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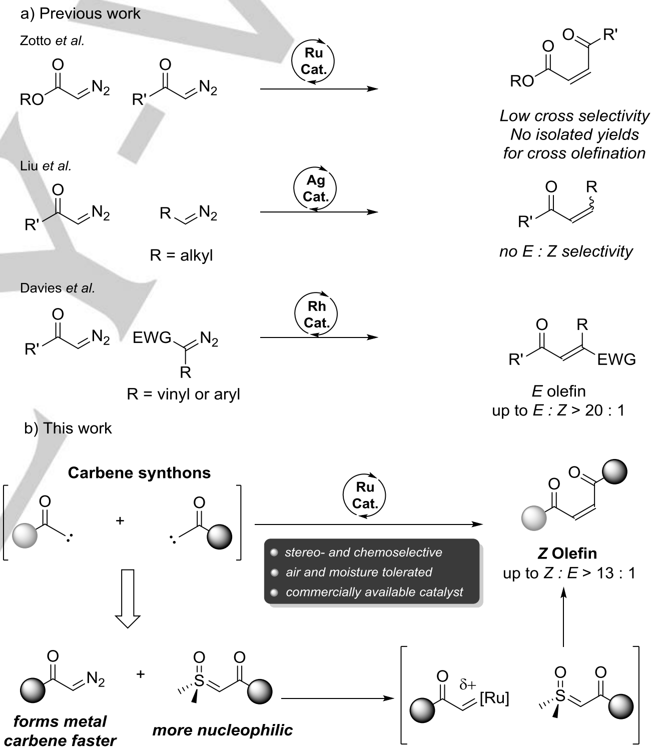
A Catalytic Cross-Olefination of Diazocompounds with Sulfoxonium Ylides

James D. Neuhaus,[a,+] Adriano Bauer,[a,+] Alexandre Pinto[a] and Nuno Maulide*[a]

Abstract: A novel ruthenium-catalysed cross-olefination of diazocompounds and sulfoxonium ylides is presented. Our reaction design exploits the intrinsic difference in reactivity of diazocompounds and sulfoxonium ylides as both carbene precursors and nucleophiles, resulting in a highly selective reaction.

The fascinating properties of alkenes have captured the imagination of chemists ever since in 1795 a team of Dutch researchers observed that the reaction between ethylene and chlorine forms a colourless liquid.[1] This observation led the authors to name ethene “gaz huileux” (*i.e.* oil-forming gas). Soon the term was renamed “gaz oléfiant” and today, over 200 years later, it is still common practice to use the word “olefin” when referring to an alkene.

In the last 70 years tremendous developments in the ability to form C=C double bonds, recognized with Nobel prizes, have become textbook knowledge such as the Wittig and related reactions[2,3] or olefin metathesis.[4] A conceptually appealing but seldom realized retrosynthetic disconnection of alkenes relies on the union of two carbenes. Indeed, early work showed that the metal-catalyzed homocoupling of diazocompounds is a valuable alternative for the generation of symmetrical alkenes.[5] Later investigations into the intermolecular cross-coupling of diazocompounds demonstrated that more effective coupling can be achieved when the nature of the two coupling partners is sufficiently different.[6,7] An early example by Zotto and coworkers showed that acceptor-substituted diazocompounds can be selectively cross-coupled with TMS diazomethane with high stereoselectivity.[6a] This concept was recently extended by Liu *et al.*, whereby alkyl-substituted diazocompounds were generated *in situ* and selectively cross-coupled to acceptor-substituted diazocompounds *via* silver catalysis.[7e] However, poor stereoselectivity, with 1:1 mixtures of *E*/*Z* olefin products, was observed. Earlier, Davies and coworkers showed that donor-acceptor diazocompounds can be cross-coupled selectively to acceptor-substituted diazocompounds *via* rhodium catalysis. Stereoselectivity was generally high in favor of the *E* olefin.[7a] Although the scope was extended by Sun and coworkers, this methodology requires both an electron-withdrawing and an electron-donating group adjacent to the diazomethane moiety of at least one of the reaction partners.[7a,7c-7e] An additional report by Wang and coworkers relies on the use of cyclopropenes as carbene precursors. These are then coupled to diazocompounds.[6d] The same group published an interesting coupling of diazocompounds with *in situ* generated difluorocarbene.[6e]



Scheme 1. Previously reported cross-olefinations and this work.

Sulfonium and sulfoxonium ylides have witnessed a renaissance in contemporary catalysis beyond the well-known Johnson-Corey-Chaykovsky reactions[8] in C-H functionalization,[9] N-H insertion[10] and cycloisomerization reactions.[11] Their popularity is owed to the fact that they are easy to prepare, readily purified and considerably safer to handle than their diazo counterparts.

