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Nitrogen Heterocycles via Palladium-Catalyzed Carbocyclization. Formal Synthesis of (+)-α-Allokainic Acid

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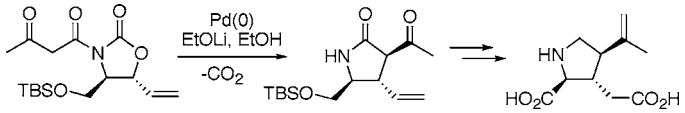
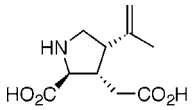
ABSTRACT

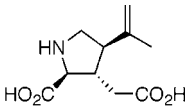


The Pd-catalyzed carbocyclization of ketoamides was investigated and found to be highly dependent on the phosphine ligand as well as the presence of coordinating counterions. Nitrogen heterocycles were formed without erosion of the stereochemical integrity. The utility of the lactam products was demonstrated by the formal synthesis of (+)-α-allokainic acid.

Over the last two decades, the kainoid family of glutamate analogues have become increasingly appealing targets for total synthesis.[1] This is a result of their biological activity as excitatory neurotransmitters in the central nervous system. Thus, numerous reports on the preparation of kainic acid (**1**)[2] and α-allokainic acid (**2**)[3] have appeared. In response to demand by biological researchers and a global deficiency of kainic acid,[4] new strategies for the synthesis of kainoids are still ardently being sought. Herein we report our approach utilizing a novel palladium-catalyzed carbocyclization.



1 kainic acid



2 allokainic acid

Recent work from our laboratory has illustrated the utility of 5-vinyloxazolidinones as useful precursors to dynamic π-allylpalladium complexes. Thus, when treated with Pd(0) catalysts, oxazolidinones **3** readily convert into oxazolines **4** with high levels of diastereoselectivity via rapidly isomerizing allyl−Pd intermediates (Scheme 1).[5,6] Integral to the success of the thermodynamic equilibration is the reversible nature of the cyclization reaction. We have demonstrated the efficacy of these chiral oxazolines for the synthesis of a variety of biologically relevant targets, including balanol,[7] lactacystin,[8] and sphingolipids.[9] We have also shown that the rapidly equilibrating π-allylpalladium complexes can be trapped with added imide-like nucleophiles to afford kineti-

(1) For reviews on kainoid chemistry, see: (a) Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149. (b) Maloney, M. G. *Nat. Prod. Rep.* **2002**, *19*, 597.

(2) For recent approaches, see: (a) Trost, B. M.; Rudd, M. T. *Org. Lett.* **2003**, *5*, 1467. (b) Greenwood, E. S.; Hitchcock, P. B.; Parson, P. J. *Tetrahedron* **2003**, *59*, 3307. (c) Anderson, J. C.; Whiting, M. *J. Org. Chem.* **2003**, *68*, 6160. (d) Clayden, J.; Knowles, F. E.; Menet, C. J. *Tetrahedron Lett.* **2003**, *44*, 3397. (e) Clayden, J.; Menet, C. J.; Mansfield, D. J. *Chem. Commun.* **2002**, 38. (f) Xia, Q.; Ganem, B. *Org. Lett.* **2001**, *3*, 485. (g) Nakagawa, H.; Sugahara, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 3181. (h) Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3194. (i) Chevliakov, M. V.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 11139. (j) Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *Chem. Commun.* **1999**, 245.

(3) For recent approaches, see: (a) Anada, M.; Sugimoto, T.; Watanabe, N.; Nakajima, M.; Hashimoto, S. *Heterocycles* **1999**, *50*, 969. (b) Chevliakov, M. V.; Montgomery, J. *Angew. Chem., Int. Ed.* **1998**, *37*, 3144. (c) Miyata, O.; Ozawa, Y.; Ninomiya, I.; Aoe, K.; Hiramatsu, H.; Naito, T. *Heterocycles* **1997**, *46*, 321. (d) Hanessian, S.; Ninkovic, S. *J. Org. Chem.* **1996**, *61*, 5418. (e) Ezquerra, J.; Escribano, A.; Rubio, A.; Remuinan, M. J.; Vaquero, J. J. *Tetrahedron Lett.* **1995**, *36*, 6149. (f) Agami, C.; Cases, M.; Couty, F. *J. Org. Chem.* **1994**, *59*, 7937.

