

Palladium- and Copper-Catalyzed 1,4-Additions of Organozinc Compounds to Conjugated Aldehydes

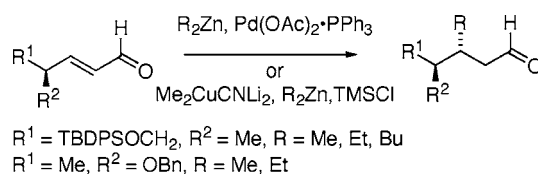
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ABSTRACT



Conjugated aldehydes undergo smooth $\text{Pd}(\text{OAc})_2\cdot\text{PPh}_3$ - or $\text{Me}_2\text{CuCNLi}_2$ -catalyzed 1,4-addition of dialkylzinc reagents.

In recent years, we have developed a methodology for converting enantiopure propargylic mesylates to chiral allenylindium and -zinc reagents. Additions of these reagents to aldehydes afford *anti*-homopropargylic alcohols of high enantiomeric and diastereomeric purity.¹ The allenyl reagents are formed in situ from the mesylate and InI or Et₂Zn in the presence of 5 mol % of $\text{Pd}(\text{OAc})_2\cdot\text{PPh}_3$ (Figure 1).

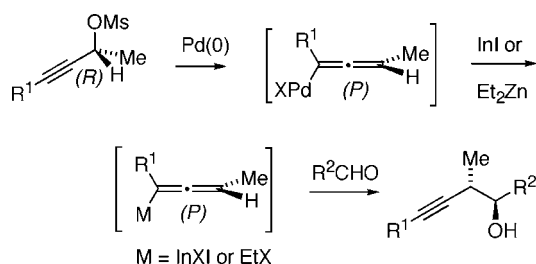


Figure 1. Preparation of allenylindium and -zinc reagents from propargylic mesylates and in situ additions to aldehydes.

In the course of recent studies on additions of allenylzinc reagents, prepared from propargylic mesylates as described above, to conjugated aldehydes, we encountered an unfore-

seen side reaction in which an ethyl group from the diethylzinc was transferred to the β -position of (*E*)-2-heptenal in a 1,4-addition reaction (Figure 2).² In a separate experi-

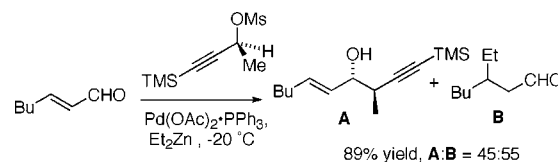


Figure 2. Unexpected 1,4-addition of diethylzinc to an enal accompanying the in situ generation of an allenylzinc reagent.

ment, we found that the 1,4-ethyl adduct was produced in high yield from the enal and diethylzinc in the presence of 5 mol % of $\text{Pd}(\text{OAc})_2$ without the propargylic mesylate. No reaction was observed in the absence of the Pd catalyst.

1,4-Additions to conjugated double bonds are generally effected with organocuprates. However, reactions of cuprates with enals typically afford mixtures of 1,4- and 1,2-adducts. The use of less-nucleophilic cyanocuprates³ or Normant magnesio cuprates^{4,5} tends to favor the 1,4-adducts compared to reactions involving Gilman-type cuprates. Also, perform-

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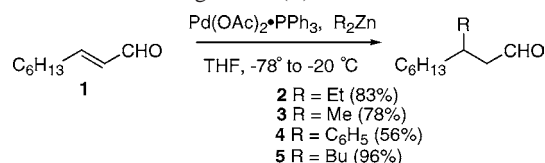
(2) Marshall, J. A.; Eidam, P.; Eidam, H. S. *J. Org. Chem.* **2006**, *71*, 4840.

ing the additions in the presence of TMSCl leads to enhanced ratios of 1,4- to 1,2-adducts.^{3,5,6} These reactions are strongly accelerated by the added TMSCl.

Kurosawa and co-workers studied Pd(0)-catalyzed 1,4-additions of disilanes to cinnamaldehyde and crotonaldehyde in the presence of TMSOTf, which led to mixtures of (*E*)- and (*Z*)-enol silanes of the 1,4-adducts together with silyl ethers of the 1,2-adducts.⁷ On the basis of X-ray crystal structures, they surmised that η^2 and η^3 palladium complexes of the enal substrates are involved in these reactions. Additionally, the Pd complex of acrolein coordinated to BF₃ undergoes O-methylation with methyl triflate to produce the corresponding enol ether Pd complex.⁸ Nickel-catalyzed 1,4-additions of organozinc reagents to enals and (mainly) enones are known,^{9,10} but analogous palladium-catalyzed additions have not been reported. To appraise the scope and potential synthetic applications of such additions, we undertook the following investigations.

