Synthesis T. Opsomer et al. Special Topic

Chemoselectivity in the Synthesis of 1,2,3-Triazoles from Enolizable Ketones, Primary Alkylamines, and 4-Nitrophenyl Azide

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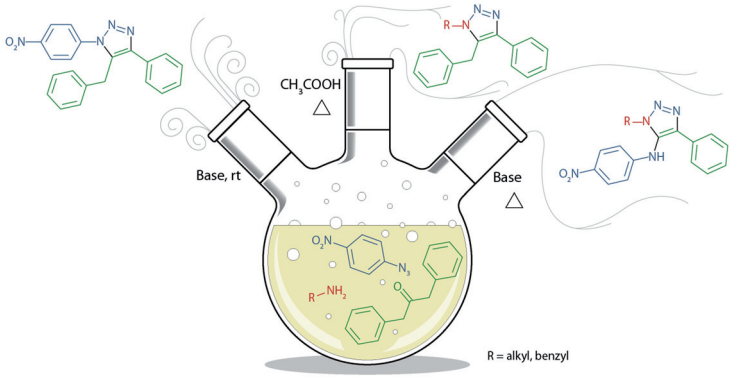

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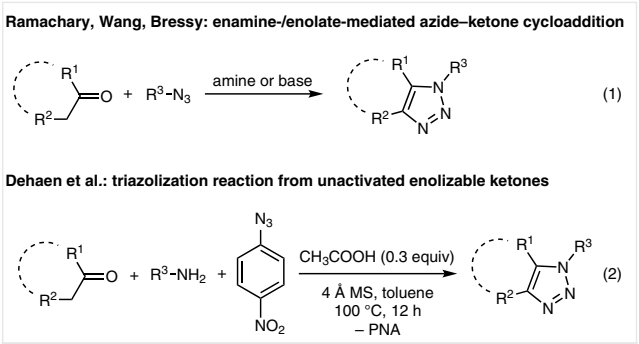
Abstract In recent years, several organocatalytic/metal-free synthetic pathways towards 1,2,3-triazoles have been reported. One of them is a general metal-free route towards the synthesis of 1,5-di- or fully-substituted 1,2,3-triazoles, designed by our group and named the 'triazolization' reaction of ketones. Limitations of this route were encountered in reactions with more activated ketones, where the corresponding 1-(4-nitrophenyl)-1,2,3-triazole was found back as the major product. Interestingly, three different triazoles are formed when 1,3-diphenylacetone is used as the ketone. In the present work, 1,3-diphenylacetone was used as a model substrate to investigate the chemoselectivity of our metal-free route under different reaction circumstances. This led to the conclusion that the formation of the desired 1,2,3-triazole is favored in apolar solvents, at high temperatures, and in the presence of acetic acid. By using one equivalent of acetic acid, previously inaccessible fully decorated 1,2,3-triazoles can be synthesized from simple α-arylketones in moderate to high yields.

Key words 1,2,3-triazole, triazolization, metal-free, multicomponent reaction, α-arylketone, Dimroth

In the past decade, 1,2,3-triazole chemistry gained a lot of attention in the field of synthetic, material, and medicinal chemistry.[2–4] With regards to the latter, the 1,2,3-triazole moiety is believed to be an effective amide isoster because of its large dipole moment, capability for H-bond formation, and metabolic stability. As examples have shown that functionalized triazoles often possess interesting biological properties, they can be seen as potential targets for drug discovery.[3e,4] The renewed interest in 1,2,3-triazoles started with the discovery of the Cu-catalyzed azide-alkyne cycloaddition (AAC) reaction towards 1,4-disubstituted 1,2,3-triazoles. The CuAAC, together with the Ru-catalyzed AAC reaction, still remains the synthetic route with the largest impact.[5] However, the use of toxic heavy metals is a limiting factor for some spectroscopy or medicinal applications, for example, perturbation of naturally occurring processes in biological systems.[6] In addition, the alkyne moieties are not always readily available and their introduction often requires a difficult multistep synthesis. Hence, in recent years, the search for metal-free and organocatalytic routes toward 1,2,3-triazoles has become a thriving area.[7]

Various amines and organic bases have been successfully applied as catalysts in reactions toward 1,2,3-triazole heterocycles.[8] Depending on the nature of the catalyst and the reagents, either an enamine, iminium ion, or enolate occurs as a dipolarophilic intermediate in the reaction mechanism.[7] The in situ formed dipolarophiles can then react with an azido compound. Many of these routes are similar to the previously reported Dimroth reaction, described by L'abbé as 'the condensation of organic azides with active methylene compounds in the presence of an equimolar amount of organic or inorganic base leading to highly substituted 1,2,3-triazoles in a regioselective manner'.[9] The organocatalytic reactions leading to diversely functionalized 1,2,3-triazoles are of high synthetic importance due to their advantages; they are metal-free, regioselective, and they make use of cheap and readily available building blocks. However, there are a number of weaknesses. First, the substituents at the N1 position are limited to aryl groups, as in most cases only aryl azides can be applied. Second, a different azide is needed for the synthesis of each analogue. These azides are potentially hazardous and in many cases commercially not available.[10]

