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Stereoselective Synthesis of P-Chiral Phosphorus Compounds from *N-tert*-Butoxycarbonyl Amino Acids

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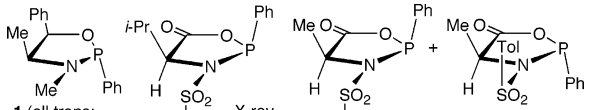
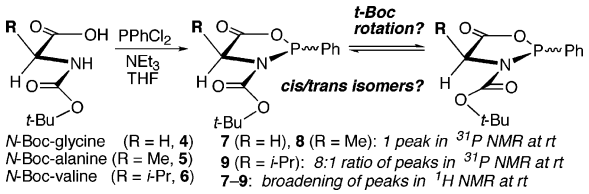
Abstract: Reaction of the *N-t*-Boc amino acids alanine and valine with $PhPCl_2$ gives the P-chiral *trans*-1,3,2-oxazaphospholidinones exclusively. Variable-temperature NMR and examination of the glycine derivative shows that the isomers observed are due to *t*-Boc rotation.

Methods for the synthesis of P-chiral phosphorus compounds have the potential to be of use in applications as varied as organometallic catalysis[1] and antisense oligonucleotides.[2−5] One of the best methods uses the reaction of the β-amino alcohol ephedrine with $PhPCl_2$,[6−8] resulting in transfer of chirality from carbon to phosphorus to give trans-substituted heterocycle **1**. The stereoselectivity



was presumed to arise by minimization of steric interactions between the phenyl groups. Like ephedrine, amino acids and their *N*-substituted derivatives have the same β-nitrogen−oxygen functionality, and have similarly been used to give 1,3,2-oxazaphospholidinones.[9−16] Until our report of the use of *N*-toluenesulfonylvaline,[12] however, none of the amino acid examples had been shown to lead to diastereomerically pure heterocycles. In contrast to the ephedrine example, the *N*-sulfonamide amino acid derivative gave the cis-substituted heterocycle **2**. Here, the stereoselectivity was shown to arise for steric reasons, since the use of *N*-toluenesulfonylalanine, having a methyl instead of an isopropyl group on the β-carbon, gave a 1:1 cis:trans ratio of **3a**:**3b**.[12,15] We proposed that the selectivity was driven by repulsive steric interactions of the toluenesulfonyl moiety with the neighboring isopropyl and phenyl groups. We have now extended this method to the use of *N-tert*-butoxycarbonyl (Boc) derivatives of amino acids, a study that was initiated to investigate the utility of other electron-withdrawing moieties on nitrogen. We report here the synthesis and surprising stereochemistry of the resultant *t*-Boc-amino acid derivatives, the X-ray crystal structure of the valine derivative, and variable-temperature NMR results on the dynamic exchange process found to take place.

SCHEME 1



Reaction of the *N*-Boc derivatives of glycine, alanine, and valine (**4**−**6**) with $PhPCl_2$ in the presence of NEt_3 gave an immediate white precipitate of $Et_3NH^+Cl^-$, and ^{31}P NMR spectra of reaction aliquots indicated clean formation of essentially one compound in each case (Scheme 1).

Standard workup consisting of filtration and solvent removal only gave oils, but the simple expedient of filtration through a large pad of silica gel gave spectroscopically pure products. Comparison of the ^1H, ^{13}C, and ^{31}P NMR spectra to those of **2**−**6** were all consistent with formation of heterocycles **7**−**9**; for instance the ^{31}P chemical shifts were all near 135 ppm as would be expected of such structures,[12,15] and **7** exhibits diastereotopic cis and trans hydrogens on the ring carbon which are absent in the achiral starting material **4**. These materials could be crystallized with some difficulty in up to 41% yield. As suggested by the initial reaction workup, these compounds are sensitive to a number of conditions that are not completely reproducible. Upon standing at room temperature under nitrogen, the lifetimes vary from 1 day to many weeks, and standing at room temperature under a vacuum gave the same variability. Surprisingly, the thermal stability depends on the ring substitution; in one unhappily serendipitous experiment involving warming for 1 day,[17] after several weeks at −30 °C **7** was found to have decomposed only slightly, **8** was about 50% decomposed, and **9** was completely decomposed. In the latter case in particular, the *tert*-butoxy group was eliminated,

