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Competitive [2,3]- and [1,2]-Oxonium Ylide Rearrangements. Concerted or Stepwise?

Deana M. Jaber,[‡] Ryan N. Burgin,[†] Matthew Helper,[†] Peter Y. Zavalij,[†] and Michael P. Doyle*[,†]

Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742, United States, and Department of Biology and Physical Sciences, Marymount University, Arlington, Virginia 22207, United States

mdoyle3@umd.edu

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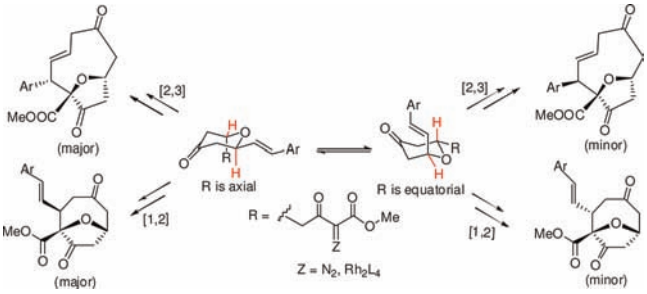
ABSTRACT



The axial−equatorial conformational isomer distribution of the reactant diazoacetoacetate or its metal carbene intermediate is reflected in Rh(II) catalyzed oxonium ylide forming reactions of 3-(*trans*-2-arylvinyl)tetrahydropyranone-5-diazoacetoacetates that afford diastereoisomeric products for both the symmetry-allowed [2,3]- and the formally symmetry-forbidden [1,2]-oxonium ylide rearrangements.

We have reported that dirhodium(II) catalyzed reactions of racemic *trans*-aryl-substituted tetrahydropyranone diazoacetoacetates **1** produce two diastereoisomeric products (***syn*-4** and ***anti*-4**) that are proposed to arise from two noninterconvertable oxonium ylide intermediates (**3A** and **3B**) via what appeared to be a concerted [1,2]-rearrangement (Scheme 1).[1] Product ratios were independent of ligand size or electron-withdrawing influence, and although para-substituents on the aromatic ring affected the yields of the ylide rearrangement products, they had limited effect on their ratios (stereoselectivity). However, increasing the steric bulk of the aryl group (ortho substituents) led exclusively to the formation of one diastereoisomer and suggested that conformational isomers in the reactant and the intermediate metal carbene are responsible for the formation of diastereoisomeric products.

The mechanism of the [1,2]-rearrangement of oxonium ylides has been interpreted as occurring via either a cleavage/recombination (either homolytic or heterolytic) or a concerted pathway.[2] Because this reaction is formally considered to be symmetry forbidden,[3] the rearrangement is regarded to occur by cleavage/recombination,[4] although other mechanistic possibilities exist.[5−7] However, convincing evidence regarding the cleavage/recombination

[†] University of Maryland.
[‡] Marymount University.

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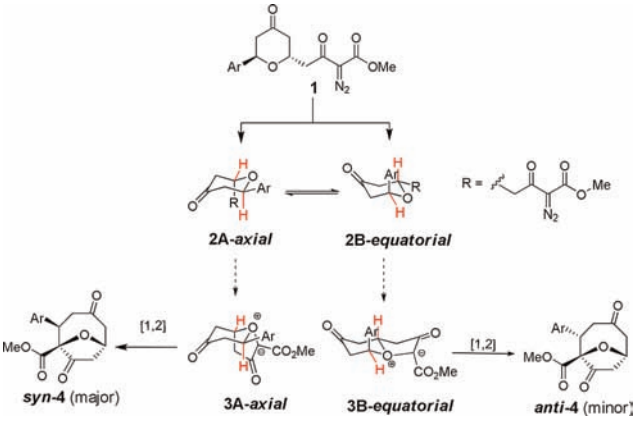
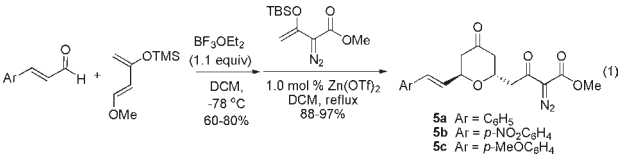
Scheme 1. Conformation-Dependent Pathway for the Formation of Two Diastereoisomers via [1,2]-Oxonium Ylide Rearrangements