Using (*E*)-2-nonenal (**1**) as our prototype aldehyde, we found that the commercially available diethyl-, dimethyl-, and diphenylzinc reagents afford the 1,4-adducts **2–4** in satisfactory yield in the presence of 5 mol % of the Pd(OAc)₂·PPh₃ precatalyst in THF (Scheme 1). Dibutylzinc,

Scheme 1. Pd(0)-Catalyzed 1,4-Additions of Organozinc Reagents to (*E*)-Nonenal



prepared according to Noller,¹¹ was also a ready participant in the 1,4-addition.

The diethylzinc additions were extended to a number of different conjugated aldehydes and a representative enone (Table 1). Comparable yields of 1,4-adducts were obtained from reactions in which the PPh₃ ligand was not present. However, purification of the products was more difficult in those reactions owing to the precipitation of persistent palladium byproducts. Attempts to effect 1,4-additions to

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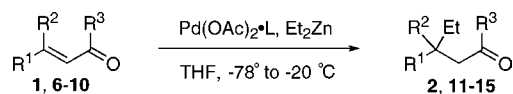
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Table 1. Pd(0)-Catalyzed 1,4-Additions of Organozinc Reagents to Conjugated Enals **1** and **6–9** and Enone **10**



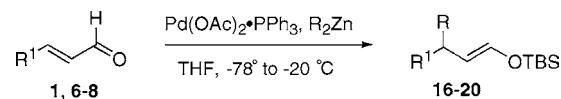
R ¹	R ²	R ³	product	yield, % ^a	yield, % ^b
C ₆ H ₁₃	H	H (1)	2	83	92
TBDPSO(CH ₂) ₃	H	H (6)	11	73	76
c-C ₆ H ₁₁	H	H (7)	12	89	90
C ₆ H ₅	H	H (8)	13	52	51
(CH ₃) ₂ C=CH(CH ₂) ₂	CH ₃	H (9)	14	80	80
c-C ₆ H ₁₁	H	CH ₃ (10)	15	79	–

^a L = PPh₃. ^b No ligand.

conjugated acyl oxazolidinones, esters, or nitriles were unsuccessful. Only starting materials were recovered from these experiments.

Following the precedent of cuprate 1,4-additions, we investigated the effect of added TMSCl on the Pd-catalyzed 1,4-addition of diethylzinc to (*E*)-2-nonenal. Unlike the enhancements observed in cuprate reactions, the presence of TMSCl in the palladium-catalyzed reactions inhibited the addition and resulted in diminished yields of the 1,4-adduct and multiple side products. On the other hand, yields of the 1,4-adducts were comparable or slightly higher when the reaction mixtures were quenched with TBSOTf to afford the isolable enol silane adducts (Table 2). Presumably, this

Table 2. Pd(0)-Catalyzed 1,4-Additions of Organozinc Reagents to Conjugated Enals and Subsequent in Situ Enolate Trapping with TBSOTf



R ¹	R	product	yield, %	(<i>E</i>)/(<i>Z</i>)
C ₆ H ₁₃ (1)	Et	16	92	>20:1
C ₆ H ₁₃ (1)	Bu	17	62	12:1
TBDPSO(CH ₂) ₃ (6)	Et	18	95	>20:1
c-C ₆ H ₁₁ (7)	Et	19	70	>20:1
C ₆ H ₅ (8)	Et	20	51	7:1

procedure minimizes side reactions of the intermediate zinc enolates such as oxidation, aldol condensation, and Michael additions.¹² The (*E*) isomers were highly favored products of these reactions. A possible mechanistic pathway is outlined in Figure 3.

Our next series of experiments was conducted to determine the effect of a γ -stereocenter on the stereoselectivity of the addition. Aldehyde **21** was prepared by Wittig homologation

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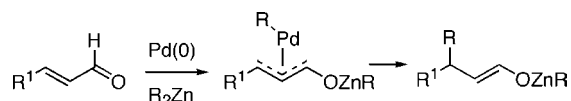
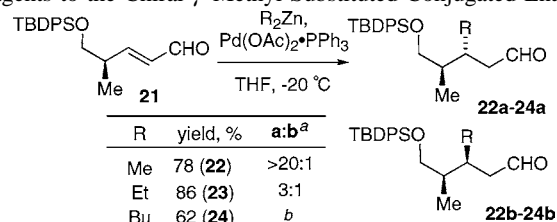


