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Pd/NHC-Catalyzed Cross-Coupling Reactions of Nitroarenes

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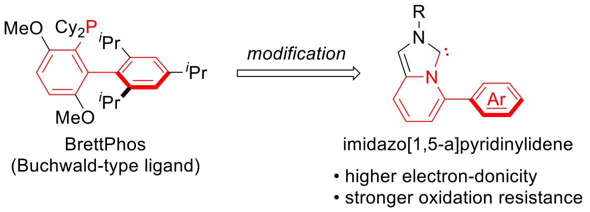
***N*-heterocyclic carbene (NHC) ligands effective for the cross-coupling of nitroarenes were identified. A rational design of the NHC ligand structures enabled significant reduction of catalyst loadings compared with the previous system employing BrettPhos as a phosphine ligand. Experimental and theoretical studies to compare these ligands gave some insgihts into high activity of the newly developed NHC ligands.**

Denitrative transformations of nitroarenes are advantageous in synthetic chemistry because they serve as an important class of chemical feedstocks readily available from simple nitration of aromatic compounds.[1] In addition, well-established functionalisations of nitroarenes including S_NAr/S_EAr/VNS and/or C–H functionalisation[2,3] to afford multi-substituted nitroarenes in a site-selective manner make the transformations highly attractive to access a variety of substituted arenes. Conventionally, the replacement of the NO_2 group with various functional groups could be achieved in 3 steps including reduction, diazotization, and Sandmeyer/cross-coupling reactions. Direct transformations of nitro groups have been therefore of high demand to upgrade the synthetic utility of nitroarenes. Some examples of such single-step transformations of Ar–NO_2 bonds have been reported but lacked generality in terms of scope of nitroarenes.[4] The difficulty in the use of nitroarenes for cross-coupling reactions is partly derived from reduction of the NO_2 group by low-valent metal catalysts.[5] Nevertheless, we previously reported that the combination of palladium as a metal center and BrettPhos[6a] as a supporting ligand enabled the unprecedented oxidative addition of Ar–NO_2 bonds to palladium(0) to enable the Suzuki–Miyaura coupling,[7a] Buchwald–Hartwig amination,[7b] and reductive denitration of nitroarenes.[7c] Although these coupling reactions opened a novel aspect in chemistry of nitroarenes, there still remained serious issues from a practical point of view such as high loadings of precious Pd (>5 mol%) and expensive Buchwald-type ligands[6] (10–20 mol%). Phosphine ligands could also be deactivated through oxidation by the NO_2 group.

To deviate from phosphine ligands, we turned our attention to the use of NHC ligands.[8] In 2005, the groups of Lassaletta and Glorius independently reported the use of imidazo[1,5-*a*]pyridinylidenes,[9a,b] which appeared to be a hybrid form of the Buchwald-type ligands and NHC ligands (Scheme 1). Subsequently, some derivatives were investigated and published.[9c–9k] Despite being structural mimics of the Buchwald-type ligands, they have rarely been applied to metal-catalysed reactions. We conceived the use of imidazo[1,5-*a*]pyridinylidene bearing an Ar group at the C5 position as a supporting ligand in the cross-coupling reactions of nitroarenes. NHC ligands generally possess higher electron-donicity and tolerance toward oxidation than phosphine ligands. We expected that the NHC ligands could facilitate the rate-determining oxidative addition of Ar–NO_2 bond and elongate a catalyst lifetime by preventing the ligand oxidation.



Scheme 1. Design of imidazo[1,5-*a*]pyridinylidene ligands for the cross-coupling of nitroarenes.

We examined the Suzuki–Miyaura coupling of 4-nitroanisole (**1a**) and phenylboronic acid (**2a**) in the presence of 1.0 mol% $Pd(acac)_2$ and 2.0 mol% **L1**[9i] (eq 1). In contrast to the use of BrettPhos, which resulted in only 6% of the desired product **3a**, the use of **L1** drastically improved the yield of **3a** to 60%.

