Palladium-Catalyzed Intramolecular α-Arylation of α-Amino Acid Esters

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The Pd-catalyzed intramolecular α-arylation of α-amino acid esters is described. Starting from readily available amino acids, the synthesis of a variety of isoindolines and tetrahydroisoquinoline carboxylic acid esters has been accomplished. Additionally, fused tricyclic systems can be efficiently prepared from cyclic amino acid esters. Reaction conditions have been found that allow the use of *tert*-butyl ester and *N*-(benzyloxycarbonyl) protecting groups.

Introduction

The synthesis of α-arylated carbonyl compounds has traditionally been a difficult transformation. Recent advances, especially in the area of palladium-catalyzed enolate arylation of ketones, have led to the development of a simple and reliable method for conducting this reaction intermolecularly.[1−7] Moreover, efficient protocols for both asymmetric arylation[8] and vinylation[9] of ketone enolates have been established.

Along with ketone arylation, the α-arylation of esters and amides is of particular interest. For example, α-aryl carboxylic acids are integral structural components of several pharmaceuticals such as ibuprofen and naproxen,[10] and α-aryl amides have potential medicinal applications.[11,12] In contrast to ketones, there are no regioselectivity issues to consider, but the lower reactivity and the relative instability of the ester moiety under basic conditions makes enolization a more challenging task. As a result, very few practical examples can be found in the literature for the synthesis of α-aryl esters.[13] Hartwig recently disclosed a successful palladium-catalyzed inter- and intramolecular α-arylation of amides using a variety of aryl bromides and chlorides.[14−16] Musco and Santi reported a palladium-mediated coupling of trimethylsilylketene acetals in the presence of thallium acetate to provide 2-(aryl) alkyl esters in moderate to good yields.[17,18] Yamanaka disclosed a palladium-catalyzed synthesis of coupling of aryl halides and ethoxy(trialkylstannyl)-acetylenes that provided 2-(aryl)ethyl acetates after an additional solvolysis step.[19,20] Kuwajima described that in situ generated tin enolates undergo palladium-catalyzed cross-coupling with aryl bromides to provide α-aryl ketones.[21] Sulikowski extended this method to the synthesis of aryl acetates in good yield by palladium-catalyzed cross-coupling of aryl bromides and copper(II) enolates.[22] Recently, a general method for the arylation of esters employing a wide variety of different aryl bromides and clorides has been developed in our laboratories.[23,24] In this case, the ester enolate was prepared in the presence of aryl halide and a palladium catalyst derived from $Pd(OAc)_2$ and biaryl-based, bulky, electron-rich phosphine ligands **1** and **2** (Figure 1).

The direct arylation of α-amino acids constitutes the most efficient method for the preparation of arylglycines. Very recently, Hartwig reported the direct arylation of a protected glycine via Pd catalysis.[24,25] Other reports detailing the direct arylation of unprotected or (protected)

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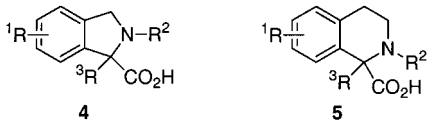

Figure 1.

glycine derivatives utilize stoichiometric amounts of toxic aryl lead,[26] aryl bismuth,[27] or chromium arene complexes.[28]

Although a fair amount of attention has been paid to intermolecular versions of carbonyl enolate arylations, less work has been reported on intramolecular variants. In 1988, Ciufolini published the first Pd-catalyzed intramolecular arylation of 1,3-dicarbonyl compounds at high temperature using Ph_3P as a ligand.[29] With less activated esters, however, the yields are generally low. Muratake reported the intramolecular α-arylation of aldehydes, ketones, and nitroalkanes to form five- to seven-membered rings in reasonable to good yields.[30−32] In some cases, aryl halide reduction was observed in up to 29% yield. Piers developed a method for the intramolecular vinylation of ketones, which was successfully employed in the synthesis of (±)-crinipellin B.[33,34] Later, the method was used by Solé and Bonjoch for the synthesis of bridged azabicyclic compounds.[35] Recently, Reissig reported a few cases of intramolecular ketone arylation to form indanes, albeit in low yield.[36] Finally, Hartwig accomplished the Pd-catalyzed synthesis of 2-oxoindoles in high yields using either BINAP,[14] Cy_3P, or a chiral carbene[15] as ligands. Attempts to apply this method to the synthesis of benzo-*δ*-lactams resulted in low yields.[14] To our knowledge, only one successful example of a Pd-catalyzed intramolecular α-arylation of amides to form a fused six-membered ring lactam has been reported as a key step employed in the synthesis of cherylline and latifine.[37]

Dihydroisoindole and tetrahydroisoquinoline carboxylic acids (**4**, **5**, Figure 2) are common structural motifs in pharmaceuticals and natural products such as Tetrazomine,[38] Bioxalomycin,[39] Excentricine[40,41] or the *Erythrina* alkaloids cocculine and erytrosine, some of them exhibiting interesting cytostatic, antineoplastic, and antiviral activity. Moreover, **4** and **5** can be regarded as a novel type of conformationally restricted amino acids, which are potentially interesting for medicinal and peptide chemistry.[42,43]

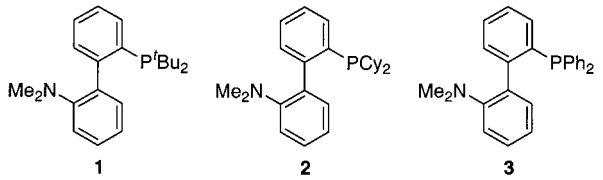

Figure 2.

Among other methods,[44,45] common synthetic pathways for the synthesis of tetrahydroisoquinoline carboxylic acids involve hydrogenations of benzo-fused cyclic imines and Pictet−Spengler-type reactions.[46,47] Both methods, however, require reasonably complex precursor compounds, and the synthesis of quarternary carbon centers adjacent to the carboxylic acid is difficult and requires the use of highly reactive α-ketoacid derivatives.[48,49] In the case of unsymmetrically substituted arenes, regioselectivity is often a problem with these Mannich-type cyclizations.[50,51]

Medicinal groups have recently reported increasing interest in dihydroisoindole derivatives, which is reflected in a number of patents[52] and publications dealing with a variety of medicinal applications.[53] In contrast, the development of efficient methods for the synthesis of substituted dihydroisoindoles seems to be a neglected area of research, and very few publications can be found in the literature.[54] Common methods for the synthesis of 1,3-unsubstituted dihydroisoindoles are the metal-catalyzed[55−58] or base-induced[59] [2 + 2 + 2] cocyclizations of bispropargylamines with alkynes. Another method employed an intramolecular Diels−Alder reaction to

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generate isoindolines with different N substituents.[60] A simple and straightforward strategy involves the alkylation of primary amines with 1,2-bisbenzyl halides to give isoindolines.[61] Further functionalization in the 1- or 3-position is feasible; however, no regioselective transformations have been reported. Alternatively, substituted oxoindoles can be reduced to the corresponding monosubstituted dihydroisoindoles.[62]

The lack of a general method for the synthesis of substituted isoindolines prompted us to explore the palladium-catalyzed intramolecular α-arylation of amino acid esters based on our previous success in α-arylation processes. Starting from readily available α-amino acid esters, our research was aimed to provide a general and efficient protocol for the regioselective synthesis of tetrahydroisoquinoline and dihydroisoindole carboxylic acid derivatives. In addition, synthetic efforts were aimed toward the synthesis of cyclic aryl-substituted amino acids bearing quarternary carbon centers.

Results and Discussion

Our initial experiments in intramolecular enolate arylation were carried out with 2-(2-bromobenzyloxy) acetic acid *tert*-butyl ester[63] screening a variety of bases and solvents. As ligands, we chose simple triaryl- or trialkylphosphines such as Ph_3P and Cy_3P as well as biaryl-based, sterically hindered phosphines **2** and **3** (Scheme 1) which are commercially available[64] or readily accessible by a one-pot procedure recently developed in our laboratories.[65] It was found that catalysts based on ligands **2** and **3** are superior to other simple commercially available phosphines in both yield and reaction rate.

Initially, we chose to use 2.3 mol % $Pd_2(dba)_3$ and a slight excess of either ligand **2** or **3** (5 mol %) as precursors for the active catalyst; reactions with $Pd(OAc)_2$ gave inferior results. The use of NaHMDS or LiHMDS in toluene, conditions which have been successfuly employed in ester arylation,[23] resulted in decomposition of starting material, presumably due to unselective Claisen condensation reactions. Weak bases such as K_3PO_4 or Cs_2CO_3 led to no conversion at all, whereas LiO-*t*-Bu in dioxane accomplished the desired cyclization in good yield. It should be noted that NaO-*t*-Bu in dioxane led to inferior results. Other solvents such as toluene, THF or DME in combination with LiO-*t*-Bu gave no or little cyclization product. It was also found that *tert*-butyl esters provide the best results under these reaction conditions. While all cyclization reactions have been conducted under an argon atmosphere, they are easy to perform. Ligands and reagents were usually kept in a desiccator and stored and weighed in the air, thus making the reaction setup very simple. The optimized reaction conditions were successfully employed for the synthesis of dihydroisoindole and tetrahydroisoquinoline carboxylic acid esters, and the results are summarized in Tables 1 and 2.

As shown in Tables 1 and 2, the formation of five- and six-membered rings can be carried out in high yield. A small amount, ca. 3%, of reduced aryl halide was observed in some cases. Using electron-rich bromoarenes, cyclization could still be accomplished in good yield albeit with longer reaction times (Table 1, entry 2; Table 2, entries 2 and 6). As shown in Tables 1 and 2, the formation of six-membered rings proceeds more slowly than five-membered rings and requires the more active catalyst based on ligand **3**. Under similar reaction conditions, ligand **3** provided increased reaction rates and yields compared to previous reactions employing ligand **2** or Ph_3P (Table 2, entries 3−5).

We also examined the effect of steric hindrance at the enolate carbon. We found that a hydrogen or a methyl group is well tolerated resulting in very good yields. In general, tertiary centers are easier to form than quarternary centers, thus resulting in shorter reaction times (Tables 1 and 2, entries 1 and 3). With an isopropyl substituent, higher catalyst loading, higher reaction temperatures and longer reaction times are required. Additionally, a significant amount of aryl halide reduction is observed (Table 1, entry 5). A remarkable exception is the phenylglycine-derived compound (Table 1, entries 6−9); the reaction proceeds quantitatively in 2 h at 90 °C, and the reaction can be conducted at 50 °C or even without a ligand at 90 °C, although longer reaction times are required.

For the synthesis of fused heterocyclic systems, cyclization precursors have been readily prepared from proline and pipecolinic acid esters (Table 1, entries 10−13, and Table 2, entries 7−9, respectively). The cyclization proceeds smoothly to give tricyclic compounds with various ring sizes in very good yields. The use of **2** and **3** is preferred over Cy_3P. Ligand **2** gives the tricyclic aminoesters in good yield (Table 1, entries 10 and 12), while the trialkylphosphine gives lower yield (Table 1, entry 11) and lower reaction rates, respectively (Table 1, entry 13). Interestingly, azatricycle **17** shows a significant increase of polarity (as judged by TLC) compared to the precusor compound **16**, presumably due to fixed geometry of the aza[3.3.0] ring system. It should be noted that compounds **17**, **19**, **29**, and **31** resemble the core structures of several alkaloids (vide infra).

