Dehydrogenation of the NH-NH Bond Triggered by Potassium *tert*-Butoxide in Liquid Ammonia

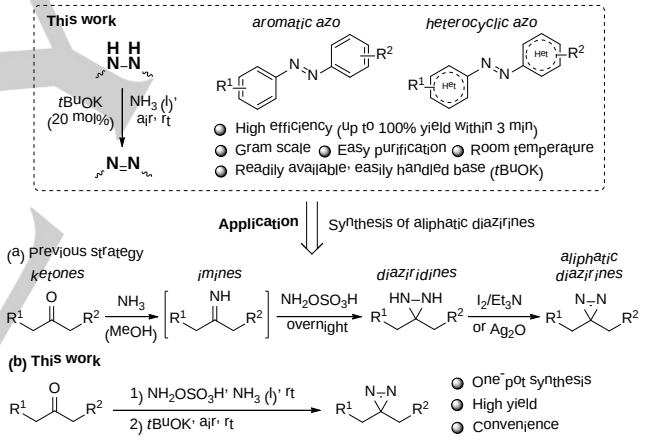
Lei Wang,* Akiko Ishida, Yasuyuki Hashidoko and Makoto Hashimoto*

Abstract: *A novel strategy for the dehydrogenation of NH-NH bond is disclosed using potassium t-butoxide (tBuOK) in liquid NH_3 under air (O_2) at room temperature. Its synthetic values are well demonstrated via highly efficient synthesis of aromatic azo compounds (up to 100% yield, 3 min), heterocyclic azo compounds, and dehydrazination of phenylhydrazine. The broad application of this strategy and its benefit to chemical biology is proved by a novel, convenient, one-pot and efficient synthesis of aliphatic diazirines, which are important photoreactive agents for photoaffinity labeling.*

Dehydrogenation of the NH-NH bond is a crucial transformation in chemistry, as the generated products which contain N=N double bond are of great interest in various fields. For instance, aromatic azo compounds, an important type of components bearing N=N bonds, are ubiquitous motifs in therapeutic agents, food additives, indicators, dyes, pigments, chemosensors, polymers, photochemical switches and radical reaction initiators.[1] The recent past has witnessed numerous methods for the synthesis of aromatic azo compounds such as oxidative coupling of anilines,[2] reduction of nitroaromatics,[3] coupling of diazo salts with aromatic compounds,[4] and Mills reaction[5]. The direct dehydrogenation of hydrazo derivatives are additional indispensable methods to prepare aromatic azo compounds. However, there are few reports on the dehydrogenation of hydrazo derivatives to afford azo compounds in the presence of catalyst or substoichiometric reagent. Utilizing O_2 or H_2O_2 as an oxidant, NH_4VO_3, Co(II) complex, $CuCl_2$, $TiCl_3$/HBr, $Pd(OAc)_2$, carbon nanotube-rhodium nanohybrid system, and reduced graphene oxide are able to catalyze this transformation.[6] Additionally, with $KClO_3/H_2SO_4$ as oxidant, a catalytic amount of $FeSO_4$ is also feasible for this reaction.[7] Nevertheless, many methods suffer from long reaction times, special catalysts, and relatively tedious post-treatment. The discovery of a novel, concise, rapid, and effective method is keenly pursued.

Aliphatic diazirines, three-membered ring structures that contain an N=N bond, are widely utilized as photoaffinity labeling agents in chemical biology.[8] Conventionally synthetic methods for aliphatic diazirines involve the preliminary treatment of ketones by NH_3 to form imines, subsequent reaction with NH_2OSO_3H to afford diaziridines (intermediates containing the NH-NH bond), and dehydrogenation to give diazirines (products containing the N=N bond) by I_2/Et_3N or freshly prepared Ag_2O (Scheme 1a).[9] Despite the prevalence of these methods,[10] they are fraught with many issues such as tedious experimental procedures, the requirement for protection under a N_2 or Ar atmosphere, inevitable filtration of the solid by-product, requirement for complete removal of NH_3 before oxidation by I_2, and relatively low reaction yields. In this respect, a convenient and effective alternative method for the synthesis of aliphatic diazirines is highly desirable.

