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1,2,3-Triazole-Mediated Synthesis of 1-Methyleneisoquinolines: A Three-Step Synthesis of Papaverine and Analogues

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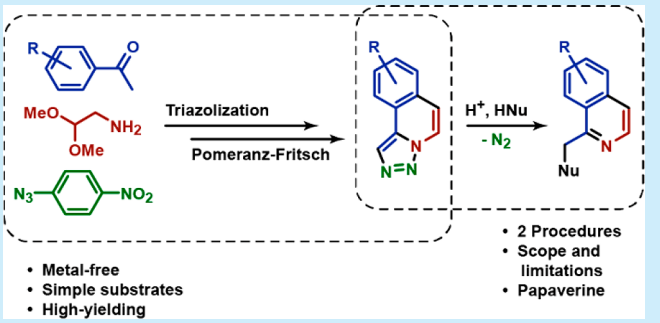
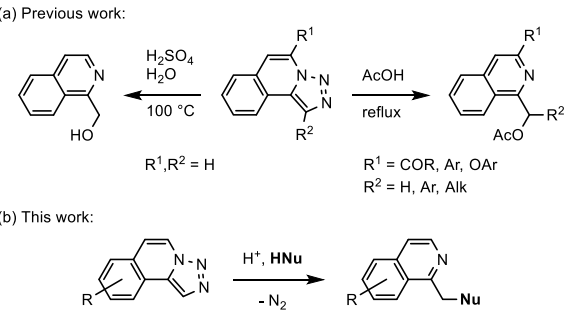
ABSTRACT: A metal-free three-step synthesis toward functionalized 1-methyleneisoquinolines from readily available substrates is reported. First, acetal-containing 1,2,3-triazoles were prepared *via* a high-yielding triazolization reaction and quantitatively converted into triazolo[5,1-*a*]isoquinolines. Next, the acid-promoted ring opening of these fused triazoles was studied in order to obtain coupling to a diverse scope of nucleophiles, including carbon nucleophiles such as veratrole. By means of non-nucleophilic strong acids under anhydrous conditions, a series of unprecedented isoquinolines and imidazo[5,1-*a*]isoquinolines was synthesized.



Isoquinolines are a valuable class of N-containing heterocycles. In particular, 1-substituted isoquinolines have been studied extensively, largely owing to their occurrence in many biologically important alkaloids.[1,2] Syntheses toward these scaffolds are numerous, and improvements of existing pathways as well as novel methods have been reported over the past decades.[3,4] However, in order to overcome limitations such as restricted substitution patterns or the use of transition metals, the development of alternative pathways for the rapid construction of functionalized isoquinolines remains an area with high level of interest.

Triazolo[5,1-*a*]isoquinolines can be put forward as potential substrates for the synthesis of isoquinolines. This was originally demonstrated by Jones, Abarca and co-workers, who studied the denitrogenative ring opening of aryl-fused triazoles with bromine, selenium dioxide, and acids.[5] Yet, the scope of acid-mediated ring opening reactions of triazoloisoquinolines has mostly remained limited to 1-hydroxymethyl- and 1-acetoxymethylisoquinolines, resulting from reactions in aqueous sulfuric acid and acetic acid, respectively (Scheme 1a).[5f,g,6a−d] In recent years, alternative methods for the denitrogenative ring opening of benzo-fused triazoles have received considerable attention. The formation of rhodium and copper carbenes has been utilized in transannulation reactions of triazolopyridines,[7] light-induced ring opening was possible for 3-aryl-1,2,3-triazolo[1,5-*a*]pyridine derivatives,[8] and tetra-*n*-butylammonium bromide (TBAB) has been applied in the metal-free ring opening of pyridotriazoles in the presence of anilines.[9] Despite these advancements, ring opening reactions of triazoloisoquinolines are underexplored, although they could be of interest, especially when the substrates are easily accessible. The reported methods for the construction of 1,2,3-triazolo[5,1-*a*]isoquinolines either start from 1-methylisoquinolines,[10] affording low product yields, or require transition metal catalysis and advanced substrates that are often not commercially available.[6]

