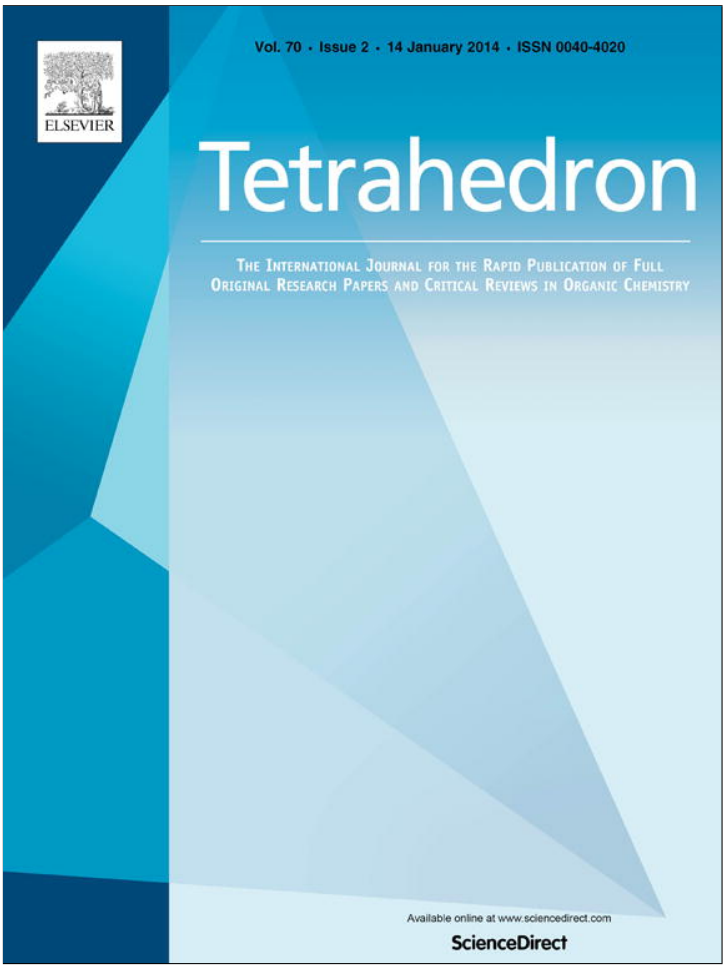

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Arylation of aryl chlorides, a convenient method for the synthesis of new potential triazolic fungicides

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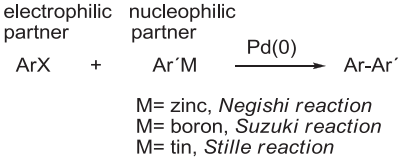
ABSTRACT

We evaluated two alternative routes for the arylation of known chlorinated fungicides. The first pathway involved a $S_{RN}1$ substitution, followed by Stille reaction, while the second consisted in a one step reaction by the Suzuki coupling. Both methodologies were useful to obtain new products that could be potential fungicides.

1. Introduction

Triazoles have been widely used as fungicides in different countries, controlling fungi, such as *Septoria tritici* or *Gibberella zeae*.[1] The triazolic plant protection fungicides include 1-(4-clorofenoxi)-3,3-dimetil-1-(1*H*-1,2,4-triazol-1-il) butan-2-one (triadimefon®) (**1**) and 1-(4-chlorophenyl)-3-cyclopropyl-2-(1*H*-1,2,4-triazol-1-yl)butan-1-ol (cyproconazole®) (**2**). Triadimefon® and cyproconazole® are chlorinated triazolic analogs, relatively stable under natural conditions, which have become prominent pollutants for soils and aquatic systems. These azoles are systemic, having a broad antifungal spectrum. Systemic azoles inhibit cytochrome P-450 enzymatic system as well as fungal 1,4-α-demethylase, avoiding the synthesis of ergosterol and, thus, decreasing the viability of the fungal cell.[2] The inhibition of demethylase involves the bind of the heme iron atom, belonging to ferric cytochrome P450, to the nitrogen-4 of triazolic compounds, which constitutes the active site of the molecule. In order to produce new fungicides, less toxic to the environment, we decided to investigate two alternative routes for the arylation of triadimefon or cyproconazole, substituting the chloride atom but retaining the triazole ring and, thus, keeping potential bioactivity of new synthetic products.

Many cross-coupling reactions are palladium-catalyzed reactions, involving the formation of a new C–C bond, which are of great importance in organic chemistry.[3] The initiation step of these cross-coupling reactions involves the assembling of two molecules to the metal, via the formation of metal–carbon bonds. In the next step, these carbon atoms couple between them, leading to the formation of a new carbon–carbon single bond. These reactions are catalyzed by zerovalent palladium and can utilize an arylhalide (ArX) as the electrophilic coupling partner. The nucleophilic coupling partner can be an organometallic compound, namely Ar′M, where M is typically zinc, boron or tin (Eq. 1).



