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Regioselective Synthesis of β-Aryl Enaminones and 1,4,5-Trisubstituted 1,2,3-Triazoles from Chalcones and Benzyl Azides

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Abstract: A highly regioselective synthesis of β-aryl enaminones and 1,4,5-trisubstituted 1,2,3-triazoles from chalcones and benzyl azides based on reaction solvent selection is reported. In the presence of a catalytic amount of $Ce(OTf)_3$, reactions of chalcones with benzyl azides in DMF at 100 °C afforded densely substituted *Z*-β-aryl enaminones in good to excellent yields, whereas treatment of chalcones with benzyl azides in toluene at 100 °C selectively produced 1,4,5-trisubstituted 1,2,3-triazoles in excellent yields.

Keywords: benzyl azides; chalcones; enaminones; rare earth metals; 1,4,5-trisubstituted 1,2,3-triazoles

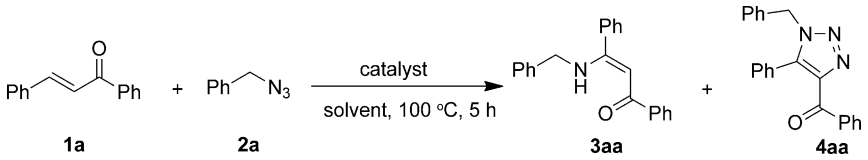
Enaminones are a highly versatile class of intermediates for the synthesis of natural products and pharmaceutical compounds.[1] These compounds have been synthesized *via* the direct condensation of 1,3-dicarbonyl compounds with amines,[2] or *via* reactions between metal enolates and imine derivatives,[3] or *via* cleavage of heterocycles in addition to some novel unconventional routes.[4] Due to their structural features, the *Z* and *E* isomers of enaminones have exhibited different chemical reactivities and electronic characteristics in synthetic and coordination chemistry.[5] However, to the best of our knowledge, reports about the highly regioselective synthesis of *Z* isomers of enaminones are very rare.[6] Besides, there is no synthetic method reported up to date for the synthesis of densely substituted *Z*-isomers of β-aryl enaminones derivatives from azides and chalcones.

1,2,3-Triazoles are an important class of heterocyclic compounds that exhibit a number of important biological properties.[7] So far, extensive works have generated many approaches for the synthesis of 1,4- or 1,5-disubstituted 1,2,3-triazoles.[8] Recently, the synthesis and applications of 1,4,5-trisubstituted 1,2,3-triazoles have received significant attention as biologically important heterocycles.[9] However, only a limited number of methods for the synthesis of fully substituted 1,2,3-triazoles have been described.[10] Therefore, the development of new methods for their synthesis from readily available starting materials is still highly desired.

In recent years, the use of rare earth metal-catalyzed reactions has emerged as a versatile tool for developing syntheses due to their numerous advantages, namely, their relatively high efficiency, water compatibility, mild reaction conditions and eco-friendly catalytic features.[11] During our studies on the use of rare earth metal-catalyzed reactions, we investigated the reactions of chalcones with benzyl azides under different conditions. As a result, we achieved the regioselective synthesis of *Z*-isomers of densely substituted β-aryl enaminones and 1,4,5-trisubstituted 1,2,3-triazoles by variation of the reaction solvent. Herein, we wish to report our preliminary results and present the involved mechanisms.

We selected chalcone **1a** as the model compound to examine its behavior under different conditions (Table 1). Upon treatment of a 1:1.2 mixture of **1a** and benzyl azide **2a** with 5 mol% $Ce(OTf)_3$ in DMF at 100 °C for 5 h, the reaction proceeded smoothly as indicated by TLC and a white solid as the major product was obtained in 82% isolated yield (Table 1, entry 1). The product was characterized as (*Z*)-3-(benzylamino)-1,3-diphenylprop-2-en-1-one **3aa** on

Table 1. Optimization of reaction conditions.[a]



