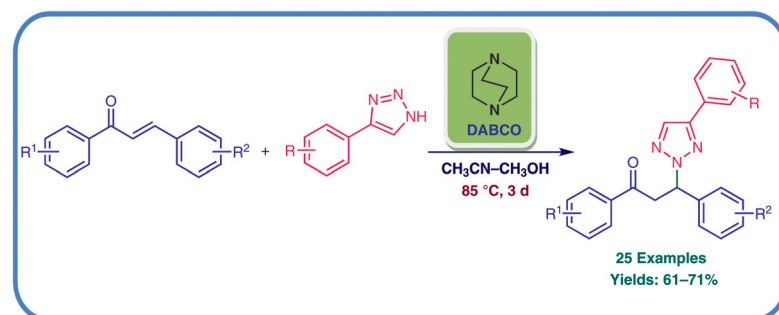


# Regiospecific Aza-Michael Addition of 4-Aryl-1*H*-1,2,3-triazoles to Chalcones: Synthesis of 2,4-Disubstituted 1,2,3-Triazoles in Basic Medium

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**Abstract** A novel metal-free and base-mediated method to display the donor ability of 1,2,3-triazoles for the synthesis of 2,4-disubstituted 1,2,3-triazoles has been developed. A DABCO-promoted aza-Michael addition of 4-aryl NH-1,2,3-triazoles to  $\alpha,\beta$ -unsaturated ketones (chalcones) is presented. The reactions proceeded with complete regioselectivity in a 3:1 mixture of acetonitrile and methanol at 85 °C to provide 2,4-disubstituted 1,2,3-triazoles as Michael adducts, and the addition products 1,3-diaryl-(4-aryl-2*H*-1,2,3-triazol-2-yl)propan-1-ones were isolated in high yields.

**Key words** triazoles, chalcones, aza-Michael addition, heterocyclic compounds

The 1,2,3-triazole motif belongs to a prominent class of heterocyclic compounds that frequently occur in many natural products, pharmaceutically active compounds, and functional materials.<sup>1</sup> Many compounds bearing the 1,2,3-triazole unit as their core structure exhibit a broad spectrum of biological properties such as anticancer, antituberculosis, antibacterial, and antiviral activities.<sup>2a,b</sup> Disubstituted 1,2,3-triazoles have also been used as chemical sensors, dendrimers, oligomers, linkers, and agrochemicals.<sup>2c-g</sup> Due to the significance of these compounds, the synthesis of 1,2,3-triazole-containing heterocycles has attracted attention from academia and industry.<sup>3</sup>

Among the methods developed for the synthesis of 1,2,3-triazoles, the Huisgen 1,3-dipolar [3+2] cycloaddition of organic azides with alkynes is one of the most popular, efficient, and powerful synthesis routes.<sup>4</sup> The classical Huisgen cycloaddition is a thermally induced reaction that gives a regioisomeric mixture of both 1,4- and 1,5-disubstituted 1,2,3-triazoles.<sup>5</sup> The Cu(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition (CuAAC) is the most effective strategy for the synthesis of 1,4-disubstituted 1,2,3-tri-

azoles as sole products, as independently exploited by Sharpless, Fokin, and co-workers<sup>6</sup> and by Meldal and co-workers.<sup>7</sup> The CuAAC-catalyzed reaction introduced by Sharpless, referred to as ‘click chemistry’, has had enormous implications in synthesis.<sup>8</sup> Subsequently, Fokin and Sharpless developed Ru-catalyzed azide-alkyne cycloaddition (RuAAC) processes for the synthesis of 1,5-disubstituted 1,2,3-triazoles with high regioselectivity.<sup>9</sup> Several other metal-catalyzed cycloaddition processes, such as the IrAAC reaction,<sup>10</sup> the AgAAC reaction,<sup>11</sup> and the PdAAC reaction,<sup>12</sup> have been developed for the regioselective synthesis of substituted 1,2,3-triazoles. Recently, a strain-promoted azide-alkyne [3+2] cycloaddition process was developed by Bertozzi and co-workers to furnish 1,4,5-trisubstituted 1,2,3-triazoles as bioorthogonal probes.<sup>13</sup> Ramachary,<sup>14</sup> Wang,<sup>15</sup> Bressy,<sup>16</sup> and their respective co-workers have recently reported new methods for enamine-mediated organocatalytic [3+2] cycloaddition processes to access trisubstituted 1,2,3-triazoles.

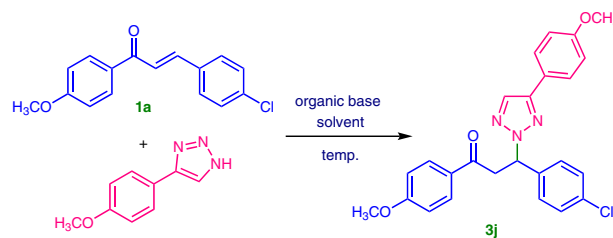
Michael additions and hetero-Michael additions, especially, aza-Michael reactions, are extremely useful transformations in which the formation of C–C and C–N bonds takes place. Such C–N bond-forming reactions are attractive in the context of synthesizing mono-, di-, or trisubstituted 1,2,3-triazoles. The aza-Michael addition reaction of nitrogen-attacking nucleophiles (Michael donors) with  $\alpha,\beta$ -unsaturated electrophiles (Michael acceptors) permits the syntheses of heterocyclic compounds containing a 1,2,3-triazole moiety. However, the nucleophilic reaction of 4-aryl-1*H*-1,2,3-triazoles is underdeveloped, because of the inherent stability of the aromatic 1,2,3-triazole moiety. Recently, Chen and co-workers have reported the selective synthesis of N(2)-substituted 1,2,3-triazoles.<sup>17</sup> Recently, we reported a metal-free, DABCO-mediated, aza-Michael addition of 4-aryl-1*H*-1,2,3-triazoles to cycloalkenones to furnish 2,4-disubstituted 1,2,3-triazoles along with 1,4-disubstituted

1,2,3-triazoles.<sup>18</sup> Under basic conditions, the nucleophilicity of N(2) is enhanced, thereby furnishing 2,4-disubstituted 1,2,3-triazoles as major products. Here, we report a DABCO-mediated aza-Michael addition of 4-aryl-1*H*-1,2,3-triazoles to chalcones under basic conditions to give 2,4-disubstituted 1,2,3-triazole derivatives exclusively.

