SPECIAL ISSUE

Flow Desulfurization

A Continuous-Flow Method for the Desulfurization of Substituted Thioimidazoles Applied to the Synthesis of Etomidate Derivatives
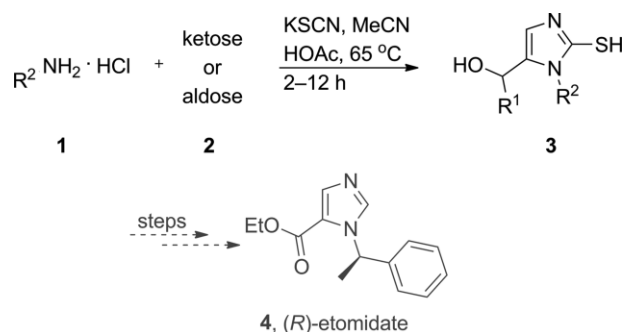
Marcus Baumann*[a] and Ian R. Baxendale[a]

Abstract: A simple yet robust flow set-up for the efficient desulfurization of a series of thioimidazoles is presented, which generates the corresponding imidazole derivatives in high yields. The strategic choice of peristaltic over piston pumps allowed reliable delivery of the heterogeneous stream of the thioimidazole substrate into a T-piece where it reacted with $NaNO_2$ in the presence of acetic acid. This approach enabled the controlled and safe formation of the reactive nitrosonium species without uncontrolled exposure to hazardous nitrous oxide byproducts as observed in related batch protocols. The value of the resulting imidazole products was further demonstrated by their conversion into various esters representing new derivatives of the known analgesic etomidate through an efficient one-pot Corey–Gilman–Ganem oxidation procedure.

Introduction

Imidazoles are amongst the most prevalent bioactive heterocyclic entities and hence can be found not only in many natural products but also in numerous pharmaceutical and agrochemical agents.[1] Consequently, a considerable number of synthetic routes has been developed for their construction.[2] Paramount to accessing structurally diverse imidazoles remains the availability of suitable building blocks that quickly furnish the desired target structures in high yield and selectivity. Addressing this requirement, we recently reported on an extension of the classical Marckwald multicomponent reaction, which produces highly substituted thioimidazoles in a single step and makes use of diverse amine and carbohydrate building blocks (dihydroxyacetone, ketoses, and aldoses) that are incorporated without erosion of stereochemical information (Scheme 1).[3]
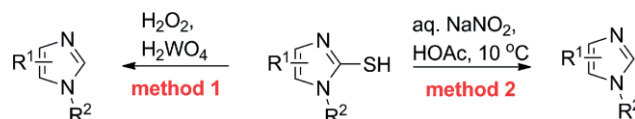

Scheme 1. Marckwald thioimidazole synthesis and structure or (*R*)-etomidate.

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http://community.dur.ac.uk/i.r.baxendale/index.html
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Building on this work, we now wish to report on a subsequent study that focuses on using these thioimidazoles as precursors for various imidazole products that hold promise as bioactive structures for example (*R*)-etomidate[4] (Scheme 1). Essential to this endeavor is the development of an efficient process allowing desulfurization and hence expansion of the thioimidazole scaffolds. To render such a process more amenable to safe and efficient scale-up we opted to harness the benefits of continuous-flow chemistry as a valuable and well-documented enabling technology.

Results and Discussion

With reliable access to diverse thioimidazole structures through the Marckwald reaction, we initially surveyed the available literature for suitable methods to accomplish the desulfurization step. Amongst the methods reported, two main options appeared attractive: (1) using a combination of hydrogen peroxide and a tungstic acid catalyst[5] or (2) treating the thioimidazole substrates with aqueous sodium nitrite in glacial acetic acid[6] (Scheme 2).

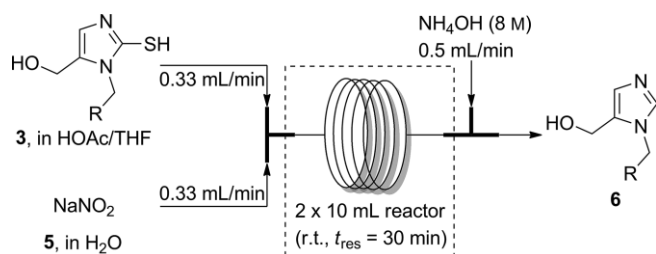Scheme 2. Selected methods for desulfurizing thioimidazoles.

While the first method is interesting due to its green credentials, it was found that prolonged reaction times were needed to obtain full conversion of the substrate (8–14 h). Typically, this also required addition of further aliquots of both catalyst and hydrogen peroxide, which makes this option less desirable over

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time. On the other hand, the second method is much faster (< 1 h), yet requires cooling of the reaction mixture due to the reaction's exothermic nature and additionally generates toxic nitrous oxide gases. Based on this pre-evaluation we decided to develop a flow process for the second method (NaNO$_2$, glacial acetic acid) with which we wished to harness the short reaction times and at the same time exploit the benefits of flow processing to mitigate risks associated with the exothermic nature of the reaction and the generation of toxic gases. Additionally, we wished to develop an efficient in-line quench process, which would neutralize the acidic reaction mixture and gaseous by-products in a controlled manner.

For this purpose, we opted to use a Vapourtec E-series flow system,[7] which utilizes peristaltic rather than more traditional piston pumps to feed streams of substrates and reagents into the reactor modules. This decision was further supported by the limited solubility of the Marckwald thioimidazoles, which, although convenient for their isolation, represents a challenge when utilizing them in further flow-based transformations. We thus suspended the desired thioimidazole substrates in a mixture of acetic acid and THF (0.5 M, 50:50 by volume, stream A) and by using the peristaltic pumps mixed this with a second stream containing NaNO$_2$ (2 M water, stream B) in a wide bore T-piece (Kinesis, 1.5 mm i.d.)[8] as depicted in Scheme 3.

Figure 1. Imidazoles 6a–j prepared by desulfurization in flow.

Scheme 3. Set-up of flow reactor.

To ensure consistent delivery of the thioimidazole suspension, it was found that a short 5 cm length of tubing leading into the peristaltic pump was beneficial. This small adjustment together with vigorously stirring of the thioimidazole suspension allowed a smooth feed of the thioimidazole substrate, which showcases how slurries can be processed in flow, a challenge that has seen considerable interest within the community.[9] Upon mixing at the T-piece, the combined reaction mixture became homogeneous, which indicates rapid formation of the key nitrosonium species and its reaction with the thioimidazole substrates. Passing the reaction mixture through a tubular flow coil (2 × 10 mL, 30 min residence time) at ambient temperature ensured quantitative conversion of all substrates into the desired imidazole products (Figure 1).

