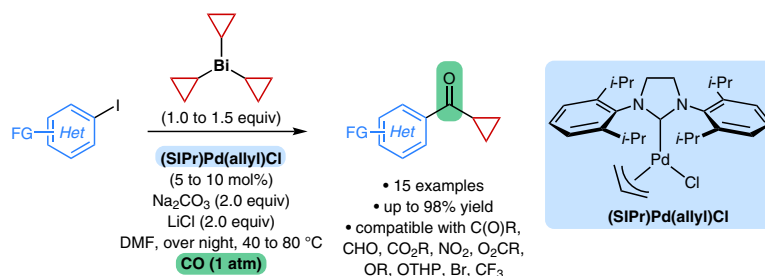


Palladium-Catalyzed Carbonylative Cross-Coupling Reaction between Aryl(Heteroaryl) Iodides and Tricyclopropylbismuth: Expedient Access to Aryl Cyclopropylketones

Emeline Benoit
Julien Dansereau
Alexandre Gagnon*

Département de Chimie, Université du Québec à Montréal, C.P. 8888, Succ. Centre-Ville, Montréal, Québec, H3C 3P8, Canada
gagnon.alexandre@uqam.ca

Dedicated to Professor Victor Snieckus on the occasion of his 80th birthday



Received: 24.05.2017

Accepted after revision: 20.06.2017

Published online: 19.07.2017

DOI: 10.1055/s-0036-1590832; Art ID: st-2017-r0394-l

Abstract The carbonylative cross-coupling reaction between aryl and heteroaryl iodides and tricyclopropylbismuth is reported. The reaction is catalyzed by (SIPr)Pd(allyl)Cl, a NHC-palladium(II) catalyst, operates under 1 atm of carbon monoxide and tolerates a wide range of functional groups. The use of lithium chloride was found to provide higher yields of the desired aryl cyclopropylketones. The conditions were also applied to the carbonylative cross-coupling of an iodoalkene to afford the corresponding alkenyl cyclopropylketone.

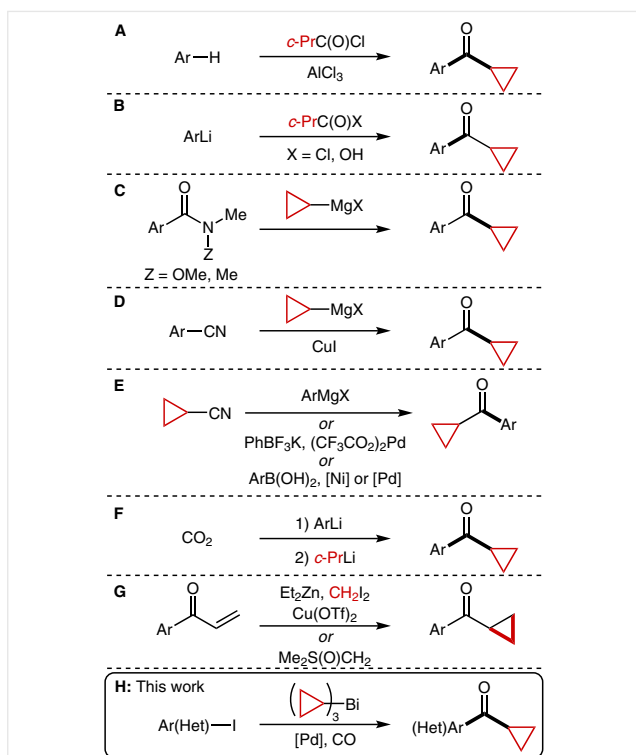
Key words aryl cyclopropylketones, carbon monoxide, carbonylative cross-coupling, NHC ligand, palladium, tricyclopropylbismuth

Aryl cyclopropylketones are highly versatile synthons that can be engaged in a multitude of reactions to prepare architecturally complex molecules. For instance, they have been used in nickel-catalyzed [3+2] cycloadditions with alkynes,¹ nickel-catalyzed dimerization and cross reactions with enones,² homo-Nazarov reactions,³ magnesium chloride induced rearrangements,⁴ reductive ring-opening reactions,⁵ radical ring opening/addition to aldehydes,⁶ Lewis acid mediated opening/condensations to α -ketoesters,⁷ aldehydes,⁸ and imines,⁹ Lewis acid promoted reactions with sulfonamides,¹⁰ mercuric salt promoted iodination/opening reactions,¹¹ nickel-catalyzed borylation reactions,¹² photochemical dimerization reactions,¹³ iodine-induced ring opening/aldol reactions,¹⁴ and rearrangement reactions via their arylhydrazones derivatives.¹⁵

Aryl cyclopropylketones have also been frequently used in medicinal chemistry to prepare biologically active molecules. For example, aryl cyclopropylketones can be found in ciproxifan,¹⁶ an extremely potent histamine H₃ agonist/antagonist, in lead molecules with antifungal¹⁷ or antitubercular activities,¹⁸ in GPR120 agonists,¹⁹ and in dual ligands for melatonin (MT₁/MT₂) and serotonin 5-HT_{2c} receptors.²⁰

