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Palladium-Catalyzed Intramolecular Alkyne-α,β-Unsaturated Carbonyl Coupling. A Formal Synthesis of (+)-Pilocarpine

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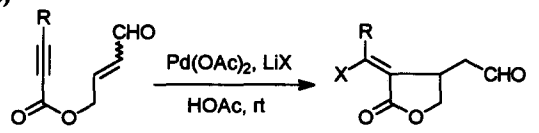
Abstract: An efficient stereoselective cyclization method by palladium-catalyzed intramolecular enyne coupling of 4'-oxo-2'-alkenyl 2-alkynoates was developed, which features in a short-step synthesis of homopilopic aldehyde. © 1997 Elsevier Science Ltd.

Intramolecular Heck reaction has been widely used in the synthesis of sophisticated natural products due to their powerful stereoselective carbon-carbon bond forming ability.[1] The cycloisomerization reaction developed by Trost was another choice for the construction of cyclic structures from acyclic enynes.[2] However, the relative strict reaction conditions and substrate limitations encountered in these reactions promoted the search for more practical synthetic methods to multi-functionalized cyclic molecules. In the context of our study in Pd(II)-catalyzed reactions of electron-deficient alkynes, we developed a series of stereoselective cyclization methods which were successfully used in the preparation of many bioactive γ-butyrolactone natural products.[3] Recently, we studied the coupling reaction of alkynes with α,β-unsaturated carbonyl compounds and found that in the presence of excess halide ion, divalent palladium catalyzed the nucleophile-alkyne-α,β-unsaturated carbonyl coupling to form γ,δ-unsaturated carbonyl compounds.[4] In this paper, we report our new results on the intramolecular alkyne-α,β-unsaturated carbonyl coupling and its application in the formal synthesis of (+)-pilocarpine.

The en-yne cyclization precursors **1** were prepared by selective monoesterification of 2-butene-1,4-diol followed by MnO_2 oxidation. The intramolecular coupling reaction of (Z)-**1a** (R=Me) was first tested under different conditions. In the presence of $Pd(OAc)_2$ (0.05 mmol), LiBr (4 mmol) and HOAc (10 mmol), the reaction could be carried out in a number of solvents such as MeCN, EtOH and CH_2Cl_2 (in this case, tetrabutylammonium bromide was used instead of LiBr) to give cyclization product **2a** (**Table 1**). The reaction rate increased with the polarity of the solvent, and in HOAc, the reaction went on smoothly and rapidly, giving the best yield of **2a** (entry 4, Table 1). So we conducted the cyclization reaction with other substrates and other halides using HOAc as solvent. The results are shown in **Table 2**.

Different alkynoates all gave good yields of en-yne cyclization products, and only one double bond isomer was obtained for each substrate under these conditions (**Table 2**). The reaction mechanism was similar to the intermolecular alkyne α,β-unsaturated carbonyl coupling reaction[4a]: first, halopalladation of **1** gives vinylpalladium intermediate, which undergoes intramolecular carbon-carbon double bond insertion followed by protonolysis of the newly formed C-Pd bond to produce **2** and regenerate the Pd(II) catalytic species. When LiX was added in small portions, several products formed in low yields,[5] showing that excess halide isindispensable for the reaction. This may be due to the fact that high concentration halide increases the stereoselectivity of halopalladation and inhibits β-H elimination side reaction.[4]

Table 1. Palladium-catalyzed Intramolecular Alkyne-α,β-Unsaturated Carbonyl Coupling of 1a (R=Me)[a]



1 2

entry	solvent	time (h)	yield (%)[b]
1	CH_2Cl_2	48	79
2	MeCN	24	79
3	EtOH	14	67
4	HOAc	2	80

[a] Reaction conditions. **1a** (1 mmol), LiBr(4 mmol), $Pd(OAc)_2$(0.05 mmol), HOAc (10 mmol) in solvent (5 mL), stirred at rt. [b] Isolated yield by column chromatography.

