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STUDIES ON PALLADIUM COMPLEX CATALYZED AZIDATION AND CARBONYLATION OF ALLYL ESTERS

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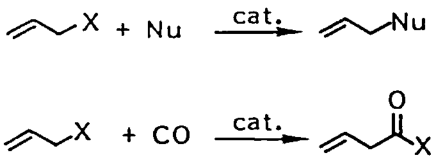
Contents

Chapter 1. General Introduction

Allylic compounds play an important role as key intermediates for various organic transformations. In particular, allyl alcohols serve as key starting compounds for the synthesis of various biologically important compounds such as medicines, e.g. vitamins, hormones and so on. Allyl alcohols occur abundantly in nature and are readily prepared by various synthetic methods. The following two transformations are fundamental; (1) substitution of allylic substituents with nucleophiles (eq 1),[1] (2) insertion of carbon monoxide into allylic positions (eq 2).[2] The displacement of allylic substrate with nucleophiles is the most fundamental transformation. Allyl halides and allyl sulfonates are commonly used as allylic substrates.[1] However, selective preparation of allylic halides (X = Cl, Br) and sulfonates (X = CH_3SO_3, p-TolSO_3) from allyl alcohols is generally difficult because elimination of HX or isomerization of the C=C double bond concurrently takes place.

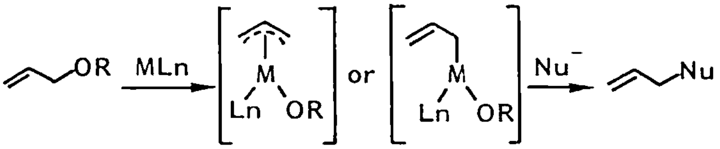


(1)

(2)

Utilization of transition metal complexes in organic synthesis leads to successful entry to the effective and selective transformation of allylic compounds. The substitution reactions of allylic compounds by the aid of transition metal complexes are known to proceed with a variety of substituents (X) such as Cl,[1,3] amines,[4] ammonium salts,[5] ethers,[6] thioethers,[7] NO_2,[8] and CN.[9] However, such transformations do not always proceed stereoselectively. Since allyl acetates are readily prepared from allyl alcohols with high regio- and stereoselectivity, stereoselective transformations are attained with these compounds. Recently, highly reactive allyl phosphates[10] and carbonates[11] have been utilized for the transformation.

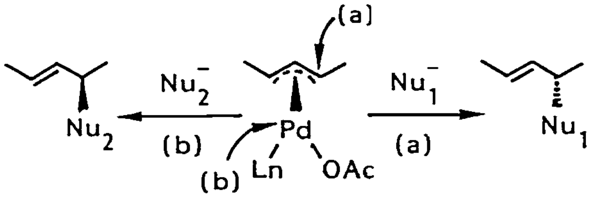
Allyl esters undergo oxidative addition to various transition metal complexes[12] to give π- or σ-allylmetal



(3)

intermediates, which undergo further reactions with various nucleophiles to give substituted allylic compounds (eq 3). Among various metal complexes, palladium complexes are especially useful for such transformations because of their multiform reactivity.

In the organic chemistry of palladium, the reactivities of π-allylpalladium intermediate toward various nucleophiles are classified by the HSAB principle.[1,13,14] Soft nucleophiles such as sodium malonates attack at the allylic carbon from the opposite side of palladium, resulting in the formation of

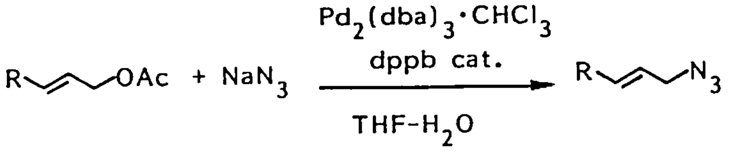


(4)

allylated compounds (path a).[15] On the other hand, hard nucleophiles such as Grignard reagents attack at palladium, and subsequent reductive elimination completes the transformation of allyl acetates (path b) (eq 4).[16] The reactivity of nucleophiles correlates with the stereochemistry of the substitution. The substitution with soft nucleophiles proceeds with retention of configuration at the allylic carbon, while the reaction with hard nucleophiles proceeds with inversion of the configuration.

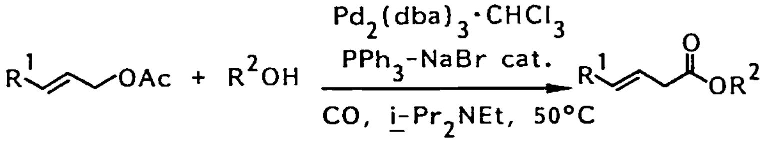
The reaction of π-allylpalladium complexes with carbanions and heteroatom nucleophiles has been extensively investigated.[17] However, there is no report on the reaction with inorganic ion. If the HSAB principle is applicable to the inorganics, the scope of the palladium chemistry will be widely opened. Keeping such a view in mind, the author has engaged in a systematic study on the reactivity of various inorganic reagents toward the π-allylpalladium.

Among many inorganic ions, sodium azide was chosen as one of the candidates of inorganic nucleophiles, since the resulting organic azide can be further transformed into various nitrogen-containing compounds such as allylamines. As the result, the author has developed a useful method for the synthesis of allyl azides from allyl acetates (eq 5).[18]



(5)

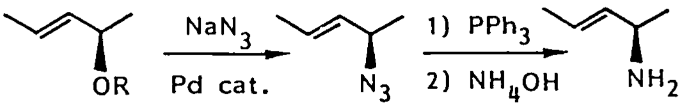
In the course of the study, the author discovered that the acetate ligand of π-allylpalladium is replaced by inorganic salts such as NaBr to give reactive π-allylpalladium halides. This finding allowed the author to develope a novel transformation of allyl acetates into β,γ-unsaturated esters by



(6)

efficient carbonylation (eq 6).[19] Carbonylation of organic compounds, which has attracted considerable attentions in view of the C_1 chemistry, is particularly useful for one-carbon homologation. Although palladium-catalyzed carbonylation of allylic halides is known to proceed, there was no report on the carbonylation of allyl acetates. Realization of the palladium-catalyzed carbonylation of allyl acetates is thought to certainly place a milestone in this field.

In this dissertation, two novel reactions with inoganic salts (NaN_3 and NaBr) are described with the following viewpoints. The growing importance of primary allylamines as enzyme inhibitors[20] and biologically active substances has led to the development of new synthetic methods of primary allylamines.[21] Palladium-catalyzed amination of allylic compounds with ammonia cannot be applied to the synthesis of primary allylamines, because polyallylation results in contamination of secondary and tertiary allylamines. The synthesis of primary allylamines has been carried on by the palladium-catalyzed preparation of N-protected primary allylamines, such as 4,4'-dimethoxybenzhydrylamine,[22] p-toluenesulfonamide,[23] phthalimide,[24] and di-t-butyl iminodicarbonate[25] and subsequent removal of the protecting groups. However, the deprotection of these N-protected group is often quite tedious. As a synthon of primary amino group, the author employed azide ion in the place of ammonia. Chapter 2 describes that the palladium(0)-catalyzed reaction of allyl acetates with sodium azide gives allyl azides with high chemo- and stereoselectivity. The azide ion acts as a soft nucleophile to π-allylpalladium complexes. The palladium catalyzed azidation of allyl esters gives allyl azides with net retention of configuration (eq 7). The stereochemical course is opposite to that of S_N2 type azidation (eq 8).[26] Primary allylamines thus obtained can be prepared from the corresponding allyl esters stereoselectively by one-pot reactions. Treatment of allyl azides with triphenylphosphine and



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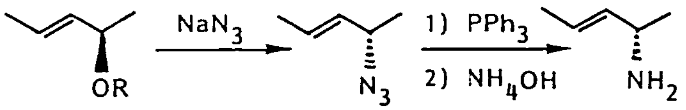
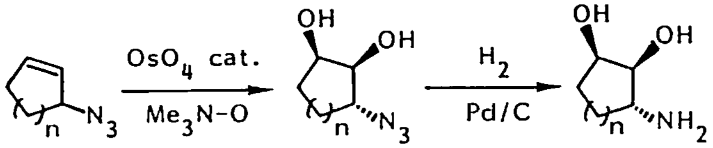


(8)

subsequently with aqueous ammonium solution gives primary allylamines highly efficiently.[27]

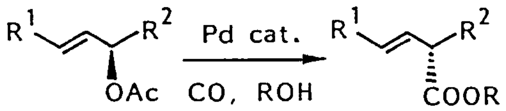
Given in Chapter 3 is an application of allyl azides to synthetic chemistry, the subject of which is OsO_4 catalyzed oxidation of allyl azides to azidodiols. Of remarkable in the



(9)

oxidation is the production of 3-aminocyclohexane-1,2-diol with high stereoselectivity (eq 9). 3-Amino-1,2-diols are potentially useful precursors for the synthesis of naturally occuring compounds such as aminosugars,[28,29] nucleosides,[30] and antibiotics.[31] In particular, the 3-amino-1,2-diol functionality in five- and six-membered ring compounds occurs in many biologically active natural products, and hence convenient synthetic routes to these compounds are desirable. The oxidation of cyclic allyl azides provides a novel synthetic route to these compounds.

β,γ-Unsaturated carbonyl compounds are useful building blocks for the synthesis of antibiotics such as rifamycin,[32] jasplakinolide,[33] domoic acid,[34] and so on.[35] Furthermore, β,γ-unsaturated esters derived from terpenoid allyl alcohols have been utilized as the precursor of various perfumes. Carbonylation of allylic compounds appears to be the most attractive route to β,γ-unsaturated carbonyl compounds. However, palladium-catalyzed carbonylation of synthetically more important allylic alcohols, ethers, amines, and acetates is difficult, and severe reaction conditions are required.[36] Carbonylation of derivatives of allyl alcohols under mild conditions is limited to that of allyl carbonates[37] and allyl phosphates.[38] Chapter 4 describes that allyl acetates are carbonylated under mild conditions using Pd(0)-NaBr catalyst in alcohols to give β,γ-unsaturated esters (eq 10). Sodium



(10)

bromide acts as hard nucleophile toward π-allylpalladium formed in situ and replaces with the acetate ligand. The carbonylation of allyl esters takes place with inversion of configuration at the allylic carbon. The scope of the carbonylation as well as the mechanism will be described in detail.

References

1. (a) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385. (b) Trost, B. M.; Verhoeven, T. R. *Compr. Organomet. Chem.* **1982**, *8*, 799. (c) Tsuji, J. *Organic Synthesis with Palladium Compounds*, Springer Verlag, Berlin, 1980.
2. **Ni**; (a) Chiusoli, G. P.; Cassar, L. *Angew. Chem.*, *Int. Ed. Engl.* **1967**, *6*, 124. **Co**; (b) Heck, R. F.; Breslow, D. S. *J. Am. Chem. Soc.* **1963**, *85*, 2779. **Pd**; (c) Dent, W. T.; Long, R.; Whitfield, G. H. *J. Chem. Soc.* **1964**, 1588. (d) Tsuji, J.; Kiji, J.; Imamura, S.; Morikawa, M. *J. Am. Chem. Soc.* **1964**, *86*, 4350. (e) Medema, D.; van Helden, R.; Kohll, C. F. *Inorg. Chim. Acta* **1969**, *8*, 255. (f) Knifton, J. F. *J. Organomet. Chem.* **1980**, *188*, 223. (g) Imamura, S.; Tsuji, J. *Tetrahedron* **1969**, *25*, 4187.
3. (a) Fitton, P.; Johnson, M. P.; McKeon, J. E. *J. Chem. Soc.*, *Chem. Commun.* **1968**, 6. (b) Hartley, F. R.; Jones, S. R. *J. Organomet. Chem.* **1974**, *66*, 465.
4. (a) Atkins, K. E.; Walker, W. E.; Manyik, R. M. *Tetrahedron Lett.* **1970**, 3821. (b) Weir, J. R.; Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1980**, *45*, 4926. (c) Kumobayashi, H.; Mitsuhashi, S.; Akutagawa, S.; Ohtsuka, S. *Chem. Lett.* **1986**, 157. (d) Chalk, A. J.; Wertheimer, V.; Magennis, S. A. *J. Mol. Catal.* **1982**, *19*, 189.
5. (a) Hirao, T.; Yamada, N.; Ohshiro, Y.; Agawa, T. *J.*

Organomet. Chem. **1982**, *236*, 409. (b) Hosomi, A.; Hoashi, K.; Kohra, S.; Tominaga, Y.; Otaka, K.; Sakurai, H. *J. Chem. Soc.*, *Chem. Commun.* **1987**, 570.

6. (a) Takahashi, K.; Miyake, A.; Hata, G. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 230. (b) Onoue, H.; Moritani, I.; Murahashi, S.-I. *Tetrahedron Lett.* **1973**, 121. (c) Fiaud, J. C.; Gournay, A. H. D.; Larcheveque, M.; Kagan, H. B. *J. Organomet. Chem.* **1978**, *154*, 175. (d) Yamamoto, T.; Akimoto, M.; Yamamoto, A. *Chem. Lett.* **1983**, 1725.

7. (a) Okamura, H.; Takei, H. *Tetrahedron Lett.* **1979**, 3425. (b) Hutchins, R. O.; Leaen, K. *J. Org. Chem.* **1982**, *47*, 4380. (c) Kotake, H.; Yamamoto, T.; Kinoshita, H.; *Chem. Lett.* **1982**, 1331. (d) Mohri, M.; Kinoshita, H.; Inomata, K.; Kotake, H. *Chem. Lett.* **1985**, 451. (e) Auburn, P. R.; Whelan, J.; Bosnich, B. *J. Chem. Soc.*, *Chem. Commun.* **1986**, 146.

8. (a) Ono, N.; Hamamoto, I.; Kaji, A. *J. Chem. Soc.*, *Chem. Commun.* **1982**, 821. (b) Tamura, R.; Hegedus, L. S. *J. Am. Chem. Soc.* **1982**, *104*, 3727. (c) Ono, N.; Hamamoto, I.; Kaji, A. *Synthesis* **1985**, 950. (d) Tamura, R.; Kai, Y.; Kakihana, M.; Hayashi, K.; Tsuji, M.; Nakamura, T.; Oda, D. *J. Org. Chem.* **1986**, *51*, 4375. (e) Tamura, R.; Kato, M.; Saegusa, K.; Kakihana, M.; Oda, D. *J. Org. Chem.* **1987**, *52*, 4121.

9. Guibe, F.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.*

1982, 23, 5055.

10. (a) Tanigawa, Y.; Nishimura, K.; Kawasaki, A.; Murahashi, S.-I.; Tetrahedron Lett. 1982, 23, 5549. (b) Murahashi, S.-I.; Imada, Y.; Taniguchi, Y.; Kodera, Y. Tetrahedron Lett. 1988, 29, 2973.

11. (a) Minami, I.; Shimizu, I.; Tsuji, J. J. Organomet. Chem. 1985, 296, 269. (b) Tsuji, J.; Minami, I. Acc. Chem. Res. 1987, 20, 140.

12. (a) Mo; Bailey, N. A.; Kita, W. G.; McCleverty, J. A.; Murray, A. J.; Mann, B. E.; Walker, N. W. J. J. Chem. Soc., Chem. Commun. 1974, 592; Brisdon, B. J.; Griffin, G. F. J. Chem. Soc., Dalton Trans. 1975, 1999; Adams, R. D.; Chodosh, D. F.; Faller, J. W.; Rosan, A. M. J. Am. Chem. Soc. 1979, 101, 2570; Trost, B. M.; Lautens, M. J. Am. Chem. Soc. 1982, 104, 5543; Tatsumi, T.; Hashimoto, K.; Tominaga, H.; Mizuta, Y.; Hata, K.; Hidai, M.; Uchida, Y. J. Organomet. Chem. 1983, 252, 105; Trost, B. M.; Lautens, M. J. Am. Chem. Soc. 1983, 105, 3343; Trost, B. M.; Lautens, M. Organometallics 1983, 2, 1687; Faller, J. W.; Chao, K.-H. J. Am. Chem. Soc. 1983, 105, 3893; Faller, J. W.; Chao, K.-H. Organometallics, 1984, 3, 927; Faller, J. W.; Linebarrier, D. Organometallics 1988, 7, 1670. (b) W; Trost, B. M.; Hung, M.-H. J. Am. Chem. Soc. 1983, 105, 7757. (c) Fe; Ladoulis, S. J.; Nicholas, K. M. J. Organomet. Chem. 1985, 285, C13; Silverman, G. S.;

Strickland, S.; Nicholas, K. M. *Organometallics* **1986**, *5*, 2117; Xu, Y.; Zhou, B. *J. Org. Chem.* **1987**, *52*, 974; Roustan, J. L.; Houlihan, F. *J. Organomet. Chem.* **1988**, *353*, 215; Zhou, B.; Xu, Y. *J. Org. Chem.* **1988**, *53*, 4421. (d) **Co**; Roustan, J. L.; Merour, J. Y.; Houlihan, F. *Tetrahedron Lett.* **1979**, 3721. (e) **Ni**; Cuvigny, T.; Julia, M. *J. Organomet. Chem.* **1983**, *250*, C21; Consiglio, G.; Morandini, F.; Piccolo, O. *J. Chem. Soc.*, *Chem. Commun.* **1983**, 112; Hiyama, T.; Wakasa, N. *Tetrahedron Lett.* **1985**, *26*, 3259; Lu, X.; Zhu, J. *J. Organomet. Chem.* **1986**, *304*, 239; Lu, X.; Zhu, J.; Huang, J.; Tao, X. *J. Mol. Catal.* **1987**, *41*, 235. (f) **Pd**; Yamamoto, T.; Saito, O.; Yamamoto, A. *J. Am. Chem. Soc.* **1981**, *103*, 5600; Yamamoto, T.; Akimoto, M.; Saito, O.; Yamamoto, A. *Organometallics* **1986**, *5*, 1559 and references cited therein.

13. (a) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533. (b) Pearson, R. G.; Songstad, J. *J. Am. Chem. Soc.* **1967**, *89*, 1827. (c) Pearson, R. G. *Symmetry Rules for Chemical Reactions*, John Wiley, New York, 1976. (d) Ho, T. L. *Chem. Rev.* **1975**, *75*, 1.
14. (a) Keinan, E.; Roth, Z. *J. Org. Chem.* **1983**, *48*, 1769. (b) Fiaud, J.-C.; Legros, J.-Y. *J. Org. Chem.* **1987**, *52*, 1907.
15. (a) Trost, B. M.; Verhoeven, T. R. *J. Org. Chem.* **1976**, *41*, 3215. (b) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730. (c) Fiaud, J. C.; Malleron, J. L.

Tetrahedron Lett. **1980**, 4437. (d) Fiaud, J. C.; Malleron, J. L. *J. Chem. Soc., Chem. Commun.* **1981**, 1159. (e) Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, 2591. (f) Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, 2595.

16. (a) Matsushita, H.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1982**, 160. (b) Hayashi, Y.; Riediker, M.; Temple, J. S.; Schwartz, J. *Tetrahedron Lett.* **1981**, *22*, 2629; Temple, J. S.; Riediker, M.; Schwartz, J. *J. Am. Chem. Soc.* **1982**, *104*, 1310. (c) Gendreau, Y.; Normant, J. F. *Tetrahedron Lett.* **1979**, *25*, 1517. (d) Consiglio, G.; Morandini, F.; Piccolo, O. *J. Am. Chem. Soc.* **1981**, *103*, 1846. (e) Keinan, E.; Greenspoon, N. *Tetrahedron Lett.* **1982**, 241.
17. Fiaud, J. C. *J. Chem. Soc., Chem. Commun.* **1983**, 1055 and Ref 14.
18. Murahashi, S.-I.; Tanigawa, Y.; Imada, Y.; Taniguchi, Y. *Tetrahedron Lett.* **1986**, *27*, 227.
19. Murahashi, S.-I.; Imada, Y.; Taniguchi, Y.; Higashiura, S. *Tetrahedron Lett.* **1988**, *29*, 4945.
20. (a) **GABA-transaminase**; Lippert, B.; Metcalf, B. W.;Jung, M. J.; Casara, P. *Eur. J. Biochem.* **1977**, *74*, 441; McDonald, I. A.; Palfreyman, M. G.; Jung, M.; Bey, P. *Tetrahedron Lett.* **1985**, *26*, 4091. (b) **Monoamine oxidase**; Rando, R. R.; Eigner, A. *Mol. Pharmacol.* **1977**, *13*, 1005; Silvermann, R. B.; Hiebert, C. K.; Vazquez, M. L. *J. Biol. Chem.* **1985**,

260, 14648; McDonald, I. A.; LaCoste, J. M.; Bey, P.; Palfreyman, M. G.; Zreika, M. *J. Med. Chem.* **1985**, *28*, 186. (c) **Dopamine β-hydroxylase;** Padgette, S. R.; Wimalasena, K.; Herman, H. H.; Sirimanne, S. R.; May, S. W. *Biochemistry* **1985**, *24*, 5826; Bargar, T. M.; Broersma, R. J.; Creemer, L. C.; McCarthy, J. R.; Hornsperger, J.-M.; Palfreyman, M. G.; Wagner, J.; Jung, M. J. *J. Med. Chem.* **1986**, *29*, 315.

21. Cheikh, R. B.; Chaabouni, R.; Laurent, A.; Mison, P.; Nafti, A. *Synthesis* **1983**, 685.
22. Trost, B. M.; Keinan, E. *J. Org. Chem.* **1979**, *44*, 3451.
23. Byström, S. E.; Aslanian, R.; Bäckvall, J.-E. *Tetrahedron Lett.* **1985**, *26*, 1749.
24. Inoue, Y.; Taguchi, M.; Toyofuku, M.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3021.
25. Connell, R. D.; Rein, T.; Åkermark, B.; Helquist, P. *J. Org. Chem.* **1988**, *53*, 3845.
26. (a) Teng, C.-Y. P.; Ganem, B. *Tetrahedron Lett.* **1982**, *23*, 313. (b) Ortar, G.; Paradisi, M. P.; Morera, E.; Romeo, A. *J. Chem. Soc.*, *Perkin Trans. I.* **1978**, 4.
27. Vaultier, M.; Knouzi, N.; Carrié, R. *Tetrahedron Lett.* **1983**, *24*, 763.
28. (a) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1981**, *46*, 227. (b) Hauser, F. M.; Ellenberger, S. R.; Clardy, J. C.; Bass, L. S. *J. Am. Chem. Soc.* **1984**, *106*, 2458. (c) Hauser, F.

M.; Ellenberger, S. R.; Rhee, R, P. J. Org. Chem. 1987, 52, 5041. (d) Whitten, J. P.; McCarthy, J. R.; Whalon, M. R. J. Org. Chem. 1985, 50, 4399.

29. (a) Castellanos, L.; Cleophax,J.; Colas, C.; Cero, S. D.; LeBoul, J.; Mercier, D.; Olesker, A.; Rolland, A.; Quillet-Sire, B.; Sepulchre, A. M. Carbohydr. Res. 1980, 82, 283. (b) Kuhlmyer, R.; Schwesinger, R.; Prinzbach, H. Tetrahedron Lett. 1984, 23, 3429. (c) Schubert, J.; Schwesinger, R.; Prinzbach, H. Angew. Chem., Int. Ed. Engl. 1984, 23, 167. (d) Georges, M.; Fraser-Reid, B. Tetrahedron Lett. 1981, 22, 4635. (e) Pauls, H. W.; Fraser-Reid, B. J. Am. Chem. Soc. 1980, 102, 3956.

30. (a) Katze, J. R.; Gunduz, U.; Smith D. L.; Cheng, C. S.; McCloskey, J. A. Biochemistry 1984, 23, 1171. (b) Arita, M.; Adachi, K.; Ito, Y.; Sawai, H.; Ohno, M. J. Am. Chem. Soc. 1983, 105, 4049.

31. Askin, D.; Angst, C.; Danishefsky, S. J. Org. Chem. 1987, 52, 622.

32. Corey, E. J.; Hase, T. Tetrahedron Lett. 1979, 335.

33. Grieco, P. A.; Hon, Y. S.; Perez-Medrano, A. J. Am. Chem. Soc. 1988, 110, 1630.

34. Ohfune, Y.; Tomita, M. J. Am. Chem. Soc. 1982, 104, 3511.

35. (a) Biloski, A. J.; Wood, R. D.; Ganem, B. J. Am. Chem. Soc. 1982, 104, 3233. (b) Rajendra, G.; Miller, M. J. J. Org. Chem. 1987, 52, 4471. (c) Barrish, J. C.; Lee, H. L.;

Pizzolato, G.; Baggiolini, E. G.; Uskokovic̈, M. R. *J. Org. Chem.* **1988**, *53*, 4282. (d) Tufariello, J. J.; Mullen, G. B.; Tegeler, J. J. Trybulski, E. J.; Wong, S. C.; Ali, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2435. (e) Takatsu, N.; Ohmiya, S.; Otomasu, H. *Chem. Farm. Bull.* **1987**, *35*, 891. (f) Chuman, T.; Sivinsky, J.; Heath, R. R.; Calkins, C. O.; Tumlinson, J. H.; Battiste, M. A.; Wydra, R. L.; Strekowski, L.; Nation, J. L. *Tetrahedron Lett.* **1988**, *29*, 6561. (g) Battiste, M. A.; Rocca, J. R.; Wydra, R. L.; Tumlinson, J. H., III.; Chuman, T. *Tetrahedron Lett.* **1988**, *29*, 6565.

36. (a) Tsuji, J.; Kiji, J.; Imamura, S.; Morikawa, M. *J. Am. Chem. Soc.* **1964**, *86*, 4350. (b) Medema, D.; van Helden, R.; Kohll, C. F. *Inorg. Chim. Acta* **1969**, *8*, 255.

37. (a) Tsuji, J.; Sato, K.; Okumoto, H. *Tetrahedron Lett.* **1982**, *23*, 5189. (b) Tsuji, J.; Sato, K.; Okumoto, H. *J. Org. Chem.* **1984**, *49*, 1341. (c) Tamaru, Y.; Bando, T.; Hojo, M.; Yoshida, Z. *Tetrahedron Lett.* **1987**, *28*, 3497.

38. Murahashi, S.-I.; Imada, Y. *Chem. Lett.* **1985**, 1477.

Chapter 2. Palladium(0)-Catalyzed Azidation of Allyl Esters. Selective Synthesis of Allyl Azides, Primary Allylamines, and Related Compounds

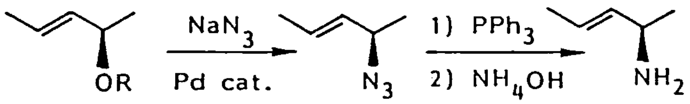
Introduction

The growing importance of primary allylamines as enzyme inhibitors[1] and biologically active substances has led to the development of new synthetic methods of primary allylamines.[2,3]

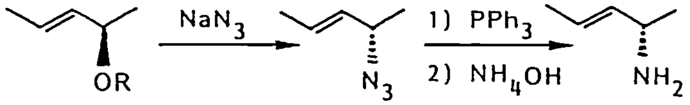
Palladium-catalyzed amination of allylic compounds with secondary amines has been extensively studied and proved to be efficient for the synthesis of tertiary amines,[4] and various nitrogen containing biologically active compounds such as alkaloids have been synthesized.[5] However, the palladium-catalyzed reactions with ammonia or primary amines cannot be applied to the synthesis of primary or secondary allylamines, because polyallylation results in contamination of secondary and tertiary allylamines. Therefore, for the synthesis of primary allylamines preparation of N-protected primary allylamines, such as 4,4'-dimethoxybenzhydrylamine,[6] p-toluenesulfonamide,[7] phthalimide,[8] and di-t-butyl iminodicarbonate[9] by palladium-catalyzed reactions and subsequent removal of the protecting groups has been utilized. For the synthesis of secondary allylamines, the author has found the palladium(0)-catalyzed synthesis of N-allylhydroxylamines, which can be readily converted into secondary allylamines by subsequent reduction of

N-hydroxylamino group.[10]

The author has also found that the palladium(0)-catalyzed reaction of allyl esters with azide ion gives the corresponding allyl azides under mild conditions. The palladium-catalyzed azidation of allyl esters gives allyl azides with net retention of configuration (eq 1).[11] The stereochemical course is opposite to that of S_N2 type azidation (eq 2).[12] Allyl azides thus



(1)



(2)

obtained are versatile synthetic intermediates such as 1,3-dipoles[13] and precursors of various substances such as nitrenes.[14] Primary allylamines can be prepared from the corresponding allyl esters stereoselectively by one-pot reactions. Treatment of allyl azides thus obtained with triphenylphosphine and subsequently with aqueous ammonium solution gives primary allylamines highly efficiently.

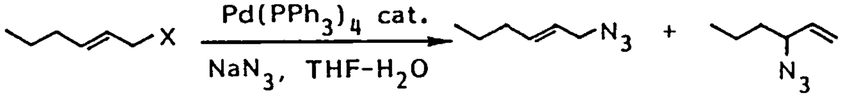
Described in this chapter is a systematic investigation of the palladium-catalyzed azidation of allyl esters, stereochemistry, mechanism, and their synthetic applications, particularly synthesis of primary allylamines.

Results and Discussion

Selective Synthesis of Allyl Azides: Nucleophilic substitutions of alkyl halide by azide ion is a well established method for the synthesis of alkyl azides. The low solubility of inorganic azides in organic solvent is important problem. The problem have been solved by the use of ammonium azides,[15] phase transfer conditions,[16] and ultrasonic irradiation.[17] Allyl azides are similarly obtained from allyl halides.[12a] Further, the direct conversion of alcohols to azides is achieved by using combination of dangerous HN_3 and BF_3:OEt_2[18] or PPh_3/azoester.[19] The azidation of allyl sulfonates and trifluoroacetates[12b] in an aprotic polar solvent, such as DMSO, DMF, and HMPA, has been used for the synthesis of allyl azides. However, these reactions requires drastic conditions. Therefore, the author has investigated palladium(0)-catalyzed transformation of allyl acetates to allyl azides under mild reaction conditions.

Palladium(0)-catalyzed reactions of allyl acetates and allyl phosphates with azide anion in aqueous THF gave allyl azides highly efficiently. The azidation of (E)-2-hexen-1-yl derivatives (**1a**-**i**) was examined in detail as a typical example. (E)-2-Hexen-1-yl phosphate (**1a**) and acetate (**1e**) did not react with sodium azide in aqueous THF. However, the addition of 2 mol% of $Pd(PPh_3)_4$ induced the azidation dramatically to give a 70:30 mixture of 2-hexen-1-yl azide (**2a**) and 1-hexen-3-yl azide (**2b**) (eq 3), the ratio being at equilibrium because of rapid

1,3-rearrangement.[20] The reactivity of the leaving groups of various esters has been found to be in the order of $(EtO)_2PO_2$-



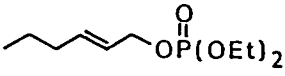
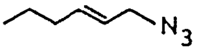
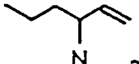
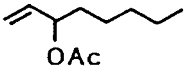
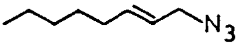
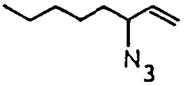
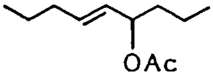
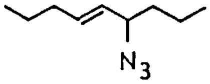
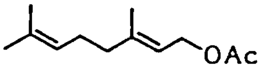
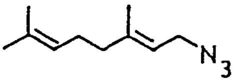
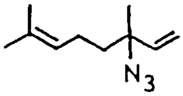
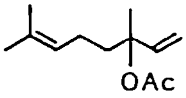
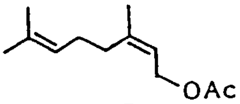
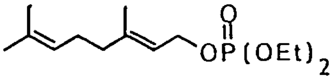
(3)

1a-i 2a 2b

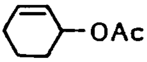
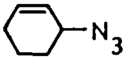
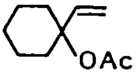
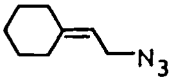
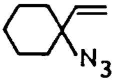
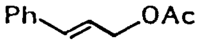
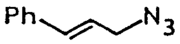
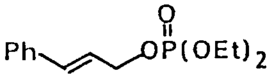
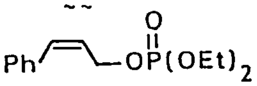
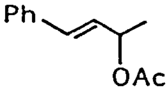
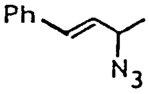
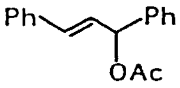
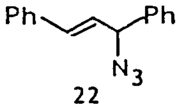
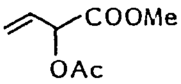
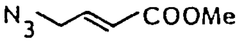
(1a) $\sim$ $EtOCO_2$- (1b) $\sim$ CF_3CO_2- (1c) $\sim$ $PhCO_2$- (1d) ≥ CH_3CO_2- (1e). The catalytic activity of various palladium complexes for the azidation of cis-5-methoxycarbonyl-2-cyclohexen-1-yl acetate (3) at 50 °C is in the order of $Pd(PPh_3)_4$ $\sim$ $Pd_2(dba)_3{\cdot}CHCl_3$-$4PPh_3$ > $Pd(acac)_2$-$2PPh_3$. $Pd_2(dba)_3{\cdot}CHCl_3$-$4PPh_3$ is more reactive than $Pd(dba)_2$-$2PPh_3$. The reaction requires about 20% of water in order to solve sodium azide. The solvent effect for the conversion of 3 and the product yield is in the order of THF > DME > DMF $\sim$ acetone > CH_3CN $\sim$ EtOH $\sim$ hexane $\sim$ toluene.

The representative results for the azidation of various allyl esters catalyzed by $Pd(PPh_3)_4$ in aq THF are summarized in Table I. The azidations of geranyl (5), linalyl (6), and neryl acetates (7) at 40 °C for 30 min gave a same mixture of geranyl azide (8a) and linalyl azide (8b) (80:20), respectively, although the conversions of 5 and 7 were 25% and that of 6 was 94%. The azidations of 5 and 7 at 50 °C for 2 h gave 8a-b in 64% and 79% isolated yields, respectively. (E)- and (Z)-Cinnamyl diethyl phosphates (18 and 19) were converted into (E)-cinnamyl azide (17), irrespective of the stereochemistry of the starting

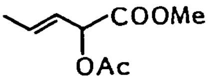
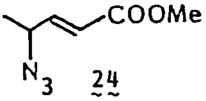
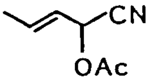
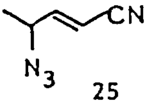
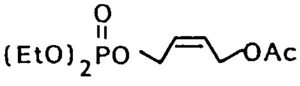
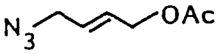
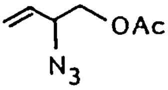
Table I. The Palladium Catalyzed Azidation of Allyl Esters.[a]

entry	allyl ester	allyl azide	yield,[b] % (ratio of α:γ[c])
1	 1a	 2a  2b	78[d] (70:30)
2		 10a  10b	97 (70:30)
3		 11	94
4	 5	 8a  8b	64 (80:20)
5	 6	8a + 8b	91 (80:20)
6	 7	8a + 8b	79 (80:20)
7	 12	8a + 8b	83, 85[e] (80:20)

(continued Table I)

8		 13	70
9	 14	 15a  15b	78 (50:50)
10	 16	 17	92
11	 18	17	82, 85^e
12	 19	17	73
13	 20	 21	95
14		 22	96
15		 23	96

(continued Table I)

16		 24	60
17		 25	80
18	 26	 27a  27b	92 (80:20)

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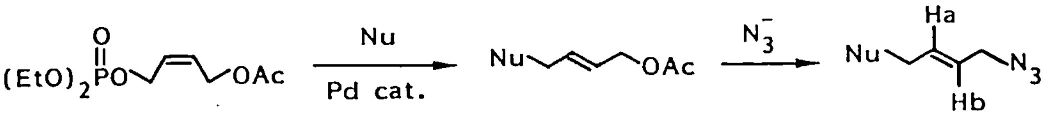
[a] The reaction was carried out according to the general procedure described in the experimental section. [b] Isolated yield by column chromatography (SiO_2). [c] The ratio of α and γ allyl azides was determined by ^1H NMR analysis. [d] The solvent is diethyl ether. [e] $TMSN_3-Bu_4NF$ was used in dry THF.

substrate. The reaction of allyl acetates bearing an electron withdrawing substituents such as Ph, CN, and COOR gave exclusively 3-substituted allyl azides which are thermodynamically stable.

