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Synthesis of optically active imidazopyridinium salts and the corresponding NHCs

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Abstract—A convergent synthesis of chiral imidazo-[1,5-*a*]-pyridinium salts is described by facile introduction of a stereogenic center via the N2 substituent. Conversion of these optically active salts to the corresponding *N*-heterocyclic carbenes (NHCs) and their trapping with sulfur followed by optical activity measurements are discussed.

The isolation of stable *N*-heterocyclic carbene (NHC) derivatives by Arduengo has led to recent studies of their utility and chemistry.[1] Imidazolium, triazolium, and thiazolium salts are employed in a wide range of transformations for organic synthesis. NHCs have served as superb ligands in metal-catalyzed reactions[2] in addition to providing an unique chemistry enabling the use of these heterocycles as organic catalysts.[3] Importantly, the use of optically active NHCs (Fig. 1) has led to the development of a variety of new catalytic asymmetric transformations for organic synthesis.[3,4] Subtle stereoelectronic effects are known to have a dramatic impact on the chemistry of NHCs. Lassaletta[5a] and Glorius[5b] have reported the synthesis of NHC derivatives based on the imidazo-[1,5-*a*]-pyridinium ring system **10** (R′=H) and Miyashita has disclosed the use of imidazopyridinium iodide **11** as a highly reactive catalyst.[6] Herein we describe a convergent synthesis of optically active imidazo-[1,5-*a*]-pyridinium salts and the in situ trapping of the corresponding carbene derivatives.

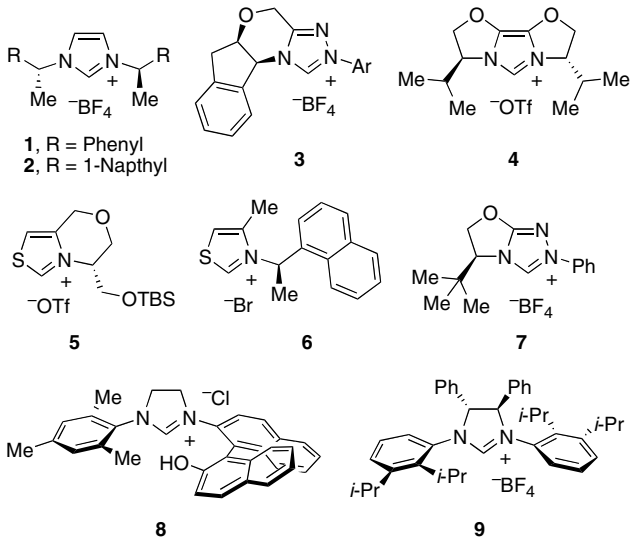
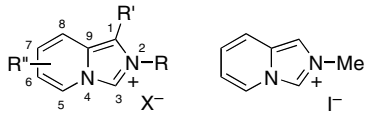


Figure 1. Representative chiral azolium salts.



Many of the transformations catalyzed by NHCs[3,4] employ the necessary catalyst by the in situ deprotonation of the corresponding azolium salt. Excellent examples of the applications of this strategy in accessing the NHCs of interest are seen in Enders and Rovis's studies employing chiral triazolium salt precatalysts (e.g., **7** and **3**, Fig. 1) in a variety of catalytic asymmetric reactions. Additionally, the representative use of optically active imidazolium salts (e.g., **8** and **9**, Fig. 1) by in situ deprotonation and organometallic complex formation is seen in the preparation of catalysts by Hoveyda[4k] and Grubbs[4w] for the olefin metathesis reaction.

