

Zinc(II)-Mediated Carbene Insertion into C–H Bonds in Alkanes

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S Supporting Information

ABSTRACT: The cationic zinc adduct $\{[\text{HB}(3,5\text{-(CF}_3)_2\text{Pz})_3]\text{Zn}(\text{NCMe})_2\}\text{ClO}_4$ catalyzes the functionalization of tertiary, secondary, and primary C–H bonds of alkanes via carbene insertion. Ethyl diazoacetate serves as the $:\text{CHCO}_2\text{Et}$ carbene precursor. The counteranion, supporting ligand, and coordinating solvents affect the catalytic activity. An in situ generated $\{[\text{HB}(3,5\text{-(CF}_3)_2\text{Pz})_3]\text{Zn}\}^+$ species containing a bulkier $\{\text{B}[3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3]_4\}^-$ anion gives the best results among the zinc catalysts used.

The activation of unfunctionalized C–H bonds is of significant importance because it allows the synthesis of a variety of complex organic compounds from more widely available hydrocarbon precursors.^{1–4} Among the routes available for the functionalization of aliphatic C–H bonds, metal-mediated carbene insertion processes are some of the most promising and attracted the interest of several groups.^{3–8} Diazoacetates like ethyl diazoacetate (EDA) are the most common carbene source, while copper- and rhodium-based compounds are the earliest and most widely used catalysts for this process.^{3,5,7,9,10}

We have been working on the development of highly fluorinated tris(azolyl)borates (scorpionates)¹¹ and their utility in the stabilization of molecules possessing very electrophilic metal sites.^{6,12,13} During the course of this work, Dias, Lovely, and co-workers discovered that silver(I) adducts like $[\text{HB}(3,5\text{-(CF}_3)_2\text{Pz})_3]\text{Ag}(\text{THF})$ containing highly fluorinated scorpionates [where $[\text{HB}(3,5\text{-(CF}_3)_2\text{Pz})_3]^-$ = hydrotris[3,5-bis(trifluoromethyl)pyrazolyl]borate] very effectively catalyze carbene insertion into unfunctionalized C–H bonds including primary C–H bonds under remarkably mild conditions.¹⁴ We have also showed that it is possible to modulate this reactivity by using sterically and electronically different ligands like $[\text{MeB}(3\text{-(C}_2\text{F}_5)_2\text{Pz})_3]^-$, $[\text{HB}(3,5\text{-(CF}_3)_2\text{Pz})_4\text{-(Cl)Pz})_3]^-$, and $[\text{HB}(3,5\text{-(CF}_3)_2\text{Pz})_4\text{-(NO}_2\text{)Pz})_3]^-$ or by varying the carbene source.^{13,15,16} The utility of silver adducts of fluorinated scorpionates in methane activation chemistry has also been noted.¹⁷ In this paper, we describe the use of 3d-metal-based zinc(II) scorpionates as efficient catalysts to functionalize tertiary, secondary, and primary C–H bonds of hydrocarbons via carbene insertion. We recently reported C–halogen bond functionalization via a similar route using zinc.¹⁸

The primary catalyst $\{\text{LZn}(\text{NCMe})_2\}\text{ClO}_4$ ($\text{L} = [\text{HB}(3,5\text{-(CF}_3)_2\text{Pz})_3]$; Figure 1) used in this work was synthesized in 71%