The palladium(0)-catalyzed azidation of allyl phosphates under the anhydrous conditions is performed by using trimethylsilyl azide (TMSN$_3$) in the presence of Bu$_4$NF,[20d] although the same treatment with allyl acetates was unsuccessful. Generally, the reactivity of allyl phosphates is much higher than that of allyl acetates. Typically, the azidation of (*Z*)-4-acetoxy-2-buten-1-yl diethyl phosphate (**26**)[4f] with 1 equiv of azide ion gave a mixture of (*E*)-4-azido-2-buten-1-yl acetate (**27a**) and 2-azido-3-buten-1-yl acetate (**27b**) (80:20) in 92% yield.

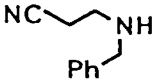
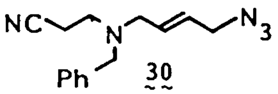
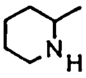
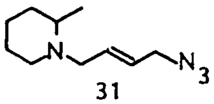
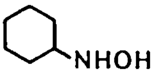
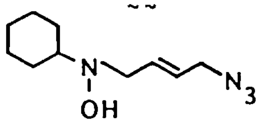
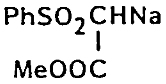
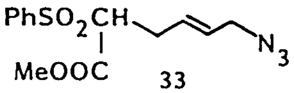
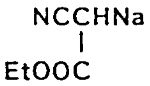
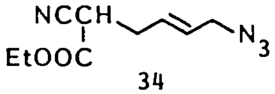
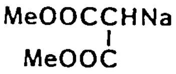
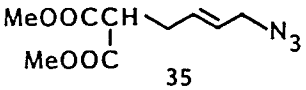
Palladium-catalyzed sequencial substitution of **26** gives (*E*)-4-substituted-2-buten-1-yl azides (**29**) selectively (Scheme I). Amination or alkylation of **26** at room temperature gives 4-substituted-2-buten-1-yl acetate (**28**), which undergoes the azidation without isolation of **28**. The representative results for the sequencial azidation of **26** using various nucleophiles are summarized in Table II. It is noteworthy that (*E*)-isomers are

Scheme I



26 **28** **29**

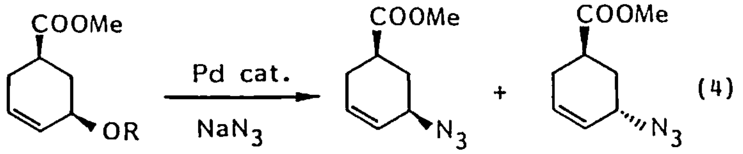
Table II. The Sequencial Reaction of (*Z*)-4-Acetoxy-2-butenyl Diethyl Phosphate (**26**).

entry	Nu_1	Nu_2	product	yield,[a] %
1		NaN_3	 **30**	76
2		NaN_3	 **31**	80
3		NaN_3	 **32**	92
4	 $PhSO_2CH(Na)COOMe$	NaN_3	 **33**	78
5	 $NCCH(Na)COOEt$	NaN_3	 **34**	75
6	 $MeOOCCH(Na)COOMe$	NaN_3	 **35**	76

[a] Isolated yields by column chromatography.

obtained exclusively, irrespective of the stereochemistry of the starting substrates. (E)-Stereochemistry was confirmed by the coupling constant of the olefinic protons (J_{Ha-b}= $\sim$15Hz). Quite recently, Waegell reported that palladium-catalyzed reaction of 1,3-diene monoepoxides with azide ion gives 4-azido-2-alkenols highly efficiently.[21]

The stereochemical course of the azidation was examined precisely concerning the azidation of cis-5-methoxycarbonyl-2-cyclohexen-1-yl esters (eq 4). The reaction of acetate **3** with sodium azide in the presence of 5 mol% of $Pd(PPh_3)_4$ at 50 °C for 2 h gave a mixture of cis- and trans-methyl 5-azido-3-cyclohexene-carboxylate (**4a** and **4b**) (38:62) in 92% yield. The addition of 2 equiv of 1,4-bis(diphenylphosphino)butane (dppb) caused a drastic change in the ratio of **4a**:**4b** (84:16), although the yield became low (38%). Therefore, the effect of various palladium catalysts was examined in detail. The typical results are summarized in Table III. The addition of a bidentate phosphine such as 1,4-bis(diphenylphosphino)butane (dppb), 1,3-bis(diphenylphosphino)propane (dppp), 1,5-bis(diphenylphosphino)pentane, and



3 OR=OAc
36 OR=OP(O)(OEt)$_2$
4a
4b

Table III. Palladium Catalysts for the Azidation of 3.[a]

entry	Pd cat.	Ligand	conv.[b] %	yield of 4[b] %	ratio[b] 4a:4b
1	$Pd(PPh_3)_4$	none	100	92	38:62
2	"	LiCl[c]	100	98	38:62
3	"	2 dppb	41	38	84:16
4	$Pd_2(dba)_3\cdot CHCl_3$	4 PPh_3	74	72	71:29
5	"	2 $Ph_2PCH_2PPh_2$	2	2	92: 8
6	"	2 $Ph_2P(CH_2)_2PPh_2$	13	5	92: 8
7	"	2 dppp	57	41	95: 5
8	"	1 dppb	22	22	88:12
9	"	2 "	71	56	91: 9
10	"	4 "	95	92	91: 9
11	"	"	80	77	96: 4[d]
12	"	8 "	99	45	91: 9
13	"	2 $Ph_2P(CH_2)_5PPh_2$	100	80	76:24
14	"	2 dppf[e]	100	86	82:18
15	"	2 TRIPHOS[f]	38	28	94: 6
16	$Pd(acac)_2$	2 PPh_3	78	65	49:51
17	"	2 dppb	14	9	79:21
18	$Pd(PCy_3)_2$	none	14	2	55:45
19	"	2 dppb	11	10	68:32

(continued Table III)

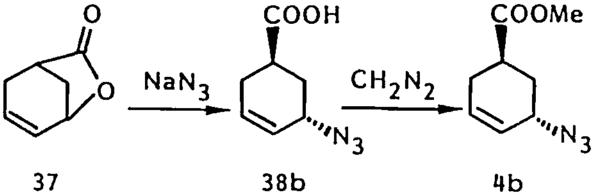
20	$Pd(dba)_2$	2 PPh_3	25	17	91: 9
21	"	2 dppb	2	2	91: 9
22	$Pd(OAc)_2$	"	1	1	90:10
23	$Pd(CF_3CO_2)_2$	2 PPh_3	1	1	62:38

[a] A mixture of **3** (0.50 mmol), palladium catalysts (5 mol%), ligand, and NaN_3 (0.55 mmol) in THF (2.0 mL) and water (0.5 mL) was stirred at 50 °C for 2 h under Ar. [b] GLC analysis. [c] An equimolar amount was used. [d] Palladium catalyst (2 mol%). [e] 1,1'-Bis(diphenylphosphino)-ferrocene. [f] Bis(2-diphenylphosphinoethyl)phenylphosphine.

1,1'-bis(diphenylphosphino)ferrocene (dppf) to $Pd_2(dba)_3 \cdot CHCl_3$ resulted in high stereoselective azidation. The reactivity of a diphosphine, $Ph_2P(CH_2)_nPPh_2$ is in the order of $n = 1 \ll 2 < 3 < 4 < 5 <$ ferrocenyl. Considering the selectivity of **4a**/**4b**, dppb seems to be the best ligand. This may be due to the formation of 7-membered π-allylpalladium diphosphine complex. The addition of 4 equiv of dppb gave the best result of the formation of **4a**, although the addition of large excess of dppb decreased the yield.

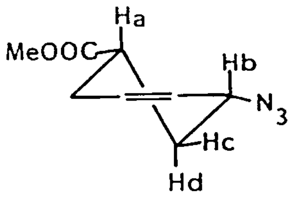
Phosphorylation of *cis*-methyl 5-hydroxyl-3-cyclohexenecarboxylate with diethyl chlorophosphate afforded *cis*-diethyl 5-methoxycarbonyl-2-cyclohexen-1-yl phosphate (**36**) stereoselectively. Stereochemical assignment of **36** was based on the ^1H NMR (100 MHz) spectrum. The proton resonance at δ 2.85 (1 H, ddd, J = 12.3, 12.3, and 9.4 Hz) was assigned as the C-6 axial hydrogen. The large geminal coupling, as well as two large vicinal coupling constants, clearly indicates that the protons at C-1 and C-5 are pseudoaxial, thus confirming the *cis*-configuration. The ^{31}P NMR spectrum of *cis*-**36** appears at δ -1.25 ppm as a single product, and no absorption corresponding to *trans*-phosphate (δ -1.53 ppm) was detected. The reaction of phosphate **36** with NaN_3 in the presence of $Pd_2(dba)_3 \cdot CHCl_3$-dppb catalyst gave **4a** highly stereoselectively in 99% yield (**4a**:**4b** = 97:3). In contrast, the direct S_N2 substitution of 7-oxabicyclo[3.2.1]oct-2-en-6-one (**37**) with NaN_3 at 50 °C gave **38b** in 83% yield along with 2% of **38a**.

The azidation of lactone 37 in the presence of $Pd(OAc)_2$-$2PPh_3$ catalyst also gave cis-azidocarboxylic acid 38a in 92% yield (38a: 38b = 95:5). The acid 38b was converted into 4b upon treatment with diazomethane.

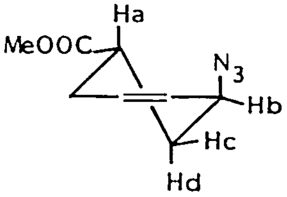


37 38b 4b

The stereochemistry of 4a and 4b was established by their NMR spectra. In the case of 4a, the proton resonance at δ 1.72 (1 H, ddd, J = 12.6, 12.6, and 10.3 Hz) is assigned as the C-6 axial hydrogen (Hd). Large geminal coupling constant, as well as



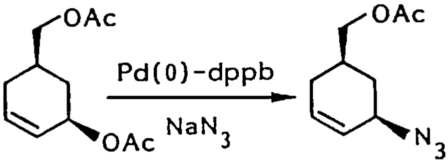
4a



4b

two large vicinal coupling constants (J_{Had} = 12.6, J_{Hbd} = 10.3, and J_{Hcd} = 12.6 Hz), clearly indicates that the protons at C-1 (Ha) and C-5 (Hb) are pseudoaxial, indicating cis-configuration. In the case of 4b, the resonances at δ 1.90 (ddd, J = 13.8, 11.9, and 4.8 Hz, Hd) and at δ 2.13 (ddd, J = 13.8, 3.09, and 3.09 Hz, Hc) are readily discernible with the expected coupling constants of J_{Hac} = 4.8, J_{Had} = 11.9, J_{Hbc} = 3.09, J_{Hbd} = 3.09, and J_{Hcd} = 13.8 Hz, suggesting that Ha and Hb are in the pseudoaxial and equatorial configuration, respectively.

The $Pd(PPh_3)_4$-catalyzed azidation of **3** gave a mixture of **4a** and **4b** (38:62) with low selectivity. In the reaction shown in eq 4, the epimerizations of **3** and **4** at the α-position of methyl carboxylate may take place under the reaction conditions. In order to avoid this, the substrate **39** was chosen for the azidation (eq 5).



(5)

cis:*trans*=96:4 **39**

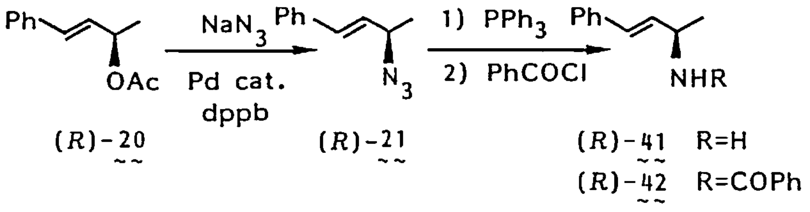
cis:*trans*=93:7 **40**

The $Pd_2(dba)_3 \cdot CHCl_3$-dppb catalyzed azidation of **39** (*cis*:*trans* = 96:4) gave *cis*-5-acetoxymethyl-2-cyclohexen-1-yl azide (**40**) in 90% yield (*cis*:*trans* = 93:7). However, the $Pd(PPh_3)_4$-catalyzed azidation of **39** under the same conditions gave a mixture of *cis*- and *trans*-**40** (54:46). The stereoselectivity seems to be strongly affected by the intermediate π-allylpalladium species.

Next, the author examined catalytic transformation of (*R*)-(*E*)-(+)-4-phenyl-3-buten-2-yl acetate (**20**) by using $Pd_2(dba)_3 \cdot CHCl_3$-dppb catalyst. The azidation of (*R*)-**20**[22] (77%

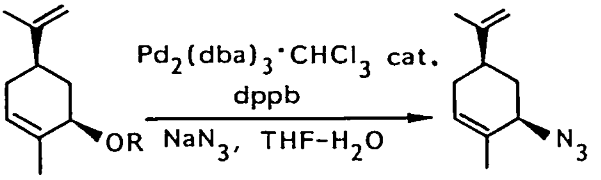
e.e.) gave (*R*)-(*E*)-(+)-4-phenyl-3-buten-2-yl azide (**21**) ($[\alpha]_D^{26}$ +65.5°, *c* 2.45, $CHCl_3$) in 80% yield as a single product with

Scheme II



retention of the configuration (Scheme II). The absolute configuration of the allyl azide **21** was determined to be (*R*) by converting it to the known (*R*)-(*E*)-(+)-4-phenyl-3-buten-2-ylamine (**41**) ($[\alpha]_D^{23}$ +10.3°, *c* 4.40, benzene).[23] The enantiomeric excess of **41** was determined to be 76.4% e.e. by HPLC analysis of *N*-[(*R*)-(*E*)-(+)-4-phenyl-3-buten-2-yl]benzamide (**42**), which was obtained upon treatment of **41** with benzoyl chloride (71%). These results clearly show that the azidation of allylic acetates proceeds with net retention of configuration. The azide ion for the palladium catalyzed reaction seems to act as a soft nucleophile, although it is assigned as a borderline nucleophile according to the HSAB principle.[24]

The azidation of optically active (1*R*,5*R*)-carvyl diethyl phosphate (**43**) (90% e.e.) (1*R*,5*R*:1*S*,5*R* = 95:5) gave racemic (1*R**,5*R**)-azide **45** (1*R**,5*R**:1*S**,5*R** = 90:10) (eq 6). The loss of enantiomeric purity is due to the formation of a symmetric π-allylpalladium intermediate and the facile 1,3-rearrangement of the product azide.[18] The azidation of the corresponding



(6)

(1*R*,5*R*)   (1*R**,5*R**)

43 R=P(O)(OEt)$_2$ **45**

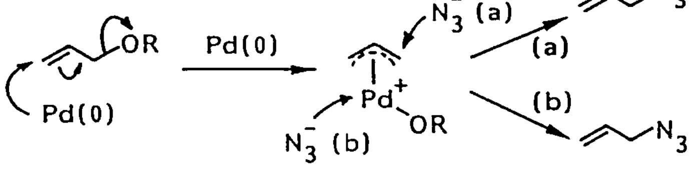
44 R=COCH$_3$

(1*R*,5*R*)-carvyl acetate (**44**) also gave the azide **45** with lower 1*R**,5*R**/1*S**,5*R** ratio (75/25).

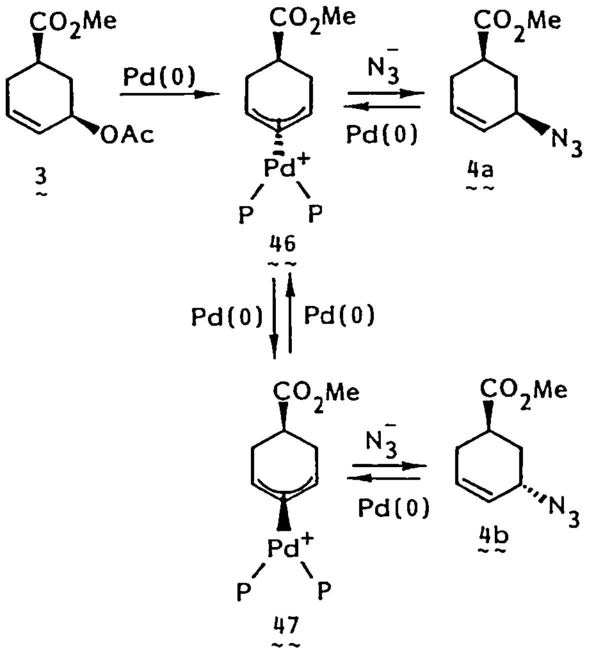
The kinetic resolution of racemic allyl acetates was attempted so far in vain by using optically active bidentate phosphine. For example, the reaction of racemic allyl acetate **20** with sodium azide (0.5 equiv) in the presence of Pd$_2$(dba)$_3$·CHCl$_3$ and (*R*)-(*S*)-BPPFA[25] at 40 °C gave (*S*)-(*E*)-allyl azide **21** (50% yield) and (*R*)-(*E*)-allyl acetate **20** (31% yield) in 2.0 and 3.4% e.e., respectively.

Mechanism: The $Pd(PPh_3)_4$-catalyzed azidation of **3** gives **4a** and **4b** without isomerization of the starting **3** under the reaction conditions. The reaction can be rationalized by assuming Scheme III. Oxidative addition of allyl esters to Pd(0) species gives π-allylpalladium intermediates, which react with N_3^- to afford allyl azides. As mentioned before, the azidations of geranyl and neryl acetates proceeds slower than that of linalyl acetate, indicating that the oxidative addition of Pd(0) species to allyl acetates proceeds in an S_N2'-fashion at the γ-position.[26] Usually, the oxidative addition of palladium(0) catalyst to allyl acetates proceeds with inversion of configuration at the allylic carbon to give π-allylpalladium complexes, which undergo subsequent reactions with soft nucleophiles with inversion of configuration [path (a)]. In contrast, hard nucleophiles attack initially at palladium, subsequent migration, and reductive elimination results in inversion of configuration [path (b)].[27] The above stereochemical outcome of the azidation with $Pd_2(dba)_3 \cdot CHCl_3$-dppb catalyst is retention of configuration. Therefore, azide ion seems to be a soft nucleophile. As shown in the reaction of 3, the addition of a bidentate ligand such as

Scheme III



dppb raised the stereoselectivity of the formation of 4a (38:62 → 91:9). The loss of stereochemistry is due to the isomerization



between anti and syn π-allylpalladium complexes (46 and 47). The isomerization of the π-allylpalldium complex bearing monodentate PPh_3 proceeds faster than that bearing bidentate dppb. The azidation of 3 with $Pd_2(dba)_3 \cdot CHCl_3$-dppb catalyst gave 4a exclusively; however, the higher concentration of the palladium catalyst decreased the selectivity of 4a/4b. Actually, the ratio of 4a/4b changed as follows 96/4, 84/16, 83/17, 76/24 in the order of the concentration of the palladium catalyst 1%, 5%, 10%, 20%, respectively. Apparently the isomerization is induced by the palladium(0) catalyst. This is consistent with the reported result that the optical yields of the asymmetric transformation of allyl carbonates are dependent on the concentration of Pd(0) species, and higher concentration results in low asymmetric transformation.[28]

It is noteworthy that the stereochemical isomerization of allyl azides takes place in the presence of palladium catalyst. Thus, the treatment of azide 4b with $Pd(PPh_3)_4$ catalyst under the similar reaction conditions gave a mixture of azides 4a and 4b (38:62) (Fig). Furthermore, the addition of excess PPh_3 decreased the yield of allyl azides. This is due to the formation of iminophosphoranes from allyl azides and phosphines.[29] The palladium(0) catalyzed isomerization of 4b proceeds relatively fast, when $Pd(PPh_3)_4$ is used. Thus, the treatment of 4b with 5 mol% of $Pd(PPh_3)_4$ at 40 °C gave an equilibriated mixture of 4a and 4b (35:65) within 1 h. However, when 2.5 mol% of $Pd_2(dba)_3 \cdot CHCl_3$-dppb was used, the isomerization of 4b does not occur even in 2 h. Probably, the palladium(0)-induced isomerization of π-allylpalldium species with bidentate ligands proceeds very slowly.

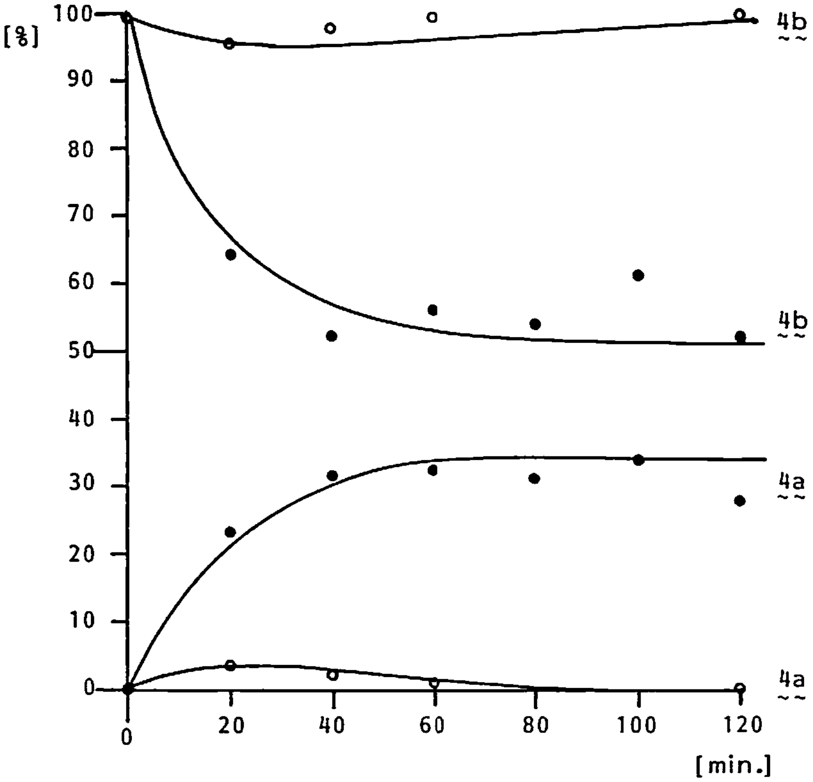
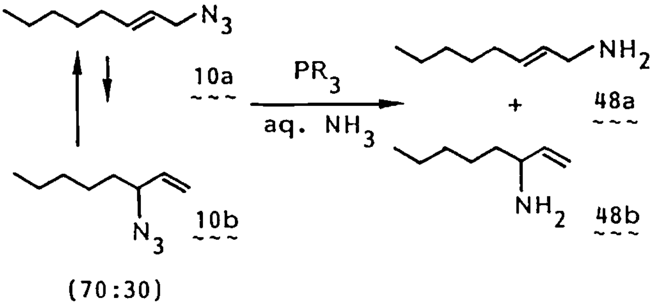


Figure. Palladium-catalyzed isomerization of **4b** at 40 °C. Azide **4b** was mixed with 5 mol% of palladium catalyst in THF at 40 °C and the reaction was followed by GLC.
○ $Pd_2(dba)_3 \cdot CHCl_3$-dppb, ● $Pd(PPh_3)_4$

Synthesis of Primary Allylamines: Although the synthesis of primary allylamines is of importance,[2,3] there is no general method for synthesis of these compounds. An attractive method is the reduction of allyl azides.[30] Catalytic hydrogenation of allyl azides over palladium catalyst has been used;[31] however, the reduction of the carbon-carbon double bonds often lowers the selectivity. Among various reducing reagents, a combination of PPh_3/NaOH[32] seems to be the most efficient for synthesis of primary allylamines. The intermediate iminophosphoranes can be used as the key intermediates for various nitrogen compounds, such as amides,[33] imines,[34] nitro compounds,[35] and secondary amines.[36]

The effect of a phosphine on the reduction of allyl azides has been examined with a mixture of octenyl azides (**10a** and **10b**, 70:30) (eq 7). The mixture was treated with various phosphines



(7)

at 50 °C for 1 h. The hydrolysis of iminophosphoranes with aqueous ammonia at 50 °C gave a mixture of 2-octen-1-ylamine (**48a**) and 1-octen-3-ylamine (**48b**). The representative results of

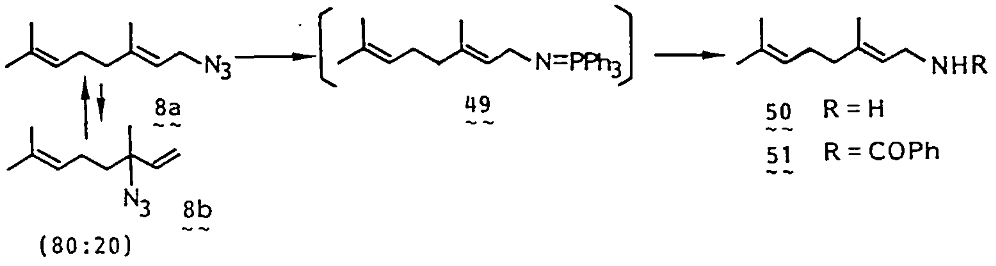
Table IV. The Phosphine Effect on the Reduction of Octenyl Azides.[a]

entry	PR_3	conv,[b] %	yield of 48,[c] %	ratio,[d] 48a:48b
1	$P(OMe)_3$	11	0	
2	$P(OEt)_3$	49	0	
3	$P(OBu)_3$	44	0	
4	PEt_3	100	98	80:20
5	PBu_3	100	80	75:25
6	PPh_3	98	82	80:20
7	PCy_3	95	0 (49)[e]	(95: 5)[e]
8	$P(o\text{-}Tol)_3$	5	0	

[a] The reactions are similar to the general procedure described in the experimental section. [b] Conversions were estimated by the amount of produced nitrogen gas. [c] Isolated yields of allylamines which were obtained by the treatment with ammonium solution. [d] The ratios of 48a:48b were determined by ^{1}H NMR analysis. [e] Treatment with 2N NaOH solution at reflux.

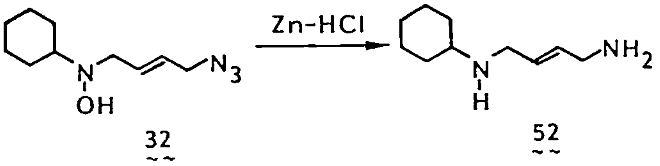
the reduction of octenyl azide are shown in Table IV. The conversion of octenyl azide was determined by measuring the amount of nitrogen gas evolved. Phosphites are not effective (entries 1-3) because of low nucleophilicity. The formation of iminophosphoranes takes place fast upon treatment with nucleophilic phosphines, although the reactivity decreases with increase of the bulkiness of phosphines (entries 7 and 8). The regioselectivity of the reduction of allyl azides is effected by steric bulkiness of phosphines. The reduction of octenyl azide with tricyclohexylphosphine proceeds highly regioselectively (95:5) in comparison with other phosphines (entry 7), although the hydrolysis of iminophosphoranes requires severe reaction conditions. Importantly, less hindered primary amines can be prepared selectively from allyl azides upon treatment with

Scheme IV



triphenylphosphine and a hydroxide solution. Typically, the treatment of an equilibriated mixture of geranyl (8a) and linalyl azide (8b) (80:20) with triphenylphosphine gave triphenyl-*N*-geranyliminophosphorane (49) selectively, and hence geranylamine

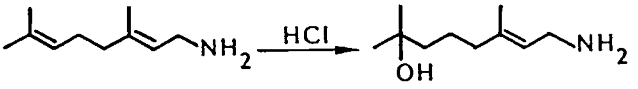
(50) was obtained exclusively. The selective formation of 49 is rationalized by assuming that less hindered 8a reacts with triphenylphosphine much faster than the equilibriated isomer 8b (Scheme IV). The transformation of optically active azide 21 to amine 41 can be performed with retention of configuration. The reduction of allyl azides is also performed efficiently by using



(8)

zinc powder. Thus, the treatment of 4-(N-cyclohexyl-N-hydroxylamino)-2-buten-1-yl azide (32) with zinc powder in an aqueous HCl solution gave 4-(N-cyclohexylamino)-2-buten-1-ylamine (52) in 72% yield (eq 8).[10]

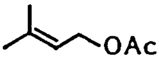
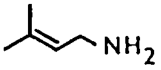
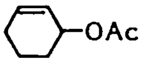
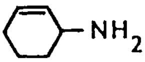
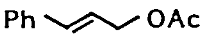
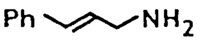
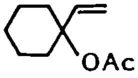
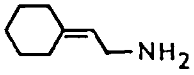
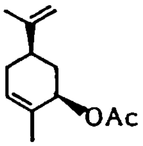
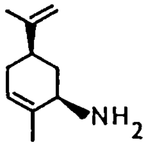
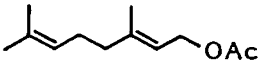
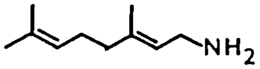
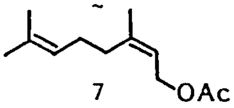
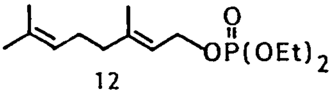
One-pot Synthesis of Primary Allylamines from Allylic Esters: Allylic acetates can be converted into primary allylamines without isolation of allyl azides upon treatment with triphenylphosphine and subsequently with aqueous ammonia solution. The representative results are listed in Table V. Primary allylamines are obtained selectively regardress of a regioisomeric mixture of allyl azides (entries 4 and 6-8). (1*R*,5*R*)-Carvyl acetate (**42**) can be converted into (1*R**,5*R**)-carvylamine (**57**) selectively with retention of configuration. The stereochemistry of **57** was determined to be (1*R**,5*R**) by converting it to the known (1*R**,5*R**)-carvyl benzamide (**58**) (mp 169°).[37] Allyl phosphates can be also converted into allylamines under mild conditions (entry 8). The sequencial amination of 4-acetoxy-2-buten-1-yl phosphate (**26**) is highly useful for the synthesis of substituted primary (*E*)-allyldiamines, which serve as the precursor of spermine alkaloids (entries 9 and 10).



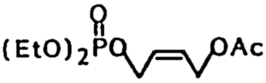
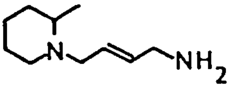
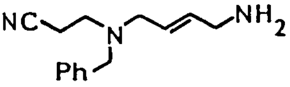
50 **61** (9)

Geranylamine thus obtained reacts with water to afford 3,7-dimethyl-7-hydroxy-2-octen-1-ylamine (**61**) under acidic solution (eq 9).[38]

Table V. The one-pot Preparation of Primary Allylamines from Allyl Esters.^{a}

entry	allyl ester	allylamine	yield,^{b} %
1		 53	61^c
2		 54	70^c
3	 16	 55	59
4	 14	 56	80
5	 44	 57	91
6	 5	 50	59
7	 7	50	62
8	 12	50	85^d

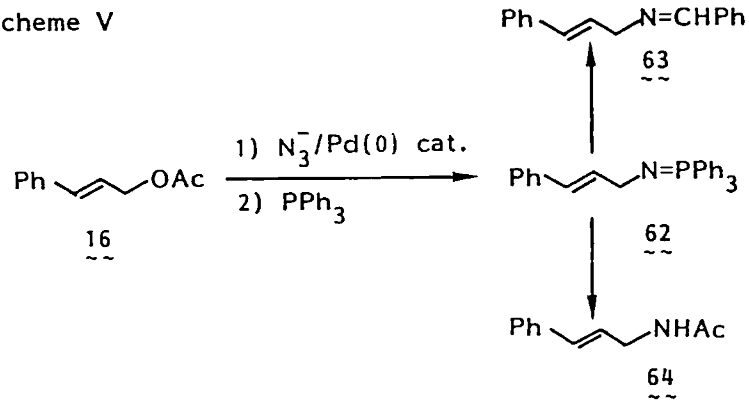
(continued Table V)

9	 26	 59	84
10	26	 60	81

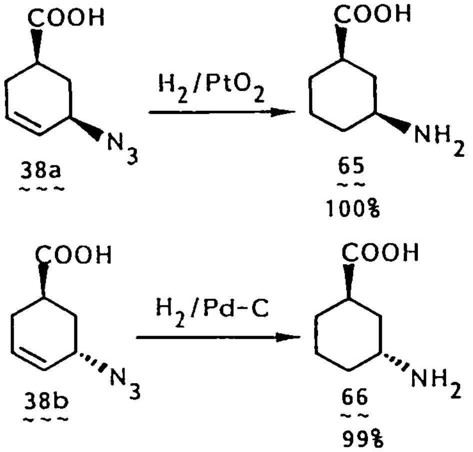
[a] The reactions are similar to the general procedure described in the experimental section. [b] Isolated yield. [c] Isolated as amine hydrochloride. [d] r.t., 2 h.

Synthetic Application of Allyl Azides: Allyl azides obtained in the aforementioned reaction can be readily converted into various nitrogen-containing allylic compounds *via* iminophosphoranes. Staudinger reaction[29,32] on *N*-cinnamyl triphenylphosphorane (**62**) with benzaldehyde in benzene at reflux gave *N*-benzylidenecinnamylamine (**63**) in >99% yield. The reaction of **62** with acetic acid in benzene at reflux afforded *N*-cinnamylacetamide (**64**) in 57% yield (Scheme V).[33] Interestingly, the

Scheme V



Scheme VI



treatment of a mixture of geranyl azide and linalyl azide (80:20) with PPh_3 and then with benzoic acid gave *N*-geranylbenzamide (**51**) selectively in 98% yield.

γ-Amino acids can be prepared by the present method. Thus, *cis*-3-aminocyclohexanecarboxylic acid (**65**) having anticonvulsant activity[39] and the corresponding *trans*-isomer **66** have been prepared by catalytic hydrogenation of the azidocarboxylic acids **38a** and **38b** respectively in quantitative yields (Scheme VI).

Conclusion

The palladium-catalyzed azidation provides an efficient method for the stereoselective transformation of allyl esters to allyl azides with *net-retention* of configuration. Higher stereoselectivity is attained by using a low concentration of palladium(0) catalyst and a chelating bidentate ligand, dppb. The non-catalyzed azidation of allyl esters proceeds with *inversion* of configuration. The allyl azides obtained can be readily converted into the corresponding primary allylamines with high selectivity.

Experimental Section

General.

NMR spectra were recorded on JEOL PMX-60 SI (60 MHz), JEOL JNM-FX 100 (^{1}H NMR at 99.60 MHz, ^{13}C NMR at 25.0 MHz, and ^{31}P NMR at 40.25 MHz), and JEOL JNM-GX 500 (500 MHz) spectrometers. Chemical shifts (δ) were expressed in parts per million relative to tetramethylsilane ($CDCl_3$) or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (D_2O). The chemical shifts of ^{31}P NMR spectra are quoted relative to external aqueous 85% phosphoric acid. IR spectra were recorded on a Hitachi 215 spectrometer. Optical rotations were measured with JASCO DIP-4 polarimeter with 1 dm-long cell at room temp. GLC analyses were carried out on a Shimadzu GC-9A flame ionization chromatography by using a 1-m x 3-mm analytical column packed with 10% SE 30 on 80-120 mesh Uniport HP and a Shimadzu GC-mini 2 flame ionization chromatography by using a 25-m x 0.25-mm PEG 20M chemical bonded on a glass capillary column (Gasukuro Kogyo, Inc. Japan). Mass spectra were obtained on a Shimadzu GCMS QP-1000 by using analytical column packed with SE 30 on Uniport HP. Elemental analyses were performed on a Yanagimoto MT-3 CHN corder.

Caution; Neat azides should be handled carefully behind a safety screen in a hood and store in a refrigerator. A solution of azides can be handled with ease.

Materials.

THF was distilled over benzophenone ketyl under argon.

