Silver-Catalyzed C–H Insertion Reactions with Donor–Acceptor Diazoacetates

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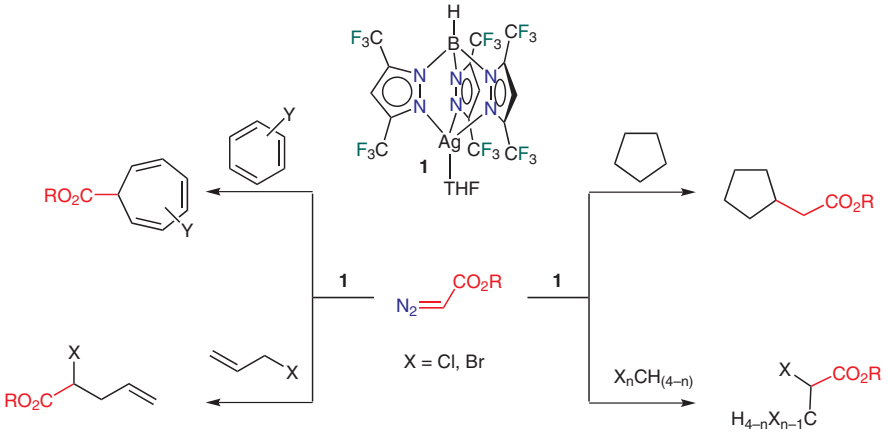
Abstract: In this paper we describe the first examples of carbene transfer with donor–acceptor diazoacetates and the silver tris(pyrazolyl)borate complex {HB[3,5-$(CF_3)_2$Pz]$_3$}Ag(THF). These reactions generally proceed in good yields and exhibit improved selectivities compared to simple diazoacetates.

Key words: organometallic, tris(pyrazolyl)borate, silver, atom transfer, chemoselective

The functionalization of unactivated C–H bonds is a topic of considerable current interest, with specific focus on accomplishing this transformation with high levels of selectivity (chemoselectivity, diastereoselectivity, enantioselectivity, etc.).[1] Several approaches to this problem have been investigated including intramolecular reactions,[2,3] appropriately placed activating groups[4–6] and varying the steric or electronic effects.[7] The derivatization of substrates lacking directing groups is more challenging and requires the development of new reagents, strategies and tactics to achieve this in a selective manner. Along these lines we have investigated the use of silver complex {HB[3,5-$(CF_3)_2$Pz]$_3$}Ag(THF) (**1**) containing the polyfluorinated and highly electron-withdrawing tris(pyrazolyl)borate ligand (Scheme 1).[1h,8,9] Previous studies from our lab have demonstrated that this complex effectively functions as a carbene-transfer catalyst with diazoacetates serving as the precursor (Scheme 1). It has been found that this combination leads to addition to and subsequent rearrangement with aromatic systems (the Büchner reaction),[10] the formation and rearrangement of halonium ylides[11,12] and C–H insertion (Scheme 1).[13] In the latter case it was determined with ethyl diazoacetate (EDA) that these reactions proceed with high efficiencies, but substrates containing heteroatoms did not participate efficiently in this reaction. Interestingly it was discovered that this catalyst showed unusual selectivities with substantial levels of C–H insertion occurring at primary sites in acyclic alkanes, although not at this point with synthetically useful selectivities.[9,13] All of these initial studies have been limited to reactions of EDA and in some limited cases with *tert*-butyl diazoacetate and therefore we have begun to investigate the utility of donor–acceptor diazoacetate derivatives to determine whether the catalyst will tolerate more substituted substrates and whether these reactions proceed with useful selectivities. Previous work, most notably by Davies and co-workers with rhodium complexes has demonstrated that these metallocarbene precursors exhibit very different reactivity profiles and quite often enhanced selectivities, including diastereo- and enantioselectivities in appropriate cases.[14]

Two diazoacetates were selected for study, methyl phenyldiazoacetate (**2**, MPDA)[14] and methyl styryldiazoacetate (**3**, MSDA),[15] which were prepared by diazo transfer to the corresponding ester according to a literature proce-



Scheme 1 Diazo transfer reactions catalyzed by {HB[3,5-$(CF_3)_2$Pz]$_3$}Ag(THF) (**1**)

