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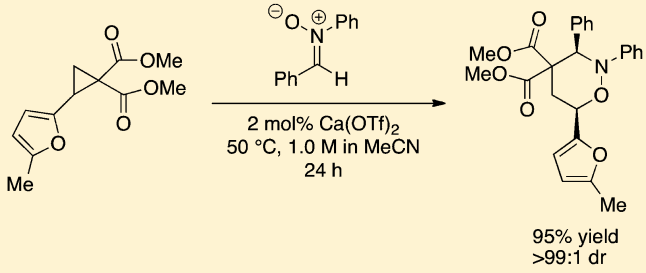
Diastereoselective 1,3-Dipolar Cycloaddition of Nitrones to Donor–Acceptor Cyclopropanes Catalyzed by a Calcium(II) Complex

Caroline M. Braun, Elizabeth A. Congdon, and Kristine A. Nolin*

University of Richmond, 28 Westhampton Way, Richmond, Virginia 23173, United States

Supporting Information

ABSTRACT: Calcium triflate has been identified as an efficient catalyst for the cycloaddition of nitrones to donor–acceptor cyclopropanes. The reaction proceeds with good to excellent yields of the corresponding tetrahydro-1,2-oxazines with high levels of diastereoselectivity. The generality of the reaction allowed for the synthesis of tetrahydro-1,2-oxazines bearing alkyl, aryl, and heteroaromatic substitution.



The stereoselective formation of heterocyclic compounds is fundamental to the development pharmaceuticals, as drug candidates frequently contain these motifs. One reliable method often employed to synthesize heterocyclic compounds is the use of a cycloaddition reaction. Cycloaddition reactions are broad in scope,[1] and in the past few decades, the methodology has expanded to include reactions of donor–acceptor (DA) cyclopropanes. DA cyclopropanes[2] have been shown to be versatile and reactive partners in cycloaddition reactions giving rise to numerous important heterocyclic structures including tetrahydrofuran,[3] pyrrolidines,[4] isoxazolidines,[5] tetrahydrocarbazoles,[6] dihydroquinolines,[7] triazinines, and azetidines.[8] Johnson and co-workers have shown that Sn(II) complexes are highly effective at catalyzing the cycloaddition of aldehydes to DA cyclopropanes.[9] Stoltz and co-workers have reported [3 + 2]-cycloadditions with heterocumulenes using stoichiometric amounts of Sn or Fe.[10] Catalytic $Yb(OTf)_3$ was used to facilitate [4 + 3]-cycloadditions[11] of DA cyclopropanes with 1,3-diphenylisobenzofuran.

Previous work in our laboratory demonstrated the ability of calcium(II) complexes to activate DA cyclopropanes.[12] Herein, we describe the expansion of this reactivity to the calcium-catalyzed 1,3-dipolar cycloaddition of nitrones and DA cyclopropanes, producing tetrahydro-1,2-oxazines. These motifs are present in a number of biologically active compounds including (+)-phyllantidine, a *Securinega* alkaloid.[13] Unlike many metals commonly used in synthetic methodologies, calcium complexes are relatively inexpensive and many are environmentally benign. The large radii and electropositive nature of the heavier alkaline earth metals (including Ca) lead to a similarity in coordination behavior and observed reactivity to lanthanide metals. In particular, the similarity of Ca^{2+} and Yb^{2+} complexes has been reported.[14] Catalytic methods for this cycloaddition have been previously reported including those by the Sibi,[15] Kerr,[16] and Tang[17] groups utilizing Ni(II) and Yb(III) complexes to facilitate the reactivity.[18]

Our experiments began with screening a selection of commercially available calcium(II) complexes as potential catalysts in the cycloaddition of cyclopropane **1** with *N*-methyl nitrone **2** (Table 1, entries 1–6). Trace reactivity was observed with calcium iodide and calcium stearate, and single turnover was observed with calcium neodecanoate. Calcium triflate ($Ca(OTf)_2$) was identified as a robust catalyst for the cycloaddition at 70 °C in toluene (entry 6). A study of dry solvents led to the identification of acetonitrile as the optimal solvent for the cycloaddition (entries 7–12).[19] Catalyst loadings as low as 2 mol % were capable of driving the reaction to full conversion without extending reaction times. Using these conditions, the scope of the reaction of nitrone **2** with various DA cyclopropanes was explored.

Cyclopropane **1** was reacted with *N*-methyl nitrone **2** under the optimized reaction conditions, in the presence 2 mol % of calcium triflate at 70 °C for 24 h. Tetrahydro-1,2-oxazine **3** was isolated in 94% yield with a 3:1 excess of the cis diastereomer (Table 2, entry 1).[16] The scope of the reaction was probed by changing the aromatic substituent on the cyclopropane. The aromatic substitution was varied to incorporate electron-donating and -withdrawing groups (Table 2, entries 2–4). The reaction of these cyclopropanes produced the corresponding tetrahydro-1,2-oxazines **5a–c**, in high yield (83–92%) with a consistent 3:1 diastereoselectivity in favor of the cis isomer.

