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Development of Non-*C*2-symmetric ProPhenol Ligands. The Asymmetric Vinylation of *N*-Boc Imines

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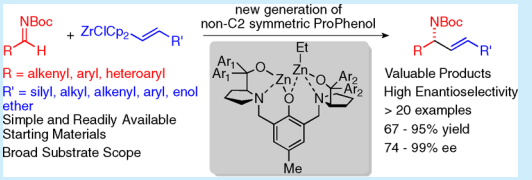
Supporting Information

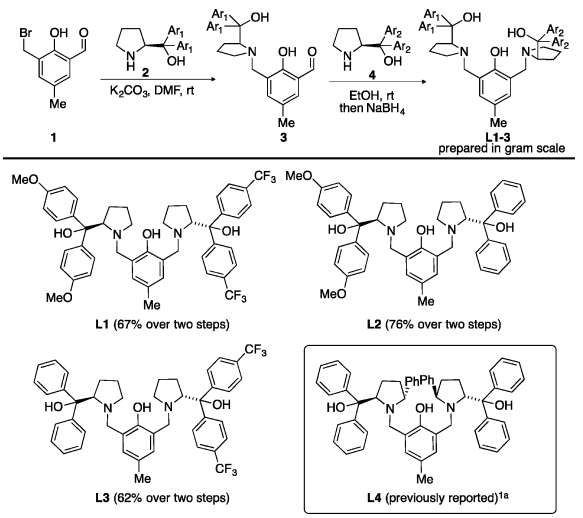
ABSTRACT: The development and application of a new generation of non-*C*2-symmetric ProPhenol ligands is reported herein. Rational design of the ProPhenol ligand paved the way to the first catalytic and asymmetric vinylation of *N*-Boc imines *via* hydrozirconation giving rise to valuable allylic amines in excellent yields and enantioselectivities. The utility of this method was demonstrated by developing the shortest reported asymmetric synthesis of the selective serotonine reuptake inhibitor (SSRI) (−)-dapoxetine.



Crafting chiral space is a major challenge for synthetic organic chemists in order to develop highly enantioselective, catalytic processes. By learning from biological mechanisms for asymmetric catalysis in nature, we set out to develop a biomimetic catalytic system tailored for asymmetric addition reactions. We and others have reported on several successful applications of the commercially available *C*2-symmetric ProPhenol ligand.[1] The versatility of this catalytic system propelled our interest in further elaborating its properties. We were driven by the question, whether electronically distinct aryl groups on each of the diphenyl prolinol subunits could affect the performance of the dinuclear catalyst. In other words, can one induce differences in the electronic nature of the zinc centers by perturbation of electronics in a remote manner?

The *C*2-symmetric ProPhenol ligand relies upon steric differentiation of the chiral space to effect asymmetric induction.[1] The ability of the ProPhenol ligand to self-assemble a dinuclear catalyst sets the stage for an interaction with both addition reaction partners through a Lewis acidic and a Lewis basic site and makes it highly attractive for further engineering. Not only the Zn-ProPhenol complex but also dinuclear ProPhenol complexes of other metals such as magnesium have been developed and proved superior in some of the investigated reactions.[2] Recently, additional steric encumbrance in the prolinol core proved to be of importance for the diastereo- and enantioselective preparation of β-hydroxy-α-amino esters through a Zn-ProPhenol catalyzed aldol reaction.[1a] In this transformation we demonstrated the differential effect of the nature of the ProPhenol ligand **L4** on the enantioselectivity of the reaction (Scheme 1). This second generation of ProPhenol adds stereocenters to the prolinol core, but still leaves the *C*2-symmetry untouched. In further pursuing the development of the ProPhenol ligand, we sought to achieve distinction of the two zinc atoms in the catalyst through electronic desymmetrization of the chiral space. We designed a non-*C*2-symmetric ligand by attaching electronically different aromatics to either prolinol (Scheme 1). The result is a push−pull system to generate a more electrophilic, Lewis acidic and a more nucleophilic, Lewis basic zinc atom in the same dinuclear catalyst. By tuning the electronic properties of the zinc centers, hence differentiating the chiral space, we sought to enhance enantioselectivity as well as reactivity in the catalytic transformation.