Water was degassed with argon prior to use. Trimethylsilyl azide,[40] $Pd(PPh_3)_4$,[41] $Pd(dba)_2$,[42] $Pd_2(dba)_3\cdot CHCl_3$,[42] $Pd(OAc)_2$,[43] $Pd(OCOCF_3)_2$,[43] $Pd(acac)_2$,[44] and $Pd[P(C_6H_{11})_3]_2$[45] were prepared by the literature procedures. cis-5-Methoxycarbonyl-2-cyclohexen-1-yl acetate (3),[46] (R)-(E)-(+)-4-phenyl-3-buten-2-yl acetate (20)[47], 7-oxabicyclo[3.2.1]oct-2-en-6-one (37),[48] and cis-5-acetoxymethyl-2-cyclohexen-1-yl acetate (39)[49] were prepared by the literature procedures. (1R,5R)-Carveol was prepared from (R)-(-)-Carvone.[50] Other allylic esters were prepared by the general procedures. Diethyl chlorophosphate was purchased from Aldrich Chemical Co and was prepared by literature procedures.[51]

General Procedure for the Preparation of Allyl Diethyl Phosphates: Diethyl chlorophosphate (7.25 g, 42.0 mmol) was added to a solution of an allyl alcohol (40.0 mmol) and pyridine (3.6 mL) in dichloromethane (40 mL) at 0 °C for 5 min. The resulting white slurry was stirred for 2 h at room temp. The reaction mixture was diluted with ether (70 mL) and was washed successively with a 10% HCl solution (30 mL x 3), a saturated $NaHCO_3$ (30 mL x 3), and brine (30 mL). The organic layer was dried over $MgSO_4$. After removal of the solvent in vacuo, distillation or column chromatography gave allyl diethyl phosphates as a colorless oil.

(E)-Diethyl 2-Hexen-1-yl Phosphate (1a): The reaction of 2-hexen-1-yl alcohol (10.0 g, 100 mmol) with diethyl chlorophosphate was carried out according to the general procedure. Phosphate **1a** (16.7 g, 71%) was obtained: bp 110-111 °C (2.0 mmHg); IR (neat) 2900 (s), 1670 (w), 1460 (m), 1400 (m), 1270 (P=O, s), 1170 (m), 1000 (P-O-C, s), 840 (w), 800 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.75-1.15 (m, 3 H, CH_3), 1.15-1.83 (m, 2 H, CH_2), 1.37 (t, J = 6 Hz, 6 H, CH_2), 1.87-2.30 (m, 2 H, CH_2), 4.06 (q, J = 7 Hz, 2 H, OCH_2), 4.18 (q, J = 7 Hz, 2 H, $POCH_2$), 4.40 (d, J = 5 Hz, 1 H, POCH), 4.57 (d, J = 5 Hz, 1 H, POCH), 5.30-6.12 (m, 2 H, CH=CH).

Diethyl Geranyl Phosphate (12): The reaction of geraniol (15.4 g, 100 mmol) with diethyl chlorophosphate was carried out according to the general procedure. Phosphate **12** (22.9 g, 79%) was obtained: IR (neat) 2970 (s), 2850 (s), 1670 (w), 1450 (m), 1390 (m), 1260 (P=O, s), 1170 (m), 1000 (P-O-C, s), 820 (m) cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 1.30 (t, J = 7 Hz, 6 H, CH_3), 1.59 (s, 3 H, CH_3), 1.65 (s, 3 H, CH_3), 1.70 (s, 3 H, CCH_3), 1.98-2.15 (m, 4 H, CH_2), 4.08 (q, J = 7 Hz, 2 H, $POCH_2$), 4.16 (q, J = 7 Hz, 2 H, $POCH_2$), 4.37 (d, J = 7 Hz, 1 H, POCH), 4.48 (d, J = 7 Hz, 1 H, POCH), 4.84-5.16 (m, 1 H, CH=), 5.35 (t, J = 7 Hz, 1 H, CH=).

(*E*)-Cinnamyl Diethyl Phosphate (18): The reaction of (*E*)-cinnamyl alcohol (13.4 g, 100 mmol) with diethyl chlorophosphate was carried out according to the general procedure. Phosphate **18** (23.2 g, 86%) was obtained: IR (neat) 3000 (m), 1480 (m), 1450 (m), 1400 (m), 1370 (m), 1280 (P=O, s), 1160 (m), 1100 (m), 1020 (P-O-C, s), 800 (m), 750 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.33 (t, J = 7 Hz, 6 H, CH_3), 4.10 (q, J = 7 Hz, 2 H, $POCH_2$), 4.18 (q, J = 7 Hz, 2 H, $POCH_2$), 4.48 (d, J = 5 Hz, 1 H, POCH), 4.60 (d, J = 5 Hz, 1 H, POCH), 6.30 (dt, J = 15 and 5 Hz, 1 H, CH=), 6.78 (d, J = 15 Hz, 1 H, ArCH=), 7.18-7.63 (m, 5 H, ArH).

(*Z*)-Cinnamyl Diethyl Phosphate (**19**): The reaction of (*Z*)-cinnamyl alcohol (0.403 g, 3.00 mmol) with diethyl chlorophosphate was carried out according to the general procedure. Phosphate **19** (0.619 g, 76%) was obtained: IR (neat) 2980, 1680, 1490, 1450, 1395, 1370, 1270 (P=O, s), 1165, 1040 (P-O-C, s), 970, 875, 800, 770, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.35 (t, J = 7 Hz, 6 H, CH_3), 4.10 (q, J = 7 Hz, 2 H, $POCH_2$), 4.18 (q, J = 7 Hz, 2 H, $POCH_2$), 4.83 (d, J = 7 Hz, 1 H, POCH), 4.96 ((d, J = 7 Hz, 1 H, POCH), 5.96 (dt, J = 11 and 7 Hz, 1 H, CH=), 6.80 (d, J = 11 Hz, 1 H, ArCH=), 7.20-7.74 (m, 5 H, ArH).

(*Z*)-4-Acetoxy-2-buten-1-yl Diethyl Phosphate (**26**): Diethyl chlorophosphate (72.3 mL, 0.50 mol) was added to a solution of (*Z*)-2-buten-1,4-diol (41.2 mL, 0.50 mol) in pyridine (79.1 mL, 2.0 mol) at 0 °C for 1 h. The resulting white slurry was stirred for 30 min at room temp. Acetic anhydride (56.5 mL, 0.60 mol) was added to the reaction mixture at 0 °C for 10 min. The reaction mixture was diluted with ether (1.0 L) and washed successively with a 10% HCl solution (500 mL x 3), a saturated $NaHCO_3$ (500 mL x 3), and brine (500 mL). The organic layer was dried over $MgSO_4$. After removal of the solvent in vacuo, distillation gave phosphate 26 (32.1 g, 24%): bp 135 °C (1.0 mmHg); IR (neat) 1743 (C=O, s), 1448, 1380, 1250 (P=O, s), 1020 (P-O-C, s) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.36 (t, J = 7 Hz, 6 H, CH_3), 2.06 (s, 3 H, CH_3CO), 4.08 (q, J = 7 Hz, 2 H, $POCH_2$), 4.16 (q, J = 7 Hz, 2 H, $POCH_2$), 4.49-4.80 (m, 4 H, CH_2), 5.72 (dt, J = 11.2 and 5.2 Hz, 1 H, CH=), 5.83 (dt, J = 11.2 and 5.1 Hz, 1 H, CH=). Anal. Calcd for $C_{10}H_{19}O_6P$: C, 45.11; H, 7.19. Found: C, 44.69; H, 7.14.

cis-5-Methoxycarbonyl-2-cyclohexen-1-yl Diethyl Phosphate (36): Diethyl chlorophosphate (7.25 g, 42.0 mmol) was added to a solution of *cis*-methyl 5-hydroxy-3-cyclohexenecarboxylate (6.24 g, 40.0 mmol) and pyridine (79.1 mL, 2.0 mol) in dichloromethane (40 mL) at 0 °C for 1 h. The resulting white slurry was stirred for 30 min at room temp. The reaction mixture was diluted with ether (70 mL) and washed successively with a 10% HCl solution (30 mL x 3), a saturated $NaHCO_3$ (30 mL x 3), and brine (30 mL) and dried over $MgSO_4$. The solvent was removed in vacuo to give phosphate 36 as a colorless oil (13.13 g, 100%). IR (neat) 2995 (s), 1735 (C=O, s), 1660 (m), 1440 (m), 1395 (m), 1375 (m), 1335 (m), 1260 (P=O, s), 1180 (s), 1000 (P-O-C, s), 900 (m), 880 (w), 845 (w), 820 (m), 800 (m), 750 (m), 700 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.33 (t, J = 6.8 Hz, 3 H, CH_3), 1.35 (t, J = 6.8 Hz, 3 H, CH_3), 2.85 (ddd, J = 12.3, 12.3, and 9.4 Hz, 1 H, $H^{6\alpha}$), 2.15-2.88 (m, 4 H), 3.68 (s, 3 H, MeO), 4.06 (q, J = 6.8 Hz, 2 H, $POCH_2$), 4.13 (q, J = 6.8 Hz, 2 H, $POCH_2$), 4.75-5.13 (m, 1 H, CHOP), 5.60-5.98 (m, 2 H, CH=CH); ^{31}P NMR ($CDCl_3$, 40.25 MHz) δ -1.25 (*cis*-phosphate; ≥99%).

A mixture of *cis*- and *trans*-5-methoxycarbonyl-2-cyclohexen-1-yl diethyl phosphate was prepared by the similar treatment of a mixture of *cis*- and *trans*-alcohol (*cis*:*trans* = 36:64) with diethyl chlorophosphate. The stereoisomeric ratio of the allyl phosphates **36** was determined by ^{31}P NMR spectra. ^{31}P NMR ($CDCl_3$, 40.25 MHz) showed δ -1.53 for *trans*-phosphate, and δ -1.25 for *cis*-phophate. The ratio (*cis*:*trans*) was 36:64.

(1*R*,5*R*)-(-)-Carvyl Diethyl Phosphate (43): The reaction of (1*R*,5*R*)-carveol (7.24 g, 48 mmol) with diethyl chlorophosphate was carried out according to the general procedure. Phosphate **43** (12.12 g, 95%) was obtained: $[\alpha]_D^{25}$ -37.0° (*c* 1.77, $CHCl_3$); IR (neat) 2980 (s), 2820 (s), 1650 (s), 1485 (w), 1455 (s), 1395 (m), 1385 (s), 1270 (P=O, s), 1170 (m), 1000 (P-O-C, s), 910 (m), 890 (m), 815 (m), 750 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 1.32 (t, J = 7.2 Hz, 3 H, CH_3), 1.34 (t, J = 7.2 Hz, 3 H, CH_3), 1.67-2.60 (m, 11 H), 4.10 (dq, J = 7.2, and 2.4 Hz, 2 H, $POCH_2$), 4.18 (dq, J = 7.2, and 2.4 Hz, 2 H, $POCH_2$), 4.65-4.80 (m, 1 H, CHOP), 4.80-5.15 (m, 1 H, CH=), 5.50-5.77 (m, 2 H, CH_2=); ^{31}P NMR signal indicated the presence of (1*S*,5*R*)-phosphate. ^{31}P NMR ($CDCl_3$, 40.25 MHz) -0.87 (1*R*,5*R*-phosphate; 95%), -1.24 (1*S*,5*R*-phosphate; 5%). Anal. Calcd for $C_{14}H_{25}O_4P$: C, 58.32; H, 8.74. Found: C, 58.70; H, 8.75.

Effect of Leaving Groups for the Azidation of (*E*)-2-Hexen-1-yl Compounds: A mixture of tetrakis(triphenylphosphine)-palladium (0.023 g, 0.02 mmol), sodium azide (90%) (0.087 g, 1.2 mmol), (*E*)-2-hexen-1-yl compounds (1.00 mmol), THF (3.0 mL), and water (1.0 mL) was stirred at 40 °C for 30 min under argon. The conversion of allylic compounds and the yield of hexenyl azides (**2a**-**b**) were determined by GLC analysis (SE 30 10%, 1-m x 3-mm) using an internal standard (*n*-tridecane and *n*-tetradecane). The conversions of (*E*)-2-hexenyl compounds are as follows: $(EtO)_2PO_2$- (**1a**, 98%), $EtOCO_2$- (**1b**, 100%), CF_3CO_2- (**1c**, 100%), $PhCO_2$- (**1d**, 97%), CH_3CO_2- (**1e**, 23%), PhO- (**1f**, 0%), Et_2N- (**1g**, 0%), Cl- (**1h**, 100%), and Br- (**1i**, 100%).

Catalytic Activity and Solvent Effect on the Azidation of Allyl Acetate 3: A mixture of palladium catalyst (0.025 mmol, 5 mol%), ligand, sodium azide (0.040 g, 0.55 mmol), *cis*-5-methoxy-carbonyl-2-cyclohexen-1-yl acetate (**3**) (0.099 mg, 0.50 mmol), water (0.5 mL) and a solvent (2 mL) was stirred at 50 °C for 2 h under argon. The conversions of allyl acetate **3** and the yields of allyl azides **4a**-**b** were determined by GLC analysis (glass capillary chemical bonded column with PEG 20M, 25-m X 0.25-mm) using an internel standard (n-docosane). The yields and the conversions (yield/conv., %) by using various solvents are as follows: THF (92/95), DME (73/91), DMF (41/73), acetone (47/73), CH_3CN (22/24), and EtOH (23/23). The results for the catalytic activity are listed in Table III.

General Procedure for the Palladium-Catalyzed Azidation of Allylic Esters: A mixture of $Pd(PPh_3)_4$ (0.5-5 mol%), sodium azide (22 mmol), and allylic compound (20 mmol) in THF (50 mL) and water (20 mL) was stirred at 50 °C for 2 h. The reaction mixture was extracted with ether (50 mL x 3). The combined extracts were washed successively with a 2N HCl (50 mL), saturated $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried over $MgSO_4$. Removal of the solvent under reduced pressure at room temp gave allyl azides. Column chromatography on SiO_2 gave pure allyl azides. The representative results are listed in Table I.

Azidation of (*E*)-2-Hexen-1-yl Diethyl Phosphate (1a): The palladium-catalyzed azidation of **1a** (4.73 g, 20.0 mmol) was carried out at room temp for 4 h. Diethyl ether was used as a solvent in place of THF, because the product azide is volatile. Column chromatography (SiO_2, pentane) gave a mixture of (*E*)-2-hexen-1-yl azide (**2a**) and 1-hexen-3-yl azide (**2b**) (2.40 g, 78%). The ratio of **2a**/**2b** was determined to be 70:30 by ^1H NMR analysis: IR (neat) 2960 (s), 2875 (m), 2100 (N_3, s), 1460 (m), 1380 (w), 1240 (s), 975 (s), 930 (m), 875 (m) cm^{-1}. For **2a**: ^1H NMR ($CDCl_3$, 60 MHz) δ 0.92 (t, J = 6.0 Hz, 3 H, CH_3), 1.14-1.80 (m, 2 H, CH_2), 2.07 (dt, J = 7.0 and 6.5 Hz, 2 H, CH_2), 3.68 (d, J = 5.0 Hz, 2 H, CH_2N_3), 4.93-6.10 (m, 2 H, CH=CH). For **2b**: ^1H NMR ($CDCl_3$, 60 MHz) δ 0.92 (t, J = 3 H, CH_3), 1.14-1.80 (m, 4 H, CH_2), 3.50-4.00 (m, 1 H, CHN_3), 4.93-6.10 (m, 3 H, $CH=CH_2$).

Azidations of Geranyl Acetate (5), Linalyl Acetate (6), Neryl Acetate (7), and Geranyl Diethyl Phosphate (12): The palladium-catalyzed azidations of geranyl acetate (0.981 g, 5.00 mmol), linalyl acetate (0.981 g, 5.00 mmol), neryl acetate (0.981 g, 5.00 mmol), and geranyl diethyl phosphate (1.45 g, 5.00 mmol) were carried out according to the general procedure. A mixture of geranyl azide (**8a**) and linalyl azide (**8b**) was obtained by column chromatography (SiO_2, hexane) in 64%, 91%, 79%, and 83% yield respectively. The ratio of **8a**/**8b** was determined to be 80:20 by the ^1H NMR analysis: IR (neat) 2920 (m), 2100 (N_3, s), 1742 (m), 1668 (w), 1450 (m), 1380 (m), 1240 (m), 878 (w) cm^{-1}. For **8a**: ^1H NMR ($CDCl_3$, 100 MHz) δ 1.35-1.79 (m, 9 H, CH_3), 2.07 (m, 4 H, CH_2), 3.74 (d, J = 7.6 Hz, 2 H, CH_2N_3), 4.94-5.90 (m, 2 H, CH=). For **8b**: ^1H NMR ($CDCl_3$, 100 MHz) δ 1.35-1.79 (m, 9 H, CH_3), 2.07 (m, 4 H, CH_2), 4.94-5.90 (m, 4 H, CH= and $CH=CH_2$). Anal. Calcd for $C_{10}H_{17}N_3$: C, 66.99; H, 9.57; N, 23.44. Found: C, 67.05; H, 9.50; N, 23.15.

Azidation of 1-Octen-3-yl Acetate (9): The palladium-catalyzed azidation of 1-octen-3-yl acetate (8.513 g, 50.0 mmol) was carried out according to the general procedure. A mixture of (*E*)-2-octen-1-yl azide (**10b**) and 1-octen-3-yl azide (**10b**) (7.46 g, 97%) was obtained by column chromatography (SiO_2, hexane). The ratio of **10a**/**10b** was determined to be 70:30 by the ^1H NMR analysis: IR (neat) 2930 (s), 2860 (s), 2100 (N_3, S), 1670 (w), 1470 (m), 1380 (w), 1240 (s), 970 (s), 930 (m), 880 (m), 725 (w)

cm^{-1}. For 10a: ^1H NMR ($CDCl_3$, 60 MHz) δ 0.60-2.40 (m, 11 H), 3.47-3.96 (m, 2 H, CH_2N_3), 5.00-6.10 (m, 2 H, CH=CH). For 10b: ^1H NMR ($CDCl_3$, 60 MHz) δ 0.60-2.40 (m, 11H), 3.47-3.96 (m, 1 H, CHN_3), 5.00-6.10 (m, 3 H, $CH=CH_2$). Anal. Calcd for $C_8H_{15}N_3$: C, 62.71; H, 9.87; N, 27.43. Found: C, 62.75; H, 9.89; N, 27.34.

(*E*)-5-Nonen-4-yl Azide (11): The palladium-catalyzed azidation of (*E*)-5-nonen-4-yl-acetate (4.607 g, 25 mmol) was carried out according to the general procedure. (*E*)-5-Nonen-4-yl azide (3.932 g, 94%) was obtained by column chromatography (SiO_2, hexane): IR (neat) 2940 (s), 2860 (m), 2090 (N_3, s), 1665 (w), 1460 (m), 1435 (m), 1380 (m), 1235 (m), 1115 (w), 1090 (w), 965 (m), 910 (w), 865 (w), 815 (w), 735 (w), 710 (w), 685 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.90 (t, J = 6.5 Hz, 6 H, CH_3), 1.10-1.70 (m, 8 H, CH_2), 2.07 (dt, J = 7.0 and 6.5 Hz, 2 H, CH_2), 3.77 (dt, J = 7.0 and 7.0 Hz, 1 H, CH), 5.30 (dd, J = 15 and 7.0 Hz, 1 H, CH=), 5.74 (dt, J = 15 and 6.5 Hz, 1 H, CH=).

2-Cyclohexen-1-yl Azide (13): The palladium-catalyzed azidation of 2-cyclohexen-1-yl acetate (0.695 g, 5.00 mmol) was carried out according to the general procedure. 2-Cyclohexen-1-yl azide (0.432 g, 70%) was obtained by column chromatography (SiO_2, pentane): IR (neat) 3030 (m), 2940 (s), 2860 (m), 2095 (N_3, s), 1650 (m), 1450 (m), 1320 (m), 1260 (s), 1235 (s), 1160 (w), 1140 (w), 1095 (m), 1045 (m), 1000 (m), 897 (m), 860 (m), 840 (w), 780 (m), 735 (m), 720 (m), 690 (w) cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 1.50-2.40 (m, 6 H), 3.58-4.40 (m, 1 H, CHN_3), 5.43-6.15

(m, 2 H, CH=CH). Anal. Calcd for $C_6H_9N_3$: C, 58.51; H, 7.37; N, 34.12. Found: C, 58.81; H, 7.42; N, 33.80.

Azidation of 1-Vinylcyclohexyl Acetate (14): The palladium-catalyzed azidation of 1-vinylcyclohexyl aceate (0.840 g, 5.00 mmol) was carried out according to the general procedure. A mixture of 1-vinylcyclohexyl azide (**15a**) and 2-cylohexylidenethyl azide (**15b**) (0.589 g, 78%) was obtained by column chromatography (SiO_2, pentane). The molar ratio of **15a** and **15b** (80:20) was determined by NMR analysis. For **15a**: ^1H NMR ($CDCl_3$) δ 1.45-2.45 (m, 10 H, CH_2), 3.71 (d, J = 8.0 Hz, 2 H, CH_2N_3), 5.00-6.10 (m, CH=). For **15b**: 1.45-2.45 (m, 10 H, CH_2), 5.00-6.10 (m, 3 H, $CH=CH_2$).

(*E*)-Cinnamyl Azide (17): The palladium-catalyzed azidations of (*E*)-cinnamyl acetate (2.00 mmol), (*E*)-cinnamyl diethyl phosphate (2.00 mmol), and (*Z*)-cinnamyl diethyl phosphate (2.00 mmol) were carried out according to the general procedure. Cinnamyl azide was obtained by column chromatography (SiO_2, benzene) in 92%, 82%, and 73% yield respectively: IR (neat) 3050 (m), 2940 (m), 2095 (N_3, s), 1600 (m), 1500 (m), 1455 (m), 1355 (m), 970 (m), 892 (m), 740 (m), 690 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 3.85 (d, J = 6.3 Hz, 2 H, CH_2), 6.16 (dt, J = 15.6 and 6.3 Hz, 1 H, CH=), 6.60 (d, J = 15.6 Hz, 1 H, CH=), 7.19-7.38 (m, 5 H, ArH). Anal. Calcd for $C_9H_9N_3$: C, 67.90; H, 5.70; N; 26.40. Found: C, 68.03; H, 5.71; N, 26.28.

(*R*)-(*E*)-(+)-4-Phenyl-3-buten-2-yl Azide (21): The palladium-catalyzed azidation of (*R*)-(*E*)-(+)-4-phenyl-3-buten-2-yl acetate (0.380 g, 2.00 mmol) was carried out according to the general procedure using $Pd_2(dba)_3 \cdot CHCl_3$ (10.3 mg, 0.01 mmol) and dppb (16.5 mg, 0.04 mmol) as a catalyst. Azide **21** (0.279 g, 81%) was obtained by column chromatography (SiO_2, benzene): $[\alpha]_D^{26}$ +65.5° (*c* 2.45, $CHCl_3$); IR (neat) 3025 (m), 2975 (m), 2925 (w), 2100 (N_3, s), 1495 (m), 1445 (m), 1375 (m), 1300 (m), 1230 (s), 1140 (m), 1070 (w), 1030 (m), 960 (m), 910 (w), 840 (w), 810 (w), 740 (s), 680 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.35 (d, J = 6.5 Hz, 3 H, Me), 4.10 (dq, J = 6.5 and 6.5 Hz, 1 H, CH), 6.07 (dd, J = 15.5 and 6.5 Hz, 1 H, CH=), 6.60 (d, J = 15.5 Hz, 1 H, CH=), 7.05-7.55 (m, 5 H, ArH).

(*E*)-1,3-Diphenylallyl Azide (22): The palladium-catalyzed azidation of (*E*)-1,3-diphenylallyl acetate (7.57 g, 30.0 mmol) was carried out according to the general procedure. (*E*)-1,3-Dipheylallyl azide (6.78 g, 96%) was obtained by column chromatography (SiO_2, benzene): IR (neat) 3030 (m), 2960 (m), 2860 (m), 2100 (N_3, s), 1600 (w), 1495 (m), 1455 (m), 1240 (s), 1065 (m), 965 (m), 900 (m), 745 (m), 700 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 5.13 (d, J = 6.5 Hz, 1 H, CHN_3), 6.22 (dd, J = 15.5 and 6.5 Hz, 1 H, CH=), 6.70 (d, J = 15.5 Hz, 1 H, CH=), 7.10-7.60 (m, 5 H, ArH).

(*E*)-Methyl 4-Azido-2-butenoate (23): The palladium-catalyzed azidation of methyl 2-acetoxy-3-butenoate (0.316 g, 2.00 mmol) was carried out according to the general procedure.

Azide **23** (0.270 g, 96%) was obtained by column chromatography (SiO_2, benzene): IR (neat) 2955 (m), 2100 (N_3, s), 1730 (C=O, s), 1660 (s), 1440 (s), 1240 (C-O, s), 1120 (m), 1035 (m), 990 (m), 840 (m), 750 (m), 720 (m), 695 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 3.78 (s, 3 H, CH_3O), 4.00 (dt, J = 5.0 and 1.5 Hz, 2 H, CH_2), 6.05 (dt, J = 15 and 1.5 Hz, 1 H, CH=), 6.88 (dt, J = 15 and 5.0 Hz, 1 H, CH=); Anal. Calcd for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.78. Found: C, 42.47; H, 4.92; N, 29.84.

Methyl (*E*)-4-Azido-2-pentenoate (24): The palladium-catalyzed azidation of methyl 2-acetoxy-3-pentenoate (3.46 g, 20.0 mmol) was carried out according to the general procedure. Azide **24** (1.85 g, 60%) was obtained by column chromatography (SiO_2, ether:pentane = 1:6): IR (neat) 2955 (m), 2100 (N_3, s), 1720 (N_3, s), 1665 (m), 1440 (m), 1260 (C-O, s), 1180 (s), 1120 (m), 1015 (m), 975 (m), 910 (w), 860 (w), 750 (w), 720 (s), 695 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.35 (d, J = 7.0 Hz, 3 H, CH_3), 3.75 (s, 3 H, CH_3O), 4.13 (dq, J = 7.0 and 6.5 Hz, 1 H, CHN_3), 5.93 (dd, J = 15 and 1.3 Hz, 1 H, CH=), 6.78 (dd, J = 15 and 6.5 Hz, 1 H, CH=).

(*E*)-4-Azido-2-pentenonitrile (25): The palladium-catalyzed azidation of (*E*)-2-acetoxy-3-pentenonitrile (6.95 g, 50.0 mmol) was carried out according to the general procedure. Azide **25** (4.88 g, 80%) was obtained by column chromatography (SiO_2, benzene): IR (neat) 2100 (N_3, s) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.37 (d, J = 7.0 Hz, 3 H, CH_3), 4.22 (dq, J = 7.0 and 6.5 Hz, 1

H, CHN_3), 5.55 (dd, J = 16 and 1.3 Hz, 1 H, CH=), 6.57 (dd, J = 16 and 5.5 Hz, 1 H, CH=).

Azidation of (*Z*)-4-Acetoxy-2-buten-1-yl Diethyl Phosphate (26): The palladium-catalyzed azidation of **26** was carried out according to the general procedure. A mixture of (*E*)-4-azido-2-buten-1-yl acetate (**27a**) and 2-azido-3-buten-1-yl acetate (**27b**) (92%) was obtained by column chromatography (SiO_2, ethyl acetate:hexane = 1:5). The ratio of **27a**/**27b** was determined to be 80:20 by ^1H NMR analysis: IR (neat) 2105 (N_3, s), 1745 (C=O, s) cm^{-1}. For **27a**: ^1H NMR ($CDCl_3$, 100 MHz) δ 2.07 (s, 3 H), 3.78 (d, J = 4.7 Hz, 2 H, CH_2N_3), 4.55 (d, J = 4.8 Hz, 2 H, CH_2OAc), 5.71 (dt, J = 15 and 4.8 Hz, 1 H, CH=), 5.87 (dt, J = 15 and 4.7 Hz, 1 H, CH=). For **27b**: ^1H NMR ($CDCl_3$, 100 MHz) δ 2.07 (s, 3 H, CH_3CO), 4.00-4.23 (m, 1 H, CHN_3), 5.24-5.66 (m, 3 H, $CH=CH_2$).

Azidation of (*E*)-Cinnamyl Diethyl Phosphate (18) with $TMSN_3$-Bu_4NF: To a solution of $Pd(PPh_3)_4$ (0.02 mmoL, 0.024 g) in THF, (*E*)-cinnamyl diethyl phosphate (**18**) (2.00 mmoL, 0.540 g), trimethylsilyl azide (2.00 mmol, 0.131 g), and a 1M solution of Bu_4NF in THF (2.0 mmol, 2.0 mL) were successively added at room temp. The reaction mixture was stirred at room temp for 1 h. To the reaction mixture, $Ca(OH)_2$ was added. The reaction mixture was diluted with ether (50 mL) and washed with a 10% $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. Short column chromatography (SiO_2, benzene) gave (*E*)-cinnamyl azide (**17**) (0.270 g, 85%).

***cis*-5-Acetoxymethyl-2-cyclohexen-1-yl Azide (40):** The palladium-catalyzed azidation of *cis*-5-acetoxymethyl-2-cyclohexen-1-yl acetate (0.436 g, 2.06 mmol) was carried out according to the general procedure using $Pd_2(dba)_3 \cdot CHCl_3$ (53 mg, 0.05 mmol) and dppb (88 mg, 0.206 mmol) as a catalyst. Azide **40** (0.359 g, 90%) was obtained by column chromatography (SiO_2, benzene:hexane = 1:1): GLC analysis of **40** indicated the presence of *trans*-isomer (7%). IR (neat) 3030 (m), 2930 (m), 2095 (N_3, s), 1740 (C=O, s), 1650 (w), 1455 (w), 1435 (w), 1365 (m), 1235 (s), 1035 (s), 900 (m), 740 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.36 (ddd, J = 12.4, 12.4, and 10.5 Hz, 1 H), 1.79-1.87 (m, 1 H), 2.00-2.17 (m, 3 H), 2.06 (s, 3 H, CH_3CO), 3.98 (dd, J = 11.0 and 6.4 Hz, 1 H, CHOAc), 4.02 (dd, J = 11.0 and 6.4 Hz, 1 H, CHOAc), 3.95-4.02 (m, 1 H, CHN_3), 5.67 (dm, J = 5.6 Hz, 1 H, CH=), 5.90 (dddd, J = 7.6, 5.0, 5.0, and 2.5 Hz, 1 H, CH=).

$(1R^{*},5R^{*})$-*p*-1,8-Menthadien-6-yl Azide (Carvyl Azide) (45): The palladium-catalyzed azidations of carvyl acetate (0.970 g, 5.00 mmol) and carvyl diethyl phosphate (5.00 mmol) were carried out according to the general procedure using $Pd_2(dba)_3 \cdot CHCl_3$ (78 mg, 0.075 mmol) and dppb (128 mg, 0.300 mmol) as a catalyst. Carvyl azide (**45**) (0.760g, 86%) was obtained by column chromatography (SiO_2, hexane). GLC analysis of **45** indicates the presence of $(1S^{*},5R^{*})$-isomer. $[\alpha]_D^{25}$ 0°, (*c* 10.0, $CHCl_3$); IR (neat) 2923 (s), 2100 (N_3, s), 1647 (m), 1450 (m), 1380 (m), 1250 (s), 1160 (w), 1050 (w), 1025 (w), 955 (w), 935 (w), 893 (m), 810 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.50-2.50 (m, 11 H), 3.57-3.83 (m, 1 H), 4.65 (s, 2 H), 5.39-5.75 (m, 1 H). Anal. Calcd for $C_{10}H_{15}N_3$: C, 67.76; H, 8.53; N, 23.71. Found: C, 68.10; H, 8.52; N, 23.38.

cis-5-Azido-3-cyclohexenecarboxylic Acid (**38a**). To a solution of palladium acetate (0.179 g, 0.800 mmol), triphenylphosphine (0.420 g, 1.60 mmol), and sodium azide (90%) (1.59 g, 22.0 mmol) in THF (50 mL), 7-oxabicyclo[3.2.1]oct-2-en-6-one (**37**) (2.48 g, 20.0 mmol) and water (20 mL) were added with stirring. After additional stirring at 50 °C for 2 h, most of the organic solvent was removed, and to the resulting aqueous residue, a 2N NaOH (20 mL) and benzene (30 mL) were added. The mixture was washed with benzene (30 mL x 2) and ether (30 mL). The combined aqueous layers were acidified with a concentrated HCl solution below 10 °C. The acidic phase was extracted with CH_2Cl_2 (30 mL x 3). The combined extracts were dried over Na_2SO_4 and evaporated to give acid **38a** as a white solid (3.08 g, 92%). An analytical sample was obtained by recrystallization from ether-pentane. mp 69-75 °C; IR (KBr) 2870 (COOH, s), 2070 (N_3, s), 1690 (C=O, s), 1420 (m), 1235 (C-O, s), 900 (m), 735 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.40-3.10 (m, 5 H), 3.75-4.30 (m, 1 H, CHN_3), 5.45-6.25 (m, 2 H, CH=CH), 10.95 (s, 1 H, COOH). Anal. Calcd for $C_7H_9N_3O_2$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.35; H, 5.42; N, 25.07.

***trans*-5-Azido-3-cyclohexenecarboxylic Acid (38b).** As described above, the reaction of lactone **37** (0.248 g, 2.00 mmol) with sodium azide (90%) (0.159 g, 2.20 mmol) in THF (5 mL) and water (2 mL) was carried out at 50 °C for 2 days in the absence of palladium catalyst. Work-up and purification as previously described afforded **38b** (0.278 g, 83%). An analytical sample was recrystallized from ether-pentane: mp 50-1 °C; IR (KBr) 2910 (COOH, brs), 2100 (N_3, s), 1685 (C=O, s), 1450 (m), 1425 (m), 1300 (m), 1275 (m), 1230 (s), 1110 (w), 1095 (w), 1050 (w), 960 (m), 930 (m), 895 (m), 810 (w), 750 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.85 (ddd, J = 13.6, 12.0, and 4.0 Hz, 1 H, CH), 2.15 (dm, J = 13.6 Hz, 1 H, CH), 2.28-2.43 (m, 2 H, CH), 2.79 (dddd, J = 12.2, 9.6, 5.7, and 3.2 Hz, 1 H, CHCOO), 3.85-4.14 (m, 1 H, CHN_3), 5.77 (dm, J = 5.0 Hz, 1 H, CH=), 6.02 (dm, J = 5.0 Hz, 1 H, CH=), 11.20 (s, 1 H, COOH).

***cis*-Methyl 5-Azido-3-cyclohexenecarboxylate (4a):** To a solution of azidocarboxylic acid **38a** (0.318 g, 1.90 mmol) in ether (10 mL), a solution of diazomethane in ether was added dropwise at 0 °C until the evolution of nitrogen ceased. The reaction mixture was quenched with acetic acid and washed with a saturated $NaHCO_3$ solution. The ethereal phase was dried over $MgSO_4$ and evaporated. Short column chromatography on silica gel (ether) gave colorless **4a** (0.306 g, 89%). GLC analysis indicated the presence of *trans*-isomer (5%): IR (neat) 2945 (m), 2090 (N_3, s), 1740 (C=O, s), 1435 (m), 1380 (w), 1250 (C-O, s), 1170 (s), 1060 (w), 1005 (w), 970 (w), 895 (w), 835 (w), 760 (w), 735 (w), 700 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.72 (ddd, J = 12.6, 12.6, and 10.3 Hz, 1 H, CH), 2.27-2.33 (m, 2 H, CH), 2.34-2.41 (m, 1 H, CH), 2.67 (dddd, J = 12.6, 9.28, 6.07, and 2.75 Hz, 1 H, CHCOO), 3.71 (s, 3 H, OCH_3), 3.95-4.03 (m, 1 H, CHN_3), 5.62-5.69 (m, 1 H, CH=), 5.88-5.93 (m, 1H, CH=); ^{13}C NMR ($CDCl_3$, 25.0 MHz) δ 174.0, 129.2, 125.6, 56.7, 51.6, 37.9, 30.5, 26.9. Anal. Calcd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 53.10; H, 6.07; N, 23.26. The palladium-catalyzed azidation of allyl acetate **3** or allyl phosphate **36** gave **4a** stereoselectively.

***trans*-Methyl 5-Azido-3-cyclohexenecarboxylate (4b):** The reaction of **38b** (0.278 g, 1.66 mmol) with a solution of diazomethane in ether gave **4b** (0.299 g, 100%). GLC analysis showed the presence of *cis*-isomer (2%): IR (neat) 2950 (m), 2090 (N_3, s), 1730 (C=O, s), 1440 (s), 1380 (m), 1200 (C-O, s), 1095 (w), 1050 (w), 1015 (w), 895 (w), 790 (w), 740 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.90 (ddd, J = 13.75, 11.92, and 4.81 Hz, 1 H, CH), 2.13 (ddd, J = 13.75, 3.09, and 3.09 Hz, 1 H, CH), 2.24 (dddd, J = 18.33, 10.20, 4.59, and 2.52 Hz, 1 H, CH), 2.40 (ddd, J = 18.33, 5.16, and 5.16 Hz, 1 H, CH), 2.77 (dddd, J = 11.92, 10.08, 5.50, and 3.21 Hz, 1 H, CHCOO), 3.71 (s, 3 H, CH_3O), 4.02 (s, 1 H, CHN_3), 5.80 (ddd, J = 9.85, 2.98, and 1.61 Hz, 1 H, CH=), 6.04 (dddd, J = 9.85, 4.82, 2.75, and 1.14 Hz, 1 H, CH=); ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 174.9, 131.2, 123.3, 54.2, 51.7, 34.8, 30.8, 27.3. This compound was also obtained from the non-catalyzed azidation of allyl phosphate **36**.

