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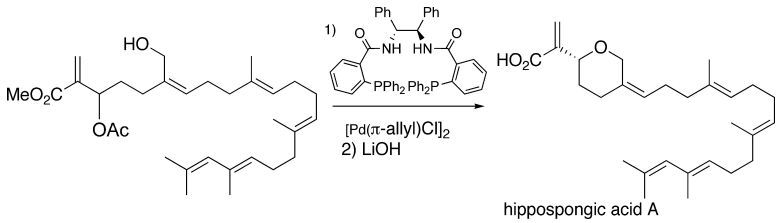

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Development of Aliphatic Alcohols as Nucleophiles for Palladium-Catalyzed DYKAT Reactions: Total Synthesis of (+)-Hippospongic Acid A

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Abstract: The ability to use aliphatic alcohols as competent nucleophiles in the palladium-catalyzed dynamic kinetic asymmetric transformation of Baylis−Hillman adducts is explored. High yield and enantioselectivity is obtained for both the kinetic transformation and dynamic kinetic transformation. The absolute stereochemistry of the products is used to explore the reactive conformation of 2-substituted π-allyl complexes with DPPBA-based chiral ligands. The utility of this method is further demonstrated in the context of a concise total synthesis of the gastrulation inhibitor (+)-hippospongic acid A. The synthesis features three palladium-catalyzed allylic alkylation reactions to introduce three different bond types: C−S, C−H, and C−O.

1. Introduction

Palladium-catalyzed asymmetric allylic alkylation (AAA) has become a powerful tool for the construction of stereogenic centers. As such, it has been used to efficiently solve many difficult problems in the context of natural product synthesis.[1] A unique feature of this method that leads to its versatility is the ability to form multiple types of bonds in the asymmetry-inducing step: C−O, C−S, C−N, and C−C bonds have all been successfully introduced.[2] The unifying quality of these reactions has been the use of "soft" functional groups as nucleophilic partners. Limited success has been achieved with "hard" nucleophiles, such as simple ketone enolates or aliphatic alkoxides, through the corresponding tin,[3] silicon,[3a] boron,[4] zinc,[5] or ammonium[6] derivatives.

More recent developments have indicated that a select group of nonstabilized nucleophiles are in fact compatible with palladium AAA reactions. Simple ketone and amide enolates afford excellent enantioselectivities in the alkylation of allyl acetate derivatives.[7] Furthemore, aliphatic alcohols are effective nucleophiles when the addition is constrained to be intramolecular.[4a,8] For example, high selectivity is achieved with alcohol **1** and vinyl epoxides in the presence of triethyl boron (Scheme 1).[9] Presumably, borate **2** forms which not only "softens" the alkoxide but also delivers the nucleophile in an intramolecular fashion. Furthermore, excellent selectivity is achieved without boron cocatalysis when the nucleophilic addition is otherwise constrained to be intramolecular (ie **4**).[8]

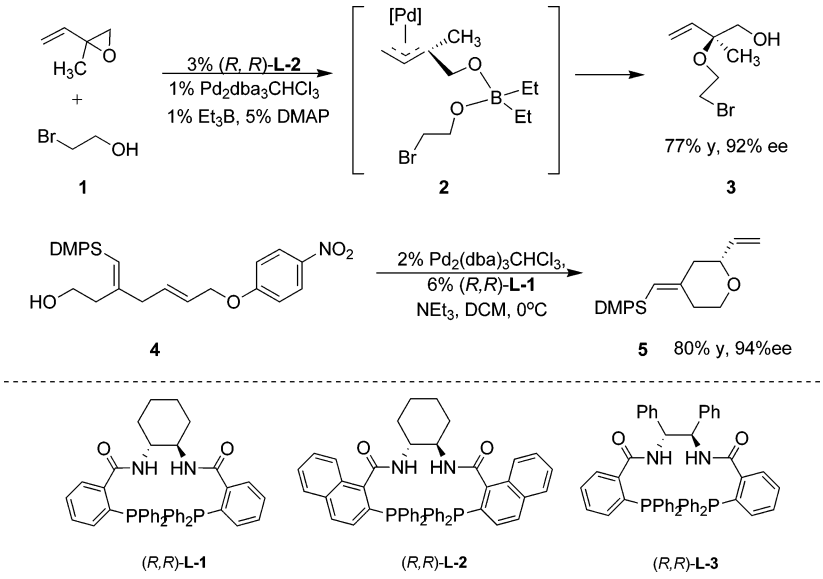
We were interested in exploring the versatility of aliphatic alcohols as nucleophiles by extending this novel nucleophilic class to other AAA processes, with a particular interest in the dynamic kinetic asymmetric transformation of Baylis−Hillman adducts. Enantiopure Baylis−Hillman adducts are versatile synthetic intermediates; as a result, much research has been devoted to designing catalytic asymmetric versions of this reaction.[10] A conceptually distinct approach was recently developed in the Trost group wherein achiral Baylis−Hillman derivatives are transformed to their chiral counterparts through a palladium-catalyzed dynamic kinetic asymmetric transformation (DYKAT) (Scheme 2).[11] Aryl alcohols were found to be competent nucleophiles for this process. Access to the deracemized parent compounds was achieved through deprotection of the chiral aryl ether products. Extension of this strategy to include alkyl alcohols would significantly expand its versatility and offer direct access to chiral alkyl ether products. Furthermore, the complex nature of this transformation represents a challenging test for determining the generality of this novel class of nucleophiles in AAA reactions.

The transformation outlined in Scheme 2 becomes most impressive when one considers the degree of control exhibited by the catalyst. Under the influence of a chiral catalyst, one enantiomer of starting material ionizes via a matched pathway,

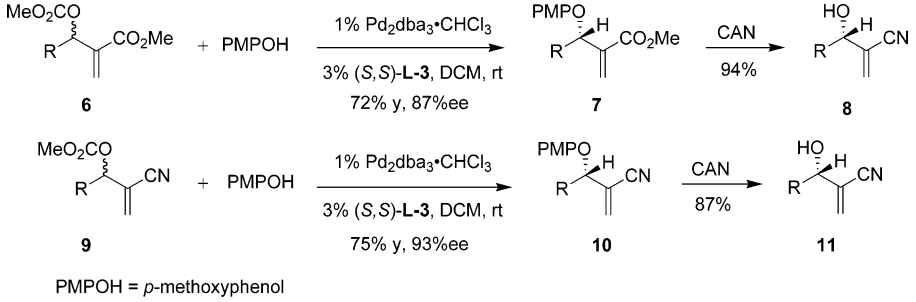
(1) Trost, B. M.; Crawley,M. L. *Chem. Rev.* **2003**, *103*, 2921. Also see Trost, B. M. *Chem. Pharm. Bull.* **2004**, *50*, 1.
(2) Trost, B. M.; Fleming, I. Eds. *Comprehensive Organic Synthesis*; Pergammon Press: Oxford, England, 1991; Vol. 4, Chapter 3.3.
(3) (a) Trost, B. M.; Tenaglia, A. *Tetrahedron Lett.* **1988**, *29*, 2927. (b) Trost, B. M.; Self, C. R. *J. Org. Chem.* **1984**, *49*, 468. (c) Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2591.
(4) (a) Trost, B. M.; MacEachern, E.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 12702. (b) Negishi, E.; Matsushita, H.; Chatterjee, S.; John, R. A. *J. Org. Chem.* **1982**, *47*, 3188.
(5) Kim, H.; Lee, C. *Org. Lett.* **2002**, *4*, 4369.
(6) Suzuki, T.; Sato, O.; Hirama, M. *Tetrahedron Lett.* **1990**, *31*, 4747.
(7) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759.
(8) Trost, B. M.; Machacek, M. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 4693.
(9) Trost, B. M.; Tang, W. *Org. Lett.* **2001**, *3*, 3409.
(10) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219. (b) Iwama, T.; Tsukiyama, S.; Kinoshita, H.; Kanematsu, K.; Tsurukami, Y.; Iwamura, T.; Watanabe, S.; Kataoka, T. *Chem. Pharm. Bull.* **1999**, *47*, 956. (c) Barrett, A. G. M.; Cook, A. S.; Kamimura, A. *Chem. Commun.* **1998**, 2533. (d) Hayase, T.; Shibata, T.; Soai, K.; Wakalsuki, Y. *Chem. Commun.* **1998**, 1271. (e) Marko, I. E.; Giles, P. R.; Hindley, N. J. *Tetrahedron* **1997**, *53*, 1015.
(11) Trost, B. M.; Tsui, H. C.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 3534.

