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Enantioselective Functionalization of Allylic C−H Bonds Following a Strategy of Functionalization and Diversification

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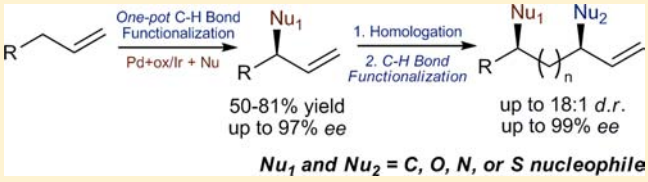
Supporting Information

ABSTRACT: We report the enantioselective functionalization of allylic C−H bonds in terminal alkenes by a strategy involving the installation of a temporary functional group at the terminal carbon atom by C−H bond functionalization, followed by the catalytic diversification of this intermediate with a broad scope of reagents. The method consists of a one-pot sequence of palladium-catalyzed allylic C−H bond oxidation under neutral conditions to form linear allyl benzoates, followed by iridium-catalyzed allylic substitution. This overall transformation forms a variety of chiral products containing a new C−N, C−O, C−S, or C−C bond at the allylic position in good yield with a high branched-to-linear selectivity and excellent enantioselectivity (ee ≤97%). The broad scope of the overall process results from separating the oxidation and functionalization steps; by doing so, the scope of nucleophile encompasses those sensitive to direct oxidative functionalization. The high enantioselectivity of the overall process is achieved by developing an allylic oxidation that occurs without acid to form the linear isomer with high selectivity. These allylic functionalization processes are amenable to an iterative sequence leading to (1,*n*)-functionalized products with catalyst-controlled diastereo- and enantioselectivity. The utility of the method in the synthesis of biologically active molecules has been demonstrated.



INTRODUCTION

The stereochemical complexity of medicinally important compounds is increasing, and recent studies have suggested that compounds containing increased numbers of sp^3 carbon centers are more successful through clinical trials.[1] Although C−H bond functionalization reactions have the potential to alter the strategies by which these compounds are prepared,[2] a major challenge encountered when developing C−H bond functionalization reactions is the control of absolute and relative stereochemistry.[2m,3]

Likewise, a major challenge facing the development of C−H bond functionalization strategies is a limited reaction scope. Reactions involving both catalyzed and uncatalyzed alkyl, aryl, and acyl substitution reactions occur with broad scope and are used, therefore, widely in medicinal chemistry to build or embellish the core of biologically active compounds.[4] Yet the same broad scope does not apply to C−H bond functionalization reactions. The functionalization of an aryl C−H bond located *ortho* to a strong directing group does occur with a range of reagents and oxidants,[2c,l,5] but the functionalization of other classes of C−H bonds does not.

One approach to create a C−H bond functionalization that occurs with broad scope is to combine one C−H bond functionalization reaction with a subsequent step that creates diversity from the initial product of C−H bond functionalization (Figure 1A). For greatest efficiency, the C−H bond functionalization and subsequent transformation should be conducted in the same reaction vessel without purification of the intermediate. The strength of this approach is illustrated by the borylation of aromatic C−H bonds. In this case, one reliable, iridium-catalyzed C−H borylation reaction leads to an intermediate that can be converted to biaryls, alkylarenes, haloarenes, arylamines, aryl ethers, aryl nitriles, and fluoroalkylarenes, among other products.[2k,5b,6]

We sought to develop a related strategy for enantioselective functionalizations of aliphatic C−H bonds. To develop a general strategy for enantioselective C−H bond functionalization reactions, the introduction of various carbon and heteroatom nucleophiles must be accomplished with control of the configuration—both absolute and relative—of any new stereogenic center generated by the C−H bond functionalization reaction.

Iridium-catalyzed allylic substitution has become one of the most general reactions that form new carbon−carbon or carbon−heteroatom bonds with control of the absolute configuration of an aliphatic stereocenter.[7] In this reaction many types of carbon, nitrogen, oxygen, and sulfur nucleophiles react with an allylic electrophile to form products in which the configuration of the new stereocenter is controlled by the catalyst, rather than existing stereogenic centers in the substrate.[7e,8]

If the electrophile for such substitution reactions could be prepared by a C−H bond oxidation process that is compatible with the substitution reaction, then a strategy for the synthesis of common structural types by C−H activation would result (Figure 1B). However, the development of such a method for C−H bond oxidation is challenging. As described in more detail

