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# (Salen)chromium(III)/DMAP: An Efficient Catalyst System for the Selective Synthesis of 5-Substituted Oxazolidinones from Carbon Dioxide and Aziridines

**Aaron W. Miller and SonBinh T. Nguyen***

*Department of Chemistry and Institute for Environmental Catalysis, Northwestern University, 2145 Sheridan Rd., Evanston, Illinois 60208-3113*

*stn@northwestern.edu*

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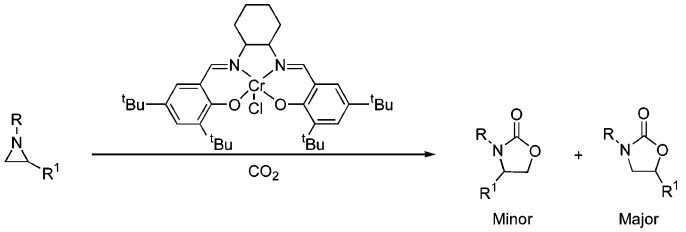
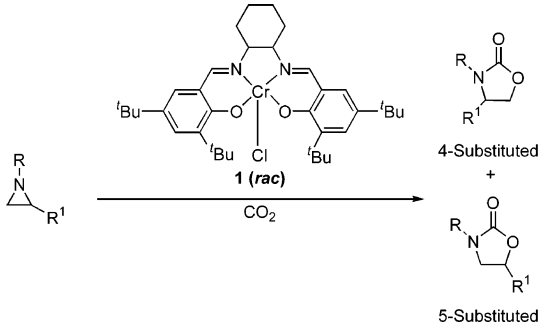
## ABSTRACT




**(Salen)chromium(III)/DMAP was found to be an active catalyst system for the coupling of $CO_2$ and aziridines. The oxazolidinone products were produced in high yield and selectivity from the opening of the aziridine at the most substituted N–C bond. This catalyst system worked well for a wide variety of monosubstituted *N*-aryl and *N*-alkyl aziridines as well as a 2,3-disubstituted *N*-alkyl aziridine.**

A number of chiral 5-substituted oxazolidinones have been shown to have high potency as antibacterial agents, and are widely used in the pharmaceutical industry.[1−8] Chiral oxazolidinones also have utility in organic synthesis as chiral synthons and auxiliaries.[9,10] An attractive route to these valuable compounds is the [2+3] coupling between aziridine and $CO_2$ (eq 1), as the variety of multiply substituted




aziridines presents the chemist with an abundance of synthetic precursors. Additionally, the chemical fixation of

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(2) Hoellman, D. B.; Lin, G.; Ednie, L. M.; Rattan, A.; Jacobs, M. R.; Appelbaum, P. C. *Antimicrob. Agents Chemother.* **2003**, *47*, 1148−1150.

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(8) Fluit, A. C.; Schmitz, F. J.; Verhoef, J.; Milatovic, D. *J. Antimicrob. Chemother.* **2002**, *50*, 271−276.

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$CO_2$ is a desirable reaction as it is an inexpensive and abundant $C_1$ feedstock.

Previous research into the aziridine/$CO_2$ coupling reaction has employed several catalyst systems—lithium iodide,[11] tin, ammonium, and antimony salts,[12] and nickel complexes[13]—albeit with limited success. Reaction 1 has also been carried out with iodine catalysts in supercritical $CO_2$.[14] While the results were promising, each of these methods suffers from either the use of high pressure or low selectivity and multiple product isomers.

