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ORIGINAL PAPER

A modular synthesis of 1,4,5-trisubstituted 1,2,3-triazoles with ferrocene moieties

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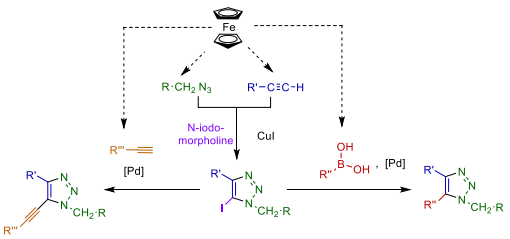
Abstract Regioselective synthesis of 1,2,3-triazoles with ferrocenyl moieties in positions 1, 4, and 5 was carried out in a two-step reaction sequence: a copper-mediated azide–alkyne cycloaddition followed by a palladium-catalyzed cross-coupling. A new route towards 5-iodo-1,2,3-triazoles was developed using *N*-iodomorpholine hydrogen iodide, instead of the corrosive and toxic ICl, as the I^+ source. The novel methodology together with a consecutive Suzuki or Sonogashira reaction was shown to be a useful procedure for the synthesis of a wide range of ferrocenyl 1,2,3-triazoles with di- and triferrocenyl derivatives among them.

Graphical abstract



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Introduction

The 1,2,3-triazole moiety can be found in a great variety of pharmacologically active compounds bearing antimicrobial, antimycobacterial, antimalarial, antiviral, or anticancer effect [1, 2]. The efficiency and action of these compounds may strongly depend on the nature and position of the substituents of the triazole ring.

Grafting a ferrocene moiety into molecules with biological interest may lead to an increase in the activity of the parent compound [3–7]. 1,4- and 1,5-disubstituted-1,2,3-triazole benzenesulfonamides obtained from ethynylferrocene showed inhibition of carbonic anhydrase, so they are possible candidates in an anticancer therapy [8]. 1-Ferrocenyl-1,2,3-triazoles were used efficiently as anion and cation sensors [9], taking advantage of the presence of the ferrocenyl moiety that enables the electrochemical detection of ferrocene derivatives or host–guest complexes derived thereof [10]. Recently, electron transfer properties of heterocycles with multiple ferrocenyl units were investigated in detail [11].

The most versatile method for the synthesis of 1,4-disubstituted triazoles is the copper-catalyzed azide–alkyne cycloaddition (CuAAC) [12, 13] that can be carried out efficiently even under flow conditions [14] with the use of suitable ligands. The CuAAC reaction has been used extensively for the synthesis of 1-ferrocenyl- or 4-ferrocenyl-1,2,3-triazoles [15]. 1,5-Disubstituted 1,2,3-triazoles can be obtained selectively by carrying out the cycloaddition in the presence of ruthenium catalysts [16]. At the same time,

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development of reaction routes towards 1,4,5-trisubstituted triazoles has gained attention only recently.

5-Alkynyl-1,2,3-triazoles can be prepared directly in the reaction of terminal alkynes and organic azides in the presence of a copper catalyst [17]. The same reaction can be carried out with organic azides formed in situ from alkyl halides and sodium azides [18]. However, in these reactions, the substituents on C-4 and C-5 cannot be varied independently, as both of them are derived from the same alkyne component.

Regiocontrolled synthesis of 1,4,5-trisubstituted triazoles can be affected either by the direct arylation of 1,4-disubstituted triazoles at elevated temperature (140 °C) in the presence of a copper catalyst, a strong base, and a threefold excess of an aryl iodide [19] or by palladium-catalyzed coupling reactions of 5-iodo-1,2,3-triazoles under mild conditions (Suzuki, Heck, and Sonogashira reaction [20], Sonogashira coupling [21–23], Suzuki coupling [24, 25], Stille coupling [26], Intramolecular Heck reaction [27, 28], Intramolecular homo coupling [29, 30]).

The starting material of the latter reaction, 5-iodo-1,2,3-triazoles, can be produced using either a catalytic or a stoichiometric amount of a copper salt. The most elegant route involves the copper-catalyzed cycloaddition of organic azides and iodoalkynes ([25], Intramolecular Heck reaction [27], Intramolecular homo coupling [29–32]) (a similar reaction for the synthesis of 5-bromo-1,2,3-triazoles from bromoalkynes was reported by Rutjes [33]). Although the two-step reaction, the conversion of the terminal alkyne into a 1-iodoalkyne in the presence of *N*-iodomorpholine hydrogen iodide as the iodine source, and the cycloaddition can be carried out in one pot [25], special ligands should be used in most cases in order to achieve good results in triazole formation. As a consequence, several methods were published for the synthesis of the iodotriazoles directly from terminal alkynes.

The copper(I) triazolide intermediate of the copper-catalyzed azide–alkyne cycloaddition can be trapped by electrophilic reagents such as ICl [34]. CuI as copper source can be used in a dual role: as a catalyst for the azide–alkyne 1,3-dipolar cycloaddition and as the source of iodine to be introduced into the triazole [35]. In these reactions, an oxidizing agent, such as NBS (Sonogashira coupling [21, 35]), NCS [36], or NIS [37] is also added to convert I^- to I^+. As a consequence, both CuI and the oxidizing agent should be present in at least equimolar amounts to the reactants. Another possibility is the application of $Cu(ClO_4)_2$ [38, 39] or $CuCl_2$ [37] together with NaI or KI to produce a copper(I) catalyst and triiodide as the electrophile [38].

During the quest for optimal conditions for the synthesis of ferrocene-substituted 5-iodo-1,2,3-triazoles, we found that *N*-iodomorpholine hydrogen iodide, instead of the corrosive and toxic ICl, can efficiently be used as the source of the I^+ electrophile to capture the copper(I) triazolide intermediate of the azide–alkyne cycloaddition. By this methodology and a further functionalization of the iodotriazoles in coupling reactions, a wide range of ferrocene-labeled 1,4,5-trisubstituted 1,2,3-triazoles were obtained.

