Organocatalysis

International Edition: DOI: 10.1002/anie.201501832
German Edition: DOI: 10.1002/ange.201501832

Asymmetric Synthesis of 1,3-Butadienyl-2-carbinols by the Homoallenylboration of Aldehydes with a Chiral Phosphoric Acid Catalyst**

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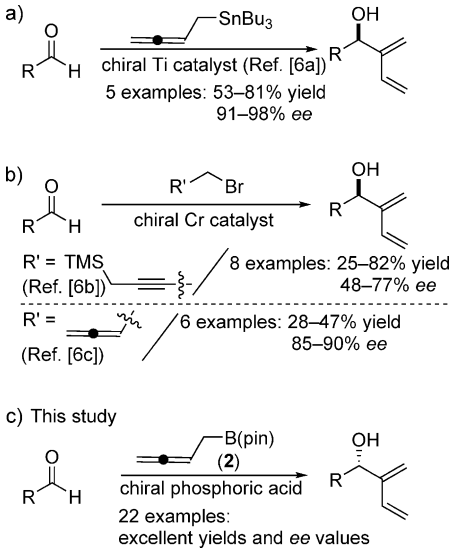
Dedicated to Professor Albert S. C. Chan on the occasion of his 65th birthday

Abstract: *Asymmetric C(sp)–C(sp^2) bond formation to give enantiomerically enriched 1,3-butadienyl-2-carbinols occurred through a homoallenylboration reaction between a 2,3-dienylboronic ester and aldehydes under the catalysis of a chiral phosphoric acid (CPA). A diverse range of enantiomerically enriched butadiene-substituted secondary alcohols with aryl, heterocyclic, and aliphatic substituents were synthesized in very high yield with high enantioselectivity. Preliminary density functional theory (DFT) calculations suggest that the reaction proceeds via a cyclic six-membered chairlike transition state with essential hydrogen-bond activation in the allene reagent. The catalytic reaction was amenable to the gram-scale synthesis of a chiral alkyl butadienyl adduct, which was converted into an interesting optically pure compound bearing a benzo-fused spirocyclic cyclopentenone framework.*

The 1,3-butadienyl-2-carbinol motif is present in many natural compounds.[1] Its conjugated-diene and allylic-alcohol substructures make this unit very versatile for multistep synthesis, as it can undergo Diels–Alder,[2] Sharpless epoxidation,[3] and cycloaddition reactions.[4] Therefore, the construction of the 1,3-butadienyl-2-carbinol scaffold,[5] especially in an asymmetric manner, is a significant task for organic chemists. However, the catalytic asymmetric synthesis of 1,3-butadienyl-2-carbinols has met with very limited success. The only three existing examples of such reactions are far from ideal,[6] as they either require a toxic tin reagent[6a] or occur in only moderate yield or with moderate enantioselectivity;[6b,c] furthermore, their scope is narrow in terms of possible substrates (Scheme 1 a,b). In this regard, the development of a rapid and efficient route to enantiomerically enriched 1,3-butadienyl-2-carbinols is highly desirable.



Scheme 1. Catalytic asymmetric synthesis of chiral 1,3-butadienyl-2-carbinols. TMS = trimethylsilyl.

The asymmetric nucleophilic addition of nontoxic and stable unsaturated organoboron reagents, such as allyl, allenyl, and propargyl boronates, to carbonyl groups enables access to synthetically and pharmaceutically important chiral secondary and tertiary alcohols.[7] Basically, two types of models involving closed and open transition states mediated by catalysts have been demonstrated.[8] In contrast to the popularly used allyl and allenyl boronates, the analogous homoallenylated boronates[9] have still not been explored in a catalytic asymmetric manner. Brown et al. showed that noncatalytic addition reactions between aldehydes and homoallenylated boronates generated racemic 1,3-butadienyl-2-carbinols at room temperature. To suppress the background reaction, a low temperature and asymmetric activation of the reactive components should be efficient tools for the development of a highly enantioselective and efficient transformation. Inspired by the previous studies on increasing the rate of allylboration by increasing the Lewis acidity of the boron center,[10] we hypothesized that the protonation of the oxygen atoms in the homoallenylated boronate **2** with