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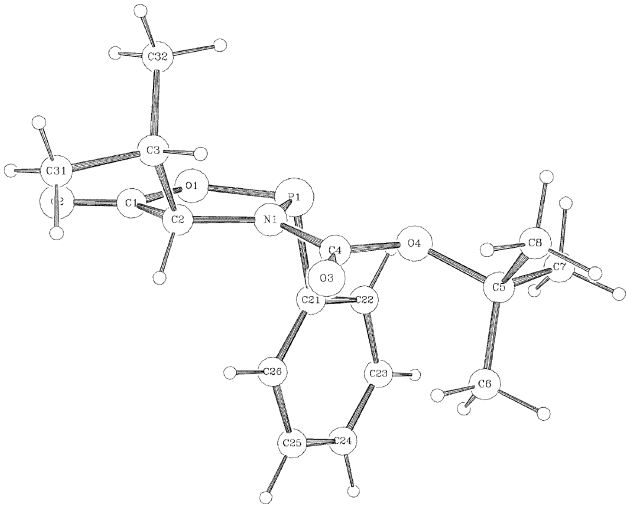

FIGURE 1. ORTEP drawing of **9**.

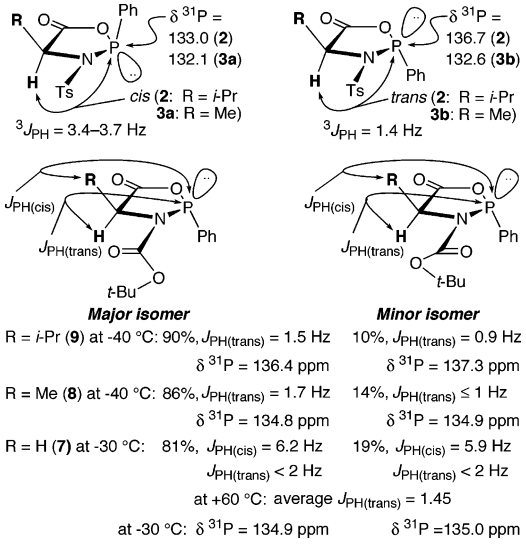

FIGURE 2. Determination of stereochemistry by phosphorus−hydrogen coupling constants.

and the amino acid moiety cleaved from phosphorus to give a complex forest of peaks in the ^{31}P NMR spectrum, and an unidentified $CDCl_3$-soluble amino acid derivative.

Crystals of **9** allowed the structure to be determined by X-ray diffraction, and the structure both confirms the heterocycle formation and shows that in contrast to **2**, the stereochemistry is trans (Figure 1). The other key feature is the *t*-Boc conformation, found in the solid state to be present in the *Z* configuration.[18−20] The structure of **9**, like that of **2**, is a rare example of a trivalent oxazaphospholidine, and these have been described by us in detail recently.[15] Bond lengths for **9** are within ±0.01−0.03 Å of those in **2** and angles about phosphorus are equally acute (i.e. ∠O−P−N = 88.7(3)°). In contrast, the amide nitrogen of **9** is nearly planar rather than pyramidalized as in **2**, and the five atoms of the heterocycle are nearly coplanar rather than exhibiting an envelope conformation like other 1,3,2-oxazaphospholidines (i.e. rms deviation from the plane = 0.027 and 0.091 Å for **9** and **2**, respectively).[15,21]

While the ^{31}P NMR spectrum of **8** gave a single peak at room temperature, that of **9** surprisingly exhibited two peaks in an ∼8:1 ratio, but the ^{1}H NMR spectra of both were broadened by a dynamic process. The glycine derivative **7** is necessarily racemic and so the observation of only one peak in the ^{31}P NMR was expected, but it too exhibited broadening in the ^{1}H NMR spectrum. While it was reasonable to suppose that the dynamic process was due to *t*-Boc rotation, a well-characterized conformational isomerism,[19,20] it was critical to rule out the alternative possibility of inversion at phosphorus.

