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Stereospecific Synthesis of Highly Substituted Skipped Dienes through Multifunctional Palladium Catalysis

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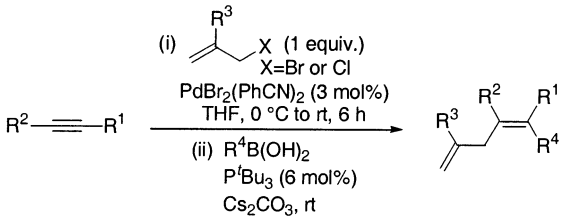
ABSTRACT



Multifunctional palladium catalysis is utilized in the one-pot stereocontrolled synthesis of tetrasubstituted alkenes. The homogeneous palladium dihalide catalyst utilized for bromo-/chloroallylation of alkynes is then reused in situ for a subsequent Suzuki cross-coupling reaction.

The growing importance of green chemistry and the concept of atom economy in organic synthesis has fueled the search for transformations that result in less waste.[1,2] A noteworthy advance in this regard is the development of multifunctional reagents capable of promoting two or more *distinct* transformations sequentially in the same pot. Such sequencing not only makes better use of precious reagents but, as an added benefit, eliminates inefficient separation and purification after each step.[3,4] Palladium reagents, known to induce a myriad of different reactions,[5] are particularly well suited for incorporation into multifunctional catalysis sequences. We report in this Letter the development of a stereospecific haloallylation/Suzuki cross-coupling sequence, in which the same Pd catalyst promotes both reactions.[6]

In connection with our work in alkaloids synthesis, we required a method for the stereocontrolled preparation of tetrasubstituted alkenes, wherein one of the substituents was an allyl unit. The plan was to utilize Pd(II) catalysis to bromoallylate an alkyne, using the procedure developed by Kaneda et al.,[7] and then, in a second step, introduce the final substituent by a Pd(0)-catalyzed Suzuki coupling (Scheme 1).[8]

(1) For reviews on green chemistry, see: Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686−694.

(2) For a discussion of atom economy, see: (a) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695−705. (b) Trost, B. M. *Science* **1991**, *254*, 1471−1477.

(3) For recent examples of tandem catalysis, see: (a) Yu, H.-B.; Hu, Q.-S.; Pu, L. *J. Am. Chem. Soc.* **2000**, *122*, 6500−6501. (b) Bielawski, C. W.; Louie, J.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 12872−12873. (c) Evans, P. A.; Robinson, J. E. *J. Am. Chem. Soc.* **2001**, *123*, 4609−4610. (d) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312−11313. (e) Zezschwitz, P.; Petry, F.; de Meijere, A. *Chem. Eur. J.* **2001**, 4035−4046. (f) Drouin, S. D.; Zamanian, F.; Fogg, D. E. *Organometallics* **2001**, 5495−5497. (g) Choudary, B. M.; Chowdari, N. S.; Jyothi, K.; Kumar, N. S.; Kantam, M. L. *Chem. Commun.* **2002**, 586−587. (h) Teoh, E.; Campi, E. A.; Jackson, W. R.; Robinson, A. J. *Chem. Commun.* **2002**, 978−979.

(4) For recent reviews of domino reactions, see: (a) Ikeda, S. *Acc. Chem. Res.* **2000**, *33*, 511−519. (b) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959−5989. (c) De Meijere, A.; Bräse, S. *J. Organomet. Chem.* **1999**, *576*, 88−110. (d) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (e) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195−206. (f) Malacria, M. *Chem. Rev.* **1996**, *96*, 289−306. (g) Heumann, A.; Réglier, M. *Tetrahedron* **1996**, *52*, 9289−9346.

(5) (a) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; John Wiley & Sons: New York, 1995 (b) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959−5989. (c) Tsuji, J. *Transition Metal Reagents and Catalysts: Innovation in Organic Synthesis*; John Wiley & Sons: New York, 2000.

(6) The sequencing of the haloallylation with Sonogashira cross-coupling and Wacker−Tsuji oxidation is described in the accompanying Letter: Thadani, A. N.; Rawal, V. H. *Org. Lett.* **2002**, *4*, 4321−4324.

