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Enantioselective Terminal Addition to Allenes by Dual Chiral Primary Amine/Palladium Catalysis

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Supporting Information

ABSTRACT: We herein describe a synergistic chiral primary amine/achiral palladium catalyzed enantioselective terminal addition to allenes with α-branched β-ketocarbonyls and aldehydes. The reactions afford allylic adducts bearing acyclic all-carbon quaternary centers with high regio- and enantioselectivity. A wide range of allenes including those aliphatic or 1,1′-disubstituted could be employed, thus expanding the scope of typical asymmetric allylic alkylation reactions.

Owing to the intriguing 1,2-diene moiety, nucleophilic addition to allenes provided one of the most atom-economic approaches for the synthesis of functionalized allylic compounds by eliminating the need for both preinstalled leaving groups and a stoichiometric amount of base.[1,2] Recently, catalytic enantioselective versions have been actively pursued. Pioneering studies by Trost and Breit et al. have demonstrated highly efficient Pd and Rh catalyzed asymmetric addition to allenes, leading to regio- and enantioselective allylic C−C,[3] C−O,[4] C−N,[5] and C−X[6] bonds formation transformations. In most of these cases, the asymmetric transformation afforded branched allylic adducts (Scheme 1, I). Linear addition to allene has been known since the 1990s by the works of Trost and Yamamoto;[7] however, a catalytic enantioselective version remains undeveloped. On the other hand, though the addition of enamine to allenes was first reported in early 1973,[8] a highly enantioselective coupling has not been achieved. In 2012, Dixon reported a catalytic asymmetric intramolecular addition to allenes by a dual Pd/chiral amine catalysis with moderate enantioselectivity.[3d] Very recently, González[9a] and López[9b] independently reported dual amine and gold catalyzed intermolecular addition to allenes with α-branched aldehydes. However, those reactions were

Scheme 1. Enantioselective Addition to Allenes

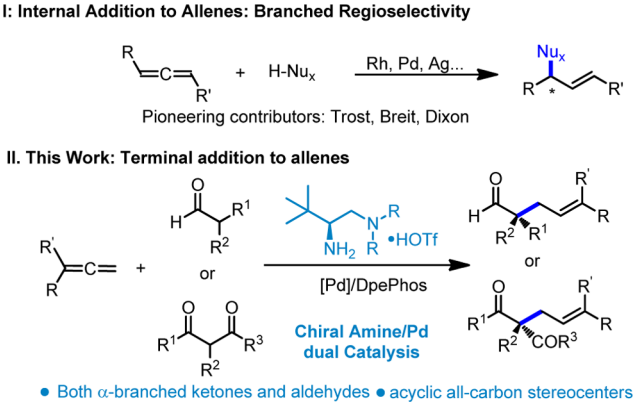
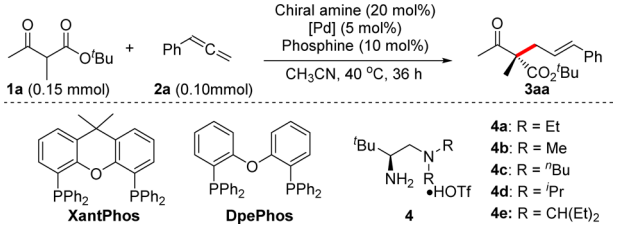


Table 1. Screening and Optimization[a]



