ChemComm

RSC Publishing

COMMUNICATION

View Article Online
View Journal | View Issue

Formal γ-alkynylation of ketones *via* Pd-catalyzed C–C cleavage†‡

Cite this: *Chem. Commun.*, 2013, **49**, 4286

Received 5th October 2012,
Accepted 29th October 2012

DOI: 10.1039/c2cc37281a

www.rsc.org/chemcomm

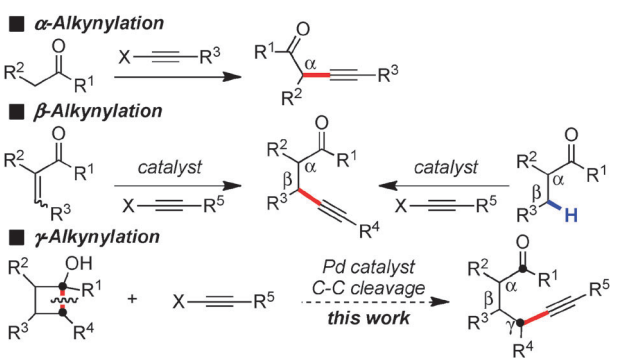
Asraa Ziadi, Arkaitz Correa and Ruben Martin*

A formal γ-alkynylation of ketones *via* Pd-catalyzed C–C bond-cleavage is presented. The method allows for the coupling of *tert*-cyclobutanols and bromoacetylenes, giving access to versatile alkynes that are beyond reach otherwise.

The high chemical versatility of alkynes and their pivotal role as key synthetic intermediates in chemical biology and material sciences have attracted the attention of organic chemists for decades.[1,2] Classical methods for preparing alkyne-containing compounds involve the classical dehydrohalogenation of halogen derivatives, alkylation of terminal alkynes, Corey–Fuchs-type reactions or Seyferth–Gilbert homologation, among others.[1] Recent catalytic strategies have shown their advantages over the classical methods in which harsh conditions are avoided with good chemoselectivities.[1] Unlike the preparation of aromatic alkyne derivatives,[3] the metal-catalyzed installation of alkynes into functionalized aliphatic backbones *via* C(sp^3)–C(sp) bond-forming processes is still a remarkable challenge.[4] Although formidable advances have been made in the α- and β-alkynylation of carbonyl compounds (Scheme 1),[5–7] the development of a general route for the catalytic γ-alkynylation of carbonyl compounds has not yet been described.[8] We wondered whether the propensity of *tert*-cyclobutanols to undergo β-carbon elimination[9,10] could step up the stage for a Pd-catalyzed C(sp)–C(sp^3) bond-formation as a means to access γ-alkynylated ketones (Scheme 1, bottom), thus constituting a complementary approach to the well-established γ-arylation processes.[11] As part of our ongoing investigations on inert bond-activation,[12] we disclose our results that demonstrate the feasibility of this hypothesis and exploit a previously unrecognized opportunity for the catalytic coupling of *tert*-cyclobutanols and haloacetylene derivatives.

We began our investigations with **1a**, readily prepared in a large scale from commercially available starting materials,[13] as the model substrate. The effects of palladium precatalyst, ligand, base, solvent and temperature were systematically examined. After considerable optimization, we pleasingly found that the combination of $Pd(OAc)_2$, SPhos and Cs_2CO_3 in toluene at 110 °C provided the best results for the desired coupling reaction, affording the γ-alkynylated ketone **3a** in 92% isolated yield. Subsequently, we found that the coupling of the chloro- and iodoethynyl derivatives also afforded **3a**, but in lower yields.[14] Similarly, solvents other than toluene and inorganic bases such as K_2CO_3, Na*t*BuO or K_3PO_4 had a deleterious effect on the reactivity, affording **3a** in much lower yields.[14]

