High yielding alkylations of unactivated sp^3 and sp^2 centres with alkyl-9-BBN reagents using an NHC-based catalyst: Pd-PEPPSI-IPr†

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Received (in Cambridge, UK) 1st October 2007, Accepted 23rd November 2007
First published as an Advance Article on the web 7th December 2007
DOI: 10.1039/b715081d

High yielding, room temperature cross couplings of unactivated alkyl bromides and aryl bromides/chlorides with alkyl-9-BBN reagents has been achieved using an NHC-based catalyst (Pd-PEPPSI-IPr) *via* a general, functional-group tolerant and easily implemented protocol.

Since its introduction in 1968 by Brown,[1] 9-borabicyclo[3.3.1]nonane (9-BBN) has been used widely as a chemo- and regioselective hydroborating reagent for alkenes and alkynes.[2] The resultant alkyl- and alkenyl-9-BBN species, respectively, are easily accessible and synthetically useful intermediates exploited in a variety of ways, including as effective transmetalating agents in Pd- and Ni-mediated cross coupling reactions.[3] This last feature made way for the first reported alkyl–alkyl coupling reaction when in 1992 Suzuki and co-workers successfully coupled unactivated sp^3-iodides with alkyl-9-BBN reagents in the presence of $Pd(PPh_3)_4$.[4] These results implied that not only were unactivated alkyl halides accessible coupling substrates but that the oxidative addition adduct (*i.e.* alkyl-Pd^{II}-I) was sufficiently stable to undergo intermolecular transmetalation rather than intramolecular β-hydride elimination (Fig. 1). Despite this finding, follow-up investigations remained scarce until 2001 when Fu and co-workers disclosed a $Pd(OAc)_2/PCy_3$ catalyst system capable of coupling alkyl-9-BBN reagents with unactivated alkyl bromides.[5] Since then, the majority of studies achieving sp^3–sp^3 Suzuki–Miyaura couplings have done so by employing exchangeable trialkylphosphines that are sufficiently electron rich to 'activate' Pd toward oxidative addition, while possessing suitable steric bulk to enhance reductive elimination and disfavor agostic Pd–H interactions and ensuing β-hydride elimination.[6]

N-Heterocyclic carbenes (NHCs) are proving to be very productive in a range of applications for a variety of reasons.[7] The NHC is an excellent σ-doner, their Pd-complexes are very insensitive to air and moisture and they have a negligible dissociation constant from the metal. In 2004, Caddick and Cloke reported the first and to-date only known alkyl–alkyl Suzuki–Miyaura coupling utilizing an NHC-based catalyst generated *in situ* from imidizaolium salt IPr·HCl and $Pd_2(dba)_3$.[8] Their attempt required slightly elevated temperatures (40 °C) to couple primary alkyl bromides in yields ranging from 28–56%.

In 2006, our group disclosed the highly active, air and moisture stable complex Pd-PEPPSI-IPr (**1**).[9] We have since relayed its successful use in the Negishi,[10] Kumada-Tamao-Corriu,[11] and sp^2–sp^2 Suzuki–Miyaura reactions.[12] Herein, we further expand the scope of Pd-PEPPSI-IPr by reporting on its success in achieving high yielding, room temperature alkylations of unactivated alkyl and aryl bromides and aryl chlorides with alkyl-9-BBN reagents.

An optimization study for the coupling of *n*-heptyl-9-BBN with 1-bromo-3-phenylpropane was carried out (Table 1). Whereas anhydrous bases CsF, K_2CO_3 and K_3PO_4 were ineffective, $K_3PO_4 \cdot H_2O$ provided excellent conversion to 1-phenyldecane (entries 1–4). Fu and co-workers have submitted that $K_3PO_4 \cdot H_2O$ generates a hydroxyl-bound "borate" complex *in situ*, which is believed to be the active transmetalating agent.[5] This is inline with mechanistic studies carried out by Soderquist and Matos,[13] and consistent with the finding that $KOH_{(s)}$ furnishes the same yield (entry 5). Comparable results were obtained when using 4 or 2 mol% of **1** while decreasing to 1 mol% resulted in a slight erosion in yield (entries 4, 6 and 7). Omission of **1** provided no product (entry 8). In all studies conducted, no β-hydride elimination product was observed.

