ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: J. M. Gil-Negrete, J. Pérez Sestelo and L. Sarandeses, *Chem. Commun.*, 2018, DOI: 10.1039/C7CC09344F.

View Article Online
DOI: 10.1039/C7CC09344F

Journal Name

COMMUNICATION

Synthesis of Bench-Stable Solid Triorganoindium Reagents and Reactivity in Palladium-Catalyzed Cross-Coupling Reactions

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

José M. Gil-Negrete, José Pérez Sestelo,* and Luis A. Sarandeses*

Bench-stable solid triorganoindium compounds have been prepared by coordination with 4-(dimethylamino)pyridine (DMAP). The solid $R_3In(DMAP)$ complexes are obtained from the corresponding solution of R_3In in quantitative yield and can be stored for up to several weeks. These reagents show excellent reactivity in palladium-catalyzed cross-coupling reactions with organic electrophiles.

In recent years, indium(III) organometallics have become an attractive alternative to classical organometallic species in organic synthesis.[1] In 1999, we discovered the palladium-catalyzed cross-coupling reactions of triorganoindium reagents R_3In,[2] which is probably their most relevant reaction and whose utility in organic synthesis is continuously increasing.[3] In this reaction the R_3In species show a high atom efficiency as all three organic groups are transferred from indium to the electrophile with excellent selectivity, high versatility and, in general, low toxicity.[4] Triorganoindium reagents are commonly prepared by transmetallation from the corresponding organolithium or organomagnesium reagents, although other protocols have also been developed.[5] A significant limitation for the use of these organometallic species is associated with their preparation and use as solutions, since attempts to isolate and store these reagents led to decomposition.[6]

The preparation of solid-salt stabilized reagents is an interesting research topic that allows the use of organometallic and other nucleophilic species as solid reagents. Organotrifluoroborates,[7] MIDA-boronates[8] and stable siloxanes[9] are useful examples of solid-salt stabilized reagents, whereas among the main-group metal derivatives, organozinc pivalates have emerged as interesting reactive solid species.[10]

In the field of indium chemistry, Schumann and co-workers reported an extensive study on the characterization of indium organometallics stabilized by intramolecular coordination using nitrogen or phosphorus atoms.[11] The isolation and characterization of allyl and 1-butenylindium halides stabilized by complexation with phosphine and pyridine ligands were also reported by Baba.[6,12] Trimethylindium complexes have also been characterized but their reactivity and synthetic utility remains unknown.[11,13] Herein, we report the preparation of stable solid triorganoindium compounds stabilized by coordination with 4-(dimethylamino)pyridine (DMAP) and their reactivity in palladium-catalyzed cross-coupling reactions.

Bearing in mind the stabilization of Group 13 derivatives by nitrogen ligands, our research started with the preparation of stable solid triphenylindium complexes by addition of different pyridines **L1**–**L5** to Ph_3In in THF solution and removal of the solvent. In general, this procedure afforded a solid material that could be manipulated in air and whose reactivity was tested in a Pd-catalyzed cross-coupling reaction with 4-bromoacetophenone (**1a**, Table 1). Initial studies using a 1:2 ratio of Ph_3In and DMAP as ligand gave the coupling product (**2a**) in moderate yield (Table 1, entries 2–6). Interestingly, on using the 1:1 complex (Ph_3In/DMAP) **2a** was obtained in 73% yield with 40 mol% of the complex and $PdCl_2(PPh_3)_2$ (5 mol%) as catalyst (Table 1, entry 7), while the use of a 50 mol% of the complex led to an excellent 91% yield of **2a** (Table 1, entry 8). The use of lower amounts (<50 mol%) of $Ph_3In(DMAP)$ afforded lower yields, probably due to some decomposition of the complex during the process. The stoichiometry of the complex was studied by NMR spectroscopy and a 1:1 ratio of Ph_3In/DMAP was found, whereas the use of larger amounts of DMAP gave rise to an equilibrium between ligated and non-ligated DMAP. Additionally, the use of a substoichiometric amount of DMAP (ratio Ph_3In/DMAP 1:0.8) resulted in the appearance of benzene due to the decomposition of non-ligated organometallic complex (Figure 1).