The use of common amine protecting groups in palladium-catalyzed ring formation is of interest. Thus, we prepared *N*-(benzyloxycarbonyl) (Cbz) protected amino acid esters to briefly investigate whether the protecting group can survive under the chosen reaction conditions. The Cbz and *tert*-butyl ester represent an orthogonal set of protecting groups so that it is possible to selectively liberate the desired functionality while the other maintains unaffected.[66,67] As shown in Table 3, both alanine and phenylglycine derived compounds give the desired product in good yield. Again, **3** was the ligand of choice in this series of transformations.

Influence of Base, Ligand, and Palladium Source. A brief comparison of ligands (see Tables 1 and 2) has shown that the more sterically hindered, biphenyl-based

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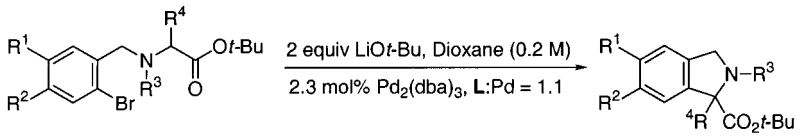
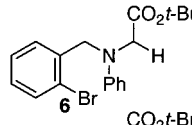
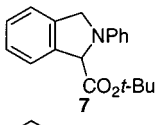
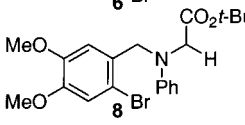
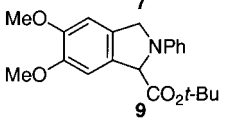
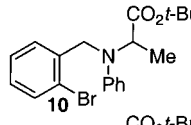
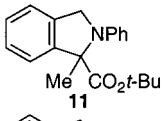
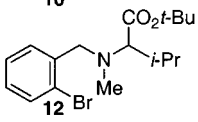
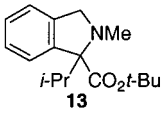
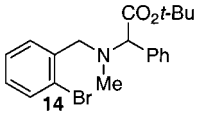
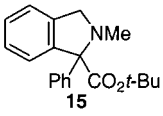
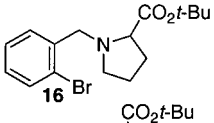
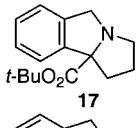
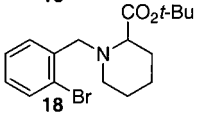
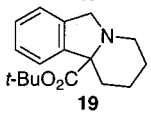
Table 1. Synthesis of Dihydroisoindole Carboxylic Acid Esters



Entry	Substrate	**L**	Conditions	Product	Yield [%][a]
1	 **6**	**2**	1 h, 85 °C	 **7**	79
2	 **8**	**2**	24 h, 85 °C	 **9**	89
3	 **10**	**2**	24 h, 85 °C	 **11**	91
4		Cy_3P	"		89[c]
5	 **12**	**3**	48 h, 110 °C	 **13**	51[b]
6	 **14**	**3**	2 h, 90 °C	 **15**	99
7		**3**	3.5 h, 70 °C		95[c]
8		**3**	20 h, 50 °C		65[d,e]
9		none	17 h, 90 °C		35[d,f]
10	 **16**	**2**	20 h, 85 °C	 **17**	62
11		Cy_3P	"		55[b]
12	 **18**	**2**	20 h, 85 °C	 **19**	84
13		Cy_3P	20 h, 85 °C		39[d,g]

[a] Isolated yields are an average of at least two runs. [b] 3.8 mol % $Pd_2(dba)_3$ and 8 mol % ligand were used, and ca. 8% of reduced arene was formed. [c] The GC yield was determined using dodecane as an internal standard. [d] The reaction was not allowed to go to completion. [e] GC yield; the reaction proceeded to 91% conversion. [f] GC yield; the reaction proceeded to 69% conversion, and 5% arene reduction was observed. [g] GC yield; the reaction proceeded to 71% conversion.

ligands **2** and **3** are superior to other simple trialkyl or triaryl phosphines such as Cy_3P and Ph_3P, respectively. Although in some cases good results have been achieved using Cy_3P as ligand (Table 1, entries 4 and 11), **2** and **3** have been shown to be both more effective and more general for the cyclization reaction. This may be related to the fact that the biphenyl backbone provides a weak coordination site to the metal via either the amino group or the arene itself.[68] Increased reactivity of catalysts based on **3** relative to those using **2** was observed in several cases. For most reactions, the use of **2** results in a very clean reaction. In contrast, with more active ligand **3** the formation of minor side products was observed. The decreased steric demand of ligand **3** relative to **2** may be important in these cyclizations. Additionally, ligand **3** is less electron-rich than **2**. Thus, the intermediate Pd(II) complex would be of enhanced elecrophilicity at the Pd center, which might affect rate and efficiency of its reaction with the enolate. At present, the deconvolution of the relative steric and electronic effects that make **3** the ligand of choice in the cyclization of sterically demanding substrates such as **12** (vide infra) is not straightforward.

The best results in the cyclization reactions have been achieved using a slight excess of either ligand **2** or **3** together with $Pd_2(dba)_3$. The use of $Pd(OAc)_2$ gave inferior results. It is possible that the dibenzylideneacetone acts as a supporting ligand.[69] Alternatively, the α-carboalkoxyalkylpalladium intermediates may be resistant to *β*-hydride elimination and thus do not provide a suitable reducing agent to generate the requisite catalyst.

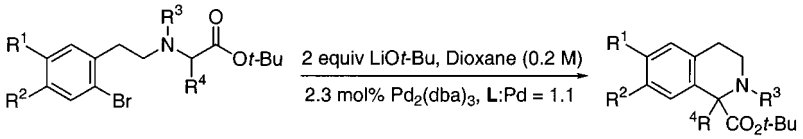
It was shown that the type of base plays an important role in the deprotonation process. Strong amide bases such as LiHMDS and NaHMDS led to decomposition of starting material. LiO-*t*-Bu in dioxane gave the best results in all cases, whereas the corresponding NaO-*t*-Bu led to inferior results. Assuming similar base strength, this indicates that the counterion plays a decisive role in the deprotonation step. In addition to the effect of the α-nitrogen, the Li^+ may form a chelating five-membered ring enolate, thus facilitating deprotonation.[70] With additional anion-stabilizing groups adjacent to the reactive

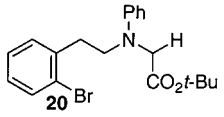
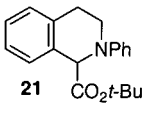
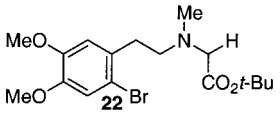
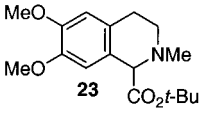
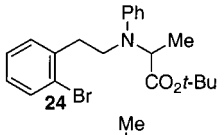
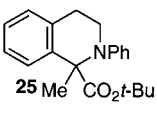
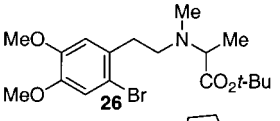
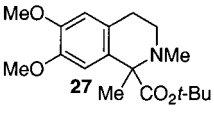
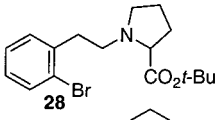
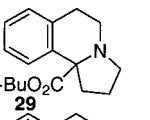
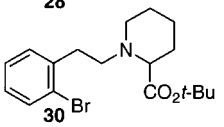
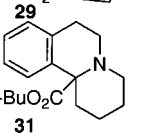
(68) Wolfe, J. P.; Tomori, H., Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

(69) For leading references of related work in this area, see: (a) Amatore, C.; Broeker, G.; Jutand, A.; Khalil, F. *J. Am. Chem. Soc.* **1997**, *119*, 5176. (b) Tschoerner, M.; Pregosin, P. S.; Albinati, A. *Organometallics* **1999**, *18*, 670.

(70) For similar effects where six-membered ring chelates with Li facilitate α-deprotonation, see: Blanchette, M. A.; Choy, W.; Davis. J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183 and references therein.

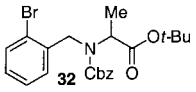
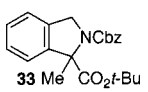
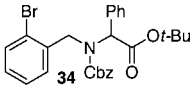
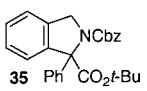
Table 2. Synthesis of Tetrahydroisoquinoline Carboxylic Acid Esters



Entry	Substrate	L	Conditions	Product	Yield [%][a]
1	 **20**	**3**	8 h, 85 °C	 **21**	79
2	 **22**	**3**	3 h, 85 °C	 **23**	75
3	 **24**	**3**	24 h, 85 °C	 **25**	62
4		**2**	24 h, 85 °C		$27^{b,c}$
5		Ph_3P	24 h, 85 °C		$12^{b,d}$
6	 **26**	**3**	45 h, 100 °C	 **27**	66
7	 **28**	**2**	24 h, 90 °C	 **29**	74
8	 **30**	**2**	24 h, 100 °C	 **31**	66
9		**3**	24 h, 90 °C		81

[a] Isolated yields are an average of at least two runs. [b] The reaction was not allowed to go to completion. [c] GC yield; the reaction proceeded to 71% conversion. [d] GC yield; the reaction proceeded to 46% conversion, and ~7% of arene reduction was observed.

Table 3. Synthesis of Cbz-Protected Dihydroisoindole Carboxylic Acid Esters

Substrate	L	Conditions[a]	Product	Yield [%][b]
 **32**	**3**	24 h, 90 °C	 **33**	67
 **34**	**3**	2 h, 90 °C	 **35**	86

[a] 2 equiv of LiO-*t*-Bu, dioxane (0.2 M), 2.3% $Pd_2(dba)_3$, L/Pd = 1.1. [b] Isolated yields are an average of at least two runs.

center, an increased rate and quantity of deprotonation should result. This is consistent with an observation on the cyclization of the phenylglycine precursor **14** (Table 1, entries 6−9).

Conclusion

A simple and flexible route to dihydroisoindole and tetrahydroisoquinoline carboxylic acid derivatives has been developed that uses the palladium-catalyzed intramolecular α-arylation of α-amino acid esters as the key step. The cyclization precursors are easily synthesized from commercially or otherwise readily available α-amino acids, followed by alkylation or acylation. We have demonstrated that the palladium-catalyzed cyclization proceeds smoothly to yield benzo-fused five- and six-membered heterocycles in good to excellent yields. The construction of quaternary carbon centers that tolerate a number of substituents at the enolate center including phenyl or bulky isopropyl groups has been accomplished. In addition, the synthesis of fused tricyclic systems bearing a bridgehead nitrogen has been demonstrated. A number of different N-substituents including alkyl, aryl, or carboxyl groups can be employed. This method is a useful extension of existing α-arylation processes and provides a simple pathway to substituted dihydroisoindoles and other complex non-natural α-amino acids. Initial results have shown that the reaction protocol is not limited to the synthesis of N-heterocycles. Investigations to develop intermolecular variants as well as asymmetric versions of this reaction are currently underway.

