Heck Coupling

DOI: 10.1002/anie.200705558

Palladium-Catalyzed Intermolecular Ene–Yne Coupling: Development of an Atom-Efficient Mizoroki–Heck-Type Reaction**

*Anders T. Lindhardt (neé Hansen), Mette Louise H. Mantel, and Troels Skrydstrup**

Palladium-catalyzed reactions have become widely accepted in organic synthesis for carbon–carbon bond assembly, and are frequently invoked by the pharmaceutical, agrochemical, and fine-chemicals industry for the production of important organic-based molecules.[1] The vast majority of such reactions (e.g. the Suzuki–Miyaura, Migita–Kosugi–Stille, Sonogashira, Hiyama, and Negishi reactions) involve the coupling of an aryl or vinyl halide with an organometallic fragment. The disadvantage of these reactions is that two functionalized starting materials are required for the C–C bond-forming step, whereby this functionality is lost in the product. Hence, atom economy is compromised in favor of reactivity. The Mizoroki–Heck reaction displays greater atom efficiency, as the functionalization of only one of the coupling partners is required for the synthesis of aryl alkenes or butadiene systems.[2] More rewarding, but highly challenging, is the development of reaction conditions for similar transformations with nonfunctionalized coupling partners[3] to improve the overall atom economy of these processes.[4] One such reaction, a powerful synthetic tool for the synthesis of cyclic dienes, is the palladium-catalyzed enyne cycloisomerization developed by Trost and co-workers.[5,6] This intramolecular isomerization of an enyne has been well developed, in contrast to the corresponding intermolecular coupling of alkynes with olefins for the preparation of 1,3-dienes.[7,8]

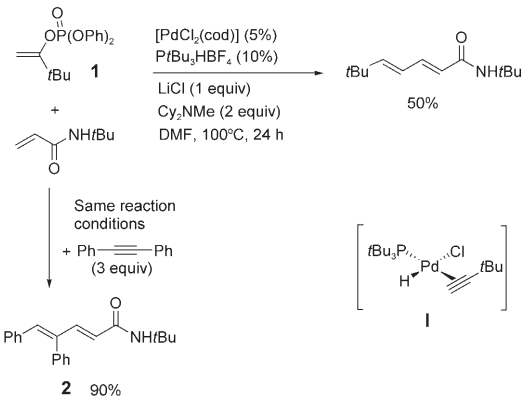
Herein, we report an effective catalyst system composed of a palladium complex with a basic, hindered alkyl phosphine for the Mizoroki–Heck-type coupling of disubstituted alkynes with electron-deficient alkenes to give 1,3-butadienes. We also reveal that these coupling reactions do not appear to proceed through a cycloaddition mechanism, but that a palladium hydride species is probably the active catalyst.

[*] Dr. A. T. Lindhardt (neé Hansen), M. L. H. Mantel, Prof. Dr. T. Skrydstrup
The Center for Insoluble Protein Structures (inSPIN)
Department of Chemistry and Interdisciplinary Nanoscience Center
University of Aarhus
Langelandsgade 140, 8000 Aarhus (Denmark)
Fax: (+45) 8619-6199
E-mail: ts@chem.au.dk

[**] We thank the Danish National Research Foundation, the Lundbeck Foundation, the Carlsberg Foundation, the OChem and INano Graduate Schools, and the University of Aarhus for generous financial support of this research. We thank Dr. Jacob Overgaard for X-ray crystallographic analysis, and we are grateful for a donation of ligands and catalysts from Degussa and Solvias. We thank Karin Dooleweerdt for synthesizing the ynamide.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

We demonstrated previously the ability of alkenyl tosylates and phosphates, such as **1**, with a bulky substituent at C1 to undergo Pd^0-catalyzed Mizoroki–Heck coupling with 1,2-migration (Scheme 1).[9,10] An alkyne-coordinated Pd^{II} hydride species **I** was proposed to be the intermediate for this reaction.