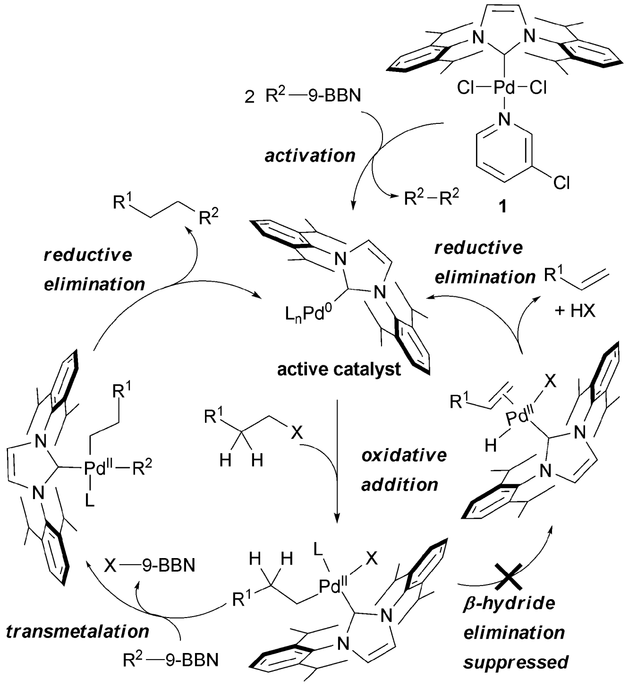

Fig. 1 Pd-PEPPSI-IPr (**1**), its proposed activation and catalytic cycle in couplings involving alkyl boranes.

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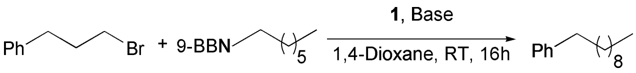
† Electronic supplementary information (ESI) available: Experimental procedures and compound data. See DOI: 10.1039/b715081d

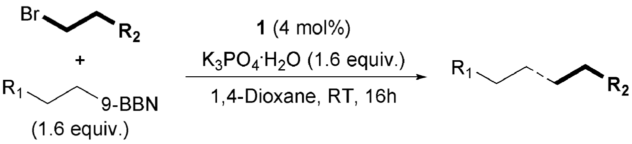
Table 1 Optimization study for Suzuki–Miyaura couplings with sp^3 centres

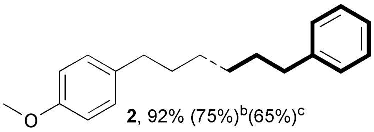


Entry	Borane equiv.[a]	Base (equiv.)[a]	1 mol%[a]	Conversion (%)[b]
1	1.6	CsF (1.6)	4	8
2	1.6	K_3PO_4 (1.6)	4	29
3	1.6	K_2CO_3 (1.6)	4	0
4	1.6	$K_3PO_4{\cdot}H_2O$ (1.6)	4	85
5	1.6	$KOH_{(s)}$ (1.6)	4	85
6	1.3	$K_3PO_4{\cdot}H_2O$ (1.3)	2	87
7	1.3	$K_3PO_4{\cdot}H_2O$ (1.3)	1	76
8	1.3	$K_3PO_4{\cdot}H_2O$ (1.3)	0	0
9[c]	1.3	$K_3PO_4{\cdot}H_2O$ (2.6)	4	77

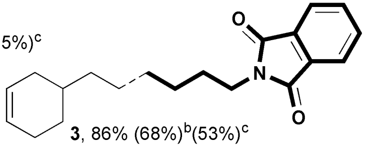
[a] Equivalents based on 3-bromo-1-phenylpropane. [b] Percent conversion was assessed by GC analysis using undecane as a calibrated internal standard; reactions were performed in duplicate. [c] THF used as solvent.