The required chalcones were synthesized by aldol condensation<sup>19</sup> of aryl aldehydes with acetophenone derivatives in the presence of KOH, and the 4-aryl-1*H*-1,2,3-triazoles were prepared from the corresponding nitrostyrene derivatives.<sup>20</sup> In our initial studies, we examined the reaction of the chalcone **1a** and 4-(4-methoxyphenyl)-1*H*-1,2,3-triazole (**2b**) in acetonitrile at 0 °C in the presence of DABCO (40 mol%). However, no reaction was observed after 10 days (Table 1, entry 1). The reaction was then tried in dichloromethane, 1,2-dichloroethane, and methanol, without any success (entries 2–4). When the reaction was carried out in the presence of DABCO in acetonitrile at room temperature for seven days, the aza-Michael adduct **3j** was isolated in 10% yield (entry 5). The reaction of **1a** and **2b** in the presence of DMAP in acetonitrile or DBU in toluene gave multiple products (entries 6 and 7). The reaction with an increased loading of DABCO in acetonitrile gave slightly improved results on increasing the temperature (entries 8–10). Subsequent reactions were therefore performed with 80 mol% of DABCO in solvents such as acetonitrile–methanol, acetonitrile, methanol, or DCE at 60–80 °C to provide adduct **3j** in moderate yield (entries 11–14). Under these conditions, the use of DMAP did not result in any improvement (entry 15). At this stage, the aza-Michael reaction between **1a** and **2b** was carried out with one equivalent of DABCO in a mixture of acetonitrile and methanol at 85 °C for three days (entries 16–20). We found that an increased amount of methanol resulted in a decreased yield of product **3j**. Thus, screening of various solvents and organic bases at different temperatures, revealed the optimal conditions to be one equivalent of DABCO in a 3:1 mixture of acetonitrile–methanol at 85 °C for three days (entry 16).

Having the optimized conditions in hand, we then proceeded to investigate the substrate scope for the aza-Michael reaction. As shown in Scheme 1, several substituted chalcones **1a–m** with electron-releasing groups in the aryl ring Ar<sup>1</sup> and electron-releasing or withdrawing groups in the aryl ring Ar<sup>2</sup> of the chalcones were evaluated. Various 4-aryl-1*H*-1,2,3-triazoles bearing electron-releasing and electron-withdrawing groups in the phenyl ring were tested for the aza-Michael reaction. The corresponding aminated products **3a–y** were isolated in yields within the narrow range of 61–71% after three days at 85 °C (Scheme 1). Chalcones bearing electron-releasing groups at the *para*-position of aryl ring Ar<sup>1</sup> and at the *ortho*- or *para*-positions of aryl ring Ar<sup>2</sup> underwent aza-Michael reaction with 4-aryl-1*H*-1,2,3-triazoles bearing aryl electron-releasing groups to give 65–66% yields of Michael adducts **3a**, **3b**, and **3p**. Halogen-substituted 4-(3-fluorophenyl)-1*H*-1,2,3-triazole af-

**Table 1** Aza-Michael Addition of 4-Methoxyphenyl-1,2,3-triazole **2b** to Chalcone **1a**<sup>a</sup>



Entry	Organic base (mol%)	Solvent (2 mL)	Temp (°C)	Time (d)	Yield <sup>b</sup> (%)
1	DABCO (40)	MeCN	0	10	nr <sup>c</sup>
2	DABCO (40)	CH <sub>2</sub> Cl <sub>2</sub>	0	10	nr
3	DABCO (40)	DCE	0	10	nr
4	DABCO (40)	MeOH	0	10	nr
5	DABCO (40)	MeCN	r.t.	7	10
6	DMAP (40)	MeCN	r.t.	7	nd <sup>d</sup>
7	DBU (40)	toluene	r.t.	7	nd
8	DABCO (60)	MeCN	r.t.	7	17
9	DABCO (60)	MeCN	60	7	32
10	DABCO (80)	MeCN	60	7	39
11	DABCO (80)	MeCN–MeOH (3:1)	60	7	46
12	DABCO (80)	MeCN	70	4	40
13	DABCO (80)	MeOH	70	4	35
14	DABCO (80)	DCE	80	4	37
15	DMAP (80)	MeCN	80	4	34
16	DABCO (100)	MeCN–MeOH (3:1)	85	3	61
17	DABCO (100)	MeCN–MeOH (1:1)	85	3	50
18	DABCO (100)	MeCN–MeOH (1:3)	85	3	44
19	DABCO (100)	MeCN–MeOH (1:2)	85	3	46
20	DABCO (100)	MeCN–MeOH (2:1)	85	3	55