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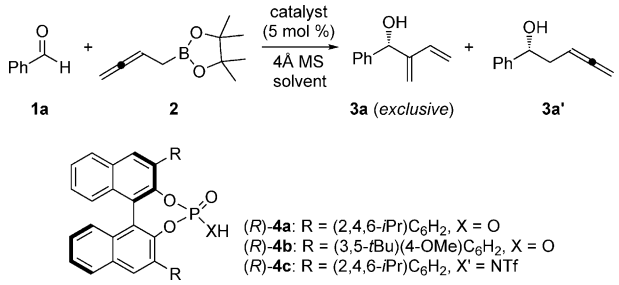
[**] We are grateful for the financial support of this investigation by the National Natural Science Foundation of China (21303128), the Research Fund for the Doctoral Program of Higher Education of China (20130143120003), and the Fundamental Research Funds for the Central Universities (WUT: 2014-Ia-002). Y.P. is supported by the National Natural Science Foundation of China (21422305).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201501832.

a strong chiral Brønsted acid could potentially increase the Lewis acidity of the boron atom and enable a highly catalytic asymmetric homoallenylation. In this study, we developed an unprecedented catalytic asymmetric dienylboration reaction between the pinacol (pin) ester **2** of 2,3-dienylboronic acid and aldehydes by virtue of the bifunctional nature of chiral phosphoric acids (CPAs; Scheme 1c).[11] A wide variety of synthetically useful enantiomerically enriched 1,3-butadienyl-2-carbinols were thus readily prepared.

For exploratory studies, we used the two reactive substrates 2,3-dienylboronic ester **2** and benzaldehyde (**1a**) in toluene at 0.2 M concentration. A control experiment revealed that the efficient background reaction between **1a** and **2** at room temperature through a facile 1,3-rearrangement (Table 1, entry 1) was completely avoided at low temperature (a trace amount of adduct **3a** was detected by TLC at −25 °C after 24 h), whereas the (*R*)-binol-derived CPA (*R*)-**4a** could catalyze the reaction to provide the (*R*)-(1,3-butadien-2-yl)methanol derivative **3a** exclusively even at very low temperature. The absolute configuration of **3a** was assigned as *R* by analogy with established cases.[6a] The use of 4 Å molecular sieves as an additive was critical to the formation of the product with a high *ee* value (Table 1, entry 3 versus entry 2); the high yield was preserved under these conditions. We reason that the hydrogen bonding in the hypothesized transition state is sensitive to minute amounts of water. A slight increase in enantioselectivity was detected when the temperature was decreased from −25 to −50 °C, but a longer reaction time was required (Table 1, entry 5). Other solvents (THF and CH_2Cl_2) and chiral Brønsted acids ((*R*)-**4b** and (*R*)-**4c**) examined at −50 °C did not give superior results (Table 1, entries 6–9). To our delight, a further decrease in the temperature to −60 °C improved the enantioselectivity significantly (99% *ee*; Table 1, entry 10); this reaction temperature was found to be the best choice. Remarkably, at a higher concentration (0.4 M of **1a**) and with a slightly higher excess of boronate **2** (1.5 equiv with respect to aldehyde **1a**), **3a** was obtained in excellent yield without erosion of the enantioselectivity after a shorter reaction time (99% yield, 99% *ee*; Table 1, entry 12). This result could be repeated on a 0.2 mmol scale under otherwise identical conditions, which were used for the following investigation (Table 1, entry 13). Thus, in terms of enantioselectivity and catalytic efficiency, the optimal reaction parameters include a 0.4 M concentration of the aldehyde **1** in toluene with 1.5 equivalents of boronate **2**, a temperature of −60 °C, and 5 mol% loading of catalyst (*R*)-**4a**. A lower loading of the chiral catalyst (2.5 mol%) was also evaluated and led to comparable results (Table 1, entry 14).

