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COMMUNICATION

Synthesis of 7-aryl/heteraryl-1,3-diphenyl-1,2,4-benzotriazinyls *via* palladium catalyzed Stille and Suzuki-Miyaura reactions†

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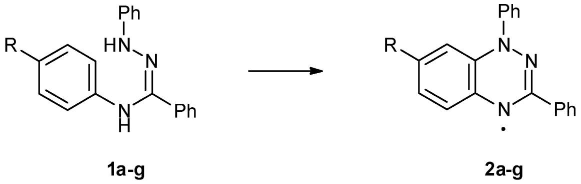
Stille and Suzuki-Miyaura reactions of 7-iodo-1,3-diphenyl-1,4-dihydro-1,2,4-benzotriazin-4-yl are presented as rare examples of cross-coupling reactions with stable organic radicals. Both the Stille and Suzuki-Miyaura reactions are in most cases high yielding but the latter are cleaner while the former are faster and are accompanied by 1,3-diphenyl-1,2,4-benzotriazin-7(*H*)-one as by-product. A range of 7-aryl and 7-heteroaryl-1,2,4-benzotriazinyls have been synthesized and characterized using standard spectroscopic and spectrometric means.

Intensive research on stable organic radicals during the past couple of decades has provided many examples of molecules comprised of light elements that demonstrate interesting magnetic and/or conducting properties.[1] Numerous reports on the synthesis and solid-state properties of several families of organic radicals, such as the nitroxide and nitronyl nitroxides,[2] the triphenylmethyls,[3] the verdazyls[4] and the heterocyclic thiazyls,[5] have appeared in the literature. 1,2,4-Benzotriazinyls are a family of radicals, first prepared by Blatter in 1968,[6] that have been less well studied. Early work on the magnetic behavior of these radicals by Neugebauer *et al.*,[7] and more recently by our group[8] showed interesting ferro- and antiferromagnetic properties. Relatively few analogues of these radicals have been prepared owing to a 5-step product specific synthesis that afforded the radicals in moderate yields and involved large excesses of HgO (toxic) or AgO (expensive) oxidants. As part of our on-going studies on the 1,2,4-benzotriazinyls, we recently, developed a mild and high-yielding method for converting *N*-phenylamidrazones **1** into stable radicals **2** using palladium-on-carbon and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in an atmosphere of air (Scheme 1).[9]



R = (a) H 85%, (b) F_3C 80%, (c) Cl 82%, (d) Br 94%, (e) I 81%, (f) Me 70%, (g) MeO 72%

Scheme 1 Synthesis of various 1,3-diphenyl-1,2,4-benzotriazinyls **2a–g** from *N*-phenylamidrazones **1a–g** (0.5 mmol) in DCM (1 ml) in the presence of DBU (0.1 equiv.) with Pd/C (1.6 mol%) at *ca.* 20 °C under an air atmosphere for 4–9 h.

We further investigated the solid-state properties of these radicals and were delighted that 7-trifluoromethyl benzotriazinyl radical **2b** exhibited, for this radical class and to the best of our knowledge, unprecedented 1D Heisenberg linear chain weak ferromagnetism at 10 K with $J/K = +1.49$ K.[8a] After submission of this present manuscript 1D ferromagnetic behaviour was reported for two 3-(3-vinylphenyl)-1,2,4-benzotriazinyls by Frank *et al.*[8b] Previous studies by Neugebauer *et al.*,[7] indicated Curie–Weiss paramagnetic behaviour for Blatter radical **2a** and 3-*tert*-butyl-1-phenyl-1,2,4-benzotriazinyl, while short range antiferromagnetic ordering was observed for 1-(4-chlorophenyl)-3-phenyl-1,2,4-benzotriazinyl. Clearly, the range of magnetic behaviour for this radical system is broader than originally anticipated. Furthermore, Blatter radical **2a** acted as the donor in an organic charge transfer salt with 7,7,8,8-tetracyanoquinodimethane (TCNQ) that demonstrated pressure-dependent conductivity.[8c] In the hope of identifying additionally interesting magnetic and/or conducting properties, we needed a rapid route to more 7-substituted benzotriazinyls. By combining Stille and Suzuki-Miyaura coupling chemistry with the now readily availabe 7-halo-1,2,4-benzotriazinyls **2c–e** we envisaged a non-product specific synthetic route to new radicals.