Scheme 1. Acid-Mediated Ring Opening Reactions of 1,2,3-Triazolo[5,1-*a*]isoquinolines



A metal-free three-component reaction for the synthesis of 1,5-di-, fully substituted and even *NH*-1,2,3-triazoles, including fused systems, was reported by our group in 2016.[11] This method was named "the triazolization reaction of ketones" and combines a broad substrate scope with the advantage of using readily available starting materials such as primary amines and the recoverable 4-nitrophenyl azide as a dinitrogen source. Resulting products have already proven their utility in post-

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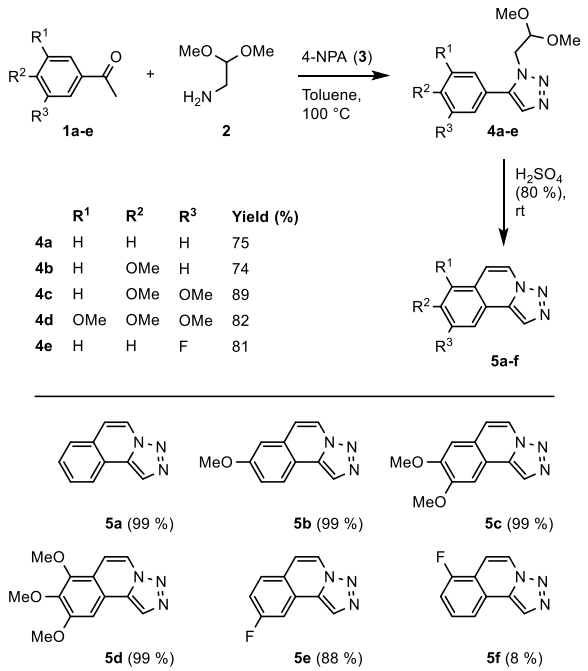
triazolization cyclization strategies, namely, toward 3-aryl-1,3*a*,6*a*-triazapentalenes,[12] allocolchicine analogues,[13] and polycyclic dihydroindoles.[14] In this work, acetal-containing 1,2,3-triazoles, derived from acetophenones, were cyclized to efficiently afford triazolo[5,1-*a*]isoquinolines. The 8,9-dimethoxytriazoloisoquinoline was considered as a potential precursor for the synthesis of the opiate papaverine, an antispasmodic and vasodilator.[15] Consequently, the acid-mediated denitrogenative ring opening of triazoloisoquinolines in the presence of nucleophiles was investigated, which led to the metal-free synthesis of functionalized 1-methyleneisoquinolines (Scheme 1b).

Dimethyl acetal-substituted triazoles **4a**−**e** were successfully prepared in a first step from the commercial aminoacetaldehyde dimethyl acetal **2**, 4-nitrophenyl azide **3** (4-NPA) and acetophenones **1** (Scheme 2). The reaction

Scheme 2. Synthesis of 1,2,3-Triazolo[5,1-*a*]isoquinolines 5a−f[a,b]



	R1	R2	R3	Yield (%)
4a	H	H	H	75
4b	H	OMe	H	74
4c	H	OMe	OMe	89
4d	OMe	OMe	OMe	82
4e	H	H	F	81

[a]Experimental conditions: 2.5 mmol of **1**, 1.1 equiv of **2**, 1.5 equiv of **3**, 2.5 mL of toluene, 17 h; 1.2 mmol of **4** in 2.5 mL of aqueous H_2SO_4 (80 wt %), 8 h. [b]Isolated yields.

proceeded smoothly under acid-free conditions, although a catalytic amount of acetic acid, as used in the optimized triazolization procedure,[11a] was not found to have a significant detrimental effect. Satisfyingly, the intermediate triazoles **4a**−**d** were then converted quantitatively *via* a modified Pomeranz−Fritsch reaction,[16] leading to the respective triazoloisoquinolines **5a**−**d** (Scheme 2). Apart from several methoxy-substituted acetophenones, 3′-fluoroacetophenone **1e** was applied as an additional example, resulting in a separable mixture of two regioisomers (**5e**,**f**). By dissolving acetal **4e** in a small portion of MeOH prior to the addition of sulfuric acid, an excellent combined yield of 96% was obtained.

