Catalytic Palladium-Mediated Tetraene Carbocyclizations: Enamine Trapping Reagents

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Summary: The palladium-catalyzed carbocyclization of a tetraene substrate in the presence of an enamine effects efficient cyclization of the substrate with concomitant formation of a second carbon-carbon bond via allylation of the enamine. A brief survey of the roles of the reaction medium, ligand, enamine reagent, and to a lesser extent the substrate and palladium catalyst in determining the catalytic efficiency, mode-selectivity, and stereoselectivity of the cyclization is described. In one example, indole is shown to also function as an efficient trapping reagent.

Catalytic and stoichiometric transition-metal-mediated carbon-carbon bond forming reactions form the basis for a rapidly increasing number of new synthetic methodologies. Many of these reactions effect the carbocyclization of an acyclic substrate as a stereo- and regioselective route to functionalized carbocyclic and heterocyclic ring systems, employing a facile metal-mediated carbon-carbon bond formation between two centers of unsaturation to effect the carbocyclization.¹ Of the these new methodologies, most of the catalytic metal-mediated cyclizations effect the desired bond construction via a net cycloisomerization of the substrate or via the metal-mediated extrusion of suitable H-X or X-Y functionality. Fewer of the methods incorporate new functionalized subunits into the cyclized product as a consequence of the carbocyclization reaction.²

We are interested in finding other new catalytic metal-mediated carbocyclization reactions in which this important aspect of convergency is satisfied. We recently reported investigations into the facile palladium-catalyzed five-membered ring carbocyclization of tetraene substrates (1), a cyclization that proceeds with incorporation of an H-X trapping reagent, to yield functionalized cyclopentanes (3) and N-acylpyrrolidines.³ The methodology, based upon the well known telomerization of butadiene⁴, presumably proceeds via the regioselective trapping of an intermediate palladacycle (2).⁵ Trapping reagents in which the X-group of the H-X reagent is a carbon nucleophile are of particular interest from the standpoint of synthetic efficiency. In such instances, the carbocyclization/H-X trapping sequence makes very efficient use of the tetraene substrate



functionality. From the acyclic starting material, two new carbon-carbon bonds are formed, two carbon-carbon double bonds are set, and new functionality is introduced into the carbon skeleton appendant to the newly formed ring. Previous studies found that nitroalkanes (e.g. nitromethane) and active methylene compounds (e.g. diethyl malonate) function as efficient carbon trapping reagents.³ We were interested finding in other such reagents. In 1973 Tsuji reported that simple cyclic enamines could be employed as trapping reagents in the palladium-catalyzed telomerization of butadiene.⁶ Hydrolysis of the allylated enamine gave the α -allylated cycloalkanone. Enamines

could provide a very versatile C-C bond forming trapping reagent for the tetraene carbocyclization and would impart useful functionality for further synthetic transformations. We have therefore investigated their palladiumcatalyzed reactions with tetraenes in some detail, focusing on the roles of the reaction medium, ligand, enamine reagent, and to a lesser extent the substrate and palladium catalyst in the cyclization reaction.

Treatment of the simple 1,3,8,10-undecatetracene derivatives 4-6 with 2 equivalents of 1-pyrrolidino-1cyclohexene (7a) and 5 mol % Pd(OAc)₂/10 mol % Ar₃P (Ar = C₆H₅ or o-CH₃C₆H₄) in refluxing methylene chloride solution effects facile carbocyclization. Hydrolysis of the crude reaction mixture yields the α -alkylated cyclohexanones 8 in good-to-excellent yield (4 - 90%, 5 - 72%, 6 - 83%) as a mixture of epimers on the cyclohexyl ring.⁷ The choice of the cyclization conditions results from empirical optimization of the reaction variables. As reported in Table 1, the chemical yields and diastereomer selectivity for the cyclization of tetraene 4 are highly dependent upon the solvent, ligand, and the nature of the enamine. In THF or benzene solution, an apparent β -hydride elimination pathway, leading to triene 9, completes with trapping by the enamine.⁸ This side reaction is suppressed in dichloromethane, chloroform, or acetonitrile. The trans/cis stereochemistry of the fivemembered ring substituents also varies as a complex function of the reaction solvent, while addition of acetic acid as a proton source has little apparent effect on the reaction. With respect to chemical yield and reaction time for the cyclization, triaryl phosphines are superior ligands to trialkyl phosphines or to phosphites. Finally, the pyrrolidino-enamine is superior to the morpholino-derivative as the trapping reagent in trapping by either cyclohexanone- or cyclopentanone-derived enamines.