To the best of our knowledge metal-catalyzed coupling reactions have been reported only for the nitronyl-nitroxide radical family.[10] These include Heck,[10a] Suzuki[10b] and Sonogashira[10c] reactions with moderate or disappointingly poor yields. The loss in yield during the Suzuki reaction of 2-iodophenyl nitronyl nitroxide was attributed to decomposition of the radical at the employed reaction temperature and during the Sonogashira reaction conditions the nitronyl nitroxide radicals suffered deoxygenation and the preceding dihydroxyimidazolinides were dehydrated.[11]

Herein we report the synthesis of 7-aryl/heteroaryl-1,2,4-benzotriazinyls *via* palladium-catalyzed Stille and Suzuki-Miyaura coupling chemistry.

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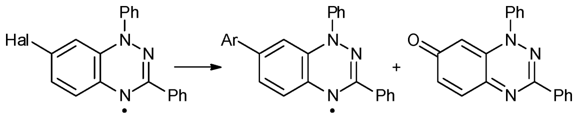
Table 1 Stille cross-coupling reactions of 7-halo-1,3-diphenyl-1,2, 4-benzotriazinyls **2c–e** (0. 12 mmol) with Pd catalyst (5 mol%) in dry DMF (2 ml) at *ca.* 100 °C under argon



2c-e **3a-c** **4**

				Yields (%)	
Hal	$ArSnBu_3$ (equiv.)	Catalyst	Time (min)	**3a–c**	**4**
Cl	$PhSnBu_3$ (3)	$Pd(OAc)_2$	24 h	[a]	—
Br	$PhSnBu_3$ (3)	$Pd(OAc)_2$	24 h	[a]	—
I	$PhSnBu_3$ (1)	$Pd(OAc)_2$	240	**3a** (53)	26
I	$PhSnBu_3$ (1.5)	$Pd(OAc)_2$	60	**3a** (56)	13
I	$PhSnBu_3$ (2)	$Pd(OAc)_2$	40	**3a** (78)	11
I	$PhSnBu_3$ (3)	$Pd(OAc)_2$	20	**3a** (76)	Trace
I	$PhSnBu_3$ (4)	$Pd(OAc)_2$	20	**3a** (82)	5
I	$PhSnBu_3$ (2)	$Pd(Ph_3P)_4$	40	**3a** (46)	19
I	$PhSnBu_3$ (3)	$Pd(Ph_3P)_4$	30	**3a** (34)	Trace
I	$PhSnBu_3$ (2)	$Pd_2(dba)_3$[b]	40	**3a** (62)	10
I	$PhSnBu_3$ (3)	$Pd_2(dba)_3$	30	**3a** (36)	Trace
I	Fur-2-yl$SnBu_3$ (2)	$Pd(OAc)_2$	30	**3b** (82)	3
I	Thien-2-yl$SnBu_3$ (2)	$Pd(OAc)_2$	30	**3c** (93)	Trace
I	*N*-Mepyrrol-2-yl$SnBu_3$ (2)	$Pd(OAc)_2$	15	[c]	—

[a] Incomplete reaction after 24 h, mainly unreacted starting radical by TLC. [b] dba = dibenzylideneacetate. [c] Complex reaction mixture and unstable products.

The reactivity of 7-chloro, bromo-, iodobenzotriazinyls **2c–e** was established in a typical Stille reaction using a three-fold excess tributylphenylstannane with $Pd(OAc)_2$ (5 mol%) as catalyst in dry DMF under an argon atmosphere. When 7-chloro, and 7-bromobenzotriazinyls **2c** and **2d** were used the reactions were incomplete even after 24 h (by TLC) and the most of the starting radicals could be recovered. Conversely, the reaction of 7-iodobenzotriazinyl **2e** with $PhSnBu_3$ (3 equiv.) finished within 20 min affording the desired 7-phenylbenzotriazinyl **3a** in 76% yield together with traces of the 1,2,4-benzotriazin-7-one **4** (Table 1).‡ The superior reactivity of the iodo was typical of the Stille reaction.[11]

The Stille reaction of the 7-iodobenzotriazinyl **2e** was then optimized with respect to organostannane equivalents and catalyst. When 2 equiv. of $PhSnBu_3$ were used the reaction time increased (40 min) and more benzotriazinone **4** was formed (11%) but the yield of the main product **3a** remained essentially the same (78%). Less $PhSnBu_3$ (1-1.5 equiv.) led to longer reaction times, lower yields of radical **3a** (53–56%) and more benzotriazinone **4**, the formation of which was presumably owed to a competitive Pd-mediated hydrodehalogenation of the 7-iodo radical, followed by oxidation.[9] While the use of 4 equiv. of $PhSnBu_3$ marginally improved the yield of the desired radical it did not improve the reaction time.

