Annulation Reactions

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Palladium-Mediated Annulation of Vinyl Aziridines with Michael Acceptors: Stereocontrolled Synthesis of Substituted Pyrrolidines and Its Application in a Formal Synthesis of (−)-α-Kainic Acid**

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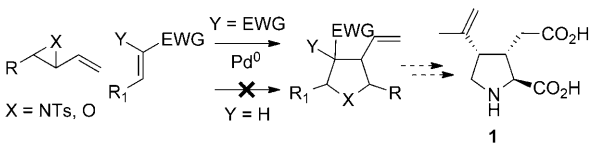
Dedicated to Professor Yun-Shan Lin

The rapid increase in molecular complexity from simple precursors is a major goal in organic synthesis.[1] Within this context, the palladium-mediated annulation reaction of Michael acceptors with vinyl epoxides,[2] and aziridines,[3] offers significant potential for the synthesis of heterocycles, but to date, this reaction has not been well developed (Scheme 1).[4] As we had established a simple, asymmetric

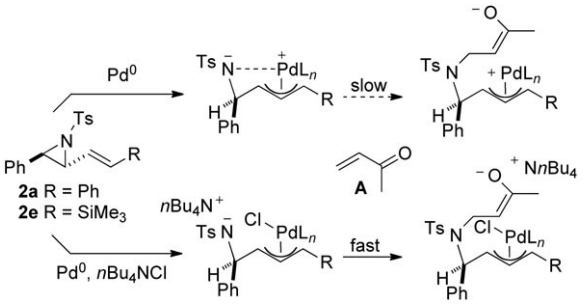


Scheme 1. Palladium-catalyzed annulation reaction of vinyl epoxides/aziridines with Michael acceptors. EWG = electron-withdrawing group, Ts = 4-toluenesulfonyl.

route to vinyl epoxides[5] and vinyl aziridines[6] via chiral sulfur ylides,[7] we were keen to develop their potential in synthesis further.[8]

It had been reported that palladium-catalyzed reactions of vinyl epoxides and aziridines with doubly activated Michael acceptors gave tetrahydrofurans and pyrrolidines in good yield but usually with poor stereocontrol.[2,3] However, related reactions with singly activated Michael acceptors were not effective.[2a,3b] Nevertheless, we recognized that if we could find a way of coercing vinyl aziridines to react with singly activated enones/acrylates, and we were able to control stereochemistry in the annulation process, then we could potentially utilize this methodology in synthesis. Herein, we describe our success in simultaneously meeting these two significant challenges and also describe its application in a formal synthesis of (−)-α-kainic acid **1**.

Our initial efforts at promoting reaction between vinyl aziridine **2a** and methyl vinyl ketone (MVK, **A**) using $[Pd_2(dba)_3{\cdot}CHCl_3]$, $(p\text{-}FC_6H_5)_3P$ in THF (conditions employed by Yamamoto[3a]), however, were fruitless—we only observed decomposition. Using trimethylsilyl-substituted *trans* vinyl aziridine **2e**, we now observed isomerization to a mixture of *trans*/*cis* aziridines (1:20).[9] With this substrate, clearly the Pd was performing its role in generating the π-allyl palladium complex as this resulted in isomerization of the vinyl aziridine. However, the amide anion that was generated did not react with the enone. This result reinforced the observations by Yamamoto and Knight[2,3] that doubly activated Michael acceptors were required to capture the relatively unreactive amide anion. We reasoned that ion pairing of the amide anion with the cationic Pd complex might compromise its reactivity, and that increased nucleophilicity should therefore be possible with an anionic Pd complex instead (Scheme 2).



Scheme 2. Possible origin of low reactivity of amide towards MVK.