Encouraged by these findings, we turned our attention to studying the generality of this reaction regarding the substitution pattern on the *tert*-cyclobutanol backbone. The results of this investigation are summarized in Table 1. As shown, the reaction manifests a broad substrate scope in which both aromatic and aliphatic groups at different positions on the *tert*-cyclobutanol backbone gave access to the corresponding γ-alkynylated ketones in good yields. The successful preparation of **3e** highlights the greater reactivity of **2a** as compared to aryl chlorides. Interestingly, the coupling reaction was not limited to 3,3-disubstituted *tert*-cyclobutanols; as shown for **3c–3e** and **3j**, 3-monosubstituted derivatives yielded the final products in comparable yields. Remarkably, 3,3-unsubstituted *tert*-cyclobutanols could be applicable as well (**3f–3i**); no competitive β-hydride elimination from the initially generated C(sp^3)–metal species was observed in the crude reaction mixtures.[15] As illustrated for **3f** and **3g** high levels of regioselectivity were found when using unsymmetrical *tert*-cyclobutanols in which the C–C bond cleavage



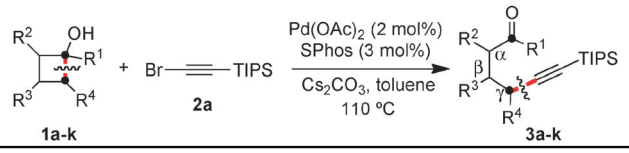
Scheme 1 Alkynylation methods of carbonyl compounds.

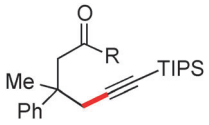
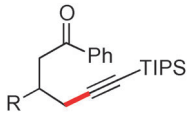
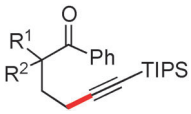
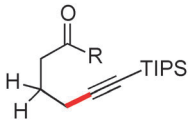
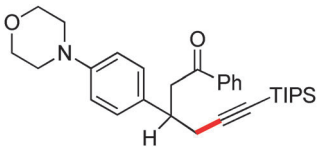
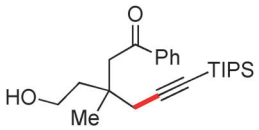
Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007, Tarragona, Spain. E-mail: rmartinromo@iciq.es; Tel: +34 977920248

† This article is part of the *ChemComm* 'Emerging Investigators 2013' themed issue.

‡ Electronic supplementary information (ESI) available. See DOI: 10.1039/c2cc37281a

Table 1 Reaction scope[a]



Entry	Product	Yield[b] (%)
1		R = Ph, 92 (**3a**)
2		R = iPr, 83 (**3b**)[c]
3		R = *n*Hex, 88 (**3c**)[c]
4		R = Ph, 78 (**3d**)
5		R = 4-ClC$_6$H$_4$, 53 (**3e**)
6		R^1 = R^2 = Ph, 76 (**3f**)
7		R^1 = Ph, R^2 = H, 69 (**3g**)
8		R = Ph, 82 (**3h**)
9		R = $CH_2C(Me)_2Ph$, 86 (**3i**)
10		62 (**3j**)
11		41 (**3k**)[d]

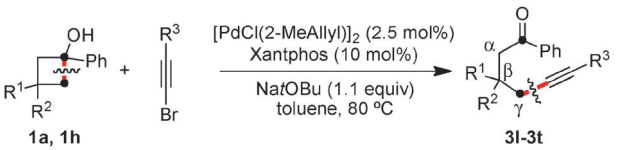
[a] Reaction conditions: **1** (0.35 mmol), **2a** (0.52 mmol), $Pd(OAc)_2$ (2 mol%), SPhos (4 mol%), Cs_2CO_3 (0.40 mmol), toluene (2 mL) at 110 °C. [b] Isolated yields, average of at least two independent runs. [c] $Pd(OAc)_2$ (4 mol%). [d] Cs_2CO_3 (2.50 equiv.).

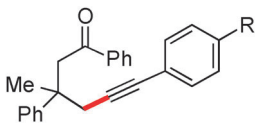
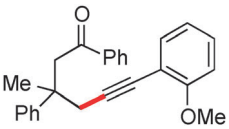
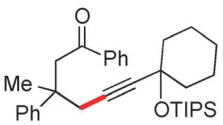
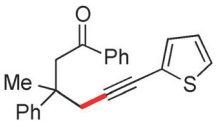
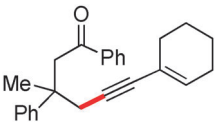
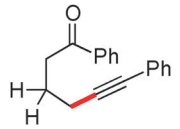
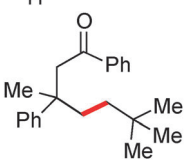
takes place at the less hindered position. The successful coupling of amine derivative **1j** demonstrates little Lewis acidity of our catalyst, if any. In line with the same notion, the method allowed for the coupling of *tert*-cyclobutanol derivatives possessing unprotected primary alcohols (**1k**); in this particular case, 2.5 equivalents of Cs_2CO_3 were required, thus yielding **3k**, albeit in lower yields.[16]

