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Rhodium Carboxylate Catalyzed Decomposition of Vinyldiazoacetates in the Presence of Heterodienes: Enantioselective Synthesis of the 6-Azabicyclo[3.2.2]nonane and 6-Azabicyclo[3.2.2]nonanone Ring Systems

Huw M. L. Davies* and L. Mark Hodges

Department of Chemistry, University at Buffalo, The State University of New York, Buffalo, New York 14260

hdavies@acsu.buffalo.edu

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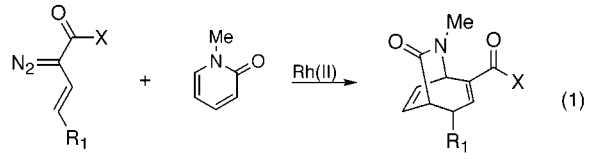
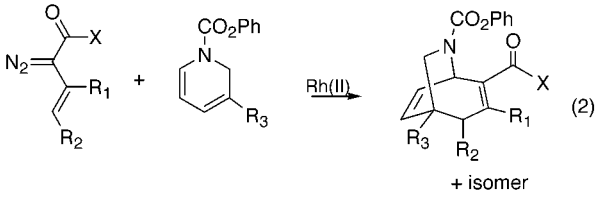
Dirhodium tetracarboxylate catalyzed decomposition of vinyldiazoacetates in the presence of *N*-phenoxycarbonyl protected 1,2-dihydropyridines or 1-methyl-2-pyridones is a direct method for the construction of the 6-azabicyclo[3.2.2]nonane ring system. The [3 + 4] cycloaddition occurs by a tandem cyclopropanation/Cope rearrangement. Asymmetric induction is possible in these transformations either by using (*S*)-lactate methyl ester as a chiral auxiliary or dirhodium tetraprolinates as chiral catalysts.

The azabicyclic ring system is a common structural unit in natural products and pharmaceutical agents.[1] Due to their inherent biological activity, there is a demand for general synthetic methods for these systems. We have previously reported that the rhodium-catalyzed decomposition of vinyldiazoacetates in the presence of *N*-BOC protected pyrroles is a very effective method for the construction of tropanes.[2] This is an example of a very general method for the construction of seven-membered rings by a [3 + 4] cycloaddition between rhodium-stabilized vinylcarbenoids and dienes.[3] Continuing with our long-standing interest in the design of novel azabicyclic structures as potential medications for cocaine addiction,[4] we report herein a study to apply the vinyldiazoacetate chemistry to the synthesis of 6-azabiyclo[3.2.2]nonadienes,[5] higher homologues of tropanes. The two central reactions that were examined were the reaction of vinyldiazoacetates with 1-methyl-2-pyridone (eq 1) and various 1,2-dihydropyridines (eq 2). In addition to evaluating the regiochemical issues of the reaction, the development of asymmetric strategies for the construction of the 6-azabiyclo[3.2.2]nonadienes was explored.





A potentially very attractive method for the synthesis of the 6-azabiyclo[3.2.2]nonane structure would be the reaction of vinyldiazoacetates with 2-pyridones. To explore the feasibility of such a reaction, the decomposition of vinyldiazoacetates was carried out in the presence of 4 equiv of 1-methyl-2-pyridone (**1**). The unsubstituted vinyldiazoacetate (**2**) gave only trace amounts of the desired azabicyclic product **3** when rhodium octanoate was used as the catalyst (eq 3). Use of the more electron deficient chiral catalyst Rh_2(*S*-TBSP)$_4$ (**4a**) improved the reaction, producing **3** in 17% yield. Even though the dirhodium tetraprolinates have resulted in high asym-

(1) For reviews on various azabicyclic systems: (a) 7-Azabicyclo-[2.2.1]heptanes: Chen, Z.; Trudell, M. L. *Chem. Rev.* **1996**, *96*, 1179. (b) 8-Azabicyclooctanes (tropanes): Lounasmaa, M.; Tamminen, T. *Alkaloids* **1993**, *44*, 1. (c) Azabicyclo[2.2.2]nonanes: Mashkovsky, M. D.; Yakhontov, L. N.; Kaminka, M. E.; Mikhlina, E. E. *Prog. Drug Res.* **1983**, *27*, 9. (d) 2-Azabicyclo[3.3.1]nonanes: Bosch, J.; Bonjoch, J. *Heterocycles* **1980**, *14*, 505. (e) 3-Azabicyclo[3.3.1]nonanes: Jeyaraman, R.; Avila, S. *Chem. Rev.* **1981**, *81*, 149. For recent reports concerning the biological utility of the 1- and 2-azabicyco[2.2.2]octane ring systems, see: (f) Brown, G. R.; Clarke, D. S.; Foubister, A. J.; Freeman, S.; Harrison, P. J.; Johnson, M. C.; Mallion, K. B.; McCormick, J.; McTaggert, F.; Reid, A. C.; Smith, G. J.; Taylor, M. J. *J. Med. Chem.* **1996**, *39*, 2971. (g) Portevin, B.; Benoist, A.; Rémond, G.; Hervé, Y.; Vincent, M.; Lepagnol, J.; De Nanteuil, G. *J. Med. Chem.* **1996**, *39*, 2379. (h) Swain, C. J.; Fong, T. M.; Haworth, K.; Owen, S. N.; Seward, E. M.; Strader, C. D. *Biorg. Med. Chem. Lett.* **1995**, *5*, 1261.

(2) Davies, H. M. L.; Matasi, J. J.; Hodges, L. M.; Huby, N. J. S.; Thornley, C.; Kong, N.; Houser, J. H. *J. Org. Chem.* **1997**, *62*, 1095.

(3) Davies, H. M. L. In *Advances in Cycloaddition*; Harmata, M., Ed.; JAI Press: Stamford, CT, 1998; Vol. 5, pp 119−164.

(4) (a) Davies, H. M. L.; Saikali, E.; Huby, N. J.; Gilliatt, V. J.; Matasi, J. J.; Sexton, T.; Childers, S. R. *J. Med. Chem.* **1994**, *37*, 1262. (b) Davies, H. M. L.; Kuhn, L. A.; Thornley, C.; Matasi, J. J.; Sexton, T.;, Childers, S. R. *J. Med. Chem.* **1996**, *39*, 2554. (c) Davies, H. M. L.; Ren, P.; Kong, N.; Sexton, T.; Childers, S. R. *Biorg Med. Chem. Lett.* **2001**, *11*, 487.

(5) For a preliminary account of this work, see: Davies, H. M. L.; Hodges, L. M.; Thornley, C. T. *Tetrahedron Lett.* **1998**, *39*, 2707.

