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One-Pot Synthesis of 2-Imidazolines via the Ring Expansion of Imidoyl Chlorides with Aziridines

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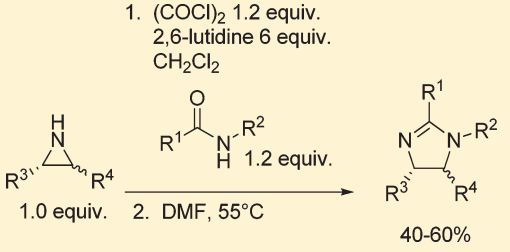
Supporting Information

ABSTRACT: We herein report a simple and convenient one-pot synthesis of highly substituted 2-imidazolines in a regiocontrolled and stereospecific matter through the ring expansion reaction of an imidoyl chloride with an aziridine, analogous to the Heine reaction.



2-Imidazolines have attracted significant attention because of their diverse pharmacological properties.[1−4] The stereochemistry of this privileged scaffold is capable of governing its diverse biological characteristics, perhaps best illustrated by the general NF-κB inhibitory scaffold **1**[5−9] and p53 activator scaffold **2**[10−12] (Figure 1). To develop a stereospecific route to 2-imidazoline scaffolds, we investigated the scope of a Heine-type ring expansion of aziridines. We anticipated aziridines to be particularly valuable building blocks, as they can be readily accessed enantiomerically pure.[13−17] The Heine reaction was first developed by Harold W. Heine, who reported the synthesis of 2-imidazolines[18] and 2-oxazolines[19−21] by the isomerization of an imidoyl aziridine and a benzoylated aziridine through NaI in acetone (Scheme 1). Many examples have been reported for the isomerization of acyl and benzoyl aziridines to 2-oxazolines by Heine and others using NaI[19−22] or Lewis acids.[23−27]

Even though there have been several reported syntheses of 2-imidazolines,[28−31] reports of a Heine-type isomerization of imidoyl aziridines have been scarce.[18,32−34] A couple reports employed the Heine reaction using the reaction of an aziridine with an alkyne and sulfonyl azide[32] and an *N*-arylketenimine.[33] However, these reports were limited in scope and required the isolation of the imidoyl aziridine prior to the subsequent rearrangement to the 2-imidazolines. We herein report a simple and convenient one-pot Heine reaction synthesis of tetrasubstituted 2-imidazolines in a regiocontrolled and stereospecific matter through the ring expansion reaction of an imidoyl chloride with an aziridine.

We first attempted to synthesize 2-imidazoline **6** by reacting aziridine **3** with imidoyl chloride **4** in a one-pot procedure via intermediate **5**. However, isomerization of the imidoyl aziridine intermediate **5** into 2-imidazoline **6** did not occur in CH_2Cl_2 with a 5:1 mixture of TEA:TEA·HCl. Instead only unreacted intermediate **5** was recovered from the reaction by removal of the excess Et_3N in vacuo followed by trituration of the Et_3N·HCl byproduct with ether. Intermediate **5** was then treated with either 1 equiv of NaI or Et_3N·HCl and was successfully transformed into the 2-imidazoline **6** by refluxing in acetone, without the formation of the 2-imidazoline **7** (Scheme 2). The regio- and stereochemistry of compound **6** was verified by NOE.

The Brønsted acid isomerization of intermediate **5** into compound **6** by Et_3N·HCl was consistent with the work by Kohn and co-worker. They reported a Brønsted acid isomerization of an ethyl aziridine carboximidate to the corresponding 2-ethoxyimidazoline.[34] The exact role of the TEA in the reaction was somewhat ambiguous. Excess TEA halted the reaction at the intermediate **5** whereas isomerizaton occurred once the excess TEA was removed leaving only Et_3N·HCl (Scheme 2). However, we hypothesized that the correct base would allow for a one-pot synthesis of 2-imidazoline **6** without stalling at the intermediate **5**. Due to the instability of the intermediate **5** to hydrolysis, we investigated the possibility of a one-pot sequence using aziridine **3** and imidoyl chloride **4**. To optimize this reaction, compound **4** was isolated by reacting *N*- benzylbenzamide with $(COCl)_2$ and 2,6-lutidine in CH_2Cl_2. The CH_2Cl_2 was removed, followed by trituration of the 2,6-lutidine hydrogen chloride salt in hexane and removal of any residual 2,6-lutidine in vacuo.[35] The imidoyl chloride **4** was treated with the aziridine **3** in toluene and multiple different bases were investigated in order to optimize the conversion to compound **6**. Initially, the reaction conditions were optimized with respect to the base and included DABCO, DMAP, Hünig's base, Et_3N, and 2,6-lutidine (Table 1). Of these bases, 2,6-lutidine performed the best (Table 1, entry 5) and rendered the product **6** in a moderate 20% overall yield.

Et_3N and Hünig's base resulted in the reaction stalling at intermediate **5** (Table 1, entries 3 and 4), which did not cyclize to compound **6**, whereas 2,6-lutidine provided product **6**. Although

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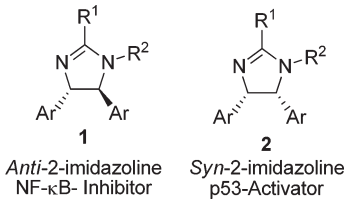
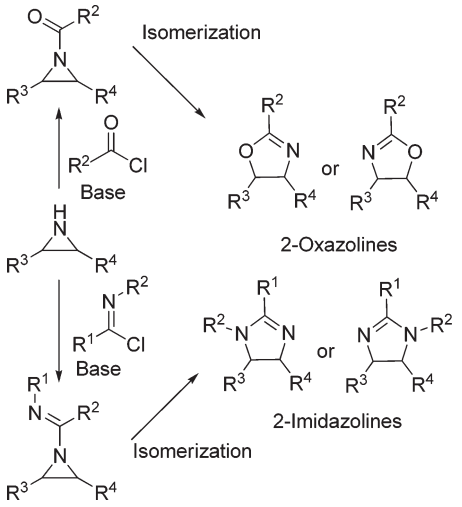
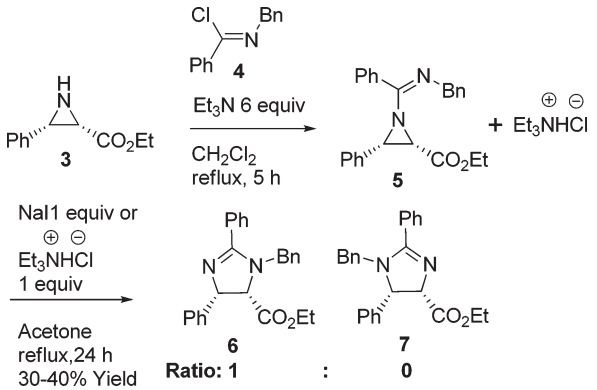


Figure 1. *Anti* and *syn* 2-imidazolines.

