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Journal Name

COMMUNICATION

[(Salcen)Cr^{III} + Lewis Base]-Catalyzed Synthesis of N-aryl-substituted Oxazolidinones from Epoxides and Aryl Isocyanates
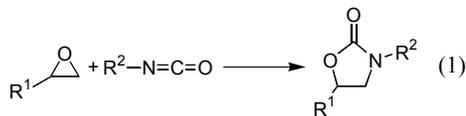
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[(Salcen)Cr^{III} + Lewis base] was found to be a highly active and selective catalyst system in the [2 + 3] cycloaddition reaction between epoxides and isocyanates to form 5-oxazolidinones. The reaction proceeds to high yield under mild reaction conditions and is applicable to a variety of terminal epoxides and aryl isocyanates.

As an important heterocycle, the oxazolidinone moiety has received significant attention due to its potential biological activity, especially as an antimicrobial agent.[1] In addition, oxazolidinones have been employed as synthons in a variety of organic transformations,[2] particularly in the synthesis of biologically active compounds or their synthetic intermediates.[3] Not surprisingly, many strategies have been designed for their synthesis,[4] the most popular of which includes the [4 + 1] condensation of ethanolamines with either urea, carbamate, carbonate, or phosgene derivatives; the [4 + 1] condensation of α-halomethyloxirane and amine; or the [2 + 3] cycloaddition reaction between either isocyanates and epoxides or between isocyanates and aziridines (to afford 2-imino oxazolidinones). Among these, the [2 + 3] cycloadditions are the most atom-economical because they do not generate inorganic wastes. In addition, the cycloaddition between isocyanates and epoxides (Eq 1) is the most attractive due to the ease of access to both classes of substrates.[5]

$$ \underset{R^1}{\triangle}\!\!\!\!O \;+\; R^2\!-\!N\!=\!C\!=\!O \;\longrightarrow\; \underset{R^1}{\overset{O}{\underset{}{\big\langle}}}O\!\!-\!\!N\!-\!R^2 \qquad (1) $$

Several catalysts have been investigated for reaction 1, including quaternary ammonium salts, lithium halides, Pd(0) complexes, organoantimony and organotin compounds.[5a, 6] However, these catalyst systems usually suffer from the need for high reaction temperatures and the use of reactive polar solvents, which lead to side reactions. In addition, they often

require the slow addition of isocyanate, or the use of excess epoxide, to suppress the undesirable trimerization of the isocyanate. Pd(0) complexes constitute one of the best catalysts for vinyl epoxides in reaction 1 because they can be used under mild reaction conditions to give oxazolidinones in yields that typically exceed 90%.[6g, 6h] North and coworkers have recently significantly expanded the utility of reaction 1 using a [(salen)Al]$_2$O catalyst that was proposed to work in a bimetallic fashion.[5b]

We have previously established that a bifunctional catalyst system comprised of a Cr^{III}(salen) complex (salen = *N,N'-bis*(3,5-di-*tert*-butylsalicylidene)-1,2-diaminoethane) in conjunction with a Lewis base is a very efficient catalyst for the [2+3] ring-opening cycloaddition reactions between CO_2 and either epoxides or aziridines.[7] Given these successes, we have extended this catalyst system to include the reaction of heterocumulenes[8] other than CO_2. Herein, we report initial results on the application of the [(salen)Cr^{III} + Lewis base] catalyst system to the coupling of isocyanates and epoxides to yield oxazolidinones. Notably, Lewis bases are synergistic cocatalysts for (salcen)Cr^{III}, in contrast to that observed for the [(salen)Al]$_2$O system,[5b] where they are inhibitors.