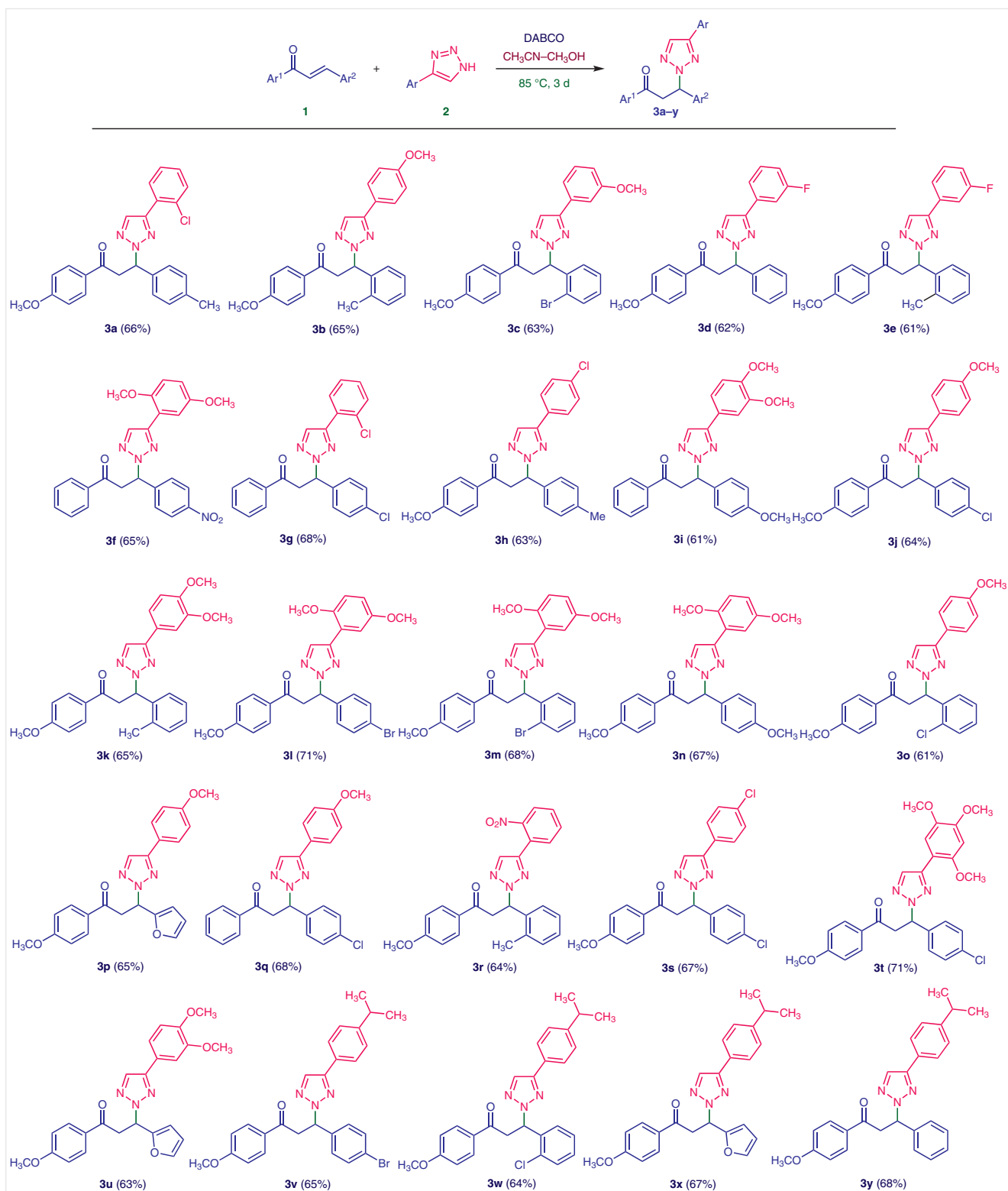
<sup>a</sup> Reaction conditions: chalcone **1a** (0.2 mmol), 1,2,3-triazole **2b** (0.2 mmol), base, solvent (2 mL).

<sup>b</sup> Isolated yield.

<sup>c</sup> nr = no reaction.

<sup>d</sup> nd = not determined.

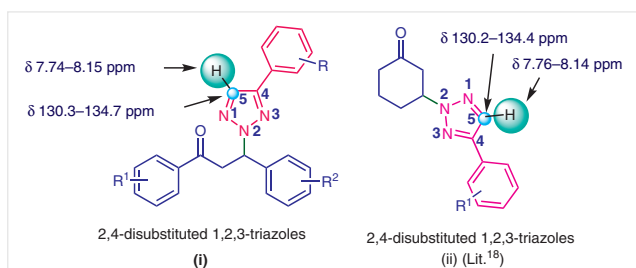
forded the adducts **3d** and **3e** in marginally lower yields of 62 and 61%, respectively. The chalcone with a bromo group at the *ortho*-position of aryl ring Ar<sup>2</sup> gave the 3-methoxyphenyltriazole derivative **3c** in 63% yield. 2,5-Dimethoxyphenyl-1,2,3-triazole underwent aza-Michael addition with chalcone derivatives having a *para*-methoxy group on the aryl ring Ar<sup>1</sup> to give the corresponding adducts **3l–n** in 67–



**Scheme 1** Aza-Michael addition of 4-aryl-1H-1,2,3-triazoles **2** to chalcones **1a-m**. Reaction conditions: chalcone **1** (0.2 mmol), 4-aryl-1H-1,2,3-triazole **2** (0.2 mmol), DABCO (1 equiv), 3:1 MeCN-MeOH (2 mL) at 85 °C, 3 d,<sup>23,24</sup> Yields of the pure and isolated products are reported.

71% yield. 2,5-Dimethoxyphenyl-1,2,3-triazole underwent 1,4-conjugation addition with a chalcone having a *para*-nitro group on Ar<sup>2</sup> to give product **3f** in 65% yield. 4-(2-Chlorophenyl)- and 4-(4-methoxyphenyl)-1*H*-1,2,3-triazoles reacted well with chalcones bearing a *para*-chloro substituent on aryl ring Ar<sup>2</sup> to give the Michael adducts **3g** and **3q**, both in 68% yield. 4-(3,4-Dimethoxyphenyl)-1*H*-1,2,3-triazole also participated in the conjugate addition reaction to give products **3i**, **3k**, and **3u** in 61–65% yield. The enhanced nucleophilicity of 4-(2,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole was reflected in the reaction in which **3t** was obtained in 71% yield. 4-(4-Isopropylphenyl)-1*H*-1,2,3-triazole also added to chalcones and provided the corresponding disubstituted 1,2,3-triazoles **3v–y** in 64–68% yields. The above results for the formation of 2,4-disubstituted triazoles suggest that electronic and steric factors of substituents on the aryl moieties of both the 1,2,3-triazole and the chalcone have a marginal effects on the outcome of this aza-Michael transformation. The addition of 1,2,3-triazoles to chalcones is regioselective and furnishes N(2)-adducts exclusively, unlike the addition to cyclohex-2-en-1-ones where N(1)-isomers were also formed;<sup>18</sup> this might be attributed to the lower reactivity of chalcones in comparison with cyclohex-2-en-1-ones. It is worthy of note that N(2)-substituted 1,2,3-triazoles cannot be obtained through click chemistry.

