# A Versatile One-Pot Synthesis of 4-Aryl-1,5-disubstituted 1,2,3-Triazoles via 1,3-Dipolar Cycloaddition Followed by Negishi Reaction under New Conditions

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**Abstract:** Several derivatives of 4-aryl-1,5-disubstituted 1,2,3-triazole were synthesized in good yields via 1,3-dipolar cycloaddition followed by Negishi reaction under new conditions.

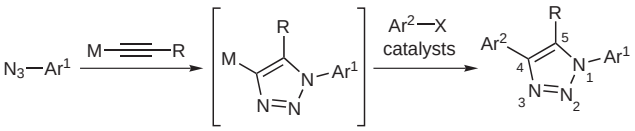
**Key words:** triazole, Negishi reaction, 1,3-dipolar cycloaddition, XANTPHOS, zinc, cross-coupling

1,2,3-Triazole substructures are emerging as valuable pharmacophores.[1,2] Among these, 4-aryl-1,5-disubstituted-1,2,3-triazole is a useful structure for development of pharmaceutical agents;[3] therefore, it is important to develop efficient synthetic methods for this compound.

N-Alkylation is a simplistic approach to synthesize substituted 1,2,3-triazoles. However, regioselectivity in this reaction is generally poor.[4] 1,3-Dipolar cycloaddition of organic azides and alkynes is a direct route to 1,2,3-triazoles.[5–7] Sharpless et al. reported a selective synthesis of 1,4-disubstituted 1,2,3-triazoles via copper-catalyzed 1,3-dipolar cycloaddition,[2] and of 1,5-disubstituted 1,2,3-triaozoles by ruthenium-catalyzed 1,3-dipolar cycloaddition.[8]

In addition, regioselective syntheses of 1,4,5-trisubstituted 1,2,3-triazoles have been reported.[9] Yamamoto et al. reported the synthesis of 5-allyl-1,4-disubstituted 1,2,3-triazoles by a cross-coupling reaction between π-allylpalladium complexes and 5-copper-1,2,3-triazoles prepared in situ.[10] Sharpless et al. reported nucleophilic substitution reactions of 4-magnesio-1,2,3-triazoles, prepared from alkynylmagnesium bromides and organic azides, to yield 1,4,5-trisubstituted 1,2,3-triazoles.[6] Wu et al. reported the synthesis of 5-aryl-1,4-disubstituted 1,2,3-triazoles by a cross-coupling reaction between 5-iodo-1,2,3-triazoles and arylboronic acids.[7]

It is expected that 1,3-dipolar cycloaddition of organic azides and alkynylmetals, followed by cross-coupling of the resulting 4-metallo-1,2,3-triazole species with arylhalides, may be developed as a particularly streamlined and regioselective synthesis method for 4-aryl-1,5-disubstituted 1,2,3-triazoles (Scheme 1).




**Scheme 1** Synthesis of 1,2,3-triazole by 1,3-dipolar cycloaddition followed by cross-coupling reaction

However, direct cross-coupling of the 4-metallo-1,2,3-triazole intermediates has not yet been reported.

Here, we report a highly effective synthetic method for 4-aryl-1,5-disubstituted 1,2,3-triazole by 1,3-dipolar cycloaddition followed by direct Negishi reaction under new conditions.

First, 1,3-dipolar cycloaddition was investigated using alkynylmetal (Li, Mg and Zn) reagents (Table 1). 1,3-Dipolar cycloaddition of azide **2a** and alkynyllithium **1a** produced triazole in mediocre yield (entry 1). As reported by Sharpless et al.[6] and Akimova et al.,[11] however, 1,3-dipolar cycloaddition using alkynylmagnesium halide **1b** gave the desired product in near-quantitative yield (entry 2).

To improve functional group compatibility, less reactive alkynylzinc halides prepared in situ were examined. With 1.05 equivalents of propynylzinc chloride, the yield was lower (entry 3). The use of dialkylzinc and zincate were also examined, but the reaction was unsuccessful (entries 4 and 5). However, with 3 equivalents propynylzinc chloride, the reaction proceeded well and the product was obtained in good yield (entry 6).

3-Phenylpropynylzinc reagents were also systematically investigated (entries 7–10). With mono- or dialkylzinc reagents, the reactions were sluggish (entries 7 and 8), but the use of zincates substantially improved the yields (entries 9 and 10).

