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Phosphine-Catalyzed Heine Reaction

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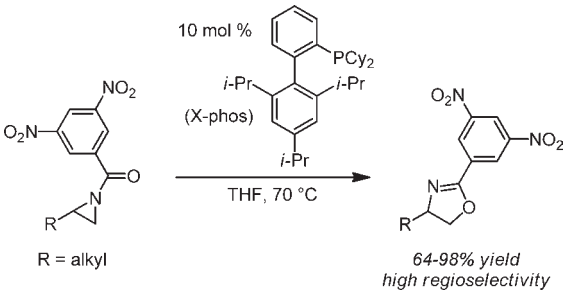
ABSTRACT



Aziridines are important synthetic intermediates which readily undergo ring-opening reactions. It is demonstrated that electron-rich phosphines are efficient catalysts for the regioselective rearrangement of *N*-acylaziridines to oxazolines. The reactions occur in excellent yield under neutral conditions. Evidence is provided for an addition/elimination mechanism by generation of a phosphonium intermediate. Similar intermediates may be useful for the development of alternate aziridine ring-opening processes and stereoselective synthesis with enantiopure phosphines.

Aziridines have a rich history as versatile intermediates in organic synthesis.[1] The strained three-membered ring is highly activated for ring-opening nucleophilic addition by a range of nucleophiles.[2] Upon functionalization by ring-opening, advanced amine synthons are produced for applications in the fine chemical industry and bioactive molecule synthesis. The aziridine structure is often chiral offering opportunities to access enantiopure intermediates. Nucleophilic derivatization is also proposed to play an important role in the biological activity of aziridine-containing natural products.

The aziridine ring-opening reaction with nucleophiles primarily serves to introduce new functionality; however, the potential of employing nucleophiles to catalyze aziridine transformations is well-known. Heine originally reported a series of intramolecular aziridine rearrangements that take place in the presence of nucleophilic inorganic salts, such as sodium iodide.[3] Specifically, the rearrangement of *N*-acylaziridines to oxazolines is known to occur under a range of Lewis acid[4] and Lewis base-catalyzed[5] conditions. Recently, organic catalysts, such as amines,[6] *N*-heterocyclic carbenes,[7] and phosphines,[8] have been investigated for intermolecular aziridine opening reactions with a variety of nucleophiles. However, phosphines have not been

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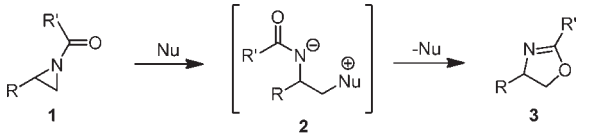
reported as catalysts for the rearrangement of aziridines to oxazolines.

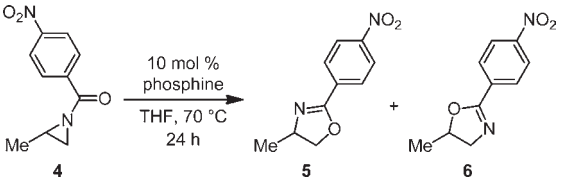
Scheme 1. Nucleophile-Catalyzed Rearrangement of Aziridines



We considered that phosphines may be active catalysts for the intramolecular rearrangement of aziridines by the mechanism outlined in Scheme 1. Nucleophile attack on the least hindered carbon of aziridine **1** should result in ring expansion by cyclization on the amide oxygen forming oxazoline **3**. If successful, the proposed intermediate (**2**) might be engineered to furnish a range of interesting heterocycles by modifying the nature of the aziridine protecting group. If phosphines could be designed to operate via this addition/elimination mechanism, we envisioned the development of novel asymmetric reactions employing enantioenriched phosphines. Herein, we describe the application of nucleophilic phosphine catalysis to the rearrangement of *N*-acylaziridines, also recognized as the Heine reaction.[9]

