

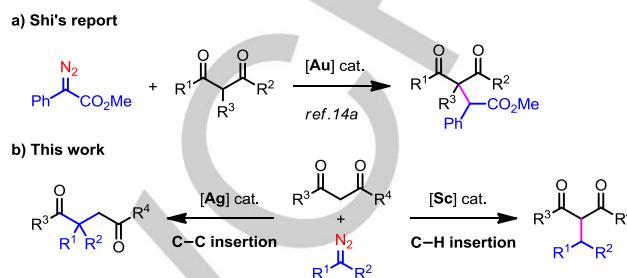
# Catalyst-dependent Chemoselective One-Carbon Insertion of Diazo Compounds into C–C or C–H Bonds of 1,3-Dicarbonyls

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**Abstract:** A catalyst-dependent chemoselective one-carbon insertion of diazo compounds into the C–C or C–H bonds of 1,3-dicarbonyls is reported. In the presence of silver(I) triflate, diazo insertion into the C(=O)–C bond of the 1,3-dicarbonyl leads to a 1,4-dicarbonyl containing an all-carbon  $\alpha$ -quaternary center, which represents the first example of the insertion of diazo-derived carbenoids into acyclic C–C bonds. By instead employing scandium(III) triflate as catalyst, the reaction path switches to formal C–H insertion, affording 2-alkylated 1,3-dicarbonyl products. Different diazo activation modes are proposed to account for this powerful catalyst-dependent chemoselectivity.

The construction of all-carbon quaternary centers by one-carbon insertions into C–C bonds is a formidable challenge, not only due to the difficulty of achieving the selective cleavage of inert C–C bonds,<sup>[1]</sup> but also the subsequent formation of the congested quaternary carbon atom.<sup>[2]</sup> Progress in this field has been especially limited in acyclic systems,<sup>[3]</sup> where insertions of diazo compounds into carbonyl compounds represent one approach to construct quaternary carbon centers.<sup>[4]</sup> In such processes, the diazo compound invariably acts as an ambiphilic species, undergoing a sequential nucleophilic addition / 1,2-rearrangement cascade.<sup>[5]</sup> While diazo compounds have also been widely explored as a source of carbenoids under transition metal catalysis,<sup>[6]</sup> the insertion of diazo-derived metal carbenoids into acyclic C–C bonds is unknown.<sup>[7]</sup> To the best of our knowledge, only one report by Wang and co-workers has described the insertion of rhodium carbenoids derived from diazo compounds into the cyclic C–C bonds of strained benzocyclobutenols to form quaternary carbons.<sup>[8]</sup>

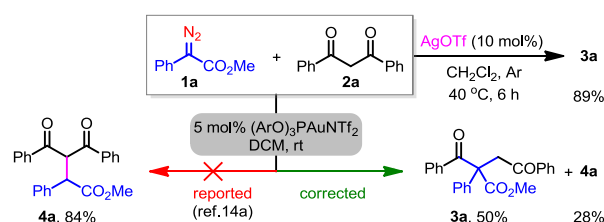
We targeted a new method to achieve the insertion of diazo-derived carbenoids into acyclic C–C bonds.<sup>[9]</sup> Based on achievements in the silver-catalyzed activation of diazo compounds by our group<sup>[15]</sup> and others,<sup>[16]</sup> we questioned whether inexpensive silver catalysts could be used to mediate C–C insertion. Although coinage metals have been extensively exploited in the alkylation of  $sp$ ,<sup>[10]</sup>  $sp^2$ ,<sup>[11]</sup> and  $sp^3$ <sup>[12]</sup> C–H bonds with diazo compounds<sup>[13]</sup> (such as Shi and co-workers' report of alkylation products, Figure 1a),<sup>[14a]</sup> equivalent C–C insertions are unknown. Here we describe the realization of this chemistry, which offers a new strategy to install all-carbon quaternary