10.1021/ja050340q CCC: $30.25

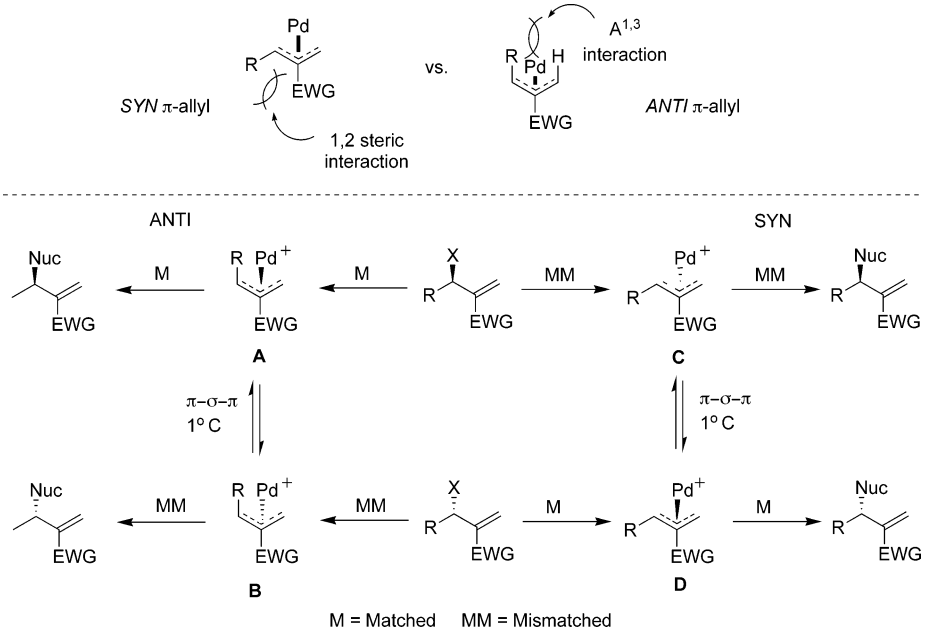
Scheme 1. AAA with Simple Aliphatic Alcohols



Scheme 2. Deracemization of Baylis−Hillman Adducts

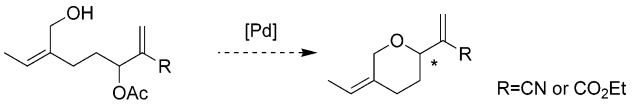


Scheme 3. Syn and Anti π-Allyl Complexes



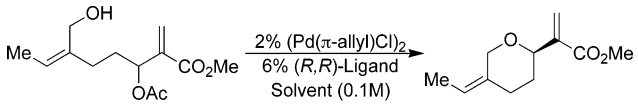
whereas the other ionizes via a mismatched pathway (Scheme 3). Direct attack onto the two diastereomeric intermediates results in racemic product. However, if equilibration of the diastereomers via a $\pi-\sigma-\pi$ mechanism is faster than nucleophilic addition, then chiral product can be obtained. Substrates such as **6** and **9** offer an additional challenge in that both syn (**C** and **D**) and anti (**A** and **B**) π-allyl complexes need to be considered. In general, the syn π-allyl complex is more stable than the anti due to unfavorable $A^{1,3}$ interactions in the anti complex.[12] However, 2-substitution on the allyl destabilizes the syn complex through developing 1,2-steric interactions. Depending on the steric size of the substituent at C2, either π-allyl

Scheme 4. Aliphatic Alcohol DYKAT



12 13

Table 1. Cyclization Optimization of **14**[a]



14 15

entry	ligand	solvent	additive[b]	temp (°C)	% conv.[c]	% ee
1	L-1	CH_2Cl_2	NEt_3[d] $N(Bu)_4Cl$	0	56	55
2	L-1	CH_2Cl_2	$N(Hex)_4Cl$	0	50	62
3	L-3	CH_2Cl_2	$N(Hex)_4Cl$	0	75	64
4	L-3	CH_2Cl_2	$N(Hex)_4Cl$	25	100[e]	68
5	L-3	CH_2Cl_2	$N(Hex)_4Cl$	50	100	50
6	**L-3**	**dioxane**	**$N(Hex)_4Cl$**	**25**	**53**	**95**
7	**L-3**	**dioxane**	**$N(Hex)_4Cl$**	**80**	**100**	**83**

[a] All reactions run in degassed solvent for 17 h. [b] 30 mol % additive was added. [c] Conversions are based on 300 MHz ^{1}H NMR ratios. Isolated yields consistently ranged between 85% and 95% for 100% conversion. [d] 100 mol % additive was added. [e] Required 21 h for complete conversion.

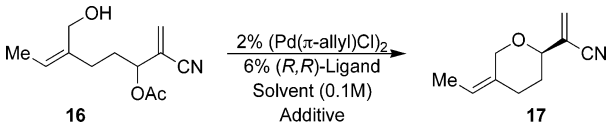
intermediate may predominate. The catalyst must effectively control the relative population of these two isomers to achieve high product enantioselectivity since matched nucleophilic attack onto the syn complex leads to absolute configuration that is opposite from that by matched attack onto the anti complex.[13]

2. DYKAT with Aliphatic Alcohol Nucleophiles

To design a system compatible with aliphatic alcohol nucleophiles, we need to constrain the nucleophilic attack to be intramolecular in nature. The tether length between electrophile and nucleophile is of ultimate importance. Short tethers may lead to fast trapping of the π-allyl intermediates, which will decrease the enantioselectivity of the products. Long tethers may lead to poor trapping of the π-allyl complexes due to unfavorable entropic and ring strain effects, which can lead to decomposition and undesirable side products. Our previous work with alkyl alcohol nucleophiles indicated that both five- and six-membered rings are efficiently formed, with pyran synthesis affording the highest % ee. Adopting pyran formation as ideal, our model substrate to test the DYKAT becomes **12** (Scheme 4).[14]

2.1. Development of the Method. We initiated our optimization with conditions similar to those employed in the cyclization of achiral substrate **4**, but found both low conversion and enantioselectivity (Table 1, entry 1). Under these conditions, the rate of π-allyl complex equilibration is slower than the rate of facile 6-exo nucleophilic attack. It is necessary to increase the rate of equilibration while at the same time decreasing the rate of nucleophilic attack. Removal of the triethylamine from the reaction should decrease the effectiveness of the alcohol nucleophile. Furthermore, since chloride ion has been shown to promote equilibration of Pd−allyl complexes, we kept this additive but switched to the tetrahexylammonium counterion.

Table 2. Cyclization Optimization of **16**



16 17

entry	ligand	solvent	additive[b]	temp (°C)	% conv.[c]	% ee
1	**L-3**	**dioxane**	**$N(Hex)_4Cl$**	**25**	**52**	**98**
2	L-3	dioxane	$N(Hex)_4Cl$	80	100	68
3	L-3	CH_3CN	$N(Hex)_4Cl$	80	100	67
4	L-3	toluene	$N(Hex)_4Cl$	80	100	81
5	**L-1**	**toluene**	**$N(Hex)_4Cl$**	**60**	**100**	**91**

[a] All reactions run in degassed solvent for 17 h. [b] 30 mol % additive was added. [c] Conversions are based on 300 MHz ^{1}H NMR ratios. Isolated yields consistently ranged between 85% and 95% for 100% conversion.

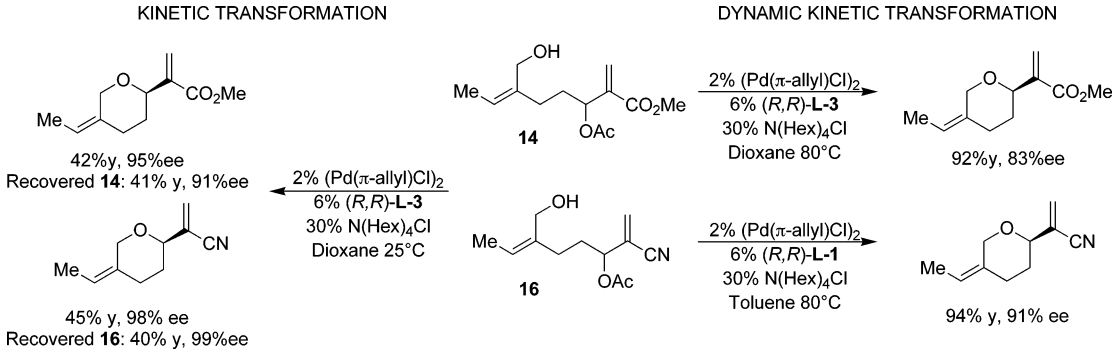
Bulky counterions are assumed to associate with the nucleophile, increasing its effective steric bulk and slowing the rate of attack.[15] These changes resulted in a slight increase in selectivity, although little change was noted in the conversion (entry 2).

