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Determining the scope of the lanthanide mediated, sequential hydroamination/C–C cyclization reaction: formation of tricyclic and tetracyclic aromatic nitrogen heterocycles

Gary A. Molander* and Shawn K. Pack

Roy and Diana Vagelos Laboratories, Department of Chemistry, 231 South 34th Street, University of Pennsylvania, Philadelphia, PA 19104-6323, USA

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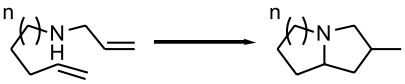
Abstract—The scope of the lanthanide mediated, sequential hydroamination/C–C cyclization reaction was determined for the formation of tricyclic and tetracyclic aromatic nitrogen heterocycles. An array of ring sizes was explored to determine the diastereoselectivity. The electronic characteristics of the aromatic ring was also varied to determine how it affected the cascade reaction. It was found that the benzo[*a*]quinolizine and the pyrido[2,1,*a*]isoindolizine ring systems formed with the highest diastereoselectivity (>20:1), regardless of the electronic characteristics of the aromatic ring. Additionally, a tetracyclic indole nitrogen heterocycle was formed with a 2.3:1 diastereomeric ratio. A novel procedure for substrate preparation is also presented.

1. Introduction

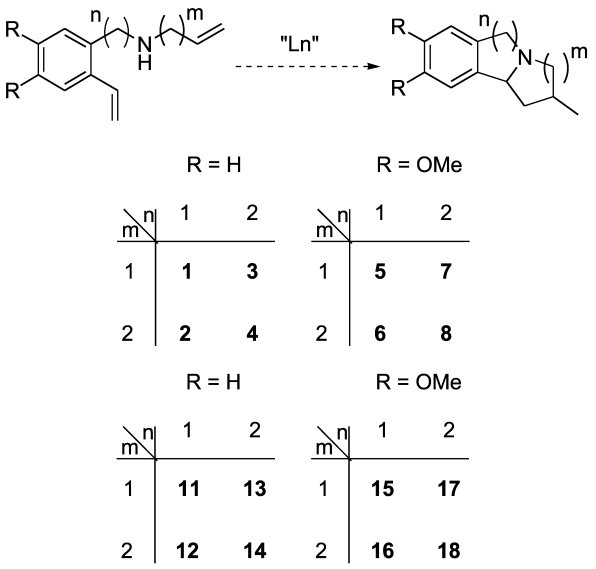
Reactions involving the formation of several bonds and ring systems in a single synthetic operation have proven to be the most powerful in the arsenal of the synthetic organic chemist. However, the utility of these reactions cannot be fully realized until the scope of the reaction is determined. Li and Marks first presented the novel lanthanide-mediated, sequential intramolecular hydroamination/C–C bond-forming cyclization reaction (Eq. (1)).[1]



(1)

In a thorough study, they have shown that, unlike other metal catalyzed intramolecular, hydroamination reactions, the organolanthanide formed after the initial hydroamination can insert into another π-system to form saturated and partially saturated indolizines and pyrrolizines (Scheme 1).

One of the primary goals of our laboratory is the development and application of various methods toward the synthesis of natural products. To apply the powerful method outlined by Li and Marks to the synthesis of complex natural products such as proteomitine, the indole alkaloids, the necine nucleus and the pumiliotoxin core, several issues must be addressed (Fig. 1). First, it was uncertain if this method could be applied to the formation of quinolizidine ring systems. Although the formation of dihydroindolizine via the hydroamination reaction is known, whether the sequential reaction would tolerate the various aromatic ring systems such as those shown for proteomitine and the indole alkaloids was unknown.[2] Lastly, the diastereoselectivity of the formation of various



(2)

Keywords: hydroamination; lanthanide; sequential reaction; aromatic nitrogen heterocycle; diastereoselectivity.
* Corresponding author. Tel.: +1-215-573-8604; fax: +1-215-573-7165; e-mail: gmolandr@sas.upenn.edu

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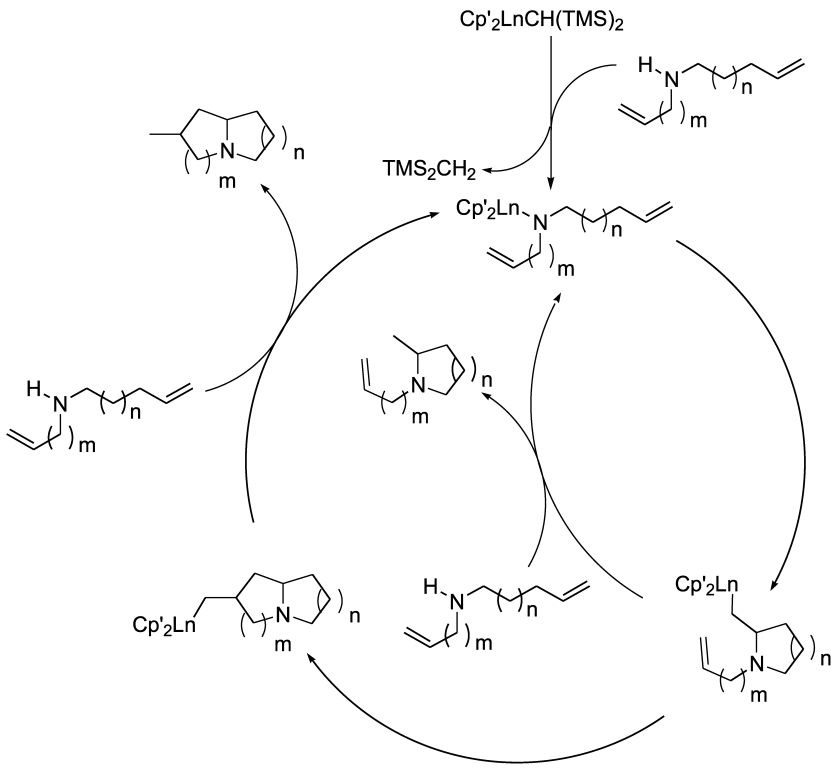


Scheme 1.

ring systems such as the necine nucleus and the pumiliotoxin core, as well as the quinolizidine ring system, has not been determined.

Herein we describe our efforts to address these questions as well as our efforts to simplify the process of substrate purification.

2. Results and discussion

To resolve some of the issues raised above, substrates **1**–**10** were prepared (Eqs. (2)–(4)).

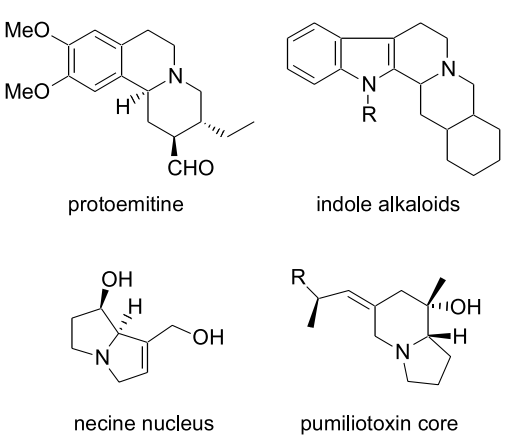
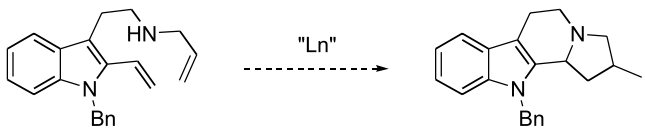


Figure 1.



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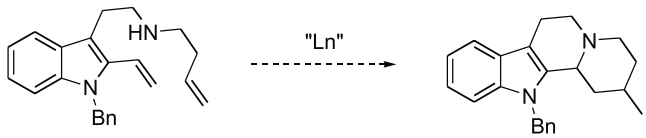
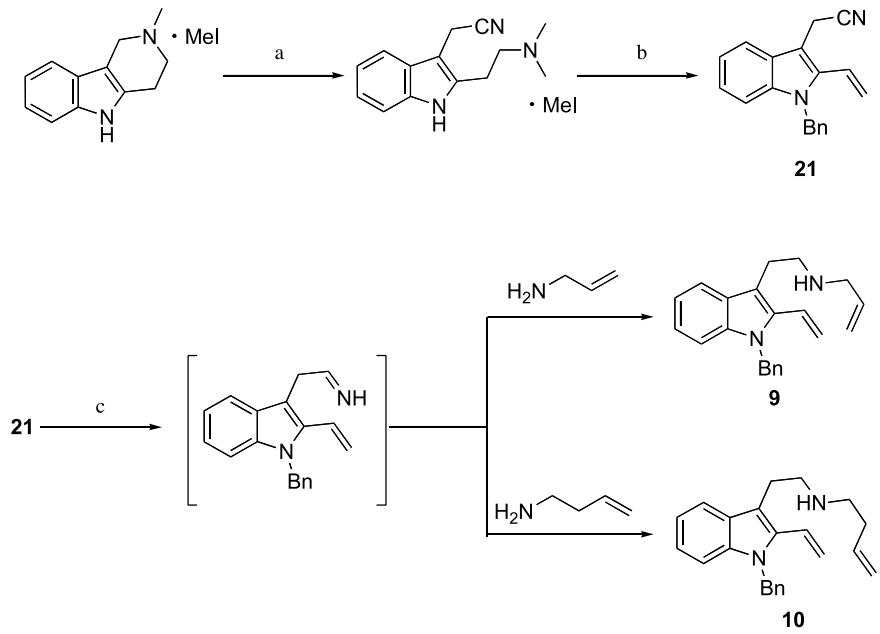


