6H, d, $J=6.6$ Hz, $NCH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2 (C) 55.6 (CH_2) 42.3 (CH_2) 29.0 (CH) 25.5 (CH) 25.2 (CH_3) 17.8 (CH_2); *m/z* (APcI) $[M+H–HCl]^+$185 (100%);

HRMS (ES) (found 185.1653 $[M+H-HCl]^+$; $C_{10}H_{21}N_2O$ requires 185.1648).

5.1.8. Methanesulfonylhydrazide hydrochloride.[33] Methanesulfonyl chloride (5.75 g, 50 mmol) was added slowly to a stirred ice-cold solution of hydrazine hydrate (2.5 g, 50 mmol) in water (7.5 mL), followed by 2 M aq NaOH (25 mL), such that the temperature did not exceed 8 °C. On completion, hydrochloric acid (25 mL) was added, which led to the precipitation of a small amount of di-methanesulfonyl hydrazide, which was filtered off. The filtrate was concentred in vacuo and the resulting residue recrystallised twice from boiling ethanol to give the title compound (2.0 g, 36%) as a coluorless crystaline solid; mp 152–153 °C; ν_{max} (nujol mull)/cm^{-1} 3440, 2652, 1953, 1461, 1376, 1146, 978; ^{1}H NMR (400 MHz, D_2O) δ 3.1 (3H, s, C*H*$_3$); ^{13}C NMR (100 MHz, D_2O) δ 38.4 (CH_3).

5.1.9. *N*-Isopropylidene-*N′*-methanesulfonylhydrazone hydrochloride. Methanesulfonylhydrazide hydrochloride (400 mg, 3.5 mmol) was stirred in an excess of acetone (20 mL) at room temperature for 24 h. The solvent was removed in vacuo and the solid residue was recrystallised twice from ethanol/ether to give the title compound as a colourless solid (824 mg, 64%); mp 120 °C dec; ν_{max} (nujol mull)/cm^{-1} 3410, 1977, 1672 (C=N), 1462, 1351 (SO_2), 1165 (SO_2), 784; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.5 (1H, s, SO_2N*H*), 3.05 (3H, s, C*H*$_3$), 2.0 (3H, s, C*H*$_3$), 1.8 (3H, s, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.74 (C) 38.59 (CH_3) 25.70 (CH_3) 17.56 (CH_3).

5.1.10. Methanesulfonic acid *N′*-isopropyl hydrazide 21·HCl. To a stirred solution of *N*-isopropylidene-*N′*-methanesulfonylhydrazone hydrochloride (0.4 g, 2.14 mmol) in methanol (3 mL) was added a solution $NaCNBH_3$ in THF (1 M, 2.14 mL, 2.14 mmol) at room temperature, followed by 2 M HCl at a rate sufficient to maintain a pH of 2–3. After 10–15 min the pH changed less rapidly and the mixture was allowed to stir for an additional 3 h. The pH was lowered to 1 and the volatiles were removed under reduced pressure. The resulting residue was taken up in water (10 mL) and the pH adjusted to 8 with 20% K_2CO_3 and extracted with ether (6×20 mL). The ethereal extracts were dried ($MgSO_4$) and concentrated to afford an oil, which was dissolved in ether (10 mL) and the solution was treated with 2 M HCl in ether to give a solid, which was recrystallised from ethanol/ether to afford the title compound **21**·HCl as a colourless solid (54 mg, 13%); mp 100–103 °C; ν_{max} (nujol mull)/cm^{-1} 1942, 1562, 1462, 1348 (SO_2), 1175 (SO_2), 795, 779; ^{1}H NMR (400 MHz, D_2O) δ 3.42 (1H, sept, J=6.5 Hz, C*H*(CH_3)$_2$), 3.1 (3H, s, C*H*$_3$), 1.14 (6H, d, J=6.5 Hz, CH(C*H*$_3$)$_2$); ^{13}C NMR (100 MHz, D_2O) δ 54.5 (CH) 39.8 (CH_3) 16.9 (CH_3).

