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# $CeCl_3$ promoted asymmetric cycloaddition of isocyanates with 2-vinylaziridines

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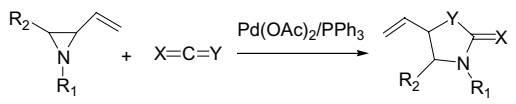
**Abstract**—The enantioselective ring-opening cyclization of 2-vinylaziridines with various isocyanates, using $Pd_2(dba)_3{\cdot}CHCl_3$, (*S*)-BINAP and $CeCl_3$ as the catalytic system, afforded chiral imidazolidinones in 58–89% yield and in up to 83% ee.


## 1. Introduction

Palladium catalyzed ring expansion reactions of heterocyclic compounds have attracted considerable attention in recent years.[1] Success has been attained in the regioselective formation of five, six and seven-membered ring heterocycles by palladium catalyzed cycloaddition reaction of oxiranes,[2] oxetanes,[3] azetidines[4] as well as pyrrolidines[5] with heterocumulenes. Recently we have shown that 2-vinylaziridines can undergo cycloaddition reactions at room temperature with various heterocumulenes in the presence of $Pd(OAc)_2$ and $PPh_3$, regioselectively affording five-membered ring products in high yield (Scheme 1).[6]

The ability to effect this cycloaddition reaction in an asymmetric manner would be significant, since it would provide a one step preparation of chiral imidazolidinones, some of which have potential biological activity.[7] To initiate this study, we chose isocyanates as the heterocumulenes in reaction with 2-vinylaziridines. During the preparation of this paper, Trost and Fandrick[8] reported the asymmetric cycloaddition of isocyanates to 2-vinylaziridines using the Trost ligand, affording imidazolidinones in good yield and ee value.




**Scheme 1.**

Readily available (*R*) or (*S*)-BINAP and its derivatives are excellent chiral ligands for many organic reactions.[9] The use of (*R*)-BINAP as a ligand for ring-opening reactions has been well documented in the literature. For example, we previously described the enantioselective synthesis of 4-vinyl-1,3-oxazolidine-2-imine in high yields and in up to 95% ee by using palladium complexes and either (*R*) or (*S*)-Tol-BINAP.[10] We envisioned that BINAP should be a good chiral ligand to promote the enantioselective ring-opening cycloaddition of isocyanates to vinylaziridines. Herein we now report the results of this investigation.

## 2. Results and discussion

In order to determine optimal reaction conditions for the asymmetric cyclization reaction, 1-cyclohexyl-2-vinylaziridine **1a** was treated with phenyl isocyanate **2a** using 2.5 mol% of $Pd_2(dba)_3{\cdot}CHCl_3$ and 10 mol% (*S*)-BINAP in 3 mL THF at room temperature for 4 h. The product, 1-cyclohexyl-3-phenyl-4-vinyl- tetrahydro-2*H*-imidazolidin-2-one **3a**, was obtained in 85% yield and 40% ee (Table 1). The enantioselectivity of the reaction could be significantly improved when catalytic amount of the Lewis acid, $CeCl_3$, was added to the reaction. When the reaction was repeated in the presence of 5 mol% $CeCl_3$, the ee increased to 75% (Table 1, entry 5). The reaction may proceed by a pathway involving intermediates **4a** and **4b** interconverting via a $\eta^1$-species

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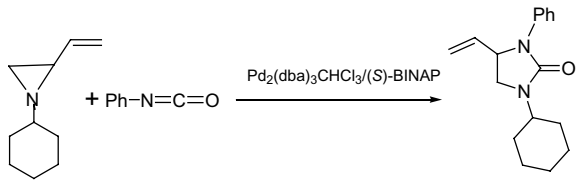
**Table 1.** Enantioselective cycloaddition of 1-cyclohexyl-2-vinyl-aziridine **1a** with phenyl isocyanate **2f** catalyzed by $Pd_2(dba)_3{\cdot}CHCl_3$/(*S*)-BINAP[a]