After establishing a quick and safe method for desulfurizing thioimidazoles in flow, we decided to also incorporate an in-line quench to neutralize the acetic acid as well as gaseous products. This was accomplished by mixing a stream of aqueous ammonia (8 M) with the reaction stream by using a standard T-piece. The reaction products were subsequently col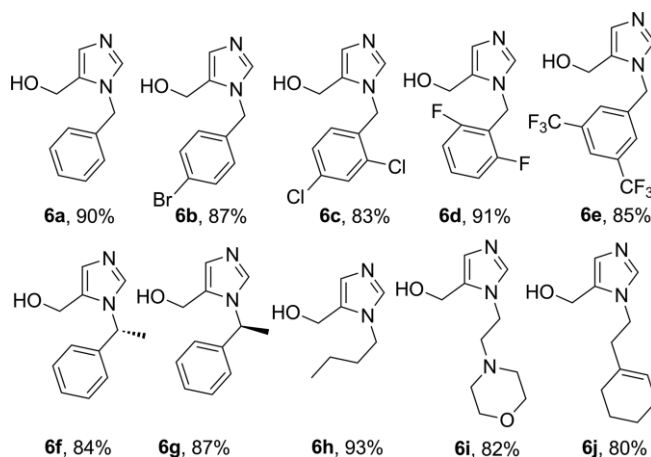lected without passing a back-pressure regulator[10] and isolated after aqueous extraction of the crude product stream yielding a series of imidazole products in high yield and purity. Crucially, it was found that this in-line quenching method not only neutralized the acetic acid, but more importantly eliminated any nitrous oxide by-products that are otherwise generated during this process. In light of this we propose a mechanism in which unreacted nitrosonium species will react with ammonia in a diazotization reaction that will generate benign nitrogen gas as the by-product (Scheme 4).[11]
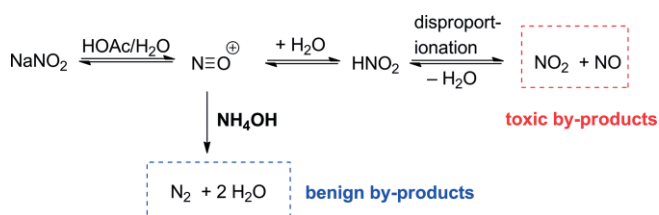

Scheme 4. Simplified mechanism for the decomposition of nitrous oxide by-products.

Pleasingly, it was found that the functional groups on the imidazole core, such as the hydroxymethyl moiety, as well as several substituted aryl and alkyl appendages are tolerated under the reaction conditions. In addition, this simple flow set-up was found to allow for successful scale-up generating multi-gram quantities of several substrates such as 6a, 6c, and 6f in equivalent yields with a typical productivity of approximately 10 mmol/h.

After accomplishing the safe and efficient desulfurization of an array of thioimidazoles, we next opted to evaluate their oxidative transformation into different ester products. To this end, we exploited imidazoles 6 that, upon oxidation of the hydroxymethyl group to an acid and subsequent ester formation, render etomidate and various derivatives[4] (Scheme 5).

Although this oxidation and esterification sequence appears to be a straightforward process, we anticipated the need for careful selection of the reaction conditions as several standard oxidation procedures could affect the imidazole core or the re-

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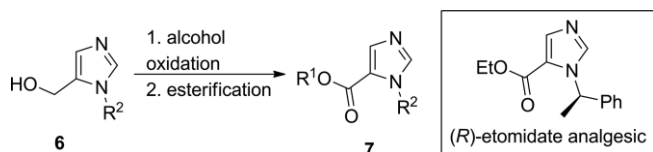
Scheme 5. Oxidation–esterification strategy to access etomidate derivatives.

active benzylic moiety. Furthermore, we were aware that the generation and isolation of the intermediate imidazole carboxylic acid might be cumbersome due to its polarity that would prohibit simple aqueous work-ups.

It was quickly established that several oxidation methods, including Swern-type, TEMPO, and MnO_2, do indeed generate the desired aldehyde derivative of our substrates, which under appropriate conditions can be further oxidized to the carboxylic acid species in a one-pot procedure (e.g. with TEMPO/BAIB).[12] However, the latter process turned out to be less desirable as it required prolonged reaction times (10–18 h) and extra care when isolating the carboxylic acid due to its polarity. Instead of optimizing this procedure we therefore opted to employ a less frequently exploited strategy for converting an alcohol substrate directly into an ester product based on the Corey–Gilman–Ganem[13] oxidation reaction. In this transformation, an activated alcohol is first oxidized with an excess of MnO_2 to the corresponding aldehyde, which then reacts in situ with cyanide to allow for subsequent oxidation of the resulting cyanohydrin to a cyano ketone, which is finally trapped as an ester upon reaction with an alcohol nucleophile (Scheme 6).
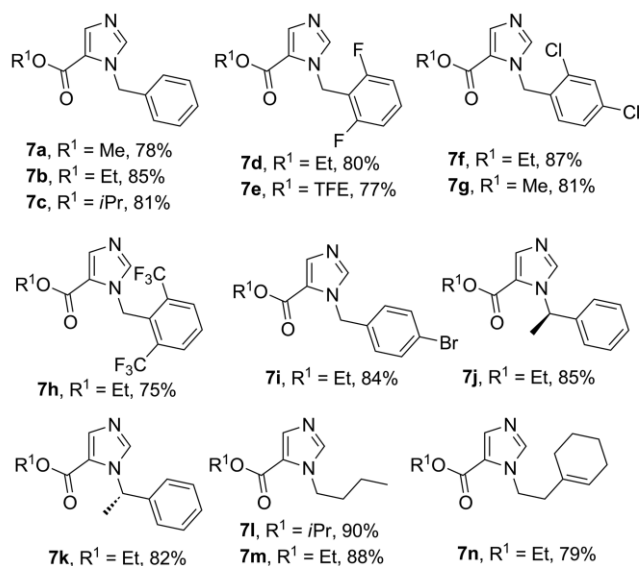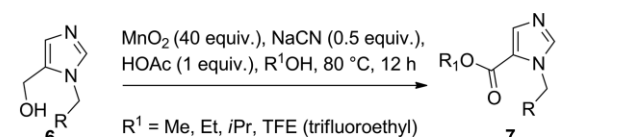
This approach not only mitigates isolation of any intermediate, but more importantly yields various ester products in a simple one-pot process. The desired structures (**7a–n**, Scheme 6) were isolated in good to excellent yields after conventional work-up and purification and include not only (R)- and (S)-etomidate[14] but also various analogues possessing unprecedented substitution patterns on the aryl ring, which we hope to evaluate for their analgesic properties in due course.

