Organic LETTERS

Letter

pubs.acs.org/OrgLett

Double Chiral Induction Enables a Stereoselective Carbonyl Allylation with Simple Alkenes under the Sequential Catalysis of Palladium Complex and Chiral Phosphoric Acid

Lu-Lu Li, Zhong-Lin Tao, Zhi-Yong Han, and Liu-Zhu Gong*

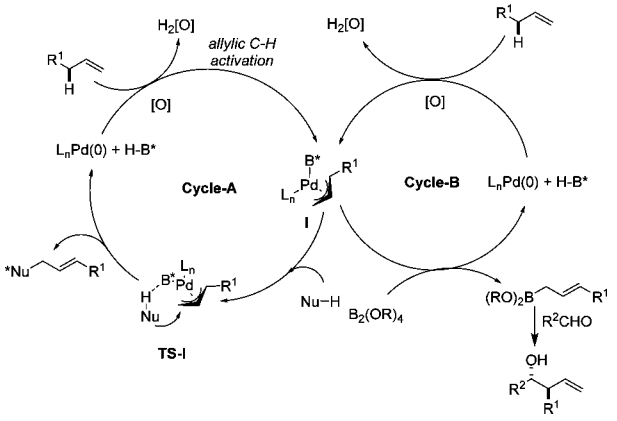
Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei 230026, China

Supporting Information

ABSTRACT: An enantioselective carbonyl allylation of aldehydes with simple alkenes has been achieved via a one-pot protocol consisting of a Pd-catalyzed allylic C−H borylation with bis(pinanediolato)diboron and a chiral Brønsted acid catalyzed asymmetric allylborylation, delivering homoallylic alcohols in high yields and with excellent diastereo- and enantioselectivities. The double chiral induction of chiral allylic borate and chiral phosphoric acid allows the reaction to give excellent stereoselectivities.

Terminal alkenes are an easily accessible and abundant feedstock, and are also among the most useful starting materials in organic synthesis, attributable to the rich chemistry capable of occurring at the carbon−carbon double bond.[1] In recent decades, the direct functionalization of allylic C−H bond of terminal alkenes has received a great deal of interest,[2] leading to the frequent appearance of new protocols.[3,4] In contrast, only a few successful examples describe catalytic, enantioselective allylic C−H functionalization reactions with the exception of the asymmetric allylic C−H oxidation catalyzed by chiral copper complexes.[5] White and co-workers found that the combination of a palladium complex and a chiral Lewis acid allowed a direct, asymmetric esterification of terminal olefins, but with modest enantioselectivity.[6] Trost demonstrated that the chiral phosphoramidite ligands were able to offer good enantioselectivity in the Pd-catalyzed asymmetric allylic alkylation of 1, 3-diketones with terminal alkenes.[7] Recently, our group established a variety of enantioselective allylic C−H functionalization reactions by virtue of cooperative catalysis of palladium and Brønsted acids.[8] These reactions basically proceed via a cascade allylic C−H oxidation and enantioselective substitution of the η^3 π-allylpalladium species **I** with different nucleophiles (**Cycle−A**, Scheme 1). On the other hand, the π-allylpalladium species **I** is principally able to react with diboron compounds to generate allylic boron intermediates,[9] which are able to undergo allylation reactions with electrophiles (**Cycle−B**, Scheme 1). However, such a principally possible transformation was not realized until recently when Szabó and co-workers[10] found that exocyclic alkenes were able to undergo a direct carbonyl allylation reaction of aldehydes, presumably proceeding via an allylic C−H borylation (eq 1, Scheme 2). Very recently, we disclosed a diastereoselective palladium-catalyzed carbonyl allylation of aldehydes directly using simple acyclic olefins as allylating reagents, which was preliminarily thought to proceed via the reaction pathway shown in **Cycle-B** in Scheme 1.[11] However, previous trials to establish an asymmetric version only led to moderate enantioselectivity (eq 2, Scheme 2). Herein, we describe a one-pot Pd/chiral phosphoric acid sequentially catalyzed process[12] consisting of an allylic C−H borylation and enantioselective allylation of aldehydes by using a double chiral

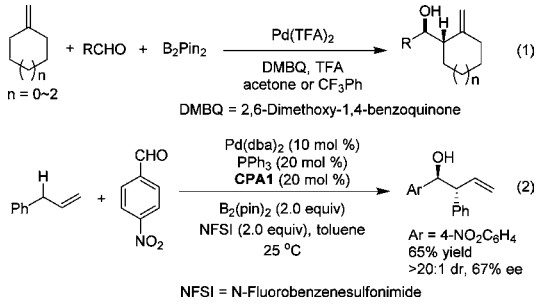
Scheme 1. Pd-Catalyzed C−H Functionalization of Terminal Olefins



Received: November 12, 2016
Published: December 20, 2016

DOI: 10.1021/acs.orglett.6b03378
Org. Lett. 2017, 19, 102−105

Scheme 2. Previous Reports on Allylation of Aldehydes with Olefins



induction strategy, to allow the formation of *anti*-homoallylic alcohols in high enantioselectivities.