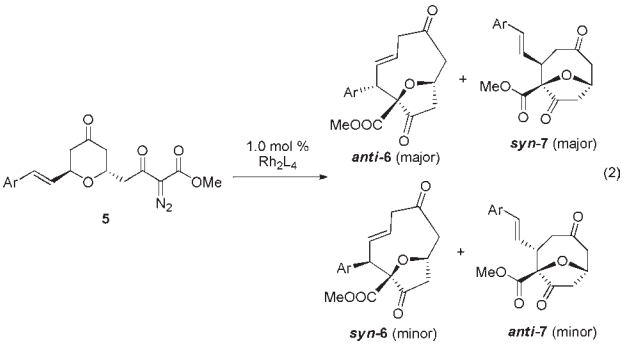


pathway is scarce. The most relevant evidence for a homolytic pathway in oxonium ylide reactions comes from detection of a "homo-dimer" in the rhodium acetate catalyzed reactions of 4-benzyloxy-1-diazo-2-butanones,[8] but similar ylide-producing reactions of the next higher homologue, 5-benzyloxy-1-diazo-2-pentanone, were not reported.[9] More elaborate evidence for radical pair and/or zwitterionic intermediates comes from ammonium ylide [1,2]-rearrangements[2,10] where, recently, substituent effects on stereoselectivity (from 4:1 to 20:1 d.r.) were obtained from aryl substituents of aryldiazoacetates in the rhodium acetate catalyzed reactions of configurationally stable Tröger bases.[11] Our proposed mechanism for oxonium ylide formation from **1** and subsequent [1,2]-Stevens rearrangement (Scheme 1) that suggests a concerted reaction is in conflict with a homolytic/heterolytic cleavage/recombination mechanism (i.e., absence of substituent effects, and steric influence on stereoselectivity), although a very fast cleavage/recombination process that is barely distinguishable from a concerted reaction is also possible. We now report analogous investigations with compounds that are structurally similar to **1** whose oxonium ylides could undergo symmetry-allowed [2,3]-sigmatropic rearrangements that are not subject to orbital symmetry restrictions.

3-(*trans*-Styryl)tetrahydropyranone-5-diazoacetoacetate and its para-substituted derivatives **5a**–**c** were selected to investigate the competition between the [2,3]-sigmatropic and [1,2]-Stevens rearrangement pathways. We anticipated that treatment of **5** with dinitrogen extrusion catalysts would form oxonium ylide(s), with the resultant reaction(s) leading to either or both products from the [2,3]-sigmatropic or the [1,2]-Stevens rearrangement, expecting the former to dominate.[12] Compounds **5** were prepared solely as the trans-diastereoisomers by $BF_3 \cdot Et_2O$-mediated hetero-Diels–Alder reactions between the cinnamaldehyde and Danishefsky's diene[13] followed by zinc triflate catalyzed Mukaiyama–Michael reaction with methyl 3-(*tert*-butyldimethylsilanoxy)-2-diazo-3-butenoate (eq 1).[14]



Rhodium(II) catalyzed decomposition of **5a**, using 1.0 mol % of dirhodium octanoate [$Rh_2(oct)_4$] in refluxing dichloromethane, afforded a mixture of [2,3]-sigmatropic **6a** and [1,2]-Stevens **7a** rearrangement products (eq 2) in 47% and 41% yield, respectively (54:46 ratio). After careful chromatographic separations and spectroscopic analyses of the reaction mixture, two diastereoisomers for both rearrangement products were isolated and identified. The crystal structure of the chromatographically separated major isomer of the [1,2]-Stevens rearrangement product was obtained (Figure 1b), and like compound **4** (Scheme 1) the major isomer was the *syn*-isomer. The minor isomer of the [1,2]-Stevens rearrangement product and the major isomer of the [2,3]-sigmatropic rearrangement product were isolated together and characterized spectroscopically, while the minor isomer of the [2,3]-rearrangement sigmatropic product (*syn*-isomer) was isolated in a separate chromatographic fraction, and its crystal structure was also obtained (Figure 1a). Table 1 reports the negligible variance in the ratio of products from [2,3]- and [1,2]-oxonium ylide rearrangements and



in the ratios of diastereoisomers formed by each process from rhodium(II) octanoate catalyzed reactions with

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para-substituted aryl derivatives **5a**–**b**. The lower yield and the difference in the ratio of products from the para-methoxy derivative **5c** is due to the formation of elimination products that, although evident in the reaction mixture, were not isolated and fully characterized.

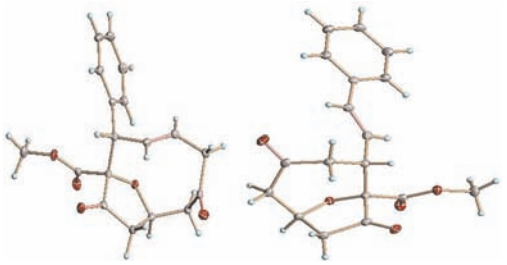


Figure 1. (a) Crystal structure (left) of ***syn*-6a** (minor isomer). (b) Crystal structure (right) of ***syn*-7a** (major isomer).