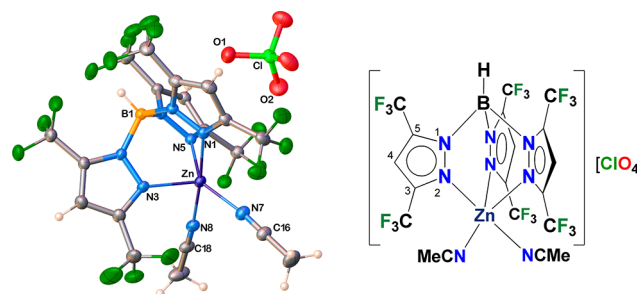


Figure 1. Zinc(II) catalyst $\{[\text{HB}(3,5\text{-(CF}_3)_2\text{Pz})_3]\text{Zn}(\text{NCMe})_2\}\text{ClO}_4$ and a view of its molecular structure. Selected bond lengths (Å) and angles (deg): Zn–N1 = 2.2028(19), Zn–N3 = 2.058(2), Zn–N5 = 2.0507(19), Zn–N7 = 1.982(2), Zn–N8 = 2.164(2); N3–Zn–N5 = 95.96(7), N5–Zn–N7 = 141.19(8), N3–Zn–N7 = 122.85(8), N1–Zn–N8 = 174.28(7), N7–Zn–N8 = 88.67(8).

isolated yield by treating LiNa with $\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ in acetonitrile in the presence of a few grains of activated molecular sieves (to remove water). Suitable crystals for X-ray analysis were obtained from a dichloromethane solution of the complex stored at -20°C . The X-ray crystal structure of the bis(acetonitrile) adduct $\{\text{LZn}(\text{NCMe})_2\}\text{ClO}_4$ is illustrated in Figure 1. It has a distorted trigonal-bipyramidal zinc center. The pyrazolyl nitrogen atoms of a κ^3 -bound L^- ligand occupy two equatorial and one axial sites with two long and one short Zn–N distances. Not surprisingly, the equatorial and axial Zn–acetonitrile bond distances are also different, e.g., Zn–N7 = 1.982(2) Å and Zn–N8 = 2.164(2) Å. The bis(isocyanide)zinc adduct $\{\text{LZn}(\text{CN}^t\text{Bu})_2\}\{\text{B}[3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3]_4\}^-$ is known, and, interestingly, it also adopts a similar trigonal-bipyramidal structure.¹⁸

In a typical catalytic process, 1 equiv of catalyst was placed in 1.5 mL of hydrocarbon (substrate and also the solvent) and stirred at 60°C . This mixture was slowly treated with a solution of 20 equiv of EDA (which is the carbene precursor) in the same hydrocarbon (5 mL) using a syringe pump (rate: 1 mL/h). After the mixture was stirred at 60°C overnight, the resulting products were analyzed using NMR spectroscopy and gas chromatography–mass spectrometry methods. The results are summarized

Received: June 26, 2015

Published: November 20, 2015



Table 1. Metal-Catalyzed Carbene Insertion into C–H Bonds of Hydrocarbons with EDA ($L = [HB(3,5-(CF_3)_2Pz)_3]$; $L' = [MeB(3-(CF_3)Pz)_3]$)^a

catalyst	substrate	total C–H % yield ^b	1° C–H ^b	2° C–H ^b	3° C–H ^b
$\{LZn(NCMe)_2\}ClO_4$	cyclohexane	91		91	
$\{LZn(NCMe)_2\}ClO_4$	2-methylpentane	75	37 (1)	30 (1.82)	8 (1.95)
$\{LZn(NCMe)_2\}ClO_4$	2,3-dimethylbutane	74	56 (1)		18 (1.93)
$LZnCl$	cyclohexane	57		57	
$\{LZn\}\{B[3,5-(CF_3)_2C_6H_3]_4\}$	cyclohexane	98		98	
$Zn(OTf)_2$	cyclohexane	23		23	
$\{LZn\}\{B[3,5-(CF_3)_2C_6H_3]_4\}$	2,3-dimethylbutane	85	66 (1)		19 (1.72)
$LA_g(THF)$	cyclohexane	99		99	
$LA_g(THF)$	2,3-dimethylbutane	95	75 (1)		20 (1.60)
$LCu(C_2H_4)$	cyclohexane	40		40	
$LCu(C_2H_4)$	2,3-dimethylbutane	10	0		10
$\{L'Zn(NCMe)\}ClO_4$	cyclohexane	12		12	