Next, the acid-mediated denitrogenative ring opening of 8,9-dimethoxytriazoloisoquinoline **5c** was investigated. Previous reports showed that 1,2,3-triazolo[1,5-*a*]isoquinolines can react with a nucleophile upon ring opening, introducing a functionalized methylene substituent onto the isoquinoline core.[5f,g,6a−d] In the search for conditions that could be applied to a variety of nucleophiles, papaverine **6a** was put forward as a target structure. This challenging aim entailed the use of veratrole as a nucleophile in initial experiments. Several acids caused conversion of **5c** at temperatures above 95 °C in polar solvents. However, when taking no precautions to exclude water from the reaction mixture, the 1-hydroxymethylisoquinoline was formed as one of the major products. Therefore, further experiments were carried out with anhydrous reagents and in dry 1,2-dichloroethane, which was selected as a suitable solvent. Based on experimental observations, it was clear that strong acids of non-nucleophilic anions would be crucial to obtain the desired outcome. Indeed, methanesulfonic acid, triflic acid, triflimidic acid, and tetrafluoroboric acid diethyl ether complex were tested and found able to induce a reaction toward papaverine at 100 °C, albeit in very low yields according to the ^{1}H NMR spectra of the crude mixtures. Due to the complexity of the spectra and therefore inconclusive results obtained from reactions with veratrole, the more reactive 1-hexanol was employed as a nucleophile in order to make a careful comparison between the different acids. Fortunately, under unoptimized conditions, nearly quantitative NMR yields of isoquinoline **7h** resulted from reactions with triflic acid and $HBF_4{\cdot}OEt_2$. Methanesulfonic acid (10% NMR yield of **7h**) appeared to still be too nucleophilic, while the use of triflimidic acid (71% NMR yield of **7h**) resulted in a significant amount of degradation. Fluoroboric acid forms an insoluble salt with **5c** in DCE, which slowly disappears in the presence of 1-hexanol, but does not react with veratrole at 100 °C. A triflic acid-promoted reaction with veratrole under the same unoptimized conditions attained full conversion after 15 h, but it produced a complex mixture with a negligible yield of papaverine. Nevertheless, based on the results with hexanol, it was kept in mind that a procedure, comprising the use of triflic acid at 100 °C, could be the method of choice for denitrogenative ring opening reactions of **5c** with potent nucleophiles.[17]

The reaction of **5c** with veratrole and fluoroboric acid was further examined at higher temperatures. This could facilitate complete solvation of the reagents and, concomitantly, the desired reaction progress. Effectively, it was found that papaverine **6a** was formed in a promising NMR yield of 41% after 1.5 h at 150 °C under microwave irradiation. One major side product was the regioisomer **6b**, furnished in an NMR yield of 15%. A subsequent optimization study was carried out by means of quantitative NMR analysis with the amounts of veratrole, acid, and solvent as variables (see the Supporting Information). In this way, papaverine could be obtained in an improved NMR yield of 64%, along with 24% of its regioisomer **6b**. Advantageously, the outcome of this reaction under conventional heating (2.5 h) was similar, and respective isolated yields of 53% and 24% were achieved for **6a** and **6b**.

Encouraged by the promising reaction with veratrole, the optimized procedure was applied to some other nucleophilic aromatic compounds (Scheme 3). For both naphthalene and thiophene, mixtures of two regioisomers (**6c**,**d** and **6e**,**f**) were obtained in acceptable combined yields of 61 and 65%, respectively. As one might expect, the α-positions of naphthalene and thiophene were the most reactive sites. The reaction of **5c** with anisole was slow and gave an inseparable mixture of products. However, starting from trimethoxytriazoloisoquinoline **5d**, the reaction with anisole proceeded