Scheme 1. Synthesis of 2-Imidazolines and 2-Oxazolines

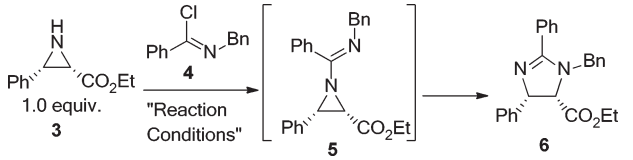


Scheme 2. Synthesis of 2-Imidazoline 6



full mechanistic details have not been exhausted, we postulated that the role of the base is to initially quench the HCl generated by substitution of aziridine **3** with imidoyl chloride **4**. Second, the protonated base generated will subsequently act as a Brønsted acid and is responsible for the isomerization of **5** to compound **6** (Table 1). This is consistent with our finding that unlike TEA (Scheme 2), excess 2,6-lutidine (Table 1, entries 9−13) did not halt the reaction at the intermediate **5**, which could be reasoned by the greater acidity of generated 2,6-lutidine·HCl ($pK_a = 6.7$) versus Et_3N·HCl (pK_a = 10.75). The choice of solvent also greatly affected the overall yield of this two-step process and solvents capable of producing a homogeneous solutions, such as DMF and DCM, performed superior over solvents that only partially solubilized the 2,6-lutidine·HCl salts, such as toluene. Further

Table 1. One-Pot Optimization of Compound 6



entry	solvent	base	temp (°C)	equiv of **4**	equiv of base	*T* (h)	yields (%)
1	toluene	DABCO	80	1.5	1.5	12	0
2	toluene	DMAP	80	1.5	1.5	12	0
3	toluene	Et_3N	80	1.5	1.5	12	0[a]
4	toluene	$(^iPr)_2NEt$	80	1.5	1.5	12	0[a]
5	toluene	2,6 lutidine	80	1.5	1.5	21	20
6	acetone	2,6-lutidine	80	1.5	1.5	21	37
7	DMF	2,6-lutidine	80	1.5	1.5	21	44
8	DMF	2,6-lutidine	rt	1.2	1.2	21	10
9	DMF	2,6-lutidine	rt	1.2	6.0	21	38
10	DMF	2,6-lutidine	80	1.2	6.0	21	47
11	DCM	2,6-lutidine	80	1.2	6.0	21	39
12	DMF	2,6-lutidine	55	1.2	6.0	21	50
13	DMF	2,6-lutidine	55	1.2	6.0	6	52
14	DMF	none	55	1.2	0.0	6	0

[a] The reaction stalled at the intermediate imidoyl aziridine **5**.

optimization of this one-pot reaction resulted in an overall yield of 52% of compound **6** based on the aziridine **3** (Table 1, entry 13).

Considering that 2,6-lutidine was used both to synthesize the imidoyl chloride **4** and for the ring expansion of aziridine **5** to the 2-imidazoline **6**, the imidoyl chloride **4** did not have to be isolated. Using this one-pot sequence, a range of different imidoyl chlorides were treated with *trans*-2,3-diphenyl aziridine to yield the *trans* imidazoline in useful yields (Table 2).

The R^1 position tolerated alkyl groups and electron-withdrawing and electron-donating aryl groups, while the R^2 position was restricted to alkyl and benzyl groups. The structural identity was supported by X-ray crystallography of compound **9j** (see the Supporting Information). The reaction did not provide the desired product when aryl groups were introduced at the R^2 position or when a *p*-NO_2-C_6H_4− group was introduced at the R^1 position.

The scope of the reaction was subsequently investigated with respect to the R^3, R^4, and R^5 positions of the aziridine. Electron-withdrawing and electron-donating aryl groups, along with vinyl, ketone, ester, and alkyl functionalities were readily tolerated at these positions (Table 3).

It was important to note that it was not possible to have just a hydrogen atom at the R^4 and R^5 positions (Table 3, entry 9). With respect to the regiochemistry, only one regioisomer was produced in all cases, except when a *p*-NO_2-C_6H_4− group was introduced at the R^3 position or a benzyl group at the R^4 position (Table 3, entries 4 and 8). Side products in this Heine reaction often included the 2-imidazole, due to oxidation of the imidazoline ring.

Of particular note is that this one-pot Heine reaction showed an overall retention of stereochemistry. In comparing the *cis* and *trans* stereoisomers of ethyl 3-phenylaziridine-2-carboxylate the stereochemistry was preserved to yield the *cis*- and *trans*-2-imidazolines, respectively (compounds **6** and Table 3, entry 2).

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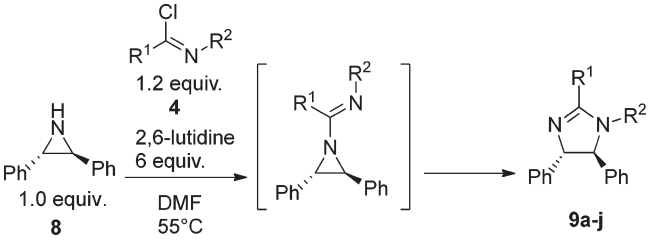
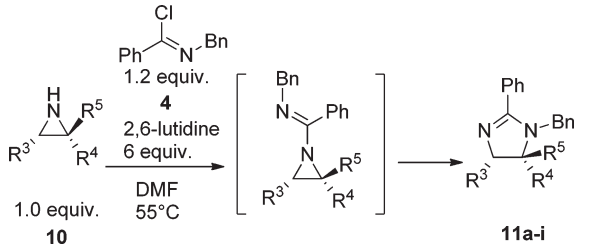
Table 2. Variation at R^1 and R^2



entry	R^1	R^2	T (h)	**9**	yield (%)
1	*p*-MeO-C_6H_4	Bn	9	**a**	59
2	Ph	Bn	9	**b**	55
3	*p*−F-C_6H_4	Bn	9	**c**	43
4	*p*-NO_2−C_6H_4	Bn	6	**d**	0
5	Cy	Bn	6	**e**	60
6	Me	Bn	9	**f**	48
7	Ph	Ph	13	**g**	0[a]
8	Ph	PMB	9	**h**	53
9	Ph	Cy	12	**i**	53
10	Ph	Me	9	**j**	60

[a] The reaction stalled at the intermediate imidoyl aziridine and did not cyclize to the 2-imidazoline

