JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

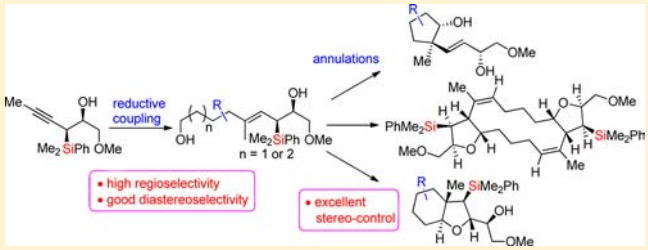
Divergent Synthesis of Functionalized Carbocycles through Organosilane-Directed Asymmetric Alkyne−Alkene Reductive Coupling and Annulation Sequence

Jie Wu, Yi Pu, and James S. Panek*

Department of Chemistry and Center for Chemical Methodology and Library Development (CMLD-BU), Boston University, Boston, Massachusetts 02215, United States

Supporting Information

ABSTRACT: An organosilane-directed alkyne−alkene reductive coupling of readily available propargylsilanes is used to access densely functionalized chiral allylsilanes. The divergent reactivity of the allylsilanes can be controlled to afford a range of novel carbocyclic ring systems through an intramolecular allylation, [3+2] annulation, and Sakurai-like homodimerization.



1. INTRODUCTION

Allylsilanes enjoy a privileged role in the realm of organic synthesis owing to their ease of preparation, handling and relatively low toxicity, allowing their use as powerful reagents for the synthesis of complex organic molecules and natural products.[1] In that context, a number of strategies have been developed to synthesize these reagents,[2,3] including the silylcupration of allenes,[1a] Claisen rearrangement,[1d] allylic C−OH functionalization,[2b] carbenoid Si−H insertion,[2c,h] allylic substitution,[2d] Pd-catalyzed intramolecular bis-silylation,[2f] and alkyne−alkene reductive cross-coupling.[3] Given this background, generation of allylsilanes from propargylsilanes, a seemingly straightforward approach, has not been realized but restricted to partial hydrogenation and/or hydride reduction.[4]

Transition metal-mediated reductive coupling reactions have proven to be extraordinarily useful transformations due to the inherent atom- and step-economical principles, thereby avoiding alkene prefunctionalization.[5] In that context, alkyne−alkene reductive coupling represents a potentially significant and difficult case due to the sluggish reactivity and control of regio- and stereoselectivity. Further complications arise when a 1,2-disubstituted olefin is used, as a new stereocenter will be created. However, the majority of previous work in this area has been restricted to racemic variants of this important bond construction.[6]

A significant breakthrough was recently documented by the Micalizio group concerning the development of a bimolecular alkyne−alkene reductive coupling with unactivated olefins.[3,7b] That study described a double asymmetric coupling where the newly formed allylic stereocenter appeared to be controlled by $A^{1,3}$-strain[8] derived from a (*Z*)-homoallylic alcohol coupling partner. However, the limited alkene substrate scope reported for the diastereoselective version thus far presents an opportunity for further development in this area.[7]

In our continuing interests in developing chiral silane reagents capable of delivering useful levels of asymmetric induction with activated C═X π-bonds,[9] we envisioned that an extension of the reductive coupling using enantioenriched propargylsilanes should allow access to highly functionalized chiral allylsilanes. While it is well known that chiral allylsilane reagents generally exhibit excellent stereocontrol in reactions with electronically activated C═X π-bonds, we were interested in whether useful selectivity can be achieved in new reactions of propargyl homologues.

In this article we detail an efficient procedure for the preparation of densely functionalized allylsilanes from readily accessible enantioenriched propargylsilane building blocks **1**,[10] that has broadened the substrate scope for the diastereoselective alkyne−alkene reductive coupling. The experiments described herein mark a substantial advance in generating complex allylsilanes, which may be used as an entry point to access carbocycles with considerable skeletal variation in a convergent and highly selective manner (Scheme 1).

2. RESULTS AND DISCUSSION

2.1. Silane-Directed Asymmetric Alkyne−Alkene Reductive Coupling. *Formation of the Alkyne−Titanium Complexes.* Our initial investigation focused on the efficiency of generating the alkyne−titanium complex from propargylsilane **1**, the key to a successful reductive coupling.[5b,11] The plausible bicyclic metallacyclopropene intermediate **I** may not be favored due to excessive ring strain associated with a fused bicyclic [3.1.0] system. Therefore, dimer **II** or higher order oligomers may play a significant role in the subsequent carbometalation (Figure 1).[12]

Received: August 28, 2012
Published: October 11, 2012

dx.doi.org/10.1021/ja3083945 | J. Am. Chem. Soc. 2012, 134, 18440−18446

Scheme 1. Silane-Directed Alkyne−Alkene Reductive Coupling and Annulation Sequence

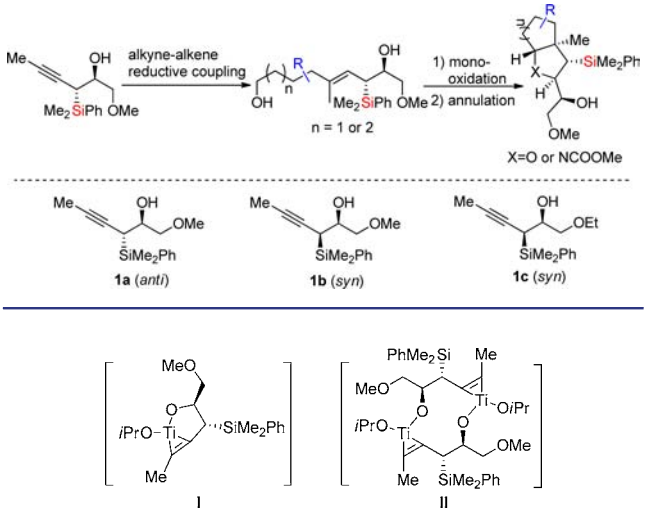
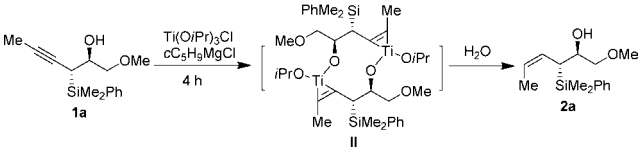


Figure 1. Proposed monomeric and dimeric alkyne−titanium complexes (higher order oligomeric structures are not shown).