We therefore added nBu_4NCl[10] and were immediately rewarded with success.[11] A 1:1 diastereomeric mixture of pyrrolidines was obtained albeit in low yield (Table 1, entry 1). Increasing the amount of MVK resulted in increased yield and diastereoselectivity (Table 1, entry 2). Further optimization of reaction conditions focused on variation of

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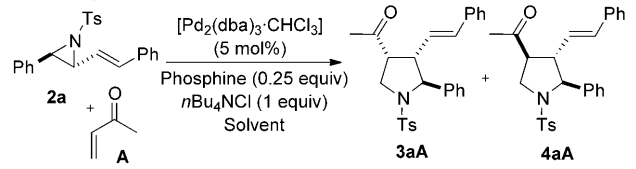
Table 1: Optimization of the annulation reaction.[a]

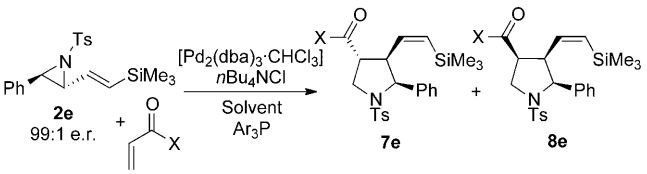


Entry	Phosphine	Solvent	Yield [%][b]	d.r. (**3aA**/**4aA**)
1[c]	$(4\text{-}FC_6H_4)_3P$	THF	21	50:50
2	$(4\text{-}FC_6H_4)_3P$	THF	38	68:32
3	Ph_3P	THF	36	65:35
4	$(2\text{-furyl})_3P$	THF	56	69:31
5	$(o\text{-tolyl})_3P$	THF	38	83:17
6	$(o\text{-tolyl})_3P$	Et_2O	60	92:8
7	$(o\text{-tolyl})_3P$	Pentane	60	93:7
8	$(o\text{-tolyl})_3P$	Pent/Et_2O[d]	65	93:7
9	$(o\text{-tolyl})_3P$	Pent/TBME[d]	66	93:7

[a] All reactions conducted at 0.1 M, 20 °C, with 10 equivalents of MVK. [b] Yield of isolated product. [c] 2 equivalents of MVK was used. [d] 3:1 mixture of solvents was used. dba = *trans*,*trans*-dibenzylideneacetone, Pent = pentane, TBME = *t*BuOMe, THF = tetrahydrofuran.

the phosphine and solvent and representative results are summarized in Table 1. Of the phosphine reagents examined (Table 1, entries 2–5), the most sterically hindered, $(o\text{-tolyl})_3P$, led to the highest diastereoselectivity but still only with moderate yield (Table 1, entry 5). Further improvements in diastereoselectivity and yield were achieved using nonpolar solvents, for example, pentane, diethyl ether, or diethyl ether/pentane mixtures (Table 1, entries 6–9). Resubjection of the pyrrolidine products to the reaction conditions did not change the diastereomeric ratio indicating that the reactions were under kinetic control.[12]

Having found conditions that gave workable yields and high diastereoselectivity in this novel annulation reaction, we briefly explored alternative aziridines and Michael acceptors (Table 2 and Scheme 3). The aziridines were easily prepared in high e.r. using our sulfur ylide methodology[5c] (e.g. as illustrated in Scheme 5) and the e.r. was maintained in the



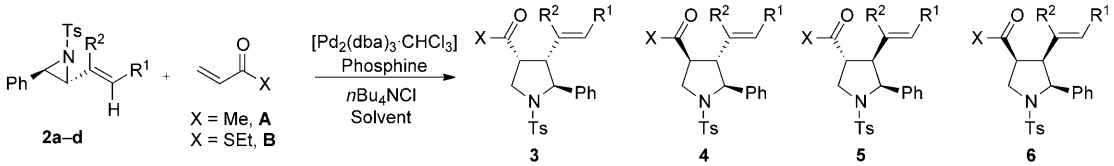
Scheme 3. Annulation of aziridine **2e** with MVK and ethyl thioacrylate.

pyrrolidine products. Alternative aryl groups in the terminal position of the vinyl aziridine **2b** could be used, albeit with decreased diastereoselectivity (Table 2, entry 2).[13] The parent vinyl aziridine **2c** was also a suitable substrate, but this time, the 2,3-*cis*-3,4-*trans*-substituted pyrrolidine **5cA** was the major diastereomer (Table 2, entry 3). The α-methyl vinyl aziridine **2d** was also effective in this process, furnishing 2,3-*trans*-3,4-*trans*-substituted pyrrolidine **4dA**, but with low diastereoselectivity (Table 2, entry 4). Investigation of alternative Michael acceptors revealed that although ethyl acrylate was unreactive towards the aziridines, ethyl thioacrylate[14] (**B**) was effective (Table 2, entries 5 and 6), and gave the pyrrolidines **3aB** and **5cB** with moderate diastereoselectivity and good yield.