(4) (a) Tremblay, J.-F. *Chem. Eng. News* **2000**, March 6, 131. (b) Tremblay, J.-F. *Chem. Eng. News* **2000**, *Jan 3*, 14.

(5) Cook, G. R.; Shanker, P. S. *Tetrahedron Lett.* **1998**, *39*, 3405.

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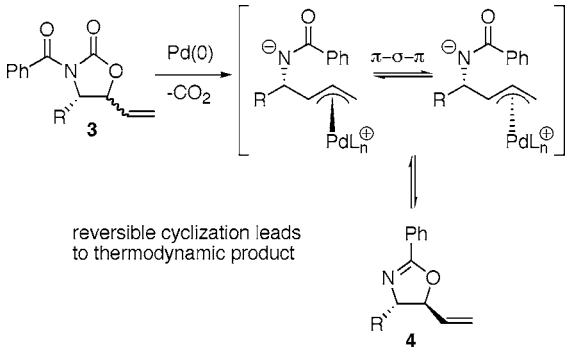
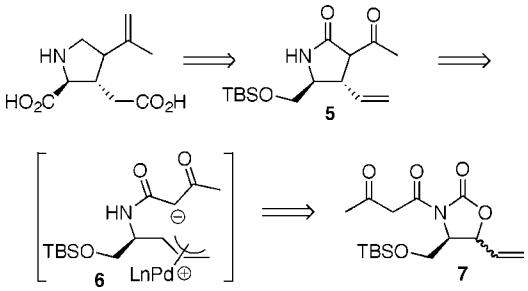
Scheme 1. Pd-Mediated Oxazoline Isomerization



cally controlled products with very high stereoselectivity.[10] Unfortunately, application of carbon-based nucleophiles such as malonates and β-diketones only afforded linear products. Thus, carbofunctionalization of the internal position was precluded. To circumvent this regiochemical problem, we envisioned that dicarbonyl derivatives tethered to the nitrogen as intramolecular nucleophiles would afford five-membered rings upon cyclization.[11] This would offer a facile route to chiral nitrogen heterocycles and provide a means for introduction of carbons on the internal position of the allyl complex.

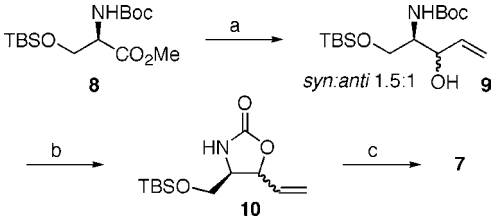
As a means to investigate the carbocyclization reaction, we conceived a route to the kainoid family of natural products (Scheme 2). The β-keto-*N*-acyloxazolidinone **7** was

Scheme 2. Retrosynthesis of Kainoids



expected to undergo Pd(0)-catalyzed ring opening and loss of carbon dioxide to give the intermediate **6**. Carbocyclization

Scheme 3. Synthesis of Oxazolidinone **7**[a]



[a] Reaction conditions: (a) (i) DIBALH, (ii) vinylmagnesium bromide, 79%. (b) NaH, THF, 93%. (c) 2,2,6-Trimethyl-1,3-dioxin-4-one, toluene, reflux, 96%.

would afford the highly functionalized nitrogen heterocycle **5**, which would be amenable to the synthesis of kainic acid.

The requisite oxazolidinone **7** was prepared from D-serine as illustrated in Scheme 3. The protected amino acid derivative **8** was treated with DIBALH followed by in situ treatment with vinylmagnesium bromide[12] to afford amino alcohol **9** as a 1.5:1 mixture of diastereomers. Treatment with NaH in THF resulted in cyclization onto the Boc carbonyl to provide oxazolidinone **10** in high yield, also as a mixture of diastereomers. Heating **10** in toluene with the acetone adduct of diketene[13] yielded the β-ketoacyl-derived oxazolidinone in 96% yield (trans:cis = 1.5:1).