Although attempted formation of titanocyclopropene failed in toluene (Table 1, entry 3), treatment of propargylsilane **1a**

Table 1. Optimization for Metallacyclopropene Complex Generation



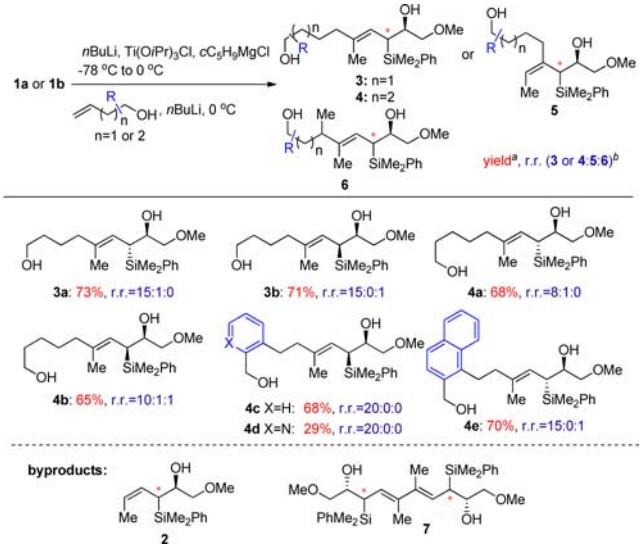
entry	solvent	additive	temp (°C)	2a:1a[a]	yield (%)[b]
1	Et_2O	none	−78 to −20	1:4	nd[d]
2	Et_2O	*n*BuLi	−78 to −20	4:1	nd
3	toluene	*n*BuLi	−78 to −20	0:1	0
4	Et_2O	*n*BuLi	0 to −78 to −20	na[c]	0
5	**Et_2O**	***n*BuLi**	**−78 to 0**	**1:0**	**80**
6	Et_2O	none	−78 to 0	1:4	nd

[a]Ratios based on crude ^{1}H NMR spectra. [b]Isolated yield. [c]na = not available. [d]nd = not determined.

with *n*BuLi (1 equiv), $Ti(OiPr)_3Cl$ (2 equiv), and cyclopentylmagnesium chloride (4 equiv, from −78 to 0 °C) using Et_2O as the solvent delivered the (*Z*)-crotylsilane **2a** in 80% yield after hydrolysis (entry 5), suggesting a clean formation of the titanocyclopropene intermediate. The presence of *n*BuLi was essential for generation of an alkoxide (entry 6), which would undergo a rapid ligand exchange to afford the polycyclic intermediate **I** or **II**.[12] Both allylic and propargylic silanes were well tolerated in the reaction, and no trace of Peterson elimination or protiodesilylation byproducts were detected.

Alkyne−Alkene Reductive Coupling with Monosubstituted Olefins. Monosubstituted terminal olefins were evaluated in the coupling with the *in situ* generated alkyne−titanium complex.[13] As depicted in Scheme 2, homoallylic alcohols as well as bis-homoallylic alcohols reacted smoothly to deliver the coupled products in good yield and regioselectivity, with new C−C bond formation selectively taking place at the carbon γ to the silyl group. The major byproducts isolated from these reactions were

Scheme 2. Silane-Directed Alkyne−Alkene Reductive Coupling with Monosubstituted Olefins



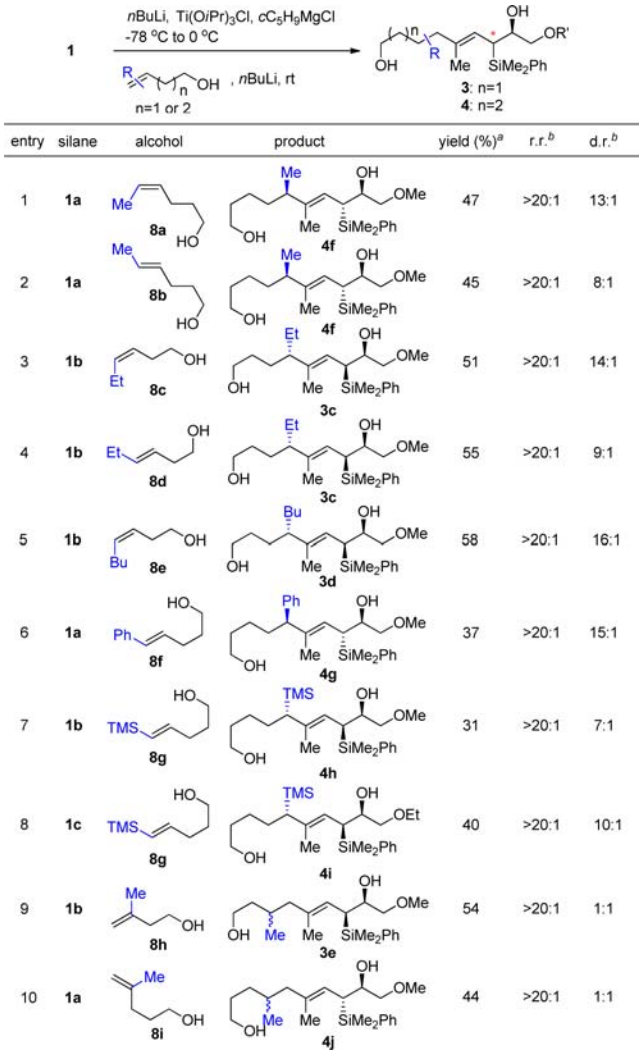
[a]Isolated yield after purification on SiO_2. [b]Regioselectivity was based on analysis of the crude ^{1}H NMR spectra; r.r. = ratio of regioselectivity.

