JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Diastereoselective Carbonyl Allylation with Simple Olefins Enabled by Palladium Complex-Catalyzed C−H Oxidative Borylation

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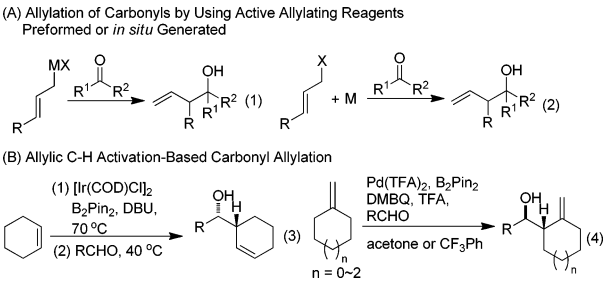
Supporting Information

ABSTRACT: A highly diastereoselective Pd-catalyzed carbonyl allylation of aldehydes and isatins directly using simple acyclic olefins as allylating reagents is described. This transformation is actually a sequential process consisting of a Pd-catalyzed oxidative allylic C−H borylation and an allylboration of carbonyls accelerated by phosphoric acid, wherein a wide scope of olefins could be tolerated. The oxidant is revealed to play a key role in the successful realization of the allylic C−H activation-based allylation.

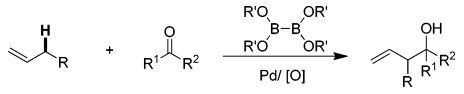
Homoallylic alcohols are arguably one of the most versatile chemicals due to the diverse range of synthetically useful transformations that can occur at the carbon−carbon double bond, thus rendering them widely applicable to the total synthesis of structurally complex natural or non-natural molecules.[1] Over the past several decades, synthetic methods to access these molecules have been established by addition reactions of allylic metal species, which could be used either in preformed (eq 1, Scheme 1A)[2] or *in situ* generated manner (eq 2, Scheme 1A),[3] to carbonyl compounds. In these cases, active allylic compounds, e.g., allylic halides (or pseudo halides), esters, or alcohols, were mainly used for the generation of allylating reagents. In sharp contrast, the use of an allylic C−H activation strategy that allows olefins to participate directly in the allylation of carbonyls appears to be rather limited (Scheme 1B).[4] Szabó and co-workers established a one-pot protocol involving an Ir-catalyzed C−H activation-based borylation of cyclic olefins and a subsequent allylation of aldehydes (eq 3, Scheme 1B).[4a] Very recently, the same group found that exocyclic alkenes were able to undergo cascade C−H activation-based borylation and carbonyl allylation reaction of aldehydes under the catalysis of palladium complexes (eq 4, Scheme 1B).[4c]

Scheme 1. Previous Allylation of Carbonyls



Simple acyclic alkenes are readily available feedstock and the most diversely useful chemicals in organic synthesis. The direct functionalization of sp^3 C−H bonds present in these molecules would increase the synthetic utility of olefins beyond the rich chemistry of the C−C double bond. As a consequence, functionalization of allylic C−H of alkenes has received a great deal of interest in recent years.[5] The most exciting achievements have been accomplished in the allylic substitution reactions, as exemplified by findings from Li,[6] White,[7] and others.[8] The alkenes in these cases act mostly as electrophiles after they undergo allylic C−H activation with transition metals. Herein, we describe a Pd-catalyzed carbonyl allylation with simple olefins, which function directly as allylating reagents after undergoing Pd-catalyzed allylic C−H borylation (Scheme 2).[9]

Scheme 2. Diastereoselective C−H Activation-Based Allylation of Carbonyls with Simple Olefins in This Study