The Pd-catalyzed cyclization envisioned in Scheme 2 would most likely occur in a nonreversible manner. Thus, to utilize **7** as a diastereomeric mixture to avoid unnecessary purification and afford a selective product, cyclization would have to be slower than isomerization of the Pd−allyl complex. Furthermore, cyclization of one diastereomeric intermediate should be kinetically faster than the other. To examine this, we carried out our initial investigation of the process on the diastereomeric mixture of **7**. Treatment of **7** under our previously reported conditions with just a Pd(0) catalyst[7] failed to yield clean conversion to products. However, as detailed in Scheme 4, deprotonation of the ketoamide in THF with *n*-BuLi followed by treatment with a Pd(0) catalyst afforded the oxazoline **11** in good yield. We were pleased to observe that the diastereomer ratio of the product favored the trans isomer almost exclusively. Although the C-cyclization was not obtained, the successful isomerization of **7** was encouraging. We found that utilizing LiOEt as the base in ethanol afforded a quantitative yield of the lactams **12** and **13**. Unfortunately, the diastereomers were obtained in equal amounts.[14]

(6) For similar examples of diastereoselective Pd-catalyzed isomerization reactions, see: (a) Ibuka, T.; Mimura, N.; Aoyama, H.; Akaji, M.; Ohno, H.; Miwa, Y.; Taga, T.; Nakai, K.; Tamamura, H.; Fujii, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 999. (b) Ibuka, T.; Mimura, N.; Ohno, H.; Nakai, K.; Akaji, M.; Habashita, H.; Tamamura, H.; Miwa, Y.; Taga, T.; Fujii, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 2982. (c) Ohno, H.; Toda, A.; Fujii, N.; Miwa, Y.; Taga, T.; Yamaoka, T.; Osawa, E.; Ibuka, T. *Tetrahedron Lett.* **1999**, *40*, 1331. (d) Ishii, K.; Ohno, H.; Takemoto, Y.; Osawa, E.; Yamaoka, Y.; Fujii, N.; Ibuka, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2155. (e) Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Osawa, E.; Yamaoka, Y.; Fujii, N.; Ibuka, T. *J. Org. Chem.* **1999**, *64*, 2992. (f) Lee, K.-Y.; Kim, Y.-H.; Park, M.-S.; Ham, W.-H. *Tetrahedron Lett.* **1998**, *39*, 8129. (g) Lee, K.-Y.; Kim, Y.-H.; Park, M.-S.; Oh, C.-Y.; Ham, W.-H. *J. Org. Chem.* **1999**, *64*, 9450. (h) Lee, K.-Y.; Kim, Y.-H.; Oh, C.-Y.; Ham, W.-H. *Org. Lett.* **2000**, *2*, 4041.

(7) Cook, G. R.; Shanker, P. S.; Peterson, S. L. *Org. Lett.* **1999**, *1*, 615.

(8) Cook, G. R.; Shanker, P. S. *J. Org. Chem.* **2001**, *66*, 6818.

(9) Cook, G. R.; Pararajasingham, K. *Tetrahedron Lett.* **2002**, *43*, 9027.

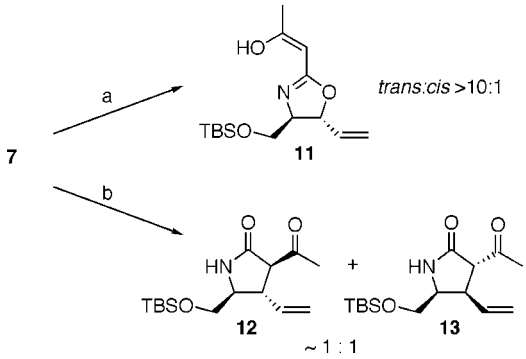
(10) (a) Cook, G. R.; Yu, H.; Sankaranarayanan, S.; Shanker, P. S. *J. Am. Chem. Soc.* **2003**, *125*, 5115. (b) Cook, G. R.; Shanker, P. S.; Pararajasingham, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 110.

(11) For examples of Pd-catalyzed oxazolidinone ring opening/carbonylation and endo cyclization, see: (a) Knight, J. G.; Ainge, S. W.; Harm, A. M.; Harwood, S. J.; Maughan, H. I.; Armour, D. R.; Hollinshead, D. M.; Jaxa-Chamied, A. A. *J. Am. Chem. Soc.* **2000**, *122*, 2944. (b) Knight, J. G.; Tchabanenko, K. *Tetrahedron* **2002**, *58*, 6659. (c) Knight, J. G.; Tchabanenko, K. *Tetrahedron* **2003**, *59*, 281. (d) Anderson, T. F.; Knight, J. G.; Tchabanenko, K. *Tetrahedron Lett.* **2003**, *44*, 757.

(12) (a) Angle, S. R.; Henry, R. H. *J. Org. Chem.* **1997**, *62*, 8549. (b) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4370.