determined to be alkene **2** and homodimer **7** derived from propargylsilane **1**. In the cases of 2,3-aryl-substituted bis-homoallylic alcohols, the coupling reactions also proceeded effectively to furnish products in excellent regioselectivity (**4c** and **4e**). However, the pyridyl-substituted olefin resulted in product **4d** in low yield, presumably due to the incompatibility of the starting alkene in the presence of *n*BuLi. Alkyne−alkene couplings with allylic or tris-homoallylic alcohols only resulted in complex product mixtures.

Alkyne−Alkene Reductive Coupling with Disubstituted Olefins. This strategy also proved to be effective in the coupling of 1,2-disubstituted olefins at higher temperature (room temperature vs 0 °C), which allowed C−C bond formation between the two π-systems accompanied by the formation of a new allylic stereogenic center. The reaction of a bis-homoallylic alkoxide derived from *cis*-4-hexen-1-ol **8a** with the *in situ* formed alkyne−titanium complex of **1a** was highly selective, delivering the coupled product **4f** as the only regioisomer with good diastereoselectivity (Scheme 3, entry 1). Notably, the reaction between *trans*-4-hexen-1-ol **8b** and silane **1a** afforded the same major diastereomer **4f** in similar yield and selectivity (entry 2). In a similar manner, reactions of **1b** with both *cis*-3-hexen-1-ol **8c** and *trans*-3-hexen-1-ol **8d** afforded the same major product **3c** in good selectivity (entries 3 and 4). The *n*-butyl-substituted alkene could be coupled with good selectivity and yield using the same condition (entry 5). Furthermore, the styrene-like reaction partner (entry 6) and silyl variant (entries 7 and 8) were suitable for the coupling to give products **4g**−**4i** with excellent selectivity, albeit in lower yield, most likely due to steric interactions associated with the substrates. Slightly larger amounts of byproducts **2** and **7** were detected compared to reactions with monosubstituted olefins. Allylsilanes **3e** and **4j** were produced in modest yield using *gem*-disubstituted olefins **8h** and **8i**; however, diastereoselectivity was not observed in these cases (entries 9 and 10). The absolute stereochemistry of **4f** and **3c** was unambiguously assigned by X-ray crystallography and NOE measurements of the corresponding [3+2] annulation product **9f** and the cyclization derivative **10c′** (Scheme 4). The remaining cases in Scheme 3 were assigned by analogy to **4f** and **3c**.

dx.doi.org/10.1021/ja3083945 | J. Am. Chem. Soc. 2012, 134, 18440−18446

Scheme 3. Silane-Directed Alkyne–Alkene Reductive Coupling with Disubstituted Olefins

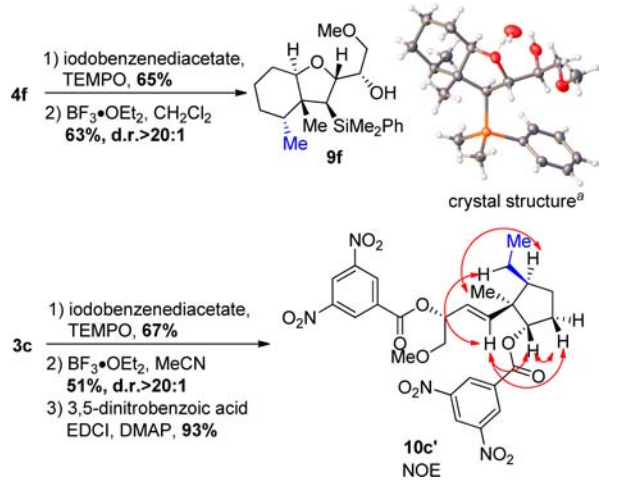


[a]Isolated yield after purification on SiO_2. [b]Selectivities were based on analysis of the crude ^1H NMR spectra; r.r. = ratio of regioselectivity; d.r. = diastereomeric ratio.

For the cases studied, the stereochemical course of the reaction appears to be independent of the olefin configuration, as both *cis*- and *trans*-olefins afforded coupled products with the same stereochemistry, and we anticipated that the coupling should occur in a stereoselective manner even with *E*/*Z* isomeric mixtures of alkenes. A control experiment was conducted using a 1:1 mixture of *E*/*Z* olefin isomers (**8c** and **8d**) to couple with propargylic silane **1b**. As expected, the major diastereomer **3c** was obtained in good yield and with high selectivity (Scheme 5). Therefore, the coupled products could be obtained in a stereoselective manner even starting with isomeric mixtures of alkenes.

