Transition-Metal-Free Diastereoselective Epoxidation of Trifluoromethylketones with *N*-Tosylhydrazones: Access to Tetrasubstituted Trifluoromethylated Oxiranes

Chuanle Zhu, Pengquan Chen, Wanqing Wu,* Chaorong Qi, Yanwei Ren, and Huanfeng Jiang*

Key Laboratory of Functional Molecular Engineering of Guangdong Province, School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, P. R. China
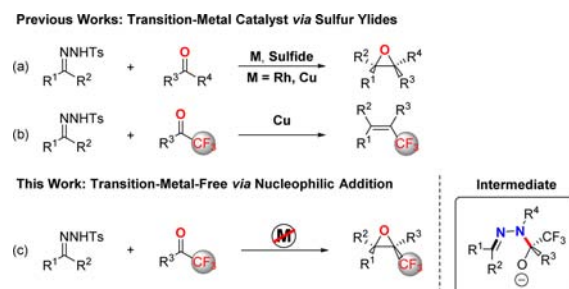
Ⓢ *Supporting Information*

ABSTRACT: The first example of the epoxidation reaction of trifluoromethylketones with *N*-tosylhydrazones under transition-metal free conditions is reported. This epoxidation reaction provided tetrasubstituted trifluoromethylated oxiranes with excellent yields and diastereoselectivities. The salient features of this reaction include readily available starting materials, mild conditions, broad substrate scope, high efficiency, and valuable further applications. Remarkably, this reaction proceeded through an unprecedented nucleophilic addition process, and the ammonium O-anion intermediate was detected and characterized by NMR and HRMS analysis.

Incorporation of the trifluoromethyl group into potential medicines has positive influences that substantially improve the lipophilicity, catabolic stability, and transport rate of the parent molecules.[1] Due to the impressive properties of the trifluoromethyl group, trifluoromethylated building blocks are privileged skeletons for library design and drug discovery.[2] Among them, trifluoromethylated oxiranes, especially di- and trisubstituted trifluoromethylated oxiranes, as all-pervading structural motifs in synthetic and medicinal chemistry have been tremendously investigated during the past decades.[3] In contrast, tetrasubstituted trifluoromethylated oxiranes, a class of important but highly sterically congested compounds, received limited attention, probably due to the lack of efficient and practical methods for their preparation.[4] In this regard, the development of a general and practical method for the diastereoselective synthesis of tetrasubstituted trifluoromethylated oxiranes not only stands as a long-pursued research subject but also as an impending challenge. Intuitively, the epoxidation reaction of trifluoromethylketones would be a highly competitive strategy.

In the past decades, the renaissance of *N*-tosylhydrazones to efficiently construct molecular complexity under transition-metal catalysis or transition-metal free conditions has already attracted the attention of many researchers.[5] The elegant early works for the epoxidation of aldehydes or ketones with *N*-tosylhydrazones under rhodium acetate and sulfide catalytic systems were reported by Aggarwal's group (Scheme 1, a).[6] In 2013, Pérez and co-workers documented that copper complex, instead of rhodium acetate, could also promote this type of epoxidation reaction.[7] However, the reaction of trifluoromethyl ketones with *N*-tosylhydrarzones was described to afford trifluoromethylated alkene compounds under copper catalysis, while the epoxidation products were not obtained (Scheme 1, b).[8] As a part of our continuous effort twoard exploiting the

Scheme 1. Reactions of *N*-Tosylhydrazones with Carbonyl Compounds

potential abilities of *N*-tosylhydrazones,[9] herein we report the epoxidation of trifluoromethyl ketones with *N*-tosylhydrazones under transition-metal free conditions, which provides various tetrasubstituted trifluoromethylated oxirane products in excellent yields and diastereoselectivities (Scheme 1, c). Remarkably, this reaction underwent an unprecedented nucleophilic addition process, and the ammonium *O*-anion intermediate was detected and characterized by NMR and HRMS analysis.
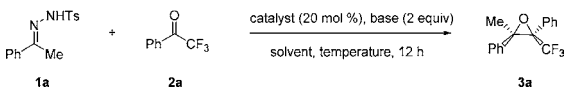
At the outset of our studies, we investigated this epoxidation reaction of *N*-tosylhydrazone (**1a**) and trifluoromethyl ketone (**2a**) under the well-established reaction conditions by Aggarwal[6] and Pérez.[7] Unfortunately, no desired product could be isolated. Inspired by our recent progress on the highly diastereoseletive cyclopropanation with *N*-tosylhydrazones,[9g] transition-metal-free catalysis became the logical follow-up consideration. To our delight, the desired oxirane product