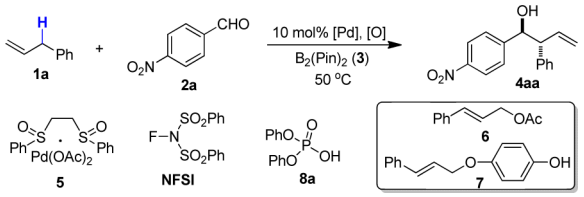


At the outset of our study, the C−H activation-based allylation reaction of 4-nitrobenzaldehyde (**2a**) with allylbenzene (**1a**) was examined under the optimal conditions that Szabó and co-workers developed for the allylation of aldehydes with exocyclic olefins.[4c] However, no desired product was detected (entry 1, Table 1). Although **1a** was completely consumed in the presence of White's catalyst **5**[7] and acetic acid, the desired product **4aa** was isolated in only trace amounts; instead, cinnamyl acetate (**6**) turned out to be a major product (entry 2). The addition of phosphoric acid as a co-catalyst led to allylation of hydroquinone formed from benzoquinone, yielding **7**, together with trace amounts of **4aa** (entry 3). A survey of oxidants (entries 4−6) found that *N*-fluorobenzenesulfonimide (NSFI) could enable the reaction to give **4aa** in 20% yield (entry 6).[10] The use of excess amounts of olefin **1a** resulted in a slightly higher conversion (entry 7). We previously found that $Pd(PPh_3)_4$ was capable of catalyzing allylic C−H activation-based allylation in the presence of appropriate oxidants;[11] thus, it was next applied to the current reaction. To our delight, a much enhanced yield was observed, compared to that obtained with White's catalyst

Received: January 16, 2015

DOI: 10.1021/jacs.5b00507
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

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



entry	1a/2a/3	Pd	oxidant	additive (*x* mol%)	yield (%)[b]
1	1/1.2/1.2	$Pd(TFA)_2$	DMBQ	TFA (50)	trace[c]
2	1/1.2/1.2	**5**	BQ	AcOH (200)	trace[d]
3	1/1.2/1.2	**5**	BQ	**8a** (20)	trace[e]
4	1/1.2/1.2	**5**	$PhI(OAc)_2$	**8a** (20)	ND
5	1/1.2/1.2	**5**	$PhI(TFA)_2$	**8a** (20)	ND
6	1/1.2/1.2	**5**	NFSI	**8a** (20)	20
7	1.2/1/1.2	**5**	NFSI	**8a** (20)	23
8	1.2/1/1.2	$Pd(PPh_3)_4$	NFSI	**8a** (20)	54
9	2/1/2	$Pd(PPh_3)_4$	NFSI	**8a** (20)	81
10	2/1/2	$Pd(PPh_3)_4$	NFSI	---	69
11	2/1/2	$Pd(dba)_2$[f]	NFSI	**8a** (20)	90 (92[j])
12	2/1/2	$Pd(TFA)_2$[f]	NFSI	**8a** (20)	71
13	2/1/2	$Pd(OAc)_2$[f]	NFSI	**8a** (20)	57
14	2/1/2	$Pd(dba)_2$[fg]	NFSI	**8a** (20)	<5
15	2/1/2	$Pd(dba)_2$[f,h]	NFSI	**8a** (20)	61
16	2/1/2	$Pd(dba)_2$[f,i]	NFSI	**8a** (20)	76

[a]Unless indicated otherwise, the reaction of **1a** (0.1 mmol), **2a** (0.12 mmol), **3** (0.12 mmol), an oxidant (0.2 mmol), and palladium complex (0.01 mmol) was carried out for 24 h in toluene (1.5 mL). [b]Isolated yield with >20/1 dr. ND = not detected. [c]Reaction was carried out in $PhCF_3$ (0.5 mL). [d]Cinnamyl acetate **6** was generated. [e]Compound **7** was generated. [f]In the presence of PPh_3 (0.02 mmol). [g]In DMSO (1.5 mL). [h]In THF (1.5 mL). [i]In $PhCF_3$ (1.5 mL). [j]1.05 g (7 mmol) of **2a** was used.

(entry 8 vs 7). Notably, a high yield of 81% could be achieved when the ratio of **1a** and $B_2(Pin)_2$ (**3**) to **2a** was tuned to 2/1 (entry 9). Interestingly, the yield was considerably sacrificed in the absence of Brønsted acid **8a** (entry 10). Screening of the palladium source found that the $Pd(dba)_2$ was the best precatalyst (entries 11−13). The examination of solvents led to the conclusion that the less polar solvents were seemingly more suitable media (entries 11 and 14−16). More significantly, the reaction conducted with >1 g of **2a** still gave **4aa** in 92% yield (entry 11).