Table 2 Substrate study for Suzuki–Miyaura coupling with alkyl bromides[a]

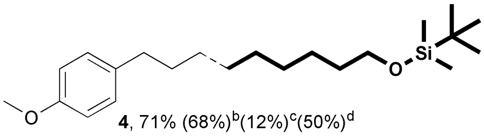




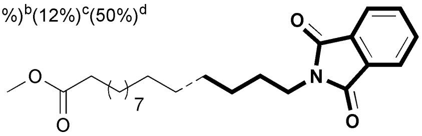
2, 92% (75%)[b](65%)[c]



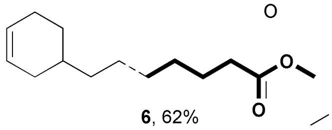
3, 86% (68%)[b](53%)[c]



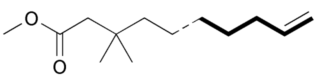
4, 71% (68%)[b](12%)[c](50%)[d]



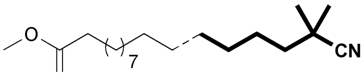
5, 81%



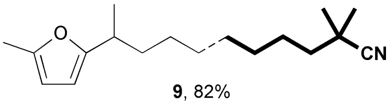
6, 62%



7, 81%



8, 73%



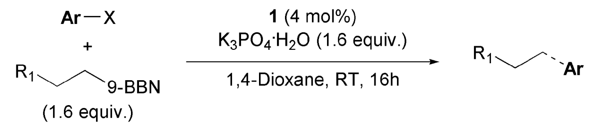
9, 82%

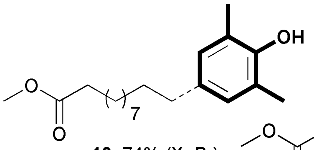
[a] All reactions were performed in duplicate and the average yield reported. Final concentration ~ 0.8 M based on alkyl bromide. [b] Reaction performed with 1.3 equiv. of alkyl-9-BBN and 4 mol% **1**. [c] Reaction performed with 1.3 equiv. of alkyl-9-BBN and 2 mol% **1**. [d] Reaction concentration ~ 0.6 M based on alkyl bromide.

Upon expanding the protocol to more elaborate substrates (Table 2), it became apparent that only moderate yields of product were accessible using a 2 mol% catalyst loading and/or less than 1.6 equivalents of the alkylborane reagent (**2**, **3** and **4**). In these experiments, the remaining mass balance was predominately unaltered alkyl bromide. Increasing the catalyst loading to 4 mol% and borane equivalents to 1.6 (based on the electrophile) generally provided optimal results. It was also discovered that diluting the reaction mixture had a detrimental effect on the yield, as can be seen with the preparation of **4**. It is not clear at which step in the catalytic cycle concentration is important because starting materials accounted for the remainder of the mass balance and no byproducts, such as β-hydride elimination, were observed. In any case, limiting the amount of solvent required and waste generated are two attractive features when considering large-scale amenability.

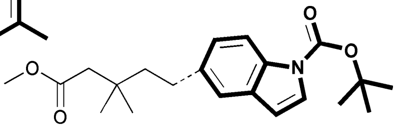
With these results in hand, the substrate scope was further expanded to include amides (**3** and **5**), nitriles (**8** and **9**), esters (**6**–**8**) and silyl ethers (**4**), providing 62–92% yields of isolated

Table 3 Substrate study for Suzuki–Miyaura coupling with aryl chlorides and bromides[a]

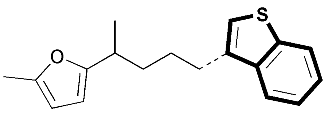




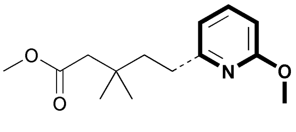
10, 74% (X=Br)



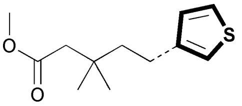
11, 88% (X=Br)



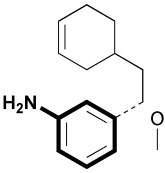
12, 77% (X=Br)



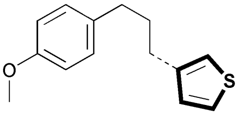
13, 89% (X=Cl)



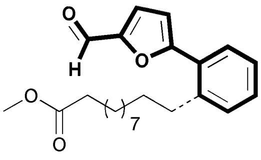
14, 79% (X=Br)



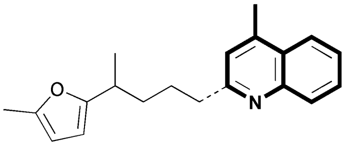
15, 76% (X=Br)



16, 88% (X=Br)



17, 58% (X=Cl)



18, 71% (X=Cl)

[a] All reactions were performed in duplicate and the average yield reported. Final concentration ~ 0.8 M based on alkyl halide.

product in less than 16 h at room temperature. Selectivity in 9-BBN hydroborations provided access to disubstituted olefins **3** and **6**. The protocol is easily implemented, requires only standard laboratory techniques, and avoids the use of an aqueous work-up.