3a was obtained in 17% isolated yield with excellent diastereoselectivity when the reaction was performed at room temperature for 6 days in the presence of BTEAC (benzyltriethylammonium chloride) as the catalyst (Table 1,

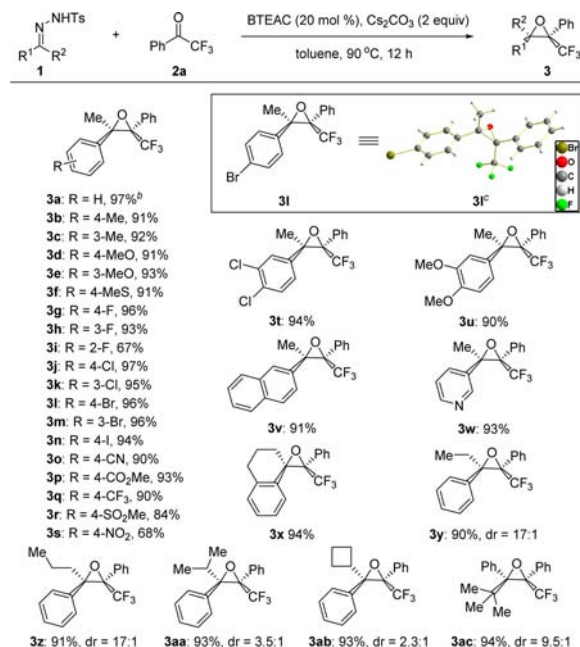**Table 1. Optimization of Reaction Conditions**[a]

entry	catalyst	base	solvent	temp (°C)	yield[b] (%)
1[c]	BTEAC	Cs_2CO_3	toluene	25	18 (17)
2	BTEAC	Cs_2CO_3	toluene	50	44
3	BTEAC	Cs_2CO_3	toluene	70	91
4	BTEAC	Cs_2CO_3	toluene	90	98 (97)
5	BTEAC	K_2CO_3	toluene	90	93
6	BTEAC	Na_2CO_3	toluene	90	91
7	BTEAC	t-BuOK	toluene	90	72
8	BTEAC	t-BuOLi	toluene	90	94
9	BTEAC	MeONa	toluene	90	91
10	BTEAC	Cs_2CO_3	toluene	90	79
11	BTEAC	Cs_2CO_3	DMF	90	43
12	BTEAC	Cs_2CO_3	MeCN	90	93
13	BTEAC	Cs_2CO_3	THF	90	94
14	BTEAC	Cs_2CO_3	DCE	90	86
15	$(n\text{-}Bu)_4N^+Br^-$	Cs_2CO_3	toluene	90	81
16	$(n\text{-}Bu)_4N^+HSO_4^-$	Cs_2CO_3	toluene	90	77
17	$(n\text{-}Bu)_4N^+I^-$	Cs_2CO_3	toluene	90	94

[a]A mixture of **1a** (0.2 mmol, 2 equiv), **2a** (0.1 mmol, 1 equiv), base (0.2 mmol, 2 equiv), catalyst (20 mol %), and solvent (2 mL) was sealed in a 25 mL Schlenk tube at 90 °C for 12 h. [b]Yields were determined by ^{19}F NMR spectroscopy with PhCF$_3$ as an internal standard, and all of the dr's (diastereomeric ratios) > 20:1. [c]The reaction time was 6 days. The isolated yield is shown in parentheses.

entry 1). Significantly, increasing the reaction temperature had a positive effect on the yield. A temperature of 90 °C was found to be optimal, affording the oxirane product **3a** in 97% isolated yield with excellent diastereoselectivity (Table 1, entries 1−4). Furthermore, different types of bases, solvents, and catalysts were investigated, but no superior results were obtained (Table 1, entries 5−17).