Aryl cyclopropylketones are commonly prepared via Lewis acid catalyzed Friedel-Crafts acylation of aromatic substrates with cyclopropanecarbonyl chloride (Scheme 1, A).^{17,21} However, to be efficient, this approach usually requires electronically rich aromatic compounds. In addition, the functional-group compatibility of this approach is usually compromised by the presence of the highly reactive Lewis acid. The addition of aryllithium to cyclopropanecarbonyl chloride²² or cyclopropane carboxylic acid²³ (Scheme 1, B) and cyclopropylmagnesium halide to *N,N*-dimethyl or *N*-methyl-*N*-methoxy benzoyl amides (Scheme 1, C)²⁴ has also been sporadically utilized to access aryl cyclopropylketones. In another approach, aryl cyclopropylketones were obtained by adding cyclopropylmagnesium halides to aryl cyanides in the presence of copper iodide (Scheme 1, D).²⁵ The uncatalyzed addition of arylmagnesium halides⁴ and the metal-catalyzed addition of potassium phenyltrifluoroborate²⁶ and arylboronic acids²⁷ onto cyclopropyl cyanide has also been utilized to prepare aryl cyclopropylketones (Scheme 1, E). Recently, the synthesis of aryl cyclopropylketones through sequential addition of an aryllithium reagent to carbon dioxide followed by cyclopropyllithium in flow chemistry mode has been reported (Scheme 1, F).²⁸ Aryl cyclopropanes can also be prepared via Simmons-Smith or Corey-Chaykovsky cyclopropanation of aryl vinylketones (Scheme 1, G).²⁹ Although methods A–G are frequently used to prepare aryl cyclopropylketones, they are not free of limitations. In fact, many of these approaches require highly reactive organometallic reagents which can severely limit the nature of functional groups that can be present on the substrate.

The preparation of diaryl and aryl alkylketones via carbonylative cross-coupling reaction between aryl halides and organometallic reagents has been extensively documented.³⁰ Surprisingly, however, to the best of our knowledge, aryl cyclopropylketones have never been prepared via



Scheme 1 Methods A–G: Selected methods for the synthesis of aryl cyclopropyl ketones. Method H: Synthesis of aryl cyclopropyl ketones via palladium-catalyzed carbonylative cross-coupling reaction between aryl(heteroaryl) iodides and tricyclopropylbismuth.

carbonylative cross-coupling reaction. This approach would provide an expedient route to this important class of compounds.

Organobismuth compounds are organometallic reagents that contain a C–Bi bond.³¹ These compounds are roughly divided into two classes: trivalent reagents and pentavalent reagents where bismuth is at the +3 and +5 oxidation state, respectively. Triarylbismuthines Ar_3Bi , introduced in 1887 by Michaelis and Polis,³² are air- and moisture-stable and can thus be purified by simple column chromatography. On the contrary, trialkylbismuthines R_3Bi , introduced by Dünhaupt,³³ Marquardt³⁴ and Breed³⁵ more than 150 years ago, are usually pyrophoric and must therefore be handled and purified under inert atmosphere. The use of organobismuth compounds in organic synthesis was greatly popularized by Barton and Finet³⁶ in the 1980s and more recently by Rao,³⁷ Condon,³⁸ and others.³⁹

Our group reported a portfolio of methods for the construction of C–C,⁴⁰ C–N,⁴¹ and C–O⁴² bond using triaryl and trialkyl organobismuth reagents.⁴³ The group of Cai⁴⁴ and our group⁴⁵ recently disclosed protocols for the carbonylative cross-coupling reaction of aryl iodides with triarylbismuthines. We envisioned that the carbonylative cross-coupling reaction between aryl halides and tricyclopropylbismuth, a reagent that we introduced in 2007⁴⁶ and used later

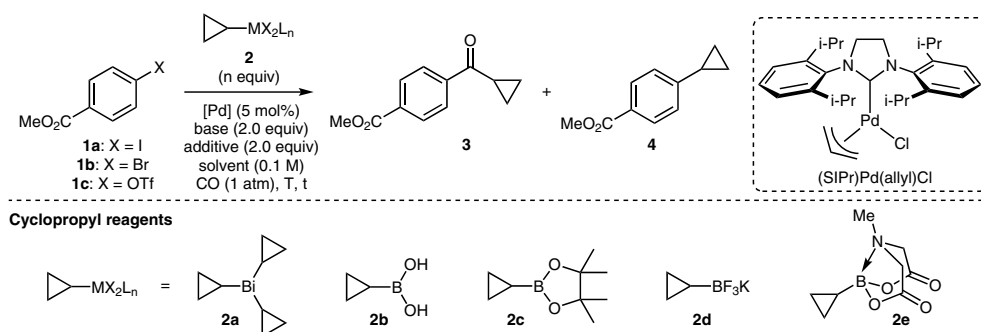
on in cross-coupling reactions,⁴⁷ could provide a highly expedient route to aryl cyclopropyl ketones (Scheme 1, H). We would like to report herein our results towards this endeavor.

