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Highly Enantioselective Allylic C−H Alkylation of Terminal Olefins with Pyrazol-5-ones Enabled by Cooperative Catalysis of Palladium Complex and Brønsted Acid

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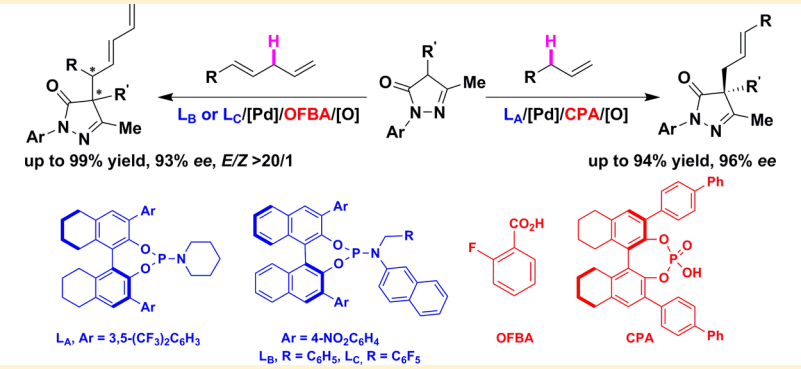
Supporting Information



ABSTRACT: A highly enantioselective allylic C−H alkylation reaction of allylarenes with pyrazol-5-ones has been established by the cooperative catalysis of a chiral palladium complex and chiral Brønsted acid to afford a wide spectrum of functionalized chiral N-heterocycles with an all-carbon quaternary stereogenic center in high yields and with high levels of enantioselectivity (up to 96% ee), wherein the chiral ligand and phosphoric acid showed synergistic effect on the control of stereoselectivity. In addition, a palladium-catalyzed asymmetric allylic C−H alkylation of 1,4-pentadienes with pyrazol-5-ones has been realized to furnish highly functionalized pyrazol-5-ones in high enantioselectivities. In this case, the chiral ligand controls the stereoselectivity while the achiral Bronsted acid, 2-fluorobenzoic acid, turns out to be a better cocatalyst than the chiral phosphoric acid. The installation of electron-deficient substituents at 3,3′-positions of binaphthyl backbone of chiral phosphoramidites is actually beneficial to the allylic C−H oxidation due to their survival in the presence of quinone derivative oxidants. These allylic C−H alkylation reactions undergo smoothly under mild conditions and tolerate a wide range of substrates. The resultant highly functionalized chiral pyrazol-5-ones have been applied to the preparation of more structurally diverse heterocycles by classical transformations.

INTRODUCTION

The stereoselective construction of carbon−carbon chemical bonds, in particular, those capable of enabling highly enantioseletive creation of all-carbon quaternary stereogenic centers in atom- and step-economy manner, holds great importance in organic synthesis but continues to be challenging for the community of synthetic organic chemistry.[1,2] As such, the development of new efficient methods to build up all-carbon quaternary stereogenic centers with high stereochemical control has long been and now is still holding great importance in synthetic organic chemistry.

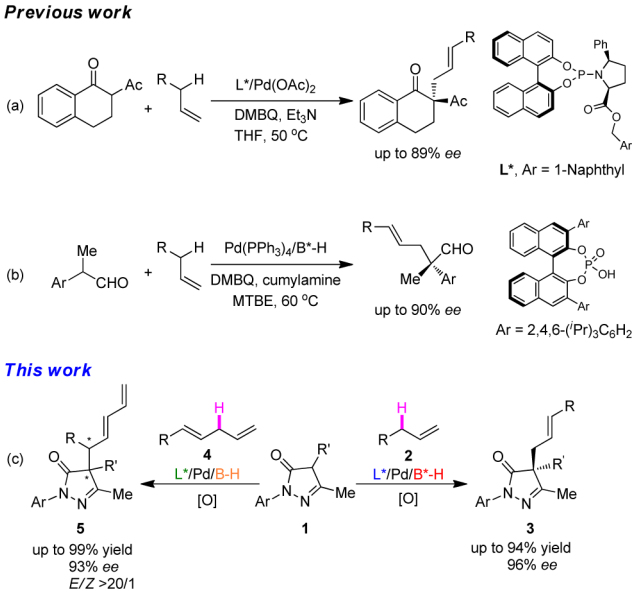
The asymmetric allylic alkylation (AAA) undoubtedly represents one of the most useful methods for the formation of carbon−carbon and carbon−heteroatom chemical bonds and has been prevalently applied to the fields of both natural product synthesis and medicinal chemistry.[3] Since the pioneering discoveries by Tsuji and Trost[4] preactivated allylic substrates, including allylic halides, esters, carbonates, and other structural analogues, have dominantly been exploited to react with either soft or hard nucleophilies.[3−5] By use of dual activation strategy, allylic alcohols are also able to undergo the AAA reaction.[6] In comparison with these traditional Tsuji−Trost type reactions, the allylic C−H activation-based alkylation of simple alkenes is considered even more challenging. In recent years, worldwide endeavors have been devoted to this field, leading to an explosive emergence of new efficient strategies for the functionalization of the relatively