With the optimized reaction conditions in hand, we turned our attention to the scope of this transformation. Gratifyingly, a broad spectrum of N-tosylhydrazones with different substitution patterns could be tolerated in this reaction, delivering the corresponding oxirane products in high yields with excellent diastereoselectivities (Scheme 2). In general, the electronic nature of the substituents on the aryl ring of N-tosylhydrazones had little influence on the product yields and diastereoselectivities (**3a−u**). It is worth noting that the reaction system could tolerate diverse valuable functional groups on the aryl ring of the N-tosylhydrazones, such as F, Cl, Br, I, CN, CO$_2$Me, CF$_3$, SO$_2$Me, and NO$_2$ substituents (products **3g−s**), providing ample potential for further synthetic applications. Significantly, product **3l** was proved to be crystalline, and the relative stereochemistry of these tetrasubstituted trifluoromethylated oxirane products was determined by means of X-ray crystallographic analysis.[10] Furthermore, 1-(naphthalen-2-yl)ethan-1-one- and 1-(pyridin-3-yl)ethan-1-one-derived N-tosylhydrazones were perfectly applicable to the current catalytic system, delivering the desired products with excellent yields (**3v,w**). Cyclic 3,4-dihydronaphthalen-1(2H)-one-derived N-tosylhy-

Scheme 2. Substrate Scope of N-Tosylhydrazones[a]

3a: R = H, 97%[b]
3b: R = 4-Me, 91%
3c: R = 3-Me, 92%
3d: R = 4-MeO, 91%
3e: R = 3-MeO, 93%
3f: R = 4-MeS, 91%
3g: R = 4-F, 96%
3h: R = 3-F, 93%
3i: R = 2-F, 67%
3j: R = 4-Cl, 97%
3k: R = 3-Cl, 95%
3l: R = 4-Br, 96%
3m: R = 3-Br, 96%
3n: R = 4-I, 94%
3o: R = 4-CN, 90%
3p: R = 4-CO$_2$Me, 93%
3q: R = 4-CF$_3$, 90%
3r: R = 4-SO$_2$Me, 84%
3s: R = 4-NO$_2$, 68%

3t 94%   **3u** 90%
3v 91%   **3w** 93%
3x 94%   **3y** 90%, dr = 17:1
3z 91%, dr = 17:1   **3aa** 93%, dr = 3.5:1   **3ab** 93%, dr = 2.3:1   **3ac** 94%, dr = 9.5:1
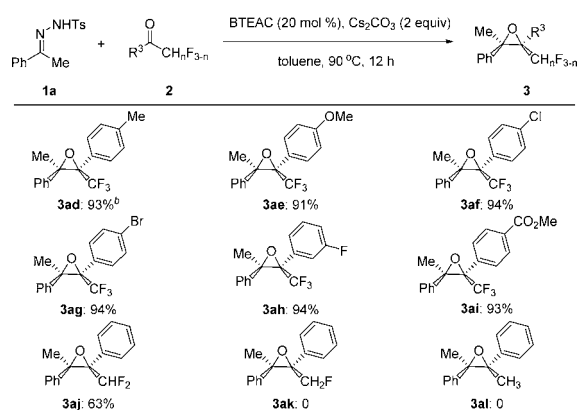
[a]Unless otherwise noted, the reaction was run at 0.1 mmol scale under standard reaction conditions. dr >20:1. [b]The average isolated yield of two parallel runs. [c]ORTEP representation with 50% probability thermal ellipsoids of a crystal structure of **3l**.

drazone was also found to be a good substrate, and the corresponding product **3x** was obtained in 94% yield. N-Tosylhydrazones derived from ethyl-, propyl-, isopropyl-, cyclobutyl-, and tert-butyl(phenyl)methanone were suitable substrates for this transformation, giving the desired oxirane products in excellent yields (**3y−ac**). It is worth mentioning that the size discrimination between aryl groups (R^1) and alkyl groups (R^2) could significantly interfere with the diastereoselectivity of these products (**3y−ab**). Interestingly, reversed relative stereochemistry was observed for **3ac**, probably due to the larger steric hindrance effect of tert-butyl group compared to that of the phenyl ring.

