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Hydrophosphination of Bicyclo[1.1.0]butane-1-carbonitriles

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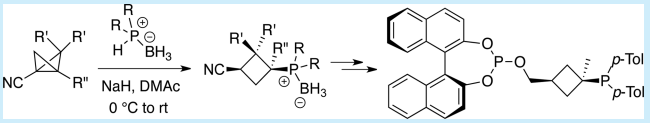
Supporting Information

ABSTRACT: Hydrophosphination of bicyclo[1.1.0]butyl nitriles with phosphine boranes and phosphites provided novel cyclobutyl-P derivatives. The reaction generally favors the *syn*-diastereomer, and the nitrile can be reduced and converted to other functional groups, thus enabling the preparation of bidentate ligands that access new conformational space by virtue of their attachment to the torsionally malleable but sterically restrictive cyclobutane scaffold. The enantioselective hydrogenation of dehydrophenylalanine using a bidentate phosphine–phosphite ligand illustrates the synthetic utility of the newly prepared scaffold.



Bicyclo[1.1.0]butanes are highly strained (ca. 65 kcal/mol) yet bench-stable, synthetically versatile carbocycles.[1,2] Bicyclobutanes with heteroatom-containing tethers, for example, can be utilized in thermal, radical, or transition-metal-mediated conversions to form structurally unique products and generally useful functionalized building blocks.[1,3]

The central bond in bicyclo[1.1.0]butanes has significant π-bond character, and homo- or heterolysis of this bond releases most of the ring strain in the carbocyle.[3] Thus, bicyclo[1.1.0]-butanes are "spring loaded" toward a variety of transformations, including protonations,[4] halogenations,[5] and photochemical processes,[6] across the central bond to afford 1,3-functionalized cyclobutanes. Nucleophilic 1,3-additions of carbon and nitrogen nucleophiles generally require electron-withdrawing activators, as shown in the recent elegant studies by Fox (esters), Baran (sulfones), and co-workers.[2,7,8] In contrast, the addition of a P-nucleophile to a bicyclobutane is, to the best of our knowledge, still unprecedented.[9]

As part of our ongoing studies to utilize phosphine boranes as convenient, air-stable reagents for hydrophosphination reactions,[10] we were interested in extending this process toward bicyclo[1.1.0]butanes to generate novel cyclobutyl phosphines. Previous work has shown that secondary phosphine borane anions effectively hydrophosphinate alkynes and carbodiimides,[10] and we are now extending this protocol to strained carbocycles (Scheme 1). The product of such an addition to a bicyclo[1.1.0]butane would be a cyclobutyl phosphine with a quaternary carbon α to the phosphorus substituent. Phosphines of this type could be of potential use in transition-metal catalysis.[11,12]

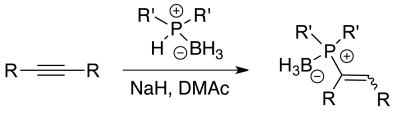
In a preliminary screen to determine the reactivity of bicyclobutanes and other strained carbocycles to the phosphine borane anion (see the Supporting Information), it became apparent that bicyclobutanes lacking an electron-withdrawing group were unreactive or showed low conversions. These results suggested that the addition reaction was not solely driven by relief of ring strain but resembled a Michael addition process. Nitriles such as 3-methylbicyclo[1.1.0]butane-1-carbonitrile **1**, obtained in two steps from commercial methylenecyclobutane-3-carbonitrile,[4b,13] reacted efficiently at ambient temperature to give a separable 1.7:1 mixture of cyclobutanes *syn*-**2** and *anti*-**2** in a combined yield of 76% (Scheme 2). The major *syn*-isomer was reduced with DIBAL-H to give aldehyde **3**, which was further reduced to alcohol **4** in an overall yield of 52%.

