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Multifunctional Palladium Catalysis. 2. Tandem Haloallylation Followed by Wacker–Tsuji Oxidation or Sonogashira Cross-Coupling

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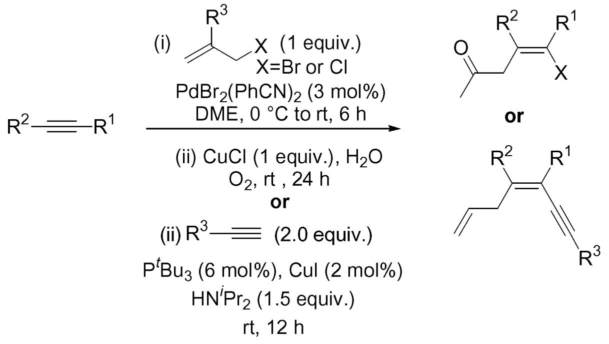
ABSTRACT



Multifunctional palladium catalysis is utilized in the one-pot stereocontrolled synthesis of tetrasubstituted methyl ketones and enynes. The homogeneous palladium dihalide catalyst utilized for the bromo-/chloroallylation of alkynes is reused in situ for subsequent Wacker–Tsuji oxidation or Sonogashira cross-coupling.

The importance of catalysis as a central tenet of the green chemistry paradigm is well established.[1] Palladium catalysis, in particular, has been the driver of many advances in modern day organic synthesis.[2] In most instances, the function of the palladium reagents is to catalyze a single type of transformation. More desirable, from the viewpoint of efficiency, are reagents capable of catalyzing multiple reactions in a single pot.[3] This multifunctional use of the catalyst would not only generate less waste but it would also obviate the tedious separation and purification of the intermediate products.[4]

In the preceding paper,[5] we reported that the atom economical addition of allyl chlorides and bromides to acetylenes, developed by Kaneda and co-workers, is ideally

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[1] For a brief review on the concept of green chemistry, see: Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686−694.

[2] (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: Innovations in Organic Synthesis*; John Wiley & Sons: New York, 2000.

[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] Thadani, A. N.; Rawal, V. H. *Org. Lett.* **2002**, *4*, 4317−4320.

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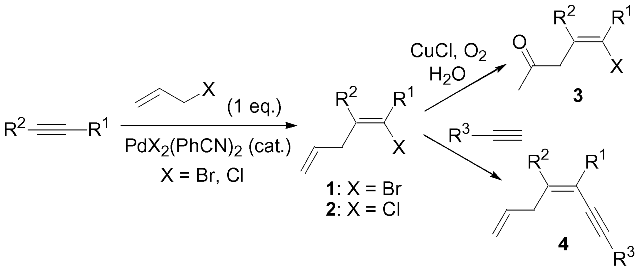
suited for “catalyst recycling”.[6−8] We showed that the haloallylation step can be followed, in the same pot and using only the initial catalyst, with a Suzuki cross-coupling reaction to afford tetrasubstituted alkenes in high yields and excellent regio- and stereoselectivities.[5] In this paper, we demonstrate that the palladium(II) catalyst from the initial bromo-/chloroallylation step can also be reused in situ for subsequent Wacker−Tsuji oxidations and Sonogashira cross-coupling reactions (Scheme 1).[9]

Scheme 1

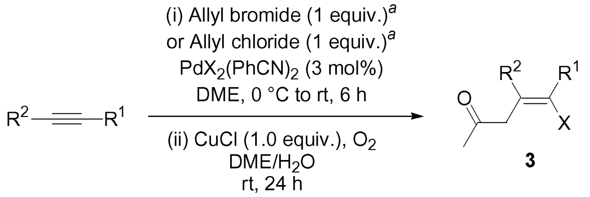


1: X = Br
2: X = Cl
3
4

The Wacker−Tsuji oxidation is particularly well-suited for incorporation in a tandem sequence with the haloallylation step, as both reactions are catalyzed by palladium(II) species.[10] A trial reaction was performed with 4-octyne and an equimolar amount of allyl bromide. The initial bromoallylation catalyzed by $PdBr_2(PhCN)_2$ (3 mol %) was carried out in DME, as previously described.[5] To the resulting crude reaction mixture containing the alkenyl bromide **1** ($R^1 = R^2 = {}^n$Pr; X = Br) and the palladium catalyst was added copper(I) chloride (1 equiv) and water.[11] The reaction mixture was then stirred for 24 h under an oxygen atmosphere. Methyl ketone **3a** was subsequently isolated in 80% yield after workup and chromatographic purification. This sequence confirmed that the palladium(II) catalyst from the initial bromo-/chloroallylation step can be effectively reused for a second palladium(II)-catalyzed reaction.