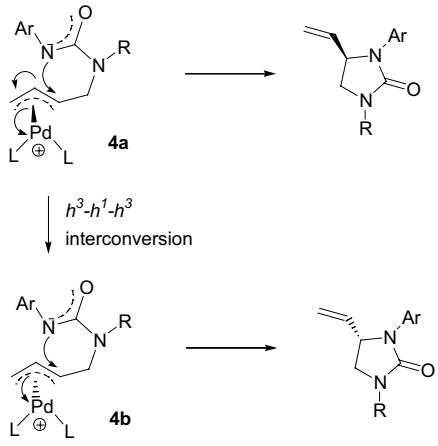



**1a** **2f** **3f**

| Entry | Solvent | (*S*)-BINAP (%) | $CeCl_3$ (%) | Yield (%)[b] | Ee (%)[c] |
|---|---|---|---|---|---|
| 1 | THF | 10 | 0 | 85 | 40 |
| 2 | THF | 2.5 | 0 | 80 | 33 |
| 3 | THF | 2.5 | 5 | 65 | 54 |
| 4 | THF | 5 | 5 | 68 | 71 |
| 5 | THF | 10 | 5 | 65 | 75 |
| 6 | THF | 10 | 10 | 70 | 75 |
| 7 | THF | 10 | 20 | 55 | 74 |
| 8 | $CH_2Cl_2$ | 10 | 10 | 80 | 50 |
| 9 | Toluene | 10 | 10 | 85 | 57 |
| 10 | Ether | 10 | 10 | 45 | 54 |
| 11 | THF | 10 | 10 | 73 | 71[d] |
| 12 | THF | 10 | 10 | 80 | 47[e] |

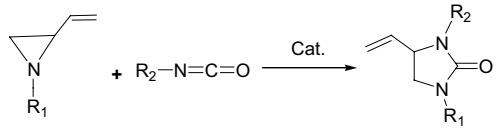
[a] Reaction conditions: 1-cyclohexyl-2-vinylaziridine (1.0 mmol), phenyl isocyanate (1.0 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.025 mmol), (*S*)-BINAP (0.1 mmol), solvent, rt 4 h.
[b] Isolated yield.
[c] The % ee was determined by HPLC using a chiral OJ column.
[d] (*R*)-BINAP was used.
[e] (*S*,*S*)-Trost ligand was used.

(Scheme 2). The presence of $CeCl_3$ may possibly increase the rate of equilibration of the π-allyl palladium intermediates, leading to the formation of the enantiomeric products.




**Scheme 2.**

Increasing the amount of $CeCl_3$ had no beneficial influence on the enantioselectivity of the product (Table 1, entries 5–7). For example, when 20% $CeCl_3$ was used, almost the same enantioselectivity (74% ee) was obtained for the cyclization reaction. The reaction was optimized by varying the ligand loading and the solvent. The amount of (*S*)-BINAP affects the ee values. When 2.5 mol% of (*S*)-BINAP was used, the product was formed in 54% ee (entry 3). When 5 mol% of (*S*)-BINAP was used, the enantiomeric excess increased to 71% (entry 4). Further increasing the ligand loading has no substantive impact on the ee. Tetrahydrofuran is the best solvent, with dichloromethane, toluene or ether, affording **3f** in modest ees [compare entry 6 (75% ee) with entries 8–10 (50–57% ee)]. Trost and Fandrick[8] reported the asymmetric cycloaddition of isocyanates to 2-vinylaziridines using the Trost ligand and acetic acid was needed in the reaction. However, under our reaction conditions, the Trost ligand only gave 47% ee in the reaction of **1a** with **2f** (entry 12) compare with entry 6 (75% ee). Also we repeated the reaction of **1a** with **2a** by using the Trost ligand instead of BINAP, **3a** was formed in 71% ee, while 81% ee was obtained by using our catalyst system. Consequently, the $Pd_2(dba)_3{\cdot}$(*S*)-BI-