Results and discussion

Homogeneous catalytic reactions were proved to be versatile tools for the functionalization of the ferrocene core [40, 41]. In the course of our ongoing interest in the use of this methodology in labeling of biologically active molecules with ferrocene [42–44], we decided to explore the possibility of the regioselective introduction of the ferrocene moiety to various positions of the 1,2,3-triazole ring. The synthetic strategy involved the synthesis of 5-iodo-1,2,3-triazoles, followed by a palladium-catalyzed coupling. The ferrocene moiety can be incorporated in any of the three reactions partners, the azide or the alkyne of the cycloaddition step, or the organometallic reagent of the palladium-catalyzed cross-coupling (Scheme 1).

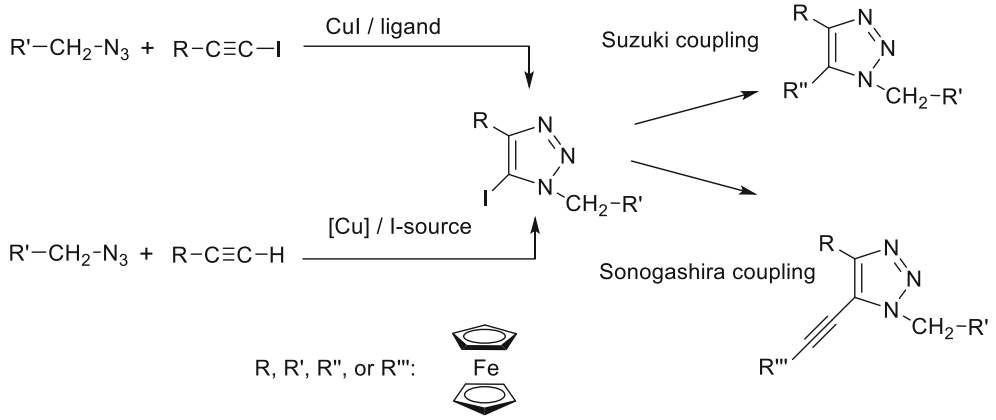
To the best of our knowledge, there is only one example for the synthesis of a ferrocene-substituted 5-iodo-1,2,3-triazole, obtained from ethynylferrocene and benzyl azide in the presence of the CuI/ICl system (Stille coupling, [26]). So we undertook to investigate and compare the efficiency of possible synthetic routes towards 5-iodo-1,2,3-triazoles bearing the ferrocene moiety in different positions.

In the model reaction, ferrocenylmethyl azide (**1a**) was chosen as the ferrocene-substituted reaction partner. First, the synthesis of 1-(ferrocenylmethyl)-5-iodo-4-phenyl-1,2,3-triazole (**3a**) was attempted in a copper-catalyzed cycloaddition with 1-iodo-2-phenylacetylene (**2**) (Scheme 2) in the presence of amine ligands (Table 1).

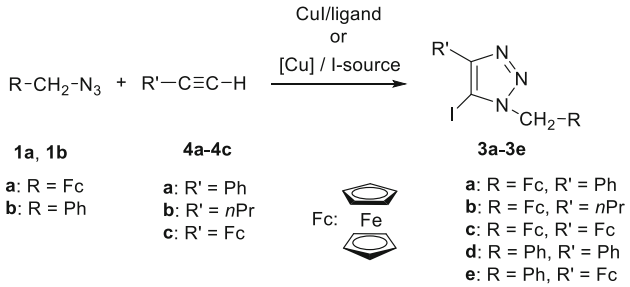
The formation of the desired product could be observed by TLC using the CuI/Et_3N catalytic system, but an isolable amount of **3a** was obtained only by increasing the ratio of the copper catalyst from 5 to 25 mol% (Table 1, entry 2). The change of the amine ligand to TBTA (*N*,*N*,*N*-tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine) clearly enhanced the reaction rate, but the yield of the product could not be increased (entry 4). Nevertheless, in the presence of TBTA, the same result was obtained in a shorter reaction time and with a lower amount of catalyst. It should also be mentioned that yields could not be increased further by the use of longer reaction times with either of the two catalytic systems.

Next, the application of a stoichiometric amount of copper was taken into consideration. Both the CuI/ICl and

Scheme 1



Scheme 2



the $CuCl_2{\cdot}2H_2O$/NaI reagents were found to give superior results (Table 2, entries 1, 2) compared to the catalytic reactions. Although $CuCl_2{\cdot}2H_2O$/NaI probably generates CuI/I_2, Brotherton et al. found that the in situ system was more reactive than the pure forms of CuI and I_2 [38]; as a consequence, we decided to test the efficiency of the former reagent. Shorter reaction times than those indicated in the table, gave considerably lower conversions. Longer reaction times led to a decrease in the yield showing the decomposition of the product (entries 3, 4).

As *N*-iodomorpholine hydrogen iodide was previously found to be an efficient iodinating agent in the copper-catalyzed conversion of terminal alkynes to iodoalkynes [45], as well as in the in situ generation of iodoalkynes during a hydroamination reaction [42–44], the possibility of the use of this compound as the iodine source was investigated. Fokin's group observed that the addition of *N*-iodomorpholine to a mixture of the organic azide and the terminal alkyne resulted in the formation of 1-iodoalkyne but failed to give the cycloaddition product [25]. Nevertheless, to our satisfaction we found that using a stoichiometric amount of copper and Et_3N as ligand, **3a** was obtained in comparable yield in the presence of *N*-iodomorpholine to that achieved with $CuCl_2{\cdot}2H_2O$/NaI, although in longer reaction time (entry 5). It should be mentioned, however, that under our conditions, the product appeared to be less sensitive to decomposition (entry 6).

