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Rhodium-Catalyzed Regio- and Enantioselective Addition of *N*-Hydroxyphthalimide to Allenes: A Strategy To Synthesize Chiral Allylic Alcohols

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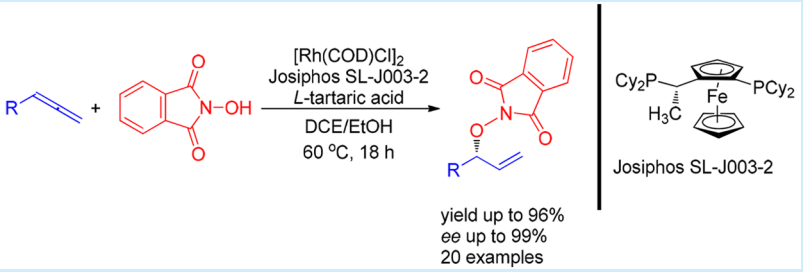
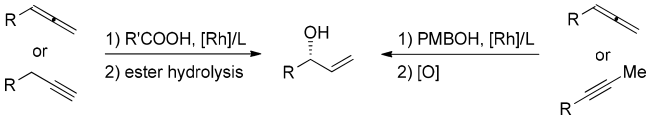
Supporting Information



ABSTRACT: We achieved the first Rh-catalyzed regio- and enantioselective additions of *N*-hydroxyphthalimide to allenes. This transformation is accomplished via mild reaction conditions, leveraging on Josiphos SL-J003-2 as a chiral ligand to furnish branched *O*-allyl compounds in good yields with moderate to excellent enantioselectivities. The substrate scope is broad, and various functional groups are tolerated. The utility of this methodology is elaborated by transformation to allylic alcohols with different functional groups as well as to chiral *O*-allyl hydroxylamines.

Since enantioenriched allylic alcohols are highly valuable and versatile building blocks as well as structural elements of natural products and bioactive molecules, efforts have been made to explore new asymmetric catalytic methods for their synthesis.[1] In addition, allylic alcohol can readily undergo subsequent diastereoselective transformations,[1] including hydrogenation, dihydroxylation, hydroboration, cyclopropanation, and epoxidation, etc., to install further functionalities in a regio- and stereoselective manner. Over the past decades, significant progress has been made for the preparation of chiral allylic alcohols, such as 1,2-reduction of α,β-unsaturated ketones,[2] addition of vinylmetal reagents to aldehydes and ketones,[3] and kinetic as well as dynamic kinetic resolution of racemic allylic alcohols.[4] In addition, enantiomerically enriched allylic alcohols could also be obtained on the basis of transition-metal-catalyzed asymmetric C−O bond formation.[5−9] In our group, we have developed Rh-catalyzed enantioselective addition of carboxylic acids[10,11] or 4-methoxybenzyl alcohol[12] (PMBOH) to allenes as well as alkynes (Scheme 1). Their deprotection furnishes branched chiral allylic alcohols. Despite the broad reaction scope, the methodology has some limitations regarding functional group compatibility; for example, an ester function usually cannot tolerate the allylic ester saponification step. In this context, we envisioned that *N*-hydroxyphthalimide (NHPI)[13] could serve as a cheap and nontoxic oxygen pronucleophile to couple with allenes. The resulting *O*-allylated addition products may undergo reductive O−N bond cleavage to furnish the corresponding allylic alcohols. Additionally, phthalimide deprotection would give access to *O*-allyl hydroxylamines.

Scheme 1. Previously Developed Asymmetric Catalytic Additions of Carboxylic Acids and Alcohols to Alkynes and Allenes for the Synthesis of Branched Allylic Alcohols



In the past few years, transition-metal-catalyzed regioselective and enantioselective coupling of allenes[10,12,14−17] and alkynes[11,12,18] with various nucleophiles has been widely explored as an atom-economic variant of the Tsuji−Trost allylation. In order to extend the utility of this new tool box for catalytic organic synthesis, we were interested in developing an asymmetric addition of NHPI to allenes to provide a new strategy to synthesize branched chiral allylic alcohols.