To further define the scope of our protocol, the substrate scope was extended to different fluorinated ketones **2** (Scheme 3). Pleasingly, trifluoromethyl ketones with both electron-donating and -withdrawing groups on the phenyl ring could undergo this reaction smoothly, delivering the desired products with excellent yields and diastereoselectivities (**3ad−ai**). In addition, when the trifluoromethyl group of **2a** was replaced with a difluoromethyl group, the epoxidation product **3aj** was also obtained in 63% yield. However, when the trifluoromethyl group was changed to a monofluoromethyl or methyl group, no desired products were observed (**3ak,al**). These results suggested that the strong electron-withdrawing di- and trifluoromethyl groups were crucial for the success of this epoxidation reaction.[2,11,12]

The synthetic utility of this transformation was next explored. A gram-scale reaction of 2.88 g of **1a** and 0.87 g of **2a** was carried out under standard reaction conditions, furnishing 1.32 g of the desired product **3a** in 95% isolated yield with dr >20:1 (Scheme 4, a). Notably, further transformation of the obtained oxirane product **3a** gave a quaternary carbon center containing trifluoromethyl ketone **4** in 96% yield, which was difficult to synthesize by other methods (Scheme 4, b).

Scheme 3. Substrate Scope of Fluorinated Ketones[a]

[a]Unless otherwise noted, the reaction was run at 0.1 mmol scale under standard reaction conditions. dr >20:1. [b]The average isolated yield of two parallel runs.

Scheme 4. Gram-Scale Synthesis and Transformation of the Products
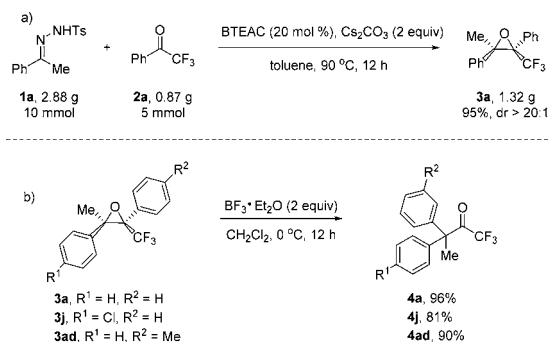
To cast some light on the mechanism details of our reaction, ^{19}F NMR and ^{13}C NMR were used to monitor the reaction process (for details, see the Supporting Information). Selected NMR spectra are shown in Figure 1. A new single peak simultaneously appeared at $\delta = -83.1$ ppm on the ^{19}F NMR spectrum as soon as trifluoromethyl ketone (2a) was added to the reaction mixture, which implied the formation of a new species. The new peak rapidly reached its maximum intensity (50%, based on ^{19}F NMR) within 60 min and remained
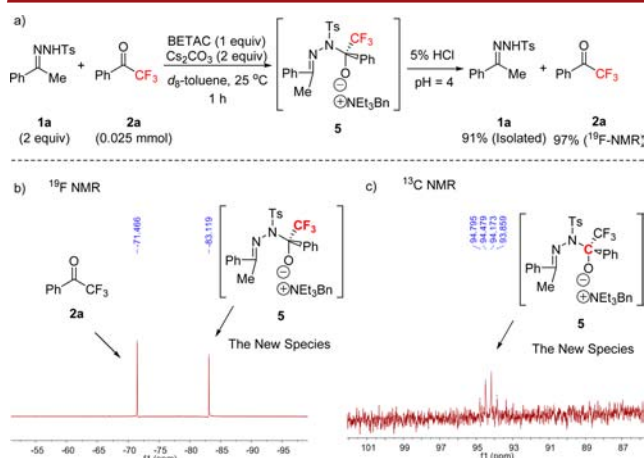

Figure 1. New species detected by NMR analysis.

