ORGANIC LETTERS

2005
Vol. 7, No. 26
5845−5848

Development of an Anomalous Heck Reaction: Skeletal Rearrangement of Divinyl and Enyne Carbinols

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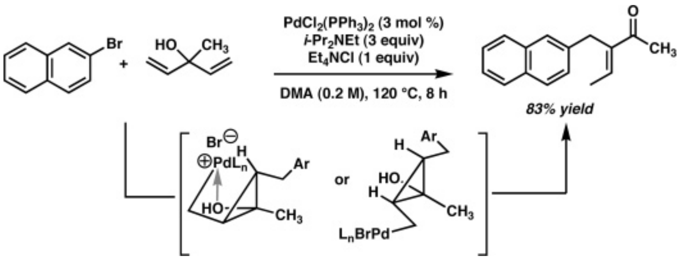
Received October 3, 2005

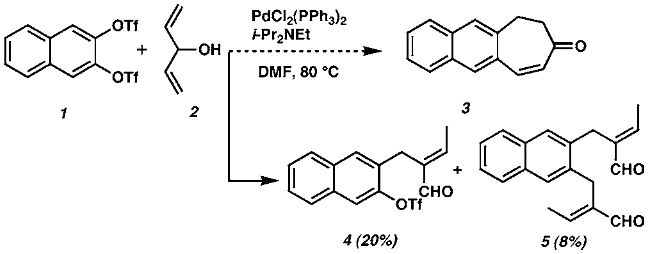
ABSTRACT



A general set of conditions that achieves the union of aryl halides and divinyl or enyne carbinols to afford tri- or tetrasubstituted olefins in good yields (up to 83%) is described. The mechanism by which this proceeds is believed to involve the intermediacy of a cyclopropanol, followed by a novel skeletal reorganization. The ability to suppress β-hydride elimination of organopalladium intermediates appears to be critical to the success of these processes.

The formation of carbon−carbon bonds is of fundamental importance in the synthesis of complex organic molecules. Among the metal-catalyzed methods available for C−C bond construction, the Heck reaction is arguably one of the most useful because it employs relatively stable and easily accessible starting materials.[1] As part of a general synthetic program aimed at the facile construction of seven-membered ring containing compounds (e.g., **3**, Scheme 1), we became interested in utilizing a Stille−Ortar variant[2] of the Heck reaction that employed ditriflate **1** and divinyl carbinols (e.g., **2**) for this purpose. Surprisingly, a complex mixture, which included enal and bisenal products (**4** and **5**, respectively), was realized under standard Heck reaction conditions employing $PdCl_2(PPh_3)_2$ (3 mol %) and Hünig's base (3 equiv) at 80 °C with DMF as solvent.

Scheme 1



We decided to pursue this transformation further with the aim of developing a wide-ranging and high-yielding method as well as added insight into the mechanism of this novel rearrangement. However, the reaction of **2** with a variety of simple aryl halides and triflates was found not to be general, as these predominantly formed the standard Heck products.

Perusal of the literature revealed a single, isolated example of this reaction reported by Gribble as part of a study of the Pd-mediated synthesis of 3-vinyl and 3- alkynyl indoles.[3]

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[1] Larhed, M.; Hallberg, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley and Sons: Hoboken, 2002; Vol. 1, pp 1133−1178.

[2] (a) Scott, W. J.; Peña, M. R.; Swärd, K.; Stoessel, S. J.; Stille, J. K. *J. Org. Chem.* **1985**, *50*, 2302−2308. (b) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, *25*, 2271−2274.

[3] Gribble, G. W.; Conway, S. C. *Synth. Commun.* **1992**, *22*, 2129−2141.

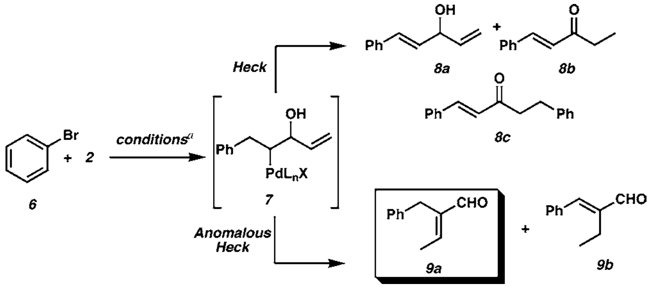
10.1021/ol052382p CCC: $30.25

In our hands, the reaction of 3-indolyl triflate with **2** under the conditions reported by Gribble proceeded in only 35% isolated yield, prompting further study.

