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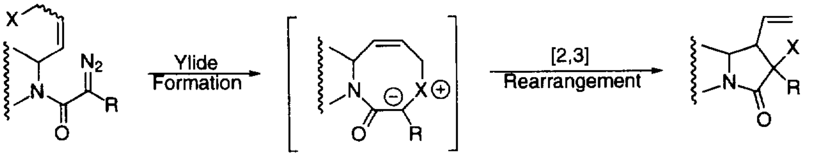
Application of Diazodecomposition Reactions in Tandem With [2,3]-Sigmatropic Rearrangements To Prepare Substituted Azabicyclic Ring Systems

Thomas A. Chappie†, R. Matt Weekly, and Mark C. McMills*

Department of Chemistry, Ohio University, Athens, Ohio 45701

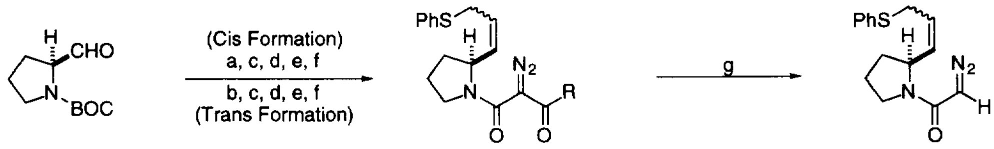
Abstract: Stereospecific [2,3]-Sigmatropic rearrangements occurring *via* ylides generated from the decomposition of α-diazoamides provided good yields of substituted azabicyclo[3.3.0]octanes. In addition some of the non-rearranged cyclopropanes were formed.

Over the past several years diazodecomposition reactions have become synthetically productive methods of forming carbon-carbon bonds when used in tandem with either sigmatropic rearrangements or cycloadditions. Ando[1a,b], Doyle[2a,b], Padwa[3a,b] and others have demonstrated the utility of electrophilic metallocarbenoid species for the formation of transient ylides. Nucleophiles such as sulfur, oxygen, and nitrogen add easily to the metallocarbenoid center, generating an ylide capable of further reaction. In a series of elegant studies, Kido and Kato have shown that sigmatropic rearrangement of large cyclic ylide intermediates can be used to prepare linearly-fused or bridged-bicyclic lactones.[4a-e] Despite the extensive investigations by Kido and Kato, very little is known for systems utilizing cyclic templates or substrates used to prepare amine or amide derivatives. We report here the preparation of functionalized azabicyclo[3.3.0]octane skeletons with a high degree of stereocontrol.



1 2 3 (1)

For this initial study, medium-sized ylide rings such as **2**, generated from a precursor diazoamide **1**, were chosen to accomplish the intramolecular [2,3]-sigmatropic rearrangement to prepare smaller azabicyclic rings (i.e. eight-membered ylide contracts to form a pyrrolidinone ring). It is proposed that the stereochemistry of the double bond and the R group attached to the diazo-containing center of diazoamide **1** would play an important role in the production of an intermediate ylide.



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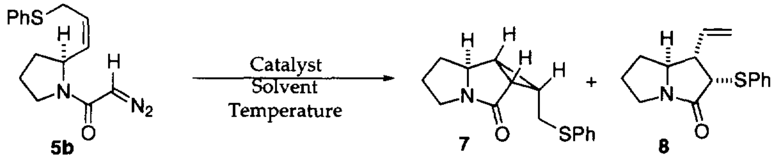
5a $R = CH_3$ (cis)
6a $R = CH_3$ (trans)

5b (cis)
6b (trans)

a) $(CF_3CH_2O)_2POCH_2CO_2CH_3$, KHMDS, 18-C-6, -78°C, 10:1 cis, 77% b) $(CH_3O)_2POCH_2CO_2CH_3$, nBuLi, 2:1 trans, 77-82% c) DIBAL, -78°C, 90-95% d) $(PhS)_2$, $(Bu)_3P$, 84% e) TFA then diketene, 80-85% f) $pCH_3CONHPhSO_2N_3$, DBU, 96% g) 5% NaOH, CH_3OH, 80-89%

