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Palladium(II)-Catalyzed Tandem Cyclic Carbopalladation–Vinylation of Enyne Compounds

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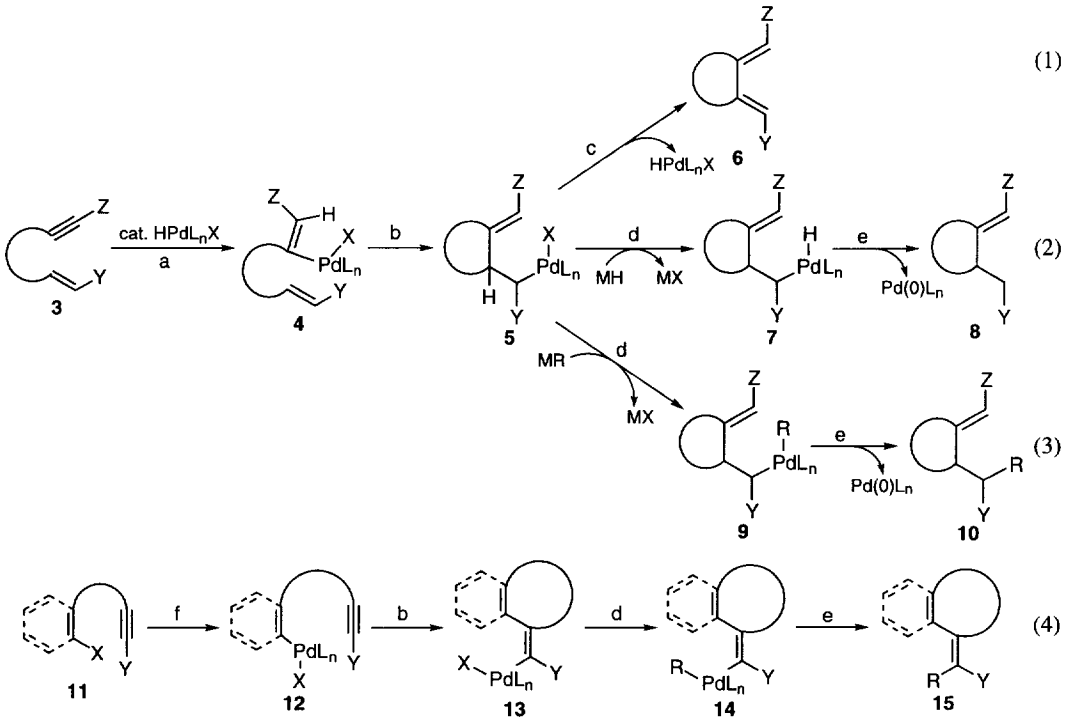
Abstract: Upon treatment with catalytic $Pd_2(dba)_3$•$CHCl_3$ in the presence of AcOH, the enyne compounds were subjected to hydropalladation followed by cyclic carbopalladation to form the homoallylpalladium complexes, which subsequently underwent in situ Stille type cross coupling with various vinyltin reagents to give the cyclized products bearing allyl appendages. © 1997 Elsevier Science Ltd.

We have recently reported[1] the total synthesis of streptazolin (**1**) and dihydrostreptazolin (**2**) utilizing palladium-mediated carbocyclization[2] as a key strategy which is based on palladium-catalyzed cycloisomerization of enynes extensively developed by Trost.[3] Such palladium-catalyzed cyclization of enynes **3** is thought to be initiated by hydropalladation of the alkyne parts to generate the alkenylpalladium derivatives **4** which is followed by cyclic carbopalladation (migratory insertion) to form the homoallylpalladium species **5**. These intermediary species can undergo subsequent dehydropalladation (β-elimination) (eq 1) or sequential hydride exchange and reductive elimination (eq 2), which pathways were successfully utilized for the synthesis of **1**[1a] or **2**,[1b] respectively, in our approach. Cyclic carbopalladation, which was commonly used as a crucial step in our synthesis of **1** and **2**, has aroused recent interest, for this step can be exploited in developing tandem and cascade processes.[4] Thus, for the tandem process, aryl- or alkenylpalladium halide complexes **12**, generated via oxidative addition of aryl or alkenyl halides **11** to Pd(0), undergo cyclic carbopalladation of alkynes leading to alkenylpalladium species **13**, which are then trapped by some other organometals via cross coupling to give **15** (eq 4).[5] These tandem reactions investigated have been rather limited by the requirement for the pathway involving the alkyne carbopalladation to form the alkenylpalladium intermediates **13**. One obvious reason for this is that the lack of hydrogens at the β position of Pd in the alkenylpalladium intermediates restricts the β-elimination pathway which prevents the further transmetalation.[6]

