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Enantioselective Construction of Tertiary C−O Bond via Allylic Substitution of Vinylethylene Carbonates with Water and Alcohols

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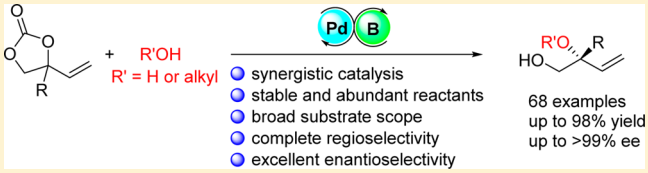
Supporting Information

ABSTRACT: An efficient method for the enantioselective construction of tertiary C−O bond via asymmetric allylic substitution of racemic vinylethylene carbonates with water and alcohols has been developed. Under the cooperative catalysis system of an in situ generated chiral palladium complex and boron reagent in mild conditions, the process allowed rapid access to valuable tertiary alcohols and ethers in high yields with complete regioselectivities and high enantioselectivities. This protocol represented the first example of direct enantioselective formation of a tertiary C−O bond with water as an oxygen donor. The synthetic utilities of the process have been demonstrated by the elaboration of the products into key intermediates of biologically relevant agents, and chiral tertiary cyclic ethers could also be provided through the sequential reactions of the allylic etherification and ring-closing metathesis.



INTRODUCTION

Chiral tertiary alcohols and ethers are ubiquitous in medicinally relevant agents and biologically active natural products.[1] Consequently, catalytic asymmetric synthesis of these skeletons from readily available precursors is a prominent objective in modern organic synthesis. A most common approach to chiral tertiary alcohols is an asymmetric addition of organometallic reagents to ketones.[1a] However, high asymmetric induction of the process invariably relies on the steric difference between the substituents bearing the carbonyl group. When the steric difference is small, the enantioselectivity is often low. Tertiary alcohols and ethers are also produced by asymmetric dihydroxylation[2] and epoxidation[3] of 1,1-disubstituted alkenes. However, the enantioselectivity of the process is also challenged on the enantiofacial discrimination between the two substituents flanking the carbon−carbon double bond. Aggarwal and co-workers reported an efficient method for the synthesis of tertiary alcohols from chiral secondary alcohols via stereospecific 1,2-metalate rearrangement of boronate complexes with broad substrate scope.[4] Although some other approaches to chiral tertiary alcohols and ethers have sporadically been reported,[5,6] the development of efficient methods for enantioselective construction of tertiary C−O bond is still highly appealing.

Transition-metal-catalyzed asymmetric allylic substitution with *O*-nucleophiles is one of the most powerful methods for the enantioselective construction of the C−O bond.[7] Although the transformation has been well developed to provide chiral secondary allylic ethers, regioselective construction of the tertiary C−O bond via allylic substitution of 1,1- or 3,3-disubstituted allylic donors remains a significant challenge.[8,9] An elegant example of forming tertiary allylic ethers with high regio- and enantioselectivity has been developed under Pd-catalyzed allylic substitution of vinyl epoxides with alcohols using trialkylborane as a cocatalyst.[10] However, this method is limited to substrates of 2-alkyl substituted 2-vinyloxirans. For vinyl epoxides, isoprene oxide can be readily made from abundant feedstock, isoprene. However, 2-vinyloxiranes bearing diverse 2-substituents are not readily accessible by the epoxidation process because the corresponding 2-substituted butadiene compounds are not easy to access. Although 2-substituted 2-vinyloxiranes can be synthesized from the corresponding α-halogenated ketones,[10b] this type of epoxides is somewhat unstable.[11] Most recently, we have developed vinylethylene carbonates (VECs) as a more stable and readily available substrate for Pd-catalyzed asymmetric decarboxylative cycloaddition with unsaturated electrophiles to construct functionalized heterocycles with quaternary stereocenters with high efficiencies.[12−14]

Based on our continuous efforts to develop efficient methods for the enantioselective construction of quaternary stereocenters, we are interested in asymmetric allylic substitution of VECs with water[15] in anticipation of the direct construction of chiral tertiary alcohols. Despite water being one of the most abundant, safe, environmentally benign, and cost-efficient resources, direct construction of the C−O bond for the production of chiral alcohols using water as an oxygen donor remains elusive.[16,17] To the best of our knowledge, corresponding protocols for enantioselective construction of a tertiary C−O bond with water are unknown. Two challenging issues should be solved for the process including how to promote the nucleophilicity of water and how to control regioselectivity to form the tertiary C−O bond. Inspired by an

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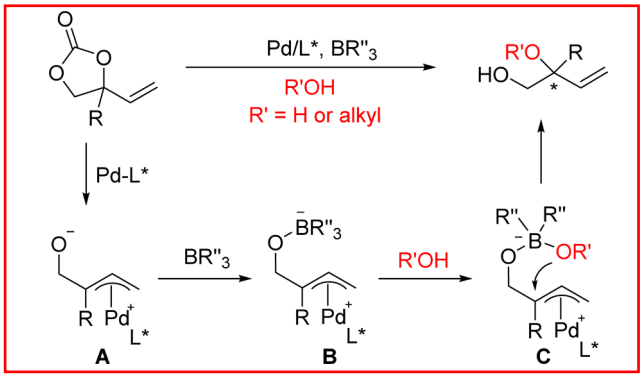
earlier report by Trost and co-workers of allylic etherification of isoprene oxide,[9a] we envisioned that the process with a boron reagent as a cocatalyst could solve these problems.[18] We hypothesized that VECs could undergo the decarboxylative process to afford the zwitterionic π-allylpalladium intermediate **A**, which with boron reagent would form boronate complex **B**. The intermediate **B** could capture water to give key intermediate **C**. This species would subsequently undergo nucleophilic addition regioselectively to form desired tertiary alcohols (Scheme 1). Herein we report the realization of this

Scheme 1. Regio- and Enantioselective Allylic Substitution of VECs with Water and Alcohols

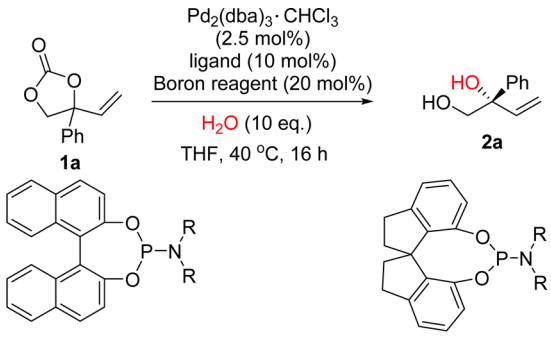


idea and present asymmetric allylic substitution of VECs with water under the cooperative catalysis system of palladium and a boron reagent, a practical approach which allows rapid access to valuable chiral tertiary 1,2-diols in high yields with complete regioselectivities and high level of enantioselectivities. The synthetic strategy is also suitable for the allylic etherification of VECs with alcohols to afford tertiary ethers with high efficiencies. The chiral tertiary cyclic ethers could also be provided through the sequential reactions of the allylic etherification and ring-closing metathesis.