Table 2. Pd(II)-Catalyzed Intramolecular Alkyne-α,β-Unsaturated Carbonyl Coupling[a]

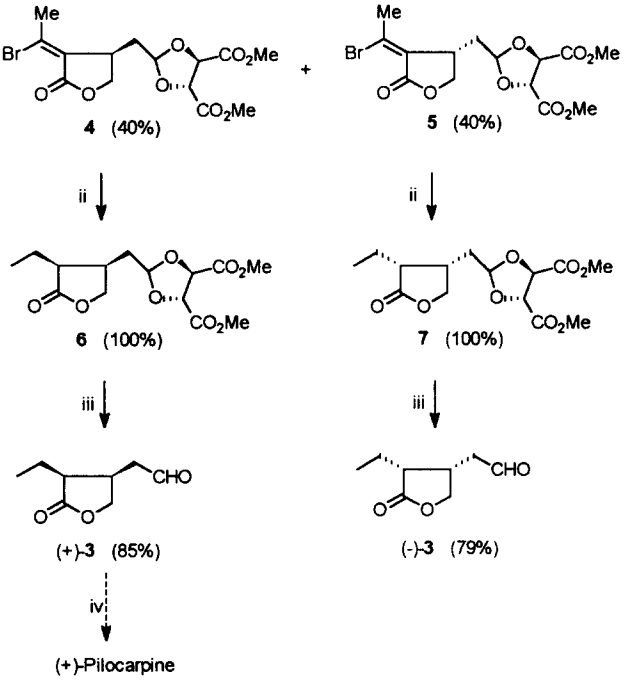
entry	substrate			product[b]		
	1	R	X	**2**	yield (%)[c]	Z/E[d]
1	(*Z*)-**1a**	Me	Br	**2a**	80	>97/3
2	(*Z*)-**1a**	Me	Cl	**2b**	82	>97/3
3	(*E*)-**1a**	Me	Br	**2a**	78	>97/3
4	(*Z*)-**1b**	H	Cl	**2c**	76	>97/3
5	(*E*)-**1b**	H	Br	**2d**	80	>97/3

[a] Reaction conditions. **1** (1 mmol), $Pd(OAc)_2$ (0.05 mmol), LiX (4 mmol) in HOAc (5 mL) at rt. [b] The products were identified by ^1H NMR, IR, MS and microanalysis.[c] Isolated yield by column chromatography.[d] The Z/E ratio (referring to the exocyclic double bond in the product) was determined by ^1H NMR spectra.

The stereochemistry of the products was determined on the basis of the ^1H NMR chemical shifts of the vinylic proton or allylic protons in CH_3 group.[6,7] It was noticed that the reaction uniformly gave products with (Z)-exocyclic double bond in high selectivity. The double bond configuration in the ester substrates had essentially no influence on the yield and stereochemical outcome (entry 1 and entry 3, **Table 2**). The (*Z*)-exocyclic double bond was generated by trans-halopalladation of the substrate. Compared to the moderate selectivity in the intermolecular coupling of benzyl butynoate with acrolein,[4a] the sole production of *Z*-isomer of **2a** from butynoate **1a** seemed surprising, but it was consistent with our previous results on other PdX_2 catalyzed intramolecular alkyne-alkene coupling,[7] implying a faster intramolecular insertion increases the *trans*-selectivity of the halopalladation-insertion sequence.

Having developed the facile method to prepare polyfunctionalized aldehydic γ-lactone, we applied it to the synthesis of the natural product, (+)-pilocarpine. Pilocarpine serves as the leading therapeutic reagent in the treatment of narrow or wide angle glaucoma.[8] Due to the important functions, it has stimulated much effort in its synthetic studies.[9] However, these syntheses all suffer from long steps of transformation and poor

overall yield and cannot avoid the isolation of undesired diastereomers. Based on the reported synthesis, we used **2a** as the key precursor to develop a more efficient synthetic method, which is shown in the **Scheme**. In order to get optically active homopilopic aldehyde **3**, we prepared the pair of diastereomeric acetals **4** and **5** from **2a** and dimethyl (+)-tartrate to achieve the racemer resolution. The acetals **4** and **5** were easily separated by column chromatography on silica gel, both in 40% yield based on **2a**. Then Pd/C catalyzed hydrogenation of **4** and **5** followed by hydrolysis in the presence of $HOAc/H_2O$ afforded enantiomeric (+)-**3** and (-)-**3**,[10] respectively. In these two reactions, no *trans*-substituted lactone isomer was obtained. The high stereoselectivity is noteworthy because direct hydrogenation of **2a** only gave a 2:3 mixture of **3** and its *trans* isomer.[11] The drastic improvement of *cis*-selectivity may be ascribed to the increased bulkiness of β-substituent through the acetal auxiliary which obliged the hydrogen delivery to occur from the other side. With (+)-**3** in hand, the aldehyde function can be transformed to imidazole ring according to literature method[9] to complete the synthesis of (+)-pilocarpine.



Scheme. Reagents and conditions: i) TsOH, benzene reflux; ii) Pd/C, NaOAc, EtOAc, H_2; iii) HOAc, H_2O. iv) Ref. 9.

