Multicomponent Synthesis of Highly Substituted Imidazolines via a Silicon Mediated 1,3-Dipolar Cycloaddition

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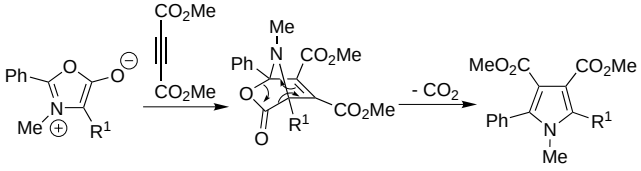
Abstract: A diastereoselective multicomponent synthesis of highly functionalized imidazolines is reported. A silicon mediated 1,3 dipolar cycloaddition of the in situ generated münchnone with an imine resulted in the formation of highly substituted imidazolines. The imidazolines contain a four-point diversity and two stereocenters and the cycloaddition reaction is applicable to aryl, alkyl, acyl, and heterocyclic substitutions.

Key words: imidazolines, 1,3-dipolar cycloaddition, diastereoselective, heterocycles, imidazoles

1,3-Dipolar cycloadditions are fundamental processes in organic chemistry for the synthesis of diverse heterocyclic compounds.[1–3] The reaction of azomethine ylides with various dipolarophiles results in highly substituted five-membered nitrogen heterocycles.[4–6] In addition to being versatile, it is also an atom economical process. Cycloaddition reactions of *N*-metalated acyclic azomethine ylides derived from glycine α-iminoesters and π-deficient alkenes affords substituted pyrrolidines with four stereogenic centers.[7,8] Achieving diastereoselectivity and enantioselectivity in this reaction is presently a field of intense scientific investigation.[9,10]

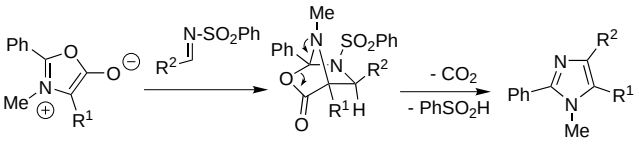
1,3-Dipolar cycloaddition reactions of *N*-methylated mesoionic oxazolones (Scheme 1), provides a general route for the syntheses of pyrroles, pyrrolines, azepines and imidazoles.[3,11–13] In the synthesis of pyrroles, the cycloaddition proceeds via a tautomerization of the parent azalactone to a mesoionic oxazolium 5-oxide, colloquially referred to as a 'münchnone'. The münchnone, undergoes a 1,3-dipolar cycloaddition with a suitable dipolarophile such as an acetylene (Scheme 1). A moderate equilibrium concentration of the mesoionic tautomer is essential for the 1,3-dipolar cycloaddition leading to heterocycle formation.[14] By *N*-methylation, the azalactones are locked in the mesoionic form, which is extremely reactive with dipoles and affords the pyrroles in very high yields.



Scheme 1

Synthesis 2003, No. 9, Print: 03 07 2003.
Art Id.1437-210X,E;2003,0,09,1433,1440,ftx,en;C01903SS.pdf.

Imidazoles can be generated by treatment of the münchnones with tosylimines. Addition of the tosylimines results in an unstable bicyclic adduct that loses carbon dioxide and benzenesulfinic acid to gain aromaticity.[12,15] The phenylsulfonyl leaving group enhances the tendency to aromatize (Scheme 2). Münchnones with different substituents, at the 2- and 4-positions lead regioselectively to products in which a bond is always formed between the 2-carbon atom of the dipole and the imine nitrogen atom. This attack was explained on the basis of a dipole–dipole interaction between partially negative nitrogen of the imine and the electrophilic C-2 atom of the münchnone. The yield reported for these reactions is low, at least partly due to self-condensation of münchnones.[12] The problem of self-condensation can be suppressed by using a solid-phase approach towards the preparation of imidazoles.[13] The münchnone generated on solid phase was condensed with tosylamines to afford the imidazoles in good yields and purities.

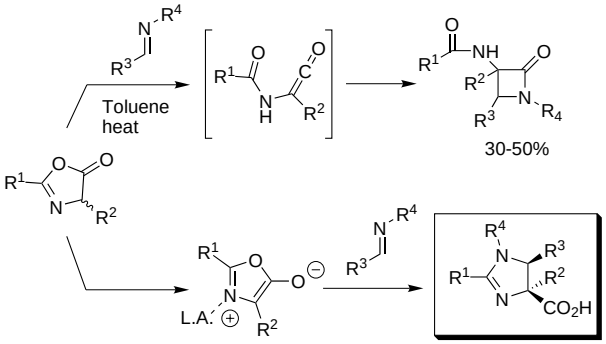


Scheme 2

Surprisingly, the utilization of oxazolones (or azalactones) has been underutilized as an efficient entry into a stereoselective synthesis of imidazolines. We have recently reported a highly diastereoselective multicomponent one-pot synthesis of substituted imidazolines.[16] These low molecular weight scaffolds contain a four point diversity applicable to alkyl, aryl, acyl, and heterocyclic substitutions. In light of the usefulness of a stereocontrolled synthesis of imidazolines for the preparation of α,β-diamino acids,[17] diaminocarbene catalysts,[18–21] peptide bond mimicks [22] and other synthetic intermediates,[23–28] we report herein the range and limitations of this extension of the 1,3-dipolar cycloaddition reaction.

It has been well documented that azalactones undergo a Staudinger-type reaction when heated with imines in toluene, yielding β-lactams.[29–31] The azalactone, which is in equilibrium with valence tautomeric ketene intermediate, undergoes a [2+2]-cycloaddition reaction with the imine (Scheme 3). It can be concluded that either mesoionic oxazolium oxide, which has the nitrogen atom unsubstituted, is not in reasonable concentration and/or the imine nitrogen is not nucleophilic enough. Hence formation of

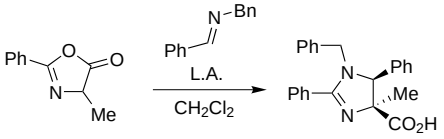
ketene is predominant, which reacts readily with the imines to afford the β-lactam.[29–31] We envisioned that a Lewis acid coordination to nitrogen of the azalactone, would increase the equilibrium concentration of münchnone intermediate and mediate the azomethine ylide-imine cycloaddition reaction (Scheme 3).



