Palladium-catalysed Regio- and Stereo-selective Synthesis of Allylic Amines

Yoshinao Tamaru,*[a] Takashi Bando,[a] Youichi Kawamura,[a] Kazuto Okamura,[a] Zen-ichi Yoshida[b] and Motoo Shiro[c]

[a] *Department of Applied Chemistry, Faculty of Engineering, Nagasaki University, Bunkyo, Nagasaki 852, Japan*
[b] *Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Sakyo, Kyoto 606, Japan*
[c] *Shionogi Research Laboratories, Shionogi Co., Sagisu, Fukushima, Osaka 553, Japan*

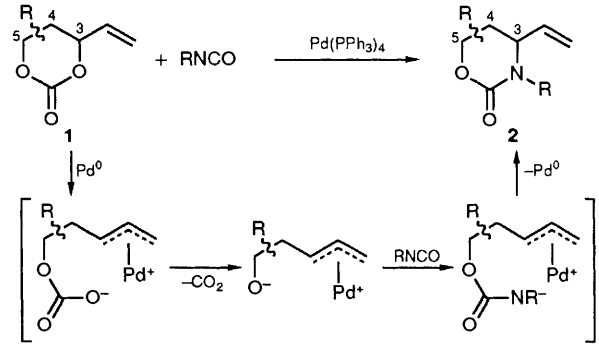
3-Vinyl-2,6-dioxacyclohexan-1-ones **1**, by treatment with *N*-tosyl or *N*-aryl isocyanates and a catalytic amount of Pd^0, are converted into *N*-tosyl- and *N*-aryl-3-vinyl-2-aza-6-oxacyclohexan-1-ones **2** in good yields and with unique stereoselectivity.

Regio- and stereo-selective preparation of allylic amines[1] still remains a synthetic challenge in organic synthesis. We needed a series of 3-amino-4-penten-1-ols of sterically defined structure not only as a key synthetic intermediates for physiologically important amino sugars[2] and rare amino acids,[3] but also as probes to examine the stereoelectronic effects of the allylic amino group on the diastereoselective addition of electrophiles (*e.g.* I_2, Pd^{2+}) to the double bond.[4]

Here, we report a convenient and stereoselective synthesis of 3-amino-4-penten-1-ols (Scheme 1), which is based on a Pd^0-catalysed transformation of cyclic carbonates **1**[5] into cyclic carbamates **2**.[6] The reaction is believed to proceed *via* a sequence of reactions, which involves an oxidative addition of Pd^0 to allylic carbonate,[7] a carbon dioxide–isocyanate exchange, followed by a nucleophilic attack by nitrogen to π-allylpalladium to regenerate palladium(0). The regioselective introduction of an amino group is achieved by the intramolecular nature of the reaction.

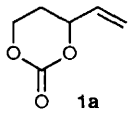
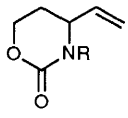
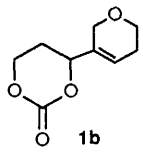
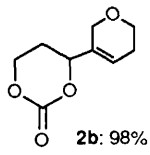
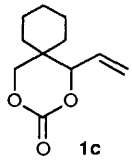
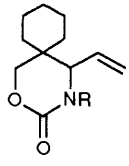
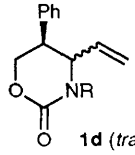
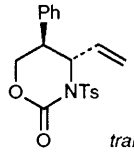
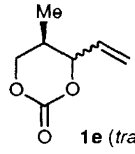
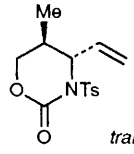
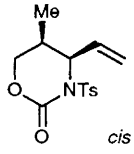
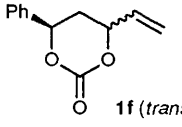
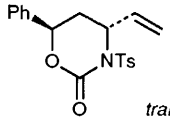
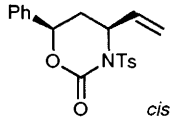
Aryl isocyanates with electron-donating and electron-withdrawing substituents and toluene-*p*-sulfonyl isocyanate react equally well (runs 1–5, Table 1). Benzyl isocyanate, however, fails to participate and an intractable mixture results (run 9, Table 1). The reaction exhibits high structural flexibility of substrates. Substituents on any carbons of **1**, except for C(3), are tolerated: 3-methyl-3-vinyl-2,6-dioxacyclohexan-1-one failed to react in a similar way and decomposed.