5.1.11. *N*-Isopropylidene-*N′*methylhydrazine. Methyl hydrazine (13.6 g, 295 mmol, 15.7 mL) was added drop wise to acetone (23.7 g, 409 mmol, 30 mL) maintaining the reaction temperature below 35 °C. The solution was stirred for 1 h after which the top layer was removed and allowed to stand over potassium hydroxide (5 g) for a further 1 h. The upper liquid was decanted from the lower aqueous layer and allowed to stand over two successive portions of potassium hydroxide (2×2.5 g) for 30 min each. Purification was by distillation (110 °C) [lit.[34] bp 116–118 °C] under nitrogen affording the title compound (17.85 g, 70%); ν_{max} (liquid film)/cm^{-1} 3394, 3262, 2911, 2794, 1711, 1631; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 (1H, br s, N*H*) 2.76, (3H, s, NHC*H*$_3$) 1.88 (3H, s, N=CC*H*$_3$ *trans*) 1.68 (3H, s, N=C–C*H*$_3$ *cis*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4 (C) 37.9 (CH_3) 25.0 (CH_3) 15.5 (CH_3); *m/z* (APcI) $[M+H]^+$87 (100%); HRMS (EI) (found 86.0841 $[M]^+$; $C_4H_{10}N_2$ requires 86.0838).

5.1.12. *N′*-Isopropyl-*N*-methylhydrazinecarboxylic acid ethyl ester hydrochloride 22·HCl. Ethyl chloroformate (1.26 g, 1.11 mL, 11.6 mmol) was added drop wise to a stirred solution of *N*-isopropylidene-*N′*-methylhydrazine (1.00 g, 11.6 mmol) in dichloromethane (10 mL) and saturated sodium bicarbonate solution (10 mL) at 0 °C. After addition the reaction mixture was allowed to warm to ambient temperature and stirred for 18 h. The organics were separated and the aqueous layer extracted with dichloromethane (2×20 mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure. The organics were added to a nitrogen flushed flask, charged with platinum oxide (132 mg, 0.58 mmol) in ethanol (20 mL) and acetic acid (10 mL). The atmosphere was replaced with hydrogen and the reaction stirred for 16 h at ambient temperature. The reaction mixture was filtered over Celite® and the filtrate was neutralised with saturated sodium bicarbonate solution (300 mL). The single phase solution was extracted with diethyl ether (3×50 mL) and the combined organics were washed with brine (20 mL), dried ($MgSO_4$) and the volatiles were removed under reduced pressure to give a clear oil, which was purified by flash column chromatography eluting with ether/light petroleum 1:1. The solvent was removed under reduced pressure and ethereal hydrochloric acid (1 M, 58.0 mmol, 58 mL, 5 equiv) was added to the solution with swirling for 30 min at ambient temperature. The precipitate was filtered under nitrogen affording the title compound **22**·HCl as a colourless powder (808 mg, 35%); mp 85–86 °C; ν_{max} (nujol)/cm^{-1} 3399, 2921, 5852, 2612, 1729, 1562, 1503, 1462, 1378, 1332, 1312, 1202, 1122, 1018; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (2H, q, J=7.2 Hz, OC*H*$_2$CH$_3$) 5.48 (1H, sept, J=6.6 Hz, NC*H*(CH_3)$_2$) 3.46 (3H, s, NC*H*$_3$) 1.50 (6H, d, J=6.6 Hz, NCH(C*H*$_3$)$_2$) 1.36 (3H, t, J=7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2 (C) 64.1 (CH_2) 54.6 (CH) 35.9 (CH_3) 17.8 (CH_3) 14.3 (CH_3); *m/z* (ES) $[M+H-HCl]^+$161 (90%) 119 (60) 115 (100); HRMS (ES) (found 161.1286 $[M+H-HCl]^+$; $C_7H_{16}N_2O_2$ requires 161.1285).