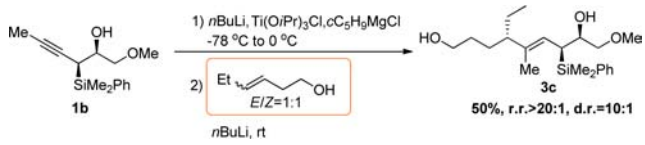
In an effort to expand the scope of this transformation, experiments were conducted using alkyne **11** (phenyl group replaced silyl group) and *cis*- and *trans*-3-hexen-1-ols (Scheme 6). Both reactions proceeded smoothly to achieve the same major product **12** in good yield and diastereoselectivity and as a single regioisomer. This control experiment also indicated that the phenyl group had sufficient steric bulk to influence the stereochemical course of the reaction.

Scheme 4. Assignment of Absolute Configuration

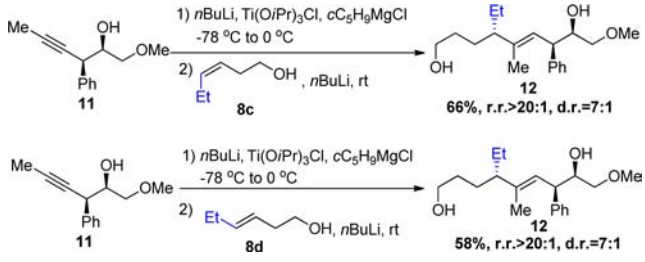


[a]The crystal structure was obtained as the monohydrate of **9f**.

Scheme 5. Reductive Coupling with an *E*/*Z* Mixture of Disubstituted Olefins



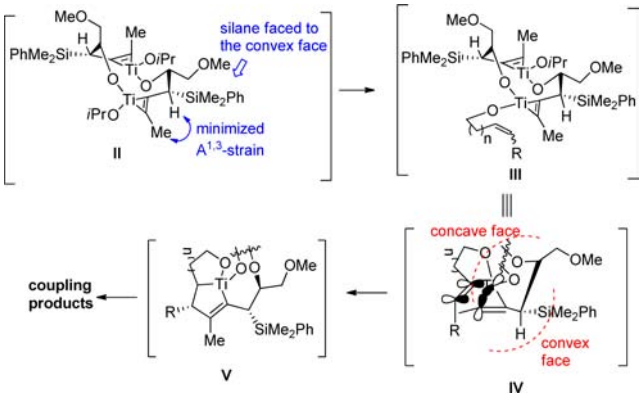
Scheme 6. Reductive Coupling Using a Phenyl-Substituted Internal Alkyne



Mechanistic Proposal. A plausible mechanistic explanation of the observed stereochemical outcome rests on a three-dimensional shape of the polycyclic metallacycle **II**, which shows a clearly defined concave nature that is influenced by the size of the silyl substituent (Scheme 7).[14] A rapid and reversible ligand exchange between alkyne–titanium complex **II** and the *in situ* generated alkoxide would deliver intermediate **III**. The subsequent transformation likely proceeds by engaging the Ti–C δ bond in a carbometalation event. Given the geometric constraints imposed by the sp^2-like nature of the metallacyclopropene, the developing bond should ensue from interaction of the alkene π system of the homoallylic alcohol partner with the C–Ti δ bond in an orientation that best accommodates the hybridization of the C=C bond of the metallacycle (intermediate **IV**). Thus, with the π system of the alkene coupling partner facing the Ti–C δ bond positioned in-plane with the metallacycle, the terminal substituent of the alkene may prefer to be oriented outside of the concave fused metallacyclic system (*syn* to the silyl substituent). In this manner, the intramolecular carbometalation will afford the metallacyclopentene **V**, followed by quenching with water to furnish the allylsilane product.[15]

dx.doi.org/10.1021/ja3083945 | J. Am. Chem. Soc. 2012, 134, 18440–18446

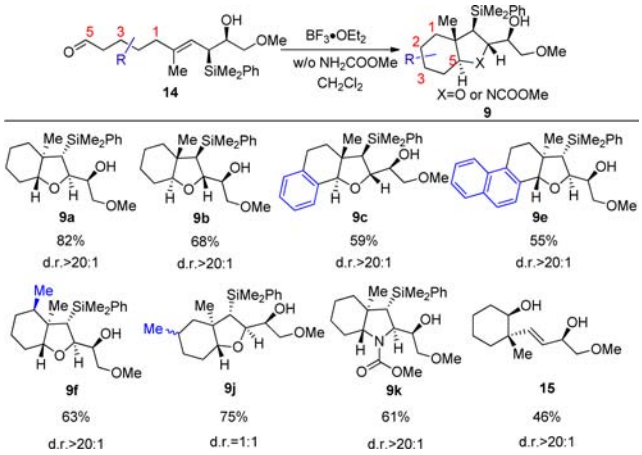
Scheme 7. Proposed Mechanism for Silane-Directed Alkyne−Alkene Reductive Coupling



2.2. Silane-Directed Asymmetric Annulation. Though the intermolecular allylsilylation has been widely documented,[9] the substrate scope for intramolecular process was limited,[16] most likely due to a lack of reliable methods to prepare complex allylsilanes. With an efficient synthesis of highly functionalized allylsilanes now accessible, we sought to demonstrate their synthetic utility. It is well documented that access to a single asymmetric quaternary carbon is regarded as a challenging problem in organic synthesis.[17] In this context, we anticipated that silyl aldehydes **14** and **13**, derived from alcohols **4** and **3** respectively,[18] could be undertaken to achieve various cyclic compounds bearing quaternary stereocenters and would present significant opportunities for structural variation.