In order to more efficiently isolate these ester products (**7a–n**) and at the same time decrease the risk of exposure to cyanide, we opted to develop a final flow-based procedure to trap the used cyanide on an ion-exchange resin (Scheme 7).
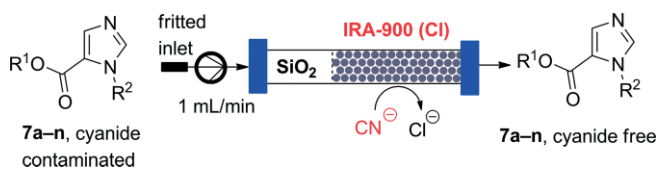
Scheme 7. Improved continuous isolation of ester products **7a–n**.

To this end, triethylamine (1 equiv.) and chloroform (10 mL) were added to the crude reaction mixture at ambient temperature. Mixing was stopped, and the MnO_2 suspension was allowed to settle. The supernatant was then pumped from the flask (1 mL/min, Vapourtec E-Series peristaltic pump) and directed into a glass column containing a small plug of silica (≈ 2 g) and Amberlite IRA-900 resin (chloride form, 10 equiv., ambient temperature). To minimize aspirating MnO_2 particles, the inlet tubing was covered with a microporous fritted filter. Upon passing through this column, residual cyanide was exchanged for benign chloride[15] that was subsequently removed by silica column chromatography to allow isolation of the desired products in very good yield and purity as before. Although not exploited in this instance, the MnO_2 slurry could also be recovered for re-use through this amendment, which would be especially worthwhile at larger scale as it allows to redefine this batch set-up as a continuously stirred tank reactor (CSTR), which could be utilized in sequential batch operations.

Conclusions

In summary, we have developed a simple flow process for the efficient desulfurization of a number of thioimidazoles to furnish the corresponding imidazole derivatives in high yield and purity. By utilizing peristaltic pumps, our approach demonstrates the reliable and accurate delivery of the substrate as a suspension that reacts with sodium nitrite in the presence of acetic acid as cosolvent prior to an in-line quench. Crucially, this flow strategy mitigates the need to perform this transformation at low temperature and at the same time does not liberate excessive amounts of toxic nitrous oxide by-products as observed in batch. Finally, we demonstrated the value of the generated imidazole products by their conversion into various analogues of the etomidate analgesic for which we exploited an efficient one-step Corey–Gilman–Ganem oxidation process in batch mode.

Scheme 6. Batch synthesis of etomidate derivatives.

Experimental Section

All solvents, substrates, and reagents were used as purchased without further purification. ^{1}H NMR spectra were recorded on 400 MHz instruments and are reported relative to residual solvent peaks: CHCl$_3$ (δ = 7.26 ppm) or [D$_6$]DMSO (δ =2.50 ppm). ^{13}C NMR spectra were recorded on the same instruments and are reported relative to CHCl$_3$ (δ = 77.16 ppm) or [D$_6$]DMSO (δ =39.52 ppm). Data for ^{1}H-NMR are reported as follows: chemical shift (δ/ppm) (integration, multiplicity, coupling constant [Hz]). 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/ppm) and multiplicity (C, CH, CH$_2$, or CH$_3$). Data for ^{19}F NMR were recorded on the above instruments at a frequency of 376 MHz using CFCl$_3$ as external standard. DEPT-135, COSY, HSQC, HMBC, and NOESY experiments were used in the structural assignment. IR spectra were recorded 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 by using the indicated techniques on instruments equipped with Acquity UPLC and a lock-mass electrospray ion source. For accurate mass measurements the deviation from the calculated formula is reported in ppm. Melting points were recorded on an automated melting point system with a heating rate of 1 °C/min and are uncorrected.

General Procedure for Flow Desulfurization: By using a Vapourtec E-series flow system a vigorously stirred suspension of thioimidazole substrate **3** (0.5 M in HOAc/THF 50:50 by volume; 0.33 mL/min) was directed into a wide-bore T-piece (Kinesis, 1.5 mm i.d.) where it was combined with a solution of sodium nitrite (2 M, water; 0.33 mL/min). Upon uniting both streams, the heterogeneous mixture quickly became homogeneous and generated gaseous byproducts. This mixture was then directed into two flow coils (10 mL each, room temperature) to give a residence time of about 30 min. Using a further T-piece a solution of ammonium hydroxide (8 M, water; 0.5 mL/min) was added to the crude reaction mixture. Upon passing a further segment of tubing ($\approx$ 15 cm), the crude mixture was collected in a flask. After partitioning between EtOAc and water, the desired product was obtained after drying (Na$_2$SO$_4$) and evaporating the organic layer.

[(1-Benzyl-1H)-imidazol-5-yl]methanol (6a): Off-white solid. Yield: 90 %. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.69 (d, J = 0.9 Hz, 1 H), 7.32–7.38 (m, 2 H), 7.26–7.32 (m, 1 H), 7.17 (d, J = 6.9 Hz, 2 H), 6.83 (s, 1 H), 5.24 (s, 2 H), 5.14 (t, J = 4.5 Hz, 1 H), 4.32 (d, J = 4.5 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 138.9 (CH), 138.1 (C), 132.1 (C), 129.1 (2CH), 128.0 (CH), 127.9 (CH), 127.5 (2CH), 53.3 (CH$_2$), 48.0 (CH$_2$) ppm. IR (neat): $\tilde{v}$ = 3182 (br. m), 2947 (m), 2868 (m), 1457 (m), 1439 (m), 1356 (m), 1248 (m), 1209 (m), 1103 (s), 1017 (s), 968 (m), 926 (m), 835 (s), 715 (s), 656 (m) cm^{-1}. HR-MS (TQF+) calculated for C$_{11}$H$_{13}$N$_2$O 189.1028, found 189.1028.

{[1-(4-Bromobenzyl)-1H]imidazol-5-yl}methanol (6b): Off-white solid. Melting range: 136.0–138.1 °C. Yield: 87 %. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.71 (s, 1 H), 7.55 (d, J = 8.0 Hz, 2 H), 7.13 (d, J = 8.0 Hz, 2 H), 6.85 (s, 1 H), 5.22 (s, 2 H), 5.19 (br. s, 1 H), 4.33 (s, 2 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 139.0 (CH), 137.5 (C), 132.1 (C), 132.0 (2CH), 129.7 (2CH), 128.0 (CH), 121.1 (C), 53.2 (CH$_2$), 47.4 (CH$_2$) ppm. IR (neat): $\tilde{v}$ = 3238 (m), 3111 (m), 2946 (m), 1488 (s), 1435 (m), 1247 (m), 1101 (m), 1073 (m), 1011 (s), 966 (m), 920 (m), 837 (s), 804 (s), 763 (m), 733 (s), 669 (m) cm^{-1}. HR-MS (TQF+) calculated for C$_{11}$H$_{12}$N$_2$OBr 267.0133, found 267.0122.