**Figure 1.** Insertions of diazo compound into 1,3-dicarbonyls.

centers in acyclic systems;<sup>[3d,e]</sup> and, tuning of the reaction pathway between C–C and C–H insertion through choice of catalyst (Figure 1b).<sup>[17]</sup>

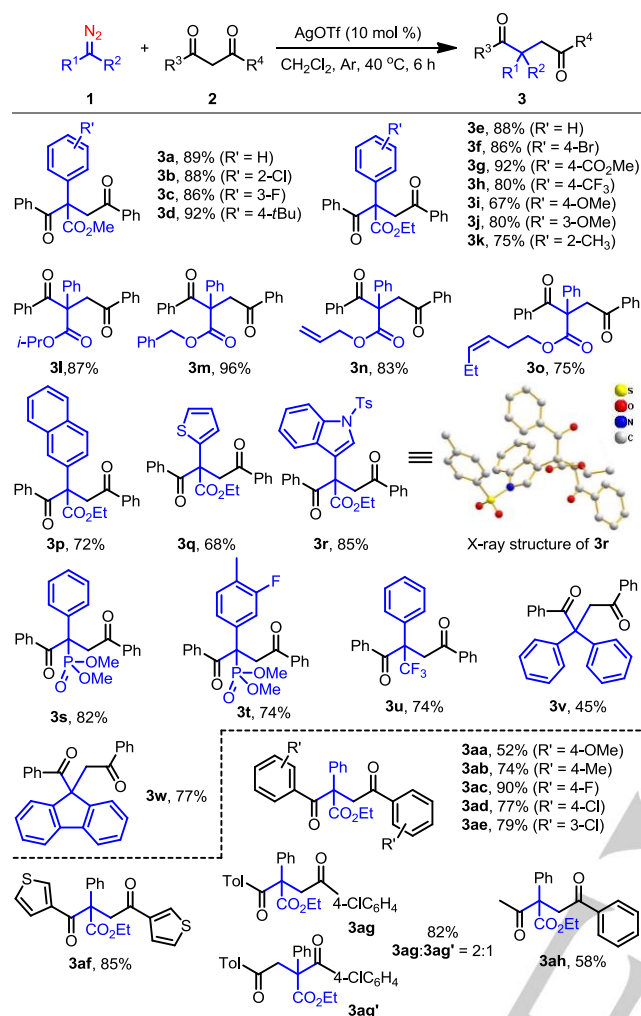
Initial studies revealed that the use of silver(I) triflate (10 mol%) as catalyst in  $CH_2Cl_2$  at 40 °C exclusively afforded the C–C insertion product **3a** in 89% yield (Figure 2).<sup>[18]</sup> Unexpectedly, the NMR data of **3a** appeared identical to that of the proposed C–H insertion product (**4a**) arising from the gold-catalyzed chemistry described by Shi.<sup>[14a]</sup> We therefore revisited the latter conditions, where in our hands **3a** and **4a** were obtained in 50% and 28% yield, respectively. While the reason for this mixture is unclear, it highlights the challenge of achieving selective C(=O)–C insertion over competing C–H<sup>[14]</sup> and O–H<sup>[19]</sup> insertions; completely selectivity for C–C insertion of diazo-derived carbenoids into 1,3-dicarbonyls, as observed with AgOTf as catalyst, has not been reported to date.



