Carbenoid Reagents

Stereoselective Synthesis of Bicyclic Pyrrolidines by a Rhodium-Catalyzed Cascade Process**

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The synthesis of complex products by a reaction between multiple components to form several carbon–carbon bonds in one operation is a strategy that has received considerable attention.[1] Often referred to as tandem or cascade processes, these operations are useful for efficient molecular constructions. Ylide chemistry with metal-stabilized carbenes has provided numerous examples of these processes, often in the context of dipolar cycloaddition reactions.[2] We recently reported versatile heterocycle syntheses by reactions of aryl and vinyl diazoacetates with aldehydes and imines catalyzed by dirhodium(II) acetate.[3] These reactions proceed through the generation of an ylide intermediate to produce epoxides, aziridines, dihydropyrroles, and, in select cases, dihydroazepines with a high degree of stereoselectivity. More recently we reported alternative pathways for the highly selective synthesis of dihydropyrrole isomers that are catalyst dependent.[4] During the course of this latter investigation, we obtained the isomeric compounds **2a**,**b** as minor products formed from two carbene units derived from methyl styryldiazoacetate and one imine (Scheme 1). However, the structure of **2a**,**b** was not determined. The constitution of these compounds was surprising, as the combination of two carbene units and an imine does not have precedence in diazo chemistry[5] or ylide processes.[1f,6] We now report the structure of this unusual product, the optimization of the reaction conditions to effect the synthesis of such compounds in good yield and selectivity, and the preliminary evaluation of the breadth of applicability of this reaction in synthesis.

The treatment of *N*-benzylidene-*p*-nitroaniline (1.0 equiv) with methyl styryldiazoacetate (1.1 equiv) in the presence of rhodium acetate (1 mol %) in refluxing dichloromethane gave a product mixture that contained two isomeric

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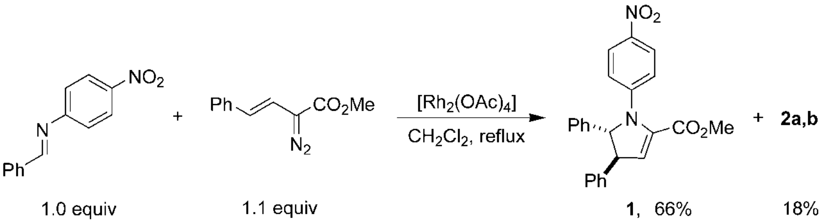


Scheme 1. Synthesis of dihydropyrrole **1**.

products whose structures were not fully revealed by their spectra (Scheme 1). The crystallization of one isomer produced a single crystal, which was identified by X-ray diffraction as **2a** (Figure 1).[7] The relative stereochemistry

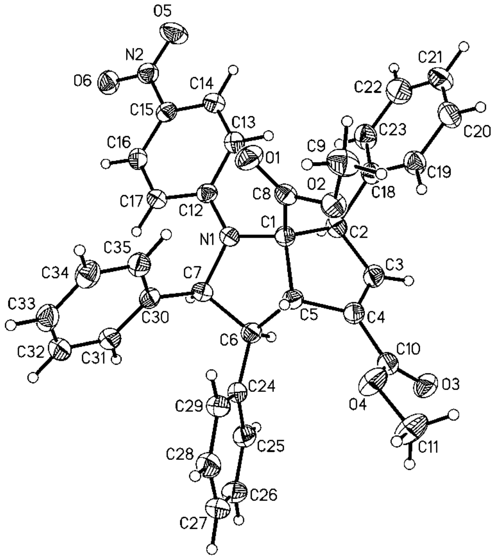
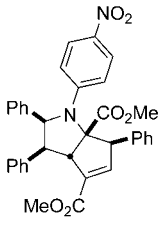
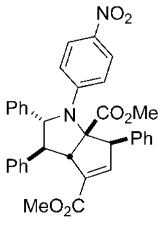


Figure 1. Crystal structure of **2a**. Selected bond lengths [Å] and angles [°]: N1-C1 1.469(2), N1-C12 1.377(2), C1-C5 1.557(2), N1-C1-C2 114.9(2), C7-N1-C12-C17 5.5(2), C30-C7-C6-C24 32.9(2).



2a



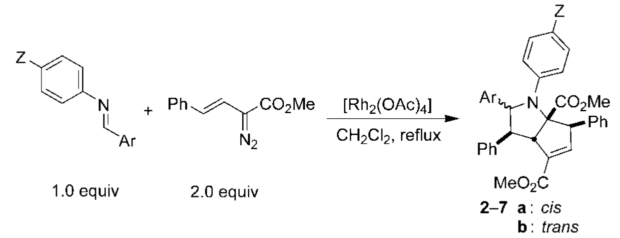
2b

of the second isomer was confirmed by NMR spectroscopy to be that of the *trans* diastereomer **2b**.[8] No other isomers of **2** were observed.