Identification of an adequate phosphine catalyst began with conversion of aziridine **4**, activated for nucleophilic ring openning, to a mixture of oxazolines **5** and **6** (Table 1). Phosphine catalysts were chosen to represent varying degrees of Lewis basicity and steric encumberance around the phosphorus atom.[10] Catalysts were screened at 70 °C in THF to minimize thermal aziridine decomposition.[11] Yield and regioselectivity trends based on phosphine structure quickly emerged. When **4** was heated in the presence of 10 mol % of PPh_3, only unchanged starting material was observed by ^{1}H NMR after 24 h (entry 1). While a less basic phosphite led to the same result (entry 2), a slight increase in basicity resulted in a dramatic enhancement in yield (entry 3). For the first time a phosphine-catalyzed rearrangement of aziridines to oxazolines had been realized. A further increase in phosphine basicity by employing tricyclohexylphosphine (PCy_3) was not tolerated (entry 4). Two tethered diphosphines with similar basicity to $PCyPh_2$ were investigated but, for unknown reasons, failed to give any rearrangement product (entries 5–6).

Table 1. Identification of Phosphine Catalysts for the Rearrangement of Aziridine **4**[a]



entry	catalyst	yield (%)[b]	**5:6**
1	PPh_3	0	—
2	$P(OPh)_3$	0	—
3	$PCyPh_2$[c]	88	10:1
4	PCy_3[c]	11	1.5:1
5	dppe[c]	0	—
6	dppb[c]	0	—
7	**7**	68	12:1
8	**8**	7	1.3:1
9	**9**	8	>20:1
10	**10**	85	11:1
11	**11**	35	>20:1

[a] Conditions: **4** (0.1 mmol), catalyst (0.01 mmol), THF (0.2 M), 70 °C, 24 h. [b] Yield determined by ^{1}H NMR of the crude reaction mixture with 1,3,5-trimethoxybenzene as internal standard. [c] Cy = cyclohexyl, dppe = bis(diphenylphosphino)ethane, dppb = bis(diphenylphosphino)butane.

Experiments to better understand the catalyst structural effects were continued with a series of phosphines developed by Buchwald and co-workers[12] for transition metal catalysis (Figure 1). The basic, sterically congested phosphines, which are generally air-stable,[13] were utilized in the rearrangement (Table 1, entries 7–11). All exhibited some reactivity; however, sterics played a vital role in reaction yield and regioselectivity. While the sterically hindered biaryl phosphine **7** resulted in good conversion, replacement of the *tert*-buyl groups with cyclohexyl substituents (**8**) was detrimental[14] (entries 7–8). The structure of the phenyl ring ortho to phosphorus also played an important role in catalytic activity. Adding substituents to the adjacent biaryl ring resulted in lower yields but higher selectivities (entries 9 and 11). We were intrigued to find that cyclohexyl-derived catalysts were viable if the ortho-aryl ring was bulkier (**10**, entry 10). The increased steric bulk in X-Phos[15] (**10**) likely prevents a catalyst decomposition pathway available to other cyclohexyl phosphines.

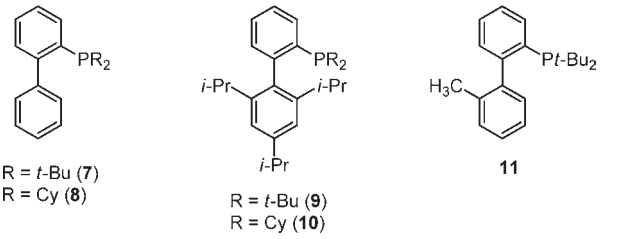


Figure 1. Structurally diverse phosphine catalysts.

(9) Kürti, L.; Czakó, B. In *Strategic Applications of Named Reactions in Organic Synthesis*; Hayhurst, J., Ed.; Elsevier Academic Press: USA, 2005; pp 198–199.

(10) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313–348.

(11) *N*-Acylaziridines are reported to undergo thermal rearrangement to allylamides. We have observed that **4** begins to undergo the same rearrangement at 90 °C in DME and 1,4-dioxane. (a) Fanta, P. E.; Walsh, E. N. *J. Org. Chem.* **1966**, *31*, 59–62. (b) Szeimies, G.; Mannhardt, K.; Junius, M. *Chem. Ber.* **1977**, *110*, 1792–1803.