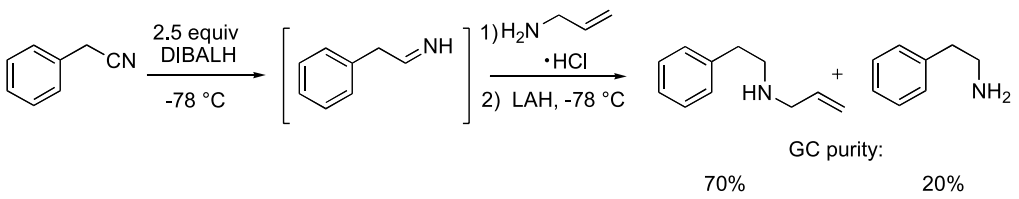
(4)

Substrates **9** and **10** were synthesized from the nitrile **21**[3] based on a modified procedure outlined by Brussee (Scheme 2).[4]

Because of the acidic protons alpha to the nitrile and the aromatic group, the following modifications were required: 1.2 equiv. of DIBALH were used rather than 2.5 equiv., the HCl salt of the amine was utilized to quench the iminium solution rather than NH_4Cl, and $NaCNBH_3$ was employed rather than $NaBH_4$ for the reduction of the secondary imine. Model studies using benzyl nitrile indicated clean formation of the primary imine (Scheme 3). However, formation of the secondary imine followed by reduction resulted in only 70% crude GC purity of product with the major impurity being the primary amine followed by some late eluting impurities. In comparison, the crude GC purity of the aliphatic counterpart is >90%.



Scheme 2. Key: (a) (i) KCN, EtOH, reflux; (ii) MeI, EtOAc/CH_2Cl_2 (91%). (b) (i) 10 wt% aq. NaOH, MeOH/H_2O, rt to 80°C; (ii) Bu_4NHSO_4, BnCl, CH_2Cl_2, 50 wt% aq. NaOH (73%). (c) (i) 1 M DIBALH in toluene, Et_2O, −20°C to rt; (ii) allylamine or homoallylamine, $NaCNBH_3$, MeOH, −20°C to rt (33–41%).

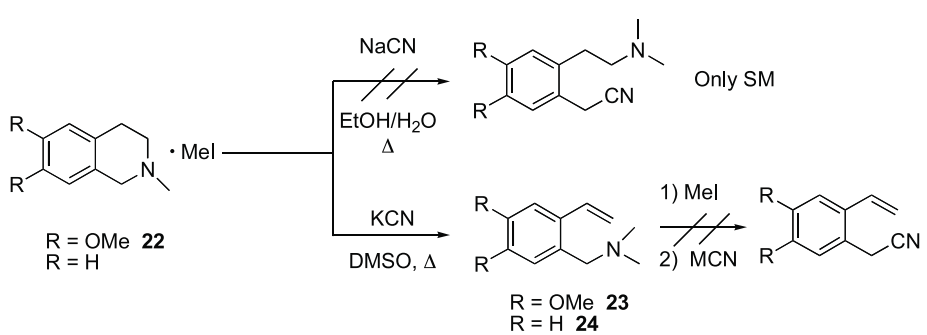


Scheme 3.

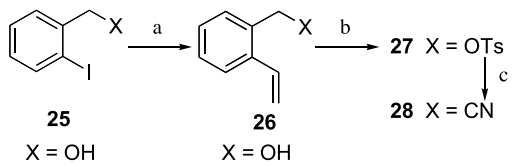
Increasing the amount of amine to 5 equiv., increasing or decreasing the pH of the transimination reaction, and changing the reducing agent of the second reduction had no effect on the outcome of the reaction. However, decreasing the number of equivalents of DIBALH to 1.5 and using $NaCNBH_3$ for the second reduction resulted in complete consumption of the primary imine. Unfortunately, this procedure also generates 5–20% of some late eluting impurities. Consequently, incorporating this procedure only resulted in a modest increase in yield, from an average of 25 to 41%.

Attempts to apply the method outlined by Sapi[3] (Scheme 2) toward the synthesis of other aromatic nitriles proved to be difficult (Scheme 4).

Efforts to open the isoquinoline ring with a nitirile source resulted in an elimination product (**23** or **24**) rather than the desired aromatic amino nitrile. Unfortunately, this product could not undergo further transformation without decomposition. NMR experiments indicated consumption of starting material and loss of the vinyl protons at 150–180°C in deuterated DMSO. It is believed that the displacement of the quaternary amine occurred at these elevated temperatures. However, the resulting product was unstable under these extreme conditions. Various nitrile sources were used

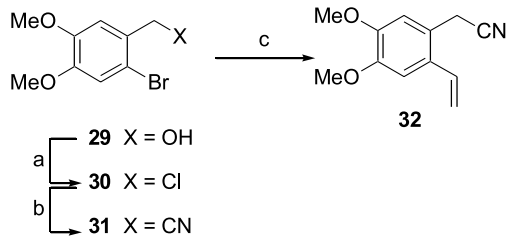


Scheme 4.



Scheme 5. Key: (a) 10% $Pd(PPh_3)_4$, 1.1 equiv. tributylvinylstannane, toluene, sealed 100–110°C (80%). (b) 5.0 equiv. KOH, 1.3 equiv. TosCl, THF, −10°C to rt (99%). (c) 3.5 equiv. KCN, MeCN, rt (95%).

including NaCN, KCN, LiCN, CuCN, and $NaCu(CN)_2$. A more conventional approach using a Stille coupling was used to install the vinyl moiety (Schemes 5 and 6) and obtain the desired nitrile derivatives **28** and **32**.[5]

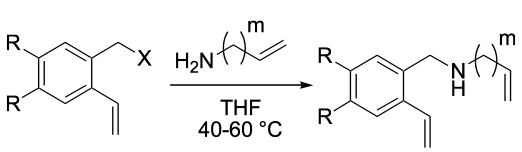


Scheme 6. Key: (a) 1.3 equiv. PPh_3, 1.35 equiv. imidazole, 1.4 equiv. NCS, CH_2Cl_2, 0°C to rt (73%). (b) 2.5 equiv. KCN, DMF (82%). (c) 10% $Pd(PPh_3)_4$, 1.1 equiv. tributylvinylstannane, toluene, sealed 100–110°C (48%).

Trace amounts of Pd result in isomerization of the allylic or homoallylic double bond (ca. 3–20%). Further, the presence of Pd in the substrate kills the catalytic cycle. Hence, the Stille coupling was incorporated as early in the synthesis as possible. In addition, multiple purifications by silica gel chromatography were required.

The instability of the dimethoxy analogs of **26** and **27** required the installation of the vinyl moiety of **32** to be last (Scheme 6). Again, multiple purifications by silica gel chromatography were required to obtain the desired purity. This purification, coupled with the inherent instability of the dimethoxy styrene core, resulted in a lower yield of nitrile **32**. Using the above mentioned transimination reaction, substrates **3**, **4**, **7**, and **8** were prepared from nitriles **28** and **32** (39–51%). The HCl salts of **3** and **4** were isolated. Treatment of the dimethoxy derivatives with HCl resulted in chlorination of the vinyl group, hence substrates **5**–**8** were isolated as the free base.

Substrates **1**, **2**, **5**, and **6** were prepared from the corresponding tosylate or chloride according to a modified procedure outlined by Fürstner (Eq. (5)).[6] Again, the HCl salts of **1** and **2** and the free base of **5** and **6** were isolated.

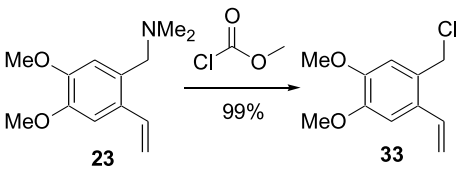


(5)

R = H, X = OTs **27**
R = OMe, X = Cl **33**

R = H, m = 1 **1**
R = H, m = 2 **2**
R = OMe, m = 1 **5**
R = OMe, m = 2 **6**

Although the dimethoxyvinylbenzyl alcohol (the dimethoxy analog of **26**) could be synthesized, it could not be manipulated further because of the electron rich aromatic ring. Attempts to make the corresponding tosylate, bromide, or chloride resulted in decomposition and unpredictable yields (10–70%). Consequently, an alternative approach was taken to prepare the precursor **33** to substrates **5** and **6** (Eq. (6)).