**1** **2** **3a-m**

**1a** $R_1$= Cy
**1b** $R_1$= *t*-Bu

**2a** $R_2$= *p*-$ClC_6H_4$
**2b** $R_2$= *o*-$ClC_6H_4$
**2c** $R_2$= *m*-$ClC_6H_4$
**2d** $R_2$= *p*-$BrC_6H_4$
**2e** $R_2$= *p*-$MeC_6H_4$
**2f** $R_2$= $C_6H_5$
**2g** $R_2$= *p*-$MeOC_6H_4$

**Scheme 3.**

**Table 2.** Asymmetric cycloaddition of 1-alkyl-2-vinylaziridines with various isocyanates in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$/(*S*)-BINAP/$CeCl_3$[a]

| Entry | Aziridine | Isocyanate | Product | Yield (%)[b] | Ee (%)[c] |
|---|---|---|---|---|---|
| 1 | **1a** | **2a** | **3a** | 74 | 81 |
| 2 | **1a** | **2b** | **3b** | 75 | 83 |
| 3 | **1a** | **2c** | **3c** | 73 | 75 |
| 4 | **1a** | **2d** | **3d** | 75 | 75 |
| 5 | **1a** | **2e** | **3e** | 78 | 75 |
| 6 | **1a** | **2f** | **3f** | 70 | 75 |
| 7 | **1b** | **2a** | **3g** | 78 | 48 |
| 8 | **1b** | **2b** | **3h** | 83 | 51 |
| 9 | **1b** | **2c** | **3i** | 85 | 66 |
| 10 | **1b** | **2d** | **3j** | 75 | 60 |
| 11 | **1b** | **2e** | **3k** | 84 | 60 |
| 12 | **1b** | **2f** | **3l** | 89 | 66 |
| 13 | **1b** | **2g** | **3m** | 58 | 70 |

[a] Reactions conditions: 2-vinylaziridine (1.0 mmol), isocyanate (1.0 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.025 mmol), (*S*)-BINAP (0.1 mmol), $CeCl_3$ (0.1 mmol) THF 2.5 mL, rt 4 h.
[b] Isolated yield.
[c] % Ee was determined by chiral HPLC using a chiral OJ column or a chiral AS column.

NAP/$CeCl_3$ system may be an effective alternative to the method described by Trost and Fandrick.

The cycloaddition of 1-alkyl-2-vinylaziridines **1a** and **1b** with various isocyanates **2a–g**, catalyzed by $Pd_2(dba)_3{\cdot}CHCl_3$/(*S*)-BINAP/$CeCl_3$, was effected under the optimized conditions (Scheme 3 and Table 2), affording products in up to 89% yield and 83% ee.[11]

Using 1-cyclohexyl-2-vinylaziridine **1a** and 4-chlorophenyl isocyanate **2a** as reactants gave **3a** in 74% isolated yield and 81% ee (Table 2, entry 1). Similar results were obtained using **2b–f** in reaction with **1a**, with the highest % ee obtained for **3b** (entries 2–6).

In contrast, reaction of 1-*t*-butyl-2-vinylaziridine **1b** with **2a–f** afforded **3g–l** in higher yields than those obtained using **1a** as the aziridine reactant (entries 7–12). However, the ees of the products were lower. *p*-Methoxylphenyl isocyanate **2g** was less active in reaction with **1b**, with **3m** being formed in 58% yield and 70% ee (entry 13).

## 3. Conclusion

In summary, we have demonstrated that the readily available BINAP ligand, in combination with $Pd_2(dba)_3{\cdot}CHCl_3$ and $CeCl_3$, is a good catalyst system for the cycloaddition reaction of 2-vinylaziridines with various isocyanates. This simple catalyst system is practical for the asymmetric synthesis of nonracemic chiral imidazolidinones.