We initially chose the [(salcen)Cr^{III} + DMAP] catalyst system (salcen = *N,N'-bis*(3,5-di-*tert*-butylsalicylidene)-1,2-*trans*-diaminocyclohexane) for the cycloaddition of phenyl isocyanate and propylene oxide (Eq 2) as it had been the optimal catalyst combination in our previous investigations of the (salen)Cr^{III}Cl-catalyzed coupling of CO_2 and epoxides.[7a] Unfortunately, this only provided a 6% yield of the desired 5-oxazolidinone product (Table 1, entry 1). This low yield is primarily due to the formation of a significant amount of 1,3,5-triphenylisocyanurate, the undesirable trimerization side product, which depleted phenylisocyanate from the reaction. Indeed, previous reports have indicated that the irreversible trimerization of isocyanates can be catalyzed by many Lewis bases, where an increase in

catalytic activity accompanies an increase in Lewis basicity.[9] Thus, we examined a broad range of Lewis bases as cocatalysts for reaction 2 to determine whether the selectivity for the desired oxazolidinone product could be improved over that for 1,3,5-triphenylisocyanurate (Table 1).

Table 1. Variation of the Lewis-base cocatalyst for reaction 2
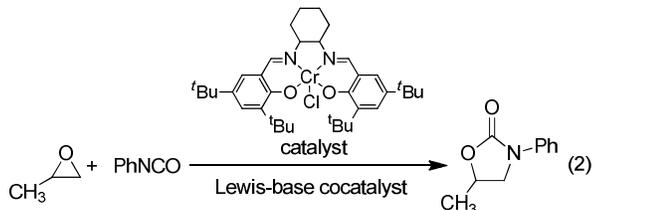
Entry	Lewis base	pKa of the conjugated acid[b]	Yield of oxazolidinone (%)[a]
1	None	-	37 (3 days)
2	DMAP	9.5	6
3	Pyridine	5.2	24
4	4-CF$_3$-pyridine	~1.9	67
5	N-Me-	7.4	18
6	NEt^{i}Pr$_2$	11.4	29
7	Pyridine-N-oxide	0.8	39
8	PPh$_3$	2.7	18
9	PCy$_3$	9.7	6
10	PPh$_3$O	0	71
11	PCy$_3$O	0	22

Reaction conditions: catalyst (3.75×10^{-5} mol), Lewis base (3.75×10^{-5} mol), PhNCO (1.25×10^{-3} mol), propylene oxide (2.5×10^{-3} mol), CH$_2$Cl$_2$, rt, 12 h. [a]Yields are relative to PhNCO and determined by GC analysis of the final reaction mixture employing tetramethylbenzene (TMB) as an internal standard. [b]References for these pKa values can be found in Table S1 in the SI.

As shown in Table 1, reducing the Lewis basicity of the cocatalyst had a significant impact on the yields of oxazolidinone in reaction 2. Replacing DMAP with the less-basic pyridine and 4-(trifluoromethyl)pyridine substantially increased the yield of oxazolidinone (Table 1, *cf* entries 1-3) with a concomitant drop in isocyanate trimer production. Several other amines and amine N-oxides were also tested as cocatalysts (Table 1, entries 4-6); however, none afforded yields that are comparable to that obtained with 4-(trifluoromethyl)pyridine. Indeed, the yield of the undesired aryl isocyanaurates trimer product can be directly correlated to the basicity of the Lewis-base cocatalysts (see Table 1 for the pKa's of the conjugate acids). Among the phosphorus-based cocatalysts investigated (Table 1, entries 7-10), the least basic PPh$_3$O provides a 71% yield of oxazolidinone, slightly higher than that obtained with 4-(trifluoromethyl)pyridine, the best amine cocatalyst. Hence, PPh$_3$O was chosen as the optimal cocatalyst for reaction 2 as it is also less expensive and easier to handle than the liquid 4-trifluoromethylpyridine. The rate for reaction 2 can be significantly increased when the PPh$_3$O/(salcen)Cr^{III} ratio is increased (SI, Fig. S1). However, the overall oxazolidinone yield

begins to suffer slightly when this ratio is increased beyond 2. Thus, we decided that 2 equivalents of PPh$_3$O cocatalyst is optimal for subsequent investigations.