At this stage, we noted that reaction conversion was consistently hovering around 50%, indicating that the ligand environment was suppressing the mismatched ionization. Fortunately, several DPPBA-based ligands with varying steric environments have been developed. In particular, stilbene-based **L-3** contains a more flexible backbone than **L-1**, which should "open" the pocket and facilitate mismatched ionization.[16] In practice, reactions utilizing **L-3** showed improved conversion and enantioselectivity (Table 1, entry 3). Increasing the reaction temperature to 25 °C was also beneficial, affording complete conversion and a small increase in enantioselectivity (entry 4). Increasing the temperature further, led to reduced selectivity. This trend with temperature points to the fact that, while heat can lead to faster equilibration of the allyl complexes and increased selectivity, it can also lead to faster nucleophilic addition and decreased selectivity. Striking a balance between these two competing processes is key. Finally, we looked at the effect of solvent. Solvents that stabilize the charged intermediates should slow nucleophilic attack and increase the selectivity. Accordingly, reactions run in dioxane at 25 °C afford **15** in an excellent 95% ee (entry 6). Interestingly, the conversion was a modest 53%, independent of the duration of the reaction, and the starting material, **14**, was recovered with 91% ee. These observations indicate that a highly selective *kinetic* resolution has been achieved wherein the mismatched ionization is not occurring. Increasing the temperature above 25 °C allows the mismatched ionization to proceed, such that full conversion with 83% ee (a DYKAT process) was obtained (entry 7).

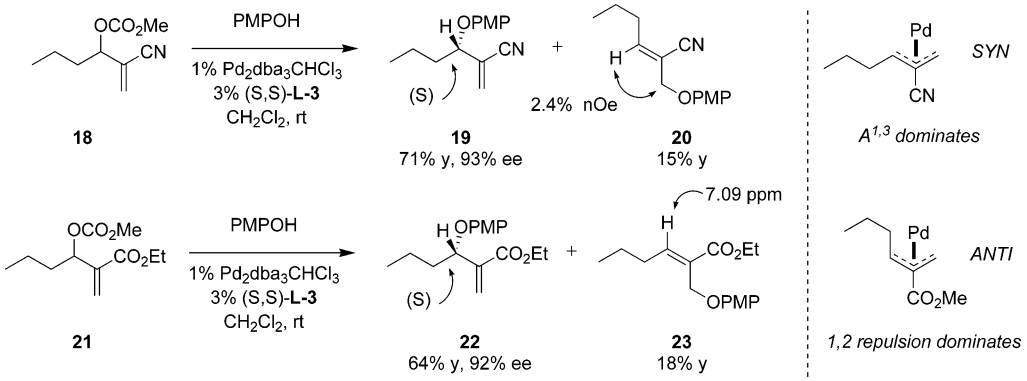
Excellent selectivity for a kinetic resolution was also obtained for **16** when the reaction was run at 25 °C in dioxane (Table 2, entry 1). However, the optimized DYKAT conditions for **14** did not transfer over to **16** (entry 2). Fortunately, reactions run in toluene returned high product selectivity. Even more gratifying was the combination of **L-1** and toluene since 91% ee was obtained at full conversion. The optimized conditions for both the kinetic and dynamic kinetic transformations are outlined in Scheme 5.

(12) (a) Faller, J. W.; Tully, M. T. *J. Am. Chem. Soc.* **1972**, *94*, 2676. (b) Faller, J. W.; Thomsen, M. E.; Mattina, M. J.. *J. Am. Chem. Soc.* **1971**, *93*, 2642.
(13) Matched implies that the reaction pathway is favored by the given enantiomer of chiral ligand.
(14) Full experimental details for all intermediates and products are reported in the Supporting Information.
(15) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1998**, *120*, 70.
(16) **L-3** has been successfully used to effect alkylations on bulky or otherwise sterically encumbered substrates. For an example relating to DYKAT reactions, see ref 11.

Scheme 5. Optimized Conditions



Scheme 6. Analysis of the Linear Isomer



3. Determination of Absolute Stereochemistry

As noted in Scheme 3, both syn and anti complexes are possible reactive intermediates in the DYKAT of 2-substituted π-allyl substrates. Importantly, the absolute stereochemistry of the products will differ, depending on the conformation of the allyl intermediate. Given the high selectivity of the DYKAT process, we assume the nucleophilic attack occurs predominantly on one of the two possible conformations. Our efforts to identify the reactive conformation of 2-substituted π-allyl complexes participating in the intermolecular DYKAT reaction revealed several interesting aspects. Unlike in the intramolecular cyclization reaction where the nucleophile is constrained to attack only at the more substituted terminus of the π-allyl complex, addition to both termini of the allyl is possible in an intermolecular reaction.[17] While the catalyst is effective at controlling the regioselectivity of addition, small amounts of the linear isomer can be isolated under unoptimized conditions. Analysis of the linear isomer indicates that with cyano substrate **18,** the double bond geometry is exclusively *Z* (Scheme 6). This stereochemistry is expected if the reactive π-allyl complex is in the syn conformation. In contrast, with ester substrate **21**, the product olefin configuration is exclusively *E*, as expected for nucleophilic addition occurring through the anti complex. The change in allyl conformation is rationalized on the basis of the different steric size of the two substituents. The linear cyano group is sterically small, and as such, the unfavorable $A^{1,3}$ interactions of an anti π-allyl complex dominate. However, the ester is sterically large enough that unfavorable 1,2-repulsion between the ester and propyl group in the syn complex dominate.

Further evidence for a reactivity dichotomy is uncovered through investigations of achiral substrates **24** and **26** (Scheme 7). These substrates ionize directly to the anti complex. If the anti complex is more reactive, this olefin geometry should be preserved in the linear products. On the other hand, if the syn complex is more reactive, then a scrambling of the olefin geometry is expected. In practice, cyano substrate **24** affords a mixture of linear products **25** and **20**. The amount of scrambling increases as an external chloride source is introduced, indicating the ability of chloride to promote the anti-to-syn interconversion. In contrast, substrate **26** affords exclusively linear product **23** independent of the amount of chloride added. This result again indicates that substrates with C2-ester substitution preferentially react through the anti π-allyl complex.

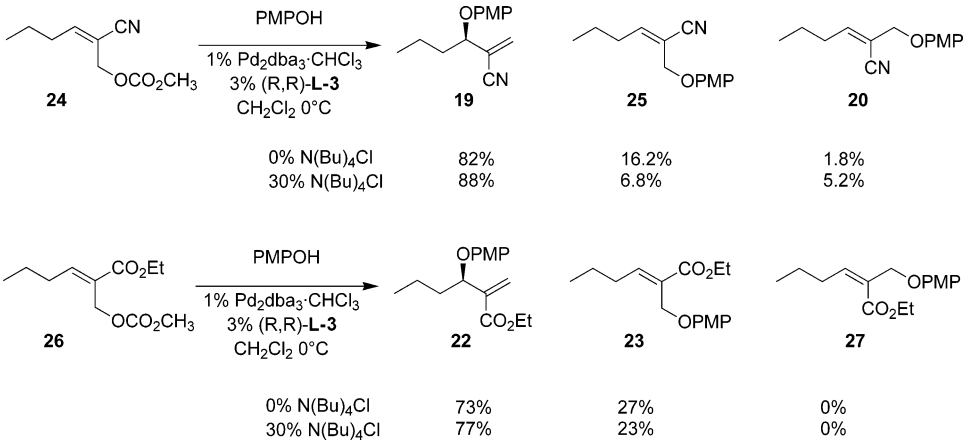
These results are curious at first glance since exo nucleophilic attack onto the syn and anti π-allyl complexes should afford products with opposite absolute stereochemistries (Scheme 8), and yet both **22** and **19** were experimentally found to have the same absolute configuration.[11] Experimental work with cyclic systems was used to shed light on this situation. In a recent report, we noted that π-allyl complexes substituted at the 2-position with an ester afford the opposite selectivity than that predicted by the working model.[18] Furthermore, the absolute stereochemistry is opposite to that observed for cyclic π-allyl complexes bearing a cyano or hydrogen[19] at C2 (Scheme 9).