We began by attempting the reaction between tricyclopropylbismuth (**2a**) and 4-iodo methyl benzoate (**1a**) using conditions that we reported for the carbonylative cross-coupling reaction of triarylbismuthines with aryl iodides.⁴⁵ Using 1.5 equivalents of tricyclopropylbismuth (**2a**), 5 mol% of tetrakis(triphenylphosphine)palladium(0) and 2.0 equivalents of rubidium carbonate in the presence of 2.0 equivalents of lithium chloride in DMF at 80 °C under 1 atm of carbon monoxide for six hours, the desired aryl cyclopropyl ketone **3**⁴⁸ was obtained in a meager 26% yield along with 58% of noncarbonylative arylcyclopropane product **4** (Table 1, entry 1), showing that tricyclopropylbismuth is much less reactive than triarylbismuthines under these conditions. With the aim of improving the efficiency of the process, we then embarked on the systematic optimization of every reaction parameter. First, increasing the reaction time to 16 hours led to a higher but still unsatisfactory yield (Table 1, entry 2). Among all the palladium catalysts and ligands that were tested, allyl[1,3-bis(2,6-diisopropylphenyl)-2-imidazolylidene]-chloropalladium(II) (SIPr)Pd(allyl)Cl provided the highest yield, affording **3** in 87% yield (Table 1, entry 3).⁴⁹ Andrus demonstrated previously that palladium catalysts containing this NHC ligand efficiently catalyze the carbonylative cross-coupling reaction of aryl diazonium ions with arylboronic acids.⁵⁰ Using conditions from entry 3, we then tested other ‘classical’ cyclopropyl boron-based donor reagents. Interestingly, and rather surprisingly, cyclopropylboronic acid (**2b**), cyclopropylboronic acid pinacol ester (**2c**), potassium cyclopropyltrifluoroborate (**2d**), and cyclopropylboronic acid MIDA ester (**2e**) gave no desired product (Table 1, entry 4). Obviously, the use of these reagents in this carbonylative cross-coupling reaction would require extensive optimization of the conditions. Consequently, we continued our journey with tricyclopropylbismuth with the intention of reinvestigating these reagents in the future. Since rubidium carbonate is quite expensive, we then tested other inorganic and organic bases in order to find a cheaper replacement (Table 1, entries 5–9). In the event, we found that potassium carbonate, sodium carbonate, and triethylamine give results comparable to rubidium carbonate. On the contrary, lower yields were obtained with potassium phosphate tribasic and cesium carbonate. Interestingly, the noncarbonylative arylcyclopropane product **4** was observed in small amount with most bases, except with cesium and sodium carbonate. In light of sodium carbonate low cost and its apparent ability to suppress the formation of the undesired noncarbonylative product, we continued our optimization with this inorganic base. Reducing the loading of sodium carbonate to 1.0 equivalent was found to have a considerable negative effect on the yield of the reaction (Table 1, entry 10). Running the reaction in acetonitrile, diox-

ane, toluene, or dimethoxyethane led to a dramatic reduction in the yield of the reaction (Table 1, entries 11–14). We then investigated the effect of lithium chloride and found a minor erosion in the yield of the reaction upon using 1.0 equivalent of LiCl (Table 1, entry 15) or no LiCl (Table 1, entry 16). We also found that the efficiency of the reaction was preserved when 1.0 equivalent of tricyclopropylbis-

muth was used in place of 1.5 equivalents (Table 1, entry 17). Reducing the loading of tricyclopropylbismuth further to 0.5 equivalents led to a considerable drop in the yield of the reaction, showing that the ability of the second cyclopropyl group to transfer is lower than the first (Table 1, entry 18). Optimization of the reaction temperature showed that it could be reduced from 80 °C to 40 °C (Table 1, entry

Table 1 Optimization of the Reaction Conditions for the Palladium-Catalyzed Carbonylative Cross-Coupling Reaction between Cyclopropyl Reagents **2a–e** and 4-Iodo- (**1a**), 4-Bromo- (**1b**), and 4-Triflyl (**1c**) Methylbenzoate