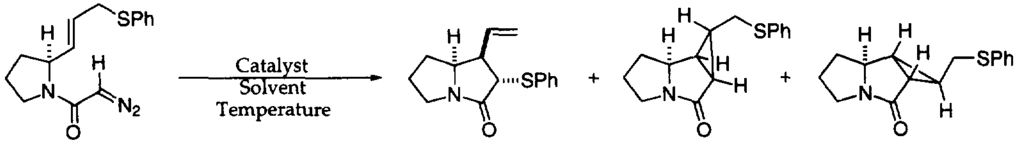
Proline was chosen as a simple template for formation of a linearly-fused azabicyclic system. Diazoamide **5a** is easily prepared by a five step sequence starting from the known BOC-protected prolinal **4**. The proline ring provides a suitable 1,2-disubstituted template for the formation of an eight-membered cyclic ylide intermediate. In addition, preparation of both the *cis* and *trans* disubstituted olefins, as well as the ability to place different nucleophilic atoms at the allylic position of the olefinic tether is easily accomplished utilizing the carboxyl group of proline. It was expected that upon sigmatropic rearrangement of the ylide, the convex/concave nature of the cyclic intermediate would stereospecifically produce the azabicyclo[3.3.0]octane ring system with the newly formed substituents *syn* to the hydrogen α to nitrogen.



Catalyst [a]	Solvent	Temperature [b]	Yield [c]	7 / 8 [d]
$Rh_2(OAc)_4$	PhH	RT	62%	1.9 / 1
$Rh_2(Cap)_4$	⇓	⇓	75%	1.4 / 1
$Rh_2(OHex)_4$	⇓	⇓	69%	5 / 1
$Rh_2(TPA)_4$	⇓	⇓	63%	2 / 1
$Rh_2(PFB)_4$	⇓	⇓	65%	4.5 / 1
$Cu(acac)_2$	⇓	⇓	52%	6 / 1
$Cu(hfacac)_2$	⇓	⇓	**61%**	**11 / 1**
$Cu(OTf)_2$	⇓	⇓	62%	7 / 1
$Pd(OAc)_2$	⇓	⇓	**63%**	**50 / 1**
$Rh_2(Cap)_4$	**PhF**	⇓	**60%**	**1 / 15**
$Rh_2(Cap)_4$	**$ClCH_2CH_2Cl$**	⇓	**55%**	**1 / 6**

a) 5 mole% based on **5b** b) Slow addition (20 mg/1h) of **5b** as a .01M solution to a refluxing solution of the catalyst in solvent c) Purified by column chromatography, yields are combined overall d) Some ratios based on GC-MS analysis of the crude reaction mixture

In an attempt to destabilize the diazo containing center relative to the series of α-diazoamides **5a** and **6a** with electron withdrawing substituents, the acetyl side chains of **5a** and **6a** were removed under basic conditions (5% NaOH, MeOH) and the resulting diazoamide **5b** was submitted to various diazodecomposition conditions including a number of different catalysts and solvents. Reaction of **5b** with both dirhodium and copper catalyst in benzene resulted in the formation of a predominance of the pyrrolizidine-cyclopropane **7** rather than the expected azabicyclooctane **8**[5] (1.4 - 11 : 1). Interestingly, only one of the two possible cyclopropanes forms in the reaction sequence. We speculate that this may be due to non-bonded interactions making only one rotamer reactive or possibly the reaction is under product control. Despite the elegant studies conducted by Doyle and Padwa, a simple change in the electronic nature of the ligands attached to rhodium provided little difference in the product ratio toward formation of the azabicyclooctane **8**.[6] It was determined that changing the polarity of the solvent might help to stabilize a more polar transition state thereby producing the azabicyclooctane **8** in excess of the pyrrolizidine-cyclopropane **7**. *Catalytic rhodium caprolactamate with either fluorobenzene or dichloroethane as solvent resulted in a complete turnover of the product ratio toward a predominance of the azabicyclooctane **8**(6 - 15 : 1, 55-60% yield).*