Alkylation of aryl bromides and chlorides were also achieved without modification of the reaction conditions (Table 3). Phenols (**10**), esters (**11**, **13**, **14** and **17**), anilines (**15**), carbamates (**11**) and aldehydes (**17**) were all coupled directly in good yield, circumventing any need to implement protecting group chemistry. Additionally, substituted furans (**12** and **18**), thiophenes (**12**, **14** and **16**), indoles (**11**) and pyridine derivatives (**13** and **18**) were found to be compatible heterocycles with these reaction conditions.

In conclusion, a general, easily implemented and high yielding protocol for the coupling of unactivated alkyl bromides and aryl bromides and chlorides with alkyl-9-BBN reagents has been established. The vast number of reports on the Suzuki–Miyaura reaction, and cross couplings in general, speaks to the difficulty associated with finding any single, generally-applicable catalyst. Although this goal may well be intrinsically unattainable, Pd-PEPPSI-IPr is being established as a broadly applicable catalyst, realizing a range of cross couplings, herein expanded to include alkylations *via* the Suzuki–Miyaura reaction.

Notes and references

1 E. F. Knights and H. C. Brown, *J. Am. Chem. Soc.*, 1968, **90**, 5280–5281.

2 M. Zaidlewicz, in *Comprehensive Organometallic Chemistry*, ed. G. Wilkinson, F. G. A. Stone and E. W. Abel, Pergamon,Oxford, 1982, **7**, pp 199–254.

3 S. R. Chemler, D. Trauner and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 2001, **40**, 4544–4568.

4 T. Ishiyama, S. Abe and A. Suzuki, *Chem. Lett.*, 1992, 691–694.

5 M. R. Netherton, C. Dai, K. Neuschutz and G. C. Fu, *J. Am. Chem. Soc.*, 2001, **123**, 10099–10100.

6 For a review, see: A. C. Frisch and M. Beller, *Angew. Chem., Int. Ed.*, 2005, **44**, 674–688.

7 (*a*) E. A. B. Kantchev, C. J. O'Brien and M. G. Organ, *Angew. Chem., Int. Ed.*, 2007, **46**, 2768–2813; (*b*) E. A. B. Kantchev, C. J. O'Brien and M. G. Organ, *ChemFiles*, 2006, **6**, 1–9; Catalysis: PEPPSI™ Catalyst; (*c*) *N-Heterocyclic carbenes in synthesis*; S. P. Nolan Ed.; Wiley-VCH: Weinheim, 2006; (*d*) W. A. Herrmann, *Angew. Chem., Int. Ed.*, 2002, **41**, 1290–1309.

8 K. Arentsen, S. Caddick, F. G. N. Cloke, A. P. Herring and P. B. Hitchcock, *Tetrahedron Lett.*, 2004, **45**, 3511–3515.

9 (1,3-Diisopropylimidazol-2-ylidene)(3-chloropyridyl)palladium(II) dichloride. PEPPSI is an acronym for Pyridine Enhanced Precatalyst Preparation Stabilization and Initiation.

10 M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien and C. Valente, *Chem.–Eur. J.*, 2006, **12**, 4749–4755.

11 M. G. Organ, M. Abdel-Hadi, S. Avola, N. Hadei, J. Nasielski, C. J. O'Brien and C. Valente, *Chem.–Eur. J.*, 2007, **12**, 150–157.

12 C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson and M. G. Organ, *Chem.–Eur. J.*, 2006, **12**, 4743–4748.

13 K. Matos and J. A. Soderquist, *J. Org. Chem.*, 1998, **63**, 461–470.