Because the **CPA1** that has been assumed to give high levels of stereochemical outcome in asymmetric allylborylation of aldehydes[13] only gave a moderate enantioselectivity and yield, some other sterically demanding chiral phosphoric acids were again evaluated for the reaction under otherwise identical conditions (Figure 1). Unfortunately, none of the phosphoric

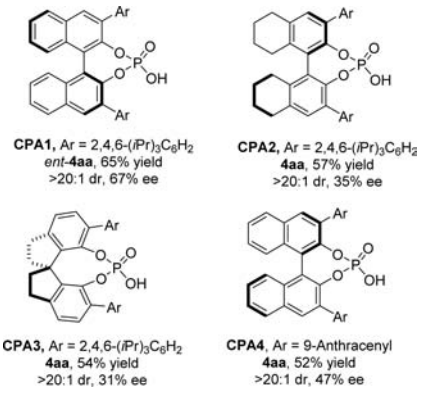
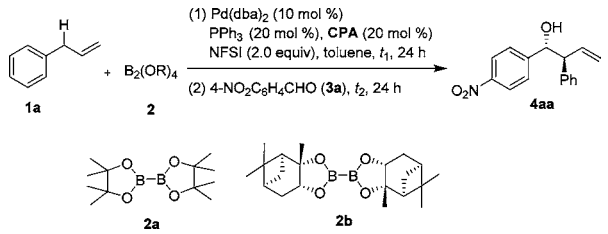


Figure 1. Evaluation of chiral phosphoric acids in the one-operation procedure.

acids was able to deliver satisfactory enantioselectivity, while **CPA1** and **CPA4** showed superior enantioselectivity. Basically, the asymmetric allylborylation reactions of aldehydes proceeding at a lower temperature gave a higher stereochemical outcome, but in contrast, the Pd-catalyzed allylic C−H borylation requires a relatively higher reaction temperature. To balance the reaction conditions of two individual steps, a one-pot sequential process was investigated. Indeed, an enhanced enantioselectivity of 75% ee was obtained from the sequential reaction going through the Pd and phosphoric acid **CPA1** cooperatively catalyzed allylic C−H borylation and Brønsted acid catalyzed allylborylation of 4-nitrobenzaldehyde (Table 1, entry 1). Elevating the allylic C−H borylation reaction temperature to 50 °C while maintaining the allylation reaction at room temperature led to a higher yield, but a considerably lower enantioselectivity was observed (entry 2). Interestingly, the use of **CPA4** to replace **CPA1** resulted in a moderate yield, but with 81% ee under otherwise identical reaction conditions (entry 3). Double chiral induction has been considered to be a powerful strategy for the development of stereoselective reactions.[14] Thus, bis(pinanediolato)diboron **2b**,[10b,15] a commercially available chiral reagent, was tested and found to give product **4a** in 49% yield and with 91% ee (entry 4). In contrast, the use of the enantiomer of **CPA4** as a cocatalyst

Table 1. Evaluation of Catalyst Systems and Optimization of Reaction Conditions[a]



entry	CPA	2	t_1 (°C)	t_2 (°C)	yield (%)[b]	ee (%)[c]
1	**CPA1**	**2a**	25	25	62	75[d]
2	**CPA1**	**2a**	50	25	81	60[d]
3	**CPA4**	**2a**	50	25	49	81
4	**CPA4**	**2b**	50	25	44	91
5	***ent*-CPA4**	**2b**	50	25	48	53[d]
6	--	**2b**	50	25	75	18
7	**CPA4**	**2b**	50	−10	34	92
8	**CPA4**	**2b**	50	−20	33	93
9[e]	**CPA4**	**2b**	50	−20	72	93
10[e,f]	**CPA4**	**2b**	50	−20	85	93

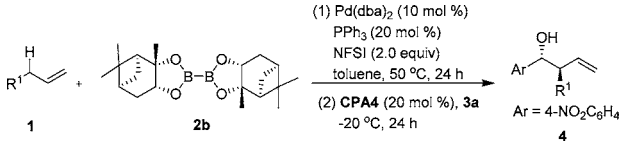
[a]Unless indicated otherwise, the reaction of **1a** (0.2 mmol), **2** (0.2 mmol), $Pd(dba)_2$ (0.01 mmol), PPh_3 (0.02 mmol), **CPA** (0.02 mmol), and *N*-fluorobenzenesulfonimide (NFSI) (0.2 mmol) was carried out in toluene (1.5 mL) at 50 °C for 24 h, and then 4-nitrobenzaldehyde **3a** (0.1 mmol) was added; resultant mixture was stirred for an additional 24 h. [b]Isolated yield with >20:1 dr. [c]Determined by chiral HPLC. [d]An opposite enantiomer of **4aa** was obtained. [e]0.3 mmol of **2b** was employed. [f]**CPA** was added to the reaction of **3a** after the allylic borylation reaction.