Scheme 1. Synthetic Approach to a New Family of Non-*C*2-symmetric ProPhenol Ligands



The synthesis of the desired ligands was achieved expediently from salicylaldehyde **1**, which can be prepared from commercially available 2-hydroxy-5-methylbenzaldehyde in one step, or more economically from *p*-cresol in two steps.[3] Nucleophilic substitution of the benzyl bromide under basic conditions with the first prolinol unit **2** followed by a reductive amination of the aldehyde **3** with the second prolinol unit **4** furnished the desired non-*C*2-symmetric ProPhenol ligands **L1**−**3** in 62−76% yields over two steps. The major assets of this

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approach are its convergence, generality, robustness, reliability, and scalability.

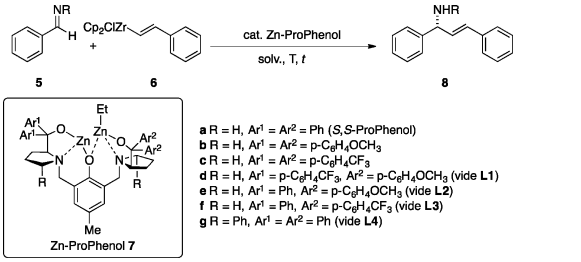
The application of this new generation of ProPhenol ligands is demonstrated through the asymmetric vinylation of *N*-Boc imines giving rise to valuable allylic amines, a process that heretofore has not been demonstrated. Allylic amines are important in their own right, but are also intermediates to more elaborate saturated amines. They occur in numerous pharmaceuticals with a broad range of biological activity such as the antiepileptic drug vigabatrin (*S*-enantiomer is pharmacologically active)[4] or the antiparkinson agent lisuride.[5] The catalytic, asymmetric synthesis of allylic amines typically involves one of two strategies, asymmetric formation of the C−N[6] or the C−C bond.[7] The utilization of an inexpensive main-group metal has economic advantages over the use of expensive transition metal catalysts. The high costs of Rh- or Ir-catalysts[7,8] previously employed as well as the requirement for the *N*-tosyl imines, a notorious amine protecting group because of the difficulties in its removal, are major drawbacks of these methods. Further the Ir-catalyzed process requires the use of disubstituted alkynes. Interestingly, the vinylation of *N*-Boc imines has never been reported to date. Given the benefits of Boc as the nitrogen protecting group (*vide infra*) the direct synthesis of allylic *N*-Boc amines became an attractive goal.

The nucleophiles of choice were vinylzirconium species resulting from the hydrozirconation of alkynes employing Schwartz' reagent deriving from DIBAL and Cp_2ZrCl_2, a gasoline additive.[9,10] The easy accessibility and the stability of alkenylzirconium species is a great asset of zirconium chemistry. However, previous reports utilizing vinylzinc species resulting from vinyl zirconium species relied on stoichiometric use of organozinc compounds in order to achieve the transmetalation from zirconium to zinc.[7,10] This prompted us to explore our newly designed Zn-ProPhenol system in the first catalytic, asymmetric transmetalation from zirconium to zinc in a C═X addition reaction to form a C−C bond. The presented method obviates the use of expensive transition metal catalysts such as Rh or Ir, but rather makes use of a biomimetic approach employing catalytic amounts of Zn in a dinuclear Zn-ProPhenol catalyst to allow for the first asymmetric vinylation of *N*-Boc imines.[1] The design of a new generation of ProPhenol ligands proved to be crucial for the success of this process.

In contradistinction to all previous reports,[7,10] we identified *N*-Boc imines as the electrophiles of choice in the presented asymmetric vinylation. Their easy synthesis and handling as well as their excellent properties as a nitrogen protecting group are major advantages of the strategy. The Boc-group can easily be removed under slightly acidic conditions, compatible with a broad range of functional groups,[11] whereas the deprotection of sulfonyl amines usually requires harsh reaction conditions hampering the further modification of the products.[12]

