

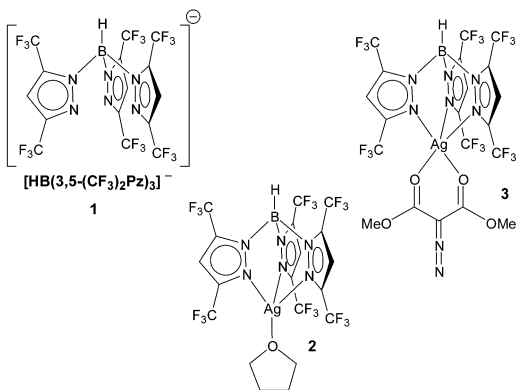
Activation of Alkyl Halides via a Silver-Catalyzed Carbene Insertion Process

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Alkyl and aryl halides serve as useful starting material for the synthesis of a wide range of products. Alkyl chlorides are the cheapest and most diverse group among these. However, they are of somewhat limited value as starting material because, as compared to bromides and iodides, C–Cl bonds in alkyl chlorides are much more difficult to activate (this serves well for the utility of compounds such as CH₂Cl₂ and CHCl₃ as solvents).^{1–3} The relatively low reactivity of alkyl chlorides is a result of the intrinsically higher bond strength of the C–Cl bond (e.g., H₃C–Cl, –Br, and –I bond energies are 84, 70, and 56 kcal mol^{–1}, respectively) and lower leaving-group ability.^{4,5} Methods (preferably catalytic) that allow the activation of carbon–halogen bonds under mild conditions are of significant current interest. Considerable progress has been achieved recently in metal (e.g., Pd)-catalyzed cross-coupling reactions involving aryl and some alkyl chlorides; however, most of these reactions occur well above room temperature.^{1–3,6} Here, we describe the discovery of a silver-catalyzed activation of carbon–halogen bonds through a carbene insertion process that occurs at room temperature. To the best of our knowledge, there is no precedent for such a metal-mediated process in the literature, although there are reports of similar products being obtained during the photochemical decomposition of methyl or ethyl diazoacetate in chlorocarbon solvents.^{7–11}



For a number of years, we have been interested in the chemistry of metal complexes containing fluorinated tris(pyrazolyl)borate ligands such as [HB(3,5-(CF₃)₂Pz)₃][–] (**1**).^{12,13} These ligands confer exceptional stability on the complexes (e.g., consider the air and thermal stability of compounds such as [HB(3,5-(CF₃)₂Pz)₃]MCO (where M = Cu, Ag, Au),¹⁴ [HB(3,5-(CF₃)₂Pz)₃]Cu₂H₄,¹³ [HB(3,5-(CF₃)₂Pz)₃]Ga,¹⁵ and [HB(3,5-(CF₃)₂Pz)₃]AgGe(Cl)(*n*-Pr)₂ATI].^{16,17} Some of these metal adducts still retain the ability to catalyze a variety of transformations.^{13,18} Part of our interest in these systems stems from the ability to isolate complexes that may be models for intermediates in catalytic cycles. For example, the reaction of [HB(3,5-(CF₃)₂Pz)₃]Ag(THF) (**2**)¹⁹ and dimethyl diazomalonnate at room temperature provided the thermally stable solid (**3**), which

Scheme 1

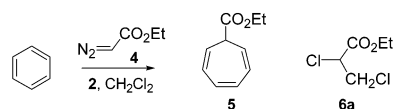


Table 1. Products and Yields of the Carbene Insertion

Substrate	Product	Yield (X = Cl)	Yield (X = Br)
(a = Cl, b = Br)		(%) ^{a,b}	(%) ^{a,b}
CH ₂ X ₂	X-CH ₂ -CO ₂ Et		
7	6	26	65
CHX ₃	X-CHX ₂ -CO ₂ Et		
8	14	60	29 ^{c,d}
CX ₄	X-CX ₃ -CO ₂ Et		
9	15	62	48 ^{c,e}
CH ₂ CH ₂ CH ₂ X	X-CH ₂ CH ₂ -CO ₂ Et		
10	16	39	78
Cl-CH ₂ -CH ₂ -X	Cl-CH ₂ -CO ₂ Et		
11	16a	70	-
Cyclohexyl-X	X-Cyclohexyl-CO ₂ Et		
12	16	63 ^{f,g}	60 ^h
Cl-CH ₂ -C(CH ₃) ₂ -X	Cl-CH ₂ -CO ₂ Et		
13	16a	73	-

^a These isolated yields are based on the average of at least two experiments and on the amount of EDA used. ^b The material balance is accounted for by dimerization of EDA (fumarate and maleate). ^c Reaction performed in CH₂Cl₂. ^d 9% of **6a** formed. ^e 3% of **6a** formed. ^f Yield determined by GC. ^g 47% (GC yield) of cyclohexene was formed. ^h 57% (GC yield) of cyclohexene formed.