Entry	[Pd] Source	Phoshine	Amine	Yield (%)	Ee (%)
1	$[Pd(allyl)Cl]_2$	PPh_3	**4a**	n.r.	–
2	$Pd_2(dba)_3$	PPh_3	**4a**	n.r.	–
3	$Pd(OAc)_2$	PPh_3	**4a**	n.r.	–
4	$[Pd(allyl)Cl]_2$	DPPE	**4a**	n.r.	–
5	$[Pd(allyl)Cl]_2$	DPPF	**4a**	trace	–
6	$[Pd(allyl)Cl]_2$	XantPhos	**4a**	65	30
7	$[Pd(allyl)Cl]_2$	DpePhos	**4a**	20	43
8	$[Pd(allyl)Cl]_2$	XantPhos	**4b**	72	4
9	$[Pd(allyl)Cl]_2$	XantPhos	**4c**	68	49
10	$[Pd(allyl)Cl]_2$	XantPhos	**4d**	78	81
11	$[Pd(allyl)Cl]_2$	XantPhos	**4e**	21	91
12[b]	$[Pd(allyl)Cl]_2$	XantPhos	**4e**	75	91
13[b]	$[Pd(allyl)Cl]_2$	DpePhos	**4e**	51	96
14[c]	$[Pd(allyl)Cl]_2$	DpePhos	**4e**	84	96
15	$[Pd(allyl)Cl]_2$	DpePhos	–	trace	–
16	–	–	**4e**	n.r.	–

[a]The reaction was performed with **1a** (0.15 mmol), **2a** (0.10 mmol), chiral amine (20 mol %), Pd precursor (5 mol %), and Phosphine (10 or 20 mol %) in 0.5 mL of CH_3CN at 40 °C for 36 h; isolated yield; the ee was determined by HPLC. [b]3 equiv of ketoester **1a** were used, and the reaction time was extended to 72 h. [c]The reaction was performed with 3 equiv of ketoester **1a** under 50 °C, 48 h.

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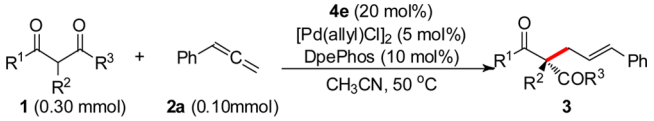
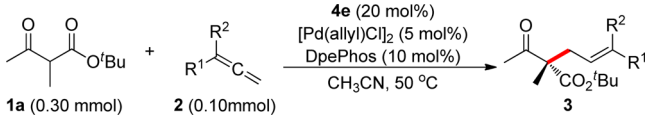
Table 2. Substrate Scope of β-Ketocarbonyls[a]



Entry	R^1	R^2	R^3	Product	Yield(%)	Ee(%)
1	Me	Me	O^{t}Bu	**3aa**	82	96
2	Me	Me	OEt	**3ba**	81	94
3	Me	Me	OAd	**3ca**	30	96
4	Me	Et	O^{t}Bu	**3da**	43	94
5	-$(CH_2)_4$-		OEt	**3ea**	78	95
6	-$(CH_2)_4$-		O^{t}Bu	**3fa**	96	95
7				**3ga**	91	93
8	Me	Me	Et	**3ha**	72	93
9	Me	Me	^{i}Pr	**3ia**	69	92
10	Me	Me	^{i}Bu	**3ja**	88	95
11	Me	Me	NHPh	**3ka**	71	65

[a]The reaction was performed with **1** (0.30 mmol), **2a** (0.10 mmol), **4e** (20 mol %), $[Pd(allyl)Cl]_2$ (5 mol %), and DpePhos (10 mol %) in 0.5 mL of CH_3CN at 50 °C for 40−72 h; isolated yield; the ee was determined by HPLC.

Table 3. Substrate Scope of Allenes 2[a]