The reaction is typically performed as follows (run 5): Into a stirred solution of $Pd(PPh_3)_4$ (0.06 mmol) in dry THF

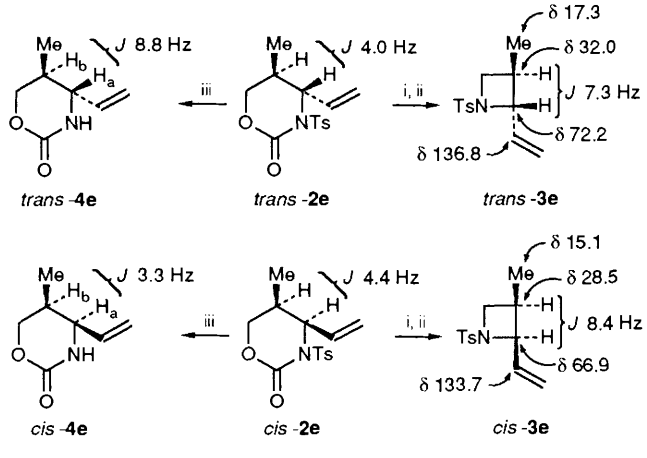


Scheme 1

Table 1 Pd^0-catalysed regio- and stereo-selective transformation of carbonates **1** into carbamates **2**

Run	Carbonate **1**	Conditions[a]	Carbamate **2**: isolated yield (%)
1	 **1a**	Dioxane, room temp., 11 h	 **2a** (R = toluene-*p*-sulfonyl, 80%)[b]
2		THF, room temp., 9 h	**2a** (R = *p*-methyphenyl, 65%)
3		THF, room temp., 8 h	**2a** (R = phenyl, 70%)
4		Dioxane, room temp., 8 h	**2a** (R = *p*-chlorophenyl, 84%)
5		THF, room temp., 9 h	**2a** (R = *p*-nitrophenyl, 87%)
6	 **1b**	Dioxane, 60 °C, 2 h	 **2b**: 98%
7	 **1c**	Dioxane, 60 °C, 2 h	 **2c** (R = toluene-*p*-sulfonyl, 98%)
8		Dioxane, 60 °C, 11 h	**2c** (R = phenyl, 90%)
9		Dioxane, 60 °C, 10 h	**2c** (R = benzyl, 0%)
10	 **1d** (*trans* : *cis* = 1.4 : 1)	Dioxane, room temp., 1 h	 *trans*-**2d**: 66%
11	 **1e** (*trans* : *cis* = 1 : 1.5)	Dioxane, 25 °C, 40 min	 *trans*-**2e**: 73%  *cis*-**2e**: 10%
	 **1f** (*trans* : *cis* = 0.8 : 1)	Dioxane, 25 °C, 40 min	 *trans*-**2f**  *cis*-**2f**
12		THF, 15 °C, 20 min	*trans*-**2f** : *cis*-**2f** = 15 : 85 (88%)[c]
13		THF, 25 °C, 2 h	*trans*-**2f** : *cis*-**2f** = >95 : <5 (90%)

[a] Carbonate (1 mmol), $Pd(PPh_3)_4$ (0.02–0.03 mmol), isocyanate (1.1 mmol) in a dry solvent (5 ml) under an argon atmosphere. [b] **2a** (91% isolated yield) with 1.5 equiv. of toluene-*p*-sulfonyl isocyanate. [c] Ratio determined by ^1H NMR spectroscopy.



Scheme 2 Structure determination of **2e**; selected ^1H and ^{13}C NMR data i, 3 mol dm^{-3} KOH (3 equiv.) in EtOH at reflux for 2 h, quantitative, ii, PPh_3 (1.2 equiv.), diethyl azodicarboxylate (1.2 equiv.) in THF (0 °C then room temp., 20 h), *ca.* 95% yield; iii, naphthalene (7 equiv.), Na (6 equiv) in THF (−78 °C then 0 °C, 15 min), *ca.* 90% yield.

(tetrahydrofuran) (12 ml) is successively added **1a** (3.0 mmol) and a solution of *p*-nitrophenyl isocyanate (3.3 mmol) in THF (3 ml) at room temperature under argon. After evolution of carbon dioxide has ceased, the mixture is stirred for an additional 8 h and then diluted with ethyl acetate and washed with aq. $NaHCO_3$. Compound **2a** (R = *p*-nitrophenyl) is isolated by recrystallization from hot benzene (m.p. 127–129 °C).†

The synthetic utility of the present reaction is furthermore augmented by the high and unique stereoselectivity (runs 10–13). Irrespective of the stereochemistry of 3,4-disubstituted carbonates **1**, were obtained *trans*-3,4-disubstituted carbamates either exclusively (**2d**, run 10) or selectively (**2e**, run 11). On the other hand, the mixture of 3,5-disubstituted carbonates **1f** furnished either *cis*-**2f** (run 12) or *trans*-**2f** (run 13) selectively depending on the reaction conditions.

