Graphical Abstract

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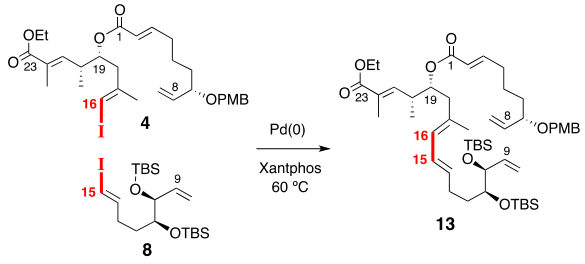

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A synthetic approach to palmerolides via Negishi cross coupling. The challenge of the C15–C16 bond formation

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ABSTRACT

The esterification of fragment C1–C8 (**2**) with fragment C16–C23 (**3**) to give iodo derivative **4**, followed by a Pd-catalyzed coupling with a C9–C15 fragment (**7** or **8**), may provide a common precursor of most palmerolides. Ligands and reaction conditions were exhaustively examined to perform the C15–C16 bond formation via Negishi reaction. With simple models, pre-activated Pd–Xantphos and Pd–DPEphos complexes were the most efficient catalysts at RT. Zincation of the C9–C15 fragment (**8**) and cross coupling with **4** required 3 equiv of *t*-BuLi, 10 mol % of Pd–Xantphos and 60 ºC.

Palmerolide A (**1A**) is a melanoma-inhibiting macrolide (LC_{50} = 18 nM) isolated from an Antarctic tunicate collected at the NSF Palmer Station.[1] Three total syntheses have been reported,[2] as well as formal syntheses[3] and several fragments.[3h–q] Some years ago we planned and started a total synthesis of **1A**, summarised in Figure 1.[4] Unfortunately, the formation of the C15–C16 single bond by coupling of two C(sp^2) carbon atoms proved to be a bottleneck in the process. We attempted a Negishi cross coupling[5] from an alkenylzinc halide (fragment C9–C15, see below, via Zr/Zn exchange), without success. A Stille reaction[6] (fragment C9–C15, with $PdCl_2(NCPh)_2$, in DMF–THF) was likewise unsuccesful.[4] In the meantime, it was reported by Nicolaou, Chen, et al.[2b,d,e] that the key C15–C16 bond could be formed in a previous step by means of a variant of the Stille reaction, with $AsPh_3$ and LiCl in NMP.[6] In this context, we have just solved the problem of the C15–C16 coupling via a Negishi reaction. It may be of help for other difficult couplings of polyfunctional substrates. We also envisage to apply the procedure to the synthesis of palmerolide D (**1D**), which is the most potent member of the series,[1c] in the near future.

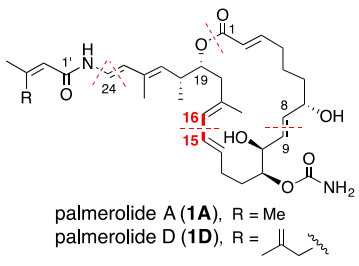
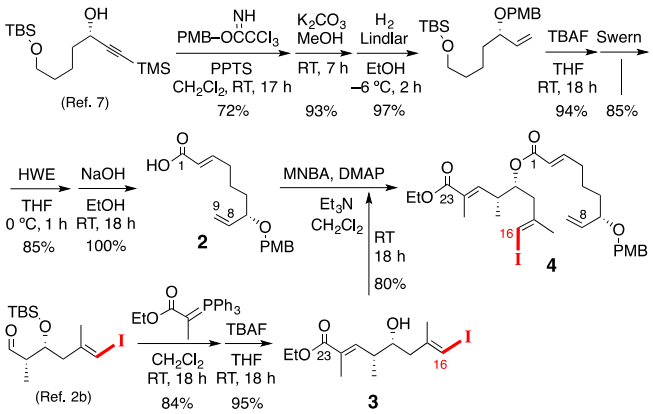


Figure 1. Chemical structures of the main palmerolides.

The synthesis of fragment C1–C8(9), **2**, where the terminal methylene (C9) would be eliminated as ethene during the ring-closing metathesis (RCM), started from a known heptynol,[7] which was subjected to protection, TMS removal, controlled reduction, TBS removal, Swern oxidation and HWE reaction (Scheme 1, see Supplementary Data for details).