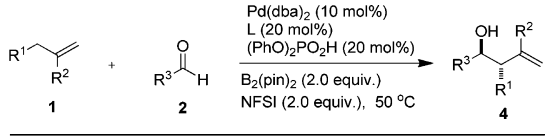
The optimal conditions were then expanded to the allylation reaction of different olefins **1** with **2a** and **3**. A variety of allylbenzene derivatives were able to smoothly undergo the allylation reaction. Generally, good yields and excellent diastereoselectivities were observed for a broad range of substituted allylarenes possessing diverse electronic and steric properties (entries 1−5, Table 2). For allyl substrates bearing an electronically neutral naphthyl group, the products were obtained in excellent yields and diastereoselectivities (entries 6 and 7). More importantly, 2-phenylpropene (**1i**), without an aryl substituent to activate the allylic C−H bond, was also able to participate in a smooth allylation reaction when triphenylphosphite was used as the ligand, leading to the generation of the desired product **4ia** in 65% yield (entry 8). Nevertheless, 2-phenylbutene (**1j**), possessing a methyl substituent at the allylic carbon to basically deactivate the C−H bond, was also nicely tolerated to undergo the transformation, giving homoallylic alcohol **4ja** in 85% yield, surprisingly with the *syn*-diastereomer as the major product (entry 9). Finally, the examination of cyclic olefins indicated that cyclohexene turned out to be an active substrate and was able to undergo the allylation reaction in a high yield and with excellent diastereoselectivity (entry 10). As for aldehyde substrates, the reaction showed a nice tolerance of different substituents in benzaldehyde derivatives (entries 11−18). Neither electronic property nor substitution pattern exerted an impact on the diastereoselectivity, whereas electron-deficient benzaldehydes generally gave higher yields than the electron-rich or neutral ones (entries 11 and 12 vs 13−18). The allylation of 2-naphthaldehyde (**2j**) with allylbenzene (**1a**) proceeded cleanly to give a high yield of 88% and perfect stereoselectivity (entry 19). Cyclohexanecarbaldehyde (**2k**), an aliphatic aldehyde, was also reactive under the conditions (entry 20).

Aside from aldehydes, isatin derivatives were tested in the allylic C−H activation-based allylation reactions (Scheme 3). Both the electronic feature and substitution pattern of the isatin have little effect on the diastereomeric ratios. Thus, fairly good yields and perfect diastereoselectivity were observed for all substrates examined.

Previous studies on Pd-catalyzed umpolung allylation of aldehydes have indicated that either allylboron[3,12] or η^1-allylpalladium[13] is a possible intermediate in the allylation with aldehydes. In principle, a similar intermediate could be involved in this Pd-catalyzed C−H activation-based allylation. Previously, Antilla reported that chiral phosphoric acids were able to catalyze asymmetric allylation of aldehydes with pinacol allylboronate.[14] If the pinacol allylboronate indeed got involved in the catalytic process, an enantioselective allylation would be accessed by using a chiral Brønsted acid to replace the achiral phosphoric acid **8a**. Thus, an allylation reaction of **1a** with **2a** was carried out in the presence of 20 mol% of chiral phosphoric acid **8b** under otherwise identical conditions. Interestingly, the desired product **4aa** was isolated with 67% ee (eq 5), which was close to that obtained from the allylation reaction between pinacol allylboronate and **2a** catalyzed by **8b** (eq 6). These control

DOI: 10.1021/jacs.5b00507
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

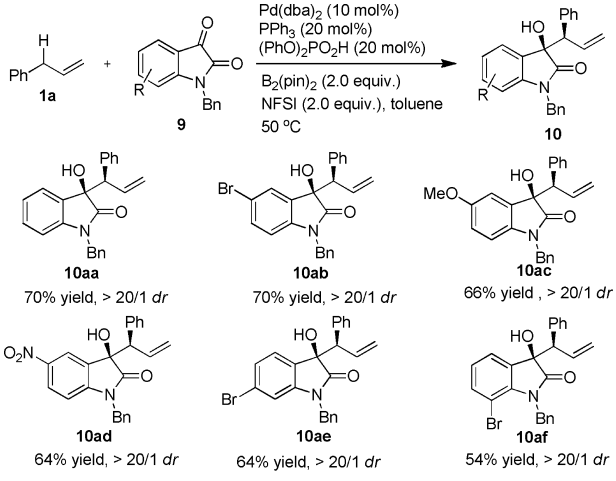
Table 2. Substrate Scope[a]