Figure 3. Possible mechanistic pathway for Pd(0)-catalyzed 1,4-additions of R_2Zn to conjugated enals.

of the known aldehyde precursor¹³ with ethyl phosphonoacetate followed by reduction of the conjugated ester and MnO_2 oxidation of the resulting allylic alcohol. Interestingly, the Me_2Zn reaction afforded a single diastereomer whereas the ethyl and butylzinc reagents yielded mixtures favoring one isomer (Table 3). The stereochemistry of the methyl adduct

Table 3. Pd(0)-Catalyzed 1,4-Additions of Organozinc Reagents to the Chiral γ -Methyl-Substituted Conjugated Enal **21**

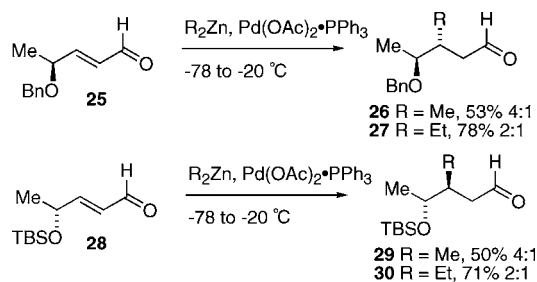


^a Ratios determined from integration of the 1H NMR spectra. ^b Not determined because of overlapping signals.

was determined by silyl cleavage and oxidation to the known *cis*- β,γ -dimethyl δ -valerolactone.¹⁴ The ethyl and butyl analogues **23** and **24** were assigned by analogy.

Additions to the γ -benzyloxy¹⁵ and silyloxy enals¹⁶ **25** and **28** by dimethyl- and diethylzinc proceeded analogously (Scheme 2). Here, too, the methyl reagent proved more

Scheme 2. Pd(0)-Catalyzed 1,4-Additions of Organozinc Reagents to Chiral γ -Benzyloxy- and Silyloxy-Substituted Conjugated Enals



selective. The stereochemistry of the 1,4-adducts **26** and **29** was ascertained through independent synthesis (see the Supporting Information for details).

In light of the previously cited findings of Kurosawa and co-workers on Pd(0) complexes of crotonaldehyde, the stereochemical preferences for the 1,4-additions must origi-

nate with η^2 and/or η^3 complexes of the palladium catalyst with the substrate enal.⁸ Likely possibilities for enals **21** and **25** are illustrated in Figure 4.¹⁷

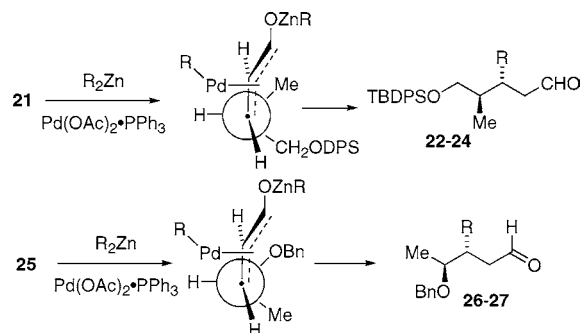
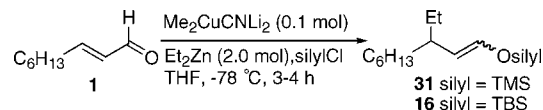


Figure 4. Transition-state rationale for stereoselectivity in 1,4-enal additions.

Considering the obvious analogy between these conjugate additions and 1,4-cuprate additions, we decided to briefly explore a direct comparison of the two. As noted in the introduction, cuprate additions to enals are typically plagued by competing 1,2-additions. Indeed, reactions of enal **21** with lithio cyanocuprate and Normant magnesiocuprate reagents afforded mixtures of 1,4- and 1,2-adducts accompanied by unidentified byproducts.⁴ Following these unsuccessful attempts, we came across a recent study by Lipschutz and co-workers in which $Me_2CuCNLi_2$ was used to catalyze the 1,4-addition of organozinc compounds to enones.⁵ The reported reactions were markedly accelerated by the presence of $TMSCl$. In the published report, 5–20 mol % of cyanocuprate was employed with up to 10 equiv of $TMSCl$, depending on the nature of the zinc reagent and the enone. We applied the Lipschutz procedure to (*E*)-2-nonenal (**1**) with 10 mol % of the cuprate catalyst. Under these conditions, the 1,4-adduct **2** was obtained in 42% yield along with 40% of the derived enol silanes **31** as a 1:1.4 mixture of the (*E*) and (*Z*) isomers (Table 4). When $TMSCl$ was replaced with $TBSCl$, the reaction rate greatly decreased and the enol silane adducts were obtained in low yield, also as a 1:1.4 *E/Z*