In this communication, we describe the development of a novel and efficient strategy for the dehydrogenation of NH-NH bond to construct N=N double bond (Scheme 1). This method uses the commercially available, cheap and easily handled *t*BuOK to trigger the dehydrogenation process. Numerous aromatic azo compounds were readily synthesized in excellent yields within 3 min. Importantly, with this strategy, a novel, convenient and effective one-pot synthesis of aliphatic diazirines is achieved, which can significantly improve the development of aliphatic diazirines for photoaffinity labeling[11] (Scheme 1b).



Scheme 1. Dehydrogenation of NH-NH bond triggered by *t*BuOK and its synthetic applications.

Initially, hydroazobenzene **1a** was used as a model substrate for the optimization of reaction conditions. By employing 20 mol% NaH in THF at room temperature, we observed a dehydrogenated product **2a** in 13% yield (Table 1, entry 1). Solvent screening indicated that DMSO was effective and the reaction at 60 °C could readily produce **2a** in 92% yield within 2 h (Table 1, entries 2-5). Remarkably, when liquid NH_3, one of the least expensive bulk chemicals, was used as solvent,[12] the reaction rapidly produced **2a** in 97% yield within 3 min at room temperature (Table 1, entry 6). Either low temperature (0 °C) or the absence of NaH resulted in a significant decrease in reaction yield (Table 1, entries 7 and 8). Further evaluation with respect to base had shown noticeable effect (Table 1, entries 9-20). Utilizing *t*BuOK, a readily available, cheap, and easily handled base, the desired product **2a** could be obtained in 99% yield within 3 min. When O_2 that existed in the sealed tube was

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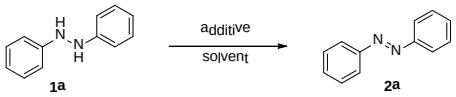
exchanged by N_2, the formation of **2a** was significantly inhibited, thus indicating the crucial role of O_2 in the reaction (Table 1, entry 21). Notably, **2a** could be easily isolated without the purification by silica gel column chromatography.

Table 1. Screening and optimization.[a]



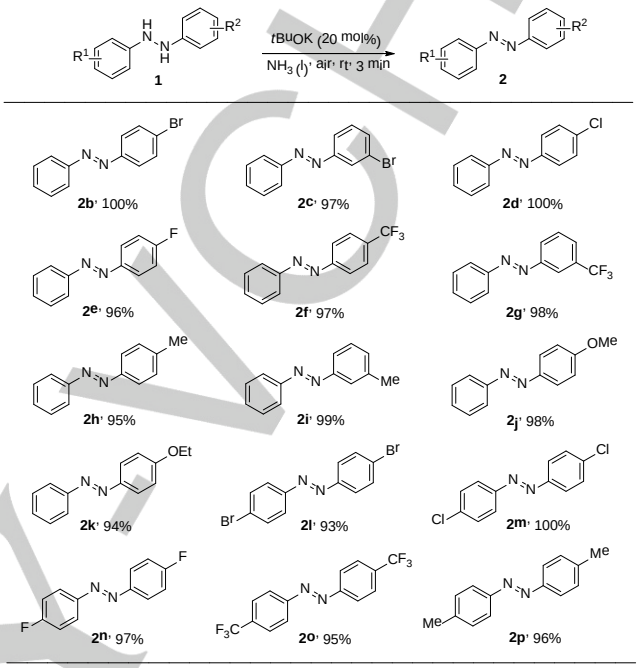
entry	solvent	additive (mol%)	temp (ºC)	time	yield (%)[b]
1[c]	THF	NaH (20)	rt	24 h	13
2[c]	MeCN	NaH (20)	rt	24 h	57
3[c]	DMF	NaH (20)	rt	24 h	89
4[c]	DMSO	NaH (20)	rt	12 h	90
5[c]	DMSO	NaH (20)	60	2 h	92
6	NH_3	NaH (20)	rt	3 min	97
7	NH_3	NaH (20)	0	3 min	33
8	NH_3		rt	3 min	0
9	NH_3	MgH_2 (20)	rt	3 min	10
10	NH_3	CaH_2 (20)	rt	3 min	22
11	NH_3	NaOH (20)	rt	3 min	11
12	NH_3	KOH (20)	rt	3 min	18
13	NH_3	$LiNH_2$ (20)	rt	3 min	30
14	NH_3	$NaNH_2$ (20)	rt	3 min	88
15	NH_3	MeONa (20)	rt	3 min	94
16	NH_3	MeOK (20)	rt	3 min	97
17	NH_3	EtONa (20)	rt	3 min	92
18	NH_3	*t*BuONa (20)	rt	3 min	97
19	**NH_3**	***t*BuOK (20)**	**rt**	**3 min**	**99**
20	NH_3	*t*BuOK (10)	rt	3 min	80
21[d]	NH_3	*t*BuOK (20)	rt	3 min	10