(13) Doyle, M. P.; Dorow, R. L.; Terpstra, J. W.; Rodenhouse, R. A. *J. Org. Chem.* **1985**, *50*, 1663.

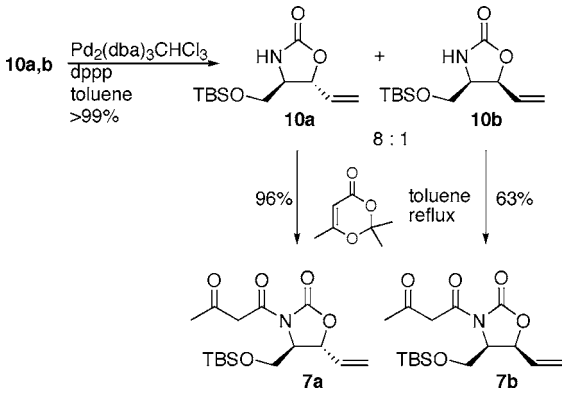
Scheme 4. Pd-Catalyzed Cyclization of **7**[a]



[a] Reaction conditions: (a) *n*-BuLi, THF followed by $[C_3H_5PdCl]_2$, dppp, 83% or $Pd_2(dba)_3CHCl_3$, dppp, bis(trimethylsilyl)acetamide, THF, 72%. (b) LiOEt, EtOH followed by $Pd_2(dba)_3CHCl_3$, dppp, 99%.

The low diastereoselectivity in the Pd-catalyzed conversion of **7** to **12** and **13** could arise either by rapid cyclization prior to Pd−allyl isomerization or by rapid isomerization followed by nonselective cyclization. To delineate the origin of the poor selectivity, we needed to examine the reaction on the pure diastereomers of **7**. Furthermore, to employ the method in an efficient synthesis of kainoids in which we utilize a pure diastereomer, we required a more selective route to **7a** (Scheme 5). Thus, we explored the Pd-catalyzed isomeriza-

Scheme 5. Pd-Catalyzed Isomerization of **10**

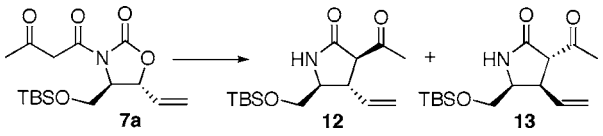


tion of the unacylated oxazolidinone **10**.[15] We were gratified to find that treatment of **10a**,**b** with $Pd_2dba_3CHCl_3$ in toluene successfully isomerized the nearly equal mixture of diastereomers to a 8:1 mixture of **10a** and **10b** in quantitative yield. These were readily separated by silica gel chromatography. Ketoamides **7a** and **7b** were prepared in 96 and 63% yields, respectively, on heating with the 1,3-dioxin-4-one.

(14) The lack of any isomerization under basic conditions established the trans relationship between the ketone and vinyl substituents in both **12** and **13**. The stereochemistry was determined by NOE between the vinyl protons and the siloxymethylene in **13**.

(15) Pd-catalyzed isomerization of similar oxazolidinones has been previously observed. See ref 11a.

Table 1. Pd-Catalyzed Isomerization of **7a**[a]



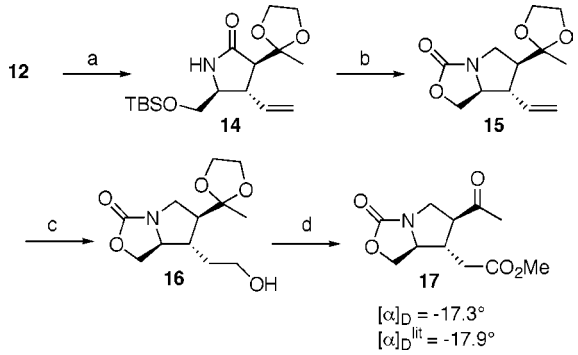
entry	catalyst[b]	ligand	additive	yield %	**12**:**13**
1	A	dppp		92	4:1
2	A	dppp	NaOAc (0.2 equiv)	82	7:1
3	A	dppp	NaOAc (0.4 equiv)	87	12:1
4	A	dppp	NaOAc (1.0 equiv)	92	10:1
5	B	dppp		96	10:1
6	A	Ph_3P		0[c]	
7	B	Ph_3P		0	
8	A	dppe		96	1:3
9	B	dppe		94	1:3
10	A	dppf		55	12:1
11	B	dppf		64	10:1
12	A	dppb		89	10:1
13	B	dppb		92	30:1
14[d]	B	dppb		93	1:40

[a] Unless otherwise indicated, the substrate was deprotonated with LiOEt in EtOH, and then the catalyst (3 mol %), ligand, (12 mol %), and additive, if present, were mixed together with the substrate at room temperature and allowed to react for 16−24 h. [b] Catalyst A = $Pd_2(dba)_3CHCl_3$; B = $[C_3H_5PdCl]_2$. [c] No reaction up to 70 °C. [d] Substrate **7b** was employed.