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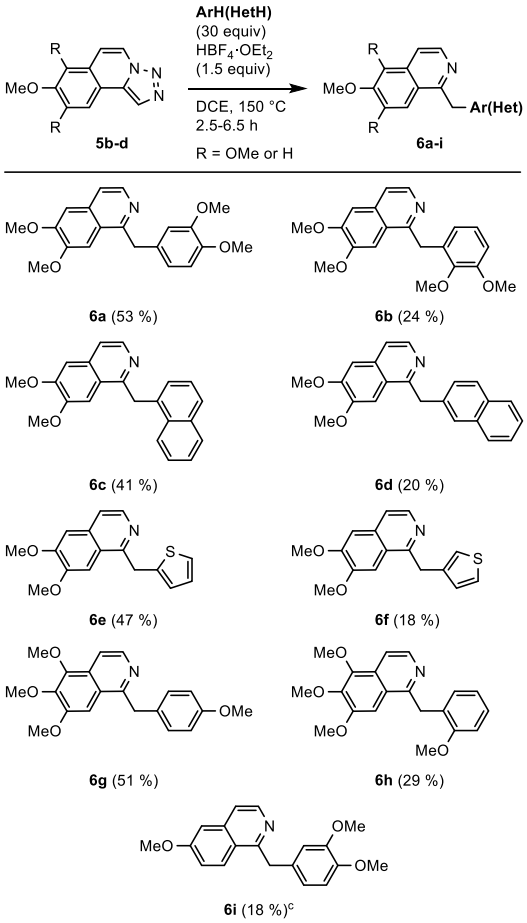
Scheme 3. Fluoroboric Acid-Mediated Ring Opening of 1,2,3-Triazolo[5,1-*a*]isoquinolines toward Isoquinolines 6a−i[a,b]

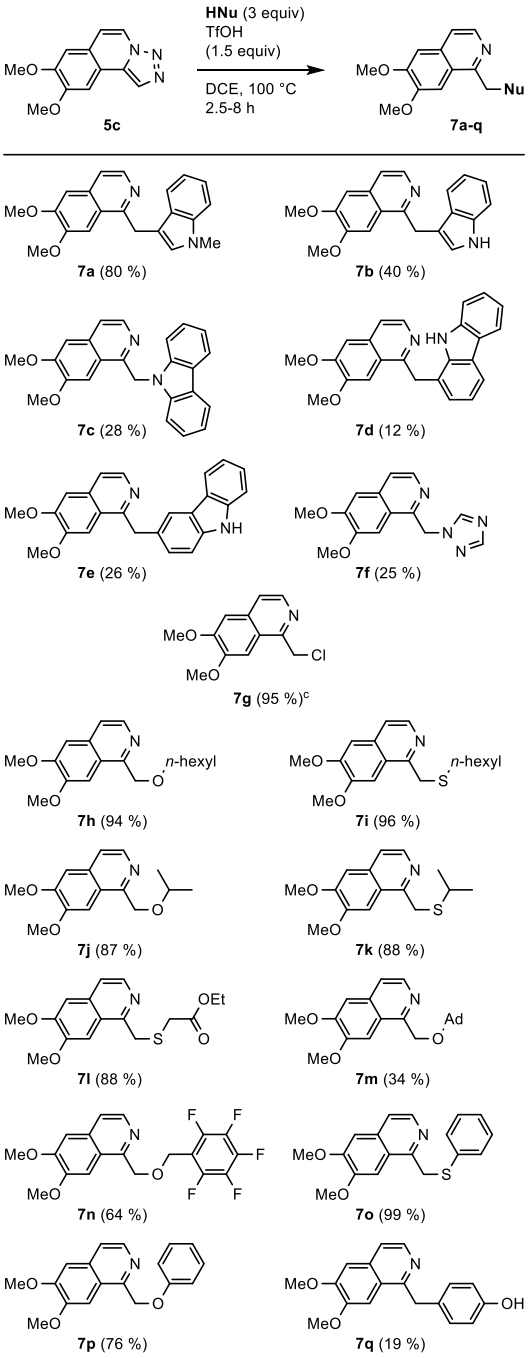


[a]Experimental conditions: 0.44 mmol of **5c**/**5d**, 7.5 mL of DCE. [b]Isolated yields. [c]0.88 mmol of **5b**, 12 mL of DCE.