Received: August 8, 2016
Published: October 9, 2016

DOI: 10.1021/jacs.6b08236
J. Am. Chem. Soc. 2016, 138, 14354−14361

inactive allylic C−H bonds.[7] However, the creation of highly enantioselective variants has continuously met with a great deal of challenge.[8] The enantioselective formation of C−O and C−N bonds from the C−H activation-based allylic substitution has been investigated for decades but only providing a limited number of successful examples.[9] In particular, even fewer reports describe the catalytic C−H allylic alkylation for the highly enantioselective formation of carbon−carbon bonds. In 2013, Trost and co-workers reported a catalytic asymmetric allylic C−H alkylation[10] and found that phosphoramidite ligands were able to accelerate both the palladium-catalyzed allylic C−H activation and the subsequent alkylation, allowing for the formation of alkylation products in good enantioselectivities (Scheme 1a). Very recently, we accomplished an

Scheme 1. Asymmetric Allylic C−H Alkylation Reactions



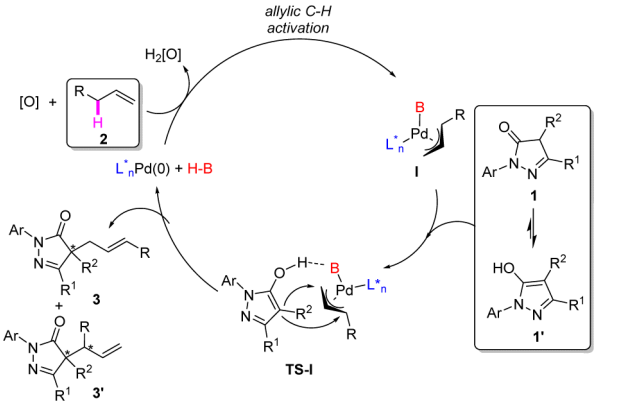
asymmetric allylic C−H alkylation of enolizable aldehydes under the asymmetric cooperative catalysis of an achiral palladium complex, a primary amine (cumylamine), and a chiral phosphoric acid (Scheme 1b).[11] Obviously, asymmetric allylic C−H alkylation reactions of terminal olefins with many other nucleophiles currently need to be created, and more importantly, new chiral catalyst systems and strategies that are generally applicable to the establishment of asymmetric allylic C−H functionalization are greatly desired.

Pyrazol-5-one derivatives have attracted much attention due to their interesting biological activities in pharmaceutical research.[12] As such, the efficient functionalization of pyrazol-5-ones, especially in the asymmetric version, can be of great importance and indeed has long been receiving a great deal of research interest.[13,14] Previously, we successfully accomplished a highly efficient functionalization of pyrazol-5-ones via palladium catalyzed asymmetric allylic alkylation with allylic alcohols.[15] These molecules showed high reactivity toward π-allyl palladium species and other electrophiles.[13,14] However, they have not been used in allylic C−H alkylation reaction as soft nucleophiles, yet. Herein, we will report that the cooperative catalysis of a chiral palladium complex and a Brønsted acid[16,17] efficiently renders a highly enantioselective allylic C−H alkylation of a broad scope of allylarenes and 1,4-pentadienes with pyrazol-5-ones, allowing for the efficient synthesis of functionalized N-heterocycles in high yields and with simultaneous creation of an all-carbon quaternary stereogenic center in excellent enantioselectivities (Scheme 1c).

RESULTS AND DISCUSSION

General Research Plan for the Creation of Asymmetric Allylic C−H Alkylation of Terminal Olefins with Pyrazol-5-ones. To address the challenges remaining in realization of highly enantioselective allylic C−H alkylation reactions, we proposed that in the presence of a chiral palladium(0) complex and a Brønsted acid, allylarene **2** could undergo an allylic C−H oxidation reaction with an appropriate oxidant to generate a chiral π-allyl palladium complex **I**,[11,18] which would presumably be able to participate in an asymmetric allylic alkylation with a pyrazol-5-one **2** via a transition state **TS-I** to give either a linear **3** or a branched alkylation product **3′** (Scheme 2). In this scenario, either

Scheme 2. Mechanistic Hypothesis for the Asymmetric Allylic C−H Alkylation of Allylarenes with Pyrazol-5-ones



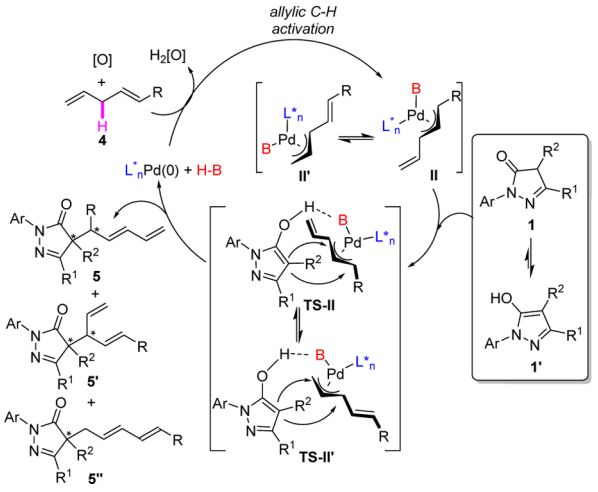
achiral or chiral Brønsted acid could be introduced to presumably assist the chiral ligand to synergistically control the stereoselectivity via the transition state **TS-1**. In addition, the presence of the Brønsted acid is actually able to facilitate the oxidation of Pd(0) into catalytic active Pd(II)[19] and to hence allow the allylic C−H activation step to proceed more smoothly.