With consistent diastereoselectivity observed for the reaction of *N*-methyl nitrone **2**, the effect of the substituents on the nitrone was examined. First, the reactivity of *N*-phenyl nitrone **7** with cyclopropane **1** was investigated. A brief optimization revealed that these reactions could be run at lower temperatures with high levels of reactivity. *N*-Phenyl nitrone **7** was

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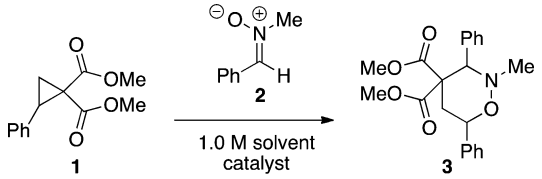
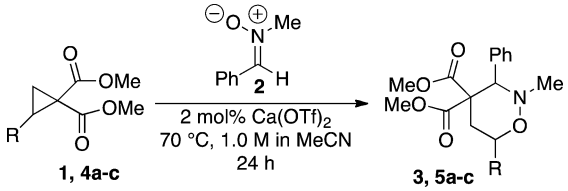
Table 1. Reaction Optimization

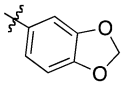


entry	solvent	equiv of **2**[a]	catalyst	catalyst loading (%)	temp (°C)	conversion (%)[b]
1	toluene	1.5	$Ca(acac)_2$	10	90	0
2	toluene	1.5	$Ca(OMe)_2$	10	90	0
3	toluene	1.5	$Ca(OAc)_2$	10	90	0
4	toluene	1.5	CaI_2	10	90	trace
5	toluene	1.5	$Ca(neodec)_2$	10	70	11
6	toluene	1.5	$Ca(OTf)_2$	10	70	100
7	toluene	1.2	$Ca(OTf)_2$	10	70	83
8	DCE	1.2	$Ca(OTf)_2$	10	70	86
9	CPME	1.2	$Ca(OTf)_2$	10	70	87
10	2-MeTHF	1.2	$Ca(OTf)_2$	10	70	86
11	BuOAc	1.2	$Ca(OTf)_2$	10	70	69
12	MeCN	1.2	$Ca(OTf)_2$	10	70	100
13	MeCN	1.2	$Ca(OTf)_2$	2	70	100

[a]Reactions were run with 0.3 mmol of **1** in dry solvents for 19−24 h. [b]Conversions were determined by ^{1}H NMR.

Table 2. Addition of *N*-Methyl Nitrone to DA Cyclopropanes



entry	R		yield (%)	*cis:trans*
1	Ph	**3**	94	3:1
2	4-OMePh	**5a**	86	3:1
3	4-ClPh	**5b**	83	3:1
4		**5c**	92	3:1

reacted with **1** in acetonitrile at 50 °C in the presence of 2 mol % of $Ca(OTf)_2$. Tetrahydro-1,2-oxazine **8** was isolated in 94% yield with 66:1 selectivity for the cis diastereomer (Scheme 1).[15] Next, differentially substituted aryl DA cyclopropanes (**4a−j**) were examined as cycloaddition partners. The reaction showed generality for the cyclopropanes of varying electronic structure when added to *N*-phenyl nitrone **7**. The tetrahydro-1,2-oxazine products (**9a−g**) were isolated in good to excellent yields (70−99%) with excellent diastereoselectivity. Incorporation of heteroaromatic rings on the cyclopropane continued to consistently result in high yields (**9h−j**, 86−95%)and cis selectivity (52−99:1).

The sensitivity of the reaction to changes in the electronic structure of the *N*-phenyl nitrones was examined (Scheme 2). Nitrones **10a−d** were reacted with cyclopropane **1** under standard reaction conditions. Electron-rich and -deficient aromatic substitutions on the nitrones were well tolerated under the reaction conditions and led to formation of the **11a−d** in very good yield (74−90%) with excellent diastereoselectivity (up to 99:1). Of note, the incorporation of *N*-tosyl indole on the nitrone led to a slightly more sluggish reaction; however, only the cis diastereomer was observed.

In conclusion, we have identified $Ca(OTf)_2$ as an efficient catalyst for the highly diastereoselective 1,3-dipolar cycloaddition of nitrones and donor−acceptor cyclopropanes. The 1,2-oxazines were isolated in good to excellent yield with selectivity for the cis diastereomer. The reactions showed generality for variations in the substitution on the cyclopropane and the nitrone.

EXPERIMENTAL SECTION

Unless otherwise noted, all commercial materials were used without purification. Calcium triflate and *N*,*α*-Diphenyl nitrone (**7**) were obtained from commercial sources and used without further purification. DA cyclopropanes[20] and nitrones[21] were synthesized according to literature procedures. Diastereomeric ratios were determined by ^{1}H NMR. NMR data for the major diastereomer has been reported. Minor diastereomers were not able to be isolated

General Procedure for the Addition of Nitrones to Cyclopropanes. In an inert glovebox, calcium triflate (6.8 mg, 0.02 mmol, 0.02 equiv) was added to a 3 mL conical glass vial with a stir bar. After the vial was removed from the glovebox, cyclopropane (1 mmol, 1.0 equiv), nitrone (1.2 mmol, 1.2 equiv), and dry MeCN (1.0 mL, 1.0 M) were added. The reaction solution was heated to 50 or 70 °C, and the reaction progress was monitored by TLC. Upon completion, the vial was removed from the heat and cooled to room temperature while stirring. The reaction was then loaded directly onto a silica gel column and purified by flash chromatography (5−20% EtOAc in hexanes).