In response to these shortcomings and the scarceness of selective pathways toward the synthesis 1,5-disubstituted 1,2,3-triazoles,[11] our group has recently developed a metal-free and regioselective three-component reaction (Scheme 1, Eq. 2).[10] This reaction was named the 'triazolization' reaction and provides synthetic access to 1,5-di- and fully-substituted 1-alkyl-1,2,3-triazoles, some of them being previously inaccessible. A major advantage is

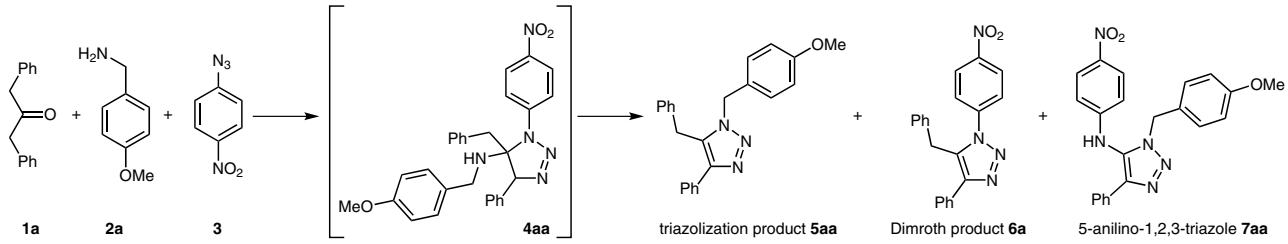


Scheme 1 Cyclization reactions with enolizable ketones for the synthesis of highly functionalized 1,2,3-triazoles

the use of readily available primary alkylamines and enolizable ketones as starting materials. In the triazolization reaction, a triazoline intermediate is formed via regioselective cycloaddition of 4-nitrophenyl azide (4-NPA) onto an enamine, this latter being derived from the condensation between the amine and ketone in situ. Subsequently, ring-opening and alternative ring-closure of the intermediate generates the desired triazole. Along with aromatization, a molecule of *p*-nitroaniline (PNA) is eliminated. The use of 4-NPA as a renewable dinitrogen source can be seen as another important feature.[10]

So far, the scope of the triazolization reaction, under the optimized conditions, has been limited to unactivated enolizable ketones. Organocatalytic routes toward 1,2,3-triazoles from different activated enolizable ketones have been described in literature, mainly by the groups of Ramachary and Wang (Scheme 1, Eq. 1).[8b,k] However, the scope of these reactions is mostly limited to 1-aryl-1,2,3-triazoles, as previously stated. Aiming to synthesize 1-alkyl-1,2,3-triazoles starting from activated methylene ketones, one can think of the triazolization reaction as a possible strategy. In this article, the relevance of this idea will be proven via investigation of the triazolization reaction between 1,3-diphenylacetone (1,3-DPA, **1a**), *p*-methoxybenzylamine (PMBA, **2a**), and 4-NPA (**3**) as reactants, which intriguingly led to the formation of three different triazole compounds (Table 1). In an acid-free reaction mixture, the desired triazolization product **5aa** represented only a minor fraction of the 1,2,3-triazoles being formed. A 1-(4-nitrophenyl)-1,2,3-triazole (**6a**), in contrast, was found back as the major product. As this triazole is formed via a Dimroth type of reaction, it is referred to as the Dimroth product. Based on known literature about azide-ketone [3+2] cycloaddition reactions, it can be stated that the Dimroth product **6a** is formed via either an enolate- or an enamine-mediated cycloaddition reaction.[8a–i,8k] Aromatization of the triazoline intermediate **4aa** occurs upon elimination of water or the amine, respectively. As the α-protons of α-arylketones are rather acidic, the C4 proton of the triazoline can

Table 1 Proportion of the 1,2,3-Triazole Products **5aa**, **6a** and **7aa**, Relative to the Total Triazole Content



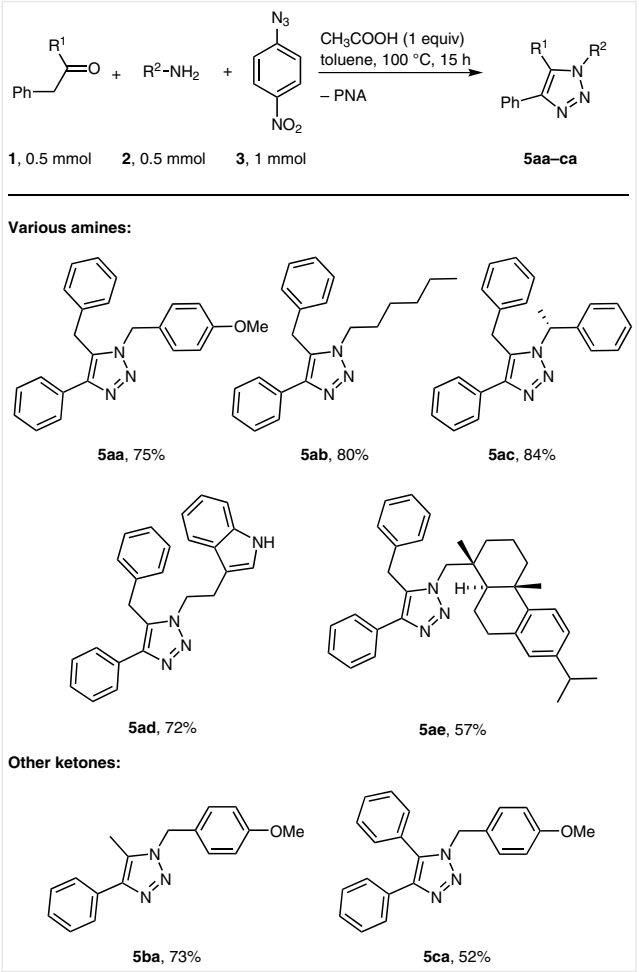
Entry	Temp (°C)	AcOH[a]	PMBA (**2a**)[a]	4-NPA (**3**)[a]	Solvent	**5aa**[b]	**6a**[b]	**7aa**[b]
1	100	–	1	2	toluene	21	48	31
2	100	–	3	2	toluene	3	59	38
3	100	–	1	2	DMF	0	88	12
4	50	–	1	2	toluene	3	74	23
5	50	0.3	1	2	toluene	12	75	13
6	100	0.3	1	2	toluene	70	27	3
7	100	1	1	2	toluene	91	7	2
8	100	–	3	3	toluene	3	54	43
9[c]	100	–	1	2[d]	toluene	61	20[d]	0