[a] Unless otherwise mentioned, all of the reactions were carried out using **1a** (0.5 mmol), additive, and solvent (6 mL) in a sealed tube with air. [b] Isolated yield. [c] Reaction was carried out in a round-bottom flask under N_2. [d] Air in the sealed tube was exchanged by N_2.

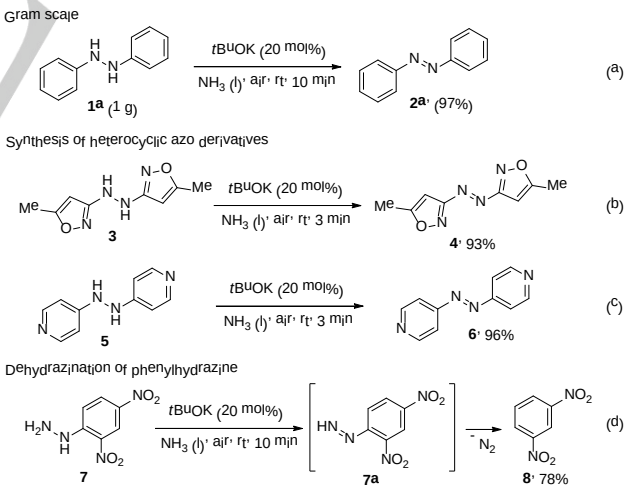
With the optimal condition in hand, we evaluated the dehydrogenation strategy to synthesize other azobenzene derivatives (Table 2). Substrates with both electron-rich and -deficient substitutions underwent efficient dehydrogenation in 3 min to afford the corresponding desired products in excellent yields. Various substituents such as –Br, –Cl, –F, –CF_3, –Me, –OMe, and –OEt were well tolerated (**2b**-**2k**). Furthermore, di-substituted hydroazobenzenes were also suitable substrates for the reaction and they afforded the desired products in high yields (**2l**-**2p**).

Follow-up chemistry was investigated to demonstrate the synthetic values of this method (Scheme 2). The novel dehydrogenation strategy could be easily scaled up to a 1 g scale in good reaction yield (Scheme 2a). Heterocyclic azo compounds were also obtained in good yields, thus indicating its application capacity for the rapid preparation of other azo compounds (Scheme 2b-2c). Interestingly, when phenylhydrazine **7** was examined by this strategy, a dehydrazinated product **8** was isolated in 78% yield. This results suggested that the dehydrogenated intermediate phenyldiazene **7a** should be generated during the reaction[13] (Scheme 2d). To our best knowledge, it is a novel and effective method to dehydrazinate phenylhydrazine.[14]

Table 2. *t*BuOK-triggered synthesis of azobenzenes.[a]



[a] Unless otherwise mentioned, all of the reactions were carried out using **1a** (0.5 mmol), *t*BuOK (20 mol%), and liquid NH_3 (6 mL) in a sealed tube at room temperature with air. Isolated yields.