(1)

These reactions begin generating an organopalladium complex ArPdX, arising from the reaction between the arylhalide and Pd(0). The insertion of palladium in a C–Cl bond requires high energy, which leads to slow initiation steps when aryl chlorides are used,[4] requiring special conditions to get good synthetic results.[5] Several advances have been reported to this respect. Buchwald studied inactive aryl chlorides (neutral or electron rich)[6] by Suzuki reactions for the first time. A study of Littke and Fu proposes a general method by the cross-coupling of aryl chlorides using Pd/$P(^tBu)_3$. However, some aryl chlorides require the use of special

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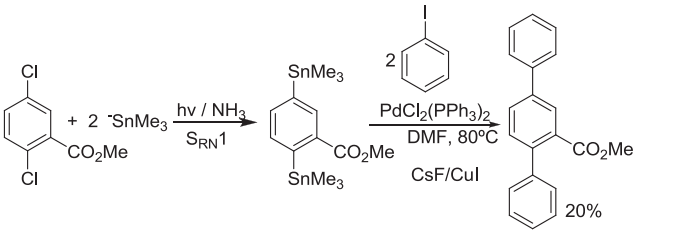
ligands for these reactions.[7] Moreover, electron deficient aryl chlorides react with arylboronic acids.[8] Also, non-active aryl chlorides require using sterically hindered phosphine ligands for these reactions.[3b,9]

One alternative way for substrates having non-reactive chlorides for the Stille reaction may be using stannyl derivatives, since stannyl compounds are good substrates in these reactions.[10] The reaction of $^{-}SnMe_3$ ions with aryl chlorides, by unimolecular Radical Nucleophilic Substitution ($S_{RN}1$),[11] is important to synthesize these stannyl intermediates. A sequence of $S_{RN}1$, followed by a cross-coupling reaction (Stille type) has been developed to obtain polyphenylated compounds as shown in Eq. 2.[12] It is also known that some organostannane compounds have also antifungal activities.[13]



(2)

Our main goal was to synthesize novel environmentally friendly fungicides. Therefore, we decided to investigate the dechlorination of chloro-fungicides in two different ways. In the first approach, we studied a sequence of $S_{RN}1$ followed by a Stille cross-coupling reaction, catalyzed by Pd(0). This methodology involves two steps, with the first providing a simple method for the preparation of compounds bearing trimethylstannyl groups. The second approach consists of a simple and efficient one step procedure for the Suzuki coupling of chloro-fungicides with organoboron compounds.

2. Results and discussion

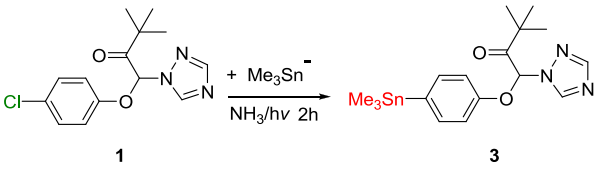
2.1. Tandem reactions: $S_{RN}1$ followed by Stille

Reactions of triadimefon (**1**) and cyproconazole (**2**) with Me_3Sn^{-} gave organostannanes as substitution products through the $S_{RN}1$ mechanism. These stannanes were used as intermediates in Stille reactions, providing arylated products. For instance, the photostimulated reaction of **1** with $^{-}SnMe_3$ ions afforded 36–77% yields of the substitution product (**3**), using liquid NH_3 as the solvent (Eq. 3) (Table 1 entries 1–3). This reaction was catalyzed by light and inhibited by inhibitors of $S_{RN}1$ reactions,[11] such as *p*-dinitrobenzene (*p*-DNB) (Table 1 entries 4 and 5).

Table 1
Reactions of triadimefon (**1**) and cyproconazole (**2**) with $^{-}SnMe_3$ ions in liquid ammonia

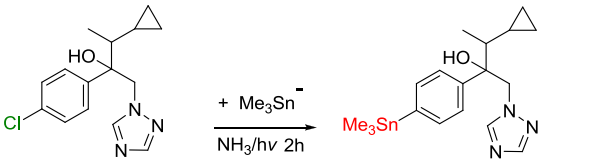
Entry	Substrate (10^{-3} M)	Nucleophile (10^{-3} M)	Conditions (min)	Cl^{-}[a] %	Yield of isolated product
1	**1** (2.0)	$^{-}SnMe_3$ (2.6)	*hν* (60)	55	**3**, 36[b]
2	**1** (2.0)	$^{-}SnMe_3$ (6.0)	*hν* (90)	100	**3**, 77[b]
3	**1** (2.0)	$^{-}SnMe_3$ (6.0)	*hν* (180)	100	**3**, 77
4	**1** (2.0)	$^{-}SnMe_3$ (6.0)	Dark (180)	—	—[c]
5	**1** (2.0)	$^{-}SnMe_3$ (6.0)	*hν*[d] (90)	10	—[c]
6	**2** (2.0)	$^{-}SnMe_3$ (6.0)	*hν* (90)	100	**4**, 98
7	**2** (2.0)	$^{-}SnMe_3$ (6.0)	Dark (90)	10	—[c]
8	**2** (2.0)	$^{-}SnMe_3$ (6.0)	*hν*[e] (90)	—	—[c]

[a] Chloride ions were determined by potentiometry.
[b] 5–10% chlorophenol was observed.
[c] Substrate was recovered.
[d] With 30% *p*-DNB added.
[e] With 20% *p*-DNB added.



1 **3** (3)

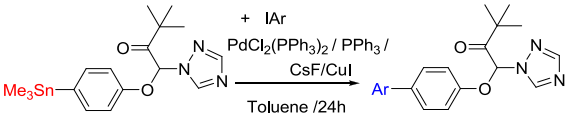
In the same way, the photostimulated reaction of **2** with $^{-}SnMe_3$ ions afforded 98% yields of the substitution product (**4**), using liquid NH_3 as the solvent (Eq. 4) (Table 1 entry 6). This reaction was also light catalyzed and inhibited with *p*-DNB (Table 1 entries 7 and 8).