Table 1. Effect of Ring Substitution on Product Formation in the Rhodium(II) Octanoate Catalyzed Reactions of 3-(*trans*-Styryl) Tetrahydropyranone-5-diazoacetoacetates **5a**–**c**[a]

	Ar	**6:7**[b]	*anti*-**6:** *syn*-**6**	*syn*-**7:** *anti*-**7**	yield, % (**6**+**7**)[c]
5a	C_6H_5	54:46	78:22	78:22	88
5b	p-$NO_2C_6H_4$	52:48	76:24	76:24	85
5c	p-$MeOC_6H_4$	69:31	79:21	70:30	60

[a] Reactions were performed in refluxing CH_2Cl_2 for 2 h using 1.0 mol % of $Rh_2(oct)_4$. Results reported are averages of two or more reactions ±2%. [b] Product ratio determined by ^1H NMR spectral analysis with a variance of ±2%. [c] NMR yield using benzaldehyde as an internal standard.

We also investigated ligand effects from dirhodium catalysts on both the [2,3]-/[1,2]-reaction pathways (**6a:7a**) and product diastereoisomer ratios from the [2,3]- and [1,2]-rearrangements to determine if the oxonium ylide intermediate was metal-associated or a free ylide. Results were obtained from reactions of **5a** with a wide spectrum of catalysts (Table 2), and they show minimal dependence on catalyst ligands. No reaction occurred with rhodium caprolactamate under the same conditions. The diastereoisomer product ratio from the [2,3]-sigmatropic rearrangement (***anti*-6a:*syn*-6a**), as well as that from the [1,2]-Stevens rearrangement (***syn*-7a:*anti*-7a**), was invariant with common ligands on dirhodium (piv = pivalate, pfb = perfluorobutyrate, tfa = trifluoroacetate, tpa = triphenylacetate) that cover a broad range of electronic influences, although results with $Rh_2(tpa)_4$ for (***anti*-6a:*syn*-6a**) suggest a minor steric effect on selectivity. These composite data are consistent with an oxonium ylide intermediate free from association with the ligated metal catalyst during product formation.

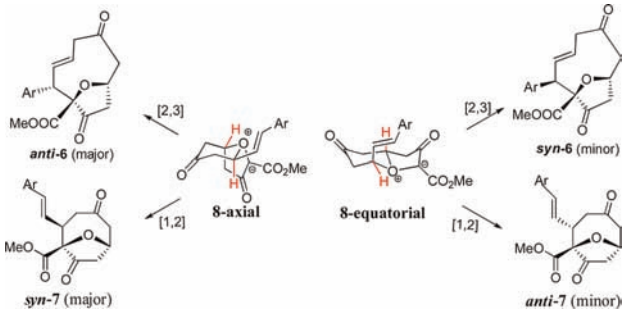
Table 2. Effect of Dirhodium(II) Ligands on Yields and Product Ratios from Oxonium Ylide Reactions of 3-(*trans*-Styryl)tetrahydropyranone-5-diazoacetoacetate **5a**[a]

catalyst	(**6a:7a**)[b]	*anti*-**6a:** *syn*-**6a**	*syn*-**7a:** *anti*-**7a**	yield, % (**6a**+**7a**)[c]
$Rh_2(oct)_4$	54:46	78:22	78:22	88
$Rh_2(OAc)_4$	51:49	80:20	77:23	94
$Rh_2(pfb)_4$	55:45	80:20	77:23	46
$Rh_2(piv)_4$	55:45	78:22	76:24	94
$Rh_2(tpa)_4$	53:47	73:27	75:25	93
$Rh_2(tfa)_4$	51:49	79:21	75:25	41

[a] Reactions were performed in refluxing dichloromethane for 2 h using 1.0 mol % of catalyst. Results reported are averages of two or more reactions. [b] Product ratio determined by ^1H NMR spectral analysis with a variance of ±2%. [c] NMR yield using benzaldehyde as an internal standard.