In summary, the best result was obtained by using alkynylmagnesium bromide. Alkynyllithiums were not effective. Reactions using alkynylzinc reagents were slow, but the yields were acceptable in some cases.

Cross-coupling of 4-metallo-1,2,3-triazole species was then investigated. Initially, Kumada–Tamao reactions were examined, but due to the narrow compatibility of this method with reactive functional groups, the focus was moved to the more versatile Negishi reaction. The reac-

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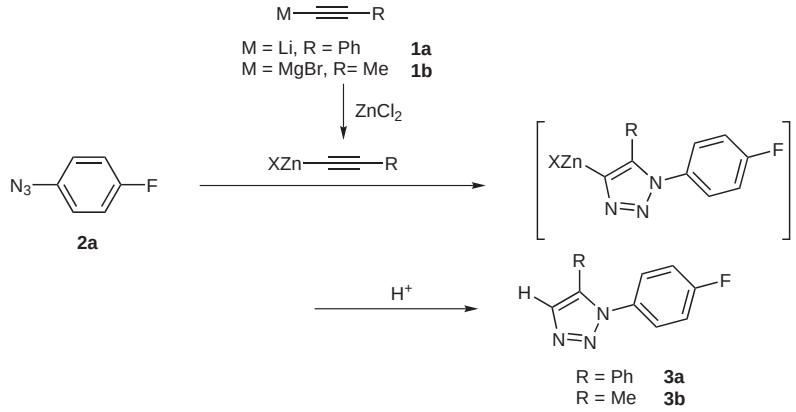
**Table 1** 1,3-Dipolar Cycloaddition of Mg, Li, and Zn Species




| Entry | **1** (equiv) | $ZnCl_2$ (equiv) | Temp (°C) | Time (h) | Yield of **3** (%)[a] |
|---|---|---|---|---|---|
| 1 | **1a** (1.05) | 0 | r.t. | 24 | 22 |
| 2 | **1b** (1.05) | 0 | r.t. | 2.5 | 96 |
| 3 | **1b** (1.05) | 1.05 | 40 | 7 | 57 |
| 4 | **1b** (1.05) | 0.53 | r.t. | 24 | 29 |
| 5 | **1b** (1.05) | 0.35 | r.t. | 24 | 34 |
| 6 | **1b** (3.00) | 3.00 | r.t. | 24 | 75 |
| 7 | **1a** (1.05) | 1.05 | r.t. | 24 | 9 |
| 8 | **1a** (1.05) | 0.53 | r.t. | 24 | 17 |
| 9 | **1a** (1.05) | 0.35 | r.t. | 24 | 74 |
| 10 | **1a** (1.05) | 0.26 | r.t. | 24 | 73 |

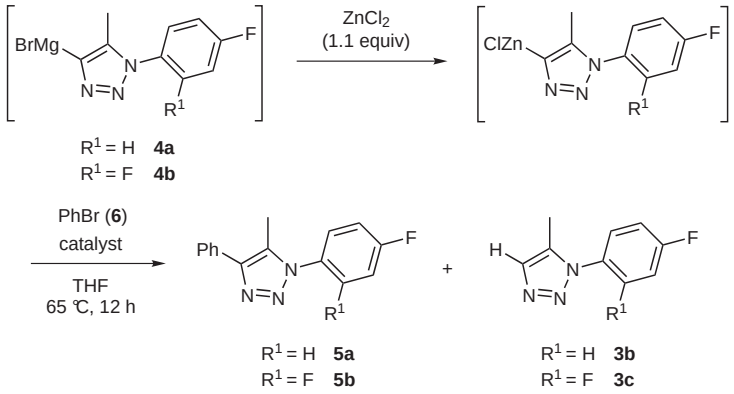
[a] Yields determined by HPLC.