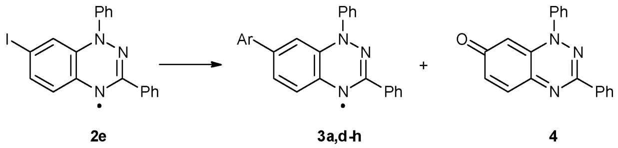
Other commercial available catalysts $Pd(Ph_3P)_4$ and $Pd_2(dba)_3$ were tested using with the same conditions but gave lower yields and more benzotriazinone. Using our best conditions: organostannane (2 equiv.) and $Pd(OAc)_2$ (5 mol%) both the fur-2-yl- and thien-2-yl-1,2,4-benzotriazinyls **3b** and **3c**, were prepared in 82 and 93% yields, respectively. The attempted synthesis of the 7-(*N*-methylpyrrol-2-yl)benzotriazinyl resulted in a complex reaction mixture and an unstable main product that could not be isolated.

The Suzuki-Miyaura reaction of the 7-iodobenzotriazinyl **2e** was cleaner and only traces of the benzotriazinone **4** were observed, however, longer reaction times were required (Table 2).§ The reactions were carried out in dry toluene at 100 °C under an argon atmosphere. When $PhB(OH)_2$ (2 equiv.) or $Pd(OAc)_2$ (5 mol%) as catalyst and K_2CO_3 (2 equiv.) as base were used the 7-phenylbenzotriazinyl **3a** was formed in 78% yield and the reaction completed in 3 h. More base (3 equiv.) reduced the reaction time by half (1.5 h) and led to a minor improvement in the yield (81%). Less than 2 equiv. of $PhB(OH)_2$ afforded the product in a significantly lower yield (59%). Conversely, when 3 equiv. of both $PhB(OH)_2$ and K_2CO_3 were used the reaction was cleaner, faster (1 h) and gave the product in exceptionally high yield (93%).

The use of wet toluene did not affect the course or yield of the reaction, however, when aqueous K_2CO_3 was used the reaction became complex and polar products were observed (baseline on TLC). Reactions in dry toluene with stronger bases such as KOH or NaOH left the yield and reaction time essentialy unchanged. Other palladium catalysts examined required either longer reaction times [$Pd_2(dba)_3$] or result in poor yield [$Pd(Ph_3P)_4$].

The optimized reaction conditions were then used to synthesize a range of 7-arylbenzotriazinyls **3d–h**. Electron rich boronic acids such as $4\text{-MeOC}_6H_4B(OH)_2$, 4-TolB(OH)_2 and $4\text{-PhC}_6H_4B(OH)_2$ gave the products **3d**, **3e** and **3g** in 83, 76 and 91% yield, respectively. However when electron deficient arylboronic acids were used either moderate yields were obtained (47% for 4-FC_6H_4-benzotriazinyl **3f**) or complicated reaction mixtures were

Table 2 Suzuki cross-coupling reactions of the 7-iodo-1,3-diphenyl-1,2,4-benzotriazinyl **2e** (0.12 mmol) with Pd catalyst (5 mol%) in dry PhMe (2 ml) at 100 °C under argon