Similarly, in the presence of the Pd(0) complex and Brønsted acid, the 1,4-pentadiene **4** would also be able to undergo the oxidation reaction to principally generate two regiomeric vinyl (π-allyl)palladium intermediates **II** and **II′**, which will respectively participate in the asymmetric allylic alkylation reaction with the pyrazol-5-one **1** to furnish the corresponding branched products **5** and **5′**, and a linear product **5″** (Scheme 3).[7k,20] In this case, the simultaneous control of the regio-, diastereo-, and enantioselectivities would bring much more challenge. According to the proposed transition states **TS-II** and **TS-II′**, the cooperative catalysis of the chiral palladium complex and Brønsted acid would also be possible to circumvent the challenges in the realization of the proposed reaction.

Recruiting Efficient Catalyst Systems and Optimization of Reaction Conditions. The palladium-catalyzed C−H activation-based asymmetric allylic alkylation basically occurs in the presence of an oxidant; therefore, the ligands must be able to survive in the oxidized conditions during the whole

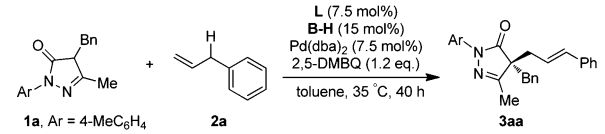
DOI: 10.1021/jacs.6b08236
J. Am. Chem. Soc. 2016, 138, 14354−14361

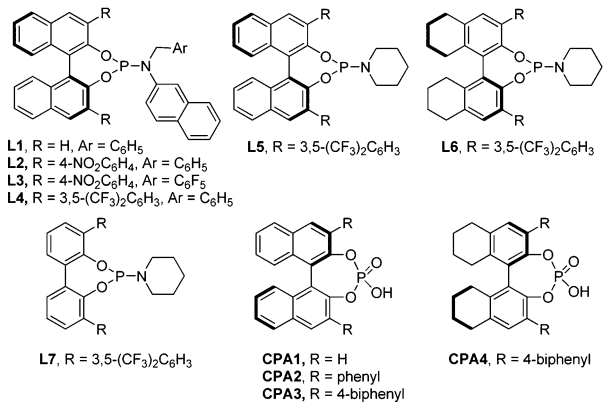
Scheme 3. Mechanistic Hypothesis for the Asymmetric Allylic C−H Alkylation of 1,4-Pentadienes with Pyrazol-5-ones



catalytic process. However, most of the phosphine ligands can be very easily oxidized to five-valence phosphorus species, which are basically unable to accelerate palladium catalysis, and thus very few available chiral ligands are applicable to asymmetric allylic C−H alkylation reaction of this type. Since some of BINOL-derived phosphoramidite ligands[21] could be compatible with quinone-type oxidants and appeared to be good ligands in the palladium-catalyzed asymmetric allylic C−H oxidation in the presence of Brønsted acid,[9k,10] their structural analogues were initially screened for an asymmetric allylic C−H alkylation of pyrazol-5-one **1a** with allylbenzene (**2a**) using 2,5-DMBQ as external oxidant and $Pd(dba)_2$ as a precatalyst in the presence of achiral $(PhO)_2PO_2H$ at 35 °C (entries 1−6, Table 1). However, the ligand **L1** without substituent at the binaphthyl backbone was unable to facilitate the reaction (entry 1). Prompted by our previous findings in the asymmetric allylic C−H oxidation that the introduction of electron-deficient substituents at 3,3′-positions of the binaphthyl moiety in the ligand would be able to enhance the catalytic activity,[9k] a variety of chiral phosphoramidite ligands **L2**−**L6** derived from BINOL were investigated. Indeed, the presence of electronically deficient 4-nitrophenyl substituents at 3,3′-positions of the binaphthyl moiety of the phosphoramidite ligands, as shown in **L2** and **L3**, allowed the desired reaction to occur and to exclusively give the linear product **3aa**, albeit in a moderate yields and with low enantioselectivities (entries 2 and 3). To our delight, the introduction of even more electronically poor 3,5-bis(trifluoromethyl)phenyl groups at 3,3′-positions of the binaphthyl backbone led to significant improvement in the stereochemical control, as indicated by the allylic C−H alkylation using **L4** as a ligand (entry 4). Fine-tuning of the amine moiety in the phosphoramidite ligands found that the incorporation of a cyclic piperidine moiety significantly improved the catalytic efficiency and enantioselectivity (entry 5). In particular, the use of H_8-BINOL-derived phosphoramidite ligand **L6** resulted in the highest enantioselectivity (entry 6). As shown in the mechanistic hypothesis (Scheme 2), the structure of Brønsted acid cocatalyst should exert an impact on the stereoselectivity. As a consequence, a variety of BINOL-derived chiral phosphoric acids[22] were screened. As anticipated, the chiral phosphoric acid cocatalyst showed a

