Tetrahedron 64 (2008) 6961–6972

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A modular synthesis of chiral aminoindanol-derived imidazolium salts

Justin R. Struble, Jeffrey W. Bode *

Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104-6354, USA

ARTICLE INFO

Article history:
Received 19 January 2008
Received in revised form 18 March 2008
Accepted 19 March 2008
Available online 22 March 2008

Dedicated to Professor John Hartwig in honor of his 2007 Tetrahedron Young Investigator Award

ABSTRACT

A modular synthesis of *N*-substituted chiral imidazolium salts derived from (1*R*,2*S*)-(+)-1-amino-2-indanol is described. A wide range of amines are amenable to late stage introduction of the *N*-substituent to provide *N*-aryl, *N*-alkyl, and *N*-amino imidazolium salts, which serve as precursors to chiral *N*-heterocyclic carbenes (NHCs). A multi-gram synthesis of the *N*-mesityl derivative provides an important imidazolium salt for ongoing studies aimed at the development and understanding of NHC-catalyzed annulations. Critical to the success of this synthetic strategy is a chemoselective alkylation, 6-*exo*-*tet* ring closure of a formamide onto an epoxide, and a heterocyclic interconversion strategy.

1. Introduction

Over the past two decades, *N*-heterocyclic carbenes (NHCs) have received increasing attention due to their storied role as ligands for transition metal complexes[1] and, more recently, their remarkable properties as catalysts in their own right.[2,3] As an increasing number of processes catalyzed by either NHCs or their transition metal complexes are reported, interest in developing highly enantioselective variants through the design and synthesis of chiral NHCs continues to grow.[4] To this end, important advances have been made by Grubbs,[5] Hoveyda,[6] Burgess,[7] Glorius,[4a] Montgomery,[8] and many others in the preparation and application of novel, chiral imidazolium-derived NHCs for catalytic applications (Fig. 1).

In our own studies, we have pioneered the development of novel NHC-catalyzed redox processes of α-functionalized aldehydes, resulting in conceptually novel approaches to ester[9,10] and amide[11,12] formation and the development of a new generation of highly selective annulation reactions from simple starting materials.[13,14] Interestingly, these novel NHC-catalyzed reactions appear to fall into two discrete categories:[15] those catalyzed by imidazolium-derived NHCs[13] and those promoted by triazolium-derived NHCs.[14] For example, our group[13] and that of Glorius[16] have independently documented the imidazolium-derived NHC-catalyzed generation of homoenolate equivalents from enals.[17,18] These species undergo nucleophilic additions to aldehydes, activated ketones, imines, and enones to give stereochemically rich annulation products under exceptionally mild and simple reaction conditions (Fig. 2).

The use of a simple organic molecule as a catalyst raises the promises of developing enantioselective variants of these annulations through the design and synthesis of chiral NHC catalysts. Indeed, chiral triazolium-derived NHCs have been employed as highly selective catalysts for benzoin and intramolecular Stetter reactions.[19,20] Our group has also reported a number of novel annulation processes that employ chiral *N*-mesityl substituted aminoindanol-derived triazolium precatalyst **1** for highly enantioselective annulations for inverse electron demand hetero-Diels–Alder reactions and benzoin-oxy-Cope reactions (Fig. 3).[14] In almost all cases, the NHC catalyst **1** affords the expected products in good yields and outstanding enantioselectivities.

In contrast, the use of **1** or other triazolium-derived NHCs uniformly fails to provide products arising from NHC-catalyzed generation of homoenolates. The lack of reactivity of the triazolium salts coupled with the relative difficulty in preparing chiral imidazolium salts that promote homoenolate-based annulations of enals has stymied the development of enantioselective variants of these promising annulation reactions.

In seeking to address this, we have recently developed a practical synthesis of chiral imidazolium-derived NHC precatalysts built onto the chiral aminoindanol backbone that has proved so successful for enantioselective NHC-catalyzed reactions. In this account, we document these studies in detail, including the application of this synthetic route to diverse chiral *N*-substituted imidazolium salts and their preparation on a multi-gram scale.

2. Results and discussion

2.1. Retrosynthetic analysis

The intense interest in the development and understanding of *N*-heterocyclic carbenes and their complexes has led to a number of

* Corresponding author. Tel.: +1 215 573 1953.
E-mail address: bode@sas.upenn.edu (J.W. Bode).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.03.072

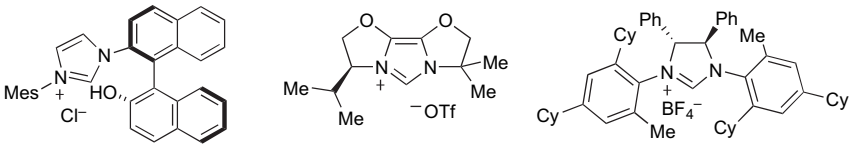


Figure 1. Selected chiral imidazolium salts as NHC precursors.

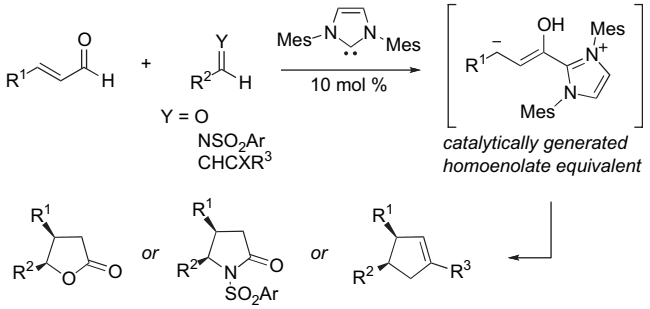
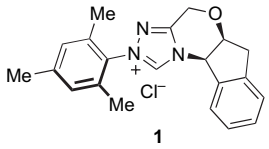


Figure 2. NHC-promoted annulations of catalytically generated homoenolates with various electrophiles.



1

Figure 3. *N*-Mesityl substituted aminoindanol-derived triazolium precatalyst.

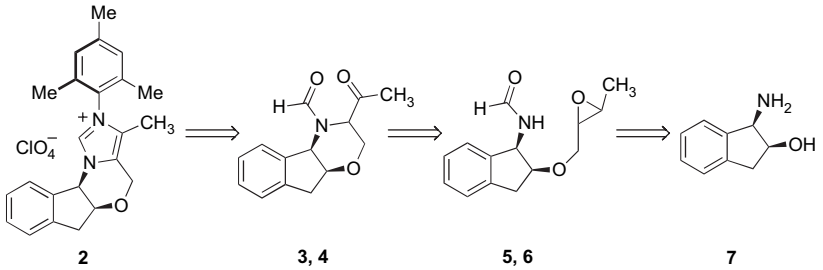
notable advances in their preparation.[21–23] Unfortunately, in our hands, we were generally unable to extend these routes to the preparation of our desired chiral bicyclic imidazolium salts. During the course of these efforts, Fürstner reported a new synthetic entry into unsymmetrically *N*,*N*′-disubstituted imidazolium salts based on a heterocyclic interconversion strategy.[24] This elegant procedure hinges on a three-step, one-pot protocol to prepare diverse imidazolium salts from *N*-formyl amino ketones or aldehydes. We reasoned that chiral aminoindanol-derived imidazolium salts such as **2** could be similarly accessed from intermediates **3** and **4**, a retrosynthetic analysis that considerably simplifies access to this highly desired class of NHC precursors. We further postulated that the diastereomeric formyl ketones **3** and **4** could be derived from epoxides **5** and **6** by intramolecular cyclization and oxidation. In turn, **5** and **6** would be obtained from readily available chiral aminoindanol **7** by N-formylation, alkylation, and epoxidation (Scheme 1).

2.2. Alkylation strategy

We began our studies with a literature procedure for the N-formylation of (1*R*,2*S*)-(+)-1-amino-2-indanol **7**.[25] We initially surmised that the *N*-formylated amide **8** would be reluctant to undergo alkylation, making possible selective O-alkylation in the subsequent step. This O-alkylation, however, proved to be difficult and yields greater than 40% were never consistently achieved even after several attempts to optimize the reaction parameters. In many cases, competing N-alkylation of the formamide reduced the isolated yields of the desired product. In contrast, excellent overall yields of the desired *N*-formyl *O*-crotylated product **10** were achieved simply by switching the order of the steps and performing the O-alkylation directly on unprotected aminoindanol (Scheme 2).

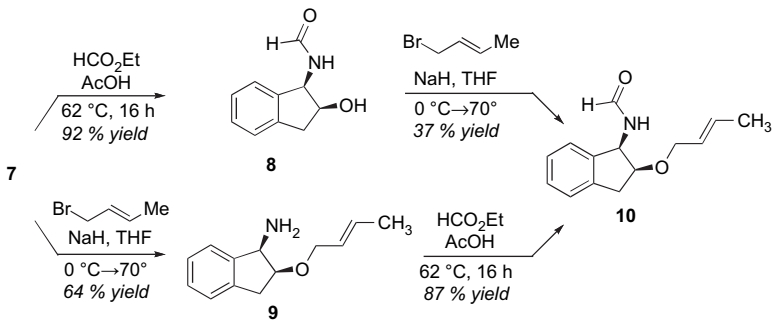
2.3. Epoxidation and cyclization

With **10** in hand, we were pleased to find that epoxidation occurred readily under a variety of straightforward conditions. Treatment of the alkene with excess *m*-CPBA (~3 equiv) in CH_2Cl_2



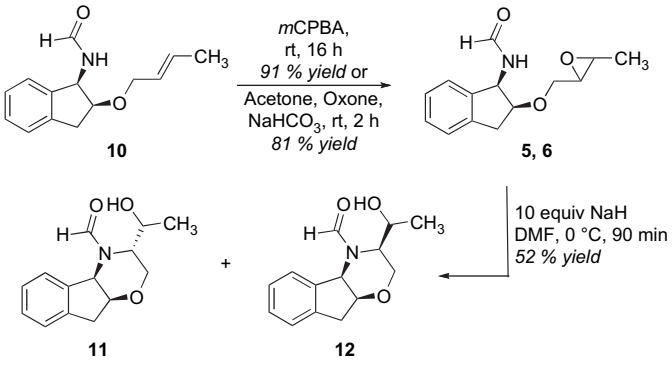
2 **3, 4** **5, 6** **7**

Scheme 1. Retrosynthetic analysis featuring *N*-formyl ketones **3** and **4**.



7 **8** **9** **10**

Scheme 2. Chemoselective alkylation and formylation of 1,2-aminoindanol.



Scheme 3. Epoxidation and intramolecular epoxide opening (*m*-CPBA=3-chloroperoxybenzoic acid).

overnight provided **5** and **6** in nearly quantitative yield, as a 1:1 mixture of diastereomers. The only drawback to this method was purification of the epoxide, which required the removal of excess peracid and the acid byproduct, and led to the formation of colored impurities that proved difficult to remove upon scale-up. We therefore turned to epoxidation via in situ generation of dimethyldioxirane (DMDO).[26] This epoxidation was clean and scalable, but afforded slightly lower conversions than *m*-CPBA. Nevertheless, this approach proved to be the method of choice for preparative scale synthesis of the diastereomeric mixture of epoxides **5** and **6** (Scheme 3).

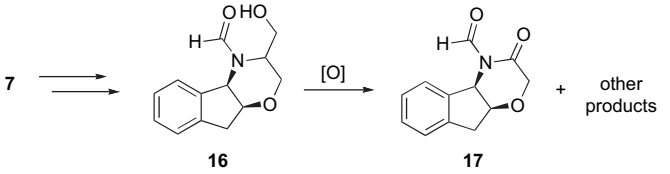
Early attempts to induce a 6-*exo*-*tet* ring closure onto the epoxide under basic conditions (NaH or KHMDS) were stymied by low yields and decomposition. A single precedent for this ring closure employed 10 equiv of NaH in DMF.[27] Indeed, ring closure ensued under these conditions, but yields were only moderate (~50%), and purification and characterization of **11** and **12** proved difficult due to the resultant mixture of diastereomers and amide rotamers.

We sought to improve the overall yield of the cyclization through the stereoselective synthesis of a single epoxide diastereomer via Shi epoxidation (Scheme 4).[28] Since the D-fructose derived Shi catalyst was more readily prepared than its enantiomer, we explored this hypothesis by using the two enantiomers of aminoindanol, **7** and ***ent*-7**, and a single enantiomer of the Shi catalyst. When formyl olefin **10**, derived from (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol, **7**, was employed, the epoxidation was quite efficient (~90% yield) but the diastereoselectivity was only moderate (5:1). However, a single diastereomer of the epoxide, **5**, was obtained after one recrystallization from hexanes/EtOAc. In evaluating the modest yield and product mixture of the cyclization, we were cognizant of the fact that the two diastereomeric epoxides **5** and **6** would likely undergo ring formation at vastly different rates, potentially leading to complications or byproducts.