[a] In equivalents with respect to the amount of 1,3-DPA (**1a**; 0.5 mmol).
[b] Percentage of the total triazole content in the crude mixture, determined from the ^{1}H NMR spectra.
[c] Reaction performed with 4-azidobenzonitrile instead of 4-NPA.
[d] This concerns the 4-cyanophenyl analogue.

be more readily abstracted compared to unactivated ketones. Therefore, it is not surprising that the Dimroth triazole is obtained as the major compound in an acid-free reaction where an amine, such as PMBA, can act as a base to facilitate the abstraction of the α-proton (Table 1, entry 1). The third compound, isolated from the reaction with 1,3-DPA, was a 5-anilino-1,2,3-triazole (5-AT) **7aa**. This type of product was previously not observed in any triazolization reaction and has, to this date, not been synthesized by other means.

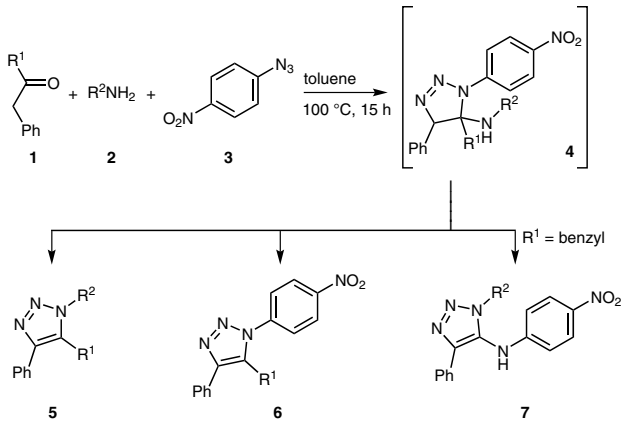
The remarkable reaction between 1,3-DPA (**1a**), PMBA (**2a**), and 4-NPA (**3**) was studied more in detail by repeating the reaction under modified conditions. For each of the reactions, the contribution of the different triazole compounds, relative to the total triazole content in the reaction mixture, was roughly determined from the crude ^{1}H NMR spectra after a reaction time of 15 hours (Table 1). Interestingly, when the reaction was performed with a large excess of amine, the triazolization product **5aa** lost ground both in favor of the Dimroth product **6a** and 5-AT **7aa** (Table 1, entry 2). This indicates that the formation of the 5-AT is favored in acid-free/basic medium. Next, few experiments were carried out to check the influence of solvent polarity and temperature. According to the observations, the use of a polar solvent and performing the reaction at lower temperatures increases the amount of Dimroth triazole (entries 3–5). One experiment was carried out to check the influence of solvent polarity. DMF was chosen as a high boiling polar solvent in which the acid-free reaction was repeated. Both the relative amount of triazolization product and the 5-AT are lower compared to the reaction in toluene. In fact, the triazolization product is not detected in the reaction mixture with DMF. The conditions that favor formation of the Dimroth product are combined in the azide-ketone cycloaddition reaction developed by Ramachary et al., who were able to synthesize fully substituted triazoles in DMSO at room temperature and in the presence of a catalytic amount of DBU.[8k] Applying the procedure of Ramachary et al. on 1,3-DPA, using 4-NPA, compound **6a** could be synthesized in 83% isolated yield. This result showed that 1,3-DPA can be added to the scope of ketones, which already included phenylacetone, deoxybenzoin, and various derivatives of these α-arylketones.