Motivated by the preliminary result, we screened various imidazo[1,5-*a*]pyridinylidenes as ligands in the reaction of **1a**

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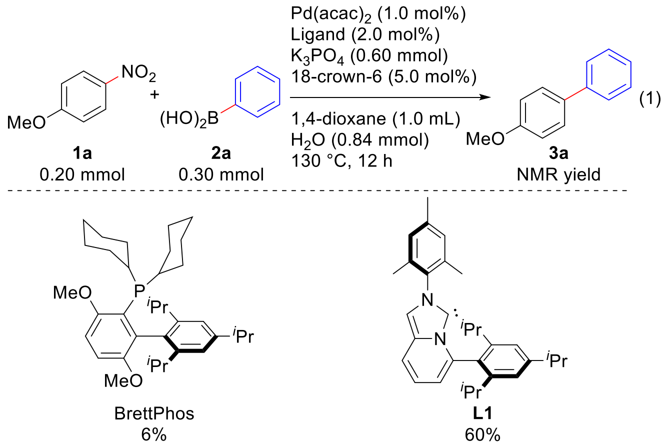
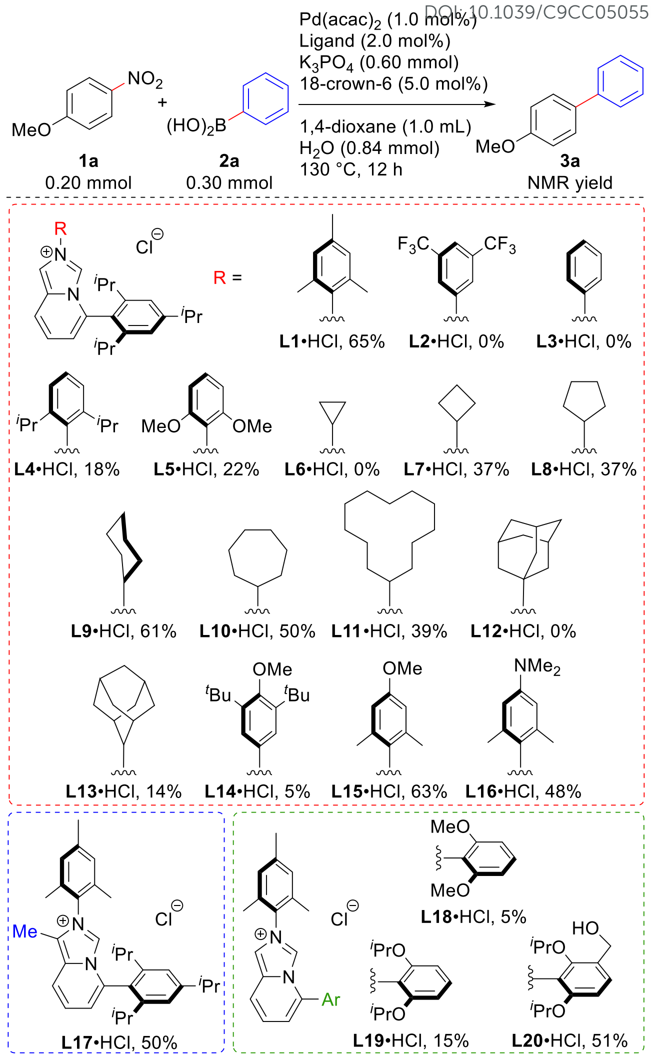


with **2a** using 1 mol% Pd (Scheme 2). The HCl adduct of **L1** could be used directly without any loss of the yield (entry 1).[10] Regarding the substituent on nitrogen, electron-withdrawing 3,5-bistrifluoromethyphenyl in **L2** and even the phenyl group in **L3** were not suitable at all, while sterically hindered 2,6-diisopropylphenyl in **L4** and 2,6-dimethoxyphenyl in **L5** deteriorated catalytic activity as well, though they were electron-donating. Cycloalkyl substituents seemed good for this system, except for the cyclopropyl group in **L6**, which could react with Pd(0).[11] **L9** showed the best performance among these, producing **3a** in 61% yield. The bulky adamantyl groups in **L12** and **L13**, and 3,5-di-*tert*-butyl-4-methoxyphenyl in **L14** retarded the reaction. **L15** and **L16**, which were expected to be more electron-donating than **L1**, unfortunately failed to improve catalytic activity. Similarly, introducing an electron-donating methyl substituent on the backbone in **L17** did not bring any positive effects. By analogy with the Buchwald-type phosphines, the properties of the C5-aryl group were found to be important. **L18** and **L19** were less active than **L1** in line with the competition of the Buchwald phosphines (SPhos and RuPhos respectively vs. XPhos or BrettPhos) in our previous report.[7a] To our surprise, NHC bearing a hydroxymethyl group **L20** marked higher yield of **3a** than **L19**.[12]



Scheme 2. Optimization of ligand structures.