At −30 to −40 °C, well-resolved NMR spectra of **7**−**9** were obtained, yielding two sets of peaks due to two isomers. Comparison of the ^{31}P NMR spectra to those of *cis*- and *trans*-**2** and **3** (Figure 2) revealed superficial similarities since both the minor isomers of **7**−**9** and the trans isomers of **2** and **3** exhibited downfield signals. However, determination of the ring stereochemistry was expected to be carried out not by chemical shift but by examination of the 3-bond coupling constant between phosphorus and the ring hydrogen. That is, we had previously shown for *cis*- and *trans*-**2** and **3** (Figure 2) that the trans coupling constant $^{3}J_{PH}$ is ∼2 Hz less than that of the cis isomer, allowing for a reliable NMR identification of the isomers *as long as both are in hand*. In the case of **8** and **9**, $^{3}J_{PH}$ = 0.9−1.7 Hz (Figure 2), suggesting that *all* observed diastereomers are trans, and that the observed isomers therefore are due to *t*-Boc rotation.

The results from glycine derivative **7** are essential for assigning the trans stereochemistry to **8** and **9**. Since there is no independent evidence for formation of the "other" phosphorus diastereomer, use of **7** allows direct measurement of the "cis" coupling constant; to allow the cis and trans designators to refer to the analogous hydrogen atoms in **7**−**9**, cis and trans here will be defined formally as the relationship between the ring hydrogen atom and the putative lone pair on phosphorus (Figure 2). As seen in Figure 3, at +20 °C two signals which exhibit a large geminal coupling constant ($^{2}J_{HH}$ = 17.8 Hz) are present, due to the cis and trans hydrogen atoms. The broad downfield signal exhibits an additional coupling of ∼4.9 Hz, while the sharper upfield signal exhibits an additional coupling (not readily visible in Figure 3) of 1.4 Hz, and on the basis of the experience with **2** and **3** these signals are assigned to the cis and trans hydrogen atoms, respectively. Cooling **7** to −30 °C eliminated the broadening of the downfield doublet, and for instance at both −30 and −20 °C, two overlapping doublets of doublets of the major and minor isomers can be seen, with $^{3}J_{PH}$ = 6.2 Hz for the major isomer and 5.9 Hz for the minor. In contrast, the major and minor isomers of the upfield trans hydrogen are still nearly coincident at low temperature, and the nonaveraged phosphorus−hydrogen coupling constant is obscured by cooling.

Definitive evidence that the exchange process exhibited by **7** is due only to *t*-Boc rotation and *not* to phosphorus

(17) A freezer warm-up during the blackout of August 14−15, 2003 most likely led to slow decomposition induced by a thermally produced initiator, but this was not evident until more than two months later.

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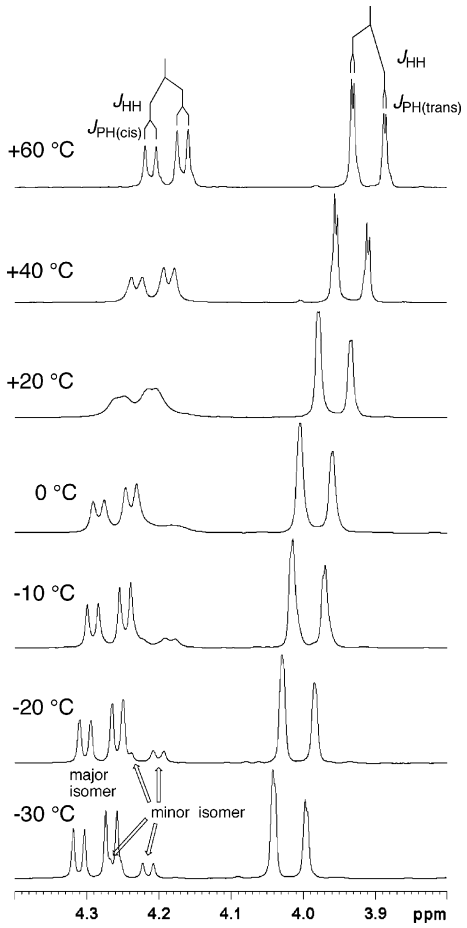

FIGURE 3. ^{1}H NMR spectra of CH_2 of **7**.