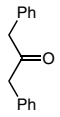
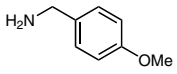
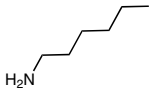
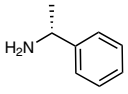
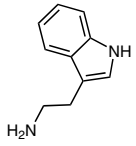
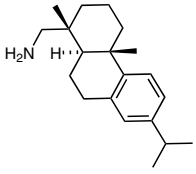
Given that the formation of the Dimroth product and the 5-AT is base-/amine-catalyzed, it was surmised that acidifying the reaction medium would change the reaction outcome. Indeed, in the presence of one equivalent of acetic acid, the triazolization product was almost exclusively formed (Table 1, entry 7). Comparing the reactions at 50 °C and 100 °C (Table 1, entries 5–6), one can conclude that the triazolization reaction is favored at higher temperatures. Complementing this with the need for an apolar solvent, a reaction in toluene at 100 °C with acetic acid can be put forward as the method of choice for the synthesis of 1-alkyl-1,2,3-triazoles from 1,3-DPA (Scheme 2). At this point, the explanation for the observed enhancement of the triazolization reaction in the presence of acetic acid still remains uncertain. However, the current findings support the idea that the N3 nitrogen of the triazoline has to be protonated in order for ring-opening to occur, an idea which was postulated earlier by our group as being part of the triazolization mechanism.[10] Another observation underpinning this hypothesis was the outcome of an acid-free reaction between 1,3-DPA, PMBA, and 4-azidobenzonitrile. The triazolization product to Dimroth triazole ratio was found to be 3, where this was 0.44 for the reaction with 4-NPA under the same conditions (Table 1, entries 1 and 9). A plausible explanation may be an increase in basicity of the N3 nitrogen of the triazoline intermediate, as a result of the less electron-withdrawing nature of the nitrile substituent, allowing protonation and subsequent ring-opening to be faster. Although the triazolization reaction is favored when using 4-azidobenzonitrile, the total yield of all triazoles combined is not higher compared to the reaction with 4-



Scheme 2 Synthesis of fully substituted 1,2,3-triazoles from α-arylketones **1**, primary amines **2**, and 4-NPA (**3**). Scope with respect to amines and ketones.

Table 2 Influence of Substrates in Acid-Free Three-Component Reactions[a]



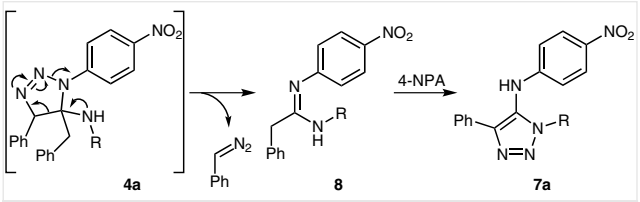
Entry	Ketone		Amine		Product, Yield (%)[b]		
1	**1a**		**2a**		**5aa**, 20	**6a**, 45	**7aa**, 29
2	**1a**		**2b**		**5ab**, n.d.	**6a**, 58	**7ab**, 34
3	**1a**		**2c**		**5ac**, 50	**6a**, 6	**7ac**, 16
4	**1a**		**2d**		**5ad**, 9	**6a**, 44	**7ad**, 35
5	**1a**		**2e**		**5ae**, 38	**6a**, 9	**7ae**, 23
6	**1b**		**2a**		**5ba**, 21	**6b**, 60	n.a.
7[c]	**1b**		**2a**		**5ba**, 73	**6b**, 15	n.a.
8	**1c**		**2a**		**5ca**, 12	**6c**, 74	n.a.
9[c]	**1c**		**2a**		**5ca**, 52	**6c**, 20	n.a.

[a] Unless indicated, all reactions were performed under the following conditions: **1** (0.5 mmol), **2** (1 equiv), **3** (2 equiv), toluene (0.5 mL), 100 °C, 15 h.
[b] Isolated yield. n.d.: Not detected; n.a.: Not applicable.
[c] CH_3COOH (1 equiv).

NPA (acid-free conditions). In the presence of one equivalent of acetic acid, the reaction with 1,3-DPA, PMBA, and 4-azidobenzonitrile furnished the triazolization product with a comparable yield of 72%.

Under the optimized conditions for the triazolization reaction, 1,2,3-triazole compounds **5aa–ae** from 1,3-DPA and various amines were synthesized in moderate to high yields (Scheme 2). The scope of ketones was also explored to some extent. An obvious example was the triazolization product **5ba** from phenylacetone, which could be isolated in 73% yield with complete regioselectivity (Table 2, entry 7). For the slightly more activated deoxybenzoin, the optimized reaction afforded the triazolization product **5ca** with an isolated yield of 52% (Table 2, entry 9). Again, the yield could not be increased by using 4-azidobenzonitrile (43%). When applying stronger acids such as *p*-toluenesulfonic acid and trifluoroacetic acid, the triazolization reaction did not proceed. This was also the case for reactions with ethyl benzoylacetate. Some attempts were made to synthesize 1-alkyl-1,2,3-triazoles from this highly activated β-keto ester. Even in the presence of one equivalent of acetic acid, only the Dimroth product was formed. Note that the aimed triazoles are accessible in another way via a method developed in our laboratory.[12]

