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Regulation of Stereoselectivity Using Lewis Acid in the Cyclization of Allenic Aldehydes Catalyzed by Palladium Complex

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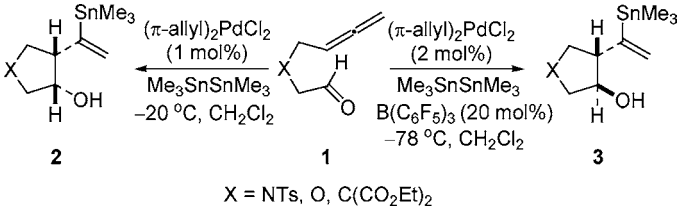
ABSTRACT



A highly diastereoselective synthesis of 3 is achieved from the reaction of 1 with hexamethylditin catalyzed by palladium complex in the presence of 20 mol % tris(pentafluorophenyl)borane as a Lewis acid additive for a reversal of diastereoselectivity, whereas 2 is formed in the absence of Lewis acid additive. The method described herein is successful with various substrates 1 in good yields and high levels of diastereoselectivity.

The availability of efficient synthetic methods in the construction of cyclic systems via organotransition metal catalysts is of considerable current interest in organic chemistry.[1] In this regard, an allene has been proven to be a useful substrate for a variety of transition metal catalytic reactions, particularly for the cyclizations in the construction of carbo- and heterocycles.[2] For example, the transition-metal-promoted cyclization of an allene and aldehyde has emerged as a highly convergent method for the stereoselective synthesis of cyclic alkenols.[3] Many advances relating to this methodology have been reported. Recently, we have disclosed our discovery of several cyclization methods using allene functionalities by transition metal catalysis,[4] as a part of the allylic transfer strategy.[5] However, a majority of the existing methods in the cylization of allene-aldehyde by transition metal catalysis provided the *cis* isomer as a major component.[3,4,6] During the past decades substantial progress has been made, and as a result, many diastereoselective synthetic routes are extensively explored.[7] Nonetheless, only a few methods exist to establish both diastereomers in a stereoselective manner, despite their plentiful synthetic

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(3) Mandai, T. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 2, pp 925−972.

(4) (a) Yu, C.-M.; Hong, Y.-T.; Lee, J. *J. Org. Chem.* **2004**, *69*, 8506−8509. (b) Yu, C.-M.; Hong, Y.-T.; Yoon, S.-K.; Lee, J. *Synlett* **2004**, 1695−1698. (c) Kang, S.; Hong, Y.-T.; Lee, J.-H.; Kim, W.-Y.; Lee, I.; Yu, C.-M. *Org. Lett.* **2003**, *5*, 2813−2816. (d) Kang, S.-K.; ha, Y.-H.; Ko, B.-S.; Lim, Y.; Jung, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 343−345.

(5) (a) Yu, C.-M.; Lee, J.-Y.; So, B.; Hong, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 161−163. (b) Yu, C.-M.: Kim, J.-M.; Shin, M.-S.; Yoon, M.-O. *Chem. Commun.* **2003**, 1744−1745.

(6) For example, Ni-catalyzed cyclizations, see: Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890−3908 and references therein.

(7) For examples, see: (a) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095−1120. (b) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121−1162.

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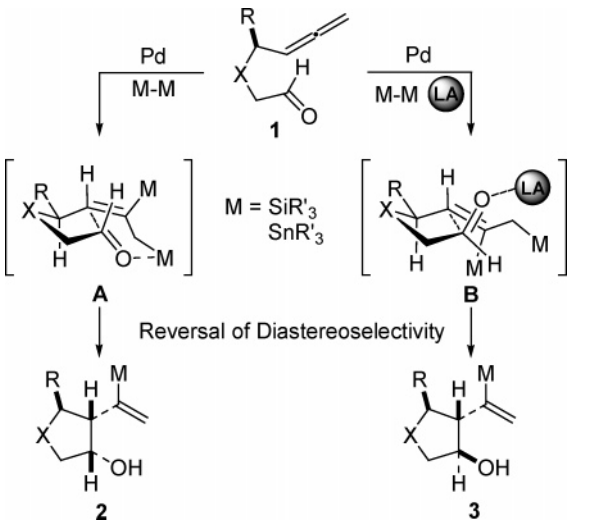
potential.[8] Therefore, the development of a synthetic route to the *trans* isomer under apropriate reaction conditions would expand the scope of reaction. This research led to the discovery of the remarkable effect of a Lewis acid additive, which causes a reversal of π-facial selectivity of the carbonyl group in the intramolecular allylic transfer reaction of an allenic aldehyde through a distannylation promoted by palladium catalyst.

