

Pyrido[1,2-*c*][1,2,4]triazol-3-ylidene: reactivity and its application in organocatalysis and organometallic catalysis†

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The reactivity and catalytic performance of 2-ethylpyrido[1,2-*c*][1,2,4]-triazol-3-ylidene **6** have been comprehensively investigated. The carbene **6** has shown unusual properties owing to the effect of the pyrido-annulation. While formohydrazide **8** and hydrazine **9** are obtained *via* the destruction of the triazole skeleton of the carbene, 3-((1*Z*,3*E*)-4-(1*H*-pyrrol-1-yl)buta-1,3-dienyl)-1-ethyl-1*H*-1,2,4-triazole **10** is achieved through the cleavage of the C–N bond of the pyridine ring. The carbene **6** has turned out to be a powerful catalyst in a variety of organocatalyzed and Pd(II)-catalyzed transformations.

Introduction

N-Heterocyclic carbenes (NHCs), as a class of nucleophilic singlet carbenes, have grown tremendously from being regarded as chemical curiosities¹ to versatile ligands in organic² and organometallic catalysis,³ and reagents in organic reactions.⁴ In the past decades, thiazol-2-ylidenes, imidazol-2-ylidenes, imidazolidin-2-ylidenes and 1,2,4-triazol-5-ylidenes have represented the typical architectures of stable nucleophilic N-heterocyclic carbenes, and the chemistry of these compounds has been studied intensively.^{1–4} Currently, much work has been devoted to the design and development of carbene species with novel structures to tune their steric and electronic properties by slight modification of the ring framework.⁵ Some new families of diaminocarbenes annulated by carbo- or heterocycles **1–5** have been developed recently.^{5d,6–10} More importantly, the morpholino-annulated triazol-5-ylidenes **5** have exhibited highly catalytic performances in various enantioselective reactions, and their chemical properties are starting to attract interest.^{9e,10}

Recent investigations indicate that pyrido-annulation, as is illustrated in **3** and **4**, significantly influences the stability and the σ -donor/ π -acceptor ligand properties of carbenes and may be a useful tool for tuning the electronic properties of

carbenes.^{5d,9a,9b} Despite detailed investigations into their structures, properties, stability and transition metal coordination chemistry, to our knowledge, their reactivity and catalysis have rarely been documented as yet. Quite recently, we have reported for the first time a highly efficient method for the preparation of the pyrido-annulated triazolium salts and described the spectroscopic properties, dimerization behavior and coordination chemistry of the corresponding triazol-3-ylidenes.¹¹ Among these triazolium salts, 2-ethylpyrido[1,2-*c*][1,2,4]triazol-2-ium tetrafluoroborate **7** has demonstrated the highest catalytic efficiency in benzoin condensation and transesterification. It is conceivable that this excellent catalytic performance could be due to the much greater stability of 2-ethylpyrido[1,2-*c*][1,2,4]triazol-3-ylidene **6**, resulting in less likelihood of dimerization or decomposition of the triazole skeleton.¹¹ In this context, we further wish to present a relatively comprehensive investigation into the reactivity as well as organocatalysis and organometallic catalysis of **6**.

Results and discussion

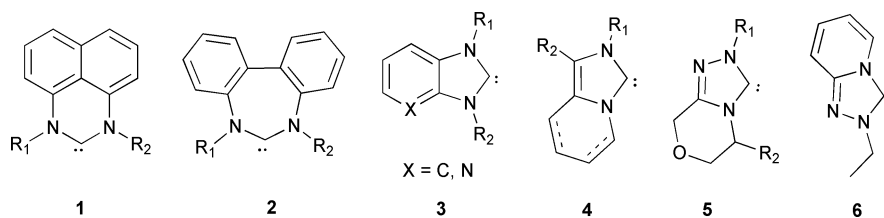
Reactivity of 2-ethylpyrido[1,2-*c*][1,2,4]triazol-3-ylidene **6**

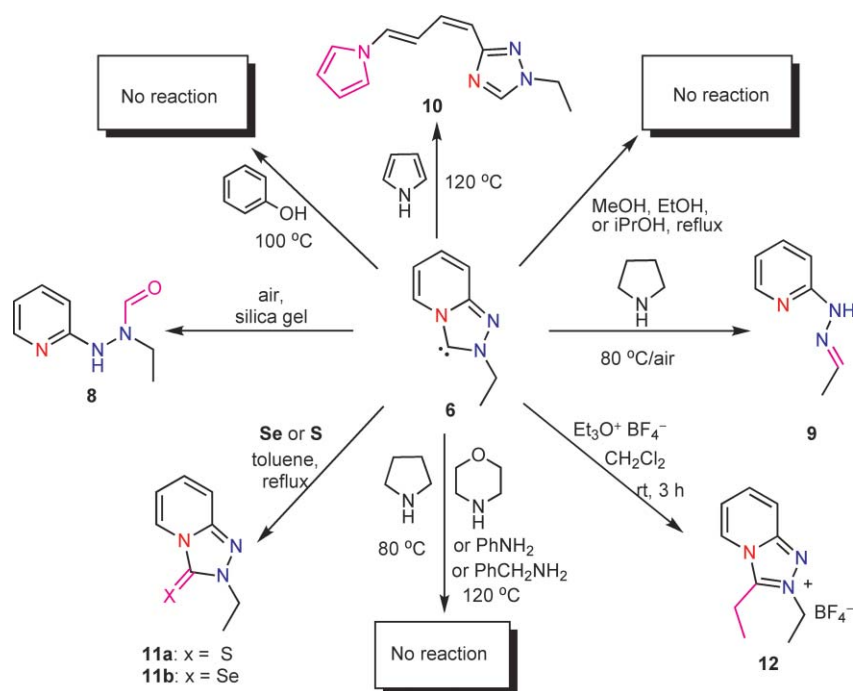
With the isolated carbene **6** now to hand, prepared by deprotonation of the triazolium salt **7** in the presence of NaH,¹¹ a variety of typical carbene reactions towards organic and inorganic substrates were performed, offering a detailed impression of its chemical nature.