Entry	1	Catalyst [Pd]	Base	Solvent	Additive	c-PrMX ₂ L _n (n equiv)	Temp (°C)	Time (h)	Yield of 3 (%) ^a	Yield of 4 (%) ^a	RSM (%) ^b
1	1a	Pd(PPh ₃) ₄	Rb ₂ CO ₃	DMF	LiCl	2a (1.5)	80	6	26	58	0
2	1a	Pd(PPh ₃) ₄	Rb ₂ CO ₃	DMF	LiCl	2a (1.5)	80	16	50	27	0
3	1a	(SiPr)Pd(allyl)Cl	Rb ₂ CO ₃	DMF	LiCl	2a (1.5)	80	16	87	7	0
4	1a	(SiPr)Pd(allyl)Cl	Rb ₂ CO ₃	DMF	LiCl	2b–e (1.5)	80	16	0	0	99
5	1a	(SiPr)Pd(allyl)Cl	K ₃ PO ₄	DMF	LiCl	2a (1.5)	80	16	67	2	0
6	1a	(SiPr)Pd(allyl)Cl	K ₂ CO ₃	DMF	LiCl	2a (1.5)	80	16	92	3	0
7	1a	(SiPr)Pd(allyl)Cl	Cs ₂ CO ₃	DMF	LiCl	2a (1.5)	80	16	76	0	0
8	1a	(SiPr)Pd(allyl)Cl	Et ₃ N	DMF	LiCl	2a (1.5)	80	16	92	5	0
9	1a	(SiPr)Pd(allyl)Cl	Na ₂ CO ₃	DMF	LiCl	2a (1.5)	80	16	99	0	0
10	1a	(SiPr)Pd(allyl)Cl	Na ₂ CO ₃ ^c	DMF	LiCl	2a (1.5)	80	16	60	35	0
11	1a	(SiPr)Pd(allyl)Cl	Na ₂ CO ₃	MeCN	LiCl	2a (1.5)	80	16	49	0	39
12	1a	(SiPr)Pd(allyl)Cl	Na ₂ CO ₃	dioxane	LiCl	2a (1.5)	80	16	4	0	78
13	1a	(SiPr)Pd(allyl)Cl	Na ₂ CO ₃	toluene	LiCl	2a (1.5)	80	16	5	0	86
14	1a	(SiPr)Pd(allyl)Cl	Na ₂ CO ₃	DME	LiCl	2a (1.5)	80	16	18	0	72
15	1a	(SiPr)Pd(allyl)Cl	Na ₂ CO ₃	DMF	LiCl ^d	2a (1.5)	80	16	92	8	0
16	1a	(SiPr)Pd(allyl)Cl	Na ₂ CO ₃	DMF	no additive	2a (1.5)	80	16	90	6	0
17	1a	(SiPr)Pd(allyl)Cl	Na ₂ CO ₃	DMF	LiCl	2a (1.0)	80	16	95	0	0
18	1a	(SiPr)Pd(allyl)Cl	Na ₂ CO ₃	DMF	LiCl	2a (0.5)	80	16	64	0	1
19	1a	(SiPr)Pd(allyl)Cl	Na ₂ CO ₃	DMF	LiCl	2a (1.0)	40	16	98	2	0
20	1a	(SiPr)Pd(allyl)Cl	Na ₂ CO ₃	DMF	LiCl	2a (1.0)	r.t.	16	0	0	99
21	1a	(SiPr)Pd(allyl)Cl	Na ₂ CO ₃	DMF	LiCl	2a (1.0)	40	6	90	0	10
22	1a	(SiPr)Pd(allyl)Cl	Na ₂ CO ₃	DMF	LiCl	2a (1.0)	40	3	50	0	50
23	1b,c	(SiPr)Pd(allyl)Cl	Na ₂ CO ₃	DMF	LiCl	2a (1.0)	80	16	0	0	99

^a Yields of isolated pure products.

^b RSM = recovered starting material.

^c Na₂CO₃ (1.0 equiv).

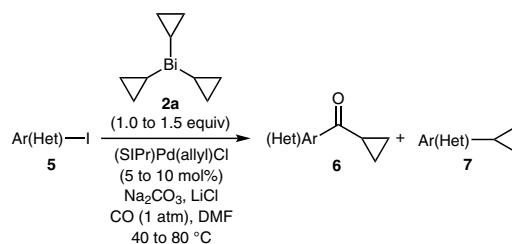
^d LiCl (1.0 equiv).

19) but not room temperature (Table 1, entry 20). The reaction time could also be reduced to six hours with a minimum impact on the yield of the reaction (Table 1, entry 21). However, reducing the reaction time to three hours had a dramatic impact on the yield of the reaction (Table 1, entry 22). Last, to our surprise, no reaction was observed when the reaction was performed on aryl bromide **1b** or aryl triflate **1c** (Table 1, entry 23).

Next, using the optimized reaction conditions from Table 1, entry 19 (method A),⁵¹ we investigated the substrate scope of the reaction (Table 2). We also performed every entry using more ‘forcing’ conditions which involved 1.5 equivalents of tricyclopropylbismuth and 10 mol% of (SIPr)Pd(allyl)Cl (method B)⁵² at 80 °C. Our studies first demonstrated that the carbonylative cross-coupling reaction can be done on aryl iodides that are *para*-, *meta*-, and *ortho*-substituted (Table 2, entries 1–3) and that possess electron-withdrawing and electron-donating groups (Table 2, entries 4 and 5). Our results also indicate that the reaction tolerates a wide array of functional groups such as a THP-protected phenol (Table 2, entry 6), a dioxolane (Table 2, entry 7), an ester (Table 2, entry 8), a methyl ketone (Table 2, entry 9), an aldehyde (Table 2, entry 10), a pivalate (Table 2, entry 11), and a benzyl-protected alcohol (Table 2, entry 12). Interestingly, the reaction was also found to be compatible with a bromide (Table 2, entry 13), thus offering a handle for further functionalization of the product via other palladium-catalyzed cross-coupling reactions. Heteroaryl iodides could also be successfully engaged in this reaction, as shown by 2-iodothiophene (**5n**). It is worth mentioning that when the yield of the desired aryl cyclopropylketone **6** was low using method A, substantial amounts of unreacted starting material could often be recovered, accounting for almost complete mass balance in many cases (Table 2, entries 5, 6, 11, 12). Oftentimes, the yield of **6** could be improved by using method B (Table 2, entries 1–3, 5–7, 11, and 12). Surprisingly, in some cases, a reduction in the yield of the aryl cyclopropylketone was observed upon using method B (Table 2, entries 4, 8–10, 13, and 14). In those cases, the noncarbonylative cross-coupling arylcyclopropane **7**⁵³ was also isolated, suggesting that higher catalyst loading favors both products **6** and **7**.

