Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 4699

www.rsc.org/obc

COMMUNICATION

Palladium-catalyzed synthesis of 2-amino ketones from propargylic carbonates and secondary amines†

Sandro Cacchi,*[a] Giancarlo Fabrizi,[a] Eleonora Filisti,[a] Antonella Goggiamani,[a] Antonia Iazzetti[a] and Loredana Maurone[b]

Received 4th April 2012, Accepted 10th May 2012
DOI: 10.1039/c2ob25670c

A novel palladium-catalyzed approach to 2-amino ketones from arylpropargylic carbonates bearing neutral, electron-rich, and electron-poor aromatic rings and cyclic secondary amines containing useful functional groups such as cyano, chloro, and bromo substituents has been developed.

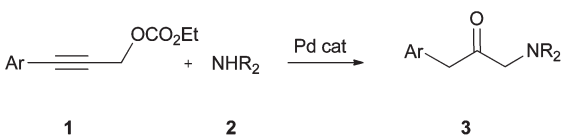
The 2-amino ketone structural motif is present in a number of biologically active compounds such as mersingines A and B[1] and a small family of linear peptides including the antitumor agent eponemycin.[2] Endogenous 2-amino ketones show pro-oxidant properties.[3] 2-Amino ketones have also been studied as candidates for the reactivation of mutant p53[4] and are used for the preparation of cosmetic compositions for the treatment of skin wrinkles.[5] Furthermore, they are useful synthetic intermediates.[6] Despite their importance, however, direct syntheses of 2-amino ketones are rather limited. Current general synthetic approaches are based on the α-amination of ketones[7] and enolsilanes[8] (in some cases taking advantage of copper catalysis[8b,d]), on the osmium-catalyzed ketamination of alkenes,[9] on the conversion of the carboxylic group of amino acids into a ketonic group,[10] and on the formation of carbon–carbon bonds between carbonyl and amino-containing fragments.[11] Recently, 2-amino ketones have been prepared *via* reaction of *N*-sulfonyl-1,2,3-triazoles with water in the presence of a rhodium catalyst.[12] Palladium catalysis has been rarely applied in this area. To the best of our knowledge, it has been used only in the preparation of 2-amino ketones from α-sulfonamidoorganostannanes and benzoyl chloride.[11b]

Herein we report on a new palladium-catalyzed approach to 2-amino ketones **3** from readily available propargylic carbonates **1** and secondary amines **2** that involves a formal anti-Markovnikov addition of water to the carbon–carbon triple bond and the substitution of the $C_{propargylic}$–N bond for the $C_{propargylic}$–O bond (Scheme 1).

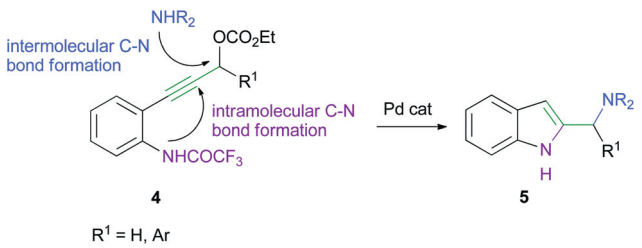
On the basis of our previous studies showing that 2-aminomethyl indoles **5** could be prepared from 3-(*o*-trifluoroacetamidophenyl)-1-propargylic carbonates **4** and amines through a process involving sequential intramolecular/intermolecular C–N bond forming steps (Scheme 2),[13] we hypothesized that a similar reaction, omitting the trifluoroacetamido group bound to the aromatic ring, might provide access to 2-amino ketones *via* sequential intermolecular C–N bond forming steps, leading to enamine intermediates **A**, and hydrolysis (Scheme 3).

We set out to use the reaction of 1 equiv. of **1a** (Ar = R^1 = Ph) with 3 equiv. of morpholine as a probe for evaluating the feasibility of the reaction. First attempts, however, met with failure. Under the same conditions employed for the synthesis of 2-aminomethyl indoles[13] a smooth palladium-catalyzed decarboxylation–propargylation[14,15] of **1a** took place and the ether **6a** was formed in almost quantitative yield (Scheme 4a).

