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Intramolecular Cyclopropanation Reactions En Route to Novel P-Heterocycles

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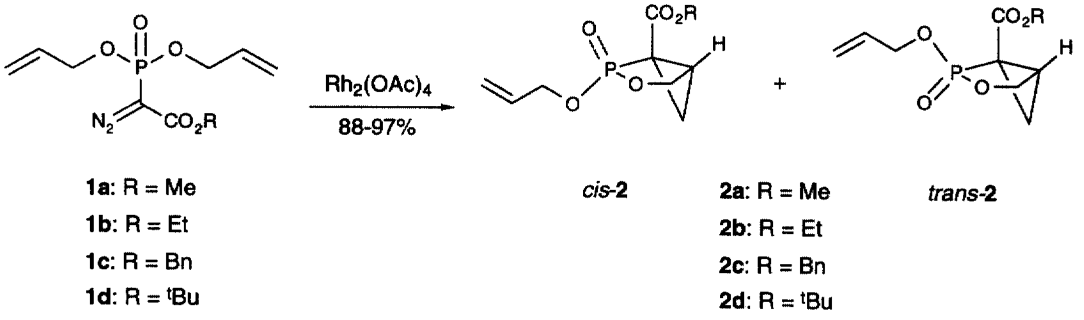
Abstract: The first examples of intramolecular cyclopropanation reactions on a phosphonate template catalyzed by $Rh_2(OAc)_4$ are described. These reactions proceed in excellent yield and give mixtures of the P-heterocycles *cis*-**2a-d** and *trans*-**2a-d** with moderate levels of diastereoselectivity. The diastereoselectivity of this transformation is dependent upon the size of the alkyl group R contained in the alkyl α-diazodiallylphosphonoacetate starting materials **1a-d**.

Cyclopropane rings continue to be the targets of organic synthesis due to their wide occurrence in natural products and biological systems.[1] Recently, phosphorus analogs of 2,3-methanoamino acids (cyclopropyl ring containing α-amino acids) have gained pharmaceutical interest due to their potential to inhibit GABA-receptors, and are of agricultural interest due to their potential to block amino acid producing enzymes.[2] Currently, there are numerous methods of synthesizing cyclopropane containing compounds, however, the transition metal catalyzed breakdown of α-diazo carbonyl compounds in the presence of olefins is one of the more popular approaches.[3] Both intermolecular and intramolecular cases[4] are prominent in the literature using various transition metal catalysts such as rhodium, palladium, and copper. These reactions have been shown to occur with both high diastereoselectivity[5] and enantioselectivity.[6] The reactions of a number of α-diazo systems[7] have been studied, including α-diazo-ketones and vinylcarbenoids. Relatively few studies exist, however, for the transition metal catalyzed reactions of α-diazophosphonoacetates.[8] To date, a single example exists on the intramolecular cyclopropanation of allyl α-diazodialkylphosphonoacetate.[8] As part of our program aimed at developing organometallic approaches to diverse phosphorus containing compounds,[9] we herein report the first examples of intramolecular cyclopropanation reactions of alkyl α-diazo-diallylphosphonoacetate substrates **1a-d** (Scheme 1) to yield the novel P-heterocycles **2a-d**.

Scheme 1



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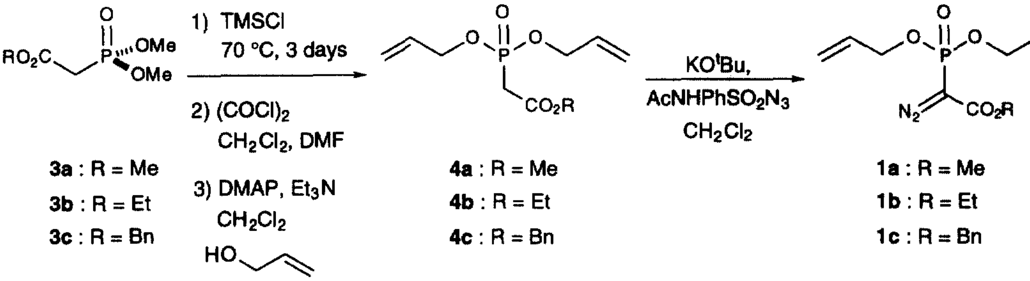
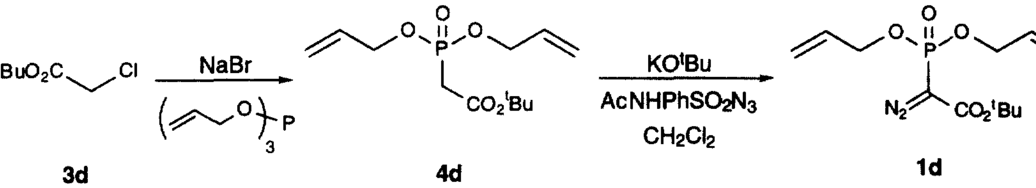
Our initial interest in this area is the development of an intramolecular cyclopropanation desymmetrization strategy en route to the synthesis of nonracemic P-heterocycles such as **2** (Scheme 1). Thus, the starting alkyl dimethylphosphonoacetates **3**[10] were deprotected under mild conditions with TMSCl (Scheme 2). Subsequent allylation led to the alkyl diallylphosphonoacetate substrates **4** (85-95% over 3 steps). Final diazo transfer with N-acetylsulfanilyl azide and KO^{t}Bu at 0°C gave the corresponding alkyl α-diazodiallylphosphonoacetate substrates **1a-c** in excellent yields (85%).