Alkenyl cyclopropylketones are interesting substrates in organic chemistry as they can be used in a variety of reactions.⁵⁴ The carbonylative cross-coupling reaction between cyclopropylmetals and haloalkenes could provide an expedient access to this class of compounds. To the best of our knowledge, this approach has never been explored. To test the transferability of our reaction conditions on alkenyl substrates, we attempted the reaction of *trans*-iodoalkene **8** using method A and obtained the desired alkenyl cyclopropylketone **9** in 61% yield (Scheme 2). Method B afforded the product in a similar yield. The full scope of this reaction is currently under investigation in our laboratory and results will be reported in due course.

Table 2 Palladium-Catalyzed Carbonylative Cross-Coupling Reaction between Aryl(heteroaryl) Iodides **5** and Tricyclopropylbismuth (**2a**)



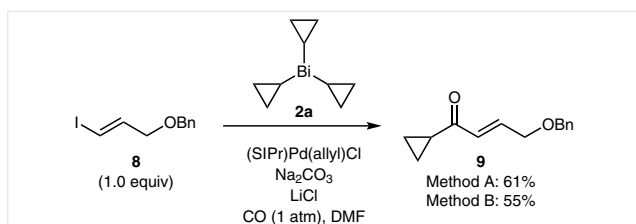
Entry	(Het)Ar 5	Yield of 6 (%) ^a	Yield of 7 (%) ^a	RSM 5 (%) ^b
1		6a 14 (A) ^c 66 (B) ^d	7a 0 (A) 0 (B)	5a 46 (A) 14 (B)
2		6b 51 (A) 62 (B)	7b 0 (A) 0 (B)	5b 0 (A) 0 (B)
3		6c 26 (A) 89 (B)	7c 0 (A) 0 (B)	5c 0 (A) 0 (B)
4		6d 93 (A) 44 (B)	7d 0 (A) 43 (B)	5d 7 (A) 0 (B)
5		6e 34 (A) 54 (B)	7e 0 (A) 0 (B)	5e 65 (A) 0 (B)
6		6f 20 (A) 68 (B)	7f 0 (A) 0 (B)	5f 67 (A) 0 (B)
7		6g 12 (A) 57 (B)	7g 0 (A) 29 (b)	5g 61 (A) 0 (B)
8		6h 82 (A) 64 (B)	7h 0 (A) 21 (B)	5h 18 (A) 0 (B)
9		6i 62 (A) 52 (B)	7i 0 (A) 23 (B)	5i 6 (A) 23 (B)
10		6j 92 (A) 36 (B)	7j 0 (A) 29 (B)	5j 5 (A) 0 (B)
11		6k 30 (A) 46 (B)	7k 0 (A) 0 (B)	5k 70 (A) 0 (B)
12		6l 17 (A) 87 (B)	7l 0 (A) 0 (B)	5l 78 (A) 11 (B)

Table 2 (continued)

Entry	(Het)Ar 5	Yield of 6 (%) ^a	Yield of 7 (%) ^a	RSM 5 (%) ^b
13		6m 83 (A) 78 (B)	7m 0 (A) 0 (B)	5m 15 (A) 0 (B)
14		6n 90 (A) 58 (B)	7n 0 (A) 0 (B)	5n 6 (A) 0 (B)

^a Yields of isolated pure products.^b RSM = recovered starting material.^c Method A: Ar(Het)I (1.0 equiv), c-Pr₃Bi (1.0 equiv), (SIPr)Pd(allyl)Cl (5 mol%), Na₂CO₃ (2.0 equiv), LiCl (2.0 equiv), DMF (0.1 M), 40 °C, 16 h.^d Method B: Ar(Het)I (1.0 equiv), c-Pr₃Bi (1.5 equiv), (SIPr)Pd(allyl)Cl (10 mol%), Na₂CO₃ (2.0 equiv), LiCl (2.0 equiv), DMF (0.1 M), 80 °C, 16 h.

In summary, we developed a protocol for the carbonylative cross-coupling reaction of tricyclopropylbismuth with aryl and heteroaryl iodides. The reaction operates under simple and mild conditions, requires only 1 atm of carbon monoxide, shows excellent functional-group compatibility, and affords the desired aryl cyclopropylketones in good to excellent yields. The use of lithium chloride as an additive provided higher yields of the desired carbonylative products. Cyclopropylboronic acid, cyclopropylboronic acid pinacol ester, potassium cyclopropyltrifluoroborate, and cyclopropylboronic acid MIDA ester failed to afford the desired carbonylative cross-coupling product. The conditions were transposed to the carbonylative cross-coupling reaction of iodoalkene **8**, affording the corresponding cyclopropyl alkylketone in good yield.



Scheme 2 Palladium-catalyzed cross-coupling reaction between *trans*-iodoalkene **8** and tricyclopropylbismuth (**2a**)

Funding Information

This work was supported by a provincial Fonds de Recherche du Québec, Nature et Technologies (FRQNT) team grant and by the Centre in Green Chemistry and Catalysis (CGCC).

Acknowledgment

J.D. thanks UQAM for a FARE and a Fondation Hydro-Québec graduate scholarship. The authors thank Emmanuelle Allouche and Pr. André B. Charette from the chemistry department of the Université de Montréal for kindly providing iodoalkene **8**.

Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0036-1590832>.