tion conditions were optimized as shown in Table 2 and Figure 1. Since the best yields of 4-metallo-1,2,3-triazole species were obtained by 1,3-dipolar cycloaddition using a magnesium reagent, 4-zincio-1,2,3-triazoles were prepared by in situ transmetalation of 4-magnesio-1,2,3-triazoles with $ZnCl_2$. The subsequent Negishi reactions were carried out by adding bromobenzene and catalysts to the 4-zincio-1,2,3-triazole mixture, producing the desired product **5** along with the uncoupled product **3**. When typical palladium catalysts were used, 10 mol% of catalyst was required, but yields were moderate (entries 1–4).[12] Fu et al. reported that $Pd(P\textit{t}\text{-}Bu_3)_2$ functioned as a good catalyst for Negishi reactions,[13] but the use of this catalyst did not improve the yield in this case (entries 5 and 6). Various ligands for the palladium catalyst were also screened (entries 7–10). Monodentate phosphines ($PPh_3$, $P\textit{t}\text{-}Bu_3$ and X-PHOS[14]) were found to be ineffective (entries 7–9). Organ et al. reported that N-heterocyclic carbene-class ligands such as IPr were effective for Negishi reactions.[15] However, IPr was found to be ineffective in this case (entry 10).

The use of palladium catalysts containing bidentate ligands was then examined (Table 3). DPPE, (*S*)-BINAP and BIPHEP[17] were found to be ineffective (entries 1–3). The reaction using DPPF was a slight improvement (entry 4), but more bulky ligands such as D*t*BPF[16,18] shut down the reaction (entry 5).[19] Negishi et al. reported that DPEPHOS was an effective bidentate ligand for Negishi reactions.[20] However, the yield obtained from the reaction using DPEPHOS was mediocre (entry 6). Recently, XANTPHOS has been found to be an excellent ligand for a variety of palladium-mediated cross-coupling reactions.[21] When this ligand was used for our reaction (entry 7), the reaction proceeded smoothly even with 1 mol% of $Pd_2(dba)_3$.[22] The XANTPHOS ligand was also applied to the Kumada–Tamao reaction, but this was not as effective as the Negishi reaction (53% yield).[23]

Hayashi et al. reported that the use of bidentate ligands to form complexes with larger P–Pd–P angles results in acceleration of reductive elimination to form the coupling product.[24] In this case, reactions using catalysts with smaller P–Pd–P bite angles (less than 92°)[25,26] did not proceed (entries 1–3), while reactions using catalysts with larger bite angles (DPPF: 96°, DPEPHOS: 102°, XANTPHOS: 111°)[25] proceeded with conversion rates that were seemingly dependent on bite angle (entries 4,

**Table 2** Studies of Catalysts for the Negishi Reaction




| Entry | Substrate **4** | Catalyst (mol%)[a] | Yield of **5** (%)[b] | Yield of **3** (%)[b] |
|---|---|---|---|---|
| 1 | **4a** | $Pd(PPh_3)_4$ (2) | 0 | 86 |
| 2 | **4b** | $Pd(PPh_3)_4$ (10) | 64 | 10 |
| 3 | **4a** | $PdCl_2(dppf)\cdot CH_2Cl_2$ (2) | 41 | 48 |
| 4 | **4b** | $PdCl_2(dppf)\cdot CH_2Cl_2$ (10) | 62 | 0 |
| 5 | **4a** | $Pd(P\textit{t}\text{-}Bu_3)_2$ (2) | 24 | 68 |
| 6 | **4b** | $Pd(P\textit{t}\text{-}Bu_3)_2$ (10) | 67 | 16 |
| 7 | **4b** | $Pd_2(dba)_3$ (1), $PPh_3$ (4) | 0 | 80 |
| 8 | **4b** | $Pd_2(dba)_3$ (1), P*t*-$Bu_3$ (4) | 1 | 77 |
| 9 | **4b** | $Pd_2(dba)_3$ (1), X-PHOS (2) | 1 | 81 |
| 10 | **4a** | $Pd_2(dba)_3$ (1), IPr (2) | 0 | 87 |

[a] $Pd_2(dba)_3$ and the appropriate ligand were mixed for at least 1 h prior to use.
[b] Determined by HPLC.

6 and 7). From these results, it may be suggested that acceleration of the reductive elimination step is critical in these reactions.