With pure **7a** in hand, the Pd-catalyzed C-cyclization was investigated in detail (Table 1). When $Pd_2dba_3CHCl_3$ and dppp were employed as the catalyst, oxazolidinone opening and carbocyclization was efficient (entry 1); however, a modest 4:1 ratio of **12** and **13** were obtained. This suggested that Pd−allyl isomerization was occurring to some extent prior to cyclization. The addition of sodium acetate (entries 2−4) or the use of the chloride-containing catalyst, $[C_3H_5PdCl]_2$, improved the selectivity significantly. Presumably, the additive (or chloride) coordinates to the metal in the Pd−allyl, which precludes a cationic metal complex.[16] This could possibly act to retard the rate of allyl isomerization. We also explored other ligands in this process. No reaction was observed when monodentate Ph_3P was used even when heated to 70 °C. The bidentate ligand with a smaller bite angle, dppe, resulted in an inversion of the diastereoselectivity to give a 1:3 ratio of **12** and **13**. Bisphosphines with longer linkers, dppf and dppb, allowed improved selectivity of **12** over **13** (10:1). We obtained optimal results when dppb was employed with the chloride-containing catalyst (entry 13). Thus, essentially complete control (30:1) of the product stereochemistry was achieved. To confirm that this was the result of kinetic cyclization prior to allyl isomerization, these optimal conditions were applied to the other diastereomer, **7b** (entry 14). This resulted in nearly exclusive formation of **13**. The reversal of product stereochemistry suggests very

(16) We have previously reported on the influence of chloride ion in the Pd-catalyzed allylic substitution. Cook, G. R.; Shanker, P. S. *Tetrahedron Lett.* **1998**, *39*, 4991.

Scheme 6. Formal Synthesis of Allokainic Acid[a]



[a] Reaction conditions: (a) Ethylene glycol, PPTS, toluene, 43%. (b) (i) $LiAlH_4$, THF; (ii) CH_3OCOCl, NaOH; (iii) NaH, THF; 64% overall. (c) (i) Catecholborane, $RhCl(Ph_3P)_3$, THF; (ii) NaOH, H_2O_2; 90%. (d) (i) Jones reagent; (ii) $TMSCHN_2$, MeOH; (iii) *p*-TsOH, acetone; 57% overall.

strongly that the ligand and halide present are acting to impede allyl isomerization.

Having established the feasibility of the Pd-catalyzed carbocyclization for the selective preparation of lactams, we next set out to complete the formal synthesis of (+)-α-allokainic acid (Scheme 6). The ketone **12** was protected as the acetal in modest yield. Reaction of **14** with $LiAlH_4$ resulted in reduction of the lactam to the nitrogen heterocycle concomitant with deprotection of the primary alcohol. This was protected as the oxazolidinone by acylation with methyl chloroformate to give **15**. Rhodium-catalyzed hydroboration and oxidation afforded the alcohol **16**, which was subsequently oxidized to the carboxylic acid. Esterification with diazomethane and deprotection of the ketone allowed us to access **17**, an advanced intermediate in the previously reported synthesis of allokainic acid.[3d]

In summary, we have investigated the Pd-catalyzed carbocyclization of ketoamides to afford nitrogen heterocycles. The reaction was found to be highly dependent on the phosphine ligand as well as the presence of coordinating counterions. While allyl isomerization was not effective for equilibration prior to carbocyclization in these substrates, successful isomerization of the unacylated oxazolidinnones gave good diastereoselectivity. The Pd-catalyzed carbocyclization was accomplished without erosion of the stereochemical integrity. We have demonstrated the utility of these lactams via the formal synthesis of (+)-α-allokainic acid.

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Supporting Information Available: Experimental procedures and characterization data for compounds **7** and **10**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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