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Synthesis of Enantiomerically Pure 1,2,3-Trisubstituted Cyclopropane Nucleosides Using Pd-Catalyzed Substitution via Directing Group-Mediated C(sp^3)−H Activation as a Key Step

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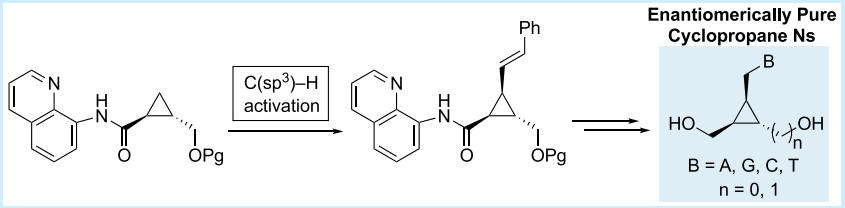
Supporting Information



ABSTRACT: A series of enantiomerically pure 1,2,3-trisubstituted cyclopropane nucleosides **Ia−Id** and **IIa−IId** of medicinal chemical interest was designed and synthesized. In the synthesis, a Pd-catalyzed substitution reaction via a directing group-mediated C(sp^3)−H activation was effectively used to construct the 1,2,3-trisubstituted cyclopropane structure as a key step.

Much attention has been focused on carbocyclic nucleosides lacking the biologically unstable *N*-ribosyl linkage in natural nucleosides, because of their significant antiviral activities,[1] typically exemplified by clinically useful entecavir[2] and abacavir[3] (Figure 1). In the course of these medicinal chemical studies on carbocyclic nucleosides, we have also studied design and synthesis of anti-RNA virus carbocyclic nucleosides such as **1** derived from antibiotic neplanosin A as a prototype.[4] Because the smallest carbocycle cyclopropane has a characteristic sterically unhindered and rigid structural feature,[5] cyclopropane nucleosides (CPNs) are of great interest.[6] Besifovir, which is a cyclopropane nucleoside phosphate derivative,[6d] was most recently approved as an antihepatitis B viral drug, and some other cyclopropane nucleosides also have potent antiviral activity.[6] We are interested in enantiomerically pure 1,2,3-trisubstituted CPNs **I** and their one-carbon-reduced congeners **II** as potential antiviral agents, because they have regioisomeric structures of A5021 with remarkable antiherpes virus effects.[6b] Furthermore, CPNs **I** and **II** are notable from the viewpoint that they correspond to conformationally restricted analogues of the potent antiherpes virus drug famcyclovir.[7]

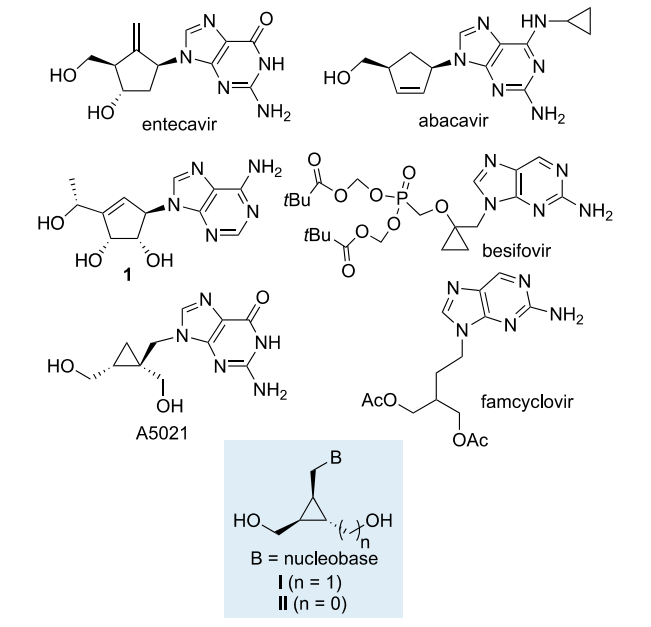


Figure 1. Carbocyclic nucleosides as antiviral agents.

Many CPNs have been synthesized, but, with regard to CPNs with a 1,2,3-trisubstituted cyclopropane structure, there are a few meso and racemic examples[6b,8a−d] and only one report of enantiomerically pure CPNs.[8e] Although considerable efforts have been devoted to developing effective methods for constructing 1,2,3-trisubstituted cyclopropanes, especially in optically pure form, it remains a distinct challenge.[9] Scheme 1 shows typical enantioselective syntheses of chiral 1,2,3-trisubstituted cyclopropanes, suggesting that the introducible substituents are limited.