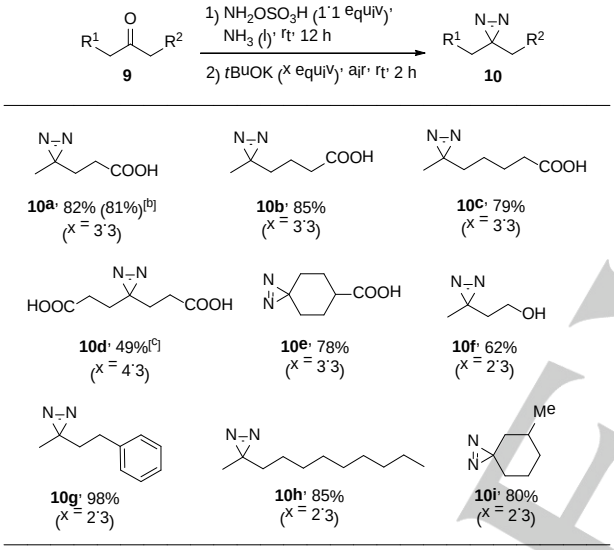


Scheme 2. Follow-up chemistry.

The above results show an effective and unique strategy for dehydrogenating the NH-NH bond to the N=N bond. To further broaden its synthetic utility, we applied this strategy to the synthesis of aliphatic diazirines as the important photoaffinity labeling agents in chemical biology. As noted earlier, conventional methods for preparing aliphatic diazirines typically involve the treatment of ketones by NH_3, subsequent reaction

with NH_2OSO_3H to form diaziridines, and formation of diazirines. Here, we explored a combination of these three reactions in a one-pot procedure based on our developed strategy, in which ketone was simultaneously treated with liquid NH_3 and NH_2OSO_3H, and then *t*BuOK was added to dehydrogenate diaziridine to afford diazirine. On the basis of screening of the reaction conditions (additives, order of the addition of reagents, and amount of reagents),[15] we successfully developed a novel synthetic method for aliphatic diazirines using a one-pot strategy (Table 3). Compared with previous methods, our developed strategy is more convenient and highly efficient. Many important aliphatic diazirines were readily synthesized in good yields. By using this one-pot method, the preparation of aliphatic diazirines-based photoaffinity labeling probes in chemical biology will be more straightforward and feasible.

Table 3. One-pot synthesis of aliphatic diazirines.[a]



[a] Unless otherwise mentioned, all of the reactions were carried out using **9** (2 mmol), NH_2OSO_3H (1.1 equiv), *t*BuOK, and liquid NH_3 (8 mL) in a sealed tube with air at room temperature. Isolated yields. [b] **9a** (1.0 g) was used for a gram-scale synthesis. [c] **9d** was treated with NH_2OSO_3H in liquid NH_3 for 24 h.

In conclusion, we have successfully developed a highly effective strategy for the dehydrogenation of the NH-NH bond to N=N bond by using substoichiometric amounts of *t*BuOK in liquid NH_3 under air. Many aromatic azo compounds were successfully prepared in excellent yields in short reaction times. Its synthetic values were demonstrated via a gram scale synthesis, the preparation of heterocyclic azo compounds and dehydrazination of phenylhydrazine. Development of a novel, convenient, and effective synthesis of aliphatic diazirines using this strategy demonstrated the potential of the method in applications in organic synthesis and chemical biology. In view of its broad utility and high efficiency, this transformation may have more applications in the future. Additional studies on the reaction scope and mechanism are currently under investigation. [16]

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Keywords: azo compounds • dehydrogenation • liquid NH_3 • photoaffinity labeling • potassium *t*-butoxide

