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Catalytic Conjugate Addition of Allyl Groups to Styryl-Activated Enones

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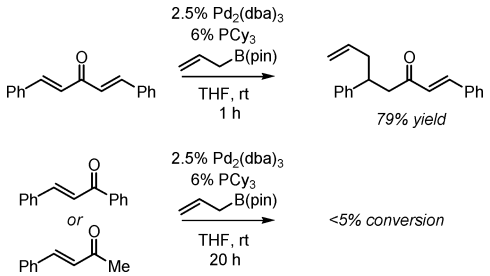
Transition-metal-catalyzed conjugate addition of organometallics to activated alkenes is an important process.[1] Intense research has focused on the utility of copper[2] and rhodium catalysts for asymmetric additions,[3] and recent efforts have led to the introduction of effective palladium[4] catalysts. Each catalyst system exhibits a unique reactivity profile. The rhodium-catalyzed asymmetric conjugate addition, first introduced by Hayashi and Miyaura,[5] is effective with many activated alkenes, and it may employ boronic acids in addition to a variety of other organometallic reagents (i.e., silanes,[6] stannanes,[7] titanates,[8] and zincates[9]). However, the reaction is limited by the requirement that the organic fragment must be an aryl or vinyl group. Copper catalysis enables the asymmetric conjugate addition of alkyl-derived organometallics, although air-sensitive organozinc and magnesium reagents are generally required.[2,10] Significantly, neither rhodium, copper, nor palladium catalysis has been extended to the enantioselective addition of allyl nucleophiles.[11] In this report, we describe the catalytic conjugate allylation of enones with the pinacol ester of allylboronic acid [allylB(pin)]. This is an unprecedented reactivity mode for allylboron compounds, reagents that typically react by 1,2-addition to carbonyls.

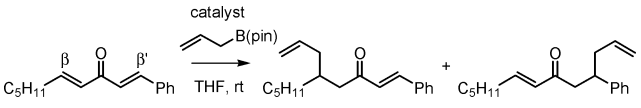
During our studies on the Pd-catalyzed asymmetric diboration of allenes, we made the surprising observation that the allylboron product undergoes conjugate addition to dibenzylidene acetone, the ligand on the $Pd_2(dba)_3$ precatalyst.[12] Examination of this side reaction was conducted with commercially available air-stable allylB(pin) and a variety of activated alkenes, in the presence of $Pd_2(dba)_3$ and PCy_3. Whereas simple unsaturated ketones, esters, amides, imides, and nitriles afford little addition product, the reaction with dibenzylidene acetone is remarkably efficient. The experiments summarized in Scheme 1 illustrate the rapidity with which the reaction occurs, so long as an appropriate catalyst is employed and the enone is activated by an auxiliary styryl unit; in the absence of either, no reaction occurs.

Scheme 1



Refinement of the catalytic conjugate allylation for use in a broad array of synthesis settings requires an efficient reaction that applies to nonsymmetric dialkylidene ketones and is highly site-selective. As depicted in Table 1, the palladium-catalyzed addition of allylB(pin) to nonsymmetric ketone **1** proceeds in good yields with electron-rich phosphine ligands such as PCy_3 and $P(NMe_2)_3$.[13] However, the reactions with these catalysts generally provide low regioselectivity. Alternatively, when $Ni(cod)_2$ and PCy_3 were used, the addition occurred with good selectivity for the alkylidene site, and the reaction product was isolated in 82% yield after only 4 h at room temperature.

Table 1. Catalyst Survey for Conjugate Allylation



1 ***β addition*** ***β' addition***

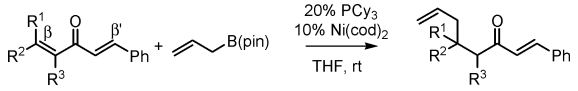
metal	ligand	time (h)	β:β' [a]	% yield[b]
2.5% $Pd_2(dba)_3$	6% PCy_3	2	n/a	<5
2.5% $Pd_2(dba)_3$	6% PCy_3	16	73:27	67
2.5% $Pd_2(dba)_3$	6% $P(NMe_2)_3$	2	50:50	76
2.5% $Pd_2(dba)_3$	6% PPh_3	2	50:50	18
2.5% $Pd_2(dba)_3$	6% $P(OPh)_3$	2	36:64	17
10% Ni(cod)$_2$	***20% PCy$_3$***	***4***	***88:12***	***82***
10% $Ni(cod)_2$	20% $P(NMe_2)_3$	4	71:29	81
10% $Ni(cod)_2$	20% PPh_3	4	52:48	55
10% $Ni(cod)_2$	20% $P(OPh)_3$	4	70:30	49

[a] Regioselectivity determined by ^{1}H NMR analysis of unpurified reaction mixture. [b] Yield of conjugate addition product after silica gel chromatography. Value is an average of two experiments in each case.