*Dimethyl 2-Methyl-3,6-diphenyl-1,2-oxazinane-4,4-dicarboxylate (**3**).* White solid, mp 84−86 °C (345.7 mg, 94% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66−7.57 (m, 2H), 7.54−7.26 (m, 8H), 4.89 (dd, J = 11.7, 3.1 Hz, 1H), 4.84 (s, 1H), 3.89 (s, 3H), 3.39 (s, 3H), 2.74 (dd, J = 14.5, 11.8 Hz, 1H), 2.63 (dd, J = 14.4, 3.2 Hz, 1H), 2.54 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.3, 168.5, 140.2, 134.8, 130.9, 128.6, 128.2, 128.1, 128.1, 126.4, 77.9, 68.0, 59.4, 53.3, 52.4, 43.4, 31.1. Spectral data was consistent with reported literature values.[17]

*Dimethyl 6-(4-Methoxyphenyl)-2-methyl-3-phenyl-1,2-oxazinane-4,4-dicarboxylate (**5a**).* White solid, mp 86−91 °C (343.2 mg, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (dd, J = 6.5, 3.0 Hz, 2H), 7.48−7.37 (m, 2H), 7.39−7.26 (m, 3H), 7.01−6.89 (m, 2H), 4.89−4.77 (m, 2H), 3.88 (s, 3H), 3.83 (s, 3H), 3.39 (s, 3H), 2.75 (dd,

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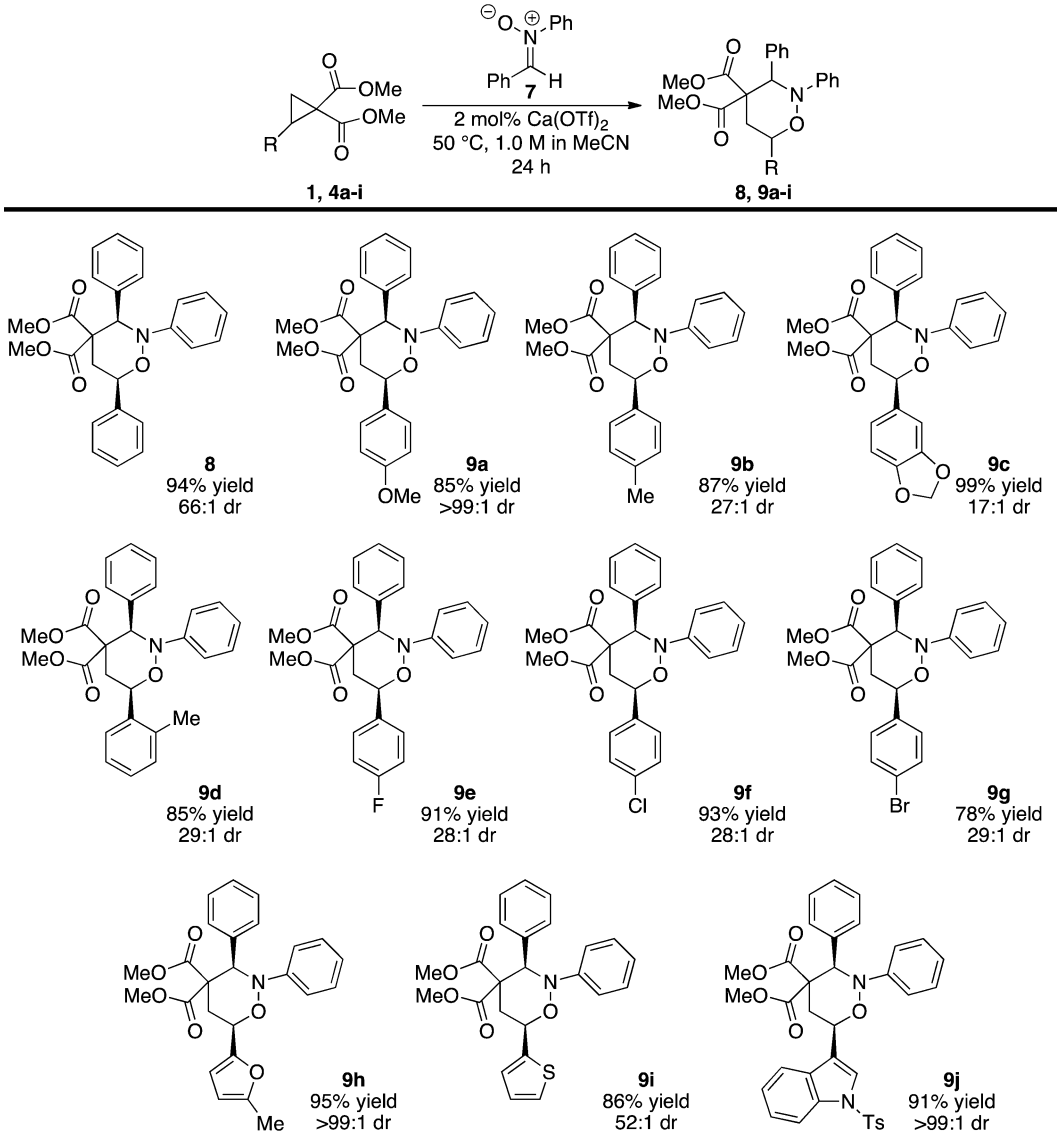
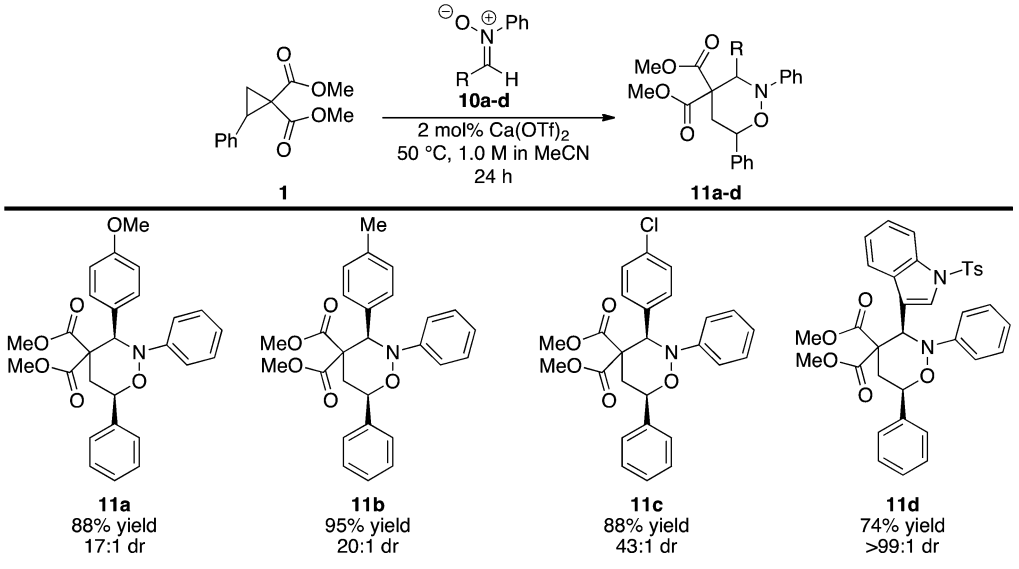
Scheme 1. Addition of Nitrone 7 to DA Cyclopropanes