Received: September 27, 2013
Published: October 24, 2013

   dx.doi.org/10.1021/ja409995w | J. Am. Chem. Soc. 2013, 135, 17983−17989

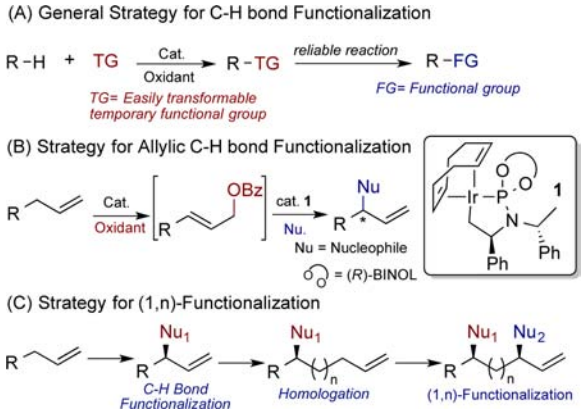


Figure 1. General strategy for aliphatic or allylic C−H bond functionalization.

below, such a reaction must form linear allylic esters with a high linear-to-branched selectivity under neutral conditions without excess of oxidant, and such allylic oxidation reactions are unknown. Published conditions for allylic oxidation are incompatible with most catalysts for subsequent transformations of the oxidation products.

However, if such a combination of oxidation and asymmetric substitution were developed, then an opportunity would be created to use a sequence of allylic C−H bond functionalization and homologation reactions to form diols, amino alcohols, and diamines, as well as products containing a new alkyl or sulfur-containing group. In these reactions the functionality and configurations would be programmed by the identity of the reagent and configuration of the catalyst. This strategy is depicted in Figure 1C. The new functional groups could be located at nearly any position along an alkyl chain.

We report the discovery of a sequence comprising C−H bond oxidation and asymmetric allylic substitution. The two steps involve a palladium-catalyzed oxidation of alkenes under neutral conditions to form linear allylic benzoates and iridium-catalyzed allylic substitution to form products containing new C−O, C−N, C−C, and C−S bonds with control over absolute and relative configuration of the stereogenic centers in the product. In contrast to recently published asymmetric allylic functionalizations,[3o] the reactants in our process are common nucleophiles lacking protecting groups and substituents that modulate their reactivity. This process forms products containing new functionalities at stereogenic centers located 1,3-, 1,4-, 1,5-, or even further removed from each other, and the absolute and relative configuration of all new stereocenters are fully controlled by the catalytic process. In addition to creating new building blocks from simple alkenes, this work introduces a strategy for aliphatic substrates to combine C−H bond functionalization with diversification of the intermediate through reliable catalytic chemistry.

■ RESULTS AND DISCUSSION

The development of a process involving the combination of palladium-catalyzed allylic C−H bond oxidation and iridium-catalyzed allylic substitution of the oxidation product confronts several challenges that would be met by development of novel conditions for allylic C−H bond oxidation. First the oxidation step must generate the terminal allylic ester with high selectivity. The branched impurity would reduce the enantioselectivity of the overall process because iridium-catalyzed allylic substitution of the branched ester leads to racemic product at full conversion. Second, the oxidant must be completely consumed in the first step. Remaining oxidant would deactivate the iridium catalyst in the second step. Third, the allylic ester must be generated in a neutral medium if a second catalyst is to be added to convert the oxidation product to a range of different products. The iridium catalyst for asymmetric allylic substitution (**1**, Figure 1B) is not stable to acidic media. This issue is a particular concern because most oxidation processes are conducted in acidic medium, and palladium-catalyzed allylic oxidations that have been published recently with oxygen or quinone as the oxidant require acid for converting the oxygen to hydrogen peroxide or the quinone to the hydroquinone. Thus, we first needed to develop a highly selective catalyst for allylic oxidation to form the terminal allylic ester with high selectivity without an excess of oxidant under neutral conditions.

