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Effect of ligands on the divalent palladium-catalyzed carbon–carbon coupling reactions. Highly enantioselective synthesis of optically active γ-butyrolactones*

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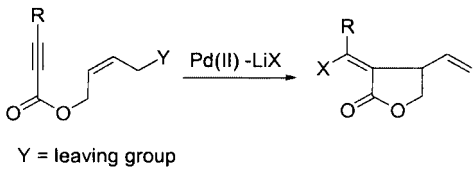
Abstract: In the palladium(II)-catalyzed enyne coupling reactions, the nitrogen-containing ligand plays the same role as the halide ion to inhibit the β-hydride elimination. Employing the pymox or bisoxazoline as ligands, the catalytic asymmetric cyclization of (Z)-4'-acetoxy-2'-butenyl 2-alkynoates initiated by acetoxypalladation was established with high efficiency (up to 92% ee) to afford the optically active γ-butyrolactones.

INTRODUCTION

The use of transition-metal catalysts in the carbocyclization of enynes offers the unique means to construct a variety of synthetically important carbocycles and heterocycles with high efficiency not normally accessible by traditional methods [1]. Despite the development of numerous catalytic carbocyclization protocols, highly enantioselective reactions remain limited [1c,2].

In our ongoing studies in the palladium(II)-catalyzed enyne coupling reactions, we have developed several efficient methods to construct the γ-butyrolactone structure from the readily available acyclic allylic 2-alkynoate precursors [3]. For example, using the versatile Pd(II)-LiX (X = halide ion) system, the α-alkylidene-γ-butyrolactones could be easily assembled from the starting material 4'-X-2'-butenyl 2-alkynoates through a halopalladation-olefinic insertion-β-heteroatom elimination sequence (Scheme 1). Our long-standing goal is to develop a corresponding enantioselective process due to the wealth of the naturally occurred chirality in biologically active γ-butyrolactones.



Scheme 1

ROLE OF HALIDE IONS

In the reaction shown in Scheme 1, halide ion concentration significantly influences the *Z/E* selectivity of the exocyclic double bond. More recently, we discovered a series of Pd(II)-catalyzed nucleophile-alkyne-α,β-unsaturated carbonyl tandem additions where the halide ligand exhibits a more dramatic

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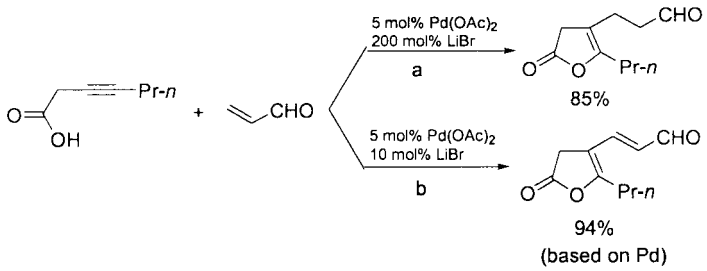
influence on the reaction course. For example, using $Pd(OAc)_2$ as the catalyst, 3-hyptynoic acid and acrolein (5 equiv) in the presence of excess LiBr (2 equiv) in HOAc gave the cyclized product in 85% yield (path a, Scheme 2). However, in the presence of decreased amounts of LiBr, compound produced by β-hydride elimination was obtained in 94% yield (based on Pd), together with precipitated palladium black (path b) [4]. The different pathway of the reaction demonstrates the presence of the excess halide ion inhibits the usual β-hydride elimination (Heck-type reaction) and promotes protonolysis of the alkyl-palladium bond α- to the carbonyl group.



Scheme 2

A stoichiometric reaction of a palladium complex with acrolein in the absence or presence of the halide ion was studied as a model reaction to explore the role of the halide ion. The reaction shows that, with no extra anion or with OAc^-, ClO_4^- or F^-, only the β-H elimination product is formed, while reactions with halide ions (Cl^-, Br^- and I^-) afford exclusively the protonolysis product. This, again, indicates the significant role of halide ion in determining the reaction outcome. It is significant that by simply applying metal halides, the reaction pathway of an alkylpalladium intermediate can be cleanly switched from the normal β-H elimination to heterolytic C–Pd bond cleavage processes, i.e., protonolysis, when the formed carbanion is stabilized by an electron-withdrawing group [5].

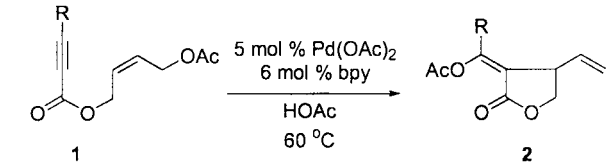
ACETOXYPALLADATION-INITIATED CYCLIZATION OF ALLYLIC ALKYNOATES

Our previous work shows that excess of halide ion is also necessary for the reaction. The key point may be the inhibition of the usual β-hydride elimination to regenerate the Pd(II) catalytic species. However, there exist problems in the way of developing the corresponding catalytic asymmetric process as shown in Scheme 1. A major one lies in the inevitable disturbance of the excess of halide ions necessary for the reaction to the coordination of chiral ligands with palladium species. In fact, the reaction dose not occur in the presence of the commonly used bidentate phosphine ligands. In the presence of chiral monophosphine ligands, the reaction rate was reduced dramatically. To overcome the difficulties of the halide ions, we turned our attention to other nucleophiles.