Other 5-iodo 1,2,3-triazoles (**3c**–**3e**) were also obtained in good yield by the same methodology (entries 11–14), which was proved to be more efficient in the synthesis of the known compound **3e** than using CuI/ICl and leading to the product in 60 % yield (Stille coupling, [26]). Besides, the corrosive and toxic ICl could be replaced by a milder reagent. Thus, it was shown that ferrocene could be introduced either into C-4 (**3e**) or N-1 (**3a**, **3b**) or both (**3c**) positions of 5-iodo-1,2,3-triazoles in a cycloaddition

Table 1 Copper-catalyzed azide–alkyne cycloaddition of **1a** and **2**

Entry	Method	CuI/mol%	Ligand	Ligand/**1a** ratio	React. time/h	Yield of **3a**/%[a]
1	A	5	Et_3N	0.4	6	Traces
2	A	25	Et_3N	2	6	23
3	B	5	TBTA	0.05	0.75	Traces
4	B	5	TBTA	0.05	3	22

Reaction conditions: 0.2 mmol **1a**, 0.2 mmol **2**, 1 cm^3 THF, rt

TBTA, *N*,*N*,*N*-tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine

[a] Isolated yield

Table 2 Azide–alkyne cycloaddition of alkynes **4a–4c** and azides **1a**, **1b** in the presence of stoichiometric amount of copper salts

Entry	Alkyne	Azide	Method	Copper salt	Reagent	Reaction time/h	Product	Yield/%[a]
1	**4a**	**1a**	C[b]	CuI	ICl	6	**3a**	32
2	**4a**	**1a**	D[c]	$CuCl_2$	NaI[c]	1.5	**3a**	39
3	**4a**	**1a**	D[c]	$CuCl_2$	NaI[c]	4.5	**3a**	38
4	**4a**	**1a**	D[c]	$CuCl_2$	NaI[c]	7	**3a**	32
5	**4a**	**1a**	E[d]	CuI	*N*-iodomorpholine.HI	5	**3a**	40
6	**4a**	**1a**	E[d]	CuI	*N*-iodomorpholine.HI	16	**3a**	40
7	**4b**	**1a**	D[c]	$CuCl_2$	NaI[c]	1.5	**3b**	47
8	**4b**	**1a**	D[c]	$CuCl_2$	NaI[c]	4.5	**3b**	39
9	**4b**	**1a**	E[d]	CuI	*N*-iodomorpholine.HI	5	**3b**	39
10	**4b**	**1a**	E[d]	CuI	*N*-iodomorpholine.HI	20	**3b**	60
11	**4c**	**1a**	E[d]	CuI	*N*-iodomorpholine.HI	16	**3c**	49
12	**4c**	**1a**	E[d]	CuI	*N*-iodomorpholine.HI	24	**3c**	74
13	**4a**	**1b**	E[d]	CuI	*N*-iodomorpholine.HI	24	**3d**	60
14	**4c**	**1b**	E[d]	CuI	*N*-iodomorpholine.HI	24	**3e**	70

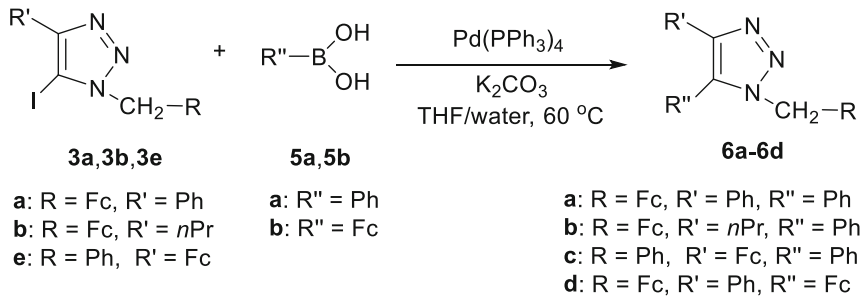
[a] Isolated yield

[b] **1a/4a**/CuI/ICl/Et_3N = 1/1/1/1/1.2, in THF, rt

[c] **1/4**/$CuCl_2$/NaI/Et_3N = 1/1/1/12/1, in acetonitrile, rt

[d] **1/4**/CuI/*N*-iodomorpholine.HI/Et_3N = 1/1/1/1/1.2, in THF, rt

Scheme 3



3a,**3b**,**3e** **5a**,**5b** **6a-6d**

a: R = Fc, R' = Ph
b: R = Fc, R' = *n*Pr
e: R = Ph, R' = Fc

a: R" = Ph
b: R" = Fc

a: R = Fc, R' = Ph, R" = Ph (72%)
b: R = Fc, R' = *n*Pr, R" = Ph (60%)
c: R = Ph, R' = Fc, R" = Ph (86%)
d: R = Fc, R' = Ph, R" = Fc (42%)

reaction starting from the corresponding terminal alkynes under mild conditions. It should be mentioned that no formation of regioisomeric 4-iodotriazoles could be detected in any of the above reactions.

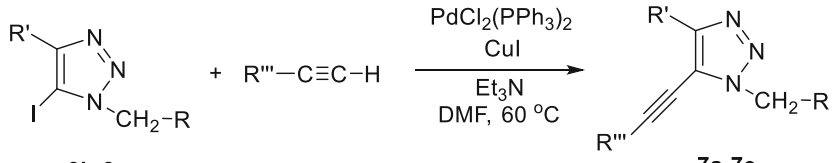
With the 5-iodo-1,2,3-triazoles **3a–3e** in hand, 1,4,5-trisubstituted derivatives were synthesized via Suzuki- (Scheme 3) and Sonogashira coupling reactions (Scheme 4).

Suzuki coupling of 5-iodo-1,2,3-triazoles **3a**, **3b**, **3e** with phenylboronic acid (**5a**) led to the products **6a–6c** in a facile reaction. Coupling of ferrocenylboronic acid (**5b**) was more sluggish but resulted in the formation of **6d** in acceptable yield.