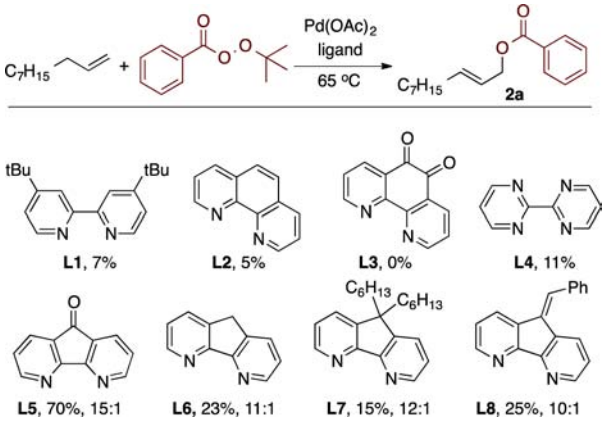
A. Development of an Allylic Oxidation under Neutral Conditions to Form Linear Products. With these challenges in mind, our initial studies focused on developing conditions for allylic oxidation to form linear allylic esters under conditions lacking acid or excess oxidant that would interfere with the allylic substitution process. Prior methods for allylic acetoxylation based on early reports from Tsuji et al.[9] and Akermark et al.[10] form linear products, but most of these reactions are conducted with excess of acid (often as solvent) or oxidant or both.[11]

To avoid these acidic conditions with excess oxidant, we investigated the reactions of alkenes with peresters, which would serve as the oxidant and could create an appropriate leaving group for the allylic substitution reaction. Copper-catalyzed allylic oxidation with peresters, such as *tert*-butyl perbenzoate (also known as the Kharasch−Sosnovsky reaction) has been studied extensively.[12] However, this reaction forms branched allylic esters as the major isomer and, therefore, is not suitable for the envisioned allylic functionalization sequence.[3g,12b,c,13] Palladium catalysts also have been used in combination with peresters for oxidation reactions,[14] but this combination has not been used for the oxidation of allylic C−H bonds. Thus we sought to develop a palladium catalyzed allylic C−H oxidation with *tert*-butyl perbenzoate as the oxidant and source of the benzoate group that would form the linear allylic ester.

The combination of $Pd(OAc)_2$ and bidentate nitrogen ligands were tested as catalyst for the benzoylation of 1-decene with *tert*-butylperbenzoate (Chart 1). The activity and regioselectivity was highest in neat alkene with a 2:1 ratio of alkene to oxidant. Reactions conducted with palladium complexes of *tert*-butylbipyridine (**L1**), phenanthroline (**L2**), 1,10-phenanthroline-5,6-dione (**L3**), and 2,2′-bipyrimidine (**L4**) provided low yields of oxidation product **2a** (7%, 5%, 0%, and 11%, respectively). The ligand 4,5-diazafluorenone (**L5**) was reported by Stahl to form the products of allylic oxidation with O_2 as reagent in acetic acid with a good linear-to-branched selectivity.[11a] Thus, we tested this catalyst system for the reaction with *tert*-butyl perbenzoate as the oxidant. Important for the implementation of the functionalization and diversification strategy, this reaction occurred in 70% yield, with a 15:1 linear-to-branched ratio.

Reactions conducted with the catalysts formed from $Pd(OAc)_2$ and derivatives of diazafluorenone ligands **L6**, **L7**, and **L8** gave lower yields of **2a** than those conducted with **L5**. Thus, the catalyst derived from $Pd(OAc)_2$ and 4,5-diazafluor-

Chart 1. Effect of Ligands on Palladium Catalyzed Benzoylation of Allylic C−H Bonds[a]

