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Chiral Dienolate-Based Remote Asymmetric Induction: The Asymmetric α-Oxylation/Pd(0)-Catalyzed Allylic Substitution Sequence Leading to γ-Chiral α,β-Unsaturated Acid Derivatives

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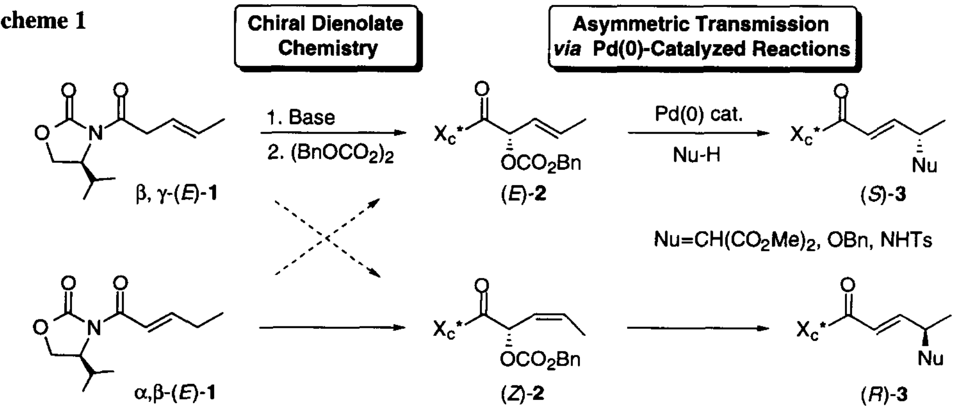
Abstract: *The asymmetric α-oxylation of the dienolates derived from chiral α,β- or β,γ-unsaturated imide with dibenzyl peroxydicarbonate followed by the Pd(0)-catalyzed reactions of the resulting allylic carbonate with various nucleophiles (alkylation, etherification, and amination) is shown to provide the γ-(S)- or -(R)-configurated α,β-unsaturated imide, respectively, with a high level of stereocontrol.*

The creation of a chiral center at a position remote from the chiral auxiliary is a challenging problem in organic synthesis.[1] Recently, we have described a general, efficient solution to this problem which relies upon a combination in tandem of the asymmetric induction *via* the allylation of chiral lithium dienolates or the aldol reaction of chiral boron dienolates with the asymmetric transmission *via* the [3,3]-sigmatropic rearrangements to afford the γ-chiral α,β-unsaturated acid derivatives in high enantiomeric purities.[2,3] As an extension of this strategy, we now disclose a new asymmetric induction/transmission sequence which involves the asymmetric α-oxylation of a chiral dienolate derived from β,γ-(*E*)- or α,β-(*E*)-**1** to afford the allylic carbonate (*E*)- or (*Z*)-**2** which is subjected to the Pd(0)-catalyzed allylic substitutions[4] to provide the γ-(*S*)- or -(*R*)-configurated α,β-unsaturated imide (**3**), respectively, in a highly stereocontrolled fashion (Scheme 1). In view of the ability to introduce various γ-substituents (Nu) and induce either configuration at the γ-position, the present synthetic sequence provides a unique, highly stereopredictable approach to remote asymmetric induction.