We envisioned a convergent and practical synthesis of optically active imidazopyridinium trifluoromethanesulfonate **12** (Scheme 1) by the condensation of a chiral

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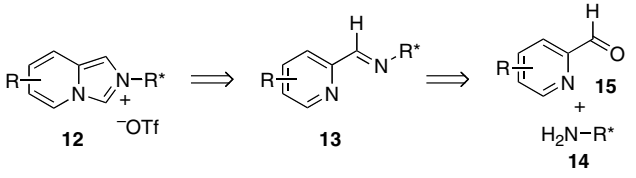
primary amine **14** with a suitable pyridine carboxaldehyde **15** followed by imidazolium formation.[7]

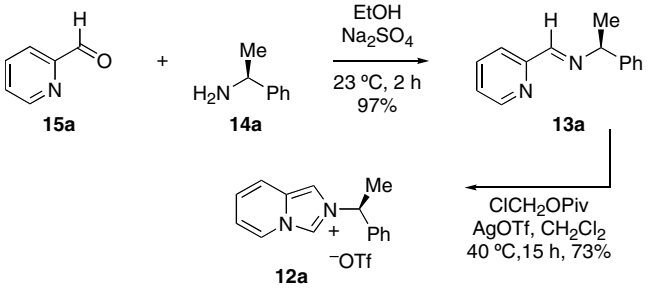
Under optimized conditions, the condensation of commercially available pyridine-2-carboxaldehyde **15a** with (*S*)-alpha-methylbenzylamine (**14a**, 98% ee) provided imine **13a** in a 97% yield (Scheme 2). The treatment of imine **13a**[8] with 2,2-dimethyl-propionic acid chloromethyl ester and anhydrous silver trifluoromethanesulfonate in dichloromethane at 40 °C for 15 h in the dark afforded the desired imidazopyridinium trifluoromethanesulfonate **12a** in a 73% isolated yield. Imidazo[1,5-*a*]-pyridinium trifluoromethanesulfonate was readily purified by flash column chromatography (Scheme 2).

Given the marked enhancement in the stability of the corresponding carbene derivative of imidazopyridinium salts with a C5-substituent,[5a] we examined their synthesis via the optimized conditions described above. The condensation of 6-methylpyridine-2-carboxaldehyde **15b**, prepared from commercially available 2,6-dibromopyridine in two steps (^{n}BuLi, MeI, THF, −78 °C; ^{n}BuLi, DMF),[9] with (*S*)-alpha-methylbenzylamine (**14a**, 98% ee) gave the corresponding imine **13b**, which was converted to the desired 5-methylimidazopyridinium trifluoromethanesulfonate (−)-**12b** ($[\alpha]_D^{20}$ −43 (*c* 0.49, $CHCl_3$)) in a 68% overall yield (Scheme 3).[10] With the 5-methyl substituent in place, deprotonation of **12b** (1.0 equiv NaH, 4 mol % KO^{t}Bu, THF (0.2 M), 23 °C, 3 h) afforded the corresponding NHC **16** as a viscous paste (80–85% yield), with characteristic ^{1}H NMR resonances[11] consistent with those reported by Lassaletta for a related optically inactive derivative.[5a]

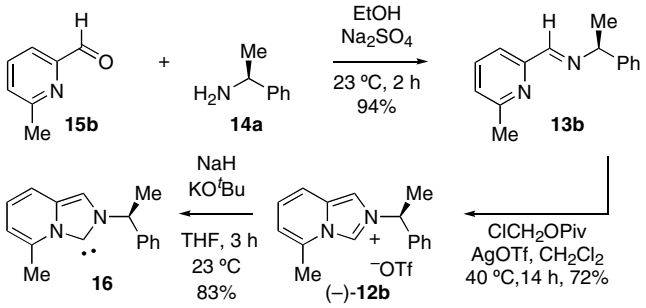
We also examined the synthesis of the doubly substituted (C1 and C5) imidazopyridinium derivative **12c** (Scheme 4). Molecular model analysis suggested that



Scheme 1.



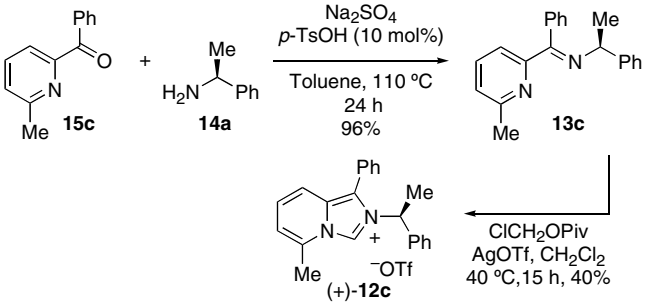
Scheme 2.