References and Notes

- Tamaki, T.; Ohashi, M.; Ogoshi, S. *Angew. Chem. Int. Ed.* **2011**, *50*, 12067.
- (a) Liu, L.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128*, 5348. (b) Tamaki, T.; Nagata, M.; Ohashi, M.; Ogoshi, S. *Chem. Eur. J.* **2009**, *15*, 10083. (c) Ogoshi, S.; Nagata, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2006**, *128*, 5350.
- De Simone, F.; Waser, J. *Chimia* **2009**, *63*, 162.
- Blake, K. W.; Gillies, I.; Denney, R. C. *J. Chem. Soc., Perkin Trans 1* **1981**, 700.
- Degueil-Castaing, M.; Rahm, A. *J. Org. Chem.* **1986**, *51*, 1672.
- (a) Enholm, E. J.; Jia, Z. *J. Org. Chem.* **1997**, *62*, 5248. (b) Enholm, E. J.; Jia, Z. *J. Org. Chem.* **1997**, *62*, 9159.
- Yang, Y.-H.; Shi, M. *J. Org. Chem.* **2005**, *70*, 10082.
- Shi, M.; Yang, Y.-H.; Xu, B. *Tetrahedron* **2005**, *61*, 1893.
- (a) Bertozzi, F.; Gustafsson, M.; Olsson, R. *Org. Lett.* **2002**, *4*, 3147. (b) Bertozzi, F.; Gustafsson, M.; Olsson, R. *Org. Lett.* **2002**, *4*, 4333. (c) Bertozzi, F.; Gundersen, B. V.; Gustafsson, M.; Olsson, R. *Org. Lett.* **2003**, *5*, 1551.
- Shi, M.; Yang, Y.-H.; Xu, B. *Synlett* **2004**, 1622.
- Barluenga, J.; Martinez-Gallo, J. M.; Najera, C.; Yus, M. *Synthesis* **1987**, 582.
- Sumida, Y.; Yorimitsu, H.; Oshima, K. *J. Org. Chem.* **2009**, *74*, 3196.
- Ranaweera, R. A. A. U.; Weragoda, G. K.; Bain, J.; Watanabe, S.; Abe, M.; Gudmundsdottir, A. D. *Phys. Org. Chem.* **2014**, 137.
- Han, Z.; Uehira, S.; Tsuritani, T.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2001**, *57*, 987.
- Salikov, R. F.; Belyy, A. Y.; Tomilov, Y. V. *Tetrahedron Lett.* **2014**, *55*, 5936.
- (a) Zaragoza, F.; Stephensen, H.; Peschke, B.; Rimvall, K. *J. Med. Chem.* **2005**, *48*, 306. (b) Eleni, P.; Dimitra, J.-L. *J. Biomol. Struct. Dyn.* **2017**, *35*, 968.
- Shi, W.; Dan, W.-J.; Tang, J.-J.; Zhang, Y.; Nandinsuren, T.; Zhang, A.-L.; Gao, J.-M. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 2156.
- Bisht, S. S.; Dwivedi, N.; Chaturvedi, V.; Anand, N.; Misra, M.; Sharma, R.; Kumar, B.; Dwivedi, R.; Singh, S.; Sinha, S. K.; Gupta, V.; Mishra, P. R.; Dwivedi, A. K.; Tripathi, R. P. *Eur. J. Med. Chem.* **2010**, *45*, 5965.
- Lombardo, M.; Bender, K.; London, C.; Kirkland, M.; Mane, J.; Pachanski, M.; Geissler, W.; Cummings, J.; Habulihaz, B.; Akiyama, T. E.; Di Salvo, J.; Madeira, M.; Pols, J.; Powles, M. A.; Finley, M. F.; Johnson, E.; Roussel, T.; Uebele, V. N.; Crespo, A.; Leung, D.; Alleyne, C.; Trusca, D.; Lei, Y.; Howard, A. D.; Ujjainwalla, F.; Tata, J. R.; Sinz, C. J. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 5724.
- Ettaoussi, M.; Pérès, B.; Errazani, A.; Boutin, J. A.; Caignard, D.-H.; Delagrèze, P.; Melnyk, P.; Berthelot, P.; Yous, S. *Eur. J. Med. Chem.* **2015**, *90*, 822.
- (a) Handlon, A. L.; Schaller, L. T.; Leesnitzer, L. M.; Merrihew, R. V.; Poole, C.; Ulrich, J. C.; Wilson, J. W.; Cadilla, R.; Turnbull, P. *ACS Med. Chem. Lett.* **2016**, *7*, 83. (b) Nandinsuren, T.; Shi, W.; Zhang, A.-L.; Bai, Y.-B.; Gao, J.-M. *Nat. Prod. Res.* **2016**, *30*, 1166.
- Castelló-Micó, A.; Herbert, S. A.; León, T.; Bein, T.; Knochel, P. *Angew. Chem. Int. Ed.* **2016**, *55*, 401.
- Alonso, F.; Lorenzo, E.; Yus, M. *J. Org. Chem.* **1996**, *61*, 6058.