The potential utility of the enyne cyclic carbopalladation-based strategies, coupled with the interest in the termination of the carbopalladation process (**13** → **15** in eq 4), have prompted us to further exploit the use of the enyne cyclic carbopalladation strategy in developing an intramolecular tandem process involving a cross coupling pathway as shown in eq 3. In this process, the active catalyst, $HPdL_nX$, can be regenerated via oxidative addition of HX to Pd(0). This strategy we envisioned involves, unlike the alkyne carbopalladation affording the alkenylpalladium complex **13** (eq 4), the *alkene carbopalladation* process generating the *alkylpalladium species* **5** having the β-hydrogen(s), which are capable of being subjected to the β-hydrogen elimination (**5** → **6**) competing with the transmetalation (**5** → **9**). Thus, achievement of the tandem process



(a) hydropalladation; (b) carbopalladation; (c) dehydropalladation; (d) transmetalation; (e) reductive elimination; (f) oxidative addition

(eq 3) affording **10** must meet the requirement for the transmetalation of **5** with an appropriate organometal (leading to eq 3) to be significantly faster than the β-elimination of **5** (leading to eq 1). In general, this limitation can not be imposed on the alkylpalladium complex like **5** in the catalytic cycle, since the β-elimination step is kinetically more favorable than the transmetalation. However, the use of organotin(IV) reagents as trapping agents has been noted to be effective for promoting the transmetalation step in the competing process (**5** → **9** vs. **5** → **6**).[4, 6c, 7] In this regard, we explored the possibility of combining the cyclic carbopalladation step with the Stille type coupling[7] of **5** with alkenyltin reagents. Herein, we disclose the results of our investigation on the palladium-catalyzed tandem cyclic carbometalation–Stille type vinylation of enyne compounds.

We first explored the optimized conditions using the enyne compound **16** to effect the palladium-catalyzed tandem process. Thus, **16** was treated with tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct ($Pd_2(dba)_3$•$CHCl_3$) as the catalyst and vinyltributyltin (2 equiv to **16**) with triphenyl- or tri-*o*-tolylphosphine as the ligand (2 equiv to Pd) in refluxing THF including AcOH (2 equiv to **16**). As shown in Scheme 1 and Table 1 (entries 1–3), the reactions afforded the desired cyclization–coupling product **18** in 28% to 39% yield, arising from the cyclic carbopalladation to form the homoallylpalladium species **17** and the subsequent vinylation, accompanied by the formation of significant quantities of a chromatographically inseparable mixture of 1,3-dienes **19** and **20** (the initially formed *s-cis*-diene **19** and the double-bond isomerized product **20** with the internal olefin) generating via the competitive β-elimination of **17**. Changing the solvent to acetonitrile in the presence of tri-*o*-tolylphosphine (Table 1, entry 4), considerably improved the yield of **18** up to 44%; however, it failed to prevent the formation of the β-elimination products **19/20** (37% yield). Switching the ligand to tri-2-furylphosphine with less electron donating character (and using