Although sulfoxonium ylide dimerization has been observed indirectly, it has never been used for the effective synthesis of olefins. This is probably also due to the fact that the generated products (electron-poor olefins) are also good substrates for Johnson-Corey-Chaykovsky cyclopropanation under the reaction conditions. [12] Indeed, sulfoxonium ylides are generally better

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[a] Dr. J. D. Neuhaus[+], A. Bauer[+],Dr. A. Pinto and Prof. Dr. N. Maulide
Institute of Organic Chemistry, University of Vienna
Währinger Straße 38, 1090 Vienna (Austria)
E-Mail: nuno.maulide@univie.ac.at
Homepage: http://maulide.univie.ac.at

[+] These authors contributed equally
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nucleophiles than their diazo analogues, but tend to undergo decomposition to the metal carbene at much slower rates than their diazo counterparts, rendering a catalytic, hypothetical sulfoxonium ylide (cross)-coupling a difficult prospect.[13]

This led us to speculate that the catalytic cross-coupling of a diazocompound with a sulfoxonium ylide should be possible. We proposed that formation of a metal carbene should take place faster from the diazocompound precursor, and that the resulting electrophilic carbene would be attacked preferentially by the more nucleophilic sulfoxonium ylide. However, we were uncertain whether the coupling product (a Michael acceptor) would be prone to undergoing conjugate addition by the sulfoxonium ylide.

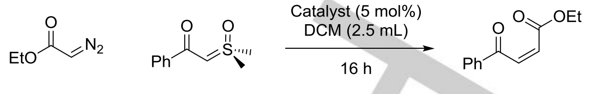
In our first trials, a range of iridium(II) and rhodium(II) catalysts were investigated for the cross olefination of diazoester **1a** and sulfoxonium ylide **2a**, due to their well-documented proficiency in metallocarbene formation.[7a],[14] Those preliminary experiments (Table1, entries 1-2; see the Supporting Information for further experiments) led to low but promising yields of the desired product accompanied by diethylmaleate/diethyl fumarate resulting from homodimerization of diazoester **1a** as the main side product. Importantly, homodimerization of the sulfoxonium ylide **2a** *was virtually absent*, corroborating our initial hypothesis. Unreacted sulfoxonium ylide could be removed completely along with the catalyst during workup, resulting in a clean and easy to analyze crude ^{1}H NMR spectrum. Cyclopropanation by-products were never observed.[15] In the course of catalyst screening, we found that the cheap ruthenium complex [Ru(*p*-cymene)Cl$_2$]$_2$ [16] displays the highest efficiency for this cross-olefination. Further optimization of the conditions led to good isolated yields above 70% with a *Z*/*E* ratio of 9:1 (Table 1, entry 5).

With optimized conditions in hand, we examined the scope of ylides (Scheme 2).[17] Pleasingly, electron-poor (**2b**-**d**, **2h**) sulfoxonium ylides afforded similar yields as well as *Z*/*E* selectivities. *Para*-substituted substrates (**2b/h**) gave particularly selective olefination with *Z*/*E* ratios up to 13:1. Electron-rich substrates (**2e/i**) show lower selectivity. Noteworthy, the aryl iodide **2f** reacted smoothly without competing oxidative addition. The product **3ai**, which has shown antimicrobial activity (*M. tuberculosis*), could be prepared in a single step.[18]

The ketone moiety on the ylide was not a prerequisite for successful cross-olefination, as sulfone (**3ak**) afforded comparable yields and high selectivities.

At this juncture, the substrate scope for the diazocompound was investigated (Scheme 3). As depicted, the reaction is general for a range of diazoesters. Notably, several alkenes (**1c/i**), a silane (**1e**) and even an alkyne (**1b**) were well tolerated with *Z*/*E* ratios of up to 11:1. No trace of competing cyclopropanation of the unsaturated moieties was observed. Furthermore, esters of functionalized terpene alcohols such as cholesterol (**1f**), citronellol (**1l**) or a β-pinene derivative (**1j**) were smoothly converted to the desired olefin. [19]

Under these conditions, donor-acceptor diazoesters, (popularised by the elegant work of Davies[20]), such as ethyl (*E*)-2-diazo-4-phenylbut-3-enoate **4**, were typically recovered suggesting that conversion to the metal carbene did not take place.