(6)

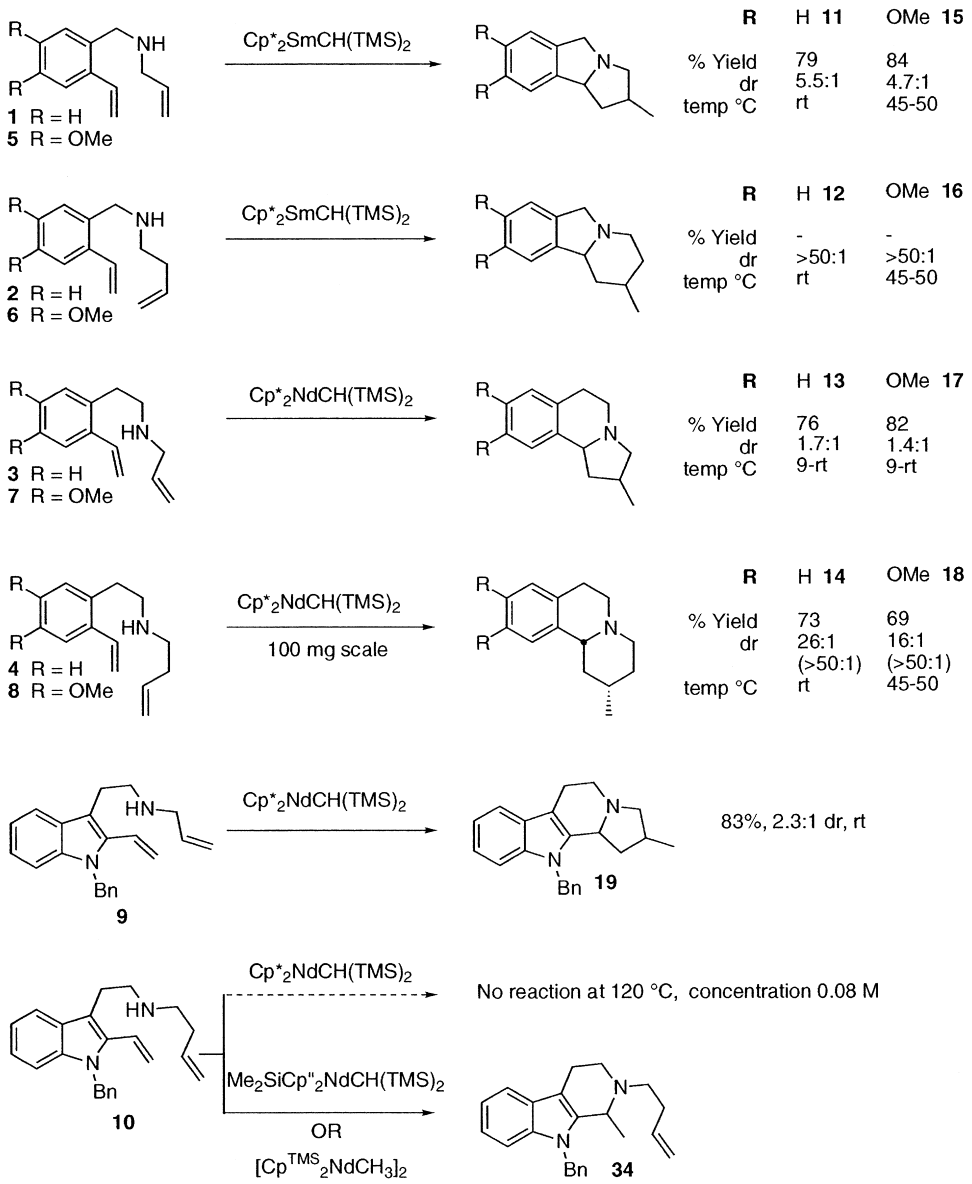
The tertiary amine **23**, prepared according to the procedure outlined above, was treated with methylchloroformate to provide the chloride **33**.[7] It should be noted that this procedure could also be used to make the chloro analog of **27** from the corresponding amine **24**.

Several advantages were realized by isolating the HCl salts of the substrates. First, handling solids are much easier than handling liquids, especially in milligram quantities. Second, oxidation of the amines was greatly inhibited, allowing for easy, prolonged storage. Third, loss of substrate owing to the volatility of the free amine is not an issue. Lastly, the requisite purity for catalytic reactions could be achieved on milligram scale. In comparison, gram quantities of material are desired to obtain comparably pure material by distillation.

Unfortunately, the HCl salt of the amine destroys the catalyst. Consequently, a simple free base protocol was required. An anhydrous, easily filtered, polymer base that is active enough to neutralize the HCl salt in a tri-phasic system (HCl salt, benzene, and polymer) would be ideal. However, to our knowledge, such a polymer does not exist. Several anhydrous bases such as the metal hydrides and metal carbonates were unsuccessful or the requisite process too complicated. Eventually, the free amine was liberated with aqueous NaOH and extracted with benzene. Drying the benzene solution of the amine over activated molecular sieves proved, to our delight, adequate enough to remove the residual moisture without absorbing significant amounts of the free amine. The benzene solution was then degassed and taken into a glove box where it was treated with the catalyst.

With the required substrates in hand, the cyclization studies were begun. Previous results in our laboratory indicated that the pre-catalyst $Cp^*_2SmCH(TMS)_2$ gave the best diastereoselectivity for the five-membered hydroamination reaction. Further, the pre-catalyst $Cp^*_2NdCH(TMS)_2$ gave the best diastereoselectivity for the six-membered hydroamination reaction. The subtle difference in atomic radii could explain this result where the smaller metal, Sm, stereoelectronically favors the formation of the smaller five-membered ring. The formation of the polycyclic nitrogen heterocycles proceeded smoothly in all but one case, substrate **10** (Table 1). This is an anomaly that cannot be readily explained at this point of time. It is somewhat surprising that the dimethoxy derivatives did not deactivate the catalytic cycle by complexation to the metal center, given the oxophilic nature of the lanthanide catalysts. Substrates **4** and **8** gave the

Table 1. Sequential intramolecular/cyclization of aromatic amino dienes



highest diastereoselectivities. Upon silica gel chromatography, the ratio of diastereomers could be enhanced to >50:1. X-ray diffraction analysis of the HCl salt of **14** and **18** show the expected 1,3-*cis* relationship between the two stereocenters (Fig. 2).[8]

Substrates **1** and **5** show higher diastereoselectivity (>4:1) than their non-aromatic counterpart (~1:1).[1] The aromatic ring might act to stiffen the transition state of the second C–C cyclization, resulting in greater selectivity. The larger and more flexible ring system of **13** and **17** resulted in significantly lower diastereoselectivities (~1.5:1).

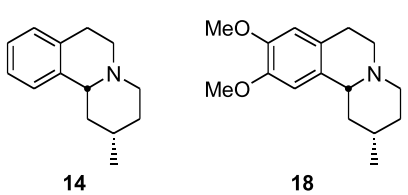
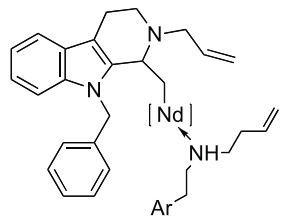


Figure 2.

All of the products are prone to air oxidation. Unfortunately, products **12** and **16** proved unusually unstable and could not be isolated. Although the HCl salt of **16** was obtained in the presence of BHT in 59% yield, it readily oxidized once the salt was in solution. Based on previous results, the relationship between the stereocenters is expected to be *cis*.

Using the standard $Cp^*_2NdCH(TMS)_2$ precatalyst, no reaction appeared to be taking place with substrate **10**, even at 120°C. The root cause of why substrate **10** did not react to form the product under these conditions is unclear at this point, in particular because substrate **9** cyclized



Coordination of a second substrate to the metal center

Figure 3.

smoothly to form **19** in a 2.3:1 diastereomeric ratio. The use of a catalyst with a more open coordination sphere such as the ansa bridged $Me_2SiCp''_2NdCH(TMS)_2$ or the dimer $[Cp''^{TMS}_2NdCH_3]_2$ resulted in mainly the hydroaminated product **34**. This might be attributable to a second amine coordinating to the more accessible metal center,[2] preventing the requisite dative interaction between the metal center and the alkene. The amine complex would serve to interrupt the second cyclization by a rapid protonolysis of the carbon–metal bond (Fig. 3).

3. Conclusions

The application of the lanthanide mediated sequential hydroamination/C–C cyclization has been applied to the synthesis of polycyclic aromatic nitrogen heterocycles, including the quinolizine ring system. The benzo[*a*]quinolizine (**14** and **18**) and the pyrido[2,1,*a*]isoindolizine (**12** and **16**) ring systems gave the greatest diastereoselectivities (>20:1), regardless of the electronic characteristics of the aromatic ring. In addition, the pyrrolo[2,1-*a*]isoindole system was formed with a surprisingly high diastereoselectivity (>4:1) compared to its aliphatic counterpart. Lastly, a novel protocol for substrate preparation involving the use of the HCl salts of the amines enabled the rapid synthesis of high purity substrates.