Experimental Section

General Considerations. All reactions were carried out in oven-dried glassware that was placed under vacuum while hot and cooled under argon. Flash chromatography was performed on Silicycle ultrapure silica gel (230−400 mesh). Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. Dichloromethane, ether, THF, and toluene were purchased from J. T. Baker in CYCLE-TAINER solvent delivery kegs and vigorously purged with argon for 2 h. The solvents were further purified by passing it through two packed columns of neutral alumina and copper(II) oxide under argon pressure.[71,72] Dioxane and dodecane (used as internal

(71) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
(72) Alaimo, P. J.; Peters, D. W.; Arnold, J.; Bergman, R. G. *J. Chem. Ed.* **2001**, *78*, 64.

standard) were purchased in small SureSeal-bottles from Aldrich Chemical Co. and used as received. Palladium acetate, tris(dibenzylideneacetone)dipalladium(0), sodium hexamethyldisilazane (NaHMDS), and lithium *tert*-butoxide (LiO-*t*-Bu) were purchased from Strem Chemical, Inc. Sodium *tert*-butoxide (NaO-*t*-Bu) was purchased from Aldrich Chemical Co. The bases were stored under nitrogen in a Vacuum Atmospheres glovebox, and small samples were taken out, stored in a desiccator on the bench, and replaced every 2 weeks. All materials were weighed in the air, except for NaHMDS, which was weighed and added to the reaction flask in a glovebox. IR spectra reported in this paper were obtained by placing neat samples directly on the DiComp probe of an ASI REACTIR in situ IR instrument. Alternatively, IR spectra for several compounds were recorded on a Perkin-Elmer FT-IR 1600. Mass spectra were taken using an Agilent GC−MS, and high-resolution mass spectra were obtained using a Bruker DALTONICS APEX, 3 T, FT-ICR-MS (Fourier transform ion cyclotron resonance mass spectrometer), with electrospray ion source (ESI). Yields in the tables refer to the isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR, GC, and combustion analysis. Melting points were taken with a MEL TEMP apparatus. Compounds that are described more than once in the same table were completely characterized once. Other samples of these compounds were characterized by comparing their ^{1}H NMR spectra to those of the fully characterized product, and their purity was confirmed by GC analysis.

General Reaction Procedure for the Cyclization of α-Amino Acid Esters. An oven-dried resealable Schlenk tube containing a stir bar was evacuated and purged with argon while cooling to ambient temperature. The Schlenk tube was charged with 2.0 equiv of LiO-*t*-Bu, 2.25 mol % of $Pd_2(dba)_3$, and 5 mol % of either 2-(dicyclohexylphosphinyl)-2′-(*N*,*N*-dimethylamino)biphenyl (**2**) or 2-(diphenylphosphinyl)-2′-(*N*,*N*-dimethylamino)biphenyl (**3**). The reaction vessel was evacuated and backfilled again with argon, and three-fourths of the dioxane was added via syringe under argon. The mixture was stirred for 5 min at room temperature, followed by addition of a solution of dodecane (0.045 mL, 0.2 mmol) and 1 equiv of the cyclization precursor in the remaining dioxane via syringe. The solution was 0.2 M in dioxane as solvent. The Schlenk tube was sealed and placed in a preheated oil bath at the given temperature for the time indicated. After the reaction was complete, as judged by either GC or TLC analysis, the reaction mixture was cooled to ambient temperature. The crude mixture was filtered through a silica gel plug which was washed thoroughly with ether. The solution was concentrated and further purified by flash column chromatography.

***N*-(2-Bromobenzyl)-*N*-phenyl *tert*-Butyl Acetate (6).** 2-Phenylaminoacetic acid *tert*-butyl ester[73] (1.04 g, 5 mmol) was dissolved in DMF (4 mL), and K_2CO_3 (0.83 g, 6 mmol) and a solution of 2-bromobenzyl bromide (1.25 g, 5 mmol) in DMF (1 mL) were added subsequently. The mixture was stirred for 3.5 h at 60 °C, cooled to ambient temperature, and then filtered through a silica gel plug and washed with ether. The organic layer was submitted to an aqueous workup (water, 3× ether, brine), dried over $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography (ether/hexanes 1:20) yielding **6** as a highly viscous yellow oil (0.97 g, 2.58 mmol, 52%) that solidified upon storage. Mp: 44 °C. ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.39−7.36 (dd, 1H, J = 1.1, 7.95 Hz), 7.28−7.24 (m, 1H), 7.10−7.04 (m, 2H), 6.90−6.85 (dt, 1H, J = 1.1, 7.6 Hz), 6.73−6.67 (m, 2H), 6.60−6.56 (m, 2H), 4.55 (s, 2H), 3.61 (s, 2H), 1.30 (s, 9H). ^{13}C NMR (C_6D_6, 100 MHz) δ: 170.3, 149.0, 138.1, 133.3, 129.9, 129.2, 129.1, 128.3, 123.3, 118.4, 113.1, 81.4, 57.9, 54.2, 28.4 ppm. IR (neat, cm^{-1}) ν: 3062, 2975, 2930, 2867, 1743, 1600, 1505, 1441, 1391, 1368, 1349, 1260, 1220, 1151, 1025, 990, 964, 846, 748, 690. Anal. Calcd for $C_{19}H_{22}BrNO_2$: C, 60.65; H, 5.89. Found: C, 60.80; H, 6.03.

(73) Skiles, J. W.; Suh, J. T.; Williams, B. E.; Menard, P. R.; Barton, J. N.; Loev, B.; Jones, H.; Neiss, E. S.; A., S.; Mann, W. S.; Khandwala, A.; Wolf, P. S.; Weinryb, I. *J. Med. Chem.* **1986**, *29*, 784.

2-Phenyl-2,3-dihydro-1*H*-isoindole-1-carboxylic Acid *tert*-Butyl Ester (7) (Table 1, Entry 1). Following the general procedure, **6** (0.188 g, 0.5 mmol) in dioxane (2.5 mL) was allowed to react for 1 h at 85 °C using ligand **2**. Flash column chromatography (ether/hexanes 1:15) yielded **7** as a pale yellow oil (0.115 g, 0.39 mmol, 78%) that solidified upon storage. Mp: 72 °C. ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.47−7.41 (m, 1H), 7.32−7.26 (m, 2H), 7.10−7.03 (m, 2H), 6.97−6.91 (m, 1H), 6.86−6.81 (m, 1H), 6.70−6.55 (m, 2H), 5.36−5.33 (d, 1H, J = 3.5 Hz), 4.59−4.53 (dd, 1H, J = 3.5, 12.9 Hz), 4.36−4.31 (d, 1H, J = 12.9 Hz), 1.19 (s, 9H). ^{13}C NMR (C_6D_6, 100 MHz) δ: 171.2, 146.9, 139.1, 138.0, 130.0, 128.7, 127.8, 123.4, 123.0, 117.7, 112.8, 81.5, 68.3, 57.8, 54.3, 28.1 ppm. IR (CH_2Cl_2, cm^{-1}) ν: 3043, 2979, 2933, 2875, 2840, 1740, 1603, 1505, 1468, 1368, 1146, 1094, 1036, 1003, 955, 839, 750, 690. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17. Found: C, 77.12; H, 7.17.

***N*-Phenyl-6-bromoveratrylamine.** (a) 6-Bromoveratrylamine (0.98 g, 4 mmol) and aniline (0.37 mL, 4 mmol) were dissolved in dichloromethane (12 mL), and $MgSO_4$ (1 g) was added. The slurry was stirred for 1 h at ambient temperature, the $MgSO_4$ was filtered off, and the solvent was removed under reduced pressure. The crude imine was taken up in MeOH (16 mL), acetic acid (0.34 mL, 6 mmol) and $NaCNBH_3$ (0.25 g, 4 mmol) were added, and the mixture was stirred overnight. Water and solid sodium bicarbonate were added, the aqueous layer was extracted four times with ether, and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (ether/hexanes 1:8) yielding the title compound as a white solid (1.25 g, 3.87 mmol, 97%). Mp: 86 °C. ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.16−7.06 (m, 2H), 6.94 (s, 1H), 6.77 (s, 1H), 6.76−6.70 (m, 1H), 6.45−6.49 (m, 1H), 4.17−4.12 (s+s, 2H), 3.50 (s, 1H), 3.22 (s, 3H), 2.97 (s, 3H). ^{13}C NMR (C_6D_6, 100 MHz) δ: 150.1, 150.0, 148.7, 131.0, 129.9, 118.4, 116.6, 113.6, 113.3, 113.0, 55.9, 55.8, 48.7 ppm. IR (CH_2Cl_2, cm^{-1}) ν: 3415, 3010, 2962, 2937, 2842, 1603, 1501, 1465, 1437, 1385, 1314, 1256, 1208, 1156, 1030, 955, 864, 799, 754, 692. Anal. Calcd for $C_{15}H_{16}BrNO_2$: C, 55.92; H, 5.01. Found: C, 56.06; H, 5.09.

***N*-(2-Bromo-4,5-dimethoxybenzyl)-*N*-phenyl *tert*-Butyl Acetate 8.** A round-bottomed flask was charged with 6-bromo-*N*-(methyl)veratrylamine (1.24 g, 3.87 mmol), 2-bromo-*tert*-butyl acetate (0.575 mL, 4.25 mmol), NaOAc (0.35 g, 4.25 mmol) and dry ethanol (0.5 mL), purged with argon and stirred for 6 h at 75 °C. After the mixture was cooled to room temperature, water and ether were added, the aqueous layer was extracted three times with ether, and the combined organic layers were washed with aqueous sodium bicarbonate and brine and dried over $MgSO_4$. The solvent was removed, and the crude product was purified by flash column chromatography (ether/hexanes 1:8) to yield **8** as an orange oil (0.86 g, 2.06 mmol, 54%) that solidified upon storage. Mp: 91 °C. ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.18 (s, 1H), 7.14−7.09 (m, 2H), 6.97 (s, 1H), 6.75−6.70 (m, 1H), 6.70−6.56 (m, 2H), 4.56 (s, 2H), 3.71 (s, 2H), 3.33 (s, 3H), 3.20 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (C_6D_6, 100 MHz) δ:_170.3, 150.5, 150.2, 149.2, 130.1, 129.9, 128.3, 118.5, 116.9, 113.4, 113.0, 112.6, 81.3, 57.7, 56.1, 56.0, 54.6, 28.4 ppm. IR (CH_2Cl_2, cm^{-1}) ν: 2979, 2937, 2842, 1740, 1602, 1503, 1465, 1439, 1383, 1370, 1349, 1256, 1221, 1210, 1150, 1030, 951, 849, 800, 754, 692. Anal. Calcd for $C_{21}H_{26}BrNO_4$: C, 57.80; H, 6.01. Found: C, 57.93; H, 6.07.

5,6-Dimethoxy-2-phenyl-2,3-dihydro-1*H*-isoindole-1-carboxylic Acid *tert*-Butyl Ester (9) (Table 1, Entry 2). Following the general procedure, **8** (0.218 g, 0.5 mmol) in dioxane (2.5 mL) was allowed to react for 4 h at 85 °C using ligand **2**. Flash column chromatography (ether/dichloromethane/hexanes 10:1:1) yielded **9** as pale yellow crystals (0.158 g, 0.445 mmol, 78.6%). Mp: 130 °C. ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.36−7.30 (m, 2H), 7.00 (s, 1H), 6.88−6.83 (m, 1H), 6.78−6.73 (m, 2H), 6.41 (s, 1H), 5.41−5.39 (d, 1H, J = 3.8 Hz), 4.65−4.58 (dd, 1H, J = 3.8, 12.2 Hz), 4.35−4.30 (d, 1H, J = 12.2 Hz), 3.41 (s, 3H), 3.37 (s, 3H), 1.24 (s, 9H). ^{13}C NMR (C_6D_6, 100 MHz) δ: 171.7, 151.2, 150.5, 147.1, 130.8, 130.1, 129.4, 117.7, 112.7, 107.0, 106.7, 81.4, 68.5, 56.1, 56.0, 54.5, 28.2 ppm. IR (CH_2Cl_2, cm^{-1}) ν: 3064, 2979, 2939, 2836, 1740, 1600, 1505,

1468, 1368, 1333, 1277, 1221, 1148, 1104, 1036, 997, 864, 852, 690. Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09. Found: C, 70.90; H, 7.21.