The 2,4-disubstituted 1,2,3-triazoles **3a–y** have a narrow range of chemical shifts ( $\delta = 7.74$ – $8.15$  ppm) for the C5-H proton (Table 1, Figure 1-i). These values are comparable with the range of chemical shifts ( $\delta = 7.76$ – $8.14$  ppm) for the C5 hydrogen of the aza-Michael adducts derived from 4-aryl-1,2,3-triazoles and cyclic enones [Figure 1(ii)].<sup>18</sup> Similarly, the <sup>13</sup>C chemical shifts ( $\delta = 130.3$ – $134.7$  ppm) for C5 of the 1,2,3-triazole moiety of **3a–y** [Table 2 and Figures 1(i)] compare closely with those ( $\delta = 130.2$ – $134.4$  ppm) of the adducts shown in Figure 1(ii).



**Figure 1** Selected chemical shifts of disubstituted triazoles from aza-Michael addition

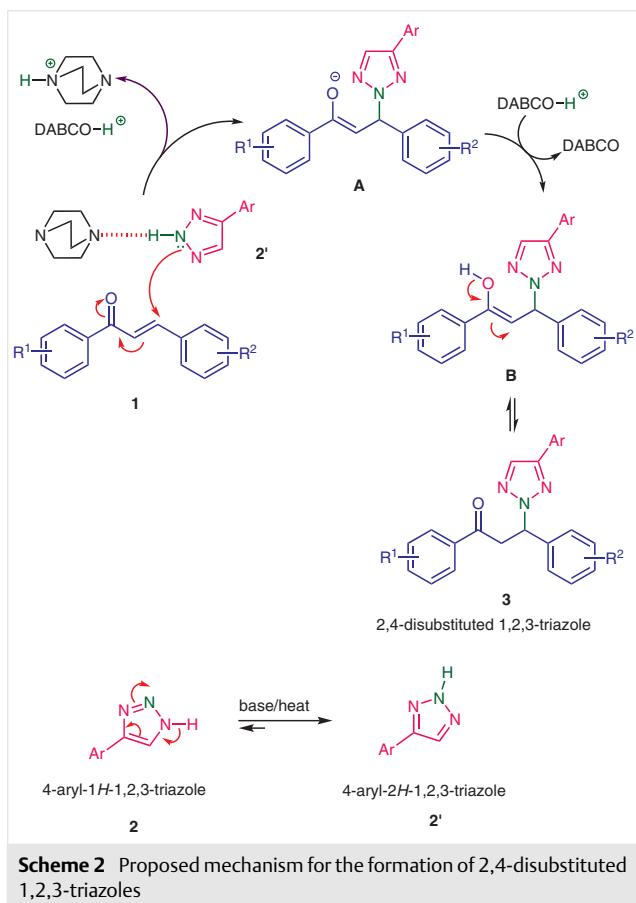
**Table 2** Chemical Shifts of C5-H and C5 of 2,4-Disubstituted 1,2,3-Triazoles **3**

Entry	Product	Chemical shift of C5-H ( $\delta$ , ppm)	Chemical shift of C5 ( $\delta$ , ppm)
1	<b>3a</b>	8.12	130.3
2	<b>3b</b>	7.74	130.3
3	<b>3c</b>	7.85	130.5
4	<b>3d</b>	7.82	131.1
5	<b>3e</b>	7.81	131.0
6	<b>3f</b>	8.12	133.7
7	<b>3g</b>	8.15	134.3
8	<b>3h</b>	7.79	130.9
9	<b>3i</b>	7.76	130.5
10	<b>3j</b>	7.74	130.6
11	<b>3k</b>	7.75	130.8
12	<b>3l</b>	8.07	134.7
13	<b>3m</b>	8.11	134.7
14	<b>3n</b>	8.06	134.5
15	<b>3o</b>	7.79	130.6
16	<b>3p</b>	7.75	130.8
17	<b>3q</b>	7.76	130.6
18	<b>3r</b>	7.74	130.9
19	<b>3s</b>	7.80	131.1
20	<b>3t</b>	8.01	134.1
21	<b>3u</b>	7.76	130.9
22	<b>3v</b>	7.80	131.0
23	<b>3w</b>	7.85	130.9
24	<b>3x</b>	7.80	–
25	<b>3y</b>	7.83	130.8

This trend is in accordance with data reported for 2,4-disubstituted 1,2,3-triazoles derived from the base-mediated reactions of 1,2,3-triazoles.<sup>17,21</sup> In addition, Creary and co-workers recently distinguished between 1,4- and 1,5-disubstituted 1,2,3-triazoles by simple one-dimensional <sup>13</sup>C NMR spectroscopy through gated decoupling experiments.<sup>22</sup>

A plausible mechanism for the conjugate addition of 4-aryl-1*H*-1,2,3-triazoles to 2-chalcones **1** is depicted in Scheme 2. The reaction is initiated by the activation of the 4-aryl-1*H*-1,2,3-triazole with DABCO by hydrogen-bonding with the N–H group of the 1,2,3-triazole. In a basic medium and at elevated temperature, the nucleophilicity of the middle nitrogen of 4-aryl-1*H*-1,2,3-triazoles is high.<sup>21b</sup> Subsequently, the activated aryl 1,2,3-triazole attacks the electron-deficient  $\beta$ -carbon of the electrophile. The middle ni-

trogen, having a greater propensity to undergo nucleophilic addition with the  $\beta$ -carbon of the chalcone, generates the enolate intermediate **A**. Proton transfer to intermediate **A** releases the less stable enol form **B**, which in turn undergoes tautomerization to liberate the 2,4-disubstituted 1,2,3-triazole.



