Stereoselective Generation of Cis or Trans Olefins from the $RuCl_2(PPh_3)_3$-Catalyzed Diazo Coupling of Ethyldiazoacetate

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Summary: The $RuCl_2(PPh_3)_3$-catalyzed diazo coupling of ethyl diazoacetate was manipulated to generate either diethyl fumarate (DEF) or diethyl maleate (DEM) with high stereoselectivity. A mechanism was proposed which contained separate pathways for DEM and DEF formation and explained how reaction conditions were controlled to favor either pathway.

Introduction

Catalytic carbon−carbon bond formation via metal-catalyzed carbene transfer has been the subject of significant research efforts over the past three decades.[1−19] Recent major advances in metal-catalyzed diazo coupling have allowed these reactions to be carried out with high stereoselectivity.[20,21] Metal complexes of nickel,[22] copper,[23] iridium,[24] osmium,[25] tantalum,[19,26,27] rhenium,[28,29] and chromium[30] have been shown to successfully generate the cis olefin diethyl maleate (DEM) from ethyl diazoacetate (EDA) with high stereoselectivity (Scheme 1). A variety of ruthenium catalysts have shown particular adeptness at generating DEM in high stereoselectivity.[20,21,31−37]

Although it is generally accepted that olefin formation via metal-catalyzed diazo coupling proceeds through a metal carbene intermediate,[20,21,31−37] little is known about the actual mechanism of this reaction. Various studies have established the reaction as being first order in the metal catalyst and, in some cases, have isolated the metal carbene intermediate to demonstrate its ability to further react with EDA to stereoselectively form DEM.[21,23,32] Many factors hamper efforts to elucidate mechanistic details, including the low catalyst concentrations often employed (usually around 1 mol % Ru vs EDA), the inherent instability of some ruthenium carbene intermediates, and the short reaction times needed for reaction completion, often occurring in only a few minutes.[20,21,31−37] Although generic catalytic cycles are often proposed in passing, mechanistic details rationalizing the high stereoselectivity seen in recent reports have been noticeably lacking.

Herein, we report our results on the study of $RuCl_2(PPh_3)_3$-catalyzed diazocoupling of EDA to generate DEM and diethyl fumarate (DEF). Although $RuCl_2(PPh_3)_3$ has been reported to generate DEM with only low stereoselectivity,[20] we have found that, by changing