Table 3. Variation at R^3, R^4, and R^5

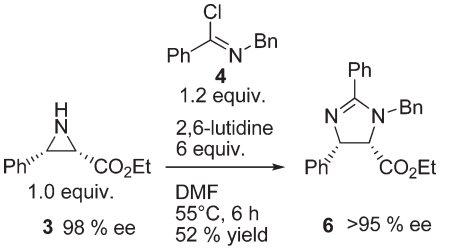


entry	R^3	R^4	R^5	T (h)	**11**	yield (%)
1	*p*-MeO-C_6H_4	H	CO_2Et	10	**a**	45
2	Ph	H	CO_2Et	12	**b**	42
3	Ph	Me	CO_2Et	12	**c**	59
4	*p*-NO_2-C_6H_4	H	CO_2Et	6	**d**	40[a]
5	PhCH=CH	H	CO_2Et	20	**e**	41
6	*n*-C_6H_{13}	H	CO_2Et	12	**f**	40
7	Ph	H	COPh	12	**g**	41
8	Ph	Bn	H	12	**h**	40[a]
9	Ph	H	H	12	**i**	0

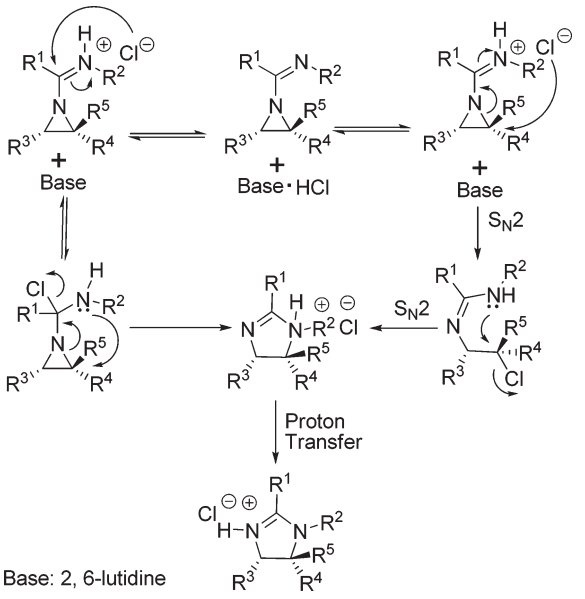
[a] The compound was synthesized as a 2:1 mixture of regioisomers.

The 2-imidazoline, compound **6**, was synthesized from both racemic aziridine **3** and enantiopure aziridine **3** (98% ee). This would presumably yield the 2-imidazoline as a racemate or enantiopure (98% ee) depending on the enantiopurity of the starting aziridine **3**. The racemate, compound **6**, was treated with (*S*)-Mosher's acid, and analysis by ^{1}HNMR showed a 1:1 ratio of diasteromeric salts. However, the enantiopure compound **6** gave only one diasteromeric salt by ^{1}H NMR. Thus the enantiopurity of compound **6** was preserved in the ring expansion reaction therefore demonstrating the utility to access enantiopure 2-imidazolines (Scheme 3).

Scheme 3. Synthesis of Enantiopure 2-Imidazoline 6



Scheme 4. Proposed Reaction Mechanism



The synthesis of a 2-imidazoline with a quaternary carbon at the C-5 position (**11c**) proceeded with complete retention of stereochemistry (Table 3, entry 3). The identity of compound **11c** was supported by X-ray crystallography (see the Supporting Information). This retention of stereochemistry could be accomplished by S_N2 attack of the chlorine anion at the 2-position of the imidoyl aziridine ring carbon and then ring closure through a second S_N2.[18−21] However, another possible mechanism could involve attack of the imidoyl carbon atom by the chloride anion followed by ring closure. This mechanism would be analogous to the earlier proposed mechanism of attack of the imidoyl carbon by the iodine anion from NaI and subsequent ring closure (Scheme 4).[18,32]

The latter mechanism would suggest that the imidoyl aziridines would undergo ring expansion by a 4-endo-tet ring closure. Both a S_Ni or a stepwise process are plausible mechanisms; evidence for these mechanisms has been supported by Tomasini and co-workers[36] via the ring expansion of *N-tert*-butoxycarbonyl aziridines to oxazolidinones. These mechanisms would likely involve activation of the imidoyl aziridine intermediate by the Brønsted acid, 2,6-lutidine·HCl. Nitrogen−carbon bond formation occurred at the most electropositive carbon atom in the imidoyl aziridine intermediate. This was the C-2 position of the aziridine in all cases except when a *p*-NO_2-C_6H_4− group was introduced at the C-3 position or a benzyl group at the C-2

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position. In this case the C-3 and C-2 positions of the aziridine ring had similar electronics and resulted in a mixture of 2-imidazoline regioisomers (Table 3, entries 4 and 8).

In conclusion, we have developed a simple one-pot stereospecific synthesis of 2-imidazolines from the ring expansion of an aziridine with an imidoyl chloride consistent with a Heine reaction. The scope of the reaction indicated that the reaction tolerated many diverse functional groups. The purification of imidoyl chlorides and imidoyl aziridine intermediates was not needed, therefore creating a simple one-pot method to synthesize these biologically significant highly substituted 2-imidazolines.

EXPERIMENTAL SECTION

General. Acetonitrile, Et_3N, and DMF were distilled from calcium hydride under nitrogen. Toluene and DCM were purified through a column packed with dry alumina and were dispensed by a nitrogen pressure delivery system. THF and ether were distilled from sodium under nitrogen. Acetone, 1,2-dichloroethane, and chloroform were distilled from calcium sulfate under nitrogen. All other reagents and solvents were purchased from commercial sources and used without further purification. All flasks were oven-dried overnight and cooled under argon or nitrogen. All reactions were monitored by TLC with 0.25 μM precoated silica gel plates and UV light was used to visualize the compounds. It some cases phosphomolybdic acid (PMA) stain or I_2 was used to visualize the compounds. Column chromatography silica gel was provided by EM Science (230−400 mesh). All NMR spectra were recorded on a 500 or 300 MHz spectrometer. Chemical shifts are reported relative to the solvent peak of chloroform (δ 7.24 for ^{1}H and δ 77.0 for ^{13}C).

General Procedure To Neutralize Silica Gel. Silica gel was saturated with Et_3N; the slurry was mixed for 5 min and then concentrated under reduced pressure to remove the excess Et_3N to give a free-flowing powder once again.

