Enantioselective Addition of Allylzinc Reagent to Alkynyl Ketones

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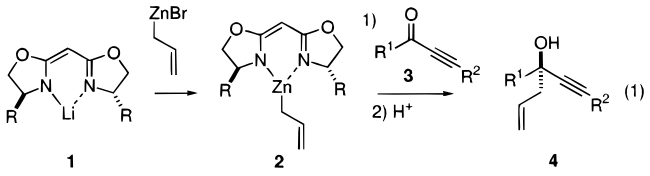
Enantioselectivity over 95% enantiomeric excess (ee) has been achieved routinely in the asymmetric addition of organometallics to various aldehydes.[1] It is not the case for the addition to ketones, in which selectivity is generally lower than 90% ee, and high selectivities have been recorded mainly for alkyl aryl ketones.[2] We report in this paper asymmetric allylation of alkyl alkynyl ketones **3** with the aid of an allylic zinc reagent (**2**), which differentiates a primary alkyl/ethynyl substituent pair in a 95:5 ratio, a *sec*-alkyl/ethynyl pair in 99:1, and a *tert*-alkyl/ethynyl pair in >99.9:0.1. Thus, excellent to virtually complete enantioface selectivity has been achieved in the addition of a carbon nucleophile to a ketone.

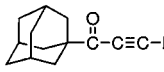
The present allylation reaction makes use of the chiral allylzinc reagent **2** prepared by treatment of allylzinc bromide with a lithiated bisoxazoline (**1**, eq 1).[3] Slow addition of an alkyl alkynyl ketone **3**, to a THF solution of this reagent results in smooth production of the desired allylation product **4** with excellent enantioselectivity (Table 1). High yield could be achieved with



essentially stoichiometric amounts of allylzinc bromide, the chiral ligand, and the ketone, and the ligand can be recovered in 70−90% yield. The following procedure describes the reaction for 1-adamantyl ethynyl ketone, which takes place at −78 °C with 99.6% ee.[4]

A 1.06-M THF solution of allylzinc bromide (6.31 mL, 6.56 mmol) was added to a solution of lithiated bisoxazoline **1** (R = Ph) prepared from bisoxazoline (R = Ph, 2.11 g, 6.87 mmol) and BuLi (1.58-M hexane solution, 4.40 mL) at 0 °C in THF.[3] After 30 min, 1-adamantyl ethynyl ketone (**3**, R^1 = 1-adamantyl, R^2 = H) (1.10 g, 6.25 mmol) in THF (9 mL) was added at −78 °C. After 1 h, the reaction was quenched with 0.25 mL of MeOH/H_2O (1:1) and then diluted with Et_2O. The organic layer was washed with 0.5 N aqueous NaOH, dried (Na_2SO_4), and filtered.

Table 1. Enantioselective Allylation of Alkynyl Ketones **3** with **2** (R = Ph)[a]

entry	Ketone **3**	% ee ($[\alpha]_D^{27}$, *C*)[b]	yield (%)[c]	temp, time (°C, h)
1		>99.9[e] (-29.2, 1.02)	93	-100, 5
		99.6	88	-78, 1
2	*t*-Bu−C(=O)−C≡C−Me	95.4[e]	74	-78, 1
3	*t*-Bu−C(=O)−C≡C−Ph	95.5[d] (-75.9, 0.75)	89	-25, 120
4	*c*-Hex−C(=O)−C≡C−H	98.0[e] (-39.9, 0.87)	65	-100, 5
5	*c*-Hex−C(=O)−C≡C−Me	92.5[e] (-37.3, 1.13)	79	-78, 1
6	$Ph(CH_2)_2$−C(=O)−C≡C−H	90.3[d] (-24.7, 1.04)	86	-100, 5
7	$Ph(CH_2)_2$−C(=O)−C≡C−Me	86.4[e]	82	-78, 1
8	*i*-Pr−C(=O)−C≡C−Me	88.2[e]	82	-25, 1
9	*i*-Pr−C(=O)−C≡C−Ph	67.4[d]	59	-25, 24
10	*i*-Pr−C(=O)−C≡C−$SiMe_3$	65.4[e]	52	-25, 0.5
11	*i*-Pr−C(=O)−C≡C−Si(*i*-Pr)$_3$	25.2[d]	54	-25, 0.5

[a] All reactions were carried out in THF/hexane according to the procedure described in the text. For reasons yet unknown, phenylethynyl ketones were much less reactive than other ketones examined. For assignment of enantioselectivity, see footnote 5. [b] Optical rotations were measured in chloroform. [c] Isolated yield. [d] Determined by HPLC analysis (Daicel CHIRALPAK OD, 4.6 mm i.d. × 250 mm, hexane/*i*-PrOH). [e] Determined by GLC analysis (CHROMPACK CP-Chirasil-DEX CB 0.25 mm i.d. × 25 m).

