ORGANIC LETTERS

2011
Vol. 13, No. 5
956–959

Copper-Free Sonogashira Coupling of Cyclopropyl Iodides with Terminal Alkynes

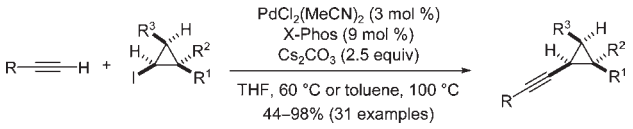
Benoît de Carné-Carnavalet,[†] Alexis Archambeau,[†] Christophe Meyer,*[,†] Janine Cossy,*[,†] Benoît Folléas,[‡] Jean-Louis Brayer,[‡] and Jean-Pierre Demoute[‡]

Laboratoire de Chimie Organique, ESPCI ParisTech, CNRS, 10 rue Vauquelin, 75231 Paris Cedex 05, France, and Diverchim, Les Marches de l'Oise, 100 rue Louis Blanc 60765 Montataire Cedex, France

christophe.meyer@espci.fr; janine.cossy@espci.fr

Received December 10, 2010

ABSTRACT



The substrate scope of the copper-free Sonogashira coupling has been successfully extended to cyclopropyl iodides, allowing an efficient access to a wide variety of functionalized alkynyl cyclopropanes.

Substituted cyclopropanes are encountered in several natural products, displaying a broad spectrum of biological activity and as key structural subunits in crop protection or therapeutic agents.[1,2] Due to their highly versatile reactivity, cyclopropane-containing compounds have attracted considerable interest,[1,2] and efficient methods have been developed for their stereoselective preparation.[3] Chemoselective reactions that allow the functionalization of the three-membered ring are also important, and in this context, palladium-catalyzed cross-coupling reactions leading to carbon−carbon bond formation and involving cyclopropyl magnesium,[4] zinc,[5] boron,[6] or tin[7] organometallic reagents as well as silanols[8] and aryl or alkenyl halides have emerged as a useful strategy.[9] Despite the well-known sp^2 character of cyclopropanes,[10] the use of electrophilic cyclopropane derivatives as partners in cross-coupling reactions has been much less explored. In 1996, Charette and Giroux demonstrated that cyclopropyl

[†] ESPCI.
[‡] Diverchim.

(1) (a) Salaün, J.; Baird, M. S. *Curr. Med. Chem.* **1995**, *2*, 511–542. (b) Salaün, J. *Top. Curr. Chem.* **2000**, *207*, 1–67. (c) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589–8627. (d) Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625–1647. (e) Pietruszka, J. *Chem. Rev.* **2003**, *103*, 1051–1070. (f) Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603–1623. (g) Brackmann, F.; de Meijere, A. *Chem. Rev.* **2007**, *107*, 4493–4537. (h) Brackmann, F.; de Meijere, A. *Chem. Rev.* **2007**, *107*, 4538–4583. (i) Reichelt, A.; Martin, S. F. *Acc. Chem. Res.* **2006**, *39*, 433–442.

(2) (a) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165–198. (b) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151–1196.

(3) For selected reviews, see: (a) Salaün, J. *Chem. Rev.* **1989**, *89*, 1247–1270. (b) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911–935. (c) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977–1050. (d) Pellissier, H. *Tetrahedron* **2008**, *64*, 7041–7095.

(4) (a) For the first report using a nickel catalyst, see: Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, A.; Kodama, S.-i.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1958–1969. (b) Limmert, M. E.; Roy, A. H.; Hartwig, J. F. *J. Org. Chem.* **2005**, *70*, 9364–9370. For an efficient synthesis of cyclopropyl Grignard reagents, see: (c) Vu, V. A.; Marek, I.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 351–352. (d) Rauhut, C. B.; Cervino, C.; Krasovskiy, A.; Knochel, P. *Synlett* **2009**, 67–70.