Prompted by the precedents shown in Table 1, we hypothesized whether the method could be extended to bromoacetylene derivatives other than (bromoethynyl)triisopropylsilane. Unfortunately, neither aromatic nor aliphatic bromoalkyne derivatives could be coupled with **1a** under the optimized reaction conditions in Table 1 based on SPhos. Indeed, not even traces of γ-alkynylated ketone could be detected by GC analysis of the crude reaction mixtures. These results manifest the remarkable and unique reactivity of **2a** as compared to other coupling partners.[6] However, after a careful re-optimization of the reaction conditions we found that the use of allylpalladium dimers in combination with Xantphos provided good yields for the coupling of (bromoethynyl)benzene (Table 2, **3l**).[17] As shown in entries 2 and 3, our method could be extended to other aromatic-substituted acetylenes possessing either electron-rich (**3m**) or electron-deficient groups (**3n**). Interestingly, the coupling of *ortho*-substituted and heteroaromatic alkynes could also be accomplished in moderate to good yields under otherwise similar reaction conditions (**3o**, **3q**). However, the coupling of bromoenynes resulted in partial decomposition, leading to **3r** in low yields. Furthermore, bromoacetylenes substituted with aliphatic backbones possessing bulky silyl-protected ethers could be tolerated under the reaction conditions based on Xantphos (**3q**). As for **3f–3i**, 3,3-unsubstituted *tert*-cyclobutanols could be utilized for the coupling with (bromoethynyl)benzene, affording **3s** in moderate yields.[16] Gratifyingly, our method was not restricted to bromoethynyl derivatives; as shown for **3t**, our protocol allowed for the coupling of alkyl halides in high yields, formally constituting a powerful catalytic manifold for preparing γ-alkylated ketones in a straightforward manner.

With substantial amounts of **3a** in hand, we focused our attention on demonstrating whether our method could be

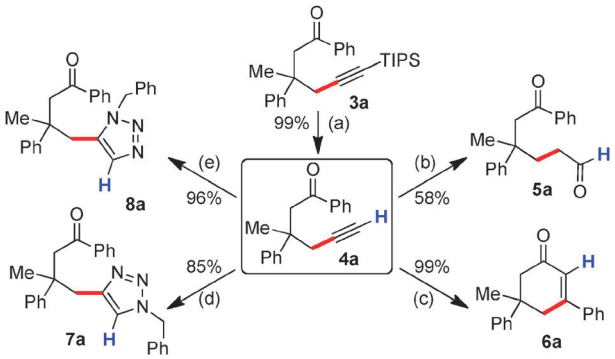
Table 2 Reaction scope[a]



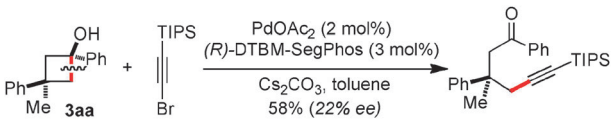
Entry	Product	Yield[b] (%)
1		R = H, 75 (**3l**)
2		R = *t*Bu, 58 (**3m**)
3		R = CF_3, 52 (**3n**)[b]
4		41 (**3o**)
5		64 (**3p**)
6		61 (**3q**)[b]
7		35 (**3r**)
8		46 (**3s**)
9		87 (**3t**)[c]

[a] Reaction conditions: **1** (0.50 mmol), **2** (1 mmol), $[PdCl(2\text{-Me-allyl})]_2$ (2.50 mol%), Xantphos (10 mol%), Nat*B*uO (0.60 mmol), toluene (1 mL) at 80 °C; isolated yields, average of two independent runs. [b] 4 equivalents of bromoacetylene were used. [c] Using reaction conditions in Table 1.