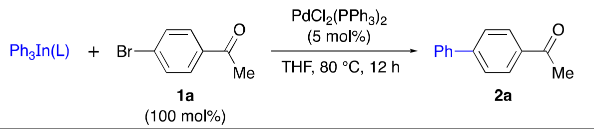
Accordingly, the addition of DMAP (1 equiv.) to a THF solution of Ph_3In at room temperature for one hour followed by evaporation of the solvent in vacuo gave a white solid with the tentative formula $Ph_3In(DMAP)\cdot 3LiCl$ (**3**, Scheme 1). This compound showed bench-stable, and was handled in air and

[a] Centro de Investigaciones Científicas Avanzadas (CICA) and Departamento de Química, Universidade da Coruña, E-15071 A Coruña, Spain.

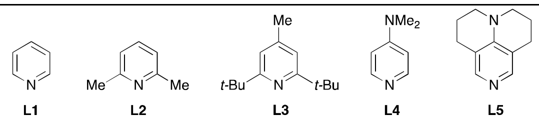
Electronic Supplementary Information (ESI) available: Tables S1 and S2, experimental procedures, compound characterization data, and copies of NMR spectra. See DOI: 10.1039/x0xx00000x

DOI: 10.1039/C7CC09344F

Table 1. Ligand optimization studies.[a]



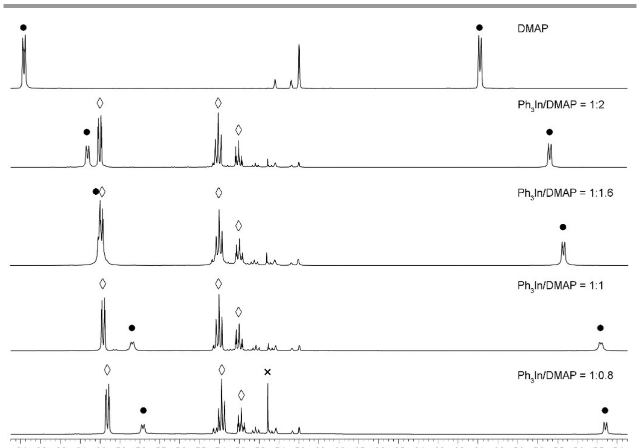
Entry	L	mol% L[b]	mol% Ph_3In[b]	Yield (%)[c]
1	–	–	40	–
2	**L1**	80	40	23
3	**L2**	80	40	15
4	**L3**	80	40	5
5	**L4**	80	40	55
6	**L5**	80	40	11
7	**L4**	40	40	73
8	**L4**	50	50	91



[a] For experimental details, see the ESI. [b] mol% of L and Ph_3In with respect to **1a**. [c] Isolated yields of reaction product after column chromatography.

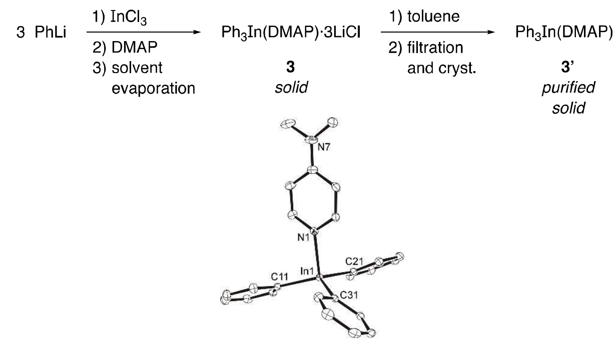
used as a solid reagent. In order to characterize this solid, the LiCl was removed by filtration after boiling in dry toluene. This process afforded a compound that was crystallized from toluene/hexane (3:1). X-ray diffraction studies on the pure crystals (**3'**) showed a trigonal pyramidal structure in which the ideal plane formed by the phenyl groups and the indium atom is distorted by the ligand (DMAP) to give an N–In–C dihedral angle of around 100° (Scheme 1). The In–N distance was 2.27 Å and the In–C distance was 2.17 Å. Interestingly, the cross-coupling reaction with 4-bromoacetophenone carried out using the purified crystals (**3'**) afforded the coupling product in excellent yield (90%) on using only 34 mol% of the solid organometallic reagent and showing the efficient transference of all three organic groups attached to the indium to the electrophile.