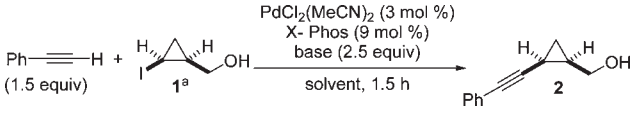
(5) (a) Piers, E.; Jean, M.; Marrs, P. S. *Tetrahedron Lett.* **1987**, *28*, 5075–5078. (b) Harada, T.; Katsuhira, T.; Hattori, K.; Oku, A. *J. Org. Chem.* **1993**, *58*, 2958–2965. (c) Martin, S. F.; Dwyer, M. P. *Tetrahedron Lett.* **1998**, *39*, 1521–1524. (d) Piers, E.; Coish, P. D. G. *Synthesis* **2001**, 251–261. (e) Coleridge, B. M.; Bello, C. S.; Leitner, A. *Tetrahedron Lett.* **2009**, *50*, 4475–4477.

10.1021/ol1029996
Published on Web 01/26/2011

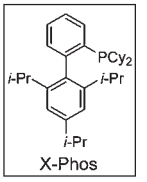
iodides could participate in Suzuki−Miyaura reactions with aryl or alkenyl organoboron species.[11] Such reactions have almost remained the only illustration of the utility of cyclopropyl iodides in cross-couplings[5c,12] besides an additional isolated example of a Negishi reaction with an arylzinc, reported during the chemical development of the non-nucleoside reverse transcriptase inhibitor MIV-150.[13]

Alkynylcyclopropanes constitute an interesting class of substituted cyclopropanes which are found in some biologically active compounds[14] and can be involved in synthetically useful transition metal-catalyzed reactions.[15] Herein, we report that a wide variety of functionalized alkynylcyclopropanes can be efficiently synthesized by copper-free Sonogashira cross-coupling between cyclopropyl iodides and terminal alkynes.

Table 1. Sonogashira Coupling between Phenylacetylene and *cis*-2-Iodocyclopropanemethanol **1**



entry	base	solvent	temperature	conversion[b]	yield[c]
1	Cs_2CO_3	MeCN	80 °C	100%	93%
2	K_2CO_3	MeCN	80 °C	75%	--[d]
3	K_3PO_4	MeCN	80 °C	100%	92%
4	K_3PO_4	THF	60 °C	90%	--[d]
5	K_3PO_4	toluene	80 °C	100%	95%
6	Cs_2CO_3	THF	60 °C	100%	97%[e]
7	Cs_2CO_3	toluene	80 °C	100%	99%



[a] 0.25−0.50 mmol scale. [b] Determined by analysis of the crude material by ^{1}H NMR spectroscopy. [c] Isolated yield of analytically pure material. [d] Not determined. Alkynylcyclpropane **2** could not be easily separated from unreacted **1** by flash chromatography [e] On a larger scale (5 mmol), $PdCl_2(MeCN)_2$ (1 mol %) and X-Phos (3 mol %) were used.

The *cis*-2-iodocyclopropanemethanol (**1**)[16] was selected as a substrate in our initial studies. Attempts to achieve a Sonogashira coupling between compound **1** and phenylacetylene, employing classical palladium and copper catalysts with an amine, were unsuccessful.[17,18] Because the oxidative addition of the palladium(0) complex into the cyclopropyl carbon−iodine bond may be difficult, the use of conditions reported by Buchwald and Gelman for less reactive substrates, such as aryl chlorides or tosylates, was considered.[19−21] We found that treatment of cyclopropyl iodide **1** with phenylacetylene (1.5 equiv) in the presence of $PdCl_2(MeCN)_2$ (3 mol %), X-Phos (9 mol %) as the ligand, and Cs_2CO_3 (2.5 equiv) as the base (MeCN, 80 °C, 1.5 h) afforded the desired alkynylcyclopropane **2** in 93% yield (Table 1, entry 1). As other palladium complexes and ligands gave inferior results,[22] only the effect of the base and the solvent was examined. In acetonitrile, Cs_2CO_3 and K_3PO_4 were almost equally efficient but K_2CO_3 provided inferior results (Table 1, entries 2 and 3). Interestingly, the reaction could be run in solvents of lower polarity than