In an effort for expand the scope of chemical transformation in the synthesis of *cis* **2**, we have focused on the design of a new reaction pathway to give *trans* **3** a reversal of diastereoselectivity as depicted in Scheme 1. From the

Scheme 1



mechanistic perspective, major functions for the stereoselectivity are immediately discernible in the catalytic process. Although the exact mechanistic aspects of this transformation have not been rigorously elucidated, Scheme 1 illustrates possible stereochemical routes for *cis* and *trans* stereoisomers. We reasoned that if a model **A**, assembled from the stereochemical route in addition of M−M (M = Si or Sn) to **1** by transition metal catalyst, was an intermediate on the reaction pathway, then it might be possible to reverse π-facial selectivity to yield *trans* **3** under a Lewis acidic condition via a model **B** in a predictable fashion. The key to this prediction is the well-defined closed arrangement (**A**, cyclic form) and an open-chained arrangement (**B**, acyclic form) for the allylic transfer reactions.[9]

With this issue in mind, our investigations began with **1a** (R = H, X = NTs), $Me_3SiSnBu_3$, and palladium complexes.[4d] Attempts of a cyclization reaction of **1a** indicated that the conversion to the corresponding *trans* **3** (M = $SiMe_3$) could not be satisfied with a variety of Lewis acids, including $SnCl_4$, $Sn(OTf)_2$, $AlMe_3$, $Al(NTf_2)_3$, Me_3SiOTf, Me_3SiNTf_2, $TiCl_2(OiPr)_2$, and $Zn(OTf)_2$ under various reaction conditions. We could not observe any notable effect of Lewis acids to invert π-facial selectivity. Reaction always produced *cis* **2** as a major product along with only trace amounts of **3** (M = $SiMe_3$, less than 5%) in lower chemical yields (20−30%) compared to those of non-Lewis acidic conditions (CH_2Cl_2, 20 °C, 1 h, 74%, **2**, M = $SiMe_3$). Fortunately, we found that $BF_3{\cdot}OEt_2$ could be an effective additive for this purpose. Initial experiment on the silastannylation of **1a** followed by intramolecular allylic transfer with $BF_3{\cdot}OEt_2$ (1 equiv) in the presence of $(\pi\text{-allyl})_2PdCl_2$ (5 mol %) at 20 °C for 3 h in CH_2Cl_2 afforded encouraging but marginal results. Although **3** (M = $SiMe_3$) was produced as a major component during the reaction, moderate selectivitvity (**3**:**2** = 72:28) and low chemical yield (37% combined yield) remained to be solved. Therefore, it was required to find a proper reagent and Lewis acid to carry out the reaction at lower temperature without disturbing stannylation of an allene by palladium catalyst. We subsequently speculated that the more bulky and acidic tris(pentafluorophenyl)borane might be a good candidate to regulate stereoselectivity.[10]

After surveying numerous reaction conditions, the remarkable observation has been made that the use of $B(C_6F_5)_3$ as a Lewis acid additive and hexamethylditin ($Me_3SnSnMe_3$) as a distannylation reagent in the presence of $(\pi\text{-allyl})_2PdCl_2$ as a promoter led to the best results in terms of chemical yields and diastereoselectivities. It was observed that the reaction can be perfomed as low as −78 °C. Treatment of **1a** with $Me_3SnSnMe_3$ in the presence of $(\pi\text{-allyl})_2PdCl_2$ (1 mol %) at −20 °C for 30 min in CH_2Cl_2 afforded **2a** as a sole product in 91% (condition A in Table 1). On the basis of the reaction conditions for *cis* **2a**, we carried out experiments to realize a reversal of distereoselectivity under various conditions. Key findings for the synthesis of *trans* **3a** are emerged as follows: (1) the use of 2 mol % $(\pi\text{-allyl})_2PdCl_2$ turned out to be optimal in terms of chemical yields and reaction rates; (2) we observed that the introduction of $B(C_6F_5)_3$ proved to be effective in comparison with other boranes including triethylborane; (3) 20 mol % of $B(C_6F_5)_3$ was needed for optimum conditions; (4) $Me_3SnSnMe_3$ was superior to other bisstannanes for a distannylation at lower temperature; (5) reaction performed at −78 °C in CH_2Cl_2 resulted in optimal chemical yields in comparison with other solvents such as toluene, THF, and CH_3CH_2CN.