In this letter, we report the development of this interesting transformation of divinyl carbinols (e.g., **2** → **4**) as well as enyne carbinols with reactive aryl and vinyl coupling partners into a general and useful reaction. This anomalous Heck reaction provides efficient access to stereochemically defined tri- and tetrasubstituted olefins, which are otherwise challenging to obtain. Importantly, this reaction manifold provides the basis for a variety of novel ring expansion and annulation reactions, examples of which are reported for the first time herein. Additionally, a series of experiments that provide insight into the mechanism of the reaction is presented.

The study was initiated using bromobenzene (**6**)[4] and 1,4-pentadien-3-ol (**2**) as substrates (Table 1). Under the initially established conditions that afford **4** and **5**, predominant formation of products resulting from the standard Heck reaction (**8a**−**c**) was observed (entry 1, Table 1), rather than the desired rearranged products. On the basis of a hypothesis that **8** and **9** formed from the same initial oxidative addition intermediate (**7**), we focused on catalyst, solvent, and additive variations that would disfavor β-hydride elimination and presumably launch the Heck insertion intermediate toward the formation of **9a/b**.[5] The use of TMEDA[6] as base resulted in a complete recovery of starting material (entry 2). This result points to the importance of Hünig's base, likely by initial reduction of the Pd(II) complex to the active Pd(0) catalyst, in initiating oxidative addition.[7] Recently, bis(tri-*tert*-butylphosphine)palladium(0) has emerged as an effective catalyst for C−C bond formation involving saturated coupling partners due in part to the stability of the organopalladium intermediates in these coupling reactions toward β-hydride elimination.[8] Although the desired product **9** was successfully realized with this catalyst (entry 3), it was obtained in low yield along with several other byproducts. An investigation of additives (entries 4−6) in an effort to suppress β-hydride elimination using the initial conditions unveiled Et$_4$NCl as the most effective.[9]

Table 1. Reaction Condition Screen for the Anomalous Heck Reaction



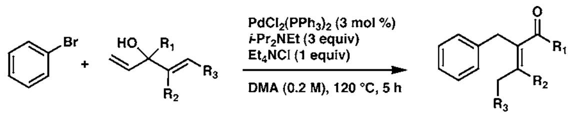
entry	catalyst	additive	base	solvent	product ratio (9:8)[b]
1	PdCl$_2$(PPh$_3$)$_2$		^{i}Pr$_2$NEt	DMF	<1:9
2	PdCl$_2$(PPh$_3$)$_2$		TMEDA	DMF	no reaction
3	Pd(P^{t}Bu$_3$)$_2$		Cy$_2$NMe	THF	1:9
4	PdCl$_2$(PPh$_3$)$_2$	Bu$_4$NCl	^{i}Pr$_2$NEt	DMF	3:4
5	PdCl$_2$(PPh$_3$)$_2$	LiBr	^{i}Pr$_2$NEt	DMF	5:6
6	PdCl$_2$(PPh$_3$)$_2$	Et$_4$NCl	^{i}Pr$_2$NEt	DMF	3:2
7	PdCl$_2$(PPh$_3$)$_2$	Et$_4$NCl	^{i}Pr$_2$NEt	DMA	10:3

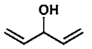
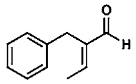
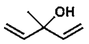
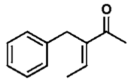
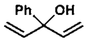
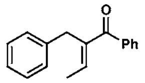
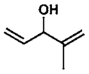
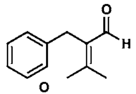
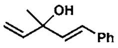
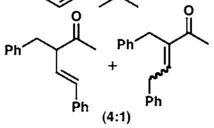
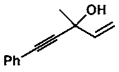
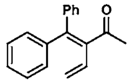
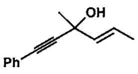
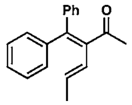
[a] All reactions were run with 3 mol % catalyst loading, 1 equiv of additive, and 3 equiv of base as a 0.2 M solution at 120 °C for 5 h. [b] Product ratios were determined using integration of ^{1}H NMR resonances.