Racemic or enantiopure ethyl 1-benzyl-2,4-diphenyl-4,5-dihydro-1*H*-imidazole-5-carboxylate (Scheme 2) (6): Benzyl benzamide (200 mg, 0.95 mmol) and DCM (4 mL) were added to a 10-mL round-bottomed flask under argon. The round-bottomed flask was cooled to 0 °C and 2,6-lutidine (0.13 mL, 1.58 mmol) was added to the round-bottomed flask via a syringe. Oxalyl chloride (0.10 mL, 1.14 mmol) was added dropwise to the reaction solution over the course of 2 min. Carbon monoxide and carbon dioxide bubbled out of the solution and the reaction was stirred at 0 °C for 1.25 h. The DCM was removed under reduced pressure at room temperature to give a yellow solid. The round-bottomed flask was put under argon and hexane (4 mL) was added via a syringe. The solution was mixed for 1 h at room temperature. The salts were removed by vacuum filtration through a plug of Celite. The hexane was removed under reduced pressure at room temperature to give (*Z*)-*N*-benzylbenzimidoyl chloride **4**: oil; 175 mg; 80% yield. The product could not be purified any further due to rapid hydrolysis to benzyl benzamide with water from the air. To another 10 mL of RBF were added either racemic or enantiopure ethyl 3-phenylaziridine-2-carboxylate (100 mg, 0.52 mmol), TEA (0.44 mL, 3.12 mmol), DCM (6 mL), and (*Z*)-*N*-benzylbenzimidoyl chloride (143 mg, 0.62 mmol). The solution was heated to reflux for 5 h and then cooled to room temperature. The reaction solution was concentrated and the excess TEA was removed in vacuo to yield crude compound **5** and 1 equiv of $Et_3N\cdot$HCl. To crude compound **5** was added acetone (5 mL) and the solution was brought to reflux for 24 h. The reaction was worked up and purified by the general procedure for synthesis of imidazolines (located below): oil; 77 mg, 38% yield. Alternatively, the $Et_3N\cdot$HCl could be removed by the addition of ether (10 mL) and the solution was allowed to sit for 15 min. The solution was then filtered through Celite and concentrated in vacuo to yield compound **5**. To crude compound **5** were added NaI (78 mg, 0.52 mmol) and acetone (5 mL) and the solution was brought to reflux for 24 h. The reaction was worked up and purified by the general procedure for synthesis of imidazolines (located below): oil; 65 mg, 32% yield.

General Procedure for the Synthesis of Imidazolines. The reaction scale was based on 100 mg of the starting aziridine. To a 10-mL round-bottomed flask under argon were added the desired amide (1.2 equiv), 2,6-lutidine (6 equiv), and DCM (4 mL). The solution was either cooled to 0 °C or left at room temperature depending on the amide (located below). Oxalyl chloride (1.2 equiv) was added to the round-bottomed flask over 3 min with a syringe. The solution was reacted for the desired time (located below) and then the DCM was removed under reduced pressure at room temperature. This gave the crude product as a mixture of the desired imidoyl chloride, excess 2,6-lutidine (bp 144 °C, 760 mmHg), and 2,6-lutidine hydrogen chloride. This round-bottomed flask was then placed under argon again and the desired aziridine (100 mg, 1 equiv) and DMF (4 mL) were added. The solution was heated to 55 °C for the desired time (see Table 2 or 3). An aliquot of the reaction solution was taken and placed under vacuum (approximately 10 mmHg) at room temperature and a ^{1}H NMR was taken to determine the imidazoline reaction times. The reactions could also be monitored by TLC 30:70 EtOAc:hexane (imidazoline·HCl salt polar). The reaction solution was then cooled to room temperature and poured into a separatory funnel followed by an addition of equal volumes of sat. aq. $NaHCO_3$ and water. The product was extracted with EtOAC, and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The imidazolines were purified by column chromatography on silica gel. In some cases the silica gel had to be neutralized with TEA to avoid product decomposition.

Racemic or enantiopure ethyl 1-benzyl-2,4-diphenyl-4,5-dihydro-1*H*-imidazole-5-carboxylate (6): Either racemic or enantiopure ethyl 3-phenylaziridine-2-carboxylate was used. The imidoyl chloride reaction time was 1.25 h at 0 °C. The imidazoline reaction time was 6 h. Silica gel chromatography; 50:50 EtOAc:hexane; R_f 0.35; oil; 105 mg; 52% yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 0.8 (3H, t, J = 7.0 Hz), 3.3−3.4 (2H, m), 4.2 (1H, d, J = 15.5 Hz), 4.4 (1H, d, J = 12.0 Hz), 4.7 (1H, d, J = 15.5 Hz), 5.6 (1H, d, J = 12.0 Hz), 7.1−7.3 (10H, m), 7.4 (3H, m), 7.7 (2H, m); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 13.4 (CH_3), 49.9 (CH_2), 60.4 (CH_2), 67.0 (CH), 71.3 (CH), 127.3 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 128.0 (CH), 128.4 (CH), 128.6 (CH), 130.0 (CH), 130.5 (CH), 130.7 (C), 136.3 (C), 139.0 (C), 146.3 (C), 169.8 (C); IR (NaCl) 3075, 2980, 1738, 1496; HRMS calcd for $C_{25}H_{25}N_2O_2$ (M + H) 385.1916, found 385.1922.

Determination of Enantiomeric Excess of Compound 6 by (*S*)-Mosher's Acid. Racemic compound **6** and (*S*)-Mosher's acid were combined in equal molar quantities in an NMR tube along with $CDCl_3$. Analysis by ^{1}H NMR revealed that the (*S*,*R*,*R*) and the (*S*,*S*,*S*) diastereomeric salts were formed in a 50:50 mixture. Enantiopure compound **6** and (*S*)-Mosher's acid were combined in equal molar quantities in an NMR tube along with $CDCl_3$. Analysis by ^{1}HNMR revealed that only one of the (*S*,*S*,*S*) diastereomeric salt was detected. (*S*,*R*,*R*) diastereomeric salt: ^{1}H NMR (500 MHz) ($CDCl_3$) δ 0.78 (3H, t, J = 7.5 Hz), 3.34 (3H, s), 3.5−3.8 (2H, m), 4.33 (1H, d, J = 15.0 Hz), 4.62 (1H, d, J = 12.5 Hz), 4.94 (1H, d, J = 15.0 Hz), 5.86 (1H, d, J = 12.5 Hz), 7.2−7.9 (20H, m), 9.2 (1H, s, br). (*S*,*S*,*S*) diastereomeric salt: ^{1}H NMR (500 MHz) ($CDCl_3$) δ 0.79 (3H, t, J = 7.5 Hz), 3.35 (3H, s), 3.5−3.8 (2H, m), 4.34 (1H, d, J = 15.0 Hz), 4.64 (1H, d, J = 12.5 Hz), 4.95 (1H, d, J = 15.0 Hz), 5.90 (1H, d, J = 12.5 Hz), 7.2−7.9 (20H, m), 9.5 (1H, s, br).