To explain this change, we invoke a change in the cant of the π-allyl complex due to coordination of the methyl ester to palladium. Normally, the 2-position of the allyl cants away from the palladium. Upon coordination of the ester, the allyl then cants toward the metal (Scheme 10). Stereoelectronic arguments dictate that the nucleophile approaches antiperiplanar relative to palladium. Therefore, the preferred trajectory for addition is via the right rear quadrant of the π-allyl−metal−ligand complex,

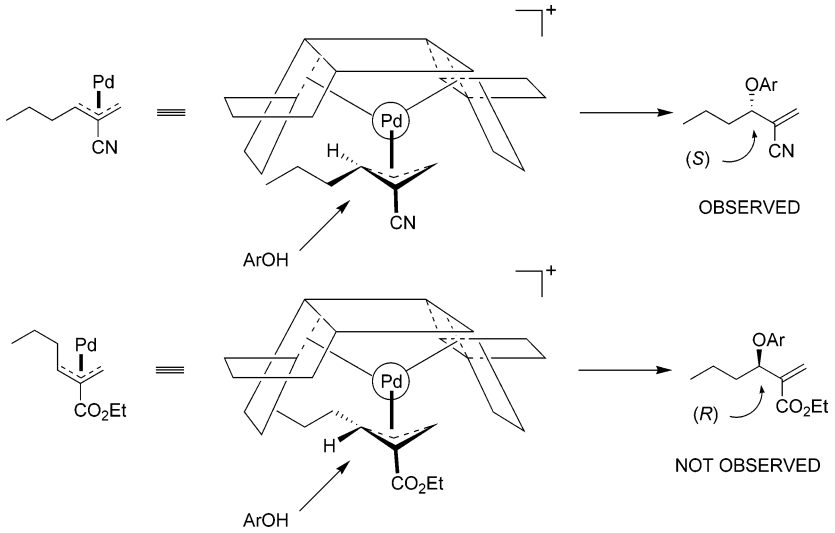
(17) Trost, B. M.; Thiel, O. R.; Tsui, H. C. *J. Am. Chem. Soc.* **2002**, *124*, 11616.

(18) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 11262.
(19) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 815.

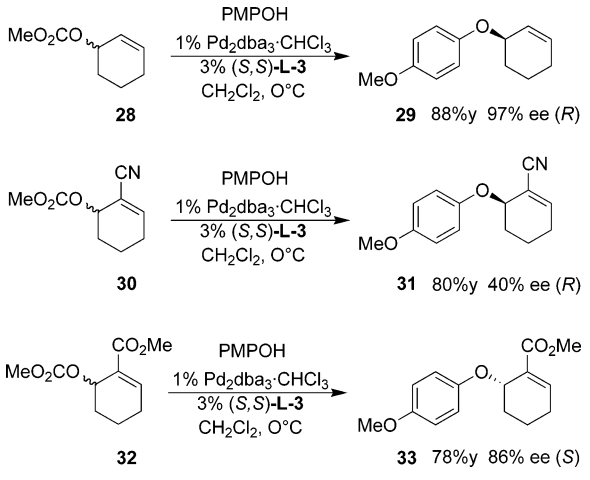
Scheme 7. Reactivities of **24** and **26**



Scheme 8. Predictions Based on Exo Nucleophilic Addition



Scheme 9. Additions onto Cyclic 2-Substituted Allyls



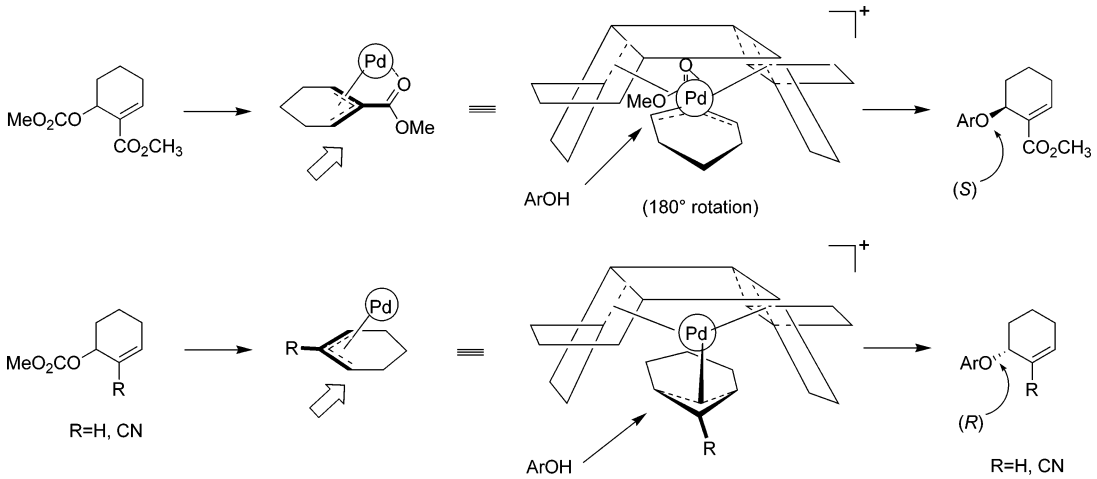
which predicts the observed stereochemistry. Interestingly, the cyano substrate, which is electronically similar to the ester, but is geometrically constrained from coordinating to the palladium metal, affords stereochemistry consistent with the typical cant of the allyl unit.

Combining these observations, we can rationalize for the acyclic cases why the selectivity does not change between the methyl ester and cyano-substituted substrates. When both the cant and the syn/anti conformation of the π-allyl changes, the same stereochemistry is predicted (Scheme 11) as is observed experimentally.

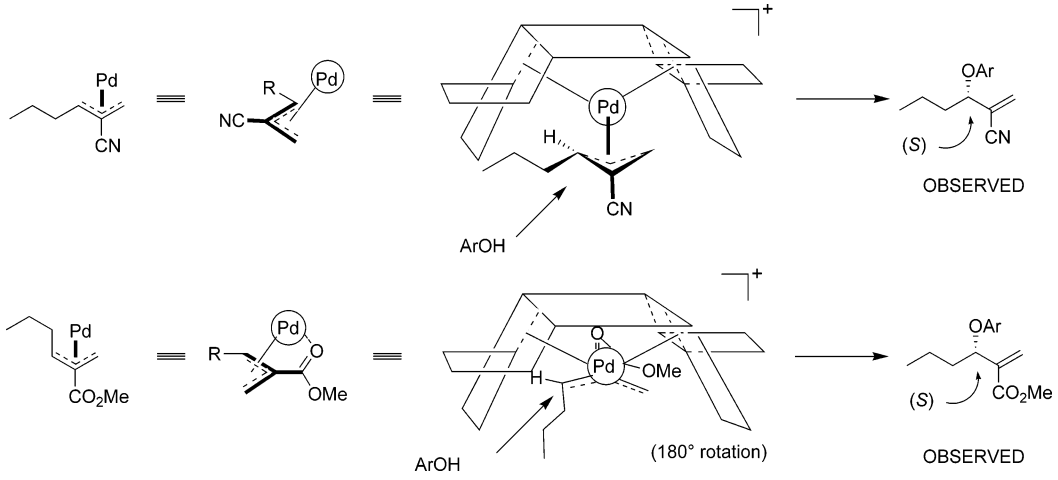
These stereochemical arguments are also consistent with the experimental observations of the cyclization DYKAT reaction. The absolute stereochemistry of the tetrahydropyran products was determined through derivitization. Ester **15** was saponified under basic conditions to afford **34**, and nitrile **17** was transformed through a DIBAl-H reduction/[20]Pinnick oxidation[21] sequence to afford **34** in an unoptimized 40% yield (Scheme 12). Comparison of the rotations indicates that both substrates afford product with the same absolute stereochemistry. Utilization of this DYKAT in the synthesis of a (+)-hippospongic acid A (vide infra) was used to assign the (*R*) configuration arising from (*R*,*R*)-ligand. These results are completely consistent with the stereochemical assignment made for **19** and **22** and with the working model (same analysis as Scheme 11). We can therefore conclude that, in the cyclization DYKAT, alkylation of **14** is occurring through the anti π-allyl complex with coordination of the ester to the palladium center, whereas alkylation of **16** is occurring through the syn complex with no cyano coordination to the metal.

(20) Campi, E.; Fitzmaurice, N. J.; Jackson, W. R.; Perlmutter, P.; Smallridge, A. J. *Synthesis* **1987**, 1032.
(21) (a) Bal, B. S.; Childers, W. E., Jr; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091. (b) Yung-Son, H.; Wei-Chih, L. *Tetrahedron Lett.* **1995**, *35*, 7693.