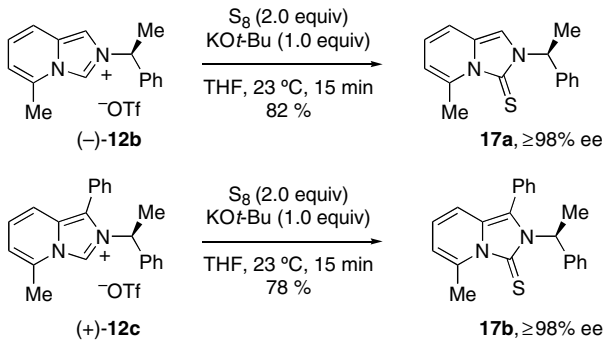
Scheme 3.

the minimization of the steric interactions between the N2-substituent (alpha-methyl benzyl group) with the C1-phenyl substituent would result in projection of the substituents at the stereogenic center toward the N2–C3–N4 environment. Aza-benzophenone derivative **15c**,[12] prepared from 2,6-dibromopyridine in two steps (^{n}BuLi, MeI, THF, −78 °C; ^{n}BuLi, PhCON(Me)OMe),[9] was condensed with amine **14a** to provide the corresponding imine **13c** in a 96% yield as a mixture of ketoimine isomers (47:53 by ^{1}H NMR). The condensation of ketone **15c** with amine **14a** required more forcing conditions as compared to that used with pyridine-2-carboxaldehyde derivatives **15a**,**b**. Ketoimine **13c,** as a mixture of isomers, was converted to the corresponding imidazopyridinium salt **12c** in a 40% isolated yield (Scheme 4).[13]

Direct measurement of the enantiomeric excess of the imidazopyridinium derivatives described above by chiral HPLC analysis was not optimal. We envisioned trapping of the corresponding in situ generated NHCs, prepared by deprotonation of the imidazopyridinium salts, in the form of stable thiourea[14] derivatives for chiral HPLC analysis (Scheme 5). The treatment of imidazopyridinium trifluoromethanesulfonates **12b** and **12c** with KO^{t}Bu in the presence of elemental sulfur provided the corresponding thiourea derivatives **17a** and **17b** in 82% and 78% yield, respectively. The enantiomeric excess of the thiourea derivatives **17a**,**b** were found to be ⩾98% ee, thus illustrating that (1) the stereocenter introduced by the chiral amine is not compromised during the synthesis of the imidazopyridinium salts, and (2) the corresponding NHCs generated by in situ deprotonation are formed without epimerization.



Scheme 4.



Scheme 5.

We have described a short and convergent synthesis of optically active imidazo-[1,5-*a*]-pyridinium derivatives. The synthesis of these imidazopyridinium salts and their in situ deprotonation to the corresponding NHCs occurs without any loss in optical activity. Trapping of the in situ generated NHC derivatives as the corresponding isolable thiourea derivatives allows a simple method for enantiomeric excess determination. This short synthetic sequence allows a multi-gram synthesis (e.g., >4 g-scale of (−)-**12b**)[10] of these optically active NHC precursors.