1a **2a** **3aa** **4aa**

Entry	Catalyst	Solvent	Yield of **3aa** [%][b]	Yield of **4aa** [%][c]
1	**$Ce(OTf)_3$ (5 mol%)**	**DMF**	**82**	<5
2[d]	none	DMF	27	<5
3	$Cu(OTf)_2$ (5 mol%)	DMF	0	0
4	$In(OTf)_3$ (5 mol%)	DMF	0	0
5	$Bi(OTf)_3$ (5 mol%)	DMF	0	<5
6	$Pd(OAc)_2$ (5 mol%)	DMF	0	0
7	CuI (5 mol%)	DMF	0	<5
8	$[Rh(COD)Cl]_2$(5 mol%)	DMF	0	<5
9	$Zn(OTf)_2$ (5 mol%)	DMF	<5	0
10	$InCl_3$ (5 mol%)	DMF	<5	0
11	$Y(OTf)_3$ (5 mol%)	DMF	<5	32
12	$Sm(OTf)_3$ (5 mol%)	DMF	75	<5
13	$Sc(OTf)_3$ (5 mol%)	DMF	65	<5
14	$Er(OTf)_3$ (5 mol%)	DMF	62	<5
15	$La(OTf)_3$ (5 mol%)	DMF	71	<5
16	$Pr(OTf)_3$ (5 mol%)	DMF	59	<5
17	**$Ce(OTf)_3$ (5 mol%)**	**toluene**	<5	**85**
18	$Ce(OTf)_3$ (5 mol%)	DMSO	0	0
19	$Ce(OTf)_3$ (5 mol%)	PhCl	<5	25
20	$Ce(OTf)_3$ (5 mol%)	CH_3CN	<5	28
21	$Ce(OTf)_3$ (5 mol%)	1,4-dioxane	0	0

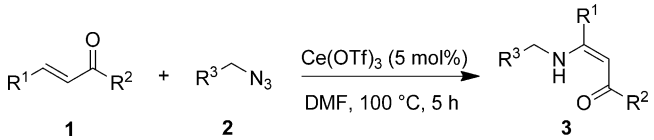
[a] Carried out with 0.5 mmol of chalcone **1a** and 0.6 mmol of benzyl azide **2a** in the presence of catalyst in solvent (2 mL) at 100 °C for 5 h (except for entry 2).
[b] Isolated yield of pure product based on **1a**.
[c] Isolated yield of pure product based on **1a**.
[d] Carried out with 0.5 mmol of chalcone **1a** and 0.6 mmol of benzyl azide **2a** in DMF (2 mL) at 100 °C for 3 days.

the basis of its spectral and analytical data. The ^1H NMR spectra of **3aa** in $CDCl_3$ shows a broad absorption peak near 11.74 ppm, suggesting that there is a strong intramolecular hydrogen bonding between the amine hydrogen and the carbonyl oxygen atom. Additionally, the doublet absorption peak of the benzylic hydrogens at about 4.37 ppm ($J = 6.5$ Hz) indicates that the benzyl group can freely rotate when dissolved in solution.[12]

Without any catalysts, chalcone **1a** reacted with benzyl azide **2a** in DMF at 100 °C to give **3aa** in a low yield (27%) after a long reaction time (3 days) (Table 1, entry 2). Scanning a variety of catalysts for the above transformation, it was found that other metal catalysts, such as $Cu(OTf)_2$, $In(OTf)_3$, $Bi(OTf)_3$, $Pd(OAc)_2$, CuI or $[Rh(COD)Cl]_2$, were not effective for this conversion (Table 1, entries 3–8), and only a trace of desired product **3aa** was detected with $Zn(OTf)_2$, $InCl_3$, and $Y(OTf)_3$ as the catalysts (Table 1, entries 9–11). Among the different rare earth metal catalysts, $Ce(OTf)_3$ was found to be the catalyst of choice for this transformation (Table 1, entry 1 *vs.* entries 12–16). The reactions were obviously restrained when they were performed in DMSO, PhCl, CH_3CN or 1,4-dioxane (Table 1, entries 18–21), however, when **1a** and benzyl azide **2a** were allowed to react in toluene in the presence of $Ce(OTf)_3$ at 100 °C for 5 h, a colorless oil was unexpectedly generated as the major product in 85% isolated yield, which was characterized as (1-benzyl-5-phenyl-1*H*-1,2,3-triazol-4-yl)(phenyl)methanone **4aa** on the basis of its spectral and analytical data (Table 1, entry 17).