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(1) Pellicciari, R.; Natalini, B.; Marinozzi, M.; Monahan, J. B.; Snyder, J. P. *Tetrahedron Lett.* **1990**, *31*, 139−142.
(2) Nishiyama, H.; Itoh, Y.; Sugawara, Y.; Matsumoto, H.; Aoki, K.; Itoh, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1247−1262.
(3) Anciaux, A. J.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyssié, P. *J. Org. Chem.* **1980**, *45*, 695−702.
(4) Zhou, S.-M.; Deng, M.-Z.; Xia, L.-J.; Tang, M.-H. *Angew. Chem., Int. Ed.* **1998**, *37*, 2845−2847.
(5) Smith, D. A.; Reynolds, D. N.; Woo, L. K. *J. Am. Chem. Soc.* **1993**, *115*, 2511−2513.
(6) Nishiyama, H.; Itoh, Y.; Matsumoto, H.; Park, S.-B.; Itoh, K. *J. Am. Chem. Soc.* **1994**, *116*, 2223−2224.
(7) Singh, V. K.; DattaGupta, A.; Sekar, G. *Synthesis* **1997**, 137−149.
(8) Lo, W.-C.; Che, C.-M.; Cheng, K.-F.; Mak, T. C. W. *Chem. Commun.* **1997**, 1205−1206.
(9) Galardon, E.; Le Maux, P.; Simonneaux, G. *Chem. Commun.* **1997**, 927−928.
(10) Wright, M. E.; Svejda, S. A.; Jin, M.-J.; Peterson, M. A. *Organometallics* **1990**, *9*, 136−146.
(11) Collman, J. P.; Brothers, P. J.; McElwee-White, L.; Rose, E. *J. Am. Chem. Soc.* **1985**, *107*, 6110−6111.
(12) Rasmussen, K. G.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1287−1291.
(13) Hansen, S. M.; Wolland, A. O.; Rominger, F.; Eisentrager, F.; Hofman, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 1273−1276.
(14) Wolf, J.; Stüer, W.; Grünwald, C.; Werner, H.; Schwab, P.; Schulz, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1124−1126.
(15) Collman, J. P.; Brothers, P. J.; McElwee-White, L.; Rose, E.; Wright, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 4570−4571.
(16) Nishiyama, H.; Park, S.-B.; Haga, M.-A.; Aoki, K.; Itoh, K. *Chem. Lett.* **1994**, 1111−1114.
(17) Vallgårda, J.; Appelberg, U.; Csöregh, I.; Hacksell, U. *J. Chem. Soc., Perkin Trans. 1* **1994**, 461−470.
(18) Djukic, J.-P.; Smith, D. A.; Young, J.; Victor, G.; Woo, L. K. *Organometallics* **1994**, *13*, 3020−3026.
(19) Masters, C.; van der Woude, C.; van Doorn, J. A. *J. Am. Chem. Soc.* **1979**, *101*, 1633−1634.
(20) Baratta, W.; Del Zotto, A.; Rigo, P. *Chem. Commun.* **1997**, 2163−2164.
(21) Baratta, W.; Del Zotto, A.; Rigo, P. *Organometallics* **1999**, *18*, 5091−5096.
(22) Simunic, J. L.; Pinhas, A. R. *Inorg. Chem.* **1989**, *28*, 2400−2406.
(23) Díaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Prieto, F.; Pérez, P. J. *Organometallics* **1999**, *18*, 2601−2609.
(24) Kubo, J.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2000**, 625−626.
(25) Woo, L. K.; Smith, D. A. *Organometallics* **1992**, *11*, 2344−2346.
(26) Berry, D. H.; Koloski, T. S.; Carroll, P. J. *Organometallics* **1990**, *9*, 2952−2962.
(27) Schrock, R. R.; Sharp, P. R. *J. Am. Chem. Soc.* **1978**, *100*, 2389−2399.
(28) Merrifield, J. H.; Lin, G.-Y.; Kiel, W. A.; Gladysz, J. A. *J. Am. Chem. Soc.* **1983**, *105*, 5811−5819.
(29) Roger, C.; Bodner, G. S.; Hatton, W. G.; Gladysz, J. A. *Organometallics* **1991**, *10*, 3266−3274.
(30) Casey, C. P.; Anderson, R. L. *J. Chem. Soc., Chem. Commun.* **1975**, 895−896.
(31) Baratta, W.; Herrmann, W. A.; Kratzer, R. M.; Rigo, P. *Organometallics* **2000**, *19*, 3664−3669.
(32) Bianchini, C.; Lee, H. M. *Organometallics* **2000**, *19*, 1833−1840.
(33) Lee, H. M.; Bianchini, C.; Jia, G.; Barbaro, P. *Organometallics* **1999**, *18*, 1961−1966.
(34) Collman, J. P.; Rose, E.; Venburg, G. D. *J. Chem. Soc., Chem. Commun.* **1993**, 934−935.
(35) Park, S.-B.; Nishiyama, H.; Itoh, Y.; Itoh, K. *J. Chem. Soc., Chem. Commun.* **1994**, 1315−1316.
(36) Galardon, E.; Le Maux, P.; Toupet, L.; Simonneaux, G. *Organometallics* **1998**, *17*, 565−569.
(37) Le Paih, J.; Derien, S.; Ozdemir, I.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2000**, *122*, 7400−7401.

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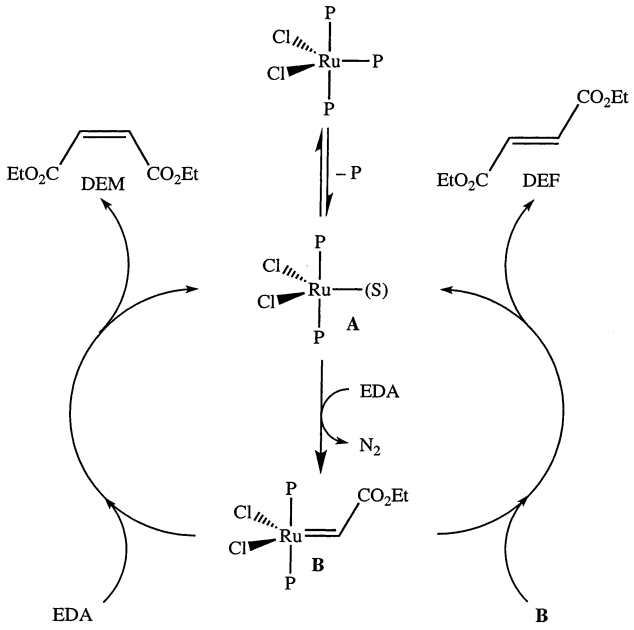
Scheme 1