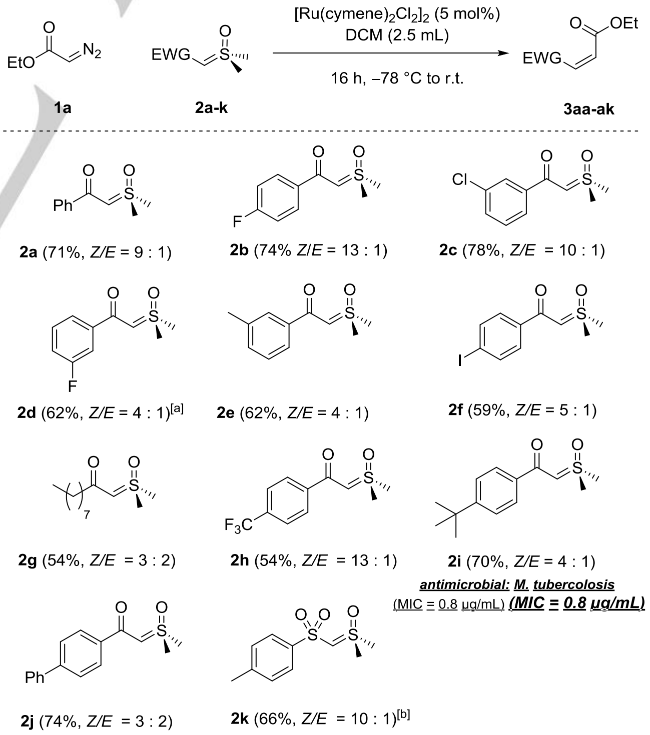


1a **2a** **3aa**

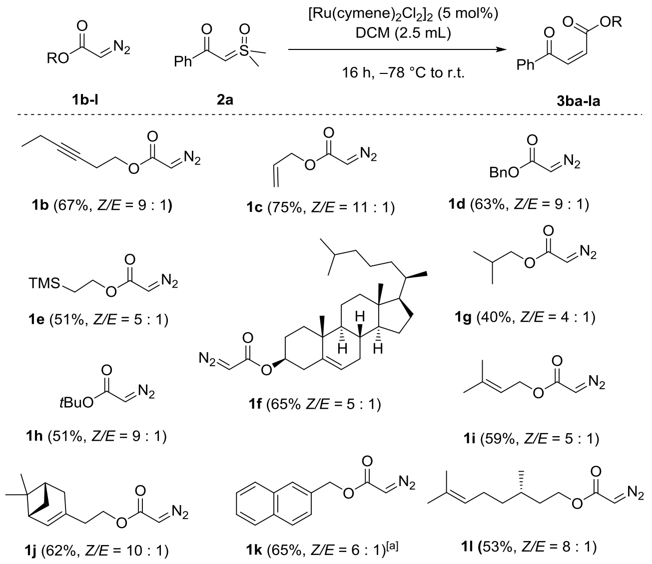
Table 1. Optimization of the cross olefination.

Entry	Catalyst	Temperature	NMR Yield **3aa**	*Z* : *E*
1	[Ir(COD)Cl]$_2$	r.t.	13%	1.0 : 1
2	Rh$_2$(OAc)$_4$	r.t.	20%	1.9 : 1
3	[Ru(*p*-cymene)Cl$_2$]$_2$	r.t.	32%	1.9 : 1
4	[Ru(*p*-cymene)Cl$_2$]$_2$	-78 °C to r.t.	53%	7.8 : 1
5[a]	**[Ru(*p*-cymene)Cl$_2$]$_2$**	**-78 °C to r.t.**	**71%[*]**	**9.0 : 1**
6[a]	Rh$_2$(Esp)$_2$	-78 °C to r.t.	10%	1 : 9.0
7[a]	Rh$_2$(OPiv)$_2$	-78 °C to r.t.	17%	1 : 7.5

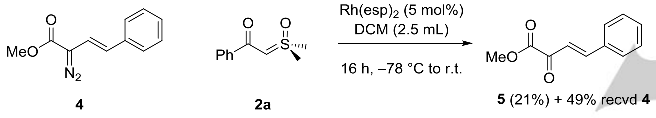
[a] 2.0 eq. of Sulfoxonium ylide used [*] Isolated yield, All reactions were performed on a 0.2 mmol scale (diazo compound) under air.



Scheme 2. Substrate scope for sulfoxonium ylides. Z/E ratios determined by crude ^{1}H NMR analysis. All yields are for pure, isolated material unless indicated otherwise. [a] ^{1}H NMR yield with Mesitylene as internal standard. [b] DMF was used as a cosolvent.



Scheme 3. Substrate scope of diazocompounds. Z/E ratios determined by crude 1H NMR analysis. All yields refer to pure, isolated material unless indicated otherwise. [a] ^{1}H-NMR yield with mesitylene as internal standard.