Acknowledgments

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10. Synthesis of 5-methyl-2-(1-(*S*)-phenylethyl)-imidazo[1,5-*a*]-pyridin-2-ium trifluoromethanesulfonate (**12b**): (*S*)-α-methylbenzylamine (**14a**, 2.09 mL, 16.4 mmol, 1.00 equiv) and anhydrous sodium sulfate (3.2 g) were added to a solution of aldehyde **15b** (1.99 g, 16.4 mmol, 1 equiv) in absolute ethanol (32 mL) and the resulting suspension was vigorously stirred at 23 °C. After 2 h, the reaction mixture was filtered and the resulting solution was concentrated to provide the desired crude imine **13b** (3.47 g). 2,2-Dimethyl-propionic acid chloromethyl ester (3.14 mL, 21.7 mmol, 1.40 equiv) and silver trifluoromethansulfonate (4.77 g, 18.6 mmol, 1.2 equiv) were added to a solution of crude imine **13b** (3.47 g) in dichloromethane (150 mL) and the resulting mixture was heated to 40 °C in the dark. After 14 h, the dark suspension was cooled to 23 °C, was filtered through a plug of Celite (7.5 cm dia. × 2.5 cm ht.). The filter cake was rinsed with methanol (2 × 20 mL) and the filtrate was concentrated in vacuo to yield a dark purple oil (8.8 g). Purification of the residue by flash column chromatography (2.5 × 26 cm, 100% CH_2Cl_2 to 2% MeOH in CH_2Cl_2) afforded imidazopyridinium salt **12b** as a light beige powder (4.14 g, 72%). Mp: 106–107 °C. TLC (10% MeOH in CH_2Cl_2), R_f: 0.48 (UV, $KMnO_4$). $[\alpha]_D^{20}$ −43 (*c* 0.49, $CHCl_3$). The ee of **12b** was determined to be 98.6% by conversion to thiourea **17a** and analysis by HPLC (Chirapak AD-H, 30% isopropanol in hexanes, 1.0 mL/min, $t_{major} = 6.99$ min, $t_{minor} = 4.83$ min). ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ 10.1 (s, 1H, C3–*H*), 7.65 (s, 1H, C1–*H*), 7.52–7.54 (m, 2H, Ph*H*), 7.38–7.49 (m, 4H, Ph*H* and C8–*H*), 7.16 (dd, $J = 9.5$ Hz, 7.0 Hz, 1H, C7–*H*), 6.86 (dt, $J = 7.0$ Hz, 1.0 Hz, 1H, C6–

H), 6.28 (q, $J = 7.0$ Hz, 1H, MeC*H*), 2.82 (s, 3H, pyr–CH_3), 2.12 (d, $J = 7.0$ Hz, 3H, CH_3CH). ^{13}C NMR (125.8 MHz, $CDCl_3$, 20 °C): δ 137.9, 133.5, 131.1, 129.7, 129.6, 127.4, 125.6, 123.5, 120.9 (q, $J_{CF} = 320.2$ Hz, *C*F_3), 116.9, 116.1, 111.8, 61.4 (Me*C*HPh), 21.0 (*C*H_3–pyr), 18.2 (*C*H_3CHPh). FTIR (neat) cm^{-1}: 3106 (m), 1662 (w), 1562 (w), 1458 (w), 1259 (s). HRMS-ESI (*m*/*z*): calcd for $C_{16}H_{17}N_2$ [M+]: 237.1392, found: 237.1393.