A variety of alkenes were subjected to the tandem bromo-/chloroallylation−Wacker−Tsuji oxidation using the above protocol (Table 1). Both internal (entries 4−6) and terminal alkynes (entries 1−3) were converted into the corresponding functionalized methyl ketones in moderate to high yields for the two-step sequence. The synthetic potential of the resulting products is highlighted by the synthesis of dihydrojasmone by Tsuji and Yasuda from methyl ketone **3** ($R^1 = C_6H_{13}$; R^2 = H; X = Cl).[11]

Table 1. One-Pot Tandem Bromo-/Chloroallylation Wacker−Tsuji Oxidation of Alkynes

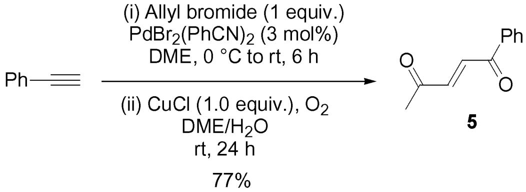


3

entry	R^1	R^2	X	yield [%]^b
1	H	CO_2Me	Br	74 (**3a**)
2	H	CO_2Me	Cl	75 (**3b**)
3	^{n}Bu	H	Br	70 (**3c**)
4	^{n}Pr	^{n}Pr	Br	80 (**3d**)
5	^{n}Pr	^{n}Pr	Cl	77 (**3e**)
6	CH_2OTBS	Me	Cl	66 (**3f**)

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

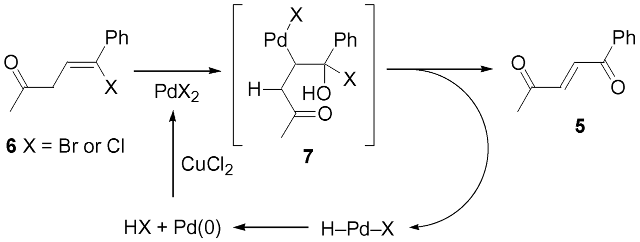
The expected methyl ketone **3** (R^1 = Ph; R^2 = H), however, was not produced when a terminal aromatic alkyne was incorporated into the two-step, one-pot sequence outlined above. Thus, subjecting phenylacetylene to the tandem process afforded, instead, vinylogous diketone **5** in 77% isolated yield (eq 1). The tandem chloroallylation/Tsuji−Wacker oxidation of phenylacetylene also resulted in diketone **5** albeit in a slightly lower yield (73%).



5 (1)

A reasonable path for the formation of the diketone is via a Saegusa-type oxidation as shown in Scheme 2. The expected product of the two-step sequence, haloenone **6**, can be hydrated with Pd(II) to yield organo-palladium halohydrin

Scheme 2



6 X = Br or Cl
7
5

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[6] (a) Kaneda, K.; Uchiyama, T.; Fujiwara, Y.; Imanaka, T.; Teranishi, S. *J. Org. Chem.* **1979**, *44*, 55−63. (b) For mechanistic studies on haloallylation, see: Bäckvall, J. E.; Nilsonn, Y. I. M.; Gatti, R. G. P. *Organometallics* **1995**, *14*, 4242−4246.

[7] For a brief review on the concept of atom economy, see: Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695−705.

[8] For other examples of halopalladation 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.

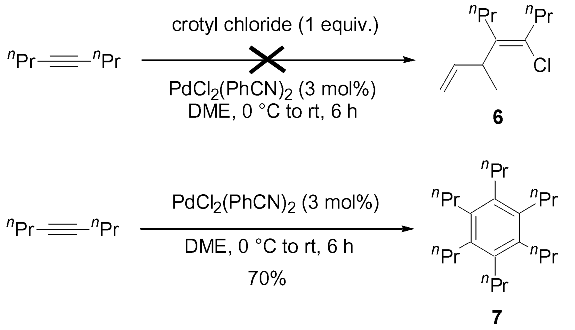
[9] The tandem bromoallylation/Stille coupling has been demonstrated, albeit in modest yields, see: Kosugi, M.; Sakaya, T.; Ogawa, S.; Migita, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3058−3061.

[10] (a) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; John Wiley & Sons: Wiley: New York, 1995; pp 22−30. (b) Tsuji, J. *Synthesis* **1984**, 369−384.

[11] **3** was synthesized via a two-pot protocol: Tsuji, J.; Yasuda, H. *Synth. Commun.* **1978**, *8*, 103−107.