The hydrophosphination of nitriles could be extended to a variety of aliphatic and aromatic phosphine boranes (Scheme 3). The overall yield is moderate to high and increases for sterically hindered phosphines (**6**), suggesting some loss of less

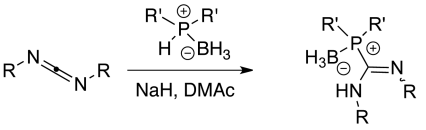
Scheme 1. Overview of Hydrophosphinations

(A) Previously reported hydrophosphinations with phosphine boranes

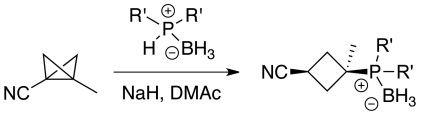
Busacca et al. (2009, 2013)



Busacca, Senanayake, Wipf et al. (2014)



(B) This work: hydrophosphination of bicyclo[1.1.0]butanes



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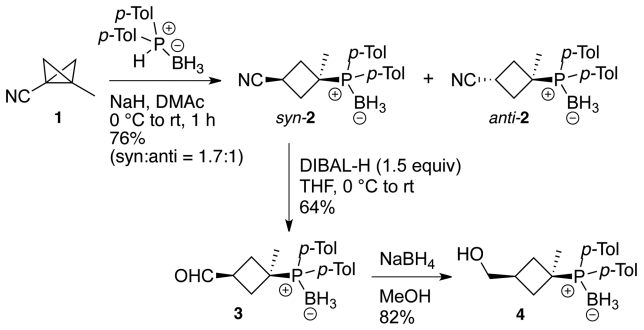
Scheme 2. Hydrophosphination of 3-Methylbicyclo[1.1.0]butane-1-carbonitrile 1 and Transformation to Phosphine Borane Alcohol 4



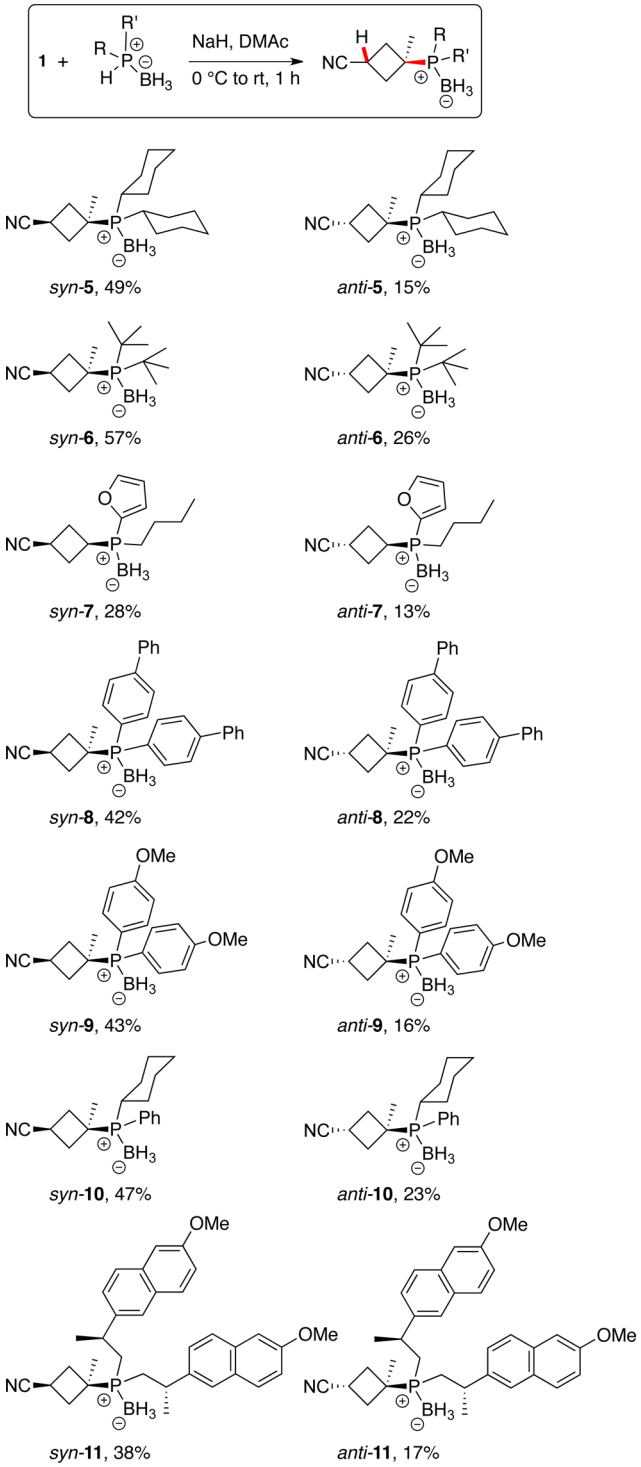
sterically shielded phosphine boranes during workup conditions. Substitutions on the aryl phosphine portion, including electron-donating groups, are well tolerated (**2**, **8**, and **9**). Mixed alkyl/aryl phosphines can be prepared (**7**, **10**) as well as chiral phosphines (**11**). In almost all cases, *syn*- and *anti*-isomers (which were readily separated using chromatography on SiO_2) were obtained in about a 2:1 ratio, regardless of the nature of the phosphine borane. Interestingly, this isomer ratio is regenerated when either isolated diastereomer is resubjected to the reaction conditions (NaH, DMAc); i.e., the hydrophosphination is under thermodynamic control. Accordingly, the minor *anti*-isomer can readily be converted to the more stable *syn*-isomer. The relative configuration was assigned by NMR (the *syn*-isomers exhibit a distinct NOE between the methyl C−H's and the methine C−H as well as a small $^4J_{CP}$ coupling of the nitrile carbon in most cases).