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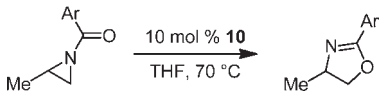
The effect of varying the benzoyl substituent on reaction yield and selectivity was investigated. A series of protected aziridines with varying sterics and electronics were synthesized and subjected to optimized conditions (Table 2).

Table 2. Effect of Aryl Substitution on Catalytic Rearrangement with **10**[a]



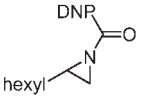
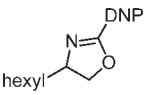
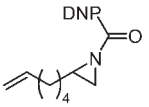
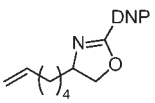
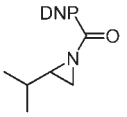
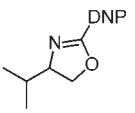
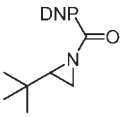
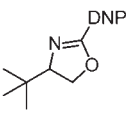
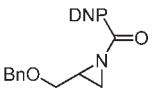
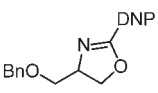
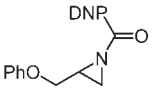
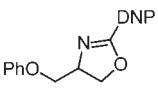
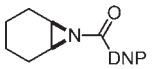
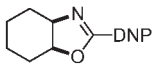
entry	Ar	yield (%)[b]	rr[c]
1	R_1 = H	21	>20:1
2	= Cl	21	8:1
3	= OMe	5	>20:1
4	= NO_2	71	10:1
5	R_2 = NO_2	77	8:1
6	= CF_3	60	12:1
7		92	7:1
8		34	6:1

[a] Conditions: aziridine (0.3 mmol), **10** (0.03 mmol), THF (0.2 M), 70 °C, 24 h. [b] Average isolated yield from two or more runs. [c] Regioisomeric ratio (rr) = 4-methyl:5-methyl.

Upon reaction scale-up, reactivity was inconsistent for $PCyPh_2$ and **7**. Fortunately, X-Phos (**10**)-catalyzed reactions were reproducible on a 0.3 mmol scale, and **10** became the catalyst of choice. Though all aziridines underwent some level of rearrangement, benzoyl rings substituted with electron-withdrawing groups were superior. The low yields in entries 1−3 are the result of low conversion, but longer reaction times did not improve the yields. Complete consumption of aziridine was observed for entries 4−8. With the best mix of yield and regioselectivity, we settled on the 3,5-dinitrobenzoyl (DNB) protecting group (entry 5) for further investigations into substrate scope.

A collection of terminal, DNB-protected aziridines (entries 1−6, Table 3) were prepared[16] and reacted under the X-Phos-catalyzed rearrangement conditions. The 3,5-dinitrophenyl (DNP) derived oxazolines were isolated with good to excellent yields as a single regioisomer in all cases. A remote alkene (entry 2) and ethers (entries 5−6) are tolerated under the neutral rearrangement conditions. For terminal aziridines, increasing the steric bulk of the substituent on the carbon backbone had no detrimental effect on the reaction yield (entries 3−4). However, the lone disubstituted aziridine did not undergo rearrangement (entry 7).

Table 3. Substrate Scope for the Phosphine-Catalyzed Rearrangement[a,e]

entry	substrate	product[c]	yield (%)[b]
1			94
2			64
3			80
4			98
5			67
6			66
7			0[d]

[a] Conditions: aziridine (0.3 mmol), **10** (0.03 mmol), THF (0.2 M), 70 °C, 24 h. [b] Average isolated yield from two or more runs. [c] Only the depicted regioisomer was observed following isolation. [d] Only the starting aziridine was observed by ^{1}H NMR. [e] DNP = 3,5-dinitrophenyl.