The synthesis of fragment C16–C23, **3**, was initiated from the known aldol (2*S*,3*R*,5*E*)-3-(*tert*-butyldimethylsilyloxy)-6-iodo-2,5-dimethyl-5-hexen-1-al[2b] (see Scheme 1, last row), although we obtained it[4] via a Ti enolate of *N*-propanoyl-1,3-thiazolidine-2-thione,[8] protection with TBSOTf and reduction with DIBALH. We converted such a 6-iodohexenal into **3** by Wittig reaction followed by cleavage of the O–TBS bond. The reaction of **2** with **3** using MNBA (the Shiina method)[9] gave the desired substrate, **4**, in 80% yield.



Scheme 1. Synthesis of **4** from **2** + **3** (C1–C8 + C16–C23).

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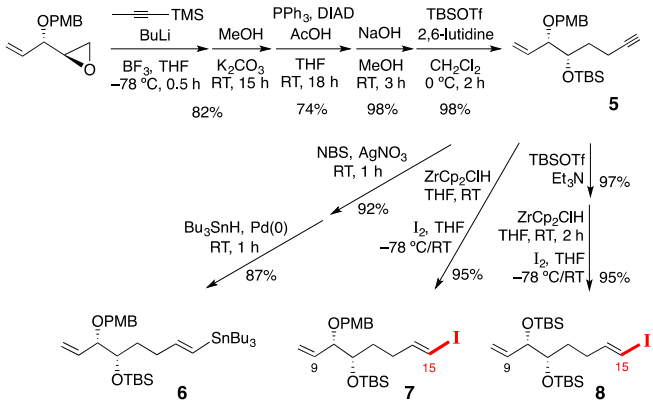
The synthesis of fragments C(8)9–C15, where C8 would disappear during the RCM to link C1–C8(9) with C(8)9–C15, is summarised in Scheme 2. Opening of the known epoxide (2*R*,3*S*)-1,2-epoxy-3-(4-methoxybenzyloxy)-4-pentene[10] with a propargylic anion[11] was followed by TMS removal, Mitsunobu inversion and protection of the free OH group with TBSOTf, to give **5**.[4] From **5**, we prepared stannane **6**, the desired iodoalkene **7** and the bis(TBS)-substituted iodoalkene **8** (through a PMB-to-TBS change with TBSOTf and Et_3N).[12]



Scheme 2. Preparation of **6**–**8** (fragments C9–C15).

Iodo derivative **4** was ready for the C15–C16 coupling with a fragment such as **6**.[13] With few further synthetic steps, a formal total synthesis of **1A** or the first total syntheses of other palmerolides would have been completed.[4,13] However, we persisted in examining the C15–C16 bond formation by Negishi coupling.[14]

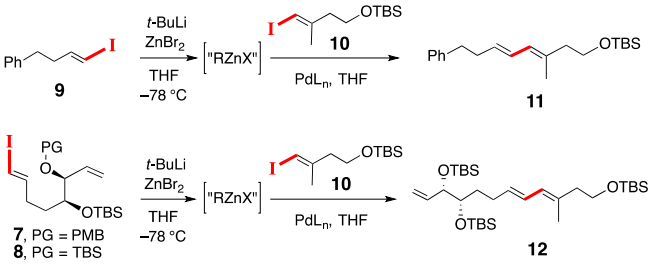
The fragments to be joined (either **4** + **7** or **4** + **8**) are both expensive advanced intermediates, so that no large excess of one of them should be used to drive the coupling reactions to completion. Thus, in our trials the molar ratios between the first partner (alkenyl–ZnX) and the second partner (alkenyl–I) should be kept around 1.1–1.2 to 1.0. The positive side would be that our results could be extrapolated to other difficult C(sp^2)–C(sp^2) couplings of advanced synthetic intermediates. To our knowledge, relatively few studies aimed at finding the best ligands and conditions to perform state-of-the-art Negishi alkenyl–alkenyl couplings involving trisubstituted olefins have been published to date.[15,16]

To find the best coupling conditions, we also had one model of **7** and **8** (see **9**, Table 1) and one model of **4** (see **10**, Table 1).[17] Since the direct insertion of various sources of Zn into alkenyl iodides shown in Table 1 (even in DMA or DMF at 80 ºC)[18] did not work, we attempted the procedure reported by Knochel et al.[19] (addition of LiCl), which is so useful for RX and many ArX, but it did not work with our iodides in refluxing THF.[20] Thus, we were forced to revisit classical lithiation reactions with *t*-BuLi, followed by Li-to-Zn exchange with ZnX_2.[21] $ZnCl_2$ and $ZnBr_2$ gave identical results, provided that the samples were anhydrous.[15,16,21] We preferred $ZnBr_2$, however, as it is less hygroscopic.