Attempt of Palladium(0)-Catalyzed Kinetic Resolution of (*E*)-4-Phenyl-3-buten-2-yl Acetate (20).

To a mixture of (*E*)-4-phenyl-3-buten-2-yl acetate (**20**) (0.380 g, 2.00 mmol), sodium azide (72 mg, 1.00 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (10.3 mg, 0.01 mmol), and (R)-(S)-BPPFA (25.0 mg, 0.04 mmol) in THF (5.0 mL) was added water (2.0 mL). After stirring at 40 °C for 2 h, the reaction mixture was extracted with ether (50 mL) and washed successively with a 2N HCl solution (20 mL), a saturated $NaHCO_3$ (20 mL), and brine (20 mL). The organic layer was dried over Na_2SO_4. Removal of the solvent, and column chromatography (SiO_2) of the residure gave (*S*)-(*E*)-allyl azide **21** ($[\alpha]_D^{23}$ -1.39°, *c* 2.52, $CHCl_3$) (R_f = 0.85 / benzene), and (*R*)-(*E*)-allyl acetate **20** ($[\alpha]_D^{23}$ +4.55°, *c* 1.41, CCl_4) (R_f = 0.45 / benzene). The optical yields of **21** and **20** are 2.0% e.e. and 3.4% e.e., respectively.

General Procedure for Sequential Amination and Azidation of (Z)-4-Acetoxy-2-buten-1-yl Diethyl Phosphate (26).

To a solution of Pd(PPh$_3$)$_4$ (0.231 g, 0.20 mmol) and 26 (1.33 g, 5.0 mmol) in THF (13 mL), an amine was added dropwise with stirring at room temp. After additional stirring for 2 h, a solution of sodium azide (90%) (0.361 g, 5.0 mmol) in water (5 mL) was added. The reaction mixtrure was stirred overnight. The ether extract (30 mL x 3) was dried over Na$_2$SO$_4$ and evaporated. Column chromatography on SiO$_2$ (benzene) gave an azide. The representative results are listed in Table II.

3-[N-((E)-4-Azido-2-buten-1-yl)-N-benzylamino]propionitrile (30): IR (neat) 3045 (m), 2945 (m), 2840 (m), 2255 (CN, w), 2100 (N$_3$, s), 1735 (w), 1660 (w), 1610 (w), 1502 (m), 1458 (m), 1430 (w), 1376 (m), 1250 (m), 1135 (m), 1080 (w), 1032 (m), 980 (m), 880 (m), 740 (m), 700 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$, 100 MHz) δ 2.38 (t, J = 4.3 Hz, 2 H, CH$_2$), 2.78 (d, J = 4.3 Hz, 2 H, CH$_2$), 3.16 (d, J = 5.0 Hz, 2 H, CH$_2$), 3.62 (s, 2 H, CH$_2$Ar), 3.73 (d, J = 5.0 Hz, 2 H, CH$_2$N$_3$), 5.71 (dt, J = 15.3 and 5.0 Hz, 1 H, CH=), 5.75 (dt, J = 15.3 and 5.0 Hz, 1 H, CH=), 7.27 (br, 5 H, ArH); mass spectrum, m/e (rel %); 255 (12), 215 (100), 173 (57). Anal. Calcd for C$_{12}$H$_{17}$N$_5$: C, 65.86; H, 6.71; N, 27.43. Found: C, 65.87; H, 6.70; N, 27.45.

(E)-4-(2-Methylpiperidino)-2-butenyl Azide (31): IR (neat) 2090 (N$_3$, s) cm^{-1}; ^{1}H NMR (CDCl$_3$, 100 MHz) δ 1.00 (d, J = 6.0 Hz, 3 H), 1.15-3.50 (m, 11 H), 3.67 (d, J = 4.5 Hz, 2 H), 5.25-6.20

(m, 2 H); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 132.6, 125.9, 55.9, 55.7, 52.6, 52.4, 34.8, 26.1, 24.1, 19.3. Anal. Calcd for $C_{10}H_{18}N_4$: C, 61.82; H, 9.34; N, 28.84. Found: C, 62.18; H, 9.41; N, 28.23; mass spectrum, m/e 194 (M^+).

(*E*)-4-(*N*-Cyclohexylhydroxylamino)-2-butenyl Azide (32): ^{1}H NMR ($CDCl_3$, 60 MHz) δ 0.77-2.67 (m, 10 H, CH_2), 2.67-2.88 (m, 1 H, CH), 3.45 (d, J = 4.5 Hz, 2 H, CH_2), 3.75 (d, J = 5 Hz, 2 H, CH_2), 5.03-6.67 (br, 1 H, NOH), 5.62 (dt, J = 15 and 4.5 Hz, 1 H, CH=), 5.98 (dt, J = 15 and 5 Hz, 1 H, CH=).

General Procedure for Sequential Alkylation and Azidation of (*Z*)-4-Acetoxy-2-butenyl Diethyl Phosphate (26).

To a solution of $Pd(PPh_3)_4$ (0.231 g, 0.20 mmol) and **26** (1.330 g, 5.0 mmol) in THF (10 mL), alkyl sodium (5.0 mmol) in THF (10 mL) was added slowly with stirring at 0 °C. After additional stirring for 2 h, a solution of sodium azide (90%) (0.361 g, 5.0 mmol) in water (5 mL) was added. The reaction mixture was stirred overnight. The ether extracts (30 mL x 3) were dried over Na_2SO_4 and evaporated. The allyl azide was purified by column chromatography (SiO_2). The results are listed in Table II.

Methyl (*E*)-2-Benzenesulfonyl-6-azido-4-hexenoate (33): IR (neat) 2955 (m), 2105 (N_3, s), 1745 (C=O, s), 1590 (w), 1450 (m), 1440 (m), 1330 (SO_2, s), 1150 (s), 1095 (m), 980 (m), 760 (m), 720 (m), 685 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 2.60-3.00 (m, 2 H, CH_2), 3.50-4.10 (m, 6 H, CH_3, CH, and CH_2), 5.40-5.84 (m, 2 H, CH=CH), 7.47-8.00 (m, 5 H, ArH).

Ethyl (*E*)-2-Cyano-6-azido-4-hexenoate (34): IR (neat) 2980 (m), 2940 (m), 2270 (CN, w), 2105 (N_3, s), 1745 (C=O, s), 1470 (w), 1450 (m), 1400 (m), 1375 (m), 1335 (m), 1200 (C-0), 1100 (w), 1030 (s), 975 (m), 935 (w), 855 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.30 (t, J = 7.0 Hz, 3 H, CH_3), 2.57-2.77 (m, 2 H, CH_2), 3.43 (s, 1 H, CH), 3.84 (d, J = 3.5 Hz, 2 H, CH_2N_3), 4.21 (q, J = 7.0 Hz, 2 H, CH_2), 5.35-6.07 (m, 2 H, CH=CH).

Methyl (*E*)-2-Methoxycarbonyl-6-azido-4-hexenoate (35): IR (neat) 2945 (m), 2100 (N_3, s), 1750 (C=O, s), 1440 (m), 1340 (m), 1240 (C-O, S), 1160 (m), 1030 (m), 980 (m), 880 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 2.67 (dd, J = 7.4 and 5.7 Hz, 2 H, CH_2), 3.45 (t, J = 7.4 Hz, 1 H, CH), 3.67 (d, J = 5.4 Hz, 2 H, CH_2N_3), 3.72 (s, 6 H, CH_3O), 5.58 (dt, J = 15 and 5.4 Hz, 1 H, CH=), 5.72 (dt, J = 15 and 5.7 Hz, 1 H, CH=); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 169.0, 131.5, 126.5, 52.5, 52.4, 51.4, 31.5. Anal. Calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.81; H, 5.73; N, 18.88.

Palladium-Catalyzed Isomerization of Allyl Azide 4b: To a solution of azide 4b (90.60 mg, 0.50 mmol) and docosane (25.0 mg) as internal standard in dry THF (2.0 ml), palladium catalyst (5.0 mol%) was added at 40 °C. The reaction was followed by GLC. These results were shown in Figure.

General Procedure for the Preparation of Primary Allyl Amines from Allyl Azides. (Effects of Phosphine).

To a solution of a phosphine (2.20 mmol) in THF (5 mL) was added a mixture of octenyl azide **10a** and **10b** (0.307 g, 2.00 mmol) with stirring at 50 °C, and the reaction mixture was stirred at 50 °C for 1 h. The conversion of allyl azides **10a-b** was determined by measuring the volume of nitrogen evolution. After aqueous ammonia (28%, 5 mL) was added, the reaction mixture was stirred at 50 °C for 1.5 h, and extracted with ether (30 mL x 3). The ether extracts (30 mL x 3) were extracted with a 2N HCl (10 mL x 3) solution. The aqueous layer was washed with benzene (10 mL) and made strongly alkaline with NaOH pellets. The aqueous layer was extracted with CH_2Cl_2 (10 mL x 3). The combined extracts were dried over $MgSO_4$ and evaporated to give a mixture of (*E*)-2-octen-1-ylamine (**48a**) and 1-octen-3-ylamine (**48b**). The results using various phosphines and phosphites are listed in Table IV.

General Procedure for the Preparation of Primary Allylamines from Allyl Azides.

To a solution of allyl azide (2.0 mmol) in THF (10 mL), PPh_3 (2.2 mmol) was added at room temperature. After the solution was stirred at 50 °C for 2 h, a 2N NaOH solution (10 mL) or a 30% aqueous ammonia (5 mL) was added. The reaction mixture was extracted with ether (30 mL x 3). The organic layer was extracted with a 2N HCl (10 mL x 3) solution. The aqueous layer was washed with benzene (10 mL) and made strongly alkaline with NaOH. The CH_2Cl_2 extracts (10 mL x 3) were dried over $MgSO_4$. Distillation gave pure allylamines.

(*R*)-(*E*)-(+)-4-Phenyl-3-buten-2-ylamine (41): The reaction of azide **21** (0.264 g, 1.524 mmol) with triphenylphosphine (0.420 g, 1.60 mmol) was carried out according to the general procedure. Amine **41** (0.211 g, 94%) was obtained: $[\alpha]_D^{23}$ +10.3° (*c* 4.4, benzene); IR (neat) 3350 (NH, br), 3270 (NH, br), 3070 (w), 3030 (w), 2970 (m), 2925 (w), 2875 (w), 1960 (w), 1880 (w), 1810 (w), 1750 (w), 1650 (m), 1600 (s), 1495 (s), 1455 (s), 1375 (s), 1265 (w), 1210 (w), 1180 (w), 1140 (m), 1085 (w), 1070 (m), 1030 (w), 965 (s), 900 (m), 850 (m), 815 (m), 745 (s), 690 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (d, J = 6.0 Hz, 3 H, CH_3), 1.45 (brs, 2 H, NH_2), 3.60 (dq, J = 6.0 and 6.0 Hz, 1 H, CHN), 6.08 (dd, J = 16 and 6.0 Hz, 1 H, CH=), 6.45 (d, J = 16 Hz, 1 H, CH=), 7.0-7.50 (m, 5 H, ArH).

The Reaction of Octenyl Azides (10) with PPh_3: The reaction of azide **10** (0.307 g, 2.00 mmol) with triphenylphosphine (0.576 g, 2.20 mmol) was carried out according to the general procedure. A mixture of 2-octen-1-ylamine (**48a**) and 1-octen-3-ylamine (**48b**) (82%) was obtained. The ratio **48a**/**48b** was determined to be 80:20 by ^1H NMR analysis: bp 59-62 °C / 4.0 mmHg (Kugelrohr); IR (neat) 3270 (NH_2, s), 2925 (s), 2855 (s), 1590 (m), 1470 (s), 1385 (m), 975 (s), 830 (m), 715 (w) cm^{-1}; An analytical sample was purified by preparative GLC (SE 30 10%, 1m x 3 mm, He). For

48a: ^{1}H NMR ($CDCl_3$, 60 MHz) δ 0.88 (t, J = 5 Hz, 3 H), 1.05-1.60 (m, 6 H), 1.75-2.30 (m, 2 H), 3.15-3.40 (m, 2 H), 5.30-5.70 (m, 2 H): For **48b**: ^{1}H NMR ($CDCl_3$, 60 MHz) δ 0.89 (t, J = 5 Hz, 3 H), 1.10-1.60 (m, 8 H), 3.10-3.50 (m, 1 H), 4.93 (ddd, J = 9.5, 1.2, and 1.2 Hz, 1 H), 5.02 (ddd, J = 16.5, 1.2, and 1.2 Hz, 1 H), 5.80 (ddd, J = 16.5, 9.5, and 6.5 Hz, 1 H). Anal. Calcd for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.01. Found: C, 75.15; H, 13.59; N, 11.15.

The Reaction of Octenyl Azide (10) with PCy_3: A solution of tricyclohexylphosphine in toluene (30.4 %, 1.54 g, 5.50 mmol) was evaporated under reduced pressure, and THF (12.5 mL) was added. A mixture of 2-octen-1-yl azide (**10a**) and 1-octen-3-yl azide (**10b**) (0.766 g, 5.00 mmol) was added, and the mixture was stirred at 60 °C for 1 h. Then, a 2N NaOH solution (15 mL) was added to the reaction mixture. The mixture was refluxed for 5 h. Isolation of amine **48** was carried out as described above. Kugelrohr distillation gave allylamine **48** (0.310 g, 49%). bp 59 °C / 4 mmHg. The ratio of **48a** and **48b** was determined to be 95:5 by ^{1}H NMR analysis as discribed above.

Geranylamine (50): The reaction of a mixture of geranyl azide and linalyl azide was carried out according to the general procedure. Amine **50** was obtained in 66% yield: bp 50-60 °C (0.15 mmHg) (lit.[52] 62-65 °C / 1.0 mmHg) (Kugelrohr); IR (neat) 3360 (NH_2, s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 1.18 (s, 2 H), 1.30-2.30 (m, 13 H), 3.23 (d, J = 7.0 Hz, 2 H), 4.80-5.48 (m, 2

H). Anal. Calcd for $C_{10}H_{19}N$: C, 78.36; H, 12.50, N, 9.14. Found: C, 78.21; H, 12.45; N, 8.98.

General Procedure for One-pot Preparation of Primary Allylamines from Allylic Esters.

To a solution of $Pd(PPh_3)_4$ (0.116 g, 0.1 mmol) and an allylic acetate (2.0 mmol) in THF (6 mL), a solution of sodium azide (90%) (0.144 g, 2.0 mmol) in water (2 mL) was added, and the mixture was stirred at 50 °C for 2 h. To the reaction mixture, PPh_3 (0.576 g, 2.2 mmol) was added. After additional stirring at 50 °C for 2 h, a 2N NaOH solution (10 mL) was added, and the mixture was stirred at 50 °C for 1 h. The reaction mixture was extracted with ether (30 mL x 3). The ethereal layer was extracted with a 2N HCl solution (10 mL x 3). The aqueous layer was washed with benzene (10 mL), made strongly alkaline with NaOH, and extracted with CH_2Cl_2 (10 mL x 3). The combined extracts were dried over $MgSO_4$ and evaporated to give allylamine. The results are summarized in Table V.

3-Methyl-2-butenylamine Hydrochloride (53). The reaction of prenyl acetate was carried out according to the general procedure. After extraction with CH_2Cl_2, the extracts were bubbled by HCl gas for 1 min. Removal of solvent affords 53 (61%): mp 196-8 °C (lit.[53] 201 °C); ^1H NMR (D_2O, 60 MHz) δ 1.90-2.50 (m, 6 H, CH_3), 4.03 (d, J = 7.0 Hz, 2 H, CH_2N), 5.65 (tq, J = 7.0 and 1.2 Hz, 1 H, CH=).

2-Cyclohexenylamine Hydrochloride (54). The reaction of cyclohexen-1-yl acetate was carried out according to the general procedure. After extraction with CH_2Cl_2, the extracts were bubbled by HCl gas for 1 min. Removal of solvent affords **54** (70%): mp 156-7 °C; IR (KBr) 2950 (NH_2, s), 2600 (m), 2500 (m), 2000 (NH, m), 1660 (w), 1600 (m), 1500 (m), 1445 (m), 1400 (m), 1360 (m), 1160 (m), 1135 (m), 1010 (m), 880 (m), 725 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.10-2.70 (m, 6 H, CH_2), 3.50-4.20 (m, 1 H, CHN), 5.59-6.30 (m, 2 H, CH=CH), 7.50-9.50 (m, 3 H, NH_3^+). Anal. Calcd for $C_6H_{12}NCl$: C, 53.93; H, 9.05; N, 10.48. Found: C, 53.81; H, 8.98; N, 10.44.

Cinnamylamine (55). IR (neat) 3280 (NH, br), 3360 (NH, br) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.13 (s, 2 H, NH_2), 3.40 (d, J = 4 Hz, 2 H, CH_2N), 5.90-6.70 (m, 2 H, CH=CH), 7.05-7.60 (m, 5 H, ArH).

2-Cyclohexylidenethylamine (56). IR (neat) 3370 (NH_2, brs), 3270 (NH_2, brs), 2925 (s), 2855 (s), 1675 (w), 1600 (m), 1450 (s), 1390 (w), 1345 (w), 1240 (w), 1135 (w), 985 (w), 935 (w), 840 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.22 (s, 2 H, NH_2), 1.36-1.80 (m, 6 H, CH_2), 1.85-2.36 (m, 4 H, CH_2), 3.22 (d, J = 7 Hz, 2 H, CH_2N), 5.18 (t, J = 7 Hz, 2 H, CH=).

(1*R*,5*R***)-*p*-1,8-Menthadien-6-ylamine (Carvylamine) (57).** IR (neat) 3200 (br, NH) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.48 (s, 2 H, NH_2), 1.50-2.50 (m, 11 H), 3.18 (t, J = 3.5 Hz, 1 H, CHN), 4.68 (s, 2 H, CH_2=), 5.25-5.58 (m, 1 H, CH=).

(*E*)-4-(2-Methylpiperidino)-2-butenylamine (59): bp 79-83

°C (0.4 mmHg) (Kugelrohr); IR (neat) 3270 (NH_2, s) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.07 (d, J = 7.0 Hz, 3 H, CH_3), 1.14-1.85 (m, 9 H), 1.85-2.45 (m, 2 H, NH_2), 2.67-3.06 (m, 2 H, CH_2), 3.14-3.47 (m, 2 H, CH_2), 5.64 (dt, J = 16.0 and 4.7 Hz, 1 H, CH=), 5.65 (dt, J = 16.0 and 4.7 Hz, 1 H, CH=). Anal. Calcd for $C_{10}H_{20}N_2$: C, 71.37; H, 11.98; N, 16.65. Found: C, 71.18; H, 11.94; N, 16.70; mass spectrum, m/e (rel %) 168 (5), 153 (100), 136 (36).

3-[*N*-((*E*)-4-Amino-2-buten-1-yl)-*N*-benzyl]aminopropionitrile (60): IR (neat) 3300 (NH_2, s), 3030 (w), 2930 (w), 2825 (m), 2250 (CN, w), 1580 (m), 1500 (m), 1458 (s), 1370 (m), 1310 (m), 1120 (m), 1075 (m), 1030 (m), 975 (m), 735 (m), 700 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.59 (br, 2 H, NH_2), 2.39 (t, J = 6.0 Hz, 2 H, CH_2), 2.68 (t, J = 6.0 Hz, 2 H, CH_2), 2.92-3.34 (m, 4 H, CH_2), 3.57 (s, 2 H, CH_2Ar), 5.35-6.01 (m, 2 H, CH=CH), 7.21 (br, 5 H, ArH).

3,7-Dimethyl-7-hydroxy-2-octen-1-ylamine (61). To a solution of $Pd(PPh_3)_4$ (0.231 g, 0.20 mmol), sodium azide (90%) (1.81 g, 25.0 mmol), and triphenylphosphine (6.55 g, 25.0 mmol) in THF (50 mL), geranyl diethyl phosphate (5.80 g, 20.0 mmol) and water (20 mL) were added. The reaction mixture was stirred at room temperature for 10 h. Most of solvents were evaporated. The residue was extracted with benzene (100 mL) and ether (50 mL x 2). The combined organic layers were extracted with a 2N HCl (50 mL x 3). The acidic phase was washed with benzene (50 mL) and ether (50 mL). The acidic phase was allowed to stand for 2 days at room temperature. Then, the aqueous phase was made strongly alkaline with NaOH, and was extracted with CH_2Cl_2 (50 mL x 3). The combined extracts were dried over $MgSO_4$, and evaporated to give amino alcohol 61. Crude amino alcohol 61 was purified by Kugelrohr distillation (2.02 g, 66%). bp 128 °C / 0.26 mmHg; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.00-2.20 (m, 18 H), 3.23 (d, J = 6.5 Hz, 2 H, CH_2N), 5.20 (t, J = 6.5 Hz, 1 H, CH=).

(*E*)-4-*N*-Cyclohexylamino-2-buten-1-ylamine (52): A mixture of azide 32 (0.183 g, 0.870 mmol) and zinc powder (0.285 g, 4.35 mmol) in a 6 N HCl (6 mL) was heated at 80 °C for 2 h with stirring. The reaction mixture was washed with ether (20 mL x 2). The aqueous layer was made alkaline with a 6N NaOH solution, re-extracted with CH_2Cl_2, and dried over K_2CO_3. Evaporation of the filtrate gave diamine 52 (0.105 g, 72%): ^1H NMR ($CDCl_3$, 60 MHz) δ 0.83-2.80 (m, 13 H), 3.17-3.47 (m, 4 H), 5.20-6.03 (m, 2 H).

Preparetion of N-Allylimines. N-Benzylidenecinnamylamine (63).

To a solution of cinnamyl azide (**17**) (0.159 g, 1.0 mmol) and benzaldehyde (0.106 g, 1.0 mmol) in dry benzene (5 mL), PPh_3 (0.262 g, 1.0 mmol) was added. The solution was refluxed for 2 h. After removal of the solvent the residue was triturated with dry hexane (10 mL). The solid precipitated (triphenylphosphine oxide) was removed by filtration. Concentration gave imine **63** (0.228 g, 100%): ^1H NMR ($CDCl_3$, 60 MHz) δ 4.42 (d, J = 4.0 Hz, 2 H), 6.10-6.90 (m, 2 H), 7.10-8.15 (m, 10 H), 8.33 (s, 1 H).

Preparation of N-Allylamides. *N*-[(*R*)-(*E*)-(+)-4-Phenyl-3-buten-2-yl]benzamide (42): To a solution of (*R*)-(*E*)-(+)-4-phenyl-3-buten-2-ylamine (0.103 g, 0.70 mmol) in CH_2Cl_2 (1.5 mL), triethylamine (0.7 mL) was added. Benzoyl chloride (93 μL, 0.80 mmol) was added to the solution slowly. The resulting slurry was stirred for 10 h at room temp. The mixture was diluted with ether (20 mL) and washed successively with a 2N HCl solution (5 mL x 2), a saturated $NaHCO_3$ (5 mL), and brine (5 mL). Evaporation gave a yellow solid. Column chromatography (SiO_2, CH_2Cl_2-hexane) gave allylamide (0.125 g, 71%). The optical purity of amide **42** was determined to be 76.4% e.e. by HPLC analysis using chiral column; $[\alpha]_D^{25}$ + 23.5° (*c* 1.12, $CHCl_3$), ^1H NMR ($CDCl_3$, 60 MHz) δ 1.35 (d, J = 6.5 Hz, 3 H, Me), 4.10 (dq, J = 6.5 and 6.5 Hz, 1 H, CH), 5.40-5.80 (br, 1 H, NH), 6.07 (dd, J = 15.5 and 6.5 Hz, 1 H, CH=), 6.60 (dd, J = 15.5 Hz, 1 H, CH=), 7.05-7.55 (m, 5 H, Ar).

N-Geranylbenzamide (51): A mixture of geranyl azide (8a) and linalyl azide (8b) (0.224 g, 12.25 mmol), PPh_3 (0.360 g, 1.38 mmol), and benzoic acid (0.168 g, 1.38 mmol) was allowed to react according to the procedure descrived above. N-Geranylbenzamide (51) (0.750 g, 98%), which contained triphenyl phosphine oxide, was obtained. The yield of 51 (98%) was determined by ^1H NMR analysis. ^1H NMR ($CDCl_3$, 60 MHz) δ 1.40-2.30 (m, 13 H), 4.05 (dd, J = 6.0 and 6.0 Hz, 2 H), 4.70-5.50 (m, 2 H), 6.70 (br, 1 H), 7.00-8.15 (m, 5 H).

(1R*,5R*)-Carvylbenzamide (58): To a solution of carvyl amine (57) (53 mg, 0.35 mmol) in CH_2Cl_2 (2.0 mL), triethylamine (0.35 mL) was added. Benzoyl chloride (58 μL) was added to the solution. The reaction mixture was stirred at room temp for 2 h. The reaction mixture was diluted with ether (10 mL) and extracted with a 2 N HCl (5 mL) and a saturated $NaHCO_3$ (5 mL). The extracts were dried over $MgSO_4$ and evaporated in vacuo. Benzamide 58 was purified by column chromatography (SiO_2, ether). An analytical sample was recrystallized from ether-hexane. Benzamide 58 (79 mg, 90%) was obtained as a colorless solid: mp 167-9 °C (lit[39] 169 °C); IR (neat) 3250 (NHCO), 2920, 1632 (C=O), 1535, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50-2.55 (m, 11 H), 4.70 (s, 2 H, CH_2=), 4.40-5.03 (m, 1 H, CHN), 5.42-5.82 (m, 2 H, CH=), 5.82-6.70 (br, 1 H, NHCO), 7.13-8.22 (m, 5 H, ArH).

N-Cinnamylacetamide (64): To a solution of cinnamyl azide

(**17**) (0.159 g, 1.0 mmol) and acetic acid (0.360 g, 6.0 mmol) in benzene (5 mL), PPh_3 (0.262 g, 1.0 mmol) was added. After the solution was heated at reflux for 30 h, a saturated $NaHCO_3$ solution (10 mL) was added. The combined benzene extracts (10 mL x 3) were washed with a saturated $NaHCO_3$ solution (10 mL x 3), dried over $MgSO_4$, and evaporated. Preparative TLC (SiO_2, CH_2Cl_2, R_f = 0.14) gave *N*-cinnamylacetamide (**64**) (0.397g, 57%), which contained triphenylphosphine oxide. The yield was determined by ^1H NMR analysis: ^1H NMR ($CDCl_3$, 60 MHz) δ 1.98 (s, 3 H), 3.90 (d, J = 6.0 Hz, 1 H), 4.00 (d, J = 6.0 Hz, 1 H), 6.07 (dt, J = 16 and 6.0 Hz, 1 H), 6.47 (d, J = 16 Hz, 1 H), 7.05-8.30 (m, 5 H).

Catalytic Hydrogenation of Azidocarboxylic Acid: A mixture of azidocarboxylic acids (**38a** or **38b**) (0.334 g, 2.00 mmol) and a catalyst in EtOH (5 mL) and water (2 mL) was stirred at room temp for 2 days under hydrogen atmosphere. Filtration through a pad of Celite using EtOH and water, and evaporation gave an amino acid. Analytically pure sample was obtained by recrystallization (EtOH-H_2O).

***cis*-3-Aminocyclohexanecarboxylic Acid (65):** PtO_2 (23 mg) was used. Quantitative yield (0.286 g, 100%): mp 277.5-8 °C (lit[39] 284 °C); ^1H NMR (D_2O, 500 MHz) δ 1.21-1.49 (m, 4 H), 1.91 (d, J = 15 Hz, 2 H), 2.02 (d, J = 12 Hz), 2.18 (d, J = 12 Hz, 1 H), 2.27 (t, J = 13 Hz), 3.19-3.28 (m, 2 H). Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78: Found: C, 58.24; H, 9.04; N, 9.57.

trans-3-Aminocyclohexanecarboxylic Acid (66): 5% Pd/C (34 mg) was used. Quantitative yield (0.284 g, 99%): mp 292.5-4 °C (lit[39] 290-1 °C); ^{1}H NMR (D_2O, 500 MHz) δ 1.48-1.59 (m, 2 H), 1.59-1.67 (m, 2 H), 1.67-1.74 (m, 1 H), 1.75-1.83 (m, 1 H), 1.86-1.95 (m, 1 H), 2.09-2.17 (m, 1 H), 2.56-2.64 (m, 1 H), 3.48-3.55 (m, 1 H). Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H,9.15; N, 9.78: Found: C, 58.36; H, 9.00; N, 9.66.

References

1. (a) For a review, Silverman, R. B.; Hoffman, S. J. *Med. Res. Rev.* **1984**, *4*, 415. (b) **GABA-transaminase**, Lippert, B.; Metcalf, B. W.; Jung, M. J.; Casara, P. *Eur. J. Biochem.* **1977**, *74*, 441; McDonald, I. A.; Palfreyman, M. G.; Jung, M.; Bey, P. *Tetrahedron Lett.* **1985**, *26*, 4091. (c) **Monoamine oxidase**, Rando, R. R.; Eigner, A. *Mol. Pharmacol.* **1977**, *13*, 1005; Rando, R. R. *J. Am. Chem. Soc.* **1975**, *95*, 4438; Silvermann, R. B.; Hiebert, C. K.; Vazquez, M. L. *J. Biol. Chem.* **1985**, *260*, 14648; McDonald, I. A.; LaCoste, J. M.; Bey, P.; Palfreyman, M. G.; Zreika, M. *J. Med. Chem.* **1985**, *28*, 186; Zreika, M.; McDonald, I. A.; Bey, P.; Palfreyman, M. G. *J. Neurochem.* **1984**, *43*, 448. (d) **Dopamine ß-hydroxylase**, Padgette, S. R.; Wimalasena, K.; Herman, H. H.; Sirimanne, S. R.; May, S. W. *Biochemistry* **1985**, *24*, 5826; Bargar, T. M.; Broersma, R. J.; Creemer, L. C.; McCarthy, J. R.; Hornsperger, J.-M.; Palfreyman, M. G.; Wagner, J.; Jung, M. J. *J. Med. Chem.* **1986**, *29*, 315. (e) **Fungal squalene epoxidase**, Stütz, A. *Angew. Chem.*, *Int. Ed. Engl.* **1987**, *26*, 320; Petrantyi, G.; Ryder, N. S.; Stütz, A. *Science* **1984**, *224*, 1239.
2. Cheikh, R. B.; Chaabouni, R.; Laurent, A.; Mison, P.; Nafti, A. *Synthesis* **1983**, 685.
3. (a) Germon, C.; Alexakis, A.; Normant, J. F. *Synthesis* **1984**,

40. (b) Inoue, Y.; Taguchi, M, Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2721. (c) Corriu, R. J. P.; Huynh, V.; Iqbal, J.; Moreau, J. J. E. *J. Organomet. Chem.* **1984**, *276*, C61. (d) Inaba, M.; Moriwake, T.; Saito, S. *Tetrahedron Lett.* **1985**, *26*, 3235. (e) Betancor, C.; Carrau, R.; Francisco, C. G.; Suárez, E. *Tetrahedron Lett.* **1986**, *27*, 4783. (f) Bargar, T. M.; McCowan, J. R.; McCarthy, J. R.; Wagner, E. R. *J. Org. Chem.* **1987**, *52*, 678.

4. (a) Atkins, K. E.; Walker, W. E.; Manyik, R. M. *Tetrahedron Lett.* **1970**, 3821. (b) Takahashi, K.; Miyake, A.; Hata, G. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 230. (c) Trost, B. M.; Genét, *J. Am. Chem. Soc.* **1976**, *98*, 8516. (d) Trost, B. M.; Keinan, E. *J. Am. Chem. Soc.* **1978**, *100*, 7779. (e) Murahashi, S.-I.; Shimamura, T.; Moritani, I. *J. Chem. Soc.*, *Chem. Commun.* **1974**, 931. (f) Tanigawa, Y.; Nishimura, K.; Kawasaki, A.; Murahashi, S.-I.; *Tetrahedron Lett.* **1982**, *23*, 5549. (g) Genét, J. P.; Balabane, M.; Bäckvall, J. E.; Nyström, J. E. *Tetrahedron Lett.* **1983**, *24*, 2745. (h) Trost, B. M.; Keinan, E. *J. Org. Chem.* **1980**, *45*, 2741. (i) Tanikaga, R.; Takeuchi, J.; Takyu, M.; Kaji, A. *J. Chem. Soc.*, *Chem. Commun.* **1987**, 386.

5. (a) Alkaloids, Trost, B. M.; Godleski, S. A.; Genét, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 3930; Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y. *Heterocycles* **1980**, *14*, 1457; Bäckvall, J. E.; Nordberg, R. E.; Nyström, J. E.; Högberg,

T.; Ulff, B. *J. Org. Chem.* **1981**, *46*, 3479. (b) Amino sugars, Baer, H. H.; Hanna, Z. S. *Can. J. Chem.* **1981**, *59*, 889. (c) Antibiotics, Nikaido, M.; Aslanian, L.; Scavo, F.; Helquist, P.; Åkermark, B.; Bäckvall, J. E. *J. Org. Chem.* **1984**, *49*, 4738.

6. Trost, B. M.; Keinan, E. *J. Org. Chem.* **1979**, *44*, 3451.
7. Byström, S. E.; Aslanian, R.; Bäckvall, J.-E. *Tetrahedron Lett.* **1985**, *26*, 1749.
8. Inoue, Y.; Taguchi, M.; Toyofuku, M.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3021.
9. Connell, R. D.; Rein, T.; Åkermark, B.; Helquist, P. *J. Org. Chem.* **1988**, *53*, 3845.
10. Murahashi, S.-I.; Imada, Y.; Taniguchi, Y.; Kodera, Y. *Tetrahedron Lett.* **1988**, *29*, 2973.
11. Murahashi, S.-I.; Tanigawa, Y.; Imada, Y.; Taniguchi, Y. *Tetrahedron Lett.* **1986**, *27*, 227.
12. (a) Teng, C.-Y. P.; Ganem, B. *Tetrahedron Lett.* **1982**, *23*, 313. (b) Ortar, G.; Paradisi, M. P.; Morera, E.; Romeo, A. *J. Chem. Soc.*, *Perkin Trans. I.* **1978**, 4.
13. Huisgen, R.; Grashey, R.; Sauer, J. in Patai, S. Ed., *The Chemistry of Alkenes*, Interscience, London, 1963, p835.
14. (a) L'abbé, G. *Chem. Rev.* **1969**, *69*, 345.
15. (a)Brändström, A.; Lamb, B.; Palmertz, I. *Acta Chem. Scand. Ser. B.* **1974**, *28*, 699. (b) Papa, A. J.; *J. Org. Chem.* **1966**, *31*, 1426. (c) Sakai, K,; Anselme, J. P. *J. Org. Chem.* **1971**,

36, 2387. (d) Hassner, A.; Stern, M. Angew. Chem., Int. Ed. Engl. 1986, 25, 478.

16. Reeves, W. P.; Bahr, M. L. Synthesis 1976, 823.

17. Priebe, H. Acta Chem. Scand., Ser. B. 1984, 38, 895.

18. Kaboré, I. Z.; Khuong-Huu, Q.; Pancrazi, A. Tetrahedron 1978, 34, 2807 and 2815.

19. Loibner, H.; Zbiral, E. Helv. Chim. Acta 1976, 59, 2100.

20. (a) Gagneux, A.; Winstein, S.; Young, W. G. J. Am. Chem. Soc. 1960, 82, 5956. (b) VanderWerf, C. A.; Heasley, V. L. J. Org. Chem. 1966, 31, 3534. (c) Arimoto, M.; Yamaguchi, H.; Fujita, E.; Ochiai, M.; Nagao, Y. Tetrahedron Lett. 1987, 28, 6289. (d) Nishiyama, K.; Karigomi, H. Chem. Lett. 1982, 1477. (e) Heyns, K.; Feldmann, J.; Hadamczyk, D.; Schwentner, J.; Thiem, J. Chem. Ber. 1981, 114, 232.