When performing the triazolization reactions from 1,3-DPA (**1a**) and various amines **2a–e** without acetic acid, a correlation between steric hindrance of the amine and the mutual ratio of triazole compounds was observed (Table 2). In general, using less sterically hindered amines such as hexylamine (**2b**) and tryptamine (**2d**) leads to higher yields of both the Dimroth triazole and 5-AT (Table 2, entries 2 and 4). In contrast, a reaction with the more sterically hindered (*R*)-(+)-α-methylbenzylamine (**2c**) clearly generates the triazolization product **5ac** as the major product (entry 3). A similar result was obtained in the case of (+)-dehydroabietylamine (**2e**) (entry 5). From the acid-free reactions, different 5-ATs **7aa–ae** were obtained. It is worth mentioning that these remarkable compounds were only generated as a side product in reactions with 1,3-DPA, which may be explained via the proposed mechanism (Scheme 3). Just as for the Dimroth and triazolization products, the 5-AT **7a** is expected to be formed from the triazoline intermediate **4a**. Triazolines bearing an electron-withdrawing substituent at the N1 position are known to be more labile. Therefore, **4a** may, to a limited extent, undergo a [3+2] cycloreversion process, generating phenyldiazomethane and the corresponding *N*′-(4-nitrophenyl)-2-phenylacetamidine (**8**) (Scheme 3).[13] Subsequent diazotransfer onto the amidine would then generate the 5-AT. The postulated mechanism is based on the report of Ugo et al., who observed cycloreversion of triazolines from tosyl azide at low temperatures.[13a] According to the postulated mechanism, two equivalents of azide are consumed in the reaction toward the 5-AT, while only one equivalent of PNA is released. By analyzing the ^{1}H NMR spectra of the crude reaction mixtures, it could be noticed that distinctly more azide was consumed compared to the amount of PNA formed. Of course, it was taken into account that azide is also consumed in the formation of the Dimroth product, without release of PNA.



Scheme 3 Cycloreversion step in the postulated mechanism for the formation of the 5-ATs **7aa–ac**

In conclusion, we can state that both solvent, temperature, and presence of acid or base influence the chemoselectivity in triazolization reactions. The results of experiments with different ketones revealed a trend of decreasing efficiency of the triazolization reaction with the acidity of the enolizable ketones. This is a valuable information in the framework of the exploration of the triazolization reaction, of which the limitations are now more specified.

All chemicals were purchased from Acros Organics, Sigma Aldrich, Alfa Aesar, and TCI Europe and used as received. Azides were prepared according to literature procedures.[10,14] All reactions were carried out in oven dried glassware, but no special precautions were taken for the exclusion of moisture. Reaction solvents (toluene) were dried using a M-Braun SPS-800 system. For column chromatography, 60–200 mesh silica gel 60 (Acros) was used as the stationary phase.

NMR spectra were recorded on commercial instruments (Bruker Avance 300 MHz, Bruker AMX 400 MHz, or Bruker Avance II+ 600 MHz) and chemical shifts (δ) are reported in parts per million (ppm) referenced to TMS (^{1}H), or the internal (NMR) solvent signal (^{13}C). High-resolution mass spectra were acquired on a quadrupole orthogonal acceleration time-of-flight mass spectrometer (Synapt G2 HDMS, Waters, Milford, MA, USA). Samples were infused at 3 µL/min and spectra were obtained in positive (or negative) ionization mode with a resolution of 15 000 (FWHM) using leucine enkephalin as lock mass. Melting points were determined on a Mettler-Toledo DSC 1 instrument, using a heating rate of 10 °C min^{-1} and under a He atmosphere.

1-Alkyl-1,2,3-triazoles 5aa–ca,7aa–ae; Modified Triazolization Procedure

To an oven-dried screw-capped reaction tube equipped with a magnetic stirring bar was added the ketone **1** (0.5 mmol) and AcOH (0.5 mmol). The mixture was dissolved in toluene (0.3 mL), after which the amine **2** (0.5 mmol) and azide **3** (1 mmol) were added in the respective order. The walls of the reaction tube were then rinsed with toluene (0.2 mL). The reaction mixture was heated immediately after addition of the reagents and left stirring for 15 h at 100 °C. The crude reaction mixtures were directly purified by column chromatog-

raphy after cooling down to r.t. CH_2Cl_2 was used at first as the eluent to remove PNA, followed by a heptane–EtOAc or CH_2Cl_2–EtOAc gradient to afford the corresponding 1,2,3-triazoles.

Note: The reactions to obtain compounds **7aa–ae** were performed without AcOH.

5-Benzyl-1-(4-methoxybenzyl)-4-phenyl-1*H*-1,2,3-triazole (5aa)

Prepared according to the triazolization procedure, using 1,3-DPA (**1a**; 105.1 mg, 0.5 mmol), PMBA (**2a**; 68.6 mg, 0.5 mmol), 4-NPA (**3**; 164.1 mg, 1 mmol), and AcOH (30 mg, 0.5 mmol); yellow solid; yield: 133.5 mg (75%); mp 104 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.68–7.65 (m, 2 H), 7.41–7.23 (m, 6 H), 7.02 (d, *J* = 8.7 Hz, 2 H), 6.98 (d, *J* = 6.5 Hz, 2 H), 6.80 (d, *J* = 8.7 Hz, 2 H), 5.26 (s, 2 H), 4.09 (s, 2 H), 3.76 (s, 3 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 159.54, 146.42, 136.01, 131.28, 130.84, 129.02, 128.74, 127.92, 127.78, 127.18, 127.08, 126.64, 114.23, 55.28, 51.75, 28.58.

HRMS (ESI-Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{21}N_3O$: 356.1757; found: 356.1761.