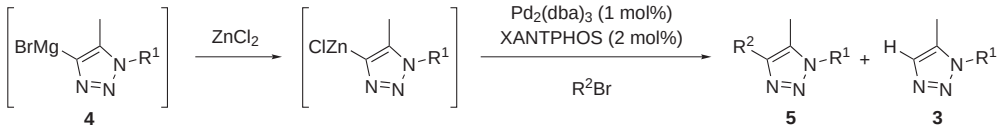
The scope and limitations of this strategy for construction of 4-aryl-1,5-disubstituted-1,2,3-triazoles are summarized in Table 4. The new conditions were applicable to bromoaryls, including those bearing reactive functional groups such as ketone **7**, ester **8**, or lactone **9** (entries 2–4). For **7**, the yield was moderate, probably due to deprotonation of the α-proton of the ketone. Reactions

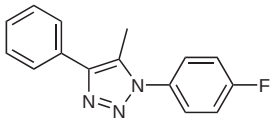
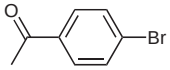
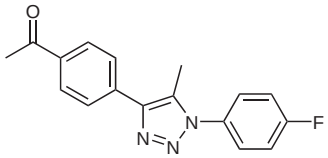
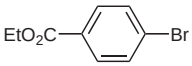
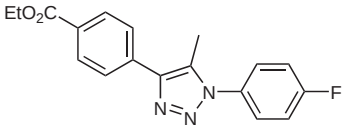
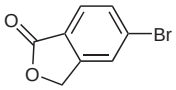
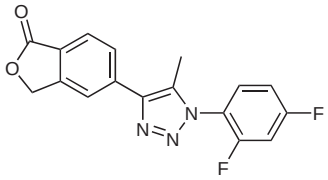
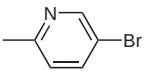
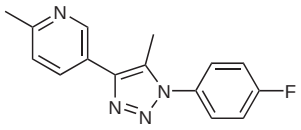
**Table 3** Negishi Reaction Using Catalysts Containing Bidentate Ligands

| Entry | Substrate **4** | Bidentate ligand (mol%)[a] | Bite angle (P–Pd–P) | Yield of **5** (%)[b] | Yield of **3** (%)[b] |
|---|---|---|---|---|---|
| 1 | **4b** | DPPE | 85° | 0 | 76 |
| 2 | **4b** | BIPHEP | 92° | 0 | 83 |
| 3 | **4b** | (*S*)-BINAP | 92° | 0 | 81 |
| 4 | **4b** | DPPF | 96° | 20 | 55 |
| 5 | **4b** | D*t*BPF | 104°[16] | 1 | 79 |
| 6 | **4b** | DPEPHOS | 102° | 30 | 53 |
| 7 | **4a** | XANTPHOS | 111° | 90 | 10 |

[a] 1 mol% of $Pd_2(dba)_3$ and 2 mol% of the appropriate ligand were mixed for at least 1 h prior to use.
[b] Determined by HPLC.

**Table 4** Application of XANTPHOS Catalyst in 1,3-Dipolar Cycloaddition Followed by Negishi Reaction[a,27,28]




| Entry | Substrate **4** | $R^2Br$ | Temp (°C) | Time (h) | Coupling product | Yield of **5** (%)[b] | Yield of **3** (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | **4a** | PhBr **6** | 65 | 12 |  **5a** | 90 | 10 |
| 2 | **4a** |  **7** | 65 | 12 |  **5c** | 51 | 19 |
| 3 | **4a** |  **8** | 55 | 17 |  **5d** | 81 | 11 |
| 4 | **4b** |  **9** | 60 | 13 |  **5e** | 70 | 14 |
| 5 | **4a** |  **10** | 55 | 12 |  **5f** | 79 | 15 |

[a] $Pd_2(dba)_3$ and XANTPHOS were mixed for at least 1 h prior to use.
[b] Determined by HPLC.

with the heteroaromatic compound **10** also proceeded efficiently (entry 5). Notably, the acidic proton of 2-methylpyridine did not disturb the coupling reaction.

In conclusion, various 4-aryl-1,5-disubstituted-1,2,3-triazoles were synthesized effectively by 1,3-dipolar cycloaddition followed by Negishi reaction catalyzed by 1 mol% of $Pd_2(dba)_3$ and 2 mol% of XANTPHOS. This methodology is applicable to many types of substrate and will contribute to the development of pharmaceutical agents. Further reports on the application of XANTPHOS in Negishi reactions will be published in the near future.