21. Tenaglia, A.; Waegell, B. Tetrahedron Lett. 1988, 29, 4851.

22. Hayashi, T.; Yamamoto, A.; Hagihara, T. J. Org. Chem. 1986, 51, 723.

23. (a) Yamamoto, Y.; Oda, J.; Inoue, Y. Bull. Chem. Soc. Jpn. 1975, 48, 3744. (b) Yamamoto, Y.; Oda, J.; Inoue, Y. J. Org. Chem. 1976, 41, 303.

24. (a) Pearson, R. G. J. Am. Chem. Soc. 1963, 85, 3533. (b) Pearson, R. G.; Songstad, J. J. Am. Chem. Soc. 1967, 89, 1827. (c) Pearson, R. G. Symmetry Rules for Chemical Reactions, John Wiley, New York, 1976. (d) Ho, T. L. Chem.

Rev. **1975**, *75*, 1.

25. (a) Hayashi, T.; Yamamoto, A.; Ito, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 1090. (b) Hayashi, T.; Mise, T.; Fukushima, M.; Kagotani, M.; Nagashima, N.; Hamada, Y.; Matsumoto, A.; Kawakami, S.; Konishi, M.; Yamamoto, K.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1138.
26. (a) Yamamoto, T.; Akimoto, M.; Yamamoto, A. *Chem. Lett.* **1983**, 1725. (b) Osakada, K.; Chiba, T.; Nakamura, Y.; Yamamoto, A. *J. Chem. Soc.*, *Chem. Commun.* **1986**, 1589.
27. (a) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385. (b) Trost, B. M.; Verhoeven, T. R. *Compr. Organomet. Chem.* **1982**, *8*, 799. (c) Tsuji, J. *Organic Synthesis with Palladium Compounds*, Springer Verlag, Berlin, 1980. (d) Keinan, E.; Roth, Z. *J. Org. Chem.* **1983**, *48*, 1769. (e) Fiaud, J.-C.; Legros, J.-Y. *J. Org. Chem.* **1987**, *52*, 1907. (f) Onoue, H.; Moritani, I.; Murahashi, S.-I. *Tetrahedron Lett.* **1973**, 121.
28. Takahashi, T.; Jinbo, Y.; Kitamura, K.; Tsuji, J. *Tetrahedron Lett.* **1984**, *25*, 5921.
29. (a) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635. (b) Staudinger, H.; Hauser, E. *Helv. Chim. Acta* **1921**, *4*, 21, 861, 873, and 887. For a review: Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L. F. *Tetrahedron* **1981**, *37*, 437.
30. Suzuki, H.; Takaoka, K. *Chem Lett.* **1984**, 1733 and references cited therein.
31. Corey, E. J.; Nicolaou, K. C.; Balanson, R. D.; Machida, Y.

Synthesis 1975, 590.

32. (a) Klioze, S. S.; Darmary, F. P. J. Org. Chem. 1975, 40, 1588. (b) Mungall, W. S.; Greene, G. L.; Heavner, G. A.; Letsinger, R. L. J. Org. Chem. 1975, 40, 1659. (c) Ranganathan, R.; Larwood, D. Tetrahedron Lett. 1978, 4341. (d) Imazawa, M.; Eckstein, F. J. Org. Chem. 1979, 44, 2039. (e) Vaultier, M.; Knouzi, N.; Carrié, R. Tetrahedron Lett. 1983, 24, 763. (f) Baum, K.; Berkowitz, P. T.; Grakauskas, V.; Archibald, T. G. J. Org. Chem. 1983, 48, 2953. (g) Koziara, A.; Osowska-Pacewicka, K.; Zawadzki, S.; Zwierzak, A. Synthesis 1985, 202. (h) Koziara, A.; Zwierzak, A. Tetrahedron Lett. 1987, 28, 6513.

33. (a) Garcia, J.; Urpi, F.; Vilarrasa, J. Tetrahedron Lett. 1984, 25, 4841. (b) Garcia, J.; Vilarrasa, J.; Bordas, X.; Banaszek, A. Tetrahedron Lett. 1986, 27, 639. (c) Kusumoto, S.; Sakai, K.; Shiba, T. Bull. Chem. Soc. Jpn. 1986, 59, 1296.

34. (a) Lambert, P. H.; Vaultier. M.; Carrié, R. J. Chem. Soc., Chem. Commun. 1982, 1224. (b) Lambert, P. H.; Vaultier, M.; Carrié, R. J. Org. Chem. 1985, 50, 5352. (c) Tsuge, O.; Kanemasa, S.; Matsuda, K. J. Org. Chem. 1984, 49, 2688.

35. Corey, E. J.; Samuelson, B.; Luzzio, F. A. J. Am. Chem. Soc. 1984, 106, 3682.

36. Zimmer, H.; Jayawant, M.; Gutsch, P. J. Org. Chem. 1970, 35, 2826.

37. Schroeter, S.; Eliel, E. L. *J. Am. Chem. Soc.* **1964**, *86*, 2066.

38. Kumobayashi, H.; Mitsuhashi, S.; Akutagawa, S.; Ohtsuka, S. *Chem. Lett.* **1986**, 157.

39. (a) Hewgill, F. R.; Jefferies, P. R. *J. Chem. Soc.* **1955**, 2767. (b) Greenstein, J. P.; Wyman, J. Jr. *J. Am. Chem. Soc.* **1938**, *60*, 2341. (c) Skaric, V.; Kovacevic, M.; Skaric, D. *J. Chem. Soc.*, *Perkin Trans. I* **1976**, 1199.

40. Birkofer, L.; Wegner, P. *Org. Synth.* **1970**, *50*, 107.

41. Coulson, D. R. *Inorg. Syn.* **1972**, *13*, 121.

42. (a) Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. *J. Organomet. Chem.* **1974**, *65*, 253. (b) Rettig, M. F.; Maitlis, P. M. *Inorg. Synth.* **1977**, *17*, 134.

43. Stephenson, T. A.; Morehouse, S. M.; Powell, A. R.; Heffer, J. P.; Wilkinson, G.; *J. Chem. Soc.* **1965**, 3632. The author modified their method; See also: Hosokawa, T.; Miyagi, S.; Murahashi, S.-I.; Sonoda, A. *J. Org. Chem.* **1978**, *43*, 2752.

44. Grinberg, A. A.; Simonova, L. K. *Zh. Prikl. Khim.* **1953**, *26*, 880.

45. Kuran, W.; Musco, A. *Inorg. Chim. Acta* **1975**, *12*, 187.

46. Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730.

47. Kenyon, J.; Partridge, S. M.; Philips, H. *J. Chem. Soc.* **1936**, 85.

48. Kato, M.; Kageyama, M.; Tanaka, R.; Kuwahara, K.; Yoshikoshi, A. *J. Org. Chem.* **1975**, *40*, 1932.

49. Keinan, E.; Sahai, M.; Roth, Z.; Nudelman, A.; Herzig, J. *J. Org. Chem.* **1985**, *50*, 3558.

50. Luche, J. L.; Rodriguez-Hahn, L.; Crabbé, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601. The stereochemical ratio (*cis*:*trans* = 95:5) was determined by GLC (PEG 20M 25m x 0.25 mm).

51. (a) Steinberg, G. M. *J. Org. Chem.* **1950**, *15*, 637. (b) Smith, T. D. *J. Chem. Soc.* **1962**, 1122. (c) Following phosphates are also available. $(EtO)_2POBr$: Górecka, A.; Leplawy, M.; Zabrocki, J.; Zwierzak, A. *Synthesis* **1978**, 474; Goldwhite, H.; Saunders, B. C. *J. Chem. Soc.* **1955**, 3564: $(EtO)_2POCN$: Shioiri, T.; Yokoyama, Y.; Kasai, Y.; Yamada, S. *Tetrahedron* **1976**, *32*, 2211: $(RO)_2PON_3$: Shioiri, T.; Yamada, S. *Chem. Farm. Bull.* **1974**, *22*, 855; Shioiri, T. Yamada, S. *Org. Synth.* **1984**, *62*, 187; Scott, F, Riordan, R.; Morton, P. D. *J. Org. Chem.* **1962**, *27*, 4255: $(t\text{-Bu})_2POX$: Gajda, T.; Zwierzak, A. *Synthesis* **1976**, 243.

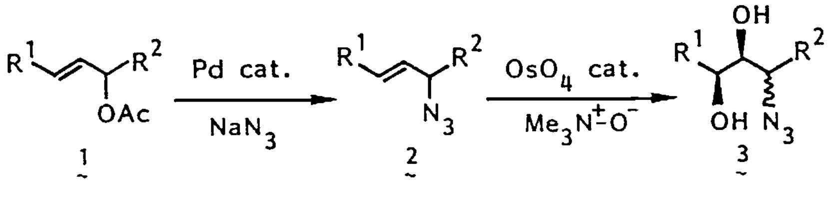
52. Kharasch, M. S.; Nudenberg, W.; Fields, E. K. *J. Am. Chem. Soc.* **1944**, *66*, 1276.

53. (a) Desvages, G.; Olomucki, M. *Bull. Soc. Chim. Fr.* **1969**, *9* 3229. (b) Deslongchamps, P.; Cheriyan, U. O.; Taillefer, R. J. *Can. J. Chem.* **1979**, *57*, 3262.

Chapter 3. Osmium Tetroxide Catalyzed Oxidation of Allyl Azides.

Introduction

In Chapter 2, the author described that allyl azides were readily prepared by the palladium-catalyzed azidation of allyl esters.[1] In order to extend the synthetic application of the azidation, metal-catalyzed oxidation of allyl azides has been studied. The oxidation of carbon-carbon double bonds with stoichiometric[2,3] and catalytic[4] amounts of OsO_4 is known to give 1,2-diols. Allylic compounds, such as allyl alcohols,[5] ethers,[5,6] esters,[6,7] amides,[8] and silanes[9] have been oxidized. The oxidation to allyl azides **2** would give 3-azido-1,2-diols **3**, and hence combining the palladium(0)-catalyzed azidation, two functional transformations of allylic esters can be performed (eq. 1). Secondary allyl acetates (**1**) (R^2=alkyl) would give two diastereomers upon oxidation with OsO_4.

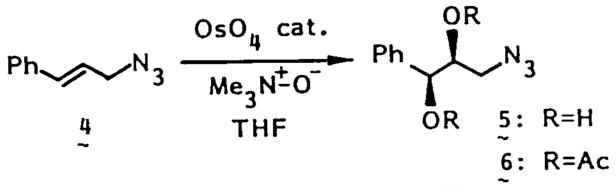


(1)

Described in this chapter is the results of the OsO_4 catalyzed oxidation of allyl azides leading to 3-azido-1,2-diols **3**. The stereochemistry of the reaction as well as the synthetic application is described.

Results and Discussion.

Synthesis of 3-Azido-1,2-diols: The reaction of allyl azides with trimethylamine *N*-oxide in the presence of a catalytic amount of OsO_4 (5 mol%) in THF at room temperature gave 3-azido-1,2-diols 3 in good yields. As shown in eqs 2 and 3, primary allyl azides 4 and 7 were smoothly oxidized to give the corresponding azidodiols 5 and 8 in high yields (91-98%). The



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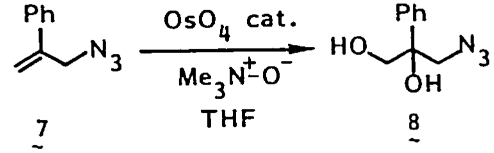

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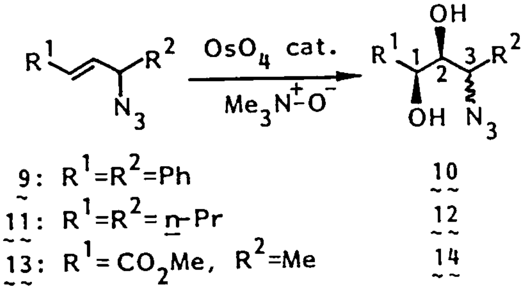
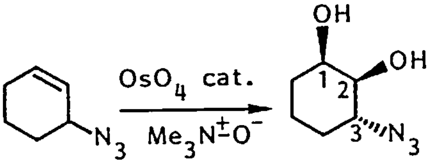


(4)

configuration of azidodiol 5 was determined to be *syn* by the ^1H NMR analysis of azidodiacetate 6 derived from 5. The oxidations of secondary allyl azides 9, 11, and 13 gave diastereoisomeric mixtures of 3-azido-1,2-diols (eq 4). The diastereoisomeric ratios of these products were determined to be 60:40 by their ^1H NMR analyses. The diastereoselectivity of the oxidation of acyclic allyl azides was not high so far; however, the oxidation of cyclic allyl azide, 2-cyclohexenyl azide (**15**) gave a single

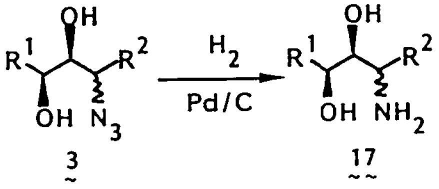


15 **16** (5)

diastereomer, 1,2-*cis*-2,3-*trans*-azidodiol **16** (eq 5). The 1,2-*cis* and 2,3-*trans* configuration of **16** was determined by the coupling constants of J_{H1-2} = 4 Hz and J_{H2-3} = 10 Hz. The oxidation occurs in the face opposite to the azido group.

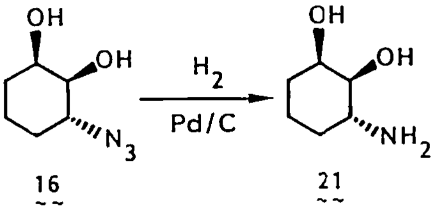
Synthesis of 3-Amino-1,2-diols: 3-Amino-1,2-diols are potentially useful precursors for the synthesis of naturally occuring compounds such as aminosugars,[8,10] nucleosides,[11] and antibiotics.[12] In particular, many biologically active natural products contain 3-amino-1,2-diol functionality in five- and six-membered ring compounds, and hence convenient method for the synthesis of these compounds are required. In view of highly selective oxidation of cyclic allyl azides, the author has examined the transformation of azidodiols to aminodiols. The catalytic hydrogenation (1.0 atm) of 3-azido-1,2-diols **3** over

Pd/C catalyst gave the corresponding 3-amino-1,2-diols (**17**) quantitatively (eq 6). The other results are summarized in Table I. Cyclic azidodiol **16** derived from 2-cyclohexenyl azide **15** was



(6)

converted into 1,2-*cis*-2,3-*trans*-aminodiol (**21**) (eq 7).[13] Thus, the overall process from allyl ester **1** to aminodiol **17** constructs the stereoselective transformation. The *cis*- and *trans*-stereochemistry of 3-aminocyclohexane-1,2-diol (**21**) with respect to 1,2- and 2,3-positions was determined based on the coupling constants of J_{H1-2} = 3 Hz and J_{H2-3} = 10 Hz, respectively.



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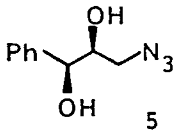
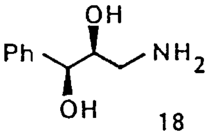
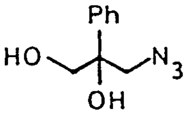
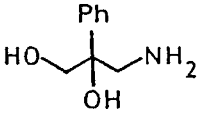
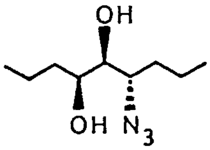
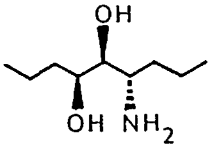
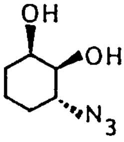
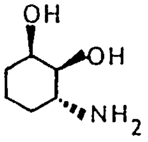
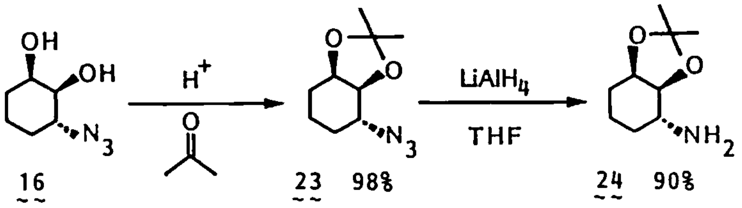
Protection of 3-Amino-1,2-diols: Selective protection of the diol moiety of azidodiols **3** can be accomplished by the usual acetalization. Thus, the treatment of **16** and **8** with acetone in the presence of a catalytic amount of *p*-toluenesulfonic acid gave

Table I. Preparation of 3-Amino-1,2-diols[a]

Azidodiol	Aminodiol	Isolated yield(%)
 5	 18	99
 8	 19	99
 12	 20	99
 16	 21	100

[a] The reaction is similar to the general procedure described in the experimental section.

azidoacetonides **23** and **25**, respectively, the azido group being not impaired under the reaction conditions (eqs 8 and 9). The azidoacetonides obtained are then transformed into the



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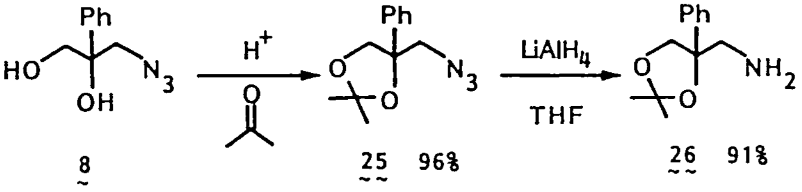
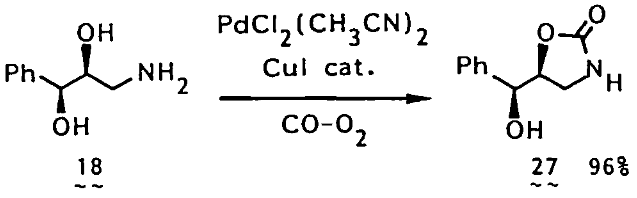


(9)

corresponding amines. Accordingly, primary amines **24** and **26** bearing a masked diol moiety can be synthesized from allyl acetates by four steps. Selective protection of the aminoalcohol



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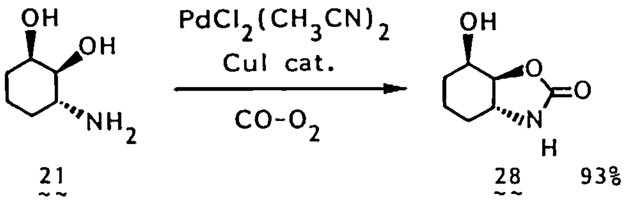
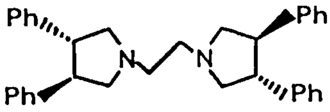


(11)

moiety is realized by appling the Pd(II)-catalyzed carbonylation of aminoalcohols which was developed by Murahashi et al.[14] Thus, the treatment of aminodiols **18** and **21** with carbon monoxide (80 kg/cm^2) in the presence of $PdCl_2(CH_3CN)_2$ (5 mol%), CuI (15 mol%) and molecular oxygen (5 kg/cm^2) gave cyclic urethanes **27** and **28**, respectively, *via* selective cross carbonylation of the aminoalcohol moiety (eqs 10 and 11). The cyclic urethanes **27** and **28** bearing OH group have potential for further synthetic transformations.

Asymmetric Oxidation of Allyl Azides: Enantioselective dihydroxylation of alkenes is one of the most efficient method for the synthesis of various optically active polyoxygenated natural products such as macrolides and carbohydrates.[5a] Promising π-face differentiations have been achieved by osmylations of either olefinic bonds attached to a chiral auxiliary such as chiral sulfoximines,[15] oxazolidines,[16] tiglate esters,[17] sulfoxides,[8b,18] acetals,[19] and enoyl sultams,[20] or prochiral alkenes in the presence of chiral ligands.

It has been reported that tertiary amines and pyridine form tight complexes with OsO_4[21] and accelerate the oxidation of olefins.[2a,22] Chiral ligands such as dihydroquinine and dihydroquinidine acetate,[23] 1,4-diamines derived from (*L*)-tartaric acid,[24] and (*R*,*R*)-*N*,*N*,*N*',*N*'-tetramethyl-1,2-cyclohexanediamine,[25] have been employed for the stoichiometric oxidations with OsO_4. However, satisfactory results have not been obtained with the enantioselectivity of the stoichiometric reactions using these ligands. Recently, the stoichiometric osmylation by using a chiral diamine 29, it is shown that, which



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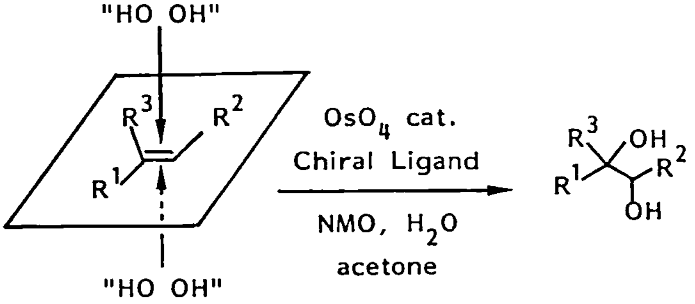
has $\underline{D}_2$-symmetry gives high enantioselectivity, and the anticancer antibiotic anthracyclinones has been synthesized by using this method.[26]

Catalytic asymmetric oxidation of alkenes with OsO_4 was firstly investigated by using a bovine serum albmin (BSA) complex.[27] Quite recentry, Sharpless et al reported asymmetric



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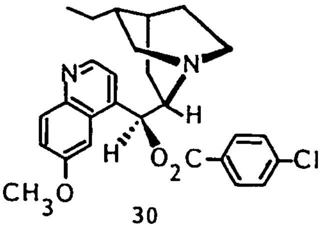

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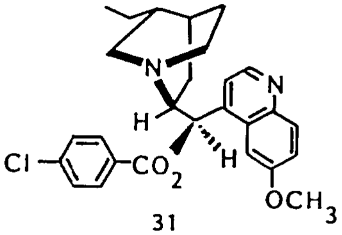
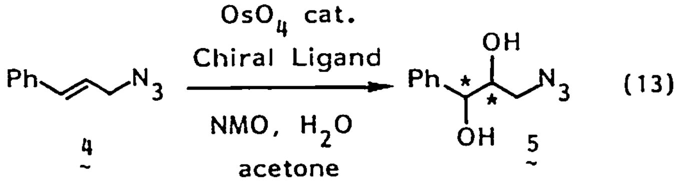
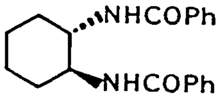


31

dihydroxylation of alkenes with N-methylmorpholine N-oxide (NMO) in the presence of chiral ligands 30 or 31, which are diastereomers bearing opposite chiral center at C-9 (eq 12).[28]

The author examined enantioselective oxidation of cinnamyl azide 4 by using Sharpless method to give optically active azidodiol 5. Osmium tetroxide catalyzed oxidation of 4 with NMO in the presence of either alkaloid ligands 30 or 31 at 0-5 °C in aqueous acetone gave (+)- or (-)-3-azido-1-phenylpropane-1,2-diol (5) in 87-89% yield (eq 13). HPLC analysis[29] showed that the enantiomeric excess of 5 is 71% and 70% e.e., respectively.





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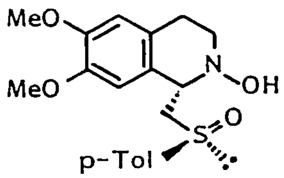
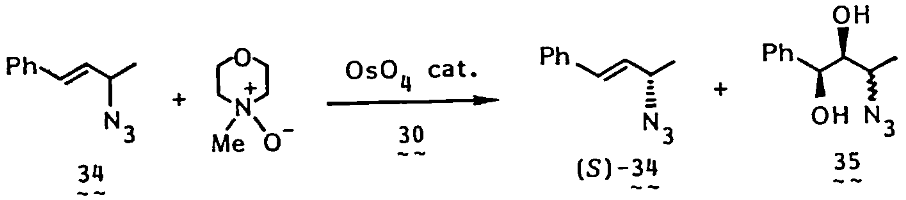


33

Considering the strong interaction of osmium tetroxide with amido group[30] and sulfoxides,[8b,18] chiral ligands, (R,R)-cyclohexanediamine dibenzamide (32) and sulfoxide 33[31] were used for the oxidation of 4, but racemic 5 was obtained in 96% yield.

The oxidation of 2-cyclohexen-1-yl azide (15) gave no sufficient asymmetric induction by the use of chiral ligand 30. The enantiomeric purity of the product 16 was ≤ 5% e.e. which was determined by HPLC analysis of the dibenzoate obtained upon treatment of azidodiol 16 with benzoyl chloride.

The kinetic resolution of racemic 4-phenyl-3-buten-2-yl azide 34 was attempted so far in vain by using chiral ligand 30 (eq 14). Thus, the reaction of racemic allyl azide 34 with *N*-methylmorphorine *N*-oxide (0.6 equiv) in the presence of OsO_4 and 30 at 0-5 °C gave (*S*)-(*E*)-allyl azide 34 (40% yield based on 34) in 5.1% e.e. along with 3-azido-1-phenylbutane-1,2-diol (35) (56% yield based on 34).



(14)

Conclusion

The osmium catalyzed oxidation of allyl azides provides an efficient method for the selective synthesis of 3-amino-1,2-diols. Osmylation of cyclic allyl azides occurs from the opposite side of the azide group with high stereoselectivity. The oxidation of cinnamyl azide 4 with OsO_4 in the presence of homochiral alkaloid ligand gave in azidodiol 5 with high enantioselectivity.

Experimental Section

General

NMR spectra were recorded on a JEOL PMX-60 SI (60 MHz), a JEOL JNM-FX 100, a JEOL JNM-GSX 270 and a JEOL JNM-GX 500 spectrometers. Chemical Shifts (δ) were expressed in parts per million relative to tetramethylsilane ($CDCl_3$) or a sodium 2,2-dimethyl-2-silapentane-5-sulfonate (D_2O, $\underline{d}_6$-DMSO, $\underline{d}_3$-MeOH). Optical rotations were measured with JASCO DIP-4 polarimeter with 1 dm-long cell at room temp. HPLC analyses were performed on a JASCO TRI ROTAR-VI system with a JASCO UVIDEC-100-VI UV detector by using a 250-mm. x 4.6-mm. analytical column packed with Chemcosorb 7 SI and Cellulose tris(3,5-dimethylphenylcarbamate) on Silica gel (Nucleosil 4000-10).[29]

Materials

Osmium tetroxide (Wako), 5% palladium on charcoal (K-type) (Nippon Engelhard), trimethylamine N-oxide (Tokyo Kasei), N-methylmorpholine N-oxide (Aldrich), hydroqunidine 4-chlorobenzoate (**30**) (Aldrich), and hydroquinine 4-chlorobenzoate (**31**) (Aldrich) are commercially available. Tetrahydrofuran (THF) was distilled from benzophenone ketyl. Acetone was distilled from $CaSO_4$ and stored over 4A molecular sieves.

General Procedure for the Osmium Catalyzed Oxidation of Allyl Azides: To a solution of allyl azide (10.0 mmol) in dry THF (50 mL) trimethylamine N-oxide dihydrate (1.67 g, 15,0 mmol) was added at room temp. A solution of OsO_4 in THF (0.386 M, 0.50 mmol, 1.30 mL) was added to the allyl azide solution by syringe in one portion at room temp. The reaction mixture was stirred at room temp for 10 h. The reaction was quenched with $Na_2S_2O_4$ (4.0 g), and Florisil (10.0 g) and water (5.0 mL) were added. The reaction mixture was stirred at room temp for 30 min and dried over $MgSO_4$ (10.0 g). The resulting slurry was filtered through a plug of silica gel (10.0 g) to give 3-azido-1,2-diols. An analytical sample was purified by silica gel column chromatography using ether as an eluent.

(1*R,2*R**)-3-Azido-1-phenylpropane-1,2-diol (5):** Oxidation of (*E*)-cinnamyl azide (**4**) (1.60 g, 10.0 mmol) was carried out according to the general procedure. (1*R**,2*R**)-3-Azido-1-phenylpropane-1,2-diol (**5**) (1.44 g, 75%) was obtained as a yellow oil: IR (neat) 3350 (OH, br), 2920 (w), 2100 (N_3, s), 1660 (s), 1500 (m), 1455 (m), 1395 (m), 1280 (s), 1200 (m), 1090 (s), 1045 (s), 925 (m), 885 (w), 765 (s), 700 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 3.01-3.30 (m, 2 H, CH_2N_3), 3.30-3.65 (br, 2 H, OH), 3.57-4.00 (m, 1 H, CHO), 4.57 (d, $J = 7.5$ Hz, 1 H, CHO), 7.10-7.40 (m, 5 H, ArH).

(1*R,2*R**)-3-Phenyl-2,3-diacetoxypropan-1-yl Azide (6):** To a solution of azidodiol **5** (1.44 g, 7.46 mmol) in dry ether (12 mL) triethylamine (3.12 mL, 22.4 mmol) and a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (91 mg, 0.75 mmol) were added. Acetic anhydride (2.12 mL, 22.5 mmol) was added to the solution at room temp. After stirring at room temp for 3 h, the reaction mixture was diluted with ether (50 mL) and was washed successively with a 2N HCl solution (20 mL x 2), brine (20 mL), and a saturated $NaHCO_3$ (20 mL x 2). The ethereal layer was dried over $MgSO_4$ and evaporated in vacuo. Diacetate **6** (1.85 g, 89%) was obtained by silica gel column chromatography as a yellow oil: IR (neat) 3040 (s), 2950 (s), 2100 (N_3, s), 1830 (s), 1740 (C=O, s), 1605 (w), 1590 (w), 1500 (m), 1440 (s), 1370 (s), 1200 (C-O-C, s), 1010 (s), 825 (m), 760 (m), 695 (m) cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 2.08 (s, 3 H, CH_3CO), 2.10 (s, 3 H, CH_3CO), 3.09 (dd, J = 13.4 and 5.6 Hz, 1 H, CHN_3), 3.38 (dd, J = 13.4 and 3.7 Hz, 1 H, CHN_3), 5.35 (ddd, J = 7.6, 5.6, and 3.7 Hz, 1 H, CHOAc), 5.96 (d, J = 7.6 Hz, 1 H, CHOAc), 7.36 (s, 5 H, ArH).

3-Azido-2-phenylpropane-1,2-diol (8): Oxidation of 2-phenyl-2-propen-1-yl azide (**7**) (0.706 g, 4.44 mmol) was carried out according to the general procedure. 3-Azido-2-phenylpropane-1,2-diol (**8**) (0.770 g, 91%) was obtained as a yellow oil: IR (neat) 3350 (s, OH), 3060 (w), 3020 (w), 2930 (m), 2870 (w), 2100 (N_3, s), 1700 (m), 1605 (w), 1585 (w), 1495 (m), 1450 (m), 1270 (s), 1180 (w), 1050 (s), 905 (m), 875 (w), 755 (m), 725 (w), 695 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 3.25-3.90 (br, 2 H, OH), 3.57 (s, 2 H, CH_2), 3.75 (s, 2 H, CH_2), 7.00-7.60 (m, 5 H, ArH).

3-Azido-1,3-diphenylpropane-1,2-diol (10): Oxidation of (*E*)-1,3-diphenyl-2-propen-1-yl azide (**9**) (0.235 g, 1.00 mmol) was carried out according to the general procedure. A mixture of (1*R**,2*S**,3*R**)- and (1*R**,2*S**,3*S**)-3-azido-1,3-diphenylpropane-1,2-diols (**10a** and **10b**) (0.184 g, 68%) was obtained as a yellow oil. The molar ratio was determined to be 6:4 by the ^{1}H NMR analysis: ^{1}H NMR ($CDCl_3$, 100 MHz) δ 2.60-3.20 (br, 2 H, OH), 3.77 (dd, J = 6.83 and 3.54 Hz, 1 H, CHO), 4.42 (d, J = 6.83 Hz, 1 H, CHN), 4.65 (d, J = 3.54 Hz, 1 H, CHO), 7.00-7.40 (m, 10 H, ArH) for **10a**. Isomer **10b** could not be assigned.

6-Azidononane-4,5-diol (12): Oxidation of (*E*)-5-nonen-4-yl azide (**11**) (1.67 g, 10.0 mmol) was carried out according to the general procedure. A mixture of (1*R**,2*S**,3*R**)- and (1*R**,2*S**,3*S**)-6-azidononan-4,5-diols (**12a** and **12b**) (1.97 g, 98%) was obtained as a colorless oil. The molar ratio was determined to be 6:4 by the ^{1}H NMR analysis: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.92-1.01 (m, 6 H), 1.35-1.73 (m, 8 H), 2.45-2.75 (br, 1 H, OH), 2.80-3.05 (br, 1 H, OH), 3.31-3.39 (m, 1 H, CHN_3), 3.43-3.48 (m, 1 H, CHO), 3.82 (ddd, J = 8.0, 4.6, and 2.3 Hz, 1 H, CHO) for **12a**; δ 0.92-1.01 (m, 6 H), 1.35-1.73 (m, 8 H), 2.45-2.75 (br, 1 H, OH), 2.80-3.05 (br, 1 H, OH), 3.31-3.39 (m, 2 H, CHN_3 and CHO), 3.67 (ddd, J = 8.3, 4.1, and 4.1 Hz, 1 H, CHO) for **12b**.

Methyl 4-Azido-2,3-dihydroxypentanoate (14): Oxidation of (*E*)-methyl 4-azido-2-pentenoate (**13**) (1.55 g, 10.0 mmol) according to the general procedure gave methyl 4-azido-2,3-dihydroxypentanoate (**14**) (1.50 g, 79%): IR (neat) 3370 (OH, s), 2960 (m), 2100 (N_3, s), 1740 (C=O, s), 1450 (m), 1385 (w), 1250 (C-O-C, s), 1130 (s), 1040 (m), 990 (w), 955 (w), 905 (w), 860 (w), 805 (w), 710 (w), 710 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 60 MHz) δ

1.35 (t, J = 6.0 Hz, 3 H), 3.00-4.50 (m, 5 H), 3.80 (s, 3 H, CH_3O).

(1*R**,2*S**,3*R**)-3-Azidocyclohexane-1,2-diol (**16**): Oxidation of 2-cyclohexen-1-yl azide (**15**) (2.46 g, 20.0 mmol) was carried out according to the general procedure. (1*R**,2*S**,3*R**)-3-Azidocyclohexane-1,2-diol (**16**) (3.14 g 100%) was obtained as a colorless crystal (1.48 g, 94%): mp 67-69 °C; IR (KBr) 3270 (OH, brs), 2930 (CH, s), 2095 (N_3, s), 1450 (m), 1365 (m), 1355 (m), 1253 (m), 1205 (w), 1115 (w), 1085 (m), 1060 (m), 995 (m), 870 (w), 835 (w), 815 (w), 710 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.34 (m, 1 H), 1.44 (m, 1 H), 1.56 (m, 1 H), 1.70 (m, 1 H), 1.90 (m, 1 H), 2.03 (m, 1 H), 2.41 (s, 1 H), 2.68 (d, J = 3.21 Hz, 1 H), 3.42 (d, J = 9.39 Hz, 1 H, CHN_3), 3.63 (ddd, J = 11.2, 9.39, and 4.35 Hz, 1 H, CHO), 4.08 (d, J = 3.43 Hz, 1 H, CHO). Anal. Calcd for $C_6H_{11}N_3O_2$: C, 45.85; H, 7.05; N, 26.74. Found: C, 45.73; H, 6.84; N, 26.95.

General Procedure for the Reduction of 3-Azido-1,2-diol: In a 200 mL round-bottomed flask were placed allyl azide (10.0 mmol) and 5% Pd/C (20 wt%). The atmosphere in the flask was replaced with hydrogen (baloon). Absolute ethanol (20 mL) was added to the flask. The suspension was stirred with vigorous stirring at room temp for 24 h. After the reaction was completed, the suspension was filtered through a plug of Celite (3.0 g, 55 x 12 mm) using ethanol as an eluent. The ethanolic solution was evaporated to give a crude aminodiol.

