

**ELECTRONIC ENCYCLOPEDIA OF REAGENTS FOR ORGANIC SYNTHESIS**

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2,6-BIS[(4*R*,5*R*)-4,5-DIHYDRO-4,5-DIPHENYL-2-OXAZOLYL]PYRIDINE

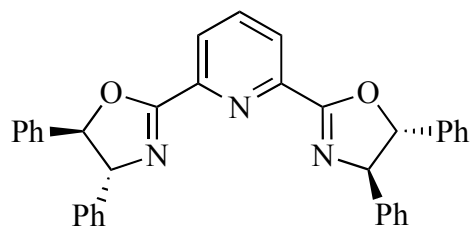
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**2,6-Bis[(4*R*,5*R*)-4,5-dihydro-4,5-diphenyl-2-oxazolyl]pyridine**



[372200-56-1]  $C_{35}H_{27}N_3O_2$  (MW 521.61)

(reagent used as a chiral tridentate ligand for various metal-catalyzed asymmetric transformations)

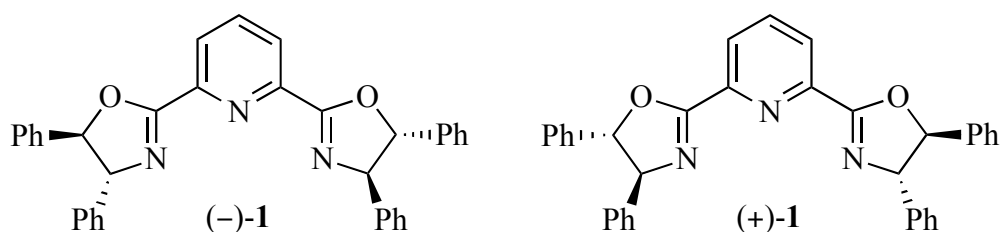
*Physical Data:* white crystalline solid, mp 201-202 °C,  $[\alpha]_D^{25} -41.4$  (c 0.5  $CHCl_3$ ).<sup>1</sup>

*Solubility:* soluble in most organic solvents.

*Analysis of Reagent Purity:*  $^1H$ -NMR (400 MHz,  $CDCl_3$ ):  $\delta$  8.41 (d,  $J= 7.8$  Hz, 2H), 7.98 (t,  $J= 7.8$  Hz, 1H), 7.30-7.40 (m, 20H), 5.54 (d,  $J= 8.3$  Hz, 2H), 5.33 (d,  $J= 8.3$  Hz, 2H);  $^{13}C$ -NMR (100 MHz,  $CDCl_3$ ):  $\delta$  163.0, 147.1, 141.3, 139.8, 137.4, 128.81, 128.79, 128.5, 127.9, 126.9, 126.6, 126.2, 90.0, 79.0.<sup>2</sup>

*Preparative Methods:* the reagent ((-)-**1**) is prepared<sup>3</sup> by a three-step sequence starting by treating 1.0 equiv of pyridine-2,6-dicarbonyl dichloride<sup>4</sup> with 2.0 equiv of the commercially available (1*S*,2*R*)-2-amino-1,2-diphenylethanol (Aldrich) and 5.1 equiv of triethylamine in anhydrous dichloromethane.<sup>1</sup> The resulting white solid (2,6-bis[(1*R*,2*S*)*N,N'*-2-hydroxyl-1,2-diphenylethyl]pyridinedicarboxamide) is isolated by filtration and subsequently treated with thionyl chloride (16 equiv) in dichloromethane to provide

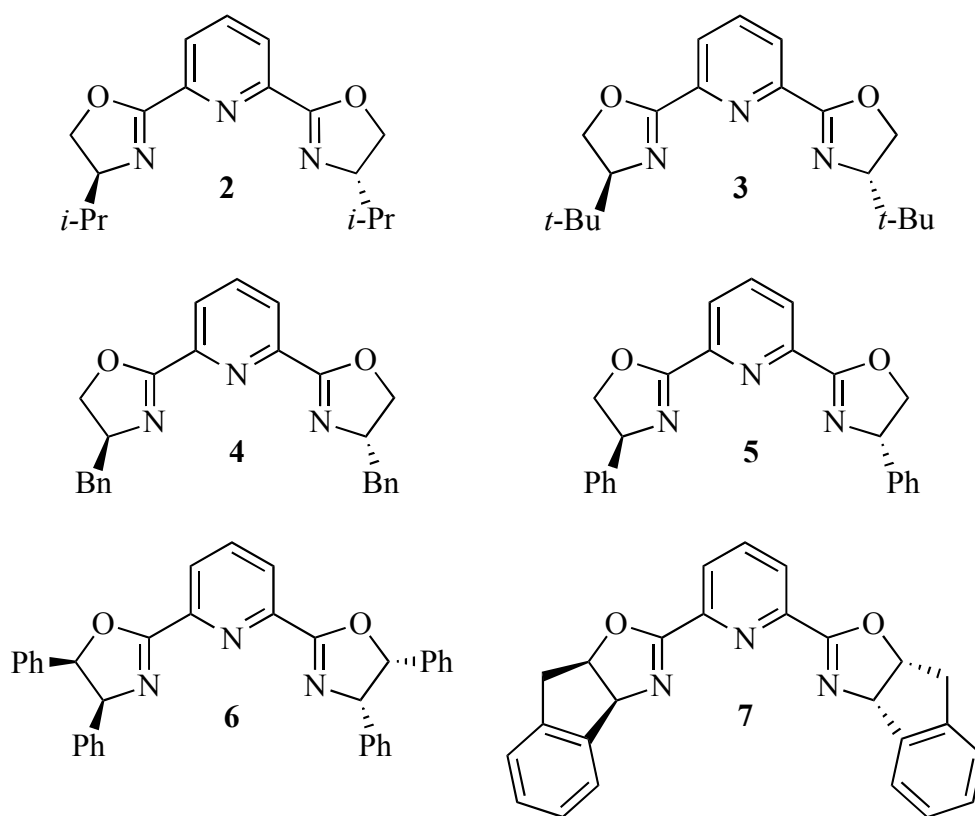
the intermediate *bis*-chloride (2,6-bis[(1*R*, 2*S*)*N,N'*-2-chloro-1,2-diphenylethyl]-pyridinedicarboxamide) that is then cyclized by treatment with an ethanolic solution of 2 N sodium hydroxide to yield the PyBox ligand (**1**).<sup>1</sup> The ligand can be purified by recrystallization from hot ethyl acetate.<sup>1</sup> The enantiomer of the title compound (2,6-bis[(4*S*,5*S*)-4,5-dihydro-4,5-diphenyl-2-oxazolyl]pyridine, (+)-**1**, 410092-98-7) can be prepared in an analogous manner.



*Handling, Storage, and Precautions:* bench stable, but generally stored in a dry-box. The toxicity of the reagent is unknown and should be handled in a well-ventilated fume-hood.

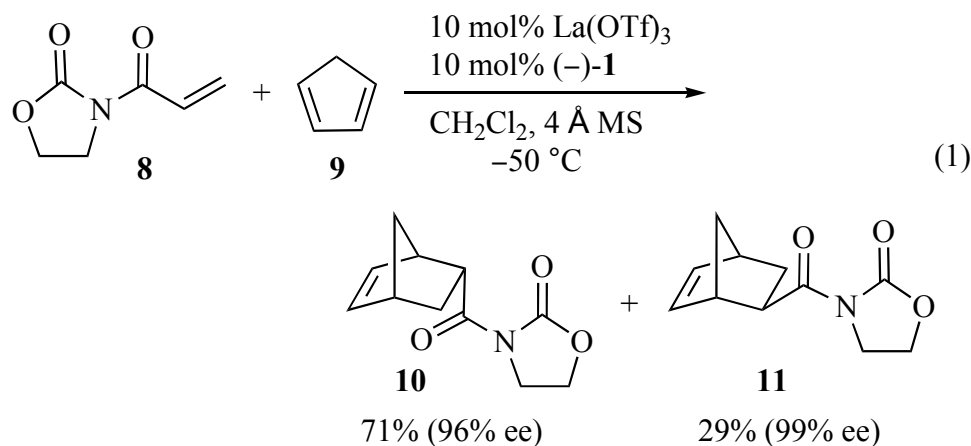
### 2,6-Bis(oxazoline)pyridine ligands.

The title reagent ((-)-**1**) is a member of a class of  $C_2$ -symmetric tridentate ligands that are generally referred to as PyBox (2,6-bis(oxazoline)pyridine) ligands.<sup>5</sup> There are a large number of substituted PyBox ligands available.<sup>5</sup> The more commonly employed ligands are compounds **1-7**. These compounds are generally used as chiral scaffolds for a variety of metal-catalyzed enantioselective reactions. The optimal PyBox ligand for a given transformation is metal, substrate, and reaction dependent.

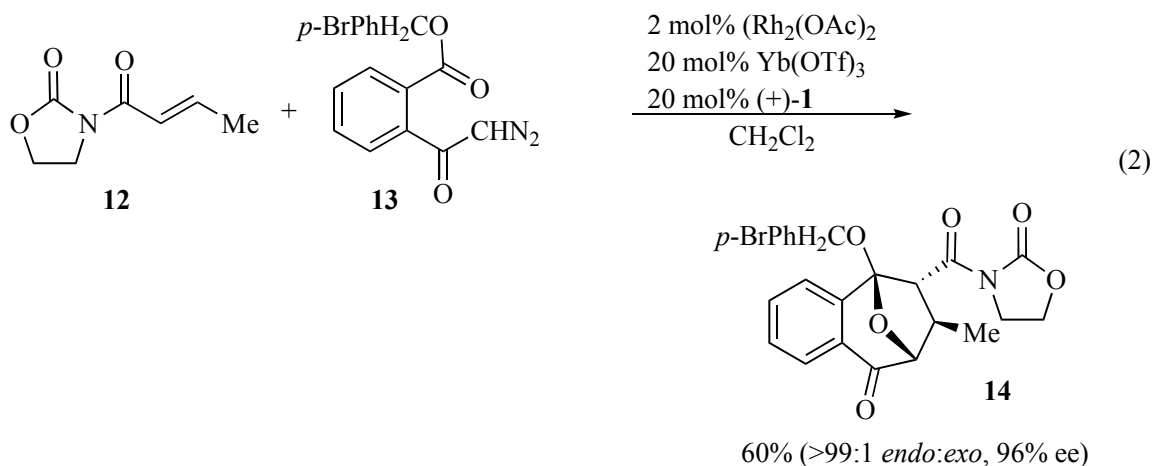


### Cycloadditions.

Impressive enantioselectivities have been observed in the endo-selective Diels–Alder reaction between 3-acryloyl-1,3-oxazolidin-3-one (**8**) and cyclopentadiene (**9**) catalyzed by the complex derived from lanthanum(III) triflate and (–)-**1** (eq 1).<sup>6</sup> However, the reaction was moderately diastereoselective (dr 71:29). Further investigation utilizing other rare-earth metals (lanthanides) and/or PyBox ligands (**2** and **5**) resulted in lower levels of diastereo- or stereoselectivity.<sup>6,7</sup>

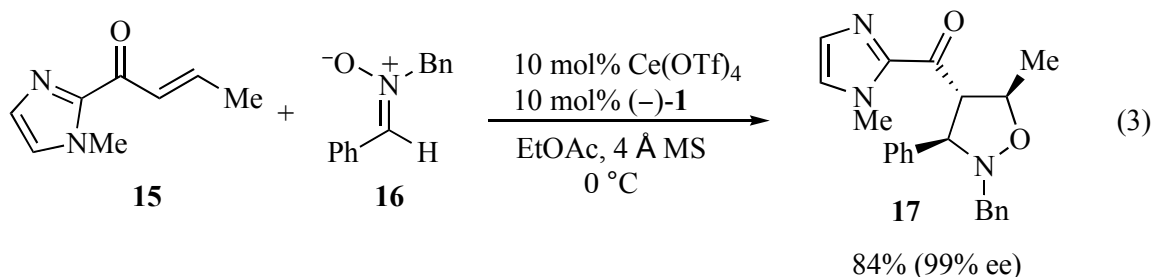


High levels of diastereo- and enantioselectivity was reported for the dipolar cycloaddition between the carbonyl ylide of **13**, formed via the dirhodium catalyzed intramolecular carbenoid-ester cyclization of **13**, and 2-acyl oxazolidinone **12** catalyzed by the ytterbium(III)-(+)-**1** triflate complex (eq 2).<sup>8</sup> The corresponding cycloaddition with the structurally similar Ph-PyBox (**5**) ligand proceeded with lower levels of enantiocontrol (84% ee).<sup>8</sup>



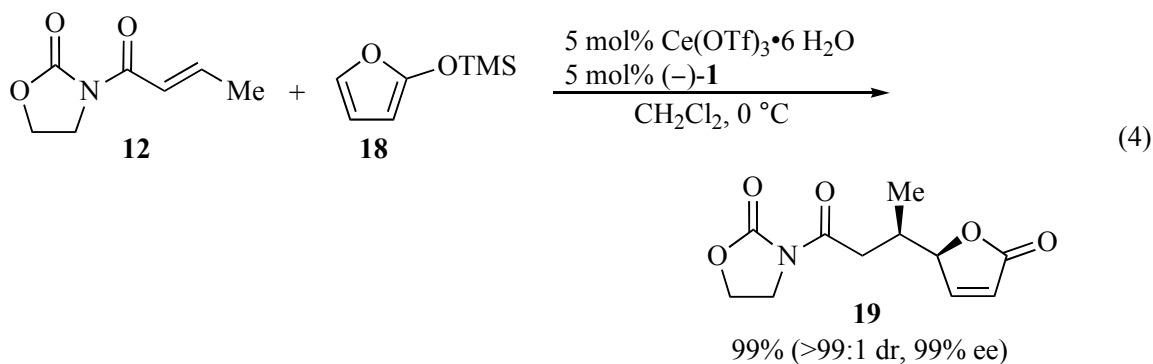
The parent ligand (-)-**1** has also been reported as an effective chiral scaffold for the cerium(IV) triflate catalyzed dipolar cycloaddition between  $\alpha,\beta$ -unsaturated 2-acyl imidazole (**15**) and nitron **16** (eq 3).<sup>9</sup> It should be noted that other PyBox ligands

(ligands **2-5** and **7**) were less efficient as lower levels of enantioselectivity or yields were observed.<sup>9</sup> Also, the structurally similar PyBox ligand **6** offered comparative selectivities in the illustrated cycloaddition.<sup>9</sup>



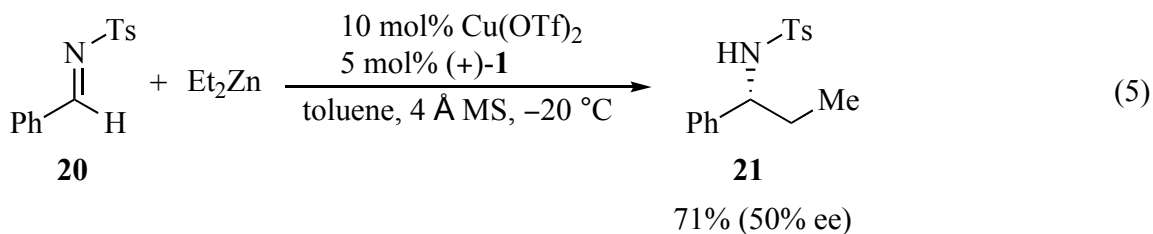
### Addition Reactions.

The Mukaiyama–Michael reaction between 2-acyl oxazolidinone **12** and 2-trimethylsilyloxyfuran **18** catalyzed by a cerium(III) triflate-(**-**)-**1** complex has been reported to proceed in very high yields, diastereoselectivity, and enantioselectivity (eq 4).<sup>1</sup> The addition reaction was shown to be considerably less selective when (**-**)-**1** was replaced with the structurally similar Ph-PyBox ligand (**5**, 50% ee).<sup>1</sup>



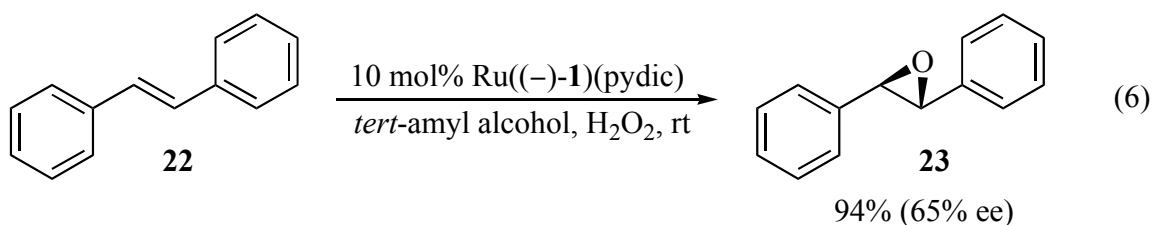
Moderate levels of selectivity were realized by employing the parent ligand (**+**)-**1** in the copper(II) triflate catalyzed diethylzinc alkylation of tosyl-imine **20** (eq 5).<sup>10</sup> Although the PyBox ligand (**+**)-**1** was shown to provide higher levels of enantiofacial bias

compared to the alkyl substituted PyBox ligands (**2-4**), the structurally similar Ph-PyBox ligand (**5**) was found to be optimal for the illustrated process (77% ee).<sup>10</sup>



### Oxidation Reactions.

A moderately enantioselective epoxidation of *trans*-stilbene **22** catalyzed by a rhodium complex derived from (–)-**1** and pyridine-2,6-dicarboxylic acid (pydic) was reported recently (eq 6).<sup>11</sup> It should be noted that the parent ligand was found to offer higher levels of enantiocontrol than the alkyl substituted PyBox ligands **2-4**, but the Ph-PyBox (**5**) ligand was optimal for the epoxidation (99% yield, 67% ee).<sup>11</sup>



### Related Reagents.

2,6-bis[(4*R*,5*S*)-4,5-dihydro-4,5-diphenyl-2-oxazolyl]pyridine (497172-36-8), 2,6-bis[(4*S*,5*R*)-4,5-dihydro-4,5-diphenyl-2-oxazolyl]pyridine (292625-77-5).

1. Desimoni, G.; Faita, G.; Filippone, S.; Mella, M.; Zampori, M. G.; Zema, M.

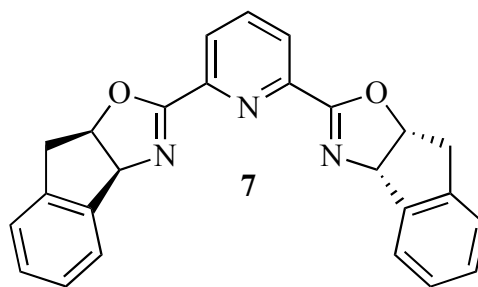
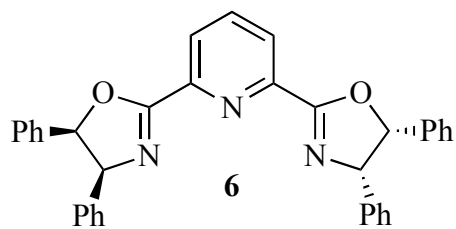
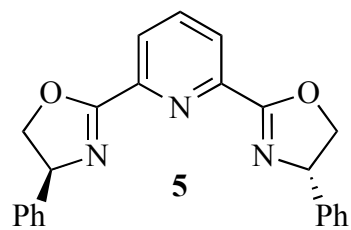
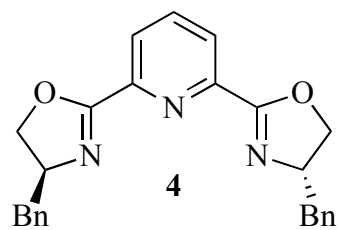
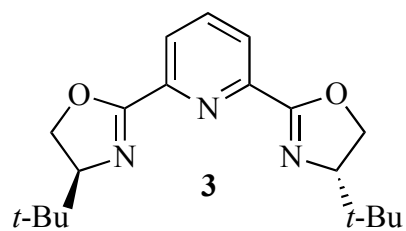
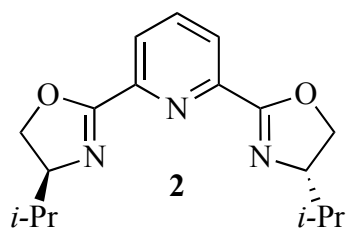
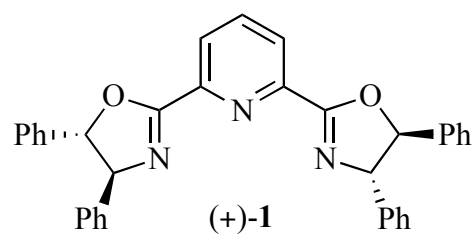
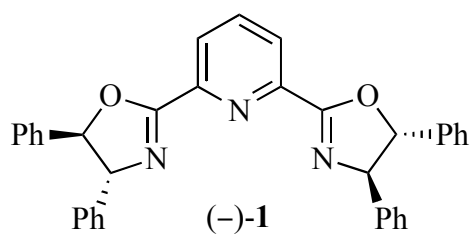
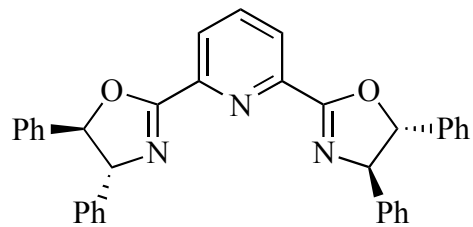
*Tetrahedron* 2001, **57**, 10203.

