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Communication

Diazo Coupling

Silver-Catalyzed Cross-Olefination of Donor and Acceptor Diazo Compounds: Use of *N*-Nosylhydrazones as Diazo Surrogate

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Abstract: The cross-olefination reaction of donor and acceptor diazo compounds was explored. The use of *N*-nosylhydrazones as diazo surrogates and the dependence on silver catalysis were crucial for the reaction development. A variety of (hetero)aryl *N*-nosylhydrazones and α-diazo esters, amides, and phosphonates were compatible, and the functionalized alkene products were afforded in good to high yields with moderate (*Z*)/(*E*) selectivities. The experimental and DFT calculation results suggest that the cross-selectivity is due to selective activation of the silver catalyst for donor diazo compounds.

Introduction

The convergent formation of alkenes occupies a central position in organic synthesis. Wittig-type reactions and olefin metathesis play dominant roles in this field.[1,2] As an alternative approach, the carbenoid-induced coupling of two diazo compounds has been emerging as a synthetically valuable olefination reaction. However, the coupling of two fragments always derives from the same diazo reagent[3] or proceeds by an intramolecular process.[4] Intermolecular diazo cross-coupling remains less developed, mainly owing to the competitive diazo homocoupling process.[5] Pioneering efforts have been devoted to exploring such an olefin synthesis in an intermolecular way (Figure 1a). The groups of Del Zotto[6] and Hodgson[7] successively studied the cross-coupling of two different acceptor diazo compounds by ruthenium catalysis to give unsymmetrical olefins in more than statistical yields. However, it was not until 2011 that Davies and co-workers described the efficient cross-coupling of two distinct donor–acceptor and acceptor diazo compounds with a rhodium-based catalytic system.[8] Pérez and co-workers subsequently revisited this reaction by using their silver complex catalyst.[9] More recently, the Sun group successfully expanded the repertoire of diazo cross-olefination to two donor–acceptor diazo components by gold or copper catalysis, which thus allowed the synthesis of tetrasubstituted alkenes.[10] These contributions have promoted the diazo olefination reaction such that it is now synthetically more useful, but the coupling components remain restricted to acceptor diazo compounds.[6–10] To the best of our knowledge, highly reactive donor diazo compounds have not been exploited in the diazo cross-olefination reaction.[11] Herein, we wish to report the first cross-coupling between donor and acceptor diazo compounds by combining the use of *N*-nosylhydrazones as diazo surrogates and silver catalysis (Figure 1b). This provides a convenient approach to β-aryl α,β-unsaturated carbonyl groups, which are key units in many pharmaceutically relevant compounds such as lacidipine, tranilast, rescinnamine, and fexaramine.[12]

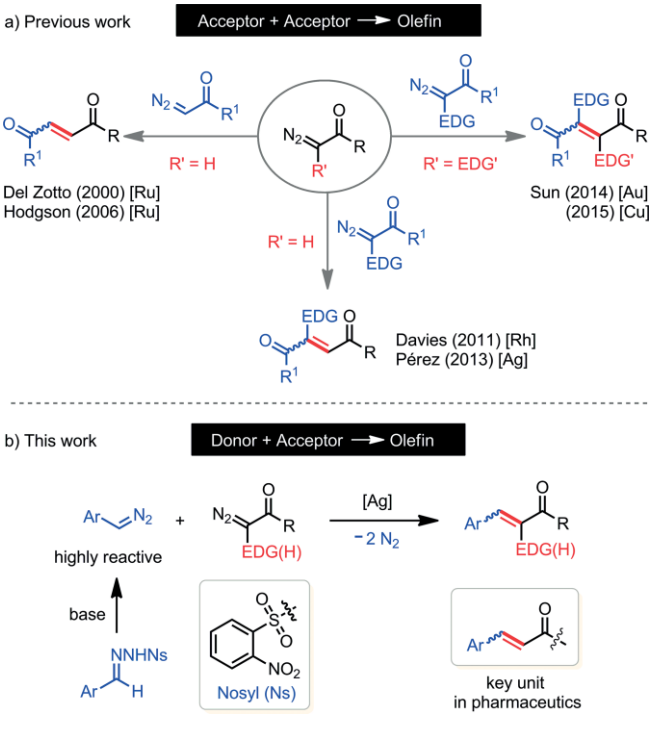

Figure 1. Cross-olefination of diazo compounds.