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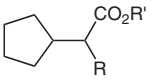
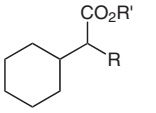
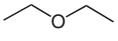
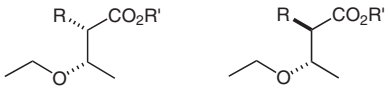
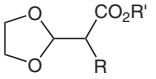
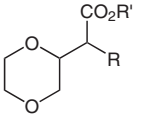
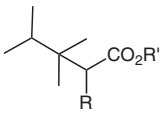
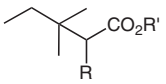
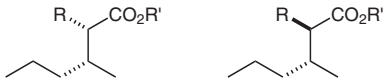
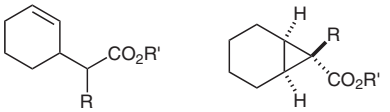
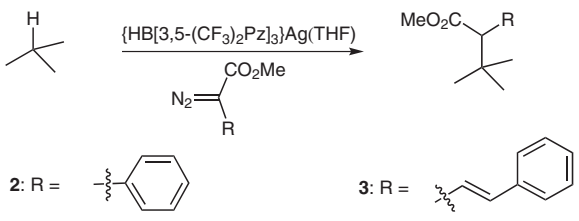
Table 1 C–H Insertion Reactions with {HB[3,5-$(CF_3)_2$Pz]$_3$}Ag(THF) (**1**) with Methyl Phenyldiazoacetate (**2**, MPDA) and Methyl Styryldiazoacetate (**3**, MSDA)[18]

Entry	Substrate	Product(s)	EDA (%) (R = H)	MPDA (%)[a] (R = Ph)	MSDA (%)[a] [R = (*E*)-CH=CHPh]
1			88[13]	87[19]	84
2			88[13]	76[19]	77
3			5	71 (3:2)[b]	88 (3:2)
4			24	91 (3:2)[b]	0
5			0	0	0
6			0	0	0
7			*85*[c,13] (2 isomers)	69[14]	66
8			*87*[d,13] (4 isomers)	74[14]	73
9			*81*[e,13] (3 isomers)	73 (1.2:1)[b,20]	85[f]
10			–	13 (1:1)/38	–

[a] Yields correspond to chromatographically isolated products and are the average of at least two independent experiments.
[b] Ratios correspond to crude reaction products, and were determined from ^{1}H NMR spectroscopy by integration of benzylic or vinylic methine signals of the crude reaction mixture.
[c] For R = H the product was isolated as mixture of C1 and C2 insertion products (C1/C2 = 80:20).
[d] For R = H the product was isolated as a mixture of C1,C2, C3, and C4 insertion products (C1 + C4/C2/C3 = 59:14:27).
[e] For R = H the product was isolated as a mixture of C1, C2, and C3 insertion products (C1/C2/C3 = 41:47:12).
[f] The diastereomeric ratio could not be determined for this product.

dure.[15] Initial experiments were conducted with cyclic hydrocarbons and 5 mol% of the tris(pyrazolyl)boratosilver catalyst **1** and the diazo compound was introduced at room temperature by syringe pump (Scheme 2). Gratifyingly, both **2** and **3** underwent efficient C–H insertion with both cyclopentane and cyclohexane in excellent yield, comparable in efficiencies to EDA (entries 1 and 2, Table 1). We had found with EDA that C–H insertion adjacent to oxygen was not efficient, a result we attributed to competitive coordination between the ether oxygen and the diazo compound (entries 3–6, Table 1).[13] With the donor–acceptor carbenoids different reactivity trends emerge. Both MPDA (**2**) and MSDA (**3**) insert efficiently into the C–H bond adjacent to the oxygen in diethyl ether and in both cases, a 3:2 mixture of diastereomers was obtained. Unlike with EDA, MPDA provided an insertion