Scheme 2. Addition of *N*-Phenyl Nitrones to 1



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J = 14.4, 12.2 Hz, 1H), 2.61−2.53 (m, 1H), 2.53 (s, 3H), 1.29−1.18 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.4, 168.5, 159.6, 130.9, 128.2, 128.0, 128.0, 120.0, 114.0, 77.6, 68.0, 59.4, 55.3, 53.3, 52.4, 43.4, 30.7, 15.3; IR (cm^{-1}): 3060, 3028, 2955, 2873, 2841, 1725, 1587, 1490, 1252, 1239, 1181, 1081. HRMS (+ve ESI/APCI TOF, $C_{22}H_{26}NO_6(MH^+)$) Calcd 400.1755, Measured Mass 400.1754.

*Dimethyl 6-(4-Chlorophenyl)-2-methyl-3-phenyl-1,2-oxazinane-4,4-dicarboxylate (**5b**).* White solid, mp 105−108 °C (334.6 mg, 83% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (d, J = 5.6 Hz, 2H), 7.47−7.28 (m, 7H), 4.85 (m, 2H), 3.89 (s, 3H), 3.38 (s, 3H), 2.78−2.57 (m, 2H), 2.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 168.3,138.7, 134.7, 133.8, 130.8, 128.7, 128.3, 128.1, 127.7, 67.8, 59.4, 53.4, 52.5, 43.4, 31.0; IR (cm^{-1}): 3037, 2993, 2955, 2892, 1736, 1492, 1429, 1255, 1169, 1150.[22] HRMS (+ve ESI/APCI TOF, $C_{21}H_{23}NO_5Cl(MH^+)$) Calcd 404.1259, Measured Mass 404.1265.

*Dimethyl 6-(Benzo[d][1,3]dioxol-5-yl)-2-methyl-3-phenyl-1,2-oxazinane-4,4-dicarboxylate (**5c**).* White solid, mp 115−117 °C (380.8 mg, 92% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64−7.54 (m, 2H), 7.39−7.26 (m, 3H), 7.04−6.90 (m, 2H), 6.84 (d, J = 8.0 Hz, 1H), 5.98 (s, 2H), 4.85−4.73 (m, 2H), 3.88 (s, 3H), 3.39 (s, 3H), 2.78−2.49 (m, 2H), 2.52 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.3, 168.4, 147.8, 147.4, 134.7, 130.9, 128.3, 128.1, 120.1, 108.3, 107.3, 101.1, 77.8, 59.4, 53.3, 52.4, 43.4, 31.0; IR (cm^{-1}): 3063, 3025, 2952, 2873, 1726, 1596, 1487, 1234, 1171, 1070, 751. HRMS (+ve ESI/APCI TOF, $C_{22}H_{24}NO_7(MH^+)$) Calcd 414.1547, Measured Mass 414.1545.