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Results and Discussion

To develop donor–acceptor diazo cross-olefination, two key problems need to be solved: (1) the easy homocoupling of donor diazo compounds; (2) the requirement for a metal catalyst preferably to promote the cross-coupling. *N*-Sulfonylhydrazones as donor diazo precursor have been widely exploited in organic synthesis.[13] We recently discovered the low-temperature decomposable properties of *N*-nosylhydrazones and, thus, overcame the inherent drawback of *N*-tosylhydrazones that require high dissociation temperatures (> 70 °C).[14] The slow release of donor diazo species from *N*-nosylhydrazones and the low reaction temperature could reduce the diazo homocoupling event drastically. Consequently, *N*-nosylhydrazones could be the ideal diazo surrogate in the study of donor diazo cross-coupling reactions. After the gold rush and traditional copper catalysis, silver catalysis has emerged as an active area in organic synthesis.[15] The application of silver salts as catalysts for the decomposition of diazo compounds is traditionally associated with the Wolff rearrangement.[16] In recent years, silver-catalyzed reactions of diazo compounds have moved beyond this classical chemistry. A number of groups such as the Dias and Lovely,[17] Pérez,[9,18] Davies,[19] and Wang[20] groups have made leading contributions to this field. Importantly, silver catalysts commonly display unique and excellent catalytic selectivity in these reactions. In continuation of our interest in silver chemistry,[21] we performed studies on the reactivity of silver carbenoids derived from *N*-nosylhydrazones and discovered the silver-catalyzed cyclopropenation of alkynes.[14] In this paper, we describe silver-catalyzed donor–acceptor diazo cross-olefination.

We commenced the study with the reaction of 4-chlorophenyl *N*-nosylhydrazone (**1a**) and ethyl diazoacetate (**2a**) as the model. Some data regarding the catalytic effects of various transition metals are shown in Figure 2. Except for the rhodium catalyst, which resulted in equal amounts of cross-coupling product **3a** (32 %) and homocoupling product **3a′** (30 %), the gold, copper, and ruthenium catalysts all dominantly produced dimer **3a′**, along with a small amount of cross-coupling product **3a**. Note that high yields of diethyl fumarate generated from the homocoupling of **2a** were obtained under gold-, copper-, ruthenium-, and rhodium-catalyzed conditions, in line with previous reports (see Table S1, Supporting Information).[5–7] In contrast to copper and gold, which were nearly inactive, silver salts preferably promoted the cross-coupling reaction. Most of the silver salts were capable of selectively affording a very high ratio of the desired product **3a**. The counteranions were found to play a critical role. Among the examined silver salts, silver trifluoromethanesulfonate (AgOTf) and silver trifluoroacetate (AgOTFA) gave the best results with 74 and 78 % yields of **3a**, respectively, without homocoupling product **3a′**. Intriguingly, no diethyl fumarate from the homocoupling of **2a** was detected under silver catalysis. Eventually, dilution of the reaction to 0.05 M led to optimal conditions, which resulted in **3a** in 90 % yield, as determined by NMR spectroscopy, and it was isolated in 86 % yield with a moderate (*Z*)/(*E*) ratio of 56:44. Notably, the handling of *N*-nosylhydrazones is easy and safe.

With the optimal conditions in hand, we set out to explore the reaction scope with respect to the *N*-nosylhydrazones