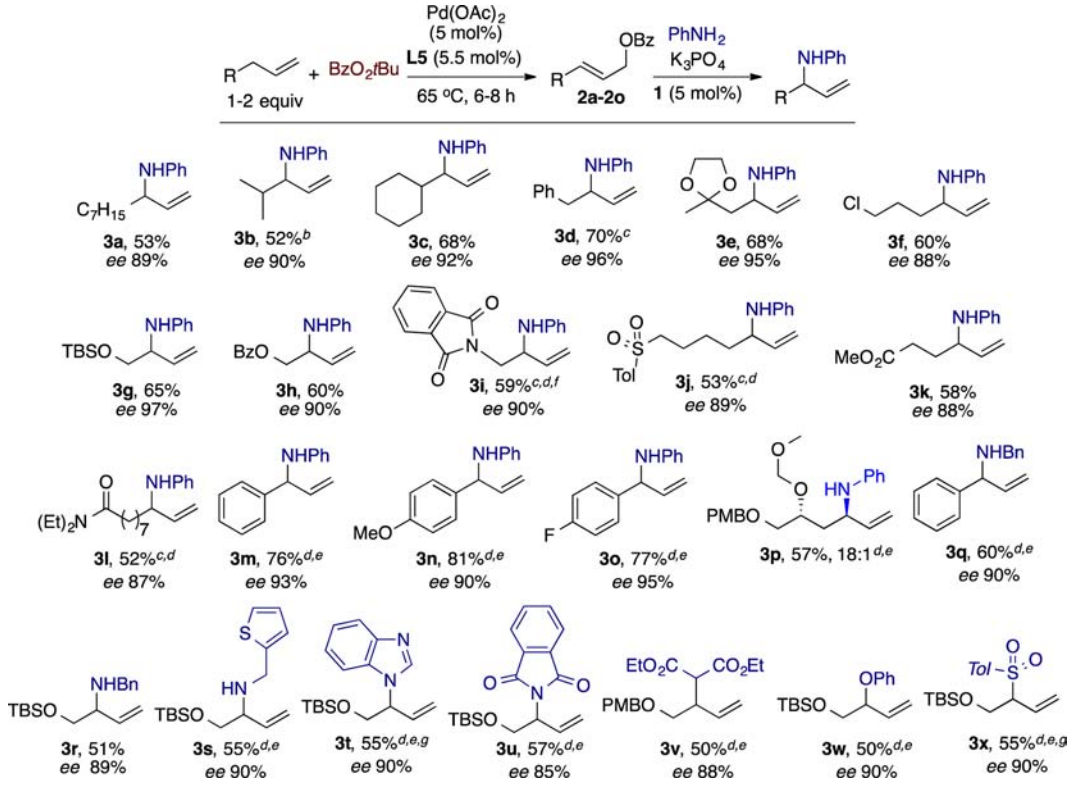


[a]Conditions: 5.0 mol % $Pd(OAc)_2$, 5.5 mol % ligand, 1-decene (0.6 mmol, 2.0 equiv) and *tert*-butyl-perbenzoate (0.3 mmol, 1.0 equiv), 65 °C. The yields and linear to branched ratios were determined by GC with dodecane as an internal standard.

eneone was used for further studies on the development of asymmetric allylic C−H bond functionalization with *tert*-butyl perbenzoate as an oxidant.

B. Compatibility and Scope of the Strategy for Asymmetric Allylic C−H Bond Functionalization and Iridium-Catalyzed Amination Reactions. If the iridium-catalyzed allylic amination would occur directly on the material generated from the allylic oxidation, then a simple process involving first adding the palladium catalyst and oxidant, followed by adding the iridium catalyst and nucleophile, would lead to a range of allylic functionalization products. To consume the benzoic acid product from the substitution reactions with neutral nucleophiles, a base is needed. Thus, we added K_3PO_4 as a base with these nucleophiles. Under these conditions, the reaction with aniline as a nucleophile resulted in complete conversion of **2a**. The final amination product (**3a**) was isolated in 53% overall yield for the two steps and 89% ee (Chart 2). The scope of alkenes that undergo the allylic amination sequence is revealed by the data in Chart 2. In addition to the linear 1-decene, branched terminal alkenes underwent the asymmetric allylic amination in good yields and excellent enantioselectivity (**3b**−**3d**). The reaction sequence was tolerant of a broad range of functional groups that could undergo further derivatization. Alkenes containing ketal and chloride functional groups were well-tolerated, affording the corresponding aromatic amines **3e** and **3f**, respectively. Alkenes containing silyl ether and benzoate functional groups reacted to afford 1,2-amino alcohol derivatives **3g** and **3h**, respectively. The C−H bond functionalization sequence was also suitable for the synthesis of the chiral 1,2-diamine **3i**. Functional groups containing weakly acidic protons, such as sulfones, esters, and amides, were also tolerated, and the sequence provided functionalized alkenes **3j**−**3l**. Finally, allylarenes bearing electron-donating or electron-withdrawing groups formed the corresponding amines in good yields with excellent regioselectivity and stereoselectivity (**3m**−**3o**).