Table 1 summarises around 90 trials (most of them unsuccessful) in which many representative catalysts, such as $Pd(PPh_3)_4$, Pd_2dba_3/Xantphos, Pd_2dba_3/DPEphos, Pd_2dba_3/XPhos and Pd_2dba_3/RuPhos, were compared.[22] The standard $Pd(PPh_3)_4$ gave rise to full consumption of the second partner only on heating (compare entries 1–4); addition of one further equiv of *t*-BuLi was not relevant. On the other hand, the bidentate ligand-containing solutions (entries 5–7) were capable of completing the reaction of **9** with **10** (to give **11**) in 4 h hours at RT. Xantphos and DPEphos gave similar excellent results, so we used them indistinctly. In these experiments at RT, a crucial step was to solve (to "activate") the catalyst by heating the suspension of Pd_2dba_3[23] in THF, under Ar, for few seconds with the diphosphine or biphenylphosphine, until clear solutions were obtained.[24] These were yellowish green in the cases of Xantphos and Ruphos, yellow with DPEphos and reddish orange with XPhos. Without this previous activation, the combination of these phosphines with $Pd_2(dba)_3$ showed no advantage over $Pd(PPh_3)_4$.

On the other hand, biphenylphosphines plus $Pd_2(dba)_3$ (entries 8 and 9) were less active, even after such a previous activation. However, when the Pd^0–XPhos complex was generated from *o*-palladacycle [$PdCl(NH_2CH_2CH_2C_6H_4)$XPhos] (XPhos-Pd-G1) and from 2-NH_2-2'-[Pd(OMs)XPhos]biphenyl (XPhos-Pd-G3),[25] conversions improved (up to 70% after 6 h, see entries 10 and 11, with 25% of recovered **10**).

Table 1
Optimisation of Ligands and Conditions for the Coupling of Iodoalkenes **7**–**9** with **10**



Entry	RI	Coupling conditions[a]	Diene, %
1	**9**	1% $Pd(PPh_3)_4$, RT, 16 h	**11**, 70
2	**9**	2% $Pd(PPh_3)_4$, RT, 4 h	**11**, 50
3	**9**	2% $Pd(PPh_3)_4$, RT, 4 h (+*t*-BuLi)	**11**, 50
4	**9**	5% $Pd(PPh_3)_4$, 60 ºC, 4 h	**11**, **85**
5	**9**	1% Pd_2dba_3, 2.5% Xantphos,[c] RT, 4 h	**11**, **88**
6	**9**	1% Pd_2dba_3·$CHCl_3$, 2.5% Xantphos,[c] RT, 4 h	**11**, **87**
7	**9**	1% Pd_2dba_3, 2.5% DPEphos,[c] RT, 4 h	**11**, **88**
8	**9**	1% Pd_2dba_3, 3% XPhos,[c] RT, 6 h	**11**, 25[d]
9	**9**	1% Pd_2dba_3, 3% RuPhos,[c] RT, 6 h	**11**, 30[d]
10	**9**	2% XPhos-Pd-G1, RT, 6 h	**11**, 70[d]
11	**9**	2% XPhos-Pd-G3, RT, 6 h	**11**, 70[d,e]
12	**7**	5% Pd_2dba_3, 12% Xantphos, 60 ºC, 16 h	0[d]
13	**7**	5% Pd_2dba_3, 12% Xantphos, 60 ºC, 16 h (+*t*-BuLi)	0[d]
14	**8**	5% Pd_2dba_3, 12% Xantphos, 60 ºC, 16 h	0[d]
15	**8**	5% Pd_2dba_3, 12% Xantphos, 60 ºC, 16 h (+*t*-BuLi)	**12**, **78**

[a] At 0.2 M concentrations. Catalyst/reagent percentages in mol %. All reactions under Ar, with 110 mol % of the first alkenyl iodide, 120 mol % of anhydrous $ZnBr_2$ (or $ZnCl_2$) and 210–220 mol % of *t*-BuLi unless otherwise indicated (as "+*t*-BuLi", where 330 mol % of *t*-BuLi was added), referred to the second iodoalkene, **10**.

[b] Conversions (by NMR) or, **in bold red**, **isolated yields** after flash column chromatography (when conversions were 100%).