5-Benzyl-1-hexyl-4-phenyl-1*H*-1,2,3-triazole (5ab)

Prepared according to the triazolization procedure, using 1,3-DPA (**1a**; 105.1 mg, 0.5 mmol), hexylamine (**2b**; 50.6 mg, 0.5 mmol), 4-NPA (**3**; 164.1 mg, 1 mmol), and AcOH (30 mg, 0.5 mmol); yellow viscous oil; yield: 128.4 mg (80%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.70–7.66 (m, 2 H), 7.41–7.36 (m, 2 H), 7.34–7.22 (m, 4 H), 7.06 (d, *J* = 7.1 Hz, 2 H), 4.24 (s, 2 H), 4.10 (t, *J* = 7.4 Hz, 2 H), 1.72 (pent, *J* = 7.4 Hz, 2 H), 1.28–1.15 (m, 6 H), 0.84 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 145.63, 136.40, 131.49, 130.66, 129.04, 128.74, 127.83, 127.78, 127.20, 127.15, 48.32, 31.12, 29.77, 28.74, 26.19, 22.35, 13.93.

HRMS (ESI-Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{25}N_3$: 320.2121; found: 320.2118.

(*R*)-5-Benzyl-4-phenyl-1-(1-phenylethyl)-1*H*-1,2,3-triazole (5ac)

Prepared according to the triazolization procedure, using 1,3-DPA (**1a**; 105.1 mg, 0.5 mmol), (*R*)-(+)-α-methylbenzylamine (**2c**; 60.6 mg, 0.5 mmol), 4-NPA (**3**; 164.1 mg, 1 mmol), and AcOH (30 mg, 0.5 mmol); off-white solid; yield: 142.8 mg (84%); mp 123 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.68–7.64 (m, 2 H), 7.40–7.34 (m, 2 H), 7.33–7.20 (m, 7 H), 7.12–7.08 (m, 2 H), 7.00–6.96 (m, 2 H), 5.26 (q, *J* = 7.0 Hz, 1 H), 4.23 (d, *J* = 17.3 Hz, 1 H), 3.91 (d, *J* = 17.3 Hz, 1 H), 1.94 (d, *J* = 7.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 146.16, 140.71, 136.27, 131.38, 130.75, 129.02, 128.84, 128.70, 127.99, 127.85, 127.68, 127.24, 127.06, 126.12, 58.76, 28.62, 22.45.

HRMS (ESI-Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{21}N_3$: 340.1808; found: 340.1815.

3-[2-(5-Benzyl-4-phenyl-1*H*-1,2,3-triazol-1-yl)ethyl]-1*H*-indole (5ad)

Prepared according to the triazolization procedure, using 1,3-DPA (**1a**; 105.1 mg, 0.5 mmol), tryptamine (**2d**; 80.1 mg, 0.5 mmol), 4-NPA (**3**; 164.1 mg, 1 mmol), and AcOH (30 mg, 0.5 mmol); off-white solid; yield: 136.5 mg (72%); mp 151 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.52 (s, 1 H, indole NH), 7.64–7.58 (m, 2 H), 7.39–7.29 (m, 4 H), 7.28–7.13 (m, 5 H), 7.09–7.03 (m, 1 H), 6.90–6.84 (m, 2 H), 6.78 (d, *J* = 2.3 Hz, 1 H), 4.34 (t, *J* = 7.3 Hz, 2 H), 3.80 (s, 2 H), 3.24 (t, *J* = 7.2 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 145.53, 136.26, 136.19, 131.48, 131.34, 128.97, 128.75, 127.89, 127.73, 127.27, 127.05, 126.91, 122.71, 122.13, 119.51, 118.14, 111.43, 111.11, 48.89, 28.12, 26.39.

HRMS (ESI-Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{22}N_4$: 379.1917; found: 379.1923.

5-Benzyl-1-{[(1*R*,4a*S*,10a*R*)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl]methyl}-4-phenyl-1*H*-1,2,3-triazole (5ae)

Prepared according to the triazolization procedure, using 1,3-DPA (**1a**; 105.1 mg, 0.5 mmol), (+)-dehydroabietylamine (**2e**; 143 mg, 0.5 mmol), 4-NPA (**3**; 164.1 mg, 1 mmol,), and AcOH (30 mg, 0.5 mmol); yellow semi-solid; yield: 143.5 mg (57%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.67–7.62 (m, 2 H), 7.41–7.23 (m, 6 H), 7.13 (d, *J* = 8.2 Hz, 1 H), 7.02–6.94 (m, 3 H), 6.91–6.88 (m, 1 H), 4.36 (d, *J* = 17.3 Hz, 1 H), 4.22 (d, *J* = 17.4 Hz, 1 H), 4.16 (d, *J* = 14.3 Hz, 1 H), 3.80 (d, *J* = 14.3 Hz, 1 H), 3.14–2.74 (m, 3 H), 2.29–2.20 (m, 1 H), 2.08–1.96 (m, 1 H), 1.90–1.55 (m, 4 H), 1.50–1.42 (m, 1 H), 1.35–1.18 (m, 11 H), 1.06 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 146.84, 145.69, 145.00, 136.27, 134.87, 132.12, 131.46, 129.09, 128.71, 127.80, 127.27, 127.16, 126.99, 124.10, 123.80, 58.19, 45.43, 39.29, 38.03, 37.63, 36.78, 33.46, 29.91, 29.07, 25.68, 24.05, 23.97, 19.40, 18.92, 18.54.

HRMS (ESI-Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{35}H_{41}N_3$: 504.3373; found: 504.3371.