RESULTS AND DISCUSSION

Enantioselective Construction of Tertiary Alcohols via Allylic Substitution of VECs with Water. Initially, we tried the reaction of Ph-VEC **1a** as a model substrate with water using the catalyst generated in situ from the $Pd_2(dba)_3{\cdot}CHCl_3$ and Feringa's phosphoramidite[19] (*R*)-**L1** as a ligand in THF at 40 °C. However, the reaction did not proceed at all, and **1a** was recovered in practically quantitative yield (Table 1, entry 1). As we expected, the reaction using a catalytic amount of triethylborane (20 mol %) under otherwise identical conditions with entry 1 afforded the desired tertiary 1,2-diol **2a** as the only regioisomer, albeit with moderate enantiomeric excess (ee) (68% ee, entry 2). We next found that the reaction could perform well with various boron sources, such as tri(2-phenylethyl)borane (entry 3), tricyclohexylborane (entry 4), boric acid (entry 5), trimethyl borate (entry 6), and phenylboronic acid (entry 7). We did not find any methoxylated product when using trimethyl borate or allylphenyl coupling product when using phenylboronic acid.[20] These results demonstrated that boron is a useful cocatalyst for the process. The reaction with phenylboronic acid gave the best enantioselectivity (82% ee). Further screening of substituted phenylboronic acids with different steric and electronic properties revealed the reaction efficiency did not improve (entries 8–11). To our delight, through the examination of

Table 1. Optimizations of Catalytic System for Allylic Substitution of Ph-VEC 1a with Water[a]



(*R*)-**L1**: R = ^{i}Pr
(*S,S,S*)-**L2**: R = (*S*)-1-phenylethyl
(*S,R,R*)-**L3**: R = (*R*)-1-phenylethyl
(*R*)-**L4**: R = ^{i}Pr
(*R,R,R*)-**L5**: R = (*R*)-1-phenylethyl
(*S,R,R*)-**L6**: R = (*R*)-1-phenylethyl

entry	ligand	boron reagent	solvent	yield (%)[b]	ee (%)[c]
1	(*R*)-**L1**	–	THF	–	–
2	(*R*)-**L1**	BEt_3	THF	73	68
3	(*R*)-**L1**	$B(2\text{-Ph-ethyl})_3$	THF	73	77
4	(*R*)-**L1**	BCy_3	THF	90	60
5	(*R*)-**L1**	$B(OH)_3$	THF	90	77
6	(*R*)-**L1**	$B(OMe)_3$	THF	84	78
7	(*R*)-**L1**	$PhB(OH)_2$	THF	90	82
8	(*R*)-**L1**	$2\text{-MeC}_6H_4B(OH)_2$	THF	84	79
9	(*R*)-**L1**	$4\text{-MeC}_6H_4B(OH)_2$	THF	83	78
10	(*R*)-**L1**	$4\text{-CF}_3C_6H_4B(OH)_2$	THF	82	70
11	(*R*)-**L1**	$C_6F_5B(OH)_2$	THF	62	83
12	(*S,S,S*)-**L2**	$PhB(OH)_2$	THF	32	−57
13	(*S,R,R*)-**L3**	$PhB(OH)_2$	THF	66	−77
14	(*R*)-**L4**	$PhB(OH)_2$	THF	96	95
15	(*R,R,R*)-**L5**	$PhB(OH)_2$	THF	–	–
16	(*S,R,R*)-**L6**	$PhB(OH)_2$	THF	26	−50
17	(*R*)-BINAP	$PhB(OH)_2$	THF	62	−20
18	(*S*)-Segphos	$PhB(OH)_2$	THF	18	20
19	Trost ligand	$PhB(OH)_2$	THF	–	–
20	(*R*)-**L4**	$PhB(OH)_2$	toluene	81	92
21	(*R*)-**L4**	$PhB(OH)_2$	CH_2Cl_2	88	76
22	(*R*)-**L4**	$PhB(OH)_2$	dioxane	92	92
23	(*R*)-**L4**	$PhB(OH)_2$	Et_2O	87	94
24	(*R*)-**L4**	$PhB(OH)_2$	CyH	61	84
25	(*R*)-**L4**	$PhB(OH)_2$	acetone	90	91
26	(*R*)-**L4**	$PhB(OH)_2$	CH_3CN	95	79
27	(*R*)-**L4**	$PhB(OH)_2$	H_2O	89	50

[a]Reaction conditions: $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), ligand (10 mol %), boron source (20 mol %), **1a** (0.2 mmol), water (2.0 mmol), solvent (1.0 mL), 40 °C, 16 h. [b]Isolated yields. [c]Determined by HPLC using a Chiralcel AD-H column. The absolute configuration was confirmed by the comparison of the sign of optical rotation with that of reported in literature.[22]

different phosphoramidite ligands (entries 12–16), we found that the reaction with the combination of $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), Zhou's ligand[21] (*R*)-**L4** (10 mol %), and phenylboronic acid (20 mol %) in THF at 40 °C gave tertiary 1,2-diol **2a** as a single regioisomer in 96% yield with 95% ee (entry 14). Low enantioselectivities were observed when the reaction with bisphosphine ligand, BINAP (entry 17) or Segphos (entry 18). The reaction did not proceed with Trost's ligand (entry 19). Further screening of solvent (entries 20–27) showed that toluene, 1,4-dioxane, ether, and acetone are also