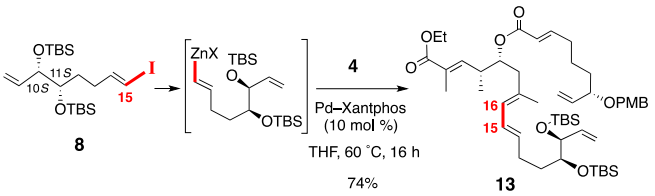
[c] The wine-red suspension of Pd_2dba_3 in THF plus the phosphine was heated for few seconds until a solution was obtained. After cooling to RT, the PdL_n solution was added via cannula to the reaction flask (all under Ar). Without this ligand exchange the reaction rates were much slower. Colour did not change with 2-(di-*tert*-butylphosphino)-2',4',6'-triisopropyl-3,6-dimethoxybiphenyl, *t*-BuBrettPhos; the mixture was inefficient at RT.

[d] Part or all of **10** was recovered unchanged; the de-iodinated alkenes from **7**–**9** were also isolated.

[e] This experiment was performed with pre-activation of the catalyst (XPhos-Pd-G3 + RCH=CHZnX for 30 s at 60 ºC, orange-to-brown colour change), cooling at RT and addition of **10**.

Compounds **7** and **8** did not react with **10** under the best conditions up to this point, with 2.2 equiv of *t*-BuLi, even with more catalyst, even on heating (see entries 12 and 14). Use of 3 equiv of *t*-BuLi, which Smith et al.[16a] had successfully applied to a difficult C(sp^3)–C(sp^2) coupling, probably involving RZn^{t}Bu as intermediates,[16a] had no effect in the case of **7** (entry 13), whereas **8** did react (entry 15, 100% conversion, 78% isolated yield of **12**).[26] Thus, the presence of PMBO groups (and presumably of other coordinating and/or prone to be lithiated PGs) is contraindicated. Moreover, for substrates with silyloxy groups, 3.3 equiv of *t*-BuLi are essential. The addition of 200 mol % of LiBr to the alkenylzinc halide, as an alternative to the use of 3.3 equiv of *t*-BuLi, so useful in other couplings,[27] did not help in our case.

We finally undertook the coupling of the organozinc halide from **8** with **4** (Scheme 3) using the optimised conditions shown in entry 15. To our delight, the conversion was complete. After flash column chromatography and preparative TLC, compound **13** was isolated in 74% yield (not optimised).



Scheme 3. Negishi cross-coupling reaction of **8** with **4**.

In conclusion, with the goal of obtaining samples of palmerolides to check their mechanism(s) of action, we first improved the difficult C15–C16 Negishi coupling using model compounds. The pre-activated Pd–Xantphos complex ("active" yellowish green solution) and the pre-activated Pd–DPEphos complex ("active" yellow solution) turned out to be the most efficient catalysts. In other words, several excellent catalysts and procedures for other cross couplings did not work so efficiently in the present case. Excess *t*-BuLi and suitable PGs (silyl groups but not PMB) are also essential when the zincates or organozinc halides to be coupled contain oxygen functional groups. We plan to synthesise again **13** (and analogues with two different silyl PGs, if necessary) in sufficient amounts to attempt a synthesis of **1D** and analogues relying on this optimised procedure.

Acknowledgments

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Supplementary data

Supplementary data associated with this article (experimental section, copies of 1D and 2D NMR spectra) can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlett.2014 .....