(1*R**,2*R**)-3-Amino-1-phenylpropane-1,2-diol (**18**):

Reduction of azidodiol **5** (1.93 g, 10.0 mmol) was carried out according to the general procedure. (1R*,2R*)-3-Amino-1-phenylpropane-1,2-diol (**18**) (1.67 g, 100%) was obtained as a yellow oil: IR (neat) 3500-2700 (NH_2 and OH, brs), 2850 (s), 1960 (w), 1890 (w), 1820 (w), 1750 (w), 1660 (w), 1595 (m), 1495 (m), 1450 (m), 1200 (m), 1100-900 (s), 760 (s), 695 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.55 (d, J = 5.0 Hz, CH_2N), 2.80-3.30 (br, 4 H, NH_2 and OH), 3.40-3.75 (m, 1 H, CHO), 4.45 (d, J = 6.5 Hz, 1 H, CHO), 7.10-7.50 (m, 5 H, ArH).

3-Amino-2-phenylpropane-1,2-diol (19): Reduction of azidodiol **8** (0.848 g, 4.39 mmol) was carried out according to the general procedure. 3-Amino-2-phenylpropane-1,2-diol (**19**) (0.727 g, 99%) was obtained as a yellow oil: IR (neat) 3500-2700 (NH_2 and OH, s), 2850 (s), 1960 (w), 1890 (w), 1820 (w), 1750 (w), 1660 (w), 1595 (m), 1495 (m), 1450 (m), 1200 (m), 1100-900 (s), 760 (s), 695 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.50-2.70 (m, 2 H, CH_2N), 3.30-3.65 (br, 4 H, OH and NH_2), 3.57-4.00 (m, 2 H, CH_2O), 7.10-7.40 (m, 5 H, ArH).

(1R*,2S*,3R*)-3-Aminocyclohexane-1,2-diol (21): Reduction of azidodiol **16** (0.734 g, 4.67 mmol) was carried out according to the general procedure. (1R*,2S*,3R*)-3-Amino-cyclohexane-1,2-diol (**21**) (0.557 g, 91%) was obtained as a colorless crystal: mp 97-99 °C; IR (neat) 3200 (NH and OH, brs), 2900 (s), 1550 (m), 1480 (s), 1365 (w), 1330 (m), 1150 (w), 1060 (s), 990 (w), 860 (w), 850 (w), 810 (w) cm^{-1}; ^1H NMR (D_2O, 500 MHz) δ 1.07-1.21 (m, 1 H), 1.40-1.60 (m, 3 H), 1.70-1.90 (m, 2 H), 2.87 (ddd, J = 11.0, 9.63, and 4.36 Hz, 1 H, CHN), 3.28 (dd, J = 9.63 and 2.98 Hz, 1 H, CHO), 3.97-4.04 (m, 1 H, CHO). Treatment of aminodiol **21** (0.131 g, 1.00 mmol) with a 2.06N HCl solution in methanol (1.00 mL, 2.06 mmol) gave amine hydrochloride **22** (0.110 g, 66%): mp 161-166 °C (lit.[11] 191-194 °C).

6-Aminononane-4,5-diol (20): Reduction of azidodiol **12** (1.01 g, 5.00 mmol) was carried out according to the general procedure. 6-Aminononane-4,5-diol (**20**) (0.867 g, 99%) was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$, 60 MHz) δ 0.65-1.15 (m, 6 H), 1.15-1.90 (m, 8 H), 2.30-3.00 (m, 5 H, CHN, OH, and NH_2), 3.00-3.50 (m, 2 H, CHO).

(1*R,2*S**,3*R**)-2,3-*O*-Isopropylidenecyclohexyl Azide (23):** Treatment of azidodiol **16** (0.314 g, 2.00 mmol) in dry acetone (5 mL) with a catalytic amount of *p*-toluenesulfonic acid (5 mg) gave (1*R**,2*S**,3*R**)-2,3-*O*-isopropylidenecyclohexyl azide (**23**) (0.386 g, 98%) as a colorless oil: IR (neat) 2940 (s), 2100 (N_3, s), 1700 (w), 1450 (m), 1380 (m), 1250 (s), 1220 (m), 1190 (w), 1150 (w), 1105 (w), 1060 (s), 1040 (s), 1000 (m), 895 (w), 865 (m), 840 (w), 815 (w), 775 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.17-1.26 (m, 1 H), 1.37 (s, 3 H, CH_3), 1.53 (s, 3 H, CH_3), 1.50-1.75 (m, 3 H), 1.85-1.92 (m, 1 H), 2.05-2.13 (m, 1 H), 3.45 (ddd, J = 12.03, 8.02, and 4.35 Hz, 1 H, CHN), 3.85 (dd, J = 8.02 and 5.04 Hz, 1 H, CHO), 4.28 (ddd, J = 5.04, 4.35, and 2.75 Hz, 1 H, CHO).

(2*R,3*S**)-2,3-*O*-Isopropylidene-2-phenylpropan-1-yl Azide**

(25): Treatment of azidodiol **8** (0.770 g, 4.00 mmol) in dry acetone (10 mL) with a catalytic amount of *p*-toluenesulfonic acid (10 mg) gave 2,3-*O*-isopropylidene-2-phenylpropan-1-yl azide (**25**) (0.894 g, 96%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.33 (s, 3 H, CH_3), 1.61 (s, 3 H, CH_3), 3.40 (dd, J = 13.5 and 12.5 Hz, 2 H, CHN_3), 4.12 (d, J = 15.5 Hz, 1 H, CHO), 4.27 (d, J = 15.5 Hz, 1 H, CHO), 7.10-7.50 (m, 5 H, ArH).

(1R*,2S*,3R*)-2,3-O-Isopropylidenecyclohexylamine (24): Reduction of azidoacetonide **23** (0.353 g, 1.79 mmol) in THF (3.6 mL) with a THF solution of $LiAlH_4$ (0.69M, 2.6 mL, 1.79 mmol) gave (1R*,2S*,3R*)-2,3-*O*-isopropylidenecyclohexylamine (**24**) (0.276 g, 90%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.00-1.09 (m, 1 H), 1.36 (s, 3 H, CH_3), 1.49 (s, 3 H, CH_3), 1.50-1.75 (m, 3 H), 1.85-1.92 (m, 1 H), 2.05-2.13 (m, 1 H), 2.82 (ddd, J = 12.03, 8.02, and 4.35 Hz, 1 H, CHN), 3.59 (dd, J = 8.02 and 5.04 Hz, 1 H, CHO), 4.24 (ddd, J = 5.04, 4.35, and 2.75 Hz, 1 H, CHO).

2,3-O-Isopropylidene-2-phenylpropylamine (26): Reduction of azidoacetonide **25** (0.906 g, 3.88 mmol) in THF (7.8 mL) with a THF solution of $LiAlH_4$ (0.69 M, 5.6 mL, 3.88 mmol) gave 2,3-*O*-isopropylidene-2-phenylpropylamine (**26**) (0.727 g, 91%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 100 MHz) δ 1.32 (s, 3 H, CH_3), 1.55 (s, 3 H, CH_3), 1.50-1.80 (br, 2 H, NH_2), 2.90 (s, 2 H, CH_2N), 4.07 (d, J = 16 Hz, 1 H, CHO), 4.18 (d, J = 16 Hz, 1 H, CHO), 7.10-7.50 (m, 5 H, ArH).

Carbonylation of Aminoalcohol 18: In a 30-mL stainless steel autoclave, bis(acetonitrile)dichloropalladium(II) (39 mg, 0.25 mmol), cuprous iodide (143 mg, 0.75 mmol), and a solution of (1*R**,2*R**)-3-amino-1-phenylpropane-1,2-diol (**18**) (0.501 g, 3.00 mmol) in methanol (6.0 mL) were placed. Carbon monoxide and oxygen gas were introduced into the autoclave to 80 kg/cm^2 (CO) and 5 kg/cm^2 (O$_2$), respectively. The mixture was stirred at room temperature for 6 h. The resulting dark brown solution was purified by column chromatography (SiO$_2$, 1.5 g, MeOH, 50 mL) to give **27** (0.556 g, 96%): mp 136-7 °C; ^{1}H NMR ($\underline{d}_6$-DMSO, 270 MHz) δ 3.29 (dd, J = 6.3 and 6.3 Hz, 1 H, CH), 3.32 (dd, J = 6.3 and 6.3 Hz, 1 H, CH), 4.62-4.77 (m, 2 H, CHO and OH), 5.77 (d, J = 4.64 Hz, 1 H, CHO), 7.20-7.50 (m, 6 H, ArH and CONH). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.18; H, 5.83; N, 7.32.

Carbonylation of Aminoalcohol 21: In a 30-mL stainless steel autoclave, bis(acetonitrile)dichloropalladium(II) (39 mg, 0.25 mmol), cuprous iodide (143 mg, 0.75 mmol), and a solution of 3-amino-1,2-cyclohexanediol (**21**) (393 mg, 3.0 mmol) in methanol (6.0 mL) were placed. Carbon monoxide and oxygen gas were introduced into the autoclave to 80 kg/cm^2 (CO) and 5 kg/cm^2 (O$_2$), respectively. The mixture was stirred at room temperature for 20 h. The resulting dark brown solution was purified by column chromatography (SiO$_2$, 1.5 g, MeOH, 50 mL) to give **28**: mp 164 °C; IR (KBr) 3370 (OH, s), 2930 (m), 2870 (w), 1735 (C=O, s), 1400 (m), 1345 (m), 1314 (m), 1226 (m), 958 (m) cm^{-1}; ^{1}H NMR ($\underline{d}_6$-DMSO, 500 MHz) δ 1.26-1.35 (m, 1 H), 1.45-1.58

(m, 3 H), 1.63-1.71 (m, 1 H), 1.86-1.92 (m, 1 H), 3.71 (dddd, J = 11.45, 11.45, 3.5, and 0.6 Hz, 1 H, CHN), 3.80 (dd, J = 11.45 and 2.06 Hz, 1 H, CHO), 4.19 (s, 1 H, CHO), 5.05 (s, 1 H, OH), 7.36 (s, 1 H, CONH).

General Procedure for the Asymmetric Oxidation of Allyl Azides: To a solution of allyl azide (2.00 mmol) in acetone (1.0 mL) and water (0.2 mL), N-methylmorpholine N-oxide (0.314 g, 2.60 mmol) and chiral amine ligands (0.10 mmol) were added at room temp. A solution of OsO_4 in toluene (0.474 M, 0.010 mmol, 21 μL) was added to the allyl azide solution by syringe in one portion at 0 °C. The mixture placed in a refrigerator at ca. 5 °C with occasional shaking during the 17 h reaction time. After 17 h, $Na_2S_2SO_4$ (50 mg) was added to the cold solution and the mixture was stirred for 5 min. The mixture was diluted with CH_2Cl_2 (2 mL), and treated with $MgSO_4$ (200 mg). The resulting slurry was filtered through a plug of silica gel (2.0 g) to give 3-azido-1,2-diols. An analytical sample was purified by silica gel column chromatography (5.0 g, 80 x 12 mm) using ether as an eluent.

Asymmetric Oxidation of Cinnamyl Azide (4): (+)-3-Azido-1-phenylpropane-1,2-diol (5): Oxidation of cinnamyl azide (0.318 g, 2.00 mmol) was carried out according to the general procedure. Hydroquinine 4-chlorobenzoate (31) (47 mg, 0.1 mmol) was used as a chiral ligand. (+)-3-Azido-1-phenylpropane-1,2-diol (5) (0.345 g, 89%) was obtained. The optical yield of 5 was determined to be 70% e.e. by HPLC analysis:

$[\alpha]_D^{22}$ +2.44° (*c* 1.11, EtOH).

(-)-3-Azido-1-phenylpropane-1,2-diol (5): Oxidation of cinnamyl azide (0.318 g, 2.00 mmol) was carried out according to the general procedure. Hydroquinidine 4-chlorobenzoate (**30**) (47 mg, 0.1 mmol) was used aa a chiral ligand. (-)-3-Azido-1-phenylpropane-1,2-diol (**5**) (0.336 g, 87%) was obtained. The optical yield of 5 was determined to be 71% e.e. by HPLC analysis: $[\alpha]_D^{22}$ -3.44° (*c* 1.14, EtOH).

Asymmetric Oxidation of 2-Cyclohexen-1-yl Azide (15): Oxidation of 2-cyclohexen-1-yl azide (**15**) (0.246 g, 2.00 mmol) was carried out according to the general procedure. Hydroquinidine 4-chlorobenzoate (**30**) (32 mg, 0.068 mmol) was used as a chiral ligand. (1*R**,2*S**,3*R**)-3-Azidocyclohexane-1,2-diol (**16**) (0.319 g, 100%) was obtained. The optical yield of **16** was determined to be 5% e.e. by HPLC analysis of azido dibenzoate.

Attempt of Osmium tetroxide Catalyzed Kinetic Resolution of (E)-4-Phenyl-3-buten-2-yl Azide (34).

To a mixture of (*E*)-4-phenyl-3-buten-2-yl azide (**34**) (0.346 g, 2.00 mmol), *N*-methylmorpholine *N*-oxide (0.117 g, 1.00 mmol), and hydroquinidine 4-chlorobenzoate (16 mg, 0.034 mmol) in acetone (1.0 mL) was added water (0.2 mL). A solution of OsO_4 (0.474 M, 0.010 mmol, 21 µL) in toluene was added to the allyl azide solution in one portion at 0 °C. The mixture placed in a refrigerator at *ca.* 5 °C with occasional shaking during the 17 h reaction time. After 17 h, $Na_2S_2SO_4$ (50 mg) was added to the cold solution and the mixture was stirred for 5 min. The mixture was diluted with CH_2Cl_2 (2 mL), and treated with $MgSO_4$ (200 mg). The resulting slurry was filtered through a plug of silica gel (2.0 g). The filtrate was evaporated in vacuo. Resulting residue was purified by silica gel column chlomatography (5.0 g, 80 x 12 mm) using ether as an eluent to give (*S*)-(*E*)-(-)-allyl azide **34** (0.137 g, 40%) ($[\alpha]_D^{24}$ -3.62°, *c* 2.79, $CHCl_3$), and 3-azido-1-phenylbutane-1,2-diol **35** (0.231 g, 56%) ($[\alpha]_D^{23}$ +1.71°, *c* 3.86, $CHCl_3$). The optical yield of **34** was determined to be 5.1% e.e. by HPLC analysis. For **34**: IR (neat) 3025 (m), 2975 (m), 2925 (w), 2100 (N_3, s), 1495 (m), 1445 (m), 1375 (m), 1300 (m), 1230 (s), 1140 (m), 1070 (w), 1030 (m), 960 (m), 910 (w), 840 (w), 810 (w), 740 (s), 680 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.35 (d, J = 6.5 Hz, 3 H, Me), 4.10 (dq, J = 6.5 and 6.5 Hz, 1 H, CH), 6.07 (dd, J = 15.5 and 6.5 Hz, 1 H, CH=), 6.60 (d, J = 15.5 Hz, 1 H, CH=), 7.05-7.55 (m, 5 H, ArH).

References

1. Murahashi, S.-I.; Tanigawa, Y.; Imada, Y.; Taniguchi, Y. *Tetrahedron Lett.* **1986**, *27*, 227.
2. (a) Criegee, R. *Justus Liebigs Ann. Chem.* **1936**, *522*, 75; Criegee, R.; Marchand, B.; Wannowius, H. *Justus Liebigs Ann. Chem.* **1942**, *550*, 99. (b) Schröder, M. *Chem. Rev.* **1980**, *80*, 187.
3. (a) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidation of Organic Compounds* p294, Academic Press (1981). (b) Haines, A. H. *Methods for Oxidation of Organic Compounds. Alkanes, Alkenes, Alkynes, and Arenes* p73, Academic Press (1985). (c) Mijs, W. J.; De Jonge, C. R. H. I. *Organic Syntheses by Oxidation with Metal Compunds* p633, Plenum Press (1986).
4. (a) VanRheenen, V.; Kelly R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973. (b) VanRheenen, V.; Cha, D. Y.; Hartley, W. M. *Organic Syntheses* Coll. Vol 6, 342p (1988). (c) Ray, R.; Matteson, D. S. *Tetrahedron Lett.* **1980**, *21*, 449.
5. (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247. (b) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943. (c) Christ, W. J.; Cha, J. K.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3947. (d) Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, *24*, 3951.
6. Vedejs, E.; McClure, C. K. *J. Am. Chem. Soc.* **1986**, *108*,

1094.

7. Trost, B. M.; Timko, J. M.; Stanton, J. L. *J. Chem. Soc., Chem. Commun.* **1978**, 436.

8. (a) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1981**, *46*, 227. (b) Hauser, F. M.; Ellenberger, S. R.; Clardy, J. C.; Bass, L. S. *J. Am. Chem. Soc.* **1984**, *106*, 2458. (c) Hauser, F. M.; Ellenberger, S. R.; Rhee, R, P. *J. Org. Chem.* **1987**, *52*, 5041. (d) Whitten, J. P.; McCarthy, J. R.; Whalon, M. R. *J. Org. Chem.* **1985**, *50*, 4399.

9. (a) Fleming, I.; Terret, N. K. *Tetrahedron Lett.* **1983**, *24*, 4151. (b) Fleming, I.; Sarkar, A. K.; Thomas, A. P.; *J. Chem. Soc., Chem. Commun.* **1987**, 157. (c) Vedejs, E.; Campbell, J. B., Jr.; Gadwood, R. C.; Rodgers, J. D.; Spear, K. L.; Watanabe, Y. *J. Org. Chem.* **1982**, *47*, 1534.

10. (a) Castellanos, L.; Cleophax,J.; Colas, C.; Cero, S. D.; LeBoul, J.; Mercier, D.; Olesker, A.; Rolland, A.; Quillet-Sire, B.; Sepulchre, A. M. *Carbohydr. Res.* **1980**, *82*, 283. (b) Kuhlmyer, R.; Schwesinger, R.; Prinzbach, H. *Tetrahedron Lett.* **1984**, *23*, 3429. (c) Schubert, J.; Schwesinger, R.; Prinzbach, H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 167. (d) Georges, M.; Fraser-Reid, B. *Tetrahedron Lett.* **1981**, *22*, 4635. (e) Pauls, H. W.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1980**, *102*, 3956.

11. (a) Katze, J. R.; Gunduz, U.; Smith D. L.; Cheng, C. S.; McCloskey, J. A. *Biochemistry* **1984**, *23*, 1171. (b) Arita,

M.; Adachi, K.; Ito, Y.; Sawai, H.; Ohno, M. *J. Am. Chem. Soc.* **1983**, *105*, 4049.

12. Askin, D.; Angst, C.; Danishefsky, S. *J. Org. Chem.* **1987**, *52*, 622.
13. Gassman, P. G.; Gremban, R. S. *Tetrahedron Lett.* **1984**, *25*, 3259.
14. Murahashi, S.-I.; Mitsue, Y.; Ike, K. *J. Chem. Soc., Chem. Commun.* **1987**, 125.
15. Johnson, C. R.; Barbachyn, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 2459.
16. Colombo, L.; Gennari, C.; Poli, G.; Scolastico, C.; Munari, S. D. *Tetrahedron Lett.* **1985**, *26*, 5459.
17. Hatakeyama, S.; Matsui, Y.; Suzuki, M.; Sakurai, K.; Takano, S. *Tetrahedron Lett.* **1985**, *26*, 6485.
18. (a) Solladié, G.; Fréchou, C.; Demailly, G. *Tetrahedron Lett.* **1986**, *27*, 2867. (b) Solladié, G.; Hutt, J.; Fréchou, C. *Tetrahedron Lett.* **1987**, *28*, 61.
19. Annunziata, R.; Cinquini, M.; Cozzi, F. *Tetrahedron Lett.* **1987**, *28*, 3139.
20. Oppolzer, W.; Barras, J.-P. *Helv. Chim. Acta* **1987**, *70*, 1666.
21. Cleare, M. J.; Hydes, P. C.; Griffith, W. P.; Wright, M. J. *J. Chem. Soc., Dalton Trans.* **1977**, 941.
22. Marzilli, L. G. *Prog. Inorg. Chem.* **1977**, *23*, 255, ed by Lippard, S. J., John Wiley and Sons, New York.

23. Hentges, S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263.

24. Yamada, T.; Narasaka, K. *Chem. Lett.* **1986**, 131.

25. Tokles, M.; Snyder, J. K. *Tetrahedron Lett.*, **1986**, *27*, 3951.

26. Tomioka, K.; Nakajima, M.; Koga, K. *J. Am. Chem. Soc.* **1987**, *109*, 6213.

27. Kokubo, T.; Sugimoto. T.; Uchida, T.; Tanimoto, S.; Okano, M. *J. Chem. Soc.*, *Chem. Commun.* **1983**, 769.

28. (a) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968. (b) *Chem. Eng. News.*, Mar. 21. 1988. p.19 (c) For additional examples of substrate scope see the Aldrich advertisement on the back of *J. Org. Chem.* **1988**, *53(12)*, June 10 issue.

29. Okamoto, Y.; Kawashima, M.; Hatada, K. *J. Chromatogr.* **1986**, *363*, 173.

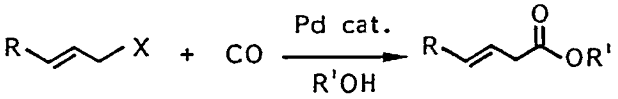
30. Che, C.-M.; Cheng, W.-K.; Mak, T. C. W. *J. Chem. Soc.*, *Chem. Commun.* **1986**, 200.

31. Murahashi, S.-I.; Shiota, T.; Tsuda, T.; Sun, J. unpublished results.

Chapter 4. Palladium(0)-Catalyzed Alkoxycarbonylation of Allyl Acetates. Synthesis of β,γ-Unsaturated Esters

Introduction

Metal-catalyzed carbonylation of allylic compounds is the fundamental and useful reaction for organic synthesis, and extensive studies have been devoted. Carbonylation of allylic halides can be readily accomplished by using transition metal catalysts such as nickel,[1] cobalt,[2] and palladium.[3] However, palladium-catalyzed carbonylations of synthetically more important allylic alcohols,[4] ethers,[5] amines,[6] and acetates[3c,d] are



(1)

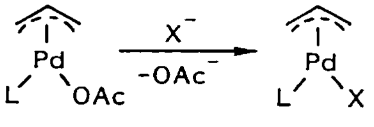
X; Hal
$EtOCO_2$, $(EtO)_2PO_2$
OAc, OMe, OPh, NEt_2, OH

difficult, and require severe reaction conditions. In the palladium(0)-catalyzed reactions of allyl acetates, allylpalladium complexes are formed readily. The study on the stoichiometric carbonylation of π-allylpalladium complexes revealed that the treatment of π-allylpalladium acetate with carbon monoxide results in back reaction to give the starting allyl acetates[3d,7,8] rather than the insertion of CO to the complex leading to the carbonylation product. In order to solve this problem, various attempts have been made. Palladium(0)-

catalyzed carbonylation of cinnamyl acetate in the presence of a stoichiometric amount of $NaCo(CO)_4$ in methanol under CO atmosphere gives methyl 4-phenyl-3-butenoate.[9] Recently, palladium(0)-catalyzed carbonylation of allyl carbonate[10] and rhodium(0)-catalyzed azacarbonylation of allyl phosphate[11] have been reported by Tsuji and Murahashi. Palladium(0)-catalyzed carbonylation of cinnamyl acetates in acetic anhydride has been also reported to give 1-naphthol derivatives.[12] The author has found that the carbonylation of allyl acetates proceeds smoothly when bromide ion is used as a co-catalyst.[13] Described in this chapter is a systematic study on the palladium-catalyzed alkoxycarbonylation of allyl acetates.

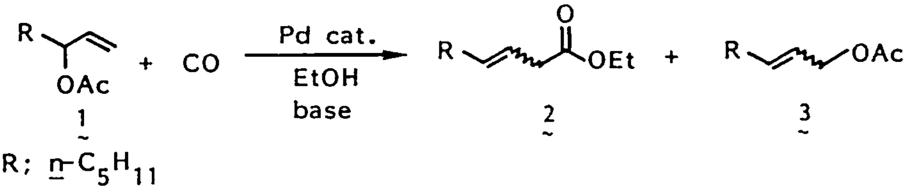
Results and Discussion

Synthesis of β,γ-Unsaturated Esters: β,γ-Unsaturated carbonyl compounds are useful building blocks for the synthesis of natural products.[14] A variety of synthetic methods of β,γ-unsaturated esters have been reported.[15] The most commonly used methods are protonation or alkylation of lithium dienolates of α,β-unsaturated carbonyl compounds.[16] Carbonylation of allylic compounds appears to be the most attractive route to β,γ-unsaturated carbonyl compounds. However, palladium-catalyzed carbonylations of synthetically more important allylic alcohols, ethers, amines, and acetates are difficult, and require severe reaction conditions. Carbonylation of derivatives of allyl alcohols under mild conditions is limited to allyl carbonates[10] and allyl phosphates.[11,13] Carbonylation of allyl halides[3] also proceed smoothly. The ligand on π-allylpalladium species may play an important role to promote the carbonylation. Since acetate ligand seems to be ineffective for the carbonylation, the effect of replacement of acetate ligand with halides has been



(2)

examined (eq 2). Various inorganic salts were employed in aiming at the exchange of the ligand in π-allylpalladium acetates.[17] Ethoxycarbonylation of 1-octen-3-yl acetate (**1**) has been examined by using a 1 mol% of $Pd_2(dba)_3 \cdot CHCl_3$, 4 mol% of PPh_3, and a 10 mol% of halide ion in ethanol at 50 °C for 20 h (eq 3). The representative results are listed in Table I. In



(3)

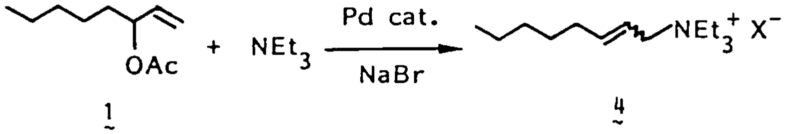
the absence of halide ion, the reaction gave a 36% yield of ethyl 3-nonenoate (2) along with 2-octen-1-yl acetate (3) (28%) which is derived from isomerization of the starting acetate.[18] The addition of 10 mol% of NaBr (entry 2) promoted the carbonylation dramatically to give ethyl 3-nonenoate in 80% yield as a mixture of (*E*)- and (*Z*)-isomers (2a and 2b) in a ratio of 81:19 (^{13}C NMR analysis). Under the conditions, the isomerization of 1 to 2-octen-1-yl acetate (3) was suppressed down to < 3% yield, indicating that the carbonylation in the presence of halide ion proceeds much faster than the isomerization induced by the intramolecular migration of acetate anion. Other halides such as *n*-Bu_4NBr and LiI also enhance the carbonylation, but are not much effective as NaBr. Sodium acetate is not effective in this carbonylation, although carbonylation of π-allylpalladium complexes under mild conditions (25 °C, 50 psi) is known to be enhanced by the presence of sodium carboxylates such as sodium acetate.[19]

Table I. The Effect of Salts for the Carbonylation of 1.[a]

entry	salt	conv. of 1,[b] %	yield of 2,[b] %
1	none	44	36
2	NaBr	96	80
3	*n*-Bu_4NBr	92	74
4	NaI	88	71
5	LiCl	90	68
6	LiI	86	68
7	LiBr	87	64
8	NaCl	82	58
9	NaSCN	55	45

[a] The reaction was carried out according to the general procedure described in the experimental section. [b] GLC analysis.

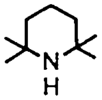
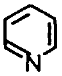
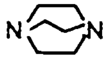
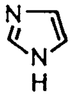
Since Pd(0) complexes react with HX (X = Cl, Br, AcO) to give inactive Pd(H)(X)(PPh$_3$)$_n$,[20] base is essential to trap acetic acid liberated. As summarized in Table II, the addition of base enhances the conversion dramatically. Basic and sterically bulky amines (p*K*a ∿ 10)[21] such as *i*-Pr$_2$NEt, *t*-BuNMe$_2$, and 2,2,6,6-tetramethylpiperidine (entries 2-4) gave the best result. The use of secondary amines such as *i*-Pr$_2$NH leads to the formation of tertiary allylamines as by-product. Although the use of simple tertiary amines such as NEt$_3$, pyridine, and DABCO results in high conversion of the carbonylation, yields are low because tertiary amines react with π-allylpalladium intermediates to give quarternary allylammonium salts.[22] For instance, 1-octen-3-yl acetate (**1**) reacts with triethylamine in the



(4)

presence of Pd(PPh$_3$)$_4$ to give triethyl 2-octen-1-ylammonium salt (**4**) (eq 4). Another reason for lower yield is ascribed to the elimination of acetic acid from allyl acetate to give 1,3-dienes.[23] The use of less basic amines such as *N*,*N*-dimethyl aniline and imidazole results in low conversion (entries 9 and 10). When an inorganic base such as NaHCO$_3$ was used, the carbonylation product was obtained again in low yield.

Table II. The Effect of Bases for the Carbonylation of **1**.[a]

entry	base	pKa[b]	conv. of **1**,[c] %	yield of **2**,[c] %
1	none		48	21
2	_i_-Pr_2NEt		100	74
3	_t_-$BuNMe_2$	9.75	95	69
4			100	61
5	NEt_3	10.72	97	45
6	_i_-Pr_2NH	11.20	99	39
7		5.23	87	34
8		8.82	74	3
9		6.99	75	4
10	$PhNMe_2$	5.07	46	8
11	$NaHCO_3$		58	29

[a] The reaction was carried out according to the general procedure described in the experimental section. [b] Reference 21. [c] GLC analysis.

The catalytic activity of various palladium catalysts (5 mol%) has been examined for the alkoxycarbonylation of 1-octen-3-yl acetate (1) in the presence of NaBr (50 mol%) at 50 °C. The representative results are summarized in Table III. Palladium complexes such as $Pd_2(dba)_3 \cdot CHCl_3$ in the absence of phosphine have no catalytic activity. As phosphine ligands, monodentate phosphines such as PPh_3 rather than bidentate phosphines are effective. The molar ratio of PPh_3 to Pd is important for the reaction. The best result was obtained when a combination of $Pd_2(dba)_3 \cdot CHCl_3$ and $4PPh_3$ was used in a PPh_3/Pd ratio of 2:1. The use of a large excess of PPh_3 decreased the yield of the carbonylation product because of the formation of quarternary allylphosphonium salts.[8e,24] The catalytic activity is in the order of $Pd_2(dba)_3 \cdot CHCl_3\text{-}4PPh_3 \sim Pd(PPh_3)_4 \sim Pd(CO)(PPh_3)_3 > Pd(OAc)_2\text{-}2PPh_3 \gg PdCl_2(CH_3CN)_2\text{-}2PPh_3 > PdCl_2(PPh_3)_2 \sim PdCl_2 \sim$ Pd (black). Generally, Pd(0) catalysts are effective, while Pd(II) catalysts such as $PdCl_2(PPh_3)_2$ and $PdCl_2$ give poor results.

In order to accelerate the carbonylation, about 30 kg/cm^2 pressure of CO is required. The yield of the carbonylation product increases with increasing CO pressure. The pressure effect (yield/conv. %) for the carbonylation of 1-octen-3-yl acetate (1) is as follows: P_{CO} 1.0 (8/24), 5.0 (36/57), 10 (53/68), 20 (60/78), and 30 (75/96) kg/cm^2. The carbonylation under the best condition (P_{CO} = 30 kg/cm^2) is still not

Table III. Palladium Catalyst for the Carbonylation of 1.[a]

entry	Pd cat.	Ligand	conv. of 1,[b] %	yield of 2,[b] %
1	$PdCl_2$	none	0	0
2	$PdCl_2(PPh_3)_2$	none	13	2
3	$PdCl_2(CH_3CN)_2$	$2PPh_3$	41	24
4	$Pd(OAc)_2$	$2P(OPh)_3$	64	49
5	"	$2PBu_3$	0	0
6	"	$2PPh_3$	63	63
7	"	2P(o-Tol)$_3$	33	19
8	"	dppe	4	0
9	"	dppf	58	42
10	$Pd(OCOCF_3)_2$	$2PPh_3$	53	44
11	$Pd(acac)_2$	$2PPh_3$	80	59
12	$Pd(PPh_3)_4$	none	100	72
13	$Pd(CO)(PPh_3)_3$	none	93	68
14	$Pd(PCy_3)_2$	none	16	11
15	$Pd(dba)_2$	$2PPh_3$	84	67
16	$Pd_2(dba)_3 \cdot CHCl_3$	none	0	0
17	"	$4P(OPh)_3$	79	43
18	"	$4PBu_3$	27	17
19	"	$4PPh_3$	94	85
20	"	$4P(NMe_2)_3$	27	4
21	"	4P(o-Tol)$_3$	40	28
22	"	2dppe	27	11

[a] The reaction was carried out according to the general procedure described in the experimental section. [b] GLC analysis.

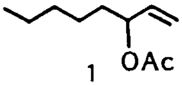
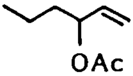
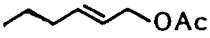
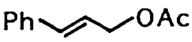
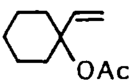
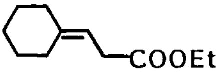
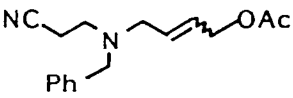
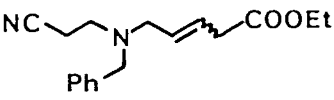
satisfactory (75% yield), this may be due to the formation of diisoproylethyl-2-octen-1-ylammonium salt even if considerably bulky diisopropylethylamine is used (Table II).

The temperature effect for the carbonylation of 1-octen-3-yl acetate (**1**) has been examined. High yields of β,γ-unsaturated ester **2a-b** were obtained at about 50 °C to 80 °C, although the carbonylation of allyl carbonate at temperature higher than 50 °C gave allyl alkyl ether.[25] The temperature effect (yield/conv. %) for the carbonylation of 1-octen-3-yl acetate is as follows: *T* 30 (46/61), 40 (69/89), 50 (81/92), 60 (81/97), 70 (75/97), and 80 (79/97) °C.

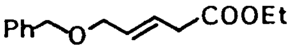
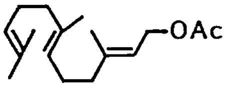
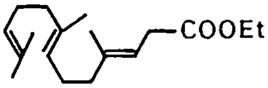
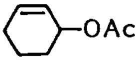
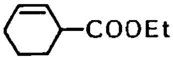
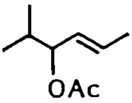
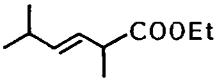
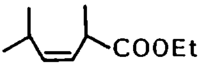
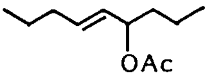
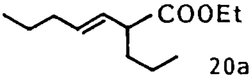
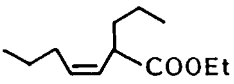
Commonly used solvents such as acetonitrile, DMF, acetone, dioxane, DME, and THF are ineffective <10% yield. When ethanol and methanol were used, the carbonylation proceeds effectively.

The representative results for the present alkoxycarbonylation of various allyl acetates using $Pd_2(dba)_3 \cdot CHCl_3$-$4PPh_3$ are summarized in Table IV. High regioselectivity is attained in all cases, where CO insertion occurs at least substituted terminal allylic carbon to give linear esters rather than branched esters. (*E*)-β,γ-Unsaturated esters have been obtained preferencially irrespective of the stereochemistry of the starting substrates. To prove the question of double bond integrity of the product, the carbonylations of 1-hexen-3-yl acetate (**5**), and (*E*)- and (*Z*)-2-hexen-1-yl acetates (**6** and **7**) were examined under the condition A (30 kg/cm^2 CO, 50 °C, 20 h, 4 mol% Pd(0) catalyst, 8

Table IV. The Palladium-Catalyzed Carbonylation of Allyl Acetates[a]

entry	allyl acetate	β,γ-unasaturated ester	conditions[b]	yield,[c] % (ratio of *E*:*Z*)[d]
1	 1	 2a  2b	A	86 (81:19)
2	 5	 8a  8b	A	78 (82:18)
3	 6	8a + 8b	A	68 (80:20)
4	 7	8a + 8b	A	74 (80:20)
5		 9	A	84 (100:0)
6	 10	 11	A	80
7	 12	 13	A	57 (68:32)

(continued Table IV)

8	 14	 15a  15b	A	85 (88:12)
9	 16	 17	B	73 (90:10)
10		 18	B	57
11		 19a  19b	B	59 (95:5)
12		 20a  20b	B	51 (87:13)

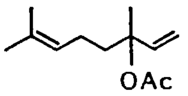
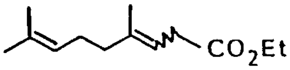
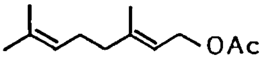
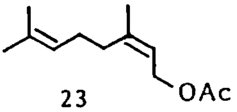
[a] The reaction was carried out according to the general procedure described in the experimental section. [b] Reaction condition A (30 kg/cm^2 CO, 50 °C), B (60 kg/cm^2 CO, 80 °C). [c] Isolated yield. [d] The ratio of *E*:*Z* was determined by ^{13}C NMR analysis or GLC analysis.

mol% PPh_3, and 20 mol% NaBr). These acetates (5, 6, and 7) produced a mixture of (E)- and (Z)-ethyl 3-heptenoate (8a and 8b) in the same ratio (80:20), irrespective of the stereochemistry of the starting substrate. Loss of the stereochemistry of the carbon-carbon double bond seems to be due to the σ-π-σ-isomerization[26] of intermediate π-allylpalladium complexes. The thermodynamically more stable (E)-isomers are thus preferencially formed, irrespective of the stereochemistry of the starting substrate. The (E)-stereochemistry of the product was confirmed by the coupling constant of the olefinic protons ($J_{Ha-b} = \sim 15$ Hz).