2-(Aminophenyl)propionic Acid *tert*-Butyl Ester. A round-bottomed flask was charged with aniline (1.86 mL, 20 mmol), 2-bromopropionic acid *tert*-butyl ester (4.18 g, 20 mmol), NaOAc (1.64 g, 20 mmol), and dry ethanol (1 mL), purged with argon, and stirred for 11 h at 80 °C. After the mixture was cooled to room temperature, water and ether were added, the aqueous layer was extracted three times with ether, and the combined organic layers were washed with aqueous sodium bicarbonate and brine and dried over $MgSO_4$. The solvent was removed, and the crude product was purified by flash column chromatography (ether/hexanes 1:4) yielding the title compound as an orange oil (3.47 g, 15.68 mmol, 78%). ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.15−6.09 (m, 2H), 6.76−6.72 (m, 1H), 6.51−6.46 (m, 2H), 4.08 (bs, 1H), 3.94−3.88 (q, 1H, J = 6.85 Hz), 1.27 (s, 9H), 1.18 (d, 1H, J = 6.85 Hz). ^{13}C NMR (C_6D_6, 100 MHz) δ: 174.2, 147.8, 129.9, 118.63, 114.2, 81.2, 53.0, 28.3, 19.2 ppm. IR (neat, cm^{-1}) ν: 3348, 2979, 1748, 1478, 1461, 1370, 1235, 1152, 1119, 1073, 841, 752, 719. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65. Found: C, 70.52; H, 8.58.

***N*-(2-Bromobenzyl)-*N*-phenylpropionic Acid *tert*-Butyl Ester (10).** 2-(Aminophenyl)propionic acid *tert*-butyl ester (1.77 g, 8 mmol) was dissolved in DMF (12 mL), followed by addition of K_2CO_3 (1.66 g, 12 mmol) and a solution of 2-bromobenzyl bromide (2.49 g, 10 mmol) in DMF (4 mL). The reaction mixture was stirred for 36 h at 60 °C, with subsequent addition of 2-bromobenzyl bromide (0.8 g, 3.2 mmol) three times during the course of reaction. After being cooled to room temperature, the mixture was filtered through a silica gel plug and washed with ether. The organic layer was submitted to an aqueous workup (water, 3× ether, brine), dried over $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography (ether/hexanes 1:15) yielding **10** as a colorless oil (1.28 g, 3.3 mmol, 47%) that solidified upon storage. Mp: 65 °C. ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.7.40−7.37 (dd, 1H, J = 1.1, 7.9 Hz), 7.37−7.33 (dd, 1H, J = 1.2, 7.7 Hz), 7.10−7.04 (m, 2H), 6.92−6.87 (dt, 1H, J = 1.0, 7.6 Hz) 6.75−6.66 (m, 4 H), 4.72−4.78 (d, 1H, J = 18.7 Hz), 4.66−4.60 (d, 1H, J = 18.7 Hz), 4.29−4.22 (q, 1H, J = 7.15 Hz), 1.27 (s, 9H), 1.22−1.25 (d, 3H, J = 7.15 Hz). ^{13}C NMR (C_6D_6, 100 MHz) δ: 172.9, 149.6, 139.6, 133.1, 129.9, 129.6, 128.9, 128.1, 122.8, 118.7, 114.2, 81.3, 58.4, 54.2, 28.3, 16.0 ppm. IR (CH_2Cl_2, cm^{-1}) ν: 2979, 2935, 1727, 1600, 1505, 1461, 1441, 1368, 1248, 1148, 1027, 914, 876, 847, 752, 690. Anal. Calcd for $C_{20}H_{24}BrNO_2$: C, 61.54; H, 6.20. Found: C, 61.80; H, 6.19.

2-Phenyl-1-methyl-2,3-dihydro-1*H*-isoindole-1-carboxylic Acid *tert*-Butyl Ester (11) (Table 1, Entry 3). Following the general procedure, **10** (0.195 g, 0.5 mmol) in dioxane (2.5 mL) was allowed to react for 24 h at 85 °C using ligand **2**. Flash column chromatography (ether/hexanes 1:20) yielded **11** as a pale yellow oil (0.142 g, 0.46 mmol, 92%). ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.29−7.21 (m, 3H), 7.08−7.02 (m, 2H), 7.01−6.97 (m, 1H), 6.83−6.76 (m, 3H), 4.57−4.52 (d, 1H, J = 12.95 Hz), 4.52−4.46 (d, 1H, J = 12.95 Hz), 1.99 (s, 3H), 1.08 (s, 9H). ^{13}C NMR (C_6D_6, 100 MHz) δ:_173.4, 146.4, 144.9, 137.5, 129.7, 128.5, 128.1, 123.0, 122.0, 117.6, 114.0, 81.1, 73.0, 55.8, 27.8, 23.4 ppm. IR (neat, cm^{-1}) ν: 3043, 2944, 2939, 2871, 2833, 1723, 1602, 1505, 1463, 1356, 1343, 1245, 1160, 1117, 991, 908, 845, 746, 692. Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49. Found: C, 77.44; H, 7.52.

***N*-(2-Bromobenzyl)valine *tert*-Butyl Ester.** To a stirred solution of valine *tert*-butyl ester (1 g, 5.77 mmol) in DMF (8 mL) was added K_2CO_3 (1.04 g, 7.5 mmol), followed by a solution of 2-bromobenzyl bromide (1.44 g, 5.8 mmol) in DMF (4 mL). The slurry was stirred for 2 h at 80 °C and then, after being cooled to room temperature, filtered through silica gel and washed with ether. The organic layer was submitted to an aqueous workup (water, 3× ether, brine), dried over $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography (ether/hexanes 1:7) yielding the title compound as a colorless oil (1.66 g, 4.84 mmol, 83%). ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.43−7.38 (dd, 1H, J = 1.45, 7.45 Hz), 7.37−7.33 (dd, 1H, J = 1.0, 7.95 Hz), 6.97−6.91 (dt, 1H, J = 1.65, 7.7 Hz), 6.82−6.76 (dt, 1H, J = 1.65, 7.7 Hz), 3.94−3.88 (d, 1H, J = 14.2 Hz), 3.78−3.72 (d, 1H, J = 14.2 Hz), 2.93−2.88 (d, 1H, J = 6.1 Hz), 1.97−1.83 (m, 2H), 1.38 (s, 9H), 1.00−0.94 (m, 6H). ^{13}C NMR (C_6D_6, 100 MHz) δ: 174.5, 140.3, 133.0, 130.5, 128.7, 127.5, 124.6, 80.5, 67.8, 52.7, 32.4, 28.3, 19.9, 18.8 ppm. IR (neat, cm^{-1}) ν: 3340, 3068, 2968, 2933, 2873, 1723, 1569, 1465, 1391, 1368, 1250, 1210, 1144, 1027, 978, 847, 802, 748. Anal. Calcd for $C_{16}H_{24}BrNO_2$: C, 56.15; H, 7.07. Found: C, 56.32; H, 7.17.

***N*-(2-Bromobenzyl)-*N*-methylvaline *tert*-Butyl Ester (12).** To a stirred solution of *N*-(2-bromobenzyl)valine *tert*-butyl ester (1.6 g, 4.67 mmol) in DMSO (10 mL) was added K_2CO_3 (0.8 g, 6.1 mmol), followed by MeI (0.35 mL, 5.6 mmol). The slurry was stirred for 18 h at ambient temperature and then filtered through silica gel and washed with ether. The organic layer was submitted to an aqueous workup (water, 3× ether, brine), dried over $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography (ether/hexanes 1:15) yielding **12** as a colorless oil (1.5 g, 4.2 mmol, 90%). ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.51−7.47 (m, 1H), 7.43−7.39 (dd, 1H, J = 1.15, 7.85 Hz), 7.03−6.97 (dt, 1H, J = 1.15, 7.55 Hz), 6.75−6.70 (dt, 1H, J = 1.75, 7.9 Hz), 3.88 (s, 2H), 2.81−2.77 (d, 1H, J = 10.8 Hz), 2.29 (s, 3H), 2.13−1.99 (m, 1H), 1.45 (s, 9H), 0.98−0.94 (d, 3H, J = 6.6 Hz), 0.93−0.87 (d, 3H, J = 6.55 Hz). ^{13}C NMR (C_6D_6, 100 MHz) δ: 171.1, 139.5, 133.4, 130.8, 128.6, 127.7, 125.2, 80.6, 74.5, 59.2, 38.0, 28.8, 28.2, 20.4, 20.0 ppm. IR (neat, cm^{-1}) ν: 3064, 2975, 2966, 2873, 2802, 1721, 1466, 1441, 1366, 1250, 1144, 1121, 1025, 980, 912, 862, 835, 796, 750. Anal. Calcd for $C_{17}H_{26}BrNO_2$: C, 57.31; H, 7.36. Found: C, 57.55; H, 7.18.

1-Isopropyl-2-methyl-2,3-dihydro-1*H*-isoindole-1-carboxylic Acid *tert*-Butyl Ester (13) (Table 1, Entry 5). Following a modification of the general procedure, **12** (0.178 g, 0.5 mmol) in dioxane (2.5 mL) was allowed to react for 48 h at 110 °C using $Pd_2(dba)_3$ (0.016 g, 7 mol %) and ligand **3** (0.0146 g, 7.5 mol %). Flash column chromatography (ether/hexanes 1:25) yielded **13** as a colorless oil (0.07 g, 0.26 mmol, 51%). ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.31−7.25 (m, 1H), 7.16−7.09 (m, 1H), 7.09−7.00 (m, 2H), 6.98−6.94 (m, 1H), 2.89−2.77 (m, 1H), 2.76 (s, 3H), 1.25 (s, 9H), 1.08−1.12 (d, 3H, J = 6.95 Hz), 0.98−0.94 (d, 3H, J = 6.8 Hz). ^{13}C NMR (C_6D_6, 100 MHz) δ: 172.5, 143.7, 141.5, 127.9, 127.0, 123.8, 122.5, 80.5, 61.7, 38.2, 34.2, 28.6, 28.4, 19.4, 18.3 ppm. IR (neat, cm^{-1}) ν: 2973, 2935, 2875, 2796, 1706, 1466, 1368, 1246, 1160, 1127, 1036, 974, 845, 758, 737, 692. Anal. Calcd for $C_{77}H_{25}NO_2$: C, 74.14; H, 9.15. Found: C, 74.79; H, 9.04.

2-[*N*-(2-Bromobenzyl)]aminophenylacetic Acid *tert*-Butyl Ester. To a stirred solution of 2-aminophenylacetic *tert*-butyl ester (1.04 g, 5.0 mmol) in DMF (7 mL) was added K_2CO_3 (1.04 g, 7.5 mmol), followed by a solution of 2-bromobenzyl bromide (1.5 g, 6 mmol) in DMF (3 mL). The slurry was stirred for 4 h at ambient temperature and then filtered through silica gel and washed with ether. The organic layer was submitted to an aqueous workup (water, 3× ether, brine), dried over $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography (ether/hexanes 1:10) yielding the title compound as a colorless oil (1.83 g, 4.86 mmol, 97%). ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.47−7.43 (m, 2H), 7.39−7.35 (dd, 1H, J = 1.6, 7.75 Hz), 7.35−7.31 (dd, 1H, J = 1.15, 7.9 Hz), 7.18−7.12 (m, 2H), 7.10−7.04 (m, 1H), 6.93−6.88 (dt, 1H, J = 1.15, 7.55 Hz), 6.70−6.64 (dt, 1H, J = 1.7, 7.7 Hz), 4.33 (s, 1H), 3.80 (s, 2H), 2.54 (s, 1H), 1.24 (s, 9H). ^{13}C NMR (C_6D_6, 100 MHz) δ: 172.4, 140.0, 139.8, 133.2, 130.7, 129.1, 129.0, 128.3, 128.2, 127.9, 124.7, 81.3, 66.0, 51.7, 28.2 ppm. IR (neat, cm^{-1}) ν: 3346, 3064, 3029, 2979, 2933, 1727, 1569, 1455, 1393, 1368, 1248, 1148, 1025, 947, 845, 748, 696. Anal. Calcd for $C_{19}H_{22}BrNO_2$: C, 60.65; H, 5.89. Found: C, 60.55; H, 5.82.