A number of enones bearing the styryl activating group participate in the catalytic conjugate allylation (Table 2). With the exception of the allylic ether in entry 5, all substrates reacted with good to excellent regioselectivity. Notably, the trisubstituted alkenes in entries 8 and 9 undergo conjugate addition exclusively at the more hindered site and provide the desired products in good yield. It is notable that the allyl ether in entry 5 delivered the conjugate addition product in good yield even though the allyl ether functionality is known to participate in allylic substitution reactions with boronic acids under Ni(0) catalysis.[14]

Strategies for manipulation and cleavage of the styryl auxiliary have been examined. As depicted in Scheme 2, the styryl unit

Table 2. Ni-Catalyzed Conjugate Allylation of Styryl Ketones



entry	R^1	R^2	R^3	time (h)	β:β' [a]	% yield[b]
1	H	C_5H_{11}	H	4	88:12	82
2	H	CH_3	H	24	95:5	75
3	H	Cy	H	4	83:17	83
4	H	*t*-Bu	H	4	>95:5	74
5	H	CH_2OTBS	H	24	61:39	66
6	H	$(CH_2)_2OTBS$	H	7	85:15	82
7	H	Ph	H	4	n/a	74
8	CH_3	CH_3	H	24	>95:5	80[c]
9	H	CH_3	CH_3	24	>95:5	76[c,d]

[a] Determined by ^{1}H NMR analysis of unpurified reaction mixture. [b] Yield of conjugate addition product after silica gel chromatography. Value is an average of two experiments in each case. [c] Reaction at 65 °C. [d] Product consists of a 1.4:1 diastereomer mixture.

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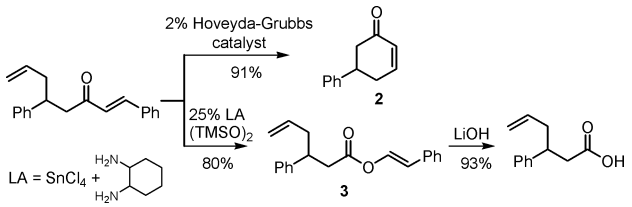
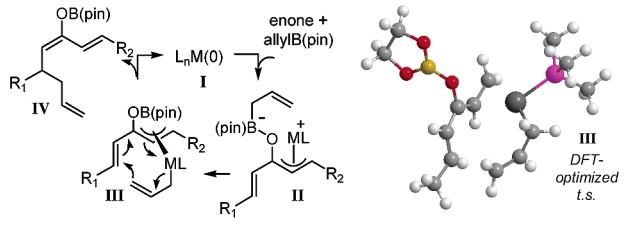
Scheme 2



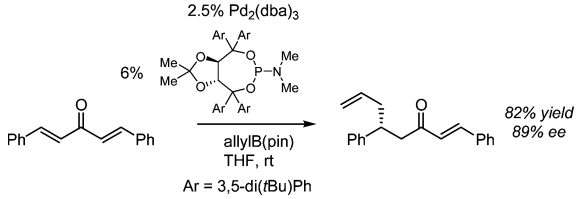
provides a convenient handle for alkene metathesis, and a ring-closing version was readily accomplished with the NHC-derived Hoveyda−Grubbs catalyst to give cyclohexenone **2**, a compound which is not readily available from other catalytic methods.[15] Alternatively, regioselective Baeyer−Villiger oxidation can be accomplished by treatment of the conjugate allylation product with trimethylsilylperoxide in the presence of Lewis acid.[16] This transformation selectively provides enol ester **3** which can be readily converted to a variety of functional groups, including the derived carboxylic acid (see Scheme 2).

Pd(trifluoroacetate)$_2$ and Ni(acac)$_2$ are ineffective catalysts for the conjugate addition of allylB(pin) (<5% conversion). This observation suggests that the reaction is not initiated by transmetalation of the boronic ester with the catalyst as is observed for Rh(I)-[17] and Pd(II)-catalyzed[4d] conjugate additions. On the basis of recent studies by Ogoshi and Kurosawa[18] and earlier work by Mackenzie,[19] it is plausible that these reactions proceed by Lewis acid induced oxidative addition of Pd(0) and Ni(0) to the enone, as depicted in Scheme 3 (**I** → **II**). The unique ability of the styryl unit to activate the adjacent enone for reaction is likely to arise from accelerated oxidative addition or reductive elimination. Recent calculations by Echavarren suggest that reductive elimination of bis(allyl)Pd complexes in the presence of donor ligands proceeds by initial conversion to a slightly higher energy bis(η^1-allyl) complex, from which reductive elimination by 3,3′-coupling is significantly more facile.[20] It is plausible that dialkylidene ketones participate in a similarly favorable 3,3′-reductive elimination (Scheme 3, **III** → **IV**) but do so without adopting the higher energy bis(η^1-allyl) bonding mode. DFT calculations (B3LYP; Stuttgart RSC 1997 ECP for Pd, 6-311+G* for others) suggest that reductive elimination of a model substrate (**III**, R_1 = Me, R_2 = H, M = Pd, L = PMe_3) faces a small barrier (1.52 kcal/mol) for a reductive coupling as shown; in contrast, a substrate with a methyl in place of the pendent alkene faces a significantly higher barrier for coupling (13.5 kcal/mol for 1,2-addition; 21.66 kcal/mol for the 1,4-adduct).[21]

Scheme 3



Scheme 4



On the basis of the hypothesis that donor ligands are intimately involved in the reductive elimination step, the conjugate allylation of dibenzylidene acetone was examined in the presence of chiral ligands. As depicted in Scheme 4, this preliminary survey revealed that appreciable levels of asymmetric induction can be observed in the catalytic conjugate allylation. Further experiments along these lines will be reported in due course.

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Supporting Information Available: Characterization and procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Consistent with the calculated lowest energy transition structure, quenching the reaction with TMS-imidazole provides the *E*-enolsilane.

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