Here, we report the efficient synthesis of a series of 1,2,3-trisubstituted CPNs **I** and **II** with high optical purity using Pd-

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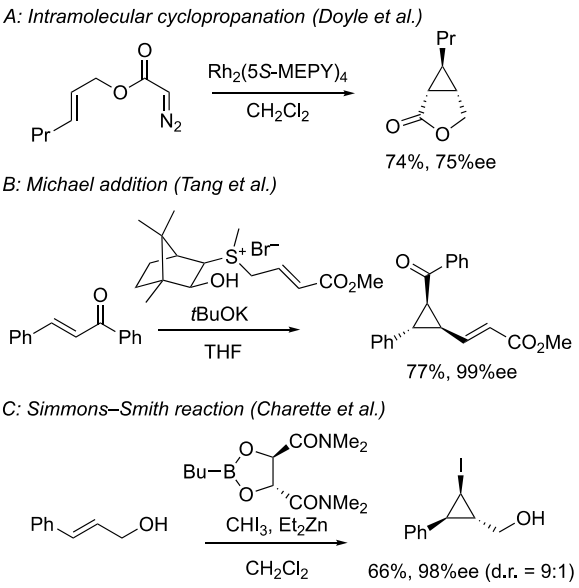
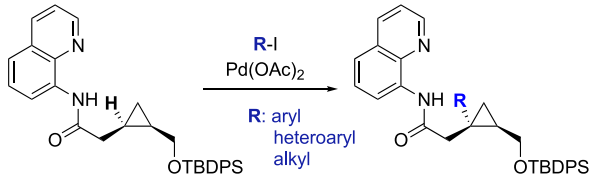
Scheme 1. Representative Enantioselective Synthesis of Chiral 1,2,3-Trisubstituted Cyclopropanes



catalyzed substitution via a directing group-mediated C(sp^3)−H activation as a key step.

We have performed synthetic and medicinal chemical studies using cyclopropane as the key structure.[5,10,11] These studies demonstrated that directing group-mediated C(sp^3)−H activation reactions effectively provide various optically active cyclopropanes with desired substituents (see examples in Scheme 2).[11,12] Based on these results, we planned to

Scheme 2. Pd-Catalyzed Substitution Constructing 1,1,2-Trisubstituted Cyclopropanes via a Directing Group-Mediated C(sp^3)−H Activation



synthesize the desired enantiomerically pure 1,2,3-trisubstituted CPNs via directing group-mediated C(sp^3)−H activation with Pd catalyst as a key step. The retrosynthetic analysis is summarized in Figure 2. Various nucleobases in **I** and **II** would be introduced via Mitsunobu reaction at a late stage. An elegant decarboxylative borylation recently reported by Aggarwal[13] would allow us to achieve one-carbon reduction for the synthesis of CPNs **II**. The introduction of third carbon at the 1-position to construct the key 1,2,3-trisubstituted

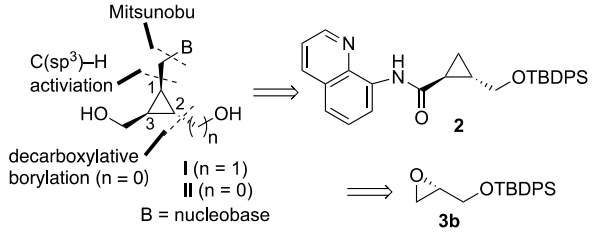
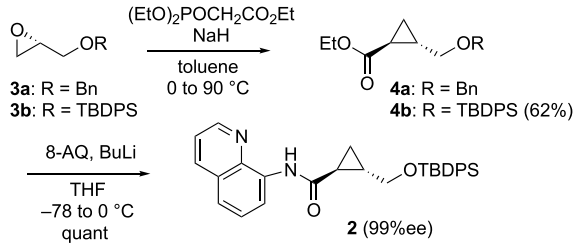


Figure 2. Retrosynthetic analysis of CPNs **I** and **II**.

cyclopropane structure was planned via the Pd-catalyzed C(sp^3)−H activation[14] of substrate **2** with an aminoquinoline as a directing group.[15] The optically active *trans*-cyclopropane structure of **2** would be constructed from protected (*R*)-glycidol **3b**.[16]

Synthesis of substrate **2** for the directing group-mediated C(sp^3)−H activation is shown in Scheme 3. Armstrong and

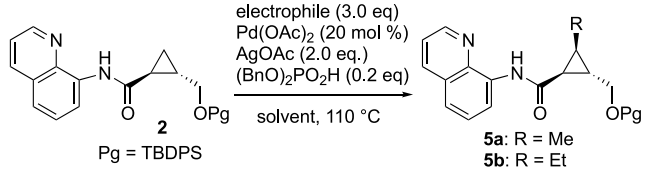
Scheme 3. Synthesis of Substrate 2 for the Directing Group-Mediated C(sp^3)−H Activation



Scutt efficiently synthesized chiral *trans*-cyclopropane **4a** in high enantiopurity from *O*-benzyl-protected (*R*)-glycidol (**3a**).[17] Based on their procedure, using the *O*-TBDPS-protected (*R*)-glycidol (**3b**) as a starting material, we successfully obtained the desired *trans*-cyclopropane **4b** in 62% yield. Treatment of **4b** with BuLi and 8-aminoquinoline in THF afforded the amide product **2** quantitatively with an optical purity of 99% ee, as confirmed by chiral HPLC.