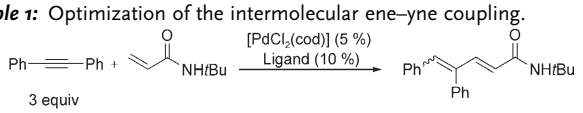


Scheme 1. Crossover experiment with diphenylacetylene. cod = 1,5-cyclooctadiene, Cy = cyclohexyl, DMF = *N*,*N*-dimethylformamide.

To confirm the existence of this palladium hydride intermediate,[11] we conducted a crossover experiment to determine whether an alkyne added to the reaction mixture could be incorporated into the final coupling product(s). The coupling of the 1-*tert*-butylvinyl phosphate **1** with *N*-*tert*-butylacrylamide[9] in the presence of diphenylacetylene (3 equiv) gave the diene **2** in 90% yield (Scheme 1).[12] However, further examination of this reaction (Table 1) revealed that the omission of the vinyl phosphate, lithium chloride, and the amine base (despite the use of the protonated ligand $PtBu_3HBF_4$), led to the same coupling product in high yield.

The structure of the phosphine ligand was found to be crucial to the effectiveness of the reaction. Of the ligands tested, only $PtBu_3$ and diadamantylbutylphosphane (cataCXium A), examples of monodentate bulky alkyl phosphines,[13] displayed good reactivity (Table 1, entries 1 and 7). None of the other ligands tested, including bidentate ligands and biphenyl phosphine ligands, showed any reactivity for this transformation (Table 1, entries 2–6). Furthermore, the conditions reported by Trost and co-workers for the cycloisomerization of enynes to cyclic dienes ($[Pd_2(dba)_3]$, P(*o*-Tol)$_3$, AcOH)[5] were ineffective in promoting this transformation. DMF was found to be the best solvent for the

Table 1: Optimization of the intermolecular ene–yne coupling.



Entry	Ligand	Solvent	*T* [°C]	Yield [%][a]	*Z*/*E*
1	$PtBu_3HBF_4$	DMF	100	86	1:0
2	S-Phos	DMF	100	NR	–
3	X-Phos	DMF	100	NR	–
4	PPh_3	DMF	100	NR	–
5	PCy_3HBF_4	DMF	100	NR	–
6	dppf[b]	DMF	100	NR	–
7	cataCXium A	DMF	100	(80)[c]	1:0
8	$PtBu_3HBF_4$	toluene	100	64	2:1
9	$PtBu_3HBF_4$	dioxane	100	77	4:1
10	$PtBu_3HBF_4$	MeCN	80	(45)[c]	1:0

[a] Yield of the isolated product after chromatographic purification. [b] Only 5 mol% of the ligand was added. [c] Conversion determined from the ^{1}H NMR spectrum of the crude reaction mixture. dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, NR = no reaction, S-Phos = 2-dicyclohexylphosphanyl-2′,6′-dimethoxybiphenyl, X-Phos = 2-dicyclohexylphosphanyl-2′,4′,6′-triisopropylbiphenyl.

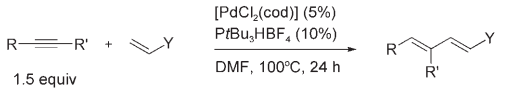
coupling; the use of other solvents led to lower yields and mixtures of the *cis* and *trans* products (Table 1, entries 8–10). The lowering of the reaction temperature had a detrimental effect on the coupling yield (results not shown).

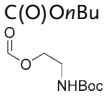
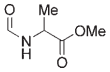
The palladium source did not appear to have a substantial impact on the outcome of the reaction. Both palladium(II) and palladium(0) complexes (e.g. $[PdCl_2(cod)]$, $Pd(OAc)_2$, $[PdCl_2(PhCN)_2]$, $[Pd(PtBu_3)_2]$, $[Pd_2(dba)_3]$) proved effective in terms of the coupling yield. Nevertheless, in certain cases (with $Pd(OAc)_2$, $[Pd(PtBu_3)_2]$), mixtures of *cis* and *trans* stereoisomers were obtained. Furthermore, we could decrease the number of equivalents of the alkene: The two coupling reagents could be used in an almost equimolar ratio without a substantial influence on the coupling yield. In the absence of either the palladium metal or the phosphine ligand, no coupling was observed.