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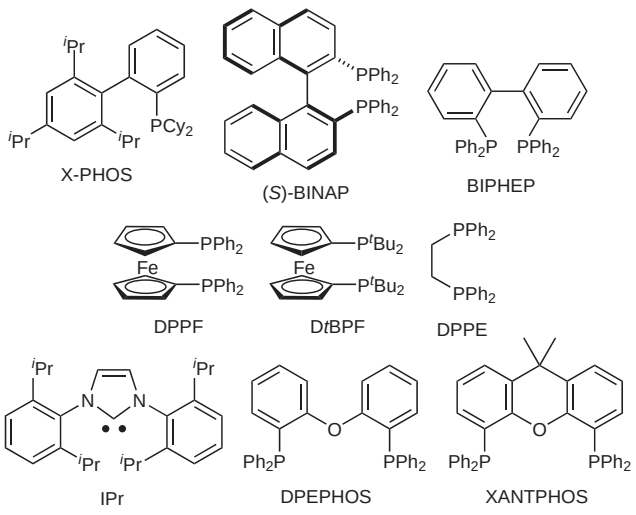


**Figure 1** Ligands for the Negishi reaction

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(22) The results of the Negishi reaction under new conditions using simple substrates are as follows. Negishi reactions were conducted using 1 mol% of $Pd_2(dba)_3$ and 2 mol% XANTPHOS in THF–NMP (2:1) at 70 °C for 12–19 h. Zinc reagents were prepared by transmetalation from the corresponding Grignard reagents. Negishi reactions of bromobenzene with phenyl-, vinyl- and propynylzinc chloride produced coupling products in almost quantitative yields. A Negishi reaction of chlorobenzene and phenylzinc chloride produced biphenyl in 78% yield. Further results from reactions using a variety of zinc reagents and halides will be reported.

(23) The reaction was conducted with magnesium species **4a** and bromobenzene(**6**) in the presence of 1 mol% of $Pd_2(dba)_3$ and 2 mol% XANTPHOS at 65 °C for 12 h.

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(27) **Typical Procedure for 1,3-Dipolar Cycloaddition Followed by Negishi Reaction.**
To a stirred solution of 8.4 wt% propynylmagnesium bromide(**1a**) in THF (d = 0.9339 g/cm$^{-3}$, 1.35 mL, 0.742 mmol) was added azide **2a** (95 mg, 0.693 mmol) in THF (0.1 mL), and the flask was washed with THF (2 × 0.1 mL). After stirring for 2 h at r.t., 1.41 M $ZnCl_2$ in THF solution (0.54 mL, 0.762 mmol) was added to the resulting yellow slurry. The resulting red solution was stirred for 1 h, and then bromobenzene (**6**; 73 μL, 0.693 mmol) and an active palladium catalyst solution prepared by mixing $Pd_2(dba)_3$ (6.3 mg, 0.00693 mmol) and XANTPHOS (8.0 mg, 0.0138 mmol) in THF (0.38 mL) for 2 h (this pre-mixing step is important in ensuring that the Negishi reaction proceeds smoothly) were added. After degassing, the mixture was stirred at 60–65 °C for 12 h. The mixture was then cooled to r.t., and the reaction mixture was added to 15% aq $NH_4Cl$ (5 mL), stirred for 10 min, and extracted with THF (10 mL and 5 mL); the volume was then adjusted to 25 mL using THF. HPLC analysis showed that product **5a** (158 mg assay) was obtained in 90% overall yield from **2a**, and protonated triazole **3a** was also recovered (12 mg assay, 10% recovery).