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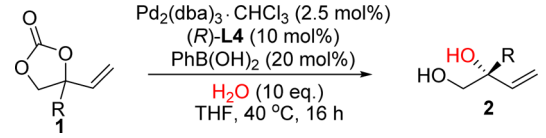
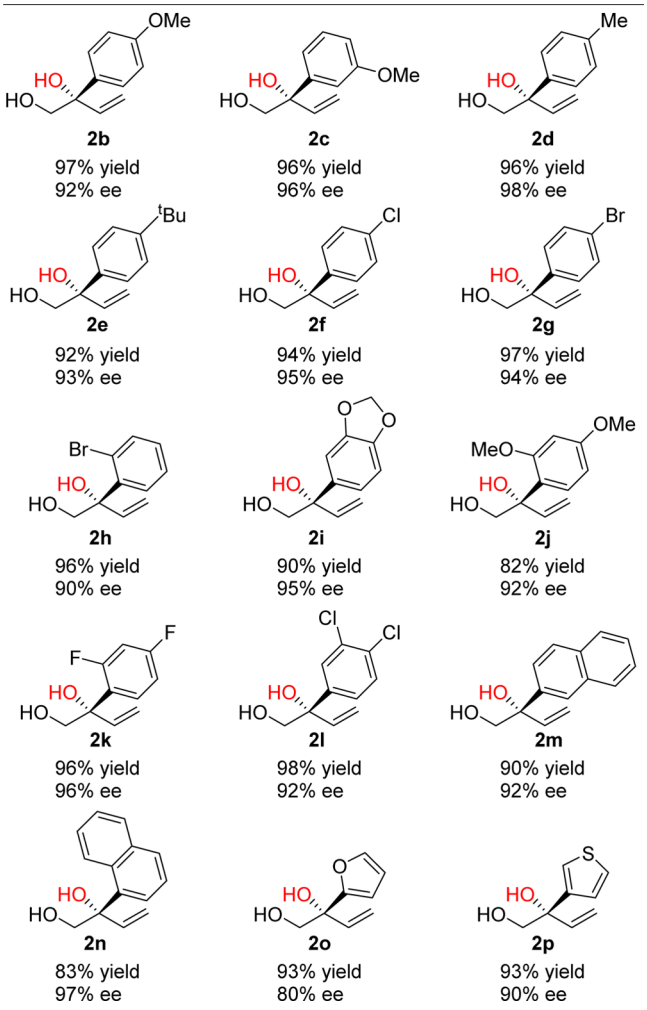
suitable solvents for the reaction, even though the enantioselectivities were slightly decreased. Notably, the reaction performed well in water as solvent to afford the product **2a** in high yield, but the enantioselectivity decreased remarkably (entry 27).

With these optimized conditions in hand (entry 14, Table 1), the generality of the protocol was evaluated with different VECs **1** (Table 2). Significantly, a wide range of substituted

Table 2. Asymmetric Allylic Substitution of VECs 1 with Water[a]



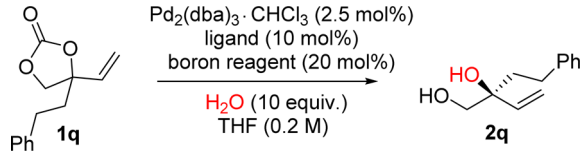


[a]Reaction conditions: $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), (*R*)-**L4** (10 mol %), phenylboronic acid (20 mol %), **1** (0.2 mmol), water (2.0 mmol), THF (1.0 mL), 40 °C, 16 h. Yields are of isolated materials. The enantioselectivities were determined by HPLC using chiral stationary phase.

phenyl-VECs having different electronic and steric properties was tolerated under the reaction conditions to convert into the corresponding tertiary 1,2-diols **2a**–**2l** in high yields with complete regioselectivities and a high level of enantioselectivities. The reaction of VECs bearing a naphthyl group also proceeded smoothly to afford 1,2-diols **2m** and **2n** in high yields with excellent enantioselectivities. The process also worked well for VECs with versatile furan and thiophene moieties to furnish corresponding tertiary 1,2-diols **2o** and **2p** in high yield with good enantioselectivities.

However, the conditions were not suitable for the reaction of alkyl substituted VEC **1q**, giving the product **2q** in 82% yield with only 30% ee (Table 3, entry 1). Therefore, we tried to find

Table 3. Optimization of Catalytic System for Allylic Substitution of VEC 1q with Water[a]



entry	ligand	boron reagent	*T* (°C)	yield (%)[b]	ee (%)[c]
1	(*R*)-**L4**	$PhB(OH)_2$	40	82	−30
2	(*R*)-**L4**	$PhB(OH)_2$	20	52	−57
3	(*R*)-**L1**	$PhB(OH)_2$	20	50	−12
4	(*S,S,S*)-**L2**	$PhB(OH)_2$	20	45	89
5	(*S,R,R*)-**L3**	$PhB(OH)_2$	20	41	8
6	(*R,R,R*)-**L5**	$PhB(OH)_2$	20	–	–
7	(*S,R,R*)-**L6**	$PhB(OH)_2$	20	–	–
8	(*S,S,S*)-**L2**	BEt_3	20	53	97
9[d]	(*S,S,S*)-**L2**	BEt_3	20	43	>99
10[e]	(*S,S,S*)-**L2**	BEt_3	20	63	>99

[a]Reaction conditions: $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), ligand (10 mol %), boron source (20 mol %), **1q** (0.2 mmol), water (2.0 mmol), THF (1.0 mL), 16 h. [b]Isolated yields. [c]Determined by HPLC using a Chiralcel AD-H column. [d]The reaction was performed with 10 mol % of Et_3B. [e]The reaction was performed with 10 mol % of Et_3B for 24 h.

optimal conditions for the reaction of VEC **1q** with water (Table 3). First, we found that the enantioselectivity could be improved when the reaction temperature reduced to 20 °C, even though the yield is decreased (entry 2). Further screening of ligands (entries 3–7) showed that the reaction with Feringa's ligand (*S,S,S*)-**L2** gave tertiary diol **2q** with 89% ee (entry 4). To our delight, the enantioselectivity could be improved to 97% by the replacement of phenylboronic acid with triethylborane (entry 8). The reaction with 10 mol % of triethylborane gave **2q** with almost a single enantiomer (entry 9). The yield can be improved to 63% by prolonging the reaction time to 24 h (entry 10).