**Figure 2.** Initial results on the gold- and silver-catalyzed diazo insertion into 1,3-dicarbonyls.

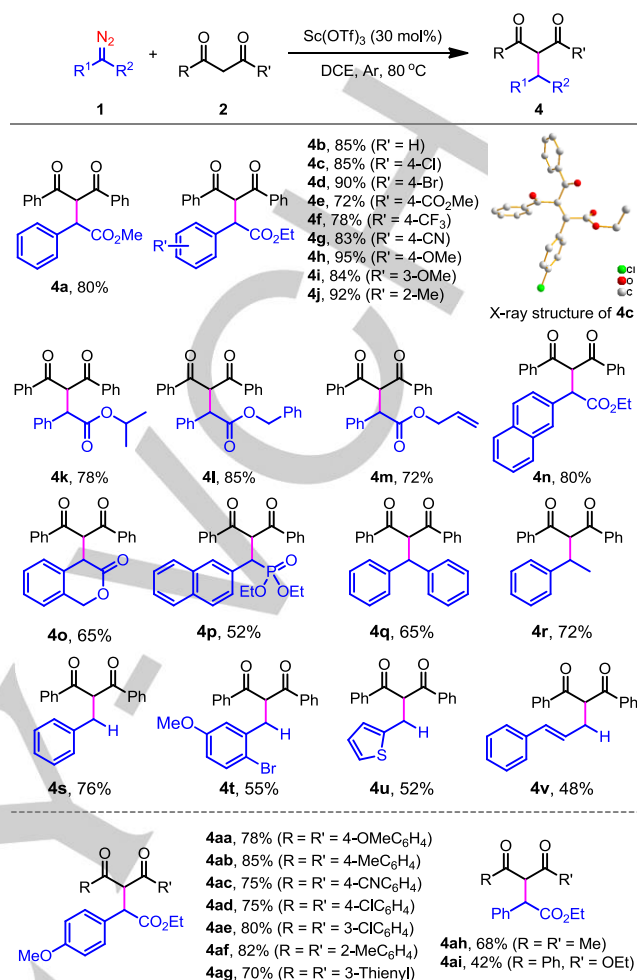
The scope of this silver-catalysed chemoselective C(=O)–C insertion was next investigated (Scheme 1). A variety of aryl diazoacetates, bearing either electron-poor (F, Cl, Br,  $CO_2Me$ ,  $CF_3$ ) or electron-rich (OMe,  $CH_3$ ,  $t$ -Bu) arenes, were successfully converted into the desired C–C insertion products (**3a–3k**) in good to excellent yields. In addition to methyl and ethyl esters, isopropyl (**1l**), benzyl (**1m**), allyl (**1n**), and 3-hexenyl phenyldiazoacetates (**1o**) were also productive substrates, affording products **3l–3o** in 75–96% yield. 2-Naphthyl (**1p**), 2-thienyl (**1q**), and 3-indolyl (**1r**) substituted diazoacetates also proved suitable reaction partners, with the

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**Scheme 1.** Scope of C(=O)–C insertion. Reaction conditions: **1** (0.3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5.0 mL) was added dropwise (1 h) to a mixture of AgOTf (10 mol%) and **2** (0.45 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) at 40 °C; Isolated yields.

connectivity of **3r** confirmed by single-crystal X-ray analysis. The present methodology was not restricted to  $\alpha$ -diazoesters, with diazophosphonates **1s** and **1t** also reacting efficiently to afford products **3s** and **3t**, featuring a phosphorus-substituted  $\alpha$ -quaternary center.<sup>[20]</sup> Relatively non-stabilized diazo compounds, such as (1-diazo-2,2,2-trifluoroethyl)benzene (**1u**), the sterically hindered diphenyldiazomethane (**1v**), and tricyclic 9-diazo-9H-fluorene (**1w**), were also compatible, delivering **3u–3w** in 45–77% yields. A variety of symmetrical diaryl 1,3-dicarbonyls could be employed, including heteroaryl diketones, affording the expected 1,4-dicarbonyls **3aa–3af** in good yields on reaction with **1e**. With an unsymmetrical diarylketone, a 2:1 mixture of isomers **3ag** and **3ag'** was obtained in 82% yield, illustrating a moderate electronic influence over the point of formal C–C insertion, while phenyl methyl-1,3-diketone delivered **3ah** exclusively in 58% yield, where reaction occurred selectively at the C(=O)–C bond to the alkyl ketone. These two observations provided an early insight into factors affecting the mechanism of the insertion process.