Using $Pd_2(dba)_3$ as the Pd(0) source and a variety of phosphine ligands such as dppp, dppe, and $[2,4,6\text{-}(MeO)_3C_6H_2]_3P$ in THF at 80 °C for 24 h led to the recovery of the starting



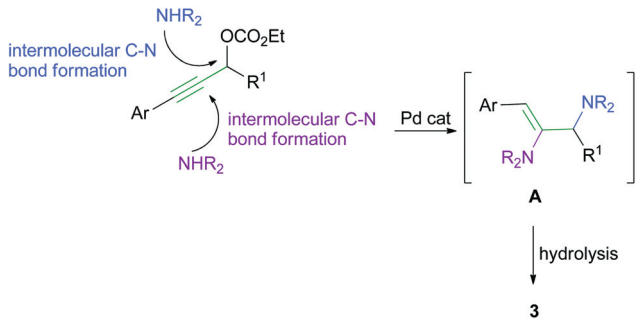
Scheme 1 Palladium-catalyzed synthesis of 2-amino ketones from propargylic carbonates and secondary amines.



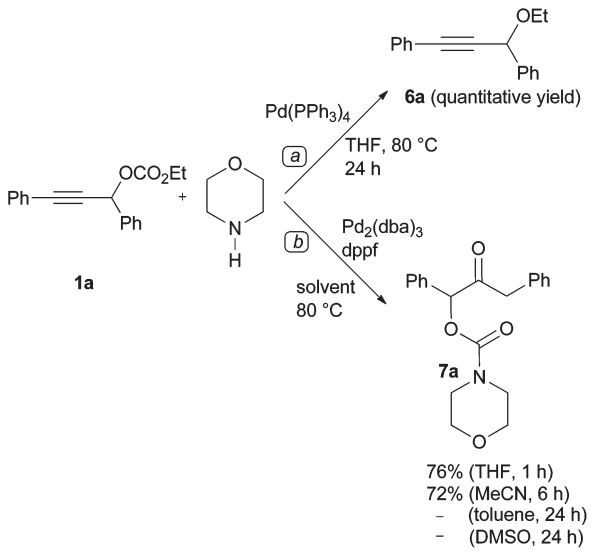
Scheme 2 Synthesis of indoles from 3-(*o*-trifluoroacetamidophenyl)-1-propargylic carbonates.

[a]*Dipartimento di Chimica e Tecnologie del Farmaco, Sapienza, Università di Roma, P.le A. Moro 5, 00185 Rome, Italy. E-mail: sandro.cacchi@uniroma1.it; Fax: +39 (06) 4991-2789; Tel: +39 (06) 4991-2795*
[b]*Dipartimento A.B.A.C., Università degli Studi della Tuscia e Consorzio Universitario "La Chimica per l'Ambiente", Via S. Camillo De Lellis, 01100 Viterbo, Italy*

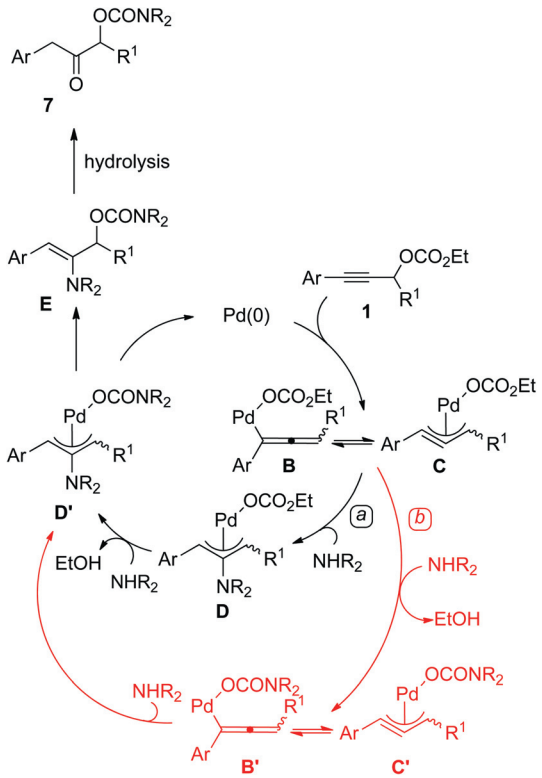
†Electronic supplementary information (ESI) available: A complete description of experimental details and product characterization. See DOI: 10.1039/c2ob25670c



Scheme 3 Our working hypothesis.