Concentration of the filtrate afforded a mixture of tertiary alcohol **4** (R^1 = adamantyl, R^2 = H) and a 2:1 complex of bisoxazoline and zinc ($Zn(BOX)_2$). Purification by silica gel chromatography afforded the desired tertiary alcohol (1.12 g, 5.50 mmol, 88% yield) and $Zn(BOX)_2$ (1.66 g, 71.5% recovery), which can be quantitatively converted to the starting BOX-H without racemization.[3] The alcohol is a 99.8:0.2 mixture of *R* and *S* isomers[5] **4** as determined by chiral GLC analysis.

The best enantioselectivity was observed for adamantyl ethynyl ketone (entry 1) which reacted at −100 °C in 93% yield with >99.9% ee as determined by comparison with an authentic mixture. To our knowledge, this is the highest selectivity recorded for asymmetric addition of a carbon nucleophile to a ketone. It is rather remarkable that **2** undergoes smooth addition even at −100 °C, since stereoselectivity in asymmetric carbonyl addition has often been achieved in the expense of reactivity. Excellent selectivity was also achieved for the *tert*-butyl propynyl ketone (95.4%) and *tert*-butyl phenylethynyl ketone (95.5%) (entries 2 and 3).

Cyclohexyl ethynyl ketone was also a highly selective substrate reacting with 98.0% ee and cyclohexyl propynyl ketone with 92.5% ee (entries 4 and 5). A 90.3% ee was also achieved for 2-phenylethyl ethynyl ketone (entry 6). *Thus, the zinc reagent effectively recognizes the small difference between an n-alkyl group and an ethynyl group.* With the ethynyl group being amenable to chain elongation and functional group transforma-

(1) For catalytic enantioselective addition of R_2Zn to aldehydes, see: (a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833−56. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994. For catalytic enantioselective allylation of aldehydes, see: (c) Cozzi, P. G.; Tagliavini, E.; Umanironchi, A. *Gazz. Chim. Ital.* **1997**, *127*, 247−54. (d) Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161−3.

(2) For catalytic reaction, see: Dosa, Peter I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445−6. Ramón, D. J.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 1239−42. For stoichiometric reaction, see: Prabhakar, K. J.; Bhat, K. S.; Perumal, T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432−9. Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 6117−28. Paulsen, H.; Graeve, C.; Hoppe, D. *Synthesis* **1996**, 141−3.

(3) (a) Nakamura, M.; Arai, M.; Nakamura, E. *J. Am. Chem. Soc.* **1995**, *117*, 1179−80. (b) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **1996**, *118*, 8489−90.

(4) Asymmetric allylation reactions were carried out on a 0.5−6.5-mmol scale. Other BOX ligands (R = *t*-Bu or *i*-Pr) gave lower enantioselectivities than BOX (R = Ph).

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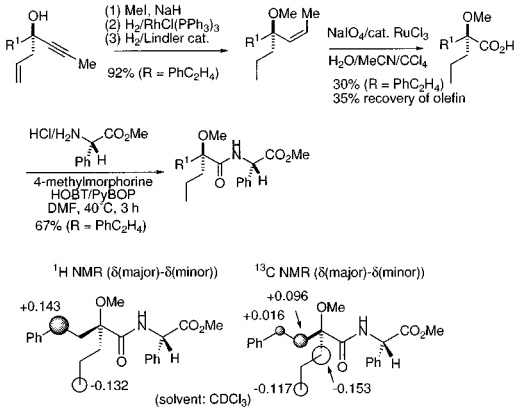
tions, the tertiary alcohol product **4** is a synthetically useful compound as partially illustrated by some transformations in footnote 5.