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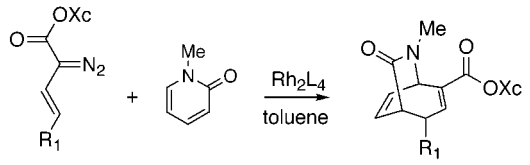
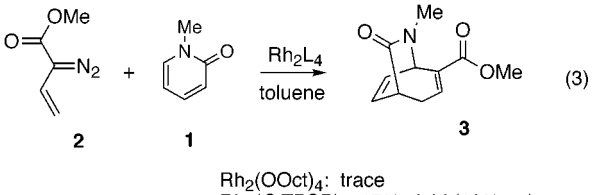
TABLE 1. Synthesis of 6-Azabicyclo[3.2.2]nonadiene-7-ones 9



8 **1** **9**

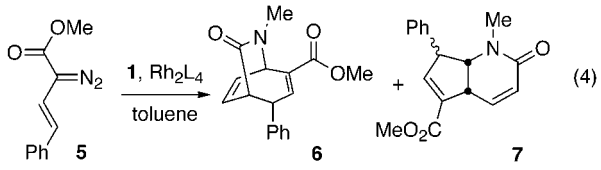
entry	compd	R_1	Xc	catalyst	yield, %	de, %
1	**a**	H	CH_2CO_2Et	$Rh_2(OOct)_4$	36	–
2	**b**	H	(*S*)-CH(Me)CO_2Et	$Rh_2(OOct)_4$	33	40
3	**b**	H	(*S*)-CH(Me)CO_2Et	Rh_2(*S*-TBSP)$_4$	40	45
4	**b**	H	(*S*)-CH(Me)CO_2Et	Rh_2(*R*-DOSP)$_4$	32	60
5	**c**	Me	(*S*)-CH(Me)CO_2Et	Rh_2(*S*-TBSP)$_4$	78	51

metric induction in various [3 + 4] cycloadditions,[3,6] in this case the enantioselectivity for the formation of **3** was only 10% ee. When the styryldiazoacetate **5** was used, higher overall yields of the azabicyclo[3.2.2]nonanone product **6** were obtained (eq 4). Use of Rh_2(*S*-DOSP)$_4$ (**4b**), a related prolinate catalyst to Rh_2(*S*-TBSP)$_4$, again resulted in enhanced overall yields of **6** (33%) compared to $Rh_2(OOct)_4$. In this reaction an isomeric [4.3.0] bicyclic product **7** was formed. The enantioselectivity in the formation of **6** (60% ee) was considerably improved over the result for **3**.



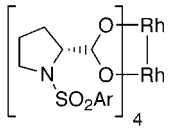
2 **1** **3**

$Rh_2(OOct)_4$: trace
Rh_2(*S*-TBSP)$_4$: 17% yield (10% ee)



5 **6** **7**

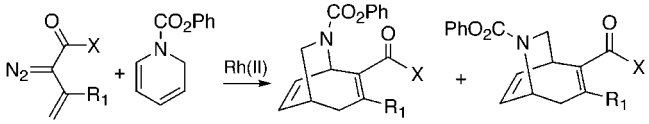
$Rh_2(OOct)_4$: **6** (22% yield), **7** (7% yield)
Rh_2(*S*-DOSP)$_4$: **6** (33% yield, 60% ee), **7** (14% yield)



4a: Ar = 4-(*tert*-Bu)C_6H_4, Rh_2(*S*-TBSP)$_4$
4b: Ar = 4-($C_{12}H_{25}$)C_6H_4, Rh_2(*S*-DOSP)$_4$

As the use of β-hydroxyesters as chiral auxiliaries has been reported to increase the yield and regioselectivity in the reaction between vinyldiazoacetates and pyrroles,[7] this strategy was applied to the reaction between vinyldiazoacetates and 2-pyridones (Table 1). Reaction of either the glycolate (**8a**) or lactate (**8b**) substituted vinyldiazoacetate resulted in a modest 30−40% yield of the desired azabicyclononadienones **9a** and **9b**. As observed with the methyl ester-substituted vinyldiazomethanes **2** and **5**, the more electron deficient chiral catalysts result in higher isolated yields of the azabicyclo[3.2.2]nonadienones **9**. Despite the yield enhancement rendered by using the α-hydroxyester auxiliary on the vinylcarbenoids, asymmetric induction was only modest (40−60% de). The use of the chiral auxiliary, terminal vinyl substitution (**8c**), and prolinate catalysis resulted in the best result, a 78% isolated yield of **9c** in 51% de (entry 5).

TABLE 2. Synthesis of 6-Azabicyclononadienes 13 and 14



12 **13** **14**

entry	diazo	X	R_1	catalyst	product	yield, % **13**	yield, % **14**
1	**2**	OMe	H	$Rh_2(OOct)_4$	**a**	30	29
2	**2**	OMe	H	$Rh_2(OPiv)_4$	**a**	56	12
3	**2**	OMe	H	$Rh_2(TPA)_4$	**a**	50	3
4	**10**	Et	H	$Rh_2(OOct)_4$	**b**	11	25
5	**10**	Et	H	$Rh_2(OPiv)_4$	**b**	27	12
6	**11**	OMe	OTBS	$Rh_2(OOct)_4$	**c**	17	24
7	**11**	OMe	OTBS	$Rh_2(OPiv)_4$	**c**	34	3

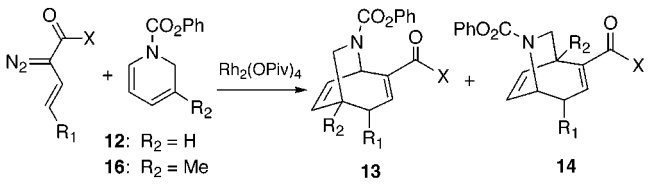
1,2-Dihydropyridines were expected to be even better substrates than 1-methyl-2-pyridone in the cycloaddition because the diene would be more electron-rich. The cycloaddition chemistry of 1,2-dihydropyridines, however, is complicated because both double bonds are accessible for cyclopropanation by the vinylcarbenoid, leading to the formation of two regioisomeric 6-azabicyclononadienes (Table 2). The regioselectivity of the reaction and the yields are affected by the functionality on the vinyldiazoacetate as well as the steric bulk of the catalyst. When the unsubstituted methyl ester vinyldiazoacetate **2** is decomposed by rhodium octanoate in the presence of *N*-phenoxycarbonyl-1,2-dihydropyridine (**12**) both the 4-substituted (**13a**) and 2-substituted (**14a**) regioisomers are formed in approximately equal amounts (entry 1, Table 2). Both regioisomers have been identified and assigned on the basis of ^{1}H NMR and decoupling data. When systematically more bulky catalysts are used such as rhodium pivalate ($Rh_2(OPiv)_4$) or rhodium triphenylacetate ($Rh_2(TPA)_4$), the predominant product is **13a**, which results from cyclopropanation at the double bond closer to the nitrogen. Similar results are obtained with the vinyldiazoketone **10** and *tert*-butyldimethylsiloxy-substituted vinyldiazoacetate **11**.

Two additional approaches were ultimately discovered that allowed highly regioselective cycloadditions to be achieved. Terminal substitution on the vinyldiazoacetate results in highly selective formation of the 4-substituted 6-azabicyclononadienes **13** (Table 3, entries 1,2). Selective formation of **13** is also achieved when 3-methyldihydropyridine **16** is used as the substrate (Table 3, entries 3−5).

Having developed appropriate systems that can generate selectively the 4-substituted 6-azabicyclononadienes **13**, the potential for the asymmetric synthesis of **13** was then explored by using chiral catalysis (Table 4). Rh_2(*S*-

(6) Davies, H. M. L.; Ahmed, G.; Churchill, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10774.
(7) Davies, H. M. L.; Matasi, J. J.; Thornley, C. *Tetrahedron Lett.* **1995**, *36*, 7205.