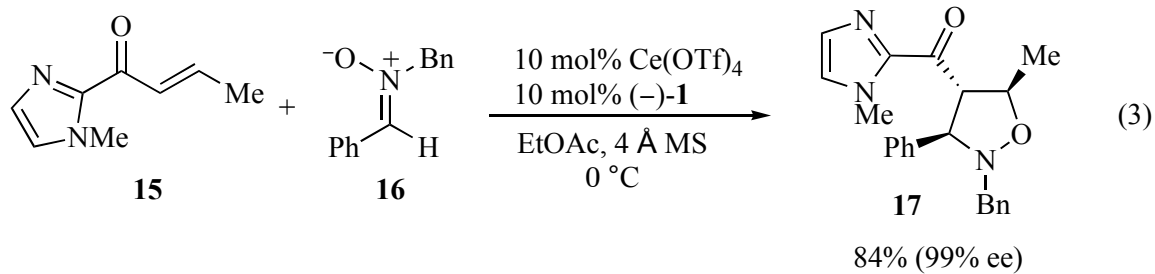
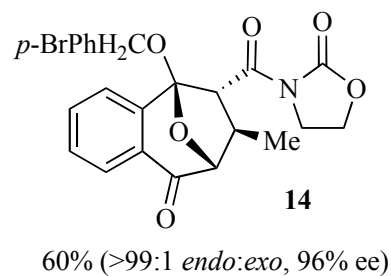
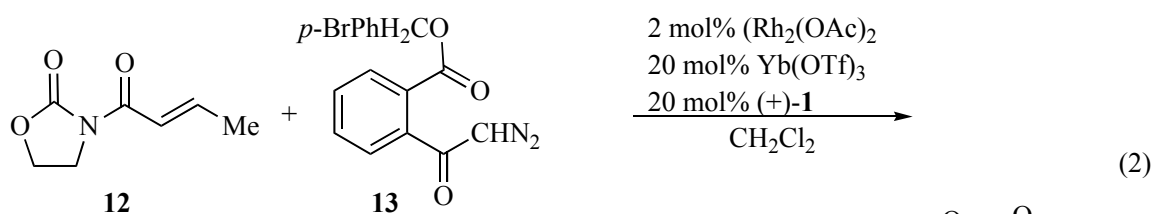
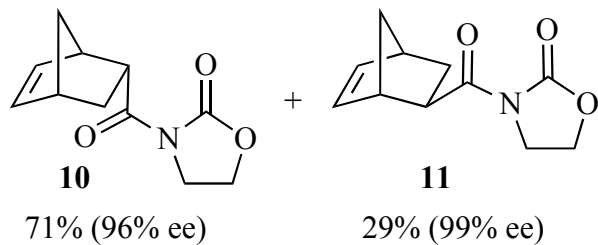
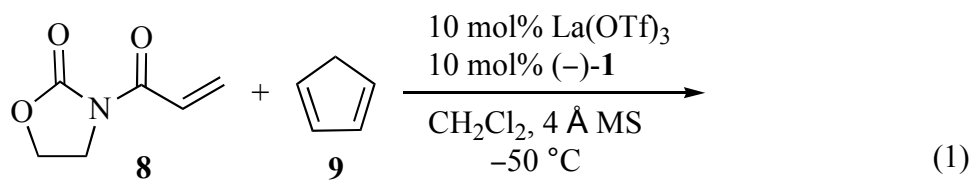
2. Evans, D. A.; Song, H.-J.; Fandrick, K. R. *Org. Lett.* 2006, **8**, 3351.
3. For alternate means for preparing PyBox ligands, see: (a) Desimoni, G.; Faita, G.; Guala, M.; Pratelli, C. *Tetrahedron: Asymm.* 2002, **13**, 1651. (b) Davies, I. W.; Gerena, L.; Lu, N.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* 1996, **61**, 9629.
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5. For a review on 2,6-bis(oxazoline)pyridine (PyBox) ligands, see: Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* 2003, **103**, 3119.
6. Desimoni, G.; Faita, G.; Guala, M.; Laurenti, A. *Eur. J. Org. Chem.* 2004, 3057.
7. Desimoni, G.; Faita, G.; Guala, M.; Pratelli, C. *Tetrahedron* 2002, **58**, 2929.
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10. Li, X.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Tetrahedron: Asymm.* 2003, **14**, 3819.
11. (a) Tse, M. K.; Bhor, S.; Klawonn, M.; Anikumar, G.; Jiao, H.; Döbler, C.; Spannenberg, A.; Mägerlein, W.; Hugl, H.; Beller, M. *Chem. Eur. J.* 2006, **12**, 1855. (b) Tse, M. K.; Bhor, S.; Klawonn, M.; Anikumar, G.; Jiao, H.; Döbler, C.; Spannenberg, A.; Mägerlein, W.; Hugl, H.; Beller, M. *Chem. Eur. J.* 2006, **12**, 1875.

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84% (99% ee)