(6) (a) Hildebrand, J. P.; Marsden, S. P. *Synlett* **1996**, 893–894. (b) Wang, X.-Z.; Deng, M.-Z. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2663–2664. (c) Yao, M.-L.; Deng, M.-Z. *Synthesis* **2000**, 1095–1100. (d) Yao, M.-L.; Deng, M.-Z. *Tetrahedron Lett.* **2000**, *41*, 9083–9087. (e) Löhr, S.; De Meijere, A. *Synlett* **2001**, 489–492. (f) Fang, G.-H.; Yan, Z.-J.; Deng, M.-Z. *Org. Lett.* **2004**, *6*, 357–360. (g) Charette, A. B.; Mathieu, S.; Fournier, J.-F. *Synlett* **2005**, 1779–1782. (h) Hohn, E.; Pietruszka, J.; Solduga, G. *Synlett* **2006**, 1531–1534. (i) Molander, G. A.; Gormisky, P. E. *J. Org. Chem.* **2008**, *73*, 7481–7485.

(7) (a) Peters, D.; Hornfeldt, A. B.; Gronowitz, S. *J. Heterocycl. Chem.* **1991**, *28*, 1629–1631. (b) Schmitz, W. D.; Romo, D. *Tetrahedron Lett.* **1996**, *37*, 4857–4860. (c) Wiedemann, S.; Rauch, K.; Savchenko, A.; Marek, I.; De Meijere, A. *Eur. J. Org. Chem.* **2004**, 631–635. (d) Heureux, N.; Marchant, M.; Maulide, N.; Berthon-Gelloz, G.; Hermans, C.; Hermant, S.; Kiss, E.; Leroy, B.; Wasnaire, P.; Markó, I. E. *Tetrahedron Lett.* **2005**, *46*, 79–83. (e) Hodgson, D. M.; Chung, Y. K.; Nuzzo, I.; Freixas, G.; Kulikiewicz, K. K.; Cleator, E.; Paris, J.-M. *J. Am. Chem. Soc.* **2007**, *129*, 4456–4462.

(8) Beaulieu, L.-P. B.; Delvos, L. B.; Charette, A. B. *Org. Lett.* **2010**, *12*, 1348–1351.

(9) For application of these cross-coupling reactions in the synthesis of arylcyclopropanes, see: Gagnon, A.; Duplessis, M.; Fader, L. *Org. Prep. Proc. Intl.* **2010**, *42*, 1–69.

(10) (a) De Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 809–826. (b) Wiberg, K. B. *Acc. Chem. Res.* **1996**, *29*, 229–234. Formation of cyclopropyllithium species by lithium−halogen exchange also illustrates this property; see: (c) Walborsky, B. H.; Impastato, F. J.; Young, A. E. *J. Am. Chem. Soc.* **1964**, *86*, 3283–3288.

(11) Charette, A. B.; Giroux, A. *J. Org. Chem.* **1996**, *61*, 8718–8719.

(12) (a) Charette, A. B.; De Freitas-Gil, R. P. *Tetrahedron Lett.* **1997**, *38*, 2809–2812. (b) Hohn, E.; Pietruszka, J. *Adv. Synth. Catal.* **2004**, *346*, 863–866.

(13) Cai, S.; Dimitroff, M.; McKennon, T.; Reider, M.; Robarge, L.; Ryckman, D.; Shang, X.; Therrien, J. *Org. Process Res. Dev.* **2004**, *8*, 353–359.

(14) (a) Liu, H.; Kerdesky, F. A.; Black, L. A.; Fitzgerald, M.; Henry, R.; Esbenshade, T. A.; Hancock, A. A.; Bennani, Y. L. *J. Org. Chem.* **2004**, *69*, 192–194. (b) Zampella, A.; D'Auria, M. V.; Minale, L.; Debitus, C.; Roussakis, C. *J. Am. Chem. Soc.* **1996**, *118*, 11085–11088. (c) Corbett, J. W.; Ko, S. S.; Rodgers, J. D.; Geahart, L. A.; Magnus, N. A.; Bacheler, L. T.; Diamond, S.; Jeffrey, S.; Klabe, R. M.; Crodova, B. C.; Garber, S.; Logue, G. L.; Trainor, G. L.; Anderson, P. S.; Erickson-Viitanen, S. K. *J. Med. Chem.* **2000**, *43*, 2019–2030.