unchanged for another 12 h at 25 °C (Figure 1, b). Accordingly, a new quartet peak was observed at $\delta = 94.3$ ppm (q, $J = 31.6$ Hz) on the ^{13}C NMR spectrum (Figure 1, c). The new species was then tentatively assigned as ammonium O-anion intermediate 5 via the nucleophilic addition of N-tosylhydrazone (1a) to trifluoromethyl ketone (2a) in the presence of BTEAC.[13] Remarkably, when the pH value of this reaction mixture was adjusted to pH = 4 with 5% aq HCl solution, the new peak ($\delta = -83.1$ ppm, ^{19}F NMR) immediately disappeared and the ratio of 2a was enhanced to 97% (based on ^{19}F NMR). Meanwhile, 1a was obtained in 91% isolated yield (Figure 1, a). These results clearly reflected the kinetic dynamic equilibrium between the tight ion-pair intermediate 5 and its precursors 2a and 1a.[14] It is noteworthy that an ESI/MS analysis of the reaction mixture permitted further identification of this counter O-anion motif of intermediate 5 with the high-resolution mass data (HRMS (ESI): [M − H]$^-$ calcd for $C_{23}H_{19}F_3N_2O_3S$ 460.1074, found 460.1079). In accordance with the ^{19}F NMR studies at 25 °C, ammonium O-anion 5 was also identified as the intermediate when the reaction was carried out at 90 °C (see the SI).

On the basis of these experimental results and previous works,[5,9] we tentatively proposed the reaction mechanism as outlined in Scheme 5. The deprotonation of N-tosylhydrazone 1 in the presence of bases afforded the insoluble cesium salt A.

Scheme 5. Possible Mechanism
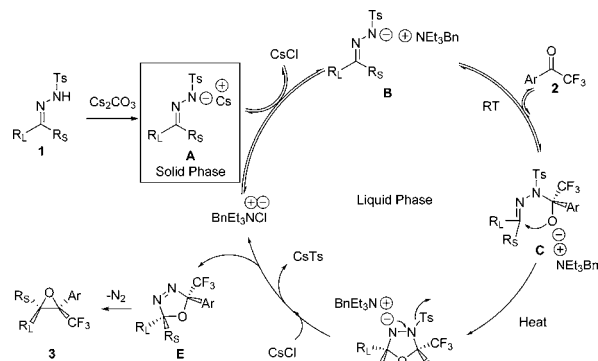
Ion exchange of the insoluble cesium salt A gave the corresponding soluble ammonium N-anion B as a tight ion pair. Subsequent nucleophilic addition of the counter N-anion of intermediate B to trifluoromethyl ketone 2 afforded the ammonium O-anion C. Further intramolecular nucleophilic attack of the O-anion species of intermediate C led to the formation of ammonium N-anion D as a tight ion pair. The elimination of Ts anion and ammonium ion from intermediate D regenerated the catalyst BTEAC and also delivered the oxadiazole compound E, which finally converted to the desired oxirane product 3 with the release of nitrogen gas.[15]

In summary, we have developed a general and practical epoxidation reaction of trifluoromethylketones with N-tosylhydrazones via an unprecedented nucleophilic process under transition-metal free conditions. This novel protocol provided an efficient method for the construction of tetrasubstituted trifluoromethylated oxirane derativites in excellent yields and diastereoselectivities. Remarkably, the ammonium O-anion intermediate of this unique transformation was characterized by NMR and HRMS analysis. Efforts are currently underway in our laboratory to elucidate the mechanistic details, investigate

the catalytic asymmetric synthesis, and explore medicinal applications of the products, the results of which will be reported in due course.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01824.

> Typical experimental procedure, characterization data for all products (PDF)
>
> X-ray cyrstallographic data for 3l (CIF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: cewuwq@scut.edu.cn.
*E-mail: jianghf@scut.edu.cn.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

REFERENCES

(1) (a) Bégué, J.-P.; Bonnet-Delpon, D.; Perez-Luna, A. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley-VCH: Hoboken, 2008. (b) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley-Blackwell: Chichester, 2009.

(2) (a) Uneyama, K.; Katagiri, T.; Amii, H. *Acc. Chem. Res.* **2008**, *41*, 817. (b) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* **2011**, *111*, 455. (c) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (d) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (e) Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8950. (f) Chu, L.; Qing, F. *Acc. Chem. Res.* **2014**, *47*, 1513. (g) Charpentier, J.; Fruh, N.; Togni, A. *Chem. Rev.* **2015**, *115*, 650. (h) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015**, *115*, 683. (i) Xu, X.; Matsuzaki, K.; Shibata, N. *Chem. Rev.* **2015**, *115*, 731. (j) Ni, C.; Hu, M.; Hu, J. *Chem. Rev.* **2015**, *115*, 765. (k) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev.* **2015**, *115*, 826. (l) Alonso, C.; Martinez de Marigorta, E.; Rubiales, G.; Palacios, F. *Chem. Rev.* **2015**, *115*, 1847. (m) Shao, X.; Xu, C.; Lu, L.; Shen, Q. *Acc. Chem. Res.* **2015**, *48*, 1227.

