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Catalytic Enantioselective Allylic Amination of Unactivated Terminal Olefins via an Ene Reaction/[2,3]-Rearrangement

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Supporting Information

ABSTRACT: The enantioselective allylic amination of unactivated terminal olefins represents a direct and attractive strategy for the synthesis of enantioenriched amines. We have developed the first use of a nitrogen-containing reagent and a chiral palladium catalyst to convert unfunctionalized olefins into enantioenriched allylic amines via an ene reaction/[2,3]-rearrangement.

The direct conversion of hydrocarbons into chiral functionalized molecules has remained an important goal in chemistry for decades.[1] Advances in this area provide more efficient and practical strategies for designing and manipulating molecular structures, with broad applications in fields such as medicine and materials science.[2] The stereoselective incorporation of nitrogen atoms into hydrocarbons, such as olefins, is of particular interest, given the prevalence of chiral amines in pharmaceutical drugs.[3] Although many powerful chemical methods have been developed for the incorporation of nitrogen atoms into hydrocarbons,[4] the catalytic enantioselective conversion of hydrocarbons into chiral amines has to date remained an unsolved problem.[5,6] In this communication, we describe a catalytic enantioselective intermolecular allylic amination of unactivated terminal olefins for the synthesis of chiral amines in high enantiomeric excess (Scheme 1).

The metal-catalyzed activation of inert C−H bonds has emerged as one efficient strategy for transforming terminal olefins into allylic amines via metal-π-allyl intermediates[7,8] or metal-nitrenoids[9] (Scheme 1, path a).[10] In theory, chiral versions of these metal complexes could facilitate the enantioselective formation of chiral amine products. Despite recent progress in metal-catalyzed enantioselective aminations of activated benzylic C−H bonds[11] and intramolecular enantioselective allylic aminations of olefins,[12] there are no general examples of intermolecular catalytic enantioselective allylic amination of unactivated terminal olefins.[13]

We were drawn to a conceptually distinct allylic amination strategy that is based on an uncatalyzed conversion of unfunctionalized olefins into *racemic* chiral amines via an ene reaction/[2,3]-rearrangement of reactive zwitterion **1** (Scheme 1, path b).[14] In this approach, an imido-sulfur or imido-selenium compound acts as the source of nitrogen. Unfortunately, since its discovery over 30 years ago, this protocol was thought to be incompatible with enantioselective catalysis because of the propensity of reactive zwitterions such as **1** to undergo facile thermal [2,3]-rearrangement in the absence of a catalyst.[15,16] We recently developed a palladium-catalyzed enantioselective [2,3]-rearrangement of zwitterionic amine *N*-oxides.[17] We hypothesized that a similar catalytic manifold may be applicable to the rearrangement of zwitterion **1**, which would provide an opportunity to develop a catalytic enantioselective allylic amination of terminal olefins.

Our initial experiments focused on the identification of a high oxidation state nitrogen source that would couple with a terminal olefin to form an ene adduct, such as **1**, which would not undergo a background [2,3]-rearrangement in the absence of a chiral catalyst. This proved challenging, since most imido-sulfur and imido-selenium oxidants that are suitable for allylic amination strategies participate in uncatalyzed thermal ene reactions followed by [2,3]-rearrangements. For example, the early work of Sharpless and Kresze highlighted the racemic allylic amination of terminal olefins at room temperature with arylsulfonyl sulfurdiimide reagents through the two-step pericyclic reaction sequence.[14]

Upon reexamination of these arylsulfonyl sulfurdiimide oxidants, we discovered that benzenesulfonyl sulfurdiimide **3** and 1-octene **2a** formed stable ene adduct **4a** at 4 °C in high yield (Table 1). This zwitterionic intermediate was purified by simple filtration without any chromatography and did not rearrange at temperatures below 0 °C, even after several days (entry 1). Coupling between nitrogen-containing oxidant **3** and terminal olefins at low temperatures was therefore selected as