2 **4** (4)

The stannanes synthesized in Eqs. 3 and 4 are stable organometallic compounds in addition to good nucleophilic coupling partners through Stille reactions, using mild reaction conditions. The Stille reaction has been used as an alternative to the Negishi and Suzuki reactions for substrates with sensitive functional groups. However, the toxicity of organotin compounds has limited their industrial use.

The reaction of **3** with iodobenzene (**5**) and $PdCl_2(PPh_3)_2$ as catalyst in DMF did not occur, showing decomposition of **3** in this solvent (Table 2, entry 1). Nevertheless, using toluene, the coupling reaction was observed. Moreover, the reaction was increased using PPh_3 as ligand, providing 77% yield of **6** (Eq. 5) (Table 2, entries 2–4).



3 **5**, IAr= **IPh** 77%, **6**
7, **1-F,4-IC$_6$H$_4$** 84%, **10**
8, **1-INaph** 5%, **11**
9, **1-I,4-An** 10%, **12**

(5)

Table 2
Stille cross-couplings of **3** with iodobenzene catalyzed by $PdCl_2(PPh_3)_2$ during 48 h[a]

	Catalyst	Ligand	Additive	Solvent	Yield of **6** (%)
1	5 mol % $PdCl_2(PPh_3)_2$	—	CsF, CuI	DMF[b]	—[c]
2	10 mol % $PdCl_2(PPh_3)_2$	—	CsF, CuI	Toluene[d]	5%[e]
3	30 mol % $PdCl_2(PPh_3)_2$	—	CsF, CuI	Toluene[d]	7%[e]
4	10 mol % $PdCl_2(PPh_3)_2$	40 mol % PPh_3	CsF, CuI	Toluene[d]	77%[f]

[a] Concentrations of substrate and nucleophile were 6.0 10^{-2} M.
[b] The reaction was carried out at 80 °C.
[c] Only substrate decomposed.
[d] Reactions were carried out at 100–110 °C.
[e] Only product observed by GC trace with respect to substrate.
[f] Isolated yield.

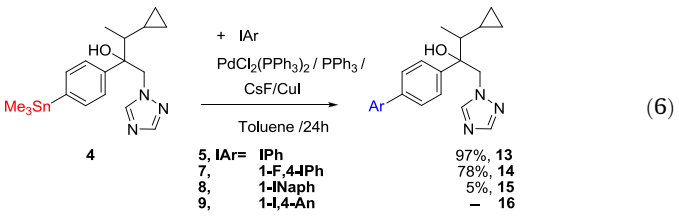
After determining the best reaction conditions for triadimefon (**3**), using **5** as electrophile, we evaluated other electrophiles. Thus, the reaction of **3** with 1-fluoro-4-iodobenzene (**7**), 1-iodonaphthalene (**8**), and 1-iodo-4-methoxybenzene (**9**), rendered 84%, 5%, and 10% yields, respectively (Eq. 4) (Table 3, entries 3, 5, and 7). The reaction using **8** as electrophile gave **11** (5%) together homocoupling product, recovering only **8** (20%) probably due to steric problems. The reaction using **9** as electrophile afforded **12** (10%) together with **6** (25%) as product. In order to understand the formation of **6**, we carried out the reaction changing the catalyst and the ligand for $Pd_2(dba)_3/P(C_6H_{12})$. In these conditions the formation of homocoupling product with Ph is not possible. However, in the reaction **6** was also formed. We can presume that **12** is probably an intermediate for the formation of **6** where the OMe group was lost. Finally, it is worthy to mention that **6** is a compound known with fungicide activity.[14]

Table 3
Stille cross-couplings of triadimefon (**3**) and cyproconazole (**4**) catalyzed by 10 mol % $PdCl_2(PPh_3)_2$, in toluene using 40 mol % PPh_3 and CsF

Entry	Electrophile	Me_3Sn–R	Yield of coupling product (%)[a]
1	**5**, PhI	R=Tr[b]	**6**, 77[c]
2	**5**, PhI	R=Cyp[d]	**13**, 97
3	**7**, 1-F,4-IPh	R=Tr[b]	**10**, 84
4	**7**, 1-F,4-IPh	R=Cyp[d]	**14**, 78
5	**8**, 1-INaph	R=Tr[b]	**11**, 5[e]
6	**8**, 1-INaph	R=Cyp[d]	**15**, 5
7	**9**, 4-IAn[f]	R=Tr[b]	**12**, 10[g]
8	**9**, 4-IAn	R=Cyp[d]	**16**, —[h]

[a] Isolated yield.
[b] Tr as triadimefonyl.
[c] Together with reduced substrate (TrH).
[d] Cyp as cyproconazoyl.
[e] Together homocoupling product, substrate (20%) and substrate decomposed.
[f] An as anisyl.
[g] Together with TrH (5%), substrate (10%) and phenol (5%). The last product indicates substrate decomposition.
[h] Substrate (80%).

In the same way, **4** reacts with iodobenzene and $PdCl_2(PPh_3)_2$ as catalyst in toluene, using PPh_3 as ligand, affording 97% yield of the coupling product (**13**) (Eq. 6) (Table 3, entry 2). In order to synthesize more derivatives; we carried out reactions starting from **4** with **7**, **8**, and **9**, which gave 78%, 5%, and 0% yield, respectively (Eq. 6) (Table 3, entries 4, 6, and 8).



