Diazo Cross-Coupling

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Rhodium(II)-Catalyzed Cross-Coupling of Diazo Compounds**

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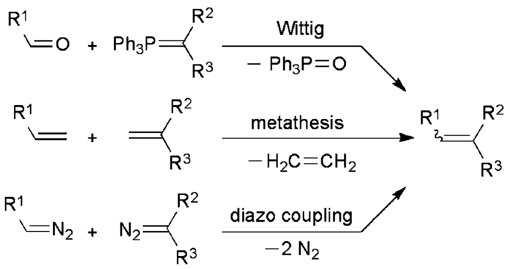
The convergent synthesis of alkenes occupies a central position as a strategic reaction in organic synthesis (Scheme 1). The Wittig reaction and its many variants are often used as key transformations in retrosynthetic analysis.[1] In recent years, olefin metathesis has become a dominant synthetic approach for the convergent synthesis of alkenes.[2] Here we describe an alternative convergent method for the synthesis of unsymmetrical alkenes by a carbenoid-induced cross-coupling of diazo compounds.



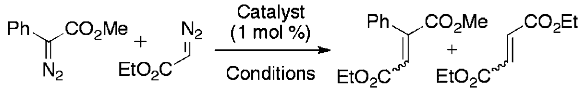
Scheme 1. Olefin formation.

Since the pioneering work of Grundmann,[3] only a few synthetically useful processes have been reported using carbenoid-induced coupling of diazo compounds.[4,5] Typically, the process is considered to be an undesired side-reaction, and the homocoupling of ethyl diazoacetate has been an especially vexing problem.[4,6] In many instances, it can only be avoided by very slow addition of the diazo compound to the reaction mixture.[6] The most useful synthetic applications to date have been intramolecular and transannular reactions of bis-diazocarbonyl compounds.[7]

The diazo coupling would be of much greater synthetic utility for the convergent synthesis of alkenes if practical procedures for intermolecular reactions were available. The cross-coupling of diazo carbonyl compounds with trimethylsilyldiazomethane has been demonstrated to be a viable process.[4b,c] In contrast, a selective cross-coupling of two diazocarbonyl compounds to form alkenes has, to our knowledge, not been reported prior to this study. In recent years, we have explored the broad synthetic potential of donor/acceptor-substituted rhodium carbenoids.[8] These carbenoids are more stabilized than conventional carbenoids lacking a donor group and have a low tendency to undergo homodimerization, which has made them useful intermediates in a range of synthetic transformations.[8d,e,9] Here, we describe that these carbenoids can undergo selective cross-coupling with diazocarbonyl compounds lacking a donor group.[5] Mechanistic studies to determine the factors that control selectivity in the dimerization chemistry will also be described.

During studies on intermolecular C–H functionalization, using two diazo compounds in the reaction mixture, it was discovered that the cross-coupling of methyl phenyldiazoacetate (**1a**) and ethyl diazoacetate (**2**) is a favorable process. This reaction was studied further in experiments that involved adding an equimolar mixture of the diazo compounds rapidly to a solution of a Rh^{II} catalyst (Table 1). The reaction affords predominantly a mixture of cross-coupling product **3a** and ethyl diazoacetate homodimerization product **4**. In order to find reaction conditions that would minimize homodimerization, and maximize the stereoselectivity of the heterodimer, several conditions were screened. Under the optimal conditions, synthetically useful selectivities could be achieved

Table 1: Optimization of cross-coupling conditions.



1a **2** **3a** **4**

Entry	Catalyst[a]	Solvent	T [°C]	Ratio[b] **3a**:**4**	E:Z **3a**[a]
1	[$Rh_2(OPiv)_4$]	CH_2Cl_2	RT	63:37	9.5:1
2	**[$Rh_2(OPiv)_4$]**	**CH_2Cl_2**	**−63**	**91:9**	**>20:1**
3	[$Rh_2(OOct)_4$]	CH_2Cl_2	−63	79:22	6.9:1
4	[$Rh_2(esp)_2$]	CH_2Cl_2	−63	77:16	12:1
5	[$Rh_2(tpa)_4$]	CH_2Cl_2	−63	64:36	20:1
6	[$Rh_2(tfa)_4$]	CH_2Cl_2	−63	75:25	7.3:1
7	[$Rh_2(OPiv)_4$]	$PhCF_3$	−63	87:13	>20:1
8	[$Rh_2(OPiv)_4$]	Et_2O	−63	72:28	13:1
9	[$Rh_2(OPiv)_4$]	*n*-Hex	−63	75:26	18:1

[a] Piv = pivaloyl; esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid; tpa = triphenylacetate; tfa = trifluoroacetate. [b] From ^1H NMR analysis of crude residue.