Scheme 2



The initial deprotection step shown in Scheme 2 proved to be problematic for the *tert*-butyl esters, presumably because of the labile nature of the *tert*-butyl group in the presence of TMSCl. This result led us to prepare compound **1d** via an alternate route shown in Scheme 3. Thus, the Arbuzov reaction of *tert*-butyl chloroacetate (**3d**) and triallylphosphite gave *tert*-butyl diallylphosphonoacetate (**4d**), albeit in poor yield (nonoptimized, 35% over 2 steps). Mild diazo transfer to derive **1d** was achieved in excellent yields (85%) through the use of KO^{t}Bu and N-acetylsulfanilyl azide at 0°C.

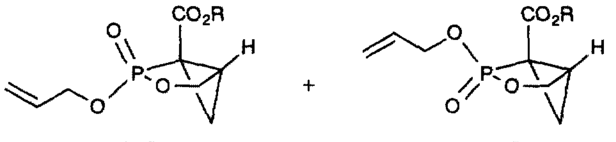
Scheme 3



Results of initial intramolecular cyclopropanation studies employing Rh$_2$(OAc)$_4$ catalysis are outlined in Table 1. All reactions proceeded in good to excellent yield giving exclusively mixtures of the P-heterocycles *cis*-**2** and *trans*-**2** with moderate levels of diastereoselectivity.[11] The diastereoselectivity of this transformation is influenced by the size of the R group with the *tert*-butyl moiety giving the highest ratio. Efforts to unambiguously assign the relative configurations using ^{1}H NMR difference nOe spectroscopic studies gave negative results and therefore have led us to pursue obtaining a crystalline derivative for x-ray crystallographic analysis.

In conclusion, we have shown that the $Rh_2(OAc)_4$ catalyzed intramolecular cyclopropanation of alkyl α-diazodiallylphosphonoacetates **1a-d** occur in good yield and with moderate levels of diastereoselectivity. Additional efforts focusing on the diastereoselective and enantioselective differentiation of substrates such as **1a-d** are actively being pursued and will be reported in due course.

Table 1



cis-**2** *trans*-**2**

entry	Products	Yield	Diastereomeric Ratio*
1	**2a** (R = Me)	97%	2.5:1
2	**2b** (R = Et)	93%	3.7:1
3	**2c** (R = Bn)	88%	4.0:1
4	**2d** (R = ^{t}Bu)	96%	5.5:1

*Note: The unambiguous assignment of each diastereomer has not been determined.

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10) The alkyldimethylphosphonoacetates (**3a-c**) are readily prepared using the standard Arbuzov procedure employing trimethyl phosphite and the appropriate alkyl haloacetate.

11) All new compounds have satisfactory ^{1}H, ^{13}C, and ^{31}P NMR and MS data.

Major Diastereomer 2b (R = Et), Colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.91-6.00 (m, 1H), 5.33-5.38 (d, J = 17.1 Hz, 1H), 5.22-5.25 (d, J = 10.4 Hz, 1H), 4.64-4.72 (m, 2H), 4.36-4.39 (dd, J = 9.3 Hz, 3.2 Hz, 1H), 4.13-4.27 (m, 2H), 4.01-4.12 (m, 1H), 2.49-2.55 (m, 1H), 1.64-1.70 (m, 1H), 1.40-1.46 (m, 1H), 1.26-1.29 (t, J = 7 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.1 (d, J_p = 8.7 Hz), 132.9 (d, J_p = 6.4 Hz), 117.8, 105.5, 68.0 (d, J_p = 6.1 Hz), 64.2 (d, J_p = 3.1 Hz), 62.0, 27.2 (d, J_p = 6.3 Hz), 17.3, 14.1; ^{31}P-NMR (161.9 Mhz, $CDCl_3$) δ 36.0; IR 2982, 2908, 1726, 1446, 1374, 1280 cm^{-1} (P=O); HRMS (CI, NH_3) calc'd for $C_{10}H_{15}O_5P$ (M^+) 246.0657 found 246.0641.

Minor Diastereomer 2b (R = Et), Colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.91-6.00 (m, 1H), 5.32-5.37 (m, 1H), 5.22-5.25 (dd, J = 10.4 Hz and 1 Hz, 1H), 4.65-4.78 (m, 2H), 4.13-4.25 (m, 3H), 4.01-4.10 (m, 1H), 2.42-2.48 (m, 1H), 1.71-1.77 (m, 1H), 1.57-1.63 (m, 1H), 1.26-1.29 (t, J = 7 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.9 (d, J_p =9.9 Hz), 132.5 (d, J_p = 5.8 Hz), 118.2, 105.5, 67.8 (d, J_p = 4.9 Hz), 64.4 (d, J_p = 5.5 Hz), 62.0, 27.1 (d, J_p = 8.0 Hz), 18.4, 14.0; ^{31}P-NMR (161.9 Mhz, $CDCl_3$) δ 36.4; IR 2909, 2982, 1727, 1448, 1376, 1274 (P=O) cm^{-1}; HRMS (CI, NH_3) calc'd for $C_{10}H_{15}O_5P$ (M^+) 246.0657 found 246.0639.