Scheme 4 The reaction of **1a** with morpholine in the presence of $Pd(PPh_3)_4$ and $Pd_2(dba)_3$/dppf.



Scheme 5 Proposed reaction mechanism for the palladium-catalyzed formation of ketocarbamates **7** from propargylic carbonates **1** and amines.

carbonate in almost quantitative yield. No evidence of the desired product was also obtained switching to the $Pd_2(dba)_3$/dppf combination. The reaction produced instead the ketocarbamate **7a** in 76% yield (Scheme 4b). Using MeCN as solvent gave **7a** in a slightly lower yield whereas only degradation products were formed in toluene and DMSO.

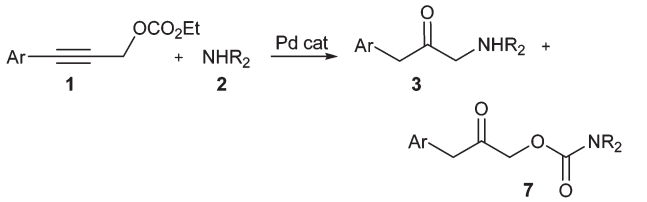
A possible rationale for the formation of **7a** is outlined in Scheme 5. The initial reaction of Pd(0) with **1a** affords the σ-allenylic palladium complex **B**, which would be in equilibrium with the π-propargylic palladium intermediate **C**.[16] The nucleophilic attack of morpholine at the central carbon of the allenylic/propargylic palladium complex **B**/**C**[17,18] (path *a*), followed by a protonation step gives the allylic palladium carbonate complex **D**. This complex is subsequently converted into the allylic carbamate palladium complex **D′** *via* displacement of the ethoxy group by morpholine. Alternatively (path *b*), morpholine can displace the ethoxy group of **B**/**C** to give **B′**/**C′** that is converted into **D′** *via* nucleophilic attack of another molecule of morpholine at the central carbon of the allenylic/propargylic palladium complex and protonation. Subsequently, the intramolecular nucleophilic attack of the carbamate oxygen at one of the allylic carbons of **D′**‡ and the hydrolysis of the resultant enamine intermediate **E** generates the ketocarbamate **7a**. The inertness of **1a** towards morpholine in the absence of palladium (the starting material was recovered in 90% yield after 3 h at 80 °C in THF) supports the view that the conversion of the carbonate fragment into the carbamate fragment occurs after the formation of a palladium complex. Experimental evidence for the intermediacy of **E** was obtained by NMR analysis of the crude reaction mixture before work-up.

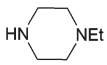
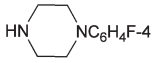
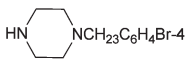
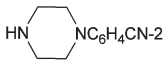
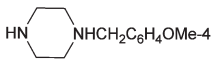
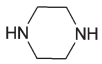
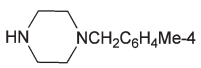
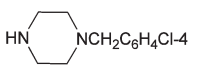
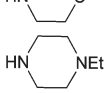
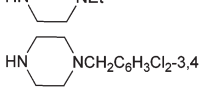
Steric effects due to the substituents of **D** or **D′** might account for the preferential intramolecular nucleophilic attack of the less hindered carbamate fragment at one of the allylic termini with respect to the intermolecular nucleophilic attack of the more sterically demanding morpholine.

Therefore, we decided to investigate the reactivity of the unsubstituted proparylic carbonate **1b** (Ar = Ph; R^1 = H). Pleasingly, its reaction with morpholine in the presence of $Pd_2(dba)_3$ and dppf in THF at 80 °C afforded the desired 2-aminoketone **3a** in 76% isolated yield after 3 h.

Using these conditions, we next explored the scope and generality of the process. As shown in Table 1, clean formation of 2-amino ketones was observed with a variety of propargylic carbonates bearing neutral, electron-rich, and electron-poor aromatic rings and cyclic secondary amines containing useful functional groups such as cyano, chloro, and bromo substituents. An acceptable yield was also obtained with the unprotected piperazine (Table 1, entry 8). The piperazine nucleus, a privileged substructure,[19] is of particular interest. Some limitations of our method were observed with acyclic secondary amines. For example, the reaction of **1b** with dibutylamine or diethylamine failed to give

Table 1 Synthesis of 2-amino ketones **3** from propargylic carbonates **1** and amines **2**[a]