The trimethylsilyl-substituted vinyl aziridine **2e** could also be employed in the annulation reaction with MVK but, surprisingly, the 2,3-*cis*-3,4-*trans* pyrrolidine bearing a *Z* olefin (**7eA**; Scheme 3) was now the major diastereomer formed—exactly opposite to that obtained from the phenyl-substituted aziridine **2a** (2,3-*trans*-3,4-*cis* bearing an *E* olefin was the major diastereomer; Table 2, entry 1). A further surprise emerged with ethyl thioacrylate (**B**), which gave rise to the all-*cis* isomer **8eB** as the major diastereomer. The relative configuration of the major diastereomers **3aA**, **7eA**, and **8eB** were determined by X-ray crystal structure analysis (see the Supporting Information).[15]

The stereoselectivity observed can be rationalized by considering the transition states involved in the final ring closure of the enolate onto the π-allyl palladium complex

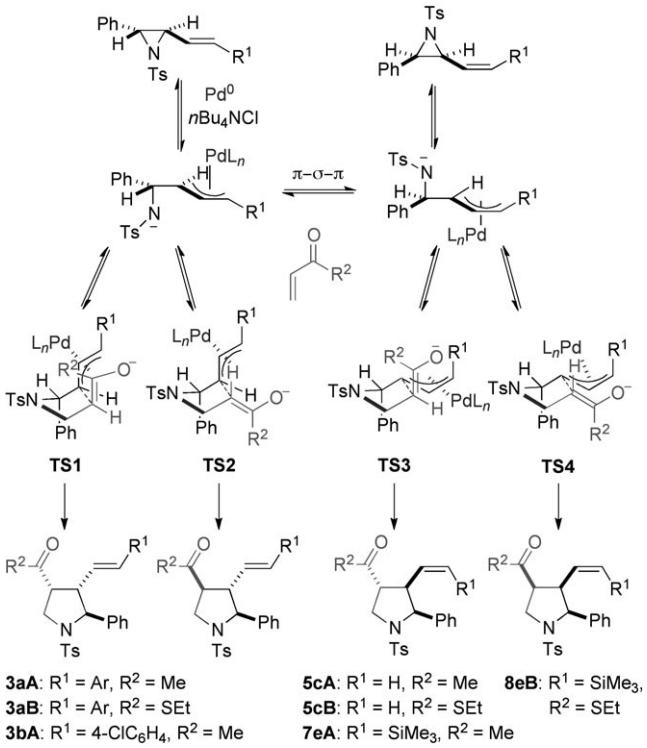
Table 2: Annulation of aziridines with Michael acceptors.[a]



Entry	**2**	Aziridine R^1	R^2	e.r.	Acceptor	Phosphine	Solvent	Product type (d.r) **3**	**4**	**5**	**6**	Yield [%][b]
1	**2a**	Ph	H	99:1	**A**	$(o\text{-tolyl})_3P$	Pent/TBME[c]	93	7	–	–	66
2	**2b**	$4\text{-}ClC_6H_4$	H	99:1	**A**	$(o\text{-tolyl})_3P$	Pentane	80	20	–	–	60
3	**2c**	H	H	94:6	**A**	$(o\text{-tolyl})_3P$	Pentane	–	–	80	20	52
4	**2d**	H	Me	99:1	**A**	$(4\text{-}FC_6H_4)_3P$	Et_2O	14	58	28	–	57
5	**2a**	Ph	H	99:1	**B**[d]	$(2\text{-furyl})_3P$	Pent/TBME[c]	75	25	–	–	50
6	**2c**	H	H	94:6	**B**[d]	$(2\text{-furyl})_3P$	Et_2O	–	–	66	33	59

[a] All reactions conducted at 0.1 M, 20 °C, with 5 mol% of $[Pd_2(dba)_3\cdot CHCl_3]$, 0.25 equivalents of phosphine, 1 equivalents of nBu_4NCl and 10 equivalents of MVK. [b] Total yield of isolated products. [c] 3:1 mixture of solvents was used. [d] 5 equivalents of ethyl thioacrylate was used.