In terms of reactivity, the NHCs behave as nucleophiles due to their lone electron pair. Initial studies of the nucleophilicity of **6** led to a surprising result (Scheme 1). Unlike other well-defined triazolylidenes available in the literature,¹² **6** did not

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† Electronic supplementary information (ESI) available: Crystallographic data in CIF format, copies of ¹H NMR and ¹³C NMR spectra. CCDC reference numbers 725112–725114. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b910073c





Scheme 1 Reactivity of the triazolylidene **6**.

react with alcohols (*i.e.*, methanol, ethanol and *iso*-propanol), phenol or amines (*i.e.*, aniline, phenylmethanamine, pyrrolidine and morpholine) *via* insertion into the O–H or N–H bond respectively, even at up to 120 °C under nitrogen. In sharp contrast, the reactions of the classic 1,3,4-triphenyl-1,2,4-triazol-5-ylidene with alcohols, phenols and amines could proceed at ambient temperature within ten minutes, affording the analytically pure alkoxytriazolines, phenoxytriazolines and aminotriazolines in good yields, respectively.¹² Our previous studies demonstrated that the pyrido[1,2-*c*][1,2,4]-triazol-3-ylidenes were quite stable in solution and in the solid state for a long period under nitrogen at room temperature. In this study, we found that the carbene **6** was converted to *N*-ethyl-*N'*-(pyridin-2-yl)formohydrazide **8** in a 78% yield after column chromatography on silica gel in the presence of air. Surprisingly, with the aid of basic pyrrolidine, the triazolylidene framework of **6** was destroyed with the formation of 1-ethylidene-2-(pyridin-2-yl)hydrazine **9** in an 80% yield in air at 80 °C. More interestingly, the replacement of amines with 1*H*-pyrrole resulted in the cleavage of the C–N bond of the pyridine ring to form 3-((1*Z*,3*E*)-4-(1*H*-pyrrol-1-yl)buta-1,3-dienyl)-1-ethyl-1*H*-1,2,4-triazole **10** in a 70% yield under N₂. Compounds **8**, **9** and **10** (CCDC 725112–725114) were characterized by X-ray structure analysis.[†] Notably, there are two independent molecules of **8** and of **10** in the relevant asymmetric units (Fig. 1).¹³

Similarly to other well-established carbenes, **6** readily underwent addition reactions with chalcogens such as sulfur and selenium to give the corresponding triazolinthione **11a** and triazolin-selenone **11b** in 95% and 98% yields, respectively. The carbene **6** could also be alkylated using triethyloxonium tetrafluoroborate, affording the 3-ethyltriazolium salt **12** in a 95% yield. These two kinds of reactivity, which were described earlier for nucleophilic carbenes, clearly exemplify the nucleophilic character of the carbene **6**.