4

5, IAr=	IPh	97%, **13**
7,	1-F,4-IPh	78%, **14**
8,	1-INaph	5%, **15**
9,	1-I,4-An	– **16**

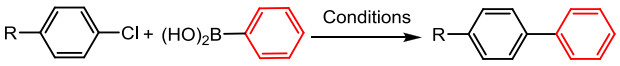
(6)

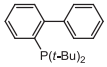
2.2. One step Suzuki coupling

The Suzuki reaction with triadimefon (**1**) and cyproconazole (**2**) can be applied to afford products similar to those found using tandem reactions. In these reactions, chlorinated fungicides react with organoboron compounds, catalyzed by Pd, which could afford cross-coupling products in one step. The stability and weak nucleophilic nature of organoboron compounds has made this reaction very practical. Furthermore, boron compounds are generally non-toxic and the reactions can be done under mild conditions. These facts have made the reaction popular in the pharmaceutical industry.

The reaction of **1** with phenylboronic acid and $Pd(OAc)_2$ at either room temperature or 85 °C did not occur, even using a bigger ligand as $[Pd_2(dba)_3]$. Homocoupling product and triphenylboroxine[15] were present in all reactions. However, **2** reacts with phenylboronic acid and $Pd(OAc)_2$ at 85 °C affording 40% of coupling product (**6**) (Table 4, entry 1).

Table 4
Suzuki cross-couplings of triadimefon (**1**) and cyproconazole (**2**) with phenylboronic acid



Entry	Halide	Catalyst	Ligand	Conditions	Yield of product %
1	**1**	$Pd(OAc)_2$[a]		3 equiv KF, THF 80 °C, 24 h	**6**, 40
2	**1**	Pd/C	DELPhos[d]	TBAB, NaOH, H_2O 140 °C, 6 h	—
3	**1**	Pd/C	Ligandless	2 equiv K_2CO_3, DMA/H_2O[e] 80 °C, 48 h	—
4	**1**	Pd/C		2 equiv K_2CO_3, DMA/H_2O[e] 80 °C, 48 h	**6**, 85[b]
5	**2**	Pd/C		2 equiv K_2CO_3, DMA/H_2O[e] 80 °C, 24 h	**13**, 100[c]

[a] Ac as acetate.
[b] Phenylboronic acid (2 equiv) was added each 12 h (6 equiv of phenylboronic acid were used).
[c] Phenylboronic acid (2 equiv) was added each 12 h (4 equiv of phenylboronic acid were used).
[d] DELPhos: bis(2-diphenylphosphinophenyl)ether.
[e] DMA/H_2O (20/1).

Various aryl chlorides reacted by Suzuki–Miyaura cross-coupling using aqueous conditions.[16] These environmentally friendly conditions utilize ligandless Pd/C (Pd concentrations 0.2–2 mol %), which allows easy separation of the catalyst at the end of the reaction. We carried out reactions of **1** with phenylboronic acid using H_2O and bis(2-diphenylphosphino phenyl)ether (DELPhos) as ligands without observing cross-coupling reaction (Table 4, entry 2).

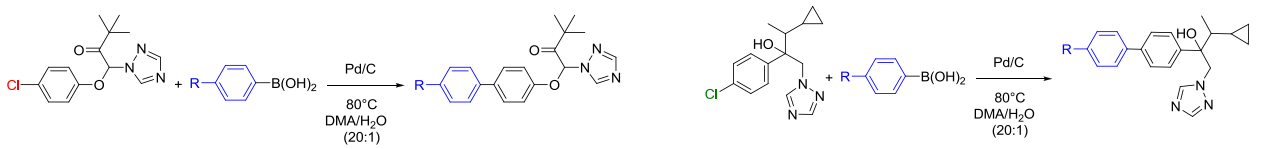
Considering reports from Sowa,[17] we tested reactions of **1** with phenylboronic acid using DMA/H_2O (20/1) with and without ligands. So, the reaction of **1** with phenylboronic acid, ligandless, and Pd/C did not gave a cross-coupling product. However, when biphenylPCy$_2$ was used, 85% **6** was obtained (Table 4, entries 3 and 4). In the same way, **2** rendered 100% cross-coupling product (**13**) using these condition (Table 4, entry 5).

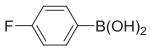
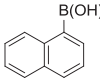
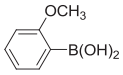
After determining the best condition for the reaction of these compounds with phenylboronic acid as electrophile, we further tested different electrophiles. Thus, the reaction of **1** with *p*-F $C_6H_4B(OH)_2$, naphthalene $B(OH)_2$, and *o*-$MeOC_6H_4B(OH)_2$ rendered 98%, 5%, and 24% yield, respectively (Table 5, entries 1–3).

In order to decrease the reaction time we used a microwave oven. Optimal reaction conditions were found using **1** with phenylboronic acid and Pd/C. We started using the dynamic mode, but the yield of the coupling product was very low (20%). So, we continued using the pulsed mode at 85 °C, which rendered 40% of the product.

