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Stereoselective Synthesis of 1,4-Bifunctional Compounds by Regioselective Pd-Catalyzed Allylic Substitution Reaction

Naoyoshi Maezaki, Yuki Hirose, and Tetsuaki Tanaka*

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565-0871, Japan

t-tanaka@phs.osaka-u.ac.jp

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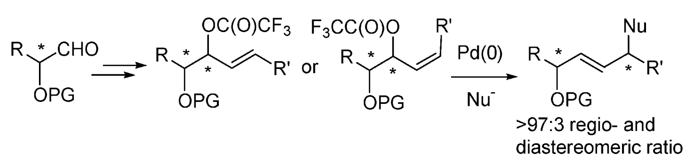
ABSTRACT



Highly stereoselective synthesis of 1,4-bifunctional compounds was accomplished via 1,2-asymmetric induction to α-oxyaldehyde followed by regio- and diastereoselective Pd-catalyzed allylic substitution reaction.

Palladium-catalyzed 1,3-chirality transfer of readily available chiral 1,2-diol derivatives is a fascinating strategy for synthesizing olefins flanking two stereogenic centers, which are synthetically useful chiral building blocks.[1] Two methods have been developed so far: Pd-catalyzed allylic substitution reactions of cyclic carbonates[2] and 1,3-diene monoepoxides.[3]

(1) For application of olefins flanking two stereogenic centers to a synthesis of natural products, see: Block, O.; Klein, G.; Altenbach, H.-J.; Brauer, D. J. *J. Org. Chem.* **2000**, *65*, 716−721. Carretero, J. C.; Arrayas, R. G. *J. Org. Chem.* **1998**, *63*, 2993−3005. Rigby, J. H.; Mateo, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 12655−12656. Hudlicky, T.; Olivo, H. F. *J. Am. Chem. Soc.* **1992**, *114*, 9694−9696. Takeda, K.; Kaji, E.; Konda, Y.; Sato, N.; Nakamura, H.; Miya, N.; Morizane, A.; Yanagisawa, Y.; Akiyama, A.; Zen, S.; Harigaya, Y. *Tetrahedron Lett.* **1992**, *33*, 7145−7148. Bäeckvall, J.-E.; Schink, H. E.; Renko, Z. D. *J. Org. Chem.* **1990**, *55*, 826−831.

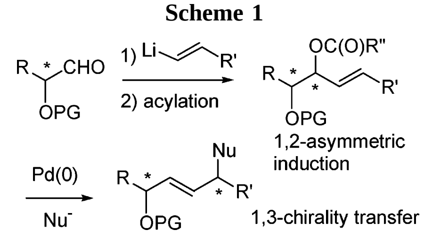
(2) (a) Kang, S.-K.; Kim, S.-G.; Lee, J.-S. *Tetrahedron: Asymmetry* **1992**, *3*, 1139−1140. (b) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385−393.

(3) Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett.* **1981**, *22*, 2575−2578.

(4) For selected recent reviews for Pd-catalyzed allylic substitutions, see: Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921−2943. Kazmaier, U. *Curr. Org. Chem.* **2003**, *7*, 317−328. Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1−14; van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741−2769. Moberg, C.; Bremberg, U.; Hallman, K.; Svensson, M.; Norrby, P.-O.; Hallberg, A.; Larhed, M.; Csöregh, I. *Pure Appl. Chem.* **1999**, *71*, 1477−1483. Poli, G.; Scolastico, C. *Chemtracts* **1999**, *12*, 822−836. Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422. Reiser, O. *Angew. Chem.* **1993**, *105*, 576−578. Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857−871. See also ref 2b.

We planned an asymmetric synthesis of 1,4-bifunctional alkenes via diastereoselective alkenylation of α-hydroxy aldehydes followed by Pd-catalyzed allylic substitution[4] as shown in Scheme 1. The stereogenic center at the protected

Scheme 1



chiral secondary alcohol not only works as a stereocontroller in the first step but also controls the regiochemistry in the diastereoselective Pd-catalyzed allylic substitution reaction. The whole transformation is formally equivalent to 1,4-asymmetric induction. The method has some advantages: (1) a variety of substrates for the allylic substitution reaction can be readily synthesized from chiral α-oxyaldehydes and vinylic anions; (2) the protecting group (PG) is adjustable so as to control the regiochemistry efficiently in the allylic

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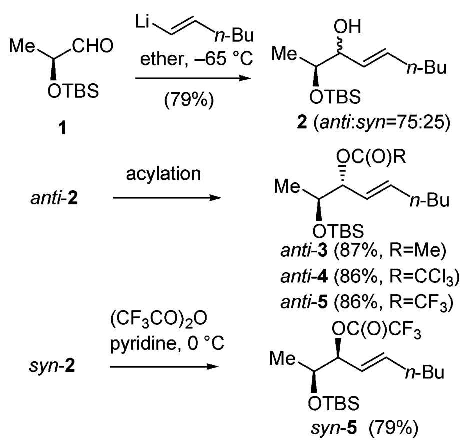
substitution reaction; and (3) the reactivity of the leaving group can also be tuned depending on the reactivity of the nucleophiles, in contrast to the previous methods. Clayden and co-workers reported the Pd-catalyzed rearrangement of allylic esters controlled by a dibenzylamino group.[5] However, the regioselectivity depends on the acyl groups and is not sufficiently high.