inversion was obtained by further heating of the sample in the NMR. As seen in Figure 3, the signals due to the *t*-Boc isomers move upfield at different rates and at first broaden and coalesce by +20 °C. Further warming resulted in sharpening of both signals, so that by +40 °C, the trans coupling constant ($^3J_{PH}$ = 1.45 Hz) can be observed readily. These results are consistent with rapid *t*-Boc rotation giving rapid interconversion of the *E* and *Z* isomers, but not interconversion of the cis and trans hydrogen atoms. That is, phosphorus inversion must be slow since there is no evidence of hydrogen exchange among the cis and trans hydrogens. A sample in toluene-d_8 at +90 °C also showed no evidence of exchange beyond the *t*-Boc rotation. Finally, the similar isomer ratios (~85/15) for each of **7**−**9** at low temperature obviously cannot be due to phosphorus inversion for **7**, but again are completely consistent with *t*-Boc rotation in all cases.

Rotation about the C−N bond of *N*-*t*-Boc amino acids is well-known. Evaluation of kinetic and thermodynamic data is complicated by the presence of cyclic structures due to hydrogen bonding of the carboxylic acid, so the best comparison is with the analogous amino acid esters. Kessler has examined the *E*,*Z* conformational equilibrium of *t*-Boc glycine methyl ester **10** (Figure 4) using a lanthanide shift reagent to give measurable shift differences. With the benefit of a higher field NMR spectrometer, we were able to carry out a variable-temperature NMR study with full line shape analysis of the CH_2 signals, and our results are in complete agreement with

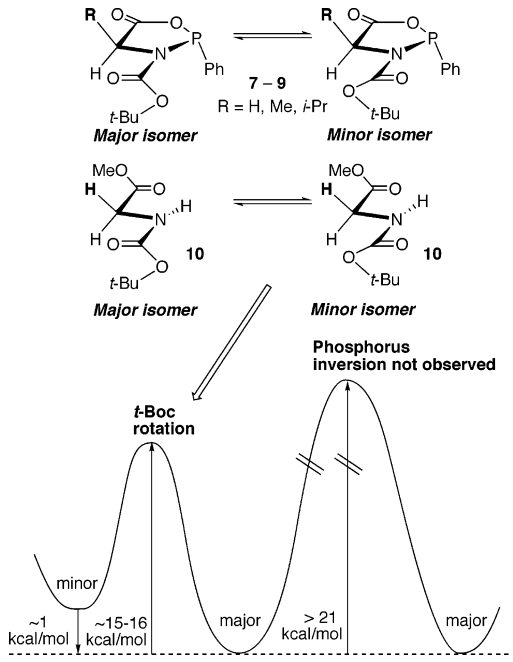

FIGURE 4. Energetics of *t*-Boc rotation.

TABLE 1. Kinetic and Thermodynamic Parameters for Isomer Exchange in 7−10[a]

	7	**8**	**9**	**10**	**10**[b]
$\Delta G°$	−0.63 ± 0.49	−0.9 ± 0.3	−1.2 ± 0.3	−1.08 ± 0.09	−1.2
$\Delta H°$	−1.0 ± 0.3	−0.7 ± 0.2	−0.8 ± 0.2	−1.31 ± 0.06	
$\Delta S°$	−1.3 ± 1.3	0.7 ± 0.9	1.4 ± 0.7	−0.8 ± 0.2	
$\Delta G^\dagger$	14.8 ± 0.9	14.8 ± 1.7	16.2 ± 0.9	16.3 ± 0.4	16.0
$\Delta H^\dagger$	16.4 ± 0.6	12.5 ± 1.1	14.5 ± 0.6	15.76 ± 0.03	15.7
$\Delta S^\dagger$	5.3 ± 2.3	−7.9 ± 4.2	−5.7 ± 2.2	−1.7 ± 1.0	1.1

[a] All values in kcal/mol; ΔG calculated at 298 K (this work) and at 7 °C for **10** (last column). [b] Determined by using a lanthanide shift reagent method (ref 20).