Table 1. Optimization of Reaction Conditions[a]





entry	L	B−H	yield (%)[b]	ee (%)[c]
1	**L1**	$(PhO)_2PO_2H$	trace	–
2	**L2**	$(PhO)_2PO_2H$	43	13
3	**L3**	$(PhO)_2PO_2H$	17	10
4	**L4**	$(PhO)_2PO_2H$	12	77
5	**L5**	$(PhO)_2PO_2H$	55	81
6	**L6**	$(PhO)_2PO_2H$	53	83
7	**L6**	**CPA1**	41	84
8	**L6**	**CPA2**	62	88
9	**L6**	**CPA3**	73	92
10	**L6**	**CPA4**	77	94
11	**L6**	***ent*-CPA4**	47	69
12	PPh_3	**CPA4**	trace	–
13	**L7**	**CPA4**	72	49
14	**L6**	HOAc	74	69
15	**L6**	OFBA	46	80
16	**L6**	–	71	68
17	**L6**	–[d]	47	58

[a]Reaction conditions: Unless indicated otherwise, reactions of **1a** (0.10 mmol), **2a** (0.20 mmol), $Pd(dba)_2$ (0.0075 mmol), **L** (0.0075 mmol), B−H (0.015 mmol), and 2,5-DMBQ (0.12 mmol) were carried out in toluene (4 mL) for 40 h. [b]Isolated yields. [c]The ee value was determined by chiral HPLC analysis. [d]In the presence of Et_3N (1.0 equiv) 2,5-DMBQ = 2,5-dimethylquinone.

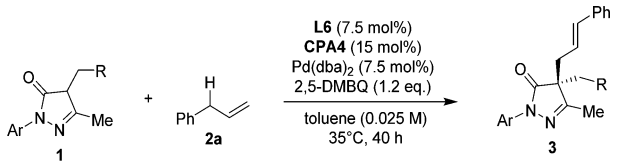
considerable effect on the reaction performance (entries 7−10) and the H_8-BINOL-derived phosphoric acid **CPA4** turned out to be the best cocatalyst and enabled the reaction to give 77% yield and 94% ee (entry 10). In contrast, the enantiomer of **CPA4** gave a much lower yield and enantioselectivity (entry 11 vs 10), suggesting that the (*R*)-configuration of **CPA4** matched the (*S*)-phosphoramidite ligand to synergistically control the stereochemistry. Surprisingly, the use of PPh_3 as a ligand[11] led to no reaction (entry 12). The use of achiral ligand **L7** and the chiral phosphoric acid **CPA4** was able to give a good yield but with a much diminished enantioselectivity (entry 13), suggesting that the stereochemical control was attributed to matched chirality of the Brønsted acid and ligand. The employment of achiral Brønsted acids as cocatalysts gave much eroded results (entries 14 and 15). Although the reaction still worked and furnished the desired product in a good yield in the absence of Brønsted acid, a moderate enantioselectivity

DOI: 10.1021/jacs.6b08236
J. Am. Chem. Soc. 2016, 138, 14354−14361

was induced (entry 16). As a control experiment in comparison with the previous process,[10] the allylic C−H alkylation reaction was conducted with Et_3N in place of chiral phosphoric acid (*R*)-**CPA4** but led to much diminished results in terms of the yield and enantioselectivity (entry 17 vs 10). These aggregative results strongly indicated that the synergistic effect between the chiral ligand and the chiral counterion indeed exists in the stereochemical control.[16,23]

Asymmetric Allylic C−H Alkylation of Pyrazol-5-ones 1 with Allylbenzene (2a). Under the optimized reaction conditions, we first explored the generality of the reaction for different pyrazol-5-ones **1** (Table 2). A wide range of pyrazol-5-ones bearing varied substituted benzyl and other alkyl groups at the C4 were nicely tolerated and underwent the asymmetric allylic C−H alkylation reaction very smoothly to furnish corresponding alkylation products in good to high yields and with excellent enantioselectivities of up to 95% ee (entries 1−14). In addition, the presence of substituents at the benzene ring of the aniline part was also permitted to participate in the desired reaction, delivering the alkylation products in good yields and with high levels of enantioselectivity (entries 15 and 16). The absolute configuration of **3ao** was assigned by X-ray analysis of its single crystal (see Supporting Information).

Table 2. Scope of Pyrazol-5-ones[a]

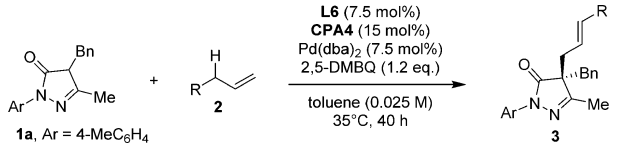


entry	R	3	yield (%)[b]	ee (%)[c]
1	4-MeC_6H_4	**3ba**	70	93
2	4-$^tBuC_6H_4$	**3ca**	82	95
3	4-$MeOC_6H_4$	**3da**	75	93
4	4-FC_6H_4	**3ea**	72	93
5	4-ClC_6H_4	**3fa**	65	94
6	4-BrC_6H_4	**3ga**	65	94
7	3-MeC_6H_4	**3ha**	73	94
8	3-$MeOC_6H_4$	**3ia**	74	94
9	3-ClC_6H_4	**3ja**	59	94
10	2-$MeOC_6H_4$	**3ka**	72	86
11	2-FC_6H_4	**3la**	68	95
12	2-naphthyl	**3ma**	52	92
13	H	**3na**	69	85
14	Me	**3oa**	65	86
15[d]	Ph	**3pa**	67	92
16[e]	Ph	**3qa**	50	92

[a]Unless indicated otherwise, reactions of **1** (0.10 mmol), **2a** (0.20 mmol), $Pd(dba)_2$ (0.0075 mmol), **L6** (0.0075 mmol), **CPA4** (0.015 mmol), and 2,5-DMBQ (0.12 mmol) were carried out in toluene (4 mL) for 40 h. Ar = 4-MeC_6H_4. [b]Isolated yields. [c]The ee value was determined by chiral HPLC analysis. [d]Ar = Ph. [e]Ar = 4-ClC_6H_4.