Table 1: Optimization of the catalytic asymmetric dienylation of benzaldehyde (**1a**).[a]

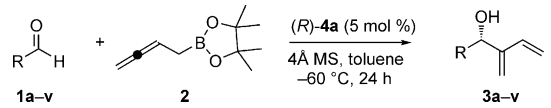


Entry	Catalyst	Solvent	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1[d]	none	toluene	25	24	86	0
2[d]	(*R*)-**4a**	toluene	−25	24	90	81
3	(*R*)-**4a**	toluene	−25	24	90	93
4	(*R*)-**4a**	toluene	−40	24	88	94
5	(*R*)-**4a**	toluene	−50	48	92	96
6	(*R*)-**4b**	toluene	−50	48	85	3
7	(*R*)-**4c**	toluene	−50	48	91	84
8	(*R*)-**4a**	THF	−50	48	60	3
9	(*R*)-**4a**	CH_2Cl_2	−50	48	84	88
10	(*R*)-**4a**	toluene	−60	48	90	99
11[e]	(*R*)-**4a**	toluene	−60	48	92	99
12[e,f]	(*R*)-**4a**	toluene	−60	24	99	99
13[f,g]	(*R*)-**4a**	toluene	−60	24	99	99
14[f,g,h]	(*R*)-**4a**	toluene	−60	24	98	98

[a] Reaction conditions, unless otherwise specified: **1a** (0.10 mmol), **2** (0.12 mmol), solvent (0.5 mL), catalyst (5 mol%). [b] Yield of the isolated product. [c] The *ee* value was determined by HPLC analysis on a chiral stationary phase. [d] The reaction was conducted in the absence of 4 Å MS. [e] The reaction was conducted in 0.25 mL of toluene. [f] The reaction was conducted with 1.5 equivalents of **2**. [g] Reaction conditions: **1a** (0.20 mmol), **2** (0.30 mmol), toluene (0.5 mL). [h] Catalyst loading: 2.5 mol%. Tf = trifluoromethanesulfonyl.

Under the optimized conditions, a wide array of aromatic, heteroaromatic, α,β-unsaturated, and aliphatic aldehydes **1a**–**v** were screened, and respectable *ee* values of 95–>99% and yields were observed for all except two cases, in which alkyl aldehydes were used (Table 2). In the case of phenyl-substituted aldehydes, electron-donating and electron-withdrawing groups at the *para* position were all tolerated, and the desired products were formed in consistently excellent yield (≥96%) and enantioselectivity (≥98% *ee*) within 24 h (Table 2, entries 2–9). When a bromo or methoxy group was introduced at the 3-position of the aromatic ring of benzaldehyde, or a methyl group at the 2-position, the yield and *ee* value of the product were extremely high (Table 2, entries 10–12). Both 1- and 2-naphthyl-substituted aldehydes were converted into the corresponding addition adducts with very satisfactory results (Table 2, entries 13 and 14), as was 9-anthryl aldehyde (Table 2, entry 15). Moreover, heterocyclic aldehydes also underwent the reaction with excellent conversion and enantiomeric induction (Table 2, entries 16 and 17), although a solvent mixture containing cyclohexane was required for 2-thiophenecarboxaldehyde. Furthermore, the effect of various two-carbon-atom linkers between the phenyl ring and the carbonyl group of the aldehyde was investigated. α,β-Unsaturated aldehydes bearing a triple or double bond were smoothly converted into the desired products with a 1,4-enyne or triene motif with uniformly satisfactory results (Table 2, entries 18–20). By tuning the reaction conditions and using a 1:1 mixture of cyclohexane and CCl_4 as the solvent, we observed a synthetically acceptable level of enantiomeric induction (92% *ee*) for aldehyde **1u** with a $-CH_2CH_2-$ linkage (Table 2, entry 21). Both the yield and *ee* value reached 90% for the challenging substrate **1v** when CCl_4 was used as the solvent (Table 2, entry 22). In all cases the regioselectivity of the reaction was perfect: no β-allenol adducts were detected.

Table 2: Asymmetric dienylation of various aldehydes.[a]