(7) Kaneda, K.; Uchiyama, T.; Fujiwara, Y.; Imanaka, T.; Teranishi, S. *J. Org. Chem.* **1979**, *44*, 55−63.

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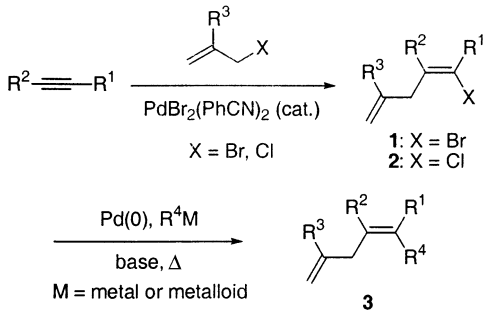
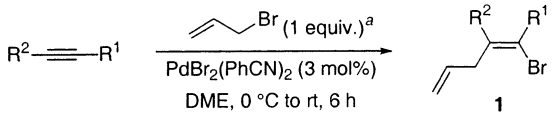
Scheme 1



The initial studies were directed at improving the original protocol of Kaneda et al., which called for the use of the allyl bromide or chloride in vast excess—often as the reaction solvent.[7] A variety of Pd catalysts were examined for the reaction between allyl bromide and 1-hexyne, but none were found to be superior to that originally employed by Kaneda and co-workers, $PdBr_2(PhCN)_2$.[9] The addition of phosphine ligands was determined to be detrimental to the haloallylation reaction. The main reason for using the allyl bromide in excess was to reduce the relative concentration of the alkyne, since it is prone to oligomerization or polymerization in the presence of the Pd catalyst. It was discovered that Pd catalyzed side reactions can be circumvented by employing dropwise addition of the alkyne. Under the optimized protocol, a solution of the alkyne (1 equiv) in dimethoxyethane (DME) is added dropwise to a solution of the allylic halide (1 equiv) and the Pd(II) catalyst (3 mol %) in DME. The modified procedure uses equimolar amounts of the two reactants and is effective for the coupling of allyl bromide to a variety of alkynes, affording the expected products cleanly and in high isolated yields (Table 1). Additionally,

Table 1. Palladium-Catalyzed Bromoallylation of Acetylenes



entry	R^1	R^2	yield [%][b]
1	H	CO_2Me	82 (**1a**)
2	^{n}Bu	H	83 (**1b**)
3	Ph	H	85 (**1c**)
4	^{n}Pr	^{n}Pr	87 (**1d**)

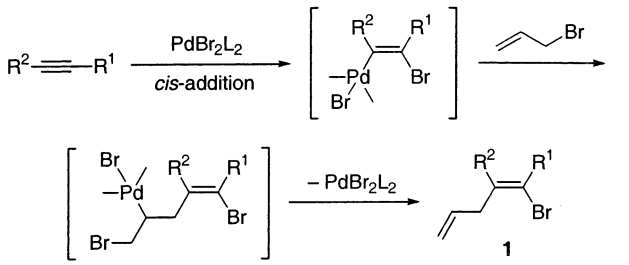
[a] Dropwise addition as a solution in DME. [b] Isolated yield.

the workup is simplified compared to the original procedure, since there is essentially no allyl bromide, a potent lacrymator, left at the end of the reaction.

(8) For other examples of bromo-/chloropalladation of alkynes, see: (a) Llebaria, A.; Camps, F.; Moretó, J. M. *Tetrahedron* **1993**, *49*, 1283−1296. (b) Ma, S.; Lu, X. *J. Org. Chem.* **1993**, *58*, 1245−1250. (c) Bäckvall, J. E.; Nilsonn, Y. I. M.; Andersson, P. G.; Gatti, R. G. P.; Wu, J. *Tetrahedron Lett.* **1994**, *35*, 5713−5716. (d) Xu, X.; Lu, X.; Liu, Y.; Xu, W. *J. Org. Chem.* **2001**, *66*, 6545−6550.

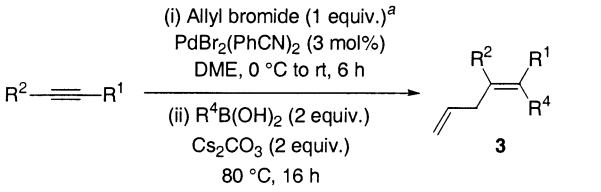
The mechanism of the initial bromoallylation of alkynes utilizing palladium dihalide catalysts has been investigated by Kaneda et al.[7] and Bäckvall and co-workers.[10] On the basis of the accepted mechanism, the catalytic cycle from the bromoallylation is expected to produce a Pd(II) species (Scheme 2).