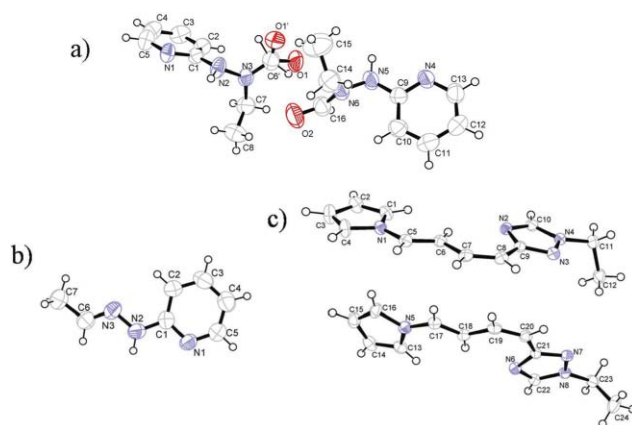


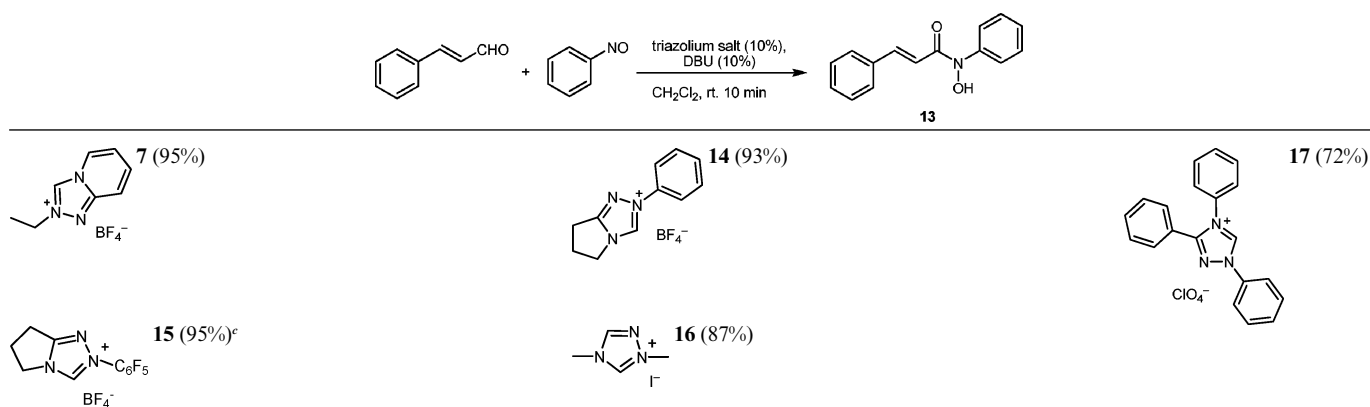
Fig. 1 ORTEP drawings of the molecular structures of **8** (a), (*E*)-**9** (b), and **10** (c). Thermal ellipsoids are set at the 50% probability level.

Overall, the pyrido-annulated carbene **6** exhibited unusual reactivity owing to the effect of the pyrido-annulation. It is therefore reasonable to assume that it would be a unique molecular architecture for the development of new organometallic processes, catalysts in organocatalytic reactions, and reagents in multicomponent coupling reactions.

Catalytic direct amidation of cinnamaldehyde with nitrosobenzene

N-Heterocyclic carbenes have been widely used as a type of efficient catalyst for metal-free carbon–carbon bond formations, which are assumed to proceed through the electrophilic “Breslow intermediate”¹⁴ or the homoenolate equivalent¹⁵ in umpolung aldehyde chemistry.

As simple neutral polyfunctional molecules, *N*-arylhydroxamic acids can not only provide novel N–OH mediators for

Table 1 Addition of cinnamaldehyde to nitrosobenzene catalyzed by the various triazolium salts^{a,b}

^a Reactions were performed with (*E*)-cinnamaldehyde (132 mg, 1 mmol), nitrosobenzene (117 mg, 1.1 mmol), triazolium salts (0.1 mmol) and DBU (0.1 mmol) in 5.0 mL of CH₂Cl₂ under N₂ at rt for 10 min. ^b Yield of isolated product. ^c See ref. 17.

oxidoreductase catalysis, but also play important roles as pharmacophores in a variety of biologically active agents.¹⁶ Quite recently, Seayad and Zhang *et al.* described the direct amidation of aldehydes with nitroso compounds catalyzed by achiral triazolium salts **15** to give *N*-arylhydroxamic acids in excellent yields, which possibly involves the “Breslow intermediates”.¹⁷ In our case, the pyrido-annulated triazolium salt **7** proved to be a powerful catalyst for this type of amidation reaction, affording a 95% yield of product (Table 1).

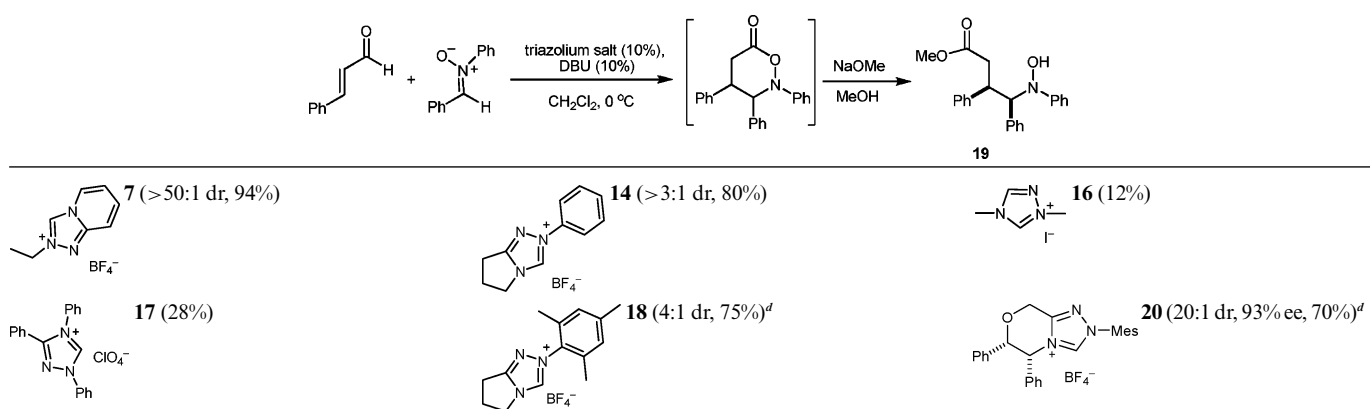
Catalytic cinnamaldehyde addition to nitrone