4. Experimental

4.1. General procedures

Et_2O, THF and C_6D_6 were distilled from sodium benzophenone ketyl. C_6D_6 was degassed prior to use. The catalysts were prepared according to a literature procedure and handled in a nitrogen filled glove box.[9] The homoallylamine was prepared according to a literature procedure.[10] All other reagents were used as received except where noted.

The substrates for catalysis were prepared by neutralizing with 10 wt% aqueous NaOH and extracted with C_6D_6. The free amine solution was dried over activated molecular sieves (cooled under high vacuum) and freeze/pump/thawed prior to transferring to the glove box. A 50 mg sample was then acidified with 2 M HCl in diethyl ether, and the solvents were removed to obtain the weight percent of amine in solution, ca. 3%. The yields of the small scale reactions were based upon this quantitation. The larger scale yields were based on the actual amount of the HCl salt used for neutralization. GC conditions: 50°C for 5 min, 5°C/min ramp, max. temp.=250°C; HP Ultra 2, cross-linked 5% phenylmethyl silicone, 25 m×0.32 mm.

4.1.1. 2-Ethenyl-benzenemethanol (26). Representative procedure for the Stille coupling. Adapted from a procedure outlined by Wipf.[5] A 100 mL sealable pressure tube, fitted with an argon line and a magnetic stirrer was charged with 2.8 g (2.4 mmol) of $Pd(PPh_3)_4$, 60 mL of toluene, 6.00 g (25.6 mmol) of iodide **25**, and 8.0 mL (8.6 g, 28 mmol) of tributylvinyltin. The mixture was cooled to −78°C and placed under vacuum for ca. 10 s prior to refilling with argon. This step was repeated four times and the mixture was allowed to warm to rt. The pressure tube was sealed and placed in a 110–120°C oil bath until the resulting solution turned black (typically 8–24 h). The pressure tube was cooled to rt. The black slurry was filtered through Celite and washed with MeOH. The solvents were removed under vacuum and the red residue was purified two times by silica gel chromatography using EtOAc/toluene as eluent to yield 2.74 g (20.4 mmol, 80%) of the title compound as a pale yellow oil. The spectral features matched the reported spectral data.[11]

4.1.2. 2-Ethenyl-benzeneacetonitrile (28). Preparation of the tosylate **27** was adapted from a procedure outlined by Nicolaou.[12] A 100 mL round bottom flask equipped with a nitrogen line, a magnetic stirrer, and an acetone/ice bath, was charged with 50 mL of THF, 5.7 g (100 mmol) of powdered KOH, 2.74 g (20.4 mmol) of alcohol **26**, and 4.9 g (26 mmol) of *p*-toluenesulfonyl chloride. The slurry was allowed to warm to rt and stirred for ca. 4 h. The slurry was filtered through Celite and the volume was reduced to ca. 10 mL. The concentrated solution was cooled to rt and charged with 100 mL of hexanes. The resulting slurry was solvent exchanged into hexanes while maintaining a bath temperature less than 35°C. The slurry was filtered and washed with hexanes to yield 5.9 g (20 mmol, 100%) of the tosylate **27** as a white crystalline solid. The solid was used immediately in the next step. It may be stored cold and under argon for only a short period of time.

A 250 mL round bottom flask, equipped with a nitrogen line and magnetic stirrer was charged with 50 mL of acetonitrile, 2.5 g (38.4 mmol) of KCN and 3.0 g (10.4 mmol) of the tosylate **27**. After allowing the slurry to stir at rt overnight, 50 mL of MTBE was charged. The slurry was filtered and the solvents were removed under vacuum. The resulting yellow mixture was separated by silica gel chromatography using HPLC grade EtOAc/hexanes as eluent. An additional purification by silica gel chromatography was required to remove trace amounts of palladium to yield 1.41 g (9.85 mmol, 95%) of the title compound as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53–7.51 (d, J=7.5 Hz, 1H), 7.41–7.40 (d, J=7.2 Hz, 1H), 7.36–7.30 (m, 2H), 6.89–6.84 (dd, J=10.8, 17.2 Hz, 1H), 5.72–5.69 (dd, J=0.8, 17.2 Hz, 1H), 5.47–5.45 (dd, J=0.8, 10.8 Hz, 1H), 3.76 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.13, 133.21, 129.04, 128.79, 128.60, 127.36, 126.94, 118.45, 117.71, 21.87; IR ($CDCl_3$) 3068.8, 2359.1, 2341.2, 2253.8, 1486.6, 1452.9, 1417.3 cm^{-1}; HRMS calcd for $C_{10}H_{10}N$ (M+H; CI$^+$): 144.0813, found: 144.0814; LRMS (CI$^+$) *m*/*z* 115 (100), 116 (85), 117 (40), 124 (23).

4.1.3. 1-Bromo-2-(chloromethyl)-4,5-dimethoxy-benzene (30). Adapted from a procedure outlined by Kita.[13] A 250 mL round bottom flask, equipped with a nitrogen line and a magnetic stirrer was charged with 120 mL of methylene chloride, 6.96 g (26.5 mmol) of PPh_3, 1.83 g (26.9 mmol) of imidazole and 3.70 g (27.7 mmol) of NCS. The resulting green/brown, hazy solution was allowed to stir for ca. 30 min. The mixture was then charged with 5.0 g (20.2 mmol) of the alcohol **29**. The mixture was allowed to stir at rt for ca. 8 h and charged with 80 g of AlO_3 and 80 mL of hexanes. The resulting slurry was stirred for ca. 30 min prior to filtration. The volume was reduced under vacuum to ca. 100 mL and charged with an additional 20 g of AlO_3. The slurry was filtered and the resulting solution was solvent exchanged into hexanes with a target volume of ca. 200 mL. The resulting slurry was cooled to 0°C, filtered, and washed with cold hexanes. The solvent was removed to yield 3.93 g (14.8 mmol, 73%) of the title compound. The spectral features matched the reported spectral data.[14] The material was used in the next step without further purification.

4.1.4. 2-Bromo-4,5-dimethoxy-benzeneacetonitrile (31). A 250 mL round bottom flask equipped with a nitrogen line and a magnetic stirrer was charged with 3.41 g (13.0 mmol) of the chloride **30**, 63 mL of DMF, and 1.46 g (22.4 mmol) of KCN. The mixture was allowed to stir at rt for ca. 6 h and cooled to 0°C. The mixture was then charged with 30 mL of diethyl ether and 30 mL of water. The mixture was separated and the aqueous layer was washed with an additional 2×30 mL of diethyl ether. The combined organic layers were washed with 30 mL of water and 30 mL of saturated brine. The organic layer was dried over K_2CO_3 and the solvents were removed under vacuum. The residue was purified by silica gel chromatography using EtOAc/hexanes as eluent to yield 2.73 g (10.7 mmol, 82%) of the title compound. The spectral features matched the reported spectral data.[15]

4.1.5. 2-Ethenyl-4,5-dimethoxy-benzeneacetonitrile (32). Prepared from bromide **31** following the Stille coupling procedure outlined above. After filtration, the solvents were removed under vacuum and the red residue was purified three times by silica gel chromatography using EtOAc/toluene as eluent to yield 1.34 g (6.60 mmol, 48%) of the title compound as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.79 (s, 1H), 6.75–6.70 (dd, J=11.0, 17.2 Hz, 1H), 5.57–5.54 (d, J=17.2 Hz, 1H), 5.31–5.28 (d, J=11.0 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.64 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.16, 149.00, 132.56, 129.24, 119.58, 117.88, 116.05, 111.89, 109.33, 56.01, 55.95, 20.97; IR ($CDCl_3$) 3090.1, 3010.4, 2964.0, 2255.0, 1607.2, 1514.7, 1465.1, 1419.0, 1343.2, 1295.9, 1269.7, 1221.8, 1202.1, 1183.4 cm^{-1}; HRMS calcd for $C_{12}H_{13}NO_2$ (M^+; CI^+): 203.0946, found: 203.0939; LRMS (CI^+) m/z 177 (67), 183 (67), 197 (90), 203 (100).