(Scheme 4). In the four transition states proposed, the phenyl group is positioned in a pseudoaxial position to minimize steric interactions with the PdL_n moiety, as previously proposed in related systems.[16] In the case of aryl-substituted

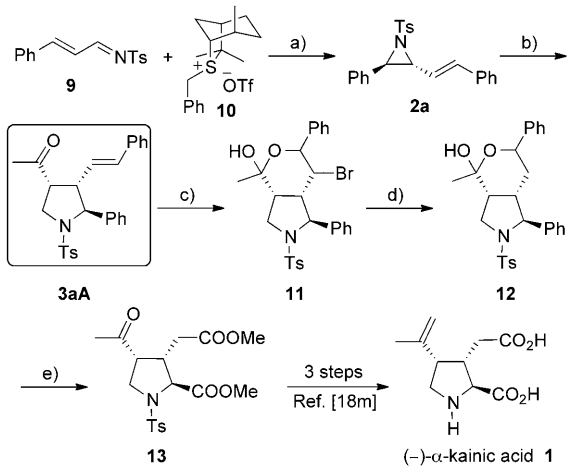


Scheme 4. Rationalization of stereochemical outcome of annulation reactions.

vinyl aziridines, the *E* π-allyl palladium complexes are favored, thus leading to **TS1** or **TS2**. Of the two transition states, **TS1** may benefit from attractive interactions between the electron-rich π system of the enolate and the electron-poor π system of the π-allyl Pd complex, thus leading to the major products **3aA**, **3bA**, and **3aB**. In the case of terminal vinyl aziridine **2c** (R^1, $R^2 = H$), all transition states are accessible but **TS3** suffers from the least steric hindrance and is favored leading to **5cA** and **5cB**. An unusual situation arises for the silyl-substituted vinyl aziridine **2e** ($R^1 = SiMe_3$), where now it seems that both *E* and *Z* π-allyl palladium complexes are equally accessible, perhaps as a result of the longer C–Si bond length.[17] With MVK, **TS3** is favored as it suffers the least steric hindrance, thus leading to **7eA**. Whereas with the thiol ester, an attractive interaction between the soft S atom and the π-allyl palladium complex may now favor **TS4**, thus leading to **8eB**. Alternatively, favorable interactions between the anionic oxygen atom of the enolate and the silyl group may also be present, thus promoting **TS3** and **TS4**.

The stereoselective formation of densely functionalized pyrrolidines **3aA**, **3aB**, **5cA**, **7eA**, or **8eB**—depending on the aziridine and Michael acceptor employed—provides a powerful synthetic method for synthesis. This is exemplified in the formal synthesis of the natural product, (−)-α-kainic acid. Kainic acid has been a popular target in synthesis,[18,19] not only because of its structure, but also because of its unique biological properties, as it is widely used as a tool in pharmacology for the investigation of a variety of neurological disorders.[20] However, a shortage of the natural material through commercial extraction[21] has led to a significant impediment to these studies, therefore fuelling a real need for a practical asymmetric synthesis.

Our synthesis of (−)-α-kainic acid (Scheme 5) began with the enantio- and diastereoselective aziridination of imine **9** using our chiral sulfur ylide methodology.[5c] Thus, treatment



Scheme 5. Reagents and conditions: a) $NaHCO_3$, CH_3CN, RT, 85%, 99% *ee*; b) $[Pd_2(dba)_3{\cdot}CHCl_3]$, nBu_4NCl, P(*o*-tolyl)$_3$, pentane, 62%, 10:1 d.r; c) NBS, H_2O, acetone, RT, 95%; d) nBu_3SnH, ACCN, benzene, reflux, 90%. e) $NaIO_4/H_5IO_6$, $RuCl_3$, $H_2O/CCl_4/CH_3CN$ (2:1:1); then $TMSCHN_2$, MeOH, toluene, RT, 37%. ACCN = 1,1′-azobis(cyclohexanecarbonitrile). NBS = *N*-bromosuccinimide, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