Interestingly, reaction 2 affords about 37% of the oxazolidinone product in the absence of any Lewis base cocatalyst (SI, Fig. S1), which is in contrast to the Cr^{III}(salen)-catalyzed coupling of CO$_2$ and epoxides that does not occur in the absence of cocatalyst.[7a] This difference can be explained by the higher reactivity of isocyanates compared to CO$_2$. That both the yield (37% after 3 days) and rate of oxazolidinone production were lowest in the absence of the Lewis-base cocatalyst confirms its importance; however, competition from the undesirable trimerization reaction must be minimized.[10]

The choice of solvent was found to dramatically effect catalytic activity in reaction 2, as both the reaction rate and yield of the oxazolidinone product were significantly impacted (SI, Fig. S2). Reactions carried out in polar solvents (THF, ether, and CH$_2$Cl$_2$) were all completed after 4 h, whereas reactions carried out in non-polar solvents (toluene and dioxane) required nearly 24 h to consume all of the isocyanate. However, the higher reaction rate exhibited in the polar solvents was accompanied by a lower yield of the oxazolidinone product (relative to reactions carried out in the non-polar solvents) due to increased isocyanate trimerization. The effects that solvent polarity and coordinating ability have on the oxazolidinone yield in reaction 2 may be attributed to the fact that polar coordinating solvents can better stabilize the charged intermediates believed to exist in the base-catalyzed trimerization of isocyanates.[9a]

Having determined that non-polar solvents afford a higher product selectivity for reaction 2 but at slower rates, we attempted to improve these rates by increasing the reaction temperature. A comparison of the profiles for reactions carried out in toluene at rt, 40 °C, and 60 °C (SI, Fig. S3) shows that both the rate and yield are significantly improved with increased temperatures: at 60 °C, the reaction is completed within 2 h with an oxazolidinone yield of > 90%.

Under our optimized reaction parameters (60 °C in toluene), the [(salcen)Cr^{III} + PPh$_3$O] catalyst system can be applied to a broad range of terminal epoxides, yielding the corresponding oxazolidinone products in near quantitative yield (Table 2, entries 1-7). Alkyl- and aryl-substituted epoxides, with both electron-withdrawing and -donating substituents, were all found to be excellent substrates. Styrene oxide gave 99% conversion; however, the product was a 2:1 mixture of the 5- and 4-substituted oxazolidinone product. In contrast, all other epoxides yielded only trace amounts of the 4-substituted oxazolidinone product.[11,12]

To understand the mechanism of reaction 2, we carried out a comprehensive computational analysis of the reaction path using [(salen)Cr^{III} + DMAP] as the model catalyst system and [propylene oxide + phenyl isocyanate] as the model substrate pair. Given our recent computational investigation of the [(salen)Cr^{III} + DMAP]-catalyzed coupling of propylene oxide and CO$_2$, where a monometallic,[13] Lewis acid-Lewis base mechanism was found to be the most probable, we eliminated the possibility of a bimetallic pathway in this reaction. As shown in Fig. 1 and

2, coordination of the epoxide to the Lewis acidic (salen)Cr$^{(III)}$ center activates it for ring-opening by DMAP ($\Delta G^{\neq}$ = 25.6 kcal mol^{-1}). Isocyanate insertion into the Cr–alkoxide bond is also energetically favorable, with a barrier of 22.2 kcal mol^{-1}. Structurally, **2-TS**, the transition state (TS) for isocyanate insertion into the Cr–alkoxide bond, is very similar to what we found for the TS for CO_2 insertion into the same bond (SI, Fig. S5).[13] Ring-closure, through an S_N2-type attack of the imine functionality on the carbon bearing DMAP, then lead to the expulsion of DMAP and formation of the coordinated 5-membered oxazolidinone product. As can be seen from Fig. 1, the C^2 carbon center in the **3-TS** structure is indeed trigonal bipyramidal in shape, with the incoming C–O bond and the outgoing C–N bond arranged in a linear fashion.

Table 2 Substrate scope for the reaction of different isocyanates with epoxides catalyzed by [(salcen)Cr^{III} + PPh$_3$O].