reaction conditions, we are able to form either DEF *or* DEM with >98% stereoselectivity. Our initial exploration into this reaction has led to the development of a catalytic cycle that accounts for various factors which influence stereoselctivity. These factors can be manipulated to direct the stereochemistry to give either the cis or trans olefin. Close examination of these factors also allows for rationalization of the high stereoselectivity shown in other ruthenium catalysts.

Experimental Section

General Methods. All preparations and manipulations, except for the solvent studies, were carried out under an oxygen-free argon atmosphere using a glovebox. The solvent studies were carried out under an oxygen-free nitrogen atmosphere using standard inert handling techniques. THF and EDA were degassed prior to use. $Ru(PPh_3)_3Cl_2$ was purchased from Strem Chemicals and used as received. EDA, DEM, and DEF were purchased from Aldrich and used without further purification. GC data were collected on HP-6890 and Varian Model GC-3350 instruments. NMR (^1H and $^{13}C\{^1H\}$) data were obtained on a Bruker AC-300 spectrometer and referenced to the solvent. GCMS data were obtained using a Hewlett-Packard 5890 Series II gas chromatograph with a RTX-1 dimethylpolysiloxane capillary column (30 m, 0.5 mm i.d.) and a Hewlett-Packard 5971A mass selective detector.

A. $Ru(PPh_3)_3Cl_2$-Catalyzed EDA Decomposition. EDA (95 μL, 5.3 M in THF, 0.505 mmol) and decalin (10 μL) were diluted with THF (0.66 mL) in a 2 mL flask equipped with a Teflon boiling chip. $RuCl_2(PPh_3)_3$ (0.235 mL, 21 mM in THF, 4.94×10^{-3} mmol, 1.0% Ru loading) was added to this solution, and the solution was agitated to ensure homogeneity. Gas release occurred at room temperature upon ruthenium addition. The reaction mixture was allowed to react for 1−2 h. The reaction mixture was then analyzed by GC. The olefin products (DEF and DEM) were isolated by column chromatography (5% ethyl acetate/95% pentane v/v on silica gel). NMR (^1H and ^{13}C) and mass spectral data for isolated DEM and DEF were identical with those of commercially obtained DEM and DEF. The only observed side products were $(CHCO_2Et)_3$, from the cyclopropanation of DEM and/or DEF, and the phosphorane $Ph_3P{=}CHCO_2Et$. The side products were identified by GCMS spectral library analysis or comparison to an authentic sample.

B. Effect of Solvent. This series of experiments examined the effect of solvent on the Ru-catalyzed EDA decomposition product distribution. $RuCl_2(PPh_3)_3$ (0.252 g, 0.263 mM, 1.0% Ru loading) and heptadecane (0.10 mL) were diluted in 50 mL of solvent in a 100 mL flask equipped with a Teflon-coated stir bar. EDA (2.76 mL, 26.3 mmol) was added to this solution and the mixture agitated until homogeneous. Gas release occurred at room temperature upon EDA addition. All samples were allowed to react at room temperature for 1−2 h and were analyzed by GC.