4.1.6. 2-Ethenyl-4,5-dimethoxy-*N*,*N*-dimethyl-benzenemethanamine (22). A 250 mL round bottom flask, equipped with a magnetic stirrer and an ice bath, was charged with 10.0 g (43.5 mmol) of the HCl salt of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 50 mL of MeOH. The solution was cooled to 0°C and charged with 34.8 g (1.74 g, 43.5 mmol) of a 5 wt% solution of NaOH in MeOH. The solution was allowed to warm to rt and stirred for ca. 1 h. The solution was dried with 5 g of K_2CO_3 and the slurry was filtered. The methanol solution was solvent exchanged into EtOAc with a final target volume of ca. 150 mL. The clear, colorless EtOAc solution was cooled to 0°C and slowly charged with 4.0 mL (9.1 g, 64.3 mmol) of MeI. The resulting slurry was allowed to warm to rt over ca. 1 h and stirred for an additional hour. The crystalline solids were filtered, washed with EtOAc, and dried under vacuum. The off white solids were charged into a 250 mL round bottom flask followed by 100 mL of water and 1.8 g (45 mmol) of NaOH. The solution was allowed to stir overnight at rt. The aqueous solution was solvent exchanged into isopropanol with a final target volume of ca. 100 mL. The resulting slurry was filtered and washed with cold isopropanol to yield 7.2 g (19 mmol, 44%) of the MeI salt **22** and 3.2 g (16.6 mmol, 38%) of the free base of **22**.

A 100 mL sealable pressure tube was charged with 4.88 g (14 mmol) of the MeI salt **22**, 730 mg (18.2 mmol) of NaOH, 40 mL of absolute EtOH, and 2 mL of DMSO. The mixture was heated to 60°C under nitrogen and sealed. The temperature was increased to ca. 90°C and stirred overnight. After cooling, the clear solution was charged into a mixture of 50 mL of water and 50 mL of diethyl ether. The organic layer was separated and the aqueous layer was washed with an additional 2×50 mL of diethyl ether. The combined organic layers were washed with 2×50 mL of water and 50 mL of saturated brine. The organic layer was dried over K_2CO_3, filtered, and the solvents were removed under vacuum to yield 2.4 g (10.8 mmol, 78%) of the title compound as a clear colorless oil. The spectral features matched the reported spectral data.[16] The material was used in the next step without further purification.

4.1.7. 1-(Chloromethyl)-2-ethenyl-4,5-dimethoxy-benzene (33). Adapted from a procedure outlined by Mariano.[7] A 100 mL round bottom flask equipped with a nitrogen line, magnetic stirrer, and an acetone/Dry Ice bath, was charged with 2.34 g (10.6 mmol) of amine **23**, 10 mL of THF, and 2.1 g (15 mmol) of K_2CO_3. After the slurry cooled to −78°C, 1.2 mL (1.5 g, 16 mmol) of methyl chloroformate was added dropwise with vigorous agitation. The thick, white paste was allowed to warm to rt and stirred for ca. 10 min. The slurry was cooled to −20°C and charged with 20 mL of water and 30 mL of Et_2O. The organic layer was separated and the aqueous layer was washed with an additional 2×30 mL of Et_2O. The combined organic layer was cooled to −20°C and washed with 20 mL of water. The organic layers were separated and dried over K_2CO_3. The slurry was filtered and the solvents were removed to yield 2.20 g (10.3 mmol, 98%) of the title compound as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04–6.98 (dd, J=10.8, 17.2 Hz, 1H), 7.03 (s, 1H), 6.82 (s, 1H), 5.66–5.63 (d, J=17.2 Hz, 1H), 5.35–5.33 (d, J=10.8 Hz, 1H), 4.64 (s, 2H), 3.91 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.74, 149.06, 133.18, 130.28, 127.19, 115.50, 113.14, 109.10, 56.19, 56.13, 44.52; IR ($CDCl_3$) 3089.3, 3010.2, 2964.3, 2254.3, 1605.9, 1514.5, 1465.0, 1420.0, 1344.1, 1270.4, 1220.1, 1102.4 cm^{-1}; HRMS calcd for

$C_{11}H_{13}O_2Cl$ (M; CI^+): 212.0604, found: 212.0598; LRMS (CI^+) *m/z* 197 (5), 212 (100).

4.1.8. 2-Ethenyl-*N*-2-propenyl-benzenemethanamine, hydrochloride (1). Representative procedure for the preparation of secondary amines from their corresponding tosylate or chloride. Adapted from a procedure outlined by Fürstner.[6] A 10 mL sealable flask, equipped with a stir bar, was charged with 750 mg (2.60 mmol) of tosylate **27**, 3 mL of THF, and 500 μL (6.7 mmol) of allylamine. The flask was sealed, heated to 60–70°C, and allowed to stir at that temperature overnight. The yellow solution was charged into 10 mL of Et_2O and allowed to stir for ca. 30 min. The resulting slurry was filtered [NMR indicates the solids are the tosylate salt of allylamine (0.99 equiv.)], cooled to −20°C, and acidified with 3.4 mL of 2 M HCl in diethyl ether. The solvents were removed under vacuum and the resulting mixture was separated by silica gel chromatography using isopropanol/EtOAc as eluent. Crystallization was achieved by solvent exchanging the combined fractions into heptane. The white crystalline solids were filtered, providing 460 mg (2.19 mmol, 84%) of the title compound. Recrystallization can be achieved using EtOAc as solvent: mp 86–88°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.03 (s, 2H), 7.72–7.71 (m, 1H), 7.48–7.46 (m, 1H), 7.34–7.32 (m, 2H), 7.06–7.01 (dd, *J*=10.8, 17.1 Hz, 1H), 6.09–6.03 (ddt, *J*=6.8, 10.4, 17.2 Hz, 1H), 5.66–5.62 (d, *J*=17.1 Hz, 1H), 5.47–5.44 (d, *J*=10.8 Hz, 1H), 5.42–5.40 (d, *J*=10.4 Hz, 1H), 5.41–5.38 (d, *J*=17.2 Hz, 1H), 4.11 (s, 2H), 3.42–3.41 (d, *J*=6.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.94, 133.88, 131.34, 129.90, 128.71, 128.10, 127.65, 127.34, 124.19, 119.26, 48.21, 45.86; IR ($CDCl_3$) 2935.7, 2744.7, 2225.3, 1583.0, 1450.8, 1216.2 cm^{-1}; HRMS calcd for $C_{12}H_{16}N$ (M−Cl; ESI^+): 174.1283, found: 174.1286; LRMS (ESI^+) *m/z* 115 (33), 174 (100).

4.1.9. 2-Ethenyl-*N*-3-butenyl-benzenemethanamine, hydrochloride (2). Prepared from tosylate **27** and homoallylamine as outlined for the preparation of secondary amines from the corresponding tosylate (1.97 mmol, 76%): mp 102–106°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.92 (s, 2H), 7.76–7.74 (m, 1H), 7.47–7.46 (m, 1H), 7.35–7.33 (m, 2H), 7.08–7.05 (dd, *J*=11.0, 17.1 Hz, 1H), 5.67–5.63 (ddt, *J*=6.6, 10.5, 16.9 Hz, 1H), 5.67–5.63 (dd, *J*=1.0, 17.1 Hz, 1H), 5.48–5.46 (dd, *J*=1.0, 11.0 Hz, 1H), 5.12–5.08 (dd, *J*=1.5, 16.9 Hz, 1H), 5.10–5.08 (dd, *J*=1.5, 10.5 Hz, 1H), 4.17 (s, 2H), 2.84–2.81 (m, 2H), 2.61–2.57 (dt, *J*=7.4, 7.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.06, 133.95, 132.80, 131.50, 130.01, 128.80, 127.58, 127.34, 119.38, 118.65, 47.05, 45.49, 30.20; IR ($CDCl_3$) 2950.6, 2750.9, 2224.9, 1584.0, 1461.7 cm^{-1}; HRMS calcd for $C_{13}H_{18}N$ (M−Cl; ESI^+): 188.1439, found: 188.1441; LRMS (ESI^+) *m/z* 115 (55), 117 (63) 188 (100).