Herein, we describe a novel method for synthesizing chiral 1,4-bifunctional compounds using regio- and diastereoselective Pd-catalyzed allylic substitution reactions.

The allylic alcohol **2** was prepared by alkenylation of (*S*)-2-(*tert*-butyldimethylsilyloxy)propanal (**1**)[6] with (*E*)-1-hexenyllithium generated in situ by iodine−lithium exchange reaction from (*E*)-1-iodohexene[7] (Scheme 2).

Scheme 2



The reaction proceeded under Felkin−Anh control, giving the adduct *anti*-**2** as a major product in a ratio of 75:25.[8] With the two diastereomeric isomers in hand, the 1,3-asymmetric transfer reaction was examined. The *anti*-adduct **2** was converted into acetate *anti*-**3** (87%, Ac_2O, pyridine, DMAP), trichloroacetate *anti*-**4** (86%, Cl_3CCOCl, pyridine), and trifluoroacetate *anti*-**5** (86%, $(CF_3CO)_2O$, pyridine). The adduct *syn*-**2** was also converted into the trifluoroacetate *syn*-**5** in 79% yield.

Scheme 3 and Table 1 show the Pd-catalyzed allylic substitution reaction of allylic acylates *anti*-**3**−**5** with dimethyl sodiomalonate. The reactions of *anti*-**3**−**5** with 3

Scheme 3

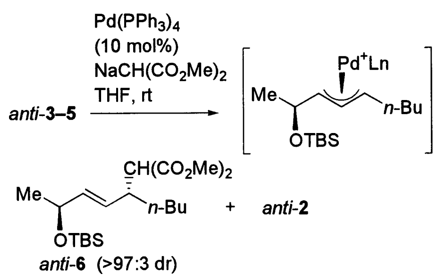


Table 1. Effect of Leaving Group and Amount of Nucleophile[a]

entry	acylates	R	Nu (equiv)	conditions	yield (%)[b] *anti*-**6**	yield (%)[b] *anti*-**2**
1	*anti*-**3**	Me	3	reflux, 5 h	0	0
2	*anti*-**4**	CCl_3	3	reflux, 2 h	32	5
3	*anti*-**5**	CF_3	3	rt, 0.5 h	74	23
4	*anti*-**5**	CF_3	2	rt, 0.5 h	93	trace
5	*anti*-**5**	CF_3	1.5	rt, 5 h	72	14
6[c]	*anti*-**5**	CF_3	3	rt to reflux, 6 h	0	78

[a] Reactions were carried out using $Pd(PPh_3)_4$ (10 mol %) in THF under Ar. [b] Isolated yield. [c] Without Pd catalyst.

equiv of dimethyl sodiomalonate exhibited a sharp contrast to each other (entries 1−3).

Use of the allylic acetate *anti*-**3** resulted in recovery of the starting material even under refluxing conditions (entry 1). The corresponding allylic trichloroacetate *anti*-**4** furnished the products *anti*-**6** in refluxing THF, but the yield was poor (32%). Nucleophilic attack to the ester moiety afforded 5% yield of the alcohol *anti*-**2** (entry 2). We found that the use of the most reactive trifluoroacetate *anti*-**5** afforded better results than the acetate and the trichloroacetate,[9] but a considerable amount of *anti*-**2** (23%) was formed (entry 3). The problem was overcome by using 2 equiv of dimethyl sodiomalonate (entry 4). The reaction proceeded quickly even at room temperature in an excellent yield. However, when 1.5 equiv of nucleophile was used, the reaction time was prolonged and the yield of *anti*-**6** was reduced (entry 5). It is noteworthy that nucleophilic attack took place exclusively at the position distal to the TBSO group with retention of the stereochemistry via double stereoinversion, giving 1,4-anti adduct as the sole product.[10] S_N2'-type reaction in the absence of Pd-catalyst did not occur; instead, nucleophilic attack took place at the ester moiety (entry 6).

Subsequently, 1,3-chirality transfer of *anti*- and *syn*-**5** was investigated using the optimized conditions (Scheme 4).