Scheme 1

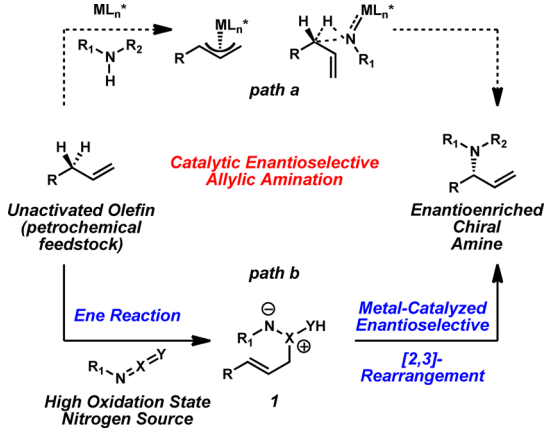

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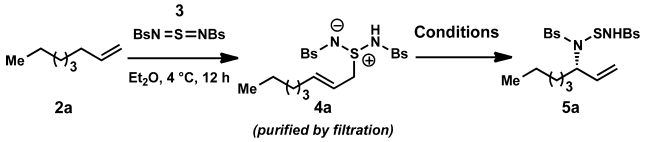
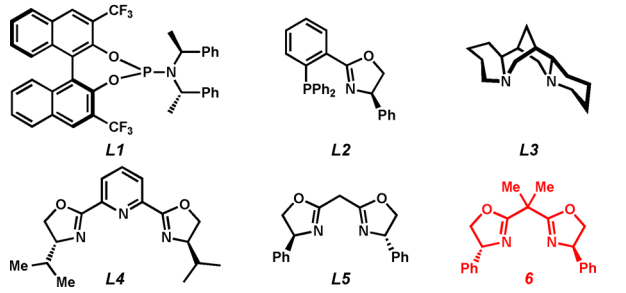
Table 1. Optimization of the Enantioselective Allylic Amination



Entry	Metal Catalyst (10 mol%)	Ligand (12 mol%)	Solvent (0.13M)	Temp (°C)	Conversion[a]	ee (%)
1	–	–	CH_2Cl_2	–10	< 5	–
2	$Pd(OAc)_2$	–	CH_2Cl_2	–10	91[b]	–
3	$Pd(OAc)_2$	*L1*	DCE	–10	99	3
4	$Pd(TFA)_2$	*L1*	DCE	–10	99	0
5	$Pd(TFA)_2$	*L2*	DCE	–10	60	4
6	$Pd(TFA)_2$	*L3*	DCE	–10	60	5
7	$Pd(TFA)_2$	*L4*	DCE	–10	99	0
8	$Pd(TFA)_2$	*L5*	DCE	–10	99	13
9	$Pd(TFA)_2$	*6*	DCE	–10	99	31
10	$Pd(TFA)_2$	*6*	Acetone	–10	63	41
11	$Pd(TFA)_2$	*6*	$PhCF_3$	–10	60	59
12	$Pd(TFA)_2$	*6*	MeOH	–15	89[b]	96

[a] Determined by ^{1}HNMR. Reaction time was 2 days. [b] Isolated yield for 2 steps.



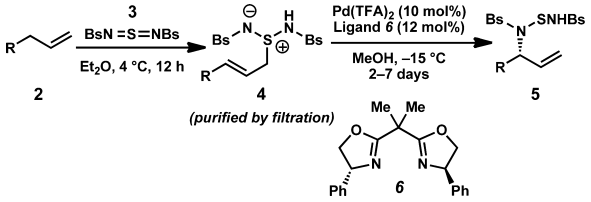
the platform for our catalytic enantioselective allylic amination of olefins.

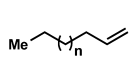
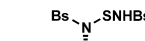
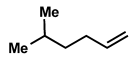
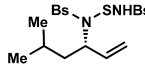
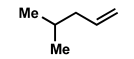
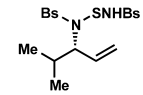
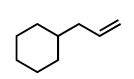
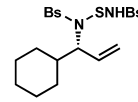
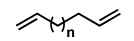
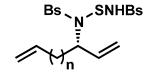
In our early attempts to accelerate the [2,3]-rearrangement of zwitterion **4a**, palladium(II) salts such as $Pd(OAc)_2$ were promising catalysts for the desired rearrangement (entry 2). After an extensive screening of reaction parameters (including solvent, chiral ligand, and palladium source), we identified $Pd(TFA)_2$ and bisoxazoline ligand **6** as the optimal catalyst complex for generating allylic sulfonamide product **5a** in 89% yield and 96% enantiomeric excess (ee) at −15 °C in anhydrous methanol (entry 12).[18] The overall two-step protocol only requires one chromatographic purification, which simplifies the operation of this reaction on large scale.

Having identified optimized reaction conditions for the enantioselective conversion of olefins into allylic amines, we explored the substrate scope of this process on a preparative scale (2−4 mmol). Table 2 highlights the efficiency of this enantioselective process in the absence of any directing functional groups in the substrate. For example, allylic amines were generated with linear hydrocarbon chains (entries 1−3) as well as hindered branched hydrocarbons (entries 4−6). In all these cases, the allylic sulfonamide products were obtained in high yields with greater than 90% ee. Given the paucity of enantioselective methods for converting achiral hydrocarbons into chiral products, the success of the enantioselective allylic amination reaction with substrates that lack directing groups is noteworthy.