We recently reported the use of the (salen)chromium(III)/DMAP catalyst system in the fixation of $CO_2$ with epoxides to form carbonates.[15] Herein, we have successfully extended the scope of this catalytic system to aziridines (eq 1). In contrast to the majority of reported catalysts, our system consistently gives 5-substituted oxazolidinones (with selectivity as high as 40:1) for a wide range of substrates. The good selectivity and high activity of our catalyst in reaction 1 is the best to date. The opening of the aziridine ring at the most substituted carbon is a behavior that is reminiscent of the classical electrophilic ring-opening of three-membered heterocycles.[16]

In contrast with the analogous epoxide/$CO_2$ coupling,[15] reaction 1 does not require a cocatalyst to proceed. The presence of a slight excess of Lewis base (LB) cocatalyst does improve the turn-over frequency (TOF) in $CH_2Cl_2$. However, a large excess of LB leads to a slight decrease in catalyst activity (Figure 1). Less basic LBs showed lower

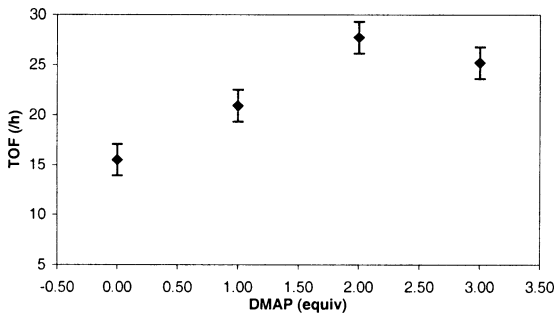


**Figure 1.** Activity of (salen)chromium(III)/DMAP as a function of DMAP concentration in the reaction of $CO_2$ and *N*-propyl-2-phenylaziridine. Reaction conditions: catalyst (12.6 mg, 0.02 mmol, 1 equiv), 400 psig of $CO_2$, *N*-propyl-2-phenylaziridine (0.322 g, 2 mmol, 100 equiv), $CH_2Cl_2$ (3.7 mL), 100 °C, 120 min.

activity, as did bulkier bases (Table 1). Of the five LBs studied, DMAP exhibits the highest activity.

Interestingly, the percentage of 5-substituted oxazolidinone product is strongly dependent on the catalyst/cocatalyst ratio. As the concentration of cocatalyst decreases, the proportion of the 5-substituted isomer increases (Figure 2). For *N*-propyl-2-phenylaziridine, reaction 1 turns over slowly and affords an 8:1 ratio of the 5- to 4-substituted products when the catalyst/cocatalyst ratio is 2. *In the absence of DMAP cocatalyst, a 40:1 selectivity was observed favoring 5-phenyl-N-propyloxazolidinone*.

**Table 1.** Activity of the (Salen)chromium(III)/LB Catalyst System in the Reaction of $CO_2$ and *N*-Propyl-2-phenylaziridine[b]

| entry | Lewis base | TOF[a] ($h^{-1}$) |
|---|---|---|
| 1 | *N*,*N*-Dimethyl-4-aminopyridine (DMAP) | 27 |
| 2 | Triethylamine | 20 |
| 3 | Triphenylphosphine oxide | 20 |
| 4 | Pyridine | 11 |
| 5 | Imidazole | 23 |

[a] TOF determined using GC yields. [b] Reaction conditions: catalyst (12.6 mg, 0.02 mmol, 1 equiv), cocatalyst (2 equiv), *N*-propyl-2-phenylaziridine (0.322 g, 2 mmol, 100 equiv), $CO_2$ (400 psig), $CH_2Cl_2$ (3.7 mL), 100 °C, 120 min.

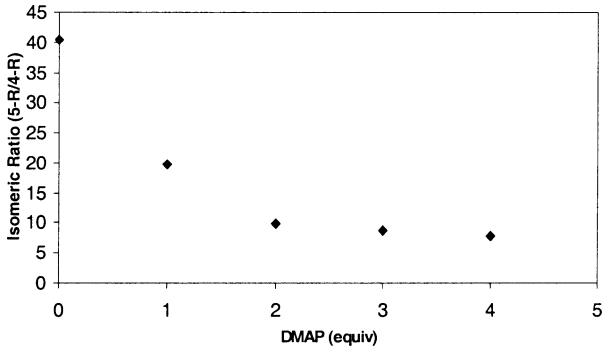


**Figure 2.** Ratio of 5-substituted to 4-substituted isomers in the reaction of $CO_2$ and *N*-propyl 2-phenylaziridine as a function of DMAP concentration. Reaction conditions: catalyst (12.6 mg, 0.02 mmol, 1 equiv), *N*-propyl-2-phenylaziridine (0.322 g, 2 mmol, 100 equiv), 400 psig of $CO_2$, $CH_2Cl_2$ (3.7 mL), 100 °C, 120 min.