Asymmetric Allylic C−H Alkylation of Allylarenes 2 with Pyrazol-5-one 1a. Next, the substrate scope with regard to allylarenes was examined under the optimized reaction conditions (Table 3). Notably, the protocol was tolerant of a broad spectrum of allylbenzene derivatives, which are installed with either electronically rich or deficient substituent in different substitution pattern, capable of offering excellent enantioselectivity ranging from 87% to 96% ee (entries 1−13). Moreover, 2-allylnaphthalene (**2o**) and 3-allylthiophene (**2p**) were also excellent substrates of the allylic C−H alkylation to generate the desired products in high yields and with excellent enantioselectivities (entries 14 and 15).

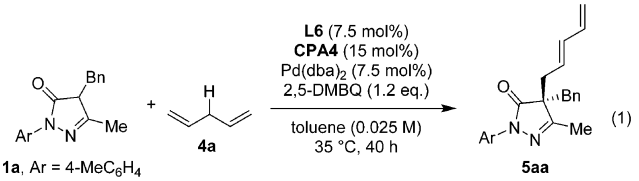
Table 3. Scope of Allylarenes[a]



entry	R	3	yield (%)[b]	ee (%)[c]
1	4-MeC_6H_4	**3ab**	63	94
2	4-$^tBuC_6H_4$	**3ac**	80	92
3	4-$MeOC_6H_4$	**3ad**	53	93
4	4-FC_6H_4	**3ae**	89	94
5	4-ClC_6H_4	**3af**	93	92
6	4-$CF_3C_6H_4$	**3ag**	88	89
7	4-CNC_6H_4	**3ah**	90	87
8	4-$(CO_2Me)C_6H_4$	**3ai**	94	90
9	3-MeC_6H_4	**3aj**	58	93
10	3-$(CO_2Me)C_6H_4$	**3ak**	81	91
11	3-ClC_6H_4	**3al**	75	89
12	2-MeC_6H_4	**3am**	63	93
13	2-FC_6H_4	**3an**	76	96
14	2-naphtyl	**3ao**	88	91
15	3-thienyl	**3ap**	72	94

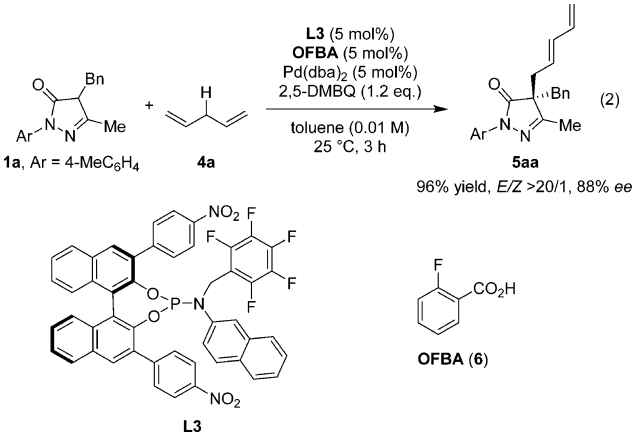
[a]Unless indicated otherwise, reactions of **1a** (0.10 mmol), **2** (0.20 mmol), $Pd(dba)_2$ (0.0075 mmol), **L6** (0.0075 mmol), **CPA4** (0.015 mmol), and 2,5-DMBQ (0.12 mmol) were carried out in toluene (4 mL) for 40 h. [b]Isolated yields. [c]The ee value was determined by chiral HPLC analysis.

Establishment of Optimal Conditions for the Allylic C−H Alkylation of 1,4-Pentadiene with Pyrazol-5-one 1a. Although the allylic C−H alkylation of 1,4-dienes with nitroacetate derivatives has been investigated by Trost and co-workers,[7k] the variants with other soft nucleophiles have not been described yet, presumably due to the paucity of efficient catalyst systems. The success of the chiral palladium complex/phosphoric acid binary catalyst in asymmetric allylic C−H alkylation prompted us to circumvent the challenge in asymmetric allylic C−H alkylation of 1,4-diene derivatives. A model reaction of 1,4-pentadiene (**4a**) with pyrazol-5-one **1a** was conducted under optimized conditions but led to a moderate yield and a poor enantioselectivity (eq 1). Thus, the reaction conditions were reoptimized (Table S1, Supporting Information) and it was found that chiral ligand **L3** was able to give a high yield, excellent *E*/*Z* selectivity, and high enantiomeric excess while achiral 2-fluorobenzoic acid (**6**) appeared to be the best cocatalyst (eq 2).