[3+2] Annulations. As described earlier in Scheme 4, upon treatment of aldehyde **14f** with $BF_3{\cdot}OEt_2$ at −30 °C, **9f** was obtained through a [3+2] annulation as the only detectable diastereomer. Thus, silyl aldehydes of type **14** with different alkyl or aryl substituents, which were originally derived from bishomoallylic alcohols, were evaluated in the [3+2] annulation to establish the generality of this transformation to deliver stereodefined, angularly substituted perhydrobenzofurans (Scheme 8).

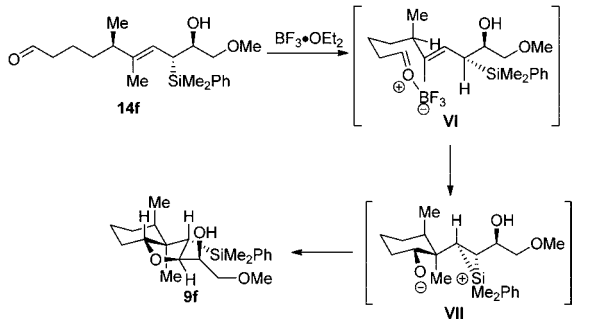
Scheme 8. [3+2] Annulation[a]



[a]Isolated yield after purification on SiO_2 is given. Diastereoselectivity was based on analysis of the crude ^1H NMR spectra. w/o = with or without.

In all cases, the resulting annulation products were obtained in moderate to good yield and with exceptional selectivity. The diastereoselectivity can be attributed to the stereocontrol effect of the chiral silyl group. As shown in Scheme 9, the intramolecular reaction is consistent with an antiperiplannar transition state

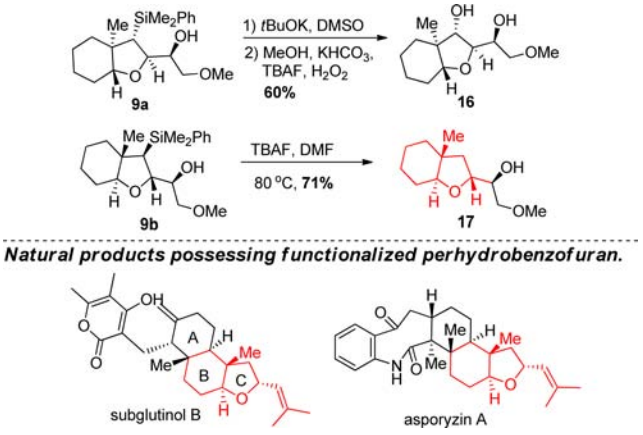
Scheme 9. Rationale for the Stereochemical Course of [3+2] Annulations



(intermediate **VI**). However, elimination of the dimethylphenylsilyl group is superseded by a [1,2]-silyl migration presumably through trapping of the silacyclopropylium cation **VII**, which delivers the bicyclic product **9**. However, simply raising the reaction temperature to 0 °C resulted in the production of cyclohexanol **15**, suggesting that the perhydrobenzofuran product may undergo a Peterson elimination at higher temperature to afford vinyl-substituted cyclohexanols.[9b] The *in situ* generation and trapping of the derived iminium ion of **14a** could also access perhydroindole **9k** through this strategy.

Furthermore, the silyl-substituted heterocycles **9** participated in a Tamao oxidation[19] or protiodesilylation,[20] thereby enhancing the diversity element of the [3+2] annulation pathway (Scheme 10). Perhydrobenzofurans bearing a fully substituted

Scheme 10. Further Diversification of [3+2] Annulation Products



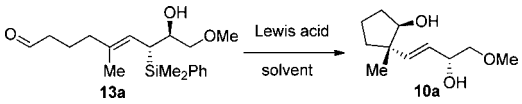
stereocenter are common structural fragments integrated into a large number of natural products. For instance, desilylated product **17** has the same stereochemistry of the BC ring fusion as natural subglutinol B and asporyzin A,[21] underscoring a potential route for their preparation.

Intramolecular Allylation. Alternatively, treatment of aldehydes of type **13**, originally generated from homoallylic alcohols, with a Lewis acid afforded highly substituted cyclopentanols **10** through an intramolecular *exo-trig* cyclization and without detection of the [3+2] annulation product. To optimize the reaction condition, a variety of Lewis acids were screened using aldehyde **13a**, and $BF_3{\cdot}OEt_2$ proved to be the

dx.doi.org/10.1021/ja3083945 | J. Am. Chem. Soc. 2012, 134, 18440−18446

most effective promoter of the annulation (Table 2). Moreover, using MeCN as the solvent resulted in a cleaner reaction than CH_2Cl_2 (entries 2 and 3).

Table 2. Optimization for the Intramolecular Allylation

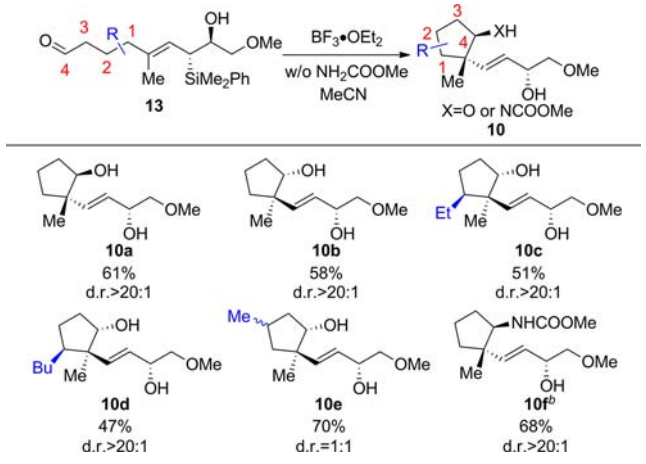


entry	Lewis acid	solvent	temp (°C)	yield (%)[a]	d.r.[b]
1	TMSOTf	CH_2Cl_2	−78	25	>20:1
2	$BF_3{\cdot}OEt_2$	CH_2Cl_2	−30	50	>20:1
3	$BF_3{\cdot}OEt_2$	MeCN	−30	61	>20:1
4	$TiCl_4$	CH_2Cl_2	−78	<20	>20:1
5	$MeAlCl_2$	CH_2Cl_2	0	0	na
6	$In(OTf)_3$	CH_2Cl_2	0	<20	>20:1
7	$Sc(OTf)_3$	CH_2Cl_2	0	0	na

[a]Isolated yield after purification on SiO_2. [b]Diastereoselectivity based on the crude ^1H NMR spectra analysis.