Finally, we increased the temperature to 105 °C, affording the best yield for the cross-coupling product **6** (97%, Table 6, entries

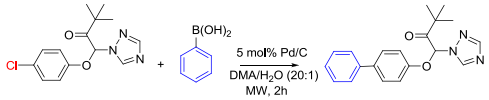
Table 5
Suzuki coupling of triadimefon (**3**) and cyproconazole (**4**) with different boronics acids and (2-biphenyl)dicyclohexylphosphine as ligand



Entry	$RC_6H_4B(OH)_2$	Yield (%) of product from **1**		Yield (%) of product from **2**	
		Conventional[a] (48 h)	MW[b] (4 h)	Conventional[a] (48 h)	MW[b] (4 h)
1		**10**, 98[c]	**10**, 95[d]	**14**, 92%[c]	**14**, 83%[d]
2		**11**, 5[e]	**11**, 5%[e]	**15**, 36%[c]	**15**, 56%[d]
3		**17**, 24%[e]	**17**, 26%[e]	**18**, 24%[e]	**18**, 23%[e]

[a] Arylboronic acid (2 equiv) was added each 12 h (4 equiv of arylboronic acid were used, except with 4-fluorophenylboronic acid that 2 equiv was used).
[b] Arylboronic acid (2 equiv) was added each 2 h (4 equiv of arylboronic acid were used, except with 4-fluorophenylboronic acid that 3 equiv and 3 h of reaction were used).
[c] Isolated yields.
[d] Products rendered with GC using internal standard.
[e] Organic products were determined by GC using relative areas.

Table 6
Microwave-mediated Suzuki coupling of triadimefon (**3**) and phenylboronic acid[a]



Entry	Conditions	Yield (%)
1	T°=80 °C. Dynamic mode	**6**, 20
2	T°=80 °C. Microwave irradiation=50 W	**6**, 40
3	T°=105 °C. Microwave irradiation=50 W	**6**, 97

[a] Arylhalide (0.5 mmol), 1 mmol of $PhB(OH)_2$, 2 mmol of K_2CO_3, 2.35 mL of DMA with 0.15 mL of water.

1–3). So, we continued subsequent reactions using this last condition. Thus, the reaction of **1** with *p*-$FPhB(OH)_2$, naphthalene $B(OH)_2$, and *o*-$MeOC_6H_4B(OH)_2$ rendered 95%, 5%, and 26% yield, respectively (Table 5, entries 1–3). It is worthy to mention that the yield of synthetized products was similar using either conventional heating or microwave irradiation. However, the use of microwave decreased the reaction time considerably.

In the same way, **2** reacted with different arylboronic acid affording cyproconazole derivates (**14**, **15**, and **18**) in variable yields. With **2** as substrate, the reaction using MW irradiation gave also similar yields but lesser reaction time (Table 5, entries 1–3).

3. Conclusions

We have studied two alternative pathways for the arylation of commercial fungicides, allowing the synthesis of new compounds with potential fungicide activity, substituting the chloride atom for less toxic groups, but retaining the triazolic moiety, which could result in new fungicides, with similar activity but less toxic to the environment. The two proposed paths allow the easy arylation of aryl chlorides and can be used alternatively. Moreover, we have shown that using Pd/C and water as solvent, it was possible to afford Suzuki cross-couplings, allowing the efficient synthesis of several substituted fungicides in one step. This catalytic system was also studied under microwave irradiation, lowering the reactiontime considerably. Despite the poor reactivity of aryl chloride in Suzuki reaction, this research shows that aryl chlorides highly functionalized can react effectively under the conditions described.

4. Experimental section

4.1. Reagents

$Sn(CH_3)_3Cl$, halobenzenes, boronic acids, catalysts, ligands, CsF, CuI, and K_2CO_3 were commercially available and used as received. Liquid ammonia was distilled under nitrogen and metallic Na. Toluene was also distilled under nitrogen. Both were used immediately after the distillation.

4.2. General methods

Irradiation was performed in a reactor equipped with two 400-W UV lamps, with maximal emission at 350 nm (Philips Model HPT, water-refrigerated). ^1H and ^{13}C NMR spectra were recorded on a High Resolution Spectrometer Advance 400 (working frequency 400 MHz and 100 MHz, respectively), at ambient temperature in $CDCl_3$ (Aldrich). Radial chromatography separations were achieved on a chromatotron 7924. Mass spectra were recorded on a Bruker, MicroTOF Q II equipment, operated with an ESI source operated in (positive/negative) mode, using nitrogen as nebulizing and drying gas and sodium formiate 10 mM as internal calibrant. MW-induced reactions were performed in a single mode instrument (CEM Focused Microwave™ Synthesis System, Model Discover) equipped with noncontact infrared sensor to measure the temperature, direct pressure control system by measurement of pressure of the reaction vessel contents, and cooling system by compressed air.

The melting points were determined on a Büchi 510 fusiometro without correction. The potentiometric titration of halides in the aqueous phases was carried out using a pH meter Model 420A Digital Seybold, equipped with Ag/Ag^+ electrode.

*4.2.1. Photostimulated reactions of **1** or **2** with $^{-}Sn(CH_3)_3$ anions in liquid ammonia.* The following procedure is representative of these reactions. $Sn(CH_3)_3Cl$ (1.5 mmol) and metallic Na (3.6 mmol, 20% excess) were added to 150 mL of distilled ammonia. Na was added slowly in small pieces until total fade occurred. Then, 20 min after the last addition, when no more solid was present, the Me_3Sn^{-} ions were ready for use (characterized by a lemon yellow solution).

Substrate **1** or **2** (0.5 mmol) was added to the solution and the reaction mixture irradiated for 90 min. The reaction was then quenched with an excess of ammonium nitrate and the ammonia allowed to evaporate under a hood. The solid was dissolved in water and extracted with dichloromethane. The organic extract was analyzed by GC and the products were isolated by vacuum distillation using a Kügelrohr equipment.

*4.2.2. Dark reactions of **1** or **2** with $^{-}Sn(CH_3)_3$ anions in liquid ammonia.* This procedure was similar to that for the previous reaction, except that the reaction flask was wrapped with aluminum foil.