Addition of homoenolate nucleophiles to nitrones would be a significant transformation since the related products may be converted to γ -amino acids as well as γ -lactam structures.¹⁸ Very recently, Scheidt *et al.* described the first formal [3+3] addition of α,β -unsaturated cinnamaldehyde to nitrones catalyzed by *N*-heterocyclic carbenes to give γ -amino ester derivatives upon addition of alcohol.¹⁹ While thiazolium and imidazolium salts failed to provide the target product, the use of 10 mol% of achiral

triazolium salt **18** afforded the γ -hydroxyl amino ester in a 75% yield with a 4:1 diastereoselectivity. In this study, the pyrido-annulated carbene **6** generated in situ from **7** proved to be a powerful catalyst for this type of addition reaction (Table 2). To our surprise, the triazolium salt **7** exhibited not only high catalytic activity giving up to 94% total yield of **19**, but also an excellent level of diastereoselectivity. Indeed, the ¹H NMR analysis of unpurified reaction mixtures indicated that the reaction afforded the γ -hydroxyl amino ester **19** as a nearly single diastereomer, which was superior to that of **20** (a 20:1 dr and 93% ee).¹⁹

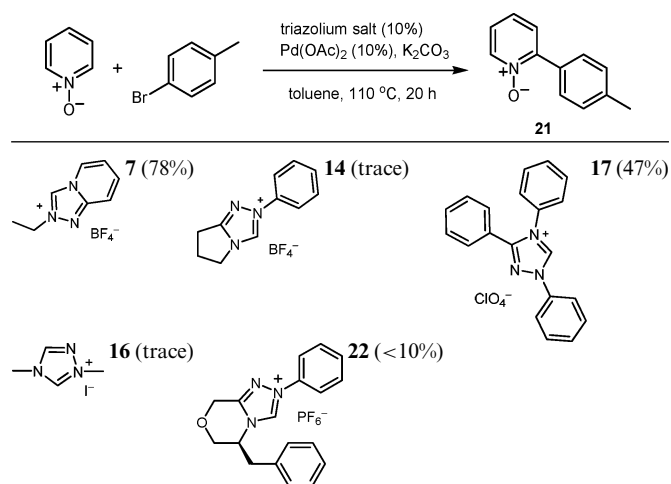
Direct C-arylation of heteroaromatics with aryl bromide catalyzed by the Pd complex of **6**

More recently, direct C-arylation of heteroaromatics has received prominent attention as an effective approach for creating aryl-heteroaryl linkages extensively throughout the natural products, pharmaceutical and materials industries.²⁰ Among these catalytic systems, a variety of transition-metal-tertiary phosphane complexes have been extensively employed as catalysts, whereas few

Table 2 Cinnamaldehyde addition to nitrone catalyzed by various achiral triazolium salts^{a,b,c}

^a Reactions were performed with (*E*)-cinnamaldehyde (0.4 mmol), (*Z*)-*N*-benzylideneaniline oxide (0.8 mmol), triazolium salts (0.04 mmol) and DBU (0.04 mmol) in 4.0 mL of CH₂Cl₂ under N₂ at 0 °C for 2 days. ^b Yield of isolated product. ^c Diastereomeric ratio determined by ¹H NMR analysis of unpurified reaction mixtures. ^d See ref. 19.

Table 3 Direct C-arylation of pyridine-*N*-oxide catalyzed by various triazolylidene-palladium complexes^{a,b}



^a Reactions were performed with K₂CO₃ (1 mmol), triazolium salts (0.05 mmol), Pd(OAc)₂ (0.05 mmol), pyridine *N*-oxide (1.5 mmol) and 4-bromotoluene (0.5 mmol) in toluene (2 mL) under N₂ at 110 °C for 20 h.
^b Yield of isolated product.

examples based on metal complexes of NHCs have been known hitherto.²¹

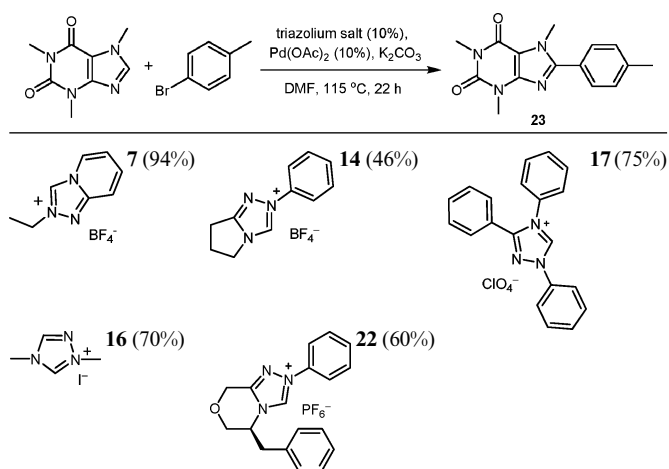
Triazolylidenes have not been as widely explored as imidazole-based carbenes in organometallic catalysis in spite of extensive application in organocatalysis.^{20–22} To our knowledge, the successful use of transition-metal-triazolylidene complexes for direct arylation reactions of arene and heterocycle C–H bonds has not yet been described. Inspired by these factors, we herein wish to evaluate the catalytic performance of the pyrido-annulated triazol-3-ylidenes in the palladium-mediated C-arylation of heteroaromatics. Our initial exploration started with the coupling of pyridine *N*-oxide with *p*-bromotoluene.²³ A screen of triazolium salts revealed that the C-arylation process smoothly occurred in a 78% yield with complete selectivity for the 2-position in the presence of **7** (10 mol%) and Pd(OAc)₂ (10 mol%). Moreover, the catalytic performance of the triazolium salt **7** turned out to be better than those of the other well-established triazolium salts investigated (Table 3).