In summary, we have illustrated the DABCO-mediated synthesis of 2,4-disubstituted 1,2,3-triazoles by regioselective aza-Michael addition of 4-aryl-1H-1,2,3-triazoles **2** to chalcones **1**. The more-stable aryl-1,2,3-triazoles produced good yields of 2,4-disubstituted 1,2,3-triazoles under metal-free conditions in presence of DABCO at the reflux temperature.

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### Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0036-1588567>.

### References and Notes

- (1) (a) Agalave, S. G.; Maujan, S. R.; Pore, V. S. *Chem. Asian J.* **2011**, *6*, 2696. (b) Muller, T.; Bräse, S. *Angew. Chem. Int. Ed.* **2011**, *50*, 11844.
- (2) (a) Tron, G. C.; Pirali, T.; Billington, R. A.; Canonico, P. L.; Sorba, G.; Genazzani, A. A. *Med. Res. Rev.* **2008**, *28*, 278. (b) Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. *Chem. Rev.* **2013**, *113*, 4905. (c) Lau, Y. H.; Rutledge, P. J.; Watkinson, M.; Todd, M. H. *Chem. Soc. Rev.* **2011**, *40*, 2848. (d) Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Fréchet, J. M. J.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem. Int. Ed.* **2004**, *43*, 3928. (e) Katritzky, A. R.; Singh, S. K.; Meher, N. K.; Doskocz, J.; Suzuki, K.; Jiang, R.; Sommen, G. L.; Ciaramitaro, D. A.; Steel, P. J. *ARKIVOC* **2006**, 43. (f) Löber, S.; Rodriguez-Loaiza, P.; Gmeiner, P. *Org. Lett.* **2003**, *5*, 1753. (g) Borgati, T. F.; Alves, R. B.; Teixeira, R. R.; de Freitas, R. P.; Perdigão, T. G.; da Silva, S. F.; dos Santos, A. A.; Bastidasc, A. de J. O. J. *Braz. Chem. Soc.* **2013**, *24*, 953.
- (3) (a) Schulze, B.; Schubert, U. S. *Chem. Soc. Rev.* **2014**, *43*, 2522. (b) Lutz, J.-F. *Angew. Chem. Int. Ed.* **2008**, *47*, 2182.
- (4) (a) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, **1984**, 1. (b) Fan, W.-Q.; Katritzky, A. R. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford, **1996**, Vol. 4 1.
- (5) (a) Huisgen, R.; Knorr, R.; Möbius, L.; Szeimies, G. *Chem. Ber.* **1965**, *98*, 4014. (b) Huisgen, R.; Szeimies, G. *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565. (c) Huisgen, R. *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 633.
- (6) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *114*, 2708. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596.
- (7) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.
- (8) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.
- (9) (a) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998. (b) Rasmussen, L. K.; Boren, B. C.; Fokin, V. V. *Org. Lett.* **2007**, *9*, 5337. (c) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 8923.
- (10) (a) Ding, S.; Jia, G.; Sun, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 1877. (b) Rasolofonjatovo, E.; Theeramunkong, S.; Bouriaud, A.; Kolodych, S.; Chaumontet, M.; Taran, F. *Org. Lett.* **2013**, *15*, 4698.
- (11) (a) McNulty, J.; Keskar, K. *Eur. J. Org. Chem.* **2012**, 5462. (b) McNulty, J.; Keskar, K.; Vemula, R. *Chem. Eur. J.* **2011**, *17*, 14727.
- (12) (a) Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333. (b) Tian, X.; Yang, F.; Rasina, D.; Bauer, M.; Warratz, S.; Ferlin, F.; Vaccaro, L.; Ackermann, L. *Chem. Commun.* **2016**, 52, 9777.
- (13) (a) Agard, N. J.; Preschner, J. A.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2004**, *126*, 15046. (b) Jewett, J. C.; Bertozzi, C. R. *Chem. Soc. Rev.* **2010**, *39*, 1272. (c) Gold, B. G.; Dudley, B.; Alabugin, I. V. *J. Am. Chem. Soc.* **2013**, *135*, 1558. (d) Agard, N. J.; Baskin, J. M.; Prescher, J. A.; Lo, A.; Bertozzi, C. R. *ACS Chem. Biol.* **2006**, *1*, 644. (e) Johnson, J. A.; Baskin, J. M.; Bertozzi, C. R.; Koberstein, J. T.; Turro, N. J. *Chem. Commun.* **2008**, 3064. (f) Sletten, E. M.; Bertozzi, C. R. *Org. Lett.* **2008**, *10*, 3097. (g) Jewett, J. C.; Sletten,