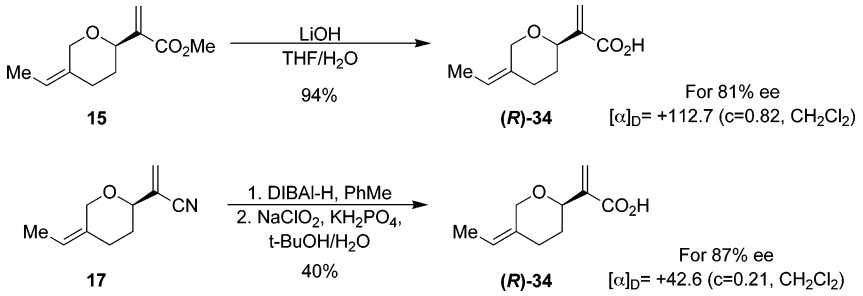
Scheme 10. Cyclic Substrates: Changing the Cant



Scheme 11. Acyclic Cases: Stereochemical Rationale

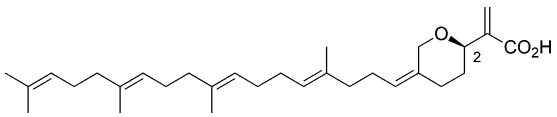


Scheme 12. Derivitization



4. Synthesis of (+)-Hippospongic Acid A

During the course of our methodology studies, we became interested in the natural product (+)-hippospongic acid A (**35**) (Figure 1).[22] This compound shows considerable activity for inhibiting gastrulation in starfish embryos. Gastrulation is a fundamental process in the development of all multicellular organisms during which differentiation of the ectoderm, endoderm, mesoderm and germ layer occurs. Inhibition of this developmental pathway would permit study of the individual stages; however, very few inhibitors are known. Recently, **35** has also been found to be a modest inhibitor of both DNA polymerase ($IC_{50} = 5.9-17.5\ \mu M$) and DNA topoisomerase I/II ($IC_{50} = 15-20\ \mu M$), both crucial enzymes for DNA replication.[23] Furthermore, **35** is effective at inducing apoptosis in the human gastric cancer cell line NUGC-3 by arresting the cell cycle at G1/G2.[23] Because of these properties, there has been considerable interest in the terpene-based natural product and

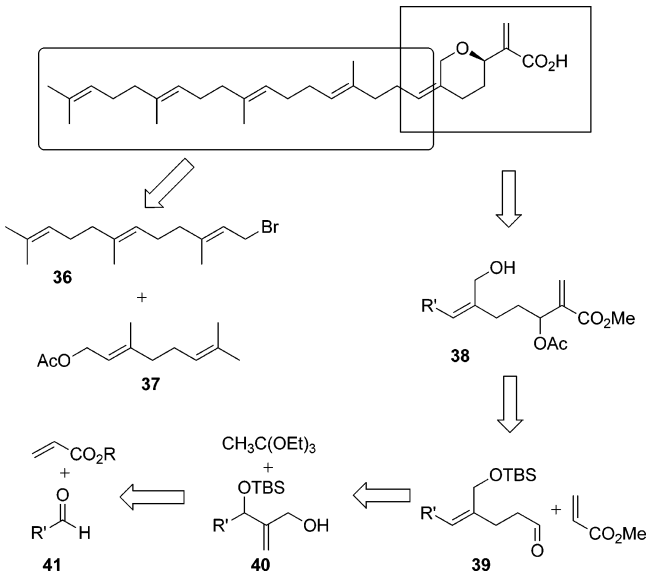


35

Figure 1. Structure of (+)-hippospongic acid A.

(22) Ohta, S.; Uno, M.; Tokumasu, M.; Hiraga, Y.; Ikegami, S. *Tetrahedron Lett.* **1996**, *37*, 7765.
(23) Mizushima, Y.; Murakami, C.; Takikawa, H.; Kasai, N.; Xu, X.; Mori, K.; Oshige, M.; Yamaguchi, T.; Saneyoshi, M.; Shimazaki, N.; Koiwai, O.; Yoshida, H.; Sugawara, F.; Sakaguchi, K. *J. Biochem.* **2003**, *133*, 541.

Scheme 13. Retrosynthetic Analysis

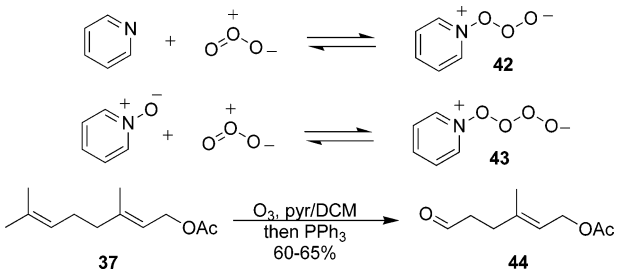


its derivatives. Several groups have completed racemic syntheses of hippospongic acid.[24] However, only two syntheses have addressed the one stereocenter: introducing the chirality through a late-stage resolution[25] and an enzyme-mediated asymmetric reduction,[26] respectively. While these syntheses provided the absolute stereochemistry of **35**, both are lengthy, requiring 23 and 33 steps, respectively.

We envisioned developing the first catalytic asymmetric route to **35** by utilizing our cyclization DYKAT reaction. A further advantage of this strategy is the simultaneous formation of both the pyran ring and the one stereocenter, which should improve the synthetic efficiency and decrease the overall step count. The DYKAT cyclization substrate was envisioned to arise through two Baylis−Hillman[27] couplings and one Claisen rearrangement (Scheme 13). The terpene side chain was disconnected through an allyl−allyl coupling sequence leading back to commercially available farnesyl bromide and geranyl acetate.

The synthesis begins with a selective oxidation of the more electron-rich olefin of geranyl acetate. While dihydroxylation and epoxidation led to mixtures of mono- and bisoxidation products, a highly selective oxidation was achieved through ozonolysis in a methylene chloride/pyridine mixed-solvent system.[28] Nucleophilic agents such as pyridine and pyridine oxide have been proposed to react with ozone to form compounds such as **42** and **43** (Scheme 14).[29] Ozonolysis using these less electrophilic agents slows the oxidation rate, allowing for small electronic differences in the olefins to impact the chemoselectivity. These conditions reliably afforded clean monooxidation product **44** in good yield.

Scheme 14. Selective Ozonolysis



We next planned to couple the geranyl subunit to farnesyl bromide using nucleophilic displacement. To transform **44** into a nucleophilic moiety, we envisioned directly transforming the allyl acetate to an allyl sulfone using palladium catalysis. Aldehyde **44** was protected as a dioxolane acetal and used without purification in the allylic alkylation step. Using phenyl sulfinic acid and conditions developed for sulfone nucleophiles[30] resulted in incomplete conversion even under extended reaction times and a 10:1 mix of S_N2- and S_N2'-like products as well as a 4:1 mix of E:Z isomers **46** and **47** (Table 3). Reasoning that too much $\pi-\sigma-\pi$ isomerization of the allyl intermediate was causing the formation of both **47** and **48**, we investigated the effect of various conditions on the reaction. Increasing the temperature allowed for full conversion but increased the formation of isomer **48**. Using the less hindered tetramethylammonium bromide as a phase transfer catalyst slightly increased the *E*:*Z* olefin ratio of the products. Ligand electronics had promising effects on selectivity (entry 5), but ligand sterics had the largest impact. Bulky ligands are known to decrease the rate of π-allyl isomerization since formation of the σ complex is disfavored. Consistent with this idea, moving from dppp to dppb to dppf systematically improved ratios of **46**:**47** and completely eliminated the formation of **48** (entries 2−4).

The isomeric mixture was then smoothly deprotonated with LDA and coupled with farnesyl bromide in the presence of DMPU to yield monoalkylated product **49** in good yield (Scheme 15). The presence of DMPU is crucial for this coupling as lower yield and bisalkylation product was observed in its absence. Attempts to remove the resulting allyl sulfone under traditional dissolving metal conditions (Li/NH_3 or Na/Hg) afforded modest yields of desulfonylated product accompanied by varying amounts of olefin regio- and stereochemical scrambling. Literature precedent indicated that allyl sulfones can be removed with retention of olefin stereochemistry in the presence of catalytic Pd and a hydride source.[31] The mechanism involves ionization of the allyl sulfone followed by trapping of the resulting η^3-intermediate with a hydride nucleophile. Reaction temperature was found to be very important since no reaction is seen at 0 °C and mixtures of olefin regioisomers are obtained at 65 °C. Running the reaction at 25 °C affords an excellent yield of desulfonylated product **50** with no observable olefin scrambling.