When the other formyl olefin, ***ent*-10**, derived from the opposite enantiomer of aminoindanol was used as the starting material, the epoxidation also proceeded cleanly to afford ***ent*-6** as a 5:1 mixture of diastereomers. A single diastereomer could be obtained after one recrystallization from hexanes/EtOAc. This diastereomer also cyclized cleanly in the presence of sodium hydride to afford **14** in 76% yield. Although yields of the morpholine products were consistently higher when pure diastereomers were employed in the ring-closing step, there does not appear to be a significant rate difference in the cyclization of the two diastereomeric epoxides. Despite the different stereochemistry, both diastereomers proved amenable to the subsequent steps and gave the identical imidazolium salts as the final product. These observations coupled with other findings on the conversion of **3** and **4** to the final product led to our decision to stay with the lower yielding, but with operationally simpler achiral epoxidation and ring closure shown in Scheme 3 for further studies.

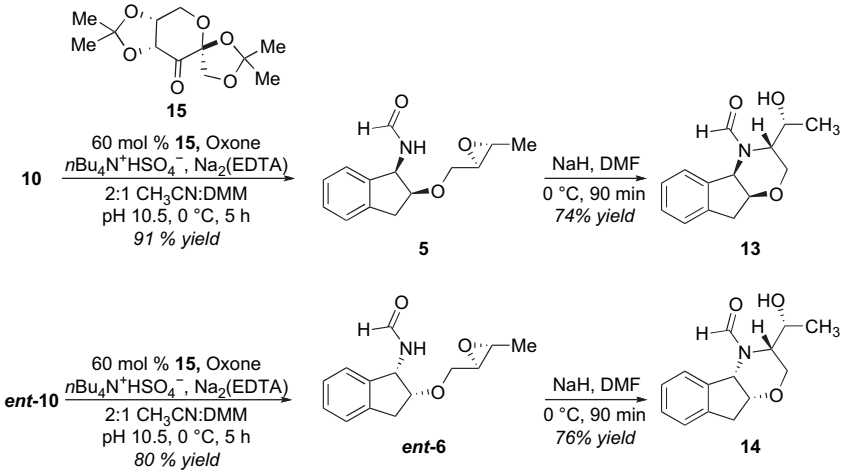
2.4. Oxidation

An early route to the chiral imidazolium salts began with allylation rather than crotylation of aminoindanol **7**. While epoxidation and cyclization proceeded cleanly, we encountered serious difficulties in obtaining the *N*-formyl aldehyde via oxidation of cyclization product **16**. Oxidation of the primary alcohol using standard protocols (TEMPO, TPAP, IBX, SO_3·pyridine, DMP) yielded little or none of the desired aldehyde but rather numerous byproducts and returned starting material, with the major side product identified as over-oxidized morpholinone **17** (Scheme 5).



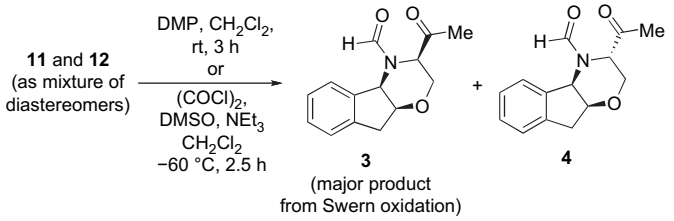
Scheme 5. Unexpected oxidative cleavage of *N*-formyl amino alcohol **18**.

To circumvent this unexpected difficulty, we elected to introduce the crotyl group during alkylation, which would subsequently lead to a secondary alcohol poised for oxidation to the ketone. We were pleased to find that Dess–Martin periodinane (DMP) gave smooth conversion to the ketone in high yield. Further

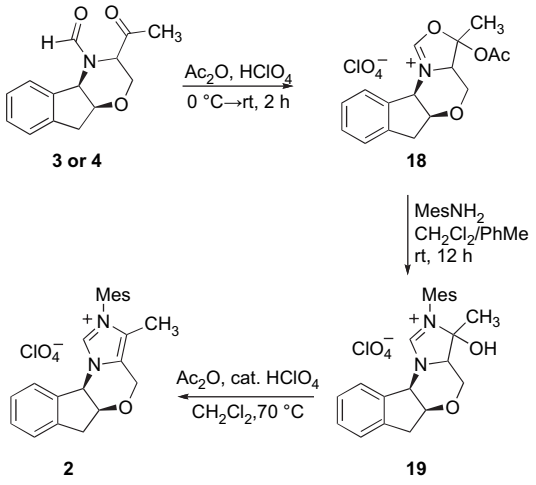


Scheme 4. Stereoselective synthesis of morpholines **13** and **14** by Shi epoxidation (DMM=dimethoxymethane).

studies, particularly for larger scale preparation of ketones **3** and **4**, also identified Swern oxidation conditions that also afforded the ketone in good yield on a 10-g scale. Under the Swern conditions, we found the *N*-formyl ketones to be sensitive toward epimerization affording **3** as the major diastereomer (Scheme 6).



Scheme 6. Oxidation of secondary alcohols **11** and **12** (DMP=1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one).



Scheme 7. Heterocyclic interconversion and elimination for the synthesis of imidazolium salts (Mes=2,4,6-trimethylphenyl).

2.5. Oxazolinium formation and conversion to *N*-substituted imidazolium salts

Ketone intermediates **3** and **4** are the key precursors to Fürstner's heterocyclic interconversion strategy for the synthesis of imidazolium salts from an oxazolinium intermediate. Although Fürstner had demonstrated a remarkably diverse range of compounds prepared with this strategy, he reported no examples of the use of sterically hindered anilines with ketone-derived amino carbonyls. Initial attempts to form the oxazolinium salt **18** by treatment of the *N*-formyl ketones with Ac_2O and aqueous or anhydrous acids HCl and HBF_4 proved unsuccessful. Reactions performed at low temperature returned only starting material; upon heating deprotection of the *N*-formyl group was observed. When $HClO_4$ was employed, a trace amount of product was observed by mass spectrometric analysis of the crude reaction mixture. From this initial hint, we quickly discerned that the oxazolinium adduct was heat sensitive. Thus, treatment of the formyl ketone with $HClO_4$ in Ac_2O was carried out at 0 °C to prevent deformylation. Furthermore, the oxazolinium salt could not be handled or stored for an extended period of time. Once triturated from the reaction mixture, residual solvent was removed in vacuo at rt since even a gentle warming of the solution upon rotary evaporation bath caused decomposition. We further found that cleaner, at least analytically, reactions occurred when diastereomers **3** and **4** were taken on separately through the modified Fürstner protocol, although the identical final product and similar yields were obtained in each case. These

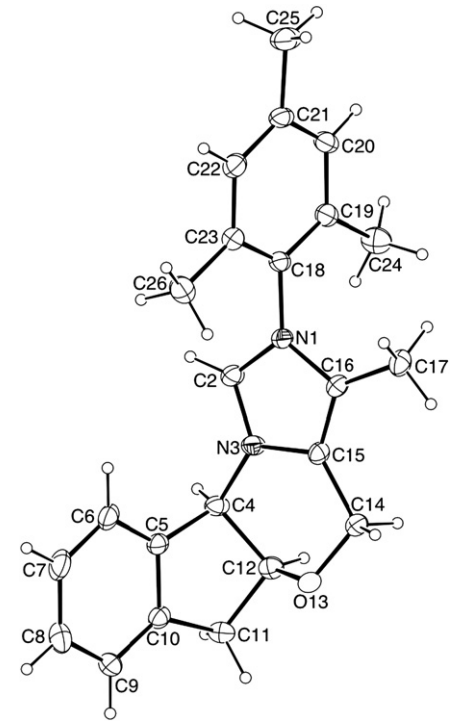
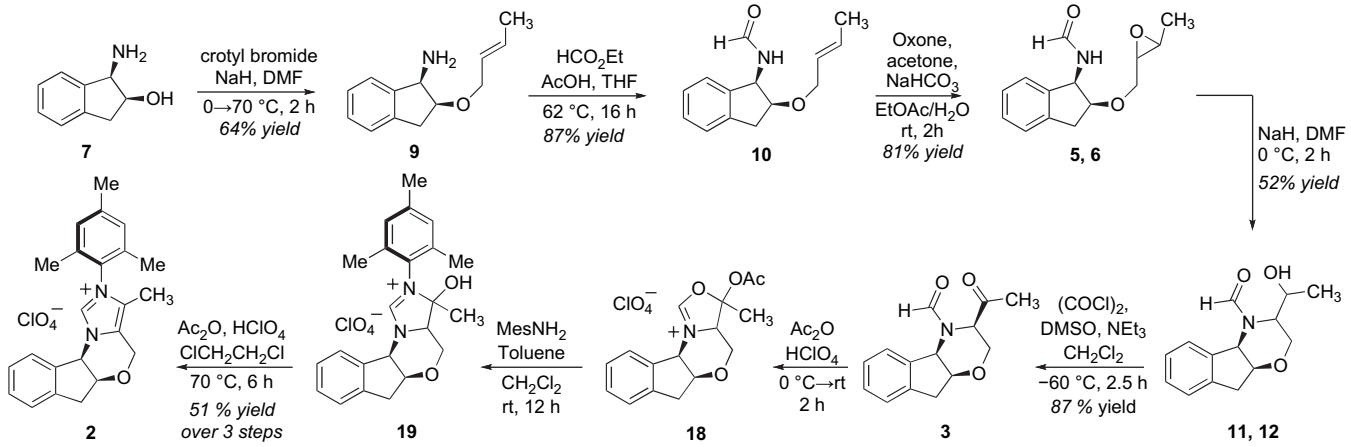


Figure 4. ORTEP plot of *N*-mesityl substituted imidazolium salt **2**.



Scheme 8. Preparative scale synthesis of *N*-mesityl substituted imidazolium salt **2** (crotyl=3-methyl-(*E*)-but-2-enyl and Mes=2,4,6-trimethylphenyl).

important modifications led to a robust and reliable procedure for the preparation of **18**, which served as the key starting material for a modular synthesis of diverse *N*-substituted NHCs (Scheme 7).

Acetal **18** was allowed to react with a variety of amines giving rise to the aminal intermediate (e.g., with 2,4,6-trimethylanilne, **19**) as a set of diastereomers. Although in several cases the aminal could be isolated, purification was difficult and most of the aminal intermediates were used directly for the elimination step without purification. Furthermore, the diastereomers could not be separated, but this was without consequence as the offending stereogenic center is destroyed upon acid elimination to give the imidazolium salt. We also improved upon Fürstner's heterogeneous protocol, which used toluene as the solvent, for a homogeneous one with CH_2Cl_2/toluene that often allowed a cleaner rearrangement to the aminal intermediate.

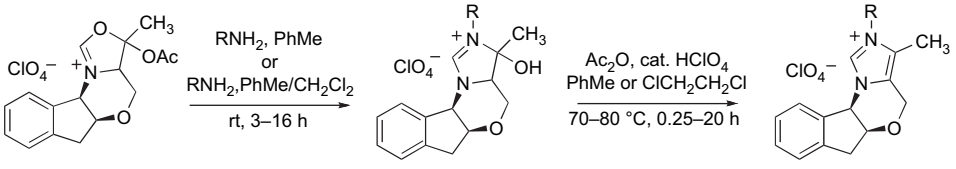
The acid-catalyzed acylation/elimination strategy originally outlined by Fürstner typically led to decomposition and only trace amounts of the desired imidazolium salt were in our hands. We found that by dramatically reducing the equivalents of Ac_2O a cleaner reaction occurred, a finding mirrored by Fürstner in a recent application of this methodology.[29] Still, in several cases, purification of the imidazolium salt was hindered by an intractable oil formed in the reaction. During the optimization of the reaction for large-scale production of **2**, we discovered that changing from a heterogeneous protocol (toluene) to a homogeneous one (1,2-dichloroethane) provided cleaner elimination allowing for easier purification of the imidazolium salt. Furthermore, under these conditions the reaction could be readily monitored by ^{1}H NMR of an aliquot from the reaction.

These conditions[30] proved (vide infra) reliable for a broad range of amines, allowing access to a diverse set of *N*-substituted imidazolium salts that can be used as precursors to *N*-heterocyclic carbene ligands and catalysts.