- (24) (a) Cowart, M.; Faghih, R.; Curtis, M. P.; Gfesser, G. A.; Bennani, Y. L.; Black, L. A.; Pan, L.; Marsh, K. C.; Sullivan, J. P.; Esbenhade, T. A.; Fox, G. B.; Hancock, A. A. *J. Med. Chem.* **2005**, *48*, 38. (b) Olah, G. A.; Prakash, G. K. S.; Arvanaghi, M. *Synthesis* **1984**, 228.
- (25) Gfesser, G. A.; Faghih, R.; Bennani, Y. L.; Curtis, M. P.; Esbenhade, T. A.; Hancock, A. A.; Cowart, M. D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2559.
- (26) Wang, X.; Liu, M.; Xu, L.; Wang, Q.; Chen, J.; Ding, J.; Wu, H. *J. Org. Chem.* **2013**, *78*, 5273.
- (27) (a) Wong, Y.-C.; Parthasarathy, K.; Cheng, C.-H. *Org. Lett.* **2010**, *12*, 1736. (b) Wang, X.; Wang, X.; Liu, M.; Ding, J.; Chen, J.; Wu, H. *Synthesis* **2013**, *45*, 2241. (c) Das, T.; Chakraborty, A.; Sarkar, A. *Tetrahedron Lett.* **2014**, *55*, 7198.
- (28) Wu, J.; Yang, X.; He, Z.; Mao, X.; Hatton, T. A.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2014**, *53*, 8416.
- (29) (a) Fujii, K.; Misaki, T.; Sugimura, T. *Chem. Lett.* **2014**, *43*, 634. (b) Paxton, R. J.; Taylor, R. J. K. *Synlett* **2007**, 633.
- (30) (a) Wu, X.-F.; Neumann, H.; Beller, H. *Chem. Soc. Rev.* **2011**, *40*, 4986. (b) Brennfürher, A.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 4114. (c) Brunet, J.-J.; Chauvin, R. *Chem. Soc. Rev.* **1995**, *24*, 89.
- (31) For reviews on organobismuth reagents, see: (a) Gagnon, A.; Dansereau, J.; Le Roch, A. *Synthesis* **2017**, *49*, 1707. (b) Condon, S.; Pichon, C.; Davi, M. *Org. Prep. Proced. Int.* **2014**, *46*, 89. (c) Finet, J.-P. *Chem. Rev.* **1989**, *89*, 1487. (d) Freedman, L. D.; Doak, G. O. *Chem. Rev.* **1982**, *82*, 15.
- (32) (a) Michaelis, A.; Polis, A. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 54. (b) Michaelis, A.; Marquardt, A. *Justus Liebigs Ann. Chem.* **1889**, *251*, 323.
- (33) (a) Dünhaupt, F. *J. Prakt. Chem.* **1854**, *61*, 399. (b) Dünhaupt, F. *Justus Liebigs Ann. Chem.* **1854**, *92*, 371.
- (34) Marquardt, A. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 1516.
- (35) (a) Breed, Dr. *Justus Liebigs Ann. Chem.* **1852**, *82*, 106. (b) Breed, Dr. *J. Prakt. Chem.* **1852**, *56*, 341.
- (36) Abramovitch, R. A.; Barton, D. H. R.; Finet, J.-P. *Tetrahedron* **1988**, *44*, 3039.
- (37) (a) Shimada, S.; Rao, M. L. N. *Top. Curr. Chem.* **2012**, *311*, 199. (b) Rao, M. L. N.; Venkatesh, V.; Dasgupta, P. *Tetrahedron Lett.* **2010**, *51*, 4975. (c) Rao, M. L. N.; Talode, J. B. *Asian J. Org. Chem.* **2016**, *5*, 98. (d) Rao, M. L. N.; Venkatesh, V.; Jadhav, D. N. *J. Organomet. Chem.* **2008**, *693*, 2494. (e) Rao, M. L. N.; Dhanorkar, R. J. *RSC Adv.* **2016**, *6*, 1012. (f) Rao, M. L. N.; Venkatesh, V.; Banerjee, D. *Tetrahedron* **2007**, *63*, 12917. (g) Rao, M. L. N.; Venkatesh, V.; Jadhav, D. N. *Tetrahedron Lett.* **2006**, *47*, 6975. (h) Rao, M. L. N.; Jadhav, D. N.; Venkatesh, V. *Tetrahedron Lett.* **2009**, *50*, 4268.
- (38) (a) Urgin, K.; Aubé, C.; Pichon, C.; Pipelier, M.; Blot, V.; Thobie-Gautier, C.; Léonel, E.; Dubreuil, D.; Condon, S. *Tetrahedron Lett.* **2012**, *53*, 1894. (b) Urgin, K.; Aubé, C.; Pipelier, M.; Blot, V.; Thobie-Gautier, C.; Sengmany, S.; Lebreton, J.; Léonel, E.; Dubreuil, D.; Condon, S. *Eur. J. Org. Chem.*; **2013**, 117. (c) Cassirame, B.; Condon, S.; Pichon, C. *J. Mol. Catal. A: Chem.* **2016**, *425*, 94. (d) Kutudila, P.; Linguerrri, R.; Al-Mogren, M. M.; Pichon, C.; Condon, S.; Hochlaf, M. *Theor. Chem. Acc.* **2016**, *135*, 176.