The scope of the reaction was examined with a variety of symmetrical disubstituted alkynes (Table 2). Diphenylacetylene underwent efficient coupling with acrylamides and acrylates to give 1,3-dienes in 67–88% yield (Table 2, entries 1–5). The same alkyne displayed good reactivity towards two styrene derivatives (Table 2, entries 10 and 11).[14] The coupling of diphenylacetylene with *N*-tosylallylamine also proved possible but afforded a series of isomeric alkenes, which were difficult to separate. However, hydrogenation of the product mixture afforded a single compound, *N*-tosyl-4,5-diphenylpentanamine, which was isolated in 98% yield (Table 2, entry 12). Other symmetrical alkynes were also compatible with the reaction conditions in the coupling with *N*-*tert*-butylacrylamide (Table 2, entries 6–8). However, the addition to phenyl acetylene was less effective (Table 2, entry 9), possibly as a result of the instability of this acetylene at the temperature required for the reaction.

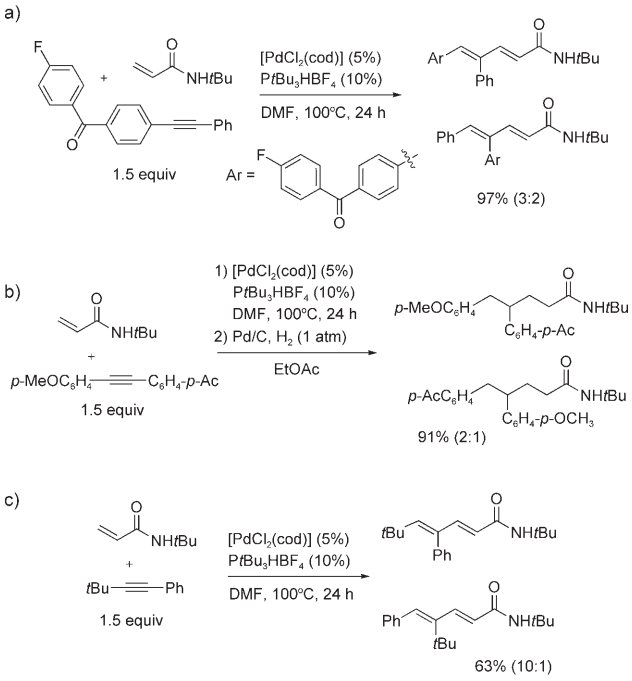
Nonsymmetrical disubstituted acetylenes were also investigated as substrates (Scheme 2). We examined substrates in which *para*-substituted phenyl groups with either electron-withdrawing or electron-donating substituents were present

Table 2: Palladium-catalyzed intermolecular coupling of alkynes with alkenes.



Entry	R	R′	Y	Yield [%][a,b]
1	Ph	Ph	C(O)NH*t*Bu	88
2	Ph	Ph	C(O)O*n*Bu	84 (2:1)
3	Ph	Ph		67
4	Ph	Ph		76
5	Ph	Ph	$C(O)NH_2$	80 (3:1)
6	*p*-CNC_6H_4	*p*-CNC_6H_4	C(O)NH*t*Bu	77 (2:1)
7	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	C(O)NH*t*Bu	72
8	EtOC(O)	EtOC(O)	C(O)NH*t*Bu	63 (2:1)
9	Ph	H	C(O)NH*t*Bu	24
10	Ph	Ph	*p*-(CONH*t*Bu)C_6H_4	76
11	Ph	Ph	*p*-$OMeC_6H_4$	71 (4:1)
12	Ph	Ph	CH_2NHTs	98[c]

[a] Yield of the isolated product after chromatographic purification. [b] Isomer ratios (*Z*/*E*) are given in parentheses. [c] A mixture of a minimum of five stereoisomers was obtained. However, after hydrogenation, a single compound, *N*-tosyl-4,5-diphenylpentanamine, was isolated. Boc = *tert*-butoxycarbonyl, Ts = *p*-toluenesulfonyl.