With optimal conditions now defined, reactions of five different aldehydes of type **13** proceeded effectively in the intramolecular allylation, affording the cyclopentane products as a single diastereomer based on the starting aldehyde (Scheme 11,

Scheme 11. Stereocontrolled Synthesis of Vinylcyclopentanes[a]

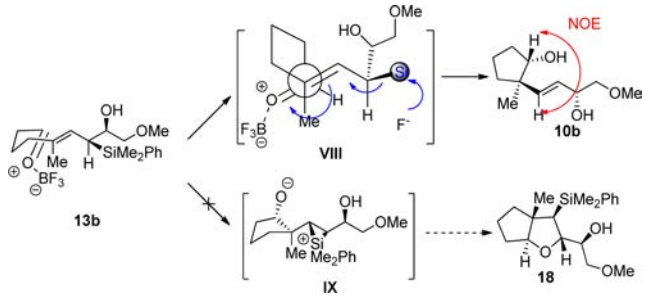


[a]Isolated yield after purification on SiO_2. Diastereoselectivity was based on the crude ^1H NMR spectra analysis. w/o = with or without. [b]Reaction for **10f** was conducted in CH_2Cl_2 instead of MeCN.

10a–**10e**). The chirality of the emerging stereocenter solely originated from and was controlled by the nature of the silicon-bearing stereocenter, which was consistent with the well-established antiperiplanar transition state (Scheme 12). In contrast to the [3+2] process that proceeds through a bridged silyl cation intermediate as observed in the cases of aldehyde **14f**, the *β*-silyl cation in the reaction with aldehyde **13** was terminated by elimination of the silyl group to form an alkene. This result was most likely due to the high energy barrier that must be overcome for the Lewis acid-coordinated alkoxide to trap the bridged silyl cation **IX** via formation of a strained *trans*-fused bicyclic [3.3.0] ring system **18**.

To extend the utility of this methodology, an *in situ* generated iminium ion was subjected to intramolecular allylation to

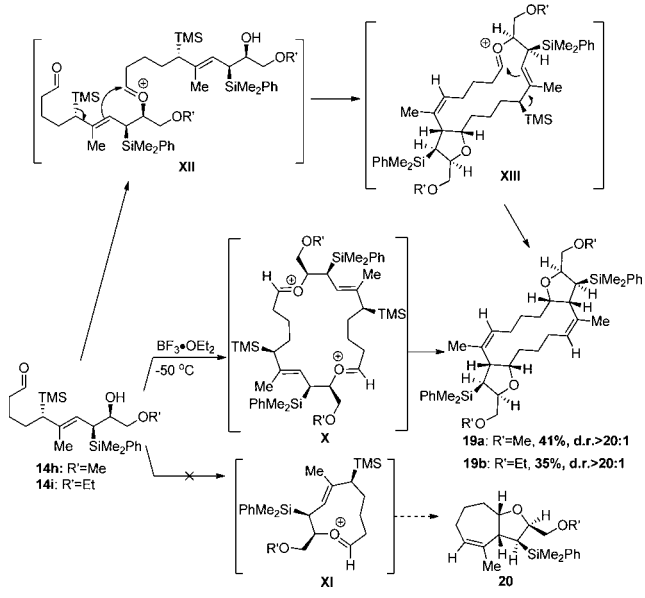
Scheme 12. Stereochemical Model for Intramolecular Allylation



afford aminocyclopentane **10f** in good yield and complete stereoselectivity (Scheme 11).

Sakurai-like Dimerization. In an effort to further explore the skeletal diversity with the generated allylsilane reagents, we evaluated the reactivity of bis-silyl reagents **14h** and **14i**. Gratifyingly, when the bis-silyl reagents were treated with $BF_3{\cdot}OEt_2$ (2 equiv) in CH_2Cl_2 (0.1 M) at −50 °C, Sakurai-type dimerization[22] products **19** with desilylation of the TMS group were obtained as single stereoisomers, without any monomer **20** detected, probably owing to the conformational rigidity and strain in cyclization of mono-oxonium ion intermediates **XI** (Scheme 13).[23] The dimerization may proceed through either

Scheme 13. Sakurai-like Dimerization

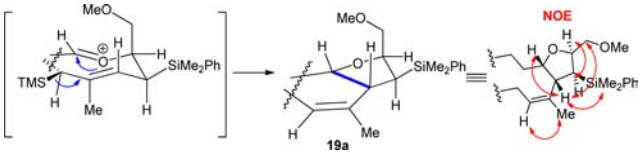


the bis-oxonium ion intermediates **X** or a stepwise procedure involving the intermediates **XII** and **XIII**.

