Novel Substituent and Chelating Effects in the Pd-Catalyzed Reaction of 2,3-Allenols, Aryl Iodides, and Amines. Highly Regio- and Stereoselective Synthesis of 2-Amino-3-alken-1-ols or 4-Amino-2(*E*)-alken-1-ols

Shengming Ma* and Shimin Zhao

State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences, 354 Fenglin Lu
Shanghai 200032, P. R. China

Received October 2, 2000

Control of regio- and stereoselectivity is a formidable challenge in organic synthesis. Although the nucleophilic substitution reaction of π-allylmetal species has become one of the most important reactions in organic synthesis, the control of regio- and stereoselectivity is still of current interest.[1] In this paper, we report the first example of unusual regioselectivity controlability of the substituent at the 1-position of 2,3-allenols in π-allylmetal chemistry, the effects controlling the diastereoselectivity, and the application in the synthesis of highly optically active amino alcohols,[2] an important class of compounds which have huge impact on organic synthesis,[2] especially as key intermediates for the synthesis of targets with pharmaceutical importance[3] and chiral auxiliaries[4]/ligands[5] in asymmetric synthesis.

The combination of an allene moiety[6] and a functional group in the same molecule provides many opportunities for the synthesis of both carbocycles and heterocycles.[7,8] In the case of 2,3-allenols, the hydroxyl group can be considered as a chelating group; with the addition of external nucleophiles such as amines, amino alcohols with special structural features can be synthesized conveniently providing that the following two formidable challenges can be tackled: (1) the control of regioselectivity of nucleophilic substitution reaction[9] in the presence of both the chelating hydroxyl group and the substitutent at the 1-position of 2,3-allenols and (2) the control of stereoselectivity in an *acyclic* environment (Scheme 1).

Scheme 1

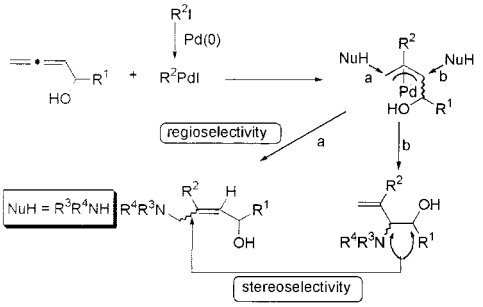
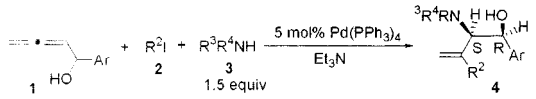


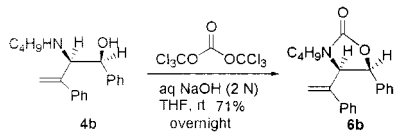
Table 1. Pd(0)-Catalyzed Reaction of 1-Aryl-2,3-allenols and Aryl Iodides[a]



entry	**1** Ar	**2** R^2	**3**	temp (°C)	time (h)	yield of **4** (%)
1	Ph (**1a**)	Ph	Et_2NH[a]	reflux	50	82 (**4a**)
2	Ph (**1a**)	Ph	Et_2NH[b]	reflux	46	79 (**4a**)
3	Ph (**1a**)	Ph	*n*-$BuNH_2$[c]	77	47	66 (**4b**)
4	Ph (**1a**)	Ph	*n*-$BuNH_2$	77	46	78 (**4b**)
5	Ph (**1a**)	Ph	$BnNH_2$	70	72	63 (**4c**)
6	Ph (**1a**)	*p*-Me-C_6H_4	$BnNH_2$	70	72	67 (**4d**)
7	Ph (**1a**)	*p*-Me-C_6H_4	*n*-$BuNH_2$	70	72	44 (**4e**)
8	*p*-MeO−C_6H_4 (**1b**)	Ph	*n*-$BuNH_2$	75	69	53 (**4f**)
9	*o*-CF_3−C_6H_4 (**1c**)	Ph	*n*-$BuNH_2$	75	66	85 (**4g**)

[a] Instead of Et_3N, Et_2NH was also used as the solvent. [b] 2 equiv of Et_2NH was used. [c] 11 equiv was used.