{[1-(2,4-Dichlorobenzyl)-1H]imidazol-5-yl}methanol (6c): Off-white solid. Melting range: 144.2–146.8 °C. Yield: 83 %. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.49 (s, 1 H), 7.42 (d, J = 2.3 Hz, 1 H), 7.20 (dd, J = 8.3, 2.3 Hz, 1 H), 6.87 (s, 1 H), 6.72 (d, J = 8.3 Hz, 1 H), 5.29 (s, 2 H), 5.11 (br. s, 1 H), 4.37 (s, 2 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 138.8 (CH), 133.9 (C), 133.8 (C), 133.2 (C), 132.0 (C), 129.6 (CH), 129.2 (CH), 128.1 (CH), 127.7 (CH), 53.4 (CH$_2$), 45.7 (CH$_2$) ppm. IR (neat): $\tilde{v}$ = 3070 (br. m), 1589 (w), 1563 (w), 1504 (m), 1477 (m), 1401 (m), 1318 (m), 1241 (m), 1103 (s), 1027 (s), 925 (s), 887 (m), 925 (s), 857 (m), 827 (s), 778 (s), 732 (s), 653 (s) cm^{-1}. HR-MS (TQF+) calculated for C$_{11}$H$_{11}$N$_2$OCl$_2$ 257.0248, found 257.0242.

{[1-(2,6-Difluorobenzyl)-1H]imidazol-5-yl}methanol (6d): Off-white solid. Yield: 91 %. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.52 (s, 1 H), 7.45–7.50 (m, 1 H), 7.16 (app t, J = 8.2 Hz, 2 H), 6.79 (s, 1 H), 5.30 (s, 2 H), 5.14 (s, 1 H), 4.44 (s, 2 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 161.2 (dd, J = 249, 8 Hz, 2CF), 138.5 (CH), 132.1 (C), 131.7 (t, J = 11 Hz, CH), 127.6 (CH), 112.8 (t, J = 19 Hz, C), 112.4 (m, 2CH), 53.1 (CH$_2$), 36.3 (t, J = 4 Hz, CH$_2$) ppm. ^{19}F NMR (367 MHz, [D$_6$]DMSO): δ = –114.5 ppm. IR (neat): $\tilde{v}$ = 3094 (br. m), 2828 (m), 1624 (m), 1591 (m), 1505 (m), 1468 (s), 1451 (m), 1360 (m), 1273 (m), 1255 (m), 1235 (m), 1212 (m), 1112 (m), 1029 (s), 1017 (s), 933 (m), 833 (s), 793 (s), 767 (s), 677 (s), 660 (s), 533 (m) cm^{-1}. HR-MS (TQF+) calculated for C$_{11}$H$_{11}$N$_2$OF$_2$ 225.0839, found 225.0841.

({1-[3,5-bis-(Trifluoromethyl)benzyl]-1H}imidazol-5-yl)methanol (6e): Off-white solid. Melting range: 102.3–105.0 °C. Yield: 85 %. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.82 (s, 1 H), 7.59 (s, 2 H), 7.46 (s, 1 H), 6.88 (s, 1 H), 5.38 (2 H), 4.50 (s, 2 H), 3.77 (br. s, 1 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 139.1 (C), 138.5 (CH), 132.4 (q, J = 34 Hz, 2 C), 131.4 (C), 128.6 (CH), 127.2 (m, 2CH), 122.9 (q, J = 274 Hz, 2CF$_3$), 120.2 (CH, m), 54.0 (CH$_2$), 47.9 (CH$_2$) ppm. ^{19}F NMR (367 MHz, CDCl$_3$): δ = –63.0 ppm. IR (neat): $\tilde{v}$ = 3150 (br. m), 1500 (w), 1379 (w), 1350 (w), 1275 (s), 1169 (s), 1124 (s), 1021 (m), 910 (m), 844 (m), 704 (m), 682 (s), 661 (m) cm^{-1}. HR-MS (TQF+) calculated for C$_{13}$H$_{11}$N$_2$OF$_6$ 325.0776, found 325.0775.

1-[(1S)-1-Phenylethyl]-5-hydroxymethylimidazole (6f): Beige solid. Melting range: 110.6–112.3 °C. Yield: 87 %. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.63 (d, J = 1.0 Hz, 1 H), 7.24–7.36 (m, 3 H), 7.08–7.13 (m, 2 H), 6.93 (s, 1 H), 5.61 (q, J = 7.1 Hz, 1 H), 4.51 (d, J = 13.5 Hz, 1 H), 4.34 (d, J = 13.5 Hz, 1 H), 2.79 (br. s, 1 H), 1.86 (d, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 141.7 (C), 136.2 (CH), 131.2 (C), 129.0 (2CH), 128.7 (CH), 127.9 (CH), 125.8 (2CH), 54.8 (CH), 54.4 (CH$_2$), 22.5 (CH$_3$) ppm. IR (neat): $\tilde{v}$ = 3090 (m), 2990 (m), 2843 (m), 1497 (m), 1450 (m), 1323 (m), 1236 (m), 1212 (m), 1110 (m), 1020 (s), 931 (s), 867 (m), 821 (m), 706 (s), 667 (s) cm^{-1}. HR-MS (TQF+) calculated for C$_{12}$H$_{15}$N$_2$O 203.1184, found 203.1184.

1-[(1R)-1-Phenylethyl]-5-hydroxymethylimidazole 6 g: Beige solid. Melting range: 111.0–112.8 °C. Yield: 84 %. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.69 (d, J = 1.0 Hz, 1 H), 7.27–7.37 (m, 3 H), 7.08–7.12 (m, 2 H), 7.00 (s, 1 H), 5.60 (q, J = 7.1 Hz, 1 H), 4.53 (d, J = 13.4 Hz, 1 H), 4.35 (d, J = 13.4 Hz, 1 H), 1.88 (d, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 141.8 (C), 136.4 (CH), 130.9 (C), 129.1 (CH), 129.0 (2CH), 128.0 (CH), 125.7 (2CH), 54.8 (CH), 54.6 (CH$_2$), 22.5 (CH$_3$) ppm. IR (neat): $\tilde{v}$ = 3090 (m), 2989 (m), 2841 (m), 1497 (m), 1450 (m), 1323 (m), 1236 (m), 1212 (m), 1110 (m), 1020 (s), 931 (s), 867 (m), 821 (m), 788 (m), 743 (m), 705 (s), 667 (s) cm^{-1}. HR-MS (TQF+) calculated for C$_{12}$H$_{15}$N$_2$O 203.1184, found 203.1186.