*Dimethyl 2,3,6-Triphenyl-1,2-oxazinane-4,4-dicarboxylate (**8**).* White solid, mp 161−162 °C (406.5 mg, 94% yield); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62−7.54 (m, 4H), 7.49−7.44 (m, 2H), 7.42−7.37 (m, 1H), 7.23−7.17 (m, 3H), 7.17−7.08 (m, 4H), 6.81 (tt, J = 7.2, 1.3 Hz, 1H), 5.80 (s, 1H), 5.04 (dd, J = 12.1, 2.6 Hz, 1H), 3.93 (s, 3H), 3.47 (s, 3H), 2.87 (dd, J = 14.4, 12.0 Hz, 1H), 2.79 (ddd, J = 14.4, 2.7, 0.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.1, 168.3, 148.6, 139.4, 135.0, 130.4, 128.6, 128.5, 128.3, 128.1, 128.0, 126.5, 121.6, 115.8, 78.8, 65.8, 59.6, 53.5, 52.6, 31.7. Spectral data were consistent with reported literature values.[16c]

*Dimethyl 6-(4-Methoxyphenyl)-2,3-diphenyl-1,2-oxazinane-4,4-dicarboxylate (**9a**).* Pale yellow solid, mp 137−139 °C (394.2 mg, 85% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67−7.55 (m, 2H), 7.55−7.46 (m, 2H), 7.25−7.05 (m, 7H), 7.05−6.95 (m, 2H), 6.85−6.76 (m, 1H), 5.79 (s, 1H), 4.97 (dd, J = 12.1, 2.4 Hz, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 3.49 (s, 3H), 2.90 (dd, J = 14.4, 12.1 Hz, 1H), 2.74 (ddd, J = 14.4, 2.6, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 168.4, 159.7, 148.6, 135.1, 131.3, 130.4, 128.5, 128.2, 128.1, 128.0, 121.5, 115.7, 114.0, 78.5, 65.5, 59.6, 55.4, 53.5, 52.7, 31.2; IR (cm^{-1}): 2949, 2892, 2854, 1733, 1597, 1242, 1169, 1043. HRMS (+ve ESI/APCI TOF, $C_{27}H_{28}NO_6(MH^+)$) Calcd 462.1911, Measured Mass 462.1927.

*Dimethyl 2,3-Diphenyl-6-(p-tolyl)-1,2-oxazinane-4,4-dicarboxylate (**9b**).* Pale yellow solid, mp 147−149 °C (385.9 mg, 87% yield); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62−7.55 (m, 2H), 7.48−7.42 (m, 2H), 7.31−7.24 (m, 2H), 7.24−7.04 (m, 7H), 6.80 (tt, J = 7.2, 1.3 Hz, 1H), 5.79 (s, 1H), 4.99 (dd, J = 12.2, 2.4 Hz, 1H), 3.92 (s, 3H), 3.47 (s, 3H), 2.87 (dd, J = 14.4, 12.2 Hz, 1H), 2.76 (ddd, J = 14.4, 2.5, 0.9 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 168.3, 148.6, 138.2, 136.3, 135.1, 130.4, 129.3, 128.5, 128.1, 128.0, 126.6, 121.5, 115.7, 78.7, 65.6, 59.5, 53.5, 52.7, 31.4, 21.3; IR (cm^{-1}): 3028, 2958, 2927, 2873, 1735, 1593, 1241, 1179, 1076. HRMS (+ve ESI/APCI TOF, $C_{27}H_{28}NO_5(MH^+)$) Calcd 446.1962, Measured Mass 446.1962.

*Dimethyl 6-(Benzo[d][1,3]dioxol-5-yl)-2,3-diphenyl-1,2-oxazinane-4,4-dicarboxylate (**9c**).* White solid, mp 152−155 °C (474.7 mg, 99% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63−7.50 (m, 2H), 7.22−7.06 (m, 8), 7.02 (ddd, J = 8.0, 1.8, 0.6 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.81 (tt, J = 6.7, 1.4 Hz, 1H), 6.02 (s, 2H), 5.78 (s, 1H), 4.93 (dd, J = 11.9, 2.6 Hz, 1H), 3.92 (s, 3H), 3.48 (s, 3H), 2.84 (dd, J = 14.4, 11.9 Hz, 1H), 2.72 (ddd, J = 14.4, 2.7, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 168.3, 148.5, 147.9, 147.6, 135.0, 133.1, 130.4, 128.6, 128.1, 128.0, 121.6, 120.3, 115.8, 108.4, 107.4, 101.2, 78.7, 65.6, 59.5, 53.5, 52.7, 31.5; IR (cm^{-1}): 2946, 2895, 1730, 1600, 1492, 1249, 1033. HRMS (+ve ESI/APCI TOF, $C_{27}H_{26}NO(MH^+)$) Calcd 476.1704, Measured Mass 476.1710.