Besides the usual homogeneous catalytic conditions, the reaction of 5-iodo-triazoles **3a**, **3e** with **5a** was carried out in the presence of a supported palladium catalyst (**SILP-Pd**, Fig. 1). In our group, an immobilized palladium catalyst had been produced by supporting palladium on an ionic liquid modified silica that had shown high efficiency in Heck reactions [46]. The same catalyst was found to give excellent results in the Suzuki reaction of the 5-iodo-1,2,3-triazoles giving **6a** and **6c** in 95 and 96 % yields, respectively. Moreover, the catalyst could be recycled with a small loss of activity leading to **6a** in 93 and 88 % yield in the second and third runs, respectively.

Another possibility for the functionalization of 5-iodo-1,2,3-triazoles is the Sonogashira reaction (Scheme 4). The coupling of 4-ferrocenyl derivatives **3c** and **3e** was less facile than their 4-propyl- (**3b**) or 4-phenyl substituted (**3d**)

Scheme 4



3b-3e

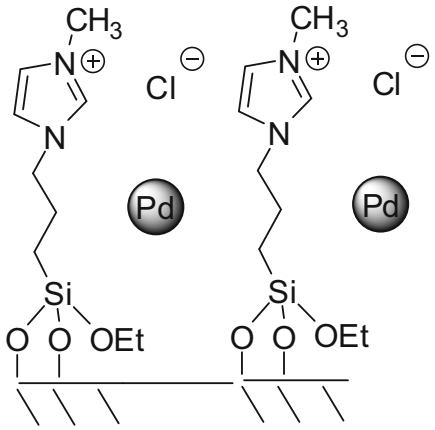
b: R = Fc, R' = *n*Pr
c: R = Fc, R' = Fc
d: R = Ph, R' = Ph
e: R = Ph, R' = Fc

4a, **4c**

a: R''' = Ph
c: R''' = Fc

7a-7e

a: R = Fc, R' = *n*Pr, R''' = Ph (68%)
b: R = Ph, R' = Fc, R''' = Ph (45%)
c: R = Fc, R' = Fc, R''' = Fc (29%)
d: R = Ph, R' = Ph, R''' = Fc (59%)
e: R = Ph, R' = Fc, R''' = Fc (43%)



SILP-Pd

Fig. 1 The supported palladium catalyst (**SILP-Pd**) used in the Suzuki coupling of **3a**, **3e**, and **5a**

counterparts, but even the triferrocenyl triazole **7c** could be produced in 26 % yield.

Conclusions

It was shown that *N*-iodomorpholine hydrogen iodide could be used as an efficient I^+ source in the synthesis of 5-iodo-1,2,3-triazoles starting from terminal alkynes and organic azides. In case of ferrocene substituted substrates, the novel method was proved to be clearly superior to those reported previously. Supplemented by a palladium-catalyzed cross-coupling, such as Suzuki or Sonogashira reaction, 1,4,5-trisubstituted triazoles with ferrocenyl groups in the desired substitution pattern can be obtained. It was demonstrated with two examples that the efficiency of this methodology can be further enhanced by the application of a heterogeneous catalyst in the Suzuki reaction.

Experimental

1-Pentyne (**4b**), ethynylferrocene (**4c**), phenylboronic acid (**5a**), ferrocenylboronic acid (**5b**), copper salts, and palladium complexes were supplied by Sigma-Aldrich, phenylacetylene (**4a**) was a Merck product. 1-Iodo-2-phenylacetylene (**2**) and *N*-iodomorpholine hydrogen iodide [25], TBTA [47], and benzyl azide (**1b**) [48] were synthesized by literature methods. Ferrocenylmethyl azide (**1a**) was obtained [49] from ferrocenylmethanol [50]. Preparation and characterization of the SILP-Pd catalyst has been reported recently [46].

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Inova 400 spectrometer at 400.13 MHz and 100.62 MHz, respectively. Chemical shifts are reported in ppm relative to $CHCl_3$ (7.26 and 77.00 ppm for ^{1}H and ^{13}C, respectively). GC–MS analysis was carried out on a Shimadzu GC–MS-QP2010SE instrument. Mass spectra of **3c**, **6d**, **7c**, and **7e** were obtained by using triple quadruple (QqQ) Micromass Quattro Micro mass spectrometer (Waters, Milford, MA, USA), which was operated in positive electrospray ionization mode. The capillary voltage was 3.0 kV, cone voltage 25 V, source temperature 140 °C. Data acquisition and processing were performed using MassLynx 4.1 software (Waters, Milford, MA, USA). IR spectra were made using a Thermo Nicolet Avatar 330 FT-IR instrument. Samples were prepared as KBr pellets.

Synthesis of 1-(ferrocenylmethyl)-5-iodo-4-phenyl-1,2,3-triazole (3a) with a catalytic amount of copper

Method A 45.6 mg 1-iodo-2-phenylacetylene (**2**, 0.2 mmol) and 48.2 mg ferrocenylmethyl azide (**1a**, 0.2 mmol) were dissolved in 1 cm^3 THF. CuI (0.05 mmol, 9.5 mg) and 55 mm^3 triethylamine (0.4 mmol) were added to the mixture and stirred under argon at room temperature for 6 h. The reaction mixture was purified by column

chromatography (silica, eluent: toluene/ethyl acetate 8/1). **3a** was obtained in 23 % yield (21.6 mg, 0.05 mmol).

Method B 1.9 mg CuI (0.01 mmol) and 5.3 mg TBTA (0.01 mmol) were dissolved in 2 cm^3 THF and stirred for 20 min until a homogeneous solution was formed. 1-Iodo-2-phenylacetylene (**2**, 0.2 mmol, 45.6 mg) and 48.2 mg ferrocenylmethyl azide (**1a**, 0.2 mmol) were solved in 1 cm^3 THF and added to the homogeneous solution. The mixture was stirred for 3 h. The reaction mixture was purified by column chromatography (silica, eluent: toluene/ethyl acetate 8/1). **3a** was obtained in 22 % yield (20.6 mg, 0.04 mmol).