With the optimal conditions of the combination of $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), Feringa's ligand (*S,S,S*)-**L2** (10 mol %), and triethylborane (10 mol %) in THF at 20 °C for 24 h, the generality of the allylic substitution of alkyl-substituted VECs with water was next examined (Table 4). For alkyl substituted VECs, Me-VEC **1r** and Bn-VEC **1s** could convert into the tertiary 1,2-diols **2r** and **2s** respectively in high yields with good enantioselectivities. For the reaction of long chain substituted VEC **1t**, excellent enantioselectivity (95% ee) was observed, albeit in relatively low yield (62%). Meaningfully, more functionalized tertiary 1,2-diols could also be prepared using this allylic hydroxylation process. Thus, versatile 1,2-diols **2u**–**2w** bearing four different functional groups at one carbon stereogenic center were obtained in good yields with acceptably high enantioselectivities. Notably, the reaction conditions described in Table 2 for aryl substituted VECs were more suitable for the reaction of VEC **1v** having a benzyloxymethyl group, thus giving the 1,2-diols **2v** in 83% yield with 98% ee

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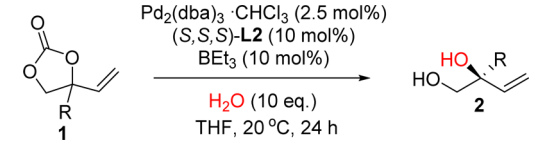
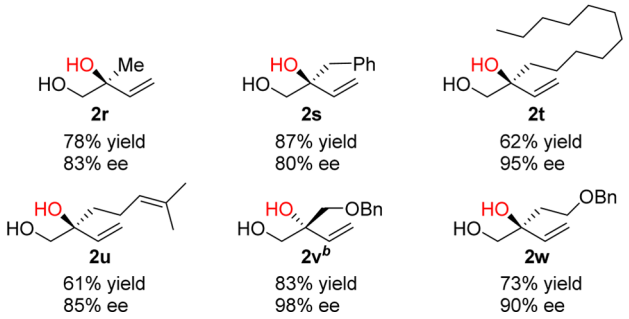
Table 4. Asymmetric Allylic Substitution of Alkyl-Substituted VECs with Water[a]





[a]Reaction conditions: $Pd_2(dba)_3$·$CHCl_3$ (2.5 mol %), (*S*,*S*,*S*)-**L2** (10 mol %), triethylborane (10 mol %), **1** (0.2 mmol), water (2.0 mmol), THF (1.0 mL), 20 °C, 24 h. Yields are of isolated materials. The ee values were determined by HPLC analysis. The ee values of **2r**, **2t**, and **2u** were determined by HPLC analysis of their diol monobenzoyl esters. [b]The reaction was carried out under the conditions as described in Table 2.

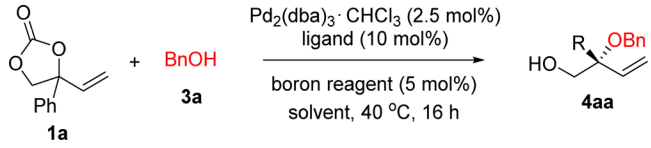
(60% yield and 73% ee were obtained under the conditions described in Table 4). Remarkably, for all of the examples in Tables 2 and 4, we did not find any corresponding byproducts, which are potentially produced from the primary alcohol of the products **2** acting as nucleophiles to the substrates.

Enantioselective Construction of Tertiary Ethers via Allylic Substitution of VECs with Alcohols. After successful realization of the asymmetric substitution of VECs with water, we subsequently turned our attention toward the expansion of this process with alcohols as nucleophiles to construct tertiary ethers. First, the studies focused on the allylic substitution of Ph-VEC **1a** with benzyl alcohol (**3a**). We began our investigation by examining the reaction of **1a** with **3a** in the presence of triethyl borane (5 mol %) and a palladium catalyst bearing different phosphoramidite ligands in THF at 40 °C for 16 h. As shown in Table 5, the reaction proceeded smoothly with Zhou's ligand (*R*)-**L4** giving the desired tertiary ether **4aa** in 88% yield with complete regioselectivity and good enantioselectivity (89% ee, entry 5). Further screening of different solvents revealed that the reaction efficiency was slightly improved by using toluene as solvent (entry 7).

Although the reaction efficiency did not improve further by using other boron reagents (entries 12−17), it is noteworthy that the reaction could proceed reasonably with various boron reagents, such as tributylborane, tricyclohexylborane, triphenylborane, boric acid, trimethyl borate, and phenylboronic acid. The reaction could be further improved by the addition of 4 Å molecular sieves, providing the product **4aa** in high yield (94%) with high enantioselectivity (93% ee, entry 18).

With the optimized conditions in hand (entry 18, Table 5), the generality of this allylic etherification process was evaluated by the reaction of Ph-VEC **1a** with various alcohols **3** (Table 6). A wide variety of allylic tertiary ethers could be produced in high yields with complete regioselectivities and high levels of enantioselectivities. The reactions proceeded well with simple alcohols, such as methanol, ethanol, 2-phenylethanol, and

Table 5. Condition Optimizations for the Allylic Substitution of Ph-VEC 1a with Benzyl Alcohol (3a)[a]



entry	ligand	boron reagent	solvent	yield (%)[b]	ee (%)[c]
1	(*R*)-**L1**	BEt_3	THF	92	80
2	(*S*,*S*,*S*)-**L2**	BEt_3	THF	80	−86
3	(*S*,*R*,*R*)-**L3**	BEt_3	THF	89	−70
4	(*R*)-**L4**	BEt_3	THF	88	89
5	(*R*,*R*,*R*)-**L5**	BEt_3	THF	28	65
6	(*S*,*R*,*R*)-**L6**	BEt_3	THF	–	–
7	(*R*)-**L4**	BEt_3	toluene	92	90
8	(*R*)-**L4**	BEt_3	CH_2Cl_2	72	63
9	(*R*)-**L4**	BEt_3	Et_2O	75	89
10	(*R*)-**L4**	BEt_3	cyclohexane	82	80
11	(*R*)-**L4**	BEt_3	1,4-dioxane	36	86
12	(*R*)-**L4**	B^nBu_3	toluene	86	90
13	(*R*)-**L4**	BCy_3	toluene	73	88
14	(*R*)-**L4**	BPh_3	toluene	48	85
15	(*R*)-**L4**	$B(OH)_3$	toluene	78	80
16	(*R*)-**L4**	$B(OMe)_3$	toluene	69	88
17	(*R*)-**L4**	$PhB(OH)_2$	toluene	62	83
18[d]	(*R*)-**L4**	BEt_3	toluene	94	93