TABLE 3. Synthesis of 6-Azabicyclononadienes 13 and 14

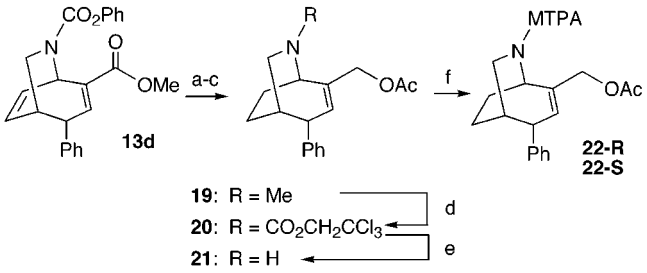


						yield, %	
entry	diazo	X	R_1	R_2	product	**13**	**14**
1	**5**	OMe	Ph	H	**d**	69	trace
2	**15**	OMe	Me	H	**e**	58	3
3	**10**	Et	H	Me	**f**	32	0
4	**15**	OMe	Me	Me	**g**	50	0
5	**5**	OMe	Ph	Me	**h**	71	0

DOSP)$_4$ catalyzed decomposition of the unsubstituted vinyldiazoacetate **2** in the presence of *N*-phenoxycarbonyl-1,2-dihydropyridine (**12**) gives an overall 32% yield of **13a** in 50−60% ee. As expected, a small amount (5% yield) of the isomeric 6-azabicyclononadiene **14a** was formed. Repeating the reaction of **2** with the 3-methyl-1,2-dihydropyridine **16** gave only a single isomer of the azabicyclononane **13i** in 30% yield and 58% ee. Reactions with the substituted vinyldiazoacetates (entries 3−5) were more efficient than the reactions with **2**. Rh$_2$(*S*-TBSP)$_4$ catalyzed decomposition of the styryldiazoacetate **5** in the presence of **12** was especially good as **13d** was formed in 68% yield and 82% ee. By a slight modification of the reaction conditions, **13d** could be isolated in an enantiomerically pure form. Rh$_2$(*S*-DOSP)$_4$ reaction with **5** in a 3:1 hexanes/toluene mixture results in selective crystallization (12%) of a *racemic* mixture of **13d** during the reaction process; workup of the remainder of the reaction mixture results in isolation of **13d** in >96% ee (51% yield).

The absolute configuration of **13d** was determined to be 1*S*,5*R* by using the Mosher amide method developed by Hoye.[2,8] The azabicyclononadiene **13d** (97% ee) was first converted to the nitrogen-unsubstituted acetate derivative **21**, which was subsequently converted to each of the Mosher (methoxyphenyltrifluoromethyl; MTPA) amides (Scheme 1). This was accomplished first by hydrogenation of the C(8)−C(9) double bond followed by lithium aluminum hydride reduction of the phenoxycarbonyl group and subsequent acylation of the primary

SCHEME 1

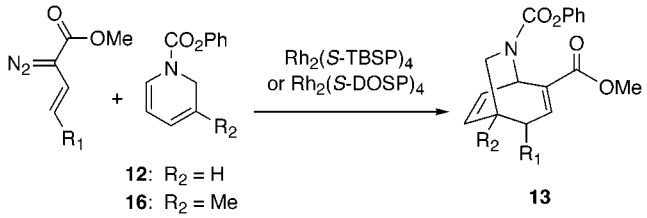


(a) H_2, $(PPh_3)_3RhCl$; (b) LAH, THF; (c) Ac_2O, DMAP; (d) Cl_3CCH_2OCOCl; (e) Zn, HOAc; (f) *R* or *S*-MTPA-Cl, *i*-Pr_2EtN

alcohol to give **19**. Demethylation via the TROC-derivative **20** followed by final *N*-acylation with each of the Mosher acid chlorides gave Mosher amides **22-*R*** and **22-*S***. Note that the *R*-acid chloride gives the corresponding *S*-amide due to changes in priority of the groups around the chiral center.

Each amide was analyzed by ^{1}H NMR (500 MHz) to establish the absolute stereochemistry of the original 6-azabicyclononane (Figure 1, Table 5). Since the most stable conformation of the Mosher amides derived from secondary amines has the trifluoromethyl group in an anti-periplanar relationship relative to the nitrogen, the phenyl group on the amide shields one of four possible quadrants of the molecule depending on the specific rotamer and the absolute stereochemistry of the amide. In the case of **22**, the major rotamer (2.2 to 1) was assigned to the anti rotamer since the phenyl group was shielding the half of the molecule (carbons 1−3 and 9) away from the C(4) substituent as determined by the chemical shifts differences of the protons on that side of the molecule (Figure 1). Furthermore, since the protons on carbons 1−3 as well as the ortho protons on the C(2)-phenyl substituent were being shielded by the phenyl group of the *S*-Mosher amide (resulting in negative $\delta S - \delta R$ values), the absolute stereochemistry of **22** was assigned as shown in Figure 1. Accordingly, the protons on the C(4)-substituent for the minor syn-rotamer were effectively shielded for the *R*-amide (positive $\delta S - \delta R$ values) as evidenced by the 1.7 ppm shift of the methylene protons next to the acetoxy group, again consistent with the absolute stereochemistry shown in Figure 1.

TABLE 4. Asymmetric Synthesis of Azabicylononadiene 13



entry	diazo	R_1	R_2	catalyst	solvent	product	yield, %	ee, %
1	**2**	H	H	Rh$_2$(*S*-DOSP)$_4$	toluene	**a**	32	50−60
2	**2**	H	Me	Rh$_2$(*S*-TBSP)$_4$	toluene	**i**	30	58
3	**15**	Me	H	Rh$_2$(*S*-TBSP)$_4$	toluene	**e**	48	65
4	**5**	Ph	H	Rh$_2$(*S*-TBSP)$_4$	toluene	**d**	68	82
5	**5**	Ph	H	Rh$_2$(*S*-DOSP)$_4$	hex−tol (3:1)	**d**	63	80

TABLE 5. ^{1}H NMR Chemical Shift Differences ($\delta S - \delta R$) of Mosher Amides 22

rotamer	H(1)	H(2β)	H(3)	*o*-Ph (C2)	H(5)	H(7)	CH_2OAc	CH$_2$O*Ac*
anti	−0.14	−1.10	−0.17	−0.26	−0.31	+0.22[a]	+0.11[a]	+0.01
syn	−0.08	0.00	+0.20	*b*	*b*	−0.03[a]	+1.69[a]	+0.02

[a] Average of two diastereotopic proton resonances. [b] Resonances not assigned.