We subsequently turned our attention to xanthine derivatives.²⁴ 8-Aryl-substituted xanthines are highly potent and selective antagonists at human A_{2B} adenosine receptors. We were pleased to find that the C-arylation of caffeine with *p*-bromotoluene could proceed in the presence of 10 mol% of **7** and 10 mol% of Pd(OAc)₂, affording the 8-aryl-substituted caffeine **23** in a 94% yield (Table 4). Further investigation indicated that the catalytic efficiency of **7** was superior to the other classic types of triazolium salts examined.

Conclusions

In summary, the pyrido[1,2-*c*][1,2,4]triazol-3-ylidene **6** has shown unusual properties owing to the effect of the pyrido-annulation. As compared with other well-defined triazolylidenes described in the literature, **6** is not capable of reacting with alcohols, phenol, or amines to form the corresponding alkoxytriazolines, phenoxytriazolines and aminotriazolines. However, the triazole

Table 4 Direct C-arylation of caffeine catalyzed by various triazolylidene-palladium complexes^{a,b}



^a Reactions were performed with K₂CO₃ (1 mmol), triazolium salts (0.05 mmol), Pd(OAc)₂ (0.05 mmol), caffeine (0.5 mmol) and 4-bromotoluene (1 mmol) in DMF (1 mL) under N₂ at 115 °C for 22 h.
^b Yield of isolated product.

framework of this “bottle stable” carbene can be destroyed to form formohydrazide **8** and hydrazine **9** in the presence of air. The C–N bond of the pyridine ring can also be broken by reacting with 1*H*-pyrrole, with the formation of the 1,2,4-triazole derivative **10**. Moreover, the carbene **6** has turned out to be a powerful catalyst in a variety of organocatalyzed and palladium-mediated direct C-arylations of heteroaromatics, and was comparable with or even superior to other well-established triazolylidenes. Further investigations into other types of organocatalysis and organometallic catalysis are currently underway and will be reported in due course.

Experimental section

General

¹H NMR spectra were obtained with a Bruker AV-300, Bruker AV II-400, Bruker AV II-600, Varian Inova-400 or a Varian Inova-600 spectrometer, while ¹³C NMR spectra were recorded with a Bruker AV-300, Bruker AV II-400, Varian Inova-400 or a Varian Inova-600. The ¹H chemical shifts were measured relative to tetramethylsilane as the internal reference, while the ¹³C NMR chemical shifts were recorded with CDCl₃ as the internal standard. Elemental analyses were performed with a CARLO ERBA1106 instrument. The mass spectra (ESI) were obtained by a Finnigan-LCQDECA spectrometer. Unless otherwise noted, all liquid reagents were freshly distilled under reduced pressure prior to use. Solvents were dried by refluxing for at least 24 h over CaH₂ (CH₂Cl₂), or sodium/benzophenone (THF or diethyl ether), and freshly distilled prior to use. Unless otherwise indicated, all syntheses and manipulations were carried out under a dry N₂ atmosphere.

X-Ray crystallography

X-Ray single-crystal diffraction data for **8** and **9** were collected on an Enraf-Nonius CAD-4 diffractometer at room temperature with Mo K α radiation ($\lambda = 0.71073$ Å) with $\omega/2\theta$ scan mode, and

for **10** was collected on a Bruker SMART 1000 CCD areadetector diffractometer at 100 K with graphite monochromated Cu K α radiation ($\lambda = 1.54184 \text{ \AA}$) with ω scan mode. All the structures were solved by direct methods using the SHELXS program and refined by full-matrix least-squares methods with SHELXL.²⁵ All non-hydrogen atoms were located in successive difference Fourier syntheses and refined with anisotropic thermal parameters on F². Hydrogen atoms were included in calculated positions and refined with constrained thermal parameters riding on their parent atoms. Drawings were produced with PLATON.²⁶