(3)

Entry	R^1	R^2	Time	Yield (%)^a
1	CH$_3$	Ph	3.5	97
2	CH$_2$Cl	Ph	3.5	100
3	CH$_2$Ph	Ph	6	98
4	C$_4$H$_9$	Ph	6	90
5	CH$_2$OPh	Ph	4.5	99
6	Ph	Ph	6	99^b
7	(R)-CH$_3$	Ph	3.5	97^c
8	CH$_3$	4-MeO-Ph	4.5	97
9	CH$_3$	1-napthyl	3.5	96
10	CH$_3$	2,6-(^{i}Pr)$_2$-	7	85

Reaction conditions: **1** (1.58 × 10^{-5} mol), PPh$_3$O (3.16 × 10^{-5} mol), PhNCO (5.80 × 10^{-4} mol,), epoxide (5.27 × 10^{-4} mol), toluene, 60 °C. ^{a}relative to epoxide, determined by GC analysis employing TMB as an internal standard. ^{b} Product was a mixture of 3,5-diphenyl-1,3-oxazolidin-2-one/3,4-diphenyl-1,3-oxazolidin-2-one (63:36). ^{c}Complete retention of stereochemistry.
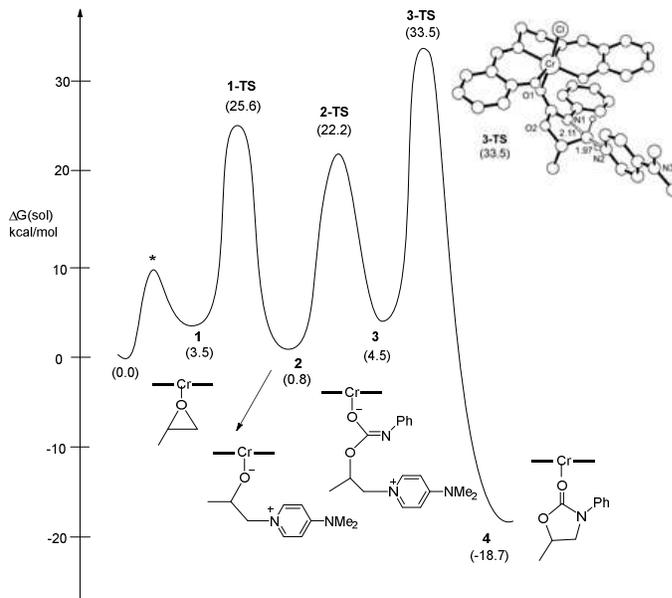
Fig. 1 The energy landscape for reaction 2 using [(salen)Cr^{III} + DMAP] as the model catalyst system and [propylene oxide + phenyl isocyanate] as the model substrate pair along with the structure of **3-TS** in the inset.

Given the aforementioned mechanism, the low selectivity of styrene oxide (Table 2, entry 6, footnote *b*) can be understood if ring opening of the (salcen)Cr^{III}-activated styrene oxide can occur spontaneously to give a carbocationic intermediate that was then intercepted by the external base. This will compete with our proposed cocatalyst-mediated ring-opening process (SI, Fig. S4), which is regulated by steric demand. In an activated epoxide such as **1**, substantial elongation of the substituted O–C bond, and eventual ring-opening at this bond, can indeed occur if the incipient carbocationic charge developed at the substituted carbon is stabilized by a phenyl substituent.[5b]
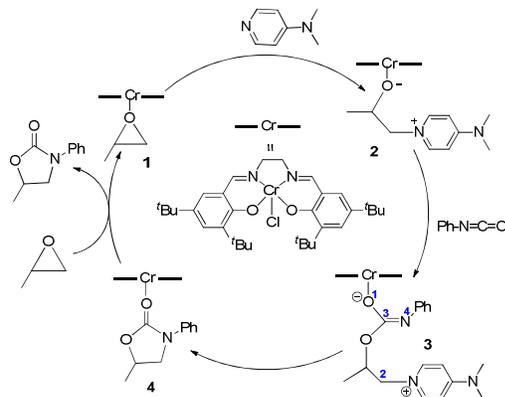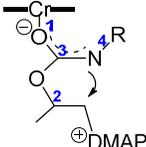

Fig. 2 Proposed mechanistic cycle for [(salen)Cr^{III} + DMAP] catalyzed coupling of propylene oxide and PhNCO, which has been computationally investigated. For the Wiberg BO discussion (see below), the relevant atoms are numbered in blue.