smoothly and two regioisomers (**6g**,**h**) could be isolated in good yields. These results demonstrate the beneficial role of the methoxy groups on the isoquinoline core in the ring opening reaction. The 8-methoxytriazoloisoquinoline **5b** reacted much slower with veratrole compared to the dimethoxy analogue **5c**, which further substantiates the rate-enhancing effect of the methoxy groups. The expected product **6i** was isolated in only 18% yield, together with two side products, which resulted from reaction with fluoride (**6j**) and demethylation reactions (**6k**).

The reactions with **5c** and 1-hexanol showed that the denitrogenative ring opening of triazoloisoquinolines could be carried out efficiently at 100 °C. Hence, for a selection of stronger nucleophiles,[17] the use of fewer equivalents of the nucleophile in combination with milder conditions could be considered. 1-Methylindole was chosen as a starting point. Applying the optimized procedure with fluoroboric acid to this nucleophile and **5c** resulted in negligible conversion at 100 °C. As anticipated, a suspension of the fluoroboric acid salt of **5c** was observed. In contrast, the homogeneous triflic acid-mediated reaction was completed in 7 h, while the amount of nucleophile could be reduced to three equivalents. By means of this modified procedure, isoquinoline **7a** was obtained in a favorable yield of 80% (Scheme 4).

Scheme 4. Triflic Acid-Mediated Ring Opening of 1,2,3-Triazolo[5,1-*a*]isoquinolines toward Isoquinolines 7a−q[a,b]



[a]Experimental conditions: 0.44 mmol of **5c**, 7.5 mL of DCE. [b]Isolated yields. [c]Tetrabutylammonium chloride (3.92 equiv) was used as the nucleophile.

Subsequently, the scope of nucleophiles of the triflic acid-promoted ring opening was explored (Scheme 4). Reactions with 1*H*-Indole and 9*H*-carbazole are interesting examples to examine the regioselectivity. The reaction between **5c** and 1*H*-indole was clearly more delicate compared to the reaction with its methylated analogue. Due to the difficult purification, 1-(indol-3-yl)methylisoquinoline **7b** was the only product that could be isolated. On the other hand, from the reaction with carbazole, a mixture of three regioisomers **7c**−**e** was obtained

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in an approximate 2:2:1 ratio and with a combined yield of 66%.

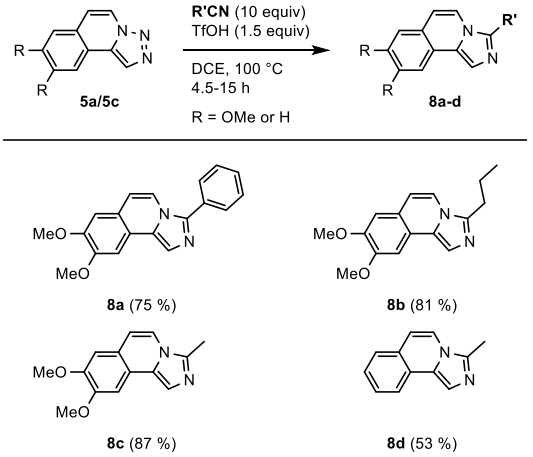
More *N*-containing heterocycles were tested. When the parent 1,2,4-triazole was used, the reaction proceeded slowly, which can be attributed to its basic properties. The reaction was stopped after 8 h, and the expected product **7f** could be isolated in yield 25%, while 41% of the triazoloisoquinoline **5c** was recovered. Interestingly, the reaction with imidazole did not show any conversion after 8 h. These results confirm that only nucleophiles with a limited basicity fall within the scope of this reaction. Correspondingly, ring opening of triazoloisoquinolines in the presence of amines was not feasible under the investigated conditions. Instead, one might propose a substitution reaction with 1-chloromethylisoquinolines and amines as an alternative pathway, which has already been described in literature.[18] The chloromethylisoquinoline **7g** has been successfully prepared in a very high yield *via* this methodology, using tetrabutylammonium chloride as a reactant.