[a]Reaction conditions: $Pd_2(dba)_3$·$CHCl_3$ (2.5 mol %), ligand (10 mol %), boron reagent (5 mol %), **1a** (0.2 mmol), benzyl alcohol (**3a**) (0.22 mmol), solvent (0.1 M), 40 °C, 16 h. [b]Isolated yield. [c]Determined by HPLC using chiral stationary phase. [d]The reaction was performed by the addition of 4 Å molecular sieves (100 mg).

cyclohexylmethanol, providing the corresponding tertiary ethers **4ab**−**4ae** in high yields with good to high enantioselectivities. Significantly, various functional groups such as keto-, cyano-, ester-groups could be introduced via the allylic etherification process to afford **4af**−**4ah** in high yields with good to high enantioselectivities. The reaction conditions were also suitable for the reaction of **1a** with *N*-boc protected amino alcohol to afford tertiary ether **4aj** with good efficiency. However, relatively low enantioselectivities were observed for the reaction with *N*-benzoyl and *N*-tosyl protected amino alcohols. Nevertheless, the reaction did not proceed at all with α-hydroxy ethyl acetate. The reaction of **1a** with 1-hexanol bearing a terminal chlorine group proceeded well to furnish corresponding product **4am** in high yield with high enantioselectivity. Various alkenyl and alkynyl moieties could also be introduced under the optimal conditions, giving corresponding tertiary ethers **4an**−**4at** in high yields with good to high enantioselectivities. The reaction also proceeded well with 2-naphthylmethanol as well as 4-methoxyl- and 4-nitrobenzyl alcohols to afford corresponding tertiary ethers **4au**−**4aw** with high efficiencies. Alcohols with heteroaromatics moieties were also suitable substrates for the reaction, providing **4ax** and **4ay** with high efficiencies. It should be noted that the reaction conditions were not suitable for secondary and tertiary alcohols such as isopropanol and *tert*-butanol.

After the successful realization of the allylic etherification of Ph-VEC **1a** with various alcohols, the generality of the process was next examined by the reaction of various substituted VECs with allylic alcohol (**3q**). As shown in Table 7, Various VECs with a substituted phenyl ring bearing different electronic and

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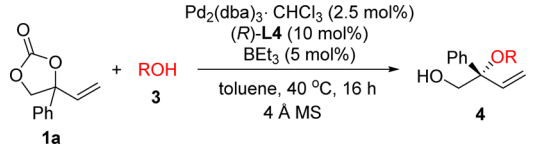
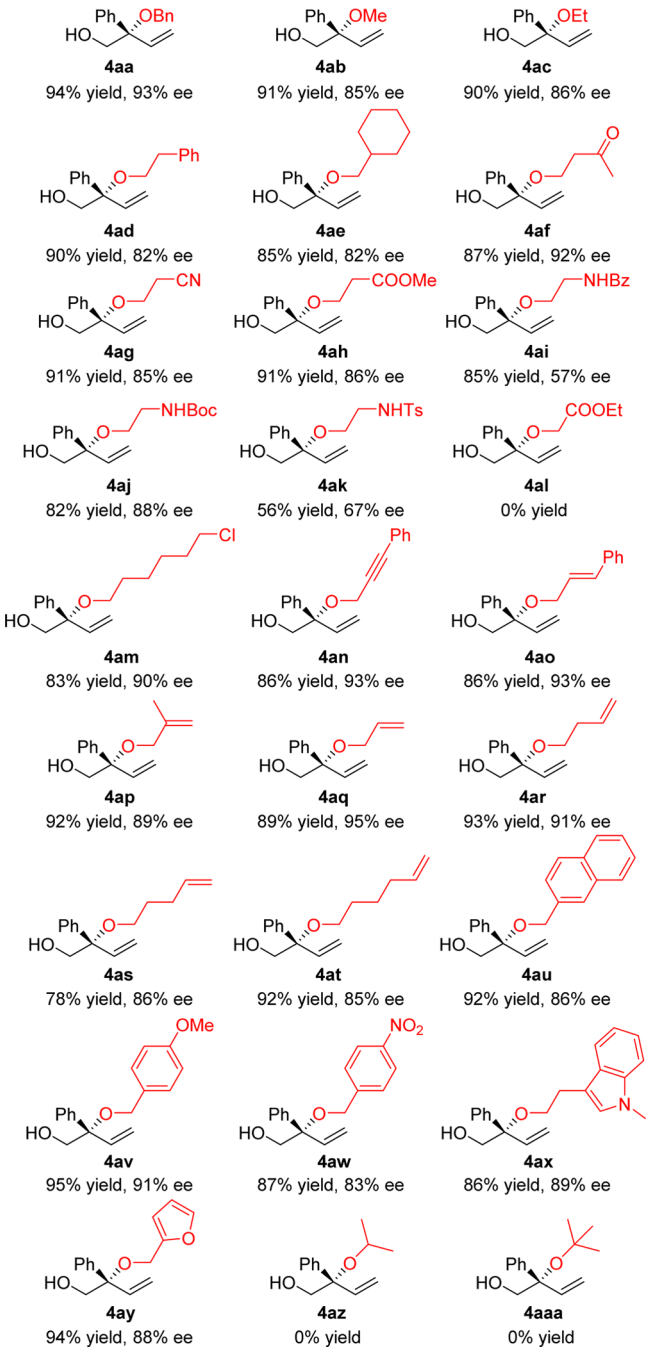
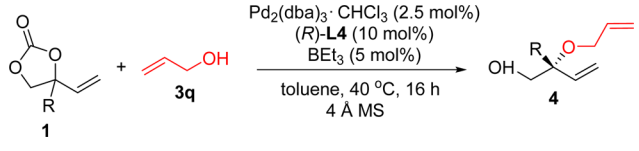
Table 6. Asymmetric Allylic Substitution of Ph-VEC 1a with Various Alcohols[a]