Using our optimized experimental conditions, the scope of the $Ce(OTf)_3$-catalyzed formation of β-aryl enaminones was examined. Thus, a series of chalcones was surveyed in reactions with benzyl azide under identical conditions as described for **3aa** (Table 1, entry 1), and the results are summarized in Table 2. It was observed that a wide range of R^1 and R^2 groups (aromatic and heteroaromatic) were well tolerated, providing the corresponding β-aryl enaminones with complete regioselectivities, and the *Z* double bond geometry was assigned based on spectroscopic trends throughout the series. Chalcones bearing electron-

Table 2. Substrate scope for the reaction of chalcones **1** and benzyl azides **2** in DMF.[a]



1 2 3

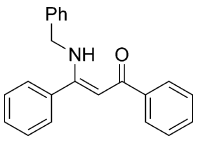
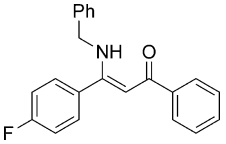
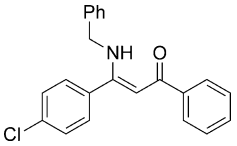
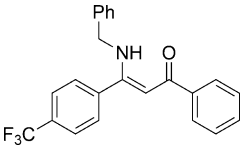
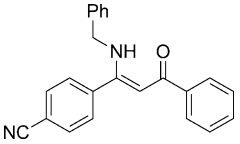
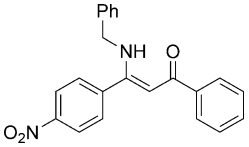
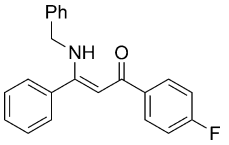
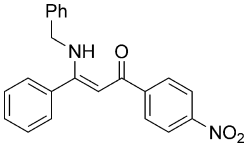
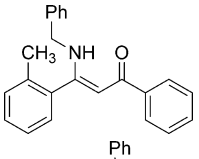
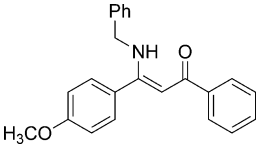
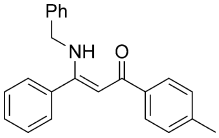
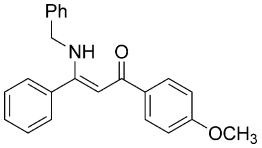
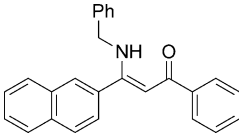
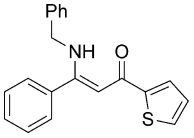
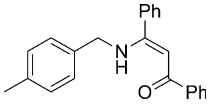
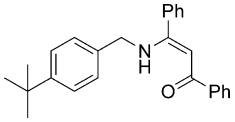
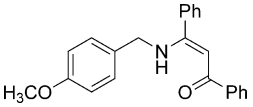
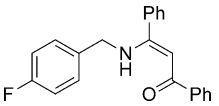
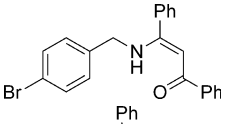
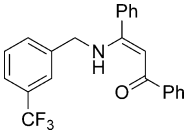
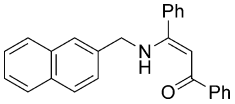
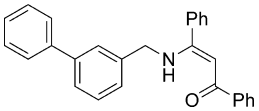
Entry	Chalcone	Azide	Product	Yield [%][b]
1	**1a:** R^1 = Ph; R^2 = Ph	**2a:** R^3 = Ph	**3aa** 	82
2	**1b:** R^1 = 4-F-C_6H_4; R^2 = Ph	**2a:** R^3 = Ph	**3ba** 	89
3	**1c:** R^1 = 4-Cl-C_6H_4; R^2 = Ph	**2a:** R^3 = Ph	**3ca** 	92
4	**1d:** R^1 = 4-CF_3-C_6H_4; R^2 = Ph	**2a:** R^3 = Ph	**3da** 	90
5	**1e:** R^1 = 4-CN-C_6H_4; R^2 = Ph	**2a:** R^3 = Ph	**3ea** 	88
6	**1f:** R^1 = 4-NO_2-C_6H_4; R^2 = Ph	**2a:** R^3 = Ph	**3fa** 	86
7	**1g:** R^1 = Ph; R^2 = 4-F-C_6H_4	**2a:** R^3 = Ph	**3ga** 	85
8	**1h:** R^1 = Ph; R^2 = 4-NO_2-C_6H_4	**2a:** R^3 = Ph	**3ha** 	87
9	**1i:** R^1 = 2-Me-C_6H_4; R^2 = Ph	**2a:** R^3 = Ph	**3ia** 	78
10	**1j:** R^1 = 4-MeO-C_6H_4; R^2 = Ph	**2a:** R^3 = Ph	**3ja** 	73