Chart 2. Scope of the Alkenes and Nucleophiles in the Allylic C−H Bond Functionalization[a]



[a]See Supporting Information for reaction conditions; yields are for isolated products; ee was measured by HPLC, *dr* is measured by ^{1}H NMR spectroscopy (500 MHz). [b]3.0 equiv of alkene was used. [c]1.5 equiv of alkene was used. [d]The oxidation step was conducted at 80 °C for 2.5 h. [e]1.0 equiv of alkene was used. [f]CH_2Cl_2 was used as solvent in the oxidation step. [g]Reaction mixture was filtered on silica after the palladium catalyzed oxidation step.

dx.doi.org/10.1021/ja409995w | J. Am. Chem. Soc. 2013, 135, 17983−17989

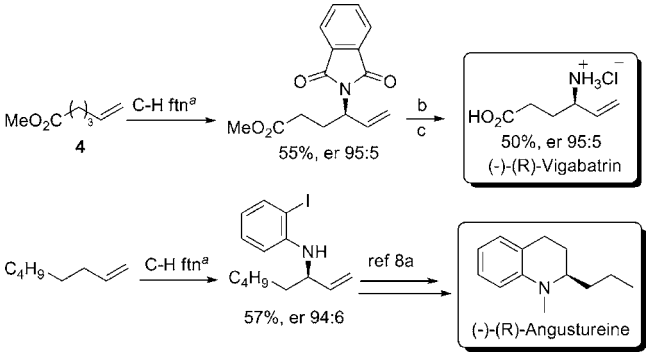
Because the iridium catalyst controls the configuration of the new stereocenter,[7e,8] the allylic substitution provides a method to control the diastereoselectivity of the amination of chiral, nonracemic alkenes. For example, the chiral alkene (ee >99%) containing a MOM-protected alcohol (MOM = methoxy methyl) reacted to form the substitution product **3p** in 57% yield with 18:1 diastereoselectivity.

Because the oxidation and functionalization steps occur sequentially, the process occurs with a range of nucleophiles that would be incompatible with direct oxidative functionalization reactions. The data in Chart 2 reveal the broad scope of this asymmetric allylic functionalization process with a variety of nitrogen, oxygen, carbon, and sulfur nucleophiles. For example, the protocol we developed occurred with alkylamines and nitrogen heterocycles to form the allylamine and *N*-allyl heteroarene derivatives **3q**−**3t** in good isolated yields with excellent enantioselectivity. Potassium phthalimide also reacted to give the corresponding amination product **3u** in similar yield to that obtained with the other nitrogen nucleophiles. In addition, sodium dimethyl malonate (carbon-), sodium phenoxide (oxygen-), and sodium *p*-toluenesulfinate (sulfur) nucleophiles reacted to form products **3v**−**3x** containing new C−C, C−O, and C−S bonds at the stereogenic center.

C. Short Synthesis of Biologically Active Molecules. By exploiting this asymmetric allylic C−H bond functionalization, we were able to conduct short, asymmetric syntheses of two biologically active compounds (−)-(*R*)-vigabatrin and (−)-(*R*)-angustureine from simple commercially available alkenes, in part to assign the absolute configuration of the functionalization products.

(−)-(*R*)-vigabatrin was synthesized from unsaturated ester **4** using the (*R,R,R*)-**1** enantiomer of the catalyst, followed by basic workup and removal of phthalimide protecting group (Scheme 1). Similarly, (−)-(*R*)-angustureine was synthesized from 1-octene using 2-iodoaniline as nucleophile and (*R,R,R*)-**1** as catalyst. The *N*-allylamine product was subjected to the previously reported sequence of hydroboration, intramolecular Suzuki−Miyaura cross-coupling, and alkylation to provide (−)-angustureine.[8a] The relative configuration of the product and iridium catalyst shows that the allylic substitution step of the functionalization sequence occurs with the same stereoselectivity as previously reported substitutions of allylic carbonates.[7c,15]

Scheme 1. Synthesis of Biologically Active Molecules



[a]C−H ftn: $Pd(OAc)_2$/**L5** (5 mol %), 65 °C, 8 h; **1** (5 mol %), K_3PO_4 (1.5 equiv), nucleophile (2 equiv). [b]10 M NaOH, 12 h. [c]$NaBH_4$, H_2O:EtOH.

Previously reported mechanistic studies from our group on iridium-catalyzed allylic substitution reactions[7d,16] have shown that the reaction occurs by a highly diastereoselective oxidative addition of an allylic benzoate to an iridium complex **1**, followed by attack of the nucleophile onto the allyl ligand from the side opposite to the metal for all of the nucleophiles in the current study. This nucleophilic attack is faster than the $\eta^3-\eta^1-\eta^3$ isomerization of the allyl complex.