At this stage, we needed to reveal the aldehyde functionality for the first of our two planned Baylis−Hillman reactions. However, deprotection of the dioxolane was nontrivial. Both

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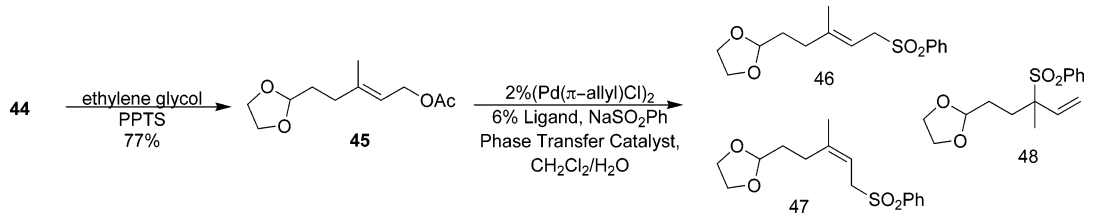
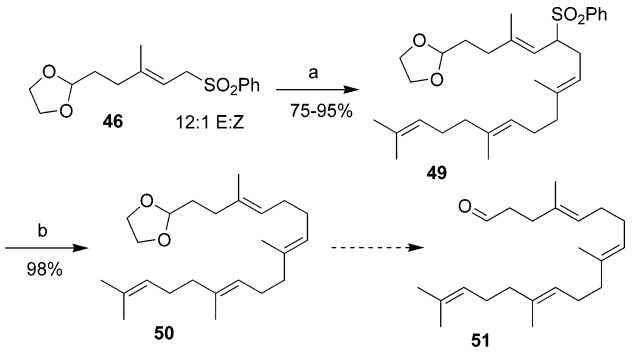
Table 3. Optimizing Formation of **46**



entry	ligand	PTC[a]	temp (°C)	ratio **46**:**47**	ratio **46**+**47**:**48**	total yield (%)[b]
1	dppp	$N(Hex)_4Br$[c]	0	4:1	10:1	53
2	dppp	$N(Me)_4Br$	25	5:1	2.5:1	63
3	dppb	$N(Me)_4Br$	25	7:1	>23:1	75
4	**dppf**	**$N(Me)_4Br$**	**25**	**12:1**	**>23:1**	**98**
5	$P(furyl)_3$	$N(Me)_4Br$	25	7:1	6:1	70

[a] 9% PTC (phase transfer catalyst) was added. [b] Represents isolated yields after chromatography of all isomers. [c] 20% $N(Hex)_4Br$ was added.

Scheme 15. Synthesis of **51**[a]



[a] Reactions and conditions: a) LDA, DMPU, then farnesyl bromide; b) $LiBHEt_3$, 12% dppp, 4% $(Pd(\pi\text{-allyl})Cl)_2$.

protic and nonprotic acid conditions caused decomposition of starting material and product. Since acyclic acetals are much less stable than their cyclic counterparts, switching to a diethoxy acetal was expected to avoid the problems we were facing. Importantly, the diethoxy acetal behaved similarly to the dioxolane in the steps preceding deprotection (Scheme 16). Furthermore, clean deprotection of **54** to aldehyde **51** was achieved in 91% yield under mild conditions using Amberlist-15.

The Morita−Baylis−Hillman reaction of **51** with either methyl acrylate or acrylonitrile was exceedingly slow and accompanied by large amounts of decomposition products under either DABCO or trialkylphosphine-catalyzed[32] conditions (Scheme 17). Lewis acid/Lewis base catalysis[33] resulted in rapid dimerization of **51** to its self-aldol condensation product. Furthermore, aqueous conditions[34] failed with **51** presumably due to the high hydrophobicity of the substrate. An alternative to the Morita−Baylis−Hillman reaction is to add the vinyl moiety through metal-mediated coupling. Chromium/nickel-mediated coupling of vinyl halides with aldehydes to yield allylic alcohols has been demonstrated to be a mild method for carbon−carbon bond formation.[35] Using vinyl bromide **56**[36] has the added advantage that the side chain comes in at the correct oxidation state, thereby eliminating a reduction step. In practice the coupling reaction worked quite well, affording a quantitative yield of addition product **57**. The choice of the TBDPS protecting group on **56** was crucial to avoid the formation of inseparable mixtures of products resulting from silyl transfer to the neighboring alkoxide.

Allyl alcohol **57** was then subjected to a Johnson ortho ester Claisen rearrangement at 100 °C, affording **58** as 16:1 *Z*:*E* olefin mixture in excellent yield (Scheme 18). Higher temperatures showed decreased selectivity, whereas lower temperatures showed slightly increased selectivity but decreased yields. The small amount of undesired double bond isomer is a result of reaction through the alternate chair form, which removes steric interactions with the bulky TBDPS ether. Reduction of **58** with DIBAl-H followed by oxidation with Dess−Martin periodinane afforded **59** in 75% yield. Direct formation of **59** from **57** via an ethyl vinyl ether Claisen rearrangement was appealing, yet low yielding due to the formation of multiple products under simple heating. Many transition metals are known catalyze this rearrangement, but substitution in the beta position of the allyl alcohol is not well tolerated in the reaction.[37,38] Consistent with these observations, reaction of **57** with ethyl vinyl ether catalyzed by either $Hg(OAc)_2$ or $(PhCN)_2PdCl_2$ or organic catalysts such as dimethoxyphenol[38a] led to no aldehyde products.

With aldehyde **59** in hand, we were not surprised to see that the Morita−Baylis−Hillman reaction gave similarly poor results as with **51**. We therefore turned to an alternative originally explored by Tsuda who noticed that, when DIBAl-H is precomplexed with HMPA, propiolate esters undergo 1,4- rather than 1,2-reduction.[39,40] Furthermore, NMR studies indicated that the resulting organoaluminum species is carbon-bound rather than oxygen-bound, indicating the possibility of forming carbon−carbon bonds by quenching with electrophiles. When aldehydes are used as electrophiles, the resulting products are equivalent to Morita−Baylis−Hillman adducts, yet they are

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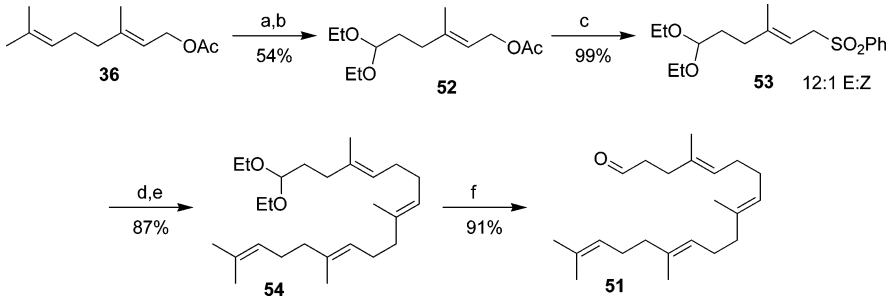
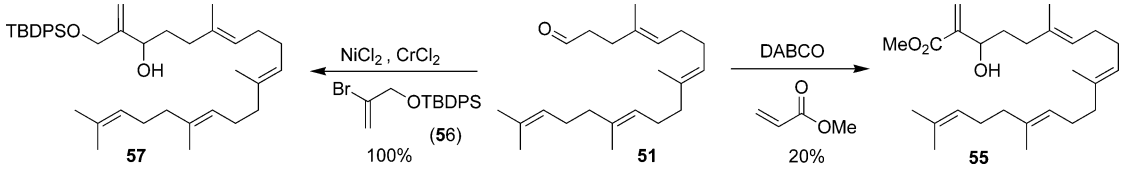
Scheme 16. Diethoxyacetal as Protecting Group[a]