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## References and notes

1. (a) El Ali, B.; Alper, H. New Approaches to the Synthesis of Heterocycles by Transition Metal Catalysis. In *Transition Metal Catalyzed Reaction*; Murahashi, S. I., Davies, S. G., Eds.; Blackwell Science: Oxford, 1999; (b) Wei, L. M.; Wei, L. L.; Pan, W. B.; Wu, M. J. *Tetrahedron Lett.* **2003**, *44*, 595; (c) Nagao, Y.; Ueki, A.; Asano, K.; Tanaka, S.; Sano, S.; Shiro, M. *Org. Lett.* **2002**, *4*, 455; (d) Jeong, Y. I.; Shiro, M.; Nagao, Y. *Heterocycles* **2000**, *52*, 85; (e) Nagao, Y.; Tanaka, S.; Ueki, A.; Jeong, Y. I.; Sano, S.; Shiro, M. *Synlett* **2002**, 480; (f) Richard, C. L.; Kishan, R. C. *J. Org. Chem.* **2002**, *67*, 2027; (g) Richard, C. L.; Kishan, R. C. *Org. Lett.* **2000**, *2*, 3325.
2. Larksarp, C.; Alper, H. *J. Org. Chem.* **2001**, *66*, 3502.
3. Larksarp, C.; Alper, H. *J. Org. Chem.* **1999**, *64*, 4152.
4. (a) Inman, G. A.; Butler, D. C. D.; Alper, H. *Synlett* **2001**, 914; (b) Martorell, A.; Inman, G. A.; Alper, H. *J. Mol. Catal. A: Chem.* **2003**, *204–205*, 91.
5. (a) Zhou, H. B.; Alper, H. *J. Org. Chem.* **2003**, *68*, 3439; (b) Zhou, H. B.; Alper, H. *Tetrahedron* **2004**, *63*, 73.
6. Butler, D. C. D.; Inman, G. A.; Alper, H. *J. Org. Chem.* **2000**, *65*, 5887.
7. (a) Katrizky, A. R.; Rees, C. W. In *Comprehensive Heterocyclic Chemistry*; Pergamon: Oxford, 1984, parts 1 and 4B; (b) John, R. S.; Anthony, M. A.; Claude, P. J.; Ronald, S. M.; Martin, M. E. PCT, Int, Appl. **2002**, 216; (c) Marvin, C.; Wilson, L. R. U.S. Patent 2,985,663 19,610,523, **1961**.
8. Trost, B. M.; Fandrick, D. R. *J. Am. Chem. Soc.* **2003**, *125*, 11836.
9. (a) Noyori, R. *Adv. Synth. Catal.* **2003**, *345*, 15; (b) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345; (c) Jerry, G. S. *Pharma Chem.* **2003**, *2*, 20; (d) Kitagawa, O.; Takahashi, M.; Kohriyama, M.; Taguchi, T. *J. Org. Chem.* **2003**, *68*, 9851; (e) Guylaine, C.; Michele, B. C.; Jeiping, Z. *Angew. Chem., Int. Ed.* **2003**, *42*, 4774; (f) Tanaka, K.; Shirasaka, K. *Org. Lett.* **2003**, *5*, 4697; (g) Suh, W. H.; Choi, M.; Lee, S. I.; Chung, Y. K. *Synthesis* **2003**, *14*, 2169; (h) Sandoval, C. A.; Ohkuma, T.; Muniz, K.; Noyori, R. *J. Am. Chem. Soc.* **2003**, *125*, 13490.
10. (a) Larksarp, C.; Alper, H. *J. Am. Chem. Soc.* **1997**, *119*, 3709; (b) Larksarp, C.; Alper, H. *J. Org. Chem.* **1998**, *63*, 6229.

11. Representative procedure for the asymmetric cycloaddition of 2-vinylaziridines with isocyanates: A mixture of $Pd_2(dba)_3{\cdot}CHCl_3$ (0.025 mmol), (*S*)-BINAP (0.1 mmol) and THF (2 mL) was stirred at room temperature for 30 min. Then $CeCl_3$ (0.1 mmol) was added, and after 10 min, 2-vinylaziridine (1.0 mmol) and isocyanate (1.0 mmol) were added and the mixture was then stirred under a nitrogen atmosphere at room temperature, until the conversion of isocyanate was complete (4h). The solution was subjected to rotary evaporation and the residue was purified by preparative silica gel TLC (ether/hexane = 1:2).