1-Benzyl-2-(4-methoxyphenyl)-4,5-diphenyl-4,5-dihydro-1*H*-imidazole (9a): The imidoyl chloride reaction time was 1.25 h at 0 °C. The imidazoline reaction time was 9 h. Silica gel column chromatography; 50:50 EtOAc:hexane; R_f 0.4; oil, 126 mg; 59% yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 3.9 (3H, s), 4.0 (1H, d, J = 16.0 Hz),

4.4 (1H, d, J = 8.5 Hz), 4.8 (1H, d, J = 15.5 Hz), 5.0 (1H, d, J = 8.5 Hz), 68.0 (2H, dd, J_1 = 7.5 Hz, J_2 = 2.5 Hz), 7.1 (2H, d, J = 9.0 Hz), 7.2 (2H, d, J = 7.0 Hz), 7.4 (8H, m), 7.4−7.5 (3H, m), 7.8 (2H, d, J = 9.0 Hz); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 49.7 (CH_2), 55.2 (CH_3), 72.5 (CH), 76.5 (CH), 114.1 (CH), 122.3 (C), 126.5 (CH), 127.0 (CH), 127.1 (CH), 127.5 (CH), 127.8 (CH), 127.9 (CH), 128.4 (CH), 128.5 (CH), 128.8 (CH), 130.2 (CH), 136.0 (C), 141.2 (C), 143.3 (C), 161.3 (C), 165.7 (C); IR (NaCl) 3028, 2925, 1512; HRMS calcd for $C_{29}H_{27}N_2O$ (M + H) 419.2123, found 419.2123.

1-Benzyl-2,4,5-triphenyl-4,5-dihydro-1*H*-imidazole (9b): The imidoyl chloride reaction time was 1.25 h at 0 °C. The imidazoline reaction time was 9 h. Silica gel column chromatography; 50:50 EtOAc:hexane; R_f 0.4; oil; 109 mg; 55% yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 4.0 (1H, d, J = 15.5 Hz), 4.4 (1H, d, J = 8.5 Hz), 4.8 (1H, d, J = 15.5 Hz), 5.0 (1H, d, J = 8.5 Hz), 7.0 (2H, dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz), 7.1 (2H, dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz), 7.2−7.4 (11H, m), 7.5 (3H, m), 7.8−7.9 (2H, m); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 49.5 (CH_2), 72.5 (CH), 77.7 (CH), 126.6 (CH), 126.9 (CH), 127.0 (CH), 127.3 (CH), 127.6 (CH), 127.8 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 130.0 (CH), 131.1 (C), 136.2 (C), 141.6 (C), 143.7 (C), 165.8 (C); IR (NaCl) 3028, 2922, 1495; HRMS calcd for $C_{28}H_{25}N_2$ (M + H) 389.2023, found 389.2023.

1-Benzyl-2-(4-fluorophenyl)-4,5-diphenyl-4,5-dihydro-1*H*-imidazole (9c): The imidoyl chloride reaction time was 1.25 h at 0 °C. The imidazoline reaction time was 9 h. Silica gel column chromatography; 50:50 EtOAc:hexane; R_f 0.4; oil; 90 mg; 43% yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 4.1 (1H, d, J = 15.5 Hz), 4.4 (1H, d, J = 8.5 Hz), 4.7 (1H, d, J = 15.5 Hz), 5.0 (1H, d, J = 8.5 Hz), 7.0 (2H, dd, J_1 = 9.5 Hz, J_2 = 3.5 Hz), 7.1−7.4 (15H, m), 7.8−7.9 (2H, m); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 50.1 (CH_2), 73.1 (CH), 78.2 (CH), 116.2 (d, $^2J_{C/F}$ = 86.5 Hz) (CH), 127.0 (CH), 127.4 (CH), 127.5 (CH), 127.8 (d, $^4J_{C/F}$ = 17 Hz) (C), 127.9 (CH), 128.1 (CH), 128.2 (CH), 128.7 (CH), 128.9 (CH), 129.2 (CH), 131.0 (d, $^3J_{C/F}$ = 33 Hz) (CH), 136.6 (C), 142.1 (C), 144.1 (C), 163.1 (C), 165.1 (d, $^1J_{C/F}$ = 119.5 Hz) (C); IR (NaCl) 3030, 2957, 1512; HRMS calcd for $C_{28}H_{24}FN_2$ (M + H) 407.1929, found 407.1927.

1-Benzyl-2-cyclohexyl-4,5-diphenyl-4,5-dihydro-1*H*-imidazole (9e): The imidoyl chloride reaction time was 1.25 h at room temperature. The imidazoline reaction time was 6 h. Silica gel column chromatography; 50:50 EtOAc:hexane; R_f 0.35; oil; 122 mg; 60% yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 1.2−1.3 (3H, m), 1.7−1.8 (2H, m), 1.8−1.9 (3H, m), 2.0−2.1 (2H, m), 2.4−2.5 (1H, m), 3.9 (1H, d, J = 16.5 Hz), 4.2 (1H, d, J = 8.0 Hz), 4.6 (1H, d, J = 16.0 Hz), 4.8 (1H, d, J = 8.0 Hz), 7.0−7.4 (15H, m); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 26.0 (CH_2), 26.2 (CH_2), 26.4 (CH_2), 30.6 (CH_2), 31.9 (CH_2), 36.6 (CH), 47.2 (CH_2), 72.7 (CH), 76.8 (CH), 126.6 (CH), 126.9 (CH), 127.1 (CH), 127.1 (CH), 127.4 (CH), 127.7 (CH), 128.4 (CH), 128.6 (CH), 128.8 (CH), 137.0(C), 141.9 (C), 144.3 (C), 169.9 (C); IR (NaCl) 3028, 2928, 1495; HRMS calcd for $C_{28}H_{31}N_2$ (M + H) 395.2487, found 395.2494.