The activity of our catalyst system is strongly dependent on the solvent used in the reaction (Figure 3). Toluene and benzene do not facilitate fast reaction rates while DME worked reasonably well. However, dichloromethane (DCM) affords the fastest TOF.

The above results can be explained by a mechanism in which the aziridine is first activated by coordination to the Lewis acidic (salen)Cr metal center, resulting in the formation of a partially cationic nitrogen (Scheme 1). This is followed by the nucleophilic ring-opening of the aziridine by the LB cocatalyst at the more substituted carbon to give an ionic intermediate. The presence of too much LB would inhibit the reaction due to the competitive coordination of the LB to the Lewis acidic Cr site.

(11) Hancock, M. T.; Pinhas, A. R. *Tetrahedron Lett.* **2003**, *44*, 5457−5460.
(12) Nomura, R.; Nakano, T.; Nishio, Y.; Ogawa, S.; Ninagawa, A.; Matsuda, H. *Chem. Ber.* **1989**, *122*, 2407−2409.
(13) Tascedda, P.; Dunach, E. *Chem. Commun.* **2000**, 449−450.
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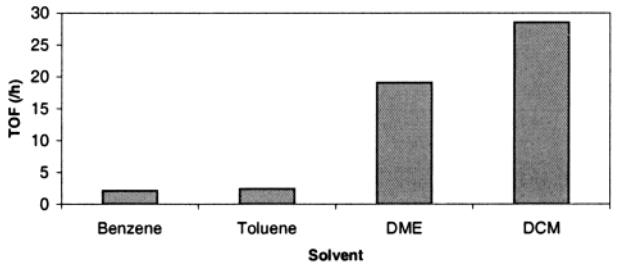
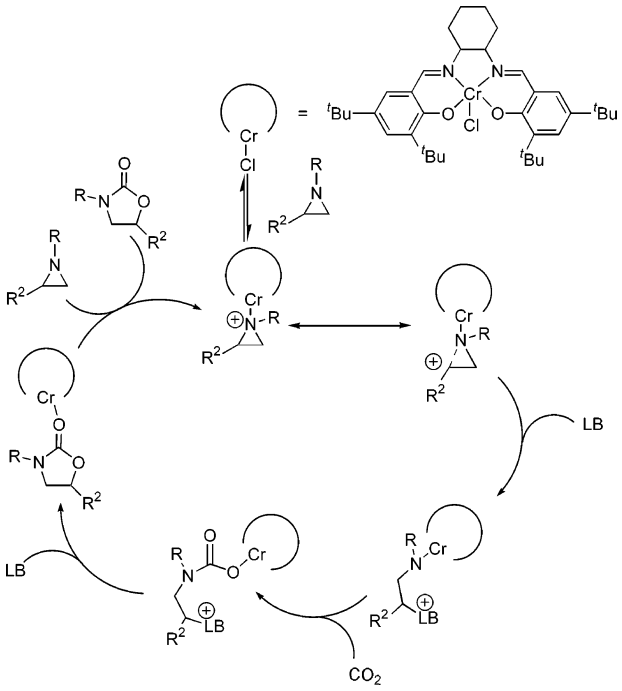



**Figure 3.** Activity of the (salen)chromium(III)/DMAP catalyst as a function of solvent in the reaction of $CO_2$ and *N*-propyl-2-phenylaziridine. Reaction conditions: catalyst (12.6 mg, 0.02 mmol, 1 equiv), DMAP (2 equiv), *N*-propyl-2-phenylaziridine (0.322 g, 2 mmol, 100 equiv), solvent (3.7 mL), 400 psig of $CO_2$, 100 °C, 120 min.