Substitutions on the bicyclo[1.1.0]butane are also well tolerated in this reaction. 3-Phenylbicyclo[1.1.0]butane-1-carbonitrile **13** was prepared from dibromocyclopropane **12** by dilithiation and subsequent trapping with dimethyl malononitrile (Scheme 4).[14] It should be noted that this is the first example of a synthesis of a bicyclobutane nitrile by transnitrilation. Bicyclobutane **13** underwent a smooth hydrophosphination with aromatic or aliphatic phosphine boranes to give cyclobutanes **14** and **15** in 60−70% yield. In contrast to methyl-substituted **1**, phenyl-substituted **13** provided a slight preference for the *anti*-isomer **14**. The origin of this reversal of selectivity is not obvious. Interestingly, the sterically hindered 2,2-dimethylbicyclo[1.1.0]butane-1-carbonitrile **16** (which lacks substitution at the bridgehead position) provided only the *syn*-isomers **17** and **18**, albeit in low yields of 27−34% (Scheme 5).

For mechanistic reasons, the conversion of **1** to **5** was also performed in the presence of a galvinoxyl (0.15 equiv) radical trap and in the dark, leading to comparable yields, ratios, and reaction times, and thus, a radical pathway could be excluded.

The addition of P-nucleophiles other than phosphine boranes to bicyclobutane nitriles was also investigated (Scheme 6). Initial attempts to accomplish the addition of an *H*-phosphonate in the same manner as phosphine boranes was unsuccessful. However, in accord with observations of Montchamp and co-workers,[15] DBU was found to be an effective base, and dibenzyl phosphite (which is slightly more acidic than the more common diethyl phosphite) led to an efficient conversion. Under these conditions, the cyclobutyl phosphonates **19** and **20** were obtained in yields of 59% and 62%, respectively, as inseparable mixtures of *syn*/*anti*-stereoisomers.

Scheme 3. Hydrophosphination of Nitrile 1 with Various Phosphine Boranes



Bidentate phosphine−phosphites and phosphine−phosphoramides have frequently been utilized in catalysis, particularly in asymmetric hydrogenations and hydroformylations.[16] In order to assess the potential of cyclobutyl phosphines as a new ligand class in asymmetric catalysis, alcohol **4** was deprotected with DABCO and subsequently treated with a BINOL-derived chlorophosphite to afford bidentate phosphine−phosphite **21** (Scheme 7). In the presence of 3 mol % of **21**, 1 mol % of cationic rhodium complex $Rh(NBD)BF_4$,[17] and hydrogen gas