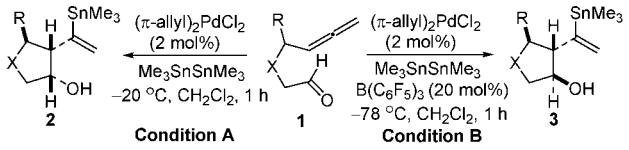
Upon optimal conditions, the reaction was conducted by a dropwise addition of a mixture of **1a** (1 equiv) and $Me_3SnSnMe_3$ (1.2 equiv) in CH_2Cl_2 for 40 min to a solution of $(\pi\text{-allyl})_2PdCl_2$ (1 mol %) and $B(C_6F_5)_3$ (20 mol %) at −78 °C in CH_2Cl_2. After 20 min at −78 °C, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$, workup, and chromatography on silica gel to afford *trans* **3a** in 81% yield as a disatereomerically pure form.

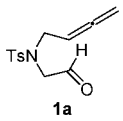
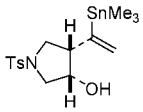
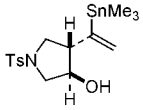
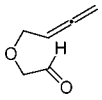
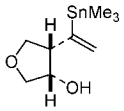
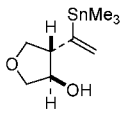
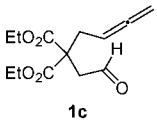
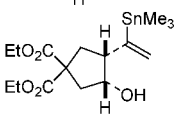
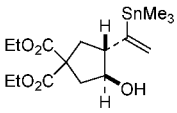
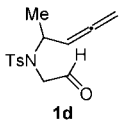
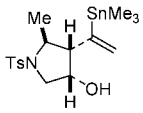
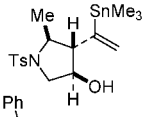
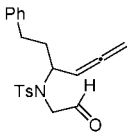
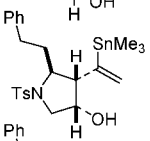
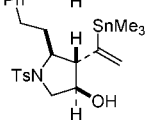
(8) For allylation, see: Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J. Ed.; Wiley-VCH: Weinheim, 2000; pp 403−490.

(9) For general discussions, see: (a) Santelli, M.; Pons, J.-M. *Lewis Acids and Selectivity in Oganic Synthesis;* CRC Press: Boca Raton, 1996; pp 91−184. (b) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry;* Otera, J. Ed.; Wiley-VCH: Weinheim, 2000; pp 299−401.

(10) (a) Erker, G. *Dalton Trans.* **2005**, 1883−1890. (b) Nakashima, D.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 1251−1253. (c) Britovsek, G. J. P.; Ugolotti, J.; White, A. J. P. *Organometallics* **2005**, *24*, 1685−1691. (d) Motita, M.; Inoue, K.; Yoshida, T.; Ogoshi, S.; Kurosawa, H. *J. Orgnomet. Chem.* **2004**, *689*, 894−898.