Entry	R^1	R^2	Product	Yield (%)	Ee (%)
1	2-MeC_6H_4	H	**3ab**	73	92
2	3-MeC_6H_4	H	**3ac**	91	95
3	4-MeC_6H_4	H	**3ad**	74	95
4	2,6-$Me_2C_6H_3$	H	**3ae**	84	93
5	4-FC_6H_4	H	**3af**	60	94
6	4-ClC_6H_4	H	**3ag**	74	93
7	4-BrC_6H_4	H	**3ah**	70	96
8	2-Naphthyl	H	**3ai**	71	92
9	C_6H_5	Me	**3aj**	58	90
10	C_6H_5	C_6H_5	**3ak**	n.r.	
11	*c*-C_6H_{11}	H	**3al**	59	90
12	$Ph(CH_2)_3$−	H	**3am**	60	90
13	$CH_3(CH_2)_9$−	H	**3an**	67	96
14	$BnO(CH_2)_2$−	H	**3ao**	36	90
15	$MeO_2C(CH_2)_3$−	H	**3ap**	60	91
16	$AcO(CH_2)_3$−	H	**3aq**	65	90
17	$NC(CH_2)_3$−	H	**3ar**	52	92
18[b]	$PhthN(CH_2)_4$−	H	**3as**	75	78

[a]The reaction was performed with **1a** (0.30 mmol), **2** (0.10 mmol), **4e** (20 mol %), $[Pd(allyl)Cl]_2$ (5 mol %), and DpePhos (10 mol %) in 0.5 mL of CH_3CN at 50 °C for 40−72 h; isolated yield; the ee was determined by HPLC. [b]Ethyl 2-methyl-3-oxobutanoate **1b** (0.30 mmol) and XantPhos (10 mol %) were were used under otherwise identical conditions.

limited to allenamides and occurred through a gold-zwitterionic intermediate to afford the linear product with moderate enantioselectivity.[9] Highly enantioselective terminal addition to a broad range of allenes remains to be explored.

Herein, we reported a dual chiral primary amine/palladium catalysis for asymmetric terminal addition to allenes via enamine intermediates. The reaction could be applied to both α-branched aldehydes and ketones, leading to the formation of acyclic all-carbon stereocenters with high enantioselectivity.[10−12] Besides being highly atom-economic, the present allene addition protocol encompasses a wide range of allenes including aryl, aliphatic and 1,1′-disubstituted ones, thus significantly enlarging the scopes of the typical asymmetric allylic alkylation processes.

Mechanistically, the success of the current reaction relies on the generation of active π-allylic palladium species via hydrometalation as well as the compatibility of such a process with enamine formation. Based on our initial successes on achiral palladium/chiral primary amine catalysis,[13] different phosphine ligands were first examined in the reaction of *tert*-butyl 2-methyl-3-oxobutanoate **1a** (0.15 mmol) and allene **2a** (0.10 mmol) in the presence of chiral primary-tertiary amine **4a** (20 mol %), $[PdCl(C_3H_5)Cl]_2$ (5 mol %). Simple PPh_3 (20 mol %) did not work, not even with other palladium precursors such as $Pd_2(dba)_3$ and $Pd(OAc)_2$ (Table 1, entries 1−3). We speculated that a more electron-rich phosphine ligand may promote the formation of π-allylic palladium intermediates; a series of electron-rich and bidentate phosphine ligands were then tested (Table 1, entries 4−7). XantPhos was identified as an efficient ligand to afford the desired product **3aa** with a 65% yield and 30% ee; the less electron-rich and more flexible ligand DpePhos slightly increased the enantioselectivity, but the yield decreased dramatically (entry 7). We then investigated a variety of *tert*-leucine derived primary-tertiary amine catalysts (Table 1, entries 8−11) with variations on the tertiary amine moiety. It was found that the enantioselectivity was significantly influenced by the bulkiness of an amine catalyst. The most bulky catalyst **4e** gave a 91% ee (entries 11 and 12), a significant improvement over its smallest counterpart dimethylated **4b** (4% ee Table 1, entry 8). Eventually, aminocatalyst **4e** and DpePhos were identified to be the optimal combination, resulting in 96% ee and 84% yield under elevated temperature and a prolonged reaction time (Table 1, entries 13 and 14). Control experiments revealed that the reaction did not work in the absence of either a chiral primary amine catalyst or palladium complex, highlighting the synergistic nature of the dual catalysis.