allowed the reaction to give an opposite enantiomer with a much eroded enantioselectivity (entry 5). In addition, the use of bis(pinanediolato)diboron **2b** as a sole chiral element provided a much diminished stereochemical outcome (entry 6). These results indicated that the double chiral induction indeed existed and the (*R*)-configuration of chiral phosphoric acid matches the chirality of **2b** to induce higher enantioselectivity. Although with a reduced yield, performing the allylation step at −20 °C did provide a slightly enhanced enantioselectivity of 93% ee (entry 8). When the ratio of chiral diboronate **2b** to **1a** was tuned to 3:2, the sequential reaction proceeded more cleanly to deliver a 72% yield, without sacrificing the enantioselectivity (entry 9). Interestingly, the desired product **4aa** was isolated in a much improved yield and with a maintained enantioselectivity by introducing the Brønsted acid catalyst **CPA4** after the borylation step completely consumed the allylbenzene **1a** (entry 10).

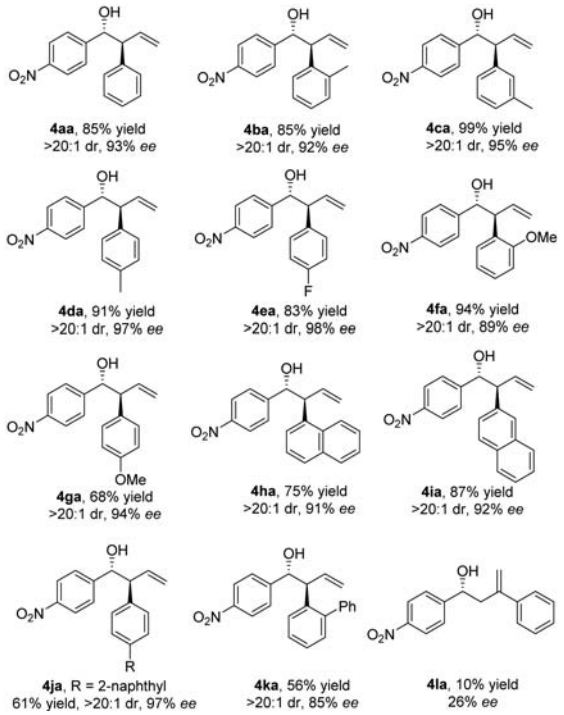
With the optimal conditions in hand, the substrate scope of allylbenzene derivatives was examined. A variety of allylbenzene derivatives underwent the Pd/Brønsted acid sequentially catalyzed allylic borylation and asymmetric carbonyl allylation reaction to give corresponding products **4** in good yields and with excellent diastereo- and enantioselectivities (Table 2). In general, the substitution pattern of the benzene ring exhibited a subtle effect on either the yield or stereochemical outcome, as illustrated by reactions to generate chiral homoallylic alcohols **4ba** to **4da**. Both electron-donating and -withdrawing substituents on the allylbenzene provided the desired products with satisfactory yields and stereoselectivity (**4ea**−**4ga**). In addition, 1-allyl- and 2-allylnaphthalenes were both well tolerated, delivering the desired products in good yields and with good enantioselectivities (**4ha** and **4ia**). The substrates with aryl substituents on the benzene ring could also be transformed into

DOI: 10.1021/acs.orglett.6b03378
Org. Lett. 2017, 19, 102−105

Table 2. Substrate Scope of Allylbenzene[a]

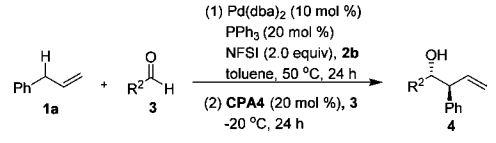


4 (yield[b], dr[c], ee[d])