To make this system more efficient, we made an attempt to use (**L1**)Pd complexes as catalyst precursors (Table 1). (**L1**)Pd(acac)Cl was prepared and examined first, but the yield was similar to the case where Pd(acac)$_2$ and **L1**•HCl were independently used. Another complex (**L1**)Pd(allyl)Cl proved to be effective to afford **3a** in 76%.

Table 1. Optimization of catalyst precursors.

Pd/**L1**	Yield (%)
Pd(acac)$_2$ (1.0 mo%) + **L1**•HCl (2.0 mol%)	65
(**L1**)Pd(acac)Cl (1.0 mol%)	61
(**L1**)Pd(allyl)Cl (1.0 mol%)	76

We then carried out some analyses to verify the properties of **L1**. Figure 1 shows the time-course of the Suzuki–Miyaura coupling of **1a** with **2a** catalysed by 5.0 mol%Pd/BrettPhos and 1.0 mol%Pd/**L1**. The former system turned out to be deactivated within 3 h,[13] whereas the coupling proceeded with the latter system much faster and the yield of **3a** kept increasing even after 4 h. These reaction profiles obviously revealed two significant effects associated with **L1**: rate-acceleration and longer catalyst lifetime. The higher reaction rate was also supported by DFT calculations. The activation barrier for the rate-limiting oxidative addition of **1a** to (**L1**)Pd^0 was calculated to be 27.2 kcal/mol, which was smaller than that to (BrettPhos)Pd^0 (30.1 kcal/mol).[14] This difference was likely to derive from their HOMO energies. The higher HOMO level of (**L1**)Pd^0 could enable the faster oxidative addition of the Ar–NO_2 bond (see Supporting Information for details). Experimentally, a large difference of $\%V_{Bur}$[15] between (BrettPhos)AuCl and (**L1**)AuCl was noted (59.5% vs. 51.9%,[9i] respectively), illustrating that **L1** occupied less space around the Pd center, possibly allowing easier access of the substrate to Pd than with BrettPhos. Furthermore, the rigid skeleton of **L1** could inhibit its flip in the coordination sphere, unlike BrettPhos which could show two different coordination modes. This rigidity could partly contribute to the robustness of (**L1**)Pd system in collaboration with reluctance to oxidation by nitroarenes.

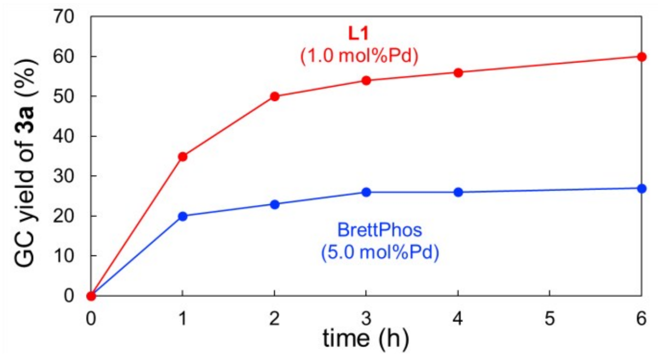


Figure 1. Time-courses of the coupling of 4-nitroanisole (**1a**) and phenylboronic acid (**2a**).

We also checked the reactivity of the new catalyst to several other substrate sets (Scheme 3). The use of boronic acid neopentylglycol ester in combination with a catalyst derived from $Pd(acac)_2$ and **L1**•HCl slightly improved the yield of **3a**. Couplings of nitronaphthalene and F-containing arylboronic acids proceeded very smoothly to give **3b** and **3c**. A nitroarene bearing an electron-withdrawing trifluoromethyl group could be reacted, though the yield of biaryl **3d** was relatively low as observed in our original report.[7a] In all the cases, the new catalytic system performed much better than 1 mol% Pd/BrettPhos. Moreover, 2,6-dimethylnitrobenzene, which was too sterically demanding to cross-couple under the previous conditions, afforded biaryl **3e** by the Pd/**L1** catalyst, possibly due to the reduced $\%V_{Bur}$ of **L1** compared with BrettPhos.