*Dimethyl 2,3-Diphenyl-6-(o-tolyl)-1,2-oxazinane-4,4-dicarboxylate (**9d**).* White solid, mp 173−175 °C (376.9 mg, 85% yield); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71−7.65 (m, 1H), 7.64−7.57 (m, 2H), 7.39−7.32 (m, 1H), 7.29 (td, J = 7.4, 1.4 Hz, 1H), 7.25−7.06 (m, 8H), 6.80 (tt, J = 7.2, 1.3 Hz, 1H), 5.82 (s, 1H), 5.18 (dd, J = 11.8, 2.4 Hz, 1H), 3.94 (s, 3H), 3.47 (s, 3H), 2.82 (dd, J = 14.4, 11.8 Hz, 1H), 2.74 (ddd, J = 14.4, 2.5, 1.0 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 168.3, 148.6, 137.8, 135.7, 135.0, 130.6, 130.4, 128.6, 128.1, 128.0, 126.4, 125.2, 121.6, 115.7, 76.3, 66.0, 59.6, 53.5, 52.7, 31.1, 19.0; IR (cm^{-1}): 3022, 2955, 2927, 2870, 1727, 1600, 1432, 1239, 1176, 1070. HRMS (+ve ESI/APCI TOF, $C_{27}H_{28}NO_5(MH^+)$) Calcd 446.1962, Measured Mass 446.1970.

*Dimethyl 6-(4-Fluorophenyl)-2,3-diphenyl-1,2-oxazinane-4,4-dicarboxylate (**9e**).* White solid, mp 134−137 °C (409.9 mg, 91% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62−7.47 (m, 4H), 7.24−7.04 (m, 9H), 6.88−6.76 (m, 1H), 5.79 (s, 1H), 5.01 (dd, J = 11.4, 3.2 Hz, 1H), 3.93 (s, 3H), 3.48 (s, 3H), 2.92−2.69 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 168.2, 162.7 (d, J = 246.9 Hz), 148.5, 135.2 (d, J = 3.3 Hz), 134.9, 130.4, 128.6, 128.4 (d, J = 8.2 Hz), 128.1, 128.0, 121.7, 115.8, 115.6 (d, J = 21.5 Hz), 78.2, 65.8, 59.5, 53.6, 52.7, 31.6; IR (cm^{-1}): 3034, 2955, 1739, 1597, 1508, 1226, 1176. HRMS (+ve ESI/APCI TOF, $C_{26}H_{25}NO_5F(MH^+)$) Calcd 450.1711, Measured Mass 450.1714.

*Dimethyl 6-(4-Chlorophenyl)-2,3-diphenyl-1,2-oxazinane-4,4-dicarboxylate (**9f**).* White solid, mp 164−170 °C (432.1 mg, 93% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61−7.38 (m, 6H), 7.27−7.01 (m, 7H), 6.83 (tt, J = 7.1, 1.3 Hz, 1H), 5.78 (s, 1H), 5.00 (dd, J = 10.6, 4.1 Hz, 1H), 3.93 (s, 3H), 3.48 (s, 3H), 2.89−2.69 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 168.1, 148.5, 137.9, 134.9, 134.2, 130.4, 128.8, 128.6, 128.1, 128.0, 127.8, 121.8, 115.9, 78.2, 66.0, 59.5, 53.5, 52.7, 31.7; IR (cm^{-1}): 2949, 2898, 1739, 1597, 1492, 1230, 1174. HRMS (+ve ESI/APCI TOF, $C_{26}H_{25}NO_5Cl(MH^+)$) Calcd 466.1416, Measured Mass 466.1418.

*Dimethyl 6-(4-Bromophenyl)-2,3-diphenyl-1,2-oxazinane-4,4-dicarboxylate (**9g**).* White solid, mp 180−181 °C (395.5 mg, 78% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64−7.49 (m, 4H), 7.48−7.39 (m, 2H), 7.24−7.02 (m, 7H), 6.83 (tt, J = 7.0, 1.3 Hz, 1H), 5.78 (s, 1H), 5.00 (dd, J = 10.0, 4.6 Hz, 1H), 3.93 (s, 3H), 3.47 (s, 3H), 2.89−2.69 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 168.1, 148.5, 138.4, 134.9, 131.8, 130.4, 128.6, 128.1, 128.0, 121.8, 115.9, 78.2, 66.0, 59.5, 53.5, 52.7, 31.6; IR (cm^{-1}): 2949, 2920, 1739, 1591, 1496, 1258, 1173, 1068. HRMS (+ve ESI/APCI TOF, $C_{26}H_{25}NO_5Br(MH^+)$) Calcd 510.0911, Measured Mass 510.0902.