Having successfully prepared the complex $Ph_3In(DMAP)$, the protocol was applied to other triorganoindium species and the reactivity of the resulting complexes was studied in palladium-catalyzed cross-coupling reactions. With this purpose, a series



• DMAP. ◊ Ph_3In. × Benzene (resulting from Ph_3In decomposition).

Figure 1. $Ph_3In(DMAP)$ stoichiometry experiments.



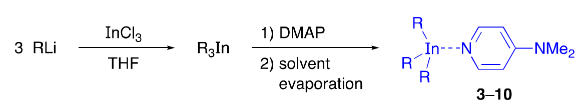
Scheme 1. Preparation of $Ph_3In(DMAP)$ (**3'**) and ORTEP drawing (showing 40% probability displacement ellipsoids) of the crystal structure of $Ph_3In(DMAP)$. The hydrogen atoms are omitted for clarity.[a] [a] CCDC-1579360.

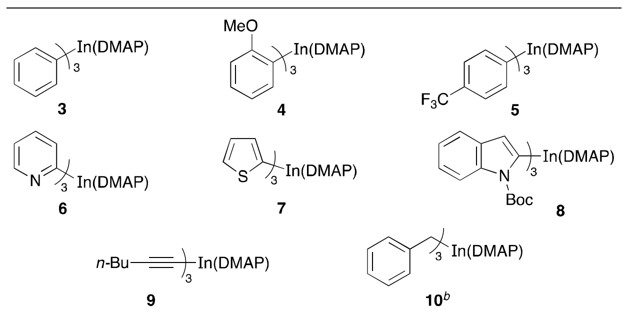
of complexes $R_3In(DMAP)·3LiCl$ abbreviated as $R_3In(DMAP)$ for clarity was prepared (Table 2) including aromatic and heteroaromatic indium reagents (**3–8**), a trialkynylindium complex (**9**) and the tribenzylindium complex (**10**).

The reactivity of the solid triorganoindium reagents was tested in palladium-catalyzed cross-coupling reactions using common electrophiles under the established conditions reported for R_3In prepared *in situ* in THF solution. The reaction of the $Ph_3In(DMAP)$ complex (**3**) with the aryl triflate **1b** or the aryl bromide **11** proceeded efficiently (92–94%, Table 3). The coupling with other electrophiles such as β-bromostyrene and benzyl bromide also gave the corresponding products **2c–d** in good yields (81–88%). Additionally, the Pd-catalyzed allylic substitution[14] with cinnamyl bromide gave regioselectively the α-substitution product **2e** in excellent yield (87%).

To our delight, other solid derivatives of triarylindium reagents, such as the tri(2-methoxyphenyl)indium(DMAP) (**4**) and tris(4-trifluoromethylphenyl)indium(DMAP) (**3**) also reacted efficiently with the electrophiles **1a** and **11–14** to give the corresponding cross-coupling products in good to excellent yields (81–96%, Table 3). In all cases the reaction proceeded under mild reaction conditions and in short reaction times using 50 mol% of the solid indium reagents, thus showing the feasibility of using these compounds in cross-coupling

Table 2. Preparation of solid triorganoindium complexes.[a]