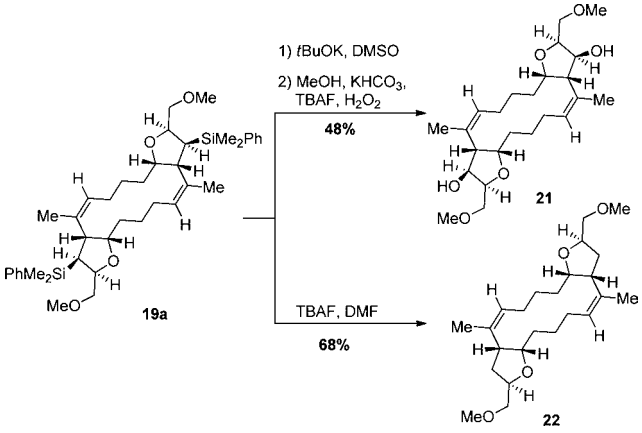
The stereochemical course of the process maybe controlled by both TMS and dimethylphenylsilyl groups. In the proposed transition state, the TMS group appeared to be perpendicular and orientated antiperiplanar to the oxonium ion (Scheme 14). The dimethylphenylsilyl group occupied the pseudoequatorial position to give the most stable conformation, which led to the final product **19**. The configuration of **19a** was determined by NOE measurement. The dimer products could efficiently undergo oxidative cleavage or protiodesilylation as well to enhance the synthetic utility of this dimerization process (Scheme 15).

dx.doi.org/10.1021/ja3083945 | J. Am. Chem. Soc. 2012, 134, 18440–18446

Scheme 14. Stereochemical Explanation for Sakurai-like Dimerization



Scheme 15. Further Diversification of Dimers



3. CONCLUSION

In summary, a sterically influenced and economical alkyne–alkene reductive coupling has been developed to generate a range of novel chiral allylsilanes that participated in Lewis acid-promoted carbocyclization with excellent levels of selectivity. Readily available chiral propargylsilanes are shown to be versatile building blocks for the construction of complex allylsilanes by reductive coupling, where the silyl group exhibits a significant steric influence on the stereochemical course of the reaction. Our study paved the way for rapid access to densely functionalized allylsilanes through an alkyne reductive coupling (e.g., alkyne–alkyne, alkyne–aldehyde). Moreover, silane-directed asymmetric alkyne–alkene reductive couplings exhibit an enhanced alkene substrate scope, achieving products with useful selectivity even from isomeric mixtures of alkenes. The subsequent annulations underscore the reliability of a silyl group with C-centered chirality as a stereocontrol element and establish a concise pathway for the convergent assembly of complex carbocycles with potential pharmacological value.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data have also been deposited with the Cambridge Crystallographic Data Centre under CCDC 869781.

■ AUTHOR INFORMATION

Corresponding Author

Panek@bu.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support from the NIGMS CMLD initiative (P50-GM067041). We are grateful to Prof. John A. Porco, Jr., Prof. Aaron Beeler (BU-CMLD), and Mr. Jihoon Lee in Boston University for helpful discussion. We thank Dr. Paul Ralifo, Dr. Norman Lee, and Dr. Jeff Bacon (Boston University) for assistance with NMR spectroscopy, HRMS, and X-ray measurements.

■ REFERENCES

(1) For selected reviews on allylsilanes, see: (a) Barbero, A.; Pulido, F. J. *Acc. Chem. Res.* **2004**, *37*, 817. (b) Chabaud, L.; James, P.; Landais, Y. *Eur. J. Org. Chem.* **2004**, 3173. (c) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063. (d) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293.

(2) For recent literatures on synthesizing allylsilanes, see: (a) Saito, N.; Kobayashi, A.; Sato, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 1228. (b) Selander, N.; Paasch, J. R.; Szabó, K. J. *J. Am. Chem. Soc.* **2011**, *133*, 409. (c) Wu, J.; Chen, Y.; Panek, J. S. *Org. Lett.* **2010**, *12*, 2112. (d) Kacprzynski, M. A.; May, T. L.; Kazane, S. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4554. (e) Shintani, R.; Ichikawa, Y.; Hayashi, T.; Chen, J.; Nakao, Y.; Hiyama, T. *Org. Lett.* **2007**, *9*, 4643. (f) Suginome, M.; Ito, Y. *J. Organomet. Chem.* **2003**, *685*, 218. (g) Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920. (h) Davies, H. M.; Hansen, T.; Rutberg, J.; Bruzinski, P. R. *Tetrahedron Lett.* **1997**, *38*, 1741.

(3) Reichard, H. A.; Micalizio, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 1440. A single example of generation of an allylsilane (racemic version) employing Ti-mediated alkyne–alkene reductive cross-coupling using an internal alkyne and a vinylsilane has been documented.

(4) (a) Gonzalez, A. Z.; Soderquist, J. A. *Org. Lett.* **2007**, *9*, 1081. (b) Betson, M. S.; Fleming, I. *Org. Biomol. Chem.* **2003**, *1*, 4005.

(5) For recent reviews, see: (a) Reichard, H. A.; Micalizio, G. C. *Chem. Sci.* **2011**, *2*, 573. (b) Reichard, H. A.; Mclaughlin, M.; Chen, M. Z.; Micalizio, G. C. *Eur. J. Org. Chem.* **2010**, 391. (c) Jeganmohan, M.; Cheng, C.-H. *Chem.—Eur. J.* **2008**, *14*, 10876. (d) Moslin, R. M.; Miller-Moslin, K.; Jamison, T. F. *Chem. Commun.* **2007**, *43*, 4441. (e) Broene, R. D. *Top. Curr. Chem.* **2007**, *279*, 209. (f) Gibson, S. E.; Mainolfi, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 3022.