[(1-Butyl-1H)-imidazol-5-yl]methanol (6h): Off-white solid. Yield: 93 %. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.19 (s, 1 H), 6.61 (s, 1 H), 6.38 (br. s, 1 H), 4.44 (s, 2 H), 3.84 (t, J = 7.4 Hz, 2 H), 1.56–1.66 (m, 2 H), 1.18 (app hex, J = 7.4 Hz, 2 H), 0.78 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 137.3 (CH), 131.7 (C), 127.0 (CH), 53.2

(CH$_2$), 44.8 (CH$_2$), 32.8 (CH$_2$), 19.8 (CH$_2$), 13.5 (CH$_3$) ppm. IR (neat): $\tilde{v}$ = 3171 (br. s), 2958 (s), 2873 (s), 1503 (s), 1460 (m), 1368 (m), 1251 (m), 1211 (m), 1111 (s), 1021 (s), 926 (m), 822 (s), 758 (m), 663 (s) cm^{-1}. HR-MS (TQF+) calculated for C$_8$H$_{15}$N$_2$O 155.1184, found 155.1193.

[1-(2-Morpholinoethyl)-1H-imidazol-5-yl]methanol (6i): Yellow oil. Yield: 82 %. ^{1}H NMR (400 MHz, d$_4$-MeOH): δ = 7.87 (d, J = 1.0 Hz, 1 H), 6.99 (s, 1 H), 4.63 (s, 2 H), 4.24 (app t, J = 6.1 Hz, 2 H), 3.65–3.73 (m, 4 H), 2.78 (app t, J = 6.1 Hz, 2 H), 2.50–2.57 (m, 4 H) ppm. ^{13}C NMR (101 MHz, d$_4$-MeOH): δ = 138.3 (CH), 131.8 (C), 125.6 (CH), 66.3 (2CH$_2$), 58.6 (CH$_2$), 53.5 (2CH$_2$), 52.5 (CH$_2$), 42.0 (CH$_2$) ppm. IR (neat): $\tilde{v}$ = 2900–3200 (broad), 2854 (w), 1707 (m), 1564 (m), 1453 (m), 1363 (m), 1262 (s), 1112 (s), 1010 (m), 854 (m), 660 (m), 608 (m) cm^{-1}. HR-MS (TQF+) calculated for C$_{10}$H$_{18}$N$_3$O$_2$ 212.1399, found 212.1392.

{1-[2-(Cyclohex-1-en-1-yl)ethyl]-1H-imidazol-5-yl}methanol (6j): Colourless oil. Yield: 80 %. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.33 (s, 1 H), 6.73 (s, 1 H), 5.35 (br. s, 1 H), 4.56 (s, 2 H), 4.26 (br. s, 1 H), 4.04 (app t, J = 7.2 Hz, 2 H), 2.36 (app t, J = 7.2 Hz, 2 H), 1.85–1.97 (m, 4 H), 1.54–1.65 (m, 2 H), 1.43–1.52 (m, 2 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 137.9 (CH), 133.5 (C), 131.3 (C), 127.6 (CH), 124.5 (CH), 53.8 (CH$_2$), 43.9 (CH$_2$), 39.2 (CH$_2$), 28.3 (CH$_2$), 25.2 (CH$_2$), 22.8 (CH$_2$), 22.2 (CH$_2$) ppm. IR (neat): $\tilde{v}$ = 3110 (broad), 2925 (m), 2835 (m), 1501 (m), 1437 (m), 1361 (m), 1110 (m), 1019 (s), 919 (m), 820 (m), 728 (s), 661 (s) cm^{-1}. HR-MS (TQF+) calculated for C$_{12}$H$_{19}$N$_2$O 207.1497, found 207.1474.

General Procedure for Batch Oxidation: To a solution of alcohol **6** in the desired alcohol solvent (0.3 M) were added MnO$_2$ (40 equiv.), NaCN (0.5 equiv.), and acetic acid (2 drops). This mixture was heated at 80 °C until TLC and ^{1}H-NMR indicated complete conversion of the substrate into the desired ester species (typically 12 h). The reaction mixture was cooled to 25 °C and filtered through a pad of celite yielding the crude product after evaporation of the solvents. Final purification was accomplished by silica column chromatography using EtOAc/hexanes (10–30 % EtOAc) as eluent.

Methyl 1-Benzyl-1H-imidazole-5-carboxylate (7a): Off-white solid. Yield: 78 %. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.76 (d, J = 1.0 Hz, 1 H), 7.61 (s, 1 H), 7.28–7.35 (m, 3 H), 7.13–7.18 (m, 2 H), 5.50 (s, 2 H), 3.80 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 160.6 (C), 142.2 (CH), 138.0 (CH), 136.2 (C), 128.9 (2CH), 128.1 (CH), 127.3 (2CH), 122.5 (C), 51.5 (CH$_3$), 50.0 (CH$_2$) ppm. IR (neat): $\tilde{v}$ = 1709 (s), 1541 (m), 1436 (m), 1363 (s), 1295 (m), 1222 (s), 1200 (m), 1107 (s), 918 (w), 809 (m), 765 (m), 711 (s), 657 (s) cm^{-1}. HR-MS (TQF+) calculated for C$_{12}$H$_{13}$N$_2$O$_2$ 217.0977, found 217.0980.

Ethyl 1-Benzyl-1H-imidazole-5-carboxylate (7b): Off-white solid. Melting range: 53.0–54.9 °C. Yield: 85 %. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.76 (d, J = 1.0 Hz, 1 H), 7.60 (s, 1 H), 7.25–7.33 (m, 3 H), 7.13–7.16 (m, 2 H), 5.49 (s, 2 H), 4.24 (q, J = 7.1 Hz, 2 H), 1.29 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 160.2 (C), 142.2 (CH), 137.9 (CH), 136.3 (C), 128.9 (2CH), 128.1 (CH), 127.2 (2CH), 122.8 (C), 60.5 (CH$_2$), 50.0 (CH$_2$), 14.2 (CH$_3$) ppm. IR (neat): $\tilde{v}$ = 2983 (w), 1708 (s), 1539 (w), 1373 (m), 1293 (m), 1221 (s), 1124 (s), 1103 (s), 1019 (w), 921 (w), 840 (w), 765 (m), 713 (s), 658 (m) cm^{-1}. HR-MS (TQF+) calculated for C$_{13}$H$_{15}$N$_2$O$_2$ 231.1134, found 231.1132.

Isopropyl 1-Benzyl-1H-imidazole-5-carboxylate (7c): Off-white solid. Yield: 81 %. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.76 (d, J = 1.0 Hz, 1 H), 7.59 (s, 1 H), 7.27–7.39 (m, 3 H), 7.14–7.18 (m, 2 H), 5.51 (s, 2 H), 5.14 (sept, J = 6.3 Hz, 1 H), 1.28 (d, J = 6.3 Hz, 6 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 159.8 (C), 142.0 (CH), 137.8 (CH), 136.3 (C), 128.9 (2CH), 128.1 (CH), 127.2 (2CH), 123.2 (C), 68.2 (CH), 50.1 (CH$_2$), 21.9 (2CH$_3$) ppm. IR (neat): $\tilde{v}$ = 2983 (w), 1708 (s), 1543 (w),

1459 (w), 1374 (s), 1294 (w), 1225 (s), 1124 (m), 1100 (s), 715 (m), 657 (w) cm^{-1}. HR-MS (TQF+) calculated for C$_{14}$H$_{17}$N$_2$O$_2$ 245.1290, found 245.1262.

Ethyl 1-(2,6-Difluorobenzyl)-1H-imidazole-5-carboxylate (7d): Off-white solid. Yield: 80 %. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.72 (d, J = 1.0 Hz, 1 H), 7.50 (s, 1 H), 7.32 (app tt, J = 8.4, 6.5 Hz, 1 H), 6.93 (dd, 8.4, J = 7.6 Hz, 2 H), 5.63 (s, 2 H), 4.33 (q, J = 7.1 Hz, 2 H), 1.35 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 161.4 (dd, J = 252, 7 Hz, 2CF), 160.3 (C), 141.7 (CH), 137.5 (CH), 131.1 (t, J = 10 Hz, CH), 122.9 (C), 111.7 (m, 2CH), 111.5 (C, m), 60.6 (CH$_2$), 38.0 (CH$_2$), 14.3 (CH$_3$) ppm. ^{19}F NMR (376 MHz, CDCl$_3$): δ = –114.0 ppm. IR (neat): $\tilde{v}$ = 2984 (w), 1710 (s), 1627 (m), 1471 (s), 1374 (m), 1351 (m), 1220 (s), 1101 (s), 1025 (s), 902 (w), 834 (m), 792 (s), 763 (m), 655 (s) cm^{-1}. HR-MS (TQF+) calculated for C$_{13}$H$_{13}$N$_2$O$_2$F$_2$ 267.0945, found 267.0949.

2,2,2-Trifluoroethyl 1-(2,6-Difluorobenzyl)-1H-imidazole-5-carboxylate (7e): Off-white solid. Yield: 77 %. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.83 (d, J = 1.0 Hz, 1 H), 7.58 (s, 1 H), 7.35 (app tt, J = 8.5, 6.5 Hz, 1 H), 6.95 (dd, J = 8.5, 6.5 Hz, 2 H), 5.61 (s, 2 H), 4.65 (q, J = 8.3 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 161.4 (dd, J = 252, 7 Hz, 2CF), 158.3 (C), 142.8 (CH), 139.2 (CH), 131.2 (t, J = 10 Hz, CH), 122.9 (q, J = 277 Hz, CF$_3$), 121.1 (C), 111.7 (m, 2CH), 111.3 (t, J = 19 Hz, C), 60.0 (q, J = 37 Hz, CH$_2$), 38.1 (t, J = 4 Hz, CH$_2$) ppm. ^{19}F NMR (376 MHz, CDCl$_3$): δ = –73.7, –114.0 ppm. IR (neat): $\tilde{v}$ = 1728 (s), 1628 (m), 1537 (m), 1472 (m), 1365 (m), 1273 (m), 1219 (m), 1164 (s), 1102 (s), 1028 (m), 971 (m), 840 (m), 791 (m), 757 (m), 651 (s) cm^{-1}. HR-MS (TQF+) calculated for C$_{13}$H$_{10}$N$_2$O$_2$F$_5$ 321.0662, found 321.0665.

Ethyl 1-(2,4-Dichlorobenzyl)-1H-imidazole-5-carboxylate (7f): Off-white solid. Melting range: 90.5–91.6 °C. Yield: 87 %. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.76 (d, J = 1.0 Hz, 1 H), 7.61 (d, J = 1.0 Hz, 1 H), 7.37 (d, J = 2.1 Hz, 1 H), 7.12 (dd, J = 8.4, 2.1 Hz, 1 H), 6.70 (dd, J = 8.4, 0.8 Hz, 1 H), 5.53 (s, 2 H), 4.22 (q, J = 7.1 Hz, 2 H), 1.26 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 160.0 (C), 142.4 (CH), 138.0 (CH), 134.9 (C), 133.3 (C), 133.0 (C), 129.5 (CH), 129.0 (CH), 127.6 (CH), 122.7 (C), 60.7 (CH$_2$), 47.2 (CH$_2$), 14.2 (CH$_3$) ppm. IR (neat): $\tilde{v}$ = 3097 (w), 2993 (w), 1698 (s), 1541 (m), 1470 (m), 1373 (s), 1347 (m), 1295 (m), 1264 (m), 1234 (s), 1194 (m), 1121 (s), 1101 (s), 1047 (m), 1022 (m), 864 (m), 834 (m), 817 (m), 766 (s), 658 (m) cm^{-1}. HR-MS (TQF+) calculated for C$_{13}$H$_{13}$N$_2$O$_2$Cl$_2$ 299.0354, found 299.0352.

Methyl 1-(2,4-Dichlorobenzyl)-1H-imidazole-5-carboxylate 7 (g): Off-white solid. Melting range: 102.4–105.0 °C. Yield: 81 %. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.72 (d, J = 1.1 Hz, 1 H), 7.60 (d, J = 1.1 Hz, 1 H), 7.33 (d, J = 2.1 Hz, 1 H), 7.09 (dd, J = 8.3, 2.1 Hz, 1 H), 6.69 (d, J = 8.3 Hz, 1 H), 5.51 (s, 2 H), 3.73 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 160.4 (C), 142.5 (CH), 138.1 (CH), 134.5 (C), 133.3 (C), 132.9 (C), 129.5 (CH), 129.0 (CH), 127.6 (CH), 122.4 (C), 51.6 (CH$_3$), 47.1 (CH$_2$) ppm. IR (neat): $\tilde{v}$ = 3024 (w), 2963 (w), 1698 (s), 1532 (m), 1473 (m), 1426 (m), 1365 (s), 1298 (m), 1262 (m), 1225 (s), 1196 (s), 1115 (s), 1047 (m), 953 (m), 831 (s), 771 (s), 655 (s) cm^{-1}. HR-MS (TQF+) calculated for C$_{12}$H$_{11}$N$_2$O$_2$Cl$_2$ 285.0198, found 285.0189.

Ethyl 1-[3,5-Bis(trifluoromethyl)benzyl]-1H-imidazole-5-carboxylate (7h): Off-white solid. Melting range: 63.8–65.0 °C. Yield: 75 %. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.78 (m, 2 H), 7.73 (s, 1 H), 7.59 (s, 2 H), 5.62 (s, 2 H), 4.24 (q, J = 7.1 Hz, 2 H), 1.28 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 160.1 (C), 142.1 (CH), 139.1 (C), 138.3 (CH), 132.2 (q, J = 34 Hz, 2 C), 127.3 (m, 2CH), 123.0 (q, J = 274 Hz, 2CF$_3$), 122.6 (C), 122.1 (dt, J = 8, 4 Hz, CH), 60.8 (CH$_2$), 49.0 (CH$_2$), 14.1 (CH$_3$) ppm. ^{19}F NMR (376 MHz, CDCl$_3$): δ = –63.0 ppm. IR (neat): $\tilde{v}$ = 1711 (m), 1543 (w), 1477 (w), 1376 (m), 1353

(m), 1276 (s), 1170 (s), 1123 (s), 905 (m), 843 (m), 704 (m), 682 (m), 659 (m) cm^{-1}. HR-MS (TQF+) calculated for C$_{15}$H$_{13}$N$_2$O$_2$F$_6$ 367.0881, found 367.0876.