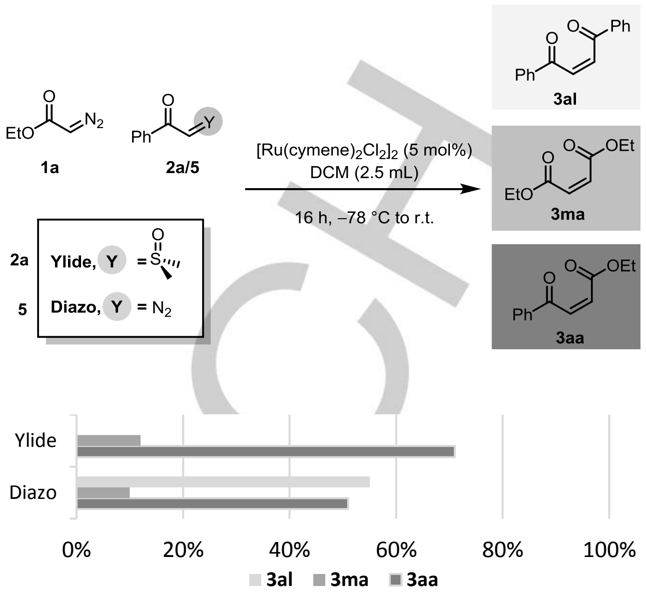


Scheme 4**.** Unexpected reaction of a donor-acceptor diazo compound. ^{1}H NMR yields with mesitylene as internal standard.

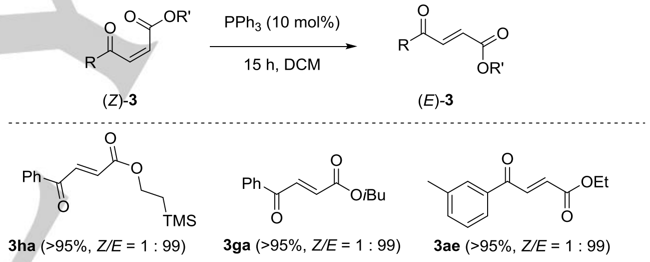
Changing to *rhodium(II)* catalysis instead of ruthenium(II) (cf. Scheme 4), the corresponding α-ketoester **5** was observed (21% and 49% starting material, NMR yield).
This suggests that our procedure is orthogonal to the work of Davies. [7a]

A direct comparison of the cross-olefination protocol reported herein with the cross olefination of two diazocompounds reveals that yield and selectivity are considerably higher when sulfoxonium ylides are employed (Scheme 5). Moreover, while the cross-olefination of sulfoxonium ylides and diazoesters delivers the homo-dimerization of the ester moiety (product **3ma**, cf. Scheme 5) as the only undesired byproduct in small amounts, cross-olefination of two diazocompounds results in a mixture of all the three possible coupling products with virtually no selectivity (in the event, the desired cross-couple product **3aa** is not even the major product).

During optimization studies, several quenching agents were investigated. While pyridine, pyrimidine and dimethylsulfide shut down the reaction, triphenylphosphine had an additional effect: *Z*/*E* diastereomeric mixtures were converted completely to the *E* isomer when substoichiometric amounts of PPh$_3$ were added to the reaction mixture. Further studies showed that this isomerization[21] takes place not only under the reaction conditions but also in solutions of isolated products (Scheme 6).



Scheme 5. Direct comparison of the cross-olefination procedure with the cross-coupling of two different diazocompounds. Conditions: EDA 1.0 eq., Acetophenone derivative 2.0 eq., Z/E ratio determined by crude 1H NMR analysis, 1H NMR yields with mesitylene as internal standard



Scheme 6. Isomerization to (E)-olefins.

In conclusion, a novel ruthenium-catalysed cross-olefination of diazocompounds and sulfoxonium ylides is presented. Our reaction design exploits the intrinsic difference in reactivity of diazocompounds and sulfoxonium ylides as both carbene precursors and nucleophiles, resulting in a highly selective reaction that nicely complements known, often less selective diazo-diazo coupling reactions. This results in olefin products with high *Z*-selectivity.

Acknowledgements

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Keywords: Cross olefination • Homogenous catalysis • sulfur ylide • diazocompound • ruthenium

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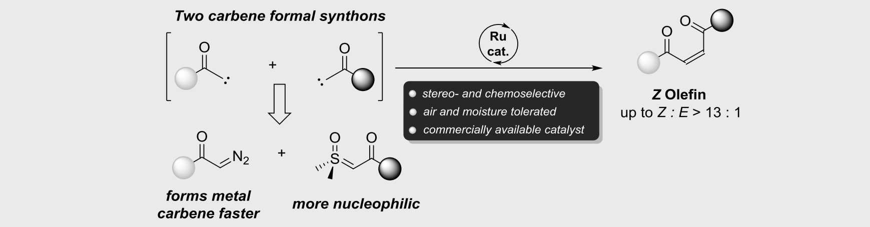

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