those of Kessler (Table 1). The same type of line shape analysis, using the *tert*-butyl and α-hydrogen peaks and the phosphorus peaks in the ^{31}P NMR, was carried out for **7**−**9**, and the similarity of the thermodynamic and kinetic parameters for these heterocycles and **10** provides further circumstantial evidence that the dynamic process is due to *t*-Boc rotation in all cases. The alternative explanation, that phosphorus inversion coincidentally occurs at the same rate in **8** and **9** as does *t*-Boc rotation in **7** and **10**, is not likely. The ^{1}H NMR line-shape data from **7** at 60 and 90 °C allow a lower limit for the barrier to phosphorus inversion to be calculated. Given a rate of exchange of less than 1 s^{-1}, since no broadening due to exchange of the coupled CH_2 hydrogens was observed, a barrier of >21 kcal/mol is obtained. In fact, this is not a stringent number, given observed barriers in saturated cyclic analogues of 27−37 kcal/mol.[22,23]

In conclusion, we have found that use of the *t*-Boc protecting group on the nitrogen of alanine and valine gives rise to exclusive formation of trans-substituted phospholidinones. In contrast to the use of the toluenesulfonyl group described previously, where alanine gave a 1:1 diastereomer ratio and valine a 10:1 ratio, there is,

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surprisingly, no variation that correlates with the differing degrees of steric hindrance of these groups. In comparison to other oxazaphospholidine cyclizations, no other system gives exclusive or even high diastereoselectivity with as little steric impetus as does **8**, in which the methyl and phenyl groups are mutually trans; in other systems both ring substituents are phenyl groups,[6−8] or P-3′-O-nucleoside substituents[2−5] or bicyclic systems[2,24,25] are involved.

This work does not answer the question of *why* the trans diastereomer forms exclusively; that is, how does the methyl group of alanine derivative **8** generate high diastereoselectivity, and is the explanation thermodynamic or kinetic? Preliminary calculations suggest that the energies of the diastereomers are similar. If this is so, the effect must be kinetic, in contrast to the sulfonamide case that we have suggested could be thermodynamic,[15] and indeed possibly to all other cases.[2,4−8,24,25] The two amides of **2**,**3** and **8**,**9** most likely differ greatly in pK_a; for instance in DMSO that of $PhSO_2NH_2$ is 16.1 while that of $EtOCONH_2$ is 24.2,[26,27] so the different stereochemical results could be due to different mechanisms of ring closure involving a sulfonamide anion on one hand and a neutral *t*-Boc amide on the other. Given that the acidity of Et_3NH^+ is a full 7 pK_a units lower even than the sulfonamide (i.e. the base used here was Et_3N),[28] an attack of an anionic nitrogen on phosphorus seems unlikely, especially since the sulfonamide reactions proceeded comparably under heterogeneous conditions in ether and toluene, and under homogeneous conditions in CH_2Cl_2.[15] If the cyclizations both proceed via attack of a neutral nitrogen species on phosphorus, the results hint at a novel mechanism of control of stereochemistry mediated by the *t*-Boc group; it is interesting to note that related examples of stereochemical control involving chiral *N*-*t*-Boc-substituted enolate intermediates have been proposed.[29,30] Many questions remain to be addressed, among them the identity of the initial bond to phosphorus, the reversibility and stereochemistry of the bond-forming steps, and whether epimerization at phosphorus occurs before cyclization. Here, preliminary work shows that the initial reaction is indeed complex, as many intermediates are observed by ^{31}P NMR spectroscopy at low temperature upon initial reaction. Future work will address these mechanistic questions as well as examine the synthetic utility of these chiral compounds.