Substituting DMA for DMF as solvent led to the discovery of optimal reaction conditions, whereby a 10:3 ratio of **9**/**8** was obtained (entry 7).[10]

Using these optimized conditions, we investigated the substrate scope of this novel rearrangement for the synthesis of a variety of substituted enals, enones, and dienones (Table 2). Secondary alcohols provide moderate yields of the corresponding enal products (entry 1), and tertiary alcohols

Table 2. Scope of the Carbinol Component



entry	divinyl carbinol	product[a]	yield
1			43%
2			60%
3			69%
4			18%
5			50%
6			69%
7			65%

[a] A single olefin regioisomer and stereoisomer (as shown) were obtained unless otherwise indicated.

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[4] (4) Iodobenzene and phenyl triflate react similarly to bromobenzene.

[5] (5) Only a trace amount of **9b** was observed in this initial screen and in subsequent studies.

[6] (6) TMEDA has been shown to be a useful additive for preventing β-hydride elimination in other systems. See: Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686−3687.

[7] (7) Although mixtures of TMEDA and Hünig's base did provide the desired products, thus supporting the necessity of Hünig's base, no increase in the amount of the anomalous Heck product was observed relative to entry 1.

[8] (8) Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5749−5752 and references therein.

(substitution at R_1) are well tolerated and lead to good yields of the desired enone products (entries 2 and 3). In contrast, substitution at the internal vinyl carbon (R_2) leads to diminished yields of the anomalous Heck product (entry 4), accompanied by a significant amount of the standard Heck product.[11] Although substitution only at the terminal vinyl carbon (R_3) completely favors the standard Heck products (not shown), a tertiary alcohol that is also substituted at the terminal vinyl carbon provides useful yields of the desired anomalous Heck product (entry 5). Gratifyingly, enyne carbinol substrates (entries 6 and 7) react chemoselectively and lead to good yields of dienone products. In all cases, the free alcohol on the divinyl and enyne carbinol substrates was found to be critical to the success of the reaction. The corresponding methyl and silyl ethers did not react at all or provided only trace quantities of the standard Heck products over prolonged reaction times.

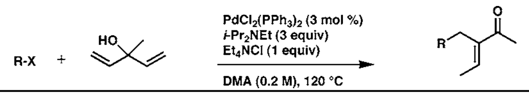
In addition to an investigation of the carbinol component (Table 2), a study of the coupling partner to establish the general applicability of the reaction conditions was also undertaken.

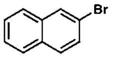
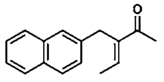
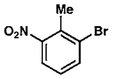
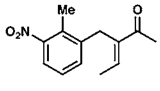
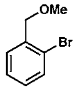
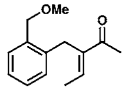
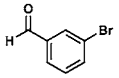
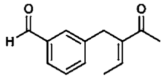
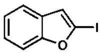
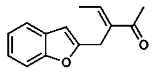
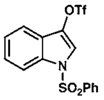
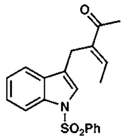
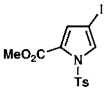
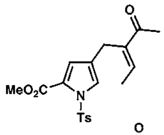
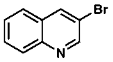
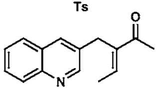
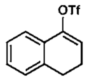
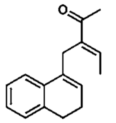
As shown in Table 3, various halides and triflates readily participate in the reaction under our conditions. Aryl halides bearing a variety of substitution patterns and functional groups engage in the reaction to provide respectable yields of the desired products (entries 1−4). Furthermore, a range of heteroaryl halides provide the α,β-unsaturated enone products in good to excellent yield (entries 5−8). Finally, vinyl triflate compounds serve as competent substrates for the reaction as well (entry 9).

The results obtained appear to be consistent with the following mechanistic picture (Scheme 2), which is illustrated with bromobenzene **6** and divinyl carbinol **2**. This mechanistic proposal is supported by experiments reported herein.[12]

Initial oxidative addition of an in situ generated Pd(0) active catalyst to **6** provides organopalladium intermediate **10** that undergoes migratory insertion of **2** to yield intermediate **11**, where addition across the olefin likely occurs on the same face that the hydroxyl resides.[13]