^aReactions at 60 °C. ^bTotal C–H insertion product yields (%) and primary, secondary, and tertiary C–H insertion product yields (%) are based on the EDA used and calculated by integration of ¹H NMR signals. The remaining EDA either was found to be unreacted or was converted into a mixture of dimethyl fumarate and maleate (see the Supporting Information for details). Normalized C–H insertion selectivity values were calculated using the ratio of :CHCO₂Et carbene insertion products and the number of each type of C–H bonds and are provided in parentheses.

in Table 1 (provided in more detail in Table S1 in the Supporting Information). Results show that $\{LZn(NCMe)_2\}ClO_4$ is an excellent catalyst for inserting a :CHCO₂Et carbene fragment from EDA into C–H bonds of cyclohexane, providing ethyl 2-cyclohexylacetate in 91% yield. The elevated temperature is necessary for higher activity. When the same process was carried out at room temperature, only 13% ethyl 2-cyclohexylacetate was produced, while about 80% EDA remained unreacted. The sluggish activity at room temperature is probably a result of acetonitrile being retained on zinc(II), which not only lowers the Lewis acidity but also hinders the interaction of EDA with zinc. Higher temperatures, in contrast, would facilitate the dissociation of acetonitrile from zinc, thus creating open coordination sites for EDA. Interestingly, $LZnCl$ is also capable of catalyzing carbene insertion into C–H bonds of cyclohexane at 60 °C, producing 57% ethyl 2-cyclohexylacetate (while 40% EDA remains unreacted). A lower product yield compared to that of the $\{LZn(NCMe)_2\}ClO_4$ -mediated reaction (which produces 91% carbene insertion product under similar conditions) is not surprising because the latter has a weakly coordinating ClO_4^- counterion, while $LZnCl$ is a neutral species with a covalently bound chloride ion. In fact, $\{LZn\}\{B[3,5-(CF_3)_2C_6H_3]_4\}$, which has one of the weakest coordinating counterions,¹⁹ shows the highest activity under comparable conditions, affording ethyl 2-cyclohexylacetate from cyclohexane and EDA in essentially quantitative yield. This catalyst was generated in situ from $LZnEt$ and $[Ph_3C]\{B[3,5-(CF_3)_2C_6H_3]_4\}$ (and in the absence of donors like acetonitrile). A less acidic $\{[MeB(3-(CF_3)Pz)_3]Zn(NCMe)\}ClO_4$ -mediated reaction produced only 12% carbene insertion product with cyclohexane (compared to the 91% $\{LZn(NCMe)_2\}ClO_4$ -catalyzed reaction), illustrating the effect of the supporting ligand on zinc(II).

We have also investigated the catalytic activity of $\{LZn(NCMe)_2\}ClO_4$ with other hydrocarbon substrates like 2,3-dimethylbutane (which contains tertiary and primary C–H bonds) and 2-methylpentane (which contains primary, secondary, and tertiary C–H bonds). With 2,3-dimethylbutane, C–H functionalization products were obtained in a total of 74% yield with a relative selectivity of 1:1.93 toward primary versus tertiary C–H bonds. When 2-methylpentane was used as the substrate, a total of 75% of the C–H functionalization products was obtained. The relative selectivities of carbene insertion into

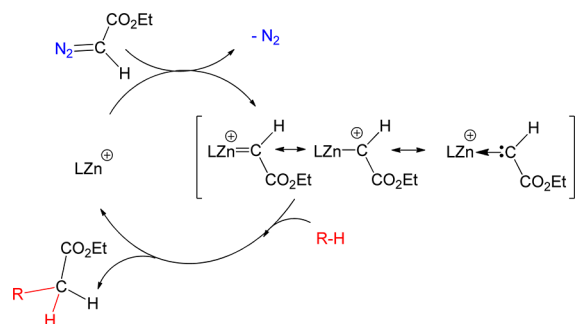
primary, secondary, and tertiary C–H bonds were found to be 1, 1.82, and 1.95, respectively, which are in line with the relative C–H bond energies^{1,7} in which the weaker tertiary bonds get activated at a relatively greater level compared to stronger primary C–H bonds. The C–H bond functionalization chemistry of cyclohexane and 2,3-dimethylbutane was also probed under similar conditions using the well-established silver catalyst $LA_g(THF)$ for comparison.^{6,15} The results show that $LA_g(THF)$ (which is a neutral complex and a 4d-metal-based catalyst and more soluble in hydrocarbons) is still the better catalyst compared to $\{LZn(NCMe)_2\}ClO_4$ (Table 1), but zinc(II) adducts like $\{LZn\}\{B[3,5-(CF_3)_2C_6H_3]_4\}$ with very weakly coordinating counterions display respectable catalytic activity, approaching those of $LA_g(THF)$ and $LA_g(C_2H_4)$.¹⁵

The related 3d-metal-based copper(I) catalyst $LCu(C_2H_4)$, in contrast, shows relatively poor C–H functionalization activity via this route under similar conditions and also demonstrates its inability to facilitate the primary C–H bond activation. Carbene dimers diethyl fumarate and maleate are formed as byproducts in significant quantities. While this study was underway, a report appeared that showed the use of copper(I) and a fluorinated scorpionate, $[HB(3,5-(CF_3)_2,4-(Br)Pz)_3]^-$, in primary C–H bond functionalization chemistry.²⁰ It features a ligand like $[HB(3,5-(CF_3)_2,4-(Cl)Pz)_3]^-$, which we reported earlier with silver(I) chemistry.¹³

The proposed C–H bond functionalization process is illustrated in Scheme 1. The cationic $\{LZn\}^+$ species reacts with EDA, resulting in a zinc carbene/zinc-bound carbocation (resonance forms), which then inserts the carbene moiety into C–H bonds of the substrate, releasing the catalyst. A detailed computational study (see the Supporting Information) of the likely intermediate suggests that it is best described as a zinc-bound carbocation rather than a zinc carbene²¹ form (although a neutral :CHCO₂Et carbene moiety gets transferred to the substrate during the reaction).

Preliminary studies indicate that $\{LZn(NCMe)_2\}ClO_4$ can also functionalize the C–H bonds of tetrahydrofuran (THF) but the activities are relatively low, presumably because of the competition between THF molecules (present in large excess) with EDA to coordinate to the Lewis acidic zinc center, which hinders the zinc-mediated decomposition of EDA. These cationic zinc adducts also mediate other types of chemistry like

Scheme 1. $\{[\text{HB}(3,5\text{-(CF}_3)_2\text{Pz)}_3]\text{Zn}\}^+$ (Denoted as $[\text{LZn}]^+$)-Mediated $:\text{CHCO}_2\text{Et}$ Carbene Insertion into C–H Bonds Involving EDA



cyclopropanation of arenes, leading to Büchner ring expansion products. For example, $\{\text{LZn}(\text{NCMe})_2\}\text{ClO}_4$ catalyzes the insertion of the carbene moiety of EDA into benzene $\text{C}=\text{C}$ bonds, affording ethyl cyclohepta-2,4,6-trienecarboxylate in 60% yield.²²

Overall, we have discovered a competent zinc catalyst that mediates the insertion of the $:\text{CHCO}_2\text{Et}$ fragment from EDA into C–H bonds of alkanes. It is a particularly noteworthy finding involving a cheap, earth-abundant, 3d metal system.²³ The supporting ligand on zinc(II) and counteranions affects the product yields. Unlike $\text{LCu}(\text{C}_2\text{H}_4)$, the cationic zinc(II) catalysts supported by the scorpionate L provide much higher yields of carbene insertion products and relatively smaller amounts of carbene dimers. We are presently exploring group 12 metal-mediated processes involving other substrates.

■ ASSOCIATED CONTENT

● Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.inorgchem.5b02134](https://doi.org/10.1021/acs.inorgchem.5b02134).

Synthesis and characterization of zinc adducts, details on catalysis, computational work, additional figures, and X-ray crystallographic data tables (PDF)

X-ray crystallographic data in CIF format (CIF)

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Science Foundation (Grant CHE-1265807) and Welch Foundation (Grant Y-1289) for support of this research. T.R.C. and S.K.K. acknowledge partial support of this research through Grant CHE-1057785.

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