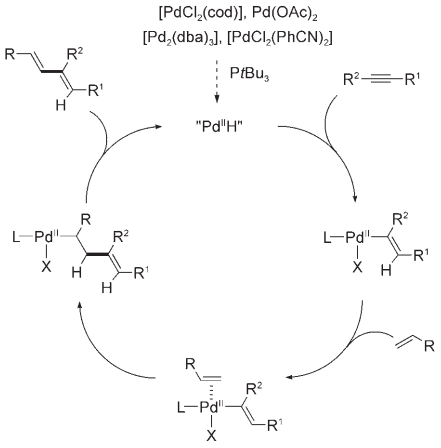


Scheme 2. Intermolecular ene–yne coupling with disubstituted nonsymmetrical acetylenes.

on the alkyne and observed no significant influence of electronic factors on the regioselectivity of the reaction (Scheme 2a,b). Steric effects were more important, as illustrated by the coupling of *tert*-butyl phenyl acetylene with *N*-*tert*-butylacrylamide to provide a 10:1 mixture of regioisom-

ers in favor of the product with a terminal *tert*-butyl group (Scheme 2c).

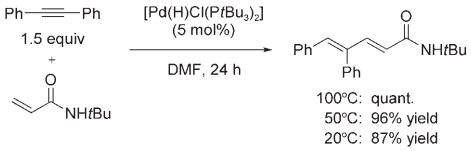
A potential mechanism for these catalytic transformations is depicted in Scheme 3. The heating of Pd^{II} or Pd^0 complexes in the presence of $PtBu_3$ in DMF could generate a Pd^{II} hydride species, which would undergo hydropalladation with the



Scheme 3. Proposed mechanism of the intermolecular ene–yne coupling. dba = dibenzylideneacetone.

alkyne to generate an alkenyl Pd^{II} intermediate similar in structure to the complex obtained from the oxidative addition of Pd^0 into a vinyl halide bond. Subsequent reaction with the alkene then occurs through a classical Heck mechanism to finally regenerate the Pd^{II} hydride for the next cycle. Bulky trialkyl phosphine ligands were found to catalyze these reactions effectively. This observation may be explained by the nature of the Pd complexes formed when such phosphine ligands are used. Pd^{II} complexes containing the ligand $PtBu_3$ have been reported previously to form a T-shaped metal species rather than the more commonly observed tetracoordinate square-planar-type complexes.[15] As alkynes are also known to coordinate strongly to Pd^{II} and Pd^0 complexes as both π-acceptor and π-donor ligands, [16] it is possible that a strong complex is formed between the alkyne and the Pd hydride species produced after the β-hydride-elimination step. Hence, the hydropalladation step may be sufficiently fast that base-promoted reduction of the Pd hydride species can not compete, as observed in our initial experiments (Scheme 1).

Alternatively, a [2+2+1] cycloaddition mechanism via a palladacyclopentene intermediate is possible, as proposed previously by Watanabe and co-workers for a ruthenium-catalyzed codimerization of acetylenes with olefins.[7a,14] In this reaction, which is similar to our Pd-catalyzed intermolecular ene–yne coupling, high reaction temperatures are required. To probe which of the two mechanisms operates in these reactions, we prepared the palladium(II) hydride complex $[HPdCl(PtBu_3)_2]$ from commercially available $[Pd(PtBu_3)_2]$ and HCl according to the procedure of Hills and Fu.[17] This complex catalyzed the coupling of diphenylacetylene with *N-tert*-butylacrylamide at both 100 and 50 °C to give the desired 1,3-diene in nearly quantitative yield (Scheme 4). Even more interestingly, the coupling product was obtained in 87% yield when the reaction was performed at 20 °C.

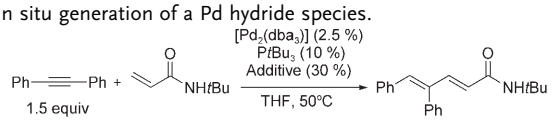


Scheme 4. Intermolecular ene–yne coupling catalyzed by $[Pd(H)Cl(PtBu_3)_2]$.