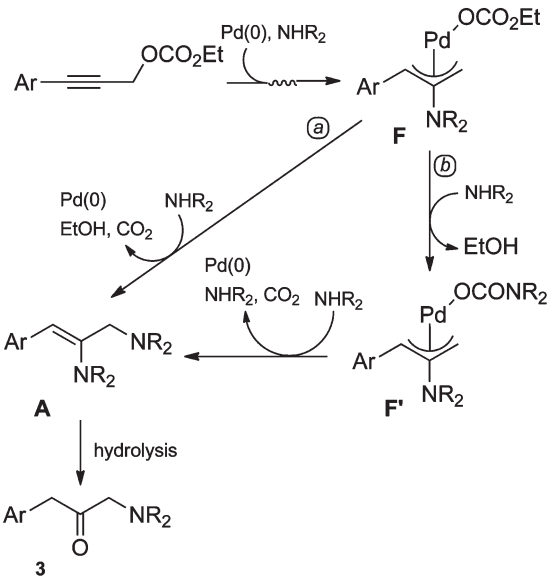


Entry	Propargylic ester **1** Ar	Amine **2**	*T* (h)	Yield %[b] **3**	Yield %[b] **7**
1	Ph		3	76 (**a**)	—
2			1.5	46 (**b**)	30
3			2	75 (**c**)	7
4			1	60 (**d**)	—
5			2	74 (**e**)	—
6			18	49 (**f**)	20
7			5.5	92 (**g**)	—
8			0.5	57 (**h**)	—
9	4-$MeOC_6H_4$		4.5	57 (**i**)	—
10			2	66 (**j**)	—
11			4	73 (**k**)	—
12	4-$MeCOC_6H_4$		7	58 (**l**)	—
13	4-$EtO_2CC_6H_4$		3	88 (**m**)	—
14			1	84 (**n**)	6
15			1.5	92 (**o**)	—
16	3-MeC_6H_4		1.5	65 (**p**)	—

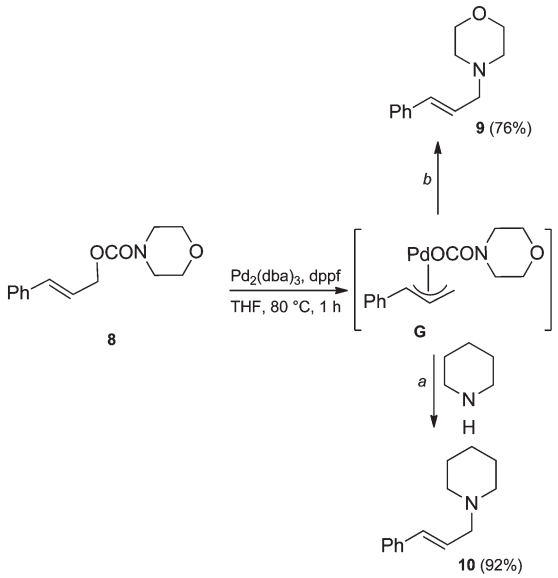
[a] Reactions were carried out on a 0.35 mmol scale at 80 °C in THF (2 mL), under a nitrogen atmosphere, using 1 equiv. of **1**, 3 equiv. of **2**, 0.025 equiv. of $Pd_2(dba)_3$, and 0.05 equiv. of dppf. [b] Yields are given for isolated products.

the desired products and the starting propargylic carbonate was recovered in 73% and almost quantitative yield, respectively.

As for the mechanism of formation of 2-amino ketones **3**, they are most probably generated through the intermolecular nucleophilic attack of the nitrogen nucleophile at the less



Scheme 6 Proposed reaction mechanism for the palladium-catalyzed synthesis of 2-amino ketones **3**.



Scheme 7 Palladium-catalyzed reaction of the allylic carbamate **8** with and without piperazine.

substituted terminus of the π-allylic palladium complex **F** followed by the hydrolysis of the resultant enamine intermediate **A** (Scheme 6, path *a*). The presence of the latter was detected by NMR analysis of the crude reaction mixture before work-up.