Scheme 3

After screening a small number of Lewis acids, we found that TMSCl promotes the reaction of oxazolones and imines to afford the imidazoline scaffold in very good yields and in most cases as single diastereomers (Table 1).[16] The oxazolones were prepared from different *N*-acyl α-amino acids by EDCI-mediated dehydration to provide the pure oxazolones in high yields.[32]

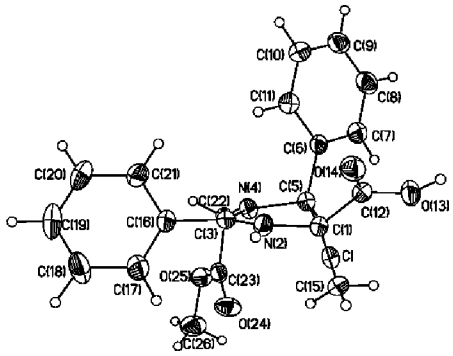
Table 1 Screening of Lewis Acids



LA	Yield (%)	LA	Yield (%)
$TiCl_4$	0	TMSCl	70
$SnCl_4$	0	TMSCl–Et_3N (1:1)	0
$ZnCl_2$	0	TMSCl–Et_3N (2 :1)	0
Et_2AlCl	0	TESCl	70
CuCl	0	PH_3SiCl	45
$B(OPh)_3$	0	CH_3COCl	55
AgOTf	0	CSA	0
YCl3	0	TMSOTf	0
Zr(*i*-PrO)$_4$	0		

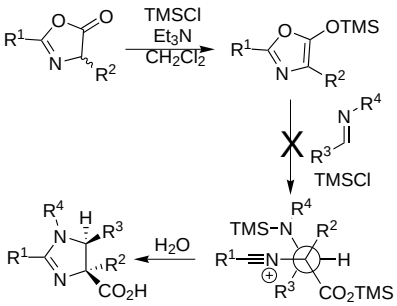
The cycloaddition reactions proceeded well with a wide variety of imines at slightly elevated temperatures to provide the highly substituted imidazolines in very good yields. Only the *trans* diastereomers (with respect to R^2 and R^3) of the imidazolines were observed in almost all cases, as determined by NOE experiments and X-ray crystallography (Figure 1).

While the complete mechanistic details of this process are still under investigation, the reaction does not seem to proceed via a ring-opened nitrilium ion intermediate (Scheme 4).[33] The possibility of a Michael-type addition via the formation of the nitrilium ion was investigated by first preparing the silyl enol ether with TMSCl (1.0 equiv) and TEA (1.0 equiv) followed by the addition of the imine and an additional one equivalent of TMSCl (Scheme 4). This resulted merely in isolation of starting materials.



Compound **2g** (Table 2)

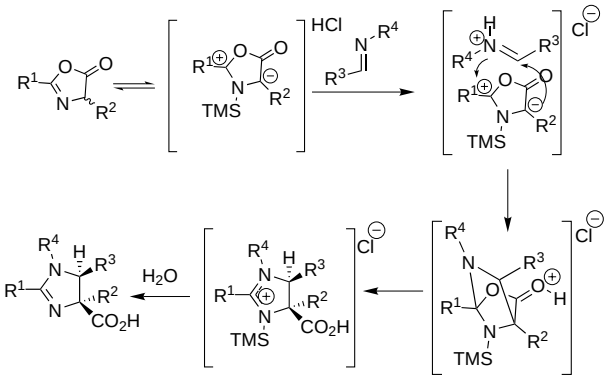
Figure 1



Scheme 4

Excess of triethylamine also halted the reaction suggesting that acidic conditions were required. However, Lewis acids such as $TiCl_4$ and $BF_3{\cdot}OEt_2$ or protic acids such as camphor sulfonic acid (CSA) and methyl sulfonic acid (MSA) did not promote product formation (Table 1). The absence of TMSCl resulted in the formation of β-lactams and *N*-acyl amino acid amide, presumably via the corresponding ketene intermediate (Scheme 3). *O*-Silylation with TMSOTf also did not result in any product formation. This indicates that a nucleophilic counterion is required to establish an equilibrium between O-silylation and N-silylation of the azalactone (Scheme 5). In light of these findings, we propose that the reaction proceeds via a 1,3-dipolar cycloaddition.

The generation of silicon mediated azomethine ylides has recently also been reported by Komatsu and co-workers.[34–36] The authors report the formation of an azomethine ylide after a 1,2-silatropic shift of α-silylimines resulting in the formation of pyrrolidines as a mixture of stereoisomers.

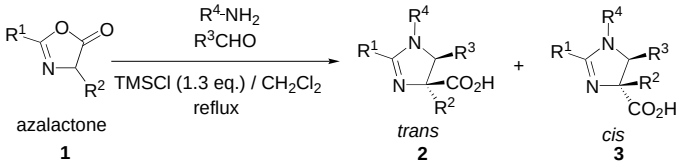


Scheme 5

Other silyl chlorides such as triphenyl silyl chloride and triethyl silyl chloride also provided the product as a single diastereomer, in notably longer reaction times and lower yields (Tables 1, 45% and 70%, respectively). Additional support of the proposed mechanism is shown in Scheme 5, we found that one equivalent of acetyl chloride resulted in the formation of the imidazoline as well, albeit in somewhat lower yields (Tables 1, 55%). A, range of structurally diverse imidazolines were prepared and are listed in Tables 2 and 3.