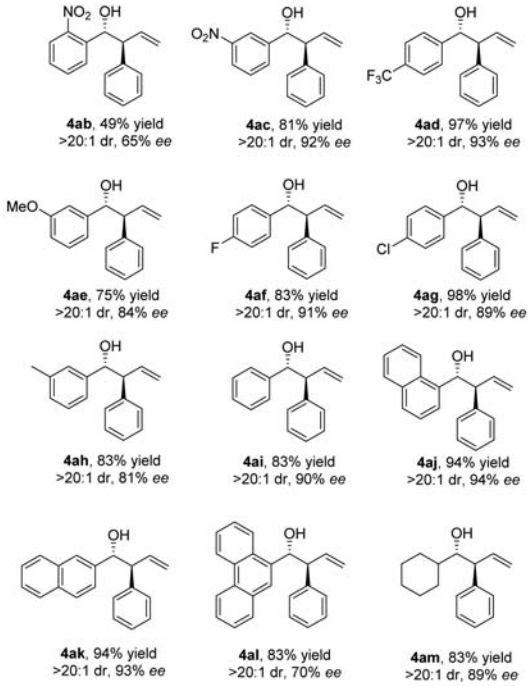


[a]Unless indicated otherwise, the reaction of **1** (0.2 mmol), **2b** (0.3 mol), $Pd(dba)_2$ (0.01 mmol), PPh_3 (0.02 mmol), and NFSI (0.2 mmol) was carried out in toluene (1.5 mL) at 50 °C for 24 h, and then 4-nitrobenzaldehyde **3a** (0.1 mmol) and **CPA4** (0.02 mmol) were added; the resultant mixture was stirred at −20 °C for an additional 24 h. [b]Isolated yield. [c]The ratio of anti/syn was determined by ^1H NMR of the crude products. [d]Determined by chiral HPLC.

Table 3. Substrate Scope of Aldehydes[a]



4 (yield[b], dr[c], ee[d])



[a]Unless indicated otherwise, the reaction of **1a** (0.2 mmol), **2b** (0.3 mol), $Pd(dba)_2$ (0.01 mmol), PPh_3 (0.02 mmol), and NFSI (0.2 mmol) was carried out in toluene (1.5 mL) at 50 °C for 24 h, and then the aldehydes **3** (0.1 mmol) and **CPA4** (0.02 mmol) were added; the resultant mixture was stirred at −20 °C for an additional 24 h. [b]Isolated yield. [c]The ratio of anti/syn was determined by ^1H NMR of the crude products. [d]Determined by chiral HPLC.

the products in moderate yields and good enantioselectivities (**4ja** and **4ka**). However, α-methylstyrene underwent a very slow reaction to give product **4la** in only 10% yield and with 23% ee. The absolute configuration of **4fa** was assigned to be (1*R*,2*S*) by X-ray analysis of its single crystal (see Supporting Information).

In addition, the protocol was amenable to a wide variety of aromatic aldehydes delivering the desired products in good to high yields and with excellent diastereo- and enantioselectivities (Table 3). However, the substitution pattern of benzaldehydes has considerable impact on the stereochemical control. Basically, both 3- and 4-substituted benzaldehyde derivatives were generally well tolerated (**4ac**−**4ah**). In contrast, 2-nitrobenzaldehyde underwent a much slower reaction and gave a diminished enantioselectivity in comparison with either 3- or 4-nitrobenzaldehydes (**4ab** vs **4ac** and **4aa** in Table 2). Neither the electronic property nor substitution pattern exhibited an impact on the diastereoselectivity, while electron-deficient benzaldehydes generally gave higher yields and enantioselectivities than the electron-rich ones (**4ac**, **4ad** and **4af** vs **4ae** and **4ah**). In addition to the benzaldehydes, other aryl aldehydes were also compatible for the transformation (**4ai**−**4al**). An aliphatic aldehyde, cyclohexanecarboxaldehyde, also turned out to be a suitable substrate for the reaction, providing **4am** in an 83% yield and with 89% enantiomeric excess.

In conclusion, we have established a one-pot protocol consisting of a Pd-catalyzed allylic borylation with a chiral diborate and a chiral Brønsted acid catalyzed asymmetric allylation of aldehydes, delivering homoallylic alcohols in high yields and with excellent diastereo- and enantioselectivities, providing an efficient method for the stereoselective functionalization of allylic C−H bonds. It turned out that the double chiral induction of chiral allylic borate and chiral phosphoric acid allows the reaction to exhibit high enantioselectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03378.

Experimental details and characterization data (PDF)

X-ray data for compound **4fa** (CIF)

DOI: 10.1021/acs.orglett.6b03378
Org. Lett. 2017, 19, 102−105

AUTHOR INFORMATION

Corresponding Author

*E-mail: gonglz@ustc.edu.cn.

ORCID

Liu-Zhu Gong: 0000-0001-6099-827X

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful for financial support from the MOST (973 project 2015CB856600), NSFC (21502183), Chinese Academy of Science (Grant No. XDB20020000), and the Fundamental Research Funds for the Central Universities (WK2060190041).

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DOI: 10.1021/acs.orglett.6b03378
Org. Lett. 2017, 19, 102−105