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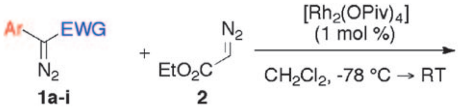
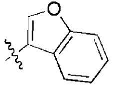
(91:9 product selectivity, >20:1 stereoselectvity favoring (E)-**3a**) using dichloromethane as solvent at low temperatures with dirhodium(II) tetrakispivaloate, [$Rh_2(OPiv)_4$], as catalyst (Table 1, Entry 2).

The cross-coupling reaction between aryldiazoesters and **2** was then examined using the optimized reaction conditions (Table 2). For a series of p-substituted aryldiazoacetates, good yields (67–73 %) and excellent stereoselection towards the E-isomer (E:Z ratio >20:1) was observed, unless the aryl substituent was very electron-withdrawing. In the case of p-trifluoromethyl substitution (**1d**), the isolated yield of **3d** was only 40 % and the E:Z-selectivity declined substantially (E:Z ratio 5.1:1). The best result was obtained with benzofuranyl diazoacetate **1f**, which afforded the E-alkene **3f** in 83 % yield, again with very good stereoselectivity. The influence of the acceptor group on the aryldiazoacetate was also investigated (Table 2, Entries 7–9), and although good overall reaction yields were obtained (71–86 %), the stereoselectivity was significantly attenuated when this group was cyano or methyl ketone. The dimethyl phosphonate-substituted compound gave no cross-coupling product, presumably because the diazo compound is too stable under the reaction conditions.[8c] These studies demonstrate that aryldiazoacetates with electron-neutral or electron-releasing substituents are optimal for achieving high chemo- and stereoselectivities.

Table 2: Cross-Coupling of aryldiazo compounds with ethyl diazoacetate.

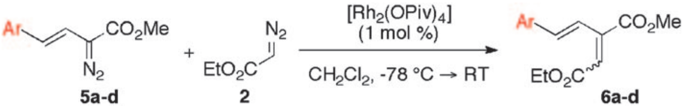


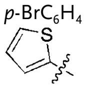
Entry	Compd.	Ar	EWG	E:Z[a]	Yield [%][b]
1	**a**	Ph	CO_2Me	>20:1	71
2	**b**	p-$MeOC_6H_4$	CO_2Me	>20:1	73
3	**c**	p-BrC_6H_4	CO_2Me	>20:1	67
4	**d**	p-$CF_3C_6H_4$	CO_2Me	5.1:1	40[c]
5	**e**	2-Naphthyl	CO_2Me	>20:1	58
6	**f**		CO_2Me	>20:1	83
7	**g**	Ph	CN	3.3:1	86[d]
8	**h**	Ph	COMe	2.0:1	71[d]
9	**i**	Ph	$PO(OMe)_2$	N/A	N/A

[a] From ^1H NMR analysis of crude residue. [b] Yields of isolated products. [c] 20–30% of homocoupled products were also formed. [d] Combined yield.

The cross-coupling of vinyldiazoacetates with **2** would form substituted dienes, a feature that would add significant value to the products. Indeed, the reaction between methyl styryldiazoacetate **5a** and **2** gave diene **6a** in 82 % yield, however with attenuated stereoselectivity (E:Z ratio 5.6:1). Moderate to good overall yields (61–82 %) can be obtained with a variety of vinyldiazoacetates **5a–d**, but with only moderate stereoselectivity across the board (Table 3).

Table 3: Cross-coupling between vinyldiazoacetates and ethyl diazoacetate.