(15) For selected references, see: (a) Barluenga, J.; Fernández-Rodríguez, M. A.; García-García, P.; Aguilar, E.; Merino, I. *Chem.−Eur. J.* **2006**, *12*, 303–313. (b) Gorin, D. J.; Dubé, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 14480–14481. (c) Zhang, J.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2006**, *45*, 6704–6707. (d) Gorin, D. J.; Watson, I. D. G.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 3736–3737. (e) Zhang, X.-M.; Tu, Y.-Q.; Jiang, Y.-J.; Zhang, Y.-Q.; Fan, C.-A.; Zhang, F.-M. *Chem. Commun.* **2009**, 4726–4728. (f) Garayalde, D.; Gómez-Bengoa, E.; Huang, X.; Goeke, A.; Nevado, C. *J. Am. Chem. Soc.* **2010**, *132*, 4720–4730. (g) Ye, S.; Yu, Z.-X. *Org. Lett.* **2010**, *12*, 804–807. (h) Li, C.-W.; Pati, K.; Lin, G.-Y.; Abu Sohel, S. M.; Hung, H.-H.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9891–9894. (i) Ye, S.; Yu, Z.-X. *Chem. Commun.* **2011**, 794–796. See also: (j) Liao, L.-a.; Fox, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 14322–14323. (k) Yin, J.; Chisholm, J. D. *Chem. Commun.* **2006**, 632–634 and references cited.

(16) Piers, E.; Coish, P. D. *Synthesis* **1995**, 47–55.

(17) (a) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp 203−239. (b) Negishi, E.-i.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979–2017. (c) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874–922. (d) Plenio, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6954–6956.

(18) Typical conditions screened were $PdCl_2(PPh_3)_2$ (4 mol %), CuI (16 mol %), Et_2NH, or Et_3N in toluene or THF (rt to reflux).

(19) Gelman, D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993–5996.

(20) For recent contributions, see: (a) R'kyek, O.; Halland, N.; Lindenschmidt, A.; Alonso, J.; Lindemann, P.; Urmann, M.; Nazaré, M. *Chem.−Eur. J.* **2010**, *16*, 9986–9989. (b) Choy, P. Y.; Chow, W. K.; So, C. M.; Lau, C. P.; Kwong, F. Y. *Chem.−Eur. J.* **2010**, *16*, 9982–9985. (c) Torborg, C.; Huang, J.; Schulz, T.; Schäffner, B.; Zapf, A.; Spannenberg, A.; Börner, A.; Beller, M. *Chem.−Eur. J.* **2009**, *15*, 1329–1336 and references cited in these articles.

(21) The Sonogashira reaction of primary alkyl halides (using carbene ligands) has also been reported; see: Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642–13643.

(22) $Pd(OAc)_2$ and other ligands such as 2-dicyclohexylphosphino-2′-methylbiphenyl (Me-Phos) or *t*-Bu_3P led to much lower conversions. BINAP, XantPhos, and dppf were unsuitable.

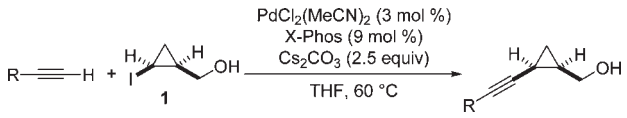
MeCN such as THF (Table 1, entries 4 and 6) or toluene (Table 1, entries 5 or 7) with minor differences in terms of reaction rates. The highest yields in alkynylcyclopropane **2** were attained with Cs_2CO_3, and the use of this latter base in THF was generally found to provide the best results in all couplings with cyclopropyl iodide **1** as substrate.

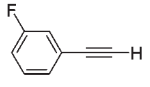
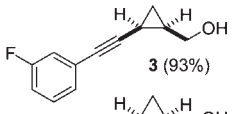
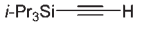
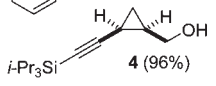
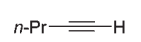
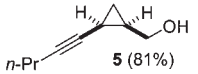
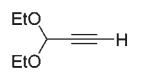
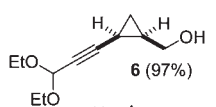
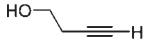
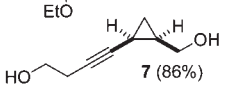
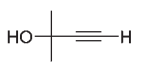
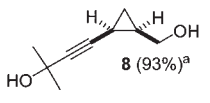
The scope of the copper-free Sonogashira coupling involving cyclopropyl iodide **1** as substrate was next examined with various terminal alkynes (Table 2).