4.2.3. Inhibited reactions with $^{-}Sn(CH_3)_3$ anions in liquid ammonia. The procedure was similar to the above reactions, except that 20 mol % of *p*-DNB was added to the solution of the nucleophile before adding the substrate.

4.2.4. Stille cross-coupling reactions catalyzed by Pd. The following procedure is representative for all Stille-type reactions. In a Schlenk tube, equipped with nitrogen and magnetic stirrer, CsF (0.474 mmol) was added and heated for 3 h in vacuum. After that $PdCl_2(PPh_3)_2$ (0.024 mmol), PPh_3 (0.096 mmol), CuI (0.024 mmol) were added, respectively. The tube was deoxygenated and refilled with nitrogen three times before adding toluene (3 mL). Next, the corresponding organotin compound (0.237 mmol in 2 mL of toluene) and PhI (0.237 mmol) were added to the reaction mixture. The solution was heated at 100 °C for 48 h. After the reaction was cooled, water was added followed by extraction with dichloromethane. Reaction products were isolated by column chromatography or by radial thin layer chromatography.

4.2.5. Suzuki cross-coupling reactions catalyzed by Pd. The following procedure is representative for all Suzuki-type reactions. In a Schlenk tube with magnetic stirring and nitrogen, Pd/C (0.025 mmol), phenylboronic acid (1 mmol), K_2CO_3 (1 mmol), and ligand (0.011 mmol) were added, respectively. Next, a mixture of dimethylacetamide (2.35 mL) and water (0.15 mL) was added to the reaction mixture. The tube was deoxygenated and refilled with nitrogen three times before adding **1** or **2** (0.5 mmol). The reaction was heated to 80 °C for 48 h. After, the reaction was cooled, water was added followed by extraction with dichloromethane. The organic extract was analyzed by GC and GC–MS. Products were isolated by column chromatography, radial thin layer chromatography or preparative chromatography plate.

4.2.6. Suzuki cross-coupling reactions catalyzed by Pd in microwave oven. This procedure was similar to that for the previous reaction, except that the reaction was irradiated with microwave.

4.3. Isolation and characterization

*4.3.1. 3,3-Dimethyl-1-(1H-1,2,4-triazol-1-yl)-1-(4-(trimethylstannyl) phenoxy)butan-2-one (**3**).* The product was isolated as dark brown oil after Kügelrohr distillation (120–125 °C/1°mmHg). MS (EI^+) *m*/*z* (%): 423 (1), 408 (86), 340 (3), 338 (1), 323 (6), 241 (14), 243 (19), 255 (4), 189 (66), 165 (30), 57 (100). ^1H NMR (400 MHz, $CDCl_3$), δ (ppm): 0.26 (s, 9H); 1.30 (s, 9H); 6.96 (s, 1H); 6.98–7.00 (d, 2H, *J*=8.54 Hz); 7.40–7.42 (d, 2H, *J*=8.54 Hz); 7.97 (s, 1H); 8.44 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): −9.18; 26.5; 44.1; 83.5; 115.8; 130.4; 137.7; 144.2; 151.8; 156.2; 203.2. HRMS $[MNa]^+$ exact mass calcd for $C_{17}H_{25}N_3O_2Sn$ 446.0866, found: 446.0898.

*4.3.2. 3-Cyclopropyl-1-(1H-1,2,4-triazol-1-yl)-2-(4-(trimethyl stannyl)phenyl)butan-2-ol (**4**).* The product was isolated as yellow oil after Kügelrohr distillation (120–125 °C/1 mmHg). MS (EI^+) *m*/*z* (%): 421 (1), 420 (2), 419 (1), 418 (2), 406 (40), 405 (18), 404 (34), 403 (18), 402 (18), 356 (15), 353 (13), 352 (69), 351 (28), 350 (54), 349 (21), 348 (30), 269 (36), 268 (14), 267 (32), 266 (15), 265 (20), 208 (25), 207 (100), 186 (40), 165 (37), 163 (30), 161 (19), 135 (19), 133 (23), 119 (17). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) −0.023–0.15 (m, 2H); 0.15–0.24 (d, *J*=2.65 Hz, 9H); 0.36–0.64 (m, 3H); 0.67–0.91 (m, 2H); 0.99 (d, *J*=6.83 Hz, 2H); 1.05–1.20 (m, 1H); 1.21–1.32 (m, 1H); 4.11–4.41 (d, 1H); 4.44–4.58 (dd, *J*=14.01, 2.54 Hz, 1H); 4.93–5.05 (dd, *J*=14.01, 6.13 Hz, 1H); 5.28 (br s, OH); 7.16 (d, *J*=7.71 Hz, 1H); 7.29–7.39 (m, 3H); 7.68 (d, 1H); 7.79 (d, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) −9.2; 3.1; 3.2; 6.4; 7.8; 13.1; 13.7; 14.7; 15.4; 47.5; 47.9; 57.4; 58.46; 79.7; 80.1; 125.0; 126.1; 135.6; 135.9; 141.20; 141.27; 141.3; 142.9; 144.3; 144.6; 151.8. HRMS $[MH]^+$ exact mass calcd for $C_{18}H_{27}N_3OSn$ 422.1252, found: 422.1231.