An extensive screening of reaction conditions was undertaken (Table 1 and Supporting Information (SI) for further details). The parent ProPhenol **7a** (Table 1, entry 1) gave promising results; however, further improvement by varying reaction conditions was not achieved. Increasing the Lewis basicity as in the tetrakis(*p*-methoxyphenyl) analog **7b** (entry 2) furnished the desired product in 42% yield. An increased Lewis acidity of both zinc atoms as in tetrakis(*p*-trifluoromethylphenyl) analog **7c** (entry 3) led to even worse results. Turning to electronically desymmetrizing the complex to enhance the differentiation of the chiral space led us to the bis(*p*-methoxyphenyl)-bis(*p*-trifluoromethylphenyl) analog **7d** wherein we maximized the

Table 1. Reaction Development[a]



entry	catalyst system (mol %)	ee (%)[b]	yield (%)[c]
1	ProPhenol **7a** (15 mol %)	82	85
2[d]	ProPhenol **7b** (15 mol %)	80	42
3	ProPhenol **7c** (15 mol %)	n.d.[e]	30
4	ProPhenol **7d** (15 mol %)	81	81
5	ProPhenol **7e** (15 mol %)	80	42
6	**ProPhenol 7f (15 mol %)**	**94**	**87**
7[f]	ProPhenol **7f** (7.5 mol %)	94	45
8[g]	ProPhenol **7f** (15 mol %)	85	51
9	ProPhenol **7g** (15 mol %)	93	52[h]
10[i]	ProPhenol **7g** (15 mol %)	81	20

[a]Conditions: **5a** (0.16 mmol), **6a** (0.24 mmol), Zn-ProPhenol **7** (15 mol %), DME/THF (4:1, 1.0 mL), 4 °C, 48 h, under Ar. [b]Ee determined by HPLC. [c]Isolated yield. [d]Reaction was performed with 1-hexyne instead of phenylacetylene. [e]Not determined due to overlapping impurity. [f]The reaction performed at rt instead of 4 °C. [g]Only DME was used as solvent. [h]Material was not entirely pure. [i]Additive: Methyl hydroxypivalate (15 mol %).

electronic differentiation. Surprisingly, the selectivity (entry 4) was similar to the parent ProPhenol **7a**. On the other hand, using the combination of phenyl and *p*-trifluoromethylphenyl in the prolinol backbone (**7f**) was found to be optimal to provide both excellent yields and enantioselectivities. The desired allyl amine was isolated in a good yield of 87% and an excellent enantioselectivity of 94% (entry 6). Control experiments revealed that only the dinuclear Zn-ProPhenol complex is an effective catalyst in this transformation. A catalyst loading of 15 mol % was required to ensure high conversions; the high enantioselectivity, however, was retained even with catalyst loadings as low as 7.5 mol % (entry 7).

Further, the new ProPhenol ligand is easily recovered in 92% yield by employing a simple acid−base extraction as we have reported for the standard ProPhenol ligand previously.[13] A mixture of DME/THF = 4:1 proved to be the solvent of choice. Only the combination of both solvents led to a high yield and enantioselectivity. The ideal reaction temperature was identified as 4 °C. Standard additives,[1,2] including triphenylphosphine oxide, *cis*-1,2-cyclopentanediol, and methyl hydroxypivalate, which are crucial in numerous reported Zn-ProPhenol catalyzed reactions were found to be counterproductive in terms of both reactivity and enantioselectivity (for a detailed screening table see SI).

With the optimized conditions in hand, we examined the scope of this catalytic, asymmetric vinylation of *N*-Boc imines (Scheme 2). To our delight, we found that a variety of electronically and sterically distinct aromatic *N*-Boc imines were competent substrates in the described transformation. Using many of these same *N*-Boc imines with the parent ProPhenol ligand gave lower enantioselectivities in the 70−81% range. Substituents in the *para*, *meta*, and even *ortho* positions of the aryl imines were successful. The electronic nature of the imine seems to have no