THF as the solvent), although rate acceleration for the Stille reaction has been observed with this ligand,[8] resulted in only a trace of **18**, but a significant increase of the formation of unwanted **19/20** (69%) (Table 1, entry 5). With these results with the phosphine ligands in mind, we then carried out the reactions without adding ligands, thereby the only product isolated was desired **18** and none of **19/20** was detected by NMR (Table 1, entries 6–8). For β-hydride elimination, Pd and β-hydrogen are required to be essentially syn periplanar. Thus, the selective formation of **18** may be explained in terms of the rapid π-complexation of Pd(II) with the proximate double bond in **17** in the absence of the triarylphosphine ligand, thereby holding the Pd–C–C–H (angular H) dihedral angle noncoplanar to disfavor β-hydrogen elimination.

Scheme 1

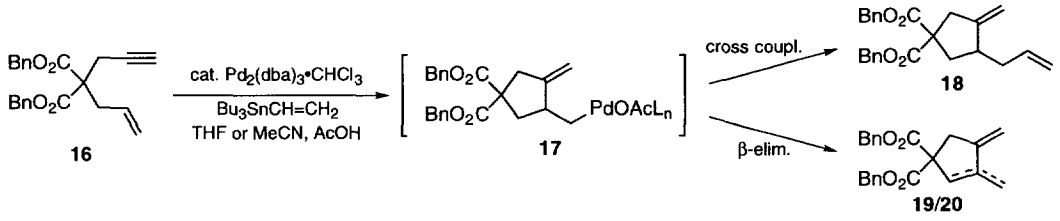


Table 1. Pd-Catalyzed Tandem Cyclic Carbopalladation–Vinylation

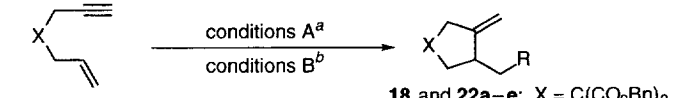
Entry	Ligand[a]	$Pd_2(dba)_3$•$CHCl_3$ (mol %)	Solvent	Time (min)	Products (%)[b] 18	Products (%)[b] 19/20
1	PPh_3	5	THF	30	28	30
2	P(*o*-tol)$_3$	5	THF	30	39	28
3	P(*o*-tol)$_3$	15	THF	30	32	43
4	P(*o*-tol)$_3$	5	MeCN	30	44	37
5	P(2-furyl)$_3$	5	THF	10	trace	69
6	none	15	THF	30	45	ND[d]
7[c]	none	5	MeCN	30	37	ND
8	none	15	MeCN	15	53	ND

[a]Two equivalents to Pd were used. [b]Isolated yield after chromatographic purification. [c]Starting material **16** was recovered in 38% yield. [d]Not detected.

As can be seen by entry 8 in the last series in Table 1, the optimal conditions for the selective preparation of the cross coupled product **18** used 15 mol % of the Pd catalyst in the absence of the phosphine ligand and acetonitrile as the solvent. Accordingly, this method was tried on the above and nitrogen-containing enynes, **16** and **21**, using various vinyltin reagents as cross coupling partners under the conditions A as presented in Table 2, entries 1–7. In all cases, the only observable reaction was the sequential carbopalladation–Stille type cross coupling reaction to give the cyclized products bearing the allyl appendages (**18**, **22**, and **23**), where, except for entry 6, retention of the alkene geometry (*E* configuration) was confirmed for the products by NMR analyses. When we carried out the vinylation reaction of **16** and **21** with addition of 18-crown-6 (conditions B in Table 2), we observed a significant enhancement of the reaction rate and yield (Table 2, entries 8–11). Although the reason for this improvement is not clear at present, the addition of 18-crown-6 may simply aid in enhancement of the solubility of the tin reagents.