Several other examples of mediocre selectivities in entries 8−11 serve for consideration of the mechanism of the face selection. Fixing the R^1 group, we changed the R^2 group from a small one to a very bulky one, i.e., methyl, phenyl, Me_3Si, and $(i\text{-}Pr)_3Si$ groups. For the sake of comparison, all reactions were carried out at the same temperature (−25 °C) to find that the enantioselectivity drops precipitously as the steric bulk of R^2 is increased. Slight decrease of the enantioselectivity was also observed for other cases (cf. entries 4/5 and 6/7). Synthetically speaking, the lower selectivity with alkynyl homologue may not be of too much concern, since the ethynyl products may be converted to these products.

On the basis of the absolute stereochemistry determined for entries 4−7, we can construct a model transition state (TS, R = phenyl) as illustrated in Figure 1 (for 3-butyn-2-one) with a line drawing as well as with a 3D picture obtained by ab initio calculations.[6] This model features the sterically less demanding alkynyl group at the axial position in the chair TS of the carbonyl addition. In addition, being differentiated from the H* vinylic hydrogen, the ethynyl group is located in such a manner that it avoids interaction with the BOX Ph group. This model is consistent not only with the increase of the selectivity with a larger R^1 group (increased propensity to be equatorial) but also with the decrease with a larger R^2 group (steric interaction with R).[7]

(5) The stereochemistry of the products in entries 5 (*R*) and 7 (*S*) were determined by the Kusumi method by conversion to the amino esters [Nagai, Y.; Kusumi, T. *Tetrahedron Lett.* **1995**, *36*, 1853. Kusumi recently established that the method is applicable to tertiary alcohols; we thank Prof. T. Kusumi at the University of Tokushima for provision of experimental data before publication (the chemical shift difference data shown below)]. The ethynyl compounds obtained in entries 4 and 6 were chemically correlated to these propynyl compounds by methylation of the acetylene moiety. Others were assigned by analogy.



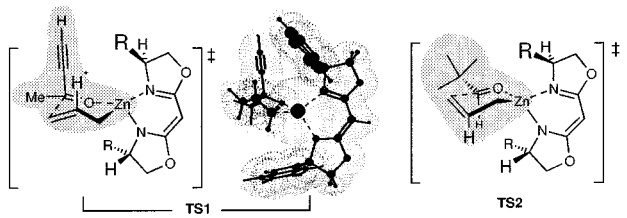


Figure 1.

Finally, we were intrigued to find that *the enantioselectivity drops for an aliphatic aldehyde* (heptanal, 27% ee, absolute configuration not assigned) and that the sense of the selectivity reverses for a bulky aldehyde (pivalaldehyde, (*S*)-62% ee). The latter selectivity conforms to **TS2**.[8] As illustrated by the shadowed areas in **TS1** and **TS2**, the shape of the six-centered TS in **TS1** would be much more readily recognizable by the BOX ligand than that in **TS2** owing to the axially projecting ethynyl group. Thus, the ethynyl group is small enough to be axial in the chair TS (local control), but is large enough to be recognized by the BOX chirality (global control). In the allylation of alkynyl ketones, the local and global factors cooperate to realized high enantioselectivity.[3]

In summary, we have achieved excellent to complete enantioface selectivity with the aid of a highly reactive allylating reagent (**2**). The principle of enantioface recognition suggested by experiments and theoretical models accounts for the uniqueness of the alkynyl ketones as a substrate in asymmetric carbonyl additions.

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Supporting Information Available: Experimental procedures and spectroscopic (GC and HPLC) data of products as well as the geometry of **TS1** and the computational details (5 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(6) The Hartree−Fock method was used with the 3-21G basis set for the core transition structure and the STO-3G basis set for the phenyl substituents of the BOX ligand. *GAUSSIAN 94, Revision D.1*; Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian, Inc.: Pittsburgh, PA, 1995. See the Supporting Information for computational details.

(7) Cf. Christopher, J. H.; Magriotis, P. A.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 10938−9.

(8) Similarly, local and global stereoselection cooperates in asymmetric allylzincation of cyclopropene and cyclic imines with **2**, which favors **TS2** because of the cis geometry of the substrates (ref 3).