- E. M.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 3688.  
 (h) Gordon, C. G.; Mackey, J. L.; Jewett, J. C.; Sletten, E. M.; Houk, K. N.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2012**, *134*, 9199.
- (14) (a) Ramachary, D. B.; Ramakumar, K.; Narayana, V. V. *Chem. Eur. J.* **2008**, *14*, 9143. (b) Ramachary, D. B.; Shashank, A. B. *Chem. Eur. J.* **2013**, *19*, 13175.
- (15) (a) Danence, L. J. T.; Gao, Y.; Li, M.; Huang, Y.; Wang, J. *Chem. Eur. J.* **2011**, *17*, 3584. (b) Wang, L.; Peng, S.; Danence, L. J. T.; Gao, Y.; Wang, J. *Chem. Eur. J.* **2012**, *18*, 6088. (c) Li, W.; Jia, Q.; Du, Z.; Wang, J. *Chem. Commun.* **2013**, *49*, 10187. (d) Yeung, D. K. J.; Gao, T.; Huang, J.; Sun, S.; Guo, H.; Wang, J. *Green Chem.* **2013**, *15*, 2384. (e) Li, W.; Du, Z.; Huang, J.; Jia, Q.; Zhang, K.; Wang, J. *Green Chem.* **2014**, *16*, 3003.
- (16) Belkheira, M. D.; Abed, E.; Pons, J.-M.; Bressy, C. *Chem. Eur. J.* **2011**, *17*, 12917.
- (17) (a) Wen, J.; Zhu, L.-L.; Bi, Q.-W.; Shen, Z.-Q.; Li, X.-X.; Li, X.; Wang, Z.; Chen, Z. *Chem. Eur. J.* **2014**, *20*, 974. (b) Zhu, L.-L.; Xu, X.-Q.; Shi, J.-W.; Chen, B.-L.; Chen, Z. *J. Org. Chem.* **2016**, *81*, 3568.
- (18) Bhagat, U. K.; Kamaluddin, ; Peddinti, R. K. *Tetrahedron Lett.* **2017**, *58*, 298.
- (19) Asundaria, S. T.; Patel, K. C. *Pharm. Chem. J.* **2011**, *45*, 725.
- (20) Quan, X.-J.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Org. Lett.* **2014**, *16*, 5728.
- (21) (a) Beryozkina, T. V.; Efimov, I. V.; Fabian, W. M. F.; Beliaev, N. A.; Slepukhin, P. A.; Isenov, M. L.; Dehaen, W.; Lubec, G.; Eltsov, O. S.; Fan, Z.; Thomas, J.; Bakulev, V. A. *Tetrahedron.* **2015**, *71*, 6189. (b) Jiang, J.; Wang, Q.; Sun, R.; Tanga, X.-Y.; Shi, M. *Org. Chem. Front.* **2016**, *3*, 744.
- (22) Creary, X.; Anderson, A.; Brophy, C.; Crowell, F.; Funk, Z. *J. Org. Chem.* **2012**, *77*, 8756.
- (23) **2,4-Disubstituted 1,2,3-Triazoles 3a–y; General Procedure**  
 DABCO (0.2 mmol) was added to a mixture of the appropriate chalcone **1** (0.2 mmol) and 4-aryl-1H-1,2,3-triazole **2** (0.2 mmol) in 3:1 MeCN–MeOH (2 mL) in a 10 mL round-bottomed flask, and the mixture was stirred at 85 °C for 3 d until almost all the reactants were converted (TLC). The product was isolated by subjecting the crude reaction mixture to column chromatography (silica gel, 10–50% EtOAc–hexanes).
- (24) **Experimental Data for Selected Compounds**  
**3-[4-(2-Chlorophenyl)-2H-1,2,3-triazol-2-yl]-1-(4-methoxyphenyl)-3-(4-tolyl)propan-1-one (3a)**  
 Pale-yellow solid; yield: 57.0 mg (66%); mp 117.5–119.0 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.12 (s, 1 H), 7.99 (d, J = 8.8 Hz, 2 H), 7.82 (dd, J = 2.4, 7.2 Hz, 1 H), 7.42 (dd, J = 2.0, 7.2 Hz, 1 H), 7.32 (d, J = 8.0 Hz, 2 H), 7.29–7.22 (m, 2 H), 7.16 (d, J = 8.0 Hz, 2 H), 6.93 (d, J = 8.8 Hz, 2 H), 6.51 (dd, J = 8.8, 5.6 Hz, 1 H), 4.49 (dd, J = 8.8, 17.6 Hz, 1 H), 3.86 (s, OCH<sub>3</sub>, 3 H), 3.71 (dd, J = 5.6, 17.6 Hz, 1 H), 2.32 (s, CH<sub>3</sub>, 3 H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 194.3 (CO), 163.7 (C), 144.6 (C), 138.0 (C), 136.4 (C), 134.1 (CH), 131.9 (C), 130.5 (2CH), 130.3 (CH), 130.2 (CH), 129.4 (2CH), 129.4 (C), 129.2 (C), 129.1 (CH), 126.8 (CH), 126.6 (2CH), 113.7 (2CH), 64.2 (CH), 55.4 (OCH<sub>3</sub>), 43.6 (CH<sub>2</sub>), 21.1 (CH<sub>3</sub>).  
**1-(4-Methoxyphenyl)-3-[4-(4-methoxyphenyl)-2H-1,2,3-triazol-2-yl]-3-(2-tolyl)propan-1-one (3b)**  
 Pale-yellow solid; yield: 55.6 mg (65%); mp 114.0–115.5 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.00 (d, J = 8.8 Hz, 2 H), 7.74 (s, 1 H), 7.65 (d, J = 8.8 Hz, 2 H), 7.21–7.12 (m, 4 H), 6.94 (d, J = 8.8 Hz, 2 H), 6.90 (d, J = 8.8 Hz, 2 H), 6.75 (dd, J = 4.8, 9.2 Hz, 1 H), 4.49 (dd, J = 9.2, 17.6 Hz, 1 H), 3.86 (s, OCH<sub>3</sub>, 3 H), 3.82 (s, OCH<sub>3</sub>, 3 H), 3.57 (dd, J = 4.4, 17.6 Hz, 1 H), 2.57 (s, CH<sub>3</sub>, 3 H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 194.6 (CO), 163.7 (C), 159.6 (C), 147.3 (C), 137.9 (C), 135.2 (C), 130.8 (CH), 130.5 (2CH), 130.3 (CH), 129.5 (C), 128.0 (CH), 127.2 (2CH), 126.4 (CH), 125.9 (CH), 123.2 (C), 114.1 (2CH), 113.8 (2CH), 60.5 (CH), 55.5 (OCH<sub>3</sub>), 55.3 (OCH<sub>3</sub>), 42.8 (CH<sub>2</sub>), 19.3 (CH<sub>3</sub>).  
