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Control of selectivity in the generation and reactions of oxonium ylides†

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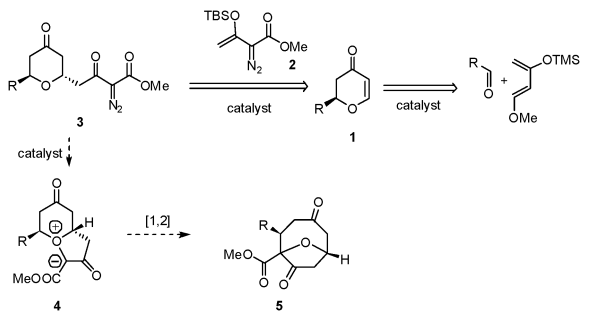
Dirhodium catalyzed reactions of aryl-substituted tetrahydropyranone diazoacetoacetates produce ylide intermediates that unexpectedly yield two oxabicyclo[4.2.1]-nonane diastereoisomers, but a single diastereoisomer is formed by increasing the steric bulk of the aryl substituent.

The synthesis and controlled reactions of oxonium ylides formed through catalytic reactions of diazocarbonyl compounds with ethers[1] have high potential for the construction of diverse natural products.[2] In our search for viable substrates that could take advantage of oxonium ylide chemistry, we considered the tetrahydro-4-pyranone framework **3** which is accessible in a two step synthetic process from synthetically available reactants (Scheme 1). The hetero-Diels–Alder reaction has numerous variants,[3] including those that are highly enantioselective.[4] The subsequent Mukaiyama-Michael reaction has recently been reported to occur in high yield[5] and exceptional diastereocontrol is well known in Lewis acid catalyzed reactions of **1** with silyl enol ethers.[6] We anticipated then that transition metal catalyzed reaction of **3** would form oxonium ylide **4** and from this reaction intermediate the resultant [1,2]-rearrangement product **5** would be obtained with high selectivity.[7] Consistent with this expectation, West and coworkers have reported that a similar six-membered ring diazoketone underwent [1,2]-rearrangement with complete stereoretention, which occurred in competition with C–H insertion and elimination (Scheme 2).[8b] The structural oxabicyclo[4.2.1]nonane framework is found in a number of



Scheme 1 Strategy for the synthesis of the oxabicyclo[4.2.1]-nonane.

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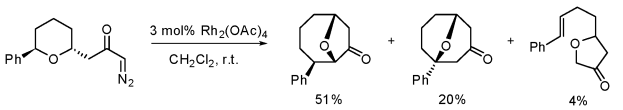
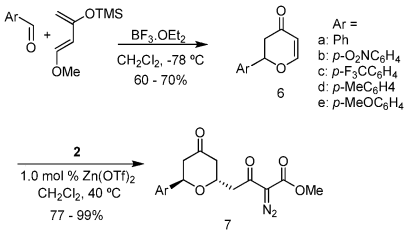
† Electronic supplementary information (ESI) available: General procedure for compounds **6a–e**, **7a–e** and **8a–e**. Characterization data and ^{1}H and ^{13}C NMR for all oxabicyclo[4.2.1]nonanes. CCDC 826314 and 826315. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc12443a



Scheme 2 Stereoretentive [1,2] rearrangement and C–H insertion.

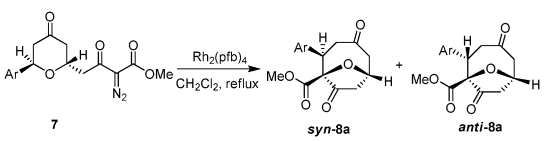


Scheme 3 Coupled hetero-Diels–Alder and highly diastereoselective Mukaiyama–Michael reactions.

natural products,[9] and a limited number of approaches have been used for their synthesis.[10]

Phenyldihydropyranone **6a** was prepared by $BF_3{\cdot}Et_2O$-mediated hetero-Diels–Alder reaction between benzaldehyde and Danishefsky's diene.[11] This process was followed by the Mukaiyama–Michael reaction of **6a** with methyl 3-(*tert*-butyldimethylsilanoxy)-2-diazo-3-butenoate **2** catalyzed by $Zn(OTf)_2$ (1.0 mol%) in refluxing dichloromethane.[5] After hydrolysis and purification, **7a** was isolated in 99% yield (Scheme 3) and was determined to be solely the *trans* isomer by NOE analysis (see supporting information†). This high stereocontrol is general for reactions of **2** with all 6-substituted 5,6-dihydro-4-pyranones.