Scheme 2

product with THF leading to a 3:2 mixture of separable adducts, whereas MSDA did not provide insertion products. Interestingly, and similar to EDA, substrates containing two oxygen atoms did not undergo reaction with MPDA or MSDA. Earlier investigations with simple acyclic alkanes and EDA had revealed that insertion occurs very effectively (entries 7 and 8, Table 1), but these reactions occur at all sites, including insertion into primary C–H bonds.[9] This was not the case with MPDA and MSDA where these reactions occurred with much higher selectivities. In the case of 2,3-dimethylbutane, this reaction led to the formation of a single insertion product in good yield, with insertion occurring at the tertiary C–H. Similarly, 2-methylbutane provided one major insertion product, again occurring at the tertiary C–H. Somewhat surprisingly, it was found that with pentane insertion into C2 was the major pathway, providing a 1:1.2 mixture of two diastereomeric adducts in good yield. Approximately 2–3% of insertion at C3 occurs, but no detectable (^{1}H NMR spectroscopy of the crude reaction mixture) insertion at the primary carbons occurs.

Davies and Thompson have shown that $AgSbF_6$ will catalyze the selective cyclopropanation of a variety of olefins with both MPDA and MSDPA with high levels of chemo- and diastereoselectivity[16] and therefore we performed one scouting experiment with cyclohexene and MPDA. Unlike the simple silver salt, it was found that both insertion and addition occur with relatively low selectivity and modest yield (entry 10, Table 1).

At this point some conclusions can be drawn from these experiments. The insertion reactions with these donor–acceptor carbenes appear to be substantially more selective compared to EDA. These results are consistent with the development of positive character at the insertion site as these reactions occur at the most substituted carbon, or in the case of the oxygen-containing substrates the α-position is most able to stabilize positive charge, this is consistent with results obtained with rhodium-based catalysts.[14,17] The result obtained with *n*-pentane is interesting in that insertion occurs at C2 with minimal insertion at the other secondary site at C3. Presumably in this case, selectivity is a result of a combination of steric and statistical factors, and it is of note that the reaction of *n*-pentane with EDA favors insertion at C2 over C3, but to a much reduced extent.[13]

In summary, our investigation demonstrates that a silver(I) complex effectively catalyzes C–H insertion of donor–acceptor carbenes. These reactions generally proceed in good to high yields and with good chemoselectivities. These observations are in contrast with the results observed with simple diazoacetates, in which substantial insertion occurs at primary sites.

Acknowledgment

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(18) **General Procedure for Catalysis by Carbene-Transfer Reactions with Catalyst {HB[3,5-$(CF_3)_2$Pz]$_3$}Ag(THF)**: Methyl phenyldiazoacetate or methyl styryldiazoacetate (0.25 mmol) dissolved in the substrate (5 mL) was added by syringe pump over a period of ca. 3 h to a stirred solution of the catalyst (0.005 g, 0.01 mmol) in the substrate (10 mL) in a foil-shielded, round-bottomed flask. The resulting mixture was stirred for 6 h at r.t., concentrated and the residue was purified by flash chromatography on silica gel (2% Et_2O–PE for hydrocarbons, 5–20% Et_2O–PE for ethers) to yield oily transparent or white solid products. The isolated yields are based on the average of at least two experiments and on the amount of diazoacetate used.
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(20) **Methyl 2-Phenyl-3-methylhexanoate**: yield: 40.2 mg (73%); diastereoisomer ratio = 1.2:1. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19–7.36 (m, 10 H, ArH), 3.624 (s, 3 H, OMe), 3.620 (s, 3 H, OMe), 3.24 (d, *J* = 10.7 Hz, 1 H, C*H*Ph), 3.23 (d, *J* = 10.3 Hz, 1 H, C*H*Ph), 2.11–2.28 (m, 2 H, CH), 1.01–1.50 (m, 8 H, CH_2), 0.98 (d, *J* = 6.5 Hz, 3 H, Me), 0.89 (t, *J* = 6.9 Hz, 3 H, Me), 0.73 (t, *J* = 6.9 Hz, 3 H, Me), 0.65 (d, *J* = 6.9 Hz, 3 H, Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.54, 174.49, 138.19, 138.14, 128.61, 128.58, 128.42, 128.39, 127.14, 58.8, 55.5, 51.7, 37.6, 36.2, 36.1, 35.6, 19.9, 19.4, 17.8, 16.6, 14.2, 14.0. IR (neat): 3087, 3064, 3029, 2959, 2932, 2873, 1738 cm^{-1}. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{21}O_2$: 221.1536; found: 221.1537.