[1] For selected examples, see: a) W. J. Sandborn, *Am. J. Gastroenterol*. **2002**, *97*, 2939; b) S. H. Lee, E. Moroz, B. Castagner, J.-C. Leroux, *J. Am. Chem. Soc*. **2014**, *136*, 12868; c) P. N. D. Ashutosh, J. K. Mehrotra, *Colourage*, **1979**, *26*, 25; d) K. Hunger, *Industrial Dyes: Chemistry, Properties, Applications*; Ed.; Wiley-VCH: Weinheim, Germany, 2003; e) N. DiCesare, J. R. Lakowicz, *Org. Lett.* **2001**, *3*, 3891; f) F. Puntoriero, P. Ceroni, V. Balzani, G. Bergamini, F. Voegtle, *J. Am. Chem. Soc.* **2007**, *129*, 10714; g) P. Commins, A. Garcia-Garibay, *J. Org. Chem*. **2014**, *79*, 1611; h) G. S. Kumar, D. C. Neckers, *Chem. Rev*. **1989**, *89*, 1915; (i) R. D. Jr. Athey, *Eur. Coat. J.* **1998**, *3*, 146.

[2] a) E. Baer, A. L. Tosoni, *J. Am. Chem. Soc*. **1956**, *78*, 2857; b) A. Grirrane, A. Corma, H. García, *Science* **2008**, *322*, 1661; c) Y. Zhu, Y. Shi, *Org. Lett*. **2013**, *15*, 1942; d) B. Dutta, S. Biswas, V. Sharma, N. O. Savage, S. P. Alpay, S. L. Suib, *Angew. Chem. Int. Ed*. **2016**, *55*, 2171.

[3] a) S. Wada, M. Urano, H. Suzuki, *J. Org. Chem.* **2002**, *67*, 8254; b) H. Zhu, X. Ke, X. Yang, S. Sarina, H. Liu, *Angew. Chem. Int. Ed*. **2010**, *49*, 9657; c) N. Sakai, K. Fujii, S. Nabeshima, R. Ikeda, T. Konakahara, *Chem. Commun*. **2010**, *46*, 3173; d) L. Hu, X. Cao, L. Shi, F. Qi, Z. Guo, J. Lu, H. Gu, *Org. Lett*. **2011**, *13*, 5640.

[4] a) J. Merrington, M. James, M. Bradley, *Chem. Commun.* **2002**, 140; b) J. Y. Kim, G. Kim, C. R. Kim, S. H. Lee, J. H. Lee, J. S. Kim, *J. Org. Chem*. **2003**, *68*, 1933; c) M. Tomasulo, F. M. Raymo, *Org. Lett*. **2005**, *7*, 4633; d) Y. He, W. He, R. Wei, Z. Chen, X. Wang, *Chem. Commun*. **2012**, *48*, 1036.

[5] a) K. Ueno, S. Akiyoshi, *J. Am. Chem. Soc.* **1954**, *76*, 3670; b) K. M. Ibne-Rasa, C. G. Lauro, J. O. Edwards, *J. Am. Chem. Soc.* **1963**, *85*, 1165; c) B. G. Gowenlock, G. B. Richter-Addo, *Chem. Rev.* **2004**, *104*, 3315; d) C. Tie, J. C. Gallucci, J. R. Parquette, *J. Am. Chem. Soc.* 2**006**, *128*, 1162.

[6] a) F. J. Trischler, *Therm. Anal*. **1979**, *16*, 119; b) S. S. B. Kim, R. B. Hommer, R. D. Cannon, *Bull. Korean Chem. Soc*. **2006**, *27*, 255; c) D. A. Blackadder, C. Hinshelwood, *J. Chem. Soc.* **1957**, 2904; d) E. Drug, M. Gozin, *J. Am. Chem. Soc.* **2007**, *129*, 13784; e) W. Gao, Z. He, Y. Qian, J. Zhao, Y. Huang, *Chem. Sci*. **2012**, *3*, 883; f) S. Donck, E. Gravel, A. Li, P. Prakash, N. Shah, J. Leroy, H. Li. I. N. N. Namboothiri, E. Doris, *Catal. Sci. Technol.* **2015**, *5*, 4542; g) L.-S. Bai, X.-M. Gao, X. Zhang, F.-F. Sun, N. Ma, *Tetrahedron Lett*. **2014**, *55*, 4545.