With the optimized reaction conditions in hand, we then explored the functional group tolerance of a variety of β-ketocarbonyls. Different ester groups were tolerated to give a comparable ee with the activity being decreased with a more bulky one (Table 2, entries 2 vs 3). Substitution on the α-position of β-ketoesters significantly influenced the reactivity. The ethyl substituted substrate **1c** afforded the desired product **3da** with a 43% yield and 92% ee, while a benzyl substituted substrate only yielded a trace amount of product. To our delight, the carbon- and nitrogen-containing cyclic β-ketoesters **1e−1g** reacted smoothly and gave corresponding products with excellent yields and enantioselectivities (Table 2, entries 5−7). In particular, unsymmetrical 1,3-diketones were demonstrated to be applicable substrates herein, even with the subtle difference of the substituents on two carbonyl moieties as in

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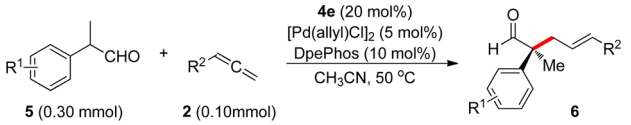
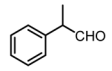
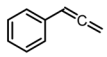
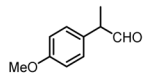
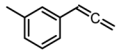
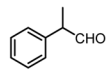
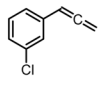
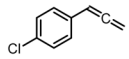
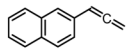
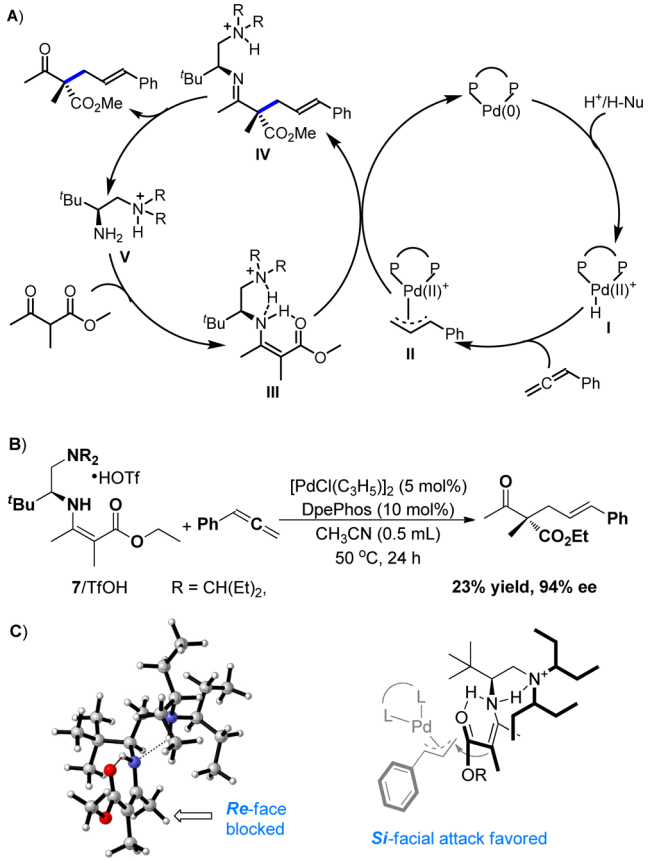
Table 4. Substrate Scope of Aldehydes and Allenes[a]



Entry	Aldehyde(**5**)	Allene(**2**)	Product	Yield (%)	Ee (%)
1			**6aa**	76	85
2			**6ba**	82	83
3			**6ab**	81	85
4			**6ac**	70	91
5			**6ad**	72	89
6			**6ae**	70	83

[a]The reaction was performed with **5** (0.30 mmol), **2** (0.10 mmol), **4e** (20 mol %), $[Pd(allyl)Cl]_2$ (5 mol %), and DpePhos (10 mol %) in 0.5 mL of CH_3CN at 50 °C for 40−72 h; isolated yield; the ee was determined by HPLC.