Ethyl 1-(4-Bromobenzyl)-1H-imidazole-5-carboxylate (7i): Off-white solid. Melting range: 66.5–68.9 °C. Yield: 84 %. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.74 (d, J = 1.0 Hz, 1 H), 7.61 (s, 1 H), 7.41 (d, J = 8.4 Hz, 2 H), 6.99 (d, J = 8.4 Hz, 2 H), 5.43 (s, 2 H), 4.23 (q, J = 7.1 Hz, 2 H), 1.28 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 160.1 (C), 142.1 (CH), 138.0 (CH), 135.4 (C), 132.0 (2CH), 128.8 (2CH), 122.6 (C), 122.0 (C), 60.6 (CH$_2$), 49.4 (CH$_2$), 14.2 (CH$_3$) ppm. IR (neat): ṽ = 3096 (w), 2983 (w), 1700 (s), 1540 (m), 1487 (m), 1368 (m), 1343 (s), 1260 (m), 1227 (s), 1184 (m), 1105 (s), 1010 (m), 917 (m), 766 (m), 752 (m), 659 (m) cm^{-1}. HR-MS (TQF+) calculated for C$_{13}$H$_{14}$N$_2$O$_2$Br 309.0239, found 309.0246.

(R)-Ethyl 1-(1-Phenylethyl)-1H-imidazole-5-carboxylate (7j): Colourless Oil. Yield: 85 %. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.78 (d, J = 1.1 Hz, 1 H), 7.73 (s, 1 H), 7.31–7.39 (m, 2 H), 7.26–7.31 (m, 1 H), 7.15–7.22 (m, 2 H), 6.37 (q, J = 7.1 Hz, 1 H), 4.19–4.34 (m, 2 H), 1.87 (d, J = 7.1 Hz, 3 H), 1.32 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 160.3 (C), 141.1 (C), 139.7 (CH), 138.0 (CH), 128.8 (2CH), 128.0 (CH), 126.2 (2CH), 122.7 (C), 60.4 (CH$_2$), 55.3 (CH), 22.2 (CH$_3$), 14.3 (CH$_3$) ppm. IR (neat): ṽ = 2982 (w), 1709 (s), 1537 (w), 1451 (m), 1373 (m), 1347 (m), 1210 (s), 1130 (s), 1107 (s), 1054 (m), 1028 (m), 921 (m), 764 (s), 699 (s), 658 (s) cm^{-1}. HR-MS (TQF+) calculated for C$_{14}$H$_{17}$N$_2$O$_2$ 245.1290, found 245.1281.

(S)-Ethyl 1-(1-Phenylethyl)-1H-imidazole-5-carboxylate (7k): Colourless Oil. Yield: 82 %. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.78 (d, J = 1.1 Hz, 1 H), 7.73 (s, 1 H), 7.31–7.37 (m, 2 H), 7.25–7.31 (m, 1 H), 7.16–7.21 (m, 2 H), 6.37 (q, J = 7.1 Hz, 1 H), 4.16–4.35 (m, 2 H), 1.86 (d, J = 7.1 Hz, 3 H), 1.32 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 160.3 (C), 141.2 (C), 139.7 (CH), 138.1 (CH), 128.8 (2CH), 128.0 (CH), 126.3 (2CH), 122.6 (C), 60.4 (CH$_2$), 55.3 (CH), 22.2 (CH$_3$), 14.3 (CH$_3$) ppm. IR (neat): ṽ = 2983 (w), 1709 (s), 1537 (w), 1451 (m), 1373 (s), 1347 (s), 1209 (s), 1130 (s), 1106 (s), 1054 (m), 1028 (m), 921 (m), 764 (s), 699 (s), 659 (s) cm^{-1}. HR-MS (TQF+) calculated for C$_{14}$H$_{17}$N$_2$O$_2$ 245.1290, found 245.1283.

Isopropyl 1-Butyl-1H-imidazole-5-carboxylate (7l): Colourless oil. Yield: 90 %. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.67 (d, J = 1.0 Hz, 1 H), 7.52 (s, 1 H), 5.15 (sept, J = 6.3 Hz, 1 H), 4.24 (t, J = 7.3 Hz, 2 H), 1.72 (tt, J = 8.3, 6.7 Hz, 2 H), 1.30 (d, J = 6.3 Hz, 6 H), 1.24–1.29 (m, 2 H), 0.90 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 159.8 (C), 141.7 (CH), 137.7 (CH), 122.8 (C), 68.0 (CH), 46.7 (CH$_2$), 33.1 (CH$_2$), 21.9 (2CH$_3$), 19.7 (CH$_2$), 13.6 (CH$_3$) ppm. IR (neat): ṽ = 2961 (w), 1706 (s), 1540 (m), 1468 (m), 1372 (m), 1300 (m), 1251 (m), 1220 (s), 1133 (s), 1094 (s), 923 (m), 839 (m), 767 (m), 658 (m) cm^{-1}. HR-MS (TQF+) calculated for C$_{11}$H$_{19}$N$_2$O$_2$ 211.1447, found 211.1444.

Ethyl 1-Butyl-1H-imidazole-5-carboxylate (7m): Colourless oil. Yield: 88 %. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.68 (d, J = 1.0 Hz, 1 H), 7.53 (s, 1 H), 4.20–4.31 (m, 4 H), 1.72 (tt, J = 8.3, 6.8 Hz, 2 H), 1.32 (t, J = 7.1 Hz, 3 H), 1.16–1.30 (m, 2 H), 0.90 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 160.2 (C), 141.8 (CH), 137.9 (CH), 122.4 (C), 60.4 (CH$_2$), 46.7 (CH$_2$), 33.1 (CH$_2$), 19.7 (CH$_2$), 14.3 (CH$_3$), 13.5 (CH$_3$) ppm. IR (neat): ṽ = 2961 (m), 1711 (s), 1539 (m), 1478 (m), 1373 (s), 1349 (s), 1250 (m), 1219 (s), 1131 (s), 1097 (s), 1019 (w), 921 (w), 766 (m), 658 (s) cm^{-1}. HR-MS (TQF+) calculated for C$_{10}$H$_{17}$N$_2$O$_2$ 197.1290, found 197.1287.