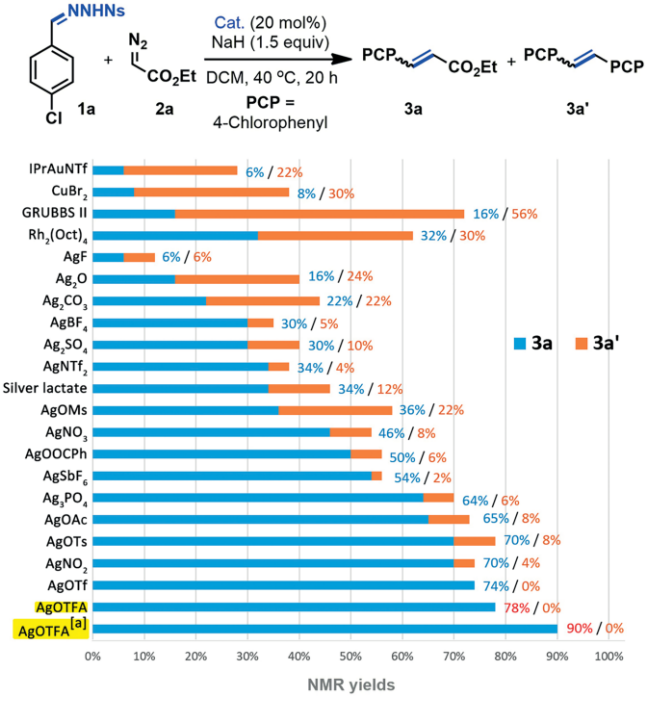
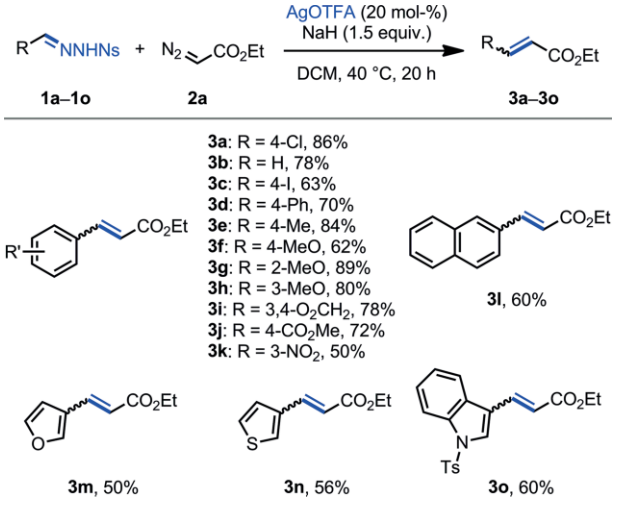


Figure 2. Optimization of the reaction conditions. Reaction conditions: **1a** (0.3 mmol), NaH (0.45 mmol), **2a** (0.45 mmol), and catalyst in CH_2Cl_2 (3 mL, 0.1 M) at 40 °C under argon for 20 h. Catalysts: $IPrAuNTf_2$ [5 mol-%; IPr = 1,3-bis(2,6-diisopropyl)phenylimidazol-2-ylidene; NTf_2 = bis(trifluoromethanesulfonyl)imidate], NaBArF {5 mol-%; BArF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate}; $CuBr_2$ (10 mol-%), Phen (10 mol-%); Grubbs II (1 mol-%); $Rh_2(Oct)_4$ (5 mol-%; Oct = octanoate); silver salts (20 mol-%); Ms = methylsulfonyl; Ts = tolylsulfonyl. Yields were determined by ^1H NMR spectroscopy by using CH_2Br_2 as an internal standard. [a] CH_2Cl_2 (6 mL, 0.05 M) was used, and the yield of the isolated product was 86 %.

(Scheme 1). The reaction scope was broad, as a variety of aryl- and heteroaryl-substituted substrates could be applied to the silver-catalyzed cross-coupling reaction with ethyl diazoacetate (**2a**) to afford diverse β-(hetero)aryl acrylates **3a**–**o** in moderate to high yields. The steric and electronic effects of the substituents on the aromatic ring showed a slight influence on the reaction outcome. For instance, the strong electron-withdrawing nitro group was tolerable, and product **3k** was delivered in 50 % yield. In addition, fused aryl and heteroaryl groups, such as naphthyl, furyl, thienyl, and indolyl, proved to be compatible with the reaction and afforded the corresponding products **3l**–**o** in 50–60 % yields.