(6) For selected examples of racemic intermolecular alkyne–alkene reductive coupling, see: (a) Li, W.; Herath, A.; Montgomery, J. *J. Am. Chem. Soc.* **2009**, *131*, 17024. (b) Herath, A.; Montgomery, J. *J. Am. Chem. Soc.* **2008**, *130*, 8132. (c) Chang, H.-T.; Jayanth, T. T.; Wang, C.-C.; Cheng, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 12032. (d) Aoki, K.; Peat, A. J.; Buchwald, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 3068. Also see ref 3.

(7) For examples on intermolecular alkyne–alkene reductive cross-coupling in an asymmetric fashion, see: (a) Wei, C.-H.; Mannathan, S.; Cheng, C.-H. *J. Am. Chem. Soc.* **2011**, *133*, 6942. (b) Canterbury, D. P.; Micalizio, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 7602. (c) Kolundzic, F.; Micalizio, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 15112. Also see ref 3.

(8) For allylic 1,3-strain, see: Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

(9) For selected examples, see: (a) Chalifoux, W. A.; Reznik, S. K.; Leighton, J. L. *Nature* **2012**, *487*, 86. (b) Wu, J.; Zhu, K.; Yuan, P.; Panek, J. S. *Org. Lett.* **2012**, *14*, 3624. (c) Wu, J.; Becerril, J.; Lian, Y.; Davies, H. M. L.; Porco, J. A.; Panek, J. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 5938. (d) Lee, J.; Panek, J. S. *Org. Lett.* **2011**, *13*, 502. (e) Brawn, R. A.; Panek, J. S. *Org. Lett.* **2010**, *12*, 4624. (f) Huber, J. D.; Leighton, J. L. *J. Am. Chem. Soc.* **2007**, *129*, 14552. (g) Tinsley, J. M.; Mertz, E.; Chong, P. Y.; Rarig, R. F.; Roush, W. R. *Org. Lett.* **2005**, *7*, 4245. (h) Mertz, E.; Tinsley, J. M.; Roush, W. R. *J. Org. Chem.* **2005**, *70*, 8035. (i) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001**, *123*, 9488. (j) Roush, W. R.; Madar, D. J.; Coffey, D. S. *Synlett* **2001**, 955. (k) Danheiser, R. L.; Dixon, B. R.; Gleason, R. W. *J. Org. Chem.* **1992**, *57*, 6094.

(10) For details concerning the preparation of propargylsilanes **1**, see Supporting Information. Also see: Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 3231.

(11) Hamada, T.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 7342.
(12) For discussion of the alkyne−titanium complex, see: Perez, L. J.; Shimp, H. L.; Micalizio, G. C. *J. Org. Chem.* **2009**, *74*, 7211.
(13) A single example of titanium-mediated coupling using an α-chiral alkyne (methyl-substituted) with an achiral monosubstituted alkene has been reported in Micalizio's synthesis of dictyostatin with low regioselectivity; see the supporting information of Shimp, H. L.; Micalizio, G. C. *Tetrahedron* **2009**, *65*, 5908.
(14) The authors are grateful to a referee for suggesting the possible empirical model of the titanium-mediated diastereoselective reductive coupling.
(15) The proposed empirical model for the coupling reaction has been described as a "Class III" alkoxide-directed coupling process in Micalizio's review of regioselective metallacycle-mediated alkyne coupling reactions; see ref 5b.
(16) For examples of asymmetric intramolecular allylsilylations, see: (a) Judd, W. R.; Ban, S.; Aube, J. *J. Am. Chem. Soc.* **2006**, *128*, 13736. (b) Masse, C. E.; Dakin, L. A.; Knight, B. S.; Panek, J. S. *J. Org. Chem.* **1997**, *62*, 9335.
(17) For selected recent examples, see: (a) Lin, M.; Kang, G.; Guo, Y.; Yu, Z. *J. Am. Chem. Soc.* **2012**, *134*, 398. (b) Aikawa, K.; Okamoto, T.; Mikami, K. *J. Am. Chem. Soc.* **2012**, *134*, 10329. (c) Jung, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 1490. (d) Chen, Z.; Duan, X.; Zhou, P.; Ali, S.; Luo, J.; Liang, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 1370. (e) Tan, B.; Candeias, N. R.; Barbas, C. F. *Nature Chem* **2011**, *3*, 473.
(18) For mono-oxidation using iodobenzenediacetate and TEMPO, see: Yadav, J. S.; Rajender, V.; Gangadhara Rao, Y. *Org. Lett.* **2010**, *12*, 348.
(19) Miura, K.; Hondo, T.; Okajima, S.; Nakagawa, T.; Takahashi, T.; Hosomi, A. *J. Org. Chem.* **2002**, *67*, 6082.
(20) For TBAF−DMF-mediated desilylation, see: Heitzman, C. L.; Lambert, W. T.; Mertz, E.; Shotwell, J. B.; Tinsley, J. M.; Va, P.; Roush, W. R. *Org. Lett.* **2005**, *7*, 2405.
(21) (a) Qiao, M.; Ji, N.; Liu, X.; Li, K.; Zhu, Q.; Xue, Q. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5677. (b) Kim, H.; Baker, J. B.; Lee, S.; Park, Y.; Bolduc, K. L.; Park, H.; Dickens, M. G.; Lee, D.; Kim, Y.; Hong, J. *J. Am. Chem. Soc.* **2009**, *131*, 3192.
(22) For a recent example of Sakurai dimerization, see: Gesinski, M. G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2011**, *133*, 9727−9729.
(23) See Supporting Information for control experiments to support the dimerization process.