Although these results do not rule out the involvement of the cycloaddition mechanism in the reactions performed with a palladium salt and trialkyl phosphine ligand at 100 °C, they do provide evidence that palladium hydride species can indeed catalyze the intermolecular ene–yne coupling reaction.

Unfortunately, the use of this palladium hydride complex was impractical. The complex is generated from expensive $[Pd(PtBu_3)_2]$ in a glove box and when isolated shows signs of decomposition after several hours under argon. Hence, we had to synthesize this complex prior to each set of coupling experiments performed. We therefore investigated the possibility of generating this hydride species in situ under the ene–yne coupling conditions. To this end, a series of additives were tested in substoichiometric quantities in the coupling of diphenylacetylene with *N-tert*-butylacrylamide in the presence of $[Pd_2(dba)_3]$ and $PtBu_3$ (Table 3), from which the Pd hydride species could in principle be generated under the reaction conditions employed. Of the wide range of additives examined, only the acid chlorides (Table 3, entries 7 and 8) catalyzed the reaction in an efficient manner at 50 °C to give the coupling product in high yield.[18] When the reaction temperature was decreased, the coupling product was obtained in lower yield after 24 h. The coupling reaction

Table 3: Optimization of the intermolecular ene–yne coupling through the in situ generation of a Pd hydride species.



Entry	Additive	Conv. [%][a]	Yield [%][b]
1	AcOH	NR	–
2	PhI	–[c]	–
3	*p*-AcC_6H_4Cl	NR	–
4	HCl in Et_2O	8	–
5	BnCl	15	–
6	butyl chloride	NR	–
7	isobutyryl chloride	100	97
8	adipoyl chloride[d]	100	96
9	–	NR	–

[a] The conversion was determined from the ^1H NMR spectrum of the crude reaction mixture. [b] Yield of the isolated product after chromatographic purification. [c] *N-tert*-Butyl cinnamide was detected in the crude product by ^1H NMR spectroscopic analysis. [c] Adipoyl chloride: 0.15 equivalents. Bn = benzyl.

was carried out in THF. The use of other solvents, such as toluene, dioxane, dimethoxyethane, and EtOAc, also led to the formation of the coupling product in at least 95% yield.

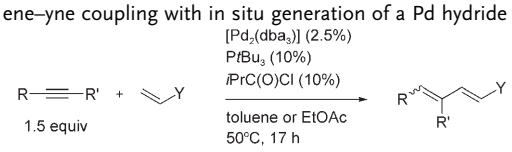
These new coupling conditions were then tested with a variety of disubstituted alkyne substrates, many of which did not undergo effective coupling under the previous conditions in DMF at 100°C (Table 4). Di(*p*-acetylphenyl)acetylene was coupled with *N*-*tert*-butylacrylamide in near quantitative yield (Table 4, entry 1). The treatment of the same coupling partners under similar conditions to those in Table 2 led to a multitude of products according to NMR analysis. Similarly, higher coupling yields were observed with di(*p*-cyanophenyl)-acetylene (Table 2, entry 2)[12] and the ynamide in entry 3 of Table 4, a heteroatom-substituted alkyne.[12] In the latter case, the best results in terms of yield and regioselectivity were obtained at 80°C with a higher catalyst loading. The alkynyl phosphonate in entry 4 of Table 4 was also a suitable substrate, the reaction of which proceeded with good regioselectivity. Diaryl acetylenes were also coupled successfully with a vinyl boronic ester and an allylic alcohol (Table 4, entries 5, 6, and 8). Finally, the reaction of diphenylacetylene with dihydrofuran provided exclusively the α-coupling product, a result that indicates a Heck-type mechanism. Again, modified reaction conditions were required to obtain the coupling products in good yields.