Scheme 1 can also be used to rationalize the dependence of reaction rate on $CO_2$ pressure. As in the case of the epoxide/$CO_2$ coupling chemistry,[15] the reaction yield increases as a function of increasing pressure up to a certain point and then slowly drops off (Figure 4). We postulate that at high $CO_2$ pressures, the amount of available DMAP for catalysis is reduced due to its reaction with $CO_2$ to form a zwitterionic complex that is not active as a cocatalyst.[17]

**Scheme 1.** A Proposed Mechanism for the Coupling of $CO_2$ and Aziridines by the (Salen)chromium(III)/DMAP Catalyst System




Further, the mechanism shown in Scheme 1 explains catalytic activity in the absence of a cocatalyst. Since the aziridine is itself a LB (p$K_b$ = 6.14),[18] it may act as its own cocatalyst. However, DMAP (p$K_b$ = 4.3)[18] is still the more effective cocatalyst under our reaction conditions.

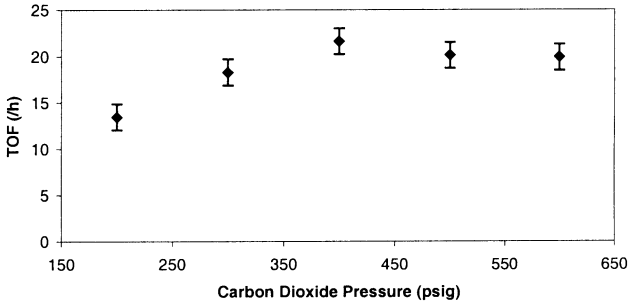



**Figure 4.** Activity of the (salen)chromium(III)/DMAP catalyst system as a function of $CO_2$ pressure in the reaction of $CO_2$ and *N*-propyl-2-phenylaziridine. Reaction conditions: catalyst (12.6 mg, 0.02 mmol, 1 equiv), DMAP (2 equiv), *N*-propyl-2-phenylaziridine (0.322 g, 2 mmol, 100 equiv), $CH_2Cl_2$ (3.7 mL), 400 psig of $CO_2$, 100 °C, 60 min.

Under optimized conditions, the (salen)chromium(III)/DMAP catalyst system is an active catalyst for the coupling of $CO_2$ with a variety of aziridine substrates. Substrates were primarily varied as to their *N*-substitution; however, 1,2-disubstituted aziridines also show good yield (albeit at longer reaction times, cf. entries 1 and 5), as do 1,2,3-trisubstituted aziridines (Table 2).

Trends in substrate reactivity show that increasing the steric hindrance of the *N*-substitution leads to a large decrease in reaction rate (cf. entries 1, 2, 3, 4, and 8), consistent with our proposed mechanism where bulky aziridines are expected to coordinate poorly to the (salen)Cr center, slowing their conversion to products. Phenyl substitution at the 2-position also seems to increase the reaction rate relative to alkyl substitutions (cf. entries 3 and 6).

In conclusion, (salen)chromium(III)/DMAP is an excellent catalyst system for the coupling of $CO_2$ and aziridines to form 5-substituted oxazolidinones selectively. Previous catalytic syntheses of oxazolidinones via aziridine/$CO_2$