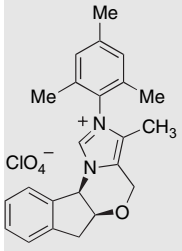
2.6. Preparative scale production of *N*-mesityl imidazolium catalyst 2

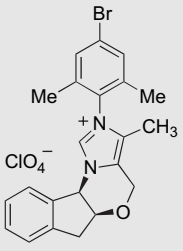
Given our success of utilizing the *N*-mesityl substituted, aminoindanol-derived triazolium salt **1** for highly enantioselective annulation reactions, we were particularly interested in undertaking a systematic survey of the differences between the imidazolium and triazolium salts of otherwise identical structure.[31] In anticipation of these studies, we applied our optimized route to the synthesis of the aminoindanol-derived NHC precursors to a preparative scale synthesis of **2**. Beginning with (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol, each step up to the oxazolinium intermediate can

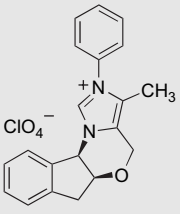
Table 1
N-Substituted chiral aminoindanol-derived imidazolium salts prepared from common acetal intermediate **18**

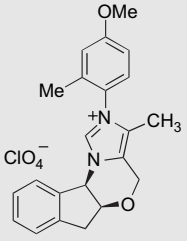


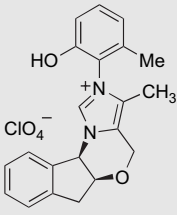
18 **2, 20–32**

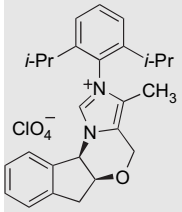

2, 78% yield

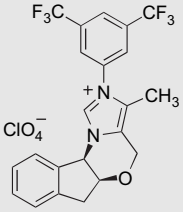

20, 51% yield

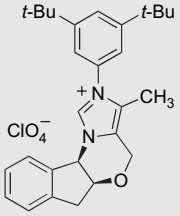

21, 70% yield

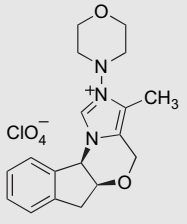

22,[33] 61% yield

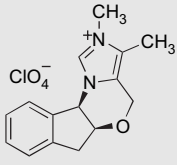

23,[33] 35% yield

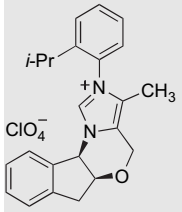

24, 48% yield

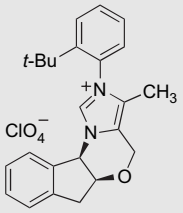

25,[33] 35% yield

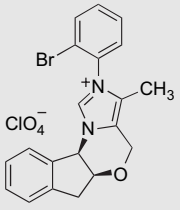

26, 75% yield

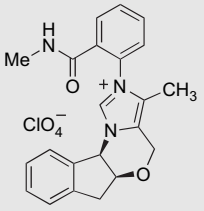

27, 63% yield


28,[33] 53% yield


29,[33] 50% yield


30,[33] 20% yield


31,[33] 22% yield


32,[33] 69% yield

be performed on >8 g scale. The final three-step sequence was performed on a 5-g scale to produce ~4.5 g of **2** in 51% yield from the formyl ketone intermediate **3** (Scheme 8). The structure of this compound was confirmed by single crystal X-ray diffraction (Fig. 4).[32]

2.7. Synthesis of other *N*-substituted chiral imidazolium salts

An important consideration in any catalyst or ligand design strategy is the ability to rapidly access structural derivatives that may enhance reactivity or selectivity in a catalytic reaction. A major attraction of the Fürstner method, and our implementation of it to prepare chiral amino alcohol-derived imidazolium salts, is the ability to introduce a wide range of *N*-substituents at the final stage of the synthesis simply by choice of the appropriate amine.

In preliminary studies, we have confirmed that this modular approach to chiral imidazolium salts is indeed viable and provides access to diverse *N*-substituents (Table 1). Indeed both hindered and unhindered anilines work well in the reaction, making possible the preparation of **2**, **20**–**26**, and **29**–**32**. Unprotected functional groups including phenols and amides do not significantly suppress the heterocyclic interconversion. Alkyl amines are also excellent reaction partners, allowing, for example, the synthesis of *N*-Me substituted imidazolium **28**. Even hydrazines are viable, providing access to *N*-morpholino imidazolium **27**.

3. Conclusion

In summary, we have documented a modular, scalable route to the preparation of chiral aminoindanol-derived imidazolium salts, which will find use as precursors to *N*-heterocyclic carbene catalysts and ligands. Our eight-step route takes advantage of a chemoselective alkylation, intramolecular epoxide opening, and a modification of the Fürstner imidazolium synthesis to achieve a robust, scalable methodology for the preparation of *N*-aryl, *N*-alkyl, and *N*-amino imidazolium salts. We have recently established that precatalysts such as **2** can serve as catalysts for enantioselective NHC-catalyzed homoenolate additions of enals to aldehydes, imines, and enones. We anticipate that the facile access to diverse and complex imidazolium salts will facilitate our own ongoing studies aimed at improving the reactivity and selectivity of these novel annulation reactions. Furthermore, our studies provide one of the first practical routes to chiral bicyclic imidazolium salts that may find use as novel ligands for transition metal mediated reactions and NHC-catalyzed transformations.

4. Experimental

4.1. General methods

All reactions utilizing air- or moisture-sensitive reagents were performed in dried glassware under an atmosphere of dry nitrogen. Dichloromethane and 1,2-dichloroethane were distilled over CaH_2. Toluene, THF, DMF, DMSO, and EtOAc were dried by passage over activated alumina under Ar atmosphere. Acetic anhydride was shaken over P_2O_5, separated, shaken over K_2CO_3, filtered, and then fractionally distilled. All commercially available anilines were fractionally distilled prior to use. Perchloric acid was purchased from Fisher Scientific as 60 or 70 wt % solutions in water. Other reagents were used without further purification. Thin-layer chromatography (TLC) was performed on Merck precoated plates (silica gel 60 F_{254}, Art 5715, 0.25 mm) and were visualized by fluorescence quenching under UV light or by staining with phosphomolybdic acid. Silica-gel preparative thin-layer chromatography (PTLC) was performed using plates prepared from Merck Kieselgel 60 PF254 (Art 7747). Column chromatography was performed on E. Merck Silica Gel 60 (230–400 Mesh) using a forced flow of 0.1–0.5 bar. ^{1}H and ^{13}C NMR were measured on a Varian Unity 400 spectrometer at 400 and 100 MHz or on Bruker Avance II at 500 and 125 MHz, respectively. Chemical shifts are expressed in parts per million (ppm) downfield from residual solvent peaks and coupling constants are reported in hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Minor diastereomers, amide rotamers, and atropisomers are marked by an asterisks (*). Infrared (IR) spectra were recorded on a JASCO FT/IR-430 spectrophotometer and are reported as wavenumbers (cm^{-1}). Optical rotations were acquired using a JASCO DIP-370 polarimeter operating at the sodium D line with a 100 mm path length cell and are reported as follows: $[\alpha]^T$ (concentration (g/mL×100), solvent).

*4.1.1. (1R,2S)-2-((E)-But-2-enyloxy)-2,3-dihydro-1H-inden-1-amine (**9**)*

A flame dried 500 mL round bottom flask equipped with a magnetic stir bar was charged with NaH (60% oil dispersion, 960 mg, 24 mmol, 1.2 equiv). NaH was washed with anhydrous pentane (1×50 mL) and the pentane removed via syringe. The flask was charged with THF (200 mL) and cooled to 0 °C. (1*R*,2*S*)-(+)-1-Amino-2-indanol (3.0 g, 20 mmol, 1.0 equiv) was added in two portions 10 min apart. The suspension was stirred until H_2(g) evolution had ceased. The flask was equipped with a water jacketed condenser and heated to 70 °C under N_2(g). A solution (66 v/v% in THF) of *trans*-crotyl bromide (85% purity, 2.7 mL, 22 mmol, 1.1 equiv) was added dropwise over 90 min. The resulting bluish-purple solution was stirred for an additional 40 min at which time it had turned light tan in color. The mixture was cooled to 0 °C and quenched with satd NH_4Cl(aq) dropwise. The suspension was poured into a separatory funnel and 250 mL of brine added. The organic phase was separated and the aqueous phase extracted with EtOAc (2×150 mL). The organic phases were combined and dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oil was dissolved in Et_2O (200 mL) and treated with 4 M HCl in dioxane (5.0 mL) at 0 °C. The white precipitate was collected by vacuum filtration and washed with excess Et_2O to afford the HCl salt of compound **9**, which was freebased with 1 N NaOH and extracted with Et_2O. Concentration of the ethereal phase yielded compound **9** as a colorless oil (2.6 g, 64%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.36 (m, 1H), 7.22–7.19 (m, 3H), 5.76–5.71 (m, 1H), 5.64–5.59 (m, 1H), 4.27 (d, 1H, J=5.4 Hz), 4.13 (dd, 1H, J=10.8, 5.4 Hz), 4.08–4.0 (m, 2H), 3.02–2.98 (m, 1H), 1.72 (dd, 3H, J=6.4, 1.4 Hz), 1.59 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.9, 140.0, 129.6, 127.8, 127.0, 125.2, 124.5, 81.3, 70.6, 65.2, 58.4, 36.0, 17.9; IR (thin film) ν 3378, 3022, 2914, 2857, 1587, 1458, 1342, 1105, 966 cm^{-1}; HRESI$^+$/TOF-MS calcd for $C_{13}H_{18}NO_2$ $[M]^+$ 203.1310, found 204.1403 (M+H).

*4.1.2. N-((1R,2S)-2-((E)-But-2-enyloxy)-2,3-dihydro-1H-inden-1-yl)formamide (**10**)*

A 0.50 M solution of (1*R*,2*S*)-2-((*E*)-but-2-enyloxy)-2,3-dihydro-1*H*-inden-1-amine (5.2 g, 26 mmol, 1.00 equiv) in THF (50 mL) was treated with ethyl formate (16 mL, 200 mmol, 7.90 equiv) and catalytic glacial acetic acid (0.070 mL, 1.3 mmol, 0.05 equiv). The flask was equipped with a water jacketed condenser and refluxed under N_2(g) in an oil bath for 15 h. The solution was concentrated in vacuo and the resulting crude solid recrystallized from a 70:30 mixture of hexanes/EtOAc and collected by vacuum filtration in two crops to afford **10** as a white solid (5.2 g, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.33–7.20 (m, 4H), 6.38 (br s, 1H), 5.73–5.58 (m, 1H), 5.57–5.51 (m, 2H), 4.32–4.30 (m, 1H), 4.05–4.01 (m, 1H), 3.96–3.92 (m, 1H), 3.08–3.0 (m, 2H), 1.70 (d, 2H, J=6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3, 141.3, 139.8, 130.3, 128.4, 127.3, 127.3, 125.2, 124.8, 79.4, 70.6, 54.5, 36.7,18.0; IR (thin film) ν 3071, 3025, 2919, 2856, 1652, 1448, 1400 cm^{-1}; mp 69–72 °C; HRESI$^+$/TOF-MS

calcd for $C_{14}H_{17}NO_2$ $[M]^+$ 231.1259, found 232.1434 (M+H), 254.1153 (M+Na).

4.1.3. Representative epoxidation procedure using m-CPBA: N-((1R,2S)-2-((3-methyloxiran-2-yl)methoxy)-2,3-dihydro-1H-inden-1-yl)formamides (**5** and **6**)

To a 0.088 M solution of *N*-((1*R*,2*S*)-2-((*E*)-but-2-enyloxy)-2,3-dihydro-1*H*-inden-1-yl)formamide (5.2 g, 22 mmol, 1.0 equiv) in CH_2Cl_2 (250 mL) was added *m*-CPBA (70–75% purity, 28 g, 80 mmol, 4.0 equiv). The solution was stirred at ambient temperature until the starting material was consumed as visualized by TLC (ca. 12 h). The solution was diluted with CH_2Cl_2 (500 mL), washed with water (1×1 L), 1 N NaOH(aq) (1×1 L), and then again with water (1×1 L). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo to a yellow oil, which was purified by flash column chromatography (gradient, hexanes/EtOAc, 1:1→1:1.5) to yield compounds **5** and **6** as a white solid as a 1:1 mixture of diastereomers (5.1 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.30–7.19 (m, 4H), 6.56 (d, 1H), 5.61–5.56 (m, 1H), 4.34–4.27 (m, 1H), 3.81–3.78 (m, 1H), 3.58 (dd, 2H, *J*=5.2, 11.6 Hz), 3.11–3.02 (m, 2H), 2.93–2.83 (m, 2H), 1.31–1.27 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 141.0, 139.7, 128.3, 127.3, 125.2, 124.6, 81.4, 69.9, 58.1, 54.7, 52.2, 37.1, 17.4; IR (thin film) ν 3307, 3030, 2990, 2924, 2859, 1684, 1497, 1384, 1119, 1084 cm^{-1}; mp 77–79 °C; HRESI$^+$/TOF-MS calcd for $C_{14}H_{17}NO_3$ $[M]^+$ 247.1208, found 248.1370 (M+H), 270.1107 (M+Na).

4.1.4. Representative epoxidation procedure using in situ DMDO

To a vigorously stirred mixture of $NaHCO_3$ (14.5 g, 171 mmol, 5.00 equiv), water (260 mL), EtOAc (170 mL), *N*-((1*R*,2*S*)-2-((*E*)-but-2-enyloxy)-2,3-dihydro-1*H*-inden-1-yl)formamide (8.0 g, 34.5 mmol, 1.00 equiv), and acetone (25.5 mL, 345 mmol, 10.0 equiv) in a 1 L round bottom flask was added dropwise a 0.235 M solution of Oxone® (42.5 g, 69.0 mmol, 2.00 equiv) in water (250 mL) over 1 h. The biphasic mixture was then stirred for an additional 1 h at ambient temperature. The organic phase was separated and the aqueous phase extracted with EtOAc (500 mL). The combined organic phases were washed with brine (500 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (gradient, hexanes/EtOAc, 50:50 →40:60→30:70→20:80) to yield **5** and **6** as a white solid and as a 1:1 mixture of diastereomers (6.45 g, 81%).