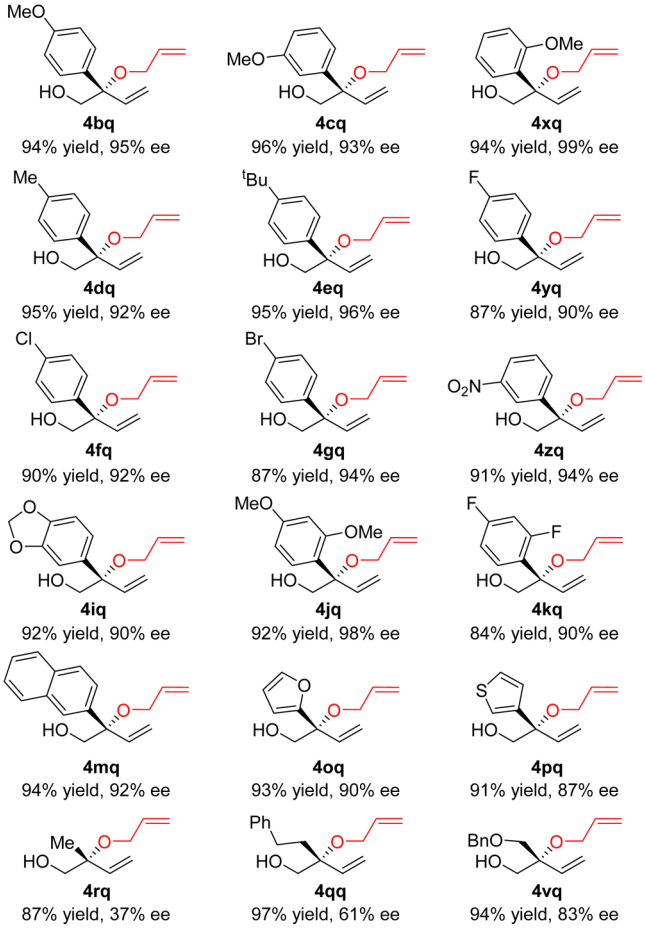




[a]Reaction conditions: $Pd_2(dba)_3$·$CHCl_3$ (2.5 mol %), (*R*)-**L4** (10 mol %), triethylborane (5 mol %), **1a** (0.2 mmol), alcohols **3** (0.22 mmol), 4 Å molecular sieves (100 mg), toluene (0.1 M), 40 °C, 16 h. Yields are of isolated materials. The ee values were determined by HPLC using chiral stationary phase. The absolute configuration was confirmed by the comparison of the sign of optical rotation of **4al** with that reported in literature.[9b] Those of the other products were assigned by analogy.

Table 7. Asymmetric Allylic Substitution of VECs 1 with Allyl Alcohol (3q)[a]





[a]Reaction conditions: $Pd_2(dba)_3$·$CHCl_3$ (2.5 mol %), (*R*)-**L4** (10 mol %), triethylborane (5 mol %), **1** (0.2 mmol), allyl alcohol (**3l**) (0.22 mmol), 4 Å molecular sieves (100 mg), toluene (0.1 M), 40 °C, 16 h. Yield of isolated product. The ee values were determined by HPLC using chiral stationary phase.

steric properties were tolerated under the reaction conditions to convert into the corresponding tertiary allylic ethers in high yields with complete regioselectivities and a high level of enantioselectivities. The reaction of VECs bearing a naphthyl group also proceeded smoothly to afford tertiary allylic ether **4mq** in high yield with high enantioselectivity. The process also worked well for VECs with versatile furan and thiophene moieties to furnish the corresponding tertiary allylic ethers **4oq** and **4pq** in high yields with good enantioselectivities. However, the reaction conditions were less effective for Me-VEC **1r** to afford the product **4rq** with only 37% ee. For the etherification of alkylated VEC **1q**, moderate enantioselectivity was observed. Notably, more functionalized tertiary allylic ether **4vq** could also be obtained in high yield with good enantioselectivity. For all of the examples in Tables 6 and 7, the byproducts, which might be formed by the primary alcohols of the products **4** acting as nucleophiles to VECs, were not observed.

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Mechanistic Consideration for the Allylic Substitution Process. First, to gain insight into the coordination mode of the phosphoramidite ligand during the catalytic reaction, we examined the correlation between the enantiopurity of ligand (*R*)-**L4** and the enantioselectivity of the allylic hydroxylation of **1a** under the conditions described in Table 1 (entry 14). As shown in Figure 1, the enantioselectivity of the reaction is

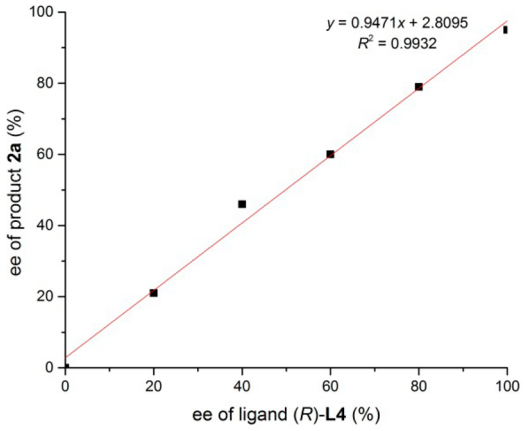
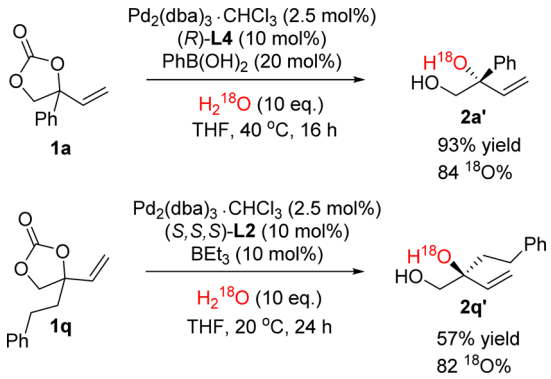