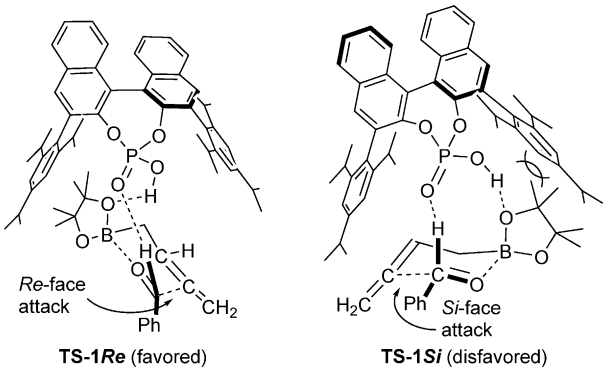
1a–v **2** **3a–v**

Entry	R	Product	Yield [%][b]	*ee* [%][c]
1	Ph(**1a**)	**3a**	99	99
2	4-MeC_6H_4 (**1b**)	**3b**	99	99
3	4-$MeOC_6H_4$(**1c**)	**3c**	98	99
4	4-FC_6H_4 (**1d**)	**3d**	96	>99
5	4-ClC_6H_4 (**1e**)	**3e**	97	98
6	4-BrC_6H_4 (**1f**)	**3f**	96	99
7	4-$CO_2MeC_6H_4$ (**1g**)	**3g**	98	98
8	4-$NO_2C_6H_4$ (**1h**)	**3h**	98	98
9	4-$CF_3C_6H_4$ (**1i**)	**3i**	97	>99
10	3-BrC_6H_4 (**1j**)	**3j**	99	>99
11	3-$MeOC_6H_4$ (**1k**)	**3k**	99	>99
12	2-MeC_6H_4 (**1l**)	**3l**	99	98
13	1-naphthyl (**1m**)	**3m**	98	99
14	2-naphthyl (**1n**)	**3n**	99	>99
15	9-anthryl (**1o**)	**3o**	96	97
16	2-furyl (**1p**)	**3p**	95	97
17[d]	2-thienyl (**1q**)	**3q**	98	98
18	PhC≡C (**1r**)	**3r**	98	99
19	(*E*)-PhCH=CH (**1s**)	**3s**	98	98
20	(*E*)-PhCH=C(CH_3) (**1t**)	**3t**	95	96
21[e]	$PhCH_2CH_2$ (**1u**)	**3u**	96	92
22[f]	c-C_6H_{11} (**1v**)	**3v**	92	90

[a] Reaction conditions, unless otherwise specified: **1** (0.20 mmol), **2** (0.3 mmol), toluene (0.5 mL). [b] Yield of the isolated product. [c] The *ee* value was determined by HPLC analysis on a chiral stationary phase. [d] The reaction was conducted in toluene/cyclohexane (1:1). [e] The reaction was conducted in cyclohexane/CCl_4 (1:1) at −20 °C. [f] The reaction was conducted in CCl_4 at −20 °C.

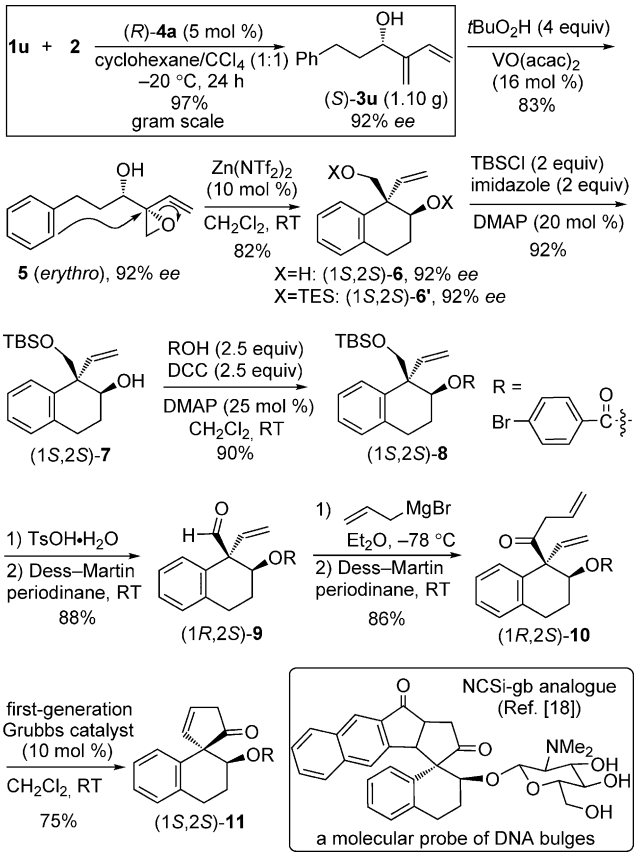
To shed light on the mode of activation and the origin of enantiomeric induction, we calculated (DFT) several possible transition states based on previous studies by other research groups (see the Supporting Information for details).[12] To reduce the calculating time, we considered a biphenol-derived phosphoric acid in the model, with methyl groups in place of the isopropyl groups in (*R*)-**4a**. In the resulting privileged chairlike transition state (**TS-1*Re***; Scheme 2), the bifunctional phosphoric acid moiety captures the two reactive components through two hydrogen bonds. The energy barrier for the formation of the *R* stereoisomer is smaller by 1.70 kcal mol^{-1} than that for the *S* isomer. This difference is attributed to steric repulsions between the large substituent at one of the 3-positions of the biphenyl group in (*R*)-**4a** and the pinacol methyl groups of **2** in the transition state **TS-1*Si*** (shortest carbon–carbon distance: 4.11 versus 3.92 Å) and would be expected to lead to the formation of the product with approximately 96 % *ee* at −60 °C. This value is consistent with the experimental value of 99 % *ee*.