Using substrate **2**, we investigated the Pd-catalyzed introduction of carbon substituents via directing group-mediated C(sp^3)−H activation (Table 1). We first examined

Table 1. Synthesis of Enantiomerically Pure 1,2,3-Trisubstituted Cyclopropanes



entry	electrophile	solvent	time (h)	yield[a] (%)
1[b]	MeI	toluene	12	25
2[b,c]	MeI	toluene	12	16
3	MeI	toluene	12	36
4	MeI	toluene	20	55
5	MeI	*t*-amyl alcohol	20	61 (59)[e]
6	EtI	*t*-amyl alcohol	20	28[e]
7[c,d]	PhCH=CHI	*t*-amyl alcohol	1	79[e]

[a]NMR yield. [b]Amount of $Pd(OAc)_2$ was 10 mol %. [c]Without $(BnO)_2PO_2H$. [d]Performed at 90 °C. [e]Isolated yield.

the alkylation of **2** with MeI as an electrophile. Treatment of **2** with MeI (3.0 equiv), $Pd(OAc)_2$ (10 mol %), AgOAc (2.0 equiv), and $(BnO)_2P(O)OH$[18] (0.2 equiv) in toluene at 110 °C for 12 h produced the desired methylated cyclopropane product **5a**, although the yield was low (25%; see Table 1, entry 1). In a similar reaction but without $(BnO)_2P(O)OH$, the yield was decreased (to 16%; see Table 1, entry 2). Increasing the amount of $Pd(OAc)_2$ (to 20 mol %; see Table 1, entry 3) and the reaction time (to 20 h; see Table 1, entry 4) improved the yield. Thus, when **2** was treated with MeI (3.0

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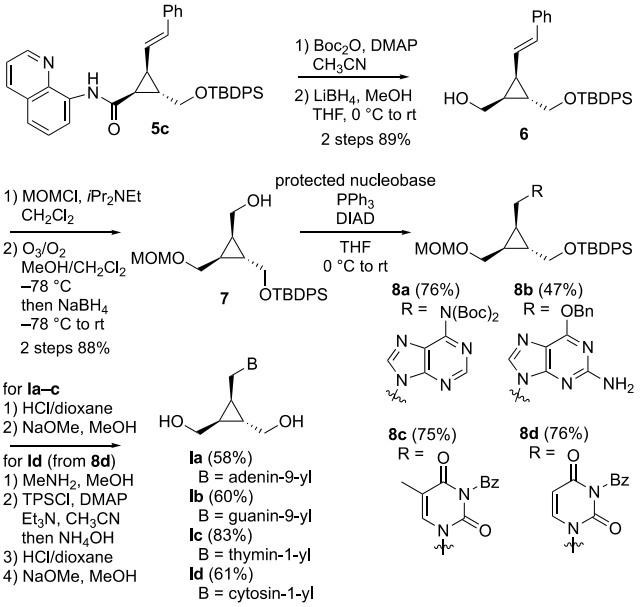
equiv), $Pd(OAc)_2$ (20 mol %), AgOAc (2.0 equiv), and $(BnO)_2P(O)OH$ (0.2 equiv) in *t*-AmylOH at 110 °C for 20 h, the methylated product **5a** was obtained in 61% yield (Table 1, entry 5). The treatment of **2** with EtI as an electrophile instead of MeI gave the corresponding ethylated product **5b** in 28% yield (Table 1, entry 6). The introduction of a styryl group, which could be potentially converted to a formyl group, was examined next. Treatment of **2** with (*E*)-(2-iodovinyl)benzene as an electrophile under the optimized conditions successfully led to the desired styryl product **5c** in 79% yield on gram scale (Table 1, entry 7).[19] Other electrophiles, such as $BrCH_2I$, $TMSCH_2I$, $PivOCH_2I$, and $BnOCH_2I$, were used in an attempt to introduce a functionalized methyl group, but all electrophiles were inactive in this reaction.