Dinitrogen extrusion catalyzed by 1.0 mol% of dirhodium (perfluorobutyrate) $[Rh_2(pfb)_4]$ in refluxing dichloromethane produced, after chromatography, a white solid that was the oxabicyclo[4.2.1]nonan-4,8-dione product **8** in 77% isolated yield (Scheme 4). No evidence was obtained for the product from C–H insertion into the C–H bond adjacent to the phenyl substituent of **7a**. Because the *trans* isomer **7a** was the reactant, and analogous to the process described in Scheme 2, we expected that the final product would also have that same stereochemistry. However, the reaction resulted in a mixture of two stereoisomers in a 71 : 29



Scheme 4 Products from Rh(II) catalyzed dinitrogen extrusion with diazo substituted tetrahydropyranones.

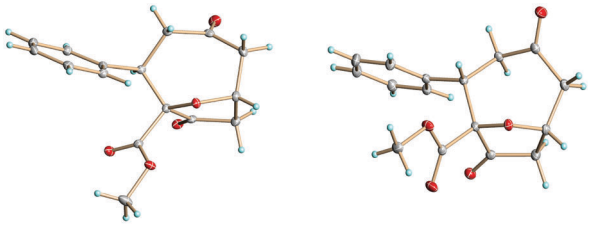


Fig. 1 Views of (a) ***syn*-8a** and (b) ***anti*-8a** showing the anisotropic atomic displacement ellipsoids for the non-hydrogen atoms at the 30% probability level. Hydrogen atoms are displayed with an arbitrarily small radius.

molar ratio that were chromatographically and spectrally distinguishable. The isomer ratio was invariant with common ligands on dirhodium (tfa = trifluoroacetate, OAc, cap = caprolactamate) that cover a broad range of electronic influences.[12] Solvent and temperature influences were also minor.[13] ^{1}H NMR spectroscopic evaluation showed that the two compounds were constitutionally identical and had the same connectivity. Spectral analysis provided their identification as the *anti* and *syn* stereoisomers of 1-carbomethoxy-2-phenyl-9-oxabicyclo[4.2.1]nonan-4,8-dione **8a**, but only through the crystal structures of the major isomer (71% of the total) and the minor isomer (29% of total) could their identities as the major and minor isomers be established (Fig. 1). Note that the original *trans*-stereochemistry of the reactant **7a** (positions 2 and 6) is formally inverted in forming ***anti*-8a**.

We investigated the influence of substituents at the *para*-position on the benzene ring in **7** on the ratio of ***syn*-8a** to ***anti*-8a**. The results from this investigation are reported in Table 1. The catalytic dinitrogen extrusion/metal carbene-derived reactions of **7** with the strongly electron-withdrawing *p*-NO_2 **7b** and *p*-CF_3 **7c** substituents were remarkably clean, and isolation of ***anti*-8** and ***syn*-8** from both substrates was achieved in very high yield. Compounds **7d** and **7e**, which have electron-donating *para* substituents, produced elimination products ***trans*-9d** and ***cis*-9e** (Fig. 2) in competition with [1,2]-rearrangement products ***anti*-8** and ***syn*-8**. The ratios of ***syn*-8**(**d** or **e**) to ***anti*-8**(**d** or **e**) from **7d** or **7e** were the same, within experimental error, as those from **7a** with the same catalyst. Also, the ***trans*-9**(**d** and **e**) to ***cis*-9**(**d** and **e**) ratios were remarkably similar to those of the corresponding ratios of ***syn*-8a** to ***anti*-8a**, suggesting that the diastereoselection established in the formation of **8** and **9** could both be determined in the ylide formation step.

How did this apparent "isomerism" arise? The most common explanation is that the cause of this erosion of stereochemical

Table 1 Influence of phenyl substituents on product ratio[a]

Entry	Z =	Yield **8**, %[b]	***syn*-8** : ***anti*-8**[c]	Yield **9**, %[d]	***trans*-9** : ***cis*-9**[c]
1	H	77	71 : 29	Trace	—
2	NO_2	94	74 : 26	Trace	—
3	CF_3	92	74 : 26	Trace	—
4	Me	55	69 : 31	14	64 : 36
5	OMe	22	69 : 31	16	58 : 42

[a] Reactions were performed in refluxing CH_2Cl_2 for 2 h using 1.0 mol% of $Rh_2(pfb)_4$. Results reported are averages of two or more reactions. [b] Weight yield of isolated ***anti*-8** and ***syn*-8** products following chromatographic separation. [c] Product ratio determined by ^{1}H NMR analysis with variance of ±4%. [d] NMR yield of ***trans*-9** and ***cis*-9** products determined by the use of benzaldehyde as an internal standard.