Observation of two diastereoisomeric products from the [2,3]-sigmatropic rearrangement with nearly identical diastereoisomer ratios (***anti*-6:*syn*-6**) as those for the [1,2]-Stevens rearrangement (***syn*-7:*anti*-7**) is inconsistent with a cleavage/rearrangement/recombination pathway in products from the [2,3]-sigmatropic rearrangement but not from the Stevens rearrangement. The fact that the diastereomer ratios are nearly identical suggests that the two processes originate from the same intermediate(s). The absence of a substituent effect on the ratio of products from [2,3]- and [1,2]-rearrangements (**6:7**) is unexpected if both sets of products arise from a cleavage/rearrangement/recombination pathway. Instead, the selectivity match between the two pathways is more likely due to the conformational equilibrium in the reactants (Scheme 1) that results in two noninterconvertable oxonium ylide intermediates and a subsequent competition between the symmetry-allowed [2,3]-sigmatropic rearrangement and the formally symmetry-forbidden [1,2]-Stevens rearrangement (Scheme 2).

Scheme 2. Conformation-Dependent Pathway for the Formation of Two Diastereoisomers via [2,3]- and [1,2]-Oxonium Ylide Rearrangements

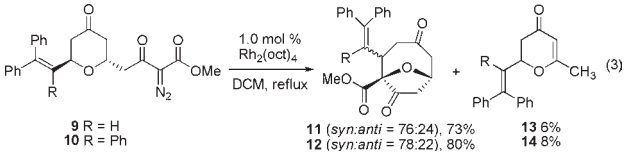


Competition between [2,3]- and [1,2]-oxonium ylide rearrangements is relatively common, especially with

diazoketones.[15,16] This competition is generally thought to be due to steric influences in structurally rigid systems. Diastereoisomeric products from the [1,2]-Stevens rearrangement have been reported, and their formation has been attributed to a cleavage/rearrangement/recombination pathway. However, the formation of two diastereoisomers for the [2,3]-sigmatropic rearrangement pathway is virtually unprecedented. The exception is a report from Clark and co-workers in a single example of structurally well-defined diastereoisomeric products for both the [1,2]-Stevens and the [2,3]-sigmatropic rearrangement pathways,[16] but the origin of these diastereoisomeric products was not explained; the explanation that we have advanced adequately accounts for their "fascinating" results.

Based on our previous demonstration that increasing the steric bulk of the aryl group of *trans*-aryl-substituted tetrahydropyranone diazoacetoacetates **1** results in the production of only one diastereoisomer in the [1,2]-Stevens rearrangement, we constructed the di- and triphenyl analogues of **5a** in order to evaluate diastereoisomer formation from the [2,3]-sigmatropic and [1,2]-Stevens rearrangement pathways, as well the influence of size on the [2,3]-/[1,2]-rearrangement ratio of products. The syntheses of diazoacetoacetates **9** and **10** were easily accessible by employing the previously described methods.

Rhodium(II) catalyzed reactions of **9** and **10** afforded [1,2]-Stevens rearrangement products **11** and **12**, respectively, in 73% and 80% yield (eq 3). The [2,3]-sigmatropic rearrangement products were not detected by either ^{1}H NMR spectra of the reaction mixtures or by HPLC analyses. However, unlike the previously established results with diortho-substituted aryl derivatives of **1**, two diastereoisomers for each of the [1,2]-Stevens rearrangement products were formed in amounts that corresponded to those found with their monophenyl counterpart **5a**. The (*syn*/*anti*) ratios of **11** and **12** are consistent with those ratios of **7a**–**c**.



(3)

In addition to the [1,2]-Stevens rearrangement products, 2-methyl-6-vinylpyran-4-ones **13** and **14** were observed as byproducts. Although these byproducts were not formed in high yields, they are ubiquitous in catalytic reactions of tetrahydropyranone- and tetrahydrofuranone-diazoacetoacetates.[17]

In conclusion, we have discovered that both the [2,3]- and [1,2]-oxonium ylide rearrangement reactions of 3-(*trans*-styryl)tetrahydropyranone-5-diazoacetoacetate and its para-substituted derivatives **5a**–**c** form diastereoisomeric products in the same ratios and that their diastereoisomer ratios are independent of electronic influences from para substituents or of catalyst ligands. These results are consistent with the involvement of catalyst-free oxonium ylides whose composition reflects the axial–equatorial conformational isomer distribution of the reactant diazoacetoacetate or its metal carbene intermediate. Furthermore, increasing the size of the styryl group of the 3-(*trans*-styryl)tetrahydropyranone-5-diazo-acetoacetate with phenyl substituents **9** and **10** removes competition with the [2,3]-oxonium ylide rearrangement, allowing the [1,2]-oxonium ylide rearrangement to occur with the production of two diastereoisomers in ratios that are identical with that from **5a**–**c**.

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Supporting Information Available. General experimental procedures, X-ray structures of ***syn*-6a** and ***syn*-7a**, and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.