4.1.5. Representative procedure for Shi epoxidation: N-((1R,2S)-2-(((2R,3R)-3-methyloxiran-2-yl)methoxy)-2,3-dihydro-1H-inden-1-yl)formamide (**5**)

A 500 mL round bottom flask was charged with magnetic stir bar, *N*-((1*R*,2*S*)-2-((*E*)-but-2-enyloxy)-2,3-dihydro-1*H*-inden-1-yl)-formamide (2.31 g, 10.0 mmol, 1.0 eqiuv), the Shi catalyst derived from D-fructose (0.775 g, 3.00 mmol, 0.300 equiv), tetrabutylammonium hydrogen sulfate (0.153 g, 0.450 mmol, 0.450 equiv), pH 10.5 buffer (100 mL) comprising 0.050 M aqueous solution of $Na_2B_4O_7$ in a 0.40 mM aqueous solution of Na_2(EDTA), and a mixture of CH_3CN/dimethoxymethane (1:2, 150 mL) and cooled to 0 °C. A solution of Oxone® (10.1 g, 16.5 mmol, 1.65 equiv) in 0.40 mM Na_2(EDTA) (70 mL) was added via syringe pump over 2.5 h; simultaneously, a 1.0 M solution of K_2CO_3 (70 mL) was added in small portions. After half of the addition was complete, another portion of Shi catalyst (0.775 g, 3.00 mmol, 0.300 equiv) was added. Once the addition was complete, the biphasic mixture was allowed to stir at 0 °C for an additional 2.5 h. Water was added (500 mL) and the mixture was extracted with CH_2Cl_2 (4×150 mL). The combined organic phases were washed with water (1×150 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to a colorless oil. Purification by flash column chromatography (gradient, hexanes/acetone, 3:1→2:1→1:1) afforded **5** and **6** as a white solid and as a 5:1 mixture of diastereomers (2.24 g, 91%). Recrystallization (heaxanes/EtOAc, 1:1) afforded diastereomerically pure **5**. Epoxide ***ent*-6** was prepared in an analogous manner from formamide ***ent*-10** (80%). Compound **5**: ^{1}H NMR (500 MHz, methanol-d_4) δ 8.25 (s, 1H), 7.25–7.19 (m, 4H), 5.47 (d, 1H, *J*=5.4 Hz), 4.32 (dd, 1H, *J*=9.9, 4.4 Hz), 3.81 (dd, 1H, *J*=11.6, 2.8 Hz), 3.47 (dd, 1H, *J*=11.6, 5.8 Hz), 3.07 (d, 2H, *J*=4.4 Hz), 2.92–2.88 (m, 2H), 1.27 (d, 3H, *J*=5.2 Hz); ^{13}C NMR (500 MHz, methanol-d_4) δ 163.8, 142.1, 141.4, 129.2, 128.0, 126.0, 125.2, 82.4, 71.2, 59.3, 55.7, 53.3, 37.5, 17.4; IR (thin film) ν 3266, 3059, 2997, 2919, 2868, 1653, 1544, 1382, 1082, 864, 727 cm^{-1}; HRESI$^+$/TOF-MS calcd for $C_{14}H_{17}NO_3$ $[M]^+$ 247.1208, found 248.1282 (M+H), 270.1097 (M+Na). Compound ***ent*-6**: ^{1}H NMR (500 MHz, methanol-d_4) δ 8.25 (s, 1H), 7.25–7.20 (m, 4H), 5.48 (d, 1H, *J*=5.4 Hz), 4.33 (dd, 1H, *J*=9.8, 4.4 Hz), 3.80 (dd, 1H, *J*=11.5, 3.1 Hz), 3.45 (dd, 1H, *J*=11.5, 6.0 Hz), 3.06 (d, 2H, *J*=4.3 Hz), 2.94–2.87 (m, 2H), 1.28 (d, 3H, *J*=5.2 Hz); ^{13}C NMR (500 MHz, methanol-d_4) δ 163.8, 142.1, 141.4, 129.2, 128.0, 126.0, 125.2, 82.2, 71.1, 59.2, 55.7, 53.3, 37.4, 17.4; IR (thin film) ν 3260, 3048, 2919, 2868, 1650, 1544, 1382, 1082, 858, 727 cm^{-1}; HRESI$^+$/TOF-MS calcd for $C_{14}H_{17}NO_3$ $[M]^+$ 247.1208, found 248.1247 (M+H), 270.1104 (M+Na).

4.1.6. (4aR,9aS)-3-(1-Hydroxyethyl)-2,3,9,9a-tetrahydroindeno-[2,1-b][1,4]oxazine-4(4aH)-carbaldehydes (**11** and **12**)

A flame dried 1 L round bottom flask equipped with a magnetic stir bar was charged with NaH (60% oil dispersion, 15.2 g, 380 mmol, 10.0 equiv). NaH was washed with anhydrous pentane (120 mL) and the pentane removed via syringe. The flask was charged with DMF (500 mL) and cooled to 0 °C. A 1.0 M solution of *N*-((1*R*,2*S*)-2-((3-methyloxiran-2-yl)methoxy)-2,3-dihydro-1*H*-inden-1-yl)formamide (9.90 g, 40.0 mmol, 1.00 equiv) in DMF (40 mL) was added dropwise over 80 min and stirred for an additional 30 min during which time it had turned blue in color. The mixture was slowly quenched with ice-cold satd aq NH_4Cl. The majority of DMF was removed in vacuo and the resultant oil diluted with EtOAc (400 mL) and water (300 mL). The organic phase was separated and the aqueous phase extracted with EtOAc (2×300 mL). The combined organic phases were washed with brine (2×500 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to a red oil, which was purified by flash column chromatography (gradient, CH_2Cl_2/acetone, 6:1→4:1→2:1) to yield compounds **11** and **12** as an inseparable complex mixture of diastereomers and amide rotamers as an orange solid (5.0 g, 52%). IR (thin film) ν 3408, 3071, 3046, 3024, 2975, 2911, 1651, 1410, 1273, 1106, 1077 cm^{-1}; HRESI$^+$/TOF-MS calcd for $C_{14}H_{17}NO_3$ $[M]^+$ 247.1208, found 248.1208 (M+H).

4.1.7. (3S,4aR,9aS)-3-((R)-1-Hydroxyethyl)-2,3,9,9a-tetrahydro-indeno[2,1-b][1,4]oxazine-4(4aH)-carbaldehyde (**13**)

A flame dried 50 mL round bottom flask equipped with a magnetic stir bar was charged with NaH (60% oil dispersion, 1.23 g, 30.8 mmol, 10.0 equiv). NaH was washed with anhydrous pentane (7.0 mL). The flask was charged with 38.0 mL of DMF and cooled to 0 °C. A 0.16 M solution of *N*-((1*R*,2*S*)-2-(((2*R*,3*R*)-3-methyloxiran-2-yl)methoxy)-2,3-dihydro-1*H*-inden-1-yl)formamide (762 mg, 3.08 mmol, 1.00 equiv) in DMF (28 mL) was added dropwise over 75 min. The mixture was stirred for an additional 25 min. The mixture was slowly poured over ice-cold satd aq NH_4Cl (250 mL). The solution was extracted with EtOAc (5×100 mL). The combined organic phases were washed with brine (2×1 L), dried over $MgSO_4$, filtered, and concentrated in vacuo to a yellow oil, which was purified by flash column chromatography (gradient, CH_2Cl_2/acetone, 8:1→4:1→2:1) to yield **13** as a white solid as a ~3:1 mixture of rotamers (564 mg, 74%). Alcohol **14** was prepared as ~1.5:1 mixture of rotamers in an analogous manner from epoxide ***ent*-6** (76%). Compound **13**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.84* (s, 1H), 8.21 (s, 1H), 7.34–7.20 (m, 4H), 7.34–7.10* (m, 4H), 5.87* (d, 1H,

J=3.9 Hz), 4.92 (d, 1H, J=4.5 Hz), 4.53–4.47 (m, 2H), 4.53–4.47* (m, 2H), 4.46* (dd, 1H, J=4.6, 1.5 Hz), 4.21 (d, 1H, J=5.7 Hz), 3.89 (dd, 1H, J=12.0, 3.3 Hz), 3.85* (d, 1H, J=2.5 Hz), 3.74 (dd, 1H, J=12.0, 9.0 Hz), 3.63* (dd, 1H, J=11.5, 10.9 Hz), 3.57–3.54 (m, 1H), 3.25–3.22* (m, 1H), 3.07–3.04 (m, 2H), 2.95* (d, 1H, J=2.6 Hz), 2.51* (d, 1H, 3.9 Hz), 1.78* (s, 1H), 1.31* (d, 3H, J=6.5 Hz), 1.23 (d, 3H, J=6.8 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 163.4, 162.0, 141.1, 141.0, 138.8, 137.2, 129.2, 128.0, 127.5, 127.1, 126.1, 125.6, 124.2, 123.4, 78.0, 77.7, 65.5, 65.2, 64.4, 64.3, 61.9, 58.9, 57.4, 56.4, 38.5, 37.1, 21.2, 19.5; IR (thin film) ν 3422, 2975, 2908, 1639, 1273, 1105, 1074, 1032, 738 cm^{-1}; HRESI$^+$/TOF-MS calcd for $C_{14}H_{17}NO_3$ [M]$^+$ 247.1208, found 248.1325 (M+H). Compound **14**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40* (s, 1H), 8.33 (s, 1H), 7.31–7.15* (m, 4H), 7.31–7.15 (m, 4H), 5.56 (d, 1H, J=4.5 Hz), 4.82* (d, 1H, J=4.3 Hz), 4.37* (t, 1H, J=4.3 Hz), 4.33–4.29* (m, 1H), 4.33–4.29 (m, 1H), 4.25 (d, 1H, J=12.0 Hz), 4.02* (dd, 1H, J=9.2, 2.8 Hz), 3.53 (dd, 1H, J=12.0, 2.9 Hz), 3.48–3.40* (m, 2H), 3.48–3.40 (m, 2H), 3.15–3.09* (m, 2H), 3.15–3.09 (m, 2H), 3.06–2.99 (m, 1H), 2.13 (d, 1H, J=4.9 Hz), 1.82* (d, 1H, J=5.5 Hz), 1.19* (d, 3H, J=6.0 Hz), 1.17 (d, 3H, J=6.2 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 163.8, 163.6, 140.1, 140.1, 139.9, 128.7, 128.1, 127.2, 127.0, 125.7, 125.3, 124.4, 123.6, 78.0, 77.8, 65.6, 64.9, 64.6, 64.4, 60.4, 59.3, 55.7, 53.7, 38.4, 38.2, 20.9, 20.4; IR (thin film) ν 3417, 2980, 2913, 1659, 1412, 1269, 1110, 1077, 1032, 912, 727 cm^{-1}; HRESI$^+$/TOF-MS calcd for $C_{14}H_{17}NO_3$ [M]$^+$ 247.1208, found 248.1316 (M+H).