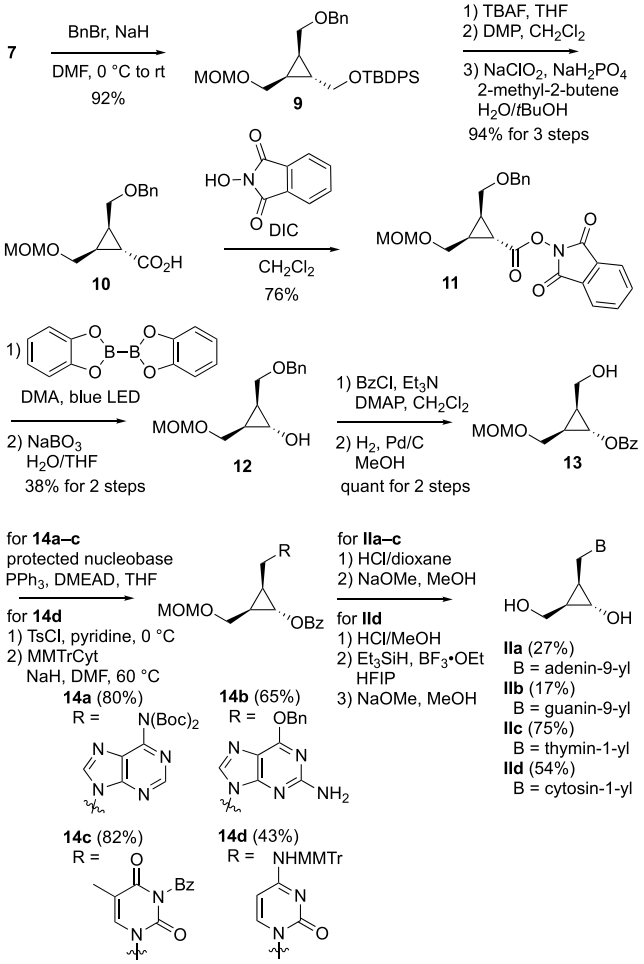
With the enantiomerically pure 1,2,3-trisubstituted cyclopropane **5c** in hand, we successfully synthesized the target CPNs **Ia**–**Id**, as shown in Scheme 4. Introduction of the Boc group to the quinolone-amide moiety of **5c**, followed by treatment with $LiBH_4$, gave alcohol **6**. The free hydroxy group of **6** was protected with a MOM group, and ozonolysis of the product afforded common triol intermediate **7**, to which various nucleobases were introduced under Mitsunobu conditions. Treatment of **7** with N^6-Boc-protected adenine[20a] in the presence of PPh_3 and DIAD in THF afforded the desired N^9-adenylated product **8a** in 77% yield.[21] Similarly, other nucleobases[20b,c] were introduced to **7**, providing **8b**, **8c**, and **8d**. Finally, the protecting groups of **8a**–**8c** were removed to furnish the target CPNs **Ia**–**1c** with adenine, guanine, and thymine as a nucleobase, respectively. The cytosine CPN **Id** was synthesized from uracil derivative **8d** via the O^4-sulfonylation and subsequent ammonolysis to form cytosine base.

Scheme 4. Synthesis of 1,2,3-Trisubstituted CPNs Ia–Id



Synthesis of one-carbon reduced CPNs **IIa**–**IId** is shown in Scheme 5. Manipulation of the protecting groups of the previously synthesized intermediate **7**, and subsequent Pinnick oxidation, gave carboxylic acid **10**, which was then coupled with *N*-hydroxyphthalimide, leading to **11**, the substrate for the decarboxylative borylation.[13] Thus, irradiation of a mixture of **11** and bis(catecholato)diboron in DMA with a blue LED lamp, followed by treatment with $NaBO_3$ in aqueous THF, effectively provided the desired decarboxylated product **12**. After manipulation of the protecting group of **12** to form **13**, coupling with nucleobases under Mitsunobu conditions with DMEAD, which was more easily separated from the products than DIAD, or alkylation of its tosylated product provided protected CPNs **14a**–**14d**. Removal of the protecting groups of **14a**–**14d** furnished the desired CPNs **IIa**–**IId** with a purine or pyrimidine natural nucleobase, respectively.[22,23]

Scheme 5. Synthesis of 1,2,3-Trisubstituted CPNs IIa–IId



In summary, we successfully developed an efficient procedure to access enantiomerically pure 1,2,3-trisubstituted CPNs **Ia**–**Id** and **IIa**–**IId** as potential antiviral agents using Pd-catalyzed substitution via directing group-mediated C-(sp^3)–H activation as the key step. It is noteworthy that the present method systematically provided the CPNs with all four natural nucleobases in high optical purity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03785.

Experimental details, spectral and analytical data for all reaction products (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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