D. Iterative C−H Bond Functionalization: Synthesis of (1,*n*)-Functionalized Chiral Fragments. To extend the utility of this process to the introduction of multiple functional groups with control of absolute and relative configurations, we developed an iterative sequence of C−H bond functionalizations and homologations to prepare (1,*n*)-functionalized alkenes (Figure 1C). In this sequence, the composition of the new functionality and the configuration of each new stereogenic center depends on the reagent and configuration of the catalyst, respectively. Various strategies have been reported for creating (1,2), (1,3), or (1,4) functionalization in molecules. Prominent examples include addition reactions to alkenes, such as dihydroxylation or halogenation reactions (1,2-functionalization), aldol reactions, 1,3 dipolar additions (1,3-functionalization), and metal-catalyzed 1,4 conjugate addition reactions (1,4-functionalization). However, no method has been reported to prepare (1,*n*)-functionalized molecules with a high diastereoselectivity and enantioselectivity containing a range of installed functional groups and programmed configurations by C−H bond functionalization.

To demonstrate this potential, we converted the simple PMB-protected but-3-en-1-ol (**5**) to a wide range of trifunctional products with controlled functionality and configuration. These results are summarized in Chart 3.

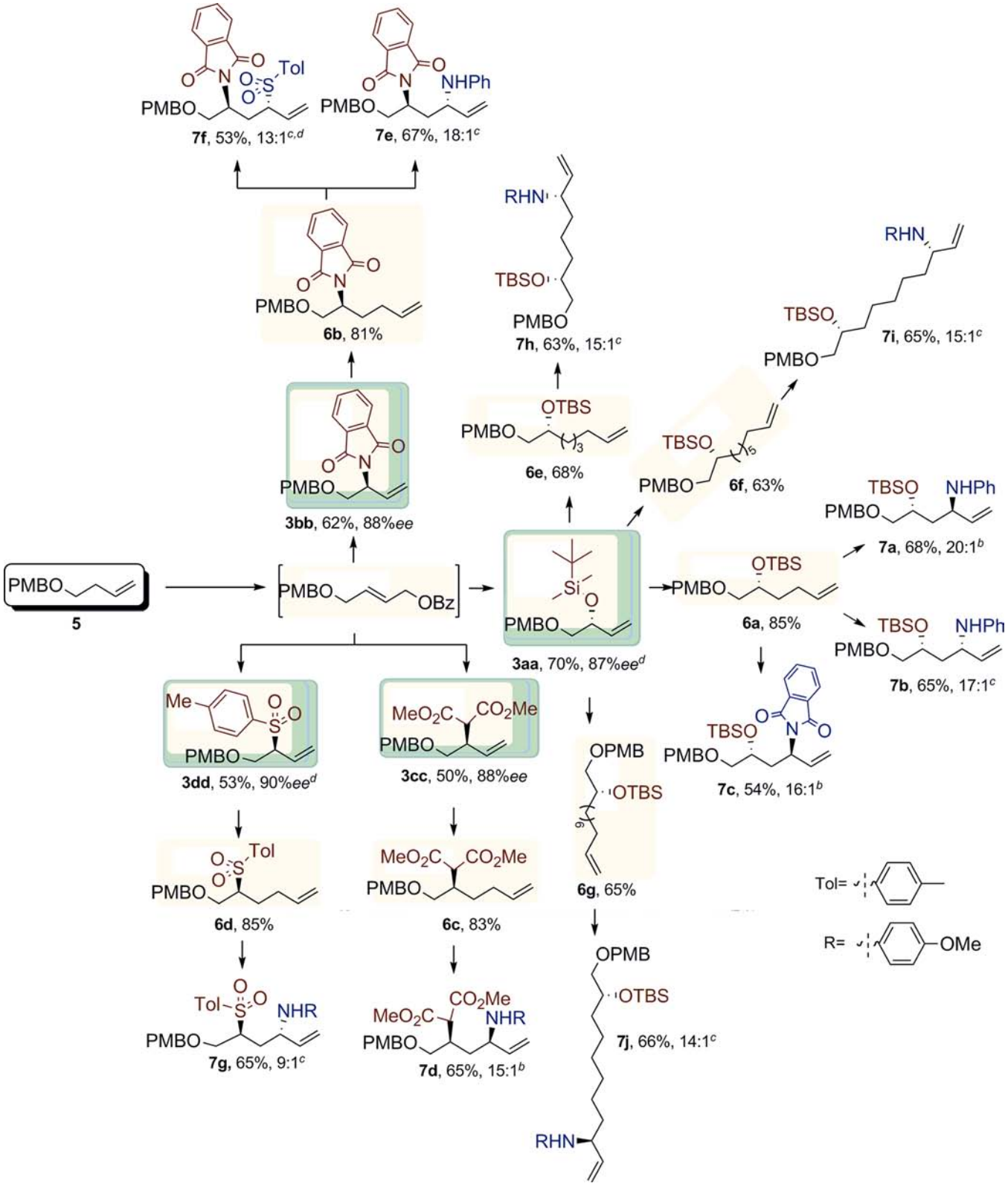
Monofunctionalized compounds derived from **5** were prepared by the C−H bond functionalization sequence described above with *tert*-butyldimethylsilanol, potassium phthalimide, sodium dimethyl malonate, and sodium 4-methylbenzenesulfinate, as the nucleophiles to form products **3aa**−**3dd**. These products were homologated to the (1,*n*,*m*) alkene intermediates **6a**−**6g** by hydroboration with 9-BBN followed by Suzuki coupling with *n*-bromoalk-1-enes, in excellent yields.