Scheme 1



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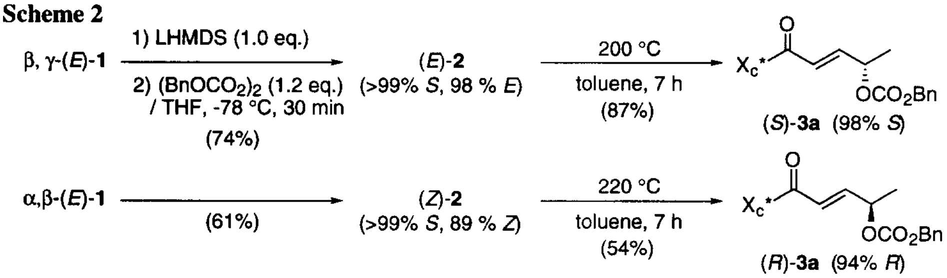
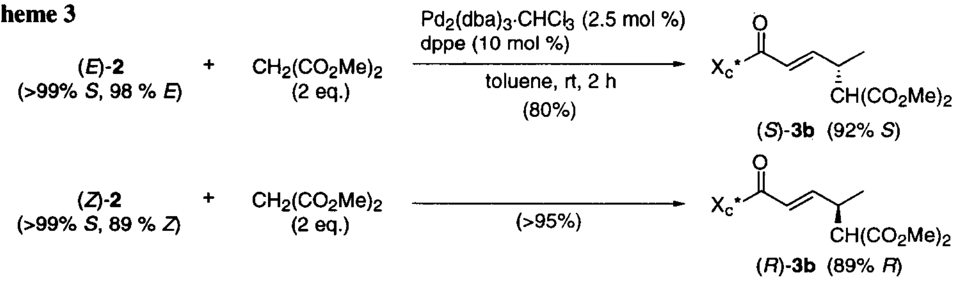
At the outset, the α-oxylation of the lithium dienolate of β,γ-(E)-**1** with dibenzyl peroxydicarbonate[5] was found to afford 74% yield of (*E*)-**2** in a high diastereofacial selectivity (>99% *S),* together with almost complete retention of the (*E*)-geometry (Scheme 2). By contrast, a similar reaction of α,β-(*E*)-**1** proceeded also with a high diastereofacial selectivity but together with changeover of the olefin geometry to provide (*Z*)-**2** in >99% *S* and 89% *Z*.[6] Recrystallization of (*Z*)-**2** from hexane was found to improve the stereopurity up to 95% *Z*. With the allylic carbonates **2** of high stereopurity in hand, we first studies their thermal [3,3]-sigmatropic rearrangements. Significantly enough, the thermolysis of (*E*)- and (*Z*)-**2** was found to proceed with a high level of asymmetric transmission to give the γ-chirally oxylated α,β-unsaturated imide (*S*)- and (*R*)-**3a**, respectively, in high stereospecificity[7] (Scheme 2).

Scheme 2



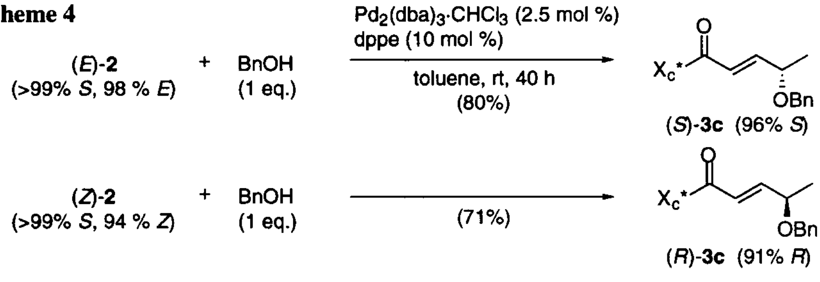
Next, our effort was directed toward the Pd(0)-catalyzed allylic substitution of (*E*)- and (*Z*)-**2** with various nucleophiles.[8] Firstly, the reaction of (*E*)-**2** with dimethyl malonate (2.0 equiv.) was carried out in toluene at room temperature using 5 mol% of $Pd(PPh_3)_4$. Rather surprisingly, the expected substitution product was formed in only 10% yield and, instead, the conjugated dienoic imide (β-elimination product) was obtained in 81% yield.[9] However, a similar use of 2.5 mol% of $Pd_2(dba)_3.CHCl_3$ with 10 mol% of $(Ph_2PCH_2)_2$ (dppe) afforded the γ-alkylated product (*S*)-**3b** in 80% yield and high enantiopurity (92% *S*) (Scheme 3).[10] In the same way, (*Z*)-**2** provided the epimer (*R*)-**3b** in >95% yield and 89% *R*.[11] It is worthwhile to note that the combined use of $Pd_2(dba)_3{\cdot}CHCl_3$-dppe as the catalyst and toluene as the solvent is indispensable to suppress the undesired β-elimination from the π-allyl Pd intermediate. Interestingly, the use of $Pd(PPh_3)_4$ or $Pd_2(dba)_3{\cdot}CHCl_3$-dppe in THF resulted in the exclusive and predominant formation of the β-elimination product, respectively. These observations suggest that, as Keinan *et al.* have claimed,[12] the dba ligand could effectively suppress the formation of the coordinatively unsaturated Pd intermediate which tends to undergo the β-elimination. As expected, a similar Pd-catalyzed reaction of (*S*)-**3a** afforded (*S*)-**3b** in an equally high yield and stereospecificity through the same chiral π-allyl Pd species as described for (*E*)-**2**.[13]