*Dimethyl 6-(5-Methylfuran-2-yl)-2,3-diphenyl-1,2-oxazinane-4,4-dicarboxylate (**9h**).* White solid, mp 124−127 °C (414.9 mg, 95% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66−7.53 (m, 2H), 7.23−7.03 (m, 7H), 6.87−6.74 (m, 1H), 6.49−6.41 (m, 1H), 6.03 (dq, J = 3.1, 1.0 Hz, 1H), 5.72 (s, 1H), 5.01 (dd, J = 12.5, 2.4 Hz, 1H), 3.89 (s, 3H), 3.48 (s, 3H), 3.09 (dd, J = 14.5, 12.5 Hz, 1H), 2.70 (ddd, J = 14.5, 2.6, 0.9 Hz, 1H), 2.37 (d, J = 1.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 168.2, 153.0, 150.1, 148.4, 134.9, 130.6, 128.5, 128.1, 128.0, 121.6, 116.0, 110.0, 106.4, 72.4, 65.9, 59.3, 53.5, 52.7, 28.2, 13.8; IR (cm^{-1}): 3006, 2958, 1736, 1591, 1489, 1252, 1198, 1154, 755. HRMS (+ve ESI/APCI TOF, $C_{25}H_{26}NO_6(MH^+)$) Calcd 436.1755, Measured Mass 436.1769.

*Dimethyl 2,3-Diphenyl-6-(thiophen-2-yl)-1,2-oxazinane-4,4-dicarboxylate (**9i**).* White solid, mp 124−127 °C (377.5 mg, 86% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62−7.51 (m, 2H), 7.41 (dd, J = 5.1, 1.2 Hz, 1H), 7.28−7.02 (m, 9H), 6.82 (tt, J = 7.4, 1.4 Hz, 1H), 5.76 (s, 1H), 5.25 (ddd, J = 11.6, 3.0, 0.9 Hz, 1H), 3.91 (s, 3H), 3.49 (s, 3H), 2.99 (dd, J = 14.3, 11.6 Hz, 1H), 2.88 (ddd, J = 14.3, 3.1, 0.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 168.1, 148.4, 141.9, 134.8, 130.5, 128.6, 128.2, 128.0, 126.8, 126.0, 125.5, 121.8, 115.9, 74.7, 66.0, 59.5, 53.6, 52.7, 31.7; IR (cm^{-1}): 2980, 2965, 1730, 1600, 1492, 1236, 1176, 1147, 701. HRMS (+ve ESI/APCI TOF, $C_{24}H_{24}NO_5S(MH^+)$) Calcd 438.1370, Measured Mass 438.1376.

*Dimethyl 2,3-Diphenyl-6-(1-tosyl-1H-indol-3-yl)-1,2-oxazinane-4,4-dicarboxylate (**9j**).* White solid, mp 118−125 °C (569.7 mg,

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91% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (dt, J = 8.3, 0.9 Hz, 1H), 7.90−7.81 (m, 2H), 7.78 (d, J = 1.1 Hz, 1H), 7.75−7.68 (m, 1H), 7.58−7.45 (m, 2H), 7.37 (ddd, J = 8.4, 7.2, 1.3 Hz, 1H), 7.32−7.22 (m, 3H), 7.22−7.10 (m, 5H), 7.10−7.02 (m, 2H), 6.83 (tt, J = 7.4, 1.3 Hz, 1H), 5.80 (s, 1H), 5.28 (ddd, J = 11.6, 2.9, 1.1 Hz, 1H), 3.93 (s, 3H), 3.51 (s, 3H), 3.02 (dd, J = 14.2, 11.6 Hz, 1H), 2.97−2.87 (m, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 168.2, 148.6, 145.2, 135.3, 135.3, 134.8, 130.5, 130.0, 129.5, 128.6, 128.2, 128.0, 127.0, 125.1, 123.5, 123.4, 121.8, 121.0, 120.4, 115.8, 113.7, 72.3, 66.5, 59.4, 53.6, 52.7, 29.7, 21.6; IR (cm^{-1}): 3060, 3034, 2949, 1735, 1597, 1446, 1236, 1174, 1135, 680. HRMS (+ve ESI/APCI TOF, $C_{35}H_{33}N_2O_7S(MH^+)$) Calcd 625.2003, Measured Mass 625.2018.

*(Z)-N-((1-Tosyl-1H-indol-3-yl)methylene)aniline Oxide (**10d**).* Yellow-orange solid, mp 179−180 °C (1.48 g, 76% yield); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.55 (s, 1H), 8.26 (s, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.93−7.87 (m, 2H), 7.86−7.79 (m, 2H), 7.64 (d, J = 7.8 Hz, 1H), 7.56−7.45 (m, 3H), 7.41 (ddd, J = 8.4, 7.2, 1.2 Hz, 1H), 7.36−7.29 (m, 1H), 7.25 (d, J = 8.1 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.8, 145.4, 134.9, 134.3, 130.1, 130.0, 129.5, 129.3, 128.4, 127.2, 125.6, 125.5, 123.7, 121.4, 118.4, 114.0, 112.9, 21.6; IR (cm^{-1}): 3174, 3060, 2974, 1594, 1530, 1445, 1372, 1173, 1090, 742, 682, 660. HRMS (+ve ESI/APCI TOF, $C_{22}H_{19}N_2O_3S(MH^+)$) Calcd 391.1111, Measured Mass 391.1118.