[7] L. Shi, F. Pan, X. Jia, Y. Wang, *Synth. Commun*. **2001**, *31*, 1691.

[8] For selected reviews, see: a) J. Das, *Chem. Rev*. **2011**, *111*, 4405; b) P. Thirumurugan, D. Matosiuk, K. Jozwiak, *Chem. Rev*. **2013**, *113*, 4905; c) T. Bottcher, M. Pitscheider, S. A. Sieber, *Angew. Chem. Int. Ed*. **2010**, *49*, 2680; d) Y. Takaoka, A. Ojida, I. Hamachi, *Angew. Chem. Int. Ed*. **2013**, *52*, 4088; e) P. R. Wratil, R. Horstkorte, W. Reutter, *Angew. Chem. Int. Ed*. **2016**, *55*, 9482.

[9] a) E. Schmitz, R. Ohme, *Chem. Ber*. **1961**, *94*, 2166; b) R. F. R. Church, A. S. Kende, M. J. Weiss, *J. Am. Chem. Soc*. **1965**, *87*, 2665; c) R. F. R. Church, M. J. Weiss, *J. Org. Chem*. **1970**, *35*, 2465.

[10] For recent examples, see: a) P. Haberkant, R. Raijmakers, M. Wildwater, T. Sachsenheimer, B. Brugger, K. Maeda, M. Houweling, A.-C. Gavin, C. Schultz, G. van Meer, A. J. R. Heck, J. C. M. Holthuis, *Angew. Chem. Int. Ed*. **2013**, *52*, 4033; b) L. Lercher, J. F. McGouran, B. M. Kessler, C. J. Schofield, B. G. Davis, *Angew. Chem. Int. Ed*. **2013**, *52*, 10553; c) Z. Li, P. Hao, L. Li, C. Y. J. Tan, X. Cheng, G. Y. J. Chen, S. K. Sze, H.-M. Shen, S. Q. Yao, *Angew. Chem. Int. Ed*. **2013**, *52*, 8551; d) J. J. Hulce, A. B. Cognetta, M. J. Niphakis, S. E. Tully, B. F. Cravatt, *Nat. Methods* **2013**, *10*, 259; e) Z. Li, D. Wang, L. Li, S. Pan, Z. Na, C. Y. J. Tan, S. Q. Yao, *J. Am. Chem. Soc.* **2014**, *136*, 9990; f) T. Kambe, B. E. Correia, M. J. Niphakis, B. F. Cravatt, *J. Am. Chem. Soc.* **2014**, *136*, 10777; g) A. Pahl, M. Lakemeyer, M.-T. Vielberg, M. W. Hackl, J. Vomacka, V. S. Korotkov, M. L. Stein, C. Fetzer, K. Lorenz-Baath, K. Richter, H. Waldmann, M. Groll, S. A.

Sieber, *Angew. Chem. Int. Ed.* **2015**, *54*, 15892; h) T. Peng, H. C. Hang. *J. Am. Chem. Soc.* **2015**, *137*, 556; i) Z. Li, L. Qian, L. Li, J. C. Bernhammer, H. V. Huynh, J.-S. Lee, S. Q. Yao, *Angew. Chem. Int. Ed.* **2016**, *55*, 2002.