Scheme 4

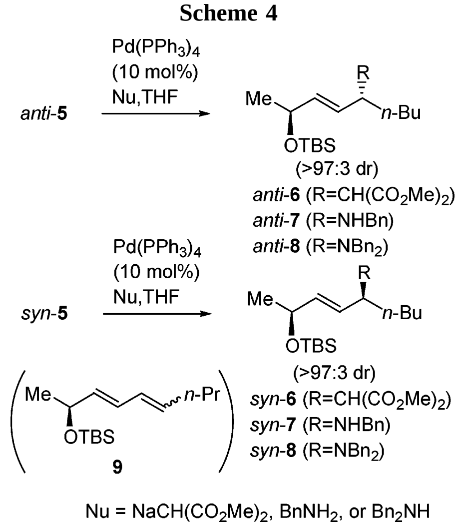


Table 2. Allylic Substitution of *anti*- and *syn*-**5** with Nucleophiles[a]

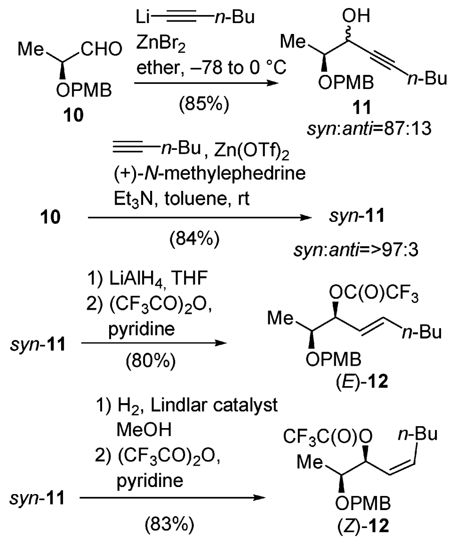
entry	product	R	conditions	yield[b] (%)
1	*anti*-**6**	$CH(CO_2Me)_2$	rt, 30 min	93 (tr)[c]
2	*anti*-**7**	BnNH	rt, 30 min	83 (10)[c]
3	*anti*-**8**	Bn_2N	reflux, 23 h	34 (45)[d]
4	*syn*-**6**	$CH(CO_2Me)_2$	rt, 30 min	98 (tr)[c]
5	*syn*-**7**	BnNH	rt, 30 min	84 (15)
6	*syn*-**8**	Bn_2N	reflux, 3 h	46 (23)[d]

[a] Reactions were carried out using *anti*-**5** (1.0 equiv), nucleophile (2 equiv), and $Pd(PPh_3)_4$ (10 mol %) in THF under Ar. [b] Isolated yield. [c] Yield in parentheses is the yield of compound **2**. [d] Yield in parentheses is the yield of compound **9**.

The results are summarized in Table 2. Benzylamine also exclusively attacked distal to the TBSO group at room temperature, giving 1,4-anti isomer *anti*-**7** (entry 2). The reaction was stereospecific, and no 1,4-syn isomer was obtained. The regiochemistry was controlled completely.[11] In the case of bulky dibenzylamine, the reaction became sluggish and no allylic substitution reaction product was produced at room temperature. When the reaction mixture was refluxed, the material disappeared, giving the adduct *anti*-**8** in 34% yield along with 45% yield of diene **9** (ca. 2.7:1 *E*/*Z* mixture) probably formed by β-hydride elimination (entry 3).[12] The syn adduct *syn*-**5** also afforded the corresponding 1,4-*syn* compounds *syn*-**6** and *syn*-**7** in good yields with high regio- and diastereoselectivity (entries 4 and 5). Although the reaction of *syn*-**5** with dibenzylamine was sluggish as in the case of *anti*-**5**, the yield of the allylic substitution reaction was higher than that in the anti isomer (entry 6). Thus, two kinds of diastereomeric 1,4-bifunctional compounds were synthesized in an enantiomerically pure form.

Next, we examined the stereodivergent synthesis of 1,4-bifunctional compounds starting from a common α-oxyaldehyde **10** by a series of reactions: (1) diastereoselective alkynylation, (2) stereoselective reduction of alkyne, and (3) 1,3-chirality transfer of (*E*)- and (*Z*)-allylic alcohols (Scheme 5), wherein we selected a PMB (*p*-methoxybenzyl) protecting group as a regio- and stereocontroller.

