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

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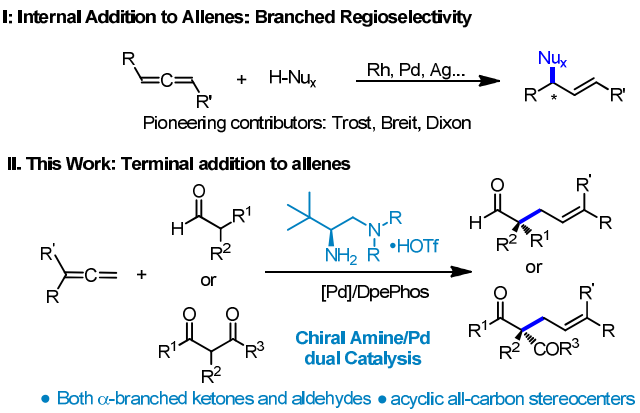
Supporting Information Placeholder

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 affords 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 scopes 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 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 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 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.

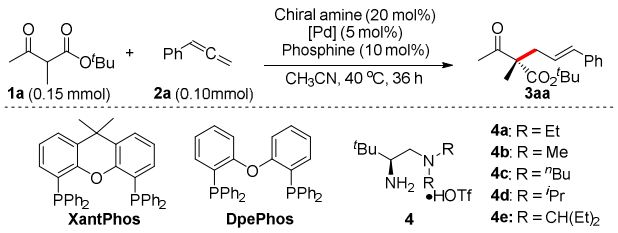
Herein, we reported a dual chiral primary amine/palladium catalysis for asymmetric terminal additions to allenes via enamine intermediates. The reactions could be applied to both α-branched aldehydes and ketones, leading to the formation of acyclic all-carbon stereocenters with high enantioselectivity.[10-12] 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.

Scheme 1. Enantioselective Addition to Allenes



Mechanistically, the success of the current reaction relies on the generation of active π-allylic palladium species via hydrometallation as well as the compatibility of such a process with enamine formation. Based on our initial successes on chiral Palladium/chiral primary amine catalysis,[11] different phosphine ligands were firstly 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, neither together with other palladium precursors such as $Pd_2(dba)_3$ and $Pd(OAc)_2$ (Table 1, entries 1-3). We speculated that 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 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 catalyst (Table 1, entries 8-11) with variations on tertiary amine moiety. It was found that the enantioselectivity was significant influenced by the bulkiness of amine catalyst. The most bulky catalyst **4e** gave 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 was identified to be the optimal combination, resulting in 96% ee and 84% yield under elevated temperature and prolonged reaction time (Table 1, entries 13 and 14). Control experiments revealed that the reaction didn't work in the absence of either chiral primary amine catalyst or palladium complex, highlighting the synergistic nature of the dual catalysis.

Table 1: Screening and Optimization[a]

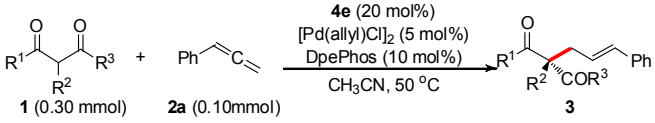


Entry	[Pd] source	Phoshine	Amine	Yield(%)	Ee(%)
1	$[Pd(allyl)Cl]_2$	PPh_3	**4a**	n. r.	-
2	$Pd_2(dba)_3$	PPh_3	**4a**	n. r.	-
3	$Pd(OAc)_2$	PPh_3	**4a**	n. r.	-
4	$[Pd(allyl)Cl]_2$	DPPE	**4a**	n. r.	-
5	$[Pd(allyl)Cl]_2$	DPPF	**4a**	trace	-
6	$[Pd(allyl)Cl]_2$	XantPhos	**4a**	65	30
7	$[Pd(allyl)Cl]_2$	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 CH_3CN at 40 °C for 36 h, isolated yield, the ee was determined by HPLC. [b] 3 equiv. of ketoester **1a** was 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.