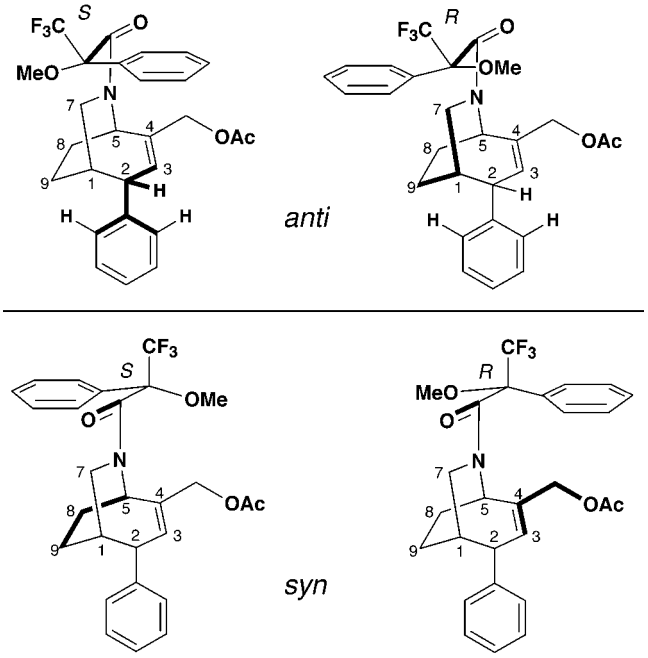


FIGURE 1. Structures of the anti (major) and syn rotamers of the Mosher amides **22-*S*** and **22-*R***. Quadrants of the molecules shielded by the phenyl group of the amide are highlighted in bold.

Discussion

The reaction of vinycarbenoids with dienes provides an efficient route to seven-membered rings. For example, tropolones, 7-oxabicyclooctanes, tropanes, and tremulanes all have been prepared in high yields with this methodology.[3] Through the use of either the chiral auxiliaries or the chiral prolinate catalysts, Rh$_2$(*S*-DOSP)$_4$ or Rh$_2$(*S*-TBSP)$_4$, these compounds can also be prepared asymmetrically. These reactions occur via a concerted, asynchronous cyclopropanation of one double bond of the diene followed by a stereoselective Cope rearrangement.

The 1-methyl-2-pyridone system reacts with vinylcarbenoids to form the 6-azabicyclononadienone ring system (**3**, **6**, and **9**). Due to the electron deficient nature of this diene, specialized reaction conditions are required to produce reasonable yields of the product. In this case, the electron deficient prolinate catalysts, Rh$_2$(*S*-DOSP)$_4$ and Rh$_2$(*S*-TBSP)$_4$, provide a more reactive carbenoid, which can react more efficiently with the pyridone. As observed in the pyrrole system, the presence of α-hydroxyesters delivers a significant increase in yield and reaction selectivity. This effect is believed to be due to interaction of the carbenoid with the ester carbonyl on the auxiliary.[2] When the glycolate or lactate auxiliaries are used in tandem with catalyst **4**, the azabicyclononadienone can be isolated in 40% yield; the yield increases to 78% when substitution is present on the vinyl portion of the vinyldiazomethane.

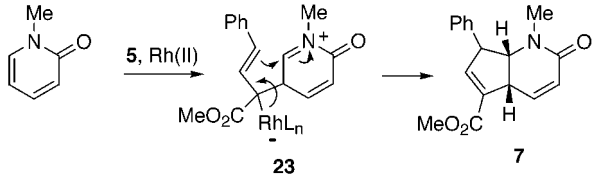


FIGURE 2.

Also formed in the reaction is the azabicyclo[4.3.0]-nonandienone product (**7**). Spectral evidence of small quantities (<10%) of azabicyclo[4.3.0]nonandienones were seen in all the reactions with *N*-methyl-2-pyridone, but except for **7**, these minor products were not fully characterized. This compound is presumably formed via a zwitterionic intermediate (**23**) formed during the cyclopropanation step (Figure 2). Alkylation of the pyridone ring followed by ring closure through the vinyl group produces **7**. The formation of side products due to the intermediacy of zwitterionic intermediates has been observed in other vinylcarbenoid reactions.[9] Catalysts with more electron withdrawing ligands such as **4**, needed to give reasonable yields of the desired [3.2.2] product, help to stabilize these zwitterionic intermediates, increasing the yield of this reaction pathway. Fortunately, this can be mitigated through the use of α-hydroxyesters on the vinyldiazomethane, which is known to minimize products resulting from zwitterionic intermediates in the reaction between vinylcarbenoids and pyrroles.[2]

In the case of the dihydropyridine ring system, the double bond regioselectivity directly leads to the formation of each of the regioisomers (Figure 3). Attack at the 5,6 double bond as in **24** generates isomer **13** while attack at the 3,4 double bond as in **25** generates isomer **14**. Bulky catalysts such as rhodium pivalate lead to a strong preference for cyclopropanation on the double bond closer to the nitrogen.[5] In accordance with this mechanism, use of the sterically robust prolinate catalysts leads to a high selectivity for formation of isomers **13**. It should be noted that the considerable electronic difference between the two catalysts does not seem to be a factor in the regioselectivity of these reactions.

In most cases, the prolinate catalysts lead to modest asymmetric induction in the resulting 6-azabicyclononadienes with the phenyl-substituted derivative **13d** showing the best result with 82% ee at room temperature. A

(8) (a) Hoye, T. R.; Renner, M. K. *J. Org. Chem.* **1996**, *61*, 2056 and references therein. (b) Rauk, A.; Tavares, D. F.; Khan, M. A.; Borkent, A. J.; Olson, J. F. *Can. J. Chem.* **1983**, *61*, 2572.

(9) (a) Davies, H. M. L.; Ahmed, G.; Chruchill, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10774. (b) Davies, H. M. L.; Clark, T. J.; Kimmer, G. F. *J. Org. Chem.* **1991**, *56*, 6440. (c) Davies, H. M. L.; Clark, T. J. *Tetrahedron* **1994**, *50*, 9883. (d) Davies, H. M. L.; Matasi, J. J.; Ahmed, G. *J. Org. Chem.* **1996**, *61*, 2305.

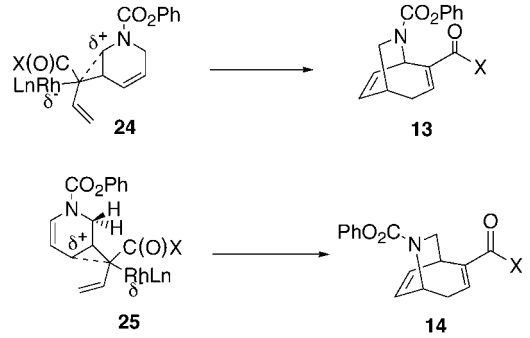


FIGURE 3.

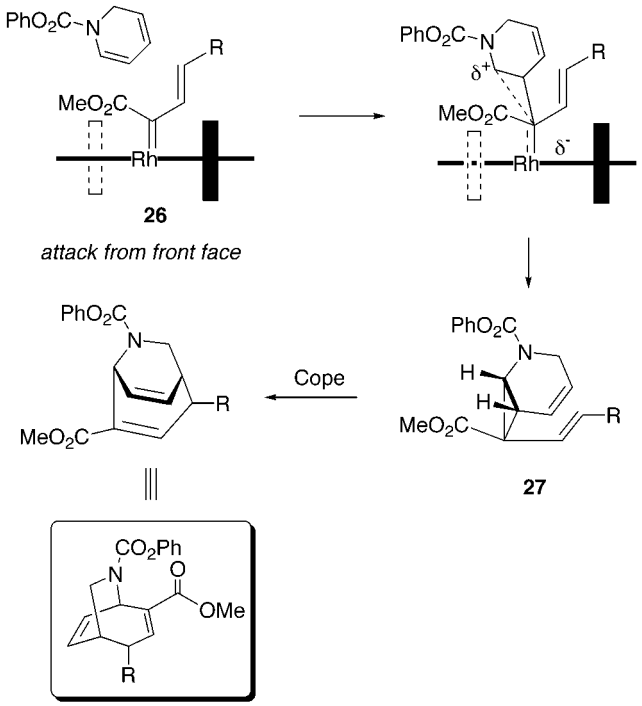


FIGURE 4.