of sulfonium salt **10** with imine **9** gave the vinyl aziridine **2a** in 85% yield and 99% *ee* (step a). Palladium-catalyzed annulation with MVK furnished pyrrolidine (+)-**3aA** in good yield and high diastereoselectivity, and a single diastereoisomer was obtained after recrystallization (step b). Conversion of the styryl group into a carboxylic ester was achieved through halohydrin formation (step c),[22] radical debromination (step d),[23] $RuCl_3/H_5IO_6/NaIO_4$ oxidation,[24] and esterification (step e). The last steps also converted the 2-phenyl group into a carboxylic ester. Although the simultaneous oxidative cleavage of both the styryl and phenyl groups was rather low yielding (step e), the high regioselectivity and brevity in the conversion of **3aA** into **13** is noteworthy. Diester **13** has been converted into (−)-α-kainic acid by Scott and Lautens in three steps involving olefination, ester hydrolysis, and removal of protecting groups.[18m] As diester **13** was identical in all respects to Lautens' diester, a formal synthesis of (−)-α-kainic acid **1** has been completed. Diester **13** was obtained in a total of only six synthetic steps from cinnamaldehyde with high diastereo- and essentially complete enantiocontrol.

In conclusion, we have described novel methodology which converts vinyl aziridines into pyrrolidines with good

diastereoselectivity to furnish 2,3-*trans*-3,4-*cis*, or 2,3-*cis*-3,4-*trans* or the all-*cis* isomer—depending on the starting materials employed. Because vinyl aziridines are readily available with high enantiomeric purity from simple precursors using sulfur ylides, this combined methodology shows significant potential. The synthetic utility of the methodology has been demonstrated in one of the shortest (formal) syntheses of (−)-α-kainic acid to date.

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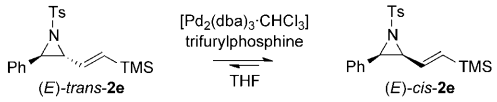
[9] Treatment of (*E*)-*trans* vinyl aziridine **2e** with $[Pd_2(dba)_3{\cdot}CHCl_3]$ and trifurylphosphine in THF resulted in rapid isomerization to a 1:20 ratio of (*E*)-*trans*-**2e**/(*E*)-*cis*-**2e** aziridines. It has been



established that *cis*-*N*-Ts aziridines are more stable than the *trans* isomers. For details, see: a) T. Ibuka, N. Mimura, H. Aoyama, M. Akaji, H. Ohno, Y. Miwa, T. Taga, K. Nakai, H. Tamamura, N. Fujii, Y. Yamamoto, *J. Org. Chem.* **1997**, *62*, 999–1015; b) T. Ibuka, N. Mimura, H. Ohno, K. Nakai, M. Akaji, H. Habashita, H. Tamamura, Y. Miwa, T. Taga, N. Fujii, Y. Yamamoto, *J. Org. Chem.* **1997**, *62*, 2982–2991. In our case, isomerization requires an S_N2 reaction of a palladium species on the cationic π-allyl palladium complex. Such processes have been reported in related systems: c) J. E. Bäckvall, K. L. Granberg, A. Heumann, *Isr. J. Chem.* **1991**, *31*, 17–24; d) K. L. Granberg, J. E. Bäckvall, *J. Am. Chem. Soc.* **1992**, *114*, 6858–6863. In the presence of nBu_4NCl, isomerization to a 35:65 ratio of (*E*)-*trans*-**2e**/(*Z*)-*cis*-**2e** isomers occurred. Evidently, Cl^- reduces the rate of the S_N2 reaction of a palladium species on the neutral π-allyl palladium complex and only π–σ–π isomerization occurred instead. See: e) A. Jutand, *Appl. Organomet. Chem.* **2004**, *18*, 574–582; f) B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **1999**, *121*, 4545–4554. For full details of the isomerization studies, see the Supporting Information.

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[11] nBu_4NOAc, nBu_4NF, KCl, LiCl, and $ZnCl_2$ were also tested but found to be ineffective.

[12] Resubjection of a 93:7 mixture of **3aA**/**4aA** to the standard reaction conditions for 14 hours resulted in a final ratio of 96:4. Resubjection of a 24:76 mixture of **3aA**/**4aA** to the standard reaction conditions resulted in a final ratio of 23:77, even after extended reaction time (48 h). These results indicate that the reaction is essentially under kinetic control. We thank one of the

reviewers for encouraging us to test whether the reaction was under kinetic or thermodynamic control.

[13] Electron-rich aryl groups (e.g. *p*-$MeOC_6H_4$) were not suitable substrates as the vinyl aziridine compounds were rather unstable and were difficult to isolate in pure form.

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[15] CCDC 826528 (**3aA**), 826526 (**7eA**), and 826527 (**8eB**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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