***N*-(2-Bromobenzyl)-*N*-methylphenylglycine *tert*-Butyl Ester (14).** To a stirred solution of *N*-(2-bromobenzyl) phenylglycine *tert*-butyl ester (1.43 g, 3.8 mmol) in DMSO (8 mL) was added K_2CO_3 (078 g, 5.7 mmol), followed by MeI (0.32 mL, 5.1 mmol). The slurry was stirred for 18 h at ambient temperature and then filtered through silica gel and washed with ether. The organic layer was submitted to an aqueous workup (water, 3× ether, brine), dried over $MgSO_4$, and

concentrated. The crude product was purified by flash column chromatography (ether/hexanes 1:20) yielding **14** as a colorless oil (1.01 g, 2.6 mmol, 68%). ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.73−7.68 (dd, 1H, J = 1.5, 7.7 Hz), 7.60−7.56 (m, 2H), 7.38−7.34 (dd, 1H, J = 1.1, 8.0 Hz), 7.16−7.10 (m, 2H), 7.07−7.03 (m, 1H), 7.03−6.98 (dt, 1H, J = 1.1, 7.6 Hz), 6.73−667 (dt, 1H, J = 1.7, 7.7 Hz), 4.40 (s, 1H), 3.99−3.93 (d, 1H, J = 14.65 Hz), 3.88−3.83 (d, 1H, J = 14.65 Hz), 2.25 (s, 3H), 1.32 (s, 9H). ^{13}C NMR (C_6D_6, 100 MHz) δ: 171.1, 139.3, 138.1, 133.0, 131.1, 129.3, 128.8, 128.5, 128.3, 127.7, 124.8, 81.0, 73.4, 58.5, 39.0, 28.2 ppm. IR (neat, cm^{-1}) ν: 3064, 2977, 2933, 2850, 2798, 1729, 1567, 1453, 1368, 1254, 1219, 1140, 1025, 945, 837, 795, 748, 698. Anal. Calcd for $C_{20}H_{24}BrNO_2$: C, 61.54; H, 6.20. Found: C, 61.80; H, 6.14.

1-Phenyl-2-methyl-2,3-dihydro-1*H*-isoindole-1-carboxylic Acid *tert*-Butyl Ester (15) (Table 1, Entry 6). Following the general procedure, **14** (0.195 g, 0.5 mmol) in dioxane (2.5 mL) was allowed to react for 2 h at 90 °C using ligand **3**. Flash column chromatography (ether/hexanes 1:12) yielded **15** as an orange oil (0.151 g, 0.49 mmol, 99%). ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.53−7.49 (m, 2H), 7.39−7.35 (m, 1H), 7.21−7.15 (m, 1H), 7.12−7.01 (m, 5H), 4.23−4.18 (d, 1H, J = 12.25 Hz), 4.15−4.00 (d, 1H, J = 12.25 Hz), 2.60 (s, 3 H), 1.24 (s, 9H). ^{13}C NMR (C_6D_6, 100 MHz) δ: 171.3, 145.2, 141.6, 141.5, 129.2, 128.5, 128.1, 127.8, 127.4, 125.3, 122.5, 81.3, 80.6, 59.0, 35.4, 28.4 ppm. IR (neat, cm^{-1}) ν: 3029, 2977, 2873, 2792, 1723, 1600, 1476, 1461, 1368, 1241, 1150, 1030, 972, 843, 766, 750, 733, 698. Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49. Found: C, 77.84; H, 7.35.

1-(2-Bromobenzyl)pyrrolidine-2-carboxylic Acid *tert*-Butyl Ester (16). To a stirred solution of proline *tert*-butyl ester (1 g, 5.84 mmol) in DMF (8 mL) was added K_2CO_3 (1.24 g, 9 mmol), followed by a solution of 2-bromobenzyl bromide (1.5 g, 6 mmol) in DMF (4 mL). The slurry was stirred for 15 h at ambient temperature and then filtered through silica gel and washed with ether. The organic layer was submitted to an aqueous workup (water, 3× ether, brine), dried over $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography (ether/hexanes 1:10) yielding **16** as a colorless oil (1.65 g, 4.84 mmol, 83%). ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.70−7.66 (dd, 1H, J = 1.1, 7.7 Hz), 7.41−7.37 (dd, 1 H, J = 1.25, 7.6 Hz), 7.04−6.98 (dt, 1H, J = 1.7, 7.6 Hz), 6.75−6.68 (dt, 1H, J = 1.7, 7.8 Hz), 4.16−4.10 (d, 1 H, J = 14.55 Hz), 3.91−3.86 (d, 1H, J = 14.55 Hz), 3.32−3.27 (dd, 1H, J = 5.2, 8.6 Hz), 2.98−2.91 (ddd, 1H, J = 4.0, 8.3, 12.6 Hz), 2.34−2.26 (dt, 1H, J = 7.6, 8.6 Hz), 2.00−1.91 (m, 1 H), 1.88−1.78 (m, 1H), 1.78−1.66 (m, 1H), 1.51−1.38 (m, 1H), 1.34 (s, 9H). ^{13}C NMR (C_6D_6, 100 MHz) δ: 173.3, 139.8, 133.1, 131.4, 128.8, 127.8, 124.6, 80.3, 66.6, 58.0, 53.4, 29.7, 28.4, 24.1 ppm. IR (neat, cm^{-1}) ν: 3061, 2975, 2833, 1725, 1567, 1439, 1367, 1255, 1213, 1153, 1025, 845, 752, 660. Anal. Calcd for $C_{16}H_{22}BrNO_2$: C, 56.48; H, 6.52. Found: C, 56.27; H, 6.40.

2,3-Dihydro-1*H*,5*H*-pyrrolo[2,1-*a*]isoindole-9b-carboxylic Acid *tert*-Butyl Ester (17) (Table 1, Entry 10). Following the general procedure, **16** (017 g, 0.5 mmol) in dioxane (2.5 mL) was allowed to react for 20 h at 85 °C using ligand **2**. Flash column chromatography (ether/hexanes) yielded **17** as a yellow oil (0.08 g, 0.31 mmol, 62%). ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.36−7.33 (m, 1H), 7.13−7.04 (m, 2H), 6.96−6.92 (m, 1H), 4.59−4.52 (d, 1H, J = 14.85 Hz), 3.66−3.58 (d, 1H, J = 14.85 Hz), 3.25−3.18 (m, 1H), 2.91−2.81 (m, 1H), 2.36−2.88 (m, 1H), 1.86−1.73 (m, 2H), 1.48−1.37 (m, 1H), 1.28 (s, 9H). ^{13}C NMR (C_6D_6, 100 MHz) δ: 173.9, 145.0, 141.6, 129.1, 127.8, 123.8, 123.2, 83.1, 80.3, 60.9, 57.7, 36.5, 28.2, 26.6 ppm. IR (neat, cm^{-1}) ν: 3072, 2971, 2931, 2865, 2809, 1721, 1457, 1366, 1283, 1252, 1237, 1154, 1111, 1086, 1055, 986, 935, 847, 762, 737, 718, 685. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16. Found: C, 74.17; H, 8.24.

1-(2-Bromobenzyl)piperidine-2-carboxylic Acid *tert*-Butyl Ester (18). To a stirred solution of *tert*-butyl pipecolinate (1 g, 5.5 mmol) in DMF (8 mL) was added K_2CO_3 (1.14 g, 8.25 mmol), followed by a solution of 2-bromobenzyl bromide (1.37 g, 5.5 mmol) in DMF (4 mL). The slurry was stirred for 8 h at ambient temperature and then filtered through silica gel and washed with ether. The organic layer was submitted to an aqueous workup (water, 3× ether, brine), dried over $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography (ether/hexanes 1:15) yielding **18** as a colorless oil (0.92 g, 2.59 mmol, 47%). ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.71−7.67 (dd, 1H, J = 1.1, 7.5 Hz), 7.42−7.38 (dd, 1H, J = 1.1, 8.0 Hz), 7.04−6.98 (dt, 1H, J = 1.0, 7.5 Hz), 6.75−6.68 (dt, 1H, J = 1.45, 7.5 Hz), 4.04−3.98 (d, 1H, J = 14.85 Hz), 3.82−3.75 (d, 1H, J = 14.85 Hz), 3.30−3.23 (m, 1H) 3.05−2.97 (ddd, 1H, J = 3.5, 8.15, 11.4 Hz), 2.26−217 (ddd, 1H, J = 4.05, 6.15, 10.7 Hz), 1.96−1.87 (m, 1H), 1.78−1.70 (m, 1H), 1.49−1.19 (m, 4H), 1.36 (s, 9H). ^{13}C NMR (C_6D_6, 100 MHz) δ: 173.1, 139.7, 133.2, 131.4, 128.8, 127.8, 125.1, 80.4, 64.8, 60.4, 49.7, 30.1, 28.5, 26.3, 22.6 ppm. IR (neat, cm^{-1}) ν: 3061, 2975, 2934, 2855, 1726, 1566, 1440, 1366, 1149, 1025, 1002, 848, 751. High resolution MS: calcd [M + H] 354.1063, found 354.1059. Anal. Calcd for $C_{17}H_{24}BrNO_2$: C, 57.63; H, 6.83. Found: C, 58.05; H, 6.93.

1,2,3,4-Tetrahydro-6*H*-pyrido[2,1-*a*]-isoindole-10b-carboxylic Acid *tert*-Butyl Ester (19) (Table 1, Entry 12). Following the general procedure, **18** (0.177 g, 0.5 mmol) in dioxane (2.5 mL) was allowed to react for 20 h at 85 °C using ligand **2**. Flash column chromatography (ether/hexanes 1:6) yields **19** as a yellow oil (0.115 g, 0.42 mmol, 84%). ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.44−7.39 (m, 1H), 7.11−699 (m, 3H), 4.43−4.36 (d, 1H, J = 11.65 Hz), 4.01−3.95 (d, 1H, J = 11.65 Hz), 3.46−3.37 (m, 1H), 2.93−2.87 (m, 1H), 2.75−2.68 (m, 1H), 1.69−1.48 (m, 4H), 1.43−1.35 (m, 1H), 1.25 (s, 9H). ^{13}C NMR (C_6D_6, 100 MHz) δ:_173.1, 145.5, 141.5, 127.9, 127.1, 132.2, 122.3, 80.6, 73.0, 56.5, 45.8, 33.2, 28.4, 24.6, 22.9 ppm. IR (neat, cm^{-1}) ν: 2973, 2931, 2854, 2811, 1720, 1611, 1473, 1459, 1391, 1367, 1343, 1289, 1245, 1164, 1139, 1093, 1009, 954, 893, 844, 758, 735, 659. High resolution MS: calcd for [$C_{17}H_{23}NO_2$ + H] 274.1802, found 274.1811.