The formation of **3** from **F′**, however, cannot be ruled out. The isolation of ketocarbamate by-products **7** in some of the reactions of unsubstituted propargylic esters with amines (Table 1, entries 2, 3, 6 and 14) might indicate its involvement as a common intermediate for the formation both of **3** and of **7** (Scheme 6, path *b*). Support for this view is provided by the results obtained by treating the allylic carbamate **8** (expected to react with Pd(0) to form the allylic intermediate **G** that could be taken as model of **F′**) with piperidine (Scheme 7, *a*). Under

standard conditions the allylic derivative **10** was isolated in excellent yield.

The alternative formation of **A** from **F′** *via* intramolecular nucleophilic attack of the nitrogen of the carbamate fragment at the less substituted allylic terminus seems unlikely in view of the known behavior of related allylpalladium carbamate intermediates in the presence of nitrogen nucleophiles[20] and of the reaction of **8** with piperidine that we carried out. Only in the absence of an external nucleophile the intramolecular nucleophilic attack of morpholine takes place affording **9** in high yield (Scheme 7, *b*).

Conclusions

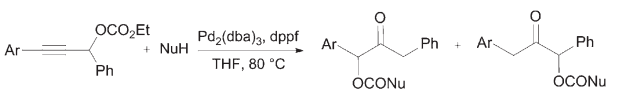
In summary, we have developed a novel palladium-catalyzed approach to 2-amino ketones from arylpropargylic carbonates unsubstituted at the propargylic carbon, bearing neutral, electron-rich and electron-poor aromatic rings, and cyclic secondary amines containing useful functional groups such as cyano, chloro, and bromo substituents. Our procedure is simple, uses readily available starting materials and may represent a useful tool for the synthesis of this class of compounds. With arylpropargylic carbonates containing aryl substituents at the propargylic carbon the reaction affords α-ketocarbamates in high yield.

Acknowledgements

We gratefully acknowledge MURST and the University "La Sapienza", Rome, for financial support.

Notes and references

‡ Electronic effects of the substituents on the aromatic rings bound to the propargylic system exert a strong influence on the regiochemistry of the reaction. In the presence of electron-withdrawing 4-ethoxycarbonyl and 3-trifluoromethyl groups the benzylic position of the phenyl ring is more electrophilic, whereas the electron-donating 4-methoxy group favors the nucleophilic attack at the benzylic position of the substituted aromatic ring. Minor differences in the electronic properties of the two aromatic rings leads to the formation of an approximately equimolar regioisomeric mixture.



NuH = morpholine

Ar = 4-$MeOC_6H_4$	2 h (73%)	**7q**	**7q'**	(65:35)
Ar = 4-$EtOCOC_6H_4$	6 h (69%)	**7r**	**7r'**	(30:70)
Ar = 3-$CF_3C_6H_4$	6 h (67%)	**7s**	**7s'**	(23:77)
Ar = 3-$MeOC_6H_4$	6 h (68%)	**7t**	**7t'**	(44:56)

1 K. Yoganathan, W.-H. Wong and T.-S. Kam, *Nat. Prod. Lett.*, 1995, **5**, 309; T.-S. Kam, K. Yoganathan and C. Wei, *J. Nat. Prod.*, 1996, **59**, 1109; G. Subramaniam and T.-S. Kam, *Helv. Chim. Acta*, 2008, **91**, 930.

2 (*a*) N. Sin, L. Meng, H. Auth and C. M. Crews, *Bioorg. Med. Chem.*, 1998, **6**, 1209; (*b*) L. Meng, B. H. Kwok, N. Sin and C. M. Crews, *Cancer Res.*, 1999, **59**, 2798; (*c*) N. Sin, K. B. Kim, M. Elofsson, L. Meng, H. Auth, B. H. Kwok and C. M. Crews, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2283; (*d*) B. Bennacer, C. Rivalle and D. S. Grierson, *Eur. J. Org. Chem.*, 2003, 4569; (*e*) J. Adams, *Nat. Rev. Cancer*, 2004, **4**, 349; (*f*) A. Ho, K. Cyrus and K.-B. Kim, *Eur. J. Org. Chem.*, 2005, 4829.

3 E. J. H. Bechara, F. Dutra, V. E. S. Cardoso, A. Sartori, K. P. K. Olympio, C. A. A. Penatti, A. Adhikari and N. A. Assuncao, *Comp. Biochem. Physiol., Part C: Toxicol. Pharmacol.*, 2007, **146**, 88.