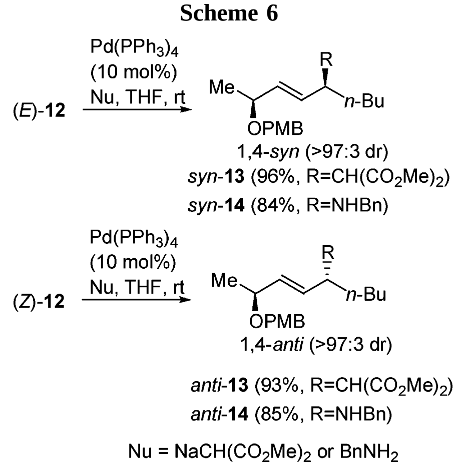
Scheme 5



(*S*)-2-(*p*-Methoxybenzyloxy)propanal (**10**)[13] was reacted with the lithium acetylide of 1-hexyne in the presence of $ZnBr_2$ in ether[14] to give the syn adduct *syn*-**11** mainly in a ratio of 87:13. The diastereoselectivity was further improved by employing Carreira's conditions.[15] The adduct *syn*-**11** was obtained in 84% yield as the sole product. Then, *syn*-**11** was reduced selectively to (*E*)-allylic alcohol (*E*)-**12** with $LiAlH_4$ in THF, and subsequent trifluoroacetylation with $(CF_3CO)_2O$ in pyridine afforded trifluoroacetate (*E*)-**12** in 80% yield in two steps.

The corresponding (*Z*)-isomer (*Z*)-**12** was synthesized via hydrogenation of *syn*-**11** with Lindlar catalyst in MeOH followed by trifluoroacetylation, giving (*Z*)-**12** in 83% in two steps.

Scheme 6



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(8) Optical purity of *anti*-**2** was confirmed by ^1H NMR spectral data after conversion into the MTPA ester. The relative configurations of *anti*- and *syn*-**2** were assigned by comparison with the reported ^1H NMR spectral data of a related compound. The assignment was confirmed by applying a modified Mosher method to *anti*-**2**. For data of the related compound, see: Kiguchi, T.; Shirakawa, M.; Honda, R.; Ninomiya, I.; Naito, T. *Tetrahedron* **1998**, *54*, 15589−15606. For the modified Mosher method, see: Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

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(10) Absolute configuration of *anti*-**6** was confirmed by comparison of the specific rotation with that reported after conversion into known (*S*)-4-butyldihydrofuran-2-one by subsequent reactions: (1) ozonolysis of the double bond followed by $NaBH_4$ reduction of the resulting aldehyde, (2) demethoxycarbonylation of the α-methoxycarbonyl γ-lactone with NaCl in aqueous DMSO. $[\alpha]^{24}_D$ −5.72 (*c* 0.25, $CHCl_3$). lit. $[\alpha]^{20}_D$ −6.00 (*c* 0.32, $CHCl_3$). For the specific rotation of (*S*)-4-butyldihydrofuran-2-one, see: Kosugi, H.; Tagami, K.; Takahashi, A.; Kanna, H.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 935−943.

(11) Absolute configuration of the amine *anti*-**7** was determined by a modified Mosher method; see: Kusumi, T.; Fukushima, T.; Ohtani, I.; Kakisawa, H. *Tetrahedron Lett.* **1991**, *32*, 2939−2942.

Conversion of these geometric isomers into the diastereomeric isomers of 1,4-bifunctional compounds was conducted by using 10 mol % $Pd(PPh_3)_4$ in THF at room temperature (Scheme 6). Thus, the geometric isomer (*E*)-**12** underwent regioselective substitution in good yield with high diastereoselectivity, giving the adducts *syn*-**13** and *syn*-**14** in 96 and 84% yields, respectively. On the other hand, the geometric isomer (*Z*)-**12** was converted into the (*E*)-isomers via $\pi-\sigma-\pi$ isomerization[16] to give *anti*-**13** and *anti*-**14** in 93 and 85% yields, respectively. Despite the comparatively small steric demand, the PMB-protected hydroxy group controlled the regiochemistry causing exclusive nucleophilic attack distal to the protected alcohol. Thus, two diastereoisomers were synthesized stereodivergently.[17]

In conclusion, we have developed a convenient method for synthesizing chiral 1,4-bifunctional compounds, which are synthetically useful. In principle, the method could be applied to other α-functionalized aldehydes and nucleophiles, giving a variety of 1,4-bifunctional compounds. Examination of other protecting groups and nucleophiles is now under way.

(12) Absolute configuration of *anti*-**8** was deduced by analogy to the reaction with benzylamine.

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(15) For the Carreira's asymmetric alkynylation, see: Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687−9688. Frants, D. E.; Fässler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373−381. Frants, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806−1807.

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Supporting Information Available: General procedures for Pd-catalyzed allylic substitution reaction and specific rotations of new chiral compounds and ^1H and ^{13}C NMR spectral data for *anti*- and *syn*-**6**−**8**, **13**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Absolute configuration of *anti*-**13** and *anti*-**14** was determined by conversion into *anti*-**6** and *anti*-**7**, respectively by deprotection of PMB ether followed by TBS protection.