In conclusion, we have developed a palladium-catalyzed intramolecular alkyne-α,β-unsaturated carbonyl coupling reaction, which leads to aldehydic γ-lactone derivatives in high yield. The simple operation, ready availability of starting materials and high selectivity in preparing such condensely functionalized compounds are noteworthy. Using this reaction, we concisely synthesized (+)-homopilopic aldehyde applying simple reagents. This route, also ensures the simultaneous synthesis of the enantiomer of (+)-homopilopic aldehyde and auxiliary-induced diastereoselectivity suggested the generality of this strategy in the asymmetric synthesis of analogous structures. Application of this strategy to other bioactive natural products and the studies of catalytic asymmetric cyclization are our current interest.

Representative procedure for palladium-catalyzed en-yne cyclization of 1: A mixture of **1** (1.0 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), LiBr (348 mg, 4.0 mmol) and HOAc (5 mL) was stirred at rt. Typically the reaction was completed in 2-3h as monitored by TLC on silica gel. The reaction mixture was fractioned by EtOAc (80 mL) and water (5 mL), the organic layer was separated, washed with brine (5 mL × 2) and then dried ($MgSO_4$). After evaporation of the solvents, the residue was subjected to column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10/3) to give cyclization product **2**.

Acknowledgments. We thank the National Natural Science Foundation and the Chinese Acedemy of Sciences for the financial support.

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5. In the reaction of **1a** with 0.2eq LiBr under the catalysis of $Pd(OAc)_2$, small amount of (E)-**2a** and the corresponding β-H elimination product were also detected besides (Z)-**2a**.
6. The configuration of the exocyclic double bond in **2** was assigned according to the deshielding effect of a *cis*-carbonyl group on ^1H NMR chemical shifts: Minami, T.; Niki, I.; Agawa, T. *J. Org. Chem.* **1974**, *39*, 3236.
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10. Spectroscopic and analytical data for important intermediates: **2a** mp 62-64°C. ^1H NMR(300MHz, $CDCl_3$) 9.80(s, 1H), 4.35(dd, J=9.5, 6.4Hz, 1H), 3.97(dd, J=9.5, 1.2Hz, 1H), 3.77-3.68(m, 1H), 2.90(dd, J=19.1, 10.2Hz, 1H), 2.68(dd, J=19.1, 3.7Hz, 1H), 2.51(s, 3H) ppm; MS m/z(%): 235[M^++1(^{81}Br)](22), 233[M^++1(^{79}Br)] (22), 153(100), 109(22), 79(38); Anal. Calcd for $C_8H_9BrO_3$: C, 41.23; H, 3.89. Found: C, 41.62; H, 3.89.
4: oil, ^1H NMR(300MHz, $CDCl_3$) 5.50-5.24(m, 1H), 4.69(d, J=3Hz, 1H), 4.61(d, J=3Hz, 1H), 4.29-4.14(m, 2H), 3.81(s, 6H), 2.54(s, 3H), 2.15-1.95(m, 2H) ppm; MS m/z(%): 395[M^++1 (^{81}Br)](7), 393[M^++1(^{79}Br)](7), 202(22), 189(100), 161(28), 117(17), 59(21); Anal Calcd for $C_{14}H_{17}BrO_8$: C, 42.77; H, 4.36. Found: C, 42.70; H, 4.11. $[\alpha]_D^{23}$ = 18.4° (c 0.53, $CHCl_3$).
6: oil, ^1H NMR(300MHz, $CDCl_3$) 5.38-5.30(m, 1H), 4.82-4.75(m, 1H), 4.75-4.67(m, 1H), 4.50-4.30(m, 2H), 3.82(s, 6H), 3.23-3.10(m, 1H), 2.65-2.50(m, 1H), 1.82-1.62(m, 4H), 1.07(t, J=7.6Hz, 3H) ppm; MS m/z(%): 317(M^++1)(7), 257(4), 202(8), 189(100), 161(28), 101(15), 69(28), 59(24); Anal. Calcd for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37. Found: C, 53.46; H, 6.22. $[\alpha]_D^{22}$ = 67° (c 0.23, $CHCl_3$).
(+)-**3**: Identical with literature data: see Ref (9).
11. Pd/C(10 mol%) catalyzed hydrogenation (1 atm H_2, rt) of **2a** in the presence of NaOAc/EtOAc gave both *cis* and *trans* lactones. The diastereomeric ratio was determined to be 2 : 3 (cis : trans) by the 300MHz ^1H NMR spectra of the product mixture.

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