We began by investigating the reaction of hexa-4,5-dien-1-ylbenzene (**1a**) with NHPI (**2a**). Initial experiments were done using 4 mol % of $Rh[(COD)Cl]_2$ and 8 mol % of 1,4-bis(dicyclohexylphosphino)butane (DCPB) in 1,2-dichloroethane (DCE)/EtOH (4/1),[19] affording the branched allylic product **3aa** in 74% yield (Table 1, entry 1) at 70 °C for 18 h. After further screening of chiral diphosphine ligands, we were delighted to identify that Josiphos SL-J003-2 was the most

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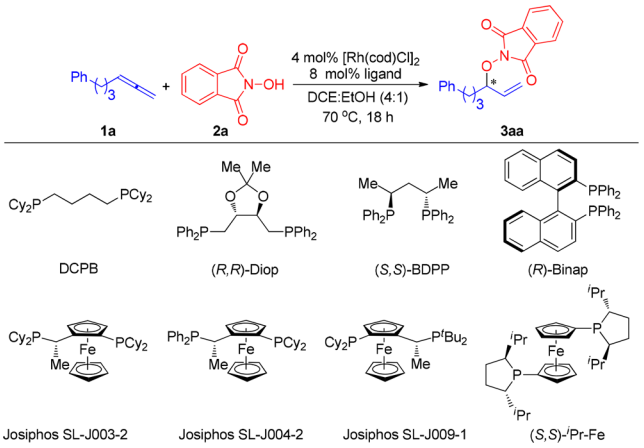
Table 1. Optimization of the Reaction Conditions[a]



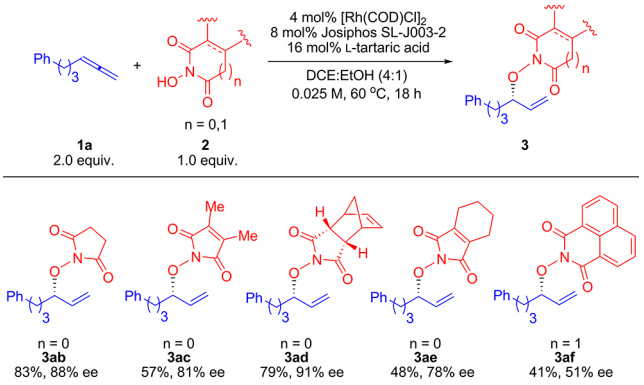
entry	ligand	yield[b] (%)	ee[c] (%)
1	DCPB	74	rac
2	(*R*,*R*)-Diop	13	20
3	(*S*,*S*)-BDPP	29	−11
4	(*R*)-Binap	12	5
5	Josiphos SL-J003-2	86	56
6	Josiphos SL-J004-2	27	−16
7	Josiphos SL-J009-1	22	54
8	(*S*,*S*)-^{i}Pr-Fe	85	−49
9[d]	Josiphos SL-J003-2	79	69
10[e]	Josiphos SL-J003-2	91	88
11[e,f]	Josiphos SL-J003-2	78	89
12[e,g]	Josiphos SL-J003-2	78	89
13[e,h]	Josiphos SL-J003-2	69	90
14[e,h,i]	Josiphos SL-J003-2	71	91
15[e,h,i,j]	Josiphos SL-J003-2	88	90

[a]All reactions were carried out in a scale of 0.2 mmol of **2a**, 1.5 equiv of **1a**, 4 mol % of $[Rh(COD)Cl]_2$, 8 mol % of ligand in DCE/EtOH (4/1, 0.4 M) at 70 °C for 18 h. [b]Isolated yield. [c]Determined by chiral HPLC. [d]0.2 M. [e]0.025 M. [f]8 mol % of L-tartaric acid. [g]8 mol % D-tartaric acid. [h]16 mol % L-tartaric acid. [i]60 °C. [j]2.0 equiv of **1a**.

promising ligand, furnishing **3aa** in 86% yield with 56% ee (Table 1, entry 5). Interestingly, lowering the substrate concentration from 0.4 M to 0.2 M to 0.025 M increased the enantiomeric excess of **3aa** up to 88% (Table 1, entries 9 and 10). When 8 mol % of either L-tartaric acid or D-tartaric acid was used as cocatalyst,[20] **3aa** was obtained in 78% yield with 89% ee (Table 1, entries 11 and 12). Further increasing the loading of L-tartaric acid to 16 mol % led to a slight increase in the ee value to 90%, although the yield decreased (Table 1, entry 13). Finally, further optimizing the reaction parameters (reaction temperature and the amount of allene) provided the product **3aa** in 88% yield and 90% ee (Table 1, entry 15).[21]

With the optimized reaction conditions in hand, we explored the scope of different *N*-hydroxylimides upon coupling with allene **1a** as the model substrate (Table 2). *N*-Hydroxysuccinimide participated in the reaction leading to **3ab** in a slightly lower yield and enantioselectivity. Moreover, the reaction substrates, 2,3-dimethyl-*N*-hydroxymaleimide, *N*-hydroxycyclohexene-1,2-dicarboximide, and *N*-hydroxynaphthalimide, were inferior to NHPI. Notably, the fused bicyclic system, *N*-hydroxy-5-norbornene-2,3-dicarboxylic acid imide, afforded the corresponding addition product **3ad** in 79% yield and 91% ee. We then decided to focus on **2a** as a water surrogate for further investigations.