5.1.13. Benzoic acid *N′*-isopropyl-*N*-methylhydrazine hydrochloride 23·HCl. Benzoyl chloride (817 mg, 5.8 mmol, 0.67 mL) was added drop wise to a stirred solution of *N*-isopropylidene-*N′*-methylhydrazine (500 mg, 5.8 mmol) in dichloromethane (5 mL) and saturated sodium bicarbonate solution (5 mL) at 0 °C. After addition the reaction mixture was allowed to warm to ambient temperature and stirred for 18 h. The organics were separated and the aqueous layer extracted with dichloromethane (2×10 mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure. The organics were added to a nitrogen flushed flask charged with platinum oxide (66 mg, 0.29 mmol, 5 mol%) in ethanol

(12 mL) and acetic acid (6 mL). The atmosphere was replaced with hydrogen and the reaction stirred for 16 h at ambient temperature. The reaction mixture was filtered over Celite® and the filtrate was neutralised with saturated sodium bicarbonate solution (180 mL). The single phase solution was extracted with diethyl ether (3×50 mL) and the combined organics were washed with brine (20 mL), dried ($MgSO_4$) and the volatiles were removed under reduced pressure resulting in a clear oil, which was purified by flash column chromatography eluting with diethyl ether in light petroleum 1:1. The volume of elutent was reduced and ethereal hydrochloric acid (1 M, 13.0 mmol, 13 mL, 5 equiv) was added to the solution with swirling for 30 min at ambient temperature. The precipitate was filtered under nitrogen affording the title compound **23**·HCl as a colourless solid (150 mg, 11%); mp 145–146 °C; ν_{max} (nujol)/cm^{-1} 3408, 2923, 2091, 1638, 1460, 1377, 1333, 1122, 1077; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (2H, d, J=8.0 Hz, *o*-Ar) 7.49, (1H, d, J=7.1 Hz, *p*-Ar) 7.42 (2H, dd, J=8.0, 7.1 Hz, *m*-Ar) 3.94 (1H, sept, J=6.6 Hz, NC*H*$(CH_3)_2$) 3.61 (3H, s, NCH_3) 1.51 (6H, d, J=6.6 Hz, NCH(C$H_2)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 C) 132.3 (Ar) 130.7 (Ar) 128.9 (Ar) 128.2 (Ar) 53.7 (CH_3) 38.6 (CH) 18.0 (CH_3); *m*/*z* (ES) $[M+H–HCl]^+$193 (72%) 151 (100%); HRMS (ES) (found 193.1336 $[M+H–HCl]^+$; $C_{11}H_{17}N_2O$ requires 193.1335).

5.1.14. *N*-^{t}Butyl-*N*′-isopropylidenehydrazine. *tert*-Butylhydrazine dihydrochloride (10 g, 80 mmol, 1 equiv) was added to acetone (4.66 g, 80 mmol, 5.89 mL, 1.0 equiv) maintaining the temperature under 35 °C. Potassium hydroxide (5 g) was added the mixture stirred for 1 h. The liquid portion was decanted from the solid residue and allowed to stand over two successive portions of potassium hydroxide (5 g) for 1 h each. The clear colourless liquid was purified by distillation (4 mbar, 40–41 °C) affording the title compound (6.60 g, 64%); ν_{max} (liquid film)/cm^{-1} 3418, 3265, 2972, 1705, 1441, 1385, 1361, 1279, 1237, 1116; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (1H, br s, N*H*) 1.70 (3H, s, N=C(C$H_3)_2$) 1.49 (3H, s, N=C(C$H_3)_2$) 0.95 (9H, s, NHC(C$H_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2 (C) 53.0 (C) 28.6 (CH_3) 25.5 (CH_3) 15.3 (CH_3); *m*/*z* (APcI) $[M+H]^+$129 (100%).