Table 3 Synthetic applicability



Reaction conditions: (a) TBAF (1.1 equiv.), THF, rt, 99%; (b) $(Chex)_2BH$, $NaBO_3$, THF, 58%; (c) $AuCl_3$ (5 mol%), AgOTf (15 mol%), DCM, 99%; (d) BnN_3, $Cu(OAc)_2$ (5 mol%), sodium ascorbate (25 mol%), *t*BuOH-H_2O, rt, 96%; (e) BnN_3, Cp*RuClCOD (2 mol%), toluene, rt, 85%.



Scheme 2 Enantioselective γ-alkynylation of ketones.

employed as a platform for molecular diversity. As shown in Table 3, this was indeed the case; the significant increase in molecular complexity achieved by otherwise simple and reliable transformations is quite appealing, thus giving access to structures that are difficult to obtain by other means. Notably, a formal anti-Markovnikov hydration of alkyne **4a** *via* a hydroboration–oxidation sequence[18] gave synthetically-attractive aldehyde **5a** in 58% overall yield. Interestingly, cyclohexenone **6a** could quantitatively be obtained by a Au-catalyzed cycloisomerization event in which the aromatic group formally migrates to the C3 position of the cyclohexenone motif.[19] Furthermore, we also demonstrate that triazoles **8a** and **9a** could easily be prepared as single regioisomers *via* Cu-[20] or Ru-catalyzed[21] [3+2]-type cycloadditions with benzyl azide.

Despite remarkable advances in the field of C–C bond-cleavage in recent years, particularly *via* β-carbon elimination pathways,[9] the development of enantioselective C–C bond cleavage approaches still remains a formidable challenge.[22] Although a thorough investigation awaits further studies, we have preliminarily found that a certain level of asymmetric induction can be obtained when using DTBM-SegPhos for the coupling of **3aa** and **2a** (Scheme 2). While modest, this result represents the first asymmetric route for preparing γ-alkynylated ketones and holds great promise for future developments in this area.

In summary, we have developed the first route to γ-alkynylated ketones *via* Pd-catalyzed C–C bond-cleavage. The chosen approach is highly convergent and involves a minimum number of manipulations due to the ready availability of the starting materials. Such a route provides a direct access to scaffolds that are beyond reach otherwise and allows the conversion of γ-alkynyl ketones into a diverse array of advanced synthetic intermediates. Further investigations along these lines and the development of an enantioselective route to γ-alkynyl ketones are currently ongoing in our laboratories.

The authors thank the ICIQ Foundation, the European Research Council (ERC-277883) and MICINN (CTQ2009-13840 & CTQ2012-34054) for financial support. Johnson Matthey, Umicore and Nippon Chemical Industrial are acknowledged for a gift of metal and ligand sources. R.M and A.C thank MICINN for RyC and JdC fellowships.