Procedure for the preparation of N-ethyl-N'-(pyridin-2-yl)formohydrazide (8). A mixture of the triazolium salt **7** (235 mg, 1.0 mmol) and NaH (26.4 mg, 1.1 mmol) in THF (5.0 mL) was stirred under a N₂ atmosphere at room temperature for 30 min. After the solid was filtered, the filtrate was evaporated under vacuum and purified by column chromatography on silica gel eluting with ethyl acetate/petroleum ether (1/2) to provide **8** in 78% yield under air. Single crystals suitable for X-ray analysis were obtained in diethyl ether under $-40 \text{ }^\circ\text{C}$. Mp: 49–51 $^\circ\text{C}$; ¹H NMR (400 MHz, CDCl₃): $\delta = 1.18$ (t, $J = 7.2$ Hz, 3H), 3.64 (q, $J = 7.2$ Hz, 2H), 6.60 (d, $J = 8.4$ Hz, 1H), 6.73–6.76 (m, 1H), 7.17 (br, 1H), 7.53–7.56 (m, 1H), 8.20 (d, $J = 5.2$ Hz, 1H), 8.33 (s, 1H); ¹³C NMR (150 MHz, CDCl₃): $\delta = 12.4, 39.8, 107.1, 116.4, 138.6, 149.1, 160.1, 165.8$ (Note: The conformation of **8** is disordered in crystal and in CDCl₃); MS (ESI⁺) $m/z = 166$ [M + H]⁺; Anal. calcd for C₈H₁₁N₃O: C, 58.17; H, 6.71; N, 25.44; Found: C, 58.01; H, 6.80; N, 25.31.

Procedure for the preparation of 1-ethylidene-2-(pyridin-2-yl)hydrazine (9). A mixture of the triazolium salt **7** (235 mg, 1.0 mmol) and NaH (26.4 mg, 1.1 mmol) in THF (5.0 mL) was stirred under a N₂ atmosphere at room temperature for 30 min. After the solid was filtered, the filtrate was evaporated under vacuum to afford the carbene **6**. Pyrrolidine (0.71 g, 10 mmol) was then added at ambient temperature. The solution was stirred at 80 $^\circ\text{C}$ for 10 h, and the excess pyrrolidine was then removed in vacuo. The resulting residue was purified by column chromatography on silica gel eluting with ethyl acetate/petroleum ether (1/5) to provide **9** in 80% yield. Single crystals suitable for X-ray analysis were obtained by slow evaporation of diethyl ether solution. Mp: 57–60 $^\circ\text{C}$; ¹H NMR (400 MHz, CDCl₃): $\delta = 1.98$ (d, $J = 5.6$ Hz, 3H), 6.68–6.71 (m, 1H), 7.14–7.18 (m, 2H), 7.52–7.56 (m, 1H), 8.06–8.08 (m, 1H), 8.12 (br, 1H); ¹³C NMR (100 MHz, CDCl₃): $\delta = 18.1, 106.9, 114.6, 137.8, 138.5, 146.9, 157.5$ (Note: Compound **9** is a mixture of (*E*)- and (*Z*)- isomers in CDCl₃); MS (ESI⁺) $m/z = 136$ [M + H]⁺; Anal. calcd for C₇H₉N₃: C, 62.20; H, 6.71; N, 31.09. Found: C, 62.11; H, 6.80; N, 30.97.

Procedure for the preparation of 3-((1*Z*,3*E*)-4-(1*H*-pyrrol-1-yl)buta-1,3-dienyl)-1-ethyl-1*H*-1,2,4-triazole (10). A mixture of the triazolium salt **7** (235 mg, 1.0 mmol) and NaH (26.4 mg, 1.1 mmol) in THF (5.0 mL) was stirred under a N₂ atmosphere at room temperature for 30 min. After the solid was filtered, the filtrate was evaporated under vacuum to afford the carbene **6**. Pyrrole (335 mg, 5 mmol) was then added to **6** at room temperature. The solution was stirred at 120 $^\circ\text{C}$ for 12 h, and the excess pyrrole was then removed in vacuo. The resulting residue was purified by column chromatography on silica gel eluting with ethyl acetate/petroleum ether (1/2) to provide **10** as colorless crystal in

70% yield. Mp: 56–57 $^\circ\text{C}$; ¹H NMR (400 MHz, CDCl₃): $\delta = 1.53$ (t, $J = 7.2$ Hz, 3H), 4.20 (q, $J = 7.2$ Hz, 2H), 6.25–6.30 (m, 3H), 6.39 (t, $J = 11.2$ Hz, 1H), 7.00–7.03 (m, 3H), 7.87–7.99 (m, 1H), 8.03 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): $\delta = 15.2, 44.7, 110.7, 112.5, 116.5, 119.4, 130.8, 132.7, 142.3, 162.0$; MS (ESI⁺) $m/z = 215$ [M + H]⁺; Anal. calcd for C₁₂H₁₄N₄: C, 67.27; H, 6.59; N, 26.15. Found: C, 67.15; H, 6.64; N, 26.08.

Procedure for the preparation of 2-ethylpyrido[1,2-*c*][1,2,4]-triazol-3-thione (11a). A mixture of the triazolium salt **7** (117.5 mg, 0.5 mmol) and NaH (13.2 mg, 0.55 mmol) in THF (5.0 mL) was stirred under a N₂ atmosphere at room temperature for 30 min. After the solid was filtered, the filtrate was evaporated under vacuum, and the resulting carbene **6** further reacted with elemental sulfur (19.2 mg, 0.6 mmol) in toluene (5 mL) at reflux for 6 h. The mixture was cooled to room temperature and concentrated in vacuo. The resulting residue was recrystallized from hexane to afford the thiourea **11a** as colorless crystals in 95% yield. Mp: 59–60 $^\circ\text{C}$; ¹H NMR (300 MHz, CDCl₃): $\delta = 1.43$ (t, $J = 7.2$ Hz, 3H), 4.40 (q, $J = 7.2$ Hz, 2H), 6.74 (t, $J = 6.5$ Hz, 1H), 7.20–7.35 (m, 2H), 8.28 (d, $J = 7.1$ Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): $\delta = 13.3, 44.9, 113.0, 115.1, 126.2, 130.7, 145.3, 158.5$; MS (ESI⁺) $m/z = 181$ [M + H]⁺; Anal. calcd for C₈H₉N₃S: C, 53.61; H, 5.06; N, 23.44; S, 17.89. Found: C, 53.46; H, 5.23; N, 22.23; S, 17.70.