The reaction is not only compatible with aryl alkynes (Table 2, entry 1) but also with triisopropylsilylacetylene (Table 2, entry 2) as well as with alkynes substituted by aliphatic groups (Table 2, entry 3), possibly bearing an acetal moiety or a free alcohol (Table 2, entries 4 and 5). The corresponding alkynylcyclopropanes **3**−**7** were isolated in high yields (81−97%). Longer reaction times were required when the substituent on the triple bond was bulky, which is in agreement with the fact that coordination of the terminal alkyne to the cyclopropylpalladium(II) iodide species, generated by oxidative addition, has to occur prior to deprotonation.[23] When the tertiary alcohol 2-methylbut-3-yn-2-ol was used as a coupling partner, the desired alkynylcyclopropane **8** was isolated in rather low yield (49%) if the reaction was carried out at 60 °C, presumably because the coupling product **8** underwent elimination of acetone under those conditions. Decreasing the temperature to 40 °C slowed the coupling but raised the yield in the alkynylcyclopropane **8** to 93% (Table 2, entry 6).

The behavior of the readily available 1,1,2- and 1,2,3-trisubstituted 2-iodocyclopropanemethanols **9** and **10**,[24] respectively, was next investigated in copper-free Sonogashira couplings with various terminal alkynes. Except for compound **14**, generated by the coupling of iodocyclopropane **9** with triisopropylsilylacetylene (44%), the other desired alkynylcyclopropanes **13**, **15**−**19** were isolated in good to excellent yields (77−97%) (Scheme 1). As the iodocyclopropanes investigated so far as substrates invariably possess a hydroxymethyl group *cis* to the iodine atom, it was necessary to ascertain whether the latter functional group was required for the success of the Sonogashira coupling. The epimeric *trans*-2-iodocyclopropanemethanol (**11**) (*trans*/*cis* = 95:5) was synthesized, and this latter compound underwent efficient Sonogashira coupling with several representative terminal alkynes, leading to the *trans*-2-alkynylcyclopropylcarbinols **20**−**22** (72−86%). Iodocyclopropane **12**, devoided of the free hydroxyl group and prepared by protection of *cis*-2-iodocyclopropanemethanol (**1**) as a *para*-methoxybenzyl ether, was also a suitable partner in copper-free Sonogashira coupling as illustrated by the formation of the alkynylcyclopropanes **23**−**25** in high yields (79−95%) (Scheme 1).

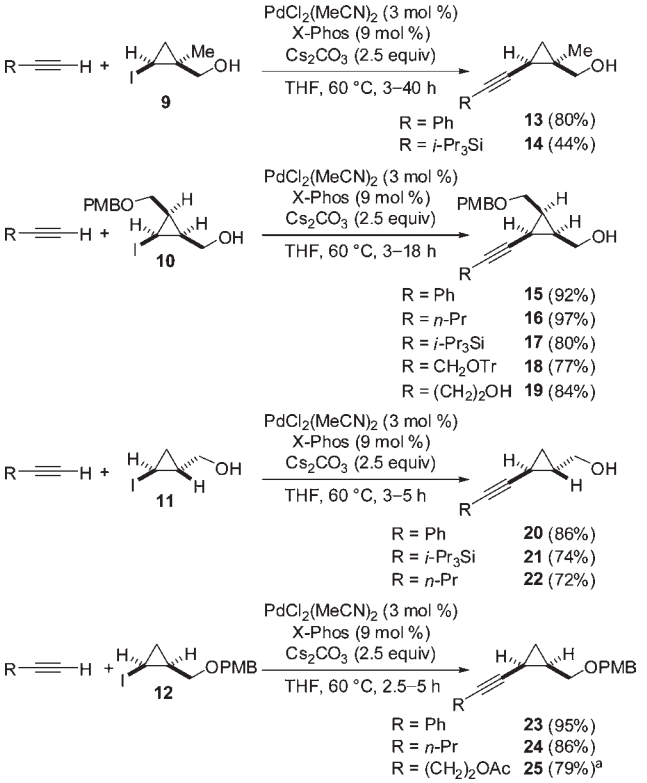
Table 2. Copper-Free Sonogashira Coupling between Cyclopropyl Iodide **1** and Various Terminal Alkynes