reasonable model to rationalize the asymmetric induction is shown Figure 4. This model is an extension of the predictive model that has been developed for the dirhodium tetraprolinate transformations,[10] in which the catalyst behaves as a D_2-symmetric complex and the chiral influence can be simplified to two blocking groups as illustrated in **26**. In the case of the 1,2-dihydropyridine **12**, only one carbon for each double bond is activated for electrophilic attack. To form **13d**, the initial C5−C6 double bond cyclopropanation would occur preferentially on the C-5 carbon. A subsequent Cope rearrangement of the divinylcyclopropane **27** would lead to the formation of **13d** with the observed absolute configuration (1*S*,5*R*). The analogous reaction between carbenoids and pyrroles shows a modest 51% ee in the resulting tropanes.[2] In this case since attack of the pyrrole ring by the carbenoid can occur at either the electronically favored α-position or sterically favored *β*-position, these competing orientations of attack lead to opposite asymmetric induction.[2]

(10) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897 and references therein.

In summary, these studies demonstrate the versatility of the [3 + 4] cycloaddition between rhodium-stabilized vinylcarbenoids and dienes. The reaction of these vinylcarbenoids with 2-pyridones and 1,2-dihydropyridines is a direct approach for the construction of 6-azabicyclo-[3.2.2]nonanes. Current studies are directed toward elaboration of these 6-azabicyclo[3.2.2]nonanes to novel monoamine re-uptake inhibitors, and the synthetic and biological results of these studies will be described in due course.

Experimental Section

^{1}H NMR spectra were run at either 300, 400, or 500 MHz, and ^{13}C NMR spectra were run at either 75 or 125 MHz in $CDCl_3$ unless otherwise noted. Mass spectral determinations were carried out at 70 eV. Hexanes, THF, and Et_2O were dried over and distilled from sodium metal with benzophenone as the indicator. Acetonitrile, toluene, and methylene chloride were dried over and distilled from CaH_2. Column chromatography was carried out on Merck silica gel 60 (230−400 mesh). Commercially available reagents were used without additional purification unless noted. Melting points are uncorrected. The chiral rhodium prolinate catalysts **4a** and **4b**[10,11] and vinyldiazomethanes **2**, **5**, **8a**−**c**, **10**, **11**, and **15** were synthesized by literature procedures.[12] *N*-Phenoxycarbonyl-1,2-dihydropyridine (**12**) and *N*-phenoxycarbonyl-3-methyl-1,2-dihydropyridine (**16**)[13] were prepared according to the literature procedure and purified via recrystallization from either absolute ethanol or methanol. Commercial 1-methyl-2-pyridone (**1**, Aldrich) was vacuum distilled before use.

Synthesis of 6-Azabicyclo[3.2.2]nona-3,8-dien-7-ones, Typical Procedure. A solution of methyl 2-diazo-3-butenoate (**2**, 705 mg, 5.59 mmol) in 30 mL of dry toluene was added dropwise over 30 min to a solution of 1-methyl-2-pyridone (**1**, 2.49 g, 22.9 mmol, 4 equiv) and tetrakis[*N*-(4-*n*-dodecylphenylsulfonyl)prolinato]dirhodium [Rh_2(DOSP)$_4$] (**4b**, 208 mg, 0.112 mmol, 2 mol %) in 40 mL of toluene at room temperature. The reaction was stirred overnight, and the excess pyridone was removed via Kugelrohr distillation (100 °C, 0.1 Torr). The crude product was then chromatographed (EtOAc) to give methyl (6-methyl-6-azabicyclo[3.2.2]nona-3,8-diene-7-one)-4-carboxylate (**3**, 17%). For compounds **6**, **7**, and **8a**−**c**, the catalyst, chromatography solvent system, and yield are given in that order in parentheses. ^{1}H NMR (**3**, 400 MHz, $CDCl_3$) δ 6.73 (m, 1 H), 6.55 (dd, J = 7.9, 6.7 Hz, 1 H), 6.16 (dd, J = 7.9, 6.7 Hz, 1 H), 4.64 (d, J = 6.1 Hz, 1 H), 3.78 (s, 3 H), 3.19 (br s, 1 H), 2.97 (s, 3 H), 2.76 (ddd, J = 20.4, 4.0, 3.6 Hz, 1 H), 2.35 (ddd, J = 21.2, 3.6, 3.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 166.2, 141.2, 134.0, 133.4, 127.9, 53.4, 52.1, 41.9, 32.7, 27.6; IR (neat) 1707, 1669, 1636 cm^{-1}; MS *m*/*z* (rel intensity) 207 (M^+, 65), 148 (19), 91 (100). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.49; H, 6.44; N, 6.57.

Methyl (6-methyl-2α-phenyl-6-azabicyclo[3.2.2]nona-3,8-diene-7-one)-4-carboxylate [6] (**4b**, 2:1 EtOAc/hexanes, 33%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.25 (m, 3 H), 7.16 (d, J = 7.3 Hz, 2 H), 6.80 (m, 1 H), 6.63 (dd, J = 7.3, 6.7 Hz, 1 H), 5.75 (dd, J = 7.3, 7.3 Hz, 1 H), 4.71 (d, J = 6.4 Hz, 1 H), 4.00 (dd, J = 3.4, 3.1 Hz, 1 H), 3.81 (s, 3 H), 3.46 (m, 1 H), 3.01 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 166.3, 143.6, 138.1, 134.3, 134.1, 128.6, 128.0, 127.5, 127.3, 53.5, 52.3, 50.2, 42.8, 33.2; IR (neat) 1708, 1640 cm^{-1}. HRMS calcd for $C_{17}H_{17}NO_3$ 283.1208; found 283.1213.

Methyl 7-phenyl-1-azabicyclo[4.3.0]nona-3,5-diene-2-one-5-carboxylate [7] (**4b**, 2:1 EtOAc/hexanes, 14%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.31 (m, 2 H), 7.28 (t, 1 H),

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(12) Davies, H. M. L. *Curr. Org. Chem.* **1998**, *2*, 463.
(13) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 4836.

7.18 (d, J = 7.6 Hz, 2 H), 6.70 (d, J = 1.5 Hz, 1 H), 6.38 (dd, J = 10.1, 1.8 Hz, 1 H), 5.99 (dd, J = 9.8, 2.4 Hz, 1 H), 4.06−3.97 (m, 3 H), 3.80 (s, 3 H), 2.64 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8, 162.5, 146.0, 140.9, 136.2, 134.8, 129.0, 127.7, 127.6, 123.6, 70.4, 58.3, 51.9, 42.8, 34.8; IR (neat) 1718, 1669, 1616 cm^{-1}; MS *m/z* (rel intensity) 283 (M^+, 100), 251 (33), 224 (79), 115 (52). Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.06; H, 6.12; N, 4.84.

Synthesis of 6-Azabicyclo[3.2.2]nonadiene Carboxylates [13, 14], Typical Procedure. A chilled solution of freshly purified **2** (3.82 g, 30.3 mmol) in 50 mL of dry toluene was added dropwise to a solution of **12** (7.61 g, 37.8 mmol, 1.25 equiv) and $Rh_2(OOct)_4$ (476 mg, 0.611 mmol, 2.0 mol %) in 100 mL of toluene over 30 min. The reaction was stirred for 1.5 h and then heated to reflux for 30 min. The reaction mixture was allowed to cool to room temperature and the mixture was concentrated under reduced pressure. The residue was chromatographed (4:1 to 1:1 petroleum ether/Et_2O) to give methyl (6-phenoxycarbonyl-6-azabicyclo[3.2.2]nona-2,8-diene)-2-carboxylate (**14a**, 2.59 g, 8.64 mmol, 29%) and methyl (6-phenoxycarbonyl-6-azabicyclo[3.2.2]nona-3,8-diene)-4-carboxylate (**13a**, 2.69 g, 8.98 mmol, 30%). For compounds **13b**−**i** and **14b**−**h**, the catalyst used, chromatography solvent system, and yield are given in that order in parentheses. In many cases, the usually favored and more polar 4-carboxylate isomers (**13**) exist as solids. The presence of rotamers caused by the phenoxycarbonyl substituent complicates the ^{13}C data of **13** and **14** and these data are not reported. When the reaction was carried out with [Rh_2(*S*-DOSP)$_4$] in toluene, **13a** was formed in 32% yield and 50−60% ee (determined by HPLC: Chiralcel OD, 2.0% *i*-PrOH in hexane, 1.0 mL/min, λ = 254 nm, t_R = 48.0 min, major; t_R = 51.1 min, minor).

^{1}H NMR (**14a**, 9:5 ratio of rotamers, 500 MHz, $CDCl_3$)[14] δ 7.36 (m, 2 H), 7.19 (q, J = 7.3 Hz, 1 H), 7.11 (d, J = 8.0 Hz, 2 H), 6.84 (dd, J = 3.4, 3.3 Hz, 1 H), 6.51 (m, 1 H), 6.24 (m, 1 H), 4.84, 4.78 (dd, J = 5.5, 5.2 Hz, 1 H total), 3.98, 3.89 (dd, J = 11.3, 1.5 Hz, 1 H total), 3.77 (s × 2, 3 H total), 3.73 (m, 1 H), 3.55, 3.42 (dd, J = 11.3, 3.7 Hz, 1 H total), 2.96, 2.92 (ddd, J = 20.4, 4.6, 4.0 Hz, 1 H total), 2.46, 2.40 (ddd, J = 20.1, 2.7, 2.4 Hz, 1 H total); IR (neat) 1712, 1638 cm^{-1}; MS *m/e* (rel intensity) 299 (M^+, 85), 206 (74), 174 (100). Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72; N, 4.68. Found: C, 68.09; H, 5.80; N, 4.56.

^{1}H NMR (**13a**, 1:1 ratio of rotamers, 500 MHz, $CDCl_3$) δ 7.33 (t, J = 7.6 Hz, 2 H), 7.14 (m, 3 H), 6.81 (m, 1 H), 6.58 (m, 1 H), 6.19 (m, 1 H), 5.69, 5.67 (d, J = 7.3 Hz, 1 H total), 3.82, 3.73 (d, J = 12 Hz, 1 H total), 3.76, 3.75 (s, 3 H total), 3.68, 3.52 (ddd, J = 11.6, 4.6, 4.6 Hz, 1 H total), 2.76−2.53 (m, 3 H); IR (neat) 1715, 1638, 1591 cm^{-1}; MS *m/e* (rel intensity) 299 (M^+, 100), 206 (66). Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72; N, 4.68. Found: C, 68.28; H, 5.74; N, 4.63. Mp = 96.5−99 °C.

2-Propionyl-(6-phenoxycarbonyl-6-azabicylo[3.2.2]nona-2,8-diene) [14b] and **4-propionyl-(6-phenoxycarbonyl-6-azabicylo[3.2.2]nona-3,8-diene) [13b]** ($Rh_2(OOct)_4$, 4:1 petroleum ether/Et_2O to 1:1 petroleum ether/Et_2O) to give both **14b** (25%) and **13b** (11%).

^{1}H NMR (**14b**, 2:1 ratio of rotamers, 500 MHz, $CDCl_3$) δ 7.35 (m, 2 H), 7.19 (m, 1 H), 7.12 (m, 2 H), 6.71 (m, 1 H), 6.48 (m, 1 H), 6.25 (m, 1 H), 4.86, 4.81 (br t, 1 H total), 3.97 (br s, 1 H), 3.85, 3.76 (d, J = 11.0 Hz, 1 H total), 3.54, 3.41 (dd, J = 11.6, 3.7 Hz, 1 H total), 2.99, 2.96 (ddd, J = 20.4, 4.6, 4.3 Hz, 1 H), 2.70 (m, 2 H), 2.54, 2.48 (d, J = 20.1 Hz, 1 H total), 1.13 (m, 3 H); IR (neat) 1716, 1668, 1630 cm^{-1}; MS *m/e* (rel intensity) 297 (M^+, 80), 147 (100). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.60; H, 6.47; N, 4.58.

^{1}H NMR (**13b**, 3:2 ratio of rotamers, 500 MHz, $CDCl_3$) δ 7.31 (m, 2 H), 7.15 (m, 1 H), 7.11, 7.08 (d, J = 8.0 Hz, 2 H), 6.65 (m, 1 H), 6.52 (m, 1 H), 6.18 (m, 1 H), 5.85, 5.74 (d, J = 7.0 Hz, 1 H total), 3.86, 3.75 (d, J = 11.5 Hz, 1 H total), 3.65, 3.51 (ddd, J = 11.5, 4, 4 Hz, 1 H total), 2.80−2.71 (m, 2 H), 2.70−2.60 (m, 3 H), 1.10 (m, 3 H); IR (neat) 1715, 1666, 1633 cm^{-1}; MS *m/e* (rel intensity) 297 (M^+, 80), 204 (39), 161 (13), 147 (100). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.89; H, 6.49; N, 4.79. Mp = 109−111 °C.

Methyl (3-*tert*-butyldimethylsiloxy-6-phenoxycarbonyl-6-azabicyclo[3.2.2] nona-2,8-diene)-2-carboxylate [14c] and methyl (3-*tert*-butyldimethylsiloxy-6-phenoxycarbonyl-6-azabicyclo[3.2.2]nona-3,8-diene)-4-carboxylate [13c] ($Rh_2(OOct)_4$, 4:1 to 2:1 petroleum ether/Et_2O) to give both **14c** (24%) and **13c** (17%).

^{1}H NMR (**14c**, 2:1 ratio of rotamers, 400 MHz, $CDCl_3$) δ 7.36 (m, 2 H), 7.20 (m, 1 H), 7.11 (d, J = 9.2 Hz, 2 H), 6.61 (m, 1 H), 6.23 (m, 1 H), 4.84, 4.79 (br t, 1 H total), 4.02, 3.90 (d, J = 14.4 Hz, 1 H total), 3.75, 3.73 (s, 3 H total), 3.66 (m, 1 H), 3.46, 3.34 (dd, J = 14.2, 4.6 Hz, 1 H total), 2.94, 2.91 (dd, J = 22.9. 6.0 Hz, 1 H total), 2.41, 2.36 (dd, J = 22.9, 2.3 Hz, 1 H total), 0.94, 0.93 (s, 9 H total), 0.18, 0.17 (s, 6 H total); IR (neat) 1720, 1609 cm^{-1}; MS *m/e* (rel intensity) 429 (M^+, 0.2), 372 (M^+ − *t*-Bu, 100). Anal. Calcd for $C_{23}H_{31}NO_5Si$: C, 64.31; H, 7.27; N, 3.26. Found: C, 64.28; H, 7.33; N, 3.25.