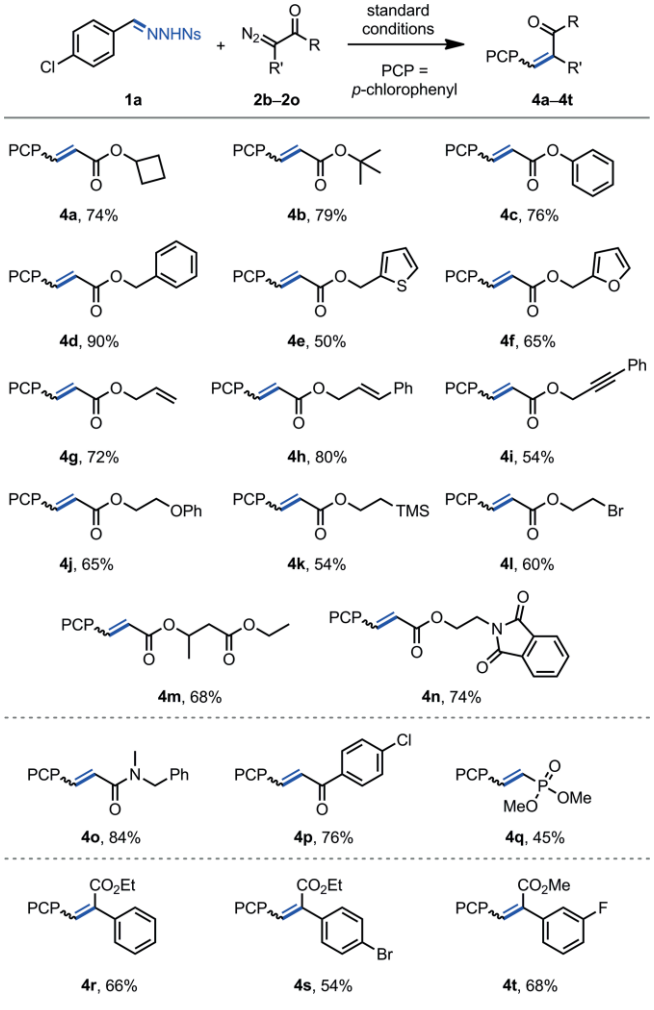
The substrate scope of the acceptor diazo compounds was also examined in the reaction with 4-chlorophenyl *N*-nosylhydrazone (**1a**) as the coupling partner (Scheme 2). The wide variation in the O-substituents of the α-diazo esters demonstrated the excellent functional-group tolerance of this reaction. For example, in addition to alkyl, aryl, and heteroaryl groups (see products **4a**–**f**, 50–90 % yield), unsaturated functional groups including terminal and internal alkenes (see products **4g** and **4h**) as well as an internal alkyne (see product **4i**) were tolerable, without the formation of cyclopropane or cyclopropene products. Other functional groups such as ether, TMS, Br, ester, and amide groups were also compatible under the



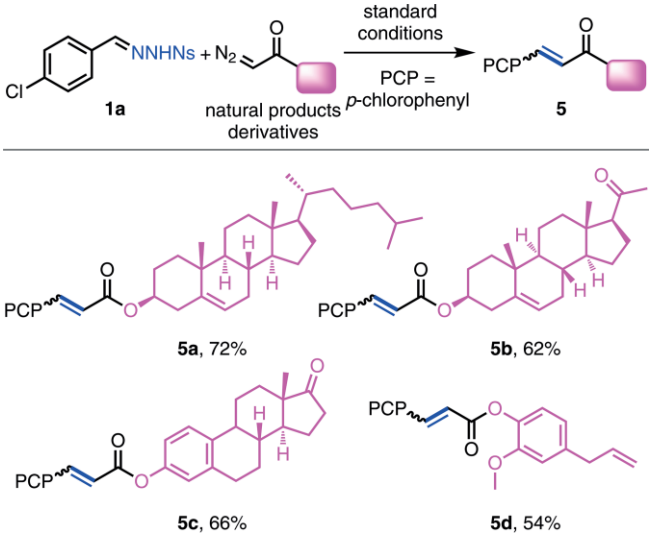
Scheme 1. Substrate scope of the *N*-nosylhydrazones. (*Z*)/(*E*) ratios were in a range of 1:1 to 3:2 and were determined by ^{1}H NMR spectroscopy.