Scheme 2



During the course of the optimization studies, we observed that the catalyst remains completely homogeneous throughout the reaction; Pd black does not precipitate out even after the reaction has gone to completion. This observation suggested the possibility of accomplishing the second transformation, a Suzuki−Miyaura cross-coupling,[11] in the same flask, using the Pd(II) catalyst already present.[12] Addition of the boronic acid was expected to reduce the Pd(II) to Pd(0), the catalytically active species for the Suzuki reaction. As a test case, upon completion of the reaction between allyl bromide and methyl propiolate (entry 1, Table 2), the reaction mixture

Table 2. One-Pot Tandem Bromoallylation/Suzuki Cross-Coupling of Alkynes



entry	R^1	R^2	R^4	yield [%][b]
1	H	CO_2Me	4-$MeOC_6H_4$	82 (**3a**)
2	CH_2OTBS	H	3-Me(O)CC_6H_4	82 (**3b**)
3	$C(Me)_2OH$	H	4-$MeOC_6H_4$	86 (**3c**)
4	Ph	H	4-$MeOC_6H_4$	80 (**3d**)
5	^{n}Pr	^{n}Pr	3-$O_2NC_6H_4$	78 (**3e**)
6	CH_2OTBS	Me	Ph	74 (**3f**)

[a] Dropwise addition as a solution in DME. [b] Isolated yield.

was treated with cesium carbonate (2 equiv) and 4-methoxyphenylboronic acid (2 equiv) and heated to 80 °C for 16 h

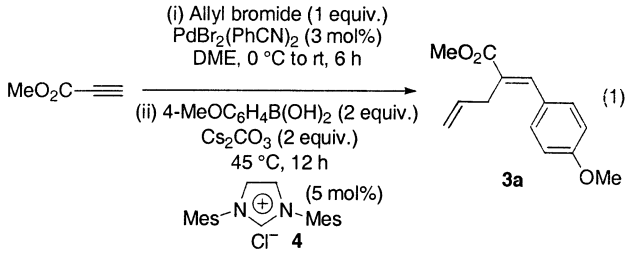
(9) The following are among the catalysts screened: $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $Pd_2(dba)_3$, and $Pd(OAc)_2$.

(10) Bäckvall, J. E.; Nilsonn, Y. I. M.; Gatti, R. G. P. *Organometallics* **1995**, *14*, 4242−4246.

in the same reaction vessel.[13] The desired tetrasubstituted alkene **3a** was obtained in high isolated yield (82%). The success of the two-reaction process confirmed the presence of the active palladium catalyst upon completion of the bromoallylation step.

The tandem, one-pot bromoallylation/Suzuki coupling sequence was extended to a variety of other alkynes, the results of which are shown in Table 2. The coupling process was effective for terminal and internal alkynes. Aliphatic and aromatic substituents on the alkyne were compatible with the process. The reaction tolerates both electron-donating and electron-withdrawing substituents on the alkyne. The scope of the tandem reaction was also established with a variety of electron-rich (entries 1, 3, and 4) and electron-poor (entry 5) arylboronic acids as cross-coupling partners. The resulting tetrasubstituted skipped dienes **3** were generated in good yields and excellent regio- and stereoselectivities. Thus, this tandem process represents the execution of two mechanistically distinct reactions catalyzed sequentially by the same palladium catalyst in one pot.