4.1.10. 2-Ethenyl-*N*-2-propenyl-benzeneethanamine, hydrochloride (3). Representative procedure for the formation of secondary amines from their corresponding nitriles. Adapted from Brusse's procedure.[4] A 100 mL round bottom flask fitted with a nitrogen line, magnetic stirrer and an acetone/ice bath, was charged with 1.33 g (500 mg, 3.49 mmol) of a 37.6 wt% solution of nitrile **28** in diethyl ether and 30 mL of diethyl ether. The solution was cooled to ca. −15°C and charged with 4.2 mL (4.2 mmol) of a 1 M solution of DIBALH in toluene while maintaining an internal temperature less than 0°C. The hazy solution was allowed to warm to rt and stirred for ca. 30 min. The mixture was then cooled to ca. −15°C and charged with 393 mg (4.2 mmol) of the HCl salt of allylamine and 341 μL (260 mg, 4.5 mmol) of allylamine. The resulting slurry was sealed and allowed to warm to rt. After stirring at rt overnight, the mixture was cooled to ca. −15°C and charged with 400 mg (6.4 mmol) of $NaCNBH_3$. The slurry was sealed and held at −15 to 0°C for ca. 6 h prior to warming to rt. After stirring at rt for ca. 1 h, the slurry was charged with 50 mL of 10 wt% aqueous NaOH. The mixture was separated and the aqueous layer was washed with 2×20 mL of diethyl ether. The combined organic layer was dried over K_2CO_3. The slurry was filtered and the resulting solution was cooled to ca. −15°C. The solution was acidified with 5 mL (10 mmol) of 2 M HCl in diethyl ether. The solvents were removed under vacuum and the resulting mixture was separated by silica gel chromatography using isopropanol/EtOAc as eluent. Crystallization was achieved by solvent exchanging the combined fractions into heptane. The white crystalline solids were filtered, providing 310 mg (1.39 mmol, 40%) of the title compound: mp 114–120°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.01 (s, 2H), 7.50–7.49 (d, *J*=7.2 Hz, 1H), 7.26–7.21 (m, 3H), 7.11–7.06 (dd, *J*=11.0, 17.2 Hz, 1H), 6.15–6.10 (ddt, *J*=6.8, 10.4, 17.4 Hz, 1H), 5.68–5.65 (d, *J*=17.2 Hz, 1H), 5.51–5.47 (d, *J*=17.4 Hz, 1H), 5.46–5.44 (d, *J*=10.4 Hz, 1H), 5.39–5.36 (d, *J*=11.0 Hz, 1H), 3.64–3.62 (d, *J*=7.0 Hz, 2H), 3.38–3.35 (m, 2H), 3.10–3.07 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.25, 134.07, 134.03, 130.23, 128.44, 127.99, 127.89, 126.48, 124.31, 117.32, 49.76, 47.10, 30.13; IR ($CDCl_3$) 2946.1, 2760.2, 2225.9, 1586.0, 1451.2 cm^{-1}; HRMS calcd for $C_{13}H_{18}N$ (M−Cl; ESI^+): 188.1439, found: 188.1445; LRMS (ESI^+) *m/z* 117 (19), 131 (37) 188 (100).

4.1.11. 2-Ethenyl-*N*-3-butenyl-benzeneethanamine, hydrochloride (4). Prepared from **28** and both the HCl salt and free base of homoallylamine as outlined for the preparation of secondary amines from their corresponding nitriles (1.35 mmol, 39%): mp 146–148°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.94 (s, 2H), 7.49–7.48 (d, *J*=7.3 Hz, 1H), 7.24–7.20 (m, 3H), 7.09–7.07 (dd, *J*=11.0, 17.2 Hz, 1H), 5.82–5.73 (ddt, *J*=6.6, 10.3, 17.0 Hz, 1H), 5.67–5.64 (d, *J*=17.2 Hz, 1H), 5.37–5.35 (d, *J*=11.0 Hz, 1H), 5.18–5.14 (dd, *J*=1.3, 17.0 Hz, 1H), 5.14–5.11 (dd, *J*=1.3, 10.3 Hz, 1H), 3.41–3.38 (m, 2H), 3.13–3.12 (m, 2H), 3.05 (m, 2H), 2.73–2.69 (dt, *J*=6.6, 7.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.21, 133.99, 133.98, 132.60, 130.16, 128.43, 127.87, 126.46, 118.84, 117.32, 48.43, 47.14, 30.27, 30.04; IR ($CDCl_3$) 2948.6, 2764.0, 2449.5, 2223.1, 1643.8, 1626.4, 1587.9, 1485.5, 1467.4 cm^{-1}; HRMS calcd for $C_{14}H_{20}N$ (M−Cl; ESI^+): 202.1596, found: 202.1604; LRMS (ESI^+) *m/z* 129 (12), 160 (8) 202 (100).

4.1.12. 2-Ethenyl-4,5-dimethoxy-*N*-2-propenyl-benzenemethanamine (5). Prepared from chloride **33** and allylamine as outlined for the preparation of secondary amines from the corresponding chloride. After the reaction was complete, the acidic mixture was neutralized with 5 mL of 10 wt% aqueous NaOH and extracted with 3×5 mL of diethyl ether. The combined organic layers were dried over

K_2CO_3 and the slurry was filtered to obtain a clear colorless solution. The solvents were removed under vacuum and the resulting residue was separated by silica gel chromatography using isopropanol/EtOAc as eluent to provide the title compound as a clear colorless oil (1.80 mmol, 75%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (s, 1H), 7.01–6.95 (dd, J=11.0, 17.4 Hz, 1H), 6.85 (s, 1H), 5.95–5.91 (ddt, J=5.9, 10.6, 17.0 Hz, 1H), 5.60–5.56 (dd, J=1.1, 17.4 Hz, 1H), 5.25–5.23 (dd, J=1.1, 11.0 Hz, 1H), 5.22–5.19 (dd, J=1.3, 17.0 Hz, 1H), 5.13–5.11 (dd, J=1.3, 10.6 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.78 (s, 2H), 3.30–3.29 (d, J=5.9 Hz, 2H), 1.22 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.01, 148.40, 137.12, 133.91, 130.54, 129.37, 116.19, 114.07, 112.81, 108.96, 56.16, 56.14, 52.25, 50.58; IR ($CDCl_3$) 3084.4, 3007.6, 2960.9, 2937.1, 2912.0, 2833.6, 2256.6, 1605.3, 1511.8, 1464.6, 1418.4, 1338.5, 1309.3, 1266.4, 1219.7, 1187.9, 1106.8 cm^{-1}; HRMS calcd for $C_{14}H_{20}NO_2$ (M+H; ESI$^+$): 234.1494, found: 234.1495; LRMS (ESI$^+$) m/z 131 (17), 146 (30), 177 (100), 234 (23).

4.1.13. 2-Ethenyl-4,5-dimethoxy-*N*-3-butenyl-benzenemethanamine (6). Prepared from chloride **33** and homoallylamine as outlined for the preparation of secondary amines from the corresponding chloride. The free base was isolated according to the procedure outlined above (0.93 mmol, 47%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (s, 1H), 7.00–6.94 (dd, J=11.0, 17.4 Hz, 1H), 6.85 (s, 1H), 5.83–5.77 (ddt, J=6.8, 10.3, 17.0 Hz, 1H), 5.59–5.56 (d, J=17.4 Hz, 1H), 5.25–5.23 (d, J=11.0 Hz, 1H), 5.11–5.07 (dd, J=1.3, 17.0 Hz, 1H), 5.04–5.02 (dd, J=1.3, 10.3 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.78 (s, 2H), 2.74–2.72 (t, J=7.0 Hz, 2H), 2.30–2.26 (dt, J=6.8, 7.0 Hz, 2H), 1.22 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.93, 148.29, 136.67, 133.87, 130.60, 129.25, 116.46, 114.11, 112.62, 108.80, 56.12, 51.19, 48.80, 34.43; IR ($CDCl_3$) 3081.9, 3005.4, 2936.6, 2911.6, 2833.3, 2256.5, 1639.9, 1605.3, 1574.3, 1511.5, 1464.3, 1418.4, 1338.6, 1266.4, 1216.0, 1187.1, 1109.3 cm^{-1}; HRMS calcd for $C_{15}H_{21}NO_2Na$ (M+Na; ESI$^+$): 270.1470, found: 270.1467; LRMS (ESI$^+$) m/z 146 (43), 177 (100), 248 (43).

4.1.14. 2-Ethenyl-4,5-dimethoxy-*N*-2-propenyl-benzeneethanamine (7). Prepared from **32** and both the HCl salt and free base of allylamine as outlined for the preparation of secondary amines from their corresponding nitriles (0.81 mmol, 41%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (s, 1H), 6.98–6.93 (dd, J=11.0, 17.4 Hz, 1H), 6.68 (s, 1H), 5.90–5.89 (ddt, J=6.1, 10.3, 17.2 Hz, 1H), 5.58–5.54 (dd, J=1.3, 17.4 Hz, 1H), 5.23–5.21 (dd, J=1.3, 11.0 Hz, 1H), 5.17–5.14 (dq, J=1.6, 17.2 Hz, 1H), 5.09–5.07 (dq, J=1.3, 10.3 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.28–3.26 (dt, J=1.3, 6.1 Hz, 2H), 2.85–2.81 (m, 4H), 1.20 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.00, 147.85, 136.99, 134.17, 130.38, 129.08, 115.99, 113.67, 113.12, 108.77, 56.13, 52.59, 50.63, 33.62; IR ($CDCl_3$) 3085.0, 3008.0, 2937.5, 2832.6, 2256.5, 1605.5, 1511.6, 1464.5, 1418.7, 1339.7, 1309.5, 1264.7, 1217.8, 1197.5, 1183.4, 1102.2 cm^{-1}; HRMS calcd for $C_{15}H_{22}NO_2$ (M+H; ESI$^+$): 248.1650, found: 248.1647; LRMS (ESI$^+$) m/z 145 (14), 160 (35), 191 (47), 248 (100).