Fortunately, alcohols and thiols proved to be ideal substrates for the triflic acid-mediated ring opening of triazoloisoquinoline **5c**. Very good yields of 87% or higher were afforded from reactions with hexanol (**7h**), hexanethiol (**7i**), isopropyl alcohol (**7j**), 2-propanethiol (**7k**), and ethyl thioglycolate (**7l**). 1-Adamantanol (**7m**), on the contrary, gave a much lower yield, and the reaction with 1-adamantanethiol did not yield the expected product. The use of benzyl alcohol did also not result in the desired reaction outcome. However, in case of pentafluorobenzyl alcohol, the 1-methyleneisoquinoline **7n** could be easily purified in a reasonable yield of 64%. Products from reactions with phenol (**7p**) and thiophenol (**7o**) were obtained in very high yields, although phenol did not react regioselectively. Benzylisoquinoline **7q**, also known as the alkaloid crykonisine, was isolated as a side product.

In the literature, examples of metal-free denitrogenative ring opening reactions of triazolo[1,5-*a*]pyridines with nitriles have been reported.[19] These transannulation reactions are interesting pathways toward various imidazopyridines. As a last part of this work, the acid-mediated ring opening of triazoloisoquinolines in the presence of nitriles was evaluated and has, to the best of our knowledge, not been explored to date. Pleasingly, the condition with triflic acid at 100 °C provided a highly effective method toward these fused systems (Scheme 5). For both benzonitrile and aliphatic nitriles, the desired imidazoisoquinolines **8a–d** were furnished in moderate to good yields when using 10 equiv of nitrile. Also for the triflic acid-promoted reaction, the absence of methoxy groups on the triazoloisoquinoline resulted in a decreased yield, which is due the slower reaction progress and concomitantly increased degradation.

In conclusion, a triazolization/Pomeranz–Fritsch sequence was successfully applied to generate 4,5-unsubstituted 1,2,3-triazolo[5,1-*a*]isoquinolines in high yields. The use of readily available starting materials can be seen as the major advantage. Next, the acid-mediated denitrogenative ring opening reaction of triazoloisoquinolines in the presence of nucleophiles was studied. For two sets of nucleophiles, a respective procedure has been put forward that allows for attaining conversion toward the desired isoquinoline products. Interestingly, the results proved that the methoxy groups on the phenyl ring of the isoquinoline core have a rate-enhancing effect on the ring opening reaction. The combination of the methods reported herein provides access to papaverine and analogues as well as a series of unprecedented functionalized (imidazo)isoquinolines. It is believed that this methodology could be expanded to other aryl methylene ketones, which may provide synthetic access to diverse polyheterocyclic scaffolds.

Scheme 5. Synthesis of Imidazo[5,1-*a*]isoquinolines 8[a,b]



[a]Experimental conditions: 0.44 mmol of **5a/5c**, 7.5 mL of DCE. [b]Isolated yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01069.