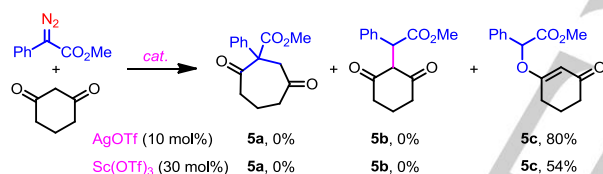


**Scheme 2.** Scope of C–H insertion. Reaction conditions: **1** (0.6 mmol) in DCE (5.0 mL) was added dropwise (1 h) to a mixture of 4Å MS (40 mg), Sc(OTf)<sub>3</sub> (30 mol%) and **2** (0.3 mmol) in DCE (1.0 mL) at 80 °C; Isolated yields.

Achieving catalyst control over the site of reactions such as insertion processes is an attractive goal.<sup>[17]</sup> To our delight, we found that a switch from C(=O)–C insertion to C–H insertion of the 1,3-dicarbonyl could be accomplished by employing Sc(OTf)<sub>3</sub> as catalyst instead of AgOTf; at 80 °C, complete selectivity for the C–H insertion reaction was observed using **1a** and diketone **2a** (to give **4a**, 80%, Scheme 2).<sup>[18,21]</sup> The scope of this complementary protocol proved equally as broad as the silver-catalyzed process, with the reactions of various ethyl aryl diazoacetates, bearing both electron-withdrawing and electron-donating groups, affording the C–H insertion products **4b–4j** in good to excellent yields. The structure of compound **4c** was unambiguously assigned by X-ray analysis. Isopropyl, benzyl, and allyl phenyldiazoacetate were also productive substrates, giving the expected products **4k–4m** in good yields. 2-Naphthyl ethyldiazoacetate and cyclic 4-diazoisochroman-3-one also smoothly underwent selective C–H insertion to furnish **4n** and **4o** in 80% and 65% yield respectively. A diazophosphonate again proved successful, affording 1,3-diketone **4p** in 52% yield. Excitingly, non-stabilized diazo compounds such as diphenyl,

aryl and alkenyldiazomethanes were accommodated, giving products **4r–4v** in 48–76% yield. Variation of the 1,3-dicarbonyl in this Sc-catalyzed insertion was evaluated using ethyl phenyldiazoacetate and ethyl 4-methoxyphenyldiazoacetate. Pleasingly, the reaction proceeded smoothly irrespective of the electronic character of the diaryl dicarbonyl: electron-donating and withdrawing groups (at various positions of the aryl rings), and a dithiophene substrate, all afforded the C–H insertion products in excellent yields (**4aa–4af**). An alkyl-1,3-diketone and an aryl- $\beta$ -ketoester were also tested as substrates, and afforded the expected products **4ah** and **4ai** in 68% and 42% yield respectively.

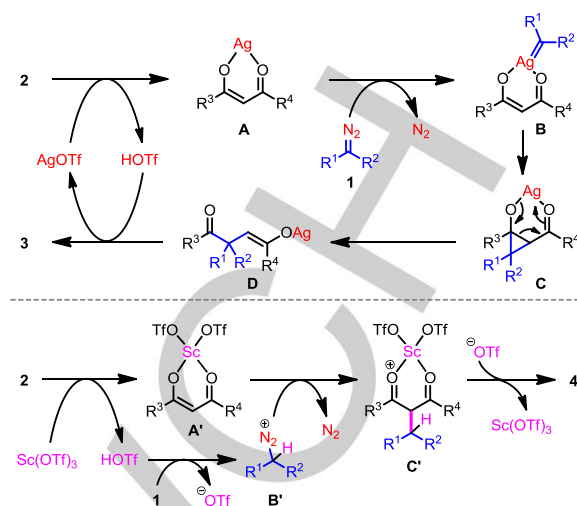
Reaction of methyl phenyldiazoacetate and 1,3-cyclohexanedione using either AgOTf or Sc(OTf)<sub>3</sub> as catalyst offered insight into the mechanisms of these different insertion processes (Scheme 3): to our surprise, both catalysts exclusively furnished the O–H insertion product **5c** in 80% and 54% yield, respectively, without formation of the anticipated C(=O)–C or C–H insertion products **5a** and **5b**. We considered that **5c** might arise from coordination of the enol form of the cyclic 1,3-diketone to the metal ion (or to a metal carbenoid), subsequently leading to the formal O–H insertion product. 1,3-cyclohexanedione differs from the previous substrates in being able to form only a *trans*-enol,<sup>[22]</sup> which may suggest that the formation of a *cis*-enol, potentially as a bidentate complex with the metal, is critical in mediating the C(=O)–C and C–H insertion reactions of acyclic 1,3-dicarbonyls.