42% yield, *E*/*Z* >20/1, 21% *ee*

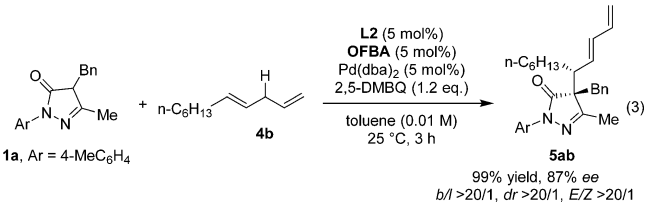
DOI: 10.1021/jacs.6b08236
J. Am. Chem. Soc. 2016, 138, 14354−14361



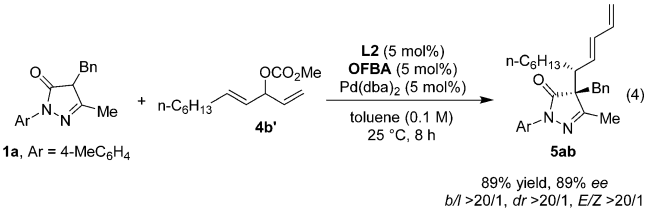
Asymmetric Allylic C−H Alkylation of 1,4-Pentadienes with Pyrazol-5-ones. The reoptimized reaction conditions were then applied to the asymmetric allylic C−H alkylation of 1,4-pentadiene (**4a**) with pyrazol-5-ones **1** (Table 4). The presence of benzyl group bearing either an electron-donating or withdrawing substituent at either meta- or para-position was allowed to undergo the asymmetric allylic C−H alkylation to give desired products in excellent yields and with high levels of enantioselectivity of up to 93% ee (entries 1−6). The installation of an ethyl substituent, as shown in **1o**, again underwent the desired allylic C−H alkylation in excellent yield and with good *E*/*Z* selectivity (14/1) and enantioselectivity (entry 8). The absolute configuration of **5fa** was assigned by X-ray analysis of the single crystal of its hydrazone derivative **7** prepared from the oxidative cleavage of the terminal carbon−carbon double bond and followed by a condensation with *N*-aminophthalimide (Scheme 4).

However, the enantioselectivity of allylic C−H alkylation is quite sensitive to the chiral ligands. Thus, when **L3**, the optimal ligand used for the reaction of 1,4-pentadiene (**4a**), was expanded to (*E*)-1,4-undecadiene (**4b**), a moderate enantioselectivity was obtained (entry 1, Table S2). Consequently, the evaluation of chiral ligands was again conducted and identified that the chiral phosphoramidite **L2** was able to induce the highest enantioselectivity (Table S2).

More interestingly, the branched allylic alkylation product **5ab** with 87% ee, >20/1 *E*/*Z*- and diastereoselectivity was isolated in a high yield, while neither the regiomer **5ab′** nor **5ab″** was isolated (eq 3).



As a comparison, a control experiment of typical allylic alkylation reaction using *n*-hexyl substituted pentadienyl carbonate **4b′** was conducted in the presence of chiral palladium complex of **L2** and 2-fluorobenzoic acid (eq 4).



Interestingly, the branched product **5ab** was also obtained in a good yield and with high regio- and enantioselectivities at a same level as the C−H activation one (eq 3 vs eq 4). Therefore, the two different protocols share a similar vinyl (π-allyl)palladium intermediate. As reported previously,[20,24] the regioselection of the allylic alkylation reaction involving either pentadienyl or allyl ester substrates highly depends on the nucleophiles and chiral ligands. The highly sterically demanding phosphoramidite ligands[24] and high nucleophil-

Scheme 4. Determination of the Absolute Configuration of Products 5fa and 5ad

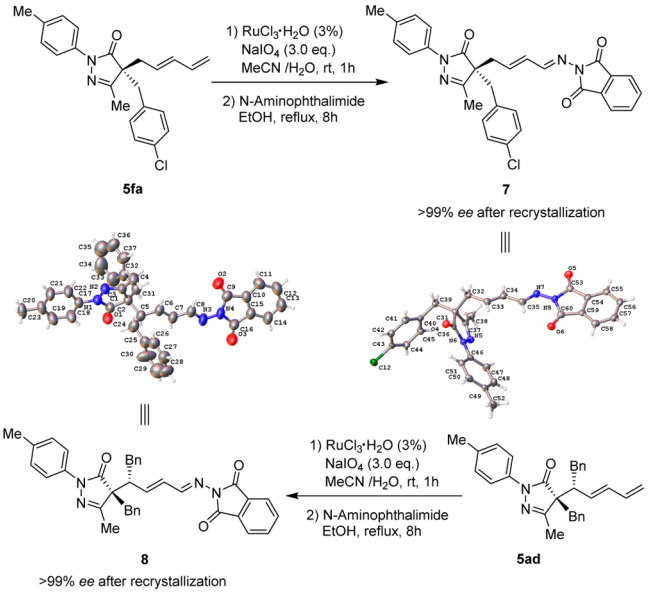
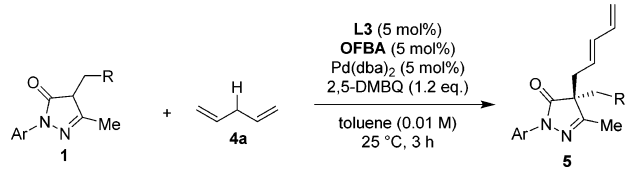