^{1}H NMR (**13c**, 3:2 ratio of rotamers, 500 MHz, $CDCl_3$) δ 7.33 (t, J = 7.9 Hz, 2 H), 7.16 (t, J = 7.4 Hz, 2 H), 7.10 (m, 2 H), 6.62 (m, 1 H), 6.20 (m, 1 H), 5.67, 5.66 (d, J = 7.0 Hz, 1 H total), 3.78, 3.68 (d, J = 11.6 Hz, 1 H total), 3.57, 3.42 (ddd, J = 11.3, 4.6, 4.3 Hz, 1 H total), 3.71 (s, 3 H), 2.77 (br s, 1 H), 2.63, 2.59 (dd, J = 11.6, 3.7 Hz, 1 H total), 2.50 (m, 1 H), 0.94 (s, 9 H), 0.19, 0.17 (s, 6 H total); IR (neat) 1716, 1615 cm^{-1}; MS *m/e* (rel intensity) 429 (M^+, 3), 372 (M^+ − *t*-Bu, 100). Anal. Calcd for $C_{23}H_{31}NO_5Si$: C, 64.31; H, 7.27; N, 3.26. Found: C, 64.38; H, 7.33; N, 3.25.

Methyl (4α-phenyl-6-phenoxycarbonyl-6-azabicyclo-[3.2.2]nona-2,8-diene)-2-carboxylate [14d] and methyl (2α-phenyl-6-phenoxycarbonyl-6-azabicyclo[3.2.2]nona-3,8-diene)-4-carboxylate [13d] ($Rh_2(OPiv)_4$, 4:1 to 2:1 petroleum ether/Et_2O) to give both **14d** (trace) and **13d** (69%). When the reaction was carried out with [Rh_2(*S*-TBSP)$_4$] in toluene, **13d** was formed in 68% yield and 82% ee (determined by HPLC: Chiralcel OD, 10% *i*-PrOH in hexane, 1.0 mL/min, λ = 254 nm, t_R = 17.3 min, major; t_R = 21.5 min, minor).

^{1}H NMR (**14d**, 2:1 ratio of rotamers, 500 MHz, $CDCl_3$) δ 7.45−7.16 (m, 10 H), 6.94 (m, 1 H), 6.58 (m, 1 H), 5.77 (m, 1 H), 5.00, 4.94 (dd, J = 5.5, 4.9 Hz, 1 H total), 4.25, 4.22 (dd, J = 4.3, 4.0, 1 H total), 4.00, 3.90 (d, J = 11.0 Hz, 1 H total), 3.85 (m, 1 H), 3.80, 3.79 (s, 3 H total), 3.57, 3.45 (dd, J = 11.0, 3.4 Hz, 1 H total); IR (neat) 1716 cm^{-1}. HRMS Calcd for $C_{23}H_{21}NO_4$ 375.1471, found 375.1492.

^{1}H NMR (**13d**, 1:1 ratio of rotamers, 500 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5 H), 7.19 (t, J = 7.3 Hz, 1 H), 7.14 (m, 4 H), 6.88 (m, 1 H), 6.64 (m, 1 H), 5.84 (m, 1 H), 5.77, 5.74 (d, J = 6.9 Hz, 1 H total), 4.04, 3.91 (d, J = 11.6 Hz, 1 H total), 3.88, 3.86 (dd, J = 3.4, 3.1 Hz, 1 H total), 3.79 (s, 3 H), 3.77, 3.62 (dd, J = 11.9, 4.6 Hz, 1 H total), 3.00 (m, 1 H); IR (neat) 1718, 1642 cm^{-1}; MS *m/e* (rel intensity) 375 (M^+, 41), 250 (22), 225 (100). Anal. Calcd for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.69; H, 5.71; N, 3.75. Mp = 137−139.5 °C.

Methyl (2α-phenyl-6-phenoxycarbonyl-6-azabicyclo-[3.2.2]nona-3-ene)-4-carboxylate [17]. A solution of **13d** (3.1 g, 8.3 mmol, 97% ee (HPLC)) in 125 g of absolute ethanol was prepared in a Parr hydrogenation flask. Wilkinson's catalyst (115 mg, 0.124 mmol, 1.5 mol %) was added, and the system was flushed with hydrogen four times and pressurized to 50 psi. The mixture was agitated for 23 h after which no starting material was observed by ^{1}H NMR. The solvent was removed under reduced pressure and the crude product chromatographed on silica gel with 2:1 petroleum ether/Et_2O to give the title compound as a white solid. Yield: 3.0 g (8.0 mmol, 97%). Mp = 98.5−100 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 3:2 ratio of rotamers) δ 7.39−7.10 (m, 11 H), 5.38, 5.35 (br s, 1 H total), 4.05, 3.99 (ddd, J = 12.4, 2, 2 Hz, 1 H total), 4.04 (br s, 1 H), 3.80, 3.61 (dd, J = 12.4, 3.3 Hz, 1 H total), 3.79, 3.78 (s, 3 H total), 2.33 (m, 1 H), 2.19 (m, 1 H), 2.07 (m, 1 H), 1.81 (m, 1

(14) The ^{1}H NMR resonances corresponding to the major rotamer are underlined.

H), 1.56 (m, 1 H); IR (neat) 1715 cm^{-1}; MS *m/e* (rel intensity) 377 (M^+, 8), 284 (100). Anal. Calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.23; H, 6.17; N, 3.76.

4-(Hydroxymethyl)-2α-phenyl-6-methyl-6-azabicyclo-[3.2.2]nona-3-ene [18] and 4-(Acetoxymethyl)-2α-phenyl-6-methyl-6-azabicyclo[3.2.2]nona-3-ene [19]. A solution of **17** (2.17 g, 5.75 mmol) in 75 g of dry THF was prepared and cooled to 0 °C. Lithium aluminum hydride (1.21 g, 31.9 mmol) was added, and the mixture was stirred for 3 h. The reaction was quenched at 0 °C by the slow addition of EtOAc (100 mL) followed by stirring for 1.5 h. Brine (100 mL) was then added, and the mixture was stirred for an additional 2 h. The mixture was filtered and the cake washed with 50 mL each of EtOAc and water, and the layers were separated in the filtrate. The organic layer was washed twice with 50 mL of 5% aq KOH followed by 100 mL of brine. The organic solution was dried ($MgSO_4$), and the solvent was evaporated to give ∼1.5 g of crude product that contained the desired compound along with the acetate ester (the desired product of the next reaction) from base-promoted ester exchange with ethyl acetate during workup. The crude material was chromatographed (5% Et_3N in Et_2O followed by 5% Et_3N in Et_2O with 20% added methanol to elute the alcohol) to give the acetate ester **19** (169 mg, 0.59 mmol, 10%) and the desired alcohol **18** (767 mg, 3.15 mmol, 55%).