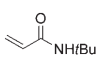
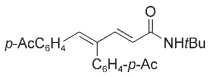
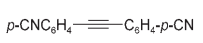
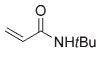
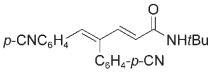
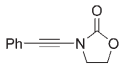
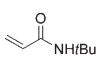
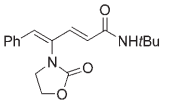
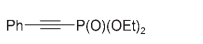
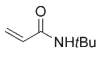
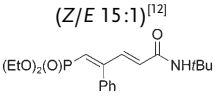
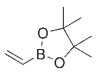
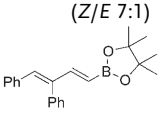
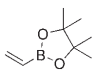
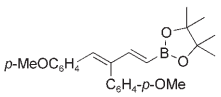
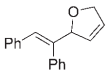
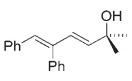
In conclusion, we have demonstrated the potential for carrying out intermolecular ene–yne coupling reactions between disubstituted acetylenes and olefins. These reactions appear to be catalyzed by a palladium hydride species. Further studies are in progress to increase the scope of these reactions, for example, to the use of monosubstituted acetylene substrates, by modifying the reaction conditions.

Experimental Section

(2*E*,4*Z*)-**2**: Diphenylacetylene (104.3 mg, 0.59 mmol), *tert*-butylacrylamide (49.6 mg, 0.39 mmol), $PtBu_3HBF_4$ (11.3 mg, 0.04 mmol), and $[PdCl_2(cod)]$ (5.6 mg, 0.02 mmol) were dissolved in DMF (3 mL) in a glove box under an argon atmosphere. The sample vial was fitted with a Teflon-sealed screw cap and removed from the glove box. The reaction mixture was heated at 100°C for 24 h. The crude product was purified by flash chromatography on silica gel (EtOAc/pentane 1:9) to afford (2*E*,4*Z*)-**2** (105 mg, 88%) as a single isomer. ^{1}H NMR

Table 4: Palladium-catalyzed intermolecular ene–yne coupling with in situ generation of a Pd hydride species.[a]



Entry	Alkyne	Alkene	Product	Yield [%][a]
1[b]				95
2[b] [12]				92
3[c]			 (*Z*/*E* 15:1)[12]	59
4[d]			 (*Z*/*E* 7:1)	78
5[e]				61
6[c,f]			 (*Z*/*E* 7:1)	88
7[g]				63
8[e,h]			 (*Z*/*E* 4:1)	92

[a] Yield of the isolated product after chromatographic purification. [b] The reaction was carried out in EtOAc/toluene (1:1). [c] The reaction was carried out in toluene at 80°C with $[Pd_2(dba)_3]$ (5 mol%), $PtBu_3$ (20 mol%), isobutyryl chloride (20 mol%), and acrylamide (3 equiv). [d] The reaction was carried out in EtOAc for 42 h. Ratio of product regioisomers: 19:1. [e] The reaction was carried out in EtOAc. [f] The reaction was carried out in toluene at 80°C with 2 equivalents of the alkene. [g] The reaction was carried out in dioxane. [h] Alkene: 4 equivalents.

(400 MHz, C_6D_6): $\delta = 8.40$ (d, $J = 14.8$ Hz, 1H), 7.60–7.51 (m, 6H), 7.32–7.29 (m, 4H), 7.08 (s, 1H), 5.92 (d, $J = 14.8$ Hz, 1H), 5.06 (br s, 1H), 1.62 ppm (s, 9H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 164.9$, 145.6, 140.2, 138.7, 137.2, 136.6, 130.3, 129.8, 129.4, 128.3, 128.0, 127.8, 125.2, 50.9, 28.8 ppm; HRMS: *m/z* calcd for $C_{21}H_{23}NO$: 328.1677 $[M+Na]^+$; found: 328.1680.