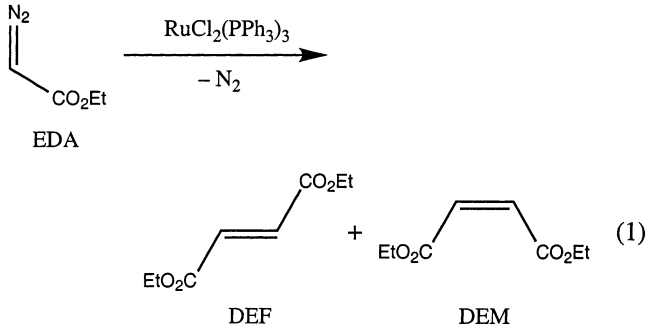
C. Effect of EDA Concentration with 1% Ru Loading. This series of experiments examined the effect of overall reaction concentration on the Ru-catalyzed EDA decomposition product distribution. Samples were prepared as described in **A** to maintain an EDA/Ru ratio of 100/1, except more or less THF was used to cover the EDA concentration range of 0.2−2.0 M. All samples were allowed to react at room temperature for 1−2 h and were analyzed by GC. DEM/DEF ratios as a function of reaction concentration are reported in Table 1.

D. Effect of EDA Concentration with Constant Ru Concentration. This series of experiments examined the effect of changing [EDA] on the Ru-catalyzed EDA decomposition product distribution. Samples were prepared as described in **A**, except different amounts of EDA were used to cover the EDA concentration range of 0.1−4.0 M while a Ru concentration of 5 mM was maintained. All samples were allowed to react at room temperature for 1−2 h and were analyzed by GC. DEM/DEF ratios as a function of EDA concentration are reported in Table 1.

E. Effect of Ru Concentration with Constant EDA Concentration. This series of experiments examined the effect of changing Ru concentration on the Ru-catalyzed EDA decomposition product distribution. Samples were prepared as described in **A**, except different amounts of $Ru(PPh_3)_3Cl_2$ were used to cover the Ru concentration range of 0.5−15 mM while an EDA concentration of 0.5 M was maintained. All samples were allowed to react at room temperature for 1−2 h and were analyzed by GC. DEM/DEF ratios as a function of Ru concentration are reported in Table 1.

Results and Discussion

The ruthenium complex $RuCl_2(PPh_3)_3$ catalyzes the diazo coupling reaction of ethyl diazoacetate (EDA) to yield diethyl fumarate (DEF) and diethyl maleate (DEM) (eq 1). An earlier report described that the



(1)

reaction in eq 1 in toluene at 60 °C formed the carbene dimers with DEM/DEF = 5.[38] However, our experiences with $RuCl_2(PPh_3)_3$ as a hydrosilylation catalyst[39,40]

(38) Demonceau, A.; Lemoine, C. A.; Noels, A. F.; Chizhevsky, I. T.; Sorokin, P. V. *Tetrahedron Lett.* **1995**, *36*, 8419−8422.

(39) Yardy, N. M.; Lemke, F. R. *Main Group Chem.* **2000**, *3*, 143−147.

(40) Yardy, N. M. Dichlorotris(triphenylphosphine)ruthenium(II): Reactions with Tertiary-Hydrosilanes and the Catalytic Hydrosilylation of Phenylacetylene. Ph.D. Dissertation, Ohio University, Athens, OH, 2001.

Table 1. Concentration Effects on the DEM/DEF Ratio for the $Ru(PPh_3)_3Cl_2$-Catalyzed Coupling of EDA

[reacn][a]					[EDA][b]					[Ru][c]				
[EDA], M	product distribn (%)[d] olefins	trimer	$Ph_3P{=}CR_2$	DEM/DEF	[EDA], M	product distribn (%)[d] olefins	trimer	$Ph_3P{=}CR_2$	DEM/DEF	[Ru], mM	product distribn (%)[d] olefins	trimer	$Ph_3P{=}CR_2$	DEM/DEF
0.1	56	33	11	1.13	0.1	20	6	74	0.78	0.5	72	26	2	97.7
0.25	70	14	16	0.28	0.2	38	6	56	0.70	2.5	68	25	7	2.8
0.5	76	10	13	0.18	0.5	76	0	13	0.18	5	76	10	13	0.18
1.0	70	7	22	0.02	1.0	74	13	14	0.41	10	63	12	26	0.03
					2.0	80	14	7	1.66	15	53	12	32	0.02