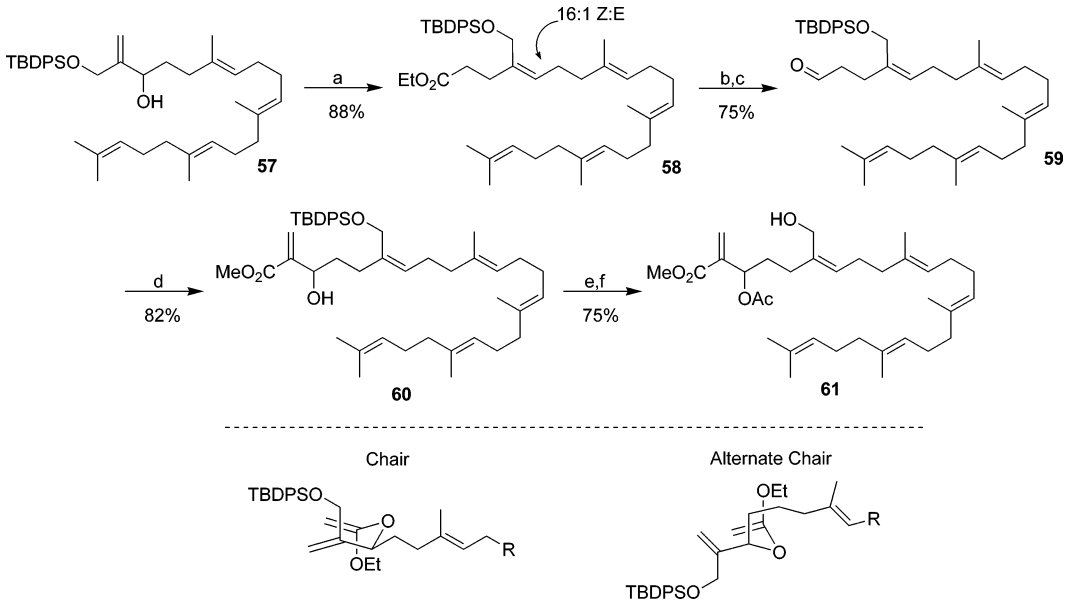


[a] Reactions and conditions: a) O_3, pyridine, then PPh_3; b) EtOH, PPTS; c) 2%($Pd(\pi$-allyl)Cl)$_2$, 6% dppf, $PhSO_2Na$, 9% TMAB; d) LDA, DMPU, then farnesyl bromide; e) $LiBHEt_3$, 12% dppp, 4% ($Pd(\pi$-allyl)Cl)$_2$; f) Amberlist-15.

Scheme 17. First Baylis−Hillman



Scheme 18. Setting up the Cyclization DYKAT Reaction[a]



[a] Reactions and conditions: a) $CH_3C(OEt)_3$; b) DIBAl-H; c) Dess−Martin-periodinane, pyridine; d) methyl propiolate, HMPA, DIBAl-H; e) AcCl; f) TBAF, AcOH.

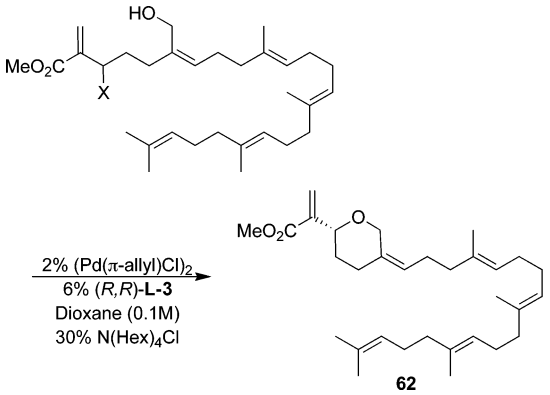
formed with significantly shortened reaction times and under mild temperatures. In our hands, the transformation was quite successful, affording good yields of coupled product **60**.

All that remained to set up the key DYKAT cyclization step was to install the allylic leaving group and reveal the pendant nucleophile. Both steps proceeded smoothly to afford palladium cyclization precursor **61** in 75% overall yield. Both the optimized kinetic transformation and dynamic kinetic transformation conditions were applied to **61** (Table 4). While the optimized conditions were successful for obtaining a kinetic transformation (entry 1), the conditions for a dynamic kinetic transformation afforded only 55% conversion to **62** with 91% enantioselectivity. Recovered **61** was enriched, indicating that the mismatched isomer was not ionizing under these conditions. Presumably, the bulk of the geranylgeranyl side chain prohibits the mismatched ionization at temperatures that afford clean ionization for the model substrate (**14**). Unfortunately, heating the reaction to 100 °C afforded full conversion, but at the cost of selectivity. Again, the bulk of the side chain is assumed to be the cause since the necessary $\pi-\sigma-\pi$ isomerization may be slowed by the bulk of the side chain. The rate of mismatched ionization can be increased through the use of more activated allylic leaving groups such as trichloroethyl carbonate and *tert*-butyl carbonate (entries 4 and 5). Unfortunately, the selectivity in these cases decreased, presumably due to an increase in the background reaction.

Nevertheless, **62** can be obtained in a satisfying 50% isolated yield and 91% ee. To finish the synthesis the methyl ester is saponified with LiOH in aqueous THF to afford the natural product in 98% yield (Scheme 19).[41] The absolute stereochem-

(41) Our spectral data matched those previously reported in refs 25 and 26.

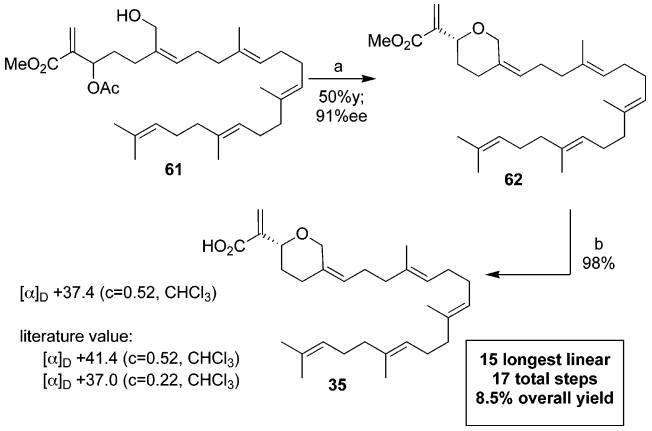
Table 4. Optimizing the Key Cyclization[a]



entry	X	temp (°C)	% conv.[b]	% ee
1	OAc	25	45	94
2	OAc	80	55[c]	91
3	OAc	100	100[d]	65
4	OTroc	25	47	87
5	OBOC	25	53	23

[a] All reactions run in degassed solvent under argon for 17 h. [b] Conversions based on 300 MHz ^{1}HNMR ratios. [c] Isolated yield 50%. [d] Isolated yield 93%.

Scheme 19. Completion of the Synthesis[a]



[a] Reactions and conditions: a) 2% (Pd(π-allyl)Cl)$_2$, 6% (*R,R*)-**L-3**, 30% N(Hex)$_4$Cl, dioxane; b) LiOH, THF/H$_2$O.

ical assignment of the DYKAT cyclization was confirmed by comparison of the rotation of **35** to natural (+)-hippospongic acid. This synthesis is the shortest to date, furnishing the natural product in only 15 longest linear and 17 total steps with an 8.5% overall yield.

5. Conclusions

Chiral Baylis−Hillman adducts represent an important class of asymmetric building blocks. We have demonstrated a concise and highly selective deracemization of achiral Baylis−Hillman adducts using aliphatic alcohol nucleophiles. Both a kinetic transformation and a dynamic kinetic transformation were developed to afford substituted pyran products with high yields and selectivities. Furthermore, we have shown the generality of aliphatic alcohols to function as competent nucleophiles in palladium-catalyzed AAA reactions. We also contributed to the body of knowledge on AAA with 2-substituted π-allyl complexes. As in previous cases, the orientation of the π-allyl complex is determined by the substitution at C2. Ester substitution affords products that result from reaction through the anti π-allyl with ester coordination to the metal center. In contrast, cyano substitution affords products that result from reaction through the syn π-allyl with no cyano coordination to the metal center.

We have further demonstrated the utility of this cyclization DYKAT through a concise and high-yielding synthesis of (+)-hippospongic acid A. Specifically, we employed three palladium-catalyzed alkylation reactions to form three different types of bonds: C−S, C−H, and C−O. Furthermore, these alkylation reactions address important selectivity issues in the synthetic sequence. Palladium-catalyzed reductive desulfonylation allowed for selective removal of an allyl sulfone without concomitant isomerization of the delicate tetraene system. The palladium-catalyzed DYKAT cyclization allowed an efficient approach to the one chiral center present in (+)-hippospongic acid A. Using the described synthetic sequence, we completed the shortest synthesis to date of (+)-hippospongic acid A, which demonstrates the power of palladium-catalyzed allylic alkylation reactions in total synthesis.

Experimental Section

All reactions were performed under an atmosphere of dry argon in flame-dried glassware. Solvents were distilled under an atmosphere of argon before use and transferred via an oven-dried syringe.