1-Benzyl-2-methyl-4,5-diphenyl-4,5-dihydro-1*H*-imidazole (9f): The imidoyl chloride reaction time was 1.25 h at 0 °C. The imidazoline reaction time was 9 h. Silica gel was neutralized with TEA by the general procedure. Silica gel chromatography; 40:55:5 EtOAc:hexane:TEA; R_f 0.4. oil; 81 mg; 48% yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 2.2 (3H, s), 3.9 (1H, d, J = 16.5 Hz), 4.3 (1H, d, J = 9.0 Hz), 4.5 (1H, d, J = 16.5 Hz), 4.8 (1H, d, J = 9.0 Hz), 7.1 (2H, d, J = 7.5 Hz), 7.1 (2H, m), 7.2−7.4 (11H, m); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 14.8 (CH_3), 47.8 (CH_2), 73.0 (CH), 77.3 (CH), 126.6 (CH), 126.9 (CH), 127.1 (CH), 127.3 (CH), 127.4 (CH), 127.7 (CH), 128.3 (CH), 128.6 (CH), 128.7 (CH), 136.7 (C), 141.0 (C), 143.6 (C), 162.9 (C); IR (NaCl) 3028, 2924, 1495; HRMS calcd for $C_{23}H_{23}N_2$ (M + H) 327.1861, found 327.1867.

1-(4-Methoxybenzyl)-2,4,5-triphenyl-4,5-dihydro-1*H*-imidazole (9h): The imidoyl chloride reaction time was 1.25 h at 0 °C. The imidazoline reaction time was 9 h. Silica gel chromatography; 50:50 EtOAc:hexane; R_f 0.4; solid; mp 110−112 °C; 114 mg; 53% yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 3.8 (3H, s), 3.9 (1H, d, J = 15.0 Hz), 4.4 (1H, d, J = 9.0 Hz), 4.7 (1H, d, J = 15.5 Hz), 5.0 (1H, d, J = 8.5 Hz), 6.8 (2H, dd, J_1 = 6.5 Hz, J_2 = 2.0 Hz), 6.9 (2H, dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz), 7.2 (2H, dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz), 7.2−7.4 (8H, m), 7.5 (3H, m), 7.8−7.9 (2H, m); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 49.1 (CH_2), 55.1 (CH_3), 72.4 (CH), 77.9 (CH), 113.8 (CH), 126.8 (CH), 126.9 (CH), 127.1 (CH), 127.7 (CH), 128.3 (CH), 128.3 (C), 128.6 (CH), 128.7 (CH), 128.8 (CH), 129.2 (CH), 130.0 (CH), 131.4 (C), 141.9 (C), 143.9 (C), 158.9 (C), 166.0 (C); IR (NaCl) 3028, 2928, 1512; HRMS calcd for $C_{29}H_{27}N_2O$ (M + H) 419.2123, found 419.2125.

1-Cyclohexyl-2,4,5-triphenyl-4,5-dihydro-1*H*-imidazole (9i): The imidoyl chloride reaction time was 3 h at room temperature. The imidazoline reaction time was 12 h. Silica gel column chromatography; 50:50 EtOAc:hexane; R_f 0.33; 104 mg; 53% yield; solid; mp 138−140 °C; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 0.7 (2H, m), 0.8−0.9 (2H, m), 1.3 (3H, m), 1.4−1.5 (3H, m), 3.4−3.5 (1H, m), 4.4 (1H, d, J = 7.0 Hz), 4.7 (1H, d, J = 7.0 Hz), 7.1 (4H, m), 7.3 (6H, m), 7.3 (3H, m), 7.7 (2H, m); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 25.5 (CH_2), 25.7 (CH_2), 26.3 (CH_2), 30.4 (CH_2), 33.8 (CH_2), 56.9 (CH), 70.1 (CH), 78.9 (CH), 126.4 (CH), 126.8 (CH), 127.4 (CH), 127.5 (CH), 128.7 (CH), 128.9 (CH), 129.0 (CH), 130.4 (CH), 132.2 (CH), 145.0 (C), 146.5 (C), 165.8 (C), 167.6 (C); IR (NaCl) 3028, 2933, 1451; HRMS calcd for $C_{27}H_{29}N_2$ (M + H) 381.2331, found 381.2330.

1-Methyl-2,4,5-triphenyl-4,5-dihydro-1*H*-imidazole (9j): The imidoyl chloride reaction time was 1.25 h at 0 °C. The imidazoline reaction time was 9 h. Silica gel chromatography; 50:50 EtOAc:hexane; R_f 0.35; solid; mp 86−88 °C; 96 mg; 60% yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 2.7 (3H, s), 4.3 (1H, d, J = 10.0 Hz), 5.0 (1H, d, J = 10.0 Hz), 7.3−7.4 (10H, m), 7.5 (3H, m), 7.7 (2H, m); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 35.0 (CH_3), 77.8 (CH), 78.6 (CH), 126.9 (CH), 127.1 (CH), 127.1 (CH), 127.8 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 128.9 (CH), 130.0 (CH), 131.3 (C), 141.9 (C), 144.1 (C), 167.0 (C); IR (NaCl) 3028, 2925, 1498; HRMS calcd for $C_{22}H_{21}N_2$ (M + H) 313.1705, found 313.1707.

Ethyl 1-benzyl-4-(4-methoxyphenyl)-2-phenyl-4,5-dihydro-1*H*-imidazole-5-carboxylate (11a): The imidoyl chloride reaction time was 1.25 h at 0 °C. The imidazoline reaction time was 10 h. Silica gel chromatography; 50:50 EtOAc:hexane; R_f 0.45; oil; 98 mg; 45% yield; ^{1}H NMR (500 MHz) $CDCl_3$: 1.3 (3H, t, J = 7.0 Hz), 3.9 (3H, s), 4.0 (1H, d, J = 16.0 Hz), 4.3 (2H, m), 4.6 (1H, d, J = 8.0 Hz), 4.6 (1H, d, J = 16.0 Hz), 4.9 (1H, d, J = 8.0 Hz), 6.9 (2H, m), 7.1 (2H, d J = 7.0 Hz), 7.2−7.3 (5H, m), 7.4−7.5 (3H, m), 7.7 (2H, m); ^{13}C NMR (500 MHz) ($CDCl_3$) δ 14.4 (CH_3), 40.0 (CH_2), 55.6 (CH_3), 61.5 (CH_2), 66.1 (CH), 76.0 (CH), 114.6 (CH), 127.7 (CH), 127.7 (CH), 128.7 (CH), 128.7 (CH), 128.9 (CH), 128.9 (CH), 130.6 (CH), 130.7 (C), 132.8 (C), 136.6 (C), 159.8 (C), 167.2 (C), 172.2 (C); IR (NaCl) 3031, 2934, 1734, 1512, 1249; HRMS calcd for $C_{26}H_{27}N_2O_3$ (M + H) 415.1977, found 415.2022.