Ethyl 1-[(2-Cyclohex-1-en-1-yl)ethyl]-1H-imidazole-5-carboxylate (7n): Colourless Oil. Yield: 79 %. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.69 (d, J = 1.1 Hz, 1 H), 7.48 (s, 1 H), 5.28 (br. s, 1 H), 4.32 (t, J = 7.0 Hz, 2 H), 4.29 (q, J = 7.1 Hz, 2 H), 2.33 (t, J = 7.0 Hz, 2 H), 1.83–

1.95 (m, 4 H), 1.55–1.64 (m, 2 H), 1.45–1.52 (m, 2 H), 1.34 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 160.3 (C), 142.0 (CH), 137.8 (CH), 133.2 (C), 124.6 (CH), 122.3 (C), 60.4 (CH$_2$), 45.6 (CH$_2$), 39.5 (CH$_2$), 28.2 (CH$_2$), 25.2 (CH$_2$), 22.8 (CH$_2$), 22.2 (CH$_2$), 14.3 (CH$_3$) ppm. IR (neat): ṽ = 2927 (m), 2857 (w), 1711 (s), 1539 (m), 1478 (m), 1373 (m), 1350 (m), 1220 (s), 1124 (s), 1104 (s), 1022 (m), 922 (m), 835 (w), 766 (m), 659 (m) cm^{-1}. HR-MS (TQF+) calculated for C$_{14}$H$_{21}$N$_2$O$_2$ 249.1603, found 249.1613.

[1] a) S. M. Weinreb, *Nat. Prod. Rep.* **2007**, *24*, 931–948; b) L. Zhang, X.-M. Peng, G. L. V. Damu, R.-X. Geng, C.-H. Zhou, *Med. Res. Rev.* **2014**, *34*, 340–437.

[2] M. Baumann, I. R. Baxendale, S. V. Ley, N. Nikbin, *Beilstein J. Org. Chem.* **2011**, *7*, 442–495. Also, see ref.[1a].

[3] M. Baumann, I. R. Baxendale, *Org. Lett.* **2014**, *16*, 6076–6079.

[4] a) J. M. Bergen, D. C. Smith, *J. Emerg. Med.* **1997**, *15*, 221–230; b) D. C. Smith, J. M. Bergen, H. Smithline, R. Kirschner, *J. Emerg. Med.* **2000**, *18*, 13–16; c) J. F. Cotten, S. S. Husain, S. A. Forman, K. W. Miller, E. W. Kelly, H. H. Nguyen, D. E. Raines, *Anesthesiology* **2009**, *111*, 240–249; d) E. Pejo, P. Santer, S. Jeffrey, H. Gallin, S. S. Husein, D. E. Raines, *Anesthesiology* **2014**, *121*, 290–301.

[5] a) K. Sato, M. Aoki, J. Takagi, R. Noyori, *J. Am. Chem. Soc.* **1997**, *119*, 12386–12387; b) J. H. Chang, K. W. Lee, D. H. Nam, W. S. Kim, H. Shin, *Org. Process Res. Dev.* **2002**, *6*, 674–676.

[6] a) P. E. Maligres, M. S. Waters, S. A. Weissman, J. C. McWilliams, S. Lewis, J. Cowen, R. A. Reamer, R. P. Volante, P. J. Reider, D. Askin, *J. Heterocycl. Chem.* **2003**, *40*, 229–240; b) D. Przybyla, U. Nubbemeyer, *Eur. J. Org. Chem.* **2017**, 695–703; c) J. P. Collman, M. Zhong, S. Costanzo, C. Zhang, *J. Org. Chem.* **2001**, *66*, 8252–8256.

[7] Further details on the Vapourtec E-series flow system can be obtained from their website: https://www.vapourtec.com/products/e-series-flow-chemistry-system-overview/.

[8] 3-Way connectors (T-pieces) were purchased from Kinesis: http://kinesis.co.uk/knowledgebase/low-volume-flow-paths.

[9] a) R. L. Hartman, *Org. Process Res. Dev.* **2012**, *16*, 870–887; b) T. Horie, M. Sumino, T. Tanaka, Y. Matsushita, T. Ichimura, J. Yoshida, *Org. Process Res. Dev.* **2010**, *14*, 405–410; c) J. Sedelmeier, S. V. Ley, I. R. Baxendale, M. Baumann, *Org. Lett.* **2010**, *12*, 3618–3821; d) C. S. Polster, K. P. Cole, C. L. Burcham, B. M. Campbell, A. L. Frederick, M. M. Hansen, M. Harding, M. R. Heller, M. T. Miller, J. L. Phillips, P. M. Pollock, N. Zaborenko, *Org. Process Res. Dev.* **2014**, *18*, 1295–1309; e) P. Koos, D. L. Browne, S. V. Ley, *Green Process Synth.* **2012**, *1*, 11–18; f) P. Filipponi, A. Gioiello, I. R. Baxendale, *Org. Process Res. Dev.* **2016**, *20*, 371–375.

[10] It was noted that using a back-pressure regulator can in some cases increase the likelihood of solids depositing in the peristaltic pump of stream A, which can lead to inaccurate flow rates and even to blocking of the pump. Despite forming gaseous by-products, it was found that an open reactor exit mitigates this risk and still allows for the reaction to reach completion within the flow coils.

[11] Alternative mechanisms can be postulated in which nitrous acid (HONO) or nitrite anion reacts with ammonium hydroxide, either of which exist in equilibria with the nitrosonium species we propose. Please see: a) N. Takenaka, I. Takahasi, H. Suekane, K. Yamamoto, Y. Sadanga, H. Bandow, *J. Phys. Chem. A* **2011**, *115*, 14446–14451; b) J. H. Dusenbury, R. E. Powell, *J. Am. Chem. Soc.* **1951**, *73*, 3266–3268.

[12] J. B. Epp, T. S. Widlanski, *J. Org. Chem.* **1999**, *64*, 293–295.

[13] a) E. J. Corey, N. W. Gilman, B. E. Ganem, *J. Am. Chem. Soc.* **1968**, *90*, 5616–5617; b) N. W. Gilman, *J. Chem. Soc., Chem. Commun.* **1971**, 733–734; c) J. S. Foot, H. Kanno, G. M. P. Giblin, R. J. K. Taylor, *Synthesis* **2003**, *7*, 1055–1064; d) Corey–Gilman–Ganem Oxidation, *Compr. Org. Name Reactions Reagents* **2010**, *158*, 722–725.

[14] To rule out possible racemization of compounds **7j/7k** (and hence **6f/6g**) chiral HPLC analysis on these structures was used, see the Supporting Information for details.

[15] Using a commercially available cyanide test kit confirmed that ≈ 99 % of cyanide was removed by this ion-exchange procedure.