11. ^{1}H NMR (500 MHz, C_6D_6, 20 °C): δ 7.01–7.15 (m, 5H, Ph*H*), 6.84 (d, $J = 9.0$ Hz, 1H, C8–*H*), 6.76 (s, 1H, C1–*H*), 6.33 (dd, $J = 9.3$ Hz, 6.3 Hz, 1H, C7–*H*), 5.87 (d, $J = 6.0$ Hz, 1H, C6–*H*), 5.74 (q, $J = 7.0$ Hz, 1H, MeC*H*), 2.76 (s, 3H, pyr–CH_3), 1.82 (d, $J = 7.0$ Hz, 3H, CH_3CH).
12. Ketone **15c**: ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ 8.10 (app d, $J = 7.5$ Hz, 2H, PhH_o), 7.76–7.80 (m, 2H, C3–*H* and C4–*H*), 7.60 (app t, $J = 7.5$ Hz, 1H, PhH_p), 7.49 (app t, $J = 7.8$ Hz, 2H, PhH_m), 7.35 (dd, $J = 6.8$ Hz, 2.3 Hz, 1H, C5–*H*), 2.65 (s, 3H, CH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$, 20 °C): δ 194.0, 157.8, 154.7, 137.1, 136.3, 133.0, 131.3, 128.2, 125.9, 121.8, 24.6.
13. Synthesis of 5-methyl-1-phenyl-2-(1-(*S*)-phenylethyl)-imidazo[1,5-*a*]pyridin-2-ium trifluoromethanesulfonate (**12c**): (*S*)-α-Methylbenzylamine (**14a**, 107 μL, 0.837 mmol, 1.10 equiv), *p*-toluenesulfonic acid monohydrate (14.5 mg) and anhydrous sodium sulfate (1.00 g) were added to a solution of ketone **15c** (150 mg, 0.760 mmol, 1 equiv) in toluene (4.00 mL) and the resulting suspension was heated to 110 °C. After 24 h, the mixture was cooled to an ambient temperature, and was concentrated in vacuo. The resulting light orange residue was diluted with hexanes (2.0 mL) and filtered. The filter cake was washed with hexanes (3×2 mL) and the filtrate was concentrated in vacuo to give the desired imine **13c** (220 mg, 96%) as a mixture of ketoimine isomers (47:53). 2,2-Dimethylpropionic acid chloromethyl ester (150 μL, 1.02 mmol, 1.40 equiv) and silver trifluoromethanesulfonate (226 mg, 0.878 mmol, 1.20 equiv) were added to a solution of the imine **13c** (220 mg, 0.732 mmol, 1 equiv) in CH_2Cl_2 (7.00 mL) and the resulting mixture was heated to 40 °C in the dark. After 15 h, the black suspension was cooled to 23 °C and was filtered through a plug of Celite (2.5×1.75 cm). The filter cake was rinsed with MeOH (3×3 mL) and the filtrate was concentrated in vacuo to yield a viscous red oil. Purification of the residue by flash column chromatography (2.5×25 cm, 1% MeOH in CH_2Cl_2 to 10% MeOH in CH_2Cl_2) afforded **12c** as a red oil. The product was triturated from CH_2Cl_2 (1 mL) by the addition of Et_2O (10 mL). Collection of the solid and removal of the volatiles afforded imidazopyridinium salt **12c** as an off-white solid (136 mg, 40%). Mp: 125–127 °C. TLC (10% MeOH in CH_2Cl_2), R_f: 0.48 (UV, $KMnO_4$). $[\alpha]_D^{20}$ +5 (*c* 0.505, $CHCl_3$). The ee of **12c** was determined to be 98.3% by conversion to thiourea **17b** and analysis by HPLC (Chirapak AD-H, 100% hexanes to 30% isopropanol in hexanes over 10 min, 2.0 mL/min, $t_{major} = 5.14$ min, $t_{minor} = 4.75$ min). ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ 10.07 (s, 1H, C3–*H*), 7.63, (app t, $J = 7.8$ Hz, 1H), 7.56 (t, $J = 7.8$ Hz, 2H), 7.24–7.28 (m, 5H), 7.25 (d, $J = 10.0$ Hz, 1H, C8–*H*), 7.16 (m, 2H), 7.12 (dd, $J = 9.5$ Hz, 7.0 Hz, 1H, C7–*H*), 6.90 (dt, $J = 6.5$ Hz, 0.5 Hz, 1H, C6–*H*), 5.80 (q, $J = 7.0$ Hz, 1H, C*H*Ph), 2.95 (s, 3H, pyr–CH_3), 2.24 (d, $J = 7.5$ Hz, 3H, CHCH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$, 20 °C): δ 138.4, 134.5, 131.2, 129.8, 129.5, 129.3, 129.1, 126.9, 125.9, 125.6, 124.9, 123.3, 120.9 (q, $J = 320.5$ Hz, *C*F_3), 117.1, 115.2, 60.3 (CH_3*C*HPh), 21.7 (*C*H_3–pyr), 18.3 (*C*H_3CH). FTIR (neat) cm^{-1}: 3106 (m), 2989 (w), 1661 (m), 1554 (m), 1456 (s). HRMS-ESI (*m*/*z*): calcd for $C_{22}H_{21}N_2$ [M+]: 313.1699, found: 313.1692.
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