Figure 1. Correlation between the enantiopurity of ligand (*R*)-**L4** and the enantioselectivity in the allylic hydroxylation of **1a** to **2a**.

linearly correlated to the enantiopurity of the ligand (*R*)-**L4** within experimental error. These results implied that the palladium complex coordinated with one phosphoramidite ligand is likely to be a true active catalytic species during the reaction.[23]

Next, in order to trace the source of the hydroxyl oxygen in the products of tertiary 1,2-diols, isotropic labeling experiments were conducted by using $H_2{}^{18}O$ instead of H_2O. As outlined in Scheme 2, the reactions of **1a** and **1q** with $H_2{}^{18}O$ under two

Scheme 2. Allylic Substitution of 1a and 1q with $H_2{}^{18}O$



different sets of optimized conditions (Tables 2 and 4) afforded ^{18}O labeled products **2a′** and **2q′** in 84 and 82 ^{18}O% respectively.[16d] These results demonstrated that the process likely undergoes formation of key intermediate **C** and a subsequent nucleophilic addition pathway as proposed in Scheme 1. Thus, the enantioselective allylic substitution of VECs with water could be achieved under the cooperative catalysis system of palladium and a boron reagent.

To further gain insight into the reaction pathway, we conducted ^{11}B NMR studies for the allylic etherification reaction (Figure 2). In control experiments, we found that

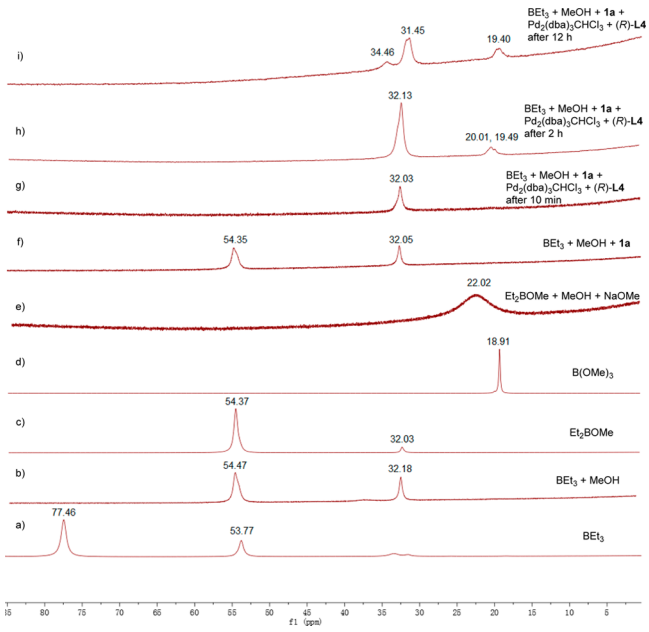


Figure 2. ^{11}B NMR spectra in THF (reference to $BF_3{\cdot}OEt_2$).

Et_3B could be converted quantitatively into Et_2BOMe and $EtB(OMe)_2$ by mixing Et_3B with methanol in THF (Figure 2a and 2b),[24] which was confirmed by comparing it with ^{11}B NMR spectra of Et_2BOMe. Upon mixing Et_2BOMe with methanol in THF, conversion of Et_2BOMe into $EtB(OMe)_2$ was also found, but no signal of $B(OMe)_3$ was observed. Upon subsequent addition of NaOMe to the solution, a new broad resonance at 22.02 ppm was formed (Figure 2e), which is likely to be characteristic of an −ate complex, $Na[EtB(OMe)_3]$.[25]

With model studies in hand, the reaction of Ph-VEC **1a** with methanol was tracked by ^{11}B NMR. Accordingly, two resonances at 54.35 (Et_2BOMe) and 32.05 [$EtB(OMe)_2$] ppm were observed by mixing Et_3B (20 mol %) with Ph-VEC **1a** (1 equiv) and MeOH (1.1 equiv) in THF (Figure 2f). Subsequently, $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol %) and ligand (*R*)-**L4** (20 mol %) were added to the mixture, in which only one signal for $EtB(OMe)_2$ at 32.02 ppm was observed (Figure 2g). When the reaction was continued for an additional 2 h (about 30% conversion determined by TLC), two new resonances at 20.01 and 19.49 ppm appeared (Figure 2h). One of the signals (20.01 ppm) might be attributed to the −ate complex of $EtB(OMe)_2$ with an oxygen anion of a zwitterionic π-allylpalladium intermediate as shown in our proposed reaction pathway in Scheme 1. After **1a** converted completely into product **4ab** within 12 h, the resonance of $EtB(OMe)_2$ remained as a major signal with a resonance at 19.40 ppm, and a new peak at 34.46 ppm was observed (Figure 2i). The resonance at 34.46 and 19.40 ppm might be attributed to the borate generated from the transesterification equilibrium of $EtB(OMe)_2$ and $B(OMe)_3$ with **4ab**. These ^{11}B NMR studies indicated that the real boron-*co*-catalyst should be $EtB(OR)_2$, or maybe a mixture of $Et_2B(OR)$, $EtB(OR)_2$, or $B(OR)_3$ in some cases. Thus, the more likely reaction pathway in the asymmetric allylic etherification process includes reaction of $EtB(OR)_2$ with allylpalladium intermediate **A** to generate an −ate intermediate, which undergoes nucleophilic addition to afford product **4** regioselectively. The chiral palladium complex and $EtB(OR)_2$ are released to the next catalytic cycle.