Table 2. Exploration of Pronucleophiles[a,b]



[a]Yield of isolated product. [b]The ee values were determined by chiral HPLC.

Next, substrate generality with respect to the allene coupling partner was evaluated. As depicted in Table 3, a diverse set of allenes underwent regio- and enantioselective rhodium-catalyzed addition reaction with NHPI to furnish the corresponding coupling products **3aa**−**ta** in moderate to high yields and enantioselectivities ranging from 82% to 99% ee. Primary and secondary alkyl-substituted allenes behaved well (**1a**−**f**). Even substrates with primary alkyl cloride and alkyl iodide functions were tolerated (**1g**,**h**). Allenes containing differently protected hydroxyl groups (**1i**−**l**) were introduced in the asymmetric addition with acceptable to high yields and good enantioselectivities. A series of allenes bearing nitrile (**1m**), ester (**1n**,**o**), amide (**1p**), phthalimide (**1q**), ether (**1r**), thioether (**1s**), and sulfone (**1t**) functions furnished the corresponding addition products effectively as well. Unfortunately, aryl-substituted allene, tertiary alkyl-substituted allene, and 1,1-disubstituted allene were not compatible in this coupling reaction. In addition, the *O*-allyl product **3aa** was synthesized under standard conditions on a 1.0 mmol scale with 85% yield and 87% ee.

The observed allylic adducts **3** could be readily transformed to the corresponding allylic alcohols or *O*-allyl hydroxylamine species (Scheme 2), thereby certifying the synthetic utility of the allylic products **3**. Compound **3aa** was converted to the corresponding hydroxylamine compound **4aa** in 65% isolated yield with 90% ee. In addition, to study the practicality of this protocol to obtain allylic alcohol, **5aa**, **5ba**, **5ja**, and **5qa** were prepared in the presence of molybdenum hexacarbonyl and triethylamine with preservation of enantiopurity in 71−75% yields, respectively. At this stage, the absolute configuration of **5ba** was assigned as *S* by comparison with known literature data.[9]

As allylic alcohols are significant structural motifs for organic synthesis, subsequent assorted functionalizations of allylic alcohol were elucidated (Scheme 3). The Simmons−Smith cyclopropanation led to cyclopropane **6aa** with 88% yield and 89% ee. Epoxidation by treatment with $VO(acac)_2$ and TBHP generated the corresponding epoxide **7aa** in 90% yield with 89% ee. The relative configuration of **7aa** was determined by inspecting diagnostic NOE correlations of its derivative (for details, see the Supporting Information). Hydroboration of **3aa** with BH_3·THF followed by oxidative workup provided 1,3-diol **8aa**.

Inspired by the above results, the new NHPI allylation was applied to the formal total synthesis of putaminoxin E, which

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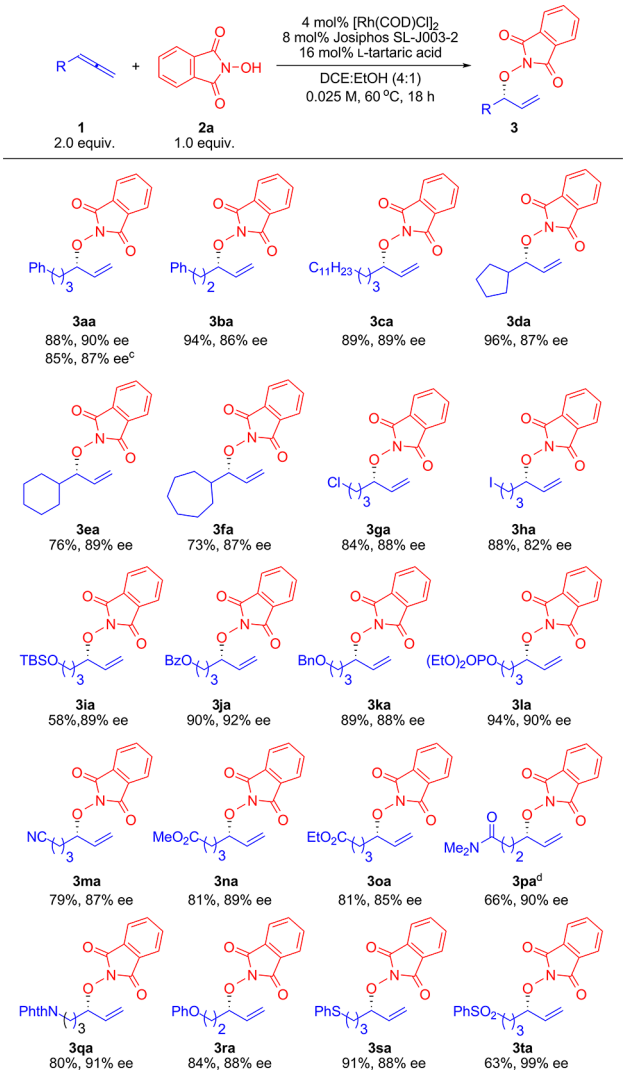
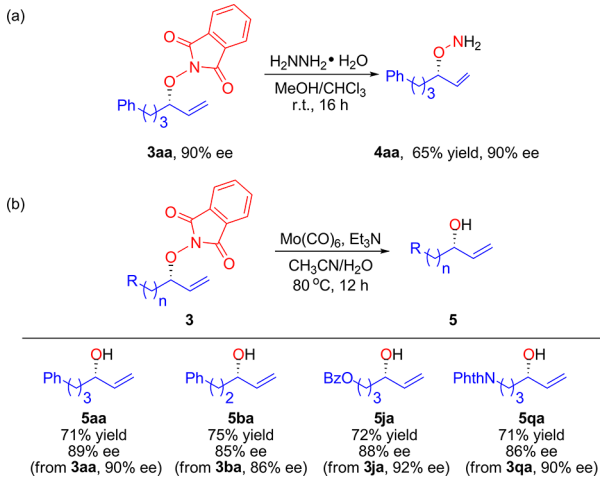
Table 3. Substrate Scope of Regio- and Enantioselective Addition of Allenes to NHPI[a,b]