5.1.15. *N*-^{t}Butyl-*N*′-isoproylidenehydrazinecarboxylic acid ethyl ester. To a suspension of *N*-*tert*-butyl-*N*′-*iso*propylidene-hydrazine (1.00 g, 7.80 mmol, 1.0 equiv) in dichloromethane (10 mL) at 0 °C was added saturated sodium bicarbonate solution (10 mL). Ethyl chloroformate (1.02 g, 9.36 mmol, 0.89 mL, 1.2 equiv) was added drop wise to the suspension and stirring was continued at 0 °C for 30 min and at ambient temperature overnight. The organic layer was separated and the aqueous layer extracted with dichloromethane (2×5 mL). The combined organics were dried (Na_2SO_4) and the volatiles removed in vacuo to give a yellow oil. Purification by flash chromatography eluting with diethyl ether in light petroleum 1:1 afforded the title compound (662 mg, 64%) as a colourless oil; ν_{max} (liquid film)/cm^{-1} 2975, 2923, 1698, 1652, 1482, 1456, 1393, 1367, 1304, 1257, 1224, 1170, 1086; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (2H, q, J=7.1 Hz, OCH_2CH$_3$) 1.91 (3H, s, NC(C$H_3)_2$) 1.71 (3H, s, NC(C$H_3)_2$) 1.21 (9H, s, NC(C$H_3)_3$) 1.04 (3H, t, J=7.1 Hz, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0 (C) 153.6 (C) 60.8 (CH_2) 58.3 (CH_2) 28.2 (CH_3) 24.5 (CH_3) 19.5 (CH_3) 14.6 (CH_3); *m*/*z* (APcI) $[M+H]^+$201 (100%); HRMS (ES) (found 201.1597 $[M+H]^+$; $C_{10}H_{21}N_2O_2$ requires 201.1598).

5.1.16. *N*-^{t}Butyl-*N*′-isopropylhydrazinecarboxylic acid ethyl ester 24. Platinum oxide (28 mg, 0.12 mmol, 5 mol%) was placed in a nitrogen flushed flask with ethanol (6 mL) and acetic acid (3 mL). *N*-*tert*-butyl-*N*′-isoproylidene-hydrazinecarboxylic acid ethyl ester (500 mg, 2.50 mmol) was added, the flask was charged with hydrogen and stirring was continued for 24 h at ambient temperature. The reaction mixture was filtered over Celite® and the filtrate was neutralised with saturated sodium bicarbonate solution (25 mL), which caused the product to precipitate. The suspension was extracted with diethyl ether (5× 15 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced in vacuo to give the title compound **24** (467 mg, 93%) as a colourless oil; ν_{max} (liquid film)/cm^{-1} 3314, 2971, 1702, 1467, 1396, 1367, 1308, 1250, 1223, 1168, 1081; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (2H, q, J=7.1 Hz, OCH_2CH$_3$) 3.80 (1H, br s, N*H*) 3.01 (1H, sept, J=6.4 Hz, NC*H*$(CH_3)_2$) 1.28 (9H, s, NC(C$H_3)_3$) 1.22 (3H, t, J=7.1 Hz, OCH$_2$CH_3) 0.92 (6H, d, J=6.4 Hz, NCH(C$H_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3 (C) 61.2 (CH_2) 58.9 (CH_3) 50.6 (CH) 29.0 (CH_3) 21.3 (CH_3) 20.8 (CH_3) 14.5 (CH_3); *m*/*z* (APcI) $[M+H]^+$203 (100%); HRMS (ES) (found 203.1756 $[M+H]^+$; $C_{10}H_{23}N_2O_2$ requires 203.1754).

