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Group 13 Lewis acid-mediated formation of 5-oxazolone derivatives from *tert*-butyl isocyanoacetate†

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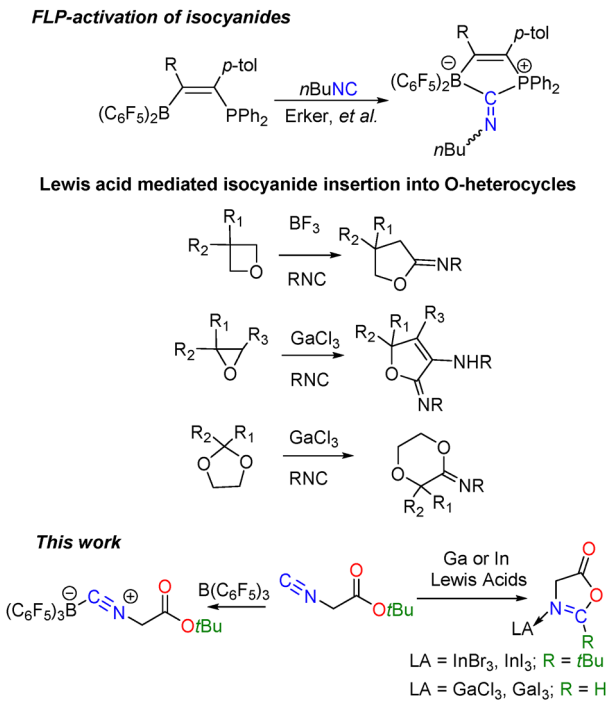
***tert*-Butyl isocyanoacetate 1 reacted with $B(C_6F_5)_3$ to give a Lewis acid–base adduct 2. $GaCl_3$ and GaI_3 promoted cyclization affording the N-bound Lewis acid adducts of the cyclized product 5-oxazolone derivatives 3 and 4, resulting from isocyano insertion into the ester C–O bond, with the loss of isobutylene. In contrast, the reactions with $InBr_3$ and InI_3 afforded the analogous adducts of 5(4*H*)-oxazolone derivatives 5 and 6, without the loss of the *tert*-butyl group. A proposed reaction mechanism is provided for these reactions of 1.**

Isocyanides and their derivatives are valuable synthetic intermediates and are widely used in pharmaceuticals,[1] materials science,[2,3] and organic synthesis.[4–7] They are frequently used in multicomponent reactions (*e.g.*, Passerini, Ugi, Barton–Zard and Van Leusen reactions),[8–10] which exploit the acidity of the α-C–H bonds to enable efficient cyclization or coupling reactions.[11] Additionally, isocyanides can insert into C–X (X = halogen, C, O, S and H)[12–14] or metal–carbon bonds[12,15,16], mediated or catalyzed by transition metal complexes (*e.g.* Pd and base metals).

Group 13 Lewis acids have been widely exploited as reagents or catalysts in organic synthesis,[17–22] as Lewis acid activation can induce the transformation of small molecules and functional groups.[23–28] For example, the Lewis acids $AlCl_3$ and $GaCl_3$ are known to mediate the Friedel–Crafts reactions[29,30] as well as cyclocondensations.[31–33] In recent years, highly active group 13 Lewis acids such as $B(C_6F_5)_3$ and $Al(C_6F_5)_3$ have attracted considerable attention.[27,28,34,35] Perhaps most notably, such Lewis acids generate "encounter complexes" with bulky Lewis bases prompting frustrated Lewis pair (FLP) chemistry of a variety of small molecules and affording new reaction types.[36–41] While these group 13 Lewis acids have been used to effect cyclization reactions of alkynes,[42–48] the corresponding reactions of isocyanides have not been reported. However, reactions of a phosphorus/boron FLP with isocyanides have been reported to generate a heterocyclic zwitterionic product of 1,1-addition of the FLP to the terminal carbon atom (Scheme 1).[49]



Scheme 1 Group 13 Lewis acid-mediated isocyanide activation.

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Despite the presence of a triple bond in both alkynes and isocyanides, the latter are strong sigma donors due to the lone pair of electrons on the terminal carbon atom. As a consequence, these species form stable adducts with Lewis acids, although group 13 Lewis acids have been used to mediate the insertion of isocyanide groups into heterocycles containing C–O bonds, effecting ring expansion (Scheme 1).[50–52] In the present study, we probe the reactivity of *tert*-butyl isocyanoacetate with various group 13 Lewis acids. The findings demonstrate that, depending on the Lewis acid used, the reaction pathway can provide Lewis acid–base adducts, effect intramolecular cyclization and in some cases also induce degradation of the *tert*-butyl group and transfer of the hydrogen atom to the isocyanide carbon atom, thus providing facile and unique access to 5-oxazolone derivatives[53] (Scheme 1).

Initially, density functional theory (DFT) calculations for the molecular orbitals of *tert*-butyl isocyanoacetate **1** were performed at the B3LYP-D3/def2-TZVP level of theory. The lone pairs of electrons at the carbonyl oxygen atom contribute to the highest occupied molecular orbital (HOMO) of **1**, while the HOMO−1 of **1** is mainly associated with the lone pair at the terminal carbon atom of the isocyanide group (Fig. 1a). Interestingly, computations for the corresponding interactions of $B(C_6F_5)_3$ with **1** showed that isocyanide-binding to $B(C_6F_5)_3$ is energetically favoured (−91.3 kJ mol^{-1}) over interaction with the carbonyl group. This may be in part attributed to the steric hindrance between $B(C_6F_5)_3$ and the *tert*-butyl group, but the focused directionality of the lone pair at the terminal carbon atom of the isocyanide group may also be important here.

To probe this experimentally, a mixture of **1** and $B(C_6F_5)_3$ in toluene solution was stirred at ambient temperature for 1 hour (Scheme 2). This afforded a new set of ^{19}F NMR resonances at −132.9, −154.9 and −162.7 ppm, as well as a new singlet at −21.2 ppm in the ^{11}B NMR spectrum. These data are suggestive of a tetracoordinate boron center.[54] Colourless crystals of **2** suitable for X-ray diffraction (XRD) analysis were obtained from toluene solution at −30 °C. The structural solution affirmed the tetracoordinated nature of the boron center and the formulation

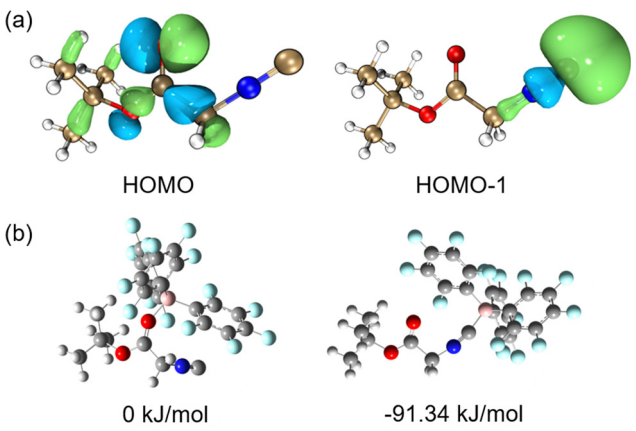
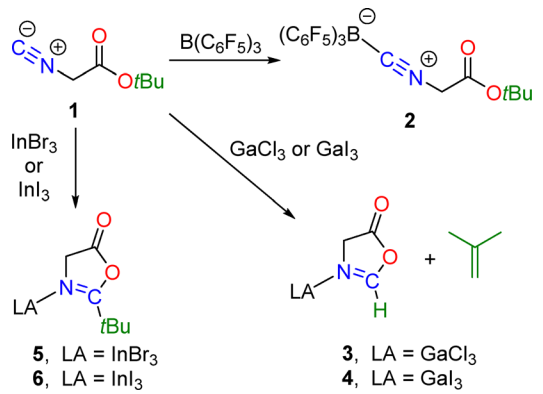


Fig. 1 (a) HOMO and HOMO−1 of **1** and (b) different coordination modes of **1** with $B(C_6F_5)_3$, each accompanied by its gas-state single-point energy.



Scheme 2 Synthesis of **2–6**.

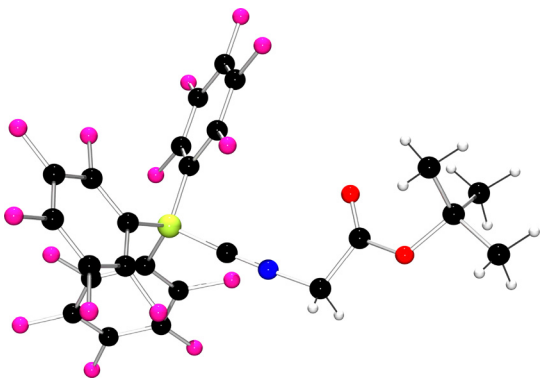


Fig. 2 POV-ray image of **2**. Solvents are omitted for clarity. H: white, C: black, F: hot pink, N: blue, O: red, and B: yellow-green.

of **2** as $(tBuO_2CCH_2NC)B(C_6F_5)_3$ (Fig. 2). The binding of the isocyanide to boron gave a $B–C_{isocyano}$ bond length of 1.613(5) Å. This value is very close to the $B–C_{isocyano}$ bond length found for the $(Ph_3PNNC)B(C_6F_5)_3$ adduct,[55] while the N–C bond length in **2** (1.133(4) Å) of the isocyano group is consistent with a triple bond.

In contrast, treating **1** with one equivalent of BCl_3 or $BF_3(OEt_2)$ gave complex and inseparable mixtures of products. On the other hand, a reaction with $GaCl_3$ in a toluene solution (Scheme 2) led to a new singlet in the ^1H NMR spectrum at 6.36 ppm. The singlet at 164.80 ppm in the ^{13}C NMR spectrum was assigned to the carbonyl group, while no methyl resonances were observed in the ^1H or ^{13}C NMR spectra. Colourless crystals of product **3** were isolated from a toluene solution after standing at −30 °C overnight. The molecular formulation of **3** (Fig. 3a) was crystallographically determined to be $(CH_2CO_2CHN)GaCl_3$ featuring a five-membered 5(4*H*)-oxazolone ring coordinated to a $GaCl_3$ moiety *via* the N atom. This was consistent with the degradation of the *t*-butyl group. The Ga–N bond (1.978(6) Å) and three Ga–Cl bonds (2.1349(19), 2.1562(18) and 2.158(2) Å) complete the pseudo-tetrahedral coordination spheres of the Ga atom. The C_3NO ring is nearly planar with a C–N–C angle of 107.0(6)°. The two N–C bonds with lengths of 1.260(9) and 1.465(9) Å can be attributed to a N=C double bond and a N–C single bond, respectively. The IR spectrum of **3**

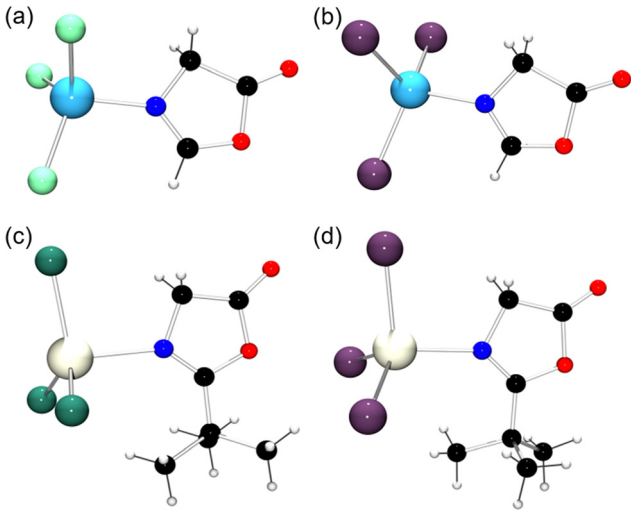


Fig. 3 POV-ray images of (a) **3**, (b) **4**, (c) **5** and (d) **6**. Solvents and disorders are omitted for clarity. H: white, C: black, N: blue, O: red, Ga: sky blue, In: wheat, and I: violet.

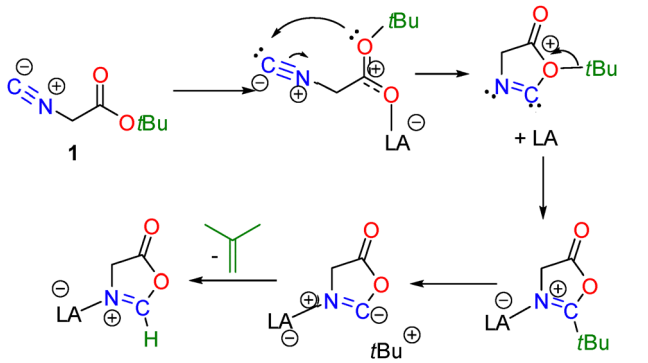
features a strong resonance around 1733 cm^{-1}, which was attributed to the carbonyl moiety.

The analogous reaction of **1** with GaI_3 in a toluene solution results in the formation of compound **4** (Scheme 2). The singlet ^1H and ^{13}C NMR spectra were similar to those observed for **3** and compound **4** also showed a strong C=O resonance peak at 1731 cm^{-1}. Colourless crystals of **4** suitable for single-crystal XRD analysis were obtained after storing the toluene solution at −30 °C overnight. The molecular structure of (CH_2CO_2CHN)-GaI_3 **4** (Fig. 3b) is similar to that of **3**, with a Ga–N bond length of 2.023(11) Å and three Ga–I bond lengths of 2.5321(18), 2.504(2) and 2.4978(19) Å.

The corresponding reaction of **1** with $InBr_3$ (Scheme 2) proceeded in CH_2Cl_2 solution at room temperature. In contrast to the Ga products **3** and **4**, a new singlet was observed at 1.57 ppm in the ^1H NMR spectrum and a corresponding singlet at 26.31 ppm in the ^{13}C NMR spectrum. These were attributed to a *tert*-butyl group in the product. The IR spectrum of product **5** showed a strong absorption peak around 1904 cm^{-1}, again consistent with the presence of a carbonyl fragment. Single-crystal X-ray crystallographic analysis of **5** (Fig. 3c) confirmed the formulation $((t\text{Bu})COC(O)CH_2N)InBr_3$. In this case, analogous cyclization and binding of the Lewis acid to the oxazolone ring is observed; however, the C-*t*Bu moiety is retained. The In–N bond length was determined to be 2.315(4) Å.

Using InI_3, the related adduct $((t\text{Bu})COC(O)CH_2N)InI_3$ **6** showed similar spectral data and its formulation was confirmed by crystallographic data (Fig. 3d). The planar five-membered 5(4*H*)-oxazolone ring was bound to InI_3 with an In–N bond length of 2.280(6) Å, while the carbonyl fragment exhibited an IR absorption peak around 1901 cm^{-1}.

The formation of these oxazolone products **2–6** is thought to be initiated *via* initial coordination of **1** to the group 13 Lewis acids (Scheme 3). The steric demands of $B(C_6F_5)_3$ result in a preference for interaction with the HOMO−1 of **1** located on



Scheme 3 Proposed reaction mechanism for the reactions of **1** with group 13 Lewis acids.

the isocyanide fragment, affording the isolation of adduct **2**. In contrast, binding of gallium and indium Lewis acids to the HOMO on oxygen induces cyclization, with concurrent migration of the *tert*-butyl group to the isocyanide carbon as well as migration of the Lewis acid to the more basic imine nitrogen atom (Scheme 2) as in the indium derivatives **5** and **6**. However, in the Ga reactions, the resulting steric congestion between the GaX_3 and *tert*-butyl fragments induces degradation of the *tert*-butyl group, resulting in the loss of isobutylene leaving a C–H bond on the heterocycle providing gallium derivatives **3** and **4**. Similar degradation of *tert*-butyl ester fragments has been reported for the reactions of di-*tert*-butyl diazodicarboxylate with $B(C_6F_5)_3$[56] or BF_3.[57]

In conclusion, we have demonstrated the varying reactivities of *tert*-butyl isocyanoacetate **1** with a series of group 13 Lewis acids. The reaction of **1** with $B(C_6F_5)_3$ gave the classic Lewis acid–isocyanate adduct **2**, while reactions employing gallium and indium Lewis acids induced cyclizations, yielding 5(4*H*)-oxazolone derivatives **3–6**. It is further proposed that the steric congestion of adjacent *tert*-butyl and GaX_3 fragments results in the elimination of isobutylene, affording the C–H fragments in **3** and **4**. It is interesting to note that the present study illustrates that variations of the Lewis acidity and steric properties of group 13 Lewis acid centers can be exploited in the synthesis of 5(4*H*)-oxazolone derivatives. Moreover, the variation of the Lewis acids affords products that model the various stages of the reaction pathway. We are continuing to explore the utility of group 13 Lewis acid mediated transformation in our effort to uncover novel strategies to heterocyclic species.

Z. H. performed the experiments. S. J. carried out the DFT calculations. T. C. assisted Z. H. with data collection. X. Z., D. W. S. and Y. W. prepared the manuscript and managed the project.

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Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the ESI.†

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