In the presence of the [(salcen)Cr^{III} + PPh$_3$O] catalyst, chirally pure (R)-propylene oxide were converted into the corresponding oxazolidinone with complete retention of stereochemistry, yielding the enantiomerically pure product (Table 2, entry 7) in excellent yield. As chiral epoxides are readily accessible via

numerous effective catalytic methods,[14] reaction 2 represents an attractive route to valuable chiral 5-oxazolidinones.[5b]

The [(salcen)Cr^{III} + PPh$_3$O] catalyst system can be readily extended to other aromatic isocyanates, with 4-methoxyphenyl and 1-napthyl isocyanates affording near quantitative yield of the corresponding oxazolidinone (Table 2, entries 8-10). As expected for the steric-demanding insertion step shown in Fig. 1, the bulky 2,6-^{i}Pr$_2$-PhNCO derivative affords slightly lower yields. While we have investigated several alkyl isocyanates as potential substrates, they did not yield any oxazolidinone even after 24 h at 60 °C. This lack of reactivity can be explained by the required hybridization change of the C=N bond in **3** upon S$_N$2 attack by the N lone pair at the DMAP-bearing carbon (C^2 in **3**) to form the desired product. This attack is more likely if the substituent on the nitrogen can facilitate the change in hybridization. As shown in Table 3, when the substituent for the isocyanate is changed from an alkyl (Me or Bn) to an aromatic (Ph or p-NO$_2$-Ph) group, the Wiberg bond order (BO) for O^1–C^3 is increased and that for C^3=N^4 is decreased. This in turn facilitates the attack by the N lone pair on C^2 and the subsequent rehybridization of the C^3=N^4 bond into a single bond. This trend is additionally supported by the observation that the TS-barrier for the aryl isocyanates are less energetically demanding than those for the alkyl isocyanates.

Table 3 Computed BO of O^1–C^3 and C^3–N^4 bonds in the rate-determining TS for different R^2-substituted isocyanates.

R	BO		TS-energy (kcal mol^{-1})
	O^1-C^3	C^3-N^4	
Ph	1.36	1.36	33.5
p-NO$_2$-Ph	1.38	1.30	31.0
Me	1.31	1.45	36.5
Bn	1.32	1.44	34.5

We note in passing that the lack of reactivity displayed by the alkyl isocyanates in reaction 1 is not a major drawback: access to virtually any N-substituted oxazolidinone is easily afforded via the CAN-promoted oxidative dearylation of N-(4-methoxyphenyl) oxazolidinone.[15] The resultant N-unsubstituted oxazolidinone can then be readily alkyl-functionalized.

In conclusion, the [(salcen)Cr^{III} + PPh$_3$O] combination is a highly efficient and selective catalyst for the synthesis of 5-aryl-substituted oxazolidinones from the [2+3] cycloaddition reaction of a broad range of epoxides and arylisocyanates under mild reaction conditions. Mechanistic computational analysis reveals that this reaction proceeds through the same pathway as the [(salen)Cr$^{(III)}$ + DMAP]-catalyzed coupling of epoxides and CO$_2$,[13] but is thermodynamically more favorable owing to the reactive nature of isocyanates. In this manner, PPh$_3$O behaves as a synergistic Lewis-base cocatalyst for the Lewis-acidic (salcen)Cr^{III} center, in contrast to that observed for the [(salen)Al]$_2$O system,[5b] where it is an inhibitor. The use of the PPh$_3$O cocatalyst, with its low Lewis basicity, in conjunction with non-polar organic solvents was important to limit the competitive trimerization of the isocyanate. In addition, access to enantiopure oxazolidinones is possible when enantiopure epoxides are employed as substrates.

Notes and references

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11. We note in passing that Saito and coworkers (see ref. 12) have observed that nickel iodide can catalyze the coupling of isocyanate with strained aziridine ring to afford the thermodynamically less-stable iminooxazolidine product (by 19.7 kcal/mol, see SI) that eventually rearranged to the oxazolidinone.

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