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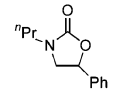
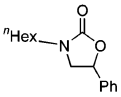
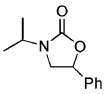
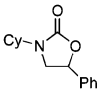
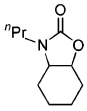
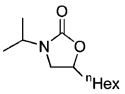
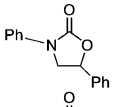
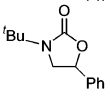
(20) **General Experimental Procedure.** On the benchtop, a 45-mL Parr high-pressure reactor equipped with a magnetic stir bar was charged with catalyst **1** (12.6 mg, 2 × $10^{-5}$ mol), DMAP (4.9 mg, 4 × $10^{-5}$ mol), and a solution of the aziridine (2 mmol) in $CH_2Cl_2$ (4 mL, 0.5 M solution). Finally, undecane (100 $\mu$L, 0.474 mmol, internal standard) was placed in the reactor. The reactor was sealed and placed under constant $CO_2$ pressure for 5 min to allow equilibration, the $CO_2$ valve was closed, and the reactor was placed in a magnetically stirred 100 °C oil bath. After 2 h the reactor was removed from the oil bath, quickly cooled in running cold tap water, and vented to a hood. A small aliquot was then removed from the solution for GC analysis. (The catalyst was removed by eluting the aliquot in $CH_2Cl_2$ (20 mL) through a solvent-wet silica plug that was doped with triethylamine (100 $\mu$L) before introduction of the aliquot. Yield was determined via GC, using peak areas and undecane internal standard.) Further purification by column chromatography over neutral alumina (150 mesh, 58 Å, hexanes: ethyl acetate 60:40) gave pure oxazolidinone product (mixture of 4- and 5-substituted isomers).

**Table 2.** Substrate Scope of the (Salen)chromium(III)/DMAP Catalyst System in the Reaction of $CO_2$ and *N*-Substituted Aziridines[g] (refs 19 and 20)

| entry | substrate | time (h) | major product structure | major product (%)[e] | minor product (%)[c] | isolated yield (%)[f] |
|---|---|---|---|---|---|---|
| 1 |  | 5 |  | 90 | 10 | 93 |
| 1a* | | 14 | | 94 | 2.3 | 90 |
| 2 |  | 8 |  | 87[b] | 11 | 91 |
| 3 |  | 12 |  | 92 | 3 | 86 |
| 4 |  | 16 |  | 97[b] | 2 | 91 |
| 5 |  | 18 |  | 94 | NA[d] | 92 |
| 6 |  | 20 |  | 92 | 7 | 93 |
| 7 |  | 28 |  | 89[c] | 0 | 82 |
| 8 |  | 120[a] |  | 92 | 2 | 89 |

[a] 5 mol% catalyst. [b] Isomers can be separated by recrystallization from hexanes. [c] Remainder is 1,2,4,5-tetraphenyl-1,4-piperazine formed from the dimerization of aziridine. [d] All cis as determined by $^1$H NMR spectroscopy. [e] GC yields. [f] Mixture of isomers. [g] Reaction conditions: catalyst (12.6 mg, 0.02 mmol, 1 equiv), DMAP (2 equiv), substrate (2 mmol, 100 equiv), $CH_2Cl_2$ (3.7 mL), 400 psig of $CO_2$, 100 °C. * No cocatalyst was used in that reaction.

coupling have only been possible by using less reactive catalysts that give multiple product isomers. To the best of our knowledge, ours is the first catalyst system to give a large excess of the 5-substituted isomer over the 4-substituted one, along with high catalyst activity. Recent investigations into the antibiotic properties of oxazolidinones show that the 5-substituted oxazolidinone comprises the active isomer. These include linezolid,[4] ranbezolid,[2] DuP-721 and DuP-105,[7] and AZD2563.[8] These fully synthetic compounds show great antibacterial potential for widespread use against staphylococci, pneumococci, and enterococci bacteria, many strains of which are resistant to traditional antibiotics.[4] While the work presented herein does not directly contribute to the synthesis of the 5-(*S*)-substituted oxazolidinone isomers which have exhibited antibacterial properties, our strategy suggests an atom-economic pathway toward the synthesis of such compounds, especially when the chirality of the 5-position can be controlled. We are actively pursuing this latter direction along with investigating the mechanism and substrate scope of reaction 1, especially concerning possible synthetic applications of this $CO_2$/aziridine coupling method. These results will be reported in due course.

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**Supporting Information Available:** Characterization data for 5-oxazolidinone products ($^1$H, $^{13}$C, 2D NOESY NMR spectra, IR spectra, HREIMS, and elemental analysis). This material is available free of charge via the Internet at http://pubs.acs.org.

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