2-Bromo-*N*-phenylphenethylamine.[74,75] To a stirred solution of KO-*t*-Bu (1.12 g, 10 mmol) in DMSO (30 mL) was added dropwise aniline (1.08 mL, 12 mmol), followed by slow addition of 2-bromostyrene (1.29 mL, 10 mmol). The mixture was stirred for 15 h at 40 °C, cooled to 0 °C, and quenched with water. Ether was added, the aqueous layer was neutralized (pH = 7) with 4 N H_2SO_4 and extracted three times with ether, and the combined organic layers were dried over $MgSO_4$. After evaporation of the solvent, the crude product was further purified by flash column chromatography (ether/hexanes 1:15) to yield the title compound as an orange oil (2.18 g, 7.9 mmol, 79%). ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.39−7.35 (dd, 1H, J = 1.0, 7.95 Hz), 7.21−7.14 (m, 2H), 6.87−6.73 (m, 3H), 6.69−6.63 (dt, 1H, J = 2.0, 7.9 Hz), 6.47−6.41 (m, 2H), 3.12−3.06 (m, 3H), 2.75−2.69 (m, 2H). ^{13}C NMR (C_6D_6, 100 MHz) δ: 148.62, 139.67, 133.5, 131.6, 130.0, 128.0, 125.3, 118.0, 113.7, 113.5, 43.7, 36.3 ppm. IR (neat, cm^{-1}) ν: 3392, 3053, 2979, 2935, 2877, 1727, 1603, 1507, 1455, 1368, 1316, 1256, 1219, 1146, 1050, 849, 746, 692. Anal. Calcd for $C_{14}H_{14}BrN$: C, 60.89; H, 5.11. Found: C, 61.07; H, 5.06.

2-[[2-(2-Bromophenyl)ethyl]phenylamino]acetic Acid *tert*-Butyl Ester (20). A round-bottomed flask was charged with 2-bromo-N-(phenyl)phenethylamine (2.18 g, 7.9 mmol), 2-bromoacetic acid *tert*-butyl ester (1.17 mL, 7.9 mmol), NaOAc (0.65 g, 7.9 mmol), and dry ethanol (0.5 mL), purged with argon, and stirred for 5 h at 75 °C. After the mixture was cooled to room temperature, water and ether were added, the aqueous layer was extracted three times with ether, and the combined organic layers were washed with aqueous sodium bicarbonate and brine and dried over $MgSO_4$. To remove residual amine (not separable by chromatography), the crude product was dissolved in dichloromethane (16 mL) and treated with acetyl chloride (0.14 mL, 2 mmol) and triethylamine (0.34 mL, 2.4 mmol). The mixture was stirred for 1 h at ambient temperature and submitted to aqueous workup (water, 3× ether, brine). The organic layer was dried over $MgSO_4$ and concentrated, and the crude product was purified by flash

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column chromatography (ether/hexanes 1:5) yielding **20** as an orange oil (2.59 g, 6.64 mmol, 84%). ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.35−7.31 (d, 1H, J = 7.8 Hz), 7.26−7.21 (m, 2H), 6.84−6.74 (m, 5H), 6.68−6.61 (m, 1H), 3.72 (s, 2H), 3.57−3.50 (m, 2H), 3.02−2.95 (m, 2H), 1.27 (s, 9H). ^{13}C NMR (C_6D_6, 100 MHz) δ:_170.4, 148.5, 139.6, 133.4, 131.7, 130.0, 129.0, 125.2, 117.7, 112.7, 81.2, 54.5, 52.8, 35.0, 28.3 ppm. IR (neat, cm^{-1}) ν: 3060, 2976, 2931, 1743, 1599, 1506, 1470, 1391, 1367, 1255, 1219, 1150, 1022, 848, 746, 691, 659. High resolution MS: calcd for $C_{20}H_{24}BrNO_2$ [M + Na] 412.0883, found 412.0900.

2-Phenyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid *tert*-Butyl Ester (21) (Table 2, Entry 1). Following the general procedure, **20** (0.197 g, 0.5 mmol) in dioxane (2.5 mL) was allowed to react for 9 h at 85 °C using ligand **3**. Flash column chromatography (ether/hexanes 1:15) yielded **21** as a colorless oil (0.121 g, 0.39 mmol, 79%). ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.50−7.46 (m, 1H), 7.29−7.22 (m, 2H), 7.09−7.01 (m, 2H), 6.97−6.87 (m, 3H), 6.86−6.81 (dt, 1H, J = 0.9, 7.3 Hz), 5.30 (s, 1H), 3.76−3.68 (ddd, 1H, J = 4.7, 7.4, 11.6 Hz), 3.34−3.23 (ddd, 1H, J = 5.1, 6.8, 11.6 Hz), 3.00−2.92 (ddd, 1H, J = 4.85, 6.6, 15.45 Hz), 2.60−2.69 (ddd, 1H, J = 5.1, 7.25, 15.45 Hz), 1.19 (s, 9H). ^{13}C NMR (C_6D_6, 100 MHz) δ: 172.3, 150.2, 136.3, 133.2, 129.0, 128.0, 126.8, 118.8, 114.6, 81.4, 63.6, 43.3, 29.6, 28.1 ppm. IR (neat, cm^{-1}) ν: 3062, 3028, 2975, 2927, 2867, 1737, 1599, 1503, 1389, 1367, 1293, 1231, 1144, 1035, 956, 847, 747, 690. Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49. Found: C, 77.47; H, 7.52.

2-[[2-(2-Bromo-4,5-dimethoxyphenyl)ethyl]methylamino]acetic Acid *tert*-Butyl Ester (22). A round-bottomedflask was charged with 5-bromo-(*N*-methyl)homoveratrylamine[76] (1.5 g, 5.47 mmol), 2-bromoacetic acid *tert*-butyl ester (0.81 mL, 6.02 mmol), NaOAc (0.49 g, 6.02 mmol), and dry ethanol (0.5 mL), purged with argon, and stirred for 22 h at 75 °C. After the mixture was cooled to room temperature, water and ether were added, the aqueous layer was extracted three times with ether, and the combined organic layers were washed with aqueous sodium bicarbonate and brine and dried over $MgSO_4$. After removal of solvent, the crude product was purified by flash column chromatography (ether/dichloromethane 1:10) yielding **22** as an orange oil (0.83 g, 2.14 mmol, 54%), which solidified upon storage. Mp: 91 °C. ^{1}H NMR (C_6D_6, 400 MHz) δ: 6.91 (s, 1H), 6.68 (s, 1H), 3.37 (s, 3H), 3.19 (s, 2H), 3.17 (s, 3H), 2.95−2.82 (m, 4H), 2.42 (s, 3H), 1.37 (s, 9H). ^{13}C NMR (C_6D_6, 100 MHz) δ: 170.5, 149.9, 149.6, 132.3, 116.7, 114.9, 114.8, 80.4, 59.8, 57.5, 56.0, 53.6, 42.4, 34.9, 28.5 ppm. IR (neat, cm^{-1}) ν: 3055, 2974, 2934, 2840, 2801, 1737, 1603, 1573, 1509, 1463, 1381, 1367, 1257, 1215, 1162, 1036, 962, 853, 799, 735, 602. Anal. Calcd for $C_{17}H_{26}BrNO_4$: C, 52.58; H, 6.75. Found: C, 52.68; H, 6.71.

6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid *tert*-Butyl Ester (23) (Table 2, Entry 2). Following the general procedure, **22** (0.194 g, 0.5 mmol) in dioxane (2.5 mL) was allowed to react for 3 h at 85 °C using ligand **3**. Flash column chromatography (ether/dichloromethane/hexanes 3:5:2) yielded **23** as a yellow oil (0.112 g, 0.36 mmol, 73%) that solidified upon storage. Mp: 134−136 °C. ^{1}H NMR (C_6D_6, 400 MHz) δ: 6.97 (s, 1H), 6.40 (s, 1H), 4.34 (s, 1H), 3.55−3.46 (m, 1H), 3.50 (s, 3H), 3.37 (s, 3H), 2.81−2.72 (m, 1H), 2.71−2.66 (dt, 1H, J = 4.8, 15.75 Hz), 2.57−2.49 (m, 1H), 2.53 (s, 3H), 1.35 (s, 9H). ^{13}C NMR (C_6D_6, 100 MHz) δ: 172.3, 149.7, 148.8, 127.6, 125.3, 113.0, 110.9, 80.8, 68.0, 56.0, 55.8, 48.5, 43.7, 29.3, 28.5 ppm. IR (neat, cm^{-1}) ν: 2972, 2932, 2852, 2804, 1728, 1611, 1518, 1464, 1368, 1324, 1290, 1260, 1225, 1147, 1071, 1016, 982, 938, 851, 815, 784. Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.43; H, 8.20. Found: C, 66.36; H, 8.29.

2-[[2-(2-Bromophenyl)ethyl]phenylamino]propionic Acid *tert*-Butyl Ester (24). A round-bottomed flask was charged with 2-bromo-*N*-(phenyl)phenethylamine (1.73 g, 6.25 mmol), 2-bromopropionic acid *tert*-butyl ester (2.88 g, 13.75 mmol), NaOAc (0.52 g, 6.25 mmol), and dry ethanol (0.5 mL), purged with argon, and stirred for 96 h at 75 °C. After the mixture was cooled to room temperature, water and ether were added, the aqueous layer was extracted three times with ether, and the combined organic layers were washed with aqueous sodium bicarbonate and brine and dried over $MgSO_4$. To remove residual amine (not separable by chromatography), the crude product was dissolved in dichloromethane (10 mL) and treated with acetyl chloride (0.27 mL, 3.75 mmol) and triethylamine (0.57 mL, 4.06 mmol). The mixture was stirred for 1 h at ambient temperature and submitted to an aqueous workup (water, 3× ether, brine). The organic layer was dried over $MgSO_4$ and concentrated, and the crude product was purified by flash column chromatography (ether/hexanes 1:20) yielding **24** as an orange oil (1.1 g, 2.73 mmol, 44%). ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.38−7.34 (dd, 1H, J = 1.1, 8 Hz), 7.28−7.23 (m 2H), 6.97−6.92 (m, 3H), 6.88−6.78 (m, 2H), 6.68−6.63 (dt, 1H, J = 1.7, 7.7 Hz), 4.24−4.16 (q, 1H, J = 7.2 Hz), 3.67−3.52 (m, 2H), 3.15−3.07 (m, 2H), 1.34−1.31 (d, 1H, J = 7.2 Hz), 1.25 (s, 9H). ^{13}C NMR (C_6D_6, 100 MHz) δ:_173.0, 149.1, 140.1, 133.4, 131.7, 129.9, 128.5, 128.1, 125.2, 118.5, 114.9, 80.9, 59.3, 47.9, 36.1, 28.7, 16.4 ppm. IR (neat, cm^{-1}) ν: 3060, 2979, 2935, 2873, 1725, 1600, 1505, 1472, 1368, 1258, 1214, 1146, 1063, 1040, 1027, 930, 849, 746, 692. Anal. Calcd for $C_{21}H_{26}BrNO_2$: C, 62.38; H, 6.48. Found: C, 62.44; H, 6.46.