Table 1. Stannylcarbocyclization of Allenyl-aldehydes

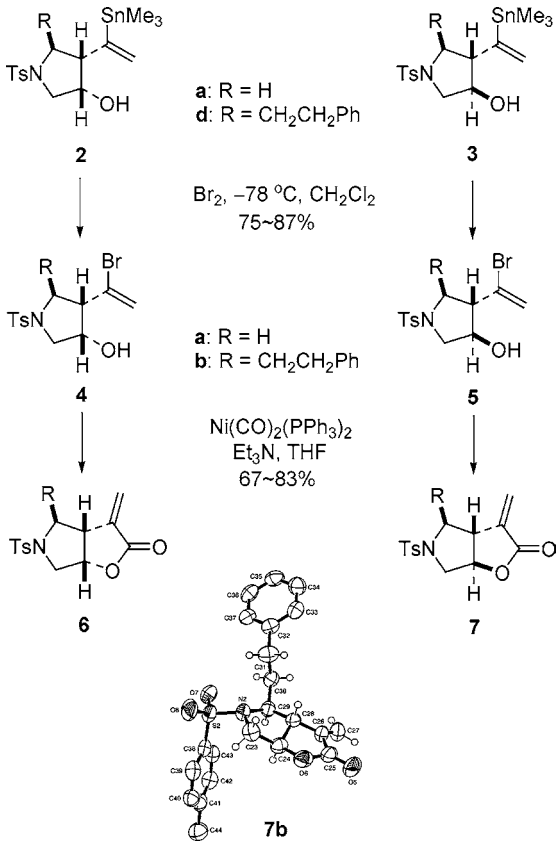


Entry	Substrate (**1**)	Condition	Product		Yield (%)
1	 **1a**	**A**		**2a**	91
2		**B**		**3a**	81
3	 **1b**	**A**		**2b**	77
4		**B**		**3b**	63
5	 **1c**	**A**		**2c**	78
6		**B**		**3c**	71
7	 **1d**	**A**		**2d**	81
8		**B**		**3d**	83
9	 **1e**	**A**		**2e**	86
10		**B**		**3e**	81

With the notion that this protocol might lead to a general and efficient method for the synthesis of multifunctional substances, we set out to determine the scope of reaction with various **1**. Indeed, the method is successful with a variety of **1** and affords products of high diastereomeric purity, as can be seen in Table 1. It is worthy of note that the reaction produced none or only trace amounts of minor products (less than 2%) according to the analysis of 500 MHz ^{1}H NMR spectra of crude products. We also observed that the internal chirality transfer of substituted **1d** and **1e** turned out to be excellent.

The products **2** and **3** are readily amenable for further conversion to useful synthetic intermediates by the functional group transformations of vinylstannane. For this purpose we decided to undertake synthesis of bicyclic *cis*- and *trans*-α-methylene-γ-butyrolactones **6** and **7**, not only to show synthetic applicability for both isomers but also to prove stereochemical relationships of products as demonstrated in Scheme 2. Bromovinylic alcohols **4** and **5** were obtained by

Scheme 2



the treatment of **2** and **3** with bromine at −78 °C in 75−87% yield.[11] Finally, synthesis of the α-methylene-γ-butyrolactones **6** and **7** was accomplished by the carbonylative cyclization of **4** and **5** with $Ni(CO)_2(PPh_3)_2$ in the presence of Et_3N under reflux conditions for 2 h in THF in 67−83% yields.[12] Stereochemical relationships of **6a**,**b** were confirmed by the comparison of the NMR specrta with those of authentic samples prepared by the method developed by our laboratory.[4a] The relative configurations of *cis* **4a** and *trans* **7b** were also unambiguously established by X-ray crystallography. Thus the stereochemical outcomes for **2** and **3** from **1** were also ascertained by these experiments.

In summary, this paper describes synthetic routes to *cis* **2** and *trans* **3** to realize a reverse diastereoselection in a general and efficient way that promises to be synthetically useful.

(11) Paquette, L. A.; Hong, F.-T.*J. Org. Chem.* **2003**, *68*, 6905−6918.
(12) (a) Martin, L. D.; Stille, J. K. *J. Org. Chem.* **1982**, *47*, 3630−3633. (b) Semmelhack, M. F.; Brickner, S. J. *J. Org. Chem.* **1981**, *46*, 1723−1725.

This highly stereocontrolled transformations involves the distannylation of allene by palladium catalyst followed by the intramolecular allylic transfer reaction with aldehyde. We observed that Lewis acid additive has a crucial role to reverse the π-facial selectivity. Studies are in progress to incorporate with chiral Lewis acid into catalytic asymmetric synthesis.

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Supporting Information Available: General experimental procedure details and chracterization data for all products, and crystal structures of **4a** and **7b** in CIF file format. This material is available free of charge via the Internet at http://pubs.acs.org.

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