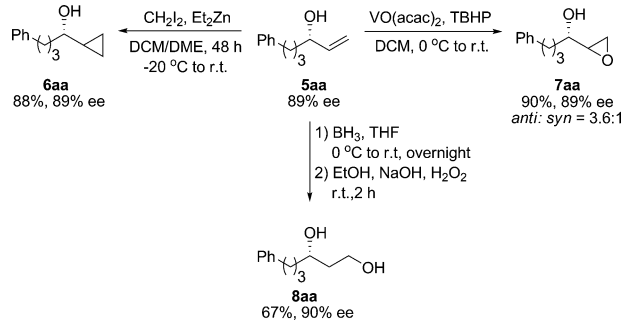


[a]Yield of isolated product. [b]The ee values were determined by chiral HPLC. [c]The reaction was conducted on a 1.0 mmol scale. [d]1.5 equiv of allene, without L-tartaric acid, at 70 °C. TBS = *tert*-butyldimethylsilyl, Bz = benzoyl, Bn = benzyl, Phth = phthaloyl.

Scheme 2. Transformations of Branched Allylic Adducts 3

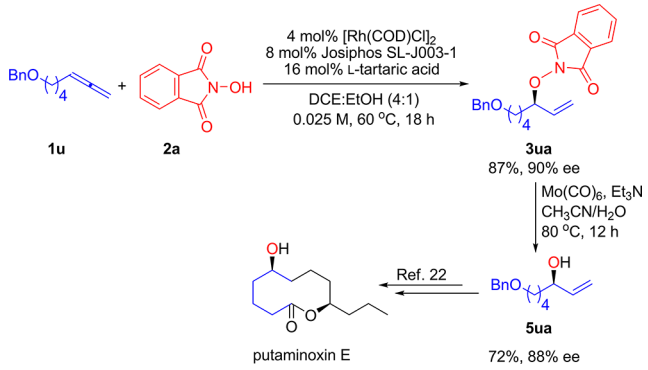


Scheme 3. Functionalization of Branched Allylic Alcohol 5aa



possesses interesting cyctotoxic activity.[22] As shown in Scheme 4, **1u** could be regioselectively and enantioselectively allylated to

Scheme 4. Utilization of Allylic Alcohol To Access Putaminoxin E



supply the corresponding product **3ua** in 87% yield with 90% ee. Allylic alcohol **5ua**, which has been used as an important intermediate in a total synthesis of putaminoxin E, was derived from subsequent deprotection of *N*-phthalimide in 72% yield and 88% ee.[22]

In conclusion, we developed a regio- and enantioselective addition of NHPI to allenes giving access to important functional motif *O*-allylic addition products which provide an alternative access to preparing enantiomerically pure allylic alcohols as well as *O*-allyl hydroxylamines. Various substituted allenes could participate in this reaction to furnish the corresponding branched allylic compounds with moderate to good yields and good to high enantioselectivities. Follow-up chemistry for such cyclopropanation, epoxidation, and hydroboration reactions highlights the synthetic potential of these building blocks. Furthermore, the value and versatility of this methodology were demonstrated through a formal total synthesis of putaminoxin E.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03709.

Experimental details and analytic data (NMR, HRMS, GC, and HPLC) (PDF)

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Notes

The authors declare no competing financial interest.

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