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13. One of us (A.G., Ref. 4) had linked **6** and *epi*-**4** (epimer at C7 of **4**) in 62% isolated yield by Stille coupling, under the conditions of Ref. 2b and 6a for the reaction of an analog of **6** (MOM instead of PMB, $CONH_2$ instead of TBS) with an analog of **4** (CH_2OTBS instead of COOEt, free OH).
14. As we were interested in determining (alternative) mechanisms of action for palmerolides, impurities of organotin compounds could confuse us. For reviews of organotins as antitumor agents, see: (a) Alama, A.; Tasso, B.; Novelli, F.; Sparatore, F. *Drug Discov. Today* **2009**, *14*, 500–508; (b) Hadjikakou, S. K.; Hadjiliadis, N. *Coord. Chem. Rev.* **2009**, *253*, 235–249; for reviews of the toxicity of organotin compounds, see: (c) Nath, M. *Appl. Organomet. Chem.* **2008**, *22*, 598–612; (d) Nakanishi, T. *J. Toxicol. Sci.* **2008**, *33*, 269–276; (e) Jensen, K. G.; Oenfelt, A.; Wallin, M.; Lidums, V.; Andersen, O. *Mutagenesis* **1991**, *6*, 409–416 (interaction with tubulin and microtubules); (f) Chow, S. C.; Orrenius, S. *Toxicol. Appl. Pharmacol.* **1994**, *127*, 19–26 (interaction with actin).
15. (a) See articles cited in Ref. 5a and 5b; (b) Yi, N.; Wang, G.; Qian, M.; Negishi, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 2916–2920 (2 *t*-BuLi, 0.05 $PdCl_2$DPEphos); (c) Huang, Z.; Negishi, E. *J. Am. Chem. Soc.* **2007**, *129*, 14788–14792; (d) Wang, C.; Tobrman, T.; Xu, Z.; Negishi, I. *Org. Lett.* **2009**, *11*, 4092–4095; (e) Wang, G.; Mohan, S.; Negishi, E. *Proc. Natl. Acad. Sci.* (*USA)* **2011**, *108*, 11344–11349 (dienoates and trienoates); (f) Xu, S.; Truex, N. L.; Mohan, S.; Negishi, E. *Arkivoc* **2012**, 242–252 (high TON with PEPPSI-IPr for alkenyl-$ZrCp_2Cl$ + BrCH=CHCOOEt); (g) Lee, J.; Panek, J. S. *Org. Lett.* **2009**, *11*, 4390–4393 and reference 6 therein (4 equiv of the cheapest alkenyl–I, 2.5 *t*-BuLi, 0.1 $Pd(PPh_3)_4$); (h) Wu, J.; Panek, J. S. *J. Org. Chem.* **2011**, *76*, 9900–9918 (1.5 alkenyl–I, 3.0 *t*-BuLi, 0.1 $Pd(PPh_3)_4$); (i) Reichard, H. A.; Rieger, J. C., Micalizio, G. C. *Angew. Chem., Int. Ed*. **2008**, *47*, 7837–7840 (1.5 alkenyl–I/$ZnCl_2$, 4.5 *t*-BuLi, 0.05 $Pd(PPh_3)_4$).
16. Couplings between alkylzinc halides and alkenyl halides have been more investigated. For representative examples, see: (a) Smith, A. B.; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654–8664 (premixing RI and $ZnCl_2$); (b) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719–2724; (c) Huang, Z.; Qian, M.; Babinski, D.; Negishi E. *Organometallics* **2005**, *24*, 475–478 (high TON, *E*-iodoolefins included); (d) Lai, K. W.; Paquette, L. A. *Org. Lett.* **2008**, *10*, 2115–2118; (e) Hatakeyama, T.; Nakagawa, N.; Nakamura, M. *Org. Lett.* **2009**, *11*, 4496–4499; (f) Krasovskiy, A.; Lipshutz, B. H. *Org. Lett.* **2011**, *13*, 3818–3821; couplings that provide biaryls have also been investigated; see: (g) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028–13032 (RuPhos, the biphenylphosphine of choice); (h) Li, J.; Jin, L.; Liu, C.; Lei, A. *Org. Chem. Front.* **2014**, *1*, 50–53 (trans-metalation studies) and references therein; (i) Hernán-Gómez, A.; Herd, E.; Hevia, E.; Kennedy, A. R.; Knochel, P.; Koszinowski, K.; Manolikakes, S. M.; Mulvey, R. E.; Schnegelsberg, C. *Angew. Chem., Int. Ed.* **2014**, *53*, 2706–2710 (use of RZnOPiv).
17. Sidera, M.; Costa, A. M.; Vilarrasa, J. *Org. Lett.* **2011**, *13*, 4934–4937.
18. Appropriate for RX (RBr + I_2 cat. and RCl + LiBr + I_2). See: Huo, S. *Org. Lett.* **2003**, *5*, 423–425.
19. Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 6040–6044.
20. Harsher conditions were not examined, as they may be unsuitable for advanced steps of a total synthesis and, moreover, there are precedents of configuration scrambling (*E/Z* mixtures from a pure *E*-iodoalkene): Majid, T. N.; Knochel, P. *Tetrahedron Lett.* **1990**, *31*, 4413–4416.