Various trifunctional building blocks (Chart 3, **7a**−**7j**) containing a (1,3)-, (1,5)-, (1,7)-, and (1,8)-relationship between two stereogenic centers were then formed from alkenes (**6a**−**6g**) in good yield. The diastereoselectivities of these reactions were high, and the relative configurations were controlled by the catalyst. For example, both diastereomers of a silyl protected enantioenriched amino alcohol (**7a** and **7b**) were prepared using catalyst **1** and the enantiomer of **1** respectively, with dr values similar to the er values of the reactions of achiral alkenes.[8b,c] The chiral alkene prepared from malonate addition was further functionalized with the aromatic amine in high diastereoselectivity (**7d**). A chiral 1,3-diamine containing different substituents at nitrogen also formed with high diastereoselectivity (**7e**). The 1,3-amino-sulfones, which could serve as a precursor to amino-sulfone ligands, were prepared with similarly high diastereoselectivity (**7f** and **7g**). Alkenes (**6e**−**6g**) provided (1,4), (1,5), and (1,6)-functionalized fragments **7h**−**7j** in excellent diastereo- and enantioselectivity simply by choosing the appropriate chain length of the 1-bromoalkene.

This iterative sequence also was followed to prepare chiral fragment **8** that was used in the synthesis of spongistatin

dx.doi.org/10.1021/ja409995w | J. Am. Chem. Soc. 2013, 135, 17983−17989

Chart 3. Iterative C−H Functionalization: Synthesis of (1,*n*)-Functionalized Alkenes

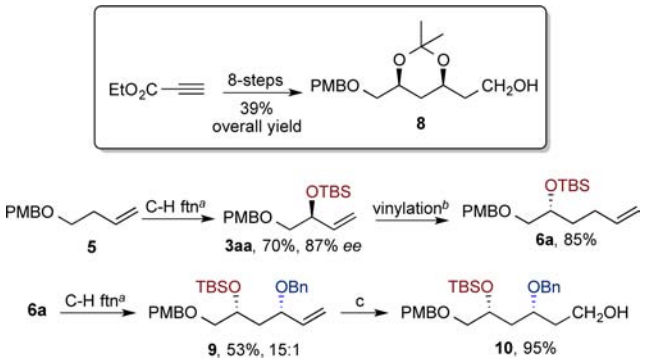


[a]For reaction conditions see Supporting Information; overall yields of isolated compounds; dr is measured by ^{1}H NMR spectroscopy (500 MHz). [b]**1** was used as a catalyst in the second step. [c]Enantiomer of **1** was used as a catalyst in the second step. [d]Reaction mixture was filtered over silica prior to the iridium-catalyzed substitution step.