silver-catalyzed conditions, and the corresponding functionalized acrylates **4j**–**n** were obtained in 54–74 % yield. In addition to diazoacetates, other kinds of α-diazo carbonyl compounds such as an α-diazo amide, ketone, and phosphonate were examined. Similarly, these diazo compounds all efficiently reacted with **1a** to produce alkenes **4o**–**q** in 45–84 % yield. Encouraged by these results, we turned our attention to donor–acceptor diazo compounds that were successful in reports by Davies[8] and Sun.[10] To our delight, α-aryl diazoacetates efficiently reacted with **1a** to give trisubstituted α-aryl acrylates **4r**–**t** in moderate yields. Notably, although the (*Z*)/(*E*) selectivity was in a range of 1:1 to 3:2, the (*Z*) and (*E*) isomers could be separated simply by column chromatography; thus, this method provides a preparative entry to (*Z*)-olefins, which are difficult to access by the Heck reaction.

Next, more complex substrates were investigated. Delightfully, several acceptor diazo-derived complex natural products succeeded in the cross-coupling with *N*-nosylhydrazone **1a** by using our method. For instance, the transformation of steroid derivatives such as cholesterol-, pregnenolone-, and estrone-derived acceptor diazo compounds afforded cross-coupling products **5a**–**c** in 62–72 % yield. A derivative of the natural perfume eugenol provided the corresponding product **5d** in 54 % yield. Note that the alkene functionality remained intact under the silver-catalyzed conditions (Scheme 3).

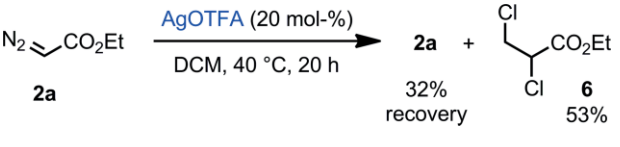


Scheme 2. Scope of the acceptor diazo compounds. (*Z*)/(*E*) ratios were in a range of 1:1 to 3:2 and were determined by ^{1}H NMR spectroscopy.



Scheme 3. Late-stage diversification of natural products.

Treatment of ethyl diazoacetate (**2a**) with silver catalyst alone, in the absence of *N*-nosylhydrazones, led to 53 % yield of C–Cl insertion product **6**,[17,19c] along with 32 % recovery of **2a** [Equation (1)]. Note that diethyl fumarate as a homocoupling product was not formed. This result clearly demonstrates that the activation ability of Ag toward acceptor diazo compounds is weaker than that of Cu, Ru, and Rh.



(1)

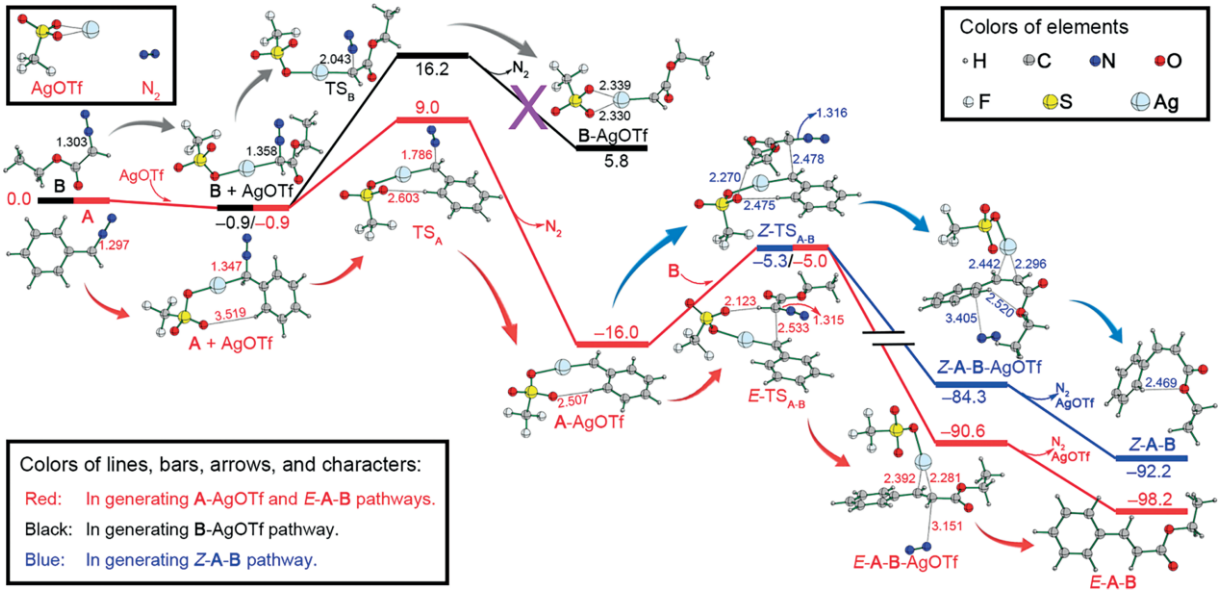


Figure 3. Energy profile for the donor–acceptor cross-olefination reaction.