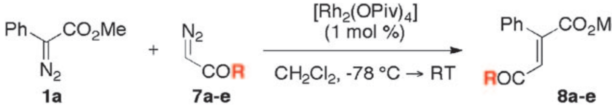


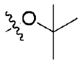
Entry	Compd.	Ar=	E:Z[a]	Yield [%][b]
1	**a**	Ph	5.6:1	82
2	**b**	p-$MeOC_6H_4$	5.5:1	67
3	**c**	p-BrC_6H_4	5.1:1	61
4	**d**		5.1:1	61

[a] From ^1H NMR analysis of crude residue. [b] Combined yields.

The next series of experiments explored methods to enhance the stereoselectivity of the cross-coupling process. By increasing the bulkiness of the unsubstituted diazo compound, significantly more selective reactions could be achieved. The reaction between *tert*-butyl diazoacetate **7a** and **1a** produced the E-alkene **8a** in 87 % yield (Table 4, Entry 1). Aryldiazoketones proved to give good coupling reactions, and produced the E-alkenes **8b–e** in >20:1 and in 79–87 % yields.

Table 4: Cross-coupling of **1a** with **7a** and diazoketones **7b–e**.



Entry	Compd.	R=	E:Z[a]	Yield [%][b]
1	**a**		>20:1	87
2	**b**	Ph	>20:1	87
3	**c**	p-$MeOC_6H_4$	>20:1	80
4	**d**	p-BrC_6H_4	>20:1	79
5	**e**	$(3,4\text{-}Cl_2)C_6H_3$	>20:1	87

[a] From ^1H NMR analysis of crude residue. [b] Yields of isolated products.

The cross-coupling of the diazo compounds is favored over the homocoupling process. A possible explanation for this would be that one of the diazo compounds is decomposed faster than the other, and then preferentially reacts with the other diazo compound.[4d,8e] In order to shed light on what factors control the cross-coupling process, the reaction progress was monitored using ReactIR. The first round of experiments explored the conversion rates of decomposition of the two diazo compounds in the presence of an external trap, styrene (6 equiv). An aliquot of catalyst (0.1 mol %) was added to a solution of diazo compound at −15 °C and trap, generating cyclopropane products (Figure 1). The reactions were monitored by the disappearance of the C=N_2 stretch bands (2088 cm^{-1} for **1a** and 2114 cm^{-1} for **2**). These studies showed that methyl phenyldiazoacetate **1a** reacted faster

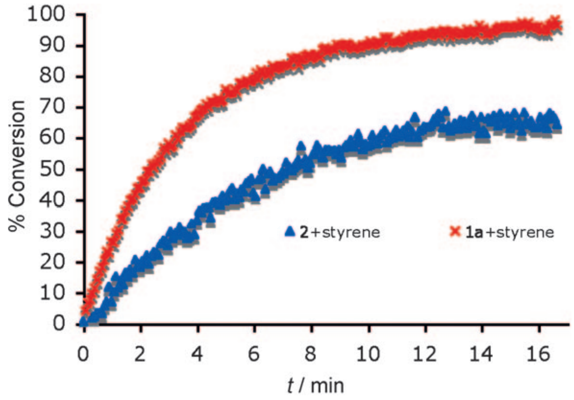


Figure 1. Reactions of **1a** (red data) and **2** (blue data) at −15 °C in the presence of styrene.

than ethyl diazoacetate **2**, which is consistent with related studies.[8e]

The second series of experiments determined the relative rates of decomposition of ethyl diazoacetate (**2**) alone (Figure 2, gray data), and an equimolar mixture of ethyl diazoacetate (**2**, blue data) and methyl phenyldiazoacetate (**1a**, red data). In the absence of styrene, the reactions are much faster, which may be an indication that the styrene has a poisoning effect on the catalyst. The cross-coupling reaction is especially fast. All of **2** is consumed within ca. 7 s, while about 30 % of **1a** is retained. The consumption of **2** is ca. 1.5-times faster than that of **1a**. Once **2** is consumed, the decomposition of **1a** is significantly slowed down (by a factor of ca. 300), presumably because the homocoupling of the donor/acceptor carbenoid is not a favorable process.[8d] The initial rate of conversion of **2** in the mixture is about 7-times faster than the homocoupling of **2** by itself. Furthermore, the latter reaction does not go to completion as poisoning of the catalyst is a problem with this diazo compound at 0.1 mol % catalyst loading.[8e] An explanation for the observed trends would be that **1a** is converted to the carbenoid faster than **2**, but both carbenoids, if formed, react quickly with **2** to form dimers. In the mixture, **2** decomposes faster than **1a** because some of it is consumed in a homodimerization process. These results are consistent with the formation of predominantly cross-dimer and some homodimer of **2**.