Ethyl 1-benzyl-2,4-diphenyl-4,5-dihydro-1*H*-imidazole-5-carboxylate (11b): The imidoyl chloride reaction time was 1.25 h at 0 °C. The imidazoline reaction time was 12 h. Silica gel column chromatography; 50:50 EtOAc:hexane; R_f 0.4; solid; 78−80 °C; 85 mg; 42% yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 1.3 (3H, t, J = 7.0 Hz), 4.0 (1H, d, J = 7.5 Hz), 4.1−4.3 (2H, m), 4.4 (1H, d, J = 15.5 Hz), 4.6 (1H, d, J = 15.5 Hz), 5.3 (1H, d, J = 7.5 Hz), 7.1 (2H, dd, J_1 = 6.0 Hz, J_2 = 1.5 Hz), 7.2−7.3 (10H, m), 7.5 (3H, m), 7.8 (2H, m); ^{13}C NMR and DEPT (500 MHz) ($CDCl_3$) δ 14.1 (CH_3), 51.3 (CH_2), 61.3 (CH_2), 69.9 (CH), 72.3 (CH), 126.6 (CH), 127.3 (CH), 127.7 (CH), 127.9 (CH), 128.4 (CH), 128.57 (CH), 128.58 (CH), 128.8 (CH), 130.3

(CH), 130.6 (C), 136.3 (C), 143.2 (C), 165.8 (C), 172.1 (C); IR (NaCl) 3030, 2980, 1734, 1497; HRMS calcd for $C_{25}H_{25}N_2O_2$ (M + H) 385.2023, found 385.2027.

Ethyl 1-benzyl-5-methyl-2,4-diphenyl-4,5-dihydro-1*H*-imidazole-5-carboxylate (11c): The imidoyl chloride reaction time was 1.25 h at 0 °C. The imidazoline reaction time was 12 h. Silica gel column chromatography; 50:50 EtOAc:hexane; R_f 0.3; solid; mp 100−102 °C; 125 mg; 59% yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 1.0 (3H, s), 1.3 (3H, t, J = 7.0 Hz), 4.2 (2H, q, J = 7.0 Hz), 4.3 (1H, d, J = 17.5 Hz), 4.6 (1H, d, J = 17.5 Hz), 5.5 (1H, s), 7.2−7.4 (13H, m), 7.6 (2H, m); ^{13}C NMR and DEPT (500 MHz) ($CDCl_3$) δ (one CH carbon not found) 14.4 (CH_3), 18.4 (CH_3), 48.4 (CH_2), 61.9 (CH_2), 73.7 (CH), 75.8 (C), 127.0 (CH), 127.3 (CH), 127.9 (CH), 128.3 (CH), 128.5 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 130.1 (CH), 131.6 (C), 138.4 (C), 139.3 (C), 167.0 (C), 175.2 (C); IR (NaCl) 3029, 2988, 1732, 1454; HRMS calcd for $C_{29}H_{27}N_2$ (M + H) 403.2174, found 403.2185.

Ethyl 1-benzyl-4-(4-nitrophenyl)-2-phenyl-4,5-dihydro-1*H*-imidazole-5-carboxylate (11d): The imidoyl chloride reaction time was 1.25 h at 0 °C. The imidazoline reaction time was 13 h. Silica gel column chromatography; 40:60 EtOAc:hexane; R_f 0.29; oil; 30 mg; 13% yield; the regiochemistry was confirmed by NOESY; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 1.3 (3H, t, J = 7.5 Hz), 3.9 (1H, d, J = 7.5 Hz), 4.2−4.4 (2H, m), 4.4 (1H, d, J = 15.0 Hz), 4.7 (1H, d, J = 15.5 Hz), 5.4 (1H, d, J = 7.5 Hz), 7.0 (2H, m), 7.2 (3H, m), 7.4 (2H, d, J = 8.5 Hz), 7.5 (3H, m), 7.8 (2H, m), 8.2 (2H, d, J = 9.0 Hz); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 14.5 (CH_3), 51.5 (CH_2), 62.0 (CH_2), 69.3 (CH), 71.5 (CH), 124.0 (CH), 127.8 (CH), 128.2 (CH), 128.3 (CH), 129.0 (CH), 129.0 (CH), 129.1 (CH), 130.4 (C), 131.0 (CH), 136.1 (C), 147.5 (C), 150.8 (C), 167.1 (C), 171.8 (C); IR (NaCl) 3028, 2918, 1734, 1523, 1350; HRMS calcd for $C_{25}H_{24}N_3O_4$ (M + H) 430.1767, found 430.1780.

Ethyl 1-benzyl-5-(4-nitrophenyl)-2-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (11d): Silica gel column chromatography; 40:60 EtOAc:hexane; R_f 0.2; oil; 60 mg; 27% yield; the regiochemistry was confirmed by NOESY; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 1.3 (3H, t, 7.0 Hz), 4.0 (1H, d, J = 15.5 Hz), 4.2−4.3 (2H, m), 4.5 (1H, d, J = 8.0 Hz), 4.6 (1H, d, J = 15.5 Hz), 5.0 (1H, d, J = 15.5 Hz), 7.0 (2H, dd, J_1 = 5.5 Hz, J_2 = 2.0 Hz), 7.2−7.3 (4H, m), 7.5 (4H, m), 7.7 (2H, m), 8.2 (2H, d, J = 9.0 Hz); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 14.2 (CH_3), 51.3 (CH_2), 61.8 (CH_2), 66.4 (CH), 76.5 (CH), 124.5 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.9 (CH), 129.0 (CH), 129.0 (CH), 130.3 (C), 131.0 (CH), 135.8 (C), 147.9 (C), 148.7 (C), 167.8 (C), 171.6 (C); IR (NaCl) 3029, 2984, 1742, 1523, 1350; HRMS calcd for $C_{25}H_{24}N_3O_4$ (M + H) 430.1767, found 430.1780.

Ethyl 1-benzyl-2-phenyl-4-styryl-4,5-dihydro-1*H*-imidazole-5-carboxylate (11e): The imidoyl chloride reaction time was 1.25 h at 0 °C. The imidazoline reaction time was 20 h. The silica gel was neutralized by the general method. Silica gel column chromatography; 40:60 EtOAc:hexane; R_f 0.48; oil; 92 mg; 41% yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 1.2 (3H, t, J = 7.0 Hz), 4.1−4.2 (2H, m), 4.2 (1H, d, J = 17.0 Hz), 4.5 (1H, d, J = 0.5 Hz), 4.5 (1H, d, J = 0.5 Hz), 4.5 (1H, d, J = 16.0 Hz), 6.1 (1H, m), 6.4 (1H, d, J = 16.0 Hz), 7.1 (2H, d, J = 5.0 Hz), 7.2−7.4 (11H, m), 7.6 (2H, m); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 14.4 (CH_3), 49.5 (CH_2), 61.6 (CH_2), 66.4 (CH), 77.1 (CH), 126.9 (CH), 127.7 (CH), 127.7 (CH), 127.8 (CH), 128.3 (CH), 128.8 (CH), 128.8 (CH), 128.9 (CH), 128.9 (CH), 130.5 (CH), 130.8 (C), 134.1 (CH), 136.4 (C), 137.1 (C), 167.4 (C), 172.1 (C); IR (NaCl) 3154, 2984, 1733, 1469, 1381; HRMS calcd for $C_{27}H_{27}N_2O_2$ (M + H) 411.2073, found 411.2086.