The Pd/NHC system developed herein catalysed not only the Suzuki–Miyaura coupling, but also the Buchwald–Hartwig amination and reductive denitration of nitroarenes (Scheme 4). Aniline (**4**) could be coupled with **1a** to afford diarylamine **5** by using 1.0 mol% (**L1**)Pd(acac)Cl as a catalyst precursor. Denitration of **1a** proceeded well with (**L9**)Pd(acac)Cl, delivering anisole (**7**) in 66% yield. Both reactions again afforded the products in yields much higher than those catalysed by 1 mol% Pd/BrettPhos.

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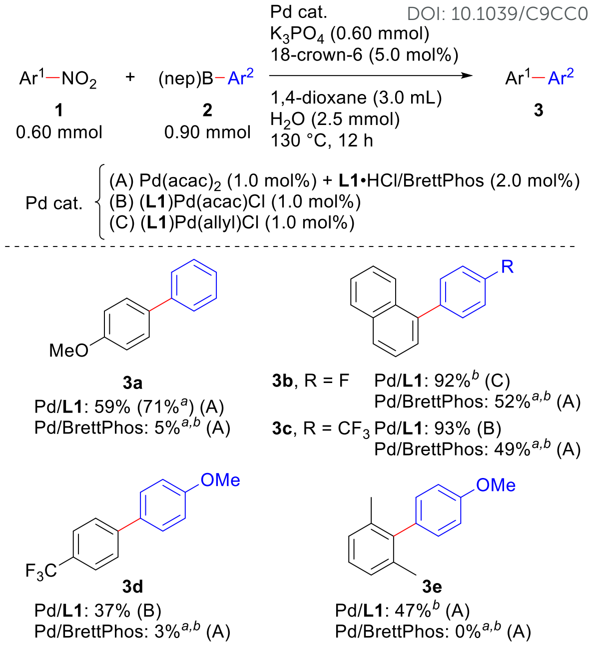
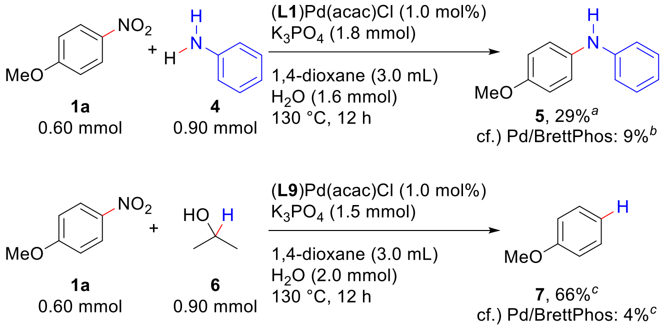


Scheme 3. Scope of the Suzuki–Miyaura coupling of nitroarenes. [a]NMR yields determined using 1,3,5-trimethoxybenzene as an internal standard. [b]Ar^2–$B(OH)_2$ was used instead of Ar^2–B(nep).



Scheme 4. The Buchwald–Hartwig amination and reductive denitration of nitroarenes. [a]Isolated yield. [b]NMR yield determined using 1,3,5-trimethoxybenzene as an internal standard. [c]GC yields determined using n-$C_{13}H_{28}$ as an internal standard.

In conclusion, we have developed new reaction conditions employing imidazo[1,5-a]pyridinylidene as NHC ligands for the cross-coupling reactions of nitroarenes. The Pd/NHC catalysts showed much higher activity than the Pd/BrettPhos system. Some insights into the reasons for the improved performance by the Pd/NHC catalyst are shown in terms of experimental and theoretical studies. Further applications of the Pd/NHC catalyst to other reactions are in progress.

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DOI: 10.1039/C9CC03053H

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (a) N. Ono, *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001; (b) G. Booth, *Nitro Compounds, Aromatic*; Ullmann's Encyclopedia of Industrial Chemistry; Wiley-VCH: New York, 2012.Citations should appear here in the format A. Name, B. Name and C. Name, *Journal Title*, 2000, **35**, 3523; A. Name, B. Name and C. Name, *Journal Title*, 2000, **35**, 3523.