Table 2. (Continued)

Entry	Chalcone	Azide		Product	Yield [%][b]
11	**1k:** R^1 = Ph; R^2 = 4-Me-C_6H_4	**2a:** R^3 = Ph	**3ka**		75
12	**1l:** R^1 = Ph; R^2 = 4-MeO-C_6H_4	**2a:** R^3 = Ph	**3la**		71
13	**1m:** R^1 = 2-naphthyl; R^2 = Ph	**2a:** R^3 = Ph	**3ma**		84
14	**1n:** R^1 = Ph; R^2 = 2-thienyl	**2a:** R^3 = Ph	**3na**		76
15	**1a:** R^1 = Ph; R^2 = Ph	**2b:** R^3 = 4-Me-C_6H_4	**3ab**		87
16	**1a:** R^1 = Ph; R^2 = Ph	**2c:** R^3 = 4-$(Me)_3C$-C_6H_4	**3ac**		83
17	**1a:** R^1 = Ph; R^2 = Ph	**2d:** R^3 = 4-MeO-C_6H_4	**3ad**		90
18	**1a:** R^1 = Ph; R^2 = Ph	**2e:** R^3 = 4-F-C_6H_4	**3ae**		75
19	**1a:** R^1 = Ph; R^2 = Ph	**2f:** R^3 = 4-Br-C_6H_4	**3af**		73
20	**1a:** R^1 = Ph; R^2 = Ph	**2g:** R^3 = 3-CF_3-C_6H_4	**3ag**		70
21	**1a:** R^1 = Ph; R^2 = Ph	**2h:** R^3 = 2-naphthyl	**3ah**		83
22	**1a:** R^1 = Ph; R^2 = Ph	**2i:** R^3 = 3-biphenyl	**3ai**		80

[a] *Reactions conditions:* 0.5 mmol of chalcone **1** and 0.6 mmol of benzyl azide **2** in the presence of $Ce(OTf)_3$ (5 mol%) in 2 mL of DMF at 100 °C for 5 h.
[b] Isolated yield of pure product based on **1**.

withdrawing substituents on the aryl ring facilitated the reaction with excellent yields (Table 2, entries 2–8). The structures of **3ca** and **3fa** were confirmed unambiguously by X-ray diffraction analysis, respectively (Figure 1 and Figure 2). Electron-rich chalcones were also found to be suitable substrates for this reac-

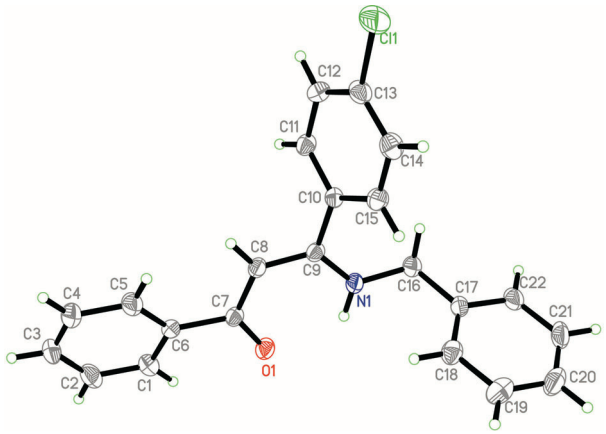


Figure 1. X-ray crystal structure of β-aryl enaminone **3ca** (CCDC 1000109 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif).