Procedure for the preparation of 2-ethylpyrido[1,2-*c*][1,2,4]-triazol-3-selenone (11b). A mixture of the triazolium salt **7** (117.5 mg, 0.5 mmol) and NaH (13.2 mg, 0.55 mmol) in THF (5.0 mL) was stirred under a N₂ atmosphere at room temperature for 30 min. After the solid was filtered, the filtrate was evaporated under vacuum, and the resulting carbene **6** further reacted with selenium (59 mg, 0.75 mmol) in toluene (5 mL) at reflux for 6 h. The mixture was then cooled to room temperature and concentrated in vacuo. The resulting residue was recrystallized from hexane to afford the selenone **11b** as a pale yellow solid in 98% yield. Mp: 103–104 $^\circ\text{C}$; ¹H NMR (400 MHz, CDCl₃): $\delta = 1.54$ (t, $J = 7.2$ Hz, 3H), 4.58 (q, $J = 7.2$ Hz, 2H), 6.88 (t, $J = 7.6$ Hz, 1H), 7.37–7.48 (m, 2H), 8.51 (d, $J = 7.1$ Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): $\delta = 13.5, 46.5, 113.9, 114.9, 127.3, 131.3, 146.8, 152.0$; MS (ESI⁺) $m/z = 227$ [M + H]⁺; Anal. calcd for C₈H₉N₃Se: C, 42.49; H, 4.01; N, 18.58. Found: C, 42.30; H, 4.12; N, 18.16.

Procedure for the preparation of 2-ethyl-3-ethyl-pyrido[1,2-*c*][1,2,4]-triazol-2-ium tetrafluoroborate (12). A mixture of the triazolium salt **7** (235 mg, 1.0 mmol) and NaH (26.4 mg, 1.1 mmol) in THF (5.0 mL) was stirred under a N₂ atmosphere at room temperature for 30 min. After the solid was filtered, the filtrate was evaporated under vacuum to afford the carbene **6**. Triethyloxonium tetrafluoroborate (228 mg, 1.2 mmol) was then added to a solution of **6** in 5 mL of CH₂Cl₂ at ambient temperature. The solution was stirred for 3 h, and ethanol (1 mL) was then added and the solvent was evaporated. To the residue was added diethyl ether, and the generated crystals were collected by filtration, washed with ether and dried in vacuo. The resulting residue was recrystallized from hexane to afford **12** as colorless crystals in 95% yield. Mp: 162–163 $^\circ\text{C}$; ¹H NMR (400 MHz, DMSO-*d*₆): $\delta = 1.28$ (t, $J = 7.6$ Hz, 3H), 1.50 (t, $J = 7.2$ Hz, 3H), 3.51 (q, $J = 7.6$ Hz, 2H), 4.61 (q, $J = 7.2$ Hz, 2H), 7.42 (t, $J = 6.8$ Hz, 1H), 7.80 (q, $J = 6.8$ Hz, 1H), 8.03 (d, $J = 9.6$ Hz,

1H), 8.83 (d, $J = 7.2$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO): $\delta = 15.6, 19.4, 21.1, 51.5, 120.5, 122.7, 130.3, 138.4, 151.5, 152.0$; MS (ESI⁺) $m/z = 176$ [M - BF₄]⁺; Anal. calcd for C₁₀H₁₄BF₄N₃: C, 45.66; H, 5.36; N, 15.97. Found: C, 45.36; H, 5.44; N, 15.81.

General procedure for synthesis of *N*-hydroxy-*N*-phenylcinnamamide (13)¹⁷

A flame-dried Schlenk tube with a magnetic stirring bar was charged with nitrosobenzene (117 mg, 1.1 mmol), triazolium salt (0.1 mmol) and dichloromethane (5 mL), followed by addition of (*E*)-cinnamaldehyde (132 mg, 1 mmol) and DBU (15 μL , 0.1 mmol). The reaction mixture was stirred at room temperature for 10 min. The solvent was removed in vacuo, and the pure product was obtained through flash silica gel column chromatography of the residue using hexane and ethyl acetate as eluents. Mp: 162–164 °C; ^1H NMR (400 MHz, DMSO-*d*₆): $\delta = 7.18$ (t, $J = 7.2$ Hz, 1H), 7.38–7.47 (m, 6H), 7.69–7.73 (m, 5H), 10.88 (s, 1H); ^{13}C NMR (50 MHz, DMSO-*d*₆): $\delta = 118.8, 121.2, 125.2, 128.2, 128.6, 129.1, 130.1, 135.1, 142.0, 142.4, 164.9$; MS (ESI⁺) $m/z = 223$ [M - O]⁺; Anal. calcd for C₁₅H₁₃NO₂: C, 75.29, H, 5.48; N, 5.85. Found: C, 75.36; H, 5.43; N, 5.82.