**Scheme 3.** Control experiments.

On the basis of these results and related precedents,<sup>[7,25]</sup> a plausible mechanism for the chemoselective one-carbon insertion of diazo compounds into acyclic 1,3-dicarbonyls is proposed (Scheme 4). In the case of the silver-catalyzed C(=O)–C insertion, 1,3-diketone **2** is first converted by AgOTf to silver enolate **A**, which engages with diazo compound **1** to give the electrophilic silver carbenoid **B** following loss of molecular nitrogen. The cyclopropanation of **B** leads to intermediate **C**,<sup>[23]</sup> which then undergoes a retro-aldol fragmentation to afford intermediate **D**.<sup>[24]</sup> Upon protonation by HOTf, **D** releases the 1,4-diketone product **3**, with concomitant regeneration of the silver catalyst. In contrast to existing catalytic methods for insertion of nucleophilic diazo compounds into ketones,<sup>[4]</sup> the transient formation of an *electrophilic* silver carbenoid (**B**) and subsequent cyclopropanation would represent a novel mode of carbenoid reactivity.<sup>[15,16]</sup> Notably, the formation of product **3ah** (Scheme 1) would be consistent with such a mechanism, where cyclopropanation occurs at the double bond of the predominant enol form (i.e., that of the methyl ketone), rather than a pathway that relies on migrating group ability, in which migration of the C2 carbon would likely be disfavored.

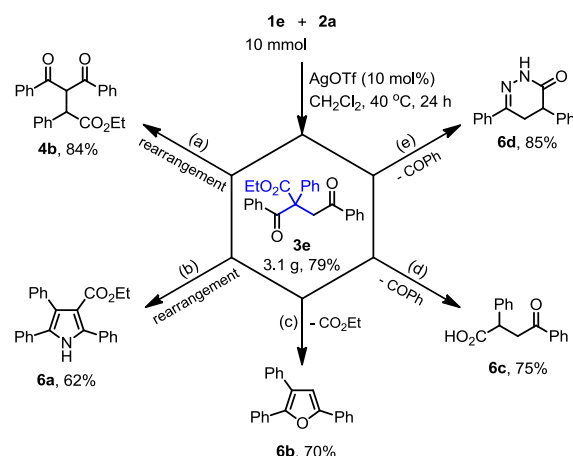
In the complementary scandium-catalyzed C–H insertion,



**Scheme 4.** Proposed reaction mechanisms for the Ag-catalyzed C–C and the Sc-catalyzed C–H insertions.

protonation of the diazo compound **1** by HOTf could yield the diazonium ion **B'**, which displays carbocation-like reactivity,<sup>[25]</sup> undergoing facile nucleophilic attack by the scandium enolate **A'** to give complex **C'**. The C–H insertion product **4** is then released, with regeneration of Sc(OTf)<sub>3</sub>. In the absence of this chelate **A'** (Scheme 4), direct reaction on the more reactive enolate oxygen atom may instead be possible (to give **5c**). The divergent reactivity of the diazo compounds under different modes of catalysis is therefore rationalized by the putative formation of an electrophilic silver carbenoid species in the presence of AgOTf, whereas in the presence of Sc(OTf)<sub>3</sub> the diazo compound instead behaves as a carbocation source.