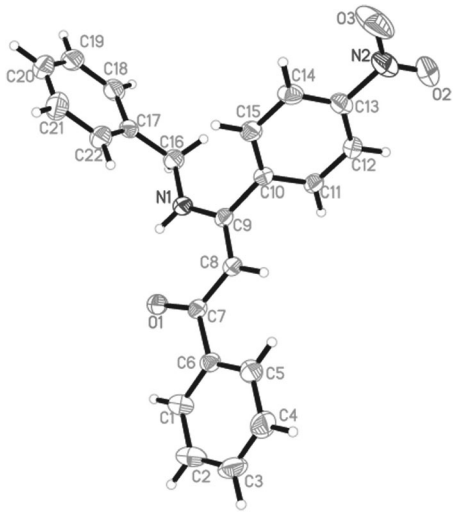


Figure 2. X-ray crystal structure of β-aryl enaminone **3fa** (CCDC 1000110 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif).

tion (Table 2, entries 9–12). A substrate with steric hindrance (*o*-CH_3) participated well under the reaction conditions (Table 2, entry 9).

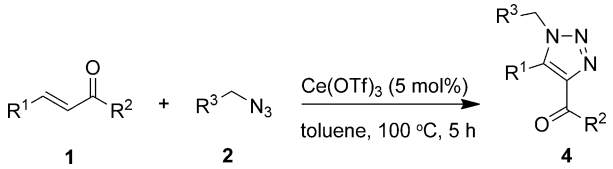
As for the azide substrates, obviously, electron-rich benzyl azides provided the desired products in higher yields than did electron-poor benzyl azides (Table 2, entries 15–17 *vs.* entries 18–20). Besides, polycyclic aromatic benzyl azides furnished the corresponding enaminones in good yields (Table 2, entries 21 and 22). Unfortunately, the phenyl and other aliphatic azides are not appropriate starting materials under the reaction conditions described herein.

The above findings led us to envisage that under appropriate conditions, the regioselective synthesis of 1,4,5-trisubstituted 1,2,3-triazoles may be realized. Thus, optimization of the 1,4,5-trisubstituted 1,2,3-triazole synthesis was also investigated. After a series of experiments, the optimal results could be obtained when the reaction of chalcone **1a** and benzyl azide **2a** were conducted in toluene at 100 °C for 5 h, whereby 1,4,5-trisubstituted 1,2,3-triazole **4aa** was obtained in 85% isolated yield (see Table S1, entry 2 in the Supporting Information).

Under the optimal conditions as for **4aa**, a range of reactions of selected chalcones **1** and benzyl azide **2** was carried out, aiming to determine the scope of the 1,4,5-trisubstituted 1,2,3-triazole synthesis, and the results are summarized in Table 3. It was found that the nature of the substituent and its position in the aromatic ring (R^1 or R^2) little influenced the reactivity of the substrate. All the reactions proceeded smoothly to afford the corresponding 1,4,5-trisubstituted 1,2,3-triazoles in good to excellent yields (77–93%). Especially, substrates bearing one or two halogen groups on the aromatic ring gave the most desirable results, providing the corresponding products **4ba**, **4oe**, **4pa** and **4ga** in 90%, 93%, 89% and 87% isolated yields, respectively, and in these cases, the other regioisomeric products were not even detected (Table 3, entries 2–4 and entry 9). Heterocyclic substrates also provided good results (Table 3, entries 15 and 16). In the case of benzyl azides, the substituent effect on the benzene rings was not apparent, either with an electron-donating or an electron-withdrawing group on the benzene ring, benzyl azides gave the corresponding 1,4,5-trisubstituted 1,2,3-triazoles in high yields (Table 3, entries 17 and 18). Unfortunately, phenyl and other aliphatic azides failed to generate the desired products under these reaction conditions.