With the optimized reaction conditions in hand, we then explored the functional group tolerance of a variety of ß-ketocarbonyls. Different ester group was tolerated to give comparable ee with the activity being decreased with more bulky one (Table 2, entries 2 vs 3). Substitution on α-position of β-ketoesters significant infulent the reactivity, the ethyl substituted substrate **1c** afforded the desired product **3da** with 43% yield and 92% ee, while benzyl substituted substrate only yielded trace amount product. To our delight, the carbon and nitrogen containing cyclic β-ketoesters **1e-1g** reacted smoothly and gave corresponding products with excellent yield and enantioselectivies (Table 2, entries 5-7). In particular, unsymmetrical 1,3-diketones were demonstrated applicable substrates herein, even with subtle difference of the substitutents on two carbonyl moieties such as methyl and ethyl can be successfully recongnized and afforded the product with 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 71% yield and 65% *ee*.

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

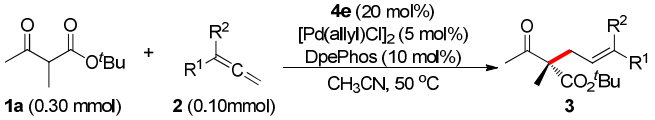


Entry	R^1	R^2	R^3	Product	Yield(%)	Ee(%)
1	Me	Me	O^{t}Bu	**3aa**	82	96
2	Me	Me	OEt	**3ba**	81	94
3	Me	Me	OAd	**3ca**	30	96
4	Me	Et	O^{t}Bu	**3da**	43	94
5	-$(CH_2)_4$-		OEt	**3ea**	78	95
6	-$(CH_2)_4$-		O^{t}Bu	**3fa**	96	95
7				**3ga**	91	93
8	Me	Me	Et	**3ha**	72	93
9	Me	Me	^{i}Pr	**3ia**	69	92
10	Me	Me	^{t}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 CH_3CN at 50 °C for 40-72 h, isolated yield, the ee was determined by HPLC.

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 electron-withdrawing or electron-donating groups on *para*-, *meta*- or *ortho*- position all reacted smoothly to afford desired adducts with good to high yields and excellent enantioselectivities (Table 2, entries 1-10, 70-91% yields, 92-96% ee). The 2-naphthylallene was tested and yielded the product with 71% yield and 93% ee. In addition, 1,1'-disubstituted allenes **2j** was also tolerated and afforded the corresponding adduct with 58% yield and 90% ee, whereas the reaction was suppressed with 1,1'-diphenyl allene, only the allene protonation product was observed, implicate that large steric hindrance was disfavored to the reaction. A series of alkyl substituted allenes also showed good reactivities and high enantioselectives (Table 3, entries 14-17). 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 enantioselectives, significantly expanding the scope of the allylic reaction with typical allylic reagents.[11,13]

Table 3: Substrate Scope of Allenes 2[a]

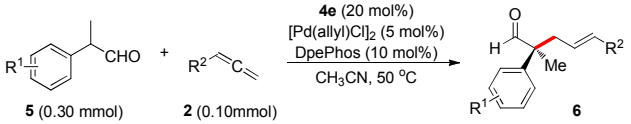


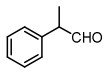
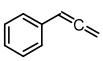
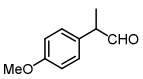
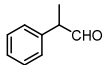
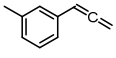
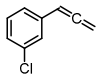
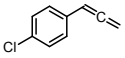
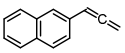
Entry	R^1	R^2	Product	Yield(%)	Ee(%)
1	2-MeC_6H_4	H	**3ab**	73	92
2	3-MeC_6H_4	H	**3ac**	91	95
3	4-MeC_6H_4	H	**3ad**	74	95
4	2,6-$Me_2C_6H_3$	H	**3ae**	84	93
8	4-FC_6H_4	H	**3af**	60	94
9	4-ClC_6H_4	H	**3ag**	74	93
10	4-BrC_6H_4	H	**3ah**	70	96
11	2-Naphthyl	H	**3ai**	71	92
12	C_6H_5	Me	**3aj**	58	90
13	C_6H_5	C_6H_5	**3ak**	n. r.	
14	*c*-C_6H_{11}	H	**3al**	59	90
15	$Ph(CH_2)_3$-	H	**3am**	60	90
16	$CH_3(CH_2)_9$-	H	**3an**	67	96
17	$BnO(CH_2)_2$-	H	**3ao**	36	90
18	$MeO_2C(CH_2)_3$-	H	**3ap**	60	91
19	$AcO(CH_2)_3$-	H	**3aq**	65	90
20	$NC(CH_2)_3$-	H	**3ar**	52	92
21[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 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.