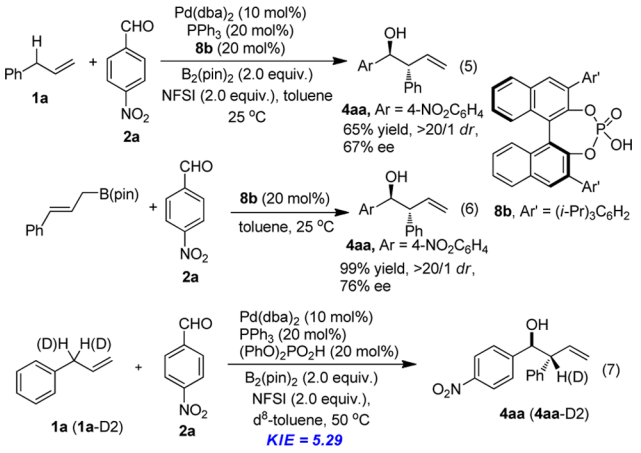


entry	1 (R^1, R^2)	2 (R^3)	4	Yield (%)[b,c]
1	**1b** (4-FC_6H_4, H)	**2a** (4-$NO_2C_6H_4$)	**4ba**	67
2	**1c** (4-ClC_6H_4, H)	**2a** (4-$NO_2C_6H_4$)	**4ca**	68
3	**1d** (4-$MeOC_6H_4$, H)	**2a** (4-$NO_2C_6H_4$)	**4da**	74
4	**1e** (4-$^tBuC_6H_4$, H)	**2a** (4-$NO_2C_6H_4$)	**4ea**	61
5	**1f** (C_6F_5, H)	**2a** (4-$NO_2C_6H_4$)	**4fa**	86
6	**1g** (1-Naphthyl, H)	**2a** (4-$NO_2C_6H_4$)	**4ga**	93
7	**1h** (2-Naphthyl, H)	**2a** (4-$NO_2C_6H_4$)	**4ha**	97
8[d,e]	**1i** (H, Ph)	**2a** (4-$NO_2C_6H_4$)	**4ia**	65
9[d,e]	**1j** (Me, Ph)	**2a** (4-$NO_2C_6H_4$)	**4ja**	85[f]
10[d]	**1k** cyclohexene	**2a** (4-$NO_2C_6H_4$)	**4ka**	73
11	**1a** (Ph, H)	**2b** (Ph)	**4ab**	67
12	**1a** (Ph, H)	**2c** (3-$MeOC_6H_4$)	**4ac**	64
13	**1a** (Ph, H)	**2d** (4-FC_6H_4)	**4ad**	87
14	**1a** (Ph, H)	**2e** (4-ClC_6H_4)	**4ae**	89
15	**1a** (Ph, H)	**2f** (4-BrC_6H_4)	**4af**	85
16	**1a** (Ph, H)	**2g** (2-$NO_2C_6H_4$)	**4ag**	99
17	**1a** (Ph, H)	**2h** (3-$NO_2C_6H_4$)	**4ah**	99
18	**1a** (Ph, H)	**2i** (4-$CF_3C_6H_4$)	**4ai**	81
19	**1a** (Ph, H)	**2j** (2-Naphthyl)	**4aj**	88
20	1a (Ph, H)	2k (c-C_6H_{11})	**4ak**	44

[a]Unless indicated otherwise, the reaction of **1** (0.2 mmol), **2** (0.1 mmol), $B_2(Pin)_2$ (**3**) (0.2 mmol), $Pd(dba)_2$ (0.01 mmol), PPh_3 (0.02 mmol), **8a** (0.02 mmol), and NFSI (0.2 mmol) was carried out in toluene (1.5 mL) at 50 °C for 24 h. [b]Isolated yield. [c]Unless indicated otherwise, the ratio of *anti*/*syn*, which was determined by ^{1}H-NMR of the crude product, was >20/1. [d]$P(OPh)_3$ (0.01 mmol) was added instead of PPh_3. [e]$(PhO)_2PO_2H$ was not added. [f]The ratio of *anti*/*syn* was 1/2.5.