Experimental Section

(2*R*,4*S*)-3-*tert*-Butyloxycarbonyl-4-isopropyl-5-oxo-2-phenyl-1,3,2-oxazaphospholidine (9). The procedure for **9** is similar to those for **7** and **8**. In a nitrogen-filled glovebox, a solution of 1.66 g (9.27 mmol) of $PhPCl_2$ in 7 mL of THF was added dropwise over 5 min to a stirred solution of *t*-Boc valine (2.00 g, 9.205 mmol) and NEt_3 (1.95 g, 19.27 mmol) in 33 mL of THF. A voluminous white precipitate formed immediately, giving a thick suspension. After 45 min, the reaction mixture was filtered through a short column of silica gel (filling 20 mL of a 30-mL fritted funnel) packed in THF, and the column was washed with another 20 mL of THF. Following solvent removal with use of a vacuum pump, 1.7 g (57% crude yield) of a sticky white solid was obtained. This material was taken up in 8 mL of hexane and cooled to −30 °C overnight, giving 1.27 g of a slightly sticky white crystalline product. A second crop of 0.15 g was obtained, and this combined material was recrystallized from 9 mL of hexane and cooled slowly in an insulated flask to give 0.98 g (33% yield) of spectroscopically pure material. Final purification was achieved by partially dissolving this material in 5 drops of ether, and then adding 7 mL of hexane and cooling at −30 °C, to give 0.64 g of analytically pure product as white crystals. The residue from this crystallization (a waxy white solid) was dissolved in 10 drops of ether and 4 mL of hexane was added; the resultant solution was allowed to stand at −30 °C for 6 days to give (after washing with cold hexane) 91 mg of product as well-formed slab-like clear crystals used for the X-ray diffraction study. $[\alpha]^{26}_D$ 296.8 (*c* 1.87, C_6H_6); IR ($CHCl_3$) 1780 (s), 1710 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.57 (m, 3H), 7.46 (m, 2H), 4.46, 4.3 (br s, ∼6:1 ratio, 1H), 2.67, 2.6 (br m, ∼6:1, 1H), 1.41, 1.19 (br s and s, ∼1:6, 9H), 1.22 (d, $^3J_{HH}$ = 7.0 Hz, 3H), 1.01 (d, $^3J_{HH}$ = 7.0 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 138.1 (13%), 137.3 (87%) ppm; ^{13}C NMR ($CDCl_3$) δ 170.8 (d, J_{PC} = 11.7 Hz), 152.0, 140.5 (d, J_{PC} = 48.3 Hz), 132.7, 130.4 (d, J_{PC} = 26.9 Hz), 128.9 (d, J_{PC} = 7.8 Hz), 82.8, 60.0, 30.5, 28.3 (minor isomer), 27.9 (major isomer), 18.1, 16.3 ppm. Anal. Calcd for $C_{16}H_{22}NO_4P$: C, 59.44; H, 6.86; N, 4.33. Found: C, 59.38; H, 6.81; N, 4.26.

Variable-Temperature NMR Spectra. Samples of **7**−**10** (∼10 mg) were prepared in $CDCl_3$ (∼0.5 mL) with 1% TMS as the nonexchanging reference peak, and for **9** 1.5 mg of PPh_3 was added as a nonexchanging ^{31}P reference peak. Spectra were recorded over the range of −60 to +60 °C (albeit not for each sample). Integration of peaks for the *t*-Boc *tert*-butyl CH_3 hydrogens of **7**−**9**, the *cis*-CHN hydrogen of **7**, the CHN hydrogen of **8** and **9**, the CH_2 peaks of **10**, and the phosphorus of **9** for each isomer in the nonexchanging region was used to determine the equilibrium ratios of the isomers, and the calculated values from a plot of ln(*K*) vs 1/*T* (where *K* = [major isomer]/[minor isomer]) were used for determination of thermodynamic parameters and for isomer ratios at the temperatures used to determine the exchange rates. For **10**, it was necessary to simulate the observed spectra and extract the integrations from these fits, since the observed peaks were too broad to give accurate integrals. Chemical shift differences of these peaks were plotted as a function of temperature in the approximately nonexchanging region and the linear fit was used to calculate all chemical shift differences for the exchanging region. Simulation of the NMR spectra by using gNMR v3.6 on a Macintosh computer was carried out for each exchanging pair of peaks, using these data and the measured line widths of TMS and PPh_3, and the best fit rate constants were determined by visual comparison of the observed and simulated spectra. Activation parameters were determined from a plot of ln(*k*/T) vs 1/*T*, where *k* is the rate constant for the reaction major isomer → minor isomer.

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Supporting Information Available: Experimental procedures and ^1H, ^{13}C, ^{31}P, and IR spectra of **7**−**9**, VT NMR data, the X-ray structure of **9**, and comparison of selected bond lengths and angles of **2** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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