Initial investigations focused on reaction stoichiometry and the influence of substituents on the *N*-benzylidene *p*-Z-aniline reagent on product formation in reactions with methyl styryldiazoacetate (2.0 equiv). In these reactions the yield of the bicyclic pyrrolidine was proportional to the number of equivalents of styryldiazoacetate used (up to 2.0 equiv). The highest yields of the bicyclic pyrrolidine were obtained when Z was H (70% when the benzylidene group was unsubstituted); imines with *para* substitutents on the benzylidine moiety were selected for further investigation of substitution effects on the reaction (Table 1).[9]

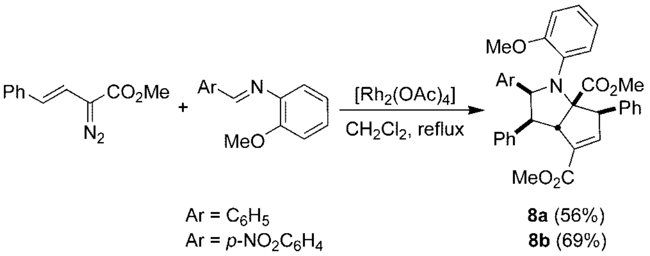
Variation of the substituents on the benzylidene group had no effect upon diastereoselectivity; however, the yield decreased with imines bearing electron-donating substituents. Exclusive formation of the *cis* diastereomer of type **8** was observed when *ortho*-substituted imines were used (Scheme 2).

Table 1: Preparation of bicyclic pyrrolidines from *N*-benzylidene *p*-Z-anilines.[a]



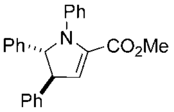
Ar	Z	Product	a/b[b]	Yield [%][c]
Ph	NO_2	**2**	54:46	18[d]
Ph	H	**3**	54:46	70
Ph	OMe	**4**	61:39	38
p-MeC_6H_4	H	**5**	52:48	51
p-ClC_6H_4	H	**6**	52:48	71
p-$NO_2C_6H_4$	H	**7**	50:50	84

[a] A solution of methyl styryldiazoacetate (2.0 mmol) in CH_2Cl_2 (2 mL) was added by a syringe pump over 1 h to a solution of $[Rh_2(OAc)_4]$ (0.01 mmol) and the imine (1.0 mmol) in CH_2Cl_2 (8 mL) at reflux. [b] Determined by the integration of characteristic ^1H NMR signals in the range $\delta = 5.47$–4.22 ppm prior to chromatography. [c] Combined yield of product **a** and **b** after chromatography. [d] Compound **1** was isolated in 47% yield.



Scheme 2. Exclusive formation of the *cis* isomer in reactions with benzylidene *o*-anisidines.

Our previous investigations are consistent with the initial step being the generation of an azomethine ylide through reaction of the imine with a carbene unit formed by catalytic dinitrogen extrusion from the diazo compound. Initially, we considered the possibility that this ylide intermediate cyclized to form a dihydropyrrole, which then reacted with a second carbene unit to generate the bicyclic pyrrolidine. However, the exposure of isolated **1** or **9** (formed from benzylideneaniline and methyl styryldiazoacetate) to methyl styryldiazoacetate (1.1 equiv) under the standard reaction conditions failed to produce any quantity of the corresponding bicyclic pyrrolidines, thus ruling out the intermediacy of the dihydropyrrole. Furthermore, *trans* dihydropyrroles are formed with a high degree of selectivity from styryldiazoacetate and *N*-benzylidine *p*-Z-anilines (Scheme 1), whereas the bicyclic products **2**–**7** are mixtures of *cis* and *trans* isomers and could therefore not be derived from the *trans* dihydropyrrole isomer.



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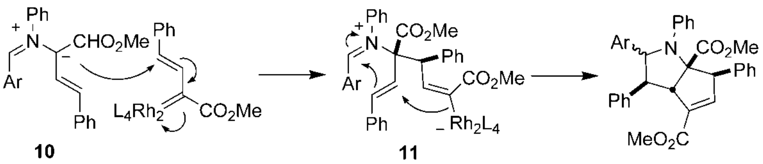
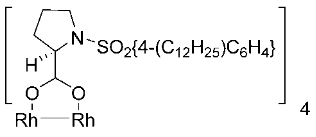
As dihydropyrroles are not intermediates in bicycle formation, an alternative explanation is that the azomethine ylide **10** reacts with a second metal–carbene unit prior to cyclization. Reports by Davies and co-workers have shown that rhodium(II)-stabilized vinyl carbenes are capable of undergoing nucleophilic attack at the vinylogous position.[10] In a similar manner, this mode of nucleophilic addition of **10** to a rhodium(II)-stabilized vinyl carbene would, after the cascade ring closure of **11**, generate the observed products (Scheme 3).



Scheme 3. Mechanism of formation of bicyclic pyrrolidines.