4.1.15. 2-Ethenyl-4,5-dimethoxy-*N*-3-butenyl-benzeneethanamine (8). Prepared from **32** and both the HCl salt and free base of homoallylamine as outlined for the preparation of secondary amines from their corresponding nitriles (1.25 mmol, 51%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (s, 1H), 6.98–6.92 (dd, J=10.8, 17.2 Hz, 1H), 6.68 (s, 1H), 5.79–5.75 (ddt, J=6.8, 10.3, 17.2 Hz, 1H), 5.57–5.53 (dd, J=1.1, 17.2 Hz, 1H), 5.23–5.20 (dd, J=1.1, 10.8 Hz, 1H), 5.08–5.04 (dq, J=1.6, 17.2 Hz, 1H), 5.03–5.00 (d, J=10.3 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 2.83–2.80 (m, 4H), 2.72–2.69 (t, J=6.1 Hz, 2H), 2.27–2.24 (q, J=6.8 Hz, 2H), 1.15 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.09, 147.92, 136.61, 134.24, 130.54, 129.16, 116.49, 113.66, 113.23, 108.97, 56.18, 56.16, 51.12, 49.06, 34.57, 33.68; IR ($CDCl_3$) 3082.4, 3005.5, 2936.8, 2832.1, 2257.2, 2183.3, 1639.8, 1605.5, 1573.9, 1511.6, 1464.4, 1418.8, 1339.0, 1308.8, 1264.8, 1217.3, 1197.5, 1101.9 cm^{-1}; HRMS calcd for $C_{16}H_{23}NO_2Na$ (M+Na; ESI$^+$): 284.1626, found: 284.1628; LRMS (ESI$^+$) m/z 160 (30), 179 (28), 191 (40), 262 (100).

4.1.16. 2-Ethenyl-1-(phenylmethyl)-*N*-2-propenyl-1*H*-indole-3-ethanamine (9). Prepared from **21** and both the HCl salt and free base of allylamine as outlined for the preparation of secondary amines from their corresponding nitriles (0.49 mmol, 33%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71–7.69 (d, J=7.7 Hz, 1H), 7.30–7.15 (m, 6H), 7.07–7.05 (d, J=7.7 Hz, 2H), 6.74–6.72 (dd, J=11.9, 18.0 Hz, 1H), 5.98–5.90 (ddt, J=5.9, 10.3, 17.2 Hz, 1H), 5.60–5.57 (dd, J=1.1, 18.0 Hz, 1H), 5.47–5.44 (dd, J=1.1, 11.9 Hz, 1H), 5.41 (s, 2H), 5.20–5.16 (dq, J=1.6, 17.2 Hz, 1H), 5.09–5.07 (dq, J=1.3, 10.3 Hz, 1H), 3.34–3.32 (d, J=5.9 Hz, 2H), 3.16–3.13 (t, J=7.2 Hz, 2H), 3.02–2.99 (t, J=7.3 Hz, 2H), 1.20 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.24, 137.61, 137.21, 135.06, 128.93, 128.35, 127.40, 126.15, 126.03, 122.66, 119.75, 119.30, 118.76, 115.72, 112.89, 109.79, 52.60, 50.27, 47.56, 25.85; IR ($CDCl_3$) 3063.2, 3030.2, 2923.9, 2822.1, 2245.1, 1626.3, 1605.7, 1495.9, 1464.6, 1453.4, 1354.9, 1336.6, 1300.8, 1179.5, 1108.9, 1028.4 cm^{-1}; HRMS calcd for $C_{22}H_{25}N_2$ (M+H; ESI$^+$): 317.2018, found: 317.2012; LRMS (ESI$^+$) m/z 317 (100).

4.1.17. 2-Ethenyl-1-(phenylmethyl)-*N*-3-butenyl-1*H*-indole-3-ethanamine (10). Prepared from **21** and both the HCl salt and free base of homoallylamine as outlined for the preparation of secondary amines from their corresponding nitriles (0.73 mmol, 43%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67–7.66 (d, J=7.5 Hz, 1H), 7.29–7.13 (m, 6H), 7.05–7.04 (d, J=7.0 Hz, 2H), 6.75–6.72 (dd, J=11.7, 17.6 Hz, 1H), 5.82–5.75 (ddt, J=7.0, 10.3, 17.0 Hz, 1H), 5.57–5.53 (dd, J=1.1, 17.6 Hz, 1H), 5.44–5.42 (dd, J=1.1, 11.7 Hz, 1H), 5.40 (s, 2H), 5.06–5.02 (dq, J=1.5, 17.0 Hz, 1H), 5.00–4.98 (dd, J=0.9, 10.3 Hz, 1H), 3.12–3.09 (t, J=7.3 Hz, 2H), 2.99–2.96 (t, J=7.5 Hz, 2H), 2.76–2.73 (t, J=6.8 Hz, 2H), 2.28–2.24 (dt, J=7.0, 13.8 Hz, 2H), 1.20 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.26, 137.58, 136.64, 135.02, 128.96, 128.30, 127.43, 126.16, 126.00, 122.66, 119.73, 119.29, 118.75, 116.49, 112.90, 109.79, 50.72, 49.10, 47.56, 34.62, 25.84; IR ($CDCl_3$) 3062.8, 3030.2, 2929.6, 2827.9, 2245.0, 1626.4, 1605.7, 1495.9, 1464.7, 1453.4, 1355.1, 1300.8, 1179.5, 1117.3, 1028.5 cm^{-1}; HRMS calcd for $C_{23}H_{27}N_2$ (M+H; ESI$^+$): 331.2174, found: 331.2184; LRMS (ESI$^+$) m/z 248 (47), 260 (100), 331 (90).

4.1.18. 2-Methyl-2,3,5,9b-tetrahydro-1*H*-pyrrolo[2,1-*a*]-isoindole (11). Representative procedure for the sequential hydroamination/C–C cyclization reaction. A sealable NMR tube was charged with 551 mg (5.51 mg, 9.53 μmol) of a 1 wt% solution of $Cp^*_2SmCH(TMS)_2$ in C_6D_6. The catalyst solution was then charged with an additional 400 mg of C_6D_6 and 730 mg (16.5 mg, 95.2 μmol) of a 2.26 wt% solution of the free amine of **1** in C_6D_6. The NMR tube was sealed and allowed to sit at rt. Upon completion of the reaction completion, ca. 22 h, the green solution was charged with 3 mL of heptane and allowed to oxidize for ca. 2 h. The yellow slurry was filtered through Celite and the clear, pale yellow solution was analyzed by GC (5.5:1 dr). The solvents were removed under vacuum and the resulting residue was separated by silica gel chromatography using EtOAc/hexanes and isopropanol/EtOAc as eluent to yield 13.1 mg (75.6 μmol, 79%) of the title compound as a 5.5:1 mixture of diastereomers: ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.31, 144.70, 140.93, 139.99, 127.46, 127.37, 127.19, 127.08, 123.18, 122.92, 122.60, 122.54, 70.76, 70.46, 64.44, 63.98, 61.78, 59.79, 41.00,. 40.74, 35.60, 32.84, 18.32, 17.51; IR ($CDCl_3$) 2958.6, 2929.6, 2872.3, 2359.7, 2251.8, 2171.5, 1477.4, 1456.1, 1378.4, 1340.8, 1091.5, 1042.9 cm^{-1}; HRMS calcd for $C_{12}H_{14}N$ (M−H; CI$^+$): 172.1126, found: 172.1129; LRMS (ESI$^+$) *m*/*z* 118 (25), 145 (18), 174 (100).

4.1.19. 1,2,3,5,6,10b-Hexahydro-2-methyl-pyrrolo[2,1-*a*]-isoquinoline (13). The general procedure for the sequential hydroamination/C–C cyclization reaction was followed with the noted exceptions (68 μmol, 76%): ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.55, 139.32, 134.60, 134.54, 128.69, 128.66, 126.17, 126.03, 126.00, 125.91, 125.85, 125.61, 63.42, 63.12, 62.49., 60.93, 48.98, 48.71, 40.83, 39.18, 31.56, 30.49, 28.91, 27.94, 20.92, 20.71; IR ($CDCl_3$) 2957.4, 2929.1, 2870.4, 2793.4, 2738.5, 2248.8, 2182.3, 1492.9, 1473.0, 1452.8, 1433.0, 1374.5, 1354.1, 1310.3, 1282.3, 1248.7, 1217.8, 1161.9, 1135.2, 1116.3, 1040.0 cm^{-1}; HRMS calcd for $C_{13}H_{18}N$ (M+H; ESI$^+$): 188.1439, found: 188.1448; LRMS (ESI$^+$) *m*/*z* 132 (15), 188 (100).