Synthesis of 5-iodo-1,2,3-triazoles 3a–3e with stoichiometric amount of copper

Method C 48.2 mg ferrocenylmethyl azide (**1a**, 0.2 mmol), 38 mg CuI (0.2 mmol), 22 mm^3 phenylacetylene (**4a**, 0.2 mmol) and 32.5 mg ICl (0.2 mmol) were stirred under argon in the presence of 33 mm^3 triethylamine (0.24 mmol) and 2 cm^3 THF under argon at room temperature. The reaction mixture was concentrated and purified by column chromatography (silica, eluent: toluene/ethyl acetate 8/1). **3a** was obtained in 32 % yield (30.0 mg, 0.06 mmol).

Method D 34 mg $CuCl_2 \cdot 2H_2O$ (0.2 mmol) was dissolved under argon in 2 cm^3 acetonitrile. Alkyne **4a** or **4b** (0.2 mmol) and 28 mm^3 triethylamine (0.2 mmol) was added to the solution. NaI (12 eq., 2.4 mmol, 360 mg) was dissolved in 0.2 cm^3 distilled water and the aqueous solution was added to the organic phase. Ferrocenylmethyl azide (**1a**, 0.2 mmol, 48.2 mg) was added to the mixture and stirred at room temperature. The yellow reaction mixture was concentrated and purified by column chromatography (silica, eluent: toluene/ethyl acetate 8/1). The products were obtained in 39 % (**3a**, 36.6 mg, 0.08 mmol) and 47 % (**3b**, 40.9 mg, 0.09 mmol) yield.

Method E (general procedure for the synthesis of 5-iodo-1,2,3-triazoles **3a**–**3e**): The alkyne **4a**–**4c** (0.4 mmol), azide **1a**, **1b** (0.4 mmol), 76 mg CuI (0.4 mmol), and 136.4 mg *N*-iodomorpholine hydrogen iodide (0.4 mmol) were stirred under argon in the presence of 66 mm^3 triethylamine (0.48 mmol) in 2 cm^3 THF at room temperature. The reaction mixture was concentrated and purified by column chromatography (silica, eluent: toluene/ethyl acetate 8/1, toluene/ethyl acetate 15/1).

1-(Ferrocenylmethyl)-5-iodo-4-phenyl-1,2,3-triazole (**3a**, $C_{19}H_{16}FeIN_3$)
Yellow solid; 40 % yield; m.p.: 184–186 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.87$ (d, $J = 7.2$ Hz, 2H), 7.46 (t, $J = 7.2$ Hz, 2H), 7.33 (t, $J = 7.2$ Hz, 1H), 5.34 (s, 2H), 4.50 (s, 2H), 4.28 (s, 5H), 4.24 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 149.9$, 130.5, 128.7, 128.7, 127.6, 81.5, 75.8, 69.5, 69.0, 68.8, 50.8 ppm; IR (KBr): $\bar{\nu} = 3084$, 2925, 2848, 1442, 1328, 1225, 1107, 1041, 976, 813, 776, 698, 482 cm^{-1}; MS (70 eV): m/z (%) = 469 (M^+, 100), 343 (13), 248 (8), 207 (16), 199 (34), 167 (14), 153 (7), 152 (6), 121 (40), 89 (26), 56 (18); $R_f = 0.4$ (toluene/ethyl acetate 15/1).

1-(Ferrocenylmethyl)-5-iodo-4-propyl-1,2,3-triazole (**3b**, $C_{16}H_{18}FeIN_3$)
Yellow solid; 60 % yield; m.p.: 91–93 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.26$ (s, 2H), 4.35 (t, $J = 1.8$ Hz, 2H), 4.15 (s, 5H), 4.12 (t, $J = 1.8$ Hz, 2H), 2.57 (t, $J = 7.3$ Hz, 2H), 1.67 (sext, $J = 7.3$ Hz, 2H), 0.92 (t, $J = 7.3$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 151.9$, 81.7, 77.6, 69.4, 69.0, 68.7, 50.4, 28.2, 22.5, 13.9 ppm; IR (KBr): $\bar{\nu} = 3101$, 2962, 2921, 2848, 1426, 1197, 1102, 1029, 800, 478 cm^{-1}; MS (70 eV): m/z (%) = 435 (M^+, 100), 370 (11), 264 (19), 199 (40), 183 (7), 134 (10), 121 (52), 56 (13); $R_f = 0.25$ (toluene/ethyl acetate 15/1).

4-Ferrocenyl-1-(ferrocenylmethyl)-5-iodo-1,2,3-triazole (**3c**, $C_{23}H_{20}Fe_2IN_3$)
Orange solid; 74 % yield; m.p.: 212–215 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.32$ (s, 2H), 4.98 (t, $J = 1.9$ Hz, 2H), 4.37 (t, $J = 1.9$ Hz, 2H), 4.29 (t, $J = 1.9$ Hz, 2H), 4.17 (s, 5H), 4.15 (t, $J = 1.9$ Hz, 2H), 4.09 (s, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 149.3$, 81.6, 74.8, 73.9, 69.4, 69.0, 68.9, 68.7, 68.5, 66.9, 50.2 ppm; IR (KBr): $\bar{\nu} = 3089$, 2917, 2851, 1409, 1234, 1099, 1021, 997, 805, 478 cm^{-1}; MS (ESI): $m/z = 577$ (M^+); $R_f = 0.34$ (toluene/ethyl acetate 15/1).

*5-Iodo-4-phenyl-1-(phenylmethyl)-1,2,3-triazole (**3d**)*
White solid; 60 % yield; m.p.: 135–138 °C; its spectroscopic data were identical with those reported before [19, 33]; $R_f = 0.43$ (toluene/ethyl acetate 15/1).

*4-Ferrocenyl-5-iodo-1-(phenylmethyl)-1,2,3-triazole (**3e**)*
Yellow solid; 70 % yield; m.p.: 167–170 °C; its spectroscopic data were identical with those reported before [19]; $R_f = 0.38$ (toluene/ethyl acetate 15/1).