The carbonylation of amino acetate 12 gave lower yield of the product probably because of the formation of ammonium salt as mentioned above.[22] The acetates of secondary allyl alcohols (entries 10-12) require relatively severe condition B (60 kg/cm^2 CO, 80 °C, 20 h, 4 mol% Pd(0), 8 mol% PPh_3, 50 mol% NaBr). The insertion of palladium into secondary acetates seems to be depressed by steric effects.

The reactivity of linalyl (21), geranyl (22), and neryl acetate (23) was examined in detail (Table V). The carbonylation of linalyl acetate (21) under condition A gave a 60:40 mixture of (E)- and (Z)-isomer of ethyl 4,8-dimethyl-3,7-nonadienoate (24a and 24b) in >99% yield. The isomeric ratio of 24a and 24b was determined by GLC analysis. The carbonylation of geranyl acetate (22) under the same conditions gave (E)-24a stereoselectively (24a:24b = 93:7) in 6% yield. These results indicate that the

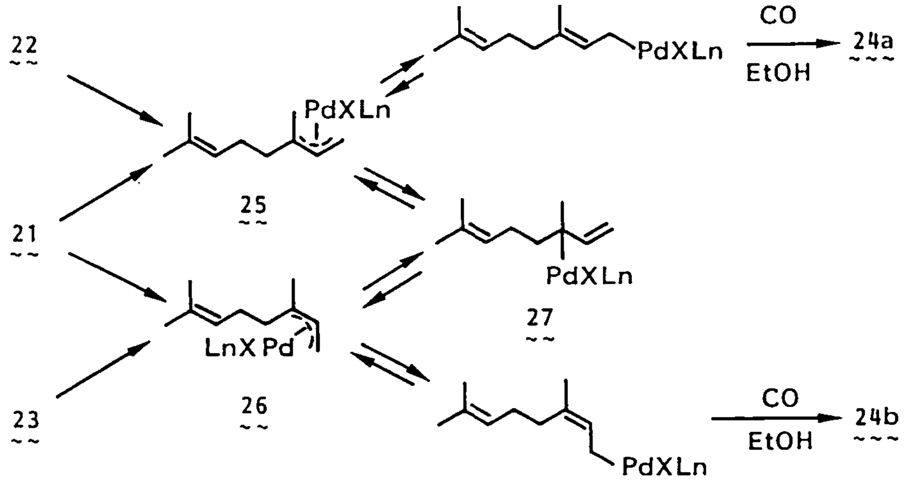
Table V. The Reactivity of Linaryl, Geranyl, and Neryl Acetates.

acetate	product	conditions[a]	yield, %[b]	*E*:*Z* ratio
 21	 24a-b	A	90 (100)	60:40
 22	24a + 24b	A	(6)	93:7
		B	74 (74)	93:7
		C	(74)	85:15
 23	24a + 24b	B	68 (78)	14:86
		C	(89)	32:68

[a] Conditions: A; CO(30 kg/cm^2), 50°C. B; CO(60 kg/cm^2), 80°C C; CO(60 kg/cm^2), 100°C. [b] Yields in parentheses were determined by GLC.

oxidative addition of palladium(0) complex to allyl acetates occurs in an S_N2'-fashion at the γ-position.[27] Under severe condition B, the carbonylation of geranyl acetate (22) gave a mixture of (E)-24a and (Z)-24b (93:7) in 74% yield, while the carbonylation of neryl acetate gave a 78% yield of products in a reverse ratio of 14:86. Virtually, the geometric integrity of the double bonds in 22 and 23 is maintained during the reaction. By contrast, the carbonylation of the corresponding allyl diethyl phosphates[13] proceeds highly selectively (E:Z = 96:4) in comparison with the carbonylation of allyl acetate. This observation has

Scheme I.

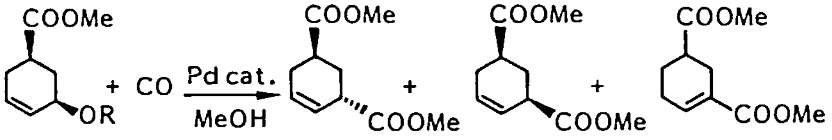


been recently discovered by the author, the details of which is an interesting subject of futher study. Under more severe condition C (60 kg/cm^2 CO, 100 °C, 20 h, 4 mol% Pd(0), 8 mol%

PPh_3, 50 mol% NaBr), the carbonylations of geranyl acetate (**22**) and neryl acetate (**23**) afforded a mixture of **24a** and **24b** in 74% (**24a**:**24b** = 85:15) and 89% (**24a**:**24b** = 32:68) yields, respectively. Control experiments show that thermal isomerization of (*Z*)-**24b** to (*E*)-isomer (**24a**) does not occur. Therefore, the product ratio of the carbonylation seems to reflect the equilibrium ratio of π-allylpalldium complexes under the reaction condition. The *syn*- and *anti*-isomerization (σ-π-σ-mechanism) of intermediates π-allylpalladium **25** and **26** (Scheme I)[22,26] *via* sterically hindered tertially σ-allylpalladium **27** is difficult, resulting in higher selectivity. On the other hand, the σ-π-σ-isomerization of the secondary σ-allylpalladium derived from (*Z*)-2-hexen-1-yl acetate (**7**) takes place to loose the stereoselectivity.

The stereochemical course of the carbonylation was examined with *cis*-5-methoxycarbonyl-2-cyclohexen-1-yl acetate (**28**) (eq 5). In the presence of 5 mol% of $Pd(PPh_3)_4$, a mixture of *cis*- and *trans*-dimethyl 2-cyclohexene-1,5-dicarboxylate (**29**) (28%) and dimethyl 1-cyclohexene-1,5-dicarboxylate (**30**) (40%) was obtained. The carbonylation is non-selective with **29**, and *trans*- and *cis*-isomers were obtained in 56:44 ratio. This is due to the palladium-induced *syn*-*anti* isomerization[28] of π-allylpalladium complexes which occurs by displacement of the palladium of π-allyl complex with the additional Pd(0) species from the opposite side. There are two explanations for the formation of α,β-unsaturated ester (**30**). One is the thermal isomerization[29] of β,γ-unsaturated ester 29 to α,β-unsaturated ester 30 under the reaction conditions. Alternatively, the isomerzation may proceed *via* a π-allylpalladium complex derived from β,γ-unsaturated ester 29.[30]

The author found that the carbonylation of *cis*-diethyl

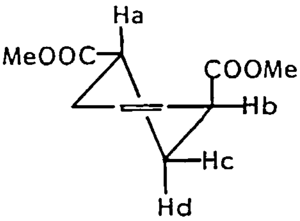


(5)

28; OR=OAc 29a 29b 30

31; $OR=OP(O)(OEt)_2$

5-methoxycarbonyl-2-cyclohexen-1-yl phosphate (31) takes place with inversion of configuration at the allylic carbon to afford



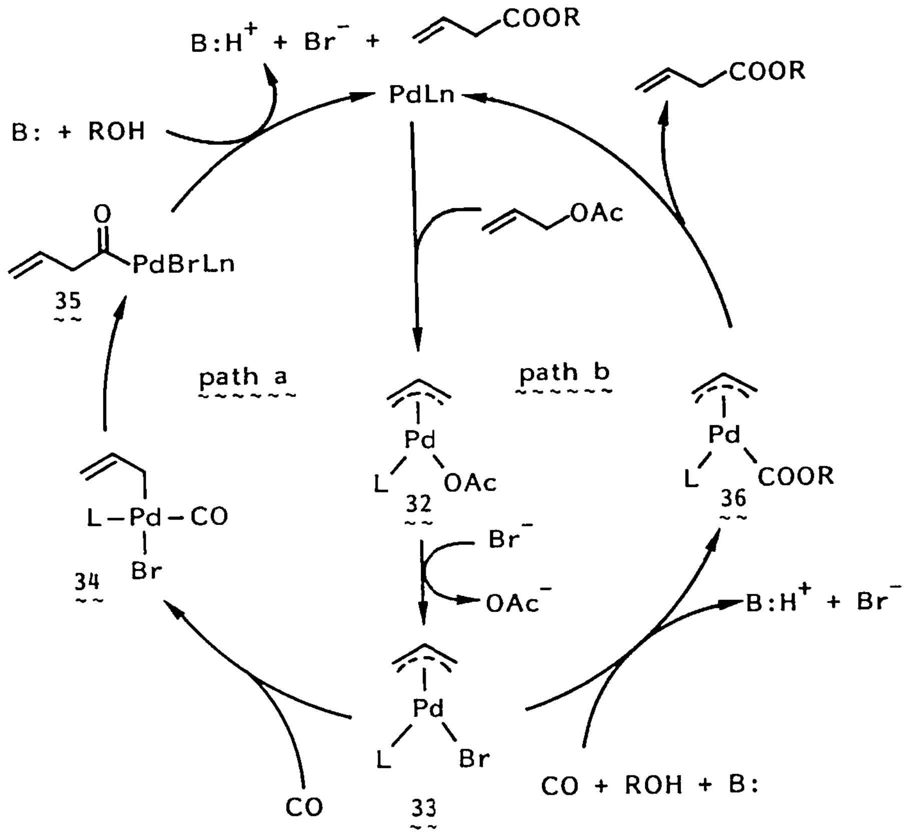
29a

trans-dimethyl 2-cyclohexene-1,5-dicarboxylate (29a) stereoselectively.[13] This result indicates that the insertion of carbon monoxide to alkylpalladium complexes proceeds with retention of configuration, which also agrees with the observations in related systems.[31] The stereochemistry of *trans*-diester 29a obtained from phosphate 31 was established by

NMR spectral analysis. The absorptions at δ 1.88 (ddd, J = 13.52, 10.77, and 6.19 Hz, Hd) and at δ 2.82 (dddd, J = 10.77, 8.93, 5.73, and 3.21 Hz, Ha) were readily discernible with the expected coupling constants of J_{Hcd} = 13.52, J_{Had} = 10.77, J_{Hbd} = 6.19, and J_{Hac} = 5.73 Hz, indicating *trans*-configuration.

Mechanism: As shown in Scheme III of Chapter 2, the oxidative addition of Pd(0) to allyl esters gives π-allylpalladium intermediates, which react with various nucleophiles. The carbonylation of geranyl and neryl acetate proceeds slower than that of linalyl acetate, indicating that the oxidative addition of Pd(0) species to allyl acetate occurs by an S_N2'-fashion at the γ-posisions. The enhancement of the carbonylation upon addition of NaBr is ascribed to the ligand exchange of π-allylpalladium acetate (**32**) with bromide ion. The resulting π-allylpalladium bromide (**33**) undergoes facile carbonylation (path a). Control experiments show that the carbonylation of allyl bromides proceeds fast. The reaction pathways of π-allylpalladium bromide (**33**) with carbon monoxide can be envisioned as shown in Scheme II. σ-Allylpalladium complex (**34**) is assumed to be formed, and the insertion of CO gives 3-butenoylpalladium complex (**35**). The carbonylations of (*E*)- and (*Z*)-2-hexen-1-yl acetates (**6** and **7**) proceed by the σ-π-σ-isomerization of allylpalladium complexes to result in the formation of **8a** and **8b** in the same ratio of 85:15, indicating that the

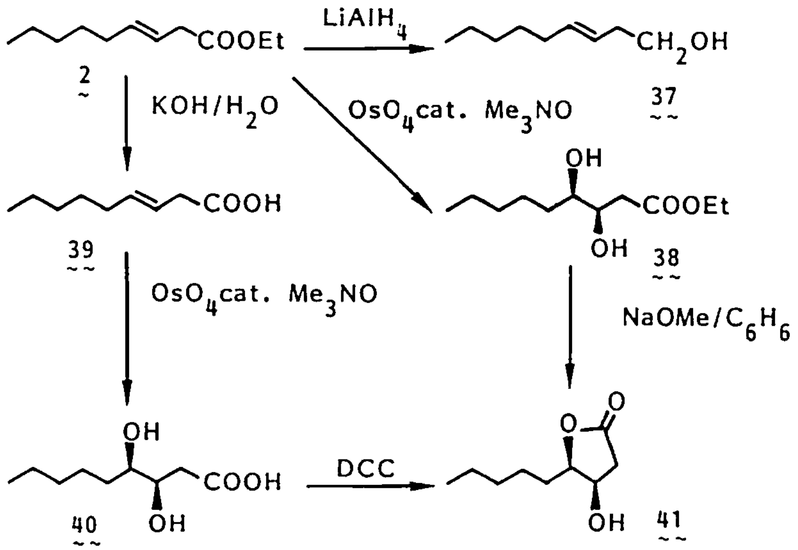
Scheme II.


B:H$^+$ + Br$^-$ +
COOR
PdLn
B: + ROH
COOR
OAc
PdBrLn
35
path a
path b
Pd
L
OAc
32
Pd
L
COOR
36
L–Pd–CO
Br
34
Br$^-$
OAc$^-$
B:H$^+$ + Br$^-$
Pd
L
Br
33
CO
CO + ROH + B:

formation of π-allypalladium intermediate rather than σ-allylpalladium. If the carbonylation of (*E*)- and (*Z*)-2-hexen-1-yl acetates proceed through σ-allylpalladium complex, the geometric integrity of the double bond should be maintained during the reactions. Subsequent alcoholysis of 3-butenoylpalladium complexes (**35**) affords β,γ-unsaturated ester. An alternative pathway which involves (alkoxycarbonyl)(π-allyl)palladium complexes (**36**) cannot be completely eliminated. Direct base-induced nucleophilic attack of alcohol on coordinated CO,[32,33] would give **36** which undergoes reductive elimination to give β,γ-unsaturated ester and Pd(0) species (path b).

Synthetic Application: β,γ-Unsaturated esters obtained from allyl esters are useful synthetic intermediates.[14,34] The double bond can be converted into various functional groups. For example, halo-lactonization and 1,3-dipolar cycloaddition with nitrones are utilized for the synthesis of biologically active compounds such as β-lactams and alkaloids.[14] Homoallyl alcohols can be prepared readily from allyl alcohols *via* β,γ-unsaturated esters. Thus, reduction of ethyl 3-nonenoate (**2**) with $LiAlH_4$ gave 3-nonenol (**37**) in 95% isolated yield. Oxidation[35] of the double bond of β,γ-unsaturated ester **2** with trimethylamine

Scheme III.



N-oxide in the presence of a catalytic amount of OsO_4 gave ethyl 3,4-dihydroxynonanoate (**38**) in quantitative yields. Hydrolysis of β,γ-unsaturated ester **2** (2N KOH) gave 3-nonenoic acid (**39**) quantitatively, which upon treatment with Me_3NO and OsO_4 gave 3,4-dihydroxynonanoic acid (40) in 98% yield. Lactonizations of 38 and 40 of NaOMe or DCC (dicyclohexylcarbodiimide) gave a 3-hydroxy-4-pentyl-4-butanolide (41) in 76 and 100% isolated yields, respectively.

Conclusion

The palladium(0)-catalyzed alkoxycarbonylation of allyl acetates in the presence of bromide ion gave β,γ-unsaturated esters selectively. The present reaction provides a new methodology for the synthesis of homoallyl skeleton.

Experimental Section

General

NMR spectra were recorded on a JEOL PMX-60 SI (60 MHz), a JEOL JNM-FX 100 (^{1}H NMR at 99.60 MHz, ^{13}C NMR at 25.0 MHz) and a JEOL JNM-GX 500 (^{1}H NMR at 500 MHz) spectrometer. Chemical shifts (δ) were expressed in parts per million relative to tetramethylsilane. GLC analyses were carried out on a Shimadzu GC-9A flame ionization chromatography by using a 1-m x 3-mm analytical column packed with 10% SE 30 on 80-120 mesh Uniport HP and a Shimadzu GC-mini 2 flame ionization chromatography by using a 25-m x 0.25-mm PEG 20M chemical bonded on a glass capillary column (Gasukuro Kogyo, Inc. Japan). Mass spectra were obtained on a Shimadzu GCMS QP-1000 by using analytical column packed with SE 30 on Uniport HP and a JEOL JMS-DX303 mass spectrometer.

Materials

$Pd(CO)(PPh_3)_3$,[36] $PdCl_2(CH_3CN)_2$,[37] $P(o\text{-}Tol)_3$,[38] 1-vinyl cyclohexan-1-ol,[39] (Z)-4-benzyloxy-2-buten-1-ol,[40] and 4-[N-benzyl-N-(2-cyanoethyl)amino]-2-buten-1-yl acetate (**12**) (E:Z = 88:12)[41] were prepared by the literature procedures. Sodium bromide (Wako) and n-Bu_4NBr (Wako). were commercially available. Diisopropylethylamine was purchased from Aldrich Chemical Co. and distilled over CaH_2 prior to use. (Z)-2-Hexen-1-ol and (2E,6E)-farnesol were purchased from Aldrich chemical Co. Other allylic esters were prepared by the general procedures.

1-Vinylcyclohexan-1-yl Acetate (10): To a solution of 1-vinylcyclohexan-1-ol (5.16 g, 41.0 mmol) and catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (0.98 g, 8.0 mmol) in dry triethylamine (8.5 mL, 61 mmol), acetic anhydride (4.8 mL, 51 mmol) was added at 0 °C for 30 min. The mixture was stirred at room temp for 72 h. The reaction mixture was diluted with ether (150 mL) and was washed with a 2N HCl (50 mL x 2). The acidic aqueous phase was extracted with ether (50 mL). The combined ethereal layers were washed successively with a 2N HCl solution (50 mL x 2), brine (50 mL x 2), a saturated $NaHCO_3$ (50 mL x 2), and brine (50 mL x 2). The organic phase was dried over $MgSO_4$ and evaporated to give a yellow oil (6.65 g, 96%). The residue was distilled to give 1-vinylcyclohexan-1-yl acetate (**10**) (3.85 g, 56%) as a colorless oil: bp 63-68 °C (10 mmHg); IR (neat) 3100 (w), 2950 (CH, s), 2870 (CH, s), 2680 (w), 1740 (C=O, s), 1645 (C=C, s), 1455 (s), 1420 (m), 1375 (CH, s), 1270 (s), 1240 (C-O, s), 1170 (w), 1140 (s), 1070 (w), 1020 (s), 960 (s), 930 (s), 910 (s), 900 (m), 850 (w), 820 (w), 740 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.00-2.50 (m, 10 H, $(CH_2)_5$), 2.00 (s, 3 H, $OCOCH_3$), 4.80-5.40 (m, 2 H, CH_2=), 6.15 (dd, *J* = 16 and 9.6 Hz, 1 H, =CH). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.09; H, 9.57.

(*Z*)-4-Benzyloxy-2-buten-1-yl Acetate (14): To a solution of (*Z*)-4-benzyloxy-2-buten-1-ol (*Z* ≥99%) (1.00 g, 5.61 mmol) and a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (50 mg, 0.04

mmol) in pyridine (0.91 mL, 11.2 mmol), acetic anhydride (0.64 mL, 6.7 mmol) was added at 0 °C for 1 min. The mixture was stirred at room temp for 12 h. The reaction mixture was diluted with ether (15 mL) and was washed with a 2N HCl (10 mL) solution. The acidic aqueous phase was extracted with ether (5 mL). The combined ethereal layers were washed successively with a 2N HCl (10 mL) solution, a saturated $NaHCO_3$ (10 mL), and brine (10 mL). The organic phase was dried over $MgSO_4$ and evaporated to give 14 as a colorless oil (1.19 g, 96%): IR (neat) 3070 (CH, s), 3040 (CH, s), 2950 (CH, s), 2860 (CH, s), 2460 (w), 2060 (w), 1970 (w), 1880 (w), 1740 (C=O, s), 1610 (w), 1590 (w), 1500 (s), 1460 (s), 1380 (s), 1340 (m), 1310 (m), 1240 (s), 1100 (s), 1040 (s), 960 (s), 900 (m), 840 (m), 740 (s), 700 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.02 (s, 3 H, $COCH_3$), 4.12 (d, J = 5.0 Hz, 2 H, OCH_2), 4.47 (s, 2 H, $PhCH_2$), 4.62 (d, J = 5.0 Hz, 2 H, CH_2OCO), 5.63 (dt, J = 11 and 5.0 Hz, 1 H, CH=), 5.85 (dt, J = 11 and 5.0 Hz, 1 H, CH=), 7.10-7.50 (m, 5 H, ArH).

Palladium-Catalyzed Carbonylation of Allyl Acetates.

(1) Salt Effects: In a 10-mL stainless steel autoclave, $Pd_2(dba)_3 \cdot CHCl_3$ (0.010 g, 0.01 mmol), PPh_3 (0.010 g, 0.04 mmol), salt (0.10 mmol), and 1-octen-3-yl acetate (**1**) (0.170 g, 1.00 mmol) were placed. After the atmosphere in the autoclave was replaced with argon, diisopropylethylamine (0.17 mL, 1.00 mmol) and absolute ethanol (1.0 mL) were added. Carbon monoxide was introduced up to 30 kg/cm^2. The mixture was stirred at 50 °C for 20 h. The yield and conversion were determined by GLC analysis using octadecane as an internal standard. These results and conditions are listed in Table I.

(2) Base Effects: In a 10-mL stainless steel autoclave, $Pd(PPh_3)_4$ (0.058 g, 0.05 mmol), NaBr (0.051 g, 0.50 mmol), and 1-octen-3-yl acetate (**1**) were placed. After the atmosphere in the autoclave was replaced with argon, a base (1.5 mmol) and absolute ethanol (3.0 mL) were added. Carbon monoxide was introduced up to 30 kg/cm^2. The mixture was stirred at 50 °C for 5 h. The yield and conversion were determined by GLC analysis using octadecane as an internal standard. These results and conditions are listed in Table II.

(3) Catalyst Effects: The carbonylation of 1-octen-3-yl acetate was carried out as described above. Instead of $Pd(PPh_3)_4$, the combinations of various pallaium catalysts and phoshines were examined. The yield and conversion were determined by GLC analysis using octadecane as an internal

standard. These results and conditions are listed in Table III.

*Reaction of Triethylamine with 1-Octen-3-yl Acetate (**1**):* In a 10-mL stainless steel autoclave, Pd(PPh$_3$)$_4$ (0.058 g, 0.050 mmol) and NaBr (0.052 g, 0.50 mmol) were placed. The atmosphere of the autoclave was replaced with argon. Absolute ethanol (1.0 mL), triethylamine (0.21 mL, 1.5 mmol), and 1-octen-3-yl acetate (**1**) (0.170 g, 1.00 mmol) were successively added. Carbon monoxide was introduced up to 30 kg/cm^2. The mixture was stirred at 50 °C for 20 h. After removal of solvents, the reaction mixture was filtrated through a pad of Celite 545 (0.5 x 5 cm, CHCl$_3$). Triethyl-2-octenylammonium salt (**4**) was obtained in 23% yield, which was determined by ^{1}H NMR analysis, along with ethyl 3-nonenoate (45% GLC yield): ^{1}H NMR (CDCl$_3$, 60 MHz) δ 0.50-1.80 (m, 6 H), 0.88 (t, J = 6 Hz, 3 H, CH$_3$), 1.36 (t, J = 7 Hz, 9 H, CH$_3$), 1.80-2.50 (m, 2 H, CH$_2$), 3.40 (q, J = 7 Hz, 6 H, CH$_2$), 4.00 (d, J = 6 Hz, 2 H, CH$_2$N), 5.70-6.50 (m, 2 H, CH=CH).

General Procedure for Carbonylation of Allyl Acetates:

Condition A: In a 10-mL stainless steel autoclave, $Pd_2(dba)_3 \cdot CHCl_3$ (0.020 g, 0.02 mmol), PPh_3 (0.021 g, 0.08 mmol), NaBr (0.020 mg, 0.20 mmol), and allyl acetate (1.00 mmol) were placed. The atmosphere in the autoclave was replaced with argon. Absolute ethanol (1.0 mL) and diisopropylethylamine (0.17 mL, 1.0 mmol) were added. Carbon monoxide was introduced up to 30 kg/cm^2. The mixture was stirred at 50 °C for 20 h. The reaction mixture was diluted with methylene chloride (20 mL) and washed with water (20 mL x 3). The organic phase was dried over $MgSO_4$. After removal of the solvents, the residue was chromatographed on silica gel to afford β,γ-unsaturated ester.

Condition B: In a 10-mL stainless steel autoclave, $Pd_2(dba)_2 \cdot CHCl_3$ (0.020 g, 0.02 mmol), PPh_3 (0.021 g, 0.08 mmol), NaBr (0.052 g, 0.50 mmol), and allyl acetate (1.00 mmol) were placed. The atmosphere in the autoclave was replaced with argon. Absolute ethanol (1.0 mL) and diisopropylethylamine (0.17 mL, 1.0 mmol) were added. Carbon monoxide was introduced up to 60 kg/cm^2. The mixture was stirred at 80 °C for 20 h. The reaction mixture was diluted with methylene chloride (20 mL) and washed with water (20 mL x 3). The organic phase was dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel to afford β,γ-unsaturated ester.

Condition C: Carbonylation of allyl acetate was carried out at 100 °C. Other reaction conditions were same to condition B.

Carbonylation of 1-Octen-3-yl Acetate (1): The Carbonylation of 1-octen-3-yl acetate (**1**) (170 mg, 1.0 mmol) was carried out under the reaction condition A. Ethyl 3-nonenoate (**2**) (0.129 g, 70%) was obtained as a yellow oil: $\underline{R_f}$ = 0.23 (SiO_2, methylene chloride:hexane = 3:7); bp 70-71 °C / 4 mmHg; IR (neat) 2960 (CH, s), 2940 (CH, s), 2860 (CH, s), 1740 (C=O, s), 1470 (CH, m), 1450 (m), 1410 (w), 1370 (CH, s), 1330 (m), 1300 (m), 1250 (C-O, s), 1160 (s), 1120 (m), 1035 (s), 970 (s), 940 (w), 860 (w), 780 (w), 725 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.60-1.10 (m, 3 H, CH_3), 1.25 (t, J = 6.4 Hz, 3 H, CH_3), 1.10-1.73 (m, 6 H, CH_2), 1.73-2.40 (m, 2 H, CH_2), 2.90-3.30 (m, 2 H, CH_2CO), 4.12 (q, J = 7.0 Hz, 2 H, CH_2), 5.16-5.90 (m, 2 H, CH=CH); The stereoisomeric ratio of E/Z was determined to be 81/19 by the ^{13}C NMR analysis; ^{13}C NMR ($CDCl_3$, 25 MHz) δ 172.1, 134.7, 121.6, 60.4, 38.2, 32.5, 31.4, 28.9, 22.6 14.2, 14.0 for (E)-**2a**; 171.9, 133.4, 120.9, 60.4, 33.1, 31.5, 29.0, 27.4, 22.6, 14.2, 14.0 for (Z)-**2b**. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.62; H, 10.90.

Carbonylation of 1-Hexen-3-yl Acetate (5): The carbonylation of 1-hexen-3-yl acetate (**5**) (0.284 g, 2.00 mmol) was carried out under the reaction condition A. A mixture of (E)- and (Z)-ethyl 3-heptenoate (**8**) (0.244 g, 78%) was obtained as a colorless oil. The isomeric ratio was determined to be 82:18 by the ^{13}C NMR analysis: bp 80-85 °C / 9 mmHg (Kugelrohr); IR (neat) 2980 (CH, s), 2930 (CH, s), 2880 (CH, s), 2850 (m), 1740

(C=O, s), 1470 (CH, m), 1450 (w), 1420 (w), 1370 (CH, m), 1330 (m), 1300 (m), 1250 (C-O, s), 1170 (s), 1120 (m), 1100 (w), 1040 (s), 970 (s), 930 (w), 860 (w), 780 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.89 (t, J = 7.3 Hz, 3 H, CH_3), 1.25 (t, J = 7.1 Hz, 3 H, $OCCH_3$), 1.39 (dq, J = 7.3 and 7.1 Hz, 2 H, CH_2), 2.11 (dt, J = 7.3 and 5.7 Hz, 2 H, CH_2), 3.01 (d, J = 5.7 Hz, 2 H, CH_2CO), 4.13 (q, J = 7.1 Hz, 2 H, OCH_2), 5.52 (dt, J = 5.7 and 15.5 Hz, 1 H, CH=), 5.57 (dt, J = 5.7 and 15.5 Hz, 1 H, CH=); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 172 (C=O), 134 (C^3), 121 (C^4), 60 (ethyl C^1), 38 (C^2), 34 (C^5), 22 (ethyl C^2), 14 (C^6), 13 (C^7) for (E)-8a; 171 (C=O), 133 (C^3), 121 (C^4), 60 (ethyl C^1), 33 (C^2), 29 (C^5), 22 (ethyl C^2), 14 (C^6), 13 (C^7) for (Z)-8b. Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 68.75; H, 10.21.

Carbonylation of (E)-2-Hexen-1-yl Acetate (6): The carbonylation of (E)-2-hexen-1-yl acetate (0.284 g, 2.00 mmol) was carried out as described above. A mixture of (E)- and (Z)-ethyl 3-heptenoate (8) (0.213 g, 68%) was obtained as a colorless oil. The isomeric ratio was determined to be 80:20 by the ^{13}C NMR analysis.

Carbonylation of (Z)-2-Hexen-1-yl Acetate (7): The carbonylation of (E)-2-hexen-1-yl acetate (0.284 g, 2.00 mmol) was carried out as described above. A mixture of (E)- and (Z)-ethyl 3-heptenoate (8) (0.230 g, 74%) was obtained as a colorless oil. The isomeric ratio was determined to be 80:20 by the ^{13}C NMR analysis.

Ethyl 4-Phenyl-3-butenoate (9): The carbonylation of cinnamyl acetate (0.176 g, 1.00 mmol) was carried out under the reaction condition B. Ethyl 4-phenyl-3-butenoate (**9**) (85%, GLC yield) was isolated (0.160 g, 84%). An analytical sample was purified by preparative GLC (SE-30, 10%, 1 m x 2 mm, 200 °C). The yield of **9** was determined by GLC using dodecane as an internal standard: $\underline{R_f} = 0.2$ (SiO_2, methylene chloride:hexane = 3:7); bp 75-80 °C / 0.2 mmHg (Kugelrohr); IR (neat) 3040 (m), 2980 (CH, s), 2900 (w), 1950 (w), 1880 (w), 1735 (C=O, s), 1650 (C=C, w), 1600 (w), 1580 (w), 1500 (m), 1465 (w), 1450 (CH, s), 1410 (m), 1370 (m), 1350 (CH, w), 1295 (m), 1250 (C-O, s), 1150 (br), 1195 (w), 1025 (s), 985 (s), 940 (w), 860 (w), 740 (m), 695 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.25 (t, J = 7.0 Hz, 3 H, CH_3), 3.16 (d, J = 5.5 Hz, 2 H, CH_2), 4.12 (q, J = 7.0 Hz, 2 H, CH_2O), 6.15 (dt, J = 15.5 and 5.5 Hz, 1 H, CH=), 6.45 (d, J = 15.5 Hz, 1 H, CH=), 6.90-7.50 (m, 5 H, ArH); The stereoisomeric ratio of *E*/*Z* was determined to be 100/0 by the ^{13}C NMR analysis; ^{13}C NMR ($CDCl_3$, 25 MHz) δ 171.2 (C=O), 136,9 (i), 133.2, 128.5, 127.5 (p), 126.3, 121.9, 60.6, 38.3, 14.2. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.51; H, 7.45.

Ethyl 3-Cyclohexylidenepropanoate (11): The carbonylation of 1-vinylcyclohexen-1-yl acetate (**10**) (0.840 g, 5.00 mmol) was carried out under the reaction condition A. Ethyl 3-cyclohexylidenepropanoate (**11**) (0.730 g, 80%) was obtained as a yellow oil: $\underline{R_f} = 0.35$ (SiO_2, methylene chloride:hexane = 1:1); bp 90-95

°C / 6 mmHg (Kugelrohr); IR (neat) 2940 (CH, s), 2860 (s), 1740 (C=O, s), 1450 (CH, m), 1410 (w), 1370 (CH, s), 1350 (w), 1330 (m), 1305 (m), 1260 (m), 1240 (C-O, s), 1160 (s), 1130 (m), 1100 (m), 1080 (w), 1030 (s), 990 (w), 940 (w), 890 (w), 840 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.08 (t, J = 7 Hz, 3 H, CH_3), 1.40-1.83 (m, 6 H, $(CH_2)_3$), 1.83-2.33 (m, 4 H, $(CH_2)_2$), 3.02 (d, J = 7.5 Hz, CH_2CO), 4.13 (q, J = 7 Hz, 2 H, OCH_2), 5.25 (t, J = 7.5 Hz, 2 H, CH=); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 172.2, 143.1, 112.8, 60.4, 37.1, 33.0, 29.0, 28.6, 27.7, 26.9, 14.3. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.28; H, 9.93.

Carbonylation of 4-(N-Benzyl-N-2-cyanoethylamino)-2-buten-1-yl Acetate (12): The carbonylation of 4-(N-benzyl-N-2-cyanoethylamino)-2-buten-1-yl acetate (0.272 g, 1.00 mmol) (E:Z = 88:12) was carried out (reaction condition B). Isolation of ester 13 from the reaction mixture is as follows: The reaction mixture was evaporated and chromatographed on silica gel (9 g, 2.2 x 6.0 cm, methylene chroride) to give a mixture of (E)- and (Z)-ethyl 5-(N-benzyl-N-2-cyanoethylamino)-3-pentenoate (13) (0.164 g, 57%) as a yellow oil: IR (neat) 2950 (br), 2830 (m), 2260 (CN, m), 1740 (C=O, s), 1600 (m), 1500 (m), 1460 (s), 1375 (s), 1250 (m), 1160 (s), 1130 (m), 1100 (m), 1080 (m), 1025 (s), 975 (s), 930 (m), 850 (w), 800 (w), 740 (s), 700 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.24 (t, J = 7.0 Hz, 3 H, CH_3), 2.40 (t, J = 6.4 Hz, 2 H, CH_2CN), 2.78 (t, J = 6.4 Hz, 2 H, CH_2CCN), 2.90-3.30 (m, 4 H, $CH_2C=C$), 3.60 (s, 2 H, CH_2Ph), 4.12 (q, J = 7.0 Hz, 2 H,

OCH_2), 4.87 (dt, J = 15.4 Hz and 5.8 Hz, 1 H, CH=), 6.46 (dt, J = 15.4 and 5.8 Hz, 1 H, CH=), 7.00-7.70 (m, 5 H, ArH); The stereoisomeric ratio of E/Z was determined to be 68/32 by the ^{13}C NMR analysis; ^{13}C NMR ($CDCl_3$, 25 MHz) δ 171.5, 138.5, 130.6, 128.6, 128.3, 127.2, 125.8, 118.8, 60.6, 58.2, 55.6, 48.7, 37.8, 16.5, 14.2 for (E)-13; 171.2, 138.4, 129.6, 128.6, 128.6, 128.3, 124.7, 118.8, 60.8, 58.3, 50.5, 49.0, 33.3, 16.6, 14.2 for (Z)-13; mass spectrum (EI), m/e 286 (12), 246 (100), 199 (31), 173 (18), 146 (6), 120 (17), 99 (4), 91 (100), 81 (8), 65 (13), 55 (8), 41 (5); high resolution mass spectrum for $C_{17}H_{22}O_2N_2$, calcd 286.1681, found 286.1704.