Scheme 3



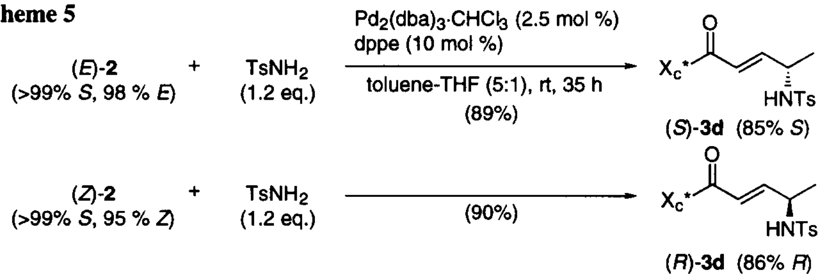
Secondly, the Pd-catalyzed allylic etherification of **2** was examined using the $Pd_2(dba)_3 \cdot CHCl_3$-dppe catalyst under the optimized conditions. Initially, the intramolecular way was attempted by simply exposing (*E*)-**2** to the catalyst solution. Unfortunately, the desired product (**3c**) was obtained in only 47% yield. However, the etherification of (*E*)- and (*Z*)-**2** in the presence of 1.0 equiv. of benzyl alcohol afforded the γ-benzyloxy-substituted compounds (*S*)- and (*R*)-**3c**, respectively, in good yields together with almost complete asymmetric transmission (Scheme 4).[14] Notably, no regiochemical complication was encountered in this substitution process.

Scheme 4



Finally, the Pd-catalyzed allylic amination of (*E*)- or (*Z*)-**2** with *p*-toluenesulfonamide was carried out using the $Pd_2(dba)_3 \cdot CHCl_3$-dppe catalyst under similar conditions. For these reactions a mixture of toluene and THF (5:1 vol) was used as the solvent to solubilize the sulfonamide. Thus, the reaction of (*E*)- and (*Z*)-**2** with $TsNH_2$ (1.2 equiv.) was found to afford the γ-amino-substituted compounds (*S*)- or (*R*)-**3d**, respectively, in good yields but with a slightly lower level of asymmetric transmission (Scheme 5).[15] Again, neither the α-substitution product nor the β-elimination product was detected.

Scheme 5



In summary, we have developed a new, efficient synthetic sequence to effect the net remote asymmetric induction which involves the asymmetric α-oxylation of the dienolates of α,β– or β,γ-(*E*)-imide **1** followed by the Pd(0)-catalyzed allylic substitutions, thereby permitting ready access to various types of the γ-chirally substituted α,β-unsaturated acid derivatives (**3**) of high enantiopurity in either enantiomeric form, which are useful for syntheses of natural products and bioactive molecules.[16] Work is underway to apply the present methodology in bioactive molecule synthesis and to further extend the present strategy.

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References and Notes

1. Recent review: Mikami, K.; Shimizu, M. *J. Synth. Org. Chem., Jpn.* **1993**, *51*, 21-29.
2. Tomooka, K.; Nagasawa, A.; Wei, S.-Y.; Nakai, T. *Tetrahedron Lett.* **1996**, *49*, 8895-8898.
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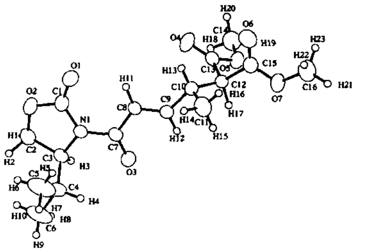
4. Recent reviews: (a) Tsuji, J. In *Palladium Reagents and Catalysts;* John Wiley & Sons: Chichester, 1995, pp290-406. (b) Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Eds.; Pergamon: Oxford, 1991; Vol. 4, Chapter 3.3, pp585-661. (c) Frost, C. G.; Howarch, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089-1122.
5. Gore, M. P.; Vederas, J. C. *J. Org. Chem.* **1986**, *51*, 3700-3704: They have reported α-oxylations of chiral enolates with Evans' chiral auxiliaries. However, their applications to the chiral dienolate, especially their *E*/*Z* control, remain largely unexplored.
6. A similar changeover has been observed in the asymmetric alkylation and aldol reaction of the chiral dienolates (ref 2, 3).
7. The diastereomeric ratios of **3a** were determined by the HPLC analyses on Chiralpax OD column. The absolute configuration of **3a** was determined after the conversion of (*S*)-**3a** to the known (*S*)-1,4-pentanediol via hydrogenation on PtO_2 followed by reduction $LiAlH_4$: Kitahara, T.; Mori, K. *Tetrahedron* **1984**, *40*, 2935-2938.
8. For a related approach to the net asymmetric induction by the Pd(0)-catalyzed allylic alkylation: Braun, M.; Opdenbush, K.; Unger, C. *Synlett* **1995**, 1174-1176.
9. The dienoic imide was assigned to have the (*E*)-geometry by ^{1}H NMR analysis. The concentration of a nucleophile (0.2 *M*) is also important to prevent the formation of this diene. Actually, the reaction of (*Z*)-**2** with dimethyl malonate (0.1 *M*) resulted in poor yield of (*R*)-**3b** (54%) with the diene (32%).
10. A representative procedure: To a solution of $Pd_2(dba)_3\cdot CHCl_3$ (2.5 mol%) and dppe (10 mol%) in toluene (0.5 m*L*) was added the solution of (*E*)-**2** (0.13 mmol) and dimethyl malonate (0.26 mmol) in toluene (0.5 m*L*). The reaction mixture was stirred at room temperature for 2 hr. Usual work up followed by silica gel chromatography gave (*S*)-**3b** in 83% yield (37 mg). The diastereomers of **3b** are distinguishable by ^{1}H NMR analysis: the δ value (ppm) of the β-vinylic proton, 7.08 (dd, *J* = 15.5, 7.5 Hz) for (*S*)-**3b** and 7.05 (dd, *J* = 15.6, 8.1 Hz) for (*R*)-**3b**. The diastereomeric ratios of **3b** were determined by the HPLC analyses on inertsil SIL 100-5 column. The absolute configuration of (*R*)-**3b** was assigned by the X-ray crystallography. The data will be described in the full paper.



11. The stereochemical outcome of the reaction of (*Z*)-**2** to (*R,E*)-**3** can be rationalized by assuming the well-established π–σ–π interconversion of the π-allyl palladium intermediate (ref 4).
12. Keinan, E.; Roth, Z. *Israel J. Chem.* **1990**, *30*, 305-313.
13. The reaction of (*S*)-**3a** (98% *S*) provided (*S*)-**3b** (96% *S*, 88% yield).
14. The diastereomeric ratios of **3c** were determined by the HPLC analyses on CHIRALPAK AD column. The absolute configuration of **3c** was determined by the same way as described in ref 7.
15. The diastereomeric ratios of **3d** were determined by the HPLC analyses on inertsil SIL 100-5 column. The absolute configuration of **3d** was determined by the comparison of the optical rotation of (*S*)-*N*-tosyl-2-amino-1-propanol derived by ozonolysis of (*S*)-**3d** and an authentic sample derived from (*S*)-alanine methyl ester hydrochloride via *N*-tosylation and $LiAlH_4$-reduction.
16. For examples, γ-hydroxy acid derivatives: a) Fischer, N. H.; Olivier, E. J.; Fischer, H. D. *Fortschr. Chem. Org. Naturst.*, **1979**, *38*, 47. b) Devon, T. K.; Scott, A. I. In Handbook of Naturally Occurring Compounds; Academic Press: New York, 1975, vol. 1.; γ-amino acid derivatives: c) Ikota, N. *Heterocycles* **1995**, *41*, 983-994; d) Wei, Z. Y.; Knaus, E. E. *Org. Prep. & Proc. Int.* **1994**, *26*, 243-248 and references cited therein.