The diastereoselectivity appears to primarily arise from the steric interaction of the bulky silyl group of the azalactone and the R^3 moiety of the imine (Figure 2). This re-

Table 2 Diverse Range of Imidazolines Prepared



	R^1	R^2	R^3	R^4	Yield **1** (%)	Ratio **2:3**	Yield **2** (%)
a	Ph	Me	Ph	Bn	75	>95:5	75
b	Ph	Me	4-methoxyphenyl	Bn	75	>95:5	78
c	Ph	Me	Ph	4-fluorophenyl	75	>95:5	74
d	Ph	Me	4-pyridinyl	Bn	75	>95:5	76
e	Ph	Me	$-CO_2Et$	4-fluorophenyl	75	>95:5	72
f	Ph	Me	Ph	benzhydryl	75	–	0
g	Ph	Me	Ph	$-CH_2CO_2Me$	75	>95:5	70
h	Ph	Me	Ph	$-CH(CH_3)CO_2Me$	75	>95:5	66
i	Ph	Me	Ph	$-CH_2CH_2CO_2Et$	75	75:25	51
j[a]	Ph	Me	Ph	Bn	75	–	75
k[a]	Ph	Me	4-pyridinyl	Bn	75	–	76
l[b]	Ph	Me	Ph	Bn	75	–	79
m[c]	Ph	Me	Ph	H	75	>95:5	71
n	Ph	Ph	Ph	Bn	70	>95:5	65
o	Ph	Ph	4-pyridinyl	Bn	70	>95:5	55
p	Ph	Ph	$-CO_2Et$	4-fluorophenyl	70	>95:5	68
q	Ph	indolyl-3-methyl	Ph	Bn	80	>95:5	68
r	Ph	$-CH_2CH_2CO_2Me$	Ph	Bn	69	>95:5	60
s	Ph	Ph	Ph	Bn	90	75:25	30
t	Bn	Me	Ph	Bn	76	67:33	n.o.[d]
u	Bn	Me	Ph	Bn	60	50:50	n.o.

[a] Derivative **j** is the ethyl ester of **2a** and derivative **k** is the ethyl ester of **2d**; isolated yields after esterification with $(COCl)_2$, EtOH.
[b] Isolated yield after reduction of **2a** with $LiAlH_4$.
[c] Isolated yield after hydrogenation of **2a** with 10% Pd/C , H_2.
[d] n.o. = not optimized.

sults in the imine approaching from one direction of the racemic azalactone resulting in the *trans*-isomer as the major/sole product. The electronic effects of the R^1 position also appear to play a significant role in the reactivity of the azalactone as well as the diastereoselectivity of the reaction. Reducing the resonance of the stabilized carbocation of the dipolarophile by changing R^1 from a phenyl to a methyl or benzyl group resulted in a significant decrease in diastereoselectivity (Table 3). The more reactive and unstable methyl-azalactone provided a 1:1 mixture of the *cis*- and *trans*-products. No reactions were found in which the *cis*-product was the major product.

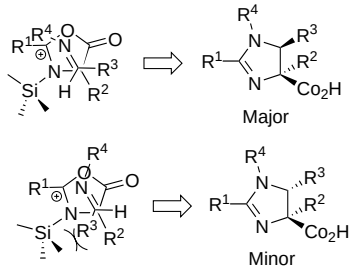


Figure 2

Table 3 Analytical Data

Compound	IR (cm^{-1})	^1H NMR (300 MHz), δ	^{13}C NMR (75 MHz), δ
2a	3350, 1738	1.80 (3 H, s), 4.05 (1 H, d, *J* = 15 Hz), 4.95 (1 H, d, *J* = 14.8 Hz), 5.05 (1 H, s), 7.05 (2 H, s), 7.25–7.54 (8 H, m), 7.74 (2 H, t, *J* = 7.2 Hz), 7.83 (1 H, t, *J* = 6.9 Hz), 8.0 (2 H,d, *J* = 8.4 Hz)[a]	25.2, 48.8, 70.4, 73.3, 122.3, 127.8, 128.3, 128.5, 128.9, 129.1, 129.3, 129.6, 129.7, 132.3, 133.2, 134, 166.1, 169.5[a]
2b	3388, 1738	1.80 (3 H, s), 3.80 (3 H, s), 3.95 (1 H, d, *J* = 15.3 Hz), 4.5 (1 H, s), 4.9 (1 H, d, *J* = 15 Hz), 6.83–6.92 (4 H, m), 7.08–7.19 (3 H, m), 7.30–7.40 (3 H, dd, J_1 = 5.1 Hz, J_2 = 1.8 Hz), 7.54–7.62 (2 H, t, *J* = 7.2 Hz), 762–7.68 (1 H, t, *J* = 7.2 Hz), 7.9 (2 H, d, *J* = 6.9 Hz)[b]	25.3, 48.8, 55.6, 70.9, 74.1, 115.2, 122.2, 123, 125.5, 127.9, 128.4, 129.2, 129.3, 129.6, 129.9, 132.8, 134.2, 161.1, 166.3, 168.4[c]
2c	3450, 1744	1.98 (3 H, s), 5.98 (1 H, s), 7.05–7.65 (14 H, m)[a]	25.2, 71.2, 77.9, 116.9, 117, 117.1, 117.3, 123, 125.1, 125.3, 129.3, 129.4, 129.6, 130.1, 130.3, 130.4, 130.5, 132.5, 133.3, 134.5, 160.4, 163.7, 165.3, 170.4[a]
2d	3400, 1746	1.80 (3 H, s), 4.24 (1 H, d, *J* = 15.9 Hz), 4.90 (1 H, d, *J* = 14.8 Hz), 5.15 (1 H, s), 7.00–7.15 (2 H, m), 7.25–7.35 (3 H, m), 7.40–7.50 (2 H, m), 7.70–7.90 (3 H, m), 7.95–8.05 (2 H, m), 8.6–8.7 (2 H, m)[a]	25.1, 49.1, 70.6, 71.7, 122.1, 123, 127.9, 128.4, 128.8,129.2, 129.4, 132.8, 133.9, 141.4, 149.8, 166.5, 169.05[a]
2e	3450, 1743	1.20 (3 H, t, *J* = 7.2 Hz), 2.03 (3 H, s), 4.9 (2 H, dq, J_1 = 7.2 Hz, J_2 = 2.1 Hz), 5.48 (1 H, s), 7.10–7.80 (9 H, m)[c]	12.8, 24.2, 62.9, 69.1, 75.1, 116.7, 116.9, 121.8, 129.3, 129.5, 129.6, 129.7, 131.5, 134.4, 162.1, 164.0, 166.2, 169.9[c]
2g	3468, 1747	1.99 (3 H, s), 3.67 (3 H, s), 3.96 (1 H, d, *J* = 18.3 Hz), 4.53 (1 H, d, *J* = 18.3 Hz), 5.39 (1 H, s), 7.47–7.50 (5 H, m), 7.74–7.87 (5 H, m)[c]	24.23, 52.09, 70.83, 75.38, 121.84, 128.26, 128.69, 129.52, 129.75, 131.78, 134.02, 167.59, 168.62, 169.19[c]
2h	3431, 1740	1.19 (d, *J* = 6.9, 3 H), 2.06 (s, 3 H), 3.38 (s, 3 H), 4.89 (q, *J* = 6.9, 1 H), 5.44 (s, 1 H), 7.43–7.46 (5 H, m), 7.75–7.85 (5 H, m).	14.9, 25.6, 52.7, 56.7, 71.9, 72.5, 122.2, 128.8, 128.9, 129.6, 130.0, 134.5, 135.8, 169.2, 169.4, 170.4[c]
2i	3481, 1743	1.17 (3 H, t, *J* = 7.5, 3 H), 1.9 (3 H, s), 2.47–2.52 (1 H, m), 2.52–2.71 (1 H, m), 3.34–3.39 (1 H, m), 3.40–4.09 (3 H, m), 5.42 (1 H, s), 7.46–7.49 (5 H, m,), 7.72–7.87 (5 H, m)[d]	13.3, 24.8, 30.6, 41.6, 61.0, 70.9, 73.5, 122.7, 128.9, 129.2, 129.8, 130.1, 132.7, 134.0, 167.3, 169.8, 170.9[c]
2j[f]	1730, 1595	0.84 (3 H, t, *J* = 7.2 Hz), 1.57 (3 H, s), 3.60 (2 H, q, *J* = 7.2 Hz), 3.85 (1 H, d, *J* = 15.3 Hz), 4.32 (1 H, s), 4.74 (1 H, d, *J* = 15.3 Hz), 6.98 (2 H, dd, J_1 = 6.9 Hz, J_2 = 2.1 Hz), 7.27–7.35 (m, 8 H), 7.49–7.51 (2 H, m), 7.76–7.79 (2 H, m)[d]	13.80, 27.13, 49.12, 60.06, 71.31, 127.98, 128.03, 128.12, 128.67, 129.02, 129.11, 130.96, 136.40, 136.80, 166.11, 171.78[d]
2k[g]	1734, 1597	0.86 (3 H, t, *J* = 7.2 Hz), 1.57 (3 H, s), 3.64 (2 H, q, *J* = 7.2 Hz), 3.83 (1 H, d, *J* = 15.3 Hz), 4.27 (1 H, s), 4.77 (1 H, d, *J* = 15.3 Hz), 6.97 (2 H, dd, J_1 = 7.2 Hz, J_2 = 2.4 Hz), 7.22–7.54 (6 H, m), 7.31–7.54 (2 H, m), 7.78–7.81 (2 H, m), 8.59–8.61 (2 H, m)[d]	13.45, 27.13, 49.47, 60.83, 71.87, 77.94, 122.56, 127.79, 127.93, 128.55, 128.70, 130.21, 130.51, 135.82, 146.59, 149.75, 166.02, 171.37[d]