4.1.8. *(4aR,9aS)-3-Acetyl-2,3,9,9a-tetrahydroindeno[2,1-b][1,4]-oxazine-4(4aH)-carbaldehydes (**3** and **4**)*

A 0.50 M solution of (4a*R*,9a*S*)-3-(1-hydroxyethyl)-2,3,9,9a-tetrahydroindeno[2,1-*b*][1,4]oxazine-4(4a*H*)-carbaldehyde (3.73 g, 15.1 mmol, 1.00 equiv) in CH_2Cl_2 (30.0 mL) was added to a suspension of Dess–Martin periodinane (8.4 g, 22.5 mmol, 1.50 equiv) in CH_2Cl_2 (115 mL). The solution was stirred at rt until all the starting material was consumed as indicated by TLC (ca. 3 h). The solution was diluted with CH_2Cl_2, and washed with 1 N NaOH (1×150 mL), water (2×225 mL), and brine (150 mL). The solution was filtered through Celite, dried over Na_2SO_4, and concentrated in vacuo to afford a crude solid, which was purified by flash column chromatography (hexanes/acetone, 3:2) to give the ketones as a set of diastereomer **3** and its amide rotamer and diastereomer **4** as tan and white solid (3.25 g, 88%). The diastereomers could be separated by flash column chromatography. Compound **3**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.39* (s, 1H), 7.34–7.18 (m, 4H), 7.32–7.18* (m, 4H), 5.58* (d, 1H, J=4.1 Hz), 4.96 (d, 1H, J=4.2 Hz), 4.71 (d, 1H, J=3.3 Hz), 4.44* (d, 1H, J=3.4 Hz), 4.42–4.40 (m, 2H), 4.32* (t, 1H, J=4.5 Hz), 3.83–3.78* (m, 2H), 3.61 (dd, 1H, J=12.2, 4.0 Hz), 3.13–3.12* (m, 1H), 3.10–3.09 (m, 1H), 3.02 (d, 1H, J=16.9 Hz), 2.98* (d, 1H, J=16.9 Hz), 2.08 (s, 3H), 2.00* (3H); IR (thin film) ν 2906, 1724, 1673, 1460, 1402, 1357, 1105, 1044 cm^{-1}; ^{13}C NMR (500 MHz, $CDCl_3$) δ 204.8, 203.1, 164.7, 163.7, 140.1, 140.0, 138.3, 138.1, 128.5, 128.1, 126.9, 126.8, 126.6, 126.5, 125.5, 125.0, 124.9, 78.2, 78.1, 65.3, 64.2, 65.3, 64.2, 60.2, 56.6, 56.2, 38.3, 38.1, 27.3, 27.3; HRESI$^+$/TOF-MS calcd for $C_{14}H_{15}NO_3$ [M]$^+$ 245.1052, found 246.1113 (M+H), 268.0951 (M+Na).Compound **4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.30–7.20 (m, 4H), 5.05 (d, 1H, J=4.6 Hz), 4.58 (q, 1H, J=4.5 Hz), 4.30 (dd, 1H, J=4.3, 7.4 Hz), 3.90 (dd, 1H, J=4.3, 12.0 Hz), 3.78 (dd, 1H, J=7.4, 12.0 Hz), 3.12 (d, 2H, J=4.0 Hz), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 163.5, 140.7, 138.6, 129.3, 127.6, 126.1, 124.1, 77.8, 64.4, 59.0, 58.0, 36.9, 28.4; IR (thin film) ν 3074, 3018, 2908, 2864, 1721, 1675, 1400, 1218 cm^{-1}; mp 174–176 °C; HRESI$^+$/TOF-MS calcd for $C_{14}H_{15}NO_3$ [M]$^+$ 245.1052, found 246.1096 (M+H), 268.0970 (M+Na).

4.1.9. *Procedure for Swern oxidation*

To a 0.256 M solution of oxalyl chloride (6.70 mL, 76.8 mmol, 2.50 equiv) in CH_2Cl_2 (300 mL) cooled to −60 °C was slowly added a 1.50 M solution of DMSO (13.6 mL, 192 mmol, 5.00 equiv) in CH_2Cl_2 (128 mL). Next, a 1.00 M solution of (4a*R*,9a*S*)-3-(1-hydroxyethyl)-2,3,9,9a-tetrahydroindeno[2,1-*b*][1,4]oxazine-4(4a*H*)-carbaldehyde (9.50 g, 38.4 mmol, 1.00 equiv) in CH_2Cl_2 (38.4 mL) was added portionwise over 30 min. The solution was allowed to warm to −20 °C and stirred for 1 h. The solution was cooled to −60 °C, NEt_3 (53.2 mL, 384, mmol, 10.0 equiv) was added dropwise over 30 min, and stirring continued for 30 min before allowing the solution to warm to rt. A white precipitate was filtered and the filtrate washed with water (2×500 mL). The combined aqueous phases were extracted with CH_2Cl_2 (2×500 mL); the combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (gradient, CH_2Cl_2/acetone, 20:1→10:1→5:1→2:1) to yield **3** and **4** as white solids (8.20 g, 87%).

4.1.10. *Conversion of N-formyl ketones **3** or **4** to acetal **18***

To an oven dried 25 mL round bottom flask equipped with a magnetic stir bar and charged with either **3** or **4** (245 mg, 1.00 mmol, 1.00 equiv) was added Ac_2O (1.5 mL, 16 mmol, 16 equiv). The mixture was cooled to 0 °C and $HClO_4$ (70%, 0.10 mL, 1.2 mmol, 1.2 equiv; or 60%, 0.12 mL, 1.2 mmol, 1.2 equiv) was added dropwise over 20 min. The brown solution was allowed to warm to rt and then stirred for 2–3 h. The solution was twice triturated with Et_2O and the supernatant decanted each time. Residual solvent was removed from the resulting white solid in vacuo at ambient temperature to afford the crude oxazolinium salt **18** either as a white solid or as a brown oil (388 mg, quant.), which was immediately used in the subsequent conversion to the imidazolium salts.

4.1.11. *Procedure for multi-gram synthesis of N-mesityl substituted imidazolium salt **2***[15]

To an oven dried 100 mL Schlenk flask equipped with a magnetic stir bar and charged with ketone **3** (5.0 g, 20 mmol, 1.0 equiv) was added Ac_2O (30 mL, 326 mmol, 16 equiv). The mixture was cooled to 0 °C and $HClO_4$ (60%, 2.6 mL, 25 mmol, 1.2 equiv) was added dropwise over 20 min. The brown solution was allowed to warm to rt and then stirred for 2 h. The solution was twice triturated with Et_2O and the supernatant decanted each time. The resulting white solid was dried in vacuo and dissolved in a minimal amount of CH_2Cl_2 before 1 vol equiv of toluene was added. Next, 2,4,6-trimethyl aniline (32 mL, 31 mmol, 1.5 equiv) was added and the solution stirred overnight. The brown solution was concentrated in vacuo to an oil. The oil was dissolved in a minimal amount of CH_2Cl_2 and triturated with Et_2O in a sonicating bath. The white precipitate was collected by vacuum filtration and washed with excess Et_2O to give the aminal intermediate as a white solid and as a mixture of diastereomers (5.9 g, 63%). This white solid (5.9 g, 13 mmol, 1.0 equiv) was transferred to an oven dried 200 mL round bottom flask equipped with a magnetic stir bar and dissolved in 85 mL of 1,2-dichloroethane (0.15 M). Next, Ac_2O (2.4 mL, 25 mmol, 2.0 equiv) and $HClO_4$ (60%, 0.26 mL, 2.5 mmol, 0.20 equiv) were added and the solution heated to 70 °C. The reaction was monitored by ^{1}H NMR analysis of aliquots from the reaction. After 4 h, another 0.26 mL of $HClO_4$ was added in order to drive the reaction to completion. The reaction was complete as indicated from NMR after an additional 2 h of stirring. The solution was cooled to rt and concentrated in vacuo. The resulting oil was dissolved in a minimal amount of CH_2Cl_2 and triturated with Et_2O in a sonicating bath. The precipitate was collected by vacuum filtration to afford **2** as a white crystalline solid (4.6 g, 81%, 51% over three steps).

4.1.12. *Preparation of N-mesityl substituted imidazolium salt **2***

To a round bottom flask charged with a magnetic stir bar and oxazolinium salt **18** (700 mg, 1.8 mmol, 1.0 equiv) were added

toluene (10 mL) and 2,4,6-trimethyl aniline (0.38 mL, 2.7 mmol, 1.5 equiv). The heterogeneous mixture was stirred at ambient temperature for 3 h. The solvent was decanted and the precipitate washed with Et_2O (2×10 mL). Residual solvent was removed in vacuo to afford the aminal intermediate as a light white solid and as a mixture of diastereomers (835 mg, quant.). A mixture of the aminal intermediate (98 mg, 0.21 mmol, 1.0 equiv) in toluene (1.0 mL) was treated with Ac_2O (0.40 μL, 0.42 mmol, 2.0 equiv) and $HClO_4$ (70%, 7.0 μL, 0.082 mmol, 0.20 equiv) and heated at 80 °C for 2.5 h. The solution was allowed to cool to rt and concentrated in vacuo. The crude solid was suspended in Et_2O and placed in a sonicating bath. Once the precipitate had become white, it was collected by vacuum filtration and washed with EtOAc to yield **2** (73 mg, 78% over three steps). ^{1}H NMR (500 MHz, acetone-d_6) δ 9.71 (s, 1H), 7.64 (d, 1H, J=7.6 Hz), 7.44 (d, 2H, J=7.4 Hz), 7.40 (t, 1H, J=7.4 Hz), 7.22 (s, 2H), 6.10 (d, 1H, J=4.0 Hz), 5.11 (d, 1H, J=15.0 Hz), 5.06 (t, 1H, J=4.5 Hz), 4.98 (d, 1H, J=15.0 Hz), 3.49 (dd, 1H, J=4.8, 17.0 Hz), 3.23 (d, 1H, J=17.0 Hz), 2.40 (s, 3H), 2.14 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 141.9, 141.5, 137.8, 136.0, 135.9, 135.2, 130.3, 130.2, 129.8, 129.6, 127.8, 126.2, 125.8, 125.2, 124.0, 78.0, 61.4, 60.0, 38.0, 20.8, 17.1, 7.6; IR (thin film) ν 3122, 3047, 2925, 2860, 1539, 1461, 1214, 1097 cm^{-1}; HRESI$^+$/TOF-MS calcd for $C_{23}H_{25}N_2O^+$ $[M]^+$ 345.1961, found 345.1931; $[\alpha]_D^{20}$ −134.0 (*c* 0.55, CH_2Cl_2).

4.1.13. Preparation of N-2,6-dimethyl-4-bromophenyl substituted imidazolium salt **20**

To a round bottom flask charged with a magnetic stir bar and oxazolinium salt **18** (388 mg, 1.00 mmol, 1.00 equiv) were added toluene (10 mL) and 4-bromo-2,6-dimethyl aniline (300 mg, 1.50 mmol, 1.50 equiv). The heterogeneous mixture was stirred at ambient temperature for 13 h. The precipitate was collected by vacuum filtration and washed with Et_2O to afford the aminal intermediate as a white powder and as a mixture of diastereomers (300 mg, 57%). A 0.25 M solution of the aminal intermediate (200 mg, 0.38 mmol, 1.0 equiv) in 1,2-dichloroethane (1.5 mL) was treated with Ac_2O (0.070 mL, 0.76 mmol, 2.0 equiv) and $HClO_4$ (70%, 6.0 μL, 0.080 mmol, 0.20 equiv) and heated at 70 °C for 3 h. The solution was allowed to cool to rt, and a precipitate collected by vacuum filtration and washed with 1,2-dichloroethane to afford **20** as a yellow solid (170 mg, 89%, 51% over three steps). ^{1}H NMR (400 MHz, acetone-d_6) δ 9.78 (s, 1H), 7.65–7.63 (m, 3H), 7.44 (d, 1H, J=7.4 Hz), 7.40 (t, 1H, J=7.3 Hz), 7.33 (t, 1H, J=7.4 Hz), 6.10 (d, 1H, J=3.7 Hz), 5.13 (d, 1H, J=15.0 Hz), 5.06 (t, 1H, J=4.3 Hz), 4.98 (d, 1H, J=15.0 Hz), 3.49 (dd, 1H, J=16.9, 4.8 Hz), 3.23 (d, 1H, J=17.0 Hz), 2.21 (s, 3H), 2.13 (s, 6H); ^{13}C NMR (100 MHz, acetone-d_6) δ 141.8, 139.4, 138.1, 132.8, 132.6, 131.9, 130.1, 128.2, 126.5, 125.9, 125.8, 125.4, 124.3, 78.3, 61.8, 60.3, 38.3, 17.4, 7.9; IR (KBr pellet) ν 3115, 3042, 2913, 2852, 1533, 1460, 1203, 1099, 858, 747 cm^{-1}; HRESI$^+$/TOF-MS calcd 409.0910 $[M]^+$, found 409.0914; $[\alpha]_D^{20}$ −109.8 (*c* 0.25, CH_2Cl_2).

4.1.14. Preparation of N-phenyl substituted imidazolium salt **21**

To a round bottom flask charged with a magnetic stir bar and oxazolinium salt **18** (388 mg, 1.00 mmol, 1.00 equiv) were added toluene (5 mL) and aniline (0.13 mL, 1.50 mmol, 1.50 equiv). The heterogeneous mixture was stirred at ambient temperature for 16 h. The solution was decanted, the remaining oil washed with Et_2O (2×10 mL), and excess solvent removed in vacuo to afford the aminal intermediate as a brown foam and as a mixture of diastereomers (420 mg, quant. crude yield). A suspension of the aminal intermediate (420 mg, 1.0 mmol, 1.0 equiv) in toluene (4.0 mL) was treated with Ac_2O (0.19 mL, 2.0 mmol, 2.0 equiv) and $HClO_4$ (70%, 17 μL, 0.20 mmol, 0.20 equiv). The mixture was stirred at 80 °C for 45 min. After allowing the reaction to cool to rt, the supernatant was decanted, excess solvent removed in vacuo, and the resulting residue triturated with Et_2O in a sonicating bath to afford 135 mg of **21** as a brown solid. The filtrate was then purified by flash column chromatography (gradient, CH_2Cl_2/acetone, 19:1 → 9:1) to afford another 145 mg of **21** as an off-white powder (230 mg, 70% over three steps). ^{1}H NMR (500 MHz, acetone-d_6) δ 9.77 (s, 1H), 7.79–7.72 (m, 5H), 7.67 (d, 1H, J=7.6 Hz), 7.41 (d, 1H, J=7.4 Hz), 7.38 (t, 1H, J=7.4 Hz), 7.30 (t, 1H, J=7.4 Hz), 5.99 (d, 1H, J=4.1 Hz), 5.08 (d, 1H, J=15.1 Hz), 4.99 (t, 1H, J=4.5 Hz), 4.95 (d, 1H, J=15.0 Hz), 3.47 (dd, 1H, J=16.9, 4.8 Hz), 3.21 (d, 1H, J=16.9 Hz), 2.23 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 141.7, 137.8, 135.6, 134.5, 131.7, 131.0, 130.0, 127.9, 127.4, 126.3, 126.1, 125.0, 124.7, 78.3, 61.5, 60.2, 38.2, 8.6; IR (thin film) ν 3121, 3059, 2928, 1545, 1460, 1217, 1094, 774 cm^{-1}; HRESI$^+$/TOF-MS calcd 303.1492 $[M]^+$, found 303.1502; $[\alpha]_D^{20}$ −177.4 (*c* 0.19, CH_2Cl_2).