(3) (a) Uchiyama, Y.; Kano, N.; Kawashima, T. *J. Am. Chem. Soc.* **2003**, *125*, 13346. (b) Wang, Q.; Deng, X.; Zhu, B.; Ye, L.; Sun, X.; Li, C.; Zhu, C.; Shen, Q.; Tang, Y. *J. Am. Chem. Soc.* **2008**, *130*, 5408. (c) Obinata, R.; Kawasaki-Takasuka, T.; Yamazaki, T. *Org. Lett.* **2010**, *12*, 4316. (d) Chu, Y.; Liu, X.; Li, W.; Hu, X.; Lin, L.; Feng, X. *Chem. Sci.* **2012**, *3*, 1996. (e) Kawai, H.; Okusu, S.; Yuan, Z.; Tokunaga, E.; Yamano, A.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 2221. (f) Wu, S.; Pan, D.; Cao, C.; Wang, Q.; Chen, F. *Adv. Synth. Catal.* **2013**, *355*, 1917. (g) Arduengo, A. J., III; Dolphin, J. S.; Gurău, G.; Marshall, W. J.; Nelson, J. C.; Petrov, V. A.; Runyon, J. W. *Angew. Chem., Int. Ed.* **2013**, *52*, 5110. (h) Nishimura, N.; Norman, M. H.; Liu, L.; Yang, K. C.; Ashton, K. S.; Bartberger, M. D.; Chmait, S.; Chen, J.; Cupples, R.; Fotsch, C.; Helmering, J.; Jordan, S. R.; Kunz, R. K.; Pennington, L. D.; Poon, S. F.; Siegmund, A.; Sivits, G.; Lloyd, D. J.; Hale, C.; Jean, D. J. S. *J. Med. Chem.* **2014**, *57*, 3094.

(4) (a) Shimizu, M.; Fujimoto, T.; Minezaki, H.; Hata, T.; Hiyama, T. *J. Am. Chem. Soc.* **2001**, *123*, 6947. (b) Shimizu, M.; Fujimoto, T.; Liu, X.; Minezaki, H.; Hata, T.; Hiyama, T. *Tetrahedron* **2003**, *59*, 9811. (c) Shimizu, M.; Fujimoto, T.; Liu, X.; Hiyama, T. *Chem. Lett.* **2004**, *33*, 438. (d) Grellepois, F.; Chorki, F.; Crousse, B.; Ourévitch, M.; Bonnet-Delpon, D.; Bégué, J. *J. Org. Chem.* **2002**, *67*, 1253. (e) Xu, J.; Wang, Y.; Gong, T.; Xiao, B.; Fu, Y. *Chem. Commun.* **2014**, *50*, 12915.

(5) For selected reviews of *N*-tosylhydrazones, see: (a) Fulton, J. R.; Aggarwal, V. K.; de Vicente, J. *Eur. J. Org. Chem.* **2005**, *2005*, 1479. (b) Barluenga, J.; Valdés, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 7486. (c) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2012**, *41*, 560. (d) Xiao, Q.; Zhang, Y.; Wang, J. *Acc. Chem. Res.* **2013**, *46*, 236. (e) Xia, Y.; Zhang, Y.; Wang, J. *ACS Catal.* **2013**, *3*, 2586.

(6) (a) Aggarwal, V. K.; Alonso, E.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Porcelloni, M.; Studley, J. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 1430. (b) Aggarwal, V. K.; Patel, M.; Studley, J. *Chem. Commun.* **2002**, 1514. (c) Aggarwal, V. K.; Alonso, E.; Bae, I.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Patel, M.; Porcelloni, M.; Richardson, J.; Stenson, R. A.; Studley, J. R.; Vasse, J.; Winn, C. L. *J. Am. Chem. Soc.* **2003**, *125*, 10926. (d) Aggarwal, V. K.; Bae, I.; Lee, H