4.1.20. 1,3,4,6,7,11b-Hexahydro-2-methyl-2*H*-benzo[*a*]-quinolizine (14). The general procedure for the sequential hydroamination/C–C cyclization reaction was followed with the noted exceptions (323 μmol, 73%). The HCl salt of the free amine was generated as outlined above. Recrystallization using acetone provided suitable crystals for X-ray analysis: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24–7.09 (m, 4H), 3.21–3.13 (m, 2H), 3.02–2.99 (m, 2H), 2.76–2.70 (dd, *J*=3.1, 16.1 Hz, 1H), 2.54–2.52 (dt, *J*=4.0, 11.6 Hz, 1H), 2.36–2.33 (m, 2H), 1.73–1.62 (m, 2H), 1.48–1.36 (dq, *J*=4.2, 12.3 Hz, 1H), 1.20–1.14 (dt, *J*=11.4, 12.8 Hz, 1H), 1.04–1.03 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.69, 134.75, 129.05, 126.07, 125.82, 124.92, 63.25, 56.94, 52.58, 40.15, 34.14, 31.98, 29.93, 22.47; IR ($CDCl_3$) 3020.5, 2947.4, 2868.9, 2800.2, 2746.4, 2285.7, 2183.8, 1492.9, 1453.1, 1390.0, 1356.1, 1307.4, 1294.3, 1250.0, 1220.5, 1198.6, 1168.1, 1122.7, 1108.3, 1090.0, 1043.5 cm^{-1}; HRMS calcd for $C_{14}H_{19}N$ (M; CI$^+$): 201.1518, found: 201.1514; LRMS (ESI$^+$) *m*/*z* 117 (10), 202 (100).

4.1.21. 7,8-Dimethoxy-2-methyl-2,3,5,9b-tetrahydro-1*H*-pyrrolo[2,1-*a*]isoindole (15). The general procedure for the sequential hydroamination/C–C cyclization reaction was followed with the noted exceptions (54 μmol, 84%): ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.25, 149.21, 149.07, 148.97, 136.97, 136.25, 132.23, 131.22, 106.24, 105.96, 105.73, 105.69, 70.94, 70.64, 64.56, 64.14, 62.02, 59.97, 56.35, 56.32, 41.02, 40.85, 35.69, 32.78, 18.20, 17.50; IR ($CDCl_3$) 2958.4, 2871.3, 2835.2, 2253.7, 2167.4, 1504.5, 1465.4, 1378.4, 1339.9, 1291.4, 1279.6, 1250.1, 1217.7, 1190.1, 1175.6, 1104.5, 1012.4 cm^{-1}; HRMS calcd for $C_{14}H_{20}NO_2$ (M+H; ESI$^+$): 234.1494, found: 234.1504; LRMS (ESI$^+$) *m*/*z* 202 (19), 234 (100).

4.1.22. 8,9-Dimethoxy-1,2,3,5,6,10b-hexahydro-2-methyl-pyrrolo[2,1-*a*]isoquinoline (17). The general procedure for the sequential hydroamination/C–C cyclization reaction was followed with the noted exceptions (49.7 μmol, 82%): ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.64, 147.51, 147.48, 147.47, 131.94, 131.36, 126.64, 126.61, 111.80, 111.77, 109.28, 109.07, 62.90, 62.68, 62.22, 60.61, 56.25, 56.15, 48.82, 48.51, 41.10, 39.46, 31.63, 30.50, 28.36, 27.21, 20.80, 20.70; IR ($CDCl_3$) 2957.8, 2936.4, 2869.5, 2835.8, 2798.3, 2253.8, 2181.7, 1610.4, 1511.2, 1464.9, 1374.1, 1359.3, 1323.1, 1262.3, 1250.2, 1232.7, 1214.5, 1163.0, 1140.7, 1100.3, 1014.1 cm^{-1}; HRMS calcd for $C_{15}H_{22}NO_2$ (M+H; ESI$^+$): 248.1650, found: 248.1649; LRMS (ESI$^+$) *m*/*z* 248 (100).

4.1.23. 9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro-2-methyl-2*H*-benzo[*a*]quinolizine (18). The general procedure for the sequential hydroamination/C–C cyclization reaction was followed with the noted exceptions (264 μmol, 69%). The HCl salt of the free amine was generated as outlined above. Recrystallization using acetone provided suitable crystals for X-ray analysis: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.70 (s, 1H), 6.57 (s, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.14–3.02 (m, 2H), 2.99–2.95 (m, 2H), 2.67–2.58 (dd, *J*=3.1, 15.3 Hz, 1H), 2.49–2.47 (dt, *J*=4.0, 11.6 Hz, 1H), 2.36–2.29 (dt, *J*=2.2, 12.1 Hz, 1H), 2.23–2.19 (dq, *J*=2.8, 12.7 Hz, 1H), 1.70–1.58 (m, 2H), 1.42–1.36 (dq, *J*=4.1, 12.1 Hz, 1H), 1.19–1.07 (dt, *J*=11.4, 12.7 Hz, 1H), 1.02–1.01 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.58, 147.35, 130.68, 126.96, 111.77, 108.47, 62.88, 56.83, 56.22, 56.02, 52.70, 40.28, 34.09, 31.94, 29.47, 22.42; IR ($CDCl_3$) 3004.2, 2950.2, 2836.2, 2808.2, 2751.9, 2254.0, 2182.4, 1611.6, 1510.5, 1464.9, 1409.9, 1388.6, 1358.9, 1327.1, 1303.8, 1287.5, 1264.0, 1249.1, 1228.1, 1209.8, 1192.0, 1170.5, 1135.8, 1121.4, 1106.6, 1088.7, 1026.7, 1001.6 cm^{-1}; HRMS calcd for $C_{16}H_{22}NO_2$ (M−H; CI$^+$): 260.1650, found: 260.1638; LRMS (ESI$^+$) *m*/*z* 165 (52), 262 (100).

4.1.24. 2,3,5,6,11,11b-Hexahydro-2-methyl-11-(phenylmethyl)-1*H*-indolizino[8,7-*b*]indole (19). The general procedure for the sequential hydroamination/C–C cyclization reaction was followed with the noted exceptions (39 μmol, 83%): ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.32, 138.13, 138.04, 137.16, 128.91, 127.46, 127.44, 127.37, 126.26, 126.13, 121.42, 119.43, 118.36, 118.34, 109.69, 108.41, 107.47, 60.14, 57.88, 57.31, 56.15, 47.48, 47.45, 46.60, 40.46, 38.87, 32.90, 31.37, 20.38, 20.20, 18.84, 17.94; IR ($CDCl_3$) 2957.8, 2928.1, 2871.0, 2251.9, 2181.2,

1495.8, 1465.8, 1453.8, 1376.0, 1352.1, 1328.4, 1309.4, 1179.3, 1134.0, 1095.3, 1028.6, 1016.6 cm^{-1}; HRMS calcd for $C_{22}H_{25}N_2$ ($M+H$; ESI^+): 317.2018, found: 317.2003; LRMS (ESI^+) *m/z* 222 (28), 234 (20), 317 (60), 333 (100).

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References

1. Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 1757.
2. Gagné, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 275.
3. Sapi, J.; Grébille, Y.; Laronze, J.; Lévy, J. *Synthesis* **1992**, *4*, 383.
4. Zandbergen, P.; van den Nieuwendijk, A.; Brussee, J.; van der Gen, A.; Kruse, C. C. *Tetrahedron* **1992**, *48*, 3977.
5. Wipf, P.; Weiner, W. S. *J. Org. Chem.* **1999**, *64*, 5321.
6. Fürstner, A.; Langemann, K. *Synthesis* **1997**, *7*, 792.
7. Dai-Ho, G.; Mariano, P. S. *J. Org. Chem.* **1988**, *53*, 5113.
8. Molander, G. A.; Dowdy, E. D.; Pack, S. K. *J. Org. Chem.* **2001**, *66*, 4344.
9. Jeske, G.; Lauke, H.; Mauermann, H.; Swepston, P. N.; Schumann, H.; Marks, T. J. *J. Am. Chem. Soc.* **1985**, *107*, 8091.
10. Sato, T.; Nakamura, N.; Ikeda, K.; Okada, M.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, *18*, 2399.
11. Rao, A. V. R.; Rao, B. V.; Reddy, D. R. *Indian J. Chem.* **1991**, *30*, 723.
12. Marron, B. E.; Spanevello, R. A.; Elisseou, M. E.; Serhan, C. N.; Nicolaou, K. C. *J. Org. Chem.* **1989**, *54*, 5522.
13. Anilkumar, G.; Nambu, H.; Kita, Y. *Org. Process Res. Dev.* **2002**, *6*, 190.
14. Olivera, R.; San Martin, R.; Domínguez, E.; Solans, X.; Urtiaga, M. K.; Arriortua, M. I. *J. Org. Chem.* **2000**, *65*, 6398.
15. Kyong, D. H.; Sladkov, V. I.; Suvorov, N. N. *J. Org. Chem. USSR (Engl. Transl.)* **1987**, *23*, 1732.
16. Sato, Y.; Shirai, N.; Machida, Y.; Ito, E.; Yasui, T. *J. Org. Chem.* **1992**, *57*, 6711.