ArB(OH)$_2$ (equiv.)	Catalyst	Base (equiv.)	Time (h)	Yields (%) 3	Yields (%) 4
PhB(OH)$_2$ (2)	Pd(OAc)$_2$	K$_2$CO$_3$ (2)	3	**3a** (78)	Trace
PhB(OH)$_2$ (2)	Pd(OAc)$_2$	K$_2$CO$_3$ (3)	1.5	**3a** (81)	Trace
PhB(OH)$_2$ (1.5)	Pd(OAc)$_2$	K$_2$CO$_3$ (3)	5	**3a** (59)	Trace
PhB(OH)$_2$ (3)	Pd(OAc)$_2$	K$_2$CO$_3$ (3)	1	**3a** (93)	Trace
PhB(OH)$_2$ (3)[a]	Pd(OAc)$_2$	K$_2$CO$_3$ (3)	1	**3a** (88)	Trace
PhB(OH)$_2$ (3)[b]	Pd(OAc)$_2$	K$_2$CO$_3$ (3)[b]	19	[c]	[c]
PhB(OH)$_2$ (3)	Pd(OAc)$_2$	KOH (3)	1.3	**3a** (84)	—
PhB(OH)$_2$ (3)	Pd(OAc)$_2$	NaOH (3)	1.5	**3a** (75)	—
PhB(OH)$_2$ (3)	Pd(Ph$_3$P)$_4$	K$_2$CO$_3$ (3)	2.5	**3a** (25)	Trace
PhB(OH)$_2$ (3)	Pd$_2$(dba)$_3$[d]	K$_2$CO$_3$ (3)	3	**3a** (80)	Trace
4-MeOC$_6$H$_4$B(OH)$_2$ (3)	Pd(OAc)$_2$	K$_2$CO$_3$ (3)	1.5	**3d** (83)	Trace
4-TolB(OH)$_2$ (3)	Pd(OAc)$_2$	K$_2$CO$_3$ (3)	1.5	**3e** (76)	Trace
4-FC$_6$H$_4$B(OH)$_2$ (3)	Pd(OAc)$_2$	K$_2$CO$_3$ (3)	2.5	**3f** (47)	11
4-PhC$_6$H$_4$B(OH)$_2$ (3)	Pd(OAc)$_2$	K$_2$CO$_3$ (3)	2	**3g** (91)	Trace
4-O$_2$NC$_6$H$_4$B(OH)$_2$ (3)	Pd(OAc)$_2$	K$_2$CO$_3$ (3)	5	[c]	[c]
4-NCC$_6$H$_4$B(OH)$_2$ (3)	Pd(OAc)$_2$	K$_2$CO$_3$ (3)	3	[c]	[c]
Thien-3-ylB(OH)$_2$ (3)	Pd(OAc)$_2$	K$_2$CO$_3$ (3)	1.5	**3h** (67)	Trace
MeB(OH)$_2$ (3)	Pd(OAc)$_2$	K$_2$CO$_3$ (3)	5	[c]	[c]

[a] Non distilled toluene. [b] K$_2$CO$_3$ (3 equiv.) in H$_2$O (1 ml). [c] Complex reaction mixture; TLC indicated traces of starting radical, products **3** and **4** and intense baseline material. [d] dba = dibenzylideneacetone.

observed for 4-O$_2$NC$_6$H$_4$B(OH)$_2$ and 4-NCC$_6$H$_4$B(OH)$_2$. Use of heterocyclic thien-3-ylB(OH)$_2$ gave the corresponding product **3h** in good yield (67%).

The solid-state properties of these new 7-aryl/heteroaryl-1,2,4-benzotriazinyls will be the subject of a full paper.

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Notes and references

‡ **Stille reaction (general procedure):** A stirred mixture of 7-iodo-1,3-diphenyl-1,4-dihydro-1,2,4-benzotriazinyl **2e** (50 mg, 0.122 mmol), organo-stannane (2 equiv.) and Pd(OAc)$_2$ (5 mol%) was heated to *ca.* 100 °C in dry DMF (2 ml) for 0.5–1 h under inert conditions until all the starting material was consumed (TLC). Dry flash chromatography (Et$_2$O–hexane, 1 : 3) of the reaction mixture gave the following phenyl, fur-2-yl, thien-2-yl 7-substituted-benzotriazinyls **3a-c**, respectively.

§ **Suzuki-Miyaura reaction (general procedure):** A stirred mixture of 7-iodo-1,3-diphenyl-1,4-dihydro-1,2,4-benzotriazinyl, arylboronic acid (3 equiv.), K$_2$CO$_3$ (3 equiv.) and Pd(OAc)$_2$ (5 mol%) was heated to *ca.* 100 °C in dry toluene for 1–3 h under argon until all the starting material was consumed (TLC). Dry flash chromatography (Et$_2$O–hexane, 1 : 3) of the reaction mixture gave the following 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-FC$_6$H$_4$, 4-PhC$_6$H$_4$, thien-3-yl 7-substituted benzotriazinyls **3d–h**, respectively.

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