The smooth isomerization of *cis*-**2f** to *trans*-**2f** is quite unusual judging from the relative stability of the isomers for 1,3-disubstituted cyclohexane systems, since the *cis*-isomers

† All new compounds showed satisfactory spectral (^1H NMR, IR, MS) and analytical data.

are generally more stable than the *trans*-ones.‡ Anomaly is also observed for the very small vicinal coupling constant between H-3 and H-4 of *trans*-**2e** (Scheme 2). Accordingly, the structure of **2e** was deduced by the standard chemical transformations as illustrated in Scheme 2. All the carbons of azetidine ring and substituents of *trans*-**3e** showed the lower field resonances relative to those of the corresponding carbons of *cis*-**3e** in the ^{13}C NMR spectra, which clearly supports the structural assignment. Furthermore, *trans*- and *cis*-**4e**, obtained by the reductive removal of toluenesulfonyl group from *trans*-and *cis*-**2e**, respectively, showed vicinal coupling constants, reasonable for their structures (*trans*-**4e**, H_a: δ 3.54, t, *J* 8.8 Hz; H_b: δ 1.87, m. *cis*-**4e**, H_a: δ 4.04, dd, *J* 3.3, 8.0 Hz; H_b: δ 2.34, m. in $CDCl_3$ at 400 MHz ^1H NMR). The chemical and spectroscopic anomalies of cyclic carbamates **2e** and **2f** may be attributed to a steric repulsion owing to an eclipsing of the sulfonyl group, residing in the O–(C=O)–N plane, with an equatorial vinyl group. Indeed, a preliminary X-ray crystallographic analysis indicates that *trans*-**2e** adopts a skew-boat conformation with both the methyl and vinyl groups quasi-diaxial.

The authors acknowledge partial financial support from the Ministry of Education, the Japanese Government, and the CIBA-GEIGY Foundation and generous gift of trichloromethyl chloroformate from Hodogaya Chemical CO.

Received, 9th July 1992; Com. 2/03648G

‡ The ratio of *trans*-**2e** to *cis*-**2e** (7.3 : 1, run 11, Table 1) changed to 3.3 : 1 after a longer reaction at a higher temperature (60 °C for 24 h). *trans*-**2d** was immune to isomerization under similar conditions.

References

1 (a) S.-E. Yoo, S.-H. Lee, K.-Y. Yi and N. Jeong, *Tetrahedron Lett.*, 1990, **31**, 6877; (b) M. P. Sibi and P. A. Renhowe, *Tetrahedron Lett.*, 1990, **31**, 7407; (c) N. K. Nayyar, M. M. Reddy and J. Iqubal, *Tetrahedron Lett.*, 1991, **32**, 6965; (d) Y. Leblanc, R. Zamboni and M. A. Bernstein, *J. Org. Chem.*, 1991, **56**, 1971.

2 F. M. Hauser and S. R. Ellenberger, *Chem. Rev.*, 1986, **86**, 35.

3 (a) Y-F. Wang, T. Izawa, S. Kobayashi and M. Ohno, *J. Am. Chem. Soc.*, 1982, **104**, 6465; (b) H. Iida, K. Kasahara and C. Kibayashi, *J. Am. Chem. Soc.*, 1986, **108**, 4647.

4 (a) S. D. Kahn and W. J. Hehre, *Tetrahedron Lett.*, 1985, **26**, 3647; (b) S. D. Kahn, C. F. Pau and W. J. Hehre, *J. Am. Chem. Soc.*, 1986, **108**, 7396; (c) S. D. Kahn, C. F. Pau, A. R. Chamberlin and W. J. Hehre, *J. Am. Chem. Soc.*, 1987, **109**, 650.

5 T. Bando, S. Tanaka, K. Fugami, Z. Yoshida and Y. Tamaru, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 97.

6 Pd(0)-catalysed preparation of 2-amino-3-buten-1-ols *via* vinyl epoxide: (a) B. M. Trost and A. R. Sudhakar, *J. Am. Chem. Soc.*, 1987, **109**, 3792; (b) 1988, **110**, 7933. (c) B. M. Trost and D. L. Van Vranken, *J. Am. Chem. Soc.*, 1990, **112**, 1261, also, see: (d) T. Hayashi, A. Yamamoto and Y. Ito, *Tetrahedron Lett.*, 1988, **29**, 99; (e) M. Kimura, K. Fugami, S. Tanaka and Y. Tamaru, *Tetrahedron Lett.*, 1991, **32**, 6359.

7 J. Tsuji, *Tetrahedron*, 1986, **42**, 4361.