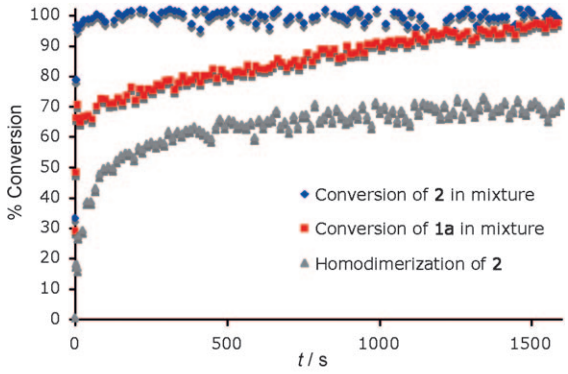


Figure 2. Decomposition of a mixture of **1a** (red data) and **2** (blue data) at 0 °C, and decomposition of **2** only (grey data) at 0 °C.

We next carried out density functional calculations to obtain an understanding of the stereoselection in the dimerization events. As a model for this we used the reaction between methyl phenyldiazoacetate (**1a**) and methyl diazoacetate (**12**) with dirhodium formate (**9**) as a catalyst. These carbenoid systems have been studied previously in cyclopropanation[11] and C–H insertion reactions.[12,13] The main discussion here is based on free energies and enthalpies calculated at the B3LYP/6-31G*[Rh-RSC+4f] level of theory.[13]

Transition structures were sought for reaction between the carbenoid complex **11**, derived from **1a**, and **12**. The most stable of these transition states, **TS-IIb**, is shown in Figure 3 a.

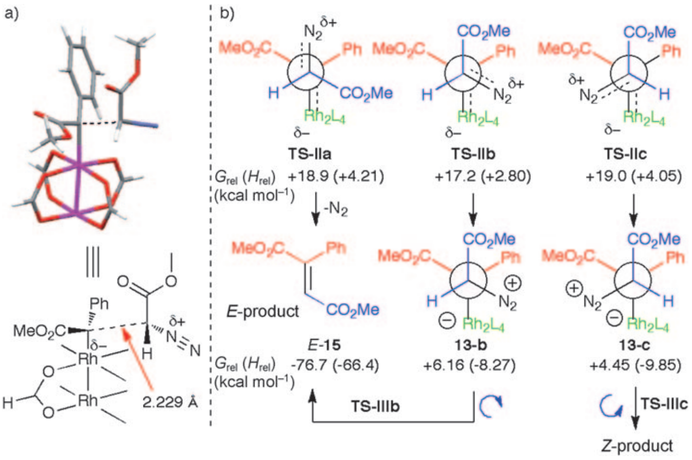
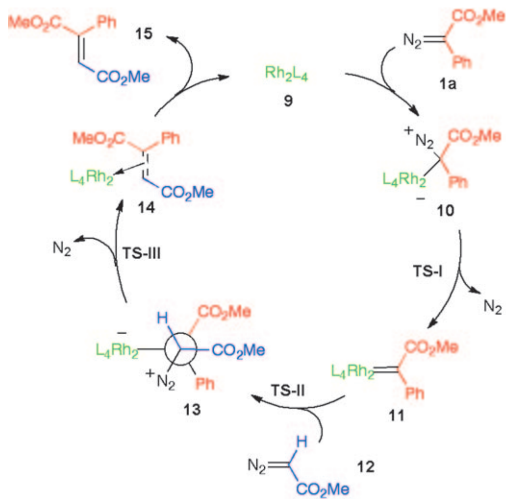


Figure 3. a) Most stable transition state **TS-IIb**. b) Dimerization stereoselectivity from three lowest-energy transition structures. Gas-phase enthalpies and Gibbs free energies reported relative to **11** + **12**.