Experimental procedures and characterization data; NMR spectra (PDF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Bentley, K. W. *Nat. Prod. Rep.* **2006**, *23*, 444−463.
(2) Quin, L. D.; Tyrell, J. A. *Fundamentals of heterocyclic chemistry: importance in nature and in the synthesis of pharmaceuticals*; John Wiley & Sons, 2010.
(3) Recent syntheses of isoquinolines: (a) Xie, L.-G.; Niyomchon, S.; Mota, A. J.; González, L.; Maulide, N. *Nat. Commun.* **2016**, *7*, 10914. (b) Chuang, S.-C.; Gandeepan, P.; Cheng, C.-H. *Org. Lett.* **2013**, *15*, 5750−5753. (c) Wan, M.; Lou, H.; Liu, L. *Chem. Commun.* **2015**, *51*, 13953−13956. (d) Nikbakht, A.; Balalaie, S.; Breit, B. *Org. Lett.* **2019**, *21*, 7645−7648. (e) Jiang, H.; Cheng, Y.; Wang, R.; Zhang, Y.; Yu, S. *Chem. Commun.* **2014**, *50*, 6164−6167. (f) Zhou, C.; Jiang, J.; Wang, J. *Org. Lett.* **2019**, *21*, 4971. (g) He, R.; Huang, Z.; Zheng, Q.; Wang, C. *Angew. Chem., Int. Ed.* **2014**, *53*, 4950−4953. (h) Gutierrez, S.; Coppola, A.; Sucunza, D.; Burgos, C.; Vaquero, J. *Org. Lett.* **2016**, *18*, 3378−3381. (i) Lu, Q.; Greßies, S.; Cembellín, S.; Klauck, F. J. R.; Daniliuc, C. G.; Glorius, F. *Angew. Chem., Int. Ed.* **2017**, *56*, 12778−12782.
(4) Recent syntheses of papaverine: (a) Wu, J.; Talwar, D.; Johnston, S.; Yan, M.; Xiao, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 6983−6987. (b) Melzer, B.; Bracher, F. *Org. Biomol. Chem.* **2015**, *13*, 7664−7672. (c) Matcha, K.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2013**, *52*, 2082−2086. (d) Chu, H.; Sun, S.; Yu, J.-T.; Cheng, J. *Chem. Commun.* **2015**, *51*, 13327−13329. (e) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558−1559.
(5) (a) Jones, G.; Abarca, B. *Adv. Heterocycl. Chem.* **2010**, *100*, 195−252. (b) Abarca, B.; Ballesteros, R.; Jones, G.; Mojarrad, F. *Tetrahedron Lett.* **1986**, *27*, 3543−3546. (c) Abarca, B.; Ballesteros, R.; Mojarred, F.; Jones, G.; Mouat, D. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, *1*, 1865−1868. (d) Abarca, B.; Mojarred, F.; Jones, G.; Phillips, C.; Ng, N.; Wastling, J. *Tetrahedron* **1988**, *44*, 3005−3014. (e) Abarca, B.; Ballesteros, R.; Gómez-Aldaraví, E.; Jones, G. *J. Chem. Soc., Perkin Trans. 1* **1985**, *1*, 1897−1901. (f) Jones, G.; Mouat, D. J.; Tonkinson, D. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, *1*, 2719−2723. (g) Abarca, B.; Ballesteros, R.; Gay, B.; Domínguez, J.-R. *ARKIVOC* **2003**, *2004*, 42.
(6) Recent syntheses of 1,2,3-triazolo[5,1-*a*]isoquinolines: (a) Fan, M.; Liu, Y.; Hu, Q.; Jia, L.; Chen, Y. *Eur. J. Org. Chem.* **2016**, *2016*, 5470−5473. (b) Wu, Y.; Meng, Y.; Liu, Z.; Zhang, M.; Song, C. *Tetrahedron Lett.* **2019**, *60*, 151287. (c) Hu, Y.-Y.; Hu, J.; Wang, X.-C.; Guo, L.-N.; Shu, X.-Z.; Niu, Y.-N.; Liang, Y.-M. *Tetrahedron* **2010**, *66*, 80−86. (d) Maurya, R. A.; Adiyala, P. R.; Chandrasekhar, D.; Reddy, C. N.; Kapure, J. S.; Kamal, A. *ACS Comb. Sci.