- (39) (a) Wang, T.; Sang, S.; Liu, L.; Qiao, H.; Gao, Y.; Zhao, Y. *J. Org. Chem.* **2014**, *79*, 608. (b) Kobiki, Y.; Kawaguchi, S.-I.; Ogawa, A. *Org. Lett.* **2015**, *17*, 3490. (c) Matano, Y.; Imahori, H. *J. Org. Chem.* **2004**, *69*, 5505. (d) Sueda, T.; Oshima, A.; Teno, N. *Org. Lett.* **2011**, *13*, 3996. (e) Robertson, A. P. M.; Burford, N.; McDonald, R.; Ferguson, M. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 3480.
- (40) (a) Petiot, P.; Gagnon, A. *Heterocycles* **2014**, *88*, 1615. (b) Petiot, P.; Gagnon, A. *Eur. J. Org. Chem.* **2013**, 5282. (c) Gagnon, A.; Albert, V.; Duplessis, M. *Synlett* **2010**, 2936.
- (41) Petiot, P.; Dansereau, J.; Gagnon, J. *RSC Adv.* **2014**, *4*, 22255.
- (42) (a) Ahmad, T.; Dansereau, J.; Hébert, M.; Grand-Maitre, C.; Larivée, A.; Siddiqui, A.; Gagnon, A. *Tetrahedron Lett.* **2016**, *57*, 4284. (b) Petiot, P.; Dansereau, J.; Hébert, M.; Khene, I.; Ahmad, T.; Samaali, S.; Leroy, M.; Pinsonneault, F.; Legault, C. Y.; Gagnon, A. *Org. Biomol. Chem.* **2015**, *13*, 1322. (c) Crifar, C.; Petiot, P.; Ahmad, T.; Gagnon, A. *Chem. Eur. J.* **2014**, *20*, 2755.
- (43) Hébert, M.; Petiot, P.; Benoit, E.; Dansereau, J.; Ahmad, T.; Le Roch, A.; Ottenwaelder, X.; Gagnon, A. *J. Org. Chem.* **2016**, *81*, 5401.
- (44) Hao, W.; Liu, H.; Yin, L.; Cai, M. *J. Org. Chem.* **2016**, *81*, 4244.
- (45) Dansereau, J.; Gautreau, S.; Gagnon, A. *ChemistrySelect* **2017**, *2*, 2593.
- (46) Gagnon, A.; St-Onge, M.; Little, K.; Duplessis, M.; Barabé, F. *J. Am. Chem. Soc.* **2007**, *129*, 44.
- (47) Gagnon, A.; Duplessis, M.; Alsabeh, P.; Barabé, F. *J. Org. Chem.* **2008**, *73*, 3604.
- (48) **Analytical Data for Compound 3**
Pale yellow solid; $R_f = 0.21$ (10% EtOAc/hexane); mp 62.6 °C. ^1H NMR (300 MHz, CDCl_3): $\delta = 8.12$ (d, $J = 8.7$ Hz, 2 H), 8.07 (d, $J = 8.7$ Hz, 2 H), 3.94 (s, 3 H), 2.71–2.62 (m, 1 H), 1.29–1.24 (m, 2 H), 1.11–1.05 (m, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 200.4$, 166.4, 141.4, 133.6, 129.9, 128.0, 52.6, 17.8, 12.3 ppm. IR (neat): 2953, 2852, 1720, 1667, 1439, 1407, 1278, 1216, 1107, 1016, 993, 720 cm^{-1} . ESI-HRMS: m/z calcd for $\text{C}_{12}\text{H}_{12}\text{O}_3$; 204.0786; found: 205.0855 $[\text{M} + \text{H}]^+$.
- (49) For all the details, see the Supporting Information.
- (50) Andrus, M. B.; Ma, Y.; Zang, Y.; Song, C. *Tetrahedron Lett.* **2002**, *43*, 9137.
- (51) **Method A**
A sealed tube equipped with a magnetic stirring bar was charged with the aryl halide **1** or **5** (1.0 equiv), Na_2CO_3 (2.0 equiv), anhydrous LiCl (2.0 equiv) and (SIPr)Pd(allyl)Cl (0.05 equiv). Tricyclopropylbismuth (**2a**, 1.0 equiv) was dissolved in anhydrous DMF (0.1 M) under argon and was added into the sealed tube. CO was bubbled in the reaction mixture for 45 s, then the tube was sealed and heated at 40 °C for 16 h. The reaction mixture was cooled to r.t., transferred in a separatory funnel containing 20 mL of an aq sat. NaHCO_3 solution, and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford the desired aryl cyclopropyl ketone **3** or **6**.
- (52) **Method B**
Same as method A except that 1.5 equiv of tricyclopropylbismuth (**2a**) instead of 1.0 equiv and 0.1 equiv of (SIPr)Pd(allyl)Cl instead of 0.05 equiv were used, and that the reaction was heated at 80 °C instead of 40 °C.
- (53) For a review on arylcyclopropanes, see: (a) Gagnon, A.; Duplessis, M.; Fader, L. *Org. Prep. Proced. Int.* **2010**, *42*, 1. (b) Talele, T. T. *J. Med. Chem.* **2016**, *59*, 8712.
- (54) For selected examples of reactions involving alkenyl cyclopropylketones, see: (a) Tsuge, O.; Kanemasa, S.; Otsuka, T.; Suzuki, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2897. (b) De Simone, F.; Saget, T.; Benfatti, F.; Almeida, S.; Waser, J. *Chem. Eur. J.* **2011**, *17*, 14527.