After some trial and error, it was observed that the $Pd(PPh_3)_4$-catalyzed reaction of 1-phenyl-2,3-butadienol (**1a**) and PhI in Et_2-NH under reflux for 48 h afforded 2-(*N*,*N*-diethylamino)-1,3-diphenyl-3-butenol (**4a**) in 82% yield (entry 1, Table 1). The reaction can also be carried out with Et_2NH (2.0 equiv) using Et_3N as the solvent to afford **4a** in 79% yield (entry 2, Table 1). Similar reaction with primary amines, i.e., *n*-butylamine and benzylamine, afforded **4b** and **4c** in 78% and 63% yields, respectively (entries 4 and 5, Table 1). The relative configurations of the two chiral centers in **4** were determined by converting **4b** to **6b** with triphosgene (eq 1). The NOE experiment of **6b** revealed



(1)

that the relative configuration in **4b** is (1R*,2S*). The ^1H NMR spectra of the crude reaction mixture indicated that both the regio-[10,11] and stereoselectivity are extremely high, i.e., only **4b** was formed.

(1) (a) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1998**, *96*, 395. (b) Trost, B. M. *J. Organomet. Chem.* **1986**, *300*, 263. (c) For a review on the selectivity in metal-catalyzed allylic substitution, see: Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089.

(2) Amino alcohols are usually prepared via the reduction of amino acids; for a typical example, see: McKennon, M. J.; Meyer, A. I.; Drautz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568. For the importance of amino alcohols, see the references therein.

(3) Zhao, S.; Freeman, J. P.; Bacon, C. L.; Fox, G. B.; O'Driscoll, E.; Foley, A. G.; Kelly, J.; Farrell, U.; Regan, C.; Mizsak, S. A.; Szmuszkovicz, J. *Bioorg. Med. Chem.* **1999**, *7*, 1647. Lucas, R.; Ubeda, A.; Paya, M.; Alves, M.; Olmo, E.; Lopez, J. L.; Feliciano, A. S. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 285; *Chem. Abstr*. **1999**, *130*, 119589s. Inokuchi, K.; Jinbo, M.; Yamana, H.; Yamakishi, M.; Nojiri, H. Japanese Kokai Tokkyo Koho Jp 10,338,636; *Chem. Abstr*. **1997**, *126*, 263856m. Fransesco, D. V.; Silvana, L.; Gabriele, M. US Patent US 5,618,842.

(4) For the use of 1,2-amino alcohols as chiral auxiliaries in asymmetric synthesis, see: Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.

(5) For reviews, see: Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. Bolm, C. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 542.

(6) Landor, S. R. *The Chemistry of the Allenes*; Academic Press: New York, 1982; Vol. 3, pp 587−590. Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; John Wiley & Sons: New York, 1988. *The Chemistry of Ketenes, Allenes, and Related Compounds*, Part 1; Patai, S., Ed.; John Wiley & Sons: New York, 1980.

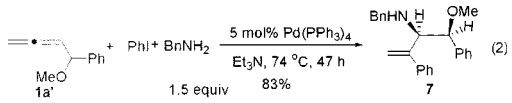
(7) For the synthesis of carbocycles, see: Ahmar, M.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1985**, *26*, 3795. Ahmar, M.; Cazes, B.; Gore, J. *Tetrahedron* **1987**, *43*, 3453. Besson, L.; Bazin, J.; Gore, J.; Cazes. B. *Tetrahedron Lett.* **1994**, *35*, 2881. Gamez, P.; Ariente, C.; Gore, J.; Cazes, B. *Tetrahedron* **1998**, *54*, 14835. Ma, S.; Zhao, S. *Org. Lett*. **2000**, *2*. 2495.

(8) For the synthesis of heterocycles, see: Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1997**, *62*, 367. Marshall, J. A.; Bartley, G. S.; Wallace, E. M. *J. Org. Chem.* **1996**, *61*, 5729. Walkup, R. D.; Guan, L.; Mosher, M. D.; Kim, S. W.; Kim, Y. S. *Synlett* **1993**, 88. Hashmi, A. S. K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1581−1583. Walkup, R. D.; Guan, L.; Kim, Y. S.; Kim, S. W. *Tetrahedron Lett*. **1995**, *36*, 3805. Ma, S.; Shi, Z. *J. Org. Chem.* **1998**, *63*, 6387−6389. Ohno, H.; Toda, Y.; Miwa, Y.; Taga, T.; Osawa, E.; Yamaoka, Y.; Fujii, N.; Ibuka, T. *J. Org. Chem.* **1999**, *64*, 2992. Ma, S.; Duan, D.; Shi, Z. *Org. Lett.* **2000**, *2*, 1419. Ma, S.; Wu, S. *J. Org. Chem.* **1999**, *64*, 9314. Ma, S.; Zhang, J. *Chem. Commun.* **2000**, 117−118. Ma, S.; Li, L. *Org. Lett.* **2000**, *2*, 941. Ma, S.; Shi, Z.; Yu, Z. *Tetrahedron Lett.* **1999**, *40*, 2393. Ma, S.; Shi, Z.; Yu, Z. *Tetrahedron* **1999**, *55*, 12137. Ma, S.; Zhao, S. *J. Am. Chem. Soc.* **1999**, *121*, 7943.