To evaluate the propensity of the azomethine ylide to add to a second carbene unit rather than cyclize to the dihydropyrrole, we used an excess of the imine relative to methyl styryldiazoacetate. When methyl styryldiazoacetate was added to a tenfold excess of *N*-benzylideneaniline under dilute conditions, the ^{1}H NMR spectrum of the product mixture showed a 39:36:25 ratio of **3a**:**3b**:**9**.[11] That the bicyclic pyrrolidine **3** remains the dominant product under conditions which are designed to force cyclization to the dihydropyrrole emphasizes the surprising efficiency of the vinylogous intermolecular reaction. The efficiency of this mode of reactivity was also illustrated upon attempts to trap ylide **10** with a series of dipolarophiles. Similar azomethine ylides have been trapped by electron-deficient olefins and acetylenes in [3+2] cycloadditions.[2a] However, the addition of methyl styryldiazoacetate to imines in the presence of common dipolarophiles of this type, even in significant excess, failed to provide the [3+2] cycloadducts.[12] The formation of bicyclic pyrrolidines was observed in all cases.

We have recently begun to develop an asymmetric variant of this reaction with chiral dirhodium catalysts; in initial investigations *N*-benzylideneaniline and the Davies catalyst [$Rh_2\{(S)\text{-dosp}\}_4$] were used.[13] Although the yield of isolated **3a**,**b** decreased to 12 % with no significant change in the ratio of diastereomers, **3b** was formed with modest enantioselectivity (25 % *ee*).[14]



[$Rh_2\{(S)\text{-dosp}\}_4$]

The potential for using simple, readily accessible starting materials to form stereochemically complex systems in good yields provides a new entry to nitrogen-based heterocycles. Of particular note are the high levels of diastereoselectivity and the promise of future progress in enantioselectivity. Attempts to exploit this reactivity mode in the synthesis of other heterocyclic systems are currently underway.

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[7] X-ray diffraction experiments were performed with a Bruker SMART 1000 CCD detector X-ray diffractometer by using $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). The structures were solved by a full-matrix least-squares method (SHELXL-97, Bruker AXS Inc., Madison, WI, USA). Crystallographic data for **2a**: $C_{35}H_{31}N_2O_6$, triclinic, space group $P\bar{1}$, $a = 11.1175(8)$, $b = 13.5357(9)$, $c =$

13.5623(9) Å, $\alpha = 112.090(2)$, $\beta = 94.205(2)$, $\gamma = 104.502(2)^{\circ}$, $V = 1798.6(2)$ Å^3, $Z = 2$, $\rho_{\text{calcd}} = 1.061\,\text{Mg}\,\text{m}^{-3}$, $\mu = 0.09\,\text{mm}^{-1}$, $T = 170$ K, $R(F, F^2 > 2\sigma) = 0.0412$, $R_w(F^2$, all data$) = 0.0998$, $S = 0.0752$ for 7343 unique reflections ($\theta < 26.39^{\circ}$) and 469 refined parameters; final difference synthesis within $\pm 0.231\,\text{e}\,\text{Å}^{-3}$. CCDC-240323 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

[8] Determination of the relative stereochemistry of **2a** allowed that of **2b** to be assigned by NMR, as detailed in the supporting information.

[9] The reaction of the imine with Z = H, Ar = p-MeOC$_6$H$_4$ did not provide a significant quantity of the bicyclic pyrrolidine.

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[11] A solution of methyl styryldiazoacetate (77 mg, 0.38 mmol) in CH$_2$Cl$_2$ (1 mL) was added by syringe pump over 1 h to a solution of [Rh$_2$(OAc)$_4$] (4.4 mg, 0.01 mmol) and benzylideneaniline (0.690 mg, 3.81 mmol) in CH$_2$Cl$_2$ (50 mL) at reflux. After the addition was complete, the solution was heated at reflux for a further 1 h. The reaction mixture was filtered through a plug of silica gel, which was then washed with CH$_2$Cl$_2$. The product ratio was determined by ^{1}H NMR spectroscopy.

[12] Reactions were carried out under the conditions described in Table 1. The dipolarophiles diethyl maleate, diethyl fumarate, dimethyl acetylenedicarboxylate, or *N*-phenylmaleimide (10–15 equiv) or methyl acrylate (100–200 equiv) were added prior to the addition of methyl styryldiazoacetate.

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[14] Following the standard reaction protocol described in Table 1, methyl styryldiazoacetate was treated with benzylideneaniline in the presence of a catalytic amount of [Rh$_2${(S)-dosp}$_4$]. Prior to purification, ^{1}H NMR spectroscopic analysis showed a 46:54 ratio of **3a**/**3b**. HPLC analysis of **3b** indicated 25% *ee*. (Chiralpak-OD, hexane/isopropyl alcohol 90:10, 1.0 mL min^{-1}, 220 nm; $R_t = 3.2$ min (major), 4.3 min (minor); $[\alpha]_D^{27} = +62.9$ ($c = 0.20$, CH$_2$Cl$_2$)).