4 M. C. Myers, J. Wang, J. A. Iera, J.-k. Bang, T. Hara, S. Saito, G. P. Zambetti and D. H. Appella, *J. Am. Chem. Soc.*, 2005, **127**, 6152.

5 C. Boulle, M. Dalko and A. Cavezza, *Eur. Pat. Appl*, EP 1405633, 2004; C. Boulle, M. Dalko and A. Cavezza, *Chem. Abstr.*, 2004, **140**, 308957.

6 For recent selected references, see: (*a*) R. R. Singhaus, R. C. Bernotas, R. Steffan, E. Matelan, E. Quinet, P. Nambi, I. Feingold, C. Huselton, A. Wilhelmsson, A. Goos-Nilsson and J. Wrobel, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 521; (*b*) W. Yu, Z. Guo, P. Orth, V. Madison, L. Chen, C. Dai, R. J. Feltz, V. M. Girijavallabhan, S. H. Kim, J. A. Kozlowski, B. J. Lavey, D. Li, D. Lundell, X. Niu, J. J. Piwinski, J. Popovici-Muller, R. Rizvi, K. E. Rosner, B. B. Shankar, N.-Y. Shih, M. A. Siddiqui, J. Sun, L. Tong, S. Umland, M. K. C. Wong, D.-Y. Yang and G. Zhou, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 1877; (*c*) Y. Xu, C. Sheng, W. Wang, X. Che, Y. Cao, G. Dong, S. Wang, H. Ji, Z. Miao, J. Yao and W. Zhang, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 2942; (*d*) Y. Sun, N.-Y. Huang and M.-W. Ding, *Synth. Commun.*, 2010, **40**, 1985; (*e*) Y. Xiong, B. Ullman, J.-S. K. Choi, M. Cherrier, S. Strah-Pleynet, M. Decaire, P. I. Dosa, K. Feichtinger, B. R. Teegarden, J. M. Frazer, W. H. Yoon, Y. Shan, K. Whelan, E. K. Hauser, A. J. Grottick, S. Graeme and A.-S. Hussien, *J. Med. Chem.*, 2010, **53**, 5696; (*f*) B. Sun, J. Hoshino, K. Jermihov, L. Marler, J. M. Pezzuto, A. D. Mesecar and M. Cushman, *Bioorg. Med. Chem.*, 2010, **18**, 5352; (*g*) S. Yu, X. Chai, H. Hu, Y. Yan, Z. Guan, Y. Zou, Q. Sun and Q. Wu, *Eur. J. Med. Chem.*, 2010, **45**, 4435; (*h*) H. Watanabe, S. Ogata and T. Satoh, *Tetrahedron*, 2010, **66**, 5675; (*i*) M. Borthakur, S. Gogoi, J. Gogoi and R. C. Boruah, *Tetrahedron Lett.*, 2010, **51**, 5160; (*j*) M. M. Ghorab, F. A. Ragab, H. I. Heiba, H. A. Youssef and M. G. El-Gazzar, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 6316; (*k*) L. Ciofi, M. Morvillo, F. Sladojevich, A. Guarna and A. Trabocchi, *Tetrahedron Lett.*, 2010, **51**, 6282; (*l*) H. Wang, X. Han and X. Lu, *Tetrahedron*, 2010, **66**, 9129; (*m*) Q. Zhou and B. B. Snider, *Org. Lett.*, 2011, **13**, 526.

7 (*a*) T. Sasaki, Y. Ishibashi and M. Ohno, *Chem. Lett.*, 1983, 863; (*b*) T. Sasaki, K. Mori and M. Ohno, *Synthesis*, 1985, 279; (*c*) T. Sasaki, K. Mori and M. Ohno, *Synthesis*, 1985, 280; (*d*) W. Oppolzer and O. Tamura, *Tetrahedron Lett.*, 1990, **31**, 991; (*e*) W. Oppolzer, O. Tamura, G. Sundarababu and M. Signer, *J. Am. Chem. Soc.*, 1992, **114**, 5900; (*f*) W. Oppolzer, O. Tamura and J. Deerberg, *Helv. Chim. Acta*, 1992, **75**, 1965; (*g*) D. Enders, C. Poiesz and R. Joseph, *Tetrahedron: Asymmetry*, 1998, **9**, 3709; (*h*) N. Kumaragurubaran, K. Juhl, W. Zhuang, A. Bøgevig and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2002, **124**, 6254; (*i*) N. Momiyama and H. Yamamoto, *Org. Lett.*, 2002, **4**, 3579; (*j*) R. O. Duthaler, *Angew. Chem., Int. Ed.*, 2003, **42**, 975.