General procedure for the catalytic cinnamaldehyde addition to nitrone (19)¹⁹

To a Schlenk tube equipped with a magnetic stirrer were added triazolium salt (0.04 mmol), (*Z*)-*N*-benzylideneaniline oxide (158 mg, 0.8 mmol) and CH₂Cl₂ (4 mL) under a N₂ atmosphere at room temperature. The mixture was then cooled to 0 °C, followed by addition of cinnamaldehyde (50 μL , 0.4 mmol) and dry freshly distilled DBU (6 μL , 0.04 mmol). After the mixture was stirred for 2 days, NaOMe (0.4 mL, 1.0 M in MeOH) was added *via* syringe. The mixture was then diluted with diethyl ether and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel eluting with diethyl ether/hexane (1/9) to afford methyl 4-(hydroxy(phenylamino)-3,4-diphenylbutanoate **19** as a yellow solid. Mp: 89–95 °C (decomposed); ^1H NMR (600 MHz, CDCl₃): $\delta = 2.53$ (s, 2H), 3.46 (s, 3H), 4.22 (s, 1H), 4.74 (s, 1H), 4.88 (s, 1H), 6.85 (s, 3H), 7.11–7.44 (m, 12H); ^{13}C NMR (100 MHz, CDCl₃): $\delta = 38.5, 43.9, 51.2, 74.7, 117.0, 121.4, 124.1, 126.3, 127.0, 127.6, 128.0, 129.1, 129.5, 135.3, 141.8, 151.0, 171.9$; MS (ESI⁺) $m/z = 362$ [M + H]⁺; IR (film) 3531, 3061, 3024, 2955, 2941, 1737, 1488, 1267 cm⁻¹.

General procedure for synthesis of 2-(*p*-tolyl)pyridine *N*-oxide (21)

A flame-dried Schlenk test tube with a magnetic stirring bar was charged with K₂CO₃ (138 mg, 1 mmol), triazolium salt (0.05 mmol), Pd(OAc)₂ (11.2 mg, 0.05 mmol), pyridine *N*-oxide (143 mg, 1.5 mmol), 4-bromotoluene (86 mg, 0.5 mmol) and toluene (2 mL) under N₂. A rubber septum was replaced with a glass stopper, and the system was then evacuated three times and backfilled with N₂. After being heated at 110 °C for 20 hours, the reaction mixture was cooled to ambient temperature, and was directly purified by column chromatography on silica gel eluting with dichloromethane/acetone (1/1) to provide the desired product **21**. Mp: 129–131 °C; ^1H NMR (400 MHz, CDCl₃): $\delta = 2.40$ (s, 3H), 7.16–7.21 (m, 1H), 7.26–7.29 (m, 3H), 7.39–7.41 (m,

1H), 7.70 (d, $J = 8.0$ Hz, 2H), 8.30 (d, $J = 6.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl₃): $\delta = 21.4, 124.2, 125.5, 127.2, 129.0, 129.1, 130.0, 139.7, 140.5, 149.4$; MS (ESI⁺) $m/z = 186$ [M + H]⁺; HR-MS (ESI) calcd for C₁₂H₁₁NO [M]⁺ 185.0841, found: 185.0813.

General procedure for synthesis of 1,3,7-trimethyl-8-(*p*-tolyl)-xanthine (23)

A flame-dried Schlenk test tube with a magnetic stirring bar was charged with Pd(OAc)₂ (11.2 mg, 0.05 mmol), triazolium salt (0.05 mmol), caffeine (97 mg, 0.5 mmol), 4-bromotoluene (172 mg, 1 mmol), K₂CO₃ (138 mg, 1 mmol) and anhydrous DMF (1 mL) under N₂. A rubber septum was replaced with a glass stopper, and the system was then evacuated three times and backfilled with N₂. After being heated at 115 °C for 22 hours, the reaction mixture was allowed to cool to room temperature. The resulting suspension was filtered through a plug of silica gel, and washed with dichloromethane (20 mL). The filtrate was concentrated under vacuum to a volume of about 2 mL. The mixture was absorbed on silica gel and subjected to flash chromatography eluting using ethyl acetate/petroleum ether (3/2) to provide the desired product **23**. Mp: 193–194 °C; ^1H NMR (400 MHz, CDCl₃): $\delta = 2.43$ (s, 3H), 3.43 (s, 3H), 3.62 (s, 3H), 4.04 (s, 3H), 7.32 (d, $J = 8.0$ Hz, 2H), 7.56 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl₃): $\delta = 21.5, 28.0, 29.8, 33.9, 108.5, 125.5, 129.1, 129.6, 140.7, 148.3, 151.8, 152.4, 155.6$; MS (AP) $m/z = 285$ [M + H]⁺; HR-MS (ESI) calcd for C₁₅H₁₇N₄O₂ [M+H]⁺ 285.1352, found: 285.1346.

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