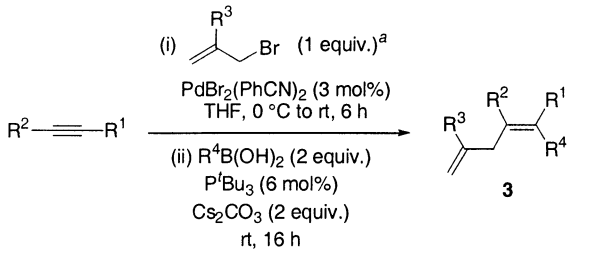
Encouraged by the results of the tandem catalysis sequence, we sought to investigate the possibility of conducting the Suzuki coupling step under milder conditions. Toward this end, various carbene and phosphine ligands were investigated as additives to generate a new, presumably more reactive, Pd(0) complex capable of catalyzing the cross-coupling reaction at lower temperatures.[14] Addition of carbene precursor **4** (5 mol %)[15] as a reagent during the Suzuki coupling step allowed for the lowering of the reaction temperature to 45 °C. Tetrasubstituted skipped diene **3a** was isolated in a slightly higher yield of 85% using this modification (cf. Table 2, entry 1).



A variety of triaryl and trialkyl phosphines were also examined for the Suzuki coupling step.[16] As expected, tri-*tert*-butylphosphine (P^tBu_3) was found to be the most effective additive in enabling the Suzuki coupling to proceed at lower temperatures.[17,18] Indeed, the addition of 6 mol % of P^tBu_3 after the initial step enabled the tandem bromoallylation/Suzuki coupling of methyl propiolate to proceed at room temperature in THF. The functionalized skipped diene **3a** was isolated in 83% yield, similar to that obtained in the absence of any phosphine ligand (Table 2, entry 1). The added P^tBu_3 is expected to convert the initial $PdBr_2(PhCN)_2$ catalyst to $PdBr_2(P^tBu_3)_2$,[19] which presumably is reduced in situ to a catalytically active Pd(0) species.

This final modification is effective for carrying out the room temperature, one-pot tandem bromoallylation/Suzuki coupling of a wide range of alkynes and boronic acids (Table 3). Methallylbromide (entries 10 and 11) was shown to be an equally effective partner in the initial bromoallylation step. The nature of the boronic acid in the Suzuki coupling step was expanded to include alkenyl (entries 8 and 9) and heterocyclic (entry 11) variants. This protocol thus allows

Table 3. One-Pot Tandem Bromoallylation/Suzuki Cross-Coupling of Alkynes at Room Temperature



entry	R^1	R^2	R^3	R^4	yield [%][b]
1	H	CO_2Me	H	4-$MeOC_6H_4$	83(**3a**)
2	CH_2OTBS	H	H	3-Me(O)CC_6H_4	86(**3b**)
3	$C(Me)_2OH$	H	H	4-$MeOC_6H_4$	81(**3c**)
4	Ph	H	H	4-$MeOC_6H_4$	83(**3d**)
5	^{n}Pr	^{n}Pr	H	3-$O_2NC_6H_4$	79(**3e**)
6	CH_2OTBS	Me	H	Ph	81(**3f**)
7	^{n}Bu	H	H	4-$MeOC_6H_4$	83(**3g**)
8	Ph	H	H	(*E*)-$C_4H_9CH{=}CH$	83(**3h**)
9	Ph	H	H	(*E*)-PhCH=CH	86(**3i**)
10	CH_2OTBS	H	Me	4-$MeOCC_6H_4$	81(**3j**)
11	^{n}Pr	^{n}Pr	Me	*N*-tosyl-3-indoyl	83(**3k**)

[a] Dropwise addition as a solution in THF. [b] Isolated yield (%).

(11) For recent reviews on the Suzuki reaction, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *J. Organomet. Chem.* **2002**, *653*, 83−90.

(12) The tandem bromoallylation/Stille coupling has been demonstrated, albeit in modest yields, see: Kosugi, M.; Sakaya, T.; Ogawa, S.; Migita, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3058−3061.

(13) Cesium carbonate was found to be the base of choice after screening a variety of other bases including K_2CO_3, KF, $NaHCO_3$, and NaOH.

(14) For leading references on the use of *N*-heterocyclic carbenes in cross-coupling reactions, see: (a) Herrmann, W. A.; Elison, M.; Fischer, J.; Köcher, C.; Artus, G. R. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2371−2373. (b) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804−3805. (c) Böhm, V. P. W.; Gstöttmayr, C. W. K.; Weskamp, T.; Herrmann, W. A. *J. Organomet. Chem.* **2000**, *595*, 186−190. (d) Grasa, G. A.; Viciu, M. S.; Huang, J.; Zhang, C.; Trudell, M. L.; Nolan, S. P. *Organometallics* **2002**, *21*, 2866−2873. (e) Hillier, A. C.; Nolan, S. P. *Platinum Metal Rev.* **2002**, *46*, 50−64.