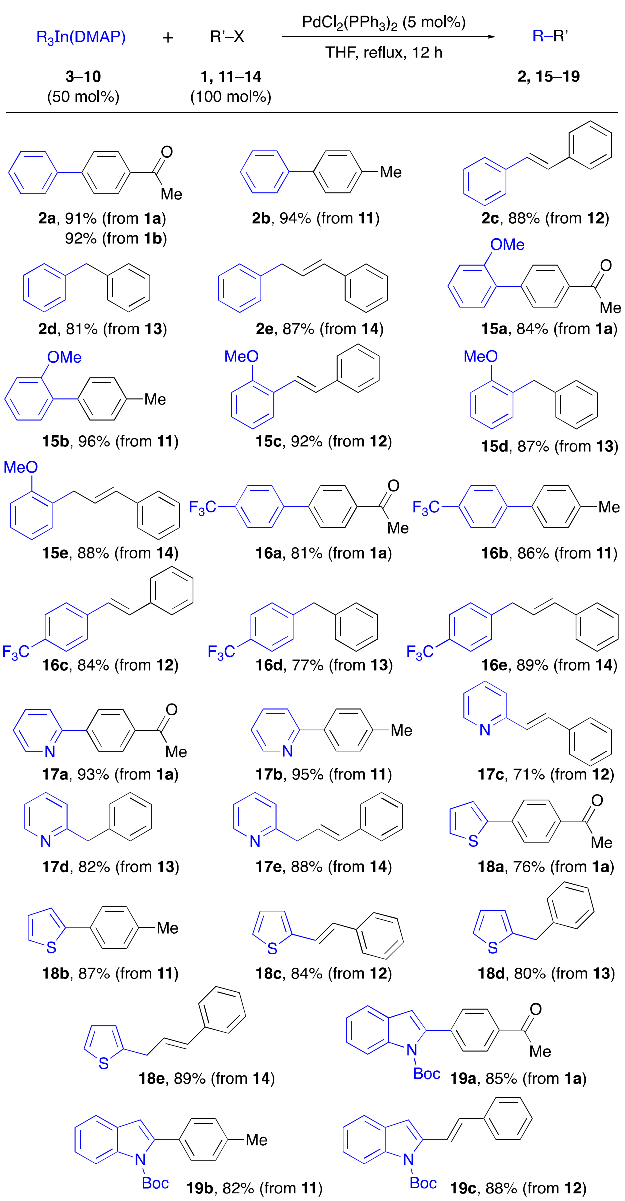




[a] LiCl in complexes is omitted for clarity. [b] Prepared from benzylmagnesium bromide.

View Article Online
DOI: 10.1039/C7CC09344F

Table 3. Palladium-catalyzed cross-coupling reactions of solid triarylindium and triheteroarylindium complexes **3–8** with organic electrophiles.[a]

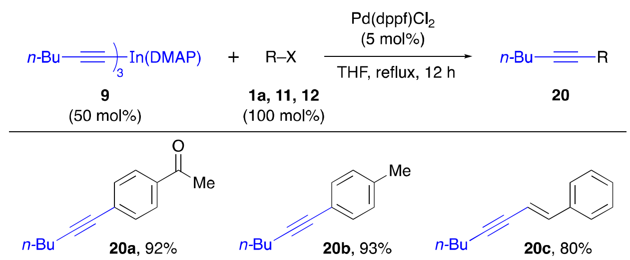


[a] **1a**: 4-Bromoacetophenone; **1b**: 4-acetylphenyl trifluoromethanesulfonate; **11**: 4-bromotoluene; **12**: β-bromostyrene; **13**: benzyl bromide; **14**: cinnamyl bromide.

reactions. The presence of DMAP as a ligand does not interfere with the reactivity of the organoindium compound since the yields are comparable to those obtained in reactions in which the R_3In was generated *in situ* in solution.

Then, we proceeded to study the reactivity of the solid heteroaryl indium compounds **6–8**. As can be seen from the results in Table 3, coupling reactions between these compounds and electrophiles **1a** and **11–14** also proceeded in good yields (71–95%, Table 3) under the same experimental conditions as before. Interestingly, the reactions involving aryl halides and also a vinyl halide, benzyl bromide and an allylic bromide as electrophiles, showed the versatility of the solid

Table 4. Palladium-catalyzed cross-coupling reactions of solid alkynylindium complex **9** with organic electrophiles.

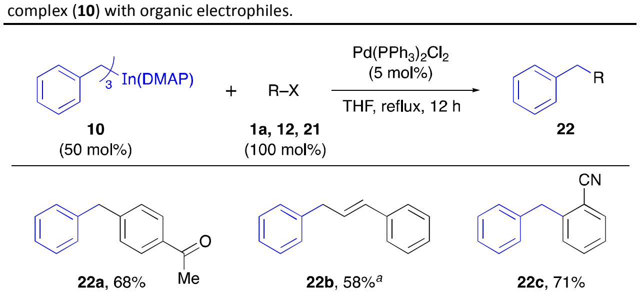


indium reagents. Furthermore, the efficient coupling achieved using the pyridylindium complex **6** showed that the nitrogen lone pair does not interfere in the complexation process with DMAP and the reactivity remains similar to that of the tripyridylindium in solution.