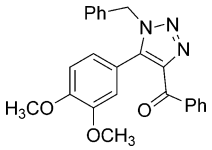
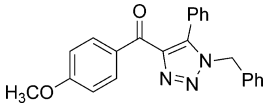
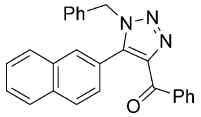
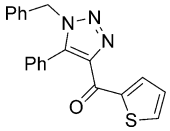
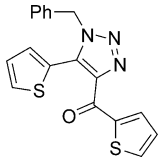
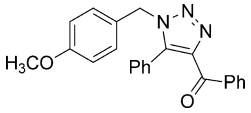
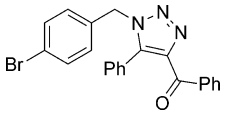
A plausible mechanism for this $Ce(OTf)_3$-promoted reaction of chalcones with benzyl azides is outlined in Scheme 1. The first step of the reaction is the regioselective 1,3-dipolar cycloaddition of benzyl azide with chalcone to form the triazoline intermediate **5**, probably rare earth metal complexes accelerated the reaction by increasing the electrophilicity of the chalcone through coordination. In toluene, the oxidation of the triazoline intermediate **5** leads to 1,4,5-trisubstituted 1,2,3-triazoles **4**.[13] However, in DMF, as pointed out by Aubé and co-workers,[4a] the unstable triazoline intermediate **5** undergoes decomposition to produce a zwitterionic species **6**, and 1,2-hydrogen migration onto the leaving diazonium species results in formation of the imine intermediate **7**, which thus yields β-aryl enaminone **3** followed by 1,3-hydrogen shift. The selective production of **3** suggested that the 1,2-hydrogen migration predominated over 1,2-phenyl (R^1) migration.

Table 3. Substrate scope for the reaction of chalcones **1** and azides **2** in toluene.[a]

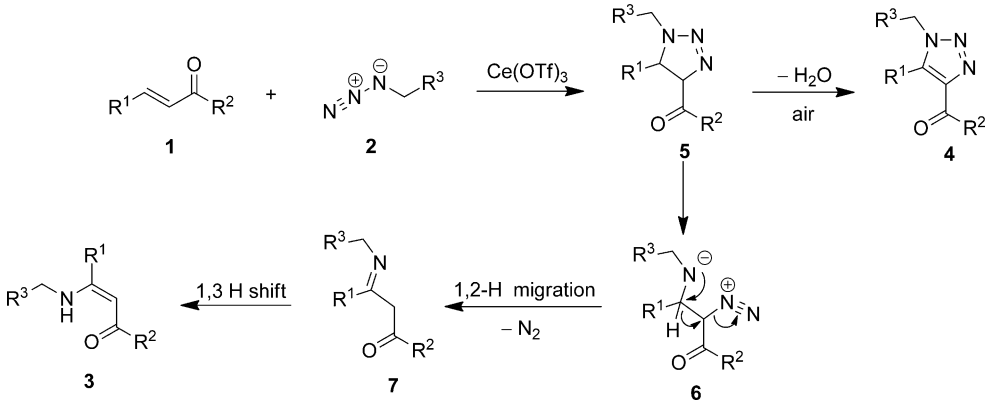


Entry	Chalcone	Azide	Product	Yield [%][b]
1	**1a:** R^1 = Ph; R^2 = Ph	**2a:** R^3 = Ph	**4aa**	85
2	**1b:** R^1 = 4-F-C_6H_4; R^2 = Ph	**2a:** R^3 = Ph	**4ba**	90
3	**1o:** R^1 = 3-Br-C_6H_4; R^2 = Ph	**2a:** R^3 = Ph	**4oa**	93
4	**1p:** R^1 = 2-F-6-Cl-C_6H_3; R^2 = Ph	**2a:** R^3 = Ph	**4pa**	89
5	**1f:** R^1 = 4-NO_2-C_6H_4; R^2 = Ph	**2a:** R^3 = Ph	**4fa**	83
6	**1q:** R^1 = 2-NO_2-C_6H_4; R^2 = Ph	**2a:** R^3 = Ph	**4qa**	80
7	**1d:** R^1 = 4-CF_3-C_6H_4; R^2 = Ph	**2a:** R^3 = Ph	**4da**	85
8	**1e:** R^1 = 4-CN-C_6H_4; R^2 = Ph	**2a:** R^3 = Ph	**4ea**	86
9	**1g:** R^1 = Ph; R^2 = 4-F-C_6H_4	**2a:** R^3 = Ph	**4ga**	87
10	**1h:** R^1 = Ph; R^2 = 4-NO_2-C_6H_4	**2a:** R^3 = Ph	**4ha**	81
11	**1i:** R^1 = 2-Me-C_6H_4; R^2 = Ph	**2a:** R^3 = Ph	**4ia**	77