6b **9** **10** **11**

					Ratios[d]	
Catalyst[a]	Solvent	Temperature[b]	Yield[c]	**9**	**10**	**11**
$Rh_2(Cap)_4$	PhH	RT	71%	9	0	1
$Rh_2(Cap)_4$	PhF		68%	1	1.2	2.1
$Rh_2(OAc)_4$	$ClCH_2CH_2Cl$		66%	0	2.5	1
$Rh_2(OAc)_4$	CH_2Cl		59%	0	2.9	1
$Rh_2(OAc)_4$	PhH		70%	0	2.2	1
$Pd(OAc)_2$	PhH		78%	0	2.7	1
$Cu(hfacac)_2$	PhH	⇓	68%	0	2.1	1

a) 5 mole% based on **6b** b) Slow addition (20 mg/1h) of **5b** as a 0.01M solution to a refluxing solution of the catalyst in solvent c) Purified by column chromatography, yields are combined overall d) Some ratios based on GC-MS analysis of the crude reaction mixture

The role that olefin geometry might play in attack of the metallocarbenoid intermediate was also investigated. It was determined from simple modeling that the *trans* olefin may place the allylic nucleophile too distant to interact with the electrophilic carbenoid center, therefore the only product that might be isolated from diazodecomposition of amide **6b** would be the cyclopropanes **10** and **11**. *Amazingly, when decomposed with electron rich catalyst rhodium caprolactamate, α-diazoamide **6b** formed the anti pyrrolizidine **9**.* [7] It was also discovered that diazodecomposition of trans diazoamide **6b** with the electron withdrawing ligands attached to rhodium or with palladium catalysis produced only cyclopropanes **10** and **11**[8] (59-78%, 2.1-2.9 : 1 ratio) with none of the sigmatropic rearrangement product formed.

We have demonstrated the utility of diazodecomposition/tandem [2,3]-rearrangements with cyclic diazoamide systems forming substituted azabicyclo[3.3.0]octane and cyclopropanated pyrrolizidine products. It has been noted that both the catalyst and solvent as well as the diazoamide substrate are critical in determining the pathway followed by the metallocarbenoid intermediate.

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† Current address: Central Research Division, Pfizer Inc., Eastern Point Rd, Groton, CT 06340

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(5) Spectral data for *Syn*-pyrrolizidine **8**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 - 7.19 (m, 5H, $-C_6H_5$), 6.09 (ddd, *J* = 17.3, 10.4 , 7.2 Hz, 1H, -CH=CHH), 5.21 (dt, *J* = 10.4, 1.2Hz, 1H, -CH=CHH), 5.16 (dt, *J* = 17.2, 1.2 Hz, 1H, CH=CHH), 3.91 (d, *J* = 7.2 Hz, 1H, S-CH-), 3.70 (dt, *J* = 5.7, 8.4 Hz, 1H, N-CH-), 3.55 (dt, *J* = 11.9, 7.5 Hz, 1H, N-CHH-), 3.05 (m, 1H, N-CHH-), 2.94 (dd, *J* = 8.5, 7.4 Hz, 1H, N-CH-CH-), 2.02 (m, 3H, $-CH_2$-CHH-), 1.25 (m, 1H, $-CH_2$-CHH-); ^{13}C NMR (100.58 MHz, $CDCl_3$) δ 171.9, 134.2, 132.4, 130.2, 128.8, 127.6, 118.2, 64.1, 57.8, 52.6, 41.5, 30.3, 26.9; IR (neat) 1696; MS (70 eV) 259, 149, 136, 120, 109, 94, 77, 70, 53, 41; High Resolution MS *m/z* calculated for $C_{15}H_{17}NOS$ (M^+) 259.1031, found 259.1028.