The reactivity of the solid alkynylindium complex **9** was also studied with aryl and alkenyl halides **1a**, **11** and **12** under standard reaction conditions. These coupling reactions also proceeded efficiently to give excellent yields (80–93%, Table 4). Finally, the reactivity of the tribenzylindium(DMAP) complex (**10**) was tested. In this case, it was found that the coupling reactions with aryl bromide **1a**, β-bromostyrene (**12**) and 2-bromobenzonitrile (**21**) gave satisfactory yields (58–71%, Table 5). In this case, 10 was prepared from benzylmagnesium bromide.

The synthetic utility of the novel solid triorganoindium species was demonstrated not only in terms of their reactivity but also due to their integrity against decomposition over time. In this respect, $Ph_3In(DMAP)\cdot 3LiCl$ (**3**) was stored on the laboratory bench at room temperature under Ar and the stability of the complex evaluated by means of palladium-catalyzed cross-coupling reactions over time. The results are presented in Table 6 and it can be seen that one month after preparation of the complex, the solid reagent remained highly reactive (78% yield of **2a**, Table 6, entry 6). Interestingly, the use of purified $Ph_3In(DMAP)$ (**3'**, without LiCl) gave compound **2a** in 95% yield after 45 days. The other organoindium complexes prepared in this study generally show high stabilities under Ar at room temperature. The stability ranges from weeks for **4** and **7**, days in the case of **5**, **9** and **10**, and >6 h for the nitrogen heterocyclic derivatives **6** and **8** (tested by studying a Pd-

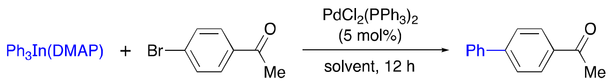
Table 5. Palladium-catalyzed cross-coupling reactions of solid tribenzylindium(DMAP) complex (**10**) with organic electrophiles.



[a] ^1H NMR yield.

View Article Online
DOI: 10.1039/C7CC09344F

Table 6. Reactivity of complex **1** over time.



3 (50 mol%) **1a** (100 mol%) **2a**

Entry	Days after preparation of $Ph_3In(DMAP)$	Yield (%)
1	3	91[a]
2	5	88[a]
3	7	93[a]
4	14	84[a]
5	21	82[a]
6	28	78[a]
7	45	95[b]

[a] Reactions with non-purified $Ph_3In(DMAP)\cdot 3LiCl$ (**3**). [b] Reaction with purified $Ph_3In(DMAP)$ (**3'**).

catalyzed cross-coupling reaction, Table S1).

In general, the use of organoindium species is limited to ethers as solvents, and to their preparation from the corresponding organolithium or organomagnesium reagents. For this reason, we studied the reactivity of the solid-stable R_3In complexes in non-ethereal solvents. The palladium-catalyzed coupling reaction of $Ph_3In(DMAP)$ with **1a** in various solvents, such as toluene, chloroalkanes or DMF, generally afforded good yields of the coupling product **2a** (45–93%, Table S3, entries 2–6).

In conclusion, a variety of bench-stable solid triorganoindium reagents have been prepared by complexation with DMAP in a 1:1 stoichiometry. The stability of the R_3In complexes ranges from days to weeks depending on the nature of the R groups. These reagents reacted with organic electrophiles under palladium catalysis to afford the coupling products in good yields. Interestingly, only 50 mol% of the solid organometallic reagent is necessary to complete the reactions. Other solvents can be used in the coupling reactions and this demonstrates the versatility and utility of these solid reagents. Further studies on the isolation of new complexes and their applications in synthesis are underway and will be published in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful to the Spanish Ministerio de Economía y Competitividad (CTQ2015-68369-P), Xunta de Galicia (GRC2014/042) and EDRF funds for financial support. We also thank Dr. Antonio L. Llamas-Díaz (RIAIDT, Universidade de Santiago de Compostela, Spain) for the X Ray structure analysis.