*4.3.3. 1-(Biphenyl-4-yloxy)-3,3-dimethyl-1-(1H-1,2,4-triazol-1-yl) butan-2-one (**6**).* The product was isolated as white solid after column chromatography using ethyl acetate. ^1H NMR (400 MHz, $CDCl_3$), δ (ppm): 1.32 (s, 9H); 6.99 (s, 1H); 7.04–7.10 (d, 2H, *J*=8.49 Hz); 7.29–7.36 (t, 1H, *J*=7.15 Hz); 7.38–7.45 (t, 2H, *J*=7.15 Hz); 7.47–7.55 (d, 2H, overlapping, *J*=8.49 Hz); 7.47–7.55 (m, 2H); 8.00 (s, 1H); 8.49 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 26.1; 44.1; 83.8; 116.4; 127.2; 127.6; 129.0; 129.2; 137.5; 140.4; 144.3; 151.9; 155.4; 203.1. MS (EI^+) *m*/*z* (%): 335 (12), 281 (5), 265 (3), 250 (100), 223 (3), 208 (10), 169 (33), 85 (15), 69 (2), 57 (85). HRMS $[MH]^+$ exact mass calcd for $C_{20}H_{21}N_3O_2$ 336.1707, found: 336.1714. Mp: 125.5–126.5 °C.

*4.3.4. 1-(4′-Fluorobiphenyl-4-yloxy)-3,3-dimethyl-1-(1H-1,2,4-triazol-1-yl)butan-2-one (**10**).* The product was isolated as white solid after column chromatography using ethyl acetate. ^1H NMR (400 MHz, $CDCl_3$), δ (ppm): 1.32 (s, 9H); 6.98 (s, 1H); 7.03–7.13 (dd, 4H, *J*=8.59 Hz); 7.41–7.48 (m, 4H); 8.00 (s, 1H); 8.49 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 26.5; 44.1; 83.7; 115.9; 116.1; 116.5; 128.7; 128.8; 128.9; 136.5; 144.3; 151.9; 155.3; 203.0. MS (EI^+) *m*/*z* (%)=284 (2), 283 (18), 282 (100), 263 (3), 207 (3), 200 (8), 199 (54), 186 (7), 171 (12), 170 (23), 83 (46), 69 (17), 55 (13). HRMS $[MH]^+$ exact mass calcd for $C_{20}H_{20}FN_3O_2$: 354.1612, found: 354.1608. Mp: 107.3–108.7 °C.

*4.3.5. 3,3-Dimethyl-1-(4-(naphthalen-1-yl)phenoxy)-1-(1H-1,2,4-triazol-1-yl)butan-2-one (**11**).* The product was isolated as colorless oil after preparative thin layer chromatography using ethyl acetate. ^1H NMR (400 MHz, $CDCl_3$), δ (ppm): 1.25 (s, 9H); 7.34–7.61 (m, 7H); 7.82 (d, 1H, *J*=6.91 Hz); 7.84–7.96 (dd, 4H, *J*=8.11 Hz); 8.41 (s, 1H); 8.43 (s, 1H). MS (EI^+) *m*/*z* (%)=387 (3), 386 (13), 385 (42), 301 (19), 300 (84), 273 (7), 272 (22), 246 (6), 245 (4), 233 (6), 232 (229), 231 (28), 222 (2), 220 (50), 219 (99), 204 (10), 203 (50), 202 (56), 201 (15), 192 (39), 191 (23), 190 (31), 189 (44), 57 (100). HRMS $[MH]^+$ exact mass calcd for $C_{24}H_{23}N_3O_2$: 386.1869, found: 386.1871.

*4.3.6. 1-(4′-Methoxybiphenyl-4-yloxy)-3,3-dimethyl-1-(1H-1,2,4-triazol-1-yl)butan-2-one (**12**).* The product was isolated as white solid after preparative thin layer chromatography using dichloromethane. ^1H NMR (400 MHz, $CDCl_3$), δ (ppm): 1.30 (s, 9H); 3.82 (s, 3H); 6.84–7.14 (m, 5H); 7.35–7.57 (dd, 4H, *J*=8.67 Hz); 7.98 (s, 1H); 8.47 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 26.4; 31,2; 55,6; 83.8; 114.6; 116.1; 116.3; 128.2; 128.5; 130.4; 133.0; 144.2; 151.8; 155.5; 207.3. MS (EI^+) *m*/*z* (%)=366 (3), 365 (13), 280 (9), 252 (5), 211 (5), 200 (15), 199 (100),

183 (6), 171 (13), 168 (5), 156 (6), 140 (5), 139 (7), 128 (8), 57 (21). HRMS $[MH]^+$ exact mass calcd for $C_{21}H_{23}N_3O_3$: 366.1818, found: 366.1820.

*4.3.7. 1-(2′-Methoxybiphenyl-4-yloxy)-3,3-dimethyl-1-(1H-1,2,4-triazol-1-yl)butan-2-one (**17**).* The product was isolated as white solid after preparative thin layer chromatography using dichloromethane. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 1.27 (s, 9H); 3.87 (s, 3H); 6.99 (s, 1H); 7.08–7.15 (dd, 4H, J=8.55 Hz); 7.45–7.51 (m, 4H); 8.11 (s, 1H); 8.57 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 25.4; 43.3; 54.1; 83.8; 115.2; 128.3; 128.6; 129.7; 129.9; 138.5; 141.6; 144.8; 154.9; 157.4; 203.7. MS (EI^+) m/z (%)=367 (1), 366 (8), 365 (32), 281 (18), 280 (100), 253 (6), 252 (29), 212 (19), 211 (23), 200 (22), 199 (39), 185 (8), 183 (15), 168 (33), 139 (14), 128 (21), 57 (78). HRMS $[MH]^+$ exact mass calcd for $C_{21}H_{23}N_3O_3$: 366.1818, found: 366.1820.