(28) **Spectroscopic Data for Products (Figure 2).**
Compound **5a**: IR (KBr): 3055, 2926, 1605, 1580, 1562, 1519, 1464, 1444, 1415, 1383, 1367, 1297, 1237, 1157, 1117, 1092, 1072, 1041, 1010 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): δ = 7.77 (br d, *J* = 8.0 Hz, 2 H), 7.52–7.47 (m, 4 H), 7.39 (br t, *J* = 7.5 Hz, 1 H), 7.29–7.25 (m, 2 H), 2.47 (s, 3 H). HRMS (ESI): *m/z* calcd for $C_{15}H_{13}N_3F$ $[M + H]^+$: 254.1094; found: 254.1091.
Compound **5b**: IR (KBr): 3052, 1610, 1526, 1495, 1460, 1442, 1278, 1260, 1151, 1110, 1006 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): δ = 7.80–7.77 (m, 2 H), 7.55 (m, 1 H), 7.49–7.46 (m, 2 H), 7.37 (m, 1 H), 7.11–7.04 (m, 2 H), 2.39 (d, *J* = 1.6 Hz, 3 H). HRMS (ESI): *m/z* calcd for $C_{15}H_{12}N_3F_2$ $[M + H]^+$: 272.0999; found: 272.1001.
Compound **5c**: IR (KBr): 3083, 1685, 1609, 1574, 1509, 1466, 1435, 1406, 1362, 1295, 1261, 1183, 1157, 1113, 1092, 1009 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): δ = 8.07 (br d, *J* = 8.3 Hz, 2 H), 7.90 (br d, *J* = 8.3 Hz, 2 H), 7.51–7.48 (m, 2 H), 7.29–7.26 (m, 2 H), 2.65 (s, 3 H), 2.51 (s, 3 H). HRMS (ESI): *m/z* calcd for $C_{17}H_{15}N_3OF$ $[M + H]^+$: 296.1199; found: 296.1202.
Compound **5d**: IR (KBr): 3087, 2986, 2944, 2904, 1696, 1657, 1611, 1563, 1518, 1474, 1448, 1432, 1410, 1390, 1365, 1312, 1279, 1222, 1176, 1160, 1106, 1011 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): δ = 8.16 (br d, *J* = 8.0 Hz, 2 H), 7.87 (br d, *J* = 8.0 Hz, 2 H), 7.51–7.49 (m, 2 H), 7.29–7.26 (m, 2 H), 4.41 (q, *J* = 7.0 Hz, 2 H), 2.50 (s, 3 H), 1.42 (t, *J* = 7.0 Hz, 3 H). HRMS (ESI): *m/z* calcd for $C_{18}H_{17}N_3O_2F$ $[M + H]^+$: 326.1305; found: 326.1306.
Compound **5e**: IR (KBr): 3060, 2977, 1749, 1617, 1523, 1444, 1347, 1271, 1227, 1152, 1109, 1054, 1029, 1013 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): δ = 8.00 (br s, 1 H), 8.00 (d, *J* = 7.5 Hz, 1 H), 7.92 (br d, *J* = 7.5 Hz, 1 H), 7.57 (m, 1 H), 7.15–7.09 (m, 2 H), 5.39 (s, 2 H), 2.47 (d, *J* = 1.6 Hz, 3 H). HRMS (ESI): *m/z* calcd for $C_{17}H_{12}N_3O_2F_2$ $[M + H]^+$: 328.0898; found: 328.0896.
Compound **5f**: IR (KBr): 2984, 2928, 1606, 1518, 1495 1466, 1443, 1415, 1383, 1351, 1294, 1257, 1235, 1156, 1116, 1091, 1007 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): δ = 8.85 (br s, 1 H), 8.10 (br d, *J* = 7.8 Hz, 1 H), 7.52–7.49 (m, 2 H), 7.33–7.26 (m, 3 H), 2.65 (br s, 3 H), 2.48 (s, 3 H). HRMS (ESI): *m/z* calcd for $C_{15}H_{14}N_4F$ $[M + H]^+$: 269.1202; found: 269.1205.

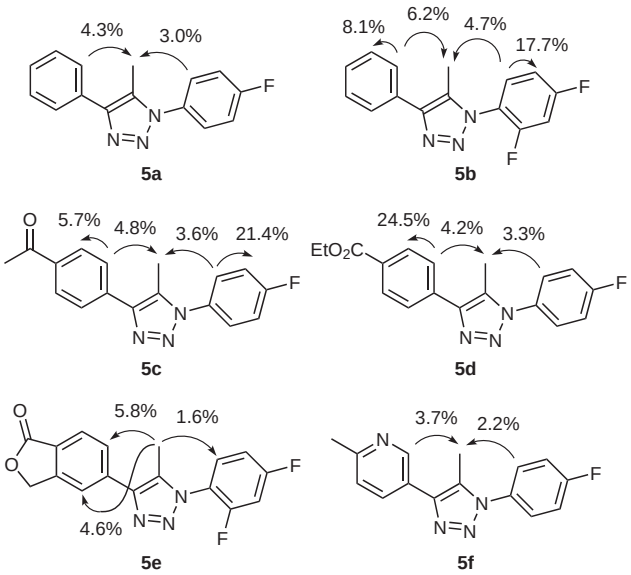


**Figure 2** NOE