4.1.15. Preparation of N-2-methyl-4-methoxyphenyl substituted imidazolium salt **22**

To a round bottom flask charged with a magnetic stir bar and oxazolinium salt **18** (388 mg, 1.00 mmol, 1.00 equiv) was added toluene (5 mL) and 4-methoxy-2-methylaniline (0.20 mL, 1.50 mmol, 1.50 equiv). The heterogeneous mixture was stirred at ambient temperature for 12 h. The supernatant was decanted, the crude oil washed with Et_2O (2×10 mL), and residual solvent removed in vacuo to afford the crude aminal intermediate as a light purple solid and as mixture of diastereomers (430 mg, 92% yield). A suspension of the crude aminal intermediate (430 mg, 0.92 mmol, 1.0 equiv) in toluene (4.0 mL) was treated with Ac_2O (0.18 mL, 1.8 mmol, 2.0 equiv) and $HClO_4$ (70%, 16 μL, 0.18 mmol, 0.20 equiv). The mixture was stirred at 80 °C for 1 h. After allowing the reaction to cool to rt, the reaction was concentrated in vacuo to a brown solid. This solid was suspended in Et_2O, at which time had turned into an oil, in a sonicating bath while methanol was dropwise added as needed until the oil began to precipitate as a light purple powder. This precipitate was collected by vacuum filtration and the purification process repeated on the filtrate to afford a second crop of **22** as a light purple solid and as a 1:1 mixture of atropisomers (370 mg, 66%, 61% over three steps). ^{1}H NMR (500 MHz, acetone-d_6) δ 9.71 (d, 1H, J=10 Hz), 7.63 (d, 1H, J=7.6 Hz), 7.56 (d, 1H, J=8.4 Hz), 7.44–7.38 (m, 2H), 7.32 (s, 1H), 7.12 (d, 1H, J=2.4 Hz), 7.05 (dd, 1H, J=8.6, 2.4 Hz), 6.04 (s, 1H), 5.09 (d, 1H, J=14.9 Hz), 5.03 (s, 1H), 4.95 (d, 1H, J=4.6 Hz), 3.91 (s, 3H), 3.48 (d, 1H, J=16.9 Hz), 3.23 (d, 1H, J=17.0 Hz), 2.20 (d, 3H, J=12.0 Hz), 2.12 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 162.4, 141.8, 137.9, 136.0, 130.0, 129.9, 128.0, 126.7, 126.4, 125.9, 125.0, 124.8, 124.4, 117.3, 113.6, 78.3, 61.5, 60.2, 56.1, 38.3, 17.5, 8.2; IR (thin film) ν 3126, 3053, 2930, 1544, 1502, 1463, 1217, 1094, 734 cm^{-1}; HRESI$^+$/TOF-MS calcd 347.1754 $[M]^+$, found 347.1768; $[\alpha]_D^{20}$ −147.5 (*c* 0.28, CH_2Cl_2).

4.1.16. Preparation of N-2-hydroxy-6-methylphenyl substituted imidazolium salt **23**

To a round bottom flask charged with a magnetic stir bar and oxazolinium salt **18** (388 mg, 1.00 mmol, 1.00 equiv) were added toluene (5 mL) and 2-hydroxy-6-methylaniline (185 mg, 1.50 mmol, 1.50 equiv). The heterogeneous mixture was stirred at ambient temperature for 14 h. The solution was triturated with Et_2O, the supernatant was decanted, and residual solvent removed in vacuo to afford a mixture of the crude aminal intermediate and parent aniline as a brown solid (482 mg, quant. crude yield). A suspension of the crude aminal intermediate (450 mg, 1.0 mmol, 1.0 equiv) in toluene (4.0 mL) was treated with Ac_2O (0.12 mL, 1.2 mmol, 1.2 equiv) and $HClO_4$ (70%, 17 μL, 0.20 mmol, 0.20 equiv). The mixture was stirred at 80 °C for 1 h. After allowing the reaction to cool to rt, the supernatant was decanted, residual solvent removed in vacuo, and the product precipitated from CH_2Cl_2. The precipitate was collected by vacuum filtration to afford **23** as a light gray powder and as a 4:1 mixture of atropisomers (150 mg, 35% over three steps). ^{1}H NMR (500 MHz, acetone-d_6) δ 9.74* (s, 1H),

9.72 (s, 1H), 9.48 (br s, 1H, OH), 9.43* (br s, 1H, OH), 7.64* (d, 1H, J=7.5 Hz), 7.58 (d, 1H, J=7.6 Hz), 7.45–7.41 (m, 3H), 7.41–7.34* (m, 3H), 7.30 (t, 1H, J=7.4 Hz), 7.09* (d, 1H, J=8.6 Hz), 7.08 (d, 1H, J=8.2 Hz), 7.03 (d, 1H, J=7.6 Hz), 6.11* (d, 1H, J=4.1 Hz), 6.08 (d, 1H, J=4.1 Hz), 5.12 (d, 1H, J=15.0 Hz), 5.12–5.09* (m, 2H), 5.06 (t, 1H, J=4.5 Hz), 4.97* (d, 1H, J=15.0 Hz), 4.96 (d, 1H, J=14.9 Hz), 3.53–3.50* (m, 1H), 3.49 (dd, 1H, J=16.9, 4.9 Hz), 3.24* (d, 1H, J=16.9 Hz), 3.22 (d, 1H, J=16.9 Hz), 2.21 (s, 3H), 2.15* (s, 3H), 2.11* (s, 3H), 2.10 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 153.9, 153.8, 141.8, 138.0, 137.8, 136.4, 133.0, 132.9, 132.8, 130.1, 130.0, 128.2, 128.0, 126.6, 126.5, 126.4, 124.8, 124.5, 124.3, 122.9, 120.8, 115.3, 115.2, 78.3, 61.6, 60.2, 38.3, 17.3, 7.9; IR (KBr pellet) ν 3350, 3132, 3053, 2924, 1592, 1544, 1477, 1298, 1105, 951, 738, 624 cm^{-1}; HRESI$^+$/TOF-MS calcd 333.1598 [M]$^+$, found 333.1607; $[\alpha]_D^{20}$ −129.6 (c 0.22, MeOH).

4.1.17. Preparation of N-2,6-diisopropylphenyl substituted imidazolium salt **24**

To a round bottom flask charged with a magnetic stir bar and oxazolinium salt **18** (388 mg, 1.00 mmol, 1.00 equiv) were added toluene (10 mL) and 2,6-diisopropyl aniline (0.28 mL, 1.50 mmol, 1.50 equiv). The heterogeneous mixture was stirred at ambient temperature for 12 h. Et_2O was added, the supernatant decanted, and the resultant oil concentrated in vacuo to afford the aminal intermediate as a light yellow foam and as a mixture of diastereomers (360 mg, 71%). A mixture of the aminal intermediate (360 mg, 0.71 mmol, 1.0 equiv) in toluene (3.0 mL) was treated with Ac_2O (0.13 mL, 1.4 mmol, 2.0 equiv) and $HClO_4$ (70%, 12 μL, 0.14 mmol, 0.20 equiv) and heated at 80 °C for 15 min. The solution was allowed to cool to rt, concentrated in vacuo, and the residue purified by flash column chromatography (gradient, CH_2Cl_2/MeOH, 98:2→95:5) to give **24** as a yellow foam (235 mg, 68%, 48% over three steps). ^{1}H NMR (500 MHz, acetone-d_6) δ 9.93 (s, 1H), 7.72–7.69 (t, 1H, J=7.8 Hz), 7.57–7.52 (m, 3H), 7.46 (d, 1H, J=7.4 Hz), 7.40 (t, 1H, J=7.4 Hz), 7.33 (t, 1H, J=7.4 Hz), 6.10 (d, 1H, J=4.0 Hz), 5.11 (d, 1H, J=15.0 Hz), 5.07 (t, 1H, J=4.4 Hz), 4.98 (d, 1H, J=15.0 Hz), 3.49 (dd, 1H, J=16.9, 4.8 Hz), 3.23 (d, 1H, J=16.9 Hz), 2.80 (d, 1H, J=16.9 Hz), 2.64 (septet, 1H, J=6.8 Hz), 2.26 (septet, 1H, J=6.8 Hz), 2.10 (s, 3H), 1.26 (dd, 6H, J=10.0, 6.8 Hz), 1.21 (dd, 6H, J=6.8, 2.5 Hz); ^{13}C NMR (125 MHz, acetone-d_6) δ 147.1, 146.9, 142.0, 138.2, 135.8, 133.0, 130.2, 129.1, 128.0, 126.9, 126.6, 126.0, 125.8, 125.8, 124.1, 123.7, 78.3, 61.8, 60.3, 38.4, 25.3, 25.2, 23.4, 23.2, 8.3; IR (thin film) ν 3116, 3045, 2965, 2929, 2871, 1538, 1462, 1202, 1099, 733, 624 cm^{-1}; HRESI$^+$/TOF-MS calcd 387.2431 [M]$^+$, found 387.2446; $[\alpha]_D^{20}$ −94.5 (c 0.22, CH_2Cl_2).

4.1.18. Preparation of N-3,5-bis(trifluoromethyl)phenyl substituted imidazolium salt **24**

To a round bottom flask charged with a magnetic stir bar and oxazolinium salt **18** (388 mg, 1.00 mmol, 1.00 equiv) were added toluene (10 mL) and 3,5-bis(trifluoromethyl)aniline (0.23 mL, 1.50 mmol, 1.50 equiv). The heterogeneous mixture was stirred at ambient temperature for 16 h. The supernatant was decanted, the crude oil washed with Et_2O (1×10 mL), and residual solvent removed in vacuo to afford the crude aminal intermediate as a yellow solid and a mixture of diastereomers (560 mg, quant. crude yield). A suspension of the crude aminal intermediate (560 mg, 1.0 mmol, 1.0 equiv) in toluene (4.0 mL) was treated with Ac_2O (0.19 mL, 2.0 mmol, 2.0 equiv) and $HClO_4$ (70%, 17 μL, 0.20 mmol, 0.20 equiv). The mixture was stirred at 80 °C for 15 min. After allowing the reaction to cool to rt, the supernatant was decanted, the residual solvent removed in vacuo, and the resulting residue suspended in a mixture of Et_2O/EtOAc (2:1, 7 mL) and sonicated until precipitation had occurred; then **25** was collected by vacuum filtration as a white solid (190 mg, 35% over three steps). ^{1}H NMR (500 MHz, acetone-d_6) δ 10.00 (s, 1H), 8.60 (s, 2H), 8.47 (s, 1H), 7.63 (d, 1H, J=7.7 Hz), 7.43 (d, 1H, J=7.5 Hz), 7.39 (t, 1H, J=7.4 Hz), 7.29 (t, 1H, J=7.4 Hz), 6.04 (d, 1H, J=4.1 Hz), 5.13 (d, 1H, J=15.1 Hz), 5.02 (t, 1H, J=4.3 Hz), 4.95 (d, 1H, J=15.1 Hz), 3.50 (dd, 1H, J=17.0, 4.8 Hz), 3.23 (d, 1H, J=17.0 Hz), 2.34 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 141.8, 137.6, 136.7, 136.3, 134.0, 133.7, 130.2, 129.3, 127.9, 126.7, 126.4, 125.0, 125.0, 78.4, 61.7, 60.2, 38.3, 8.6; IR (thin film) ν 3148, 3058, 2937, 1543, 1368, 1280, 1105, 1076, 905, 604 cm^{-1}; HRESI$^+$/TOF-MS calcd 439.1240 [M]$^+$, found 439.1246; $[\alpha]_D^{20}$ −141.9 (c 0.15, CH_2Cl_2).