Table 3 Analytical Data (continued)

Compound	IR (cm^{-1})	^1H NMR (300 MHz), δ	^{13}C NMR (75 MHz), δ
2l[g]	3314	1.25 (3 H, s), 3.48 (1 H, d, *J* = 12 Hz), 3.56 (1 H, d, *J* = 11.8), 3.75 (1 H, d, 12.9), 3.87 (s, 1 H), 3.94 (1 H, d, *J* = 12.9), 7.28–7.54 (m, 13 H), 7.77–7.79 (m, 2 H), 8.06 (1 H, br s)[b]	17.25, 51.67, 61.54, 66.28, 66.93, 127.266, 127.68, 128.26, 128.56, 128.82, 129.06, 131.77, 135.48, 138.03, 139.90, 167.91[d]
2m	3300, 1736	1.76 (s, 3 H), 5.34 (s, 1 H), 7.34–7.36 (br, 5 H), 7.69 (2 H, dd, *J* = 8.1, 7.2 Hz), 7.81 (1 H, dd, J_1 = 6.9 Hz, J_2 = 7.2 Hz), 8.15 (2 H, d, *J* = 8.4 Hz)[c]	25.32, 55.66, 70.79, 72.57, 123.12, 128.24, 128.96, 129.42, 129.67, 130.12, 135.42, 136.24, 164.24, 170.77[c]
2n	3400, 1738	3.80 (1 H, d, *J* = 15.6 Hz), 4.62 (1 H, d, *J* = 15.6 Hz), 4.98 (1 H, s), 6.58 (2 H, d, *J* = 8.1 Hz), 7.05–7.65 (16 H, m), 7.90 (2 H, d, *J* = 7.2 Hz)[d]	29.7, 48.3, 75.6, 79.1, 123.1, 125.7, 126.7, 127.3, 127.4, 127.9, 128.1, 128.2, 128.8, 128.9, 129, 129.3, 132.9, 133.8, 136, 143.1, 164.8, 168.1[d]
2o	3400, 1733	4.00 (1 H, d, *J* = 15.6 Hz), 5.00 (1 H, d, *J* = 15.6 Hz), 5.38 (1 H, s), 7.1–7.65 (17 H, m), 8.5 (2 H, d, *J* = 7.2 Hz)[d]	45.2, 66.3, 75.6, 123.7, 126.5, 126.9, 128.5, 128.6, 128.8, 129.2, 129.3, 131.9, 133.5, 134.4, 136.2, 143.4, 149.7, 166.6, 166.9[d]
2p	3331, 1736	0.84 (3 H, t, *J* = 7.2 Hz), 3.89 (2 H, dq, J_1 = 7.2 Hz, J_2 = 3 Hz), 4.73 (1 H, s), 6.70–6.84 (2 H, m), 6.89 (2 H, t, *J* = 9 Hz), 7.34–7.5 (3 H, m), 7.55 (3 H, t, *J* = 7.5 Hz), 7.65 (2 H, t, *J* = 8.1Hz), 7.83 (2 H, dd, J_1 = 8.1 Hz, J_2 = 2.1 Hz), 8.10–8.22 (2 H, m)[d]	13.3, 61.1, 66.1, 76.3, 115.3, 115.6, 117.3, 117.4, 125, 126.1, 128.2, 128.6, 133, 134.6, 142, 142.1, 155.7, 162.1, 169, 176.8[d]
2q	3420, 1741	3.95 (1 H, d, *J* = 16.2 Hz), 4.6 (1 H, d, *J* = 16.2 Hz), 5.25 (1 H, s), 6.1 (2 H, d, *J* = 7.8 Hz), 6.90–7.30 (5 H, m), 7.30–8.00 (15 H, m)[a]	32.3, 48.5, 70.4, 74.4, 105.8, 111, 119, 121.4, 122.7, 126.6, 126.7, 127.8, 127.9, 128.6, 128.7, 128.9, 129.4, 129.7, 132.3, 132.5, 133.7, 136.5, 166, 169.6[a]
2r	1734, 1653	2.05–2.25 (2 H, m), 2.30–2.50 (2 H, m), 3.55 (3 H, s), 4.38 (2 H, ddd, J_1 = 4 Hz, J_2 = 9 Hz, J_3 = 25 Hz), 4.86 (1 H, q, *J* = 3.3), 7.10–7.60 (12 H, m), 7.70–7.90 (4 H, m)[d]	27.6, 30.1, 43.3, 51.6, 52.7, 127.1, 127.2, 127.3, 128.2, 128.3, 131.5, 131.6, 133.3, 137.8, 167.5, 171.4, 173.6[d]
2s	3350, 1704	3.47 (2 H, d, *J* = 15.6 Hz), 4.31 (2 H, d, *J* = 15.6Hz), 5.80 (1 H, s), 6.40–7.40 (20 H, m)[a]	30.7, 47.5, 72.1, 100.2, 126.2, 126.6, 126.8, 127.3, 127.7, 127.9, 128.0, 128.5, 128.6, 129.0, 131.4, 132.5, 133.4, 136.4, 164.4, 171.6[a]
2t	3350, 1624	1.74 (3 H, s), 3.67 (1 H, d, *J* = 15.3 Hz), 4.11 (1 H, d, J = 14.7 Hz), 4.38 (1 H, s), 4.46 (1 H, d, *J* = 14.7 Hz) 4.59 (1 H, d, *J* = 15.3 Hz), 6.77 (2 H, d, *J* = 7 Hz), 7.00–7.60 (13 H, m)[d]	22.1, 32.4, 48.1, 70.6, 71.1, 127.6, 128.3, 128.6, 128.9, 129.1, 129.2, 129.7, 132.2, 132.8, 133.5, 164.8, 175.1[d]
3t	3350, 1738	1.14 (3 H, s), 3.94 (1 H, d, *J* = 15.6 Hz), 4.24 (2 H, q, *J* = 8.7 Hz), 4.56 (1 H, d, *J* = 15 Hz), 5.74 (1 H, s), 6.65 (2 H, d, *J* = 7.5 Hz), 7.00–7.40 (13 H, m)[d]	27.1, 38.7, 48.6, 71.5, 73.5, 127.9, 128.3, 128.5, 128.7, 128.9, 129, 129.3, 129.4, 129.5, 129.8, 120.9, 132.2, 133.5, 134.2, 165.6, 170.6 [e]

[a] DMSO-d_6.
[b] $CDCl_3$ and 2 drops of DMSO-d_6.
[c] CD_3OD.
[d] $CDCl_3$.
[e] DMSO-d_6 –CD_3OD.
[f] Derivatives **j** and **k** are ethyl esters of **2a** and **2d**, respectively.
[g] Derivative **l** is an alcohol derived from **2a**.

Reactions were carried out in oven-dried glassware under nitrogen atmosphere, unless otherwise noted. All commercial reagents were used without further purification. All solvents were reagent grade. THF was freshly distilled from sodium/benzophenone under nitrogen. Toluene, CH_2Cl_2, and TMSCl were freshly distilled from CaH_2 under nitrogen. All reactions were magnetically stirred and monitored by TLC with Analtech 0.25 mm pre-coated silica gel plates. Column chromatography was carried out on silica gel 60 (230–400 mesh) supplied by EM Science. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Melting points were determined on a Mel-Temp (Laboratory devices) apparatus with a microscope attachment. Infrared spectra were recorded on a Nicolet IR/42 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini-300 spectrometer or a Varian VXR-500 spectrometer. Chemical shifts are reported relative to the residue peaks of the solvent $CDCl_3$ (δ 7.24 for ^1H and δ 77.0 for ^{13}C) and DMSO-d_6 (δ 2.49 for ^1H and δ 39.5 for ^{13}C). HRMS were obtained at the Mass Spectrometry Laboratory of the University of South Carolina, Department of Chemistry & Biochemistry with a Micromass VG-70S mass spectrometer. Gas chromatography/low-resolution mass spectra were recorded on a Hewlet–Packard 5890 Series II gas chromatograph connected to a TRIO-1 EI mass spectrometer. All chemicals were obtained from Aldrich Chemical Co. and used as received.

Synthesis of 2-Oxazolin-5-ones; General Procedure[32]

A solution of benzoyl amino acid (2 mmol) and EDCI (2 mmol) in CH_2Cl_2 (20 mL) was stirred (0 °C for 1 h for racemic compounds, 15 min for optically active compounds). The reaction mixture was washed successively with cold (containing ice) H_2O (10 mL), aq $NaHCO_3$ (10 mL), and H_2O (10 mL) The solution was dried over anhyd $MgSO_4$, filtered, and the solvent removed in vacuo to give the oxazolones as solids or oils.

***dl*-(4*S*,5*S*)-1-Benzyl-4-methyl-2,5-diphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylic Acid (2a)**

A solution of benzaldehyde (0.06 g, 0.57 mmol), benzylamine (0.061 g, 0.57 mmol) in anhyd CH_2Cl_2 (15 mL) was refluxed under nitrogen for 2 h. 2-Phenyl-4-methyl-4*H*-oxazolin-5-one (0.1 g, 0.57 mmol) and chlorotrimethylsilane (0.08 g, 0.74 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The solvent was evaporated under vacuum. The product was precipitated using CH_2Cl_2–hexanes (1:1); yield: 75% (0.155 g); white solid; mp 185–190 °C (dec.).

HRMS (EI): *m*/*z* calcd for $C_{24}H_{21}N_2O_2$ [M – H], 369.1603; found, 369.1610.

***dl*-(4S,5S)-1-Benzyl-5-(4-methoxyphenyl)-4-methyl-2-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylic Acid (2b)**

A solution of *p*-anisaldehyde (0.077 g, 0.57 mmol), benzylamine (0.061 g, 0.57 mmol) in anhyd CH_2Cl_2 (15 mL) was refluxed under nitrogen for 2 h. 2-Phenyl-4-methyl-4*H*-oxazolin-5-one (0.1 g, 0.57 mmol) and chlorotrimethylsilane (0.08 g, 0.74 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The reaction mixture was evaporated to dryness under vacuum. The product was precipitated using CH_2Cl_2–hexanes (1:1); yield: 78% (0.180); mp 205–208 °C (dec.).

HRMS (EI): *m*/*z* calcd for $C_{25}H_{23}N_2O_3$ [M – H], 399.1709; found, 399.1717.

***dl*-(4*S*,5*S*)-1-(4-Fluorophenyl)-4-methyl-2,5-diphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylic acid 2c**

A solution of benzaldehyde (0.060 g, 0.57 mmol), 4-fluoroaniline (0.063 g, 0.57 mmol) in anhyd CH_2Cl_2 (15 mL) was refluxed under nitrogen for 2 h. 2-Phenyl-4-methyl-4*H*-oxazolin-5-one (0.1 g, 0.57 mmol) and chlorotrimethylsilane (0.08 g, 0.74 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The reaction mixture was evaporated to dryness under vacuum. The product was precipitated using CH_2Cl_2–hexanes (1:1) to give the titled compound; yield: 74% (0.160 g); white solid; mp 230–232 °C.

HRMS (EI): *m*/*z* calcd for $C_{23}H_{18}FN_2O_2$ [M – H], 373.1352; found, 373.1359.

***dl*-(4*S*,5*S*)-1-Benzyl-4-methyl-2-phenyl-5-pyridin-4yl-4,5-dihydro-1*H*-imidazole-4-carboxylic Acid (2d)**

A solution of pyridin-4-carboxylaldehyde (0.061 g, 0.57 mmol), benzylamine (0.061 g, 0.57 mmol) in anhyd CH_2Cl_2 (15 mL) was refluxed under nitrogen for 2 h. 2-Phenyl-4-methyl-4*H*-oxazolin-5-one (0.1 g, 0.57 mmol) and chlorotrimethylsilane (0.08 g, 0.74 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The reaction mixture was evaporated to dryness under vacuum. The product was precipitated using EtOAc–MeOH (4:1); yield: 76% (0.161 g); off-white solid; mp 185–190 °C.

HRMS (EI): *m*/*z* calcd for $C_{23}H_{20}N_3O_2$ [M – H], 370.1556; found, 370.1556.

***dl*-(4*S*,5*S*)-1-(4-Fluorophenyl)-4-methyl-2-phenyl-4,5-dihydro-1*H*-imidazole-4,5-dicarboxylic acid 5-ethyl Ester (2e)**

A solution of ethyl glyoxalate (0.058 g, 0.57 mmol) as a 50% solution in toluene (1.03 gmL^{-1}), 4-fluoroaniline (0.063 g, 0.57 mmol) in anhyd CH_2Cl_2 (15 mL) was refluxed under nitrogen for 2 h. 2-Phenyl-4-methyl-4*H*-oxazolin-5-one (0.1 g, 0.57 mmol) and chlorotrimethylsilane (0.08 g, 0.74 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The reaction mixture was evaporated to dryness under vacuum. The product was purified by column chromatography on silica gel using EtOAc–MeOH (4:1); yield: 72% (0.152 g); white solid; mp 190–193 °C.

HRMS (EI): *m*/*z* calcd for $C_{20}H_{18}FN_2O_4$ [M – H], 369.1251; found, 369.1255.

***dl*-(4*S*,5*S*)-1-Methoxycarbonylmethyl-4-methyl-2,5-diphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylic Acid (2g)**

To a well stirred solution of 2-phenyl-4-methyl-4*H*-oxazolin-5-one (0.5 g, 2.85 mmol) and TMSCl (0.37 g, 3.42 mmol) in anhyd CH_2Cl_2 (50 mL) was added a solution of (benzylidene-amino)-acetic acid methyl ester (0.6 g, 3.42 mmol) in anhyd CH_2Cl_2 (20 mL) and the mixture was refluxed under nitrogen for 10 h and then stirred overnight at r.t. The reaction mixture was evaporated to dryness under vacuum. The product was precipitated using CH_2Cl_2–hexanes (1:1); yield: 70% (0.70 g); white solid; mp 215–217 °C (dec.)

HRMS (EI): *m*/*z* calcd for $C_{20}H_{21}N_2O_4$ [M + H] 352.1501, found, 353.1507.

***dl*-(4*S*,5*S*)-1-(1-Methoxycarbonyl-ethyl)-4-methyl-2,5-diphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylic Acid (2h)**

To a well stirred solution of 2-phenyl-4-methyl-4*H*-oxazolin-5-one (0.25 g, 1.5 mmol) and TMSCl (0.23 ml, 1.8 mmol) in anhyd CH_2Cl_2 (50 mL) added a solution of 2-(benzylidene-amino)-propionic acid methyl ester (0.34 g, 1.8 mmol) in anhyd CH_2Cl_2 (20 mL) and the mixture was refluxed under nitrogen for 10 h and then stirred overnight at r.t. The reaction mixture was evaporated to dryness under vacuum. The product was precipitated using CH_2Cl_2–hexanes (1:1); yield: 66% (0.340 g); white solid; mp 222–226 °C.

HRMS (EI): *m*/*z* calcd for $C_{21}H_{23}N_2O_4$ [M + H], 367.1658; found, 367.1642.

***dl*-(4*S*,5*S*)-1-(2-Ethoxycarbonyl-ethyl)-4-methyl-2,5-diphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylic Acid (2i)**

To a well stirred solution of 2-phenyl-4-dimethyl-4*H*-oxazolin-5-one (1.0 g, 5.7 mmol) and TMSCl (1 mL, 6.8 mmol) in anhyd CH_2Cl_2 (80 mL) added a solution of 3-(benzylidene-amino)-propionic acid ethyl ester (1.4 gm, 6.8 mmol) in anhyd CH_2Cl_2 (60 mL) and the mixture was refluxed under nitrogen for 10 h and then stirred overnight at r.t. The reaction mixture was evaporated to dryness under vacuum. The product was precipitated CH_2Cl_2–hexanes (1:1); yield: 51%; (1.08 g); mp 218–220 °C (dec.).