Table 3. Scope of the "Halide" Component



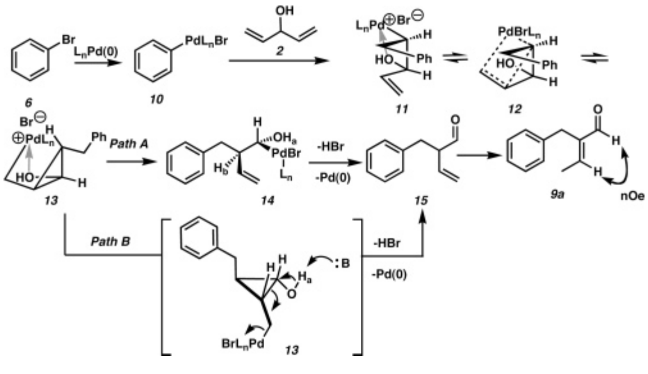
entry	substrate	product	time	yield
1			8 h	83%
2[a]			8 h	65%
3			24 h	71%
4			26 h	70%
5			6.5 h	74%
6			9 h	71%
7			6 h	52%
8			14 h	77%
9[b]			6 h	60%

[a] Reaction was run using 6 mol % catalyst loading. [b] Product is a 3:1 mixture of trans and cis isomers. Major product is shown.

The accelerated rate of reaction of substrates such as **2**, which bear a free hydroxyl, relative to the corresponding methyl and silyl ethers under our reaction conditions, strongly suggests that a precoordination of the palladium center to the hydroxyl (or corresponding alkoxide) enhances the initial migratory insertion to provide **11**, consistent with previous observations by Cacchi and Ortar and also by Oestreich.[13]

Under the conditions of the reaction, with β-hydride elimination significantly compromised by coordination to the

Scheme 2. Proposed Mechanism of the Anomalous Heck Reaction



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(9) Interestingly, ample precedent exists for the dramatic effect of quaternary ammonium salts on the efficiency of the standard Heck reaction as well. See: (a) Soderberg, B. C. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford, NY, 1995; Vol. 12, Chapter 3.5, p 259. (b) Bräse, S.; de Meijere, A. In *Metal Catalyzed Coupling Reactions*; Stang, P. J., Diederich, F., Eds.; John Wiley & Sons: New York, 1998 and references therein.

(10) Other solvents that were examined include *N*-methyl pyrrolidone, dimethylimidazolidone, and acetonitrile.

(11) See Supporting Information.

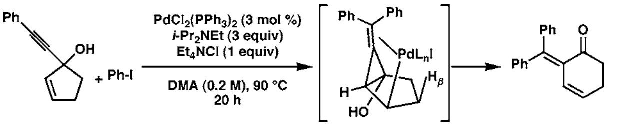
(12) Our mechanistic proposal takes into consideration our observations of reactivity of both divinyl and enyne carbinols in the anomalous Heck reaction.

(13) Coordination of hydroxyl functionality to cationic palladium intermediates during the vinylation of aryl triflates has been proposed previously and should predicate the stereochemistry indicated. See: (a) Oestreich, M.; Sempere-Culler, F.; Machotta, A. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 149−152. (b) Bernocchi, E.; Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1992**, *33*, 3073−3076.

hydroxyl (see **11**), excess halide (from the Et_4NCl additive), or alkene, ensuing migratory insertion produces cyclopropanol **13**.[14]

At this stage, two alternate pathways (path A or B) may account for product formation. In path A, which is favored in the original Gribble report of this reaction, a decarbopalladative rearrangement of **13** that has ample precedent in the work of Negishi provides organopalladium intermediate **14**.[15] Ensuing β- or β'-hydride elimination (loss of H_a or H_b, respectively) from **14** then yields β,γ-unsaturated aldehyde **15**.[16−18] Conversely, in path B, base abstraction of H_a from **13** with concomitant fragmentation of the cyclopropanol, followed by loss of Pd(0), affords **15**. Isomerization of **15** under the reaction conditions yields **9a**, the alkene geometry of which was confirmed by nuclear Overhauser effect (NOE) experiments and determined to be under thermodynamic control.[19]