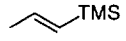
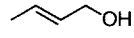
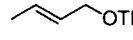
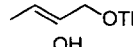
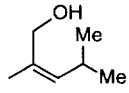
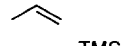
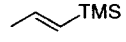
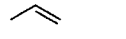
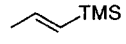
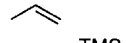
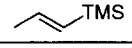
In summary, the results presented herein provide a one-pot procedure for the Pd-catalyzed tandem cyclic carbopalladation–vinylation process. Extension of this methodology toward other enyne compounds and its application to natural product synthesis are under investigation.

Table 2. Pd-Catalyzed Tandem Cyclic Carbopalladation–Vinylation in the Absence of Triarylphosphine Ligand



16: X = $C(CO_2Bn)_2$
21: X = NCOPh

18 and **22a–e**: X = $C(CO_2Bn)_2$
23a, b: X = NCOPh

Entry	Enyne	R of Bu_3SnR	Conditions	Time (min)	Product	Yield (%)[c]
1	**16**		A	15	**22a**	71
2	**16**		A	30	**22b**	42
3	**16**		A	30	**22c**	48
4	**16**		A	30	**22d**	43
5	**16**		A	30	**22e**	32
6	**21**		A	15	**23a**	47
7	**21**		A	10	**23b**	40
8	**16**		B	10	**18**	59
9	**16**		B	10	**22a**	86
10	**21**		B	10	**23a**	58
11	**21**		B	10	**23b**	63

[a]Conditions A: At a substrate concentration of 0.1 M, 2 equiv of the vinyltin reagents (Bu_3SnR), 15 mol % of $Pd_2(dba)_3$•$CHCl_3$, and 2 equiv of AcOH in acetonitrile were refluxed during the time indicated. [b]Conditions B: At a substrate concentration of 0.1 M, 2 equiv of the vinyltin reagents (Bu_3SnR), 5 mol % of $Pd_2(dba)_3$•$CHCl_3$, 2 equiv of AcOH, and 0.3 equiv of 18-crown-6 in acetonitrile were refluxed during the time indicated. [c]Isolated yield after chromatographic purification.

References and Notes

1. (a) Yamada, H.; Aoyagi, S.; Kibayashi, C. *J. Am Chem. Soc.* **1996**, *118*, 1054–1059. (b) Yamada, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1996**, *37*, 8787–8790.
2. For a recent review on transition metal-catalyzed carbocyclizations in organic synthesis, see: Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635–662.
3. For recent reviews, see: (a) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34–42. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259–281.
4. For a recent review, see: Negishi, E.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365–393.
5. (a) Burns, B.; Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakum, T. *Tetrahedron Lett.* **1989**, *30*, 1135–1138. (b) Grigg, R.; Loganathan, V.; Sukirthalingam, S. *ibid.* **1990**, *31*, 6573–6576. (c) Negishi, E.; Noda, Y.; Lamaty, F.; Vawter, E. J. *Tetrahedron Lett.* **1990**, *31*, 4393–4396. (d) Wang, R.; Chou, F.; Luo, F. *J. Org. Chem.* **1990**, *55*, 4846–4849. (e) Nuss, J. M.; Levine, B. H.; Rennels, R. A.; Heravi, M. M. *Tetrahedron Lett.* **1991**, *32*, 5243–5246. (f) Nuss, J. M.; Rennels, R. A.; Levine, B. H. *J. Am. Chem. Soc.* **1993**, *115*, 6991–6992.
6. In a few cases, in situ trapping of cyclic alkylpalladium species by organometals has been reported: (a) Oppolzer, W.; Ruiz-Montes, J. *Helv. Chim. Acta* **1993**, *76*, 1266–1274. (b) Stadtmüller, H.; Lentz, R.; Tucker, C. E.; Stüdemann, T.; Dörner, W.; Knochel, P. *J. Am. Chem. Soc.* **1993**, *115*, 7027–7028. (c) Casaschi, A.; Grigg, R.; Sansano, J. M.; Wilson, D.; Redpath, J. *Tetrahedron Lett.* **1996**, *37*, 4413–4416.
7. Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 509–524.
8. Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595.

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