Scheme 2. Proposed Mechanism (A), Stoichiometric Experiment (B), and Stereocontrol Mode (C)



the case of methyl and ethyl which can be successfully recognized, affording the product with a 72% yield and 93% ee. Variations of one keto moiety of 1,3-diketones retained high yield and enantioselectivity (Table 2, entries 8−10). In addition, the β-ketoamide **3k** was also tolerated and gave the allylation product with a 71% yield and 65% ee.

The compatibility of various aryl, alkyl, and 1,1′-disubstituted allenes were also evaluated with *tert*-butyl 2-methyl-3-oxobutanoate (**1a**) under otherwise the same conditions. A range of monoaryl substituted allenes bearing either an electron-withdrawing or -donating group on the *para*-, *meta*-, or *ortho*- position all reacted smoothly to afford desired adducts with good to high yields and excellent enantioselectivities (Table 3, entries 1−10, 70−91% yields, 92−96% ee). The 2-naphthylallene was tested and yielded the product with a 71% yield and 93% ee. In addition, 1,1′-disubstituted allenes **2j** was also tolerated and afforded the corresponding adduct with a 58% yield and 90% ee, whereas the reaction was suppressed with 1,1′-diphenyl allene, and only the allene protonation product was observed, implicating that large steric hindrance was disfavored in the reaction. A series of alkyl substituted allenes also showed good reactivities and high enantioselectivities (Table 3, entries 11−14). Alkyl allenes with various different functional groups such as benzyl ether (**2o**), ester (**2p**), acetoxyl (**2q**), nitrile (**2r**), and phthalimidoyl (**2s**) can react smoothly to furnish the allylation products with moderate yields and high enantioselectivities, significantly expanding the scope of the allylic reaction with typical allylic reagents.[11,13]

We have also examined the reaction with α-branched aldehydes, for which a highly enantioselective version has not been reported. Under the identical conditions, 2-phenylpropanal and phenyl allene were coupled successfully to give the desired product with a 76% yield and 85% ee (Table 4, entry 1). The reactions also worked with other 2-arylaldehydes and allenes, affording the desired products with high enantioselectivities and good reactivities regardless of electronic and steric variation (Table 4, entries 2−6).

On the basis of previous studies, a synergistic chiral amine/achiral palladium catalytic cycle could be proposed as depicted in Scheme 2.[2,11] A hydropalladium complex **I** *in situ* formed underwent hydrocarbonation with allene to afford the key π-allyl-palladium species **II**, which then coupled with the enamine intermediate **III** to give the allylation product after hydrolysis. Stoichiometric experiment with preformed enamine 7 gave the desired adduct in 23% yield and 94% *ee* (Scheme 2B, vs Table 2, entry 2), thus verifying the enamine catalytic nature.[14] *Si*-facial attack of π-allylpalladium to the enamine intermediate can be proposed to account for the observed stereoinduction (Scheme 2, **C**). Steric effect is the major stereocontrol factor. The DFT optimized structure of enamine **III** clearly shows that the bulky tertiary amino moiety would block attack onto the enamine *Re*-face, facilitating a favorable *Si*-facial attack. The observed bulky substituent effect of the tertiary amino moiety is clearly in agreement with this model. The steric effect may also explain the exclusive linear selectivity in the allene addition step.

In conclusion, we have developed a catalytic enantioselective terminal addition to allenes by the synergistic enamine/palladium catalysis with a chiral primary amine as the sole chiral source. The reaction could be generally applied to α-branched aldehydes and ketones to afford allylic adducts bearing acyclic all-carbon quaternary centers. The strategy

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features an atom-economical process under rather mild conditions and expands the scopes of typical allylic reagents to include 1,1-disubstituted and alkyl allyl fragments in C−C bond formation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b00437.

Experimental details, characterization of new compounds, and computational studies (PDF)

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Notes

The authors declare no competing financial interest.

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