can be readily isolated and characterized.²⁰ This is in contrast to the reaction of **2** with the more reactive ethyl diazoacetate (EDA, **4**), which provided no isolable metal complex, although the evolution of nitrogen suggested the possible formation of a carbene. Consequently, attempts were made to demonstrate the intermediacy of silver carbene by trapping experiments. In the course of investigating the reactions of the presumed metallacarbene derived from **2**¹⁹ and EDA with benzene, it was found that, in addition to reaction with the π-bond leading to the ring expanded product (**5**),²¹ an apparent insertion into the C–Cl bond of the reaction solvent CH₂Cl₂ occurred, providing **6a** (12%) as a minor byproduct. When the reaction was conducted in the absence of the arene in CH₂Cl₂, 26% of the insertion product **6a** was obtained (Scheme 1). Given

Scheme 2

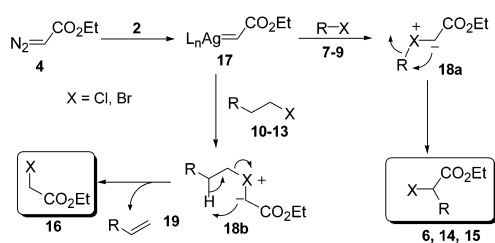


Table 2. Dependence on Catalyst

Catalyst	Products	
	Cl-CH ₂ -CO ₂ Et / %	Fumarate/Maleate / %
Ag ₂ O	2	91
AgOTf	8	17
Ag[HB(3,5-Me ₂ Pz) ₃]	0	0
AgSbF ₆	7	85
Rh ₂ (OAc) ₄	0	Nd ^a

^a Not determined; dimers were the only observed product in the ¹H NMR of the crude reaction mixture.

this result, a number of chloroalkanes were surveyed, including a number of common chlorinated solvents and chloroalkanes (Table 1, **7a–13a**), as substrates for this insertion.

In general, two reaction pathways were observed: either insertion into the C–Cl bond or 1,1-hydrochlorination (Table 1). For example, at room temperature, a mixture of CHCl₃ and EDA in the presence of 5 mol % [HB(3,5-(CF₃)₂Pz)₃]Ag(THF) afforded HCIC(CO₂Et)CCl₂H (**14a**) in 60% yield. When attempts were made to extend this reaction to primary, secondary, or tertiary alkyl chlorides, rather than the expected insertion product, ethyl chloroacetate **16a**, the net addition of H–Cl to the carbene, was obtained (see Scheme 2). Successful experiments with the analogous bromo derivative (Table 1, **7b–10b**, **12b**) suggest that this reaction is not limited to chloroalkanes.

To establish whether this reaction was restricted to complex [HB(3,5-(CF₃)₂Pz)₃]Ag(THF), other silver(I) salts were investigated. It was found that silver salts such as Ag₂O or AgOTf gave very poor yields of the insertion product with chloroform under conditions similar to those routinely employed (Table 2). Interestingly, the silver salt of the nonfluorinated ligand [HB(3,5-Me₂Pz)₃]Ag did not provide any product resulting from C–Cl insertion or from the elimination pathway.²² Either carbene dimers (diethyl fumarate and maleate) or unreacted EDA were recovered as major products from these mixtures. It was further found that the commonly employed rhodium acetate²³ does not catalyze the formation of products derived from C–Cl insertion; only maleate and fumarate are observed.

The use of silver salts with diazo compounds is well known, particularly in the Wolff rearrangement,²⁴ although normally stoichiometric quantities are employed. It has also been reported that Ag₂O has been utilized in a process to transfer the –C(N₂)CO₂Et moiety to bromo and iodo reagents. It is, however, a silver salt metathesis reaction, and it is believed to proceed via the AgC(N₂)CO₂Et intermediate.^{25,26}

Although at this point no rigorous mechanistic studies have been conducted, a working hypothesis has evolved based on the observed products and the known behavior of metallacarbenes (Scheme 2). Presumably, a silver carbenoid **17** is formed on reaction of the catalyst with ethyl diazoacetate (**4**), which then reacts with the halide to form a ylde (**18**). In the absence of a β-hydrogen, a 1,2-shift of the alkyl moiety occurs to provide the rearrangement product (**18a** → **6**, **14**, **15**). If a β-hydrogen is present, elimination occurs to provide the corresponding ethyl haloacetate (**18b** → **16**) and alkene (**19**).

In summary, we have identified a novel silver-catalyzed process involving carbene precursors and aliphatic carbon–halogen bonds. This transformation results in the formation of a new sp³–sp³ carbon–carbon bond and the net migration of a halide atom. Further attempts to extend this chemistry as well as additional applications of this catalyst are under investigation in our laboratories.

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Supporting Information Available: Experimental procedures and spectroscopic data for all of the compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- Where [(n-Pr)₂ATI] = N-(n-propyl)-2-(n-propylamino)troponimate.
- Catalytic properties of copper complexes containing nonfluorinated tris-(pyrazolyl)borates are also of significant current interest. See, for example: Caballero, A.; Díaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 1446.
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- It has been found that this complex catalyzes the addition of carbenes to aromatic rings to provide a net Buchner reaction product. Details of this study will be reported elsewhere. Dias, H. V. R.; Browning, R. G.; Diyabalanage, H. V. K.; Polach, S. A.; Lovely, C. J., manuscript in preparation.
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