Carbonylation of (Z)-4-Benzyloxy-2-buten-1-yl Acetate (14): The carbonylation of (Z)-4-benzyloxy-2-buten-1-yl acetate (0.441 g, 2.00 mmol) was carried out (reaction condition A). A mixture of (E)- and (Z)-ethyl 5-benzyloxy-3-pentenoate (15) (0.399 g, 85%) was obtained. The isomeric ratio was determined to be 88:12 by the ^{13}C NMR analysis: bp 115-120 °C / 0.2 mmHg (Kugelrohr); IR (neat) 3080 (s), 3030 (m), 2980 (s), 2940 (s), 2900 (s), 2850 (s), 2800 (m), 1740 (C=O, s), 1500 (m), 1480 (w), 1455 (s), 1410 (m), 1390 (m), 1370 (m), 1340 (m), 1250 (m), 1190 (m), 1170 (s), 1100 (s), 1060 (m), 1020 (s), 970 (s), 940 (m), 855 (m), 805 (w), 740 (m), 695 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.23 (t, J = 7 Hz, 3 H, CH_3), 2.90-3.20 (m, 2 H, CH_2CO), 3.80-4.30 (m, 2 H, CH_2O), 4.07 (q, J = 7 Hz, CH_2O), 4.43 (s, 2 H, $ArCH_2O$), 5.30-6.30 (m, 2 H, CH=CH), 7.00-7.60 (m, 5 H, ArH); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 171.1, 138.3, 130.3, 128.2, 127.6, 127.4, 125.4, 71.9, 70.1, 60.4, 37.6, 14.2 for (*E*)-**15**. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 72.10; H, 7.89.

Carbonylation of Farnesyl Acetate (16): The carbonylation of a mixture of (2*E*,6*E*)-, (2*E*,6*Z*)-, (2*Z*,6*E*)-, and (2*Z*,6*Z*)-farnesyl acetate (3:3:2:2) (0.529 g, 2.00 mmol) was carried out (reaction condition B). A mixture of (3*E*,7*E*)-, (3*E*,7*Z*)-, (3*Z*,7*E*)-, and (3*Z*,7*Z*)-ethyl 4,8,12-trimethyltrideca-3,7,11-trienoate (**17**) (0.419 g, 75%) was obtained.

The carbonylation of (2*E*,6*E*)-farnesyl acetate (**16**) (0.529 g, 2.00 mmol) was carried out (reaction condition B). A mixture of (2*E*,6*E*)-, and (2*Z*,6*E*)-ethyl 4,8,12-trimethyltrideca-3,7,11-trienoate (**17**) (0.406 g, 73%) was obtained. The ratio was determined to be 90:10 by the GLC analysis (OV-1 chemical bonded capillary column, 25-m x 0.25-mm, injection temp 200 °C, column temp 200-Δ5-300 °C, 1.5 kg/cm^2-N_2): IR (neat) 2980 (s), 2920 (s), 2850 (s), 1740 (C=O, s), 1670 (C=C, w), 1480 (w), 1460 (w), 1450 (m), 1380 (m), 1320 (m), 1300 (m), 1260 (m), 1160 (s), 1105 (m), 1100 (m), 1035 (s), 980 (w), 940 (m), 920 (w), 840 (m), 800 (w), 950 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.24 (t, J = 7.0 Hz, 3 H, CH_3), 1.56-1.83 (m, 12 H, CH_3), 1.83-2.30 (m, 8 H, CH_2), 3.00 (d, J = 7.0 Hz, 2 H, CH_2CO), 4.11 (q, J = 7.0 Hz, 2 H, OCH_2), 4.60-5.70 (m, 3 H, CH=).

Ethyl 2-Cyclohexenecarboxylate (18): The carbonylation of 2-cyclohexen-1-yl acetate (0.420 g, 3.00 mmol) was carried out (reaction condition B). The reaction mixture was diluted with methylene chloride and washed with water (20 mL x 3). After removal of the solvents, the residue was chromatographed on silica gel (10 g, R_f = 0.3, methylene chloride:hexane = 3:7). Ethyl 2-cyclohexenecarboxylate (18) (0.265 g, 57%) was isolated as a yellow oil. An analytical sample was purified by preparative GLC (SE-30, 10%, 1-m x 2-mm, 150 °C). The GLC yield was determined by using tridecane as an internal standard: bp 90-95 °C / 17 mmHg (Kugelrohr); IR (neat) 3060 (CH, m), 2980 (CH, s), 2930 (CH, s), 2860 (CH, s), 2830 (m), 2650 (w), 1890 (w), 1730 (C=O, s), 1650 (C=C, m), 1450 (CH, s), 1390 (m), 1365 (CH, s), 1300 (s), 1200 (C-O, s), 1090 (s), 1030 (s), 925 (m), 900 (m), 890 (m), 860 (m), 850 (m), 800 (w), 660 (w), 620 (s), 660 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.26 (t, J = 6.8 Hz, 3 H, CH_3), 1.45-2.43 (m, 6 H, $(CH_2)_3$), 2.76-3.30 (m, 1 H, CH), 4.16 (q, J = 6.8 Hz, 2 H, CH_2), 5.53-6.10 (m, 2 H, CH=CH); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 174.0, 129.3, 124.8, 60.4, 41.3, 25.4, 24.9, 21.0, 14.3. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.65; H, 9.09.

(E)-Ethyl 2,5-Dimethyl-3-hexenoate (19): The carbonylation of 5-methyl-2-hexen-4-yl acetate (0.312 g, 2.00 mmol) was carried out (reaction condition B). Ethyl 2,5-dimethyl-3-hexenoate (19) (0.197 g, 59%) was obtained as a yellow oil: R_f = 0.40 (SiO_2, methylene chloride:hexane = 1:1); IR (neat) 2960 (CH, s), 2880 (s), 1740 (C=O, s), 1470 (CH, m), 1380 (CH, m), 1330 (m), 1250

(C-O, s), 1170 (s), 1100 (m), 1050 (m), 970 (m), 860 (w), 760 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.98 (d, J = 6 Hz, 6 H, CH_3), 1.25 (d, J = 7 Hz, 3H, CH_3), 1.28 (t, J = 7 Hz, 3 H, CH_3), 1.56-1.86 (m, 1H, CH), 2.80-3.40 (m, 1H, CH), 4.21 (q, J = 7 Hz, 2 H, CH_2), 5.30-5.80 (m, 2 H, CH=CH); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 175.1, 139.0, 126.0, 60.3, 42.8, 30.9, 22.3, 17.6, 14.3, 14.2.

Carbonylation of 5-Nonen-4-yl Acetate: The carbonylation of 5-nonen-4-yl acetate (0.368 g, 2.00 mmol) was carried out (reaction condition B). Ethyl 2-*n*-propyl-3-heptenoate (**20**) (0.202 g, 51%) was obtained as a yellow oil: R_f = 0.40 (SiO_2, methylene chloride:hexane = 1:1); IR (neat) 2960 (CH, s), 2930 (s), 2880 (CH, s), 1740 (C=O, s), 1470 (CH, m), 1370 (CH, m), 1240 (C-O, s), 1180 (m), 1100 (m), 1030 (m), 970 (m), 850 (w), 740 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 0.88 (t, J = 8.1 Hz, 3 H, CH_3), 0.91 (t, J = 8.1 Hz, 3 H, CH_3), 1.10-1.90 (m, 6 H, CH_2), 1.33 (t, J = 7.3 Hz, 3 H, $OCCH_3$), 1.98 (dt, J = 8.6 and 5.8 Hz, 2 H, $CH_2C=C$), 2.94 (dt, J = 5.8 and 5.8 Hz, 1 H, CH), 4.12 (q, J = 7.3 Hz, 3 H, OCH_2), 5.30 (dt, J =16.4 and 8.6 Hz, 1 H, CH=), 5.55 (dd, J = 16.4 and 5.8 Hz, 1 H, CH=); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 174.6, 133.0, 128.2, 60.2, 49.2, 34.9, 34.6, 22.4, 20.4, 14.3, 13.8, 13.6.

Carbonylation of Linalyl acetate (21): The carbonylation of linalyl acetate (**21**) (0.196 g, 1.00 mmol) was carried out (reaction condition A). The mixture of (*E*)- and (*Z*)-ethyl 4,8-dimethyl-3,7-nonadienoate (**24**) was isolated (0.188 g, 90%). The GLC yield was determined to be 100% by using hexadecane as an internal standard: $\underline{R}_f$ = 0.37 (SiO_2, methylene chloride:hexane = 1:9); bp 65-70 °C / 0.2 mmHg (Kugelrohr); IR (neat) 2980 (CH, s), 2930 (CH, s), 2730 (w), 1740 (C=O, s), 1450 (CH, m), 1385 (m), 1255 (C-O, m), 1150 (s), 1105 (w), 1015 (s), 940 (w), 830 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.25 (t, J = 6.8 Hz, 3 H, $O\text{-}C\text{-}CH_3$), 1.50-1.95 (m, 9 H, CH_3), 1.95-2.40 (m, 4 H, $(CH_2)_2$), 3.02 (d, J = 6.8 Hz, 2 H, CH_2CO), 4.12 (q, J = 6.8 Hz, 2 H, OCH_2), 4.90-5.56 (m, 2 H, CH=); The stereoisomeric ratio of *E*/*Z* was determined to be 60/40 by the ^{13}C NMR analysis and by the GLC analysis (PEG 20M chemical bonded capillary column, 25-m x 0.25-mm, injection temp 200 °C, column temp 130-Δ5-230 °C, 1.5 $kg/cm^2\text{-}N_2$). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 73.96; H, 10.56.

Carbonylation of Geranyl Acetate (22): As descrived above, the carbonylation of geranyl acetate (**22**) (0.196 g, 1.00 mmol) was carried out (reaction condition A). Ethyl 4,8-dimethyl-3,7-nonadienoate (**24**) (6%, GLC yield) was also obtained. The stereoisomeric ratio was determined to be 93:7 by the GLC analysis.

The carbonylation of geranyl acetate (**22**) (0.196 g, 1.00

mmol) was also carried out (reaction condition B). Ester **24a** (74%, GLC yield) was also obtained in 74% isolated yield stereoselectively. The ratio of **24a**:**24b** was determined to be 93:7 by the ^{13}C NMR and GLC analyses: ^{13}C NMR (25 MHz, $CDCl_3$) δ 138.9, 131.4, 124.1, 116.0, 60.4, 39.7, 33.8, 26.6, 25.7, 17.7, 16.3, 14.3 for (*E*)-**24a**.

The carbonylation of geranyl acetate (0.196 g, 1.00 mmol) was carried out (reaction condition C). Ester **24a** (74%, GLC yield) was also obtained. The ratio of **24a**:**24b** was determined to be 85:15 by the GLC analysis:

Carbonylation of Neryl Acetate (23): As described above, the carbonylation of neryl acetate (0.196 g, 1.00 mmol) was carried out (reaction condition B). (*Z*)-Ethyl 4,8-dimethyl-3,7-nonadienoate (**24b**) (78%, GLC yield) was also obtained in 68% isolated yield stereoselectively. The ratio of **24a**:**24b** was determined to be 14:86 by the ^{13}C NMR and GLC analyses; ^{13}C NMR ($CDCl_3$, 25 MHz) δ 138.8, 131.8, 124.0, 116.8, 60.4, 33.7, 32.2, 26.5, 25.7, 23.4, 17.6, 14.3 for (*Z*)-**24b**.

The carbonylation of neryl acetate (0.196 g, 1.00 mmol) was carried out (reaction condition C). Ester **24b** (89%, GLC yield) was also obtained. The ratio of **24a**:**24b** was determined to be 32:68 by the GLC analysis.

Control Experiment for the Thermal Isomerization of β,γ-Unsaturated Ester 24b under the Reaction Conditions B: In a 10-mL stainless steel autoclave, control experiment for the thermal isomerization of **24b** (*E*:*Z* = 7:93) was carried out under the condition B. No change of isomer ratio was obserbed after 20 h.

Carbonylation of *cis*-5-Methoxycarbonyl-2-cyclohexen-1-yl Acetate (28): The carbonylation of *cis*-5-methoxycarbonyl-2-cyclohexen-1-yl acetate (**28**) (0.198 g, 1.00 mmol) was carried out (reaction condition B) using methanol in place of ethanol. A mixture of *trans*- and *cis*-dimethyl 2-cyclohexene-1,5-dicarboxylate (**29a** and **29b**) and dimethyl 1-cyclohexene-1,5-dicarboxylate (**30**) (0.135 g, 68%) was obtained by the column chromatography (SiO_2, hexane:methylene chloride = 8:2). The molar ratio **29a**/**29b**/**30** was determined to be 23:18:59 by the GLC analysis. An analytical sample was purified by preparative GLC (SE-30 10%, 1-m x 3-mm, He); **29a**-**b**; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.50-2.90 (m, 5 H), 3.00-3.50 (m, 1 H, CHCOO), 3.70 (s, 6 H, OMe), 5.70-5.93 (m, 2 H, CH=CH): **30**; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.40-3.00 (m, 7 H), 3.69 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 6.85-7.20 (m, 1 H, CH=).

The carbonylation of *cis*-diethyl 5-methoxycarbonyl-2-cyclohexen-1-yl phosphate (**31**) (0.292 g, 1.00 mmol, *cis*:*trans* = 100:0) was carried out at 50 °C for 5 h under CO atmosphere (60 kg/cm^2). Instead of EtOH, MeOH was used as a solvent. *trans*-Dimethyl 1-cyclohexene-1,5-dicarboxylate (**29a**) (0.121 g, 57 %) was obtained as a colorless oil. The *cis*:*trans* ratio of **29a**-**b** was determined to be 96.0:4.0 on the basis of GLC analysis (PEG 20M, 25 m x 0.25 mm): IR (neat) 3040 (w), 2900 (m), 1850 (w), 1735 (C=O, s), 1660 (m), 1620 (m), 1435 (m), 1160 (C-O-C, s), 1100 (m), 105 (m), 1010 (m), 900 (m), 870 (m), 830 (w), 800 (m), 765 (m), 690 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.88 (ddd, J = 13.52, 10.77, and 6.19 Hz, 1 H, $H^{2\alpha}$), 2.21-2.35 (m, 3 H, $H^{2\beta}$ and H^6), 2.82 (dddd, J = 10.77, 8.93, 5.73, and 3.21 Hz, 1 H, $H^{1\beta}$), 3.21 (m, 1 H, $H^{3\alpha}$), 3.69 (s ,3 H, COOMe), 3.70 (s, 3 H, COOMe), 5.75-5.87 (m, 2 H, CH=CH).

Synthetic Application

(E)-3-Nonen-1-ol (37): To a solution of ethyl 3-nonenoate (2) (0.184 g, 1.00 mmol) in THF (2.0 mL), a THF solution of lithium aluminum hydride (0.69 M, 2.5 mL, 1.73 mmol) was added at 0-5 °C for 20 min. The mixture was stirred at room temp for 60 min. The reaction was quenched with water (1.0 mL). The resulting gel was passed through a pad of Celite using ethyl acetate (20 mL) as an eluent. The eluate was evaporated to give 3-nonen-1-ol (37) (0.162 g, 95%) as a colorless oil: IR (neat) 3300 (OH, br), 2930 (s), 2860 (s), 1750 (w), 1720 (w), 1475 (m), 1470 (m), 1380 (m), 1050 (s), 970 (s), 880 (w), 720 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 0.89 (t, J = 6.2 Hz, 3 H, CH_3), 1.05-1.55 (m, 6 H, CH_2), 1.80-2.10 (m, 2 H, $CH_2C{=}C$), 2.24 (dt, J = 6.5 and 6.2 Hz, 2 H, CH2CH2O), 2.41 (s, 1 H, OH), 3.59 (t, J = 6.5 Hz, 2 H, CH_2O), 5.32 (dt, J = 14.9 and 5.8 Hz, 1 H, CH=), 5.55 (dt, J = 14.9 and 5.8 Hz, 1 H, CH=). Anal. Calcd for $C_9H_{18}O$: C, 75.99;

H, 12.76. Found: C, 75.60; H, 12.62.

(E)-3-Nonenoic Acid (39): In a 50-mL round bottomed flask, a 2N KOH (10 mL) solution was added carefully to the THF solution (10 mL) of (E)-ethyl 3-nonenoate (2) (1.87 g, 10.1 mmol) at 0 °C. The reaction mixture was stirred at room temp for 48 h. After removal of the solvents, the mixture was diluted with water and washed successively with toluene (20 mL x 3) and ether (20 mL). Then, the aqueous layer was made acidic with a 12N HCl solution at 0 °C. The acidic solution was extracted with methylene chloride (20 mL x 5) and the combined extracts were dried over $MgSO_4$. After removal of the solvents, (E)-3-nonenoic acid (39) (1.54 g, 99%) was obtained as a yellow oil.

3,4-Dihydroxynonanoic Acid (40): To a solution of 3-nonenoic acid (1.03 g, 6.3 mmol) in THF (30 mL), trimethylamine N-oxide (1.04 g, 9.4 mmol) was added. A THF solution of OsO_4 (0.348 M, 1.0 mL, 0.35 mmol) was added to the suspension. The reaction mixture was stirred for 2 h at room temp. The reaction was quenched by $Na_2S_2O_4$ (5.0 g), Florisil (12.5 g), and water (6.5 mL). The mixture was stirred at room temp for 30 min. The reaction mixture was dried over $MgSO_4$ (6 g). The resulting slurry was stirred for 1 h. The mixture was filtered through a pad of SiO_2 (12 g) using methanol (200 mL) as an eluent. The eluate was evaporated to give the crude acid 40 (1.17 g, 100%) as colorless crystals; IR (KBr) 3233 (CH, s), 3086 (CH, s), 2955 (CH, s), 1678 (C=O, s), 1456 (m), 1423 (w), 1386 (w), 1332 (m), 1275 (w), 1170 (m), 1134 (m), 1111 (m), 1087 (m), 1060 (m), 1024 (w), 1003 (w), 935 (w), 914 (w), 866 (m), 673, (m), 602 (m) cm^{-1}.

Ethyl 3,4-Dihydroxynonanoate (38). To a solution of ethyl 3-nonenoate (**2**) (1.84 g, 10.0 mmol) in THF (50 mL), trimethylamine *N*-oxide (1.67 g, 15.0 mmol) was added. The solution of OsO_4 (0.386 M, 1.3 mL, 0.5 mmol) was added to the suspension. The reaction mixture was stirred at room temp for 2 h. The reaction was quenched by $Na_2S_2O_4$ (4 g), Florisil (10 g), and water (5 mL). The mixture was stirred at room temp for 30 min. The reaction mixture was dried over $MgSO_4$ (10 g). The resulting slurry was stirred for 1 h. The mixture was filtrated through a pad of SiO_2 (20 g) using ether (300 mL) as an eluent. The eluent was evaporated to give the crude diol **38** (2.13 g, 98%) as a colorless crystal: IR (neat) 3420 (OH, brs) 2960 (m), 2930 (s), 2875 (m), 1735 (C=O, s), 1475 (m), 1400 (m), 1380 (m), 1300 (m), 1170 (C-O-C, s), 1060 (m), 1025 (m), 945 (w), 880 (w), 725 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.90 (t, J = 5.0 Hz, 3 H, CH_3), 1.05-1.80 (m, 8 H, CH_2), 1.26 (t, J = 7.0 Hz, 3 H, CH_3), 2.53 (d, J = 6.2 Hz, 2 H, CH_2), 2.70-3.00 (br, 1 H, OH), 3.10-4.00 (m, 3 H, OH and CHOCHO), 4.15 (q, J = 7.0 Hz, 2 H, CH_2).

3-Hydroxy-4-pentyl-4-butanolide (41):

Method A: In a 10-mL round bottomed flask, 3,4-dihydroxynonanoic acid (**40**) (0.190 g, 1.00 mmol) and dry benzene (2 mL) were placed. To the acid solution, dry benzene solution (1.0 mL) of dicyclohexylcarbodiimide (0.270 g, 1.2 mmol) was added.

Then the mixture was stirred at room temp for 48 h, and the mixture was changed to a white suspension. The white precipitate was removed by filtration. After removal of benzene, 3-hydroxy-4-pentyl-4-butanolide (**41**) (0.180 g, 100%) was obtained as a yellow oil: IR (neat) 3400 (OH, br), 2980 (CH, s), 2930 (CH, s), 2880 (CH, s), 1770 (C=O, s), 1650 (w), 1470 (m), 1410 (m), 1380 (m), 1360 (m), 1300 (m), 1200 (s), 1170 (s), 1140 (m), 1120 (w), 1090 (m), 1020 (m), 980 (w), 950 (m), 900 (w), 850 (w), 810 (w), 790 (w), 730 (w), 660 (w) cm^{-1}; ^{1}H NMR (CDCl$_3$, 60 MHz) δ 0.90 (t, J = 5 Hz, 3 H, CH$_3$), 1.0-2.0 (m, 8 H, (CH$_2$)$_4$), 2.5-2.7 (m, 2 H, CH$_2$CO), 3.4 (s, 1 H, OH), 4.0-4.6 (m, 2 H, CHO).

Method B: In a 50-mL round bottomed flask equipped with a reflux condenser, ethyl 3,4-dihydroxynonanoate (**38**) (0.440 g, 2.00 mmol) sodium methoxide (0.011 g, 0.2 mmol) and molecular sieves 4A (0.5 g) were placed. After the atmosphere in the flask was replaced with nitrogen, dry benzene (10 mL) was added to the flask. The mixture was refluxed for 2 h. After filtration of molecular sieves, the filtrate was evaporated to give 3-hydroxy-4-pentyl-4-butanolide (**41**) (0.260 g, 76%) as a yellow oil. The spectral data was described above.

References

1. (a) Chiusoli, G. P.; Merzoni, S. *Z. Naturforsch.* **1962**, *17b*, 850. (b) Chiusoli, G. P. *Chim. Ind.* (Milan) **1959**, *41*, 503. (c) Chiusoli, G. P. *Gazz. Chim. Ital.* **1959**, *89*, 1332. (d) Heck, R. F. *J. Am. Chem. Soc.* **1963**, *85*, 2013. (e) Chiusoli, G. P.; Cassar, L. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 124. (f) Foá, M.; Cassar, L. *Gazz. Chim. Ital.* **1979**, *109*, 616. (g) Joó, F.; Alper, H. *Organometallics* **1985**, *4*, 1775.
2. Heck, R. F.; Breslow, D. S. *J. Am. Chem. Soc.* **1963**, *85*, 2779.
3. (a) Dent, W. T.; Long, R.; Whitfield, G. H. *J. Chem. Soc.* **1964**, 1588. (b) Tsuji, J.; Kiji, J.; Morikawa, M. *Tetrahedron Lett.* **1963**, 1811. (c) Tsuji, J.; Kiji, J.; Imamura, S.; Morikawa, M. *J. Am. Chem. Soc.* **1964**, *86*, 4350. (d) Medema, D.; van Helden, R.; Kohll, C. F. *Inorg. Chim. Acta* **1969**, *8*, 255. (e) Cowell, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4193. (f) Sheffy, F. K.; Stille, J. K.; *J. Am. Chem. Soc.* **1983**, *105*, 7173. (g) Baillargeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 7175. (h) Merrifield, J. H.; Godschalx, J. P.; Stille, J. K. *Organometallics* **1984**, *3*, 1108. (i) Sheffy, F. K.; Godschalx, J. P.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4833. (j) Baillargeon, V. P.; Stille, J. K. *J. Am.*

Chem. Soc. **1986**, *108*, 452. (k) *Chem. Eng. News* **1984**, *62*, 28. (l) Kiji, J.; Okano, T.; Nishiumi, W.; Konishi, H. *Chem. Lett.* **1988**, 957.

4. (a) Knifton, J. F. *J. Organomet. Chem.* **1980**, *188*, 223. (b) Ref 3b-d.

5. (a) Imamura, S.; Tsuji, J. *Tetrahedron* **1969**, *25*, 4187. (b) Bonnet, M. C.; Neibecker, D.; Stitou, B.; Tkatchenko, I. "5th International Symposium on Homogeneous Catalysis (ISHC-5)" Abstracts, Kobe, 1986, Sept 22-26, G-7, 36. (c) Mitsudo, T.; Hasegawa, H.; Kadokura, M.; Watanabe, Y. "56th JCS Meeting, Abstracts, 1XIIA32, Tokyo, 1988.

6. Murahashi, S.-I.; Imada, Y.; Nishimura, K. *J. Chem. Soc.*, *Chem. Commun.* **1988**, 1578.

7. (a) Long, R.; Whitfield, G. H. *J. Chem. Soc.* **1964**, 1852. (b) Brewis, S.; Hughes, P. R. *J. Chem. Soc.*, *Chem. Commun.* **1965**, 157. (c) Tsuji, J.; Imamura, S.; Kiji, J. *J. Am. Chem. Soc.* **1964**, *86*, 4491. (d) Powell, J.; Shaw, B. L. *J. Chem. Soc. A* **1967**, 1840. (e) Medema, D.; van Helden, R. *Recl. Trav. Chim. Pays-Bas.*, **1971**, *90*, 304. (f) Bäckvall, J. E.; Nordberg, R. E.; Zetterberg, K.; Åkermark, B. *Organometallics* **1983**, *2*, 1625. (g) Åkermark, B.; Söderberg, B. C.; Hall, S. S. *Organometallics* **1987**, *6*, 2608. (h) Söderberg, B. C.; Åkermark, B.; Hall, S. S. *J. Org. Chem.* **1988**, *53*, 2925.

8. (a) Takahashi, Y.; Sakai, S.; Ishii, Y. *J. Chem. Soc.*,

Chem. Commun. **1967**, 1092. (b) Takahashi, Y.; Tsukiyama, K.; Sakai, S.; Ishii, Y. *Tetrahedron Lett.* **1970**, 1913. (c) Bäckvall, J. E.; Nordberg, R. E.; Björkman, E. E.; Moberg, C. *J. Chem. Soc.*, *Chem. Commun.* **1980**, 943. (d) Yamamoto, T.; Saito, O.; Yamamoto, A. *J. Am. Chem. Soc.* **1981**, *103*, 5600. (e) Yamamoto, T.; Akimoto, M.; Saito, O.; Yamamoto, A. *Organometallics* **1986**, *5*, 1559.

9. Hegedus, L. S.; Tamura, R. *Organometallics* **1982**, *1*, 1188.
10. (a) Tsuji, J.; Sato, K.; Okumoto, H. *Tetrahedron Lett.* **1982**, *23*, 5189. (b) Tsuji, J.; Sato, K.; Okumoto, H. *J. Org. Chem.* **1984**, *49*, 1341. (c) Tamaru, Y.; Bando, T.; Hojo, M.; Yoshida, Z. *Tetrahedron Lett.* **1987**, *28*, 3497.
11. Murahashi, S.-I.; Imada, Y. *Chem. Lett.* **1985**, 1477.
12. (a) Koyasu, Y.; Matsuzaka, H.; Hiroe, Y.; Uchida, Y.; Hidai, M. *J. Chem. Soc.*, *Chem. Commun.* **1987**, 575. (b) Matsuzaka, H.; Hiroe, Y.; Iwasaki, M.; Ishii, Y.; Koyasu, Y.; Hidai, M. *Chem. Lett.* **1988**, 377. (c) Matsuzaka, H.; Hiroe, Y.; Iwasaki, M.; Ishii, Y.; Koyasu, Y.; Hidai, M. *J. Org. Chem.* **1988**, *53*, 3832. (d) Iwasaki, M.; Matsuzaka, H.; Hiroe, Y.; Ishii, Y.; Koyasu, Y.; Hidai, M. *Chem. Lett.* **1988**, 1159. (e) Iwasaki, M.; Li, J.-p.; Kobayashi, Y.; Matsuzaka, H.; Ishii, Y.; Hidai, M. *Tetrahedron Lett.* **1989**, *30*, 95.
13. Murahashi, S.-I.; Imada, Y.; Taniguchi, Y.; Higashiura, S. *Tetrahedron Lett.* **1988**, *29*, 4945.

14. (a) β-Lactam. Biloski, A. J.; Wood, R. D.; Ganem, B. *J. Am. Chem Soc.* **1982**, *104*, 3233; Rajendra, G.; Miller, M. J. *J. Org. Chem.* **1987**, *52*, 4471. (b) Antibiotics. Corey, E. J.; Hase, T. *Tetrahedron Lett.* **1979**, 335; Barrish, J. C.; Lee, H. L.; Pizzolato, G.; Baggiolini, E. G.; Uskoković, M. R. *J. Org. Chem.* **1988**, *53*, 4282; Grieco,P. A.; Hon, Y. S.; Perez-Medrano, A. *J. Am. Chem. Soc.* **1988**, *110*, 1630. (c) Alkaloids: Tufariello, J. J.; Mullen, G. B.; Tegeler, J. J. Trybulski, E. J.; Wong, S. C.; Ali, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2435; Takatsu, N.; Ohmiya, S.; Otomasu, H. *Chem. Farm. Bull.* **1987**, *35*, 891; Ohfune, Y.; Tomita, M. *J. Am. Chem. Soc.* **1982**, *104*, 3511.

15. (a) Corey, H. S., Jr.; McCormick, J. R. D.; Swensen, W. E. *J. Am. Chem. Soc.* **1964**, *86*, 1884. (b) Büchi, G.; Cushman, M.; Wüest, H. *J. Am. Chem. Soc.* **1974**, *96*, 5563. (c) Salomon, M.; Pardo, S. N.; Salomon, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 2473. (d) Chiusoli, G. P.; Pallini, L. *J. Organomet. Chem.* **1982**, *238*, C85. (e) Fujisawa, T.; Sato, T.; Takeuchi, M. *Chem. Lett.* **1982**, 71 and 219; Fujisawa, T.; Sato, T.; Gotoh, Y.; Kawashima, M.; Kawara, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3555. (f) Camps, F.; Coll, J.; Guerrero, A.; Guitart, J.; Riba, M. *Chem. Lett.* **1982**, 715. (g) Ikuba, T.; Chu, G. N.; Yoneda, F. *Tetrahedron Lett.* **1984**, *25*, 3247. (h) Piva, O.; Henin, F.; Muzart, J.; Pete, J. P. *Tetrahedron Lett.* **1987**, *28*, 4825; Mortezaei, R.;

Awandi, D.; Henin, F.; Muzart, J.; Pete, J. P. *J. Am. Chem. Soc.* **1988**, *110*, 4824.

16. (a) Kende, A. S.; Toder, B. H. *J. Org. Chem.* **1982**, *47*, 163. (b) Yamaguchi, M. Hamada, M.; Nakashima, H.; Minami, T. *Tetrahedron Lett.* **1987**, *28*, 1785. (c) Ikuba, T.; Taga, T.; Shingu, T.; Saito, M.; Nishii, S.; Yamamoto, Y. *J. Org. Chem.* **1988**, *53*, 3947. (d) Ballester, P.; Costa, A.; Garcia-Raso, A. *J. Chem. Soc.*, *Perkin Trans. I* **1988**, 2797.

17. Nordberg, R.; Bäckvall, J. E. *J. Organomet. Chem.* **1985**, *285*, C24.

18. Overman, L. E.; Knoll, F. M. *Tetrahedron Lett.* **1979**, 321.

19. (a) Milstein, D. *Organometallics* **1982**, *1*, 888. (b) Milstein, D. *Acc. Chem. Res.* **1988**, *21*, 428.

20. Kudo, K.; Hidai, M.; Murayama, T.; Uchida, Y. *J. Chem. Soc.*, *Chem. Commun.* **1970**, 1701.

21. Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solution: Supplement 1972*, Butterworths, London (1972).

22. Åckermark, B.; Vitagliano, A. *Organometallics* **1985**, *4*, 1275.

23. (a) Tsuji, J.; Yamakawa, T.; Kaito M.; Mandai, T. *Tetrahedron Lett.* **1978**, 2075. (b) Trost, B. M.; Verhoeven, T. R.; Fortunak, J. M. *Tetrahedron Lett.* **1979**, 2301.

24. (a) Moreno-Manas, M.; Trius, A. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2154. (b) Tsukahara, Y.; Kinoshita, H,; Inomata, K.;

Kotake, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3013. (c) Tamura, R.; Kato, M.; Saegusa, K.; Kakihara, M.; Oda, D. *J. Org. Chem.* **1987**, *52*, 4121.

25. Guibe, F.; Saint M'Leux, Y. *Tetrahedron Lett.* **1981**, *22*, 3591.

26. (a) Bosnich, B.; Mackenzie, P. B. *Pure Appl. Chem.* **1982**, *54*, 189. (b) Faller, J. W.; Thomsen, M. E.; Mattina, M. J. *J. Am. Chem. Soc.* **1972**, *93*, 2642.

27. Osakada, K.; Chiba, T.; Nakamura, Y.; Yamamoto, A. *J. Chem. Soc.*, *Chem. Commun.* **1986**, 1589.

28. Takahashi, T.; Jinbo, Y.; Kitamura, K.; Tsuji, J. *Tetrahedron Lett.* **1984**, *25*, 5921.

29. (a) Rhoads, S. J.; Chattopadhyay, J. K.; Waali, E. E. *J. Org. Chem.* **1970**, *35*, 3352. (b) Sakai, M. Nishikawa, S.; Koike, H.; Sakakibara, Y.; Uchino, N. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2970. (c) Alcock, S. G.; Baldwin, J. E.; Bohlmann, R.; Harwood, L. M. *J. Org. Chem.* **1985**, *50*, 3526.

30. (a) Parshall, G. W.; Wilkinson, G. *Inorg. Chem.* **1962**, *1*, 896. (b) Tsuji, J.; Imamura, S. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 197.

31. (a) Stille, J. K.; Hines, L. F. *J. Am. Chem. Soc.* **1970**, *92*, 1798. (b) Hines, L. F.; Stille, J. K. *J. Am. Chem. Soc.* **1972**, *94*, 485. (c) James, D. E.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 1810. (d) Lau, K. S. Y.; Wong, P. K.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 5832. (e)

Stille, J. K.; Divakaruni, R. J. Org. Chem. 1979, 44, 3474. (f) Larock, R. C.; Leach, D. R. J. Org. Chem. 1984, 49, 2144.

32. Rivetti, F.; Romano, U. J. Organomet. Chem. 1978, 154, 323.

33. Hidai, M.; Kokura, M.; Uchida, Y. J. Organomet. Chem. 1973, 52, 431.

34. (a) Cyclization: Kasahara, A.; Izumi, T.; Sato, K.; Maemura, M.; Hayasaka, T. Bull. Chem. Soc. Jpn. 1977, 50, 1899; Kato, T.; Kumazawa, S.; Kitahara, Y. Synthesis 1972, 573; Hoye, T. R.; Kurth, M. J. J. Org. Chem. 1978, 43, 3693; Rouessac, A.; Rouessac, F.; Zamarlik, H. Tetrahedron Lett. 1981, 22, 2641; Hoye, T. R.; Caruso, A. J.; Kurth, M. J. J. Org. Chem. 1981, 46, 3550; Gnonlonfoun, N.; Zamarlik, H. Tetrahedron Lett. 1987, 28, 4053. (b) Asymmetric Hydrogenation: Ohta, T.; Takaya, H.; Kitamura, M.; Nagai, K.; Noyori, R. J. Org. Chem. 1987, 52, 3174.

35. (a) Schröder, M. Chem. Rev. 1980, 80, 187. (b) VanRheenen, V.; Kelly R. C.; Cha, D. Y. Tetrahedron Lett. 1976, 1973. (c) Glattfield, J. W. E.; Rietz, E. J. Am. Chem. Soc. 1940, 62, 974.

36. Kudo, K.; Hidai, M.; Uchida, Y. J. Organomet. Chem. 1971, 33, 393.

37. Hegedus, L. S.; Anderson, O. P.; Zetterbeg, K.; Allen, G.; Hansen, K. S.; Olsen, D. T.; Packard, A. B. Inorg. Chem. 1977, 16, 1887.

38. (a) Mann, F. G.; Chaplin, E. J. *J. Chem. Soc.* **1937**, 527.

(b) Ziegler, C. B., Jr.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2941.

39. Marcou, M. A.; Normant, H. *Bull. Soc. Chim. Fr.* **1965**, 3491.

40. Danishefsky, S.; Berman, E. M.; Ciufolini, M.; Etheredge, S. J.; Segmuller, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 3891.

41. Tanigawa, Y.; Nishimura, K.; Kawasaki, A.; Murahashi, S.-I.; *Tetrahedron Lett.* **1982**, *23*, 5549.

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