4.1.19. Preparation of N-3,5-di-tert-butylphenyl substituted imidazolium salt **26**

To a solution of oxazolinium salt **18** (388 mg, 1.00 mmol, 1.00 equiv) in CH_2Cl_2 (3 mL) were added toluene (10 mL) and 3,5-di-*tert*-butylaniline (0.23 mL, 1.50 mmol, 1.50 equiv). The solution was stirred at ambient temperature for 16 h during which a white solid had precipitated. The precipitate was collected by vacuum filtration and washed with Et_2O to afford the aminal intermediate as a white powder and as a mixture of diastereomers (420 mg, 79% yield). A 0.25 M solution of the aminal intermediate (420 mg, 0.79 mmol, 1.0 equiv) in 1,2-dichloroethane (3.1 mL) was treated with Ac_2O (0.15 mL, 1.6 mmol, 2.0 equiv) and $HClO_4$ (70%, 14 μL, 0.16 mmol, 0.20 equiv) and stirred at 70 °C for 30 min. After allowing the solution to cool to rt, the solvent was removed in vacuo and the residue purified by flash column chromatography (CH_2Cl_2/MeOH, 30:1) to afford **26** as a light yellow foam (385 mg, 95%, 75% over three steps). ^{1}H NMR (500 MHz, acetone-d_6) δ 9.75 (s, 1H), 7.80 (t, 1H, J=1.7 Hz), 7.65–7.63 (m, 3H), 7.41 (d, 1H, J=7.4 Hz), 7.35 (t, 1H, J=7.3 Hz), 7.29 (t, 1H, J=7.4 Hz), 5.97 (s, 1H, J=4.2 Hz), 5.06 (d, 1H, J=15.0 Hz), 4.96 (t, 1H, J=4.4 Hz), 4.90 (d, 1H, J=15.0 Hz), 3.46 (dd, 1H, J=16.9, 4.9 Hz), 3.20 (d, 1H, J=16.9 Hz), 2.23 (s, 3H), 1.41 (s, 18H); ^{13}C NMR (125 MHz, acetone-d_6) δ 154.0, 141.6, 137.8, 135.5, 134.2, 129.9, 127.8, 126.2, 126.0, 125.3, 124.9, 124.5, 121.6, 78.2, 61.3, 60.1, 38.1, 35.8, 31.4, 8.7; IR (thin film) ν 3126, 3053, 2952, 2868, 1608, 1597, 1538, 1477, 1365, 1248, 1096, 733, 624 cm^{-1}; HRESI$^+$/TOF-MS calcd 415.2744 [M]$^+$, found 415.2742; $[\alpha]_D^{20}$ −133.7 (c 0.25, CH_2Cl_2).

4.1.20. Preparation of N-morpholino substituted imidazolium salt **27**

To a solution of oxazolinium salt **18** (388 mg, 1.00 mmol, 1.00 equiv) in CH_2Cl_2 (5 mL) were added toluene (5 mL) and 4-aminomorpholine (0.15 mL, 1.50 mmol, 1.50 equiv). The heterogeneous mixture was stirred at ambient temperature for 18 h. Et_2O was added to the mixture causing an oil to form. The supernatant was decanted. The oil was dissolved in a minimal amount of CH_2Cl_2 (~5 mL) and triturated with Et_2O, the supernatant decanted, and residual solvent removed in vacuo to afford the aminal intermediate as a light yellow solid and as a mixture of diastereomers (360 mg, 84%). A 0.25 M solution of the aminal intermediate (360 mg, 0.84 mmol, 1.0 equiv) in 1,2-dichloroethane (3.4 mL) was treated with Ac_2O (0.15 mL, 1.6 mmol, 2.0 equiv) and $HClO_4$ (70%, 7.0 μL, 0.080 mmol, 0.10 equiv) and stirred at 70 °C for 20 h. After allowing the solution to cool to rt, the solvent was removed in vacuo and the residue purified by flash column chromatography (gradient, CH_2Cl_2/MeOH, 95:5→90:10) to afford **27** as a yellow solid (260 mg, 75%, 63% over three steps). ^{1}H NMR (500 MHz, acetone-d_6) δ 10.09 (s, 1H), 7.58 (d, 1H, J=7.7 Hz), 7.41–7.35 (m, 2H), 7.30 (t, 1H, 7.3 Hz), 5.90 (d, 1H, J=4.1 Hz), 5.00 (d, 1H, J=15.0 Hz), 4.95 (t, 1H, J=4.4 Hz), 4.82 (d, 1H, J=15.1 Hz), 3.92 (t, 4H, J=4.5 Hz), 3.47 (t, 4H, J=4.5 Hz), 3.43–3.40 (m, 1H), 3.17 (d, 1H, J=16.9 Hz), 2.35 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 141.7, 137.7, 132.9, 130.0, 127.9, 126.4, 125.8, 124.8, 122.7, 78.3, 67.3, 61.4, 60.0, 57.2, 38.2, 7.4; IR (thin film) ν 3115, 2969, 2863, 1460, 1270, 1102, 1080, 923, 741 cm^{-1}; HRESI$^+$/TOF-MS calcd 312.1707 [M]$^+$, found 312.1720; $[\alpha]_D^{20}$ −174.5 (c 0.20, CH_2Cl_2).

4.1.21. Preparation of N-methyl substituted imidazolium salt **28**

To a solution of oxazolinium salt **18** (388 mg, 1.00 mmol, 1.00 equiv) in CH_2Cl_2 (5 mL) were added toluene (5 mL) and a 2.0 M

solution (THF) of *N*-methyl amine (0.75 mL, 1.50 mmol, 1.50 equiv). The heterogeneous mixture was stirred at ambient temperature for 12 h. The precipitate was collected by vacuum filtration and washed with Et_2O to afford the aminal intermediate as a white powder and as a mixture of diastereomers (310 mg, 86% yield). A 0.25 M solution of the aminal intermediate (300 mg, 0.83 mmol, 1.0 equiv) in 1,2-dichloroethane (3.3 mL) was treated with Ac_2O (0.16 mL, 1.7 mmol, 2.0 equiv) and $HClO_4$ (70%, 7.0 μL, 0.080 mmol, 0.10 equiv) and stirred at 70 °C for 10 min. After allowing the solution to cool to rt, the solvent was removed in vacuo and the resultant residue dissolved in a minimal amount of CH_2Cl_2 and triturated with toluene. The precipitate was collected by vacuum filtration to afford **28** as a white powder (180 mg, 64%, 53% over three steps). ^{1}H NMR (400 MHz, acetone-d_6) δ 9.56 (s, 1H), 5.53 (d, 1H, J=7.6 Hz), 7.41–7.30 (m, 2H), 7.28 (t, 1H, J=7.3 Hz), 5.91 (s, 1H), 5.02 (d, 1H, J=15.2 Hz), 4.95 (t, 1H, J=4.5 Hz), 4.83 (d, 1H, J=15.0 Hz), 4.06 (s, 3H), 3.43 (dd, 1H, J=16.9, 4.9 Hz), 3.18 (d, 1H, J=17.0 Hz), 2.36 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 141.6, 138.1, 135.7, 129.9, 127.9, 126.2, 126.0, 124.7, 124.0, 78.2, 61.1, 60.0, 38.1, 34.2, 7.8; IR (thin film) ν 3137, 3076, 2930, 1636, 1558, 1446, 1253, 1096, 760, 738, 624 cm^{-1}; HRESI$^+$/TOF-MS calcd 241.1335 [M]$^+$, found 241.1338; $[\alpha]_D^{20}$ −163.7 (*c* 0.33, CH_2Cl_2).

4.1.22. Preparation of N-2-isopropylphenyl substituted imidazolium salt **29**

To a round bottom flask charged with a magnetic stir bar and oxazolinium salt **18** (388 mg, 1.00 mmol, 1.00 equiv) were added toluene (10 mL) and 2-isopropyl aniline (0.21 mL, 1.50 mmol, 1.50 equiv). The heterogeneous mixture was stirred at ambient temperature for 12 h. The precipitate was suspended in EtOAc, collected by vacuum filtration, and washed with EtOAc to afford the aminal intermediate as a white powder and as a mixture of diastereomers (325 mg, 71%). A mixture of the aminal intermediate (325 mg, 0.70 mmol, 1.0 equiv) in toluene (2.8 mL) was treated with Ac_2O (0.13 mL, 1.4 mmol, 2.0 equiv) and $HClO_4$ (70%, 13 μL, 0.14 mmol, 0.20 equiv) and heated at 80 °C for 1 h. The solution was decanted and the oil concentrated in vacuo to a brown foam, which was dissolved in a minimal amount of EtOAc, placed in a sonicating bath, and triturated with Et_2O. Isolation of the precipitate by vacuum filtration provided two crops of **29**, 100 and 120 mg, respectively, as a white powder (220 mg, 71%, 50% over three steps) and as a 50:50 mixture of atropisomers. ^{1}H NMR (500 MHz, acetone-d_6) δ 9.85 (d, 1H, J=1.6 Hz), 7.75–7.73 (m, 2H), 7.65–7.51 (m, 3H), 7.47–7.39 (m, 2H), 7.35–7.30 (m, 1H), 6.06 (dd, 1H, J=28.6, 4.2 Hz), 5.13–5.08 (m, 1H), 5.05–5.02 (m, 1H), 4.99–4.91 (m, 1H), 3.49–3.46 (m, 1H), 3.23 (dd, 1H, J=16.9, 2.7 Hz), 2.77* (septet, 1H, J=6.9 Hz), 2.59 (septet, 1H, J=6.9 Hz), 2.12 (d, 3H, J=2.6 Hz), 1.30–1.24 (m, 6H); ^{13}C NMR (125 MHz, acetone-d_6) δ 146.8, 146.6, 142.0, 141.8, 138.1, 137.8, 136.0, 135.8, 132.9, 132.9, 131.7, 130.2, 130.1, 129.0, 128.7, 128.5, 128.5, 128.4, 128.3, 128.1, 128.0, 127.0, 126.8, 126.6, 126.4, 125.0, 124.9, 124.1, 78.3, 61.7, 61.6, 60.3, 60.2, 38.4, 38.3, 28.9, 28.6, 24.8, 24.8, 23.4, 23.0, 8.4, 8.3; IR (thin film) ν 3120, 3057, 2967, 2930, 2871, 1540, 1461, 1268, 1224, 1099, 733, 623 cm^{-1}; HRESI$^+$/TOF-MS calcd 345.1916 [M]$^+$, found 345.1955; $[\alpha]_D^{20}$ −113.3 (*c* 0.12, CH_2Cl_2).

4.1.23. Preparation of N-2-tert-butylphenyl substituted imidazolium salt **30**

To a round bottom flask charged with a magnetic stir bar and oxazolinium salt **18** (388 mg, 1.00 mmol, 1.00 equiv) were added toluene (10 mL) and 2-*tert*-butyl aniline (0.24 mL, 1.50 mmol, 1.50 equiv). The heterogeneous mixture was stirred at ambient temperature for 15 h. The aminal intermediate was collected by vacuum filtration as a tan powder and as a mixture of diastereomers (410 mg, 86%). A mixture of the aminal intermediate (410 mg, 0.86 mmol, 1.0 equiv) in toluene (3.5 mL) was treated with Ac_2O (0.16 mL, 1.7 mmol, 2.0 equiv) and $HClO_4$ (70%, 16 μL, 0.17 mmol, 0.20 equiv) and heated at 80 °C for 45 min. The solution was decanted and the oil concentrated in vacuo to a brown foam, which was dissolved in a minimal amount of EtOAc, placed in a sonicating bath, and triturated with Et_2O. Isolation by vacuum filtration afforded **30** in three crops as a yellow solid and ~10:1 mixture of atropisomers (90 mg, 23%, 20% over three steps). ^{1}H NMR (500 MHz, acetone-d_6) δ 9.97* (s, 1H), 9.94 (s, 1H), 7.89 (dd, 1H, J=8.2, 1.4 Hz), 7.71–7.68 (m, 1H), 7.68* (d, 1H, J=1.5 Hz), 7.60–7.57 (m, 1H), 7.54–7.49 (m, 1H), 7.49–7.47* (m 1H), 7.46–7.41 (m, 4H), 7.40 (d, 1H, J=7.4 Hz), 7.30–7.16* (m, 7H), 6.18* (d, 1H, J=5.0 Hz), 6.01 (d, 1H, J=4.2 Hz), 5.13 (d, 1H, J=15 Hz), 5.10–5.08* (m, 2H), 5.02 (t, 1H, J=4.4 Hz), 4.93 (dd, 1H, J=15.0, 1.0 Hz), 3.50 (dd, 1H, J=16.9, 5.0 Hz), 3.31* (dd, 1H, J=16.8, 4.1 Hz), 3.24 (d, 1H, J=16.9 Hz), 3.15* (d, 1H, J=16.7 Hz), 2.16* (s, 3H), 2.14 (s, 3H), 1.32* (s, 9H), 1.29 (s, 9H); ^{13}C NMR (125 MHz, acetone-d_6) δ 147.5, 142.0, 138.1, 137.0, 132.6, 131.7, 131.5, 131.3, 130.8, 130.2, 129.0, 128.8, 128.7, 128.1, 128.0, 127.9, 126.6, 125.0, 124.3, 78.3, 61.6, 60.1, 38.3, 36.9, 32.1, 8.92; IR (thin film) ν 3123, 3056, 2967, 1540, 1482, 1213, 1099, 733, 624 cm^{-1}; HRESI$^+$/TOF-MS calcd 359.2118 [M]$^+$, found 359.2112; $[\alpha]_D^{20}$ −202.7 (*c* 0.073, CH_2Cl_2).