(9) For the reaction of π-allyl palladium with amines, see: Blart, E.; Gent, J. P.; Safi, M.; Savignac, M.; Sinou, D. *Tetrahedron* **1994**, *50*, 505. For a review, see: Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689.

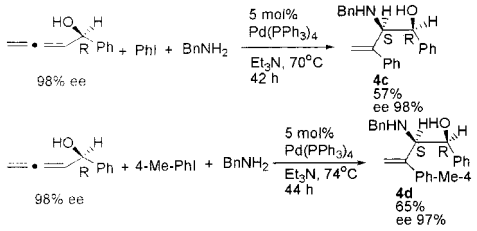
10.1021/ja0035553 CCC: $20.00
Published on Web 05/19/2001

Even the corresponding reaction of 1-phenyl-2,3-propadienyl methyl ether **1a′**, which can be viewed as the hydroxy group in **1a** was protected as the methoxy group, with PhI and $BnNH_2$ still afforded the corresponding α-aminomethoxide **7** highly regio- and stereoselectively (eq 2).



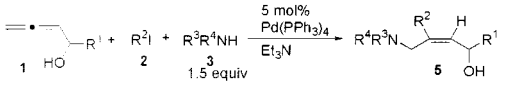
With this protocol in hand, optically enriched 2-amino alcohols **4c** and **4d**[12] were synthesized by starting from (*R*)-1-phenyl-2,3-butadienol (98% ee) (Scheme 2).[13,14]

Scheme 2



Furthermore, it is interesting to observe that when the phenyl group was replaced with the *n*-butyl group, 4-amino-2(*E*)-alken-1-ol **5b** was obtained, indicating a completely different regioselectivity[11] and high stereoselectivity[15] (entry 1, Table 2). This

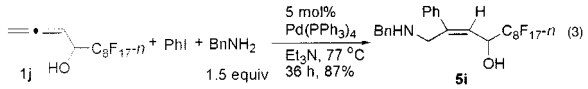
Table 2. Pd(0)-Catalyzed Reaction of 1-Alkyl or Alkenyl-2,3-allenols and Aryl Iodides



entry	**1** R^1	**2** R^2	**3**	temp (°C)	time (h)	yield of **5** (%)
1	*n*-C_4H_9 (**1e**)	Ph	$BnNH_2$	77	45	92 (**5b**)
2	*n*-C_8H_{17} (**1f**)	Ph	$BnNH_2$	70	72	72 (**5c**)
3	*n*-C_8H_{17} (**1f**)	Ph	*n*-$BuNH_2$	70	72	57 (**5d**)
4	*n*-C_8H_{17} (**1f**)	*p*-Me-C_6H_4	$BnNH_2$	70	72	78 (**5e**)
5	cyclohexyl (**1g**)	Ph	$BnNH_2$	74	47	45 (**5f**)
6	*E*−1-propenyl (**1h**)	Ph	$BnNH_2$	75	67	58 (**5g**)

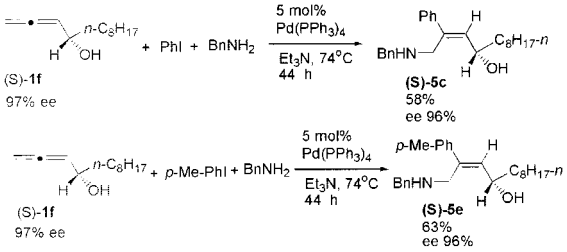
regioselectivity seems applicable to 1-primary alkyl (entries 1−4, Table 2)-, 1-secondary alkyl (entry 5, Table 2), and 1-alkenyl (entry 6, Table 2)-substituted 2,3-allenols. Both 1-alkenyl iodides (entry 3, Table 2) and differently substituted aryl iodides (entries 1−2 and 4−6, Table 2) can be used.