Table 4. Silyl-Promoted Copper-Catalyzed 1,4-Additions of Et_2Zn to (*E*)-2-Nonenal

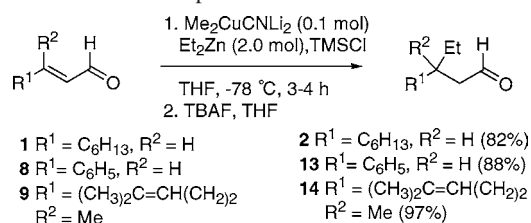


silylCl	yield, %	(<i>E</i>)/(<i>Z</i>)
$TMSCl$	40 ^a (31)	1:1.4
$TBSCl$	15 (16)	1:1.4
none ^b	15 (16)	>20:1

^a 42% of the aldehyde 1,4-adduct was obtained. ^b The reaction was quenched with $TBSOTf$.

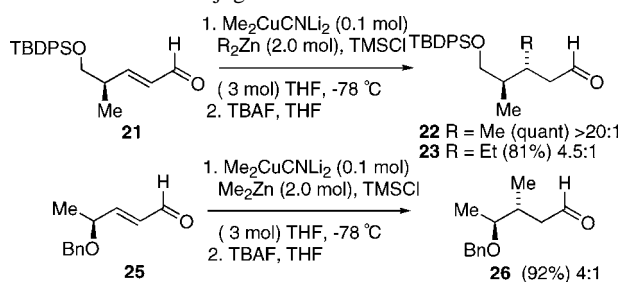
mixture. As expected, in the absence of a silylating reagent, the copper-catalyzed addition was extremely slow. However, upon quenching with TBSOTf, this reaction afforded the (*E*)-enol silane **16** as the sole product in 15% yield along with recovered enal. Evidently, the silane reagents, when initially present, play a direct role in the addition phase of the reaction.⁶ Additional examples of the copper-catalyzed additions are shown in Scheme 3.

Scheme 3. Copper-Catalyzed 1,4-Additions of Et₂Zn to Representative Enals



Extending the comparison between copper- and palladium-catalyzed 1,4-additions, we applied the Lipschutz procedure to the chiral enals **21** and **25** (Scheme 4). Both dimethyl-

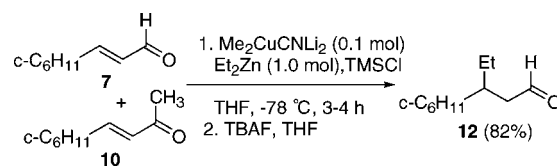
Scheme 4. Copper-Catalyzed 1,4-Additions of Organozinc Reagents to Chiral γ -Methyl- and Benzyloxy-Substituted Conjugated Enals **21** and **25**



and diethylzinc added rapidly at -78 °C affording the 1,4-adducts **22**, **23**, and **26** after brief treatment with TBAF, in high yield and with stereoselectivity comparable to that of the Pd-catalyzed reactions.

To evaluate potential selectivity issues, we conducted a competition experiment between (*E*)-3-cyclohexyl-2-propenal (**7**) and the related enone **10** for 1 equiv of diethylzinc (Scheme 5). The Pd-catalyzed reaction afforded the 1,4-

Scheme 5. Competition Experiment to Assess Relative Reactivity of Enals vs Enones in Cuprate-Catalyzed 1,4-Additions



adduct **12** in 42% yield along with an inseparable mixture of starting materials and unidentified byproducts, whereas the cuprate-catalyzed addition showed excellent selectivity for the enal. The 1,4-adduct **12** was obtained in 82% yield, and most of the unreacted enone was recovered.

In summary, we have found conditions for effecting selective Pd-catalyzed 1,4-additions of organozinc reagents to conjugated enals without competing 1,2-additions. The intermediate zinc enolates can be efficiently trapped with TBSOTf to afford (*E*)-enol silanes. We have also found that the Lipschutz methodology for cyanocuprate-catalyzed 1,4-additions of dialkylzinc reagents to conjugated ketones can be applied to aldehydes. The diastereoselectivity of additions to conjugated aldehydes possessing a stereocenter at the γ -position is consistent with the intermediacy of a π -allyl Pd or Cu species. Finally, we have conducted a preliminary experiment that suggests a useful selectivity for conjugated enals over enones in the copper-catalyzed additions.

Supporting Information Available: Experimental procedures, spectra, and analytical data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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