1-(4-Methoxybenzyl)-5-methyl-4-phenyl-1*H*-1,2,3-triazole (5ba)

Prepared according to the triazolization procedure, using phenylacetone (**1b**; 67.1 mg, 0.5 mmol), PMBA (**2a**; 68.6 mg, 0.5 mmol), 4-NPA (**3**; 164.1 mg, 1 mmol), and AcOH (30 mg, 0.5 mmol); yellow viscous oil; yield: 102.0 mg (73%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.68 (d, *J* = 7.5 Hz, 2 H), 7.42 (t, *J* = 7.5 Hz, 2 H), 7.32 (t, *J* = 7.3 Hz, 1 H), 7.16 (d, *J* = 8.3 Hz, 2 H), 6.86 (d, *J* = 8.4 Hz, 2 H), 5.47 (s, 2 H), 3.78 (s, 3 H), 2.33 (s, 3 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 159.55, 144.98, 131.66, 129.02, 128.66, 128.64, 127.59, 127.11, 126.84, 114.35, 55.30, 51.59, 9.22.

HRMS (ESI-Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}N_3O$: 280.1444; found: 280.1449.

1-(4-Methoxybenzyl)-4,5-diphenyl-1*H*-1,2,3-triazole (5ca)

Prepared according to the triazolization procedure, using deoxybenzoin (**1c**; 98.1 mg, 0.5 mmol), PMBA (**2a**; 68.6 mg, 0.5 mmol), 4-NPA (**3**; 164.1 mg, 1 mmol), and AcOH (30 mg, 0.5 mmol); off-white solid; yield: 89.0 mg (52%); mp 88 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.57–7.52 (m, 2 H), 7.51–7.40 (m, 3 H), 7.28–7.19 (m, 3 H), 7.18–7.13 (m, 2 H), 6.96 (d, *J* = 8.6 Hz, 2 H), 6.76 (d, *J* = 8.6 Hz, 2 H), 5.34 (s, 2 H), 3.76 (s, 3 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 159.43, 144.51, 133.68, 130.97, 130.16, 129.64, 129.15, 129.04, 128.41, 128.00, 127.64, 127.41, 126.70, 114.01, 55.26, 51.59.

HRMS (ESI-Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{19}N_3O$: 342.1601; found: 342.1609.

5-Benzyl-1-(4-nitrophenyl)-4-phenyl-1*H*-1,2,3-triazole (6a)

To an oven-dried screw-capped reaction tube equipped with a magnetic stirring bar was added 1,3-DPA (**1a**; 105.1 mg, 0.5 mmol) and 4-NPA (**3**; 123.1 mg, 0.75 mmol). The mixture was dissolved in DMSO (1 mL), after which DBU (0.05 mmol, 7.6 mg) was added. The reaction mixture was left stirring for 2 h at 25 °C and subsequently worked up with aq NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The product was purified by column chromatography using a heptane–EtOAc gradient: white solid; yield: 147.4 mg (83%); mp 156 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.28 (d, *J* = 9.0 Hz, 2 H), 7.77–7.73 (m, 2 H), 7.56 (d, *J* = 9.0 Hz, 2 H), 7.46–7.36 (m, 3 H), 7.32–7.23 (m, 3 H), 7.02–6.97 (m, 2 H), 4.32 (s, 2 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 147.84, 146.80, 141.19, 136.21, 131.64, 130.38, 129.28, 128.96, 128.50, 127.71, 127.41, 127.24, 125.63, 124.87, 29.33.

HRMS (ESI-Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{16}N_4O_2$: 357.1346; found: 357.1348.

1-(4-Methoxybenzyl)-*N*-(4-nitrophenyl)-4-phenyl-1*H*-1,2,3-triazol-5-amine (7aa)

Prepared according to the triazolization procedure, using 1,3-DPA (**1a**; 105.1 mg, 0.5 mmol), PMBA (**2a**; 68.6 mg, 0.5 mmol), and 4-NPA (**3**; 164.1 mg, 1 mmol); brown semi-solid; yield: 59.1 mg (29%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.01 (d, *J* = 8.9 Hz, 2 H), 7.74–7.69 (m, 2 H), 7.30–7.25 (m, 3 H), 7.08 (d, *J* = 8.5 Hz, 2 H), 6.73 (d, *J* = 8.5 Hz, 2 H), 6.48 (d, *J* = 8.9 Hz, 2 H), 6.24 (s, 1 H, NH), 5.32 (s, 2 H), 3.72 (s, 3 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 159.88, 149.34, 141.77, 140.95, 129.48, 129.36, 129.26, 128.84, 128.55, 126.17, 125.87, 125.81, 114.35, 113.23, 55.33, 51.43.

HRMS (ESI-Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{19}N_5O_3$: 402.1561; found: 402.1552.

1-Hexyl-*N*-(4-nitrophenyl)-4-phenyl-1*H*-1,2,3-triazol-5-amine (7ab)

Prepared according to the triazolization procedure, using 1,3-DPA (**1a**; 105.1 mg, 0.5 mmol), hexylamine (**2b**; 50.6 mg, 0.5 mmol), and 4-NPA (**3**; 164.1 mg, 1 mmol); brown semi-solid; yield: 62.9 mg (34%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.11 (d, *J* = 9.1 Hz, 2 H), 7.73–7.68 (m, 2 H), 7.32–7.27 (m, 3 H), 6.69–6.63 (m, 3 H), 4.15 (t, *J* = 7.4 Hz, 2 H), 1.84 (pent, *J* = 7.3 Hz, 2 H), 1.33–1.17 (m, 6 H), 0.83 (t, *J* = 6.9 Hz, 3 H). NH could not be assigned unambiguously.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 149.78, 141.09, 141.05, 129.55, 129.39, 128.87, 128.51, 126.43, 125.85, 113.22, 47.55, 31.07, 29.66, 26.23, 22.36, 13.91.