1-Methyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid *tert*-Butyl Ester (25) (Table 2, Entry 3). Following the general procedure, **24** (0.202 g, 0.5 mmol) in dioxane (2.5 mL) was allowed to react for 24 h at 85 °C using ligand **3**. Flash column chromatography (ether/hexanes 1:25) yielded **25** as a yellow oil (0.101 g, 0.31 mmol, 62%). ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.44−7.40 (m, 1H), 7.21−7.11 (m, 6H), 7.08−6.97 (m, 2H), 6.96−6.92 (m, 1H), 6.90−6.84 (m, 1H), 3.76−3.68 (ddd, 1H, J = 4.4, 7.25, 11.8 Hz), 3.21−3.29 (m, 1H), 2.82−2.70 (m, 2H), 1.86 (s, 3H), 1.16 (s, 9H). ^{13}C NMR (C_6D_6, 100 MHz) δ: 174.3, 150.6, 140.4, 135.6, 129.4, 129.29, 128.3, 127.1, 126.9, 126.6, 81.0, 67.3, 46.9, 31.4, 27.9, 26.2 ppm. IR (neat, cm^{-1}) ν: 3059, 2976, 2932, 2867, 1723, 1598, 1495, 1451, 1391, 1367, 1251, 1158, 1111, 1062, 1034, 847, 755, 695. Anal. Calcd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79. Found: C, 77.69; H, 7.82.

2-[[2-(2-Bromo-4,5-dimethoxyphenyl)ethyl]methylamino]propionic Acid *tert*-Butyl Ester (26). A round-bottomed flask was charged with 5-bromo-*N*-methylhomoveratrylamine[76] (1.6 g, 5.8 mmol), 2-bromopropionic acid *tert*-butyl ester (0.57 g, 6.96 mmol), NaOAc (0.57 g, 6.96 mmol), and dry ethanol (0.5 mL), purged with argon, and stirred for 41 h at 70 °C. After the mixture was cooled to room temperature, water and ether were added, the aqueous layer was extracted three times with ether, and the combined organic layers were washed with aqueous sodium bicarbonate and brine and dried over $MgSO_4$. After removal of solvent the crude product was purified by flash column chromatography (gradient ether/dichloromethane 1:30−1:10) yielding **26** as an orange oil (1.53 g, 3.8 mmol, 66%). ^{1}H NMR (C_6D_6, 400 MHz) δ: 6.92 (s, 1H), 6.63 (s, 1H), 3.39−3.32 (q, 1H, J = 7.1 Hz), 3.34 (s, 3H), 3.19 (s, 3H), 3.07−3.01 (m, 1H), 2.99−2.88 (m, 3H), 2.49 (s, 3H), 1.38 (s, 9H), 1.28−1.24 (d, 2H, J = 7.1 Hz). ^{13}C NMR (C_6D_6, 100 MHz) δ: 172.8, 149.8, 149.6, 132.5, 116.7, 115.0, 114.9, 80.3, 62.8, 56.0, 55.8, 55.3, 38.4, 35.8, 28.6, 16.1; IR (neat, cm^{-1}) ν: 2975, 2937, 2842, 2807, 1721, 1603, 1509, 1463, 1439, 1383, 1366, 1337, 1256, 1216, 1162, 1146, 1096, 1034, 962, 850, 793 ppm. Anal. Calcd for $C_{18}H_{28}BrNO_4$: C, 53.74; H, 7.01. Found: C, 53.97; H, 6.89.

6,7-Dimethoxy-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid *tert*-Butyl Ester (27) (Table 2, Entry 6). Following the general procedure, **26** (0.203 g, 0.5 mmol) in dioxane (2.5 mL) was allowed to react for 45 h at 100 °C using ligand **3**. Flash column chromatography (ether/hexanes 2:3) yielded **27** as a yellow oil (0.106 g, 0.33 mmol, 66%). ^{1}H NMR (C_6D_6, 400 MHz) δ: 6.98 (s, 1H), 6.38 (s, 1H), 3.47 (s, 3H), 3.37 (s, 3H), 3.36−2.29 (m, 1H), 2.96−2.87 (ddd, 1H, J = 5.2, 9.35, 14.8 Hz), 2.73−2.67 (dt, 1H, J = 4.85, 9.3 Hz), 2.64−2.56 (dt, 1H, J = 4, 15.3 Hz), 2.49 (s, 3H), 1.79 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (C_6D_6, 100 MHz) δ:_174.2, 149.2, 149.0, 131.5, 127.1, 112.7, 110.5, 80.5, 66.8, 56.1, 55.7, 48.7, 39.9, 30.4, 28.4, 25.2 ppm. IR (neat, cm^{-1}) ν: 2977, 2941, 2908,

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2834, 2804, 1717, 1613, 1515, 1465, 1451, 1368, 1329, 1254, 1221, 1162, 1106, 1067, 1027, 1001, 847, 793, 744, 704. Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47. Found: C, 67.50; H, 8.64.

1-[2-(2-Bromophenyl)ethyl]pyrrolidine-2-carboxylic Acid *tert*-Butyl Ester (28). To a stirred solution of proline *tert*-butyl ester (1.0 g, 5.84 mmol) in DMF (4 mL) and toluene (2 mL) was added K_2CO_3 (1.24 g, 9 mmol), followed by a solution of 2-bromophenethyl bromide (1.69 g, 6.42 mmol) in DMF (2 mL). The slurry was stirred for 20 h at 80 °C, at which point monitoring by GC showed that little conversion had occurred. DBU (0.88 mL, 5.84 mmol) was added, and the mixture was stirred for an additional 7 h at 80 °C and then filtered through a silica gel plug and washed with ether. The organic layer was submitted to an aqueous workup (water, 3× ether, brine), dried over $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography (gradient ether/hexanes 1:10−1:3) yielding **28** as a colorless oil (1.4 g, 3.95 mmol, 68%). ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.40−7.36 (dd, 1H, J = 1.1, 7.6 Hz), 7.13−7.09 (dd, 1H, J = 1.6, 7.5 Hz), 6.93−6.86 (dt, 1H, J = 1.1, 7.5 Hz), 6.69−6.62 (dt, 1H, J = 1.7, 7.6 Hz), 3.19−2.94 (m, 5H), 2.73−2.64 (m, 1H), 2.33−2.25 (m, 1H), 2.00−1.88 (m, 1H), 1.86−1.81 (m, 2H), 1.54−1.42 (m, 1H), 1.36 (s, 9H). ^{13}C NMR (C_6D_6, 100 MHz) δ: 173.5, 140.7, 133.3, 131.5, 128.3, 127.9, 125.3, 80.1, 66.9, 54.7, 53.5, 36.2, 29.7, 28.5, 24.1 ppm. IR (neat, cm^{-1}) ν: 2973, 2875, 2806, 1723, 1472, 1391, 1366, 1256, 1212, 1150, 1111, 1030, 978, 939, 911, 847, 748. Anal. Calcd for $C_{17}H_{24}BrNO_2$: C, 57.63; H, 7.83. Found: C, 57.77; H, 6.80.

2,3,5,6-Tetrahydro-1*H*-pyrrolo[2,1-*a*]isoquinoline-10b-carboxylic Acid *tert*-Butyl Ester (29) (Table 2, Entry 7). Following the general procedure, **28** (0.177 g, 0.5 mmol) in dioxane (2.5 mL) was allowed to react for 24 h at 90 °C using ligand **2**. Flash column chromatography (ether/hexanes 1:3) yielded **29** as a yellow oil (0.097 g, 0.36 mmol, 71%). ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.30−7.25 (m, 1H), 7.09−6.98 (m, 2H), 6.96−6.91 (m, 1H), 3.60−3.51 (ddd, 1H, J = 4.0, 10.20 Hz, 12.70 Hz), 3.20−3.13 (ddd, 1H, J = 2.1, 7.25, 12.20 Hz), 2.97−2.91 (m, 1H), 2.86−2.80 (ddd, 1H, J = 3.9, 4.9, 12.7 Hz), 2.76−2.67 (ddd, 1H, J = 3.9, 10.20, 15.8 Hz), 2.67−2.59 (dt, 1H, J = 6.25, 8.85 Hz), 2.49−2.41 (dt, 1H, J = 3.8, 15.8 Hz), 1.96−1.83 (m, 1H), 1.69−1.60 (m, 1H), 1.53−1.43 (m, 1H), 1.27 (s, 9H). ^{13}C NMR (C_6D_6, 100 MHz) δ:_173.9, 140.4, 135.5, 129.3, 127.0, 126.8, 126.7, 80.2, 70.2, 53.0, 45.8, 38.8, 28.2, 25.5, 24.4 ppm. IR (neat, cm^{-1}) ν: 2973, 2941, 2802, 1721, 1490, 1453, 1366, 1266, 1256, 1152, 1113, 1030, 974, 847, 760, 743. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48. Found: C, 74.60; H, 8.47.

1-[2-(2-Bromophenyl)ethyl]piperidine-2-carboxylic Acid *tert*-Butyl Ester (30). To a stirred solution of pipecolinic acid *tert*-butyl ester (0.75 g, 4.1 mmol) in DMF (4 mL) and toluene (2 mL) was added K_2CO_3 (1.18 mmol, 6.11 mmol), followed by a solution of 2-bromophenethyl bromide (1.18 g, 4.48 mmol) in DMF (2 mL). The slurry was stirred for 20 h at 80 °C, and after being cooled to room temperature it was filtered through silica gel and washed with ether. The organic layer was submitted to an aqueous workup (water, 3× ether, brine), dried over $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography (ether:hexanes 1:5) yielding **30** as a colorless oil (0.86 g, 2.33 mmol, 57%). ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.39−7.35 (dd, 1H, J = 1.15, 7.6 Hz), 7.09−7.06 (dd, 1H, J = 1.65, 7.5 Hz), 6.92−6.87 (dt, 1H, J = 1.2, 7.5 Hz), 6.68−6.63 (dt, 1H, J = 1.7, 7.6 Hz), 3.21−3.12 (m, 2H), 3.03−2.93 (m, 3H), 2.79−2.68 (m, 1H), 2.33−2.25 (ddd, 1H, J = 3.55, 6.9, 10.8 Hz), 1.91−1.82 (m, 1H), 1.76−166 (m, 1H), 1.58−1.38 (m, 3H), 1.35 (s, 9H), 1.28−1.17 (m, 1H). ^{13}C NMR (C_6D_6, 100 MHz) δ: 173.1, 140.8, 133.3, 131.6, 128.2, 127.9, 125.3, 80.2, 65.2, 56.9, 50.1, 35.0, 30.2, 28.5, 26.4, 22.8 ppm. IR (neat, cm^{-1}) ν: 2935, 2856, 1725, 1472, 1443, 1366, 1291, 1210, 1148, 1115, 1100, 1030, 999, 850, 831, 748. Anal. Calcd for $C_{18}H_{26}BrNO_2$: C, 58.70; H, 7.12. Found: C, 58.53; H, 7.21.

1,2,3,4,6,7-Hexahydropyrido[2,1-*a*]isoquinoline-11b-carboxylic Acid *tert*-Butyl Ester (31) (Table 2, Entry 9). Following the general procedure, **30** (0.184 g, 0.5 mmol) in dioxane (2.5 mL) was allowed to react for 23 h at 90 °C using ligand **3**. Flash column chromatography (ether/hexanes 1:5) yielded **31** as a yellow oil (0.117 g, 0.406 mmol, 81%). ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.68−7.64 (dd, 1H, J = 1.1, 7.8 Hz), 7.13−7.07 (dt, 1H, J = 1.1, 7.8 Hz), 7.06−7.01 (dt, 1H, J = 1.3, 7.4 Hz), 6.96−6.92 (dd, 1H, J = 1.3, 7.4 Hz), 4.02−3.93 (dt, 1H, J = 3.9, 11.3 Hz), 3.26−3.17 (dt, 1H, J = 2.8, 11.7 Hz), 3.13−3.03 (ddd, 1H, J = 6.5, 11.2, 15.8 Hz), 2.83−2.77 (m, 1H), 2.75−2.69 (m, 1H), 2.69−2.63 (ddd, 1H, J = 1.9, 6.5, 11.7 Hz), 2.56−2.49 (ddd, 1H, J = 1.7, 3.6, 15.8 Hz), 1.77−1.56 (m, 4H), 1.50−1.42 (m, 1H), 1.27 (s, 9H). ^{13}C NMR (C_6D_6, 100 MHz) δ: 173.4, 139.0, 136.2, 130.2, 127.4, 127.2, 126.4, 81.0, 67.2, 52.9, 49.0, 38.1, 31.1, 28.6, 26.7, 24.1 ppm. IR (neat, cm^{-1}) ν: 2975, 2931, 2861, 1717, 1453, 1391, 1368, 1302, 1237, 1158, 1144, 1123, 1081, 1054, 1015, 959, 849, 839, 791, 754, 731. Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77. Found: C, 75.00; H, 8.81.