In hydroacetoxylation of alkynoates, acetate attacks the triple bond under palladium catalyst via *trans*-acetoxypalladation followed by protonolysis [6]. It occured to us that acetate may be a good nucleophile to replace halide ions in the Pd(II)-catalyzed cyclization of enyne esters. However, acetate cannot inhibit the usual β-hydride elimination as the halide ions do [5]. In addition, halopalladation of alkynes occurs preferentially and exclusively rather than acetoxypalladation does even in the presence of small amounts of halide ion. It seems that halide ion must be excluded from the reaction system, that is, a ligand is needed to play the role of halide ion to inhibit the β-H elimination.

We initially examined the reaction of (*Z*)-4'-acetoxy-2'-butenyl 2-butynoates (**1a**) [7]. No desired cyclization product was obtained with the catalyst systems such as $Pd(OAc)_2/PPh_3$, $Pd(OAc)_2/AsPh_3$, $Pd(OAc)_2$/PhSMe, $PdCl_2(PPh_3)_2$ and $Pd_2(dba)_3{\cdot}CHCl_3$. Fortunately, the cycloisomerization of **1a** under the action of 5 mol % $Pd(OAc)_2$ and 6 mol % bpy (2,2'-bipyridine) at 60 °C led to a 87% yield of the cyclization product α-(*Z*)-acetoxyalkylidene-β-vinyl-γ-butyrolactone (**2a**) (Scheme 3). The reactions

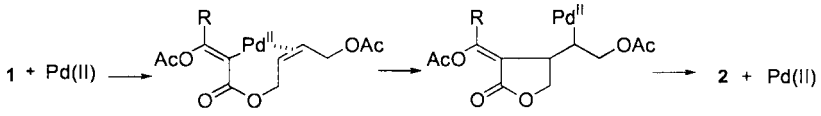
proceeded smoothly to afford the γ-butyrolactones in high yields with high stereoselectivity regarding the exocyclic double bonds (*Z*:*E* > 95:5) [8].



Scheme 3

MECHANISM

The plausible mechanism of the reaction involves *trans*-acetoxypalladation of the triple bond, followed by intramolecular olefinic insertion, and finally the carbon–palladium bond is quenched by deacetoxypalladation instead of the common β-hydride elimination (Scheme 4). Here, we found that the nitrogen-containing ligand was of critical importance in the reaction. It not only played the same role as the halide ions to inhibit the β-hydride elimination but also made the intramolecular olefinic insertion into the vinylpalladium bond more preferable to its protonolysis, thus avoiding the formation of protonolysis product.

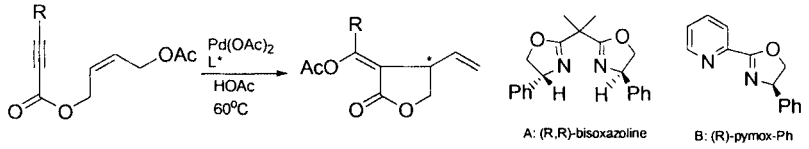


Scheme 4

CATALYTIC ASYMMETRIC CYCLIZATION OF ALLYLIC 2-ALYNOATES

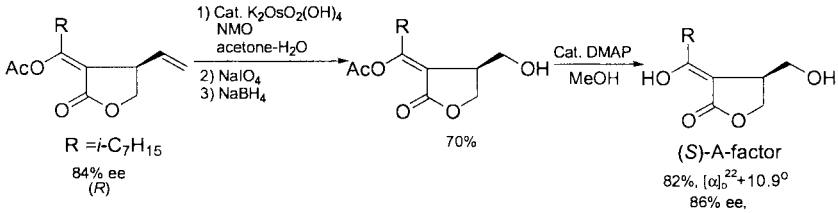
With these results in hand, further effort to the development of an asymmetric catalysis was made using the homochiral nitrogen-containing ligands. Employment of phenyl-substituted bisoxazoline (A) or (R)-pymox-Ph (B) [9] as the ligands led to high yield and enantioselectivity (up to 92 % ee) (Table 1) [8].

Table 1. Asymmetric cyclization of **1**.



R	Condition (time, h)	2, yield, (%)	% ee (config)
Me (1a)	A (18)	88	81 ((+)-R)
	B (35)	78	92 ((+)-R)
n-Pr (1b)	A (34)	83	81 ((+)-R)
	B (42)	80	80 ((+)-R)
Ph (1c)	A (48)	70	81 ((+)-R)
	B (72)	58	79 ((+)-R)
i-C_7H_{15} (1d)	A (23)	86	84 ((+)-R)
	B (48)	77	85 ((+)-R)
CH_3OCH_2 (1e)	A (41)	72	79 ((+)-R)
	B (48)	67	87 ((+)-R)

To establish the absolute configuration of the optically active γ-butyrolactones obtained above and demonstrate the synthetic utility of the asymmetric protocol, we chose A-factor as our target molecule [10]. The retrosynthetic analysis of A-factor could easily identify γ-butyrolactone **2d** as the key intermediate. Conveniently, (+)-**2d** (84% ee) (Table 1) was converted in four steps (57% total yield) to enantiomerically enriched (3S)-(+)-A-factor (86% ee, calculated from the specific rotation, $[\alpha]^{22}_{D}$ +10.9°, and the literature value, $[\alpha]^{22}_{D}$ +12.7° [10b], (Scheme 5). Thus, comparing the signs of the specific rotation of the other γ-butyrolactones with (+)-**2d** (Table 1), all other γ-butyrolactones in Table 1 were identified to be in 3R configuration.



Scheme 5

ACKNOWLEDGMENTS

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