The three most stable structures **TS-IIa–c** are shown in Figure 3 b (see Supporting Information for more details), including enthalpies and Gibbs energies relative to free reactants (carbenoid **11** + **12**). The structures are represented by Newman projections, analogous to models previously presented by Nagai,[14] Wulfman,[15] and Shechter[16] in homodimerization chemistry.

Stereoselection is indirectly governed by the stereoelectronic requirement that the elimination must occur with the Rh–C and C–N bonds arranged in a periplanar conformation.[16] Whether this affords the *E*- or *Z*-product, depends on the preferred transition state for addition to the carbenoid. The preference for **TS-IIb** is related to the steric influence of the carbenoid on the three substituents on **12**. The largest substituent of **12** (methyl ester), prefers to be oriented *anti* to the catalyst "wall", the diazonium moiety (medium bulk) towards the lower right quadrant, and hydrogen (small) oriented towards the most sterically crowded sector (between the carbenoid ester group and catalyst). The forward intrinsic reaction coordinate drive from **TS-IIb** leads to formation of an ylide **13b**, which is kinetically unstable. Clockwise rotation of the front of this ylide gives a *syn*-elimination to form the observed major E-product. The counter-clockwise rotation to give *anti*-elimination and Z-product is disfavored since the system must pass through an eclipsed conformation for this to happen. **TS-IIIb** for the conversion of **13b** to (E)-**15** could not be located computationally, presumably due to the flat nature of the potential energy surface in this region. However, a coordinate scan towards the product side indicated that a small barrier may exist (<0.5 kcal mol^{-1}). For comparison, rotation of ylide **13b** to give *anti*-elimination (Z-alkene formation), has a barrier of $\Delta G^{\ddagger} = 7.7$ kcal mol^{-1}. Transition states **TS-IIa–c** were next optimized at the B3LYP/6-311+G(d,p)[Rh-RSC+4f] level of theory, with included solvent effects from dichloromethane (IEFPCM model)[17] at −78 °C. A simple Eyring analysis, based on the re-optimized structures **TS-IIb** and **TS-IIc**, gives a predicted diastereomer ratio of 19:1. These results are in very good agreement with experimental observations (Table 1 shows E:Z ratios in the range 6.9–22:1), particularly considering potential errors in DFT calculations.[18] The mechanistic model is consistent with an increase in stereoselectivity with increasing steric bulk of the unsubstituted diazo compound (*tert*-butyl ester group or diazoketone) as it would favor the preferred trajectory even more.

We propose a catalytic cycle for the dimerization process as shown in Scheme 2. The results of the calculations, in conjunction with the ReactIR studies, suggest that productive cross-coupling occurs through reaction between the donor/acceptor-substituted carbenoid and the unsubstituted diazo compound.



Scheme 2. Proposed coupling mechanism.

In summary, we have described a convergent process for the selective cross-coupling of diazo compounds to afford trisubstituted alkenes in synthetically useful yields. Productive cross-dimerization appears to rely on: 1) a significant decomposition rate difference between the two diazo compounds and, 2) a preference for trapping of the initial carbenoid with the other diazo compound. The study represents significant progress towards synthetic utilization of diazo coupling reactions in alkene synthesis, since valuable insights into factors controlling stereo- and chemoselectivity in the dimerization events have been identified.

Experimental Section

General procedure for cross-coupling: To a flame-dried, 50 mL round-bottom flask, equipped with a magnetic stir bar, a rubber septum, and an argon inlet adaptor was added dirhodium(II) tetrakispivaloate (0.01 equiv). The flask was evacuated and purged with argon three times before placing it under a positive Ar atmosphere. Dry and degassed CH_2Cl_2 (5.0 mL) was added by syringe and the reaction flask was cooled to −78 °C in an acetone/CO_2 bath. A mixed, equimolar solution of diazo compounds (1.0 mmol each, 1.0 equiv each) was prepared by combining the appropriate diazo compounds in CH_2Cl_2 (5.0 mL). This solution was then added to the cooled reaction mixture over 1 h through a syringe pump. Following addition, the reaction flask was slowly allowed to obtain ambient temperature. The solvent was removed in vacuo and the crude material was purified by column chromatography.

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