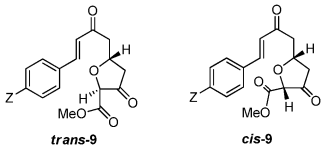
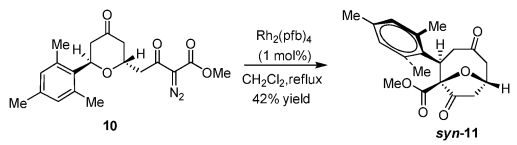


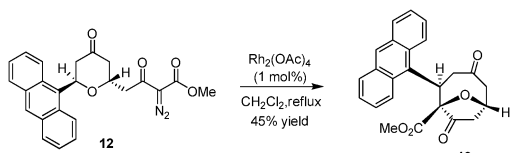
Fig. 2 Elimination products from reactions of **7d** (Z = Me) and **7e** (Z = OMe) with $Rh_2(pfb)_4$.

retention is a stepwise mechanism involving radical or ion pairs in the formation of **8** from the ylide precursor.[8,14] The lack of product dependence on catalyst suggests that the catalyst is not bound to the ylide during the product forming step. In the case of diazoacetoacetate **7** the stepwise mechanism would involve ylide formation followed by homolytic or heterolytic cleavage of the benzyl-oxygen bond, then bond rotation at the benzyl carbon and ring closure to form the observed ***anti*-8** and ***syn*-8** products. However, the absence of a substituent effect on the isomer ratio and the production of a single ylide-derived isomer from a comparable diazoketone (Scheme 2) suggests that other factors may be operating, one of which could be conformational (*e.g.*, one conformational isomer of **7** forming ***syn*-8** while a second conformer of **7** forms ***anti*-8**).

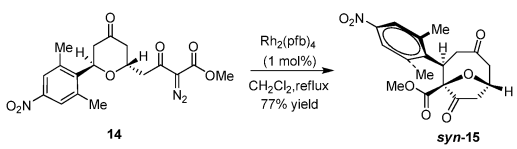
To evaluate the influence of conformational factors several bulky aryl groups of **7** were examined for their suitability in ylide formation and [1,2]-rearrangement. The mesityl (**10**) and the 9-anthranyl (**12**) derivatives were screened in the dirhodium(II) catalyzed dinitrogen extrusion reaction. Single ylide-derived isomers [***syn*-11** from **10** (eqn (1)) and ***syn*-13** from **12** (eqn (2))[15]] were observed without evidence for the anti-isomer, as determined by ^{1}H NMR data, but they were formed in less than 50% yield as mixtures with other reaction products. However, dirhodium(II)-catalyzed reaction of the 2,6-dimethyl-4-nitrophenyl derivative (**14**) proved to be relatively free of competing reactions, and dinitrogen extrusion of **14**, catalyzed by $Rh_2(pfb)_4$, formed ***syn*-15** in 77% isolated yield without a measurable contribution (^{1}H NMR) from the potential ***anti*-15** diastereomer (eqn (3)).



(1)



(2)



(3)

In conclusion, dirhodium carboxylate catalyzed ylide generation with aryl-substituted tetrahydropyranone diazo-acetoacetates and their subsequent [1,2]-rearrangement forms two diastereoisomers with the oxabicyclo[4.2.1]nonane framework.

para-Substituents on the 2-substituted aromatic ring were expected to influence the stability of intermediates for this reaction if formed from the ylide by homolytic or heterolytic cleavage, but the ratio of these two diastereoisomers was independent of *para*-substituents. However, using the same catalysts and conditions with aryl-substituted tetrahydropyranone diazoacetoacetates in which the steric bulk of the 2-aryl group is substantially increased produced a single diastereoisomer. The importance of the size of the aryl group, coupled with the absence of a substituent effect on the ratio of oxabicyclo[4.2.1]-nonane diastereomers suggests that conformational influences may be responsible for the apparent isomerism; in this case each reacting conformer forms a different ylide-derived intermediate by reaction of the rhodium carbene with either the axial or equatorial lone pair of electrons on oxygen. Rearrangement of each of these two non-equilibrating ylides would then form a distinct diastereoisomeric product. However, our results do not rule out the long held dissociation–rearrangement–recombination pathway,[8] and further investigations are underway to delineate the mechanism of this and related transformations.

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