In considering enamines as trapping reagents for the $[Pd(OAc)_2/2 Ar_3P]$ -catalyzed carbocyclization reaction, it is conceivable that catalytic amounts of acetate ion serve to shuttle the tetraene to an intermediate allylic acetate, which subsequently undergoes palladium-catalyzed reaction with the enamine.⁹ The action of the enamine trapping reagent could, in principle, be entirely independent from the carbocyclization event. In support of this hypothesis, we find that treatment of the isolated allylic acetate 10^{10} under the enamine carbocyclization conditions (2 eq 7a / 5 mol % Pd(OAc)₂/2 eq (*o*-CH₃C₆H₄)₃P / CH₂Cl₂ / 40° / 5 h) gives after hydrolysis 8a in 96% yield. It should be noted that the reaction of 10 with 7a not only defines this potential role for acetate ion in the efficient trapping by enamines, but also serves to correlate the trans relative stereochemistry of the cyclopentane substituents in the compounds described above to compounds previously reported.³ The presence of acetate ion is however not obligatory for successful allylation of the enamine. Treatment of tetraene 4 with 2 eq of 7a in the presence of 5 mol % Pd(acac)₂, in place of Pd(OAc)₂, gives 8a in 81% yield (2 eq (*o*-CH₃C₆H₄)₃P / CH₂Cl₂ / 40° / 25 h).



	4 + (CH ₂)	1. 5 mol % Pd(OAc) ₂ 2 eq Ngend / solvent 2. H _s O*		+ EK		⊌ ^{СН} ₂ ∕> _{СН₂}
	7a (n = 2), b (n = 1)		8a (n = 2), b (n = 1)	9		
n	NR ₂	Ligand	Solvent	Ketone	(trans:cis)	Triene
2	pyrrolidine	Ph ₃ P	THF / 65º / 22 h	51%	(>20:1)	34%
2	••	**	PhH / 70º / 17 h	49%	(5:1)	38%
2	"	**	CH ₃ CN / 70 ^o / 7 h	64%	(8:1)	7%
2	"	**	CH ₃ CN / cat HOAc / 70° / 5 h	64%	(10:1)	5%
2	**	**	CH ₂ Cl ₂ / 40° / 17 h	80%	(11:1)	3%
2	"	(o-H3CC6H4)3P	CH ₂ Cl ₂ / 40° / 10 h	90%	(11:1)	
2	••	**	CHCl ₃ / 60° / 4 h	85%	(11.5:1)	
2	••	Bu ₃ P	CH ₂ Cl ₂ / 40° / 24 h	NR ^a		
2	**	(C ₆ H ₁₁) ₃ P	CHCl3 / 60º / 24 h	15%	(10:1) ^b	
2		(PhO) ₃ P	CH ₂ Cl ₂ / 40º / 84 h	NR ^a		
2	morpholine	Ph ₃ P	CH ₂ Cl ₂ / 40° / 24 h	18%		
2		(o-H3CC6H4)3P	CH ₂ Cl ₂ / 40º / 21 h	49%	(4.5:1)	
1	pyrrolidine	Ph ₃ P	CH ₂ Cl ₂ / 40° / 18 h	69%	(>20:1)	9%
1		(o-H3CC6H4)3P	CH ₂ Cl ₂ / 40º / 12 h	68%	(16:1)	
1	morpholine	Ph ₃ P	CH ₂ Cl ₂ / 40° / 22 h	49%	(>20:1) ^c	

Table 1. The role of solvent, ligand and enamine reagent in the palladium-catalyzed carbocyclization of tetraene 4.

a) Only recovered tetraene. b) 51% recovered tetraene. c) 31% recovered tetraene.

The benzamide tetraene 11 proved to be a particularly good substrate for the carbocyclization with enamine 7a. The cyclization using two eq of triphenylphosphine or tri(o-tolyl)phosphine or one eq of diphenylphosphinoethane (dppe) in conjunction with the Pd(OAc)₂ catalyst proceeds in about 90% overall to yield the substituted Nacylpyrrolidine 12. The trans relative stereochemistry is assigned in analogy to 8a. Indole also proves to be an effective trapping reagent in the reaction of 11.¹¹ The adduct 13 is obtained in 91% yield from the palladium acetate-catalyzed reaction in the presence of tri(o-tolyl)phosphine.



The catalytic palladium-mediated tetraene carbocyclization methodology provides an efficient, stereoselective route to the preparation of functionalized five-membered ring systems. Trapping by enamine reagents accounts for the formation of a second carbon-carbon bond during the course of the cyclization and introduces new functionality into the tetraene framework that is suitable for further chemical elaboration. Further studies on novel tetraene carbocyclizations are in progress.