4.1.24. Preparation of N-2-bromophenyl substituted imidazolium salt **31**

To a round bottom flask charged with a magnetic stir bar and oxazolinium salt **18** (388 mg, 1.00 mmol, 1.00 equiv) were added toluene (10 mL) and 2-bromoaniline (0.140 mL, 1.50 mmol, 1.50 equiv). The heterogeneous mixture was stirred at ambient temperature for 12 h. The solution was concentrated in vacuo to a brown foam, which was suspended in Et_2O (10 mL) and EtOAc (4 mL), placed in a sonicating bath, and methanol (<1 mL) added until a solid precipitate formed. The precipitate was collected by vacuum filtration to afford two crops of the aminal intermediate as a white solid and as a mixture of diastereomers (130 mg, 26%). A mixture of the aminal intermediate (125 mg, 0.25 mmol, 1.0 equiv) in toluene (1.0 mL) was treated with Ac_2O (47 μL, 0.50 mmol, 2.0 equiv) and $HClO_4$ (70%, 4.0 μL, 0.050 mmol, 0.20 equiv) and stirred at 80 °C for 30 min. The solution was concentrated in vacuo and the residue purified by flash column chromatography (gradient, CH_2Cl_2/MeOH, 98:2→95:5→92:8→90:10) to afford **31** as a yellow solid as a 2:1 mixture of atropisomers (100 mg, 83% yield, 22% over three steps). ^{1}H NMR (500 MHz, acetone-d_6) δ 9.90* (s, 1H), 9.82 (s, 1H), 8.01 (d, 1H, J=8.0 Hz), 7.97* (d, 1H, J=7.3 Hz), 7.79–7.70 (m, 3H), 7.66* (d, 1H, J=7.6 Hz), 7.61 (d, 1H, J=7.6 Hz), 7.44 (d, 1H, J=7.4 Hz), 7.39 (t, 1H, J=7.3 Hz), 7.32 (t, 1H, J=7.3 Hz), 6.14* (d, 1H, J=3.6 Hz) 6.02 (d, 1H, J=3.8 Hz), 5.13* (d, 1H, J=15.1 Hz), 5.12 (d, 1H, J=15.0 Hz), 5.01* (t, 1H, J=4.4 Hz), 5.01 (t, 1H, J=4.4 Hz), 4.92 (d, 1H, J=15.0 Hz), 3.50* (dd, 1H, J=16.9, 4.7 Hz), 3.50 (dd, 1H, J=16.9, 4.7 Hz), 3.24* (d, 1H, J=16.9 Hz), 3.22 (d, 1H, J=16.9 Hz), 2.17* (s, 3H), 2.14 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 141.8, 138.0, 136.4, 136.1, 134.9, 134.8, 134.2, 133.5, 131.1, 130.8, 130.5, 130.4, 130.1, 128.1, 128.0, 126.6, 126.5, 126.3, 125.0, 124.7, 124.3, 121.9, 78.3, 61.7, 60.2, 38.4, 38.2, 8.4, 8.3; IR (thin film) ν 3124, 3058, 2926, 1544, 1482, 1267, 1219, 1092, 736, 622 cm^{-1}; HRESI$^+$/TOF-MS calcd 381.0597 [M]$^+$, found 381.0607; $[\alpha]_D^{20}$ −84.9 (*c* 011, CH_2Cl_2).

4.1.25. Preparation of N-2-(N-methylbenzamido) substituted imidazolium salt **32**

To a 1.0 M solution of oxazolinium salt **18** (388 mg, 1.00 mmol, 1.00 equiv) in CH_2Cl_2 in a round bottom flask charged with a magnetic stir bar was added a 1 M solution of 2-amino-*N*-methylbenzamide[34] (1.5 mL, 1.5 mmol, 1.5 equiv) in CH_2Cl_2 followed by toluene (3 mL). The cloudy solution was stirred at ambient temperature for 16 h. The solution was triturated with Et_2O, the supernatant decanted, and residual solvent removed in vacuo to afford the aminal intermediate as a light tan foam and as a mixture

of diastereomers (475 mg, 99%). A 0.25 M solution of the aminal intermediate (475 mg, 0.99 mmol, 1.0 equiv) in 1,2-dichloroethane (4.0 mL) was treated with Ac_2O (0.19 mL, 2.0 mmol, 2.0 equiv) and $HClO_4$ (70%, 17 μL, 0.20 mmol, 0.20 equiv). The solution was stirred at 70 °C for 30 min, concentrated in vacuo, and the residue purified by flash column chromatography (CH_2Cl_2/MeOH, 95:5) to afford **32** as a white solid (320 mg, 70%, 69% over three steps). ^{1}H NMR (500 MHz, acetone-d_6) δ 9.67 (s, 1H), 7.9 (br s, 1H, NH), 7.89–7.77 (m, 4H), 7.62 (d, 1H, J=7.6 Hz), 7.41 (d, 1H, J=7.4 Hz), 7.38 (t, 1H, J=7.4 Hz), 7.32 (t, 1H, J=7.4 Hz), 5.97 (s, 1H), 5.04 (d, 1H, J=15.0 Hz), 4.99 (br s, 1H), 4.89 (d, 1H, J=15.0 Hz), 3.47 (dd, 1H, J=16.9, 4.8 Hz), 3.20 (d, 1H, J=16.9 Hz), 2.81 (d, 3H, J=4.7 Hz), 2.10 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 166.4, 141.6, 138.1, 136.6, 135.4, 132.5, 132.4, 131.9, 129.9, 129.8, 129.6, 127.9, 127.2, 126.2, 124.8, 123.6, 78.3, 61.5, 60.1, 38.3, 26.8, 8.4; IR (thin film) ν 3362, 3128, 3061, 2931, 1662, 1604, 1545, 1217, 1099, 734, 623 cm^{-1}; HRESI$^+$/TOF-MS calcd 360.1707 [M]$^+$, found 360.1711; $[\alpha]_D^{20}$ −124.9 (c 0.19, CH_2Cl_2).

Acknowledgements

Partial support for this work was provided by the National Science Foundation (CHE-0449587). Unrestricted support from Amgen, AstraZeneca, Boehringer-Ingelheim, Bristol Myers Squibb, and Eli Lilly is gratefully acknowledged. We thank Donald Gauthier of Merck & Co. for a generous gift of aminoindanol. We thank Michael Rommel for his studies on the stereoselective epoxidation and ring closure of **5**. We thank Patrick J. Carroll for the X-ray crystallographic structure. J.W.B is a fellow of the Packard Foundation, the Beckman Foundation, the Sloan Foundation, and a Cottrell Scholar.

Supplementary data

Copies of ^{1}H NMR and ^{13}C NMR spectra as well as crystallographic data can be found in the online version. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.03.072.

References and notes

1. (a) Herrmann, W. A.; Köcher, C. *Angew. Chem., Int. Ed.* **1997**, *36*, 2162–2187; (b) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *37*, 1290–1309; (c) César, V.; Bellemin-Laponnaz, S.; Gade, L. H. *Chem. Soc. Rev.* **2004**, *33*, 619–636; (d) Díez-González, S.; Nolan, S. P. *Coord. Chem. Rev.* **2007**, *251*, 874–883; (e) *N-Heterocyclic Carbenes in Transition Metal Catalysis*; Glorius, F., Ed.; Springer: New York, NY, 2007.
2. (a) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726; (b) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *43*, 534–541; (c) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655; (d) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988–3000.
3. *N-Heterocyclic Carbenes in Synthesis*; Nolan, S. P., Ed.; Wiley VCH: Weinheim, Germany, 2006.
4. (a) Glorius, F.; Altenhoff, G.; Goddard, R.; Lehmann, C. *Chem. Commun.* **2002**, 2704–2705; (b) Burstein, C.; Lehmann, C. W.; Glorius, F. *Tetrahedron* **2005**, *61*, 6207–6217; (c) Tewes, F.; Schlecker, A.; Harms, K.; Glorius, F. *J. Organomet. Chem.* **2007**, *692*, 4593–4602.
5. Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225–3228.
6. Gillingham, D. G.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 3860–3864.
7. Chen, D.; Banphavichit, V.; Reibenspies, J.; Burgess, K. *Organometallics* **2007**, *26*, 855–859.
8. Chaulagain, M. R.; Sormunen, G. J.; Montgomery, J. *J. Am. Chem. Soc.* **2007**, *129*, 9568–9569.
9. (a) Chow, K. Y.-K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126–8127; (b) Sohn, S. S.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3873–3876; (c) Sohn, S. S.; Bode, J. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 6021–6024.
10. For related work, see: (a) Reynolds, N. T.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518–9519; (b) Reynolds, N. T.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *125*, 16406–16407.
11. Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798–13799.
12. Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 13796–13797.
13. (a) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370–14371; (b) He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131–3134.
14. (a) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418–8420; (b) He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15088–15089; (c) Chiang, P.-C.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 3520–3521; (d) He, M.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 418–419.
15. Struble, J. R.; Kaeobamrung, J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 957–960.
16. (a) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205–6208; (b) Burstein, C.; Tschan, S.; Xie, X.; Glorius, F. *Synthesis* **2006**, *14*, 2418–2439.
17. For a highlight, see: Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506–7510.
18. For other applications of these conditions and concepts, see: (a) Mattson, A. E.; Scheidt, K. A. *Org. Lett.* **2004**, 4363–4366; (b) Nair, V.; Poonoth, M.; Vellalath, S.; Suresh, E.; Thirumalai, R. *J. Org. Chem.* **2006**, *71*, 8964–8965; (c) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *J. Am. Chem. Soc.* **2006**, *128*, 8736–8737; (d) Nair, V.; Vellalath, S.; Poonoth, M.; Mohan, R.; Suresh, E. *Org. Lett.* **2006**, *8*, 507–509; (e) Nair, V.; Babu, B. P.; Vellalath, S.; Suresh, E. *Chem. Commun* **2008**, *6*, 747–749.
19. (a) Knight, R. L.; Leeper, F. J. *Tetrahedron Lett.* **1997**, *38*, 3611–3614; (b) Knight, R. L.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1891–1893; (c) Enders, D.; Kalfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743–1745; (d) Enders, D.; Breuer, K.; Balensiefer, T. *Synthesis* **2003**, *8*, 1292–1295; (e) Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem.* **2004**, *9*, 2025–2035; (f) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem.* **2005**, *70*, 5725–5728; (g) Enders, D.; Niemmeier, O.; Balensiefer, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1463–1467; (h) Takikawa, H.; Hachisu, Y.; Bode, J. W.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 3492–3494.
20. For highlights, see: (a) Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326–1328; (b) Christmann, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2632–2634.
21. Arduengo, A. J.; Krafczyk, R.; Schmutzler, R.; Craig, H. A.; Goerlich, J. R.; Marshall, W. J.; Unverzagt, M. *Tetrahedron* **1999**, *55*, 14523–14534.
22. Kuhn, N.; Kratz, T. *Synthesis* **1993**, 561–562.
23. Nyce, G. W.; Csihony, S.; Waymouth, R. M.; Hedrick, J. L. *Chem.—Eur. J.* **2004**, *10*, 4073–4079.
24. Fürstner, A.; Alcarazo, M.; César, V.; Lehmann, C. W. *Chem. Commun.* **2006**, 2176–2178.
25. Song, Z. J.; Zhao, M.; Desmond, R.; Devine, P.; Tschaen, D. M.; Tillyer, R.; Frey, L.; Heid, R.; Xu, F.; Foster, B.; Li, J.; Reamer, R.; Volante, R.; Grabowski, E. J. J.; Dolling, U. H.; Reider, P. J.; Okada, S.; Kato, Y.; Mano, E. *J. Org. Chem.* **1999**, *64*, 9658–9667.
26. Hashimoto, N.; Kanda, A. *Org. Process Res. Dev.* **2002**, *6*, 405–406.
27. Potter, G. W.; Monro, A. M. *J. Heterocycl. Chem.* **1972**, *9*, 299–301.
28. Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224–11235.
29. Fürstner, A.; Alcarazo, M.; César, V.; Krause, H. *Org. Synth.* **2008**, *85*, 35–44.
30. Our optimized protocol was subsequently used on substrates **22**, **28**–**30**, and **34** and scale-up of **2**.
31. The experimental details for this optimized route to *N*-mesityl substituted imidazolium salt **2** were reported in Supplementary data of our work cited in Ref. 15.
32. Crystallographic data (excluding structural factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 674712. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
33. These examples were prepared only once. The diminished yields of several of these salts reflect the difficulty in purification from an intractable brown oil formed in the reaction.
34. Witt, A.; Bergman, J. *Tetrahedron* **2000**, *56*, 7245–7253.