21. Reviews: (a) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117–2188; (b) Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, C. E. *Org. React.* **2001**, *58*, 417–731; (c) Knochel, P. In *Science of Synthesis*; Thieme: Stuttgart, **2004**, *3*, 5–90.
22. (a) For a review of bidentate ligands 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) and bis[(2-diphenylphosphino)phenyl] ether (DPEphos), see: Birkholz, M.-N.; Freixa, Z.; van Leeuwen, P. W. N. M. *Chem. Soc. Rev.* **2009**, *38*, 1099–1118; (b) for 2-dicyclohexyl-phosphino-2′,4′,6′-triisopropylbiphenyl (XPhos): Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653–6655; (c) for 2-dicyclohexylphosphino-2′,6′-bis(isopropoxy)biphenyl (RuPhos), see Ref. 16g; (d) for alkyl–alkenyl couplings, $PdCl_2$(DPEphos) and *N*-methylimidazole have been used with success: Krasovskiy, A.; Lipshutz, B. H. *Org. Lett.* **2011**, *13*, 3822–3825.
23. In entries 5, 7–9 and 12–15, Pd_2dba_3 came from the same bottle (Aldrich, 97%). NMR spectra indicated that it contained 40 mol % of free dba (and of Pd NPs). See: Zalesskiy, S. S.; Ananikov, V. P. *Organometallics* **2012**, *31*, 2302–2309. Commercially available $Pd_2dba_3{\cdot}CHCl_3$ (which contained only 25 mol % of free dba) was similarly active, however (entry 6). What matters, as expected, is the amount of Pd^0–phosphine-containing complex in the medium.
24. Pd–Xantphos, Pd–DPEphos, Pd–XPhos and Pd–RuPhos complexes containing one dba ligand may be the predominant species (but probably not the most active). For entries to the subject, see the following reviews: (a) Amatore, C.; Jutand, A. *Coord. Chem. Rev.* **1998**, *178–180*, 511–528. (b) Fairlamb, I. J. S. *Org. Biomol. Chem.* **2008**, *6*, 3645–3656; also see: (c) Jalón, F. A.; Manzano, B. R.; Gómez de la Torre, F.; López-Agenjo, A. M.; Rodríguez, A. M.; Weissensteiner, W.; Sturm, T.; Mahía, J.; Maestro, M. *J. Chem. Soc, Dalton Trans.* **2001**, 2417–2424; (d) Klingensmith, L. M.; Strieter, E. R.; Barder, T. E.; Buchwald, S. L. *Organometallics* **2006**, *25*, 82–91; (e) Grushin, V. V.; Marshall, W. J. *J. Am. Chem. Soc.* **2006**, *128*, 12644–12645; also see Ref. 23 (and references 18–25 cited therein); (f) for advantages of Pd–Xantphos in benzamido/halo replacements, see: Bosch, L.; Cialicu, C.; Caner, J.; Ariza, X.; Costa, A. M.; Terrazas, M.; Vilarrasa, J. *Tetrahedron Lett.* **2012**, *53*, 1358–1362.
25. Very useful for aromatic and heteroaromatic substrates. See: (a) Yang, Y.; Oldenhuis, N. J.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 615–619 and references therein; (b) Colombe, J. R.; Bernhardt, S.; Stathakis, C.; Buchwald, S. L.; Knochel, P. *Org. Lett.* **2013**, *15*, 5754–5757; (c) Yang, Y.; Mustard, T. J. L.; Cheong, P. H.–Y.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 14098–14102 (allylzinc halides plus ArX).
26. Furthermore, **7** did not couple with **9** or with *epi*-**4** (Ref. 13), under conditions of entries 12–15, whereas **8** did couple with **9** (100% conversion, 86% isolated yield) under the conditions of entry 15. In the reactions of **7** and **8** we added first $ZnBr_2$ (120 mol %) and then *t*-BuLi (330 mol %) (Barbier-type conditions), as in Ref. 16a, but the results were similar in the cases in which we reversed the addition order.
27. (a) It has been brilliantly demonstrated that higher-order zincates are crucial in alkyl–alkyl couplings: McCann, L. C.; Hunter, H. N.; Clyburne, J. A. C.; Organ, M. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 7024–7027 and references cited therein; also see: (b) Fleckenstein, J. E.; Koszinowski, K. *Organometallics* **2011**, *30*, 5018–5026; (c) McCann; L. C.; Organ, M. G. *Angew. Chem., Int. Ed.* **2014**, *53*, 4386–4389.