Table 4. Allylic C−H Alkylation of 1,4-Pentadiene (4a) with Pyrazol-5-ones[a]



entry	R	5	yield (%)[b]	*E*/*Z*[c]	ee (%)[d]
1	4-MeC$_6$H$_4$	**5ba**	93	>20/1	92
2	4-MeOC$_6$H$_4$	**5da**	92	15/1	93
3	4-FC$_6$H$_4$	**5ea**	96	>20/1	86
4	4-ClC$_6$H$_4$	**5fa**	86	>20/1	90
5	3-MeOC$_6$H$_4$	**5ia**	97	11/1	90
6	3-ClC$_6$H$_4$	**5ja**	96	16/1	88
7	2-MeC$_6$H$_4$	**5ra**	95	9/1	80
8	Me	**5oa**	81	14/1	81
9	Ph[e]	**5qa**	95	>20/1	80
10	Ph[f]	**5sa**	93	>20/1	87

[a]Unless indicated otherwise, reactions of **1** (0.10 mmol), **4a** (0.20 mmol), Pd(dba)$_2$ (0.005 mmol), **L3** (0.005 mmol), OFBA (0.005 mmol), and 2,5-DMBQ (0.12 mmol) were carried out in toluene (10 mL) for 3 h. Ar = 4-MeC$_6$H$_4$. [b]Isolated yields. [c]The *E*/*Z* ratio was determined by ^{1}H NMR spectroscopic analysis. [d]The ee value was determined by chiral HPLC analysis. [e]Ar = 4-ClC$_6$H$_4$. [f]Ar = 4-MeOC$_6$H$_4$.

DOI: 10.1021/jacs.6b08236
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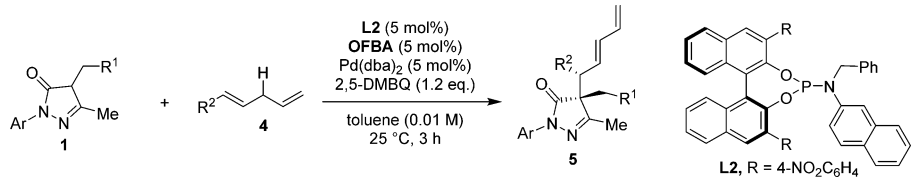
Table 5. Allylic C−H Alkylation of Substituted 1,4-Pentadienes with Pyrazol-5-ones[a]



entry	Ar	R^1	R^2	5[b]	yield (%)[c]	ee (%)[d]
1	4-MeC_6H_4	Ph	cyclohexyl	**5ac**[e]	93	92
2	4-MeC_6H_4	Ph	Bn	**5ad**	87	91
3	4-MeC_6H_4	Ph	$PhCH_2CH_2$	**5ae**	91	87
4	4-MeC_6H_4	Ph	Ph	**5af**	90[f]	90
5	Ph	Ph	Me	**5pg**	93	89
6	Ph	Ph	$PhCH_2CH_2$	**5pe**	91	93
7	4-ClC_6H_4	Ph	$PhCH_2CH_2$	**5qe**	87	85
8	4-$MeOC_6H_4$	Ph	$PhCH_2CH_2$	**5se**	89	86
9	4-MeC_6H_4	4-$MeOC_6H_4$	$PhCH_2CH_2$	**5de**	89	81
10	4-MeC_6H_4	4-ClC_6H_4	$PhCH_2CH_2$	**5fe**	92	85

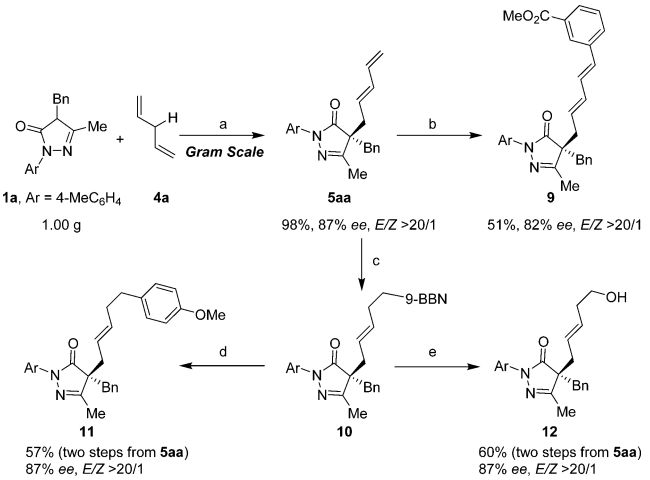
[a]Unless indicated otherwise, reactions of **1** (0.10 mmol), **4** (0.20 mmol), $Pd(dba)_2$ (0.005 mmol), **L2** (0.005 mmol), OFBA (0.005 mmol), and 2,5-DMBQ (0.12 mmol) were carried out in toluene (10 mL) for 3 h. [b]*b*/*l* > 20/1, *dr* > 20/1, *E*/*Z* > 20/1, which was determined by ^1H NMR spectroscopic analysis. [c]Unless indicated otherwise, yields were isolated yields after chromatography. [d]The ee value was determined by chiral HPLC analysis. [e]**L3** was used instead of **L2**. [f]The yield was determined by ^1H NMR spectroscopic analysis using 1,3,5-triacetylbenzene as the internal standard.

icity[20] of pyrazol-5-ones might account for the branched regioselectivity.