HRMS (EI): *m*/*z* calcd for $C_{22}H_{25}N_2O_4$ [M + H], 381.1814; found, 381.1813.

***dl*-(4*S*,5*S*)-1-Benzyl-4-methyl-2,5-diphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylic Acid Ethyl Ester (2j)**

To a well-stirred suspension of imidazoline-4-carboxylic acid **2a** (0.1 g, 0.27 mmol) in anhyd CH_2Cl_2 (30 mL) at 0°C was added a solution of oxalyl chloride (0.14 g, 1.1 mmol) in anhyd CH_2Cl_2 (5 mL). A solution of DMF (0.001 mL) in anhyd CH_2Cl_2 (1 mL) was added to the reaction mixture and the mixture was stirred at 0 °C for another 2 h. The CH_2Cl_2 was evaporated under vacuum and the reaction mixture cooled to 0 °C after which absolute EtOH (20 mL) was added. The solution was allowed to stir for an additional 1 h. The solvent was evaporated under vacuum and the reaction mixture

diluted with anhyd CH_2Cl_2 (30 mL) and washed with sat. $NaHCO_3$ (10 mL) and H_2O (10 mL). The organic layer was dried over Na_2SO_4 and was concentrated under vacuum to yield the crude product, which was further purified by silica-gel column chromatography (EtOAc); overall yield (2 steps from azlactone): 75% (0.095 g); colorless oil.

HRMS (EI): *m*/*z* calcd for $C_{26}H_{27}N_2O_2$, 399.2073; found, 399.2072

***dl*-(4*S*,5*S*)-1-Benzyl-4-methyl-2-phenyl-5-pyridin-4-yl-4,5-dihydro-1*H*-imidazole-4-carboxylic Acid Ethyl Ester (2k)**

To a well-stirred suspension of *dl*-(3*S*,4*S*)-1-benzyl-4-methyl-2-phenyl-5-pyridin-4yl-4,5-dihydro-1*H*-imidazole-4-carboxylic acid (**2d**) (0.1 g, 0.27 mmol) in anhyd CH_2Cl_2 (30 mL) at 0°C added a solution of oxalyl chloride (0.14 g, 1.1 mmol) in anhyd CH_2Cl_2 (5 mL). A solution of DMF (0.001 mL) in anhyd CH_2Cl_2 (1 mL) was added to the reaction mixture and was stirred at 0 °C for another 2 h. The CH_2Cl_2 was evaporated under vacuum and the reaction mixture cooled to 0 °C after which absolute EtOH (20 mL) was added. The solution was allowed to stir for an additional 1 h. The solvent was evaporated under vacuum and the reaction mixture diluted with CH_2Cl_2 (30 mL) and washed with sat.$NaHCO_3$ (10 mL) and H2O (10 mL). The organic layer was dried over $NaHSO_4$ and was concentrated under vacuum to yield the crude product, which was further purified by silica-gel column chromatography (ethyl acetate); overall yield (from azlactone): 76% (0.97 g); pale yellow oil.

HRMS (EI): *m*/*z* calcd for $C_{25}H_{27}N_3O_2$, 400.2025; found, 400.2038.

***dl*-(4S, 5S)-1-Benzyl-4-methyl-2,5-diphenyl-4,5-dihydro-1*H*-imidazol-4-yl)-methanol (2l)**

To a well stirred suspension of $LiAlH_4$ (0.12g, 0.3 mmol) in anhyd THF (5 mL) was added a solution of 1-benzyl-4-methyll-2,5-diphenyl-4,5-ihydro-1*H*-imidazole-4-carboxylic acid (0.1 gm, 0.27 mmol) in anhyd THF (5 mL) dropwise at 0 °C, the mixture was stirred at the same temperature for 15 min quenched with ice cold sat. NH_4Cl solution (**caution**: NH_4Cl solution kept at 0 °C for about 30 min.; and should be added with extreme care; highly exothermic reaction and the reaction mixture should be at 0 °C) followed by 10% HCl (ca 10 mL). The reaction mixture was diluted with an excess of EtOAc (100 mL) washed with H_2O (20 mL) dried over anhyd Na_2SO_4, filtered, and the solvent evaporated under reduced pressure to yield the crude product which was purified by column chromatography (EtOAc); overall yield (2 steps): 79% (0.076 g); viscous oil.

HRMS (FAB): *m*/*z* calcd for $C_{24}H_{25}N_2O$ [M + H], 357.1888; found, 357.1967.

***dl*-(4*S*,5*S*)-4-Methyl-2,5-diphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylic Acid (2m)**

To a well-stirred suspension of imidazoline-4-carboxylic acid **2a** (0.1 g, 0.27 mmol) and cyclohexene (0.1 mL, 1.25 mmol) in anhyd THF (30 mL) was added 10% Pd/C (45 mg, 0.06 mmol). The suspension was refluxed for 36 h. The reaction mixture cooled to r.t. and EtOH (10 mL) was added. The mixture was filtered through Celite, washed with EtOH, and the filtrate was evaporated under reduced pressure. The crude product was purified by column silica-gel chromatography (EtOH); overall yield: 71% (0.070 g); white solid; mp 222–224 °C (dec.).

HRMS (FAB): *m*/*z* calcd for $C_{17}H_{17}N_2O_2$ [M + H], 281.1212; found, 281.1289.

***dl*-(4*S*,5*S*)-1-Benzyl-2,4,5-triphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylic Acid (2n)**

A solution of benzaldehyde (0.6 g, 5.7 mmol), benzylamine (0.61 g, 5.7 mmol) in anhyd CH_2Cl_2 (120 mL) was refluxed under nitrogen for 2 h. 2,4-Diphenyl-4*H*-oxazolin-5-one (1.35 g, 5.7 mmol) and chlorotrimethylsilane (0.8 g, 7.4 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The product was purified by silica-gel column chromatography (EtOH–EtOAc, 1:5); yield: 65% (2.1 g); off-white solid; mp 153–155 °C.