**3-(2-Bromophenyl)-1-(4-methoxyphenyl)-3-(4-(3-methoxyphenyl)-2H-1,2,3-triazol-2-yl)propan-1-one (3c)**  
 Brown viscous liquid; yield: 62.0 mg (63%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.00 (d, J = 8.8 Hz, 2 H), 7.85 (s, 1 H), 7.61 (d, J = 8.0 Hz, 1 H), 7.32–7.26 (m, 3 H), 7.22 (td, J = 0.8, 7.6 Hz, 1 H), 7.15 (td, J = 1.6, 7.6 Hz, 1 H), 6.95–6.92 (m, 4 H), 6.86 (dt, J = 2.4, 7.2 Hz, 1 H), 4.51 (dd, J = 10.8, 17.6 Hz, 1 H), 3.86 (s, OCH<sub>3</sub>, 3 H), 3.80 (s, OCH<sub>3</sub>, 3 H), 3.57 (dd, J = 3.2, 17.6 Hz, 1 H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 193.9 (CO), 163.7 (C), 159.8 (C), 147.6 (C), 139.2 (C), 133.2 (CH), 131.5 (C), 131.3 (CH), 130.5 (2CH), 129.7 (CH), 139.5 (CH), 129.3 (C), 128.0 (CH), 127.4 (CH), 122.0 (C), 118.4 (CH), 114.2 (CH), 113.7 (2CH), 111.1 (CH), 63.5 (CH), 55.4 (OCH<sub>3</sub>), 55.2 (OCH<sub>3</sub>).  
**3-[4-(3-Fluorophenyl)-2H-1,2,3-triazol-2-yl]-1-(4-methoxyphenyl)-3-phenylpropan-1-one (3d)**  
 Pale-yellow solid; yield: 49.8 mg (62%); mp 136.0–137.0 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.00 (d, J = 8.8 Hz, 2 H), 7.82 (s, 1 H), 7.49 (d, J = 7.6 Hz, 1 H), 7.45 (dd, J = 2.0, 10.0 Hz, 1 H), 7.39 (d, J = 7.6 Hz, 2 H), 7.36–7.27 (m, 4 H), 6.99 (td, J = 2.4, 8.4 Hz, 1 H), 6.93 (d, J = 8.8 Hz, 2 H), 6.51 (dd, J = 4.8, 9.2 Hz, 1 H), 4.51 (dd, J = 9.2, 17.6 Hz, 1 H), 3.86 (s, OCH<sub>3</sub>, 3 H), 3.67 (dd, J = 5.2, 17.6 Hz, 1 H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 194.2 (CO), 163.7 (C), 163.0 (d, J = 244.1 Hz, CF), 146.4 (C), 139.3 (C), 132.5 (d, J = 8.6 Hz, C), 131.1 (CH), 130.5 (2CH), 130.2 (d, J = 7.7 Hz, CH), 129.4 (C), 128.8 (2CH), 128.3 (CH), 126.6 (2CH), 121.5 (CH), 115.0 (d, J = 21.0 Hz, CH), 113.8 (2CH), 112.8 (d, J = 22.9 Hz, CH), 64.4 (CH), 55.4 (OCH<sub>3</sub>), 43.5 (CH<sub>2</sub>).  
**3-[4-(3-Fluorophenyl)-2H-1,2,3-triazol-2-yl]-1-(4-methoxyphenyl)-3-(2-tolyl)propan-1-one (3e)**  
 Pale-yellow solid; yield: 5.7 mg (61%); mp 144.0–145.0 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.01 (d, J = 8.8 Hz, 2 H), 7.81 (s, 1 H), 7.49 (d, J = 7.6 Hz, 1 H), 7.44 (d, J = 9.6 Hz, 1 H), 7.33 (q, J = 7.6 Hz, 1 H), 7.23–7.14 (m, 4 H), 6.99 (td, J = 2.0, 8.4 Hz, 1 H), 6.95 (d, J = 8.4 Hz, 2 H), 6.68 (dd, J = 4.4, 9.6 Hz, 1 H), 4.52 (dd, J = 9.6, 17.6 Hz, 1 H), 3.87 (s, OCH<sub>3</sub>, 3 H), 3.58 (dd, J = 4.4, 17.6 Hz, 1 H), 3.59 (s, CH<sub>3</sub>, 3 H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 194.4 (CO), 163.8 (C), 163.0 (d, J = 244.1 Hz, CF), 146.3 (C), 137.7 (C), 135.2 (C), 132.6 (d, J = 7.6 Hz, C), 131.0 (CH), 130.8 (CH), 130.5 (2CH), 130.2 (d, J = 8.6 Hz, CH), 129.4 (C), 128.1 (CH), 126.5 (CH), 125.8 (CH), 121.5 (d, J = 2.9 Hz, CH), 115.0 (d, J = 21.0 Hz, CH), 113.8 (2CH), 112.8 (d, J = 22.9 Hz, CH), 60.7 (CH), 55.5 (OCH<sub>3</sub>), 42.7 (CH<sub>2</sub>), 19.33 (CH<sub>3</sub>).  
**3-[4-(2,5-Dimethoxyphenyl)-2H-1,2,3-triazol-2-yl]-1-(4-methoxyphenyl)-3-(4-nitrophenyl)propan-1-one (3f)**  
 Yellow viscous liquid; yield: 59.6 mg (65%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.17 (d, J = 8.4 Hz, 2 H), 8.12 (s, 1 H), 8.01 (d, J = 7.6 Hz, 2 H), 7.59 (t, J = 8.0 Hz, 1 H), 7.55 (d, J = 8.4 Hz, 2 H), 7.48 (d, J = 7.2 Hz, 2 H), 7.47 (t, J = 7.6 Hz, 1 H), 6.89 (d, J = 8.8 Hz, 1 H), 6.85 (dd, J = 3.2, 8.8 Hz, 1 H), 6.62 (dd, J = 6.4, 7.6 Hz, 1 H), 4.52 (dd, J = 8.0, 17.6 Hz, 1 H), 3.85 (s, OCH<sub>3</sub>, 3 H), 3.83 (dd, J = 6.0,