2 M. Mąkosza, J. Winiarski, *Acc. Chem. Res.* 1987, **20**, 282.

3 (a) L. Caron, L.-C. Campeau, K. Fagnou, *Org. Lett.* 2008, **10**, 4533; (b) P. Guo, J. M. Joo, S. Rakshit, D. Sames, *J. Am. Chem. Soc.* 2011, **133**, 16338; (c) V. O. Iaroshenko, A. Gevorgyan, O. Davydova, A. Villinger, P. Langer, *J. Org. Chem.* 2014, **79**, 2906; (d) V. O. Iaroshenko, A. Gevorgyan, S. Mkrtchyan, T. Grigoryan, E. Movsisyan, A. Villinger, P. Langer, *ChemCatChem* 2015, **7**, 316; (e) Z. Yi, Y. Aschenaki, R. Daley, S. Davick, A. Schnaith, R. Wander, D. Kalyani, *J. Org. Chem.* 2017, **82**, 6946.

4 (a) J. R. Beck, *Tetrahedron* 1978, **34**, 2057; (b) J. Holt, F. Tjosås, J. M. Bakke, A. Fiksdahl, *J. Heterocycl. Chem.* 2004, **41**, 987; (c) S. D. Kuduk, R. M. DiPardo, M. G. Bock, *Org. Lett.* 2005, **7**, 577; (d) F. Tjosås, A. Fiksdahl, *Molecules* 2006, **11**, 130; (e) L. Arias, H. Salgado-Zamora, H. Cervantes, E. Campos, A. Reyes, E. C. Taylor, *J. Heterocycl. Chem.* 2006, **43**, 565; (f) P. Beier, T. Pastýříková, N. Vida, G. Iakobson, *Org. Lett.* 2011, **13**, 1466; (g) M. Mondal, S. K. Bharadwajb, U. Bora, *New J. Chem.* 2015, **39**, 31; (h) T. Begum, M. Mondal, M. P. Borpuzari, R. Kar, P. K. Gogoi, U. Bora, *Eur. J. Org. Chem.* 2017, 3244; (i) S. S. Bahekar, A. P. Sarkate, V. M. Wadhai, P. S. Wakte, D. B. Shinde, *Cat. Commun.* 2013, **41**, 123; (j) H. Tian, A. Cao, L. Qiao, A. Yu, J. Chang, Y. Wu, *Tetrahedron* 2014, **70**, 9107; (k) T. B. Nguyen, P. Retailleau *Org. Lett.* 2017, **19**, 4858; (l) D. W. Lamson, P. Ulrich, R. O. Hutchins, *J. Org. Chem.* 1973, **38**, 2928; (m) R. Fielden, O. Meth-Cohn, H. Suschitzky, *J. Chem. Soc., Perkin Trans. 1* 1973, **1**, 696; (n) A. G. Giumanini, G. Verardo, *Can. J. Chem.* 1997, **75**, 469; (o) C. W. Rees, S. C. Tsoi, *Chem. Commun.* 2000, 415; (p) R. El-Berjawi, P. Hudhomme, *Dyes and Pigments* 2018, **159**, 551.

5 (a) R. S. Berman, J. K. Kochi, *Inorg. Chem.* 1980, **19**, 248; (b) K. Osakada, R. Sato, T. Yamamoto, *Organometallics* 1994, **13**, 4645.

6 (a) B. P. Fors, D. A. Watson, M. R. Biscoe, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 13552; (b) R. Martin, S. L. Buchwald, *Acc. Chem. Res.* 2008, **41**, 1461; (c) E. J. Cho, T. D. Senecal, T. Kinzel, Y. Zhang, D. A. Watson, S. L. Buchwald, *Science* 2010, **328**, 1679; (d) A. Aranyos, D. W. Old, A. Kiyomori, J. P. Wolfe, J. P. Sadighi, S. L. Buchwald, *J. Am. Chem. Soc.* 1999, **121**, 4369; (e) A. V. Vorogushin, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* 2005, **127**, 8146; (f) X. Wu, B. P. Fors, S. L. Buchwald, *Angew. Chem. Int. Ed.* 2011, **50**, 9943; (g) D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.* 2008, **47**, 6338; (h) B. P. Fors, S. L. Buchwald, *J. Am. Chem. Soc.* 2009, **131**, 12898; (i) A. C. Sather, S. L. Buchwald, *Acc. Chem. Res.* 2016, **49**, 2146;