Terminal aziridines contain a chiral center which is retained in the product oxazolines. To ascertain if chirality transfer was occurring, aziridine **12** was synthesized with >99% ee and subjected to the optimized rearrangement conditions. Oxazoline **13** was isolated in 94% yield without loss of enantiopurity (Scheme 2). The stereospecificity of the rearrangement not only is important for synthetic application in asymmetric synthesis but also sheds light on the reaction mechanism.

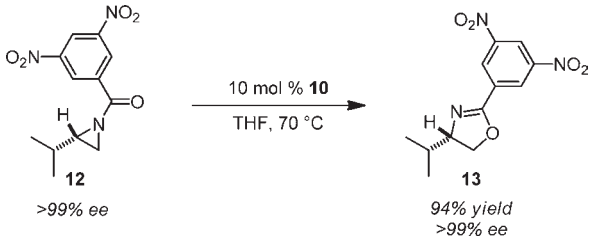
(13) Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 5096–5101.

(14) The poor regioselectivity exhibited by some cyclohexyl-derived phosphine catalysts is attributed to catalyst decomposition since low yields were also observed (Table 1, entries 4, 8).

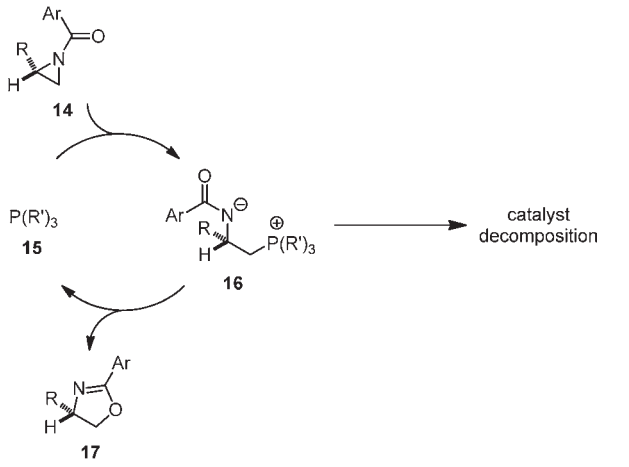
(15) Commercially available from Strem Chemicals. For seminal publications, see: (a) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653–6655. (b) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818–11819.

(16) A desirable substrate class is 2-aryl aziridines; however, we have found that such substrates readily rearrange to the 5-aryl oxazolines. This undesirable rearrangement occurs at 70 °C in THF in the absence of phosphine catalyst, is promoted by silica gel (as seen during the attempted purification of the substrate), and presumably involves rearrangement at the activated benzylic C−N bond.

Scheme 2. Phosphine-Catalyzed Rearrangement of an Enantioenriched Aziridine



Scheme 3. Proposed Catalytic Cycle



We propose a catalytic cycle similar to that orginially suggested by Heine[3a] (Scheme 3). Terminal aziridine **14** is susceptible to attack at the least hindered carbon by a nucleophilic phosphine (**15**). The intermolecular reaction would be rate limiting with a certain Lewis basicity at phosphorus required for reactivity based on data in Table 1. The balanced steric requirement for an optimal phosphine catalyst can be explained by initial phosphine attack coupled with the stability of intermediate **16**. The phosphine catalyst must be small enough to efficiently open the aziridine, but added steric bulk around phosphorus may prevent nonproductive decomposition of **16**. Following collapse of **16** on oxygen, the correct regioisomer of oxazoline (**17**) is predicted and the stereochemical integrity is maintained.

A novel phosphine-catalyzed rearrangement of aziridines has been described. Future experiments will be aimed at developing intermolecular reactions that take advantage of the proposed phosphonium intermediate. The diverse array of commercially available enantioenriched phosphines should also facilitate the development of an aziridine kinetic resolution.

Acknowledgment. We would like to thank Research Corporation (Cottrell College Science Award) and UNCW (Cahill Award) for funding.

Supporting Information Available. Detailed experimental procedures and characterization data for all unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.