To test the robustness of this chemoselective one-carbon C–C insertion, a multigram-scale experiment was performed (Scheme 5). When 10 mmol of **1e** and **2a** were subjected to the standard silver-catalyzed reaction conditions, product **3e** was isolated in 79% yield (3.1 g). The synthetic versatility of 1,4-diketone **3e** was then explored in an array of derivatizations:



**Scheme 5.** Gram scale synthesis and further transformations. Reaction conditions: (a) HCl·1,4-dioxane, 80 °C, 30 h; (b) NH<sub>4</sub>OAc/AcOH, 120 °C, 36 h;



(c) TsOH (50 mol%), toluene, 110 °C, 8 h; (d) 20 wt% NaOH, 120 °C, 30 h; (e) N<sub>2</sub>H<sub>4</sub>, H<sub>2</sub>O/EtOH, reflux, 12 h.

under strongly acidic conditions (path a), **3e** rearranged to give tricarbonyl **4b** (84%),<sup>[26]</sup> while under Paal-Knorr conditions, **3e** could be transformed into either the tetrasubstituted pyrrole **6a** (path b, 62%), or the 2,3,5-triphenylfuran **6b** (Path c, 70%), both important motifs in bioactive natural products, pharmaceuticals and photoelectric materials.<sup>[27]</sup> Alternatively, treatment of **3e** with base led to  $\gamma$ -oxo acid **6c** (path d), a key precursor for the synthesis of bioactive pyridazine derivatives,<sup>[28]</sup> while reaction with hydrazine hydrate (path e) afforded the 4,6-diarylpyridazin-3(2H)-one **6d** in 85% yield.

In summary, a catalyst-controlled chemoselective insertion of diazo compounds into acyclic 1,3-dicarbonyls has been developed. In the presence of AgOTf, a one-carbon insertion of diazo-derived carbenoids into acyclic C–C bonds is achieved, affording 1,4-dicarbonyls with an  $\alpha$ -quaternary carbon atom. In contrast, the use of Sc(OTf)<sub>3</sub> as catalyst leads to a switch in chemoselectivity, now effecting a formal C–H insertion, and leading to products of 1,3-dicarbonyl alkylation. This divergent reactivity of the diazo compounds is ascribed to the different activation modes of the Ag and Sc catalysts. This work opens a new avenue for exploration of the rarely reported one-carbon insertion into acyclic C–C bonds, and also underlines the great potential of metal catalysts in regulating the reactivity of diazo compounds. Investigations into the development of asymmetric versions of these divergent catalytic processes are underway.

## Acknowledgements

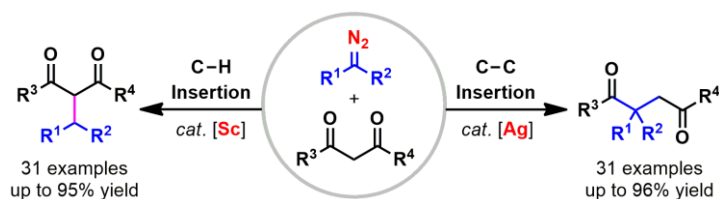
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**Keywords:** C–C insertion • C–H insertion • 1,3-dicarbonyls • diazo compound • silver catalysis

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## COMMUNICATION



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**Catalyst-dependent Chemoselective  
One-Carbon Insertion of Diazo  
Compounds into C–C or C–H Bonds  
of 1,3-Dicarbonyls**

**Chemoselectivity Switch:** Catalyst-dependent chemoselectivity in the insertion of diazo compounds into 1,3-dicarbonyls is reported. In the presence of AgOTf, the selective insertion of diazo compounds into the C(=O)–C bond was achieved, affording 1,4-dicarbonyls with an all-carbon  $\alpha$ -quaternary center. In contrast, in the presence of Sc(OTf)<sub>3</sub> the site of reaction was switched to C–H insertion, resulting in  $\alpha$ -C–H alkylation products.