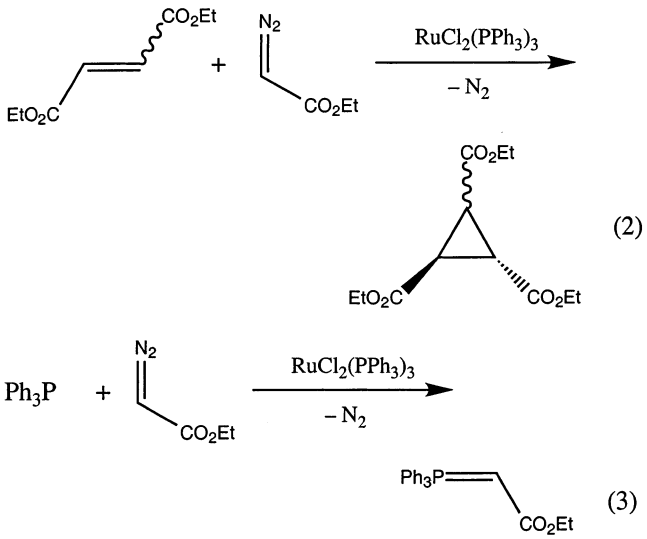
[a] Reaction conditions: EDA:Ru = 100:1 in THF at room temperature for 1−2 h. [b] Reaction conditions: [Ru] = 5 mM in THF at room temperature for 1−2 h. [c] Reaction conditions: [EDA] = 0.5 M in THF at room temperature for 1−2 h. [d] EDA totally consumed. The product distribution was determined by GC relative to decalin as internal standard. Olefins = DEM + DEF. Trimer = $(CHCO_2Et)_3$ from the cyclopropanation of DEM or DEF. $Ph_3P{=}CR_2$ = $Ph_3P{=}CH(CO_2Et)$.

suggested that the DEM/DEF ratio should be dependent on the reaction solvent and reactant concentrations. To explore the effect of solvent on the $RuCl_2(PPh_3)_3$-catalyzed diazo coupling reaction of EDA, the reaction in eq 1 was investigated in toluene, THF, CH_2Cl_2, and DMF. Under the reaction conditions of 0.5 M EDA, 1% $RuCl_2(PPh_3)_3$, room temperature, and 1−2 h, the stereoselectivity (DEM/DEF) for the EDA diazocoupling was as follows: toluene (3.8), DMF (4.1), $CHCl_3$ (4.2), and THF (5.4), with total consumption of EDA. As the stereoselective formation of DEM was maximized using THF, this was chosen as the solvent for subsequent reactions.

Concentration Effects. The effects of reactant concentration and catalyst loading on the stereoselectivity of the $Ru(PPh_3)_3Cl_2$-catalyzed diazo coupling of EDA (eq 1) are given in Table 1. The formation of DEF is favored over DEM with increasing concentration of the reactants. A 10-fold increase in overall reaction concentration (constant initial [EDA]/[Ru] = 100) resulted in a >50-fold decrease in the DEM/DEF ratio. To the best of our knowledge, no other studies of ruthenium-catalyzed diazo couplings have reported a connection between reaction concentration and final product stereoselectivity.

In an effort to further understand the DEM/DEF trend, the concentration effects of the individual reaction components (EDA and $Ru(PPh_3)_3Cl_2$) were studied separately. The stereoselectivity of the diazo coupling products was not very sensitive to changes in EDA concentration. A 20-fold change in EDA concentration, with fixed Ru concentration (5 mM), resulted in only a 9-fold increase in DEM/DEF. However, the minimum DEM/DEF was observed in the middle of the studied EDA concentration range; the DEM/DEF increased as the EDA concentration was increased or decreased from [EDA] = 0.5 M. On the other hand, diazo coupling selectivity was very sensitive to Ru concentration, with DEF formation being favored with increasing Ru concentration. A 30-fold increase in Ru concentration resulted in a nearly 5000-fold decrease in DEM/DEF. Nearly exclusive DEM formation was observed at low Ru concentration, while nearly exclusive DEF formation was observed at high Ru concentration. Thus, a relatively small change in the amount of catalyst added to the system had a disproportionately large impact on product stereoselectivity. It is important to note that the overall reaction and $Ru(PPh_3)_3Cl_2$ concentration effects on DEM/DEF exhibit similar trends, higher concentrations favoring DEF formation. However, the very dramatic effect observed with respect to Ru concentration indicates that catalyst concentration is the primary driving force behind the diazo coupling product stereoselectivity (DEM/DEF).