7 (a) M. R. Yadav, M. Nagaoka, M. Kashihara, R.-L. Zhong, T. Miyazaki, S. Sakaki, Y. Nakao, *J. Am. Chem. Soc.* 2017, **139**, 9423; (b) F. Inoue, M. Kashihara, M. R. Yadav, Y. Nakao, *Angew. Chem. Int. Ed.* 2017, **56**, 13307; (c) M. Kashihara, M. R. Yadav, Y. Nakao, *Org. Lett.* 2018, **20**, 1655.

8 For reviews, see (a) E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Angew. Chem. Int. Ed.* 2007, **46**, 2768; (b) S. Díez-González, N. Marion, S. P. Nolan, *Chem. Rev.* 2009, **109**, 3612; (c) J. C. Y. Lin, R. T. W. Huang, C. S. Lee, A. Bhattacharyya, W. S. Hwang, I. J. B. Lins, *Chem. Rev.* 2009, **109**, 3561; (d) M. Poyatos, J. A. Mata, E. Peris, *Chem. Rev.* 2009, **109**, 3677; (e) G. C. Fortman, S. P. Nolan, *Chem. Soc. Rev.* 2011, **40**, 5151; (f) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* 2014, **510**, 485.

9 (a) M. Alcarazo, S. T. Roseblade, A. R. Cowley, R. Fernández, J. M. Brown, J. M. Lassaletta, *J. Am. Chem. Soc.* 2005, **127**, 3290; (b) C. Burstein, C. W. Lehmann, F. Glorius, *Tetrahedron* 2005, **61**, 6207; (c) M. Nonnenmacher, D. Kunz, F. Rominger T. Oeser, *Chem. Commun.* 2006, 1378; (d) A. Fürstner, M. Alcarazo, H. Krause, C. W. Lehmann, *J. Am. Chem. Soc.* 2007, **129**, 12676; (e) J. T. Hutt, Z. D. Aron, *Org. Lett.* 2011, **13**, 5256; (f) E. Y. Tsui, T. Agapie, *Polyhedron* 2014, **84**, 103; (g) M. Espina, I. Rivilla, A. Conde, M. M. Díaz-Requejo, P. J. Pérez, E. Álvarez, R. Fernández, J. M. Lassaletta, *Organometallics* 2015, **34**, 1328; (h) C. T. Check, K. P. Jang, C. B. Schwamb, A. S. Wong, M. H. Wang, K. A. Scheidt, *Angew. Chem. Int. Ed.* 2015, **54**, 4264; (i) Y. Kim, Y. Kim, M. Y. Hur, E. Lee, *J. Organomet. Chem.* 2016, **820**, 1; (j) Y. Koto, F. Shibahara, T. Murai, *Chem. Lett.* 2016, **45**, 1327; (k) Y. Koto, F. Shibahara, T. Murai, *Org. Biomol. Chem.* 2017, **15**, 1810.

10 Unreacted **1a** (24%) and *p*-anisidine (5%) were also observed.

11 (a) S. Ma, L. Lu, J. Zhang, *J. Am. Chem. Soc.* 2004, **126**, 9645; (b) G. T. Jong, F. M. Bickelhaupt, *ChemPhysChem* 2007, **8**, 1170.

12 Although we confirmed that the hydroxymethyl group of **L20** was lost by ^{1}H NMR, its fate and the reason for the higher activity compared with **L19** were unclear.

13 BrettPhos was completely consumed to give BrettPhos oxide (~80%) and a certain amount of biaryl via C(sp^{2})–P bond cleavage.

14 The energy value for (BrettPhos)Pd is different from that in ref 7a because we applied a different functional (see Supporting Information for details).

15 (a) H. Clavier, S. P. Nolan, *Chem. Commun.* 2010, **46**, 841. (b) L. Falivene, R. Credendino, A. Poater, A. Petta, L. Serra, R. Oliva, V. Scarano, L. Cavallo, *Organometallics* 2016, **35**, 2286.