(15) Arduengo, A. J., III; Dias, H. V. R.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530−5534.

(16) PPh_3, PCy_3, P^tBu_3, and dppf were tested.

(17) For leading references on the use of P^tBu_3 for cross-coupling reactions, see: (a) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617−620. (b) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367−2370. (c) Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729−1731. (d) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719−2724. (e) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989−7000. (f) Littke, A. F.; Schwarz, L.; Fu. G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343−6348.

(18) For leading references on the use of P^tBu_3 for Suzuki reaction, see: (a) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028. (b) Netherton, M. R.; Dai, C.; Neuschuetz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099−10100. (c) Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1945−1947.

(19) Goel, R. G.; Ogini, W. O. *Organometallics* **1982**, *1*, 654−658.

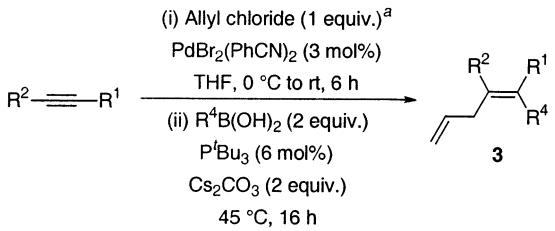
for the stereocontrolled synthesis of functionalized skipped dienes in good overall yields and under very mild conditions.

The final improvement to the process was to incorporate the use of allyl chloride in the tandem catalysis sequence. The advantages of using chlorides over bromides include lower cost, higher stability, and commercial availability of a broader range of compounds, issues that are of particular importance for large-scale applications of this methodology. During initial optmization studies, it was determined that chloroallylation of alkynes using 1 equiv of allyl chloride proceeded at a slower rate than the corresponding reaction with allyl bromide. Nevertheless, after 6 h, only trace amounts of the alkyne remained in the crude reaction mixture. The resulting crude vinyl chloride **2** (R^1 = Ph; R^2, R^3 = H) was directly subjected to the Suzuki cross-coupling conditions with 4-methoxyphenylboronic acid, P^tBu_3, and cesium carbonate. Although the cross-coupling step proceeded slowly at room temperature (<20% conversion after 24 h), it proceeded nicely to full conversion when the temperature was raised to 45 °C.

Several different alkynes were then subjected to this protocol for the one-pot tandem chloroallylation/Suzuki coupling (Table 4). As before, the desired skipped dienes (**3**) were produced with complete regio- and stereochemical integrity, albeit in slightly lower yields compared with the corresponding tandem bromoallylation/Suzuki couplings (Table 3). The lower yields are probably due to increased oligo- and polymerization of the alkyne as a result of the slow nature of the initial chloroallylation.

To summarize, we have demonstrated the capability of using a palladium catalyst for two mechanistically distinct chemical reactions—bromo- or chloroalllylation of an alkyne followed, in the same flask, by a Suzuki cross-coupling reaction. This tandem sequence produces functionalized, tetrasubstituted skipped dienes in a stereocontrolled manner. The advantages of this multifunctional catalysis include the avoidance of intermediate workup steps and the atom economy associated with not having to use a second set of reagents and solvents, as well as the time and cost savings of transforming the used catalyst in situ for a second reaction.

Table 4. One-Pot Tandem Chloroallylation/Suzuki Cross-Coupling of Alkynes



entry	R^1	R^2	R^4	yield [%][b]
1	H	CO_2Me	4-$MeOC_6H_4$	73 (**3a**)
2	CH_2OTBS	H	3-Me(O)CC_6H_4	68 (**3b**)
3	$C(Me)_2OH$	H	4-$MeOC_6H_4$	68 (**3c**)
4	Ph	H	4-$MeOC_6H_4$	70 (**3d**)
5	^{n}Pr	^{n}Pr	3-$O_2NC_6H_4$	64 (**3e**)
6	CH_2OTBS	Me	Ph	72 (**3f**)

[a] Dropwise addition as a solution in THF. [b] Isolated yield.

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Supporting Information Available: Preparation procedures and characterization data for **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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