The compatibility of this reaction with a wide range of reactive functional groups was also examined. Polyunsaturated terminal olefins selectively incorporated a single nitrogen atom via a hetero-ene reaction with one molecule of benzenesulfonyl sulfurdiimide **3** (entries 7−8). Nucleophilic functional groups,

Table 2. Substrate Scope of the Enantioselective Allylic Amination



Entry	Olefin[b]		Product	Yield (%)[a]	ee (%)
1		n = 1		89	97
2		n = 3		89	96
3		n = 9		88	98
4				93	98
5[c]				79	91
6				87	94
7		n = 5		97	96
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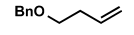
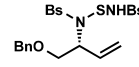
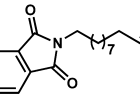
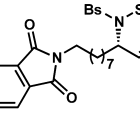
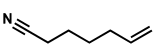
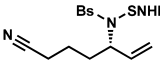
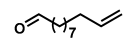
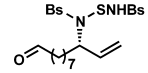
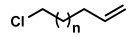
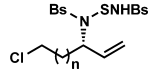
9				61	91
10[c]				82	94
11[c]				91	92
12				78	97
13		n = 2		85	97
14		n = 3		87	94
15		n = 7		94	98

[a] Isolated yield for 2 steps, based on sulfurdiimide **3**. [b] 3−5 equiv of olefin. [c] Reaction temperature was −5 °C.

such as free alcohols and carboxylic acids, were not tolerated in the enantioselective allylic amination, presumably because of competitive addition into the electrophilic benzenesulfonyl sulfurdiimide **3** prior to the hetero-ene reaction. However, the mild reaction conditions were compatible with protected heteroatoms, including a benzyl ether (entry 9) and a nitrogen-bearing phthalimide (entry 10). Reactive electrophilic functional groups, such as nitriles (entry 11), aldehydes (entry 12), and primary alkyl chlorides (entries 13−15), could be incorporated into the products without affecting the overall efficiency of the allylic amination process. The absolute stereochemistry of the allylic amination products was determined by examining crystals of the product in entry 6 that were suitable for X-ray diffraction.

As a preliminary mechanistic proposal, we hypothesize that the palladium(II)-bisoxazoline catalyst acts as a chiral π-acid to activate zwitterion **4**, which then undergoes aminopalladation to generate heterocycle **7** as an intermediate (Scheme 2). Grob-type fragmentation eventually reveals allylic amine **5** and the palladium(II)-bisoxazoline catalyst, which can reenter the

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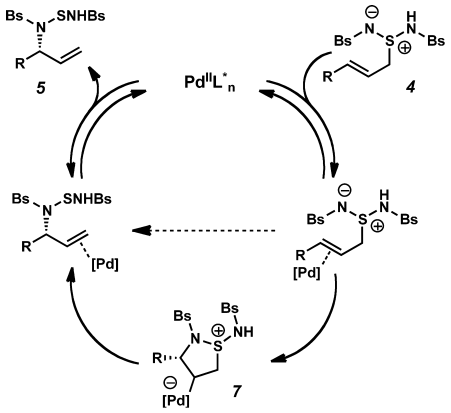
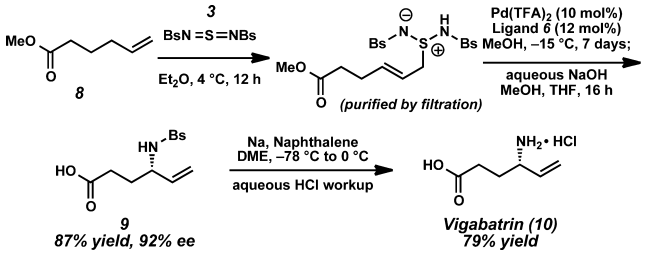
Scheme 2



catalytic cycle. This cyclization-induced mechanism, which is similar to Overman's proposal for the [3,3]-rearrangement of allylic trichloroacetimidates,[19] is consistent with a crossover experiment between two differentially substituted zwitterionic substrates that only yield non-crossover products (see Supporting Information).[20]

The utility of this enantioselective allylic amination reaction in the synthesis of biologically active, nitrogen-containing chiral molecules is exemplified by the conversion of commercially available unsaturated ester **8** into enantioenriched antiepileptic drug Vigabatrin (Scheme 3).[21] The enantioselective allylic amination protocol yielded chiral sulfonamide **9**, which was then deprotected to reveal the enantioenriched HCl salt of Vigabatrin (**10**).

Scheme 3



In conclusion, we have developed a practical method for converting terminal olefins into enantioenriched allylic amines with a chiral palladium catalyst. Our key discovery was the use of a catalyst to accelerate the enantioselective [2,3]-rearrangement of allylic zwitterion **4**, a process that was traditionally thought to be uncontrollable by chiral catalysts. This procedure for generating allylic amines is compatible with a broad range of functional groups. Moreover, the chiral rearrangement products can be easily transformed into synthetically useful allylic sulfonamides and primary amines. We are currently interested in gaining more mechanistic insight into the mode of stereoinduction in the enantioselective rearrangement step while also increasing the functional group compatibility of the transformation. We anticipate that this method will be useful for the synthesis of nitrogen-containing pharmaceutical agents from inexpensive and abundant unactivated olefins.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Complete experimental procedures and characterization 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.

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NOTE ADDED AFTER ASAP PUBLICATION

Scheme 1 was incomplete in the version published ASAP October 29, 2012. The corrected version was re-posted on October 30, 2012.