7, which upon loss of HX and reductive elimination of Pd(0) would yield the observed product.[12,13]

Scheme 3

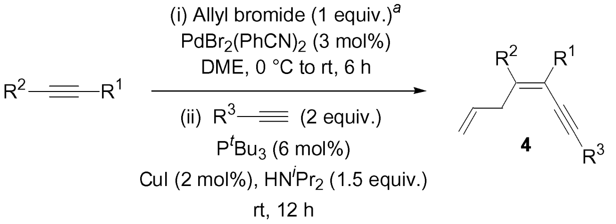


6

7

We next turned our attention toward further expanding the scope of such tandem reaction sequences. The Sonogashira cross-coupling, which is an important component in the repertoire of carbon−carbon bond-forming methodologies, was an attractive process to include in the tandem sequence.[14] Incorporation of such a reaction after the bromoallylation of alkynes would result in a one-pot stereocontrolled synthesis of highly substituted functionalized enynes.[15] After extensive screening of conditions, it was found that the Sonogashira cross-coupling step proceeded best when conducted under the conditions previously reported by Buchwald and Fu et al.[16] The tandem reaction worked well with a broad range of alkynes to afford enyne **4** stereospecifically and in good overall isolated yields (Table 2). The addition of tri-*tert*-butylphosphine (P^tBu_3) is expected to convert the palladium dihalide species that results from the bromoallylation step to $PdBr_2(P^tBu_3)_2$.[17] In turn, this palladium compound is presumably reduced in situ to a catalytically active Pd(0) species.

Table 2. One-Pot Tandem Bromoallylation−Sonogashira Cross-Coupling of Alkynes



entry	R^1	R^2	R^3	yield [%]^b
1	^{n}Bu	H	$C(Me)_2OH$	85 (**4a**)
2	$C(Me)_2OH$	H	$C(Me)_2OH$	73 (**4b**)
3	Ph	H	$C(Me)_2OH$	79 (**4c**)
4	^{n}Pr	^{n}Pr	Ph	84 (**4d**)
5	^{n}Pr	^{n}Pr	$C(Me)_2OH$	87 (**4e**)

^{a} Dropwise as a solution in DME. ^{b} Isolated yield.

Attempts at extending the tandem sequence to crotyl chloride were unsuccessful. The initial chlorocrotylation step was very sluggish and none of the desired diene (**6**) was formed. Formed, instead, was the interesting product of alkyne cyclotrimerization, a hexasubstituted benzene derivative (**7**), in 59% isolated yield (Scheme 3). The yield of **7** was increased to 70% by simply subjecting 4-ocytne, but without added crotyl chloride, to the same reaction conditions.[18]

In conclusion, the stereocontrolled synthesis of functionalized methyl ketones and enynes were accomplished via multipurpose palladium catalysis. The palladium dihalide catalyst left over from the initial bromo-/chloroallylation step was shown capable of catalyzing a subsequent Wacker−Tsuji oxidation in the same reaction vessel. The initial palladium catalyst was also shown to successfully promote a Sonogashira cross-coupling reaction, which requires in situ reduction of the Pd(II) species. The sequencing of two distinct reactions in a one-pot process, as illustrated in this and the preceding paper,[5] not only makes better use of precious reagents and solvents but also has the added benefit of eliminating inefficient separation and purification after each step. The resultant reduction in waste makes such processes environmentally desirable.

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Supporting Information Available: Preparation procedures and characterization data for **3**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] (a) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011−1013. (b) Takayama, H.; Koike, T.; Aimi, N.; Sakai, S. *J. Org. Chem.* **1992**, *57*, 2173−2176.

[13] An alternate, albeit less likely path involves the rearrangement of the haloenone **6** to afford a γ-chloroenone, which upon hydrolysis and oxidation could yield the observed product.

[14] (a) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 5. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467−4470.

[15] For an interesting domino reaction of allyl electrophiles, alkynes, and alkynyltins using Ni catalysis, see: Cui, D.-M.; Tsuzuki, T.; Miyake, K.; Ikeda, S.; Sato, Y. *Tetrahedron* **1998**, *54*, 1063−1072.

[16] Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *122*, 1729−1731.

[17] Goel, R. G.; Ogini, W. O. *Organometallics* **1982**, *1*, 654−658.

[18] Similar palladium(II)-catalyzed cyclotrimerization of alkynes was recently demonstrated: Li, J. H.; Jiang, H. F.; Chen, M. C. *J. Org. Chem.* **2001**, *66*, 3627−3629.