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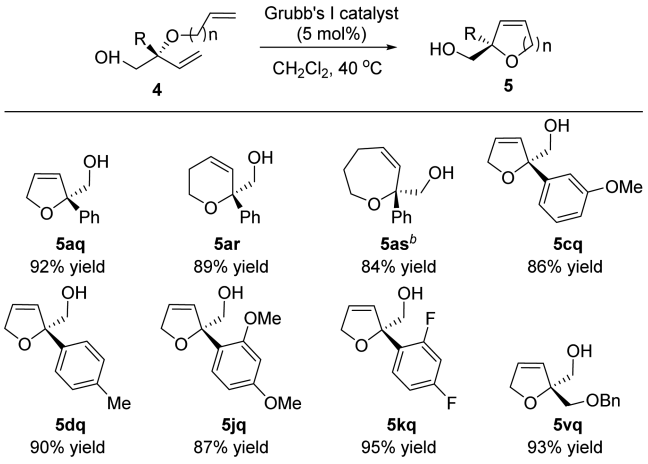
Synthetic Utility of the Allylic Substitution Process. To display the synthetic utility of the present allylic hydroxylation and etherification protocol, we tried to elaborate the products of tertiary alcohols **2** and tertiary ethers **4** to more valuable compounds. First, we applied the furnished products **4** to the convenient synthesis of biologically relevant tertiary cyclic ethers. As shown in Table 8, ring-closing metathesis of tertiary ethers **4aq**–**4as** performed well in the presence of the Grubbs' I or II catalysts to produce five-, six-, and seven-membered oxo-heterocycles with high yields. Dihydrofurans with different functional groups could also be afforded in high yields (86–95%). To further demonstrate synthetic utility of the allylic etherification method, dihydrofuran **8**, which would be a key intermediate for antifungal drug Posaconazole,[26] has been synthesized through sequential reactions of asymmetric allylic etherification and ring-closing metathesis (Scheme 3). The reaction of VEC **1k** with allylic alcohol **6** was performed smoothly to furnish desired product **7** in 92% yield with 95% ee. The tertiary ether **7** underwent ring-closing metathesis with the Hoveyda–Grubbs first generation catalyst to afford the dihydrofuran **8** in 83% yield.

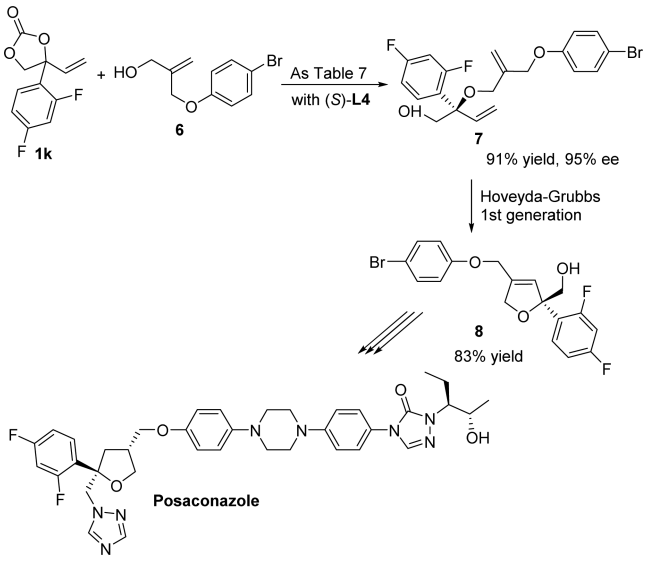
The synthetic utility of the allylic hydroxylation process was also demonstrated by the elaboration of tertiary 1,2-diol **2k** into the corresponding triol **10** (Scheme 4), which is a key intermediate for the preparation of triazole antifungal agents,[27] such as Genaconazole, Ravuconazole, and Albaconazole. The reaction of **1k** with water in 6 mmol scale using (*S*)-**L4** as a ligand proceeded smoothly to afford (*R*)-**2k** in 92% yield (1.1 g) with 94% ee. Epoxidation of **2k** with 3-chloroperoxybenzoinc acid (*m*-CPBA) under −10 °C gave epoxide **9** in 84% yield with a 7:1 diastereomeric ratio, and subsequent reduction of the epoxide by the treatment of lithium aluminum hydride afforded triol **10** in 85% yield. The absolute configuration of triol **10** was confirmed by the comparison of ^{1}H NMR data with those reported.[27]

Table 8. Ring-Closing Metathesis of 4 to Tertiary Cyclic Ethers 5[a]

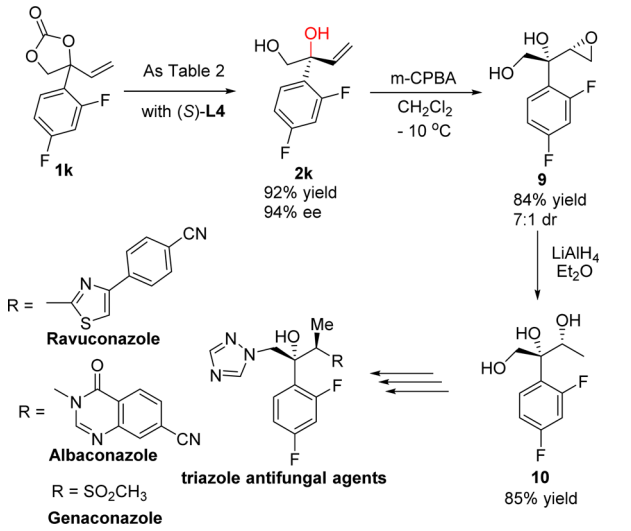


[a]Reaction conditions: Grubbs' I catalyst (5 mol %), **4** (0.2 mmol), CH_2Cl_2 (0.1 M), 40 °C, 16 h. Yields are of isolated materials. [b]The reaction was ran by using Grubbs' II catalyst.

Scheme 3. Synthesis of a Key Intermediate for Posaconazole



Scheme 4. Synthesis of a Key Intermediate for Triazole Antifungal Agents



CONCLUSIONS

In conclusion, we have developed an efficient method for the enantioselective construction of a tertiary C–O bond via asymmetric allylic substitution of VECs with water and alcohols. The process relies on a synergistic catalysis system of an in situ generated chiral palladium complex and boron reagent to rigorously control the regio- and enantioselectivity, and allows rapid access to highly functionalized chiral tertiary alcohols and ethers in high yields with complete regioselectivities and a high level of enantioselectivities. The synthetic utility of the present process was demonstrated by the synthesis of key intermediates of biologically relevant agents. The tertiary cyclic ethers with different ring sizes can also be offered through the sequential reactions of asymmetric allylic etherification and ring-closing metathesis with high efficiencies. Further investigation of this allylic substitution process with other nucleophiles is currently underway in our laboratory and will be reported in due course.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b04759.

Detailed experimental procedures; characterization data of all of the new compounds; copies of HPLC chromatographies, ^{1}H and ^{13}C NMR spectra of the products (PDF)

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Notes

The authors declare no competing financial interest.

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