The corresponding reaction of **1j**, which can be viewed as the C_8H_{17} group in **1f** being replaced by an electron-withdrawing perfluoroalkyl C_8F_{17} group, with PhI and $BnNH_2$ afforded γ-amino alcohol **5i** with the same regioselectivity in 87% yield, indicating that the switch of the electronic property of the α-substituent does not change the regiochemical outcome (eq 3).



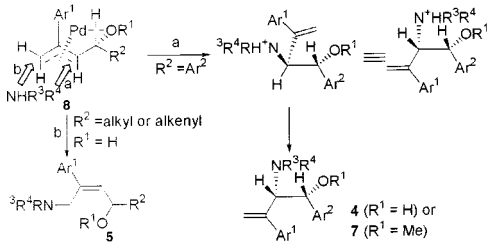
The synthetic potentials were demonstrated by the efficient preparation of the optically enriched 4-amino-2(*E*)-alken-1-ols (S)-**5c** and (S)-**5e** from (S)-1,2-dodecadien-3-ol[14,16] without obvious loss of enantiopurities (Scheme 3).

Scheme 3



A rational was provided based on a combination of steric effect and stereoelectronic effect (Scheme 4). In the most favored

Scheme 4



π-allylpalladium intermediate **8**, when R^2 = aryl, Ar^2 should be in a position remote from Ar^1 as shown in Scheme 4 to avoid the steric repulsion of two aryl groups. An amine attacks the π-allylpalladium moiety of **8** from the front side, and the α-selectivity may be caused by the electronic stabilization of the positively charged ammonium intermediate by the delocalized π-orbits of the aryl groups,[17] when R^2 = alkyl or 1-alkenyl, the γ-selectivity was determined by the steric effect of the α-substituent.

In conclusion, we have observed the unique regioselectivity controlability of the 1-substituent in 2,3-dienols. The regio- and diastereoselectivities are rationalized in terms of steric and stereoelectronic effects. Although the mechanism for the novel regioselectivity is not very clear yet at the present stage, this reaction provides efficient entries to 2- or 4-amino alkenols with high regio- and stereoselectivity. With the ready availiblity of different types of nucleophiles, this observation opens up a new area for the highly regio- and stereoselective synthesis of functionalized alkenols. Further studies on the scope of this reaction and the factors controlling the selectivity are being carried out in our laboratory.

Acknowledgment. Financial support from Chinese Academy of Sciences and the Major State Basic Research Development Program (Grant No. G2000077500) is greatly appreciated. Shengming Ma is the recipient of the 1999 Qiu Shi Award for Young Scientific Workers issued by Hong Kong Qiu Shi Foundation of Science and Technology (1999-2002) and the Special Grant for Outstanding Young Chemists issued by Shanghai Municipal Committee of Science and Technology (00XD14028).

Supporting Information Available: Typical experimental procedure and analytical data for all the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0035553

(10) For the reaction of vinylic oxiranes with phthalimide with a 16:1 1,2-/1,4-selectivity, see: Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am Chem. Soc.* **2000**, *122*, 5968. The corresponding reactions with other nucleophiles occurred in a 1,4-manner, see ref 1b.

(11) For Ru-catalyzed reaction of vinyl oxiranes with amines, see: Fagnou, K.; Lautens, M. *Org. Lett.* **2000**, *2*, 2319. Here with *alkyl groups* the reaction afforded *1,2-amino alcohols*.

(12) Percent ee was determined by HPLC with a CHIRALPAK OD or AS column (ϕ 0.46 cm × 25 cm from Daicel Chemical Ind., Ltd.). The ee values of both the crude and the purified **4c** were kept constant.

(13) Aoyagi, S.; Wang, T. C.; Kibayashi, C. *J. Am. Chem. Soc.* **1993**, *115*, 11393.

(14) Crabbé, P.; Fillion, H.; André, D.; Luche, J.-L. *J. Chem. Soc., Chem. Commun.* **1979**, 859. Crabbé, P.; Nassim, B.; Robert-Lopes, M.-T. *Org. Synth.* **1985**, *63*, 203.

(15) The configuration of the C=C double bonds in **5** was determined by the NOE experiment of **5b**.

(16) Nishizawa, M.; Yamada, M.; Noyori, R. *Tetrahedron Lett.* **1981**, *22*, 247.

(17) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983. We thank one of the referees for his constructive suggestion of stereoelectronic effect.