Table 3. (Continued)

Entry	Chalcone	Azide	Product	Yield [%][b]
12	**1r:** R^1 = 3,4-$(MeO)_2C_6H_3$; R^2 = Ph	**2a:** R^3 = Ph	**4ra** 	81
13	**1l:** R^1 = Ph; R^2 = 4-MeO-C_6H_4	**2a:** R^3 = Ph	**4la** 	82
14	**1m:** R^1 = 2-naphthyl; R^2 = Ph	**2a:** R^3 = Ph	**4ma** 	82
15	**1n:** R^1 = Ph; R^2 = 2-thienyl	**2a:** R^3 = Ph	**4na** 	85
16	**1s:** R^1 = 2-thienyl; R^2 = 2-thienyl	**2a:** R^3 = Ph	**4sa** 	83
17	**1a:** R^1 = Ph; R^2 = Ph	**2d:** R^3 = 4-OMe-C_6H_4	**4ad** 	86
18	**1a:** R^1 = Ph; R^2 = Ph	**2f:** R^3 = 4-Br-C_6H_4	**4af** 	84

[a] *Reactions conditions:* 0.5 mmol of chalcone **1** and 0.6 mmol of benzyl azide **2** in the presence of $Ce(OTf)_3$ (5 mol%) in 2 mL of toluene at 100 °C for 5 h.
[b] Isolated yield of pure product based on **1**.



Scheme 1. A plausible reaction mechanism.

In summary, we have developed a facile and efficient synthesis of β-aryl enaminones and 1,4,5-trisubstituted 1,2,3-triazoles from readily available chalcones in a highly regioselective manner by variation of the reaction solvent. Good yields, high regioselectivity, easily available starting materials and experimentally convenient catalytic process make it an attractive alternative to the contemporary synthetic

routes. Further study on extension of the scope of the present protocol to construct the biologically active molecules is ongoing in our laboratory.

Experimental Section

General Experimental Procedure for Synthesis of β-Aryl Enaminones 3

A mixture of chalcone (1.0 equiv., 0.5 mmol), benzyl azide (1.2 equiv., 0.6 mmol), $Ce(OTf)_3$ (0.05 equiv., 0.025 mmol), and 2 mL of DMF was heated (100 °C) and stirred at 100 °C for 5 h. The progress of the reaction was monitored by thin-layer chromatography. Upon cooling to room temperature, the reaction mixture was diluted with H_2O (10 mL), extracted with ethyl acetate (3×10 mL). The organic extract was washed with H_2O (3×5 mL), dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated to dryness under reduced pressure and the residue was purified by flash column chromatography (petroleum ether/ethyl acetate) to afford β-aryl enaminones **3**.

General Experimental Procedure for Synthesis of 1,4,5-Trisubstituted 1,2,3-Triazoles 4

A mixture of chalcone (1.0 equiv., 0.5 mmol), benzyl azide (1.2 equiv., 0.6 mmol), $Ce(OTf)_3$ (0.05 equiv., 0.025 mmol), and 2 mL of toluene was refluxed at 100 °C for 5 h. The progress of the reaction was monitored by thin-layer chromatography. The mixture was then cooled and evaporated under reduced pressure. The target product **4** was purified by column chromatography on silica gel using a mixture of ethyl acetate and petroleum ether. *[**CAUTION**: Sufficient care has to be exercised while handling organic azides because of their explosive nature.]*

Supporting Information

General experimental procedures, and spectral data, NMR spectra, high resolution mass spectra for all compounds, and X-ray crystallographic files (CIF) for **3ca** and **3fa** are given in the Supporting Information.

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