(Scheme 2).[17] The 1,3,4-triol derivative **9** was prepared from **5** in excellent diastereo and enantioselectivity (53%, 15:1, 99% ee). Treatment of **9** with 9-BBN, followed by oxidation formed alcohol **10** in 95% yield. By this iterative method we installed three different protecting groups in triol **9**, thus providing selective access to each hydroxyl functional group for further

dx.doi.org/10.1021/ja409995w | J. Am. Chem. Soc. 2013, 135, 17983−17989

Scheme 2. Synthesis of Chiral Fragment of Spongistatin



[a]C−H ftn: $Pd(OAc)_2$/**L5** (5 mol %), 65 °C, 8 h; **1** (5 mol %), K_3PO_4, (1.5 equiv), 1-phenyl-propyne (10 mol %), nucleophile (2 equiv). [b]Vinylation: 9-BBN, 10 h, 25 °C; $Pd(dppf)Cl_2$ (5 mol %), vinyl bromide (3 equiv), DMF, 50 °C. [c]9-BBN (1.3 equiv, 0.5 M solution in THF), 25 °C, 10 h; $NaBO_3$, H_2O, 24 h.

transformations. Moreover, the catalyst controlled the configuration of each stereogenic center, thus allowing access to all possible stereoisomers of this fragment simply by changing the choice of the enantiomer of the catalyst without changing the protocol or the starting substrate.

CONCLUSION

In conclusion, a new approach to asymmetric C−H bond functionalization of allylic C−H bonds in unactivated terminal alkenes that creates the ability to install a broad range of functional groups has been developed. This process comprises a one-pot sequence involving a palladium catalyzed allylic C−H oxidation system with a perester as both reagent and oxidant, thereby occurring under neutral conditions, and an iridium-catalyzed allylic substitution of the product with a broad range of nucleophiles with programmed stereochemistry to form the branched, chiral products containing new C−C, C−N, C−O, and C−S bonds in high yield with excellent enantioselectivity (ee up to 97%). An iterative C−H bond functionalization is also reported that can be used to form a wide range of enantioenriched (1,*n*)-functionalized products, including those used in the synthesis of spongistatin, (−)-(*R*)-vigabatrin, and (−)-(*R*)-angustureine, from trivial alkene starting materials.

This work underscores the value of developing C−H bond functionalization reactions that form common synthetic intermediates under conditions appropriate for subsequent direct diversification by a second catalytic process. Few examples of C−H bond functionalization reactions occurring in this fashion have been reported. The borylation of arene C−H bonds[2k,5b,6] is one example of a process that forms the functionalized intermediate without side products that interfere with subsequent transformations. C−H bond oxidation by P450 enzymes[18] creates a functional group that can be converted to a halogen or can be used for subsequent Mitsunobu reactions, but the products are formed in a medium that is incompatible with the second step. The development of additional C−H bond functionalization reactions that form common synthetic intermediates will be the focus of future studies in our laboratory.

REPRESENTATIVE PROCEDURE FOR ALLYLIC C−H FUNCTIONALIZATION

To a 4 mL vial containing a magnetic stir bar, $Pd(OAc)_2$ (3.3 mg, 5 mol %) and **L5** (3 mg, 5.5 mol %) were added, followed by 25.0 μL of DCM. The reaction mixture was then stirred for 15 min at room temperature. The solvent was then removed under vacuum, and dodacane (25.0 μL) and 1-decene (0.6 or 0.3 mmol) were added followed by *tert*-butyl perbenzoate (58.27 mg, 0.3 mmol). The vial was sealed with a cap containing a PTFE septum and then heated at 65 °C for 8 h (monitored by ^1H NMR for consumption of oxidant). The vial was kept at high vacuum for 3−4 h to remove volatile materials and brought into the glovebox. The reaction mixture was dissolved in 0.5 mL of dry toluene. To the resulting solution K_3PO_4 (95.5 mg, 0.45 mmol) and the aniline (2.0 mmol) were added, followed by a solution of iridium catalyst **1** (13.0 mg, 5 mol %) in 0.5 mL of dry toluene. The resulting reaction mixture was stirred at 25 °C until the linear benzoyl ester was fully consumed, as determined by GC or TLC. The crude reaction mixture was then treated with 2 mL of EtOAc and extracted with brine. The solvent was evaporated from the organic layer, and the product was purified by flash column chromatography on silica gel eluting with a mixture of hexane and ethyl acetate (99:1).

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the NIH (GM-55382 to J.F.H.) and the Swiss National Science Foundation (SNSF) (PBGEP2_139830 to A.S.) for financial support and Johnson-Matthey for $Pd(OAc)_2$ and $[Ir(COD)Cl]_2$.

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