HRMS (ESI-Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{23}N_5O_2$: 366.1924; found: 366.1924.

(*R*)-*N*-(4-Nitrophenyl)-4-phenyl-1-(1-phenylethyl)-1*H*-1,2,3-triazol-5-amine (7ac)

Prepared according to the triazolization procedure, using 1,3-DPA (**1a**; 105.1 mg, 0.5 mmol), (*R*)-(+)-α-methylbenzylamine (**2c**; 60.6 mg, 0.5 mmol), and 4-NPA (**3**; 164.1 mg, 1 mmol); brown semi-solid; yield: 30.5 mg (16%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.00 (d, *J* = 9.2 Hz, 2 H), 7.74–7.70 (m, 2 H), 7.32–7.24 (m, 6 H), 7.19–7.15 (m, 2 H), 6.44 (d, *J* = 9.1 Hz, 2 H), 5.86 (s, 1 H, NH), 5.51 (q, *J* = 7.1 Hz, 1 H), 2.01 (d, *J* = 7.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 149.25, 141.86, 140.98, 139.81, 129.51, 129.11, 129.04, 128.82, 128.52, 128.51, 126.22, 126.19, 125.86, 113.13, 58.44, 21.44.

HRMS (ESI-Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{19}N_5O_2$: 386.1611; found: 386.1610.

1-[2-(1*H*-Indol-3-yl)ethyl]-*N*-(4-nitrophenyl)-4-phenyl-1*H*-1,2,3-triazol-5-amine (7ad)

Prepared according to the triazolization procedure, using 1,3-DPA (**1a**; 105.1 mg, 0.5 mmol), tryptamine (**2d**; 80.1 mg, 0.5 mmol), and 4-NPA (**3**; 164.1 mg, 1 mmol); brown semi-solid; yield: 73.4 mg (35%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.42 (s, 1 H, indole NH), 7.81 (d, *J* = 9.1 Hz, 2 H), 7.58–7.53 (m, 2 H), 7.48–7.43 (m, *J* = 8.1, 3.1 Hz, 2 H), 7.33–7.11 (m, 5 H), 6.74 (d, *J* = 2.3 Hz, 1 H), 5.86 (d, *J* = 9.2 Hz, 2 H), 4.90 (s, 1 H, NH), 4.50 (t, *J* = 6.1 Hz, 2 H), 3.33 (t, *J* = 6.1 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 148.42, 140.54, 139.93, 136.21, 130.22, 129.55, 128.71, 128.31, 126.23, 125.90, 125.72, 123.50, 122.96, 120.41, 118.22, 112.92, 112.12, 110.80, 47.44, 26.72.

HRMS (ESI-Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{20}N_6O_2$: 425.1720; found: 425.1718.

1-{[(1*R*,4a*S*,10a*R*)-7-Isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl]methyl}-*N*-(4-nitrophenyl)-4-phenyl-1*H*-1,2,3-triazol-5-amine (7ae)

Prepared according to the triazolization procedure, using 1,3-DPA (**1a**; 105.1 mg, 0.5 mmol), (+)-dehydroabietylamine (**2e**; 143 mg, 0.5 mmol), and 4-NPA (**3**; 164.1 mg, 1 mmol); yellow semi-solid; yield: 63.1 mg (23%).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 8.09 (d, *J* = 8.9 Hz, 2 H), 7.69 (d, *J* = 7.0 Hz, 2 H), 7.30–7.23 (m, 3 H), 7.10 (d, *J* = 8.2 Hz, 1 H), 6.97 (d, *J* = 8.1 Hz, 1 H), 6.88 (s, 1 H), 6.60 (d, *J* = 8.7 Hz, 2 H), 6.28 (s, 1 H, NH), 4.15 (d, *J* = 14.0 Hz, 1 H), 3.92 (d, *J* = 14.0 Hz, 1 H), 3.04–2.90 (m, 2 H), 2.85–2.77 (m, 1 H), 2.23 (d, *J* = 12.8 Hz, 1 H), 2.05–1.99 (m, 1 H), 1.87–1.78 (m, 1 H), 1.74–1.65 (m, 1 H), 1.57–1.48 (m, 2 H), 1.40–1.34 (m, 1 H), 1.28–1.18 (m, 11 H), 1.08 (s, 3 H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ = 149.24, 146.61, 145.87, 141.15, 140.24, 134.51, 130.40, 129.50, 128.82, 128.46, 126.96, 126.43, 125.89, 124.03, 123.92, 113.25, 57.54, 45.49, 39.18, 38.00, 37.57, 36.74, 33.43, 29.80, 25.51, 23.99, 23.95, 19.33, 18.83, 18.44.

HRMS (ESI-Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{39}N_5O_2$: 550.3176; found: 550.3178.

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Supporting Information

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