Table 4, entry 2: 4,4′-Ethynediyldibenzonitrile (133.5 mg, 0.293 mmol), *tert*-butylacrylamide (49.6 mg, 0.39 mmol), P*t*Bu$_3$ (7.8 mg, 0.04 mmol), and $[Pd_2(dba)_3]$ (8.9 mg, 0.01 mmol) were dissolved in EtOAc/toluene (1:1, 4 mL) in a glove box under an argon atmosphere. Isobutyryl chloride was then added from a stock solution (0.05 mg μL^{-1}, 83.1 μL) in EtOAc. The sample vial was fitted with a Teflon-sealed screw cap and removed from the glove box. The reaction mixture was heated at 50 °C for 17 h. The crude product was purified by flash chromatography on silica gel (EtOAc/CH_2Cl_2/pentane 1:1:3) to afford (2*E*,4*Z*)-*N*-*tert*-butyl-4,5-bis(4-cyanophenyl)-penta-2,4-dienamide (127.2 mg, 92%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.71$ (d, $J = 8.4$ Hz, 2H), 7.53 (d, $J = 14.8$ Hz, 1H), 7.40 (d, $J = 8.4$ Hz, 2H), 7.28 (d, $J = 8.4$ Hz, 2H), 6.95 (d, $J = 8.4$ Hz, 2H), 6.90 (s, 1H), 5.43 (br s, 1H), 5.37 (d, $J = 14.8$ Hz, 1H), 1.34 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.4$, 143.1, 142.1, 140.9, 139.8, 135.3, 133.1, 132.1, 130.4, 130.1, 126.8, 118.5, 118.3, 112.3, 111.5, 51.7, 28.8 ppm; HRMS: *m/z* calculated for $C_{23}H_{21}N_3O$: 378.1582 $[M+Na]^+$; found: 378.1576.

Received: December 5, 2007
Published online: February 26, 2008

Keywords: alkenes · alkynes · Mizoroki–Heck reaction · palladium · phosphane ligands

[1] a) J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651; b) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed. (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**; c) J. Tsuji, *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*, Wiley, Chichester, **2004**; d) *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E. Negishi), Wiley-Interscience, New York, **2002**.

[2] For some recent reviews on the Heck reaction, see: a) R. F. Heck, *Synlett* **2006**, 2855; b) N. T. S. Phan, M. Van Der Sluys, C. W. Jones, *Adv. Synth. Catal.* **2006**, *348*, 609; c) F. Alonso, I. P. Beletskaya, M. Yus, *Tetrahedron* **2005**, *61*, 11771.

[3] For two recent examples of the Pd-catalyzed coupling of nonfunctionalized arenes by C–H activation, see: a) D. R. Stuart, K. Fagnou, *Science* **2007**, *316*, 1172; b) D. R. Stuart, E. Villemure, K. Fagnou, *J. Am. Chem. Soc.* **2007**, *129*, 12072, and references therein.

[4] a) B. M. Trost, *Science* **1991**, *254*, 1471; b) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285; *Angew. Chem. Int. Ed. Eng.* **1995**, *34*, 259; c) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695.

[5] a) B. M. Trost, G. J. Tanoury, *J. Am. Chem. Soc.* **1988**, *110*, 1636; b) B. M. Trost, *Acc. Chem. Res.* **1990**, *23*, 34; c) B. M. Trost, M. Yanai, K. Hoogsteen, *J. Am. Chem. Soc.* **1993**, *115*, 5294; d) B. M. Trost, V. K. Chang, *Synthesis* **1993**, 824; e) B. M. Trost, G. J. Tanoury, M. Lautens, C. Chan, D. T. Macpherson, *J. Am. Chem. Soc.* **1994**, *116*, 4255; f) B. M. Trost, M. J. Krische, *Synlett* **1998**, 1; g) B. M. Trost, F. D. Tosate, A. B. Pinkerton, *Chem. Rev.* **2001**, *101*, 2067.

[6] a) I. Ojima, M. Tzamarioudaki, Z. Li, R. J. Donovan, *Chem. Rev.* **1996**, *96*, 635; b) C. Aubert, O. Buisine, M. Malacria, *Chem. Rev.* **2002**, *102*, 813; c) V. Balraju, R. V. Dev, S. S. Reddy, J. Iqbal, *Tetrahedron Lett.* **2006**, *47*, 3569.

[7] For a Ru-catalyzed version of this reaction to give 1,3-dienes, see: a) T. Mitsudo, S.-W. Zhang, M. Nagao, Y. Watanabe, *J. Chem. Soc. Chem. Commun.* **1991**, 598; b) C. S. Yi, D. W. Lee, Y. Chen, *Organometallics* **1999**, *18*, 2043. In reference [7b] only coupling with ethylene was described.