entry	alkyne	time	product (yield)
1		2 h	 **3** (93%)
2		2 h	 **4** (96%)
3		3 h	 **5** (81%)
4		5.5 h	 **6** (97%)
5		2.5 h	 **7** (86%)
6		21 h[a]	 **8** (93%)[a]

[a] The reaction was carried out at 40 °C.

Scheme 1. Copper-Free Sonogashira Coupling between Cyclopropyl Iodides **9**−**12** and Various Terminal Alkynes

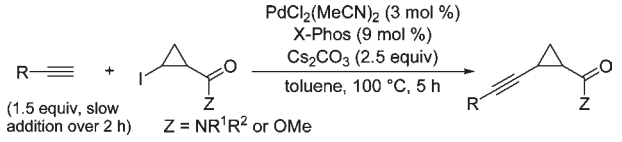


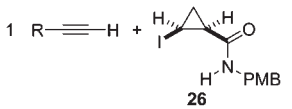
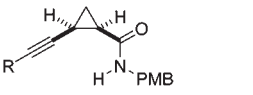
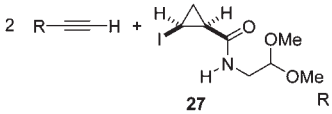
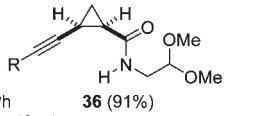
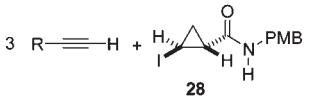
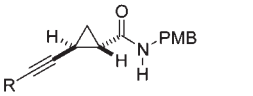
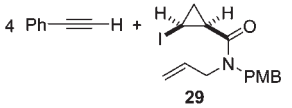
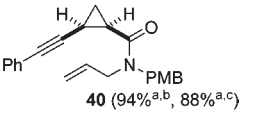
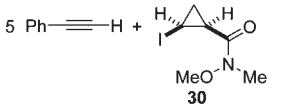
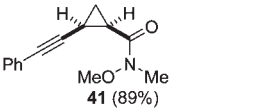
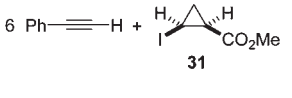
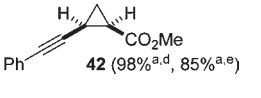
[a] Compound **25** was synthesized from but-3-yn-1-ol [R = $(CH_2)_2OH$], and the hydroxyl group was subsequently acetylated.

(23) For mechanistic investigations on the so-called copper-free Sonogashira coupling, see: (a) Tougerti, A.; Negri, S.; Jutand, A. *Chem.*−*Eur. J.* **2007**, *13*, 666–676. (b) Ljungdahl, T.; Bennur, T.; Dallas, A.; Emtenäs, H.; Martensson, J. *Organometallics* **2008**, *27*, 2490–2498.

(24) Charette, A. B.; Gagnon, A.; Fournier, J.-F. *J. Am. Chem. Soc.* **2002**, *124*, 386–387.

Table 3. Copper-Free Sonogashira Coupling with 2-Iodocyclopropanecarboxylic Acid Derivatives



entry	substrates	product (yield)
1	 **26**	 R = Ph **32** (96%); R = *n*-Pent **33** (98%); R = *i*-Pr$_3$Si **34** (78%); R = CH(OEt)$_2$ **35** (87%)
2	 **27**	 R = Ph **36** (91%); R = CH(OEt)$_2$ **37** (95%)
3	 **28**	 R = Ph **38** (92%); R = *n*-Pent **39** (76%)
4	 **29**	 **40** (94%[a,b], 88%[a,c])
5	 **30**	 **41** (89%)
6	 **31**	 **42** (98%[a,d], 85%[a,e])

[a] Slow addition of the alkyne not required. [b] Toluene, 100 °C, 2.5 h. [c] THF, 60 °C, 14 h. [d] Toluene, 100 °C, 1 h. [e] THF, 60 °C, 2 h.