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 was coupled successfully to give the desired product with 76% yield and 85% ee (Table 1, 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).

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

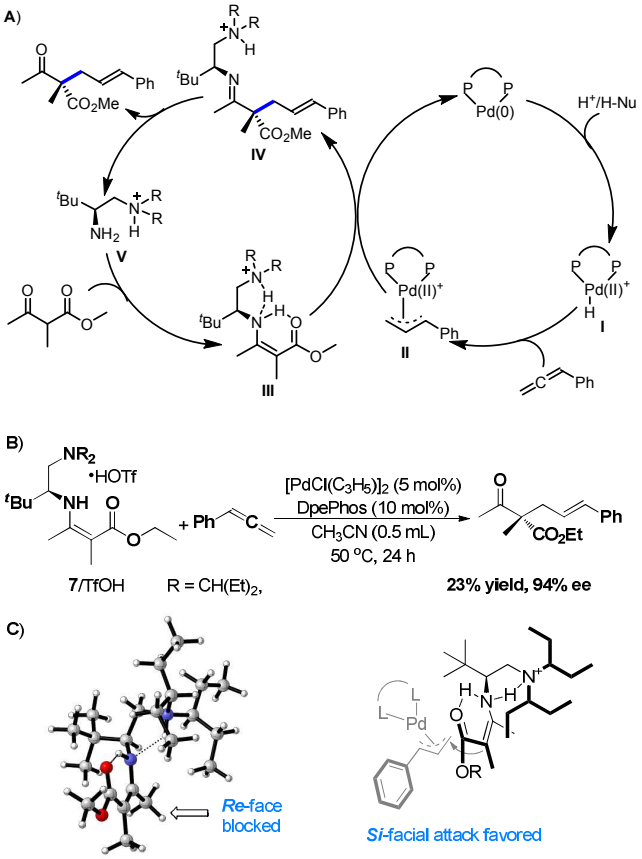


Entry	Aldehyde(**5**)	Allene(**2**)	Product	Yield (%)	Ee (%)
1			**6aa**	76	85
2			**6ba**	82	83
3			**6ab**	81	85
4			**6ac**	70	91
5			**6ad**	72	89
6			**6ae**	70	83

[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 CH_3CN at 50 °C for 40-72 h, isolated yield, the ee was determined by HPLC.

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 experiments with preformed enamine **7** gave the desired adduct in 27% yield and 94% *ee* (Scheme 2**B**, 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. 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 substituents effect of the tertiary amino moiety is clearly in line with this model. The steric effect may also explain the exclusive linear selectivity in the allene addition step.

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



In conclusion, we have developed a catalytic enantioselective terminal addition to allenes by the synergistic enamine/palladium catalysis with 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 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

Experimental details, characterization of new compounds and computational studies. 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.

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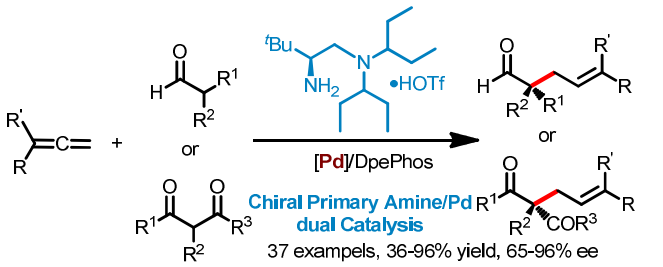
Graphic abstract



• Both α-branched ketones and aldehydes • acyclic all-carbon stereocenters