Compound 15. A solution of (Pd(π-allyl)Cl)$_2$ (0.00084 g, 0.0023 mmol) and (*R,R*)-**L-3** (0.0055 g, 0.0071 mmol) in 0.5 mL of *degassed* dioxane was added via cannula to a solution of **14** (0.030 g, 0.12 mmol), and tetrahexylammonium chloride (0.014 g, 0.036 mmol) in *degassed* dioxane (0.7 mL). The reaction was stirred at 80 °C under argon for 17 h. The resulting light-yellow solution was purified directly via flash chromatography (silica, ether/petroleum ether, gradient) to yield 0.022 g (92%) of **15** as a colorless oil. $[\alpha]_D$ +69.28 (c = 0.67, CH_2Cl_2). The enantiomeric excess was determined to be 95% via chiral GC analysis. (Cyclosil B column, 120 °C isotherm, flow rate = 2.0 mL/min, t_r: 26.19 (major), 27.47 (minor).) R_f = 0.70 in 25% ether/petroleum ether. IR (film from $CDCl_3$) 1721, 1382 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (s, 1H), 5.80 (s, 1H), 5.27 (app q, J = 6.8 Hz, 1H), 4.71 (d, J = 12.8 Hz, 1H), 4.31 (d, J = 10.8 Hz, 1H), 3.86 (d, J = 12.8 Hz, 1H), 3.75 (s, 3H), 2.32 (m, 2H), 2.00 (m, 1H), 1.60 (d, J = 8.4 Hz, 3H), 1.35 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 141.5, 133.6, 124.6, 118.9, 75.4, 66.7, 51.8, 33.9, 33.1, 12.6. HRMS calcd for $C_{11}H_{16}O_3$ (M^+): 196.1099. Found: 196.1089.

Compound 17. A solution of (Pd(π-allyl)Cl)$_2$ (0.00084 g, 0.0023 mmol) and (*R,R*)-**L-3** (0.0050 g, 0.0071 mmol) in 0.5 mL of *degassed* toluene was added via cannula to a solution of **16** (0.027 g, 0.12 mmol), and tetrahexylammonium chloride (0.014 g, 0.036 mmol) in *degassed* toluene (0.7 mL). The reaction was stirred at 80 °C under argon for 17 h. The resulting light-yellow solution was purified directly via flash chromatography (silica, ether/petroleum ether, gradient) to yield 0.018 g (94%) of **17** as a colorless oil. $[\alpha]_D$ +45.74 (c = 0.82, CH_2Cl_2). The enantiomeric excess was determined to be 98% via chiral GC analysis. (Cyclosil B column, 110 °C isotherm, flow rate = 2.0 mL/min, t_r: 37.97 (major), 45.06 (minor).) The enantiomeric excess can also be determined via HPLC analysis. (Chiralcel OD column, 99.9:0.1 heptane:^{i}PrOH, flow rate = 1.0 mL/min, 220 nm, t_r: 15.08 (major), 16.87 (minor)). R_f = 0.60 in 25% ether/petroleum ether. IR (film from $CDCl_3$) 2227, 1622, 1442 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01 (s, 1H), 5.97 (s, 1H), 5.34 (m, 1H), 4.72 (d, J = 12.9 Hz, 1H), 4.03 (d, J = 11.1 Hz, 1H), 4.85 (d, J = 12.6 Hz, 1H), 2.36 (m, 2H), 2.02 (m, 1H), 1.62 (d, J = 6.9 Hz, 3H), 1.55 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.2, 129.9, 124.5, 112.0, 117.1, 76.4, 66.5, 32.5, 32.3, 12.7. Anal. calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03. Found: C, 73.38; H, 8.00.

Compound 31. A test tube containing 4-methoxyphenol (45 mg, 0.37 mmol), Pd_2dba_3·$CHCl_3$ (3.8 mg, 0.004 mmol), and (*S*,*S*)-**L-3** (7.7 mg, 0.012 mmol) was evacuated and filled with argon three times. The test tube was charged with a solution of **30** (66 mg, 0.37 mmol) in methylene chloride (3.7 mL). The resulting orange solution was stirred at 0 °C for 3 h and directly chromatographed eluting with 6:1 petroleum ether:diethyl ether to afford **31** (67 mg, 80%, 40%ee) as a colorless film. Enantiomers were separated by HPLC using Chiralcel OD column eluting with 95:5 heptanes:2-propanol at 1.0 mL/min. Retention times: minor enantiomer (*S*) 37.20 min and major enantiomer (*R*) 41.86 min. IR (film) 2221, 1749, 1595, 1442, 1035 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.80−7.02 (m, 4H), 6.82 (br s, 1H), 3.77 (s, 3H), 2.31−2.41 (m, 1H), 2.12−2.30 (m, 1H), 1.92−2.06 (m, 1H), 1.61−1.90 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 151.4, 150.6, 149.1, 118.6 (2C), 114.6 (2C), 113.9, 72.2, 55.5, 26.9, 25.9, 16.5 HRMS for $C_{14}H_{15}NO_2$ (M^+) Calcd: 229.1103. Found: 229.1092. $[\alpha]^{22}_D$ −48.2 (*c* = 0.78, CH_2Cl_2, 48% ee, (*R*,*R*)-**L-1**).

Compound 33. A test tube containing 4-methoxyphenol (15 mg, 0.121 mmol), Pd_2dba_3·$CHCl_3$ (1.0 mg, 0.001 mmol), and (*S*,*S*)-**L-3** (2 mg, 0.003 mmol) was evacuated and filled with argon three times. The test tube was charged with a solution of **32** (25 mg, 0.117 mmol) in methylene chloride (1.0 mL). The resulting orange solution was stirred at 0 °C for 3 h and directly chromatographed eluting with 6:1 petroleum ether:diethyl ether to afford **33** (24 mg, 78%, 86%ee) as a colorless film. Enantiomers were separated by HPLC using Chiralcel OD column eluting with 98:2 heptanes:2-propanol at 1.0 mL/min. Retention times: minor enantiomer (*R*) 8.38 min and major enantiomer (*S*) 10.25 min. IR (film) 1717, 1506, 1436, 1069 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.24 (m, 1H), 6.99 (dm, *J* = 9.0 Hz, 2H), 6.81 (dm, *J* = 9.0 Hz, 2H), 5.01 (m, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 2.38 (dt, *J* = 19.8, 4.6 Hz, 1H), 2.20−2.09 (m, 2H), 1.89−1.79 (m, 1H), 1.66−1.60 (m, 1H), 1.43 (tt, *J* = 14.0, 3.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.9, 154.4, 152.0, 144.8, 129.7, 118.9 (2C), 114.5 (2C), 70.1, 55.6, 51.7, 26.3, 25.9, 15.8. HRMS Calcd for $C_{15}H_{18}O_4$: 262.1205. Found: 262.1198.

Compound 62. A solution of $(Pd(\pi\text{-allyl})Cl)_2$ (0.00044 g, 0.0012 mmol) and (*R*,*R*)-**L-3** (0.0028 g, 0.0036 mmol) in 0.3 mL of *degassed* dioxane was added via cannula to a solution of **61** (0.03 g, 0.06 mmol), and tetrahexylammonium chloride (0.007 g, 0.018 mmol) in *degassed* dioxane (0.3 mL). The reaction was stirred at 80 °C under argon for 17 h. The resulting light-yellow solution was purified directly via flash chromatography (silica, ether/petroleum ether, gradient) to yield 0.014 g (50%) of **62**. $[\alpha]_D$ +20.38 (*c* = 0.42, CH_2Cl_2) for 91% ee as determined via chiral HPLC analysis. (Chiralcel AD column, 400:1 heptane:^{i}PrOH, flow rate = 0.5 mL/min, 230 nm, t_r: 13.64 (minor), 17.22 (major).) The obtained spectral data [IR, ^1H, ^{13}C] matched the literature values.[24a] IR (film from $CDCl_3$) 1722, 1633, 1439, 955, 819 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 6.23 (t, *J* = 1.5 Hz, 1H), 5.88 (t, *J* = 1.5 Hz, 1H), 5.18 (t, *J* = 7.0 Hz, 1H), 5.12−5.06 (m, 4H), 4.67 (d, *J* = 12.5 Hz, 1H), 4.31 (d, *J* = 11.5 Hz, 1H), 3.86 (d, *J* = 12.5 Hz, 1H), 3.75 (s, 3H), 2.36−2.27 (m, 2H), 2.15−1.94 (m, 17H), 1.66 (d, *J* = 1.5 Hz, 3H), 1.58 (s, 3H), 1.57 (s, 9H), 1.33 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 141.5, 135.2, 134.9, 134.4, 132.9, 131.3, 124.8, 124.6, 124.5, 124.4, 124.2 (2C), 75.4, 67.1, 51.8, 39.8, 39.7, 33.9, 33.0, 29.7, 28.2 (2C), 26.7, 26.6, 25.7, 25.6, 17.7, 16.1, 16.0 (2C).

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Supporting Information Available: Detailed procedures and full characterization of all synthetic intermediates and products, along with spectral comparison of natural and synthetic (+)-hippospongic acid A. This material is available free of charge via the Internet at http://pubs.acs.org.

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