* **2014**, *16*, 466−477. (e) Gulevskaya, A. V.; Tyaglivy, A. S.; Pozharskii, A. F.; Nelina-Nemtseva, J. I.; Steglenko, D. V. *Org. Lett.* **2014**, *16*, 1582−1585. (f) Zhao, S.; Yu, R.; Chen, W.; Liu, M.; Wu, H. *Org. Lett.* **2015**, *17*, 2828−2831. (g) Arigela, R. K.; Samala, S.; Mahar, R.; Shukla, S. K.; Kundu, B. *J. Org. Chem.* **2013**, *78*, 10476−10484. (h) Chen, Y.; Zhou, S.; Ma, S.; Liu, W.; Pan, Z.; Shi, X. *Org. Biomol. Chem.* **2013**, *11*, 8171−8174. (i) Tao, S.; Hu, Q.; Li, H.; Ma, S.; Chen, Y. *Synth. Commun.* **2015**, *45*, 1354−1361.
(7) (a) Helan, V.; Gulevich, A. V.; Gevorgyan, V. *Chem. Sci.* **2015**, *6*, 1928−1931. (b) Kim, H.; Kim, S.; Kim, J.; Son, J.-Y.; Baek, Y.; Um, K.; Lee, P. H. *Org. Lett.* **2017**, *19*, 5677−5680. (c) Chattopadhyay, B.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 862−872. (d) Chuprakov, S.; Hwang, F. W.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 4757−4759. (e) Joshi, A.; Mohan, D. C.; Adimurthy, S. *Org. Lett.* **2016**, *18*, 464−467. (f) Shi, Y.; Gevorgyan, V. *Chem. Commun.* **2015**, *51*, 17166−17169.
(8) Zhang, Z.; Yadagiri, D.; Gevorgyan, V. *Chem. Sci.* **2019**, *10*, 8399−8404.
(9) Lamaa, D.; Lin, H.-P.; Bzeih, T.; Retailleau, P.; Alami, M.; Hamze, A. *Eur. J. Org. Chem.* **2019**, *2019*, 2602−2611.
(10) (a) Abramovitch, R. A.; Takaya, T. J. *J. Org. Chem.* **1972**, *37*, 2022−2029. (b) Reimlinger, H.; Lingier, W. R. F.; Merényi, R. *Chem. Ber.* **1975**, *108*, 3794−3798.
(11) (a) Thomas, J.; Jana, S.; John, J.; Liekens, S.; Dehaen, W. *Chem. Commun.* **2016**, *52*, 2885−2888. (b) Thomas, J.; Jana, S.; Liekens, S.; Dehaen, W. *Chem. Commun.* **2016**, *52*, 9236−9239. (c) Jana, S.; Thomas, J.; Dehaen, W. *J. Org. Chem.* **2016**, *81*, 12426−12432. (d) Opsomer, T.; Thomas, J.; Dehaen, W. *Synthesis* **2017**, *49*, 4191.
(12) Verbelen, B.; Dehaen, W. *Org. Lett.* **2016**, *18*, 6412−6415.
(13) Krasniqi, B.; Dehaen, W. *Org. Lett.* **2019**, *21*, 5002−5005.
(14) Jana, S.; Vroemans, R.; Dehaen, W. *Adv. Synth. Catal.* **2017**, *359*, 3085−3089.
(15) Liu, J. K.; Couldwell, W. T. *Neurocrit. Care* **2005**, *2*, 124−132.
(16) Cody, J. A.; Ahmed, I.; Tusch, D. J. *Tetrahedron Lett.* **2010**, *51*, 5585−5587.
(17) Mayr's scale of nucleophilicity: (a) Mayr, H.; Ofial, A. R. *Nachr. Chem.* **2008**, *56*, 871−877. (b) Mayr, H. *Reactivity Scales*; https://www.cup.lmu.de/oc/mayr/2019_MayrPoster.pdf (accessed 2020-03-20).
(18) Mikata, Y.; Yamashita, A.; Kawata, K.; Konno, H.; Itami, S.; Yasuda, K.; Tamotsu, S. *Dalt. Trans.* **2011**, *40*, 4059−4066.
(19) (a) Joshi, A.; Mohan, D. C.; Adimurthy, S. *J. Org. Chem.* **2016**, *81*, 9461−9469. (b) Chiassai, L.; Adam, R.; Drechslerová, M.; Ballesteros, R.; Abarca, B. *J. Fluorine Chem.* **2014**, *164*, 44−50.

https://dx.doi.org/10.1021/acs.orglett.0c01069
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