HRMS (EI): *m*/*z* calcd for $C_{28}H_{23}N_2$ [(M – H) – CO_2], 387.1526; found, 387.1539.

***dl*-(4*S*,5*S*)- 1-Benzyl-2,4-diphenyl-5-pyridin-4-yl-4,5-dihydro-*1H*-imidazole-4-carboxylic Acid (2o)**

A solution of pyridin-4-carboxylaldehyde (0.61 g, 0.57 mmol), benzylamine (0.61 g, 5.7 mmol) in anhyd CH_2Cl_2 (120 mL) was refluxed under nitrogen for 2 h. 2,4-Diphenyl-4*H*-oxazolin-5-one (1.35 g, 5.7 mmol) and chlorotrimethylsilane (0.8 g, 7.4 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The product was precipitated using CH_2Cl_2–Et_2O; yield 55% (1.35 g); off-white solid.

MS (EI): *m*/*z* calcd for $C_{29}H_{24}FN_3O_2$ [M +H], 434.34186; found, 434.1852.

***dl*-(4*S*,5*S*)-1-(4-Fluorophenyl)-2,4-diphenyl-4,5-dihydro-1*H*-imidazole-4,5-dicarboxylic Acid 5-Ethyl Ester (2p)**

A solution of ethyl glyoxalate (0.85 g, 8.3 mmol) as 50% solution in toluene (1.03 g/mL), 4-fluoroaniline (0.93 g, 8.3 mmol) in anhyd CH_2Cl_2 (250 mL) was refluxed under nitrogen for 2 h. 2,4-Diphenyl-4*H*-oxazolin-5-one (2 g, 8.3 mmol) and chlorotrimethylsilane (1.16, 10.8 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The reaction mixture was evaporated to dryness under vacuum. The product was precipitated using CH_2Cl_2–Et_2O; yield: 68% (2.4 g); white solid.

HRMS (FAB): *m*/*z* calcd for $C_{25}H_{22}FN_2O_4$ [M + H], 433.1486; found: 433.1565.

***dl*-(4*S*,5*S*)-1-Benzyl-4-(1*H*-indol-3-ylmethyl)-2,5-diphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylic Acid (2q)**

A solution of benzaldehyde (0.6 g, 5.7 mmol), benzylamine (0.61 g, 5.7 mmol) in anhyd CH_2Cl_2 (120 mL) was refluxed under nitrogen for 2 h. 4-(1*H*-Indol-3-ylmethyl)-2-phenyl-4*H*-oxazol-5-one (1.65 g, 5.7 mmol) and chlorotrimethylsilane (0.8 g, 7.4 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The product was purified by column chromatography on silica gel EtOH–EtOAc (1:5); yield: 68% (3.1 g); off-white solid; mp >250 °C (dec.).

HRMS (EI): *m*/*z* calcd for $C_{32}H_{26}N_3O_2$ [M – H], 484.2025; found, 484.2011.

***dl*-(4*S*,5*S*)-1-Benzyl-4-(2-methoxycarbonyl-ethyl)-2,5-diphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylic Acid (2r)**

A solution of benzaldehyde (0.252 g, 2.4 mmol), benzylamine (0.258 g, 2.4 mmol) in anhyd CH_2Cl_2 (100 mL) was refluxed under nitrogen for 2 h. 3-(5-Oxo-2-phenyl-4,5-dihydro-oxazol-4-yl)-propionic acid methyl ester (**1e**) (0.5 g, 2 mmol) and chlorotrimethylsilane (0.282 g, 2.6 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The reaction mixture was evaporated to dryness under vacuum. The product was precipitated using CH_2Cl_2–hexanes (1:1); yield: 60% (0.54 g); white solid.

HRMS (FAB): *m*/*z* calcd for $C_{27}H_{27}N_2O_4$ [M + H], 443.1893; found, 443.1971.

***dl*-(4*S*,5*S*)-1,2-dibenzyl-4,5-diphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylic Acid (2s)**

A solution of benzaldehyde (0.6 g, 5.7 mmol), benzylamine (0.61 g, 5.7 mmol) in anhyd CH_2Cl_2 (120 mL) was refluxed under nitrogen for 2 h. 2-Benzyl-4-phenyl-4*H*-oxazolin-5-one (1.43 g, 5.7 mmol) and chlorotrimethylsilane (0.8 g, 7.4 mmol) were added and the

mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The product was a mixture of diastereomers (3:1 ratio); yield: 60%. The above *trans*-diastereomer was obtained by repeated precipitation from MeOH–Et_2O.

HRMS (FAB): *m*/*z* calcd for $C_{30}H_{27}N_2O_2$ [M + H] 447.2010; found, 447.2072.

_dl_-(4*S*,5*S*)-1,2-Dibenzyl-4-methyl-5-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylic Acid (2t) and _dl_-(4*S*,5*R*)-1,2-Dibenzyl-4-methyl-5-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylic Acid (3t)

A solution of benzaldehyde (1.13g, 10.58 mmol), benzylamine (1.13g, 10.58 mmol) in anhyd CH_2Cl_2 (250 mL) was refluxed under nitrogen for 2 h. 2-Benzyl-4-methyl-4*H*-oxazolin-5-one (2g, 10.58 mmol) and chlorotrimethylsilane (1.48 g, 10.58 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The reaction mixture was evaporated to dryness under vacuum. The product *cis*-isomer **3t** was precipitated using CH_2Cl_2–Et_2O; yield: 30% (0.6 g); white solid. The *trans*-isomer **2t** was then precipitated out from the mother liquor. A small amount was then reprecipitated to remove traces of **3t**; yield: 17% (0.15g).

2t

HRMS (FAB): *m*/*z* calcd for $C_{25}H_{25}N_2O_2$ [M + H], 385.1898; found, 385.1916.

3t

HRMS (FAB): *m*/*z* calcd for $C_{25}H_{25}N_2O_2$ [M + H], 385.1898; found, 385.1917.

Acknowledgment

The authors gratefully acknowledge financial support provided by Michigan State University and the Donors of the Petroleum Research Fund, administered by the American Chemical Society. In addition, the authors thank Huang Rui for obtaining the crystallographic data.

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