2-(2-Bromobenzyl)aminopropionic Acid *tert*-Butyl Ester. To a stirred solution of alanine *tert*-butyl ester hydrochloride (1.09 g, 6.0 mmol) in DMF (8 mL) was added K_2CO_3 (2.07 g, 15 mmol), followed by a solution of 2-bromobenzyl bromide (1.5 g, 6 mmol) in DMF (4 mL). The slurry was stirred for 4 h at ambient temperature and then filtered through silica gel and washed with ether. The organic layer was submitted to an aqueous workup (water, 3× ether, brine), dried over $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography (ether/hexanes 1:5) yielding the title compound as a colorless oil (1.38 g, 4.4 mmol, 73%). ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.7.42−7.38 (dd, 1H, J = 1.55, 7.65 Hz), 7.37−7.33 (dd, 1H, J = 1.15, 7.95 Hz), 6.97−6.91 (dt, 1H, J = 1.15, 7.5 Hz), 6.72−6.66 (dt, 1H, J = 1.7, 7.45 Hz), 3.93−3.87 (d, 1H, J = 14.4 Hz), 3.88−3.83 (d, 1H, J = 14.4 Hz), 3.24−3.17 (q, 1H, J = 6.95 Hz), 1.90−1.81 (s, 1H), 1.35 (s, 9H), 1.1.21−1.88 (d, 3H, J = 6.95 Hz). ^{13}C NMR (C_6D_6, 100 MHz) δ: 175.2, 1403, 133.4, 130.5, 128.9, 127.9, 128.3, 80.6, 57.5, 52.1, 28.4, 19.7 ppm. IR (neat, cm^{-1}) ν: 3338, 3064, 2977, 1725, 1569, 1465, 1441, 1368, 1254, 1214, 1146, 1025, 849, 746. Anal. Calcd for $C_{14}H_{20}BrNO_2$: C, 53.51; H, 6.42. Found: C, 53.55; H, 6.36.

2-[*N*-(Benzyloxycarbonyl)-*N*-(2-bromobenzyl)]aminopropionic Acid *tert*-Butyl Ester (32). To a stirred solution of 2-(2-bromobenzyl)aminopropionic acid *tert*-butyl ester (1.24 g, 3.94 mmol) in dichloromethane (5 mL) was added diisopropylethylamine (0.83 mL, 4.73 mmol), followed by dropwise addition of benzyl chloroformate (0.62 mL, 4.34 mmol). The solution was stirred for 1 h at ambient temperature and then submitted to an aqueous workup (water, 3× ether, brine), dried over $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography (ether/hexanes 1:5) yielding **32** as a colorless oil (1.4 g, 3.2 mmol, 81%) that consisted of a 2:1 mixture of rotamers. ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.56−7.52 (d, 0.34H, J = 7.55 Hz), 7.39−7.35 (d, 0.66H, J = 7.65 Hz), 7.32−7.25 (m, 1.7H), 7.15−7.08 (m, 0.66H), 7.08−6.97 (m, 4.64H), 6.97−6.90 (m, 1H), 6.82−6.74 (m, 1.34H), 5.30−5.25 (d, 0.34H, J = 12.5 Hz), 5.10−5.01 (m, 1.32H), 4.92−4.86 (d, 0.66H, J = 12.5 Hz), 4.89−4.83 (d, 0.34H, J = 17.6 Hz), 4.64−4.57 (d, 0.34H, J = 16.8 Hz), 4.44−4.37 (d, 0.66H, J = 17.6 Hz), 4.30−4.24 (q, 0.66H, J = 7.2 Hz), 4.09−4.02 (q, 0.34H, J = 7.2 Hz), 1.34 (s, 6H), 1.25−120 (m, 5H), 0.91−0.86 (d, 1H, J = 7.2 Hz). ^{13}C NMR (C_6D_6, 100 MHz, major rotamer) δ: 171.0, 156.5, 138.5, 133.1, 129.9, 129.2, 129.0, 128.9, 128.8, 128.5, 127.9, 122.9, 81.3, 67.6, 57.4, 50.9, 32,2, 28.2 ppm. IR (neat, cm^{-1}) ν: 3066, 3004, 2979, 2958, 1737, 1706, 1455, 1441, 1407, 1368, 1254, 1154, 1069, 1027, 912, 849, 746, 696. Anal. Calcd for $C_{22}H_{26}BrNO_4$: C, 58.94; H, 5.85. Found: C, 59.09; H, 5.83.

2-Benzyloxycarbonyl-2-methyl-2,3-dihydro-1*H*-isoindole-1-carboxylic Acid *tert*-Butyl Ester (33) (Table 3, Entry 1). Following the general procedure, **32** (0.195 g, 0.5 mmol) in dioxane (2.5 mL) was allowed to react for 20 h at 90 °C using ligand **3**. Flash column chromatography (ether/hexanes 1:12) yielded **33** as an orange oil (0.123 g, 0.34 mmol, 67%) that consisted of a 3:2 mixture of rotamers. ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.35−7.20 (m, 2H), 7.17−6.90 (m, 6H), 6.80−6.72 (m, 1H), 5.31−5.26 (d, 0.66H, J = 12.4 Hz), 5.29−5.24 (d, 0.34H, J = 12.5 Hz), 5.21−5.16 (d, 0.34H, J = 12.5 Hz), 5.09−5.04 (d, 0.34H, J = 14.8 Hz), 5.07−5.02 (d, 0.66H, J = 12.4 Hz), 4.83−4.77 (d, 0.66H, J = 14.3 Hz), 4.80−4.73

(d, 0.34H, J = 14.8 Hz), 4.54−4.48 (d, 0.66H, J = 14.3 Hz), 1.26 (s, 6H), 1.13 (s, 3H). ^{13}C NMR (C_6D_6, 100 MHz) δ: 171.4, 155.0, 142.9, 142.7, 138.0, 137.4, 137.0, 129.0, 128.9, 128.7, 128.3, 123.4, 123.2, 122.4, 122.3, 81.3, 73.0, 72.1, 67.7, 67.3, 54.4, 53.3, 28.0, 27.9, 25.1, 24.0 ppm. IR (neat, cm^{-1}) ν: 3035, 2979, 2939, 2871, 1735, 1706, 1455, 1405, 1355, 1252, 1154, 1121, 1065, 1021, 912, 847, 750, 698. Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86. Found: C, 72.10; H, 6.87.

***N*-(Benzyloxycarbonyl)-*N*-(2-bromobenzyl)phenylglycine *tert*-Butyl Ester (34).** To a stirred solution of 2-[*N*-(2-bromobenzyl)]aminophenylacetic acid *tert*-butyl ester (0.38 g, 1.0 mmol) in dichloromethane (1 mL) was added diisopropylethylamine (0.19 mL, 1.1 mmol), followed by dropwise addition of benzylchloroformate (0.15 mL, 1.05 mmol). The solution was stirred for 1 h at ambient temperature and then submitted to an aqueous workup (water, 3× ether, brine), dried over $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography (ether/hexanes 1:20) yielding **39** as a highly viscous colorless oil (0.47 g, 0.92 mmol, 92%) that consisted of a ∼2:1 mixture of rotamers. ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.55−6.95 (m, 9H), 6.94−6.82 (m, 4H), 6.60−6.54 (m, 1H), 6.01−5.96 (s, 0.7H), 5.79−5.72 (s, 0.3H), 5.34−4.87 (m, 3H), 4.80−4.57 (m, 1H), 1.34 (s, 6H), 1.24 (s, 3H). ^{13}C NMR (C_6D_6, 100 MHz, major rotamer) δ:_170.1, 157.5, 138.4, 137.3, 135.2, 132.7, 130.3, 129.0, 128.9, 128.8, 128.3, 127.4, 122.6, 82.1, 68.0, 66.2, 65.2, 49.9, 28.2, 15.9 ppm, IR (neat, cm^{-1}) ν: 3066, 3033, 2977, 2935, 1737, 1704, 1455, 1441, 1401, 1368, 1256, 1150, 1104, 1027, 970, 916, 841, 798, 746, 698. Anal. Calcd for $C_{27}H_{28}BrNO_4$: C, 63.53; H, 5.53. Found: C, 63.61; H, 5.52.

2-Benzyloxycarbonyl-1-phenyl-2,3-dihydro-1*H*-isoindole-1-carboxylic Acid *tert*-Butyl Ester (35) (Table 3, Entry 2). Following the general procedure, **34** (0.195 g, 0.5 mmol) in dioxane (2.5 mL) was allowed to react for 2 h at 90 °C using ligand **3**. Flash column chromatography (ether/hexanes 1:12) yielded **35** as an orange oil (0.151 g, 0.49 mmol, 99%) that consisted of a 1:1 mixture of rotamers. ^{1}H NMR (C_6D_6, 400 MHz) δ: 7.82−7.78 (m, 1H), 7.61−7.57 (m, 1H), 7.36−7.32 (m, 0.5H), 7.25−7.15 (m, 1H), 7.14−6.78 (m, 10.5H), 5.25−5.21 (d, 0.5H, J = 12.35 Hz), 5.18−5.11 (d, 0.5H, J = 14.85 Hz), 5.10−5.05 (d, 0.5H, J = 12.3 Hz), 5.05−5.00 (d, 0.5H, J = 12.3 Hz), 4.98−4.93 (d, 0.5H, J = 14.85 Hz), 4.89−4.84 (d, 0.5H, J = 14.45 Hz), 4.83−4.78 (d, 0.5H, J = 12.35 Hz), 4.77−4.72 (d, 0.5H, J = 14.45 Hz), 1.29 (s, 4.5H), 1.18 (s, 4.5H). ^{13}C NMR (C_6D_6, 100 MHz) δ: 169.6, 169.6, 155.3, 154.4, 143.3, 142.8, 142.4, 141.7, 137.9, 137.8, 137.2, 136.8, 130.5, 129.5, 129.1, 129.0, 128.9, 128.8, 128.7, 128.5, 128.2, 128.0, 127.9, 127.7, 124.9, 124.8, 123.1, 123.0, 82.2, 82.0, 78.5, 77.8, 67.6, 67.4, 54.5, 53.5, 28.1, 27.9 ppm. IR (neat, cm^{-1}) ν: 3062, 3033, 3006, 2979, 1737, 1708, 1497, 1447, 1403, 1351, 1297, 1250, 1150, 1125, 984, 841, 746, 694. Anal. Calcd for $C_{27}H_{27}NO_4$: C, 75.50; H, 6.34. Found: C, 75.63; H, 6.34.

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Supporting Information Available: ^{1}H NMR data of compounds **19** and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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