Treatment with dry ethereal HCl gave the corresponding salt **24**·HCl as a colourless solid; mp 115–117 °C; ν_{max} (nujol)/cm^{-1} 2924, 2853, 1732, 1541, 1464, 1376, 1290; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (2H, br s, NH_2) 4.26 (2H, q, J= 7.1 Hz, OCH_2CH$_3$) 3.69 (1H, sept, J=6.6 Hz, NC*H*$(CH_3)_2$) 1.61 (9H, s, NC(C$H_3)_3$) 1.46 (6H, br s, NCH(C$H_3)_2$) 1.32 (3H, t, J=7.1 Hz, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0 (C) 64.4 (CH_2) 62.3 (C) 57.6 (CH) 29.0 (CH_3) 18.5 (CH_3) 14.3 (CH_3); *m*/*z* (APcI) $[M+H]^+$203 (100%); HRMS (ES) (found 203.1753 $[M+H–HCl]^+$; $C_{10}H_{23}N_2O_2$ requires 203.1754).

5.1.17. Typical experimental procedure for catalytic runs. *trans*-Cinnamaldehyde **8** (252 mg, 1.9 mmol, 0.24 mL, 1.0 equiv) was added to a solution of catalyst (10 mol%, 0.19 mmol) in methanol (2.0 mL) at 25 °C and the resulting mixture was stirred for 5 min to initiate iminium ion formation. Freshly cracked cyclopentadiene **7** (323 mg, 4.9 mmol, 0.38 mL, 2.5 equiv) was added in a single aliquot and stirring was continued for 24 h. The volatiles were removed under reduced pressure and the resulting organics were hydrolysed in a chloroform (2 mL), water (1 mL) trifluoroacetic acid (1 mL) mixture over night. Saturated sodium hydrogen carbonate solution (18 mL) was added to neutralise the solution and the aqueous phase was extracted with dichloromethane (2×20 mL). The combined organics were washed with water (10 mL) and dried (Na_2SO_4) prior to the removal of the volitiles under reduced pressure. ^{1}H NMR of the crude reaction mixture was used to establish the conversion to the products and *exo*:*endo* ratios through the integration of aldehyde peaks at: δ_H (400 MHz, $CDCl_3$) 9.8 (*exo*) 9.65 (cinnamaldehyde) 9.53 (*endo*). The products were then purified by flash column chromatography eluting with 10% ethyl acetate in light petrol

resulting in a mixture of the *exo*- and *endo*-isomers of 3-phenyl-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde **9** and **10** as a pale yellow oil. ^{1}H NMR, ^{13}C NMR and IR data were consistent with previously reported literature values;[35] ν_{max} (liquid film)/cm^{-1} 1718, 1601, 1497; *exo*-**10**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (1H, d, $J=2.02$ Hz, C*H*O) 7.4–7.0 (5H, m, Ar*H*) 6.27 (1H, dd, $J=5.63$, 3.61 Hz, C*H*=CH) 6.01 (1H, dd, $J=5.62$, 3.64 Hz, CH=C*H*) 3.66 (1H, dd, $J=5.03$, 3.42 Hz, C*H*Ph) 3.25–3.05 (2H, m, C*H*CH$_2$) 2.55–2.45 (1H, m, C*H*CHO) 1.65–1.45 (2H, m, CH$_2$); *endo*-**9**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (1H, d, $J=2.16$ Hz, C*H*O) 7.4–7.0 (5H, m, Ar*H*) 6.36 (1H, dd, $J=5.63$, 3.61 Hz, C*H*=CH) 6.10 (1H, dd, $J=5.62$, 3.64 Hz, CH=C*H*) 3.26 (1H, m, C*H*Ph) 3.05 (1H, m, C*H*CH$_2$) 3.01 (1H, m, C*H*CH$_2$) 2.91 (1H, m, C*H*CHO) 1.49 (2H, m, CH$_2$); *m/z* (EI) [M]$^{+}$198 (10%) 132 (89) 131 (100) 103 (52) 77 (21) 66 (54).

Acknowledgements

The authors wish to express their gratitude to the EPSRC, the UK Computational Chemistry Facility for a generous grant of time on the Columbus central facility and The Mass Spectrometry Service, Swansea for high resolution spectra.This work was sponsored by EPSRC under grant ref. GR/S69337/01.

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