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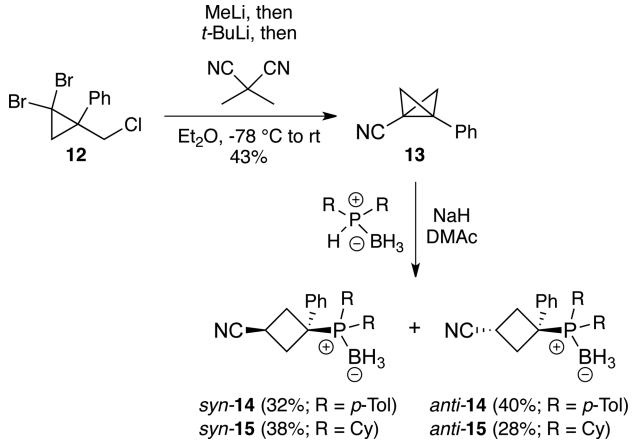
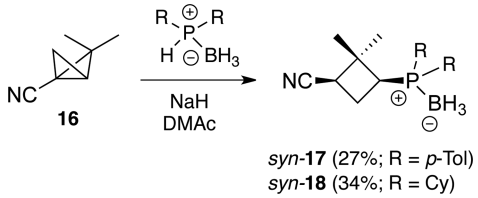
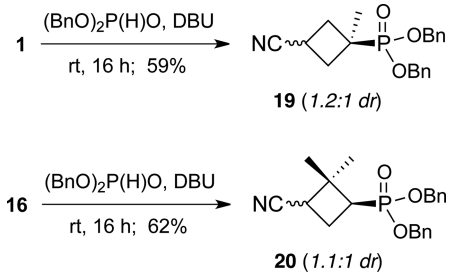
Scheme 4. Preparation and Hydrophosphination of 3-Phenylbicyclo[1.1.0]butane-1-carbonitrile 13



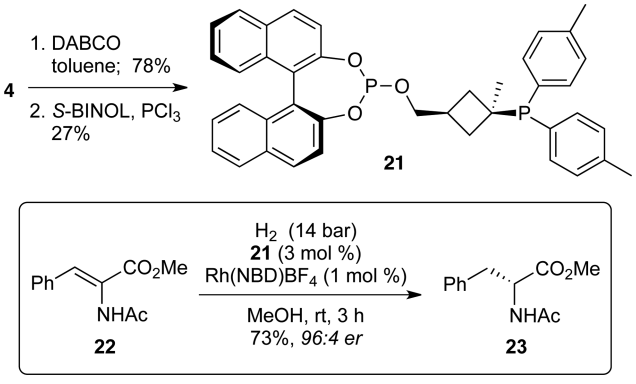
Scheme 5. Hydrophosphination of 2,2-Dimethylbicyclo[1.1.0]butane-1-carbonitrile 16



Scheme 6. Addition of *H*-Phosphonates to Bicyclo[1.1.0]butanes 1 and 16



Scheme 7. Preparation of Bidentate Phosphine Ligand 21 and Asymmetric Hydrogenation of Dehydrophenylalanine 22



in methanol, dehydrophenylalanine **22** was converted to *N*-acetyl D-phenylalanine methyl ester **23** in 73% yield and 96:4 er, suggesting an effective enantiofacial differentiation induced by the cyclobutane-linked phosphine−phosphite motif in **21**.

In summary, the first hydrophosphinations of bicyclo[1.1.0]-butane-1-carbonitriles have been achieved with secondary phosphine borane anions. In a similar fashion, *H*-phosphonates can be added across the central bond of this strained carbocycle. Most cyclobutylphosphine borane products are obtained as a readily separable mixture of *syn*- and *anti*-diastereomers that can be re-equilibrated for higher conversions. Alkyl and aryl substitutions on bicyclobutane and phosphine are readily tolerated, and the nitrile moiety in the cyclobutane product can be converted to aldehydes and alcohols, which enables the synthesis of chiral bidentate phosphine−phosphite ligands. The utility of this new scaffold has been demonstrated in the enantioselective hydrogenation of a dehydrophenylalanine derivative. Future extensions of this work include exploring applications of these phosphine derivatives in transition-metal catalysis and developing related nucleophilic ring openings of bicyclobutanes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02051.

Experimental procedures, NMR spectra for new compounds, and a differential scanning calorimetry plot for **1** (PDF)

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Notes

The authors declare no competing financial interest.

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