Scheme 3. Allylation of Isatins



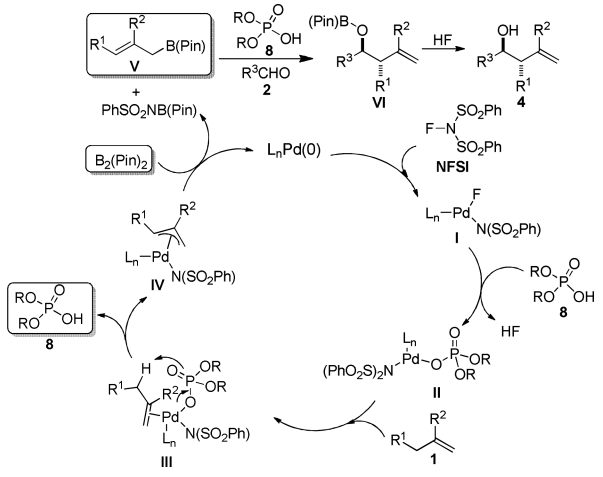


experiments suggested that the pinacol allylboronate, which was *in situ* generated from allylic C−H borylation, rather than η^1-allylpalladium, participated in the phosphoric acid-promoted allylation of aldehydes.

To further understand the reaction mechanism, kinetic studies on the allylation reaction of either (allyl-1,1-d_2)benzene (**1a-D2**) or **1a** with **2a** were conducted in d_8-toluene at 50 °C (eq 7, and Figure S1 in SI). A significant kinetic isotope effect (KIE) was observed, revealing that the allylic C−H activation was a rate-limiting step.[15]

Although the exact mechanism cannot be entirely concluded currently, a plausible catalytic cycle has been proposed to understand the transformation (Scheme 4). The Pd(0) was first

Scheme 4. Plausible Reaction Mechanism



oxidized by NFSI to generate a Pd(II) species **I**,[16] which might then be able to react with a relatively stronger Brønsted acid **8** to yield the key palladium phosphate intermediate **II**,[17] accompanied with release of one molecule of hydrogen fluoride. The allylic C−H activation of **1** would then occur with **II**, presumably via intermediate **III**, leading to the formation of allylpalladium species **IV**.[17] This transformation has been proven to be the rate-limiting step in the whole process by KIE studies (eq 7). Subsequently, the allylborylation reaction between **IV** and **3** would proceed to give pinacol allylboronates **V**,[18] which are highly active reagents in the allylation reaction with aldehydes **2** to give homoallylic alcohols **4** diastereoselectively. The allylation reaction that actually proceeds external to the catalytic cycle for the allylic C−H activation could be accelerated by the

DOI: 10.1021/jacs.5b00507
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

phosphoric acid, as indicated by the results of the enantioselective catalytic version (eq 5).

In conclusion, we have established a highly stereoselective allylation of aldehydes with simple acyclic alkenes, wherein a wide scope of aldehydes and acyclic or cyclic alkenes are nicely tolerated. The reaction is basically a cascade process consisting of a Pd-catalyzed allylic C−H borylation and an allylation of aldehydes. Actually, the oxidants play a key role in the realization of the allylic C−H activation step. The Brønsted acid was able to catalyze the allylation reaction and hence to facilitate the whole process. More importantly, the enantioselective version could be accessed using chiral Brønsted acids as co-catalysts. Improvement of the enantioselectivity and applications of the concept to the creation of new transformations involving allylic C−H activation are now being actively pursued.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures and characterization data for the prepared compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from MOST (973 project 2015CB856600) and NSFC (21232007).

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DOI: 10.1021/jacs.5b00507
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX