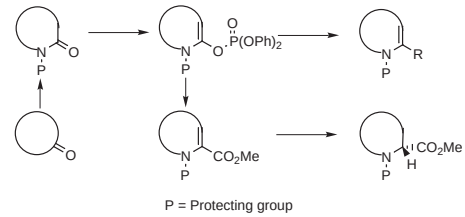
Synthesis of *N*-heterocycles *via* lactam-derived ketene aminal phosphates. Asymmetric synthesis of cyclic amino acids.

K. C. Nicolaou,* Guo-Qiang. Shi, Kenji Namoto and Federico Bernal

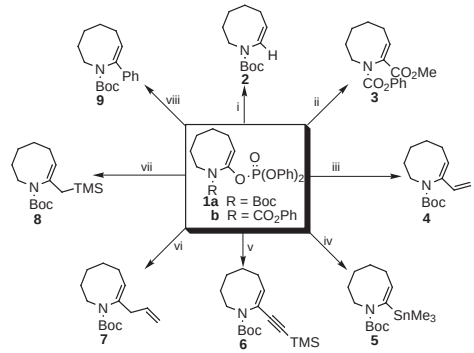
Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, USA and Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093, USA

A variety of *N*-heterocycles can be synthesized from lactams *via* Pd^0-catalyzed couplings of their corresponding enol phosphates.

Due to the rich chemistry and biology of nitrogen-containing compounds, the synthesis of *N*-heterocycles has been a central and important theme within organic chemistry. The functionalization of lactams to substituted heterocycles *via* the corresponding enol triflates has been reported.[1] However, the triflate-based methodology has been proven cumbersome due to the rather unstable, difficult-to-isolate nature of the triflates and the necessity to use unconventional and expensive triflating reagents. Here we report the synthesis of lactam-derived ketene aminal phosphates[2] and their utilization for the construction of a variety of *N*-heterocycles, including enantiomerically enriched cyclic amino acids. In contrast to their triflate counterparts, these phosphate intermediates enjoy remarkable stability, efficiency of formation and reactivity, as well as easy access and versatility (Scheme 1).[3]



Scheme 1

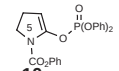
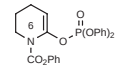
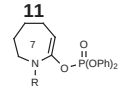
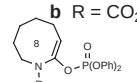
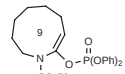
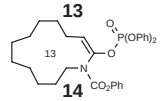
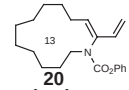
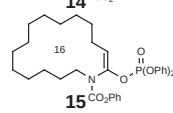
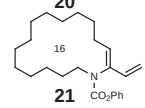


Scheme 2 *Reagents and conditions*: i, Et_3Al (1 M in hexanes, 2.0 equiv.), $Pd(PPh_3)_4$ (0.05 equiv), THF, 6 h, 92%; ii, CO (1 atm), $Pd(OAc)_2$ (0.1 equiv.), PPh_3 (0.2 equiv.), MeOH (3.0 equiv.), Et_3N (3.0 equiv.), DMF, 60 °C, 4 h, 72%; iii, $Bu_3SnCH{=}CH_2$ (2.0 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.), LiCl (3.0 equiv.), THF, heat, 3 h, 85%; iv, $(Me_3Sn)_2$ (2.0 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.), LiCl (3.0 equiv.), THF, heat, 3 h, 77%; v, $Me_3SiC{\equiv}CH$ (3.0 equiv.), $Pd(PPh_3)_4$ (0.1 equiv.), CuI (0.1 equiv.), Et_2NH–THF (2:1), 25 °C, 4 h, 84%; vi, $Bu_3SnCH_2CH{=}CH_2$ (2.0 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.), LiCl (3.0 equiv.), THF, heat, 4 h, 93%; vii, Me_3SiCH_2MgCl (3.0 equiv.), $Ni(acac)_2$ (0.05 equiv.), Et_2O, 25 °C, 1 h, 88%; viii, PhZnCl (2.0 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.), THF, 50 °C, 1 h, 87%

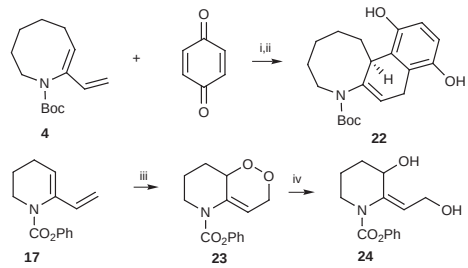
The synthesis of ketene aminal diphenylphosphates **1a**,**b** is accomplished from the eight-membered *N*-Boc or *N*-CO_2Ph protected lactams *via* their potassium enolates. These compounds proved quite stable at ambient temperatures and to silica gel flash chromatography, entering a variety of coupling reactions with appropriate partners under palladium(0) or nickel(0) catalyzed conditions, (Scheme 2). All of these reactions proceeded smoothly in good to excellent yields, furnishing a variety of products capable of further functionalization.

The generality and scope of the present technology was further illustrated by synthesizing ketene aminal phosphates of different ring sizes, as shown in Table 1. Two useful applications of the newly synthesized dienes[4] (Table 1) are shown in Scheme 3. Thus, diene **4**† enters smoothly into a Diels–Alder reaction with benzoquinone affording, after silica gel-induced tautomerization, hydroquinone **22**, while diene **17** reacted with singlet oxygen to afford endoperoxide **23**. The latter compound was reduced to diol **24** in 57% overall yield upon treatment with aluminium amalgam.

Table 1 Preparation and Stille coupling of lactam-derived ketene aminal phosphates

Entry	Phosphate[a]	Yield (%)	Coupling product[b]	Yield (%)
1	 **10**	93	 **16**	65
2	 **11**	95	 **17**	80
3	 **12a** R = Boc **b** R = CO_2Ph	91	 **18**	76
4	 **1a** R = Boc **b** R = CO_2Ph	96	 **4**	85
5	 **13**	41[c]	 **19**	94
6	 **14**	81	 **20**	81
7	 **15**	96	 **21**	73

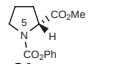
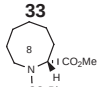
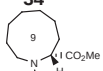
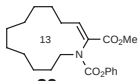
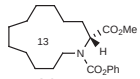
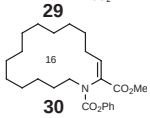
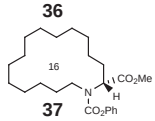
[a] Conditions: $(PhO)_2P(O)Cl$ (1.5 equiv.), KHMDS (1.2 equiv.), THF, −78 °C, 0.5 h; add base to lactam and phosphoryl chloride. [b] Coupling conditions as described in Scheme 2 for compound **1a.** [c] KHMDS (1.0 equiv.) was used.



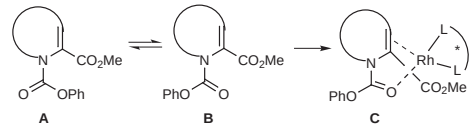
Scheme 3 *Reagents and conditions*: i, benzoquinone (5.0 equiv.), toluene, heat, 24 h; ii, silica gel, Et_2O, 12 h, 86% (2 steps); iii, O_2, tetraphenylporphine (trace), CCl_4, 500 W halogen lamp, 15 min, ; iv, Al-Hg (excess), THF–H_2O (10:1), 1.5 h, 57%

The chemistry of ketene aminal phosphates was explored further through their Pd-catalyzed carbonylation and subsequent asymmetric hydrogenation. Thus, a series of compounds arising from carbonylation of the ketene aminal phosphates were synthesized in good yields (Table 2). They were then subjected to asymmetric hydrogenation[6,7] in the presence of a catalytic amount of [Rh(COD)-(−)-(*R*,*R*)-(Et-DuPHOS)]OTf.[8] This afforded the corresponding cyclic amino acids in excellent yields and with high enantioselectivities except for the five- and six-membered rings, which resisted hydrogenation under standard conditions and gave low enantioselectivities at high pressures. Inspection of the NMR spectra of the compounds with larger ring sizes (7–16) revealed that the unsaturated esters exist as two rotamers, with rotamer **A** being

Table 2 Synthesis of cyclic dehydroamino acids from carbonylation of ketene aminal phosphates and subsequent asymmetric hydrogenation

Phosphate	Carbonylation[a]	Yield (%)	Hydrogenation[b]	Yield (%)	Ee (%)[c]
10	 **25**	70[d]	 **31**	84	0.4
11	 **26**	78	 **32**	95[e]	26.5
12b	 **27**	82	 **33**	96	94.8
1b	 **3**	72	 **34**	96	97.0
13	 **28**	79	 **35**	97	94.5
14	 **29**	89[d,f]	 **36**	96	91.3
15	 **30**	86[d,f]	 **37**	86	86.0

[a] Conditions: CO (1 atm), $Pd(OAc)_2$ (0.1 equiv.), PPh_3 (0.2 equiv.), MeOH (40 equiv.), Et_3N (2.0 equiv.), DMF, 60 °C, 3–6 h; [b] Conditions: H_2 (90 psi), [Rh(COD)-(−)-(*R*,*R*)- Et-DuPHOS)]OTf (0.06 equiv.), MeOH, room temp., 24 h. [c] Determined by HPLC on a Chiralcel OD using hexanes–Pr^{i}OH (7:1) as eluent (for compounds **31–33**) or an AD column using hexanes–Pr^{i}OH (97:3) as eluent (for compounds **34–37**). [d] (*R*)-(+)-BINAP (0.1 equiv.) was used instead of PPh_3 (see ref. 5). [e] Reaction performed under H_2 (400 psi) at 70 °C in EtOH. [f] Yield based on 77% conversion.



Scheme 4

the preferred one (Scheme 4). However, the five- and six-membered ring compounds **25** and **26** show the presence of only one rotamer, assumed to be rotamer **A**, in their NMR spectra. Through variable temperature NMR experiments, it was found that the rotamer **B** of **26** appears at around 70 °C. It is, however, rotamer **B** that enables the formation of the requisite chelation complex **C** which could result in asymmetric induction during hydrogenation.[6] This phenomenon can also explain the lack of reactivity of **25** and **26** under standard conditions.

The chemistry described herein demonstrates the potential of cyclic ketene aminal phosphates as substrates for the construction of a variety of *N*-heterocycles, including alkaloid structures and unnatural amino acids through transition metal catalyzed reactions. Multiple applications in synthesis are envisioned for this new synthetic technology.

We thank Professor K. B. Sharpless, Dr L. Gooβen, and Dr K. R. Dress for assistance with chiral HPLC and high pressure equipment. This work was financially supported by the National Institutes of Health, USA (G. M.) and The Skaggs Institute for Chemical Biology.

Notes and References

† *Synthetic procedure* for **4**: To a solution of *N*-CO_2Ph protected 2-azacyclooctanone (1.16 g, 4.7 mmol) and $(PhO)_2P(O)Cl$ (1.46 ml, 7.0 mmol) in THF (80 ml) at −78 °C was added KHMDS (0.5 M in toluene, 14.1 ml, 7.0 mmol). After being stirred at −78 °C for 30 min, the reaction mixture was treated with 1 M aq. NH_3 (80 ml) for 10 min. The organic phase was separated and the aqueous layer was extracted with Et_2O (3× 20 ml). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was subjected to flash column chromatography (silica gel, 1:1 Et_2O–hexanes containing 2% Et_3N) to give phosphate **1b** (2.18 g, 96%). A solution of **1a** (0.24 g, 0.52 mmol), anhydrous LiCl (66 mg, 1.57 mmol), tri-*n*-butyl(vinyl)tin (0.31 ml, 1.05 mmol) and $Pd(PPh_3)_4$ (53 mg, 0.046 mmol) in THF (20 ml) was heated at 70 °C under Ar for 3 h. The solution was then diluted with Et_2O and filtered through silica gel. The filtrate was concentrated and the residue was subjected to flash column chromatography (silica gel, 1:9 Et_2O–hexanes) to give diene **4** (105 mg, 85%).

1 For the use of lactam-derived enol triflates in carbon–carbon bond forming reactions, see: T. Okita and M. Isobe, *Synlett*, 1994, 589; T. Okita, and M. Isobe, *Tetrahedron*, 1995, **51**, 3737; T. Luker, H. Hiemstra and W. N. Speckamp, *Tetrahedron Lett.*, 1996, **37**, 8257; T. Luker, H. Hiemstra and W. N. Speckamp, *J. Org. Chem.*, 1997, **62**, 3592; T. Luker, H. Hiemstra and W. N. Speckamp, *J. Org. Chem.*, 1997, **62**, 8131.
2 For the use of lactone-derived ketene acetal phosphates, see: K. C. Nicolaou, G.-Q. Shi, J. L. Gunzner, P. Gärtner and Z. Yang, *J. Am. Chem. Soc.*, 1997, **119**, 5467.
3 The larger lactams were synthesized from the corresponding ketones *via* a Beckmann rearrangement, see: G. A. Olah and A. P. Fung, *Synthesis*, 1979, 537.
4 W. J. Scott and J. K. Stille, *J. Am. Chem. Soc.*, 1986, **108**, 3033.
5 BINAP has been previously used as a superior ligand to monodentate and other bidentate systems in aromatic amination; see: J. P. Wolfe, S. Wagaw and S. L. Buchwald, *J. Am. Chem. Soc.*, 1996, **118**, 7215.
6 For a catalytic hydrogenation review, see: R. Noyori, *Asymmetric Catalysis In Organic Synthesis*, Wiley-Interscience, New York, 1994, ch. 2.
7 To the best of our knowledge, there is only one example of a catalytic asymmetric hydrogenation of a cyclic dehydroamino acid derivative, see: C. J. Foti and D. L. Comins *J. Org. Chem.*, 1995, **60**, 2656.
8 M. J. Burk, M. F. Gross, T. Gregory, P. Harper, C. S. Kalberg, J. R. Lee and J. P. Martinez, *Pure Appl. Chem.*, 1996, **68**, 37.

Received in Corvallis, OR, USA, 2nd June 1998; 8/04198I