Notes and references

1 *Acetylene Chemistry*, ed. F. Diederich, P. J. Stang and R. R. Tykwinski, Wiley-VCH, Weinheim, 2005.
2 U. H. F. Bunz, *Chem. Rev.*, 2000, **100**, 1605; S. Toyota, *Chem. Rev.*, 2010, **110**, 5398; N. M. Jenny, M. Mayor and T. R. Eaton, *Eur. J. Org. Chem.*, 2011, 4965; S. I. Lee and N. Chatani, *Chem. Commun.*, 2009, 371, and articles cited therein.
3 For a recent review on the classical Sonogashira–Hagihara reaction, see R. Chinchilla and C. Nájera, *Chem. Soc. Rev.*, 2011, **40**, 5084.
4 For recent selected contributions in this area, see: F. Ye, X. Ma, Q. Xiao, H. Li, Y. Zhang and J. Wang, *J. Am. Chem. Soc.*, 2012, **134**, 5742; Z. Li and C.-J. Li, *J. Am. Chem. Soc.*, 2004, **126**, 11810; Z. Li, D. S. Bohle and C.-J. Li, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, **103**, 8928; M. Eckhardt and G. C. Fu, *J. Am. Chem. Soc.*, 2003, **125**, 13642; O. Vechorkin, D. Barmaz, V. Proust and X. Hu, *J. Am. Chem. Soc.*, 2009, **131**, 12078; G. Altenhoff, S. Würtz and F. Glorius, *Tetrahedron Lett.*, 2006, **47**, 2925; S. Nicolai, C. Piemontesi and J. Waser, *Angew. Chem., Int. Ed.*, 2011, **50**, 4680.
5 For a recent catalytic α-alkynylation event, see: D. F. González, J. P. Brand and J. Waser, *Chem.–Eur. J.*, 2010, **16**, 9457.
6 For an elegant β-alkynylation *via* C–H activation: Y. Ano, M. Tobisu and N. Chatani, *J. Am. Chem. Soc.*, 2011, **133**, 12984.
7 For selected methods on metal-catalyzed β-alkynylation of α,β-unsaturated compounds: L. Chen and C.-J. Li, *Chem. Commun.*, 2004, 2362; K. Takeishi, K. Sugishima, K. Sasaki and K. Tanaka, *Chem.–Eur. J.*, 2004, **10**, 5681; T. Nishimura, Y. Washitake and S. Uemura, *Adv. Synth. Catal.*, 2007, **349**, 2563.
8 For an isolated example, see ref. 6.
9 For selected reviews, see: T. Seiser, T. Saget, D. N. Tran and N. Cramer, *Angew. Chem., Int. Ed.*, 2011, **50**, 7740; C. Aïssa, *Synthesis*, 2011, 3389; M. Murakami, M. Makino, S. Ashida and T. Matsuda, *Bull. Chem. Soc. Jpn.*, 2006, **79**, 1315.
10 For selected examples: A. Schweinitz, A. Chtchemelinine and A. Orellana, *Org. Lett.*, 2011, **13**, 232; T. Seiser, O. A. Roth and N. Cramer, *Angew. Chem., Int. Ed.*, 2009, **48**, 6320; T. Seiser and N. Cramer, *J. Am. Chem. Soc.*, 2010, **132**, 5340; T. Matsuda, M. Shigeno and M. Murakami, *J. Am. Chem. Soc.*, 2007, **129**, 12086.
11 For selected references: T. Nishimura and S. Uemura, *J. Am. Chem. Soc.*, 1999, **121**, 11010; A. Ziadi and R. Martin, *Org. Lett.*, 2012, **14**, 1266; T. Nishimura, S. Matsumura, Y. Maeda and S. Uemura, *Chem. Commun.*, 2002, 50; S. Maysumura, Y. Maeda, T. Nishimura and S. Uemura, *J. Am. Chem. Soc.*, 2003, **125**, 8862; T. Nishimura, S. Matsumura, Y. Maeda and S. Uemura, *Tetrahedron Lett.*, 2002, **43**, 3037.
12 N. Barbero and R. Martin, *Org. Lett.*, 2012, **14**, 796; P. Novák, A. Correa, J. Gallardo-Donaire and R. Martin, *Angew. Chem., Int. Ed.*, 2011, **50**, 12236; P. Alvarez-Bercedo and R. Martin, *J. Am. Chem. Soc.*, 2010, **132**, 17352; P. Alvarez-Bercedo, A. Flores-Gaspar, A. Correa and R. Martin, *J. Am. Chem. Soc.*, 2010, **132**, 466; A. Correa and R. Martin, *J. Am. Chem. Soc.*, 2009, **131**, 15974.
13 B. D. Johnson, E. Czyzewska and A. C. Oehlschlager, *J. Org. Chem.*, 1987, **52**, 3693.
14 See ESI‡ for details.
15 J. F. Hartwig, *Inorg. Chem.*, 2007, **46**, 1936.
16 No byproducts other than the recovered starting material and homocoupling of the haloacetylene derivatives were observed.
17 For an example of using bidentate phosphines with bromoacetylenes, see: S. Nicolai and J. Waser, *Org. Lett.*, 2011, **13**, 6324.
18 G. W. Kabalka, S. Yu and N.-S. Li, *Can. J. Chem.*, 1998, **76**, 800.
19 T. Jin and Y. Yamamoto, *Org. Lett.*, 2007, **9**, 5259.
20 V. Rostovtsev, L. Green, V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596.
21 B. C. Boren, S. Narayan, L. K. Rasmussen, L. Zhang, H. Zhao, Z. Lin, G. Jia and V. V. Fokin, *J. Am. Chem. Soc.*, 2008, **130**, 8923.
22 T. Seiser and N. Cramer, *Org. Biomol. Chem.*, 2009, **7**, 2835.