General procedure for the Suzuki coupling of 5-iodo-1,2,3-triazoles 3a–3e

A mixture of the 5-iodo-1,2,3-triazole **3a**–**3e** (0.1 mmol), the boronic acid **5a**, **5b** (0.2 mmol), 5.8 mg $Pd(PPh_3)_4$ (0.005 mmol) (or the supported catalyst **SILP-Pd** with the same palladium-content) and 69 mg K_2CO_3 (0.5 mmol) in 1/1 cm^3 THF/distilled water was stirred under argon at 60 °C for 10 h. The product was extracted with CH_2Cl_2 (3 × 2 cm^3). The combined organic phases were dried

over Na_2SO_4 and concentrated. The product was purified by column chromatography (silica, eluent: toluene/ethyl acetate 15/1). In the recycling experiment, the catalyst was removed by simple filtration and was reused without purification.

1-(Ferrocenylmethyl)-4,5-diphenyl-1,2,3-triazole (**6a**, $C_{25}H_{21}FeN_3$)
Yellow solid; 72 % yield; m.p.: 162–164 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.46 (m, 5H), 7.30–7.17 (m, 5H), 5.10 (s, 2H), 4.18 (s, 5H), 4.11 (s, 2H), 4.04 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.3, 133.2, 131.2, 130.4, 129.8, 129.4, 128.5, 128.3, 127.7, 126.9, 81.8, 69.2, 68.9, 68.6, 48.4 ppm; IR (KBr): $\bar{\nu}$ = 3052, 2917, 2845, 1442, 1327, 1245, 1107, 1025, 980, 809, 764, 698, 478 cm^{-1}; MS (70 eV): *m/z* (%) = 419 (M^+, 100), 354 (8), 326 (14), 299 (7), 223 (14), 210 (8), 199 (17), 165 (16), 145 (8), 121 (23), 89 (8), 56 (16); R_f = 0.49 (toluene/ethyl acetate 8/1).

1-(Ferrocenylmethyl)-5-phenyl-4-propyl-1,2,3-triazole (**6b**, $C_{22}H_{23}FeN_3$)
Yellow solid; 60 % yield; m.p.: 90–93 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.44 (m, 3H), 7.22–7.18 (m, 2H), 5.13 (s, 2H), 4.05 (s, 5H), 4.00 (t, J = 1.8 Hz, 2H), 3.92 (t, J = 1.8 Hz, 2H), 2.52 (t, J = 7.3 Hz, 2H), 1.58 (sext, J = 7.3 Hz, 2H), 0.82 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.7, 133.8, 130.0, 129.3, 129.0, 128.1, 82.2, 69.1, 68.9, 68.5, 48.2, 27.2, 23.0, 14.0 ppm; IR (KBr): $\bar{\nu}$ = 3093, 2962, 2929, 2848, 1450, 1266, 1103, 1041, 1009, 805, 756, 702, 478 cm^{-1}; MS (70 eV): *m/z* (%) = 385 (M^+, 100), 320 (14), 292 (9), 223 (11), 199 (19), 135 (9), 121 (31), 56 (14); R_f = 0.28 (toluene/ethyl acetate 8/1).

4-Ferrocenyl-5-phenyl-1-(phenylmethyl)-1,2,3-triazole (**6c**, $C_{25}H_{21}FeN_3$)
Yellow solid; 86 % yield; m.p.: 153–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.42 (m, 3H), 7.27–7.21 (m, 3H), 7.17–7.13 (m, 2H), 7.00–6.95 (m, 2H), 5.35 (s, 2H), 4.45 (s, 2H), 4.15 (s, 2H), 3.98 (s, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.9, 135.5, 132.4, 130.2, 129.6, 128.8, 128.6, 127.9, 127.9, 127.3, 75.7, 69.3, 68.3, 66.6, 51.9 ppm; IR (KBr): $\bar{\nu}$ = 3109, 3036, 2933, 1458, 1221, 1168, 1099, 1066, 997, 808, 768, 739, 706, 498 cm^{-1}; MS (70 eV): *m/z* (%) = 419 (M^+, 100), 325 (14), 300 (69), 197 (23), 165 (11), 153 (14), 152 (12), 141 (21), 121 (46), 91 (23), 56 (13); R_f = 0.23 (toluene/ethyl acetate 15/1).

5-Ferrocenyl-1-(ferrocenylmethyl)-4-phenyl-1,2,3-triazole (**6d**, $C_{29}H_{25}Fe_2N_3$)
Orange solid; 42 % yield; m.p.: 145–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61–7.59 (m, 2H), 7.42–7.35 (m, 3H), 5.65 (s, 2H), 4.39 (s, 2H), 4.36 (s, 2H), 4.24 (s, 2H), 4.19 (s, 5H), 4.17 (s, 2H), 4.02 (s, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.2, 131.9, 129.1, 128.7, 128.1, 127.9, 83.5, 71.9, 69.5, 69.3, 69.0, 69.0, 68.1, 68.1, 47.8 ppm; IR (KBr): $\bar{\nu}$ = 3085, 2921, 2852, 1417, 1335, 1290, 1103, 1005, 821, 780, 735, 702, 486 cm^{-1}; MS (ESI): *m/z* = 528 ($[M+H]^+$); R_f = 0.28 (toluene/ethyl acetate 15/1).

General procedure for the Sonogashira coupling of 5-iodo-1,2,3-triazoles 3a–3e

A mixture of the 5-iodo-1,2,3-triazole **3a**–**3e** (0.1 mmol), the alkyne **4a**–**4c** (0.2 mmol), 3.5 mg $Pd(PPh_3)_2Cl_2$ (0.005 mmol), and 1.0 mg CuI (0.005 mmol) was stirred in 2 cm^3 DMF under argon in the presence of 28 mm^3 triethylamine (0.2 mmol) at 60 °C for 6 h. The solvent was removed in vacuo and the product was purified by column chromatography (silica, eluent: toluene/ethyl acetate 15/1).