*4.3.8. 2-(Biphenyl-4-yl)-3-cyclopropyl-1-(1H-1,2,4-triazol-1-yl)butan-2-ol (**13**).* The product was isolated as colorless oil after column chromatography using dichloromethane/ethyl acetate (80/20). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 0.28–0.72 (m, 7H); 1.06 (d, 3H, J=7.07 Hz); 1.29–1.41 (m, 1H); 4.44 (br s, OH); 4.56 (d, 1H, J=13.5 Hz, overlapping); 5.00 (d, 1H, J=13.5 Hz, overlapping) 7.36–7.61 (m, 4H, overlapping); 7.78 (s, 1H); 7.88 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 3.2; 6.5; 13.7; 14.8; 47.6; 57.5; 79.8; 125.9; 26.8; 127.0; 127.3; 127.7; 129.1; 140.1; 140.6; 140.7; 144.6; 151.9.

Minor isomer ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 0.028–0.72 (m, 7H), 0.91 (d, 3H, J=7.07 Hz); 1.16–1.29 (m, 1H); 4.25 (br s, OH); 4.56 (d, 1H, J=13.5 Hz, overlapping); 5.00 (d, 1H, J=13.5 Hz, overlapping) 7.36–7.61 (m, 4H, overlapping); 7.78 (s, 1H); 7.88 (s, 1H).

MS (EI^+) m/z (%): 267 (2), 266 (18), 265 (100), 197 (3), 196 (1), 182 (53), 180 (1), 168 (29), 154 (13), 82 (14), 69 (11). HRMS $[MH]^+$ exact mass calcd for $C_{21}H_{23}N_3O$: 334.1914, found: 334.1914.

*4.3.9. 3-Cyclopropyl-2-(4′-fluorobiphenyl-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol (**14**).* The product was isolated as colorless oil after radial chromatography using ethyl acetate. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 0.015–0.80 (m, 6H), 1.05 (d, 3H, J=6.62 Hz); 1.21–1.29 (m, 1H); 4.24 (br s, OH); 4.53 (d, 1H, J=14.03 Hz, overlapping); 4.99 (d, 1H, J=14.03 Hz, overlapping) 7.05–7.56 (m, 8H, overlapping); 7.78 (s, 1H); 7.88 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 3.2; 6.5; 13.7; 14.8; 47.6; 57.5; 79.8; 125.9; 26.8; 127.0; 127.3; 127.7; 129.1; 140.1; 140.6; 140.7; 144.6; 151.9. MS (EI^+) m/z (%): 284 (1), 283 (16), 282 (100), 264 (3), 249 (1), 214 (2), 200 (7), 199 (54), 186 (6), 185 (43), 82 (38), 69 (11). HRMS $[MH]^+$ exact mass calcd for $C_{21}H_{22}FN_3O$: 352.1820, found: 352.1823.

*4.3.10. 3-Cyclopropyl-2-(4-(naphthalen-1-yl)phenyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol (**15**).* The product was isolated as white solid after preparative thin layer chromatography using dichloromethane/ethyl acetate (75/25). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 0.016–0.77 (m, 7H); 1.12 (d, 3H, J=6.62 Hz); 1.26 (m, 1H); 4.96 (br s, OH); 4.53 (d, 1H, J=14.03 Hz, overlapping); 4.99 (d, 1H, J=14.03 Hz, overlapping) 7.11–7.53 (m, 8H, overlapping); 7.78 (s, 1H); 7.88 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 3.2; 6.6; 13.8; 14.9; 47.7; 57.5; 79.9; 125.6; 126.1; 126.4; 126.9; 127.3; 127.9; 128.0; 128.6; 129.8; 131.9; 134.1; 139.8; 140.4; 140.7; 141.8. MS (EI^+) m/z (%): 383 (1), 365 (1), 315 (26), 314 (100), 297 (6), 296 (12), 232 (10), 231 (46), 203 (26), 202 (46), 82 (18), 69 (15). HRMS $[MH]^+$ exact mass calcd for $C_{25}H_{25}N_3O$: 384.2070, found: 384.2084.

*4.3.11. 3-Cyclopropyl-2-(2′-methoxybiphenyl-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol (**18**).* The product was isolated as colorless oil after preparative thin layer chromatography using ethyl acetate. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 0.03–1.39 (m, 5H); 1.65 (s, 3H); 2.04 (s, 1H); 3.84 (s, 3H); 5.12 (br s OH overlapping); 4.82–5.25 (m, 2H, overlapping); 6.90–7.03 (m, 2H); 7.38–7.75 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 1.4; 55.7; 114.3; 114.4; 114.5; 114.6; 128.7; 128.8; 128.9; 129.0; 132.1; 132.2; 132.3; 132.4; 132.5; 132.6; 132.7; 134.2; 134.3; 134.4; 134.5; 162.8. MS (EI^+) m/z (%): 296 (2), 295 (23), 294 (100), 253 (5), 252 (10), 251 (8), 190 (7), 189 (37), 188 (18), 176 (9), 174 (10), 161 (8), 159 (9), 147 (10), 146 (10), 135 (7), 134 (14), 133 (19), 105 (58), 104 (13), 91 (22), 77 (19). HRMS $[MH]^+$ exact mass calcd for $C_{22}H_{25}N_3O_2$: 364.2025, found: 364.2030.

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