Notes and references

1 (a) Z.-L. Shen, S.-Y. Wang, Y.-K. Chok, Y.-H. Xu and T.-P. Loh, *Chem. Rev.*, 2013, **113**, 271; (b) K. Zhao, L. Shen, Z.-L. Shen and T.-P. Loh, *Chem. Soc. Rev.*, 2017, **46**, 586.

2 (a) I. Pérez, J. Pérez Sestelo and L. A. Sarandeses, *Org. Lett.*, 1999, **1**, 1267; (b) I. Pérez, J. Pérez Sestelo and L. A. Sarandeses, *J. Am. Chem. Soc.*, 2001, **123**, 4155; (c) R. Riveiros, D. Rodríguez, J. Pérez Sestelo and L. A. Sarandeses, *Org. Lett.*, 2006, **8**, 1403; (d) Á. Mosquera, M. A. Pena, J. Pérez Sestelo and L. A. Sarandeses, *Eur. J. Org. Chem.*, 2013, **2013**, 2555; (e) M. Mato, C. Pérez-Caaveiro, L. A. Sarandeses and J. Pérez Sestelo, *Adv. Synth. Catal.*, 2017, **359**, 1388, and references therein.

3 (a) K. Takami, H. Yorimitsu, H. Shinokubo, S. Matsubara and K. Oshima, *Org. Lett.*, 2001, **3**, 1997; (b) P. H. Lee, S.-Y. Sung and K. Lee, *Org. Lett.*, 2001, **3**, 3201; (c) K. Lee, D. Seomoon and P. H. Lee, *Angew. Chem. Int. Ed.*, 2002, **41**, 3901; (d) U. Lehmann, S. Awasthi and T. Minehan, *Org. Lett.*, 2003, **5**, 2405; (e) Y.-H. Chen, M. Sun and P. Knochel, *Angew. Chem. Int. Ed.*, 2009, **48**, 2236; (f) Z.-L. Shen, K. K. K. Goh, H.-L. Cheong, C. H. A. Wong, Y.-C. Lai, Y.-S. Yang and T.-P. Loh, *J. Am. Chem. Soc.*, 2010, **132**, 15852; (g) D. Lee, T. Ryu, Y. Park and P. H. Lee, *Org. Lett.*, 2014, **16**, 1144; (h) S. Kim, C.-E. Kim, B. Seo and P. H. Lee, *Org. Lett.*, 2014, **16**, 5552; (i) S. Thapa, S. K. Gurung, D. A. Dickie and R. Giri, *Angew. Chem. Int. Ed.*, 2014, **53**, 11620; (j) Y. Park, J. Min, D. Eom and P. H. Lee, *Org. Lett.*, 2015, **17**, 3934.

4 J. Burgess, *Chem. Soc. Rev.*, 1996, **25**, 85.

5 (a) J. L. W. Pohlmann, F. E. Brinckman, G. Tesi and R. E. Donadio, *Z. Naturforsch.*, 1965, **20b**, 5; (b) H. C. Clark and A. L. Pickard, *J. Organomet. Chem.*, 1967, **8**, 427; (c) E. Font-Sanchis, Á. Sastre-Santos and F. Fernández-Lázaro, *Dalton Trans*, 2009, 2470; (d) Z.-L. Shen, K. K. K. Goh, Y.-S. Yang, Y.-C. Lai, C. H. A. Wong, H.-L. Cheong and T.-P. Loh, *Angew. Chem. Int. Ed.*, 2011, **50**, 511; (e) L. Adak and N. Yoshikai, *J. Org. Chem.*, 2011, **76**, 7563; (f) S. Bernhardt, Z.-L. Shen and P. Knochel, *Chem. Eur. J.*, 2013, **19**, 828.

6 M. Yasuda, M. Haga and A. Baba, *Organometallics*, 2009, **28**, 1998.

7 (a) G. A. Molander and N. Ellis, *Acc. Chem. Res.*, 2007, **40**, 275; (b) G. A. Molander, *J. Org. Chem.*, 2015, **80**, 7837.

8 J. Li, A. S. Grillo and M. D. Burke, *Acc. Chem. Res.*, 2015, **48**, 2297.

9 D. Martinez-Solorio, B. Melillo, L. Sanchez, Y. Liang, E. Lam, K. N. Houk and A. B. Smith III, *J. Am. Chem. Soc.*, 2016, **138**, 1836.