1-(Ferrocenylmethyl)-5-(phenylethynyl)-4-propyl-1,2,3-triazole (**7a**, $C_{24}H_{23}FeN_3$)
Orange solid; 68 % yield; m.p.: 78–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.52 (m, 2H), 7.42–7.38 (m, 3H), 5.30 (s, 2H), 4.36 (s, 2H), 4.13 (s, 7H), 2.72 (t, J = 7.4 Hz, 2H), 1.75 (sext, J = 7.4 Hz, 2H), 0.96 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.7, 131.4, 129.4, 128.6, 121.7, 118.1, 100.8, 81.9, 74.8, 69.1, 68.7, 68.5, 48.7, 27.6, 22.2, 13.8 ppm; IR (KBr): $\bar{\nu}$ = 3088, 2958, 2868, 1446, 1324, 1238, 1193, 1107, 1029, 825, 760, 690, 478 cm^{-1}; MS (70 eV): *m/z* (%) = 409 (M^+, 100), 344 (9), 247 (11), 234 (12), 199 (28), 191 (17), 169 (8), 121 (31), 56 (15); R_f = 0.33 (toluene/ethyl acetate 15/1).

4-Ferrocenyl-5-(phenylethynyl)-1-(phenylmethyl)-1,2,3-triazole (**7b**, $C_{27}H_{21}FeN_3$)
Yellow solid; 45 % yield; m.p.: 72–75 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.52 (m, 2H), 7.44–7.39 (m, 3H), 7.36–7.29 (m, 5H), 5.61 (s, 2H), 5.02 (s, 2H), 4.32 (s, 2H), 4.07 (s, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.4, 135.1, 131.5, 129.7, 129.0, 128.9, 128.6, 128.1, 121.9, 116.4, 102.1, 75.8, 74.8, 69.8, 69.3, 67.1, 53.0 ppm; IR (KBr): $\bar{\nu}$ = 3082, 3031, 2925, 2843, 1437, 1266, 1074, 1017, 919, 751, 678, 527 cm^{-1}; MS (70 eV): *m/z* (%) = 443 (M^+, 100), 415 (8), 349 (12), 324 (24), 211 (10), 176 (9), 141 (10), 121 (43), 91 (27), 56 (14); R_f = 0.77 (toluene/ethyl acetate 15/1).

4-Ferrocenyl-5-(phenylethynyl)-1-(ferrocenylmethyl)-1,2,3-triazole (**7c**, $C_{35}H_{29}Fe_3N_3$)
Orange solid; 29 % yield; m.p.: 169–171 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.33 (s, 2H), 5.05 (t, J = 1.8 Hz, 2H), 4.65 (t, J = 1.8 Hz, 2H), 4.43 (t, J = 1.8 Hz, 2H), 4.40 (t, J = 1.8 Hz, 2H), 4.35 (t, J = 1.8 Hz, 2H), 4.34 (s, 5H), 4.21–4.19 (m, 7H), 4.13 (s, 5H) ppm; ^{13}C NMR

(100 MHz, $CDCl_3$): $\delta = 148.1$, 116.4, 101.8, 82.3, 74.9, 72.2, 71.5, 70.0, 69.6, 69.5, 68.9, 68.8, 68.8, 68.4, 66.7, 63.3, 48.5 ppm; IR (KBr): $\bar{\nu} = 3077$, 2925, 2848, 2210, 1413, 1319, 1209, 1099, 1029, 1005, 813, 486 cm^{-1}; MS (ESI): $m/z = 660$ ($[M+H]^+$); $R_f = 0.32$ (toluene/ethyl acetate 15/1).

5-(Ferrocenylethynyl)-4-phenyl-1-(phenylmethyl)-1,2,3-triazole (**7d**, $C_{27}H_{21}FeN_3$)
Yellow solid; 59 % yield; m.p.: 98–103 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.20$–8.18 (m, 2H), 7.46–7.42 (m, 2H), 7.38–7.29 (m, 6H), 5.62 (s, 2H), 4.50 (s, 2H), 4.31 (s, 2H), 4.19 (s, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 147.3$, 134.9, 130.5, 128.8, 128.5, 128.4, 128.3, 127.9, 125.9, 117.9, 102.6, 71.7, 71.6, 70.0, 69.6, 62.7, 52.7 ppm; IR (KBr): $\bar{\nu} = 3105$, 2921, 2848, 2214, 1458, 1352, 1319, 1221, 1102, 1005, 813, 768, 739, 694, 494 cm^{-1}; MS (70 eV): m/z (%) = 443 (M^+, 100), 324 (38), 312 (8), 176 (14), 165 (20), 121 (23), 91 (18), 56 (10); $R_f = 0.48$ (toluene/ethyl acetate 15/1).

4-Ferrocenyl-5-(ferrocenylethynyl)-1-(phenylmethyl)-1,2,3-triazole (**7e**, $C_{31}H_{25}Fe_2N_3$)
Orange solid; 43 % yield; m.p.: 98–101 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.41$–7.32 (m, 5H), 5.61 (s, 2H), 5.05 (t, $J = 1.8$ Hz, 2H), 4.55 (t, $J = 1.8$ Hz, 2H), 4.36–4.33 (m, 4H), 4.23 (s, 5H), 4.12 (s, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 148.4$, 135.1, 128.8, 128.3, 127.7, 116.9, 102.1, 74.7, 71.8, 71.4, 69.9, 69.6, 69.5, 68.8, 66.7, 63.1, 52.6 ppm; IR (KBr): $\bar{\nu} = 3089$, 2917, 2850, 2214, 1406, 1331, 1217, 1107, 1045, 1029, 997, 817, 735, 490 cm^{-1}; MS (ESI): $m/z = 552$ ($[M+H]^+$); $R_f = 0.32$ (toluene/ethyl acetate 15/1).