The byproducts observed in the concentration studies described above were the cyclopropane $(CHCO_2Et)_3$, from the cyclopropanation of DEF and DEM (eq 2), and the phosphorane $Ph_3P{=}CHCO_2Et$ (eq 3). The



$(CHCO_2Et)_3$/olefin ratio in these concentration studies ranged from 0.10 to 0.59 (based on GC results). The formation of $(CHCO_2Et)_3$ decreased with increasing EDA and Ru concentrations. The formation of $Ph_3P{=}CHCO_2Et$ was favored by low EDA and high Ru concentrations.

Diazo Coupling Mechanism. Metal carbenoids have been established as intermediates in transition-metal-catalyzed diazo coupling reactions.[20,21,31−37] It was therefore reasonable to postulate the presence of a ruthenium carbenoid intermediate in the ruthenium-catalyzed diazo coupling of EDA (eq 1), with the fate of this ruthenium carbenoid determining the DEM/DEF stereoselectivity. Early studies on isolated tantalum[19,26,27] and rhenium[28,29] carbenes demonstrated that metal carbenes decompose to give olefinic products by a reaction which was second order in the metal carbene. In the presence of nucleophilic substrates (phosphoranes or diazoalkanes), metal carbene decomposition also yields olefinic products, but the reaction was found to be first order in metal carbene.[25,35] Furthermore, the simultaneous occurrence of second-order and first-order olefin formation reactions for metal carbenes has been described in several reports.[19,26,27] Thus, a first-order

reaction mechanism, with respect to metal carbene, could be favored over a second-order reaction mechanism through simple changes in reaction conditions. The concentration effects on DEM/DEF stereoselectivity described in the previous section were consistent with a change in ruthenium carbenoid reaction order.

A mechanism for the ruthenium-catalyzed diazo coupling of EDA, based on a ruthenium carbenoid, is given in Scheme 1. Dissociation of phosphine from $RuCl_2(PPh_3)_3$ generates the solvent-stabilized species **A**.[41] EDA reacts with **A** to form the ruthenium carbenoid **B**, an analogue of Grubbs' catalyst.[42,43] Carbenoid **B** can decompose by two possible pathways. Our concentration studies and literature precedence suggest that direct attack on **B** by EDA generates DEM and **A**, while two ruthenium carbenoids could react to form DEF and **A**. The DEM/DEF stereoselectivity would be dependent on the relative reactivity of the ruthenium carbenoid **B** with either EDA, to produce DEM, or another **B**, to produce DEF.

The concentration effects on DEM/DEF stereoselectivity are consistent with the mechanism proposed in Scheme 1. Increasing the EDA concentration or decreasing the ruthenium loading favors the reaction of carbenoid **B** with EDA and, subsequently, the formation of DEM. On the other hand, DEF formation is favored by factors which increase the relative concentration of carbenoid **B** (i.e. increasing the ruthenium loading or decreasing the EDA concentration).

The mechanism in Scheme 1 was also consistent with previously reported studies on metal-catalyzed diazo couplings of EDA. Many recent reports described the use of sterically hindered metal centers to generate DEM with high stereoselectivity.[20,21,23,31−37] In these cases, the steric bulk of the metal catalyst may have prevented the second-order metal carbenoid coupling reaction, instead favoring the first-order coupling reaction with EDA to generate DEM. Conversely, isolated metal carbenes were reported to undergo carbene−carbene coupling reactions to generate olefins, with sterically demanding ligands hindering the rate of coupling.[19,27−29] Woo reported that reaction conditions could be manipulated to force a metalloporphyrin carbene to undergo either unimolecular or bimolecular coupling reactions with respect to the metalloporphyrin carbene.[25]

Conclusion

The stereoselectivity (DEM/DEF) of the $RuCl_2(PPh_3)_3$-catalyzed diazo coupling reaction of EDA was very dependent on the ruthenium loading. Nearly exclusive DEM formation was observed at low ruthenium loading, while nearly exclusive DEF formation was observed at high ruthenium loading. This dramatic change in reaction stereoselectivity was consistent with a change *in reaction order with respect to ruthenium*.

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(41) James, B. R.; Markham, L. D. *Inorg. Chem.* **1974**, *13*, 97−100.
(42) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856−9857.
(43) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29.