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An efficient synthesis of optically active five- and six-membered cyclic compounds with selectable stereo-controls by a Ti(II)-mediated cyclization of chiral secondary 2,7- and 2,8-enyn-1-ol derivatives

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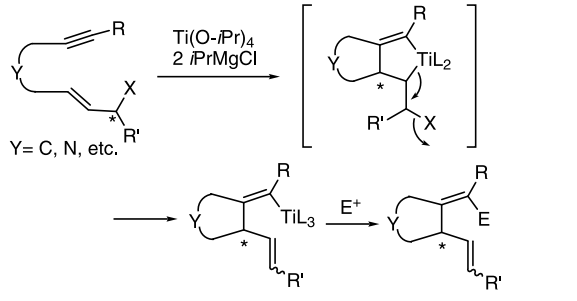
Abstract—Ti(II)-mediated cyclization of readily accessible optically active secondary 2,7- and 2,8-enyn-1-ol derivatives enables the selective preparation of any one of the four possible stereoisomers of the cyclized product with high optical purity.

Metal-mediated and -catalyzed cyclizations of bis-unsaturated compounds have recently attracted much interest as a versatile method for synthesizing cyclic compounds.[1] We have recently developed an efficient method for cyclization of 2,7- and 2,8-enynol derivatives mediated by a divalent titanium reagent, Ti(O-*i*Pr)$_4$/2*i*PrMgCl (**1**), which proceeds through formation of a titanacyclic intermediate and the following β-elimination reaction to provide carbo- and hetero-cyclic compounds as shown in Scheme 1.[2,3] Since such compounds having both a versatile exocyclic vinyl and an alkenyl moieties might serve as useful intermediates for preparing biologically active natural and artificial compounds,[4] we expected to carry out the reaction in an asymmetric way starting from optically active secondary enynol derivatives. We anticipated that the stereochemistry of the reaction could be controlled by choosing a proper leaving group and/or the olefinic geometry of the substrate, thus enabling the preparation of four possible stereoisomers of the cyclized product.

We first carried out the **1**-mediated reaction of (*E*)-(*S*)-*N*-benzyl-7-azadec-4-en-9-yn-3-ol derivatives **2** with 98.4% enantiomeric excess (ee) having a variety of leaving groups (X), the results of which are summarized in Scheme 2. All of the substrates were cyclized smoothly in high yields to afford, after hydrolysis, pyrrolidine **3** with *S* absolute configuration (vide infra) as the major stereoisomer, irrespective of the leaving group. However, the degree of chirality transfer and the olefinic geometry of the but-1-enyl side-chain in the product **3** were highly dependent on the leaving group X, and, to our satisfaction, selective preparation of **3** having either an (*E*)- or a (*Z*)-but-1-enyl substituent [(*S*)-(*E*)- or (*S*)-(*Z*)-**3**] with high optical purity could be attained by choosing a dimethylphosphoryloxy or a *tert*-butyldiphenylsilyloxy group as the leaving group, respectively. Thus, the reaction of dimethylphosphate **2** [X = OP(O)(OMe)$_2$] with **1** afforded (*S*)-(*E*)-**3** with 97:3



Scheme 1. Ti(II)-mediated cyclization of 2,7- and 2,8-enyn-1-ol derivatives.

Keywords: cyclization; titanium; chirality transfer; leaving group; olefinic geometry.

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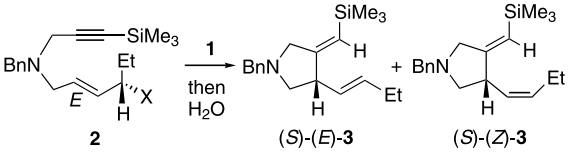
E-selectivity in respect of the but-1-enyl moiety and with 91.2% ee,[5] indicating that the degree of chirality transfer based on the ee of **2** is 93%. Meanwhile, the reaction of **2** having a *t*-$BuPh_2SiO$ group as the leaving group proceeded with almost complete *Z*-selectivity (99%) and chirality transfer (>98%) to afford (*S*)-(*Z*)-**3**[5] in excellent yield.

Although Scheme 2 summarizes the hydrolysis outcome after Ti(II)-mediated cyclization, as the reaction products contain a titanium–carbon bond, they could be further manipulated by treatment with other electrophiles, as shown in Scheme 3. Thus, the reaction products of dimethylphosphate **2** [X = $OP(O)(OMe)_2$] and silyl ether **2** [X = *t*-$BuPh_2SiO$] were, respectively, reacted with iodine to give alkenyliodides (*E*)-**4** and (*Z*)-**4** in high yields. In addition, the carbon skeleton of the product could be directly extended by using carbon electrophiles: the cyclization product of dimethylphosphate **2** was treated with benzaldehyde to afford compound **5** as a diastereomeric mixture in 55% yield, and, likewise, its allylation with allyl bromide in the presence of $Li_2Cu(CN)Cl_2$ produced the corresponding triene **6** in 81% yield.

The absolute configurations of the products thus obtained were determined to be *S* by converting alkenyliodides (*E*)- and (*Z*)-**4** to methylidenepyrrolidine **7**, respectively, by conventional organic reactions shown in Scheme 4 and comparing their $[\alpha]_D$ values with that of the authentic (*S*)-**7**.[6]

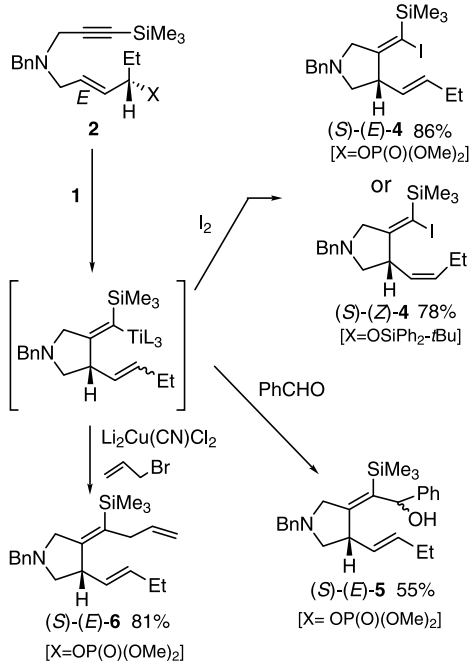
Next, we carried out the reaction using (*Z*)-(*S*)-*N*-benzyl-7-azadec-4-en-9-yn-3-ol derivatives **8**, which have the same structure as that of **2** except for the geometry of the olefin moiety. As shown in Scheme 5, the reaction of dimethylphosphate **8** [X = $OP(O)(OMe)_2$] with **1** proceeded with 99% *E*-selectivity and 76% chirality transfer to afford, after hydrolysis, (*R*)-(*E*)-**3**.[5] Similarly, the silyl ether **8** [X = *t*-$BuPh_2SiO$] was cyclized with almost complete *Z* selectivity and chirality transfer to give (*R*)-(*Z*)-**3**.[5]



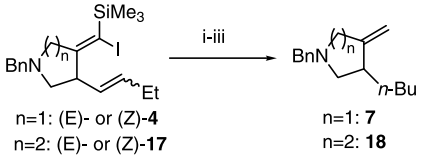
2[a]	**3**			
X	Total Yield	*E* : *Z*	E.e.[b]	Chirality Transfer[b,c]
$OP(O)(OMe)_2$	**91%**	**97 : 3**	**91.2%**	**93%**
OC(O)OEt	85%	87 : 13	65.6%	67%
OMe[d]	73%	32 : 68	—	—
$OSiMe_2$-*t*-Bu[d]	85%	14 : 86	—	—
$OSiPh_2$-*t*Bu	**90%**	**1: 99**	**>96%**	**>98%**

[a] 98.4% ee. [b]For the major olefinic isomer. [c]The values are equal to the calculated ee values simply extrapolated when the starting materials are 100% ee. [d]The reaction was carried out using a racemic substrate.

Scheme 2. Results of **1**-mediated cyclization of **2**.

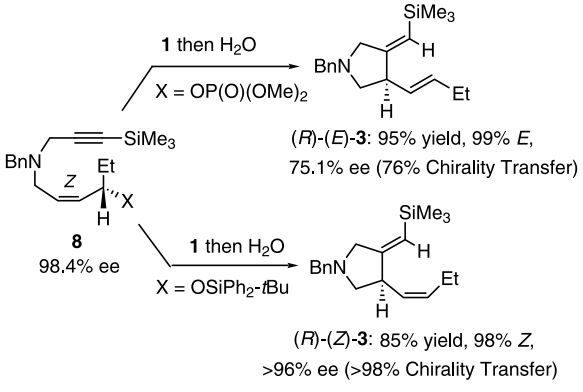


Scheme 3. Results of the reaction of the cyclized product of **2** with electrophiles other than water.



Scheme 4. Transformation of (*E*/*Z*)-**4** or (*E*/*Z*)-**17** to **7** or **18**, respectively. *Reagents and conditions*: (i) $KO_2CN = NCO_2K$, AcOH, 1,4-dioxane, 55%; (ii) Bu_4NF, THF; (iii) $LiAlH_4$, Et_2O, 68% for two steps.

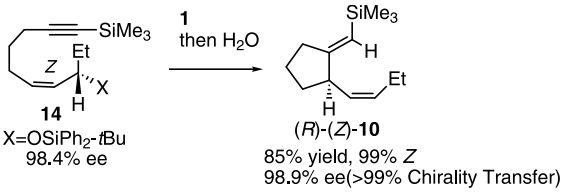
From the results described above, it could be inferred that (1) the olefinic geometry of the starting compound, regardless of its leaving group, would control the absolute configuration of the cyclized product; i.e., (*E*)-substrates would afford (*S*)-products and (*Z*)-substrates give (*R*)-products, and that (2) the leaving group of the starting compound, irrespective of its olefinic geometry,



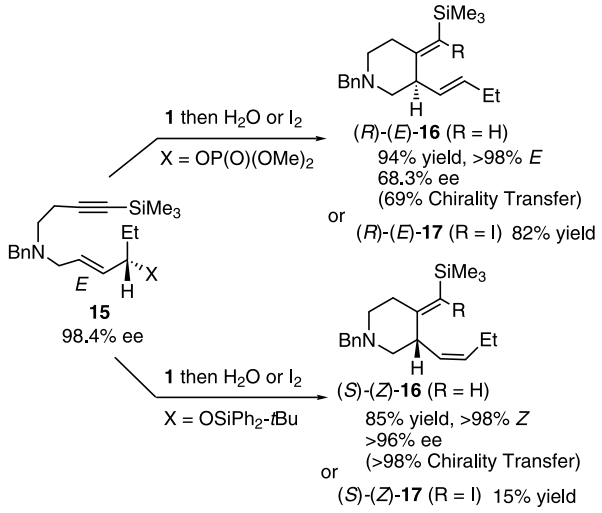
Scheme 5. Results of **1**-mediated cyclization of **8**.

would control the olefinic geometry of the but-1-enyl substituent of the cyclized product: substrates having $OP(O)(OMe)_2$ would lead to (*E*)-products and those having *t*-$BuPh_2SiO$ give (*Z*)-products. Thus, any one of the four possible stereoisomers of pyrrolidine **3** with high optical purity can be efficiently obtained starting from (*S*)-*N*-benzyl-7-azadec-4-en-9-yn-3-ol derivatives. Although metal-mediated or -catalyzed cyclization of chiral bis-unsaturated compounds affording optically active cyclic compounds having either an (*E*)- or a (*Z*)-alk-1-enyl substituent has been reported,[7] to date, no method could control both the stereogenic center and the olefinic geometry of the product simultaneously to give all four possible stereoisomers.

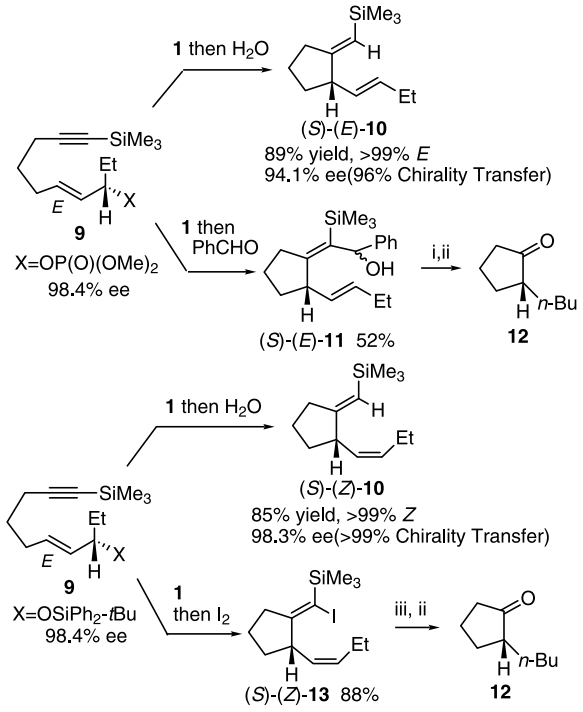
The reaction to form carbocyclic compounds also proceeds with similar stereochemical features as mentioned above. Thus, as shown in Scheme 6, the reaction of (*S*)-dec-4-en-9-yn-3-ol derivatives **9** [X = $OP(O)(OMe)_2$] proceeded with >99% *E*-selectivity and 96% chirality transfer to afford cyclopentane (*E*)-**10**[5] by hydrolysis in 89% yield and (*E*)-**11** by treatment with benzaldehyde in 52% yield. The absolute configuration of (*E*)-**11** was determined to be *S* by converting to 2-butylcyclopentanone **12** and comparing its $[\alpha]_D$ value with that reported in the literature.[8] Meanwhile, the corresponding silyl ether **9** was cyclized with complete stereoselectivity to afford (*Z*)-**10**[5] by hydrolysis and (*Z*)-**13** by iodonolysis. The absolute configuration of (*Z*)-**13** was determined to be *S* after converting to 2-butylcyclopentanone **12** (see Scheme 6). The reaction of silyl ether substrate **14** [X = *t*-$BuPh_2SiO$], which is the *Z* isomer of **9** [X = *t*-$BuPh_2SiO$], was found to proceed in a predictable fashion to give (*R*)-(*Z*)-**10**,[5] as shown in Eq. (1).



(1)



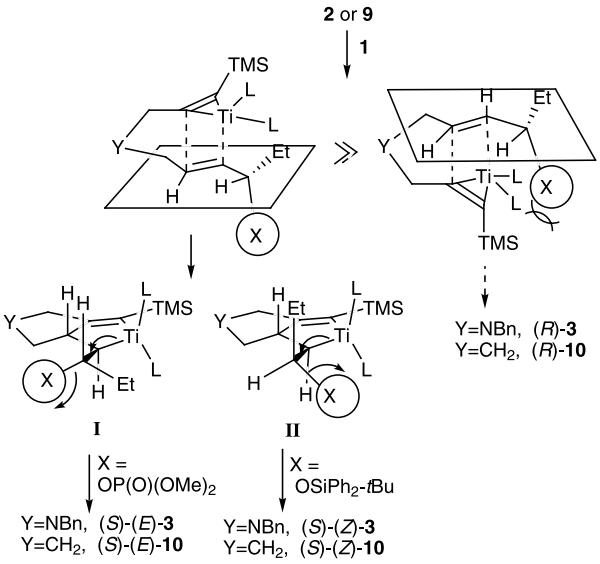
Scheme 7. Results of **1**-mediated cyclization of **15**.



Scheme 6. Results of **1**-mediated cyclization of **9**. *Reagents and conditions*: (i) H_2, $Pd(OH)_2/C$, MeOH, 85%; (ii) O_3, MeOH then Me_2S, 72%; (iii) $KO_2CN{=}NCO_2K$, AcOH, 1,4-dioxane, 66%.

Formation of optically active six-membered cyclic compounds starting from 2,8-enyn-1-ol derivatives is also feasible, as shown in Scheme 7. The dimethylphosphate substrate **15** [X = $OP(O)(OMe)_2$] was cyclized with > 98% *E*-selectivity and 69% chirality transfer to give piperidine (*E*)-**16**[5] in 94% yield by hydrolysis and (*E*)-**17** in 82% yield by iodonolysis. The absolute configuration of (*E*)-**17** was determined to be *R* by converting to methylidenepiperidine **18**, as shown in Scheme 4, and comparing its $[\alpha]_D$ value with that of the authentic (*S*)-**18**.[6] Meanwhile, the reaction of the corresponding silyl ether **15** [X = *t*-$BuPh_2SiO$] proceeded with excellent stereoselectivity to afford (*Z*)-**16**[5] by hydrolysis in 85% yield and (*Z*)-**17** by iodonolysis, albeit in a low yield (15%) probably due to its instability under the reaction conditions. To our surprise, the absolute configuration of (*Z*)-**17**, determined after converting to methylidenepiperidine **18** as shown in Scheme 4, is *S* and not *R*, which is in stark contrast to the stereochemical outcome obtained in the cyclization of the analogous 2,7-enyn-1-ol substrates **2**.

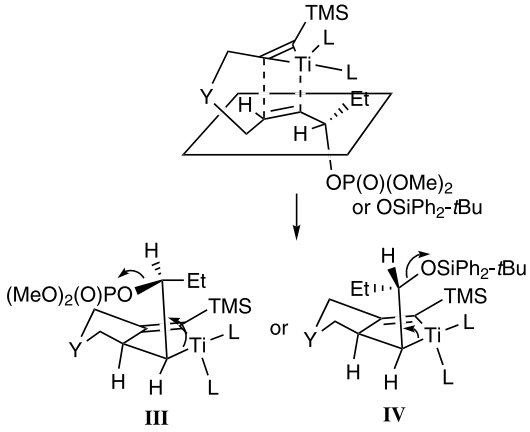
Although explanation of the difference in stereochemistry between five- and six-membered cyclization must await further study, the results of the cyclization affording the five-membered rings could be rationalized by the following reaction mechanism. For cyclization of substrate (*E*)-**2** or (*E*)-**9**, it is reasonably assumed that the (η^2-alkyne)-titanium complexes formed from the substrate and **1** would predominantly attack the double



Scheme 8. Possible reaction mechanism of **1**-mediated cyclization of **2** and **9**.

bond from the diastereo-face that is opposite to the leaving group to avoid its steric bulkiness, affording *S* absolute configuration of the products, as shown in Scheme 8. From the resulting titanacyclic intermediates, the good leaving group $(MeO)_2(O)PO$ might be eliminated through an *anti*-coplanar transition structure **I** to give (*E*)-products; while elimination of the *t*-$BuPh_2SiO$ group, which is a rather poor leaving group, might proceed through a *syn* pathway to afford (*Z*)-products via the transition structure **II**, where the intramolecular coordination of the silyloxy group to the titanium acts as a driving force for its elimination.[9] For cyclization of (*Z*)-**8** or (*Z*)-**14**, the stereochemical outcome of the reaction could be elucidated by the similar transition structure **III** and **IV**, respectively, shown in Scheme 9.

In conclusion, Ti(II)-mediated cyclization of readily accessible optically active secondary 2,7- and 2,8-enyn-1-ol derivatives provides an efficient entry to optically active five- and six-membered cyclic compounds.



Scheme 9. Possible transition structures of **1**-mediated cyclization of **8** and **14**.

Acknowledgements

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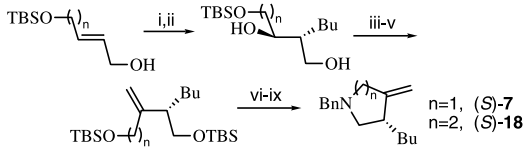
4. Recent examples: (a) Togashi, K.; Terakado, M.; Miyazawa, M.; Yamamoto, K.; Takahashi, T. *Tetrahedron Lett.* **1994**, *35*, 3333; (b) Trost, B. M.; Li, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6625; (c) Xie, X.; Lu, X. *Tetrahedron Lett.* **1999**, *40*, 8415.
5. Ee values of the products (*E*)-/(*Z*)-**3** and (*E*)-/(*Z*)-**16** were determined by ^{1}H NMR analysis in the presence of 1 equiv. (*R*)-*O*-acetylmandelic acid. Ee values of the products (*E*)-/(*Z*)-**10** were determined by chiral GLC analysis.
6. Authentic (*S*)-**7** and (*S*)-**18** were prepared as shown below:



(i) Ti(O-*i*Pr)$_4$, L-(+)-DIPT, TBHP, -20°C, 76%, (ii) Bu_2CuLi, 85%, (iii) TBSCl, NEt_3, DMAP, 91%, (iv) TPAP, NMO, 100%, (v) CH_2Br_2-$TiCl_4$-Zn, 90%, (vi) TBAF, (vii) MsCl, NEt_3, (viii) NaI, (ix) $BnNH_2$, *i*Pr_2NEt, 60°C, 62% for 4 steps. (Yields indicated were for preparation of (*S*)-**7**.)

7. Efficient Pd-catalyzed cyclization of optically active substrates was reported to afford chiral five- and six-membered cyclic compounds, which, however, always gave an (*E*)-alk-1-enyl side chain, see Refs. 4a, 4b and Oppolzer, W.; Birkinshaw, T. N.; Bernardinelli, G. *Tetrahedron*

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9. The reason why **2** having a *t*-$BuPh_2SiO$ group affords better *Z*-selectivity than **2** having a *t*-$BuMe_2SiO$ group is unclear and the explanation must await further study.