We next focused our attention on the synthetic application of the alkyl (1,3-butadien-2-yl)methanol product **3u** (Scheme 3). First, a gram-scale reaction between **1u** and **2** provided the enantiomerically pure adduct (*S*)-**3u** (1.10 g) in 97 % yield with 92 % *ee*), a result comparable to that in entry 21 of Table 2. Selective monoepoxidation directed by the hydroxy group in **3u** then readily gave the *erythro* α-epoxy alcohol **5**, frequently presented as a structural core in natural



TS-1*Re* (favored) **TS-1*Si*** (disfavored)

Scheme 2. Proposed transition structures based on DFT studies.



Scheme 3. Gram-scale synthesis of **3u** and further transformations showing its synthetic utility. acac = acetylacetonate, DCC = *N*,*N*′-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, Ts = *p*-toluenesulfonyl.

products,[13] in 83 % yield with high diastereoselectivity (>20:1).[14] The configuration of **3u** and **5** was assigned on the basis of reported data.[15] An initial attempt at the TES protection of **5** with a stoichiometric amount of TESOTf[16] led to an unexpected 6-*exo*-tet epoxy–arene cyclization to give (1*S*,2*S*)-**6′**. This result inspired us to synthesize the optically pure diol **6** by using $Zn(NTf_2)_2$ as a Lewis acid catalyst[17] and to carry out the total synthesis of **11**. As expected, compound **6** was accessed exclusively in excellent yield with preservation of the *ee* value (92 % *ee*). The absolute configuration of **6** was determined by mechanistic considerations and a 2D NOESY NMR spectroscopic study of its

derivative **8** (see the Supporting Information for details); these analyses indicated that the two adjacent stereocenters have a *cis* relative configuration. The tetrahydronaphthalene **6** contains a functionality-rich 1,3-diol motif and a quaternary stereocenter bearing a vinyl group. These features facilitated the total synthesis of **11**, which shares the benzo-fused chiral spirocyclic cyclopentenone moiety present in a molecular probe for DNA bulges,[18] via **7**, **8**, **9**, and **10** by selective protection of the secondary alcohol, Dess–Martin oxidation, allylation of the aldehyde, a second Dess–Martin oxidation, and a final olefin-metathesis reaction in satisfactory yields.

In summary, we have described an enantioselective C(sp)–C(sp^2) bond-forming reaction that occurs through the noncovalent activation of an allene reagent by a chiral Brønsted acid catalyst.[19] This environmentally benign and straightforward metal-free process avoids toxic reagents and metal leaching. A broad range of useful enantiomerically enriched butadiene-substituted secondary alcohols were available in consistently high yields (92–99%) with excellent regio- and enantioselectivity (90- > 99% *ee*). One such adduct was transformed in a practical manner into the previously unreported interesting chiral compound **11**. DFT calculations were found to be beneficial in the elucidation of the transition state, which involves essential noncovalent activation of the allene reagent, and prediction of the high level of enantioselectivity. Further exploration of the use of 2,3-dienylboronic esters in other catalytic asymmetric reactions and the design of new chiral catalysts containing structures based on **11** are under way in our laboratory.

Keywords: allylic alcohols · asymmetric dienylation · boron · enantioselectivity · organocatalysis

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 7299–7302
Angew. Chem. **2015**, *127*, 7407–7410

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Received: February 26, 2015
Published online: May 4, 2015

