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[(Salcen)Cr^{III} + Lewis base]-catalyzed synthesis of *N*-aryl-substituted oxazolidinones from epoxides and aryl isocyanates†

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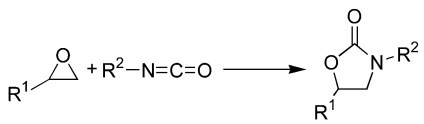
[(Salcen)Cr^{III} + Lewis base] was found to be a highly active and selective catalyst system in the [2+3] cycloaddition between epoxides and isocyanates to form 5-oxazolidinones. The reaction proceeds to high yield under mild reaction conditions and is applicable to a variety of terminal epoxides and 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 syntheses,[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 (eqn (1)) is the most attractive due to the ease of access to both classes of substrates.[5]



(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 either a slow addition of isocyanate, or an excess of the 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,h] 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, comprising a Cr^{III}(salen) complex (salen = *N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-diaminoethane) in conjunction with a Lewis base is highly efficient for the [2+3] cycloaddition 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 [(salcen)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 (eqn (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 2). 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 mixture. Indeed, previous reports have indicated that the irreversible trimerization of isocyanates can be catalyzed by

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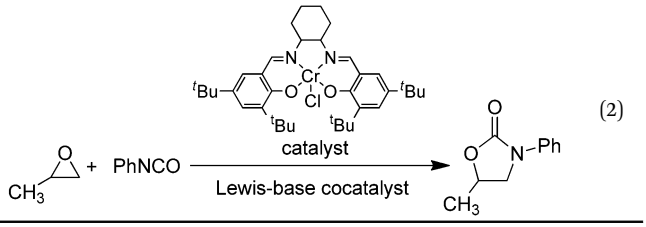
Table 1 Variation of the Lewis-base cocatalyst for reaction (2)



(2)

Entry	Lewis base	pK_a 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-imidazole	7.4	18
6	NEt^iPr_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_3O	0	71
11	PCy_3O	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_2Cl_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 pK_a values can be found in Table S1 in the ESI.

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).

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 2–4) with a concomitant drop in isocyanate trimer production. Several other amines and amine *N*-oxides were also tested as cocatalysts (Table 1, entries 5–7); 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 pK_a's of the conjugate acids). Among the phosphorus-based cocatalysts investigated (Table 1, entries 8–11), the least basic PPh_3O provides a 71% yield of oxazolidinone, slightly higher than that obtained with 4-(trifluoromethyl)pyridine, the best amine cocatalyst. Hence, PPh_3O 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_3O/(salcen)Cr^{III} ratio is increased (ESI,† 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_3O cocatalyst is optimal for subsequent investigations.

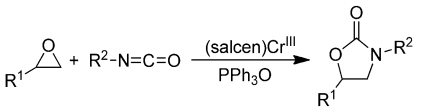
Interestingly, reaction (2) affords about 37% of the oxazolidinone product in the absence of any Lewis base cocatalyst (ESI,† Fig. S1), which is in contrast to the Cr^{III}(salen)-catalyzed coupling of CO_2 and epoxides that does not occur in the absence of cocatalyst.[7a] This difference can be explained by the higher reactivity of isocyanates compared to CO_2. That both the yield (37% after 3 days; Table 1, entry 1) 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 (ESI,† Fig. S2). Reactions carried out in polar solvents (THF, ether, and CH_2Cl_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 (ESI,† 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_3O] catalyst system can be applied to a broad range of terminal epoxides, yielding the corresponding oxazolidinone products in near quantitative yield (Table 2,

Table 2 Substrate scope for the reaction of different isocyanates with epoxides catalyzed by [(salcen)Cr^{III} + PPh_3O]



(3)

Entry	R^1	R^2	Time (h)	Yield[a] (%)
1	CH_3	Ph	3.5	97
2	CH_2Cl	Ph	3.5	100
3	CH_2Ph	Ph	6	98
4	C_4H_9	Ph	6	90
5	CH_2Oph	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-$^iPr_2$-Ph	7	85

Reaction conditions: **1** (1.58×10^{-5} mol), PPh_3O (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.