It is worth pointing out that the copper-free Sonogashira reaction involving 2-iodocyclopropanemethanols proceeded stereoselectively and with retention of configuration,[25] as previously observed for the Suzuki−Miyaura coupling involving such substrates.[10,11]

The scope of the copper-free Sonogashira coupling was then investigated with derivatives of 2-iodocyclopropanecarboxylic acid (Table 3). Under the previously used conditions (THF, 60 °C), the coupling between phenylacetylene and 2-iodocyclopropanecarboxamide **26** (Table 3, entry 1) did not reach completion even after prolonged heating. The presence of the amide group seemed to slow the cross-coupling whereas phenylacetylene was found to be consumed by competitive oligomerization.[26] The coupling was therefore carried out at a higher temperature (100 °C) in toluene since we previously showed that this nonpolar solvent was suitable. Furthermore, the alkyne partner was slowly added (portionwise over 2 h) to avoid its too rapid consumption and, under these conditions, the desired coupling product **32** could be isolated in 96% yield. The *cis*-2-iodocyclopropanecarboxamides **26** and **27** underwent successful Sonogashira coupling with different alkynes under these optimized conditions to afford the corresponding 2-alkynylcyclopropanecarboxamides **33**−**37** in high yields (78−98%) (Table 3, entries 1 and 2). Not surprisingly, the Sonogashira coupling with *trans*-2-iodocyclopropanecarboxamide **28** proceeded also successfully and provided the functionalized alkynylcyclopropanes **38** (92%) and **39** (76%) (Table 3, entry 3). The fact that compounds **32** and **33** were the epimers of **38** and **39**, respectively, confirmed that the copper-free Sonogashira coupling with 2-iodocyclopropanecarboxamides proceeded with complete stereoselectivity and retention of configuration. Additionally, no competitive β-elimination that would have generated a cyclopropenecarboxamide intermediate took place under these conditions.

The scope of the coupling reaction with 2-iodocyclopropanecarboxylic acid derivatives was successfully extended to the tertiary amide **29** and also to the Weinreb amide **30**, as illustrated using phenylacetylene as a partner, to deliver the corresponding 2-alkynylcyclopropanecarboxamides **40** (94%) and **41** (89%), respectively (Table 3, entries 4 and 5). As illustrated with compound **31**, a methyl ester was also tolerated on the cyclopropane ring and the resulting coupling product **42** was obtained in excellent yield (98%) (Table 3, entry 6). Slow addition of phenylacetylene was not required in the case of substrates **29** and **31**, but the coupling reactions still proceeded more rapidly and cleanly in toluene at 100 °C than in THF at 60 °C (Table 3, entries 4 and 6).

In conclusion, we have shown that the substrate scope of the copper-free Sonogashira cross-coupling can be extended to diversely substituted cyclopropyl iodides as substrates to afford highly functionalized alkynyl cyclopropanes in high yields. Since iodocyclopropanes are easily accessible by different strategies, also in an enantiomerically enriched form,[27] this method should find useful applications for the stereoselective preparation of a variety of substituted cyclopropanes.

Acknowledgment. B. de C.-C. thanks Diverchim for a CIFRE grant.

Supporting Information Available. Experimental procedures and ^{1}H and ^{13}C NMR data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(25) The relative configuration of the coupling products could be assigned by ^{1}H NMR spectroscopy in most cases by determination of the ^3J coupling constants between the cyclopropyl protons; see the Supporting Information for details. Comparison of the spectra of the *cis*-cyclopropanemethanols **2**, **4**, **5** and their corresponding *trans* diastereomers **20**, **21**, **22**, respectively, also confirmed the results unambiguously.

(26) Competitive consumption of aryl alkynes in slow copper-free Sonogashira coupling has already been observed as a side reaction under similar conditions; see ref 19.

(27) Beaulieu, L.-P.; Zimmer, L. E.; Charette, A. B. *Chem.−Eur. J.* **2009**, *15*, 11829–11832.