17.6 Hz, 1 H), 3.76 (s, OCH<sub>3</sub>, 3 H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 195.1 (CO), 153.6 (C), 151.0 (C), 147.6 (C), 146.5 (C), 144.6 (C), 136.0 (C), 135.1 (CH), 133.7 (CH), 128.7 (2CH), 128.1 (2CH), 127.8 (2CH), 124.0 (2CH), 119.4 (C), 114.9 (CH), 113.1 (CH), 112.4 (CH), 63.2 (CH), 55.9 (OCH<sub>3</sub>), 55.7 (OCH<sub>3</sub>), 43.8 (CH<sub>2</sub>).

**3-(4-Chlorophenyl)-3-[4-(2-chlorophenyl)-2H-1,2,3-triazol-2-yl]-1-phenylpropan-1-one (3g)**

Pale-yellow solid; yield: 57.4 mg (68%); mp 84.0–86.0 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.15 (s, 1 H), 8.01 (d, *J* = 7.6 Hz, 2 H), 7.81 (dd, *J* = 2.4, 7.6 Hz, 1 H), 7.58 (t, *J* = 7.6 Hz, 1 H), 7.46 (t, *J* = 7.6 Hz, 2 H), 7.44–7.41 (m, 1 H), 7.38 (d, *J* = 8.4 Hz, 2 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 7.29–7.22 (m, 2 H), 6.53 (dd, *J* = 5.6, 8.4 Hz, 1 H), 4.52 (dd, *J* = 8.4, 18.0 Hz, 1 H), 3.78 (dd, *J* = 5.6, 18.0 Hz, 1 H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 195.4 (CO), 144.9 (C), 137.6 (C), 136.1 (C), 134.3 (CH), 134.2 (C), 133.5 (CH), 131.9 (C), 130.3 (2CH), 129.3 (CH), 128.9 (2CH and C), 128.6 (2CH), 128.2 (2CH), 128.1 (2CH), 126.8 (CH), 63.5 (CH), 43.8 (CH<sub>2</sub>).

**3-[4-(4-Chlorophenyl)-2H-1,2,3-triazol-2-yl]-1-(4-methoxyphenyl)-3-(4-tolyl)propan-1-one (3h)**

White solid; yield: 54.4 mg (63%); mp 125.0–127.0 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.99 (d, *J* = 8.8 Hz, 2 H), 7.79 (s, 1 H), 7.66 (d, *J* = 8.0 Hz, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 7.30 (d, 8.0 Hz, 2 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 6.93 (d, *J* = 8.8 Hz, 2 H), 6.46 (dd, *J* = 5.2, 9.2 Hz, 1 H), 4.49 (dd, *J* = 8.8, 17.6 Hz, 1 H), 3.86 (s, OCH<sub>3</sub>, 3 H), 3.67 (dd, *J* = 5.2, 17.6 Hz, 1 H), 2.31 (s, CH<sub>3</sub>, 3 H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 194.3 (CO), 163.7 (C), 146.4 (C), 138.1 (C), 136.4 (C), 133.9 (C), 130.9 (CH), 130.5 (2CH), 129.4 (2CH), 129.4

(C), 129.0 (C), 128.8 (2CH), 127.1 (2CH), 126.6 (2CH), 113.7 (2CH), 64.2 (CH), 55.4 (OCH<sub>3</sub>), 43.5 (CH<sub>2</sub>), 21.1 (CH<sub>3</sub>).

**3-[4-(3,4-Dimethoxyphenyl)-2H-1,2,3-triazol-2-yl]-3-(4-methoxyphenyl)-1-phenylpropan-1-one (3i)**

Yellow viscous liquid; yield: 54.1 mg (61%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.01 (d, *J* = 7.6 Hz, 2 H), 7.76 (s, 1 H), 7.55 (t, *J* = 7.6 Hz, 1 H), 7.44 (t, *J* = 7.6 Hz, 2 H), 7.35 (d, 8.8 Hz, 2 H), 7.25 (td, *J* = 1.6, 6.0 Hz, 2 H), 6.87–6.84 (m, 3 H), 6.45 (dd, *J* = 5.2, 8.8 Hz, 1 H), 4.51 (dd, *J* = 8.8, 17.6 Hz, 1 H), 3.86 (s, OCH<sub>3</sub>, 3 H), 3.86 (s, OCH<sub>3</sub>, 3 H), 3.74 (s, CH<sub>3</sub>, 3 H), 3.70 (dd, *J* = 5.2, 17.6 Hz, 1 H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 195.9 (CO), 159.3 (C), 149.0 (C), 147.3 (C), 136.3 (C), 133.2 (CH), 131.4 (C), 130.5 (CH), 128.5 (CH), 128.0 (2CH), 128.0 (C, merged with two CH), 127.8 (2CH), 123.2 (C), 118.3 (CH), 114.0 (2CH), 111.0 (CH), 109.0 (2CH), 63.6 (CH), 55.7 (2OCH<sub>3</sub>), 55.1 (OCH<sub>3</sub>) 43.9 (CH<sub>2</sub>).

**3-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-[4-(4-methoxyphenyl)-2H-1,2,3-triazol-2-yl]propan-1-one (3j)**

White solid; yield: 57.3 mg (64%); mp 120.0–122.0 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.97 (d, *J* = 8.8 Hz, 2 H), 7.74 (s, 1 H), 7.65 (d, *J* = 8.4 Hz, 2 H), 7.33 (q, *J* = 8.4 Hz, 2 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 6.91 (dd, *J* = 6.4, 8.4 Hz, 4 H), 6.45 (dd, *J* = 5.6, 8.4 Hz, 1 H), 4.40 (dd, *J* = 8.4, 17.6 Hz, 1 H), 3.85 (s, OCH<sub>3</sub>, 3 H), 3.81 (s, OCH<sub>3</sub>, 3 H), 3.70 (dd, *J* = 5.6, 17.6 Hz, 1 H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 194.1 (CO), 163.8 (C), 159.7 (C), 147.6 (C), 138.1 (C), 134.0 (C), 130.6 (CH), 130.5 (2CH), 129.3 (C), 128.9 (2CH), 128.2 (2CH), 127.2 (2CH), 122.9 (C), 114.1 (2CH), 113.8 (2CH), 63.5 (CH), 55.5 (2OCH<sub>3</sub>), 55.3 (OCH<sub>3</sub>), 43.5 (CH<sub>2</sub>).