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(7) Spectral data for *Anti* pyrrolizidine **9**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H, C_6H_5), 5.78 (ddd J=16.5, 11.2, 7.5Hz, 1H, CH=CH_2), 5.13 (app dt, *J*=11.2, 1.2Hz, CH=CHH), 5.11 (app dt, *J*=16.5, 1.2Hz, 1H, CH=CHH), 3.82 (d, *J*=11.3Hz, 1H, S-CH), 3.53 (m. 2H, CH-N-CHH), 3.07 (m, 1H, N-CHH), 2.41 (m, 1H, N-CHCH), 1.90 (m, 3H, CH_2CHH), 1.18 (m, 1H, CH_2CHH); ^{13}C NMR (100.58 MHz, $CDCl_3$) δ 171.2, 135.6, 133.4, 129.0, 128.8, 127.8, 118.2, 63.5, 58.8, 53.2, 42.1, 30.7, 26.3; MS (70eV) *m/z* (M^+)259, 150, 121, 109, 81, 70, 53, 41.

(8) Spectral data for **Cyclopropane 10:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 - 7.15 (m, 5H, $-C_6H_5$), 4.06 (dt, *J* = 9.5, 5.7 Hz, 1H, N-CH-), 3.26 (dd, *J* = 13.4, 4.9 Hz, 1H, S-CHH-), 3.18 (dt, *J* = 11.5, 8.1 Hz, 1H, N-CHH-), 2.93 (m, 1H, N-CHH-), 2.47 (dd, *J* = 13.4, 9.2 Hz, 1H, S-CHH-), 1.99 (m, 3H, $-CH_2$-CHH-), 1.82 (m, 1H, N-CO-CH-), 1.63 (m, 1H, $-CH_2$-CHH-), 1.24 (m, 1H, N-CH-CH-), 1.14 (m, 1H, S-CH_2-CH-); ^{13}C NMR (100.58 MHz, $CDCl_3$) δ 173.2, 135.3, 130.5, 128.9, 126.7, 61.8, 40.9, 36.0, 32.2, 28.0, 27.4, 21.1, 20.9; IR (neat) 1694, 1651; MS (70 eV) *m/z* (M^+)259, 182, 150, 136, 120, 94, 79, 70, 53; High Resolution MS *m/z* calculated for $C_{15}H_{17}NOS$ (M^+) 259.1031, found 259.1023.

Cyclopropane 11: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 - 7.19 (m, 5H, $-C_6H_5$), 3.57 (dt, *J* = 11.6, 8.2 Hz, 1H, N-CHH-), 3.46 (dd, *J* = 10.8, 4.0 Hz, 1H, N-CH-), 3.11 (dd, *J* = 13.6, 5.2 Hz, 1H, S-CHH-), 2.85 (m, 1H, N-CHH-), 2.58 (dd, *J* = 13.6, 8.4 Hz, 1H, S-CHH-), 1.99 (tdd, *J* = 11.6, 8.6, 3.2 Hz, 1H, N-CO-CH-), 1.88 (dd, *J* = 6.0, 3.6 Hz, 1H, $-CH_2$-CHH-), 1.82 (m, 3H, $-CH_2$-CHH-), 1.55 (m, 1H, S-CH_2-CH-), 1.15 (dd, *J* = 10.8, 8.8 Hz, 1H, N-CH-CH-); ^{13}C NMR (100.58 MHz, $CDCl_3$) δ 177.5, 135.4, 130.4, 129.0, 126.7, 63.5, 42.0, 36.5, 29.8, 28.7, 28.2, 27.6, 24.9; IR (neat) 1694, 1598; MS (70 eV) *m/z* (M^+)259, 150, 136, 120, 81, 70, 53; High Resolution MS *m/z* calculated for $C_{15}H_{17}NOS$ (M^+) 259.1031, found 259.1025.

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