Characterization of **18**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 2 H), 7.21 (m, 3 H), 5.75 (br s, 1 H), 4.13 (s, 2 H), 3.83 (br s, 1 H), 3.13 (dd, J = 11.0, 6.1 Hz, 1 H), 3.06 (d, J = 6.4 Hz, 1 H), 2.69 (d, J = 11.0 Hz, 1 H), 2.41 (s, 3 H), 2.12 (m, 2 H), 1.76 (m, 1 H), 1.47 (m, 2 H); O*H* resonance not observed; ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.0, 143.5, 128.2, 127.9, 126.8, 126.3, 68.1, 56.8, 56.2, 53.4, 44.2, 37.0, 28.0, 18.6; IR (neat) 3400 (br) cm^{-1}; HRMS calcd for $C_{16}H_{21}NO$ 243.1623, found 243.1633.

Characterization of **19**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (t, J = 7.6 Hz, 2 H), 7.23 (t, J = 7.6 Hz, 1 H), 7.19 (d, J = 7.6 Hz, 2 H), 5.83 (br s, 1 H), 4.59 (abq, J = 12.5 Hz, 2 H), 3.83 (br s, 1 H), 3.20 (dd, J = 10.7, 6.4 Hz, 1 H), 3.01 (d, J = 6.7 Hz, 1 H), 2.61 (d, J = 10.7 Hz, 1 H), 2.40 (s, 3 H), 2.11 (s, 3 H), 2.1 (m, 2 H), 1.76 (m, 1 H), 1.50 (m, 1 H), 1.44 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 142.9, 139.0, 130.5, 128.4, 127.9, 126.4, 69.3, 56.7, 56.5, 53.6, 44.1, 36.9, 28.7, 21.0, 18.6; IR (neat) 1739 cm^{-1}; HRMS calcd for $C_{18}H_{23}NO_2$ 285.1729, found 285.1714.

4-(Acetoxymethyl)-2α-phenyl-6-(2,2,2-trichloroethoxycarbonyl)-6-azabicyclo[3.2.2]nona-3-ene [20]. A solution of **19** (147 mg, 0.515 mmol) in 10 mL of dry toluene was prepared. Anhydrous potassium carbonate (10 mg, 0.072 mmol) was added followed by 2,2,2-trichloroethyl chloroformate (0.15 mL, 1.0 mmol, 2 equiv). The reaction mixture was heated to reflux for 10 h. The mixture was diluted with Et_2O and extracted with 2 × 50 mL of $NaHCO_3$ (sat, aq) followed by 50 mL of brine. The organic solution was dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give an oil. The crude material was chromatographed (2:1 petroleum ether/Et_2O) to give the title product as a yellow oil. Yield: 200 mg (0.448 mmol, 87%). This compound could also be prepared in 70% yield from **18** first by acylation (1.2 equiv each of Ac_2O and DMAP in CH_2Cl_2) followed by demethylation of crude **19** with excess 2,2,2-trichloroethyl chloroformate. ^1H NMR (500 MHz, $CDCl_3$, 1:1 ratio of rotamers) δ 7.35 (m, 2 H), 7.27 (m, 1 H), 7.21 (d, J = 7.6 Hz, 2 H), 5.75 (br s, 1 H), 4.89−4.72 (m, 4 H), 4.66, 4.64 (br s, 1 H total), 4.48 (m, 1 H), 3.91 (br d, J = 12.2 Hz, 1 H), 3.88 (br s, 1 H), 3.71, 3.59 (dd, J = 12.0, 4.4 Hz, 1 H total), 2.25 (br d, J = 17.4 Hz, 1 H), 2.11, 2.10 (s, 3 H total), 2.10−1.98 (m, 1 H), 1.78 (m, 1 H), 1.47 (m, 1 H); IR (neat) 1740, 1715, 1601 cm^{-1}; MS *m/e* (rel intensity) 445 (M^+, 1), 385 ($(M - HOAc)^+$, 26), 181 (100). Anal. Calcd for $C_{20}H_{22}NO_4Cl_3$: C, 53.77; H, 4.96; N, 3.14. Found: C, 53.51; H, 5.00; N, 3.05.

4-(Acetoxymethyl)-2α-phenyl-6-azabicyclo[3.2.2]nona-3-ene [21]. A 4-dram vial was charged with **20** (200 mg, 0.448 mmol), glacial HOAc (5.0 mL), and zinc powder (100 mesh, 500 mg). The mixture was stirred for 18 h at room temperature. The reaction was diluted with water (25 mL), filtered, and neutralized with K_2CO_3(s) and 60 mL of NH_4OH (aq) (final pH 11). The aqueous mixture was extracted with CH_2Cl_2 (4 × 25 mL) and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give the crude product, which contained approximately 10% starting material. The crude mixture was chromatographed (Et_2O, then 5% Et_3N in Et_2O, followed by 5% Et_3N in Et_2O with 10% methanol). Yield 53 mg (0.20 mmol, 44%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (t, J = 7.6 Hz, 2 H), 7.25−7.30 (m, 3 H), 5.78 (br s, 1 H), 4.61 (br s, 2 H), 3.90 (br s, 1 H), 3.35 (br d, J = 4.9 Hz, 1 H), 3.31 (dd, J = 11.6, 4.9 Hz, 1 H), 3.20 (br d, J = 11.9 Hz, 1 H), 2.78 (br s, 1 H), 2.10 (s, 3 H), 2.07 (m, 1 H), 2.04 (m, 1 H), 1.84 (m, 1 H), 1.66 (m, 1 H), 1.55 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 143.9, 142.4, 130.6, 128.3, 127.9, 126.3, 68.5, 53.0, 49.4, 47.1, 37.4, 27.9, 21.0, 18.5; IR (neat) 3346 (br), 1738 cm^{-1}; HRMS calcd for $C_{17}H_{21}NO_2$ 271.1572, found 271.1554.

Conversion of 21 to Mosher Amides 22-*R* and 22-*S* (General Procedure). A 1-dram vial was charged with **21** (15 mg, 0.056 mmol), DIEA (18 mg, 0.14 mmol), and 0.40 g of CH_2Cl_2. The corresponding acid chloride (*R*-acid chloride for the *S*-amide; the *S*-acid chloride for the *R*-amide; 18 μL, 0.096 mmol) was added by syringe. The vial was gently flushed with Ar for 30 s and the reaction allowed to stand for ∼12 h at room temperature. The reaction mixture was diluted with 5 mL of CH_2Cl_2 and added to 10 mL of stirred NH_4Cl (sat, aq). After the solution was stirred for 30 min, the layers were separated, and the aqueous layer was back-extracted with 5 mL of CH_2Cl_2. The organic extracts were combined, dried ($MgSO_4$), and filtered through a pad of silica gel in a 15-mL coarse-fritted funnel. The solvent was evaporated under reduced pressure and the crude amide **22** dissolved in $CDCl_3$ and analyzed by ^1H NMR (500 MHz). Assignments of proton resonances were made with the assistance of COSY and nOe data.

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Supporting Information Available: Spectral data for **9a**−**c**, **13e**−**i**, and **14e**, and proton NMR spectra for **6**, **9a**, **13i**, **19**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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