10 Selected references: (a) S. Bernhardt, G. Manolikakes, T. Kunz and P. Knochel, *Angew. Chem. Int. Ed.*, 2011, **50**, 9205; (b) J. R. Colombe, S. Bernhardt, C. Stathakis, S. L. Buchwald and P. Knochel, *Org. Lett.*, 2013, **15**, 5754; (c) M. Ellwart and P. Knochel, *Angew. Chem. Int. Ed.*, 2015, **54**, 10662; (d) Y.-H. Chen, C.-P. Tüllmann, M. Ellwart and P. Knochel, *Angew. Chem. Int. Ed.*, 2017, **56**, 9236–9239.

11 Representative references: (a) H. Schumann, U. Hartmann, W. Wassermann, A. Dietrich, F. H. Görlitz, L. Pohl and M. Hostalek, *Chem. Ber.*, 1990, **123**, 2093; (b) H. Schumann, J. Kaufmann, B. C. Wassermann, F. Girgsdies, N. Jaber and J. Blum, *Z. Anorg. Allg. Chem.*, 2002, **628**, 971; (c) H. Schumann, F. Girgsdies, B. Heymer, J. Kaufmann, C. Marschall and W. Wassermann, *Z. Anorg. Allg. Chem.*, 2007, **633**, 2268.

12 (a) M. Yasuda, M. Haga and A. Baba, *Eur. J. Org. Chem.*, 2009, **2009**, 5513; (b) M. Yasuda, M. Haga, Y. Nagaoka and A. Baba, *Eur. J. Org. Chem.*, 2010, **2010**, 5359; (c) K. Kiyokawa, M. Yasuda and A. Baba, *Organometallics*, 2011, **30**, 2039.

13 (a) D. C. Bradley, H. Dawes, D. M. Frigo, M. B. Hursthouse and B. Hussain, *J. Organomet. Chem.*, 1987, **325**, 55; (b) K. M. Coward, A. C. Jones, A. Steiner, J. F. Bickley, L. M. Smith and M. E. Pemble, *J. Chem. Soc., Dalton Trans.*, 2001, 41; (c) F. Thomas, T. Bauer, S. Schulz and M. Nieger, *Z. Anorg. Allg. Chem.*, 2003, **629**, 2018; (d) X. Tian, R. Fröhlich, T. Pape and N. W Mitzel, *Organometallics*, 2005, **24**, 5294.

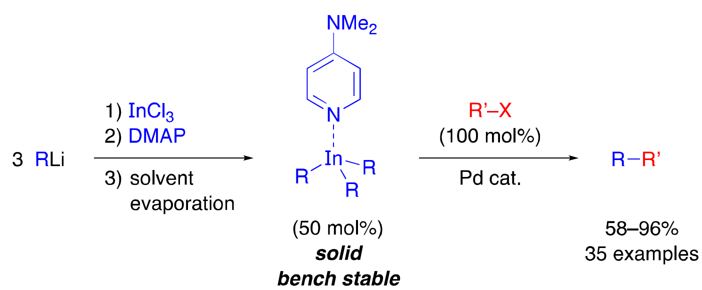
14 (a) L. Baker and T. Minehan, *J. Org. Chem.*, 2004, **69**, 3957; (b) D. Rodríguez, J. Pérez Sestelo and L. A. Sarandeses, *J. Org. Chem.*, 2004, **69**, 8136; (c) R. Riveiros, R. Tato, J. Pérez Sestelo and L. A. Sarandeses, *Eur. J. Org. Chem.*, 2012, **2012**, 3018.

View Article Online
DOI: 10.1039/C7CC09344F

Table of Contents Entry

Manuscript title: Synthesis of Bench-Stable Solid Triorganoindium Reagents and Reactivity in Palladium-Catalyzed Cross-Coupling Reactions

Authors: José M. Gil-Negrete, José Pérez Sestelo, and Luis A. Sarandeses



Triorganoindium reagents can be isolated as bench-stable solid $R_3In(DMAP)$ complexes and show excellent reactivity in palladium-catalyzed cross-coupling reactions.