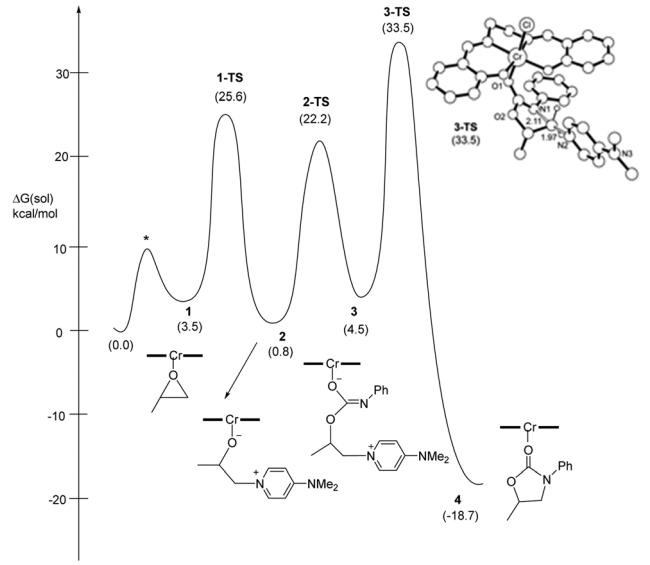


Fig. 1 The energy landscape for reaction (2) using [(salen)Cr^{III} + DMAP] as the model catalyst system and [propylene oxide + phenyl isocyanate] as the model substrate pair along with the structure of **3-TS** in the inset.

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 (Table 2, entry 6, footnote *b*). 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

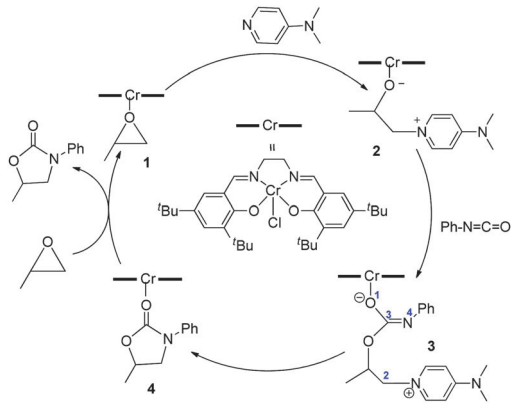


Fig. 2 Proposed mechanistic cycle for [(salen)Cr^{III} + DMAP] catalyzed coupling of propylene oxide and PhNCO, which has been computationally investigated. For the Wiberg BO discussion (see below), the relevant atoms are numbered in blue.

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 (ESI,† 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.

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 (ESI,† 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]

In the presence of the [(salcen)Cr^{III} + PPh_3O] 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 (3) represents an attractive route to valuable chiral 5-oxazolidinones.[5b]

The [(salcen)Cr^{III} + PPh_3O] 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. 2, 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 $C^3{=}N^4$ bond in **3** upon S_N2 attack at the DMAP-bearing carbon (C^2 in **3**) by the N^4 lone pair 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

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

	R	BO O^1–C^3	BO C^3–N^4	TS-energy (kcal mol^{-1})
	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

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 at C^2 by the N^4 lone pair 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.

We note in passing that the lack of reactivity displayed by the alkyl isocyanates in reaction (3) 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_3O] combination is a highly efficient and selective catalyst for the synthesis of 5-aryl-substituted oxazolidinones from the [2+3] cycloaddition reaction between 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_3O 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_3O 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.

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Notes and references

1 (*a*) K. S. Jandu, V. Barrett, M. Brockwell, D. Cambridge, D. R. Farrant, C. Foster, H. Giles, R. C. Glen, A. P. Hill, H. Hobbs, A. Honey, G. R. Martin, J. Salmon, D. Smith, P. Woollard and D. L. Selwood, *J. Med. Chem.*, 2001, **44**, 681–693; (*b*) F. Reck, F. Zhou, C. J. Eyermann, G. Kern, D. Carcanague, G. Ioannidis, R. Illingworth, G. Poon and M. B. Gravestock, *J. Med. Chem.*, 2007, **50**, 4868–4881; (*c*) T. A. Mukhtar and G. D. Wright, *Chem. Rev.*, 2005, **105**, 529–542; (*d*) M. R. Barbachyn and C. W. Ford, *Angew. Chem., Int. Ed.*, 2003, **42**, 2010–2023.