Ethyl 1-benzyl-4-hexyl-2-phenyl-4,5-dihydro-1*H*-imidazole-5-carboxylate (11f): The imidoyl chloride reaction time was 1.25 h at 0 °C. The imidazoline reaction time was 12 h. Silica gel chromatography; 50:50 EtOAc:hexane; R_f 0.4; oil; 86 mg; 40% yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 0.9 (3H, t, J = 6.5 Hz), 1.3 (3H, t, J = 7.0 Hz), 1.3−1.4 (8H, m), 1.5−1.6 (1H, m), 1.6−1.7 (1H, m), 3.7 (1H, d, J = 7.0 Hz), 4.1 (1H, m), 4.1−4.3 (2H, m), 4.3 (1H, d, J = 15.5 Hz), 4.6 (1H, d, J = 15.5 Hz), 7.1 (2H, d, J = 7.0 Hz), 7.3 (3H, m), 7.4 (3H, m), 7.7 (2H, m); ^{13}C NMR and DEPT (500 MHz) ($CDCl_3$) δ 14.1 (CH_3), 14.2 (CH_3), 22.6 (CH_2), 25.0 (CH_2), 29.1 (CH_2), 31.7 (CH_2), 36.8 (CH_2), 51.0 (CH_2), 61.1 (CH_2), 66.8 (CH), 69.8 (CH), 127.7 (CH), 127.9 (CH), 128.6 (CH), 128.6 (CH), 128.7 (CH), 130.1 (CH), 130.7 (C), 136.7 (C), 164.7 (C), 172.6 (C); IR (NaCl) 3029, 2928, 1734, 1469, 1381; HRMS calcd for $C_{25}H_{33}N_2O_2$ (M + H) 393.2542, found 393.2548.

1-Benzyl-2,4-diphenyl-4,5-dihydro-1*H*-imidazol-5-yl)(phenyl)-methanone (11g): The imidoyl chloride reaction time was 1.25 h at 0 °C. The imidazoline reaction time was 12 h. Silica gel chromatorgraphy; 50:50 EtOAc:hexane; R_f 0.45; oil; 85 mg; 41% yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 4.3 (1H, d, J = 15.5 Hz), 4.7 (1H, d, J = 15.5 Hz), 4.9 (1H, d, J = 6.5 Hz), 5.1 (1H, d, J = 6.5 Hz), 7.1 (2H, m), 7.2 (2H, m), 7.2−7.4 (6H, m), 7.4 (2H, m), 7.5 (3H, m), 7.6 (1H, m), 7.7 (2H, d, J = 8.0 Hz), 7.8 (2H, m); ^{13}C NMR and DEPT (500 MHz) ($CDCl_3$) δ 51.1 (CH_2), 73.2 (CH), 73.3 (CH), 127.3 (CH), 127.9 (CH), 128.0 (CH), 128.4 (CH), 128.8 (CH), 128.9 (CH), 128.9 (CH), 129.0 (CH), 129.0 (CH), 129.1 (CH), 130.6 (CH), 133.8 (CH), 135.0 (C), 136.7 (C), 143.0 (C), 165.8 (C), 166.3 (C), 197.7 (C); IR (NaCl) 3065, 2925, 1688, 1451; HRMS calcd for $C_{29}H_{25}N_2O$ (M + H) 417.1967, found 417.1960.

1,5-Dibenzyl-2,4-diphenyl-4,5-dihydro-1*H*-imidazole and 1,4-dibenzyl-2,5-diphenyl-4,5-dihydro-1*H*-imidazole (11h): The imidoyl chloride reaction time was 1.25 h at 0 °C. The imidazoline reaction time was 12 h. Silica gel chromatorgraphy; 50:50 EtOAc:hexane; R_f 0.45; oil; 87 mg; 41% yield; the compounds were isolated as an inseparable mixture of regioisomers (2:1 ratio). **Regioisomer 1**: ^{1}H NMR (500 MHz) ($CDCl_3$) δ 2.5 (1H, dd, J_1 = 8.5 Hz, J_2 = 5.5 Hz), 3.0 (1H, dd, J_1 = 8.0 Hz, J_2 = 6.0 Hz), 3.8 (1H, d, J = 16.0 Hz), 4.6 (1H, d, J = 11.0 Hz), 4.7 (1H, d, J = 16.0 Hz), 4.8 (1H, m), 6.8−7.9 (20H, m). **Regioisomer 2**: ^{1}H NMR (500 MHz) ($CDCl_3$) δ 2.3 (1H, dd, J_1 = 7.5 Hz, J_2 = 6.0 Hz), 2.7 (1H, dd, J_1 = 8.5 Hz, J_2 = 5.5 Hz), 3.6 (1H, d, J = 16.0 Hz), 4.1 (1H, m), 4.5 (1H, d, J = 16.0 Hz), 5.3 (1H, d, J = 10.5 Hz), 6.8−7.9 (20H, m). **Both Regioisomers**: ^{13}C NMR (500 MHz) ($CDCl_3$) δ 37.7, 39.0, 48.9, 51.3, 64.6, 66.9, 70.6, 72.8, 125.9, 126.4, 127.3, 127.7, 127.7, 127.8, 127.8, 127.8, 127.8, 128.1, 128.2, 128.2, 128.5, 128.6, 128.8, 128.8, 128.9, 128.9, 128.9, 129.1, 129.2, 129.4, 130.3, 130.6, 131.6, 131.7, 137.4, 137.8, 138.4, 139.3, 149.8, 140.0, 165.8, 167.7; IR (NaCl) 3028, 2918, 1616, 1595; HRMS calcd for $C_{26}H_{27}N_2O_2$ (M + H) 399.2073, found 399.2086.

■ ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures for all compounds synthesized, X-ray structure of compounds **9j** and **11c**, as well as all spectroscopy data. This material is available free of charge via the Internet at http://pubs.acs.org.

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