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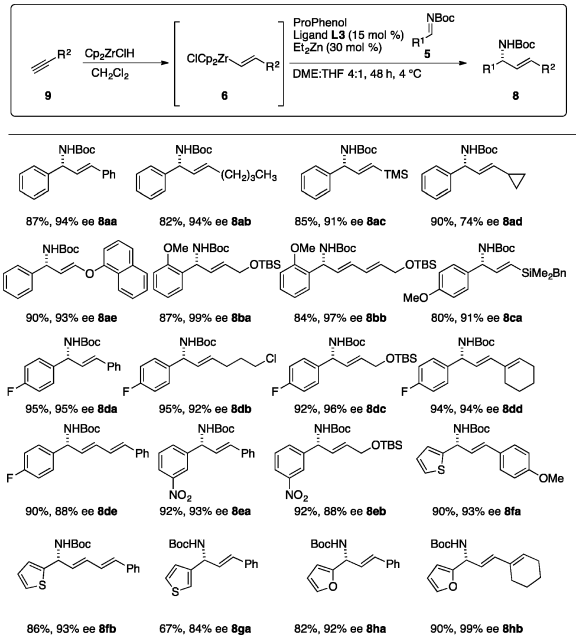
Scheme 2. Catalytic Asymmetric Vinylation of Imines under Dinuclear Zn-ProPhenol Catalysis[a,b]



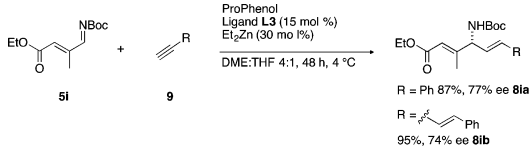
[a]Conditions: **1** (0.16 mmol), **2** (0.24 mmol), 30 mol % $ZnEt_2$, 15.0 mol % **L3** in DME/THF (4:1, 1.0 mL) at 4 °C, 48 h, under Ar; isolated yield. [b]Reactions employing **7a** generally give ee's in the range of 70−81%.

major impact on the enantioselectivity of the reaction. In most cases the ee is above 90%. We found electron-poor aromatic imines give slightly higher yields (80% to 95%) than electron-neutral and -rich aromatic imines. On the other hand, the electron-rich furan- and thiophene-derived imines performed well under the optimized reaction conditions.

The scope of the alkynes was also thoroughly investigated. Both, aromatic and aliphatic acetylenes were equally viable substrates (phenylactylene 87% yield, 94% ee; 1-hexyne 82% yield, 94% ee; see Scheme 2). Protected propargyl alcohols are effective substrates, and distant halides in an aliphatic acetylene are well tolerated. Most notably, vinyl benzyldimethylsilyl amines can be accessed setting the stage for further functionalization of the vinyl unit via Hiyama cross-coupling.[14] Gratifyingly, enynes could be employed in the desired transformation without loss of reactivity and enantioselectivity, giving rise to chiral substituted (*E*,*E*)-*α*,*β*,*γ*,*δ*-unsaturated amines never obtained by any other vinylation method before.

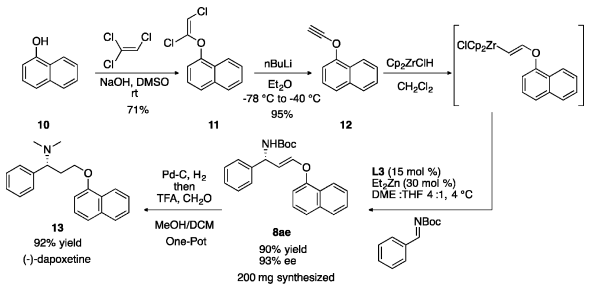
The reaction was also applicable to *α*,*β*-unsaturated imines, albeit with slightly lower enantioselectivities (Scheme 3). Unprecedented chiral diallylic amines can be readily synthesized in high yields of 87−95% with good enantioselectivities from 74 to 77% ee.

Scheme 3. Application of *α*,*β*-Unsaturated Imines for the Asymmetric Synthesis of Diallylic Amines



The unprecedented application of an alkynyl-aryl ether in a hydrozirconation reaction allowed us to report the shortest enantioselective synthesis of the selective serotonin reuptake inhibitor (SSRI) (−)-dapoxetine.[15] The drug was synthesized from 1-naphthol and trichloroethene in four simple synthetic operations (Scheme 4).

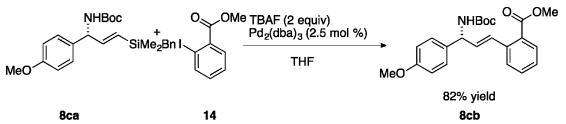
Scheme 4. Shortest Enantioselective Synthesis of (−)-Dapoextine



The alkynyl-aryl ether **12** was synthesized by a literature known method.[16] Allylic amine **8ae** was accessed in 90% yield and 93% ee by applying the optimized reaction conditions for the asymmetric vinylation. A one-pot approach making use of Pd/C catalyzed hydrogenation, *in situ* deprotection of the *N*-Boc group mediated by TFA, and final *in situ* reductive amination with formaldehyde furnished the desired (−)-dapoxetine in 92% yield.