Notably, other substituted 1,4-pentadienes were also nicely accommodated and also branched products were preferentially generated (Table 5). Basically, alkyl substituted dienes underwent the reaction in high conversion and gave the branched products with excellent regio-, *E*/*Z*- and diastereoselectivity and offered the branched products with high levels of enantioselectivity (entries 1−3 and 5−10). 1-Phenyl-1,4-pentadiene (**4f**) also participated in the desired reaction to favorably give branched product **5af** in a high yield and with excellent regio- and stereoselectivities (entry 4). The variation of substituents of pyrazol-5-ones **1** was also allowed to give branched allylic alkylation products in high yields and good stereoselectivities (entries 6−10). The absolute configuration of **5ad** was assigned by X-ray analysis of the single crystal of its hydrazone derivative **8**, which was prepared by following a procedure similar to the preparation of **7** from **5fa** (Scheme 4).

Synthetic Applications. As mentioned previously, the chiral pyrazol-5-one derivatives hold great potential in the preparation of biologically active substances, and thereby the synthetic protocol to access the compounds in structural diversity is of high importance. The chiral pyrazol-5-ones **5** are highly functionalized and can be converted into many other different optically active heterocycles (Scheme 5). Thus, a gram-scale reaction of **1a** with **4a** was performed to give the desired product **5aa** in a maintained yield and enantioselectivity in comparison with the small scale. The Heck coupling[25] of **5aa** with 3-iodobenzoic ester was able to give **9** in a good yield. On the other hand, the exposure of **5aa** to 9-borabicyclo[3.3.1]nonane (9-BBN) led to the generation of **10**,[26] a versatile synthetic intermediate capable of undergoing a diverse range of reactions. For example, the Suzuki coupling[27] of **10** with iodobenzene led to **11** in a good yield and with maintained enantiomeric excess. The oxidation[26] of **10** with hydrogen peroxide in the presence of sodium hydroxide was able to give homoallylic alcohol **12** in a good yield. As such, the chiral pyrazol-5-ones bearing a wide scope of allylic substituents could be principally accessed by available classical transformations.

Scheme 5. Scale-up and the Application in the Synthesis of Functionally Diverse Chiral Heterocycles[a]



[a]Conditions and reagents: (a) **1a** (1.00 g), **4a** (2.0 equiv), $Pd(dba)_2$ (5 mol %), **L3** (5 mol %), OFBA (5 mol %) and 2,5-DMBQ (1.2 equiv), toluene (300 mL), 25 °C, 10 h; (b) 3-$IC_6H_4CO_2Me$ (1.5 equiv), $Pd(PPh_3)_4$ (5 mol %), AgOAc (2.0 equiv), DMF, 70 °C, 24 h; (c) 9-BBN (2.0 equiv), THF, rt, 12 h; (d) 4-IC_6H_4OMe (1.2 equiv), $Pd(PPh_3)_4$ (5 mol %), $K_3PO_4·H_2O$ (2.0 equiv), THF, 85 °C, 24 h; (e) NaOH(aq.), H_2O_2, rt, 1 h.

CONCLUSION

In summary, we have found that the cooperative catalysis of palladium complexes of chiral phosphoramidite ligands and Brønsted acids is able to render highly enantioselective allylic C−H alkylation reactions of terminal alkenes with pyrazol-5-ones under mild conditions. A significant synergistic effect between the chiral ligand and the chiral counterion was observed in the stereochemical control of the allylic C−H

DOI: 10.1021/jacs.6b08236
J. Am. Chem. Soc. 2016, 138, 14354−14361

alkylation of allylarenes and pyrazol-5-ones. The palladium-catalyzed asymmetric allylic C−H alkylation of 1,4-pentadienes with pyrazol-5-ones has been established by cooperative catalysis of chiral palladium complexes and 2-fluorobenzoic acid. Both transformations show a broad substrate scope in terms of both the pyrazol-5-ones and olefins to afford a wide scope of functionalized chiral N-heterocycles with an all-carbon quaternary stereogenic center in high yields and with high levels of enantioselectivity. More importantly, a family of new chiral phosphoramidite ligands have been found to show great potential in asymmetric allylic C−H functionalization reactions and would allow their palladium complexes combined with Brønsted acids to offer a generally applicable strategy for the creation of asymmetric allylic C−H alkylation reactions with other nucleophiles bearing functionalities that can form hydrogen-bonding interaction with conjugate bases in situ generated from Brønsted acid cocatalysts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08236.

Experimental procedures and compound characterization data (PDF)
Crystallographic data for **3ao** (CIF)
Crystallographic data for **7** (CIF)
Crystallographic data for **8** (CIF)
NMR spectra and chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from MOST (973 Project 2015CB856600), NSFC (Grants 21232007, 21302177, and 21502183), Chinese Academy of Science (Grant XDB20020000), and the China Postdoctoral Science Foundation (Grant 2015M580534). We also thank professor Xue-Long Hou for his thoughtful suggestion.

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