

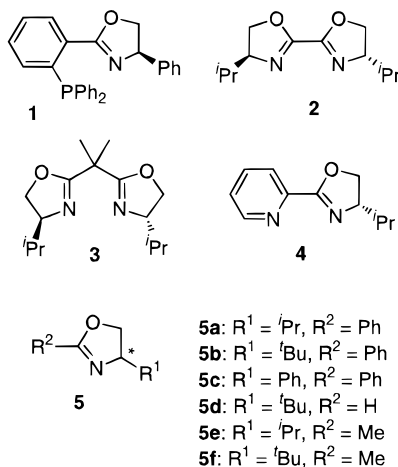
Nickel-Catalyzed Asymmetric Multiple-Component Tandem Coupling. Effects of Simple Monodentate Oxazolines as Chiral Ligands

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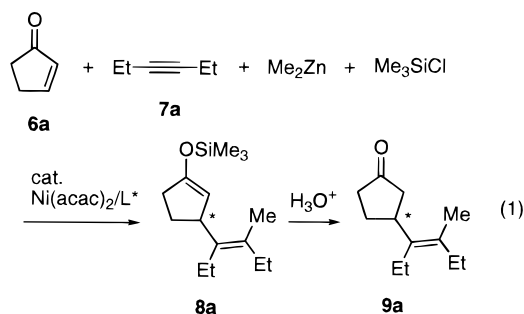
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Optically active oxazolines have been extensively used as ligands for transition metals in asymmetric catalysts.¹ However, most of them are bidentate ligands such as **1–4**. We report here a new catalytic asymmetric reaction using monodentate chiral oxazoline ligands **5**.



Tandem (also described as domino or cascade) reactions, which permit complex molecules to be reasonably well-constructed in a one-pot assembly, are an important topic in organic synthesis.² We recently found that a nickel complex catalyzed the reaction of enones, alkynes, organometallics, and Me₃SiCl to provide the tandem coupling products with high regio- and stereoselectivities.³ We next planned an enantioselective reaction and started to examine the effects of various chiral ligands.

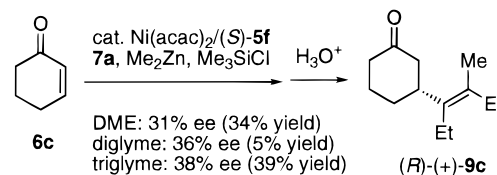
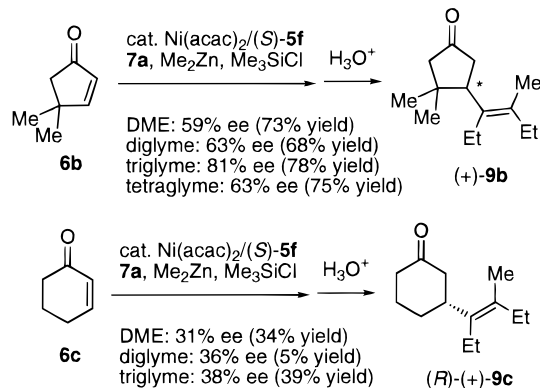
Enone **6a** was treated with alkyne **7a**, Me₂Zn, and Me₃SiCl in the presence of Ni(acac)₂ (5 mol %) and a chiral ligand (10 mol %) in THF at room temperature (eq 1).⁴ After hydrolysis of the



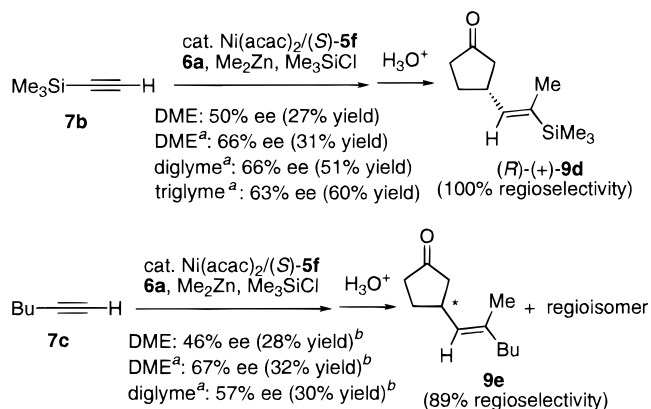
obtained **8a**, the enantiomeric excess (ee) of the corresponding **9a** was determined by chiral HPLC. Whereas phosphorus ligands

- (1) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.
 (2) (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (b) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103. (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.
 (3) (a) Ikeda, S.; Sato, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5975. (b) Ikeda, S.; Yamamoto, H.; Kondo, K.; Sato, Y. *Organometallics* **1995**, *14*, 5015. (c) Ikeda, S.; Kondo, K.; Sato, Y. *J. Org. Chem.* **1996**, *61*, 8248. (d) Cui, D.-M.; Yamamoto, H.; Ikeda, S.; Hatano, K.; Sato, Y. *J. Org. Chem.* **1998**, *63*, 2782.

Scheme 1



Scheme 2^a



^a All substrates were added in succession to the catalytic system, and the mixture stirred for 2 h at room temperature. ^b Total yield of regioisomeric mixture.