[11] a) H. Nakashima, M. Hashimoto, Y. Sadakane, T. Tomohiro, Y. Hatanaka, *J. Am. Chem. Soc.* **2006**, *128*, 15092; b) M. Hashimoto, Y. Hatanaka, *Eur. J. Org. Chem*. **2008**, 2513; c) M. Tomizawa, J. E. Casida, *Acc. Chem. Res.* **2009**, *42*, 260; d) L. Wang, Y. Murai, T. Yoshida, A. Ishida, K. Masuda, Y. Sakihama, Y. Hashidoko, Y. Hatanaka, M. Hashimoto, *Org. Lett*. **2015**, *17*, 616; e) L. Wang, Y. Hashidoko, M. Hashimoto, *J. Org. Chem*. **2016**, *81*, 4464; f) I. Coin, M. H. Perrin, W. W. Vale, L. Wang, *Angew. Chem. Int. Ed*. **2011**, *50*, 8077; g) F. Kotzyba-Hibert, I. Kapfer, M. Goeldner, *Angew. Chem. Int. Ed.* **1995**, *34*. 1296; h) G. Li, Y. Liu, Y. Liu, L. Chen, S. Wu, Y. Liu, X. Li, *Angew. Chem. Int. Ed.* **2013**, *52*, 9544.

[12] a) E. C. Franklin, *J. Am. Chem. Soc.* **1905**, *27*, 820; b) W. L. Jorgensen, M. Ibrahim, *J. Am. Chem. Soc*. **1980**, *102*, 3309; c) P. Ji, J. Atherton, M. I. Page, *Org. Biomol. Chem*. **2012**, *10*, 5732.

[13] P. C. Huang, E. M. Kosower, *J. Am. Chem. Soc*. **1968**, *90*, 2367.

[14] For selected examples, see: a) L. D. S. Yadav, R. Kapoor, *J. Org. Chem*. **2004**, *69*, 8118; b) A. Unciti-Broceta, M. J. Pineda de las Infantas, M. A. Gallo, A. Espinosa, *Chem. Eur. J.* **2007**, *13*, 1754; c) R. Xia, M.-S. Xie, H.-Y. Niu, R.-G. Qu, H.-M. Guo, *Green Chem*. **2014**, *16*, 1077; d) L. Kubovičová, K. Bürglová, J. Hlaváč, *Org. Biomol. Chem*. **2016**, *14*, 4824.

[15] See Supporting Information for details. Noted: in consideration of the cnsumption of *t*BuOK by NH_2OSO_3H and carboxyl groups of compounds **9a**-**9e,** excess *t*BuOK was used in the one-pot reaction; for example, to synthesize **10a**, excess 3.1 equiv of *t*BuOK was used to react with NH_2OSO_3H (0.1 equiv) and the generated SO_4^{2-} (2.0 equiv), and to neutralize the carboxyl group of **9a** (1.0 equiv).

[16] In the presence of a radical scavenger BHT (2,6-di-*tert*-butyl-4-methylphenol), formation of **2a** was partly inhibited in the standard condition (from 99% to 78% yield), thus indicating that a radical pathway could be involved in the reaciton. see: a): A. Dewanji, C. Mück-Lichtenfeld, A. Studer, *Angew. Chem. Int. Ed*. **2016**, *55*, 6749; b) S. Zhou, E. Doni, G. M. Anderson, R. G. Kane, S. W. MacDougall, V. M. Ironmonger, T. Tuttle, J. A. Murphy, *J. Am. Chem. Soc*. **2014**, *136*, 17818.

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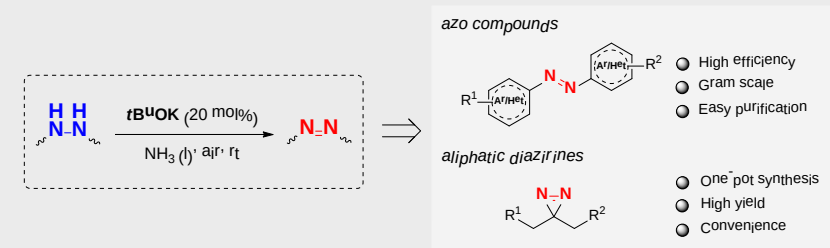

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