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References

1. Pibiri I, Buscemi S (2010) Curr Bioact Comp 6:208
2. Siddiqui N, Ahsan W, Alam MS, Ali R, Jain S, Azad B, Akhtar J (2011) Int J Pharm Sci Rev Res 8:161
3. Fouda MFR, Abd-Elzaher MM, Abdelsamaia RA, Labib AA (2007) Appl Organomet Chem 21:613
4. Ornelas C (2011) New J Chem 35:1973
5. Navarro M, Castro W, Biot C (2012) Organometallics 31:5715
6. Braga SS, Silva AMS (2013) Organometallics 32:5626
7. Kilpin KJ, Dyson PJ (2013) Chem Sci 4:1410
8. Salmon AJ, Williams ML, Wu QK, Morizzi J, Gregg D, Charman SA, Vullo D, Supuran CT, Poulsen SA (2012) J Med Chem 55:5506
9. Romero T, Orenes RA, Tárraga A, Molina P (2013) Organometallics 32:5740
10. Molina P, Tárraga A, Caballero A (2008) Eur J Inorg Chem 3401
11. Hildebrandt A, Lang H (2013) Organometallics 32:5640
12. Rostovtsev VV, Green LK, Fokin VV, Sharpless KB (2002) Angew Chem Int Ed 41:2596
13. Tornøe CW, Christensen C, Meldal M (2002) J Org Chem 67:3057
14. Orthaber A, Fuchs M, Belaj F, Rechberger GN, Kappe CO, Pietschnig R (2011) Eur J Inorg Chem 2588
15. Balogh J, Skoda-Földes R (2011) Transition-metal catalyzed reactions in the synthesis of ferrocene. In: Phillips ES (ed) Ferrocenes: compounds, properties and applications. Nova Publishers, USA, pp 107–147
16. Zhang L, Chen X, Xue P, Sun HHY, Williams ID, Sharpless KB, Fokin VV, Jia G (2005) J Am Chem Soc 127:15998
17. Li LJ, Zhang YQ, Zhang Y, Zhu AL, Zhang GS (2014) Chin Chem Lett 25:1161
18. Alonso F, Moglie Y, Radivoy G, Yus M (2012) Synlett 23:2179
19. Ackermann L, Potukuchi HK, Landsberg D, Vicente R (2008) Org Lett 10:3081
20. Deng J, Wu YM, Chen QY (2005) Synthesis 2730
21. Morris JC, Chiche J, Grellier C, Lopez M, Bornaghi LF, Maresca A, Supuran CT, Pouysségur J, Poulsen SA (2011) J Med Chem 54:6905
22. Joubert N, Schinazi RF, Agrofoglio LA (2005) Tetrahedron 61:11744
23. Ostrowski T, Januszczyk P, Cieslak M, Kazmierczak-Baranska J, Nawrot B, Bartoszak-Adamska E, Zeidler J (2011) Bioorg Med Chem 19:4386
24. García-Álvarez J, Díez J, Gimeno J, Suárez FJ, Vincent C (2012) Eur J Inorg Chem 5854
25. Hein JE, Tripp JC, Krasnova LB, Sharpless KB, Fokin VV (2009) Angew Chem Int Ed 48:8018
26. Carcenac Y, David-Quillot F, Abarbri M, Duchêne A, Thibonnet J (2013) Synthesis 45:633
27. Panteleev J, Geyer K, Aguilar-Aguilar A, Wang L, Lautens M (2010) Org Lett 12:5092
28. Schulman JM, Friedman AA, Panteleev J, Lautens M (2012) Chem Commun 48:55
29. Juríček M, Stout K, Kouwer PHJ, Rowan AE (2011) Org Lett 13:3494
30. Bogdan AR, James K (2011) Org Lett 13:4060
31. García-Álvarez J, Díez J, Gimeno J, Suárez FJ, Vincent C (2012) Eur J Inorg Chem 5854
32. Cheng W, Jilin Y, Wei Z, Lan Z, Zheng Z (2013) J South Med Univ 33:779
33. Kuijpers BHM, Dijkmans GCT, Groothuys S, Quaedflieg PJLM, Blaauw RH, van Delft FL, Rutjes FPJT (2005) Synlett 3059
34. Wu YM, Deng J, Li Y, Chen QY (2005) Synthesis 1314
35. Li L, Zhang G, Zhu A, Zhang L (2008) J Org Chem 73:3630
36. Li L, Li Y, Li R, Zhu A, Zhang G (2011) Aust J Chem 64:1383
37. Yan R, El-Emir E, Rajkumar V, Robson M, Jathoul AP, Pedley RB, Årstad E (2011) Angew Chem Int Ed 50:6793
38. Brotherton WS, Clark RJ, Zhu L (2012) J Org Chem 77:6443
39. Barsoum DN, Brassard CJ, Deeb JHA, Okashah N, Sreenath K, Simmons JT, Zhu L (2013) Synthesis 45:2372
40. Coutouli-Argyropoulou E, Tsitabani M, Petrantonakis G, Terzis A, Raptopoulou C (2003) Org Biomol Chem 1:1382
41. Mamane V (2008) Mini-Rev Org Chem 5:303
42. Kuik Á, Skoda-Földes R, Jánosi L, Kollár L (2007) Synthesis 1456
43. Szánti-Pintér E, Balogh J, Csók Z, Kollár L, Gömöry Á, Skoda-Földes R (2011) Steroids 76:1377
44. Balogh J, Skoda-Földes R, Vazdar K, Habuš I (2012) J Organomet Chem 703:51
45. Krasnova LB, Hein JE, Fokin VV (2010) J Org Chem 75:8662
46. Urbán B, Srankó D, Sáfrán Gy, Ürge L, Darvas F, Bakos J, Skoda-Földes R (2014) J Mol Catal A 395:364

47. Hein JE, Krasnova LB, Iwasaki M, Fokin VV (2011) Org Synth 88:238
48. Wilkening I, del Signore G, Hackenberger CPR (2011) Chem Commun 47:349
49. Casas-Solvas JM, Vargas-Berenguel A, Capitán-Vallvey LF, Santoyo-González F (2004) Org Lett 6:3687
50. Broadhead GD, Osgerby JM, Pauson PL (1958) J Chem Soc 655