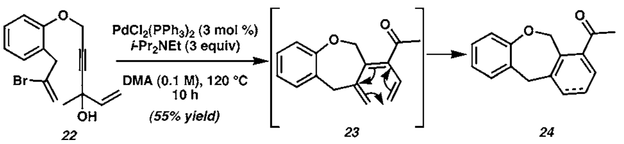
Additional insight into this unique reaction is gained by considering the mechanism by which cyclic substrates such as **18** may react (eq 1), which reveals that a potential coordination between the Pd(II) metal center and alkene is sufficient to deter β-hydride elimination of **20**. Instead, a facile ring expansive rearrangement, likely facilitated by the antiperiplanar relationship between the hydroxyl group and the C−Pd bond in **20**, results to yield **21** in fair yield. In this case, a decarbopalladative rearrangement (i.e., path A, see Scheme 2) necessary for ring expansion is highly compromised *because a coplanar arrangement between the breaking C−C bond and the C−Pd bond cannot be achieved.*



(1)

18 *19* *20* *21 (54% yield)*

The development of this anomalous Heck reaction sets the stage for a range of applications. Illustrated in eq 2 is an efficient complexity-building annulation reaction whereby dienynol **22** undergoes a tandem anomalous Heck/6-π electrocyclization reaction to provide tricyclic cyclohexadiene **24** (along with a small quantity of the corresponding aromatized compound) in an unoptimized 55% overall yield.[20]



(2)

22 *23* *24*

In summary, we report the first study of a Pd-mediated skeletal rearrangement that converts divinyl and enyne carbinols to a series of enals, enones, and dienones that cannot be readily accessed otherwise. Our mechanistic proposal suggests that suppression of β-hydride elimination is important for the formation of these products. Also of note is the importance of the hydroxyl functionality of the divinyl (or enyne) carbinol in facilitating these processes. Further studies on the scope of this reaction as well as on the mechanism and applications thereof are underway and will be reported in due course.

Acknowledgment. The authors are grateful to UC Berkeley, GlaxoSmithKline (postdoctoral support to J.M.N.), and the NSF (predoctoral fellowship to K.K.L.) for generous financial support. The authors also thank the Bartlett, Toste, Trauner, Bergman, Francis, Vollhardt, and Ellman labs for chemicals and pertinent discussions. Mr. Alexandre Savari is acknowledged for his contributions to this project.

Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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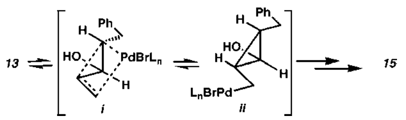
[14] Heteroatom-bound organopalladium intermediates have been shown to be recalcitrant toward β-hydride elimination. See: Oestreich, M.; Dennison, P. R.; Kodanko, J. J.; Overman, L. E. *Angew. Chem., Int. Ed.* **2001**, *40*, 1439−1442. The Et_4NCl additive may serve to augment this effect, or the added halide might competitively bind to the metal center to further minimize β-hydride elimination.

[15] (a) Owzarczyk, Z.; Lamaty, F.; Vawter, E. J.; Negishi, E.-i. *J. Am. Chem. Soc.* **1992**, *114*, 10091−10092. See also: (b) Trost, B. M.; Dumas, J. *Tetrahedron Lett.* **1993**, *34*, 19−22. (c) Brown, D.; Grigg, R.; Sridharan, V.; Tambyrajah, V.; Thornton-Pett, M. *Tetrahedron* **1998**, *54*, 2595−2606.

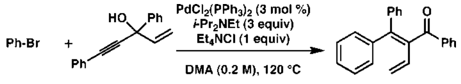
[16] The β,γ-unsaturated enal **15** may also result from alkene-bound organopalladium intermediate **i** via **ii**.



i *ii*

[17] Loss of H_b via β-hydride elimination will require a syn coplanar relationship between the C−Pd and C−H_b bonds to provide an enol that tautomerizes to **15**. The intermediacy of **15** is supported by the isolation of styrenyl products (see entry 5, Table 2).

[18] Loss of H_b via β-hydride elimination is not a strict requirement for product formation, as enynol substrates such as **16**, which lack H_b, readily undergo the anomalous Heck reaction to provide very good yields of the desired product.



6 *16* *17 (74% yield)*

[19] The enal **9a** was isomerized to a 3:1 *E*/*Z* mixture of olefin iosmers under photochemical irradiation (medium-pressure Hanovia Hg lamp), which when subjected to the reaction conditions readily reverts to **9a**.

[20] A 9:1 ratio of cyclohexadiene **29** and the corresponding aromatized compound was obtained in 55% yield, as determined by integration of ^{1}H NMR resonances using 1,2-dichloroethane as an internal standard.