Vinyldimethylbenzyl silane **8ca** was synthesized in 80% yield with 91% ee utilizing the optimized reaction conditions. To introduce functional groups, such as esters and ketones, that are generally incompatible with the hydrozirconation process, a Hiyama coupling with aryl iodides could be readily performed (Scheme 5). Employing ester substituted aryl iodide **14**, we were

Scheme 5. Synthetic Application of the Synthesized Allyl Amines



able to synthesize allylic amine **8cb** in 82% yield. This compound can readily be converted to benzazepinones which possess profound chemotherapeutic properties.[17]

The proposed catalytic cycle is depicted in Scheme 6. After the formation of the dinuclear Zn-ProPhenol complex **7**, transmetalation from the vinylzirconium species to the zinc catalyst occurs and places the nucleophile in a chiral environment (**15**). A bidentate coordination of the *N*-Boc group to both zinc atoms and the electronic differentiation by the introduction of an electron-withdrawing group to one side of the ProPhenol ligand may account for the high enantioselectivities achieved with *N*-Boc imines and the employed non-*C*2-symmetric ligand **L3**. The nucleophilic addition of the vinylzinc species into the coordinated imine takes place in a six-membered transition state leading to the enantiomerically enriched allylic amine. Finally, a transmetalation of the vinylzirconium species will then liberate carbonimidate **18**, which will later be transformed to the desired allylic amine **8** upon protonation during workup. The catalytic cycle starts again with the coordination of an additional imine **5**.

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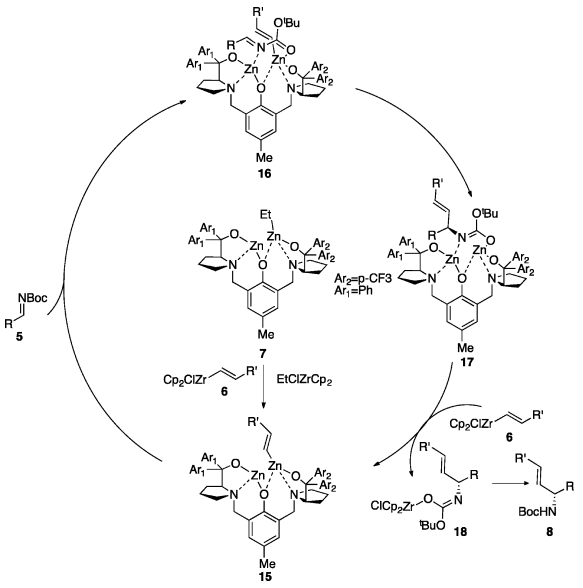
Scheme 6. Proposed Catalytic Cycle



In summary, we have developed a new generation of non-*C*2-symmetric ProPhenol ligands that proved to enhance the selectivity by electronically differentiating the chiral space in the dinuclear zinc ProPhenol catalyst. It is remarkable that such a long-range effect can have a profound impact on the selectivity. These readily prepared and quantitatively recoverable ligands allowed the first enantioselective addition of vinylzirconocenes to *N*-Boc imines. Ease of recovery and recycling the ProPhenol ligand mitigate the loading levels for a single run wherein the net effective loading becomes much less. This report displays the first asymmetric vinylation of an imine in the absence of a precious metal or a chiral auxiliary. Invoking the first catalytic transmetalation from zirconium to zinc obviating the need for preformation of a vinylzinc species provides a facile way to access valuable allylic amines in excellent yields and enantioselectivities. The scope of the reaction comprises not only aromatic but also α,β-unsaturated *N*-Boc imines. A wide range of different acetylenes, including enynes and an alkynyl ether, were employed successfully. We were able to demonstrate the synthetic utility of the generated allylic amines by presenting the shortest asymmetric synthesis of (−)-dapoxetine. The differential effect of the new ProPhenol generation on various reactions is currently being investigated in our laboratory, and results will be published in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full spectroscopic data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01755.

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Notes

The authors declare no competing financial interest.

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