[8] The Ru-catalyzed coupling of alkynes with alkenes for the synthesis of 1,4-dienes and related compounds is well known; for representative examples, see: a) B. M. Trost, A. F. Indolese, T. J. J. Müller, B. Treptow, *J. Am. Chem. Soc.* **1995**, *117*, 615; b) B. M. Trost, T. J. J. Müller, J. Martinez, *J. Am. Chem. Soc.* **1995**, *117*, 1888; c) B. M. Trost, T. J. J. Müller, *J. Am. Chem. Soc.* **1994**, *116*, 4985; d) B. M. Trost, J. A. Martinez, R. J. Kulawiec, A. F. Indolese, *J. Am. Chem. Soc.* **1993**, *115*, 10402; e) B. M. Trost, J.-P. Surivet, F. D. Toste, *J. Am. Chem. Soc.* **2001**, *123*, 2897; f) B. M. Trost, H. C. Shen, A. B. Pinkerton, *Chem. Eur. J.* **2002**, *8*, 2341; g) B. M. Trost, F. D. Toste, *Tetrahedron Lett.* **1999**, *40*, 7739; h) S. Dérien, P. H. Dixneuf, *J. Chem. Soc. Chem. Commun.* **1994**, 2551; i) S. Dérien, L. Ropartz, J. Le Paih, P. H. Dixneuf, *J. Org. Chem.* **1999**, *64*, 3524.

[9] a) A. L. Hansen, J.-P. Ebran, M. Ahlquist, P.-O. Norrby, T. Skrydstrup, *Angew. Chem.* **2006**, *118*, 3427; *Angew. Chem. Int. Ed.* **2006**, *45*, 3349; b) J. P. Ebran, A. L. Hansen, T. Gøgsig, T. Skrydstrup, *J. Am. Chem. Soc.* **2007**, *129*, 6931.

[10] For examples of 1,2-migration in the Kumada and Negishi cross-coupling reactions, see: a) M. E. Limmert, A. H. Roy, J. F. Hartwig, *J. Org. Chem.* **2005**, *70*, 9364; b) A. L. Hansen, J.-P. Ebran, T. Gøgsig, T. Skrydstrup, *J. Org. Chem.* **2007**, *72*, 6464.

[11] For a review on palladium hydride complexes, see: V. V. Grushin, *Chem. Rev.* **1996**, *96*, 2011.

[12] The structure of the product (major isomer, where applicable) was determined by X-ray structural analysis. CCDC-669443 (**2**), -669444 (diene from Table 4, entry 2), and -632284 (diene from Table 4, entry 3) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. As the alkene functionality originating from the alkyne was found to have the *Z* configuration in these three products, the products (major isomer, where applicable) of all other reactions reported were tentatively assigned this configuration.

[13] For references on the development of bulky electron-rich phosphines and their application in coupling reactions, notably by the research groups of Fu, Buchwald, Hartwig, and Beller, see: A. Zapf, M. Beller, *Chem. Commun.* **2005**, 431.

[14] Interestingly, styrene derivatives were not compatible with the Ru-mediated ene–yne coupling reported by Watanabe and co-workers (see reference [7a]). A [2+2+1] cycloaddition step with a five-membered cyclic ruthenium intermediate was proposed for these reactions.

[15] J. P. Stambuli, C. D. Incarvito, M. Bühl, J. F. Hartwig, *J. Am. Chem. Soc.* **2004**, *126*, 1184.

[16] a) M. Ahlquist, G. Fabrizi, S. Cacchi, P.-O. Norrby, *J. Am. Chem. Soc.* **2006**, *128*, 12785; b) M. Ahlquist, G. Fabrizi, S. Cacchi, P.-O. Norrby, *Chem. Commun.* **2005**, 4196.

[17] I. D. Hills, G. C. Fu, *J. Am. Chem. Soc.* **2004**, *126*, 13178.

[18] The generation of a palladium hydride species from either butyryl or adipoyl chloride most likely occurs by oxidative addition of Pd^0 into the carbon–halide bond, followed by decarbonylation and subsequent β-hydride elimination.