To better understand the excellent chemoselectivity between the donor–acceptor diazo compounds, density functional theory (DFT) calculations were performed at the m06/6-31G(d)[sdd for Ag] level[22] on the model reaction of phenyl diazomethane (**A**) and ethyl diazoacetate (**B**) by using AgOTf as the catalyst. In line with general theory, the DFT results suggest that the cross-olefination reaction may have two elementary steps. In the first step, the AgOTf catalyst leads to the decomposition of the diazo compound and the formation of the corresponding silver carbenoid. As shown in Figure 3, the formation of silver carbenoid **A**–AgOTf is an exothermic process, with an energy barrier of 9.9 kcal mol^{-1} and a reaction energy of –15.1 kcal mol^{-1}. In contrast, the generation of carbenoid **B**–AgOTf has a much higher energy barrier (17.1 kcal mol^{-1}) and is endothermic (6.7 kcal mol^{-1}). Furthermore, structural checking revealed a hydrogen bond between the phenyl ring and OTf in both silver carbenoid **A**–AgOTf and corresponding transition state TS**A**. The formation of such a hydrogen bond could lower the energies and promote the generation of **A**–AgOTf. In the second step, silver carbenoid **A**–AgOTf couples with another diazo component to form the olefin. As drawn in Figure 3 and Figure S1, the energy barriers for the cross-coupling between **A**–AgOTf and phenyl diazomethane (**A**) or ethyl diazoacetate (**B**) to form olefin (*Z*)/(*E*)-**A**-**A** or (*Z*)/(*E*)-**A**-**B** are 9.3/10.7 and 11.0/10.7 kcal mol^{-1}, respectively. The formation of self-coupling product **A**-**A** seems to be favored, but the **A**-**A** coupling event can be excluded, because of the extremely low concentration of phenyl diazomethane (**A**) in the reaction solution. Consequently, in situ generated silver carbenoid **A**–AgOTf is able to react with ethyl diazoacetate (**B**) to produce the corresponding cross-coupling product **A**-**B**.

Another question regards the (*Z*)/(*E*) selectivity of the olefin. As shown in the latter part of Figure 3, the energies released by the coupling to form (*E*)-**A**-**B** and (*Z*)-**A**-**B** are –82.2 and –76.2 kcal mol^{-1}, respectively, which suggests irreversible conversion in both pathways. Thus, the (*Z*)/(*E*) selectivity should be determined by the energy barriers rather than the reaction energies. According to our calculations, the energy barriers are 11.0 [(*Z*)-TS$_{\mathbf{A\text{-}B}}$] and 10.7 kcal mol^{-1} [(*E*)-TS$_{\mathbf{A\text{-}B}}$], respectively. The energy barrier difference ($\Delta\Delta G$) of 0.3 kcal mol^{-1} is negligible, which could not result in significant (*Z*)/(*E*) selectivity. The small energy difference of the transition states probably accounts for the lack of stereoselectivity. Such a prediction is consistent with our experimental observation of (*Z*)/(*E*) ratios in the 1:1–3:2 range.

Conclusions

The cross-olefination reaction between donor–acceptor diazo compounds was developed by using *N*-nosylhydrazones as diazo surrogates under silver-catalyzed conditions. This method enabled the cross-coupling of a variety of diazo substrates to afford a variety of functionalized alkenes in good to high yields. This work has, for the first time, expanded the repertoire of diazo cross-coupling to highly reactive donor diazo compounds and has, thus, opened a new avenue to explore diazo cross-olefination methodology.

Acknowledgments

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Keywords: Alkenes · Cross-coupling · Diazo compounds · Hydrazones · Silver

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