*Dimethyl 3-(4-Methoxyphenyl)-2,6-diphenyl-1,2-oxazinane-4,4-dicarboxylate (**11a**).* Pale yellow solid, mp 162−164 °C (404.7 mg, 88% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61−7.34 (m, 7H), 7.20−7.05 (m, 4H), 6.87−6.77 (m, 1H), 6.77−6.67 (m, 2H), 5.75 (s, 1H), 5.03 (dd, J = 11.5, 3.1 Hz, 1H), 3.92 (s, 3H), 3.71 (s, 3H), 3.50 (s, 3H), 2.86 (dd, J = 14.4, 11.5 Hz, 1H), 2.77 (ddd, J = 14.3, 3.2, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 168.3, 159.1, 148.6, 139.4, 131.6, 128.6, 128.5, 128.3, 126.9, 126.5, 121.6, 115.8, 113.3, 78.8, 65.3, 59.5, 55.0, 53.5, 52.7, 31.5. Spectral data were consistent with reported literature values.[16c]

*Dimethyl 2,6-Diphenyl-3-(p-tolyl)-1,2-oxazinane-4,4-dicarboxylate (**11b**).* White solid, mp 186−188 °C (425.2 mg, 95% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60−7.52 (m, 2H), 7.51−7.33 (m, 5H), 7.20−7.05 (m, 4H), 7.04−6.94 (m, 2H), 6.81 (tt, J = 7.3, 1.5 Hz, 1H), 5.77 (s, 1H), 5.02 (dd, J = 11.7, 2.9 Hz, 1H), 3.92 (s, 3H), 3.50 (s, 3H), 2.86 (dd, J = 14.4, 11.7 Hz, 1H), 2.76 (ddd, J = 14.3, 3.0, 0.8 Hz, 1H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 168.3, 148.6, 139.4, 137.7, 131.8, 130.3, 128.8, 128.6, 128.5, 128.3, 126.6, 121.5, 115.7, 78.8, 65.4, 59.5, 53.5, 52.7, 31.6, 21.1; IR (cm^{-1}): 3012, 2965, 2923, 2863, 1733, 1597, 1489, 1233, 1198, 1052. HRMS (+ve ESI/APCI TOF, $C_{27}H_{28}NO_5(MH^+)$) Calcd 446.1962, Measured Mass 446.1952.

*Dimethyl 3-(4-Chlorophenyl)-2,6-diphenyl-1,2-oxazinane-4,4-dicarboxylate (**11c**).* White solid, 150−152 °C (411.3 mg, 88% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59−7.34 (m, 7H), 7.22−7.11 (m, 4H), 7.11−7.02 (m, 2H), 6.90−6.78 (m, 1H), 5.77 (s, 1H), 5.03 (dd, J = 7.8, 6.7 Hz, 1H), 3.93 (s, 3H), 3.51 (s, 3H), 2.87−2.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 168.1, 148.3, 139.1, 134.1, 133.5, 131.7, 128.7, 128.7, 128.5, 128.3, 126.5, 121.9, 115.8, 78.8, 65.3, 59.4, 53.6, 52.8, 31.5; IR (cm^{-1}): 3034, 2952, 2876, 1733, 1599, 1486, 1235, 1198, 1181. HRMS (+ve ESI/APCI TOF, $C_{26}H_{25}NO_5Cl(MH^+)$) Calcd 466.1416, Measured Mass 466.1421.

*Dimethyl 2,6-Diphenyl-3-(1-tosyl-1H-indol-3-yl)-1,2-oxazinane-4,4-dicarboxylate (**11d**).* Yellow solid, mp 188−193 °C (459.2 mg, 74% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.86−7.74 (m, 1H), 7.64−7.56 (m, 2H), 7.56−7.48 (m, 3H), 7.48−7.38 (m, 3H), 7.24−7.12 (m, 2H), 7.11−6.99 (m, 6H), 6.85−6.71 (m, 1H), 6.12 (s, 1H), 5.08 (dd, J = 11.5, 3.0 Hz, 1H), 3.96 (s, 3H), 3.14 (s, 3H), 2.84 (ddd, J = 14.5, 3.1, 0.9 Hz, 1H), 2.75 (dd, J = 14.5, 11.5 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 167.9, 148.6, 144.6, 139.0, 134.8, 134.0, 131.2, 129.7, 128.9, 128.6, 128.5, 127.3, 126.5, 126.4, 124.6, 123.1, 122.1, 119.2, 116.0, 115.6, 113.5, 79.1, 58.8, 58.6, 53.6, 52.6, 31.9, 21.5; IR (cm^{-1}): 3066, 3031, 2955, 2923, 1736, 1597, 1445, 1230, 1173, 1119, 660. HRMS (+ve ESI/APCI TOF, $C_{35}H_{33}N_2O_7S(MH^+)$) Calcd 476.1704, Measured Mass 476.1710. Calcd 625.2003, Measured Mass 625.2003.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: knolin@richmond.edu.

Notes

The authors declare no competing financial interest.

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