8 (*a*) G. Fraenkel, J. Gallucci and H. S. Rosenzweig, *J. Org. Chem.*, 1989, **54**, 677; (*b*) D. A. Evans, M. M. Faul and M. T. Bilodeau, *J. Am. Chem. Soc.*, 1994, **116**, 2742; (*c*) S. Minakata, T. Ando, M. Nishimura, I. Ryu and M. Komatsu, *Angew. Chem., Int. Ed.*, 1998, **37**, 3392; (*d*) D. A. Evans and D. S. Johnson, *Org. Lett.*, 1999, **1**, 595.

9 (*a*) A. Villar, C. H. Hövelmann, M. Nieger and K. Muñiz, *Chem. Commun.*, 2005, 3304; (*b*) K. Muñiz, C. H. Hövelmann, A. Villar, R. Vicente, J. Streuff and M. Nieger, *J. Mol. Catal. A: Chem.*, 2006, **251**, 277.

10 (*a*) M. T. Reetz, *Chem.Rev.*, 1999, **99**, 1121; (*b*) L. De Luca, G. Giacomelli and A. Porcheddu, *Org. Lett.*, 2001, **3**, 1519.

11 (*a*) J. A. Murry, D. E. Frantz, A. Soheili, R. Tillyer, E. J. J. Grabowski and P. J. Reider, *J. Am. Chem. Soc.*, 2001, **123**, 9696; (*b*) K. W. Kells and J. M. Chong, *J. Am. Chem. Soc.*, 2004, **126**, 15666; (*c*) A. E. Mattson and K. A. Scheidt, *Org. Lett.*, 2004, **6**, 4363; (*d*) G.-Q. Li, L.-X. Dai and S.-L. You, *Chem. Commun.*, 2007, 852.

12 T. Miura, T. Biyajima, T. Fujii and M. Murakami, *J. Am. Chem. Soc.*, 2012, **134**, 194.

13 (*a*) I. Ambrogio, S. Cacchi and G. Fabrizi, *Org. Lett.*, 2006, **8**, 2083; (*b*) I. Ambrogio, S. Cacchi, G. Fabrizi and A. Prastaro, *Tetrahedron*, 2009, **65**, 8916.

14 For a review on palladium-catalyzed reactions of propargylic esters, see: J. Tsuji and T. Mandai, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2589.

15 For selected references on the related decarboxylation–allylation of alkyl allylic carbonates, see: F. Guibe and S. M. Leux, *Tetrahedron Lett.*, 1981, **22**, 3591; J. Tsuji and I. Minami, *Acc. Chem. Res.*, 1987, **20**, 140.

16 K. Tsutsumi, S. Ogoshi, S. Nishiguchi and H. Kurosawa, *J. Am. Chem. Soc.*, 1998, **120**, 1938.

17 M. W. Baize, P. W. Blosser, V. Plantevin, D. G. Schimpff, J. C. Gallucci and A. Wojcicki, *Organometallics*, 1996, **15**, 164.

18 For selected examples of reactions involving a nucleophilic attack at the central sp carbon of a σ-propargylic palladium complex to give a π-allyl-palladium complex which is further attacked by a second nucleophile, see: (*a*) C. Fournier-Nguefack, P. Lhoste and D. Sinou, *Synlett*, 1996, 553; (*b*) J.-R. Labrosse, P. Lhoste and D. Sinou, *Tetrahedron Lett.*, 1999, **40**, 9025; (*c*) J.-R. Labrosse, P. Lhoste and D. Sinou, *Org. Lett.*, 2000, **2**, 527; (*d*) M. Yoshida, M. Fujita, T. Ishii and M. Ihara, *J. Am. Chem. Soc.*, 2003, **125**, 4874; (*e*) M. Yoshida, Y. Morishita, M. Fujita and M. Ihara, *Tetrahedron*, 2005, **61**, 4381.
19 D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893.
20 J. Cabou, H. Bricout, F. Hapiot and E. Monflier, *Catal. Commun.*, 2004, **5**, 265.