(BINAP,^{5a} 4% ee (43% yield); MeO-MOP,^{5b} 0% ee (47% yield)) and bidentate oxazolines (**1**,⁶ <2% ee (32% yield); **2**,⁷ <2% ee (60% yield); **3**,⁷ 4% ee (20% yield); **4**,⁸ 0% ee (43% yield)) were not effective, the use of monodentate oxazolines **5**⁹ induced enantioselection to give optically active **9a**, i.e., **5a**, 33% ee (42% yield); **5b**, 34% ee (42% yield); **5c**, 20% ee (55% yield); **5d**, 50% ee (31% yield); **5e**, 43% ee (43% yield); **5f**, 65% ee (47% yield)). When a THF solution of **6a** and Me₃SiCl was added dropwise over 2 h to the reaction mixture including (*S*)-**5f**, both the ee and the chemical yield of **9a** further increased to 70 and 62%, respectively. To this end, DME was more efficient than THF (78% ee (57% yield)). Similar results were obtained when diglyme (74% ee (63% yield)) and triglyme (76% ee (61% yield)) were used as the solvent.

(4) The conjugate addition to **6** followed by the carbocyclization of **7** did not occur in the reaction.^{3b} For the nickel-catalyzed carbocyclization of aryl-substituted internal alkynes, see: Stüdenmann, T.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 93.

(5) (a) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345. (b) Uozumi, Y.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 9887.

(6) (a) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566. (b) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769. (c) Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coote, S. T. *Tetrahedron Lett.* **1993**, *34*, 3149.

(7) Phaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339.

(8) (a) Brunner, H.; Obermann, U. *Chem. Ber.* **1989**, *122*, 499. (b) Bolm, C.; Weickhardt, K.; Zehnder, M.; Ranft, T. *Chem. Ber.* **1991**, *124*, 1173.

(9) (a) Kurth, M. J.; Decker, O. H. W. *J. Org. Chem.* **1985**, *50*, 5789. (b) Leonard, W. R.; Romine, J. L.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 1961. (c) Meyers, A. I.; Shipman, M. J. *J. Org. Chem.* **1991**, *56*, 7098. (d) Kamata, K.; Agata, I.; Meyers, A. I. *J. Org. Chem.* **1998**, *63*, 3113.

The results of the enantioselective tandem coupling with cyclic enones are shown in Scheme 1. Treatment with **6b** in DME and diglyme gave **9b** of modest enantiomeric purity. Interestingly, the enantioselectivity was improved to 81% ee by the use of triglyme. The ee of **9c**¹⁰ derived from the reaction with **6c** was lower than that of **9a** and **9b**.

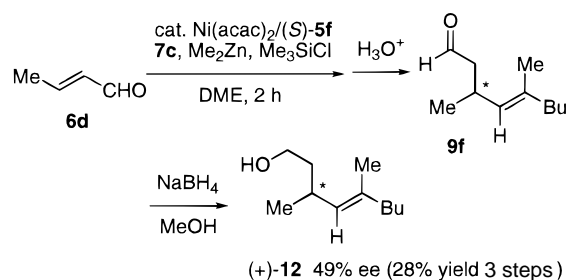
The enantioselective tandem coupling was performed also with terminal alkynes (Scheme 2). The reaction of **6a** with **7b** in DME gave **9d**¹¹ of 50% ee with perfect regioselection. The enantiomeric purity was increased to 66%, when all of the reactants were successively added to the catalytic system. Almost the same enantioselectivity (**9e**, 67% ee) was shown in the reaction with **7c**.

The present catalytic system is applied to the asymmetric reaction with crotonaldehyde (**6d**). An alcohol **12**, which was converted from the corresponding tandem coupling **9f** by treatment with NaBH₄, was obtained in 49% ee (Scheme 3).

(10) The absolute configuration of (+)-**9c** was determined to be *R*-configuration by examination of the ¹³C NMR spectra of diastereomeric ketal, which were obtained by the treatment of (+)-**9c** with (2*R*,3*R*)-2,3-butandiol; see: Lemièrre, G. L.; Dommissé, R. A.; Lepoivre, J. A.; Alderweireldt, F. C.; Hiemstra, H.; Wynberg, H.; Jones, J. B.; Toone, E. J. *J. Am. Chem. Soc.* **1987**, *109*, 1363.

(11) The absolute configuration of (+)-**9d** was determined by following previous procedures: (i) (+)-**9d** was converted to (+)-3-propylcyclopentenone (3-PrC₅H₇O)^{11a} by desilylation and hydrogenation, and (ii) the stereochemistry of (+)-PrC₅H₇O was assumed to be *R*-configuration by comparison with the sign of rotation of (*R*)-(+)-3-MeC₅H₇O,^{11b} (*R*)-(+)-3-EtC₅H₇O,^{11c} and (*S*)-(-)-3-BuC₅H₇O.^{11d} (a) Racemate was already known, see: Wenkert, E.; Davis, L. L.; Mylari, B. L.; Solomon, M. F.; da Silva, R. R.; Shulman, S.; Warnet, R. J.; Ceccherelli, P.; Curini, M.; Pellicciari, R. *J. Org. Chem.* **1982**, *47*, 3242. (b) Kokke, W. C. M. C.; Varkevisser, F. A. *J. Org. Chem.* **1974**, *39*, 1535. (c) Posner, G. H.; Frye, L. L.; Hulce, M. *Tetrahedron* **1984**, *40*, 1401. (d) Taura, Y.; Tanaka, M.; Funakoshi, K.; Sakai, K. *Tetrahedron Lett.* **1989**, *30*, 6349.

Scheme 3



In summary, we have accomplished a new asymmetric catalytic multiple-component tandem coupling.¹² It is worth noting that the catalysts involving simple monodentate chiral oxazolines **5**, which have been previously used as valuable chiral auxiliaries,¹ make the enantiofacial differentiation of **6** effectively occur to give optically active **8** (or **9**).

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Supporting Information Available: General procedure and spectral and analytical data of all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(12) For the review including the examples of the enantioselective tandem reactions in the partially intermolecular and the fully intramolecular modes, see: Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371.