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Sample Experimental Procedure. To a nitrogen-blanketed solution of $Pd(OAc)_2$ (12.0 mg, 0.05 mmol) and (o-CH₃C₆H₄)₃P (30.0 mg, 0.10 mmol) in dichloromethane (5 mL) is added 1-pyrrolidino-1-cyclohexene (302 mg, 2.0 mmol) and tetraene 4 (292 mg, 1.0 mmol). The resulting amber solution is stirred (40°, 10 h) then quenched by the addition of 10% aq HCl (5 mL), and the resulting mixture is stirred (25°, 0.5 h). The layers are separated, the aqueous layer extracted with dichloromethane, and the combined organics washed with aq NaHCO₃, then dried (MgSO₄) and concentrated. Chromatography on silica (35-70 mesh, 10:1 hexanes:EtOAc) yields 351 mg of 8 (90%) as a colorless liquid: ¹H NMR (CDCl₃, 360 MHz) & 5.64-5.72 (m, 1H), 5.33 (dt, J = 7, 15 Hz, 1H), 5.17 (dd, J = 8, 15 Hz, 1H), 4.87-4.94 (m, 2H), 4.09 (q, J = 7 Hz, 4H), 2.37-2.48 (m, 3H), 1.60-2.35 (m, 16H), and 1.16 ppm (t, J = 7 Hz, 6H); ¹³C NMR (CDCl₃, 50 MHz) & 212.31 (C=O), 172.47 & 172.45 (C=O), 136.82 (CH=C), 133.49 & 133.47 (CH=C), 129.06 & 129.04 (CH=C), 115.54 (C=CH₂), 61.20 (OCH₂), 58.16 (C(CO₂Et)₂), 50.45 & 50.41 (C(O)CH), 48.52 (CH, major trans-isomer), 45.19 (CH, minor cis-isomer), 44.74 (CH, major trans-isomer), 42,58 (CH, minor cis-isomer), 41.85 (CH₂), 27.77 & 27.74 (CH₂), 24.76 (CH₂), and 13.87 ppm (CH₃); IR (neat) 1732 (s, C=O), 1713 (s, C=O), and 1640 cm⁻¹ (m, C=C); HRMS analysis (EI, C₂3H₃₄O₅ 390.241) found *m/z* 390.240.

References and Notes.

¹ For a few recent examples see: a) Zhang, Y.; Negishi, E. J. Am. Chem. Soc. **1989**, 111, 3454-6; b) Trost, B. M.; Lee, D.C. J. Org. Chem. **1989**, 54, 2271-4; c) Oppolozer, W. Angew. Chem. Int. Ed. Engl. **1989**, 28, 38-52; d) Negishi, E.; Iyer, S.; Rousset, C.J. Tetrahedron Lett. **1989**, 30, 291-4; e) Larock, R.C.; Song, H.; Baker, B.E.; Gong, W.H. Tetrahedron Lett. **1988**, 29, 2919-22; f) Abelman, M.M.; Overman, L.E. J. Am. Chem. Soc. **1988**, 110, 2328-9; g) Wender, P.A., Ihle, N.C., Correia, C.R.D. J. Am. Chem. Soc. **1988**, 110, 2328-9; g) Wender, P.A., Ihle, N.C., Correia, C.R.D. J. Am. Chem. Soc. **1988**, 110, 5904-6; h) Stille, J.K.; Tanaka, M. J. Am. Chem. Soc. **1987**, 109, 3785-6; i) Takacs, J.M.; Anderson, L.G.; Creswell, M.W.; Takacs, B.E. Tetrahedron Lett. **1987**, 28, 5627-30.

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⁵ Jolly, P.W., Mynott, R., Raspel, B., Schick, K.-P. Organometallics 1986, 5, 473-81.

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⁷ All stable new compounds were characterized spectroscopically and the elemental composition determined by combustion analysis and/or high resolution mass spectrometry.

⁸ In the absence of a trapping reagent, the catalytic palladium-mediated cycloisomerization of tetraene 4 gives triene 9 in synthetically useful yields. These studies will be reported in due course.

⁹ Onoue, H.; Moritani, I.; Murahashi, S. Tetrahedron Lett. 1973, 121-4.

¹⁰ Allylic acetate 10 is prepared in 72% yield from 4 by treatment with 2 eq Et₃N-HOAc (5 mol % Pd(OAc)₂/2 eq (o-CH₃C₆H₄)₃P / CH₂Cl₂/40° / 48 h); see also reference 3.

¹¹ Billups, W.E.; Erkes, R.S.; Reed, L.E Synth. Commun. 1980, 10, 147-54.