2 (*a*) S. C. Bergmeier and D. M. Stanchina, *J. Org. Chem.*, 1999, **64**, 2852–2859; (*b*) H. A. McManus and P. J. Guiry, *Chem. Rev.*, 2004, **104**, 4151–4202.

3 (*a*) T. Hakogi, Y. Monden, S. Iwama and S. Katsumura, *Org. Lett.*, 2000, **2**, 2627–2629; (*b*) C. M. Orac, S. Zhou, J. A. Means, D. Boehm, S. C. Bergmeier and J. V. Hines, *J. Med. Chem.*, 2011, **54**, 6786–6795.

4 R. Robles-Machín, J. Adrio and J. C. Carretero, *J. Org. Chem.*, 2006, **71**, 5023–5026.

5 (*a*) M. E. Dyen and D. Swern, *Chem. Rev.*, 1967, **67**, 197–246; (*b*) T. Baronsky, C. Beattie, R. W. Harrington, R. Irfan, M. North, J. G. Osende and C. Young, *ACS Catal.*, 2013, **3**, 790–797.

6 (*a*) I. Shibata, A. Baba and H. Matsuda, *Tetrahedron Lett.*, 1986, **27**, 3021–3024; (*b*) G. P. Speranza and W. J. Peppel, *J. Org. Chem.*, 1958, **23**, 1922–1924; (*c*) J. E. Herweh, T. A. Foglia and D. Swern, *J. Org. Chem.*, 1968, **33**, 4029–4033; (*d*) M. Fujiwara, A. Baba and H. Matsuda, *J. Heterocycl. Chem.*, 1988, **25**, 1351–1357; (*e*) I. Shibata, A. Baba, H. Iwasaki and H. Matsuda, *J. Org. Chem.*, 1986, **51**, 2177–2184; (*f*) A. Baba, K. Seki and H. Matsuda, *J. Heterocycl. Chem.*, 1990, **27**, 1925–1930; (*g*) B. M. Trost and A. R. Sudhakar, *J. Am. Chem. Soc.*, 1987, **109**, 3792–3794; (*h*) C. Larksarp and H. Alper, *J. Am. Chem. Soc.*, 1997, **119**, 3709–3715.

7 (*a*) R. L. Paddock and S. T. Nguyen, *J. Am. Chem. Soc.*, 2001, **123**, 11498–11499; (*b*) A. W. Miller and S. T. Nguyen, *Org. Lett.*, 2004, **6**, 2301–2304.

8 (*a*) H. A. Duong, M. J. Cross and J. Louie, *J. Am. Chem. Soc.*, 2004, **126**, 11438–11439; (*b*) B. R. D'Souza and J. Louie, *Org. Lett.*, 2009, **11**, 4168–4171.

9 (*a*) A. K. Zhitinkina, N. A. Shibanova and O. G. Tarakanov, *Russ. Chem. Rev.*, 1985, **54**, 1104–1125; (*b*) Y. Taguchi, I. Shibuya, M. Yasumoto, T. Tsuchiya and K. Yonemoto, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 3486–3489.

10 In the absence of the Lewis base, formation of the isocyanurate is very slow even at 100 °C and its formation is irreversible. See: P. A. Argabright, B. L. Phillips and C. H. DePuy, *J. Org. Chem.*, 1970, **35**, 2253–2257.

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^{-1}, see ESI†) that eventually rearranged to the oxazolidinone.

12 T. Munegumi, I. Azumaya, T. Kato, H. Masu and S. Saito, *Org. Lett.*, 2006, **8**, 379–382.

13 D. Adhikari, S. T. Nguyen and M.-H. Baik, *Chem. Commun.*, 2014, **50**, 2676–2678.

14 (*a*) P. Besse and H. Veschambre, *Tetrahedron*, 1994, **50**, 8885–8927; (*b*) *Comprehensive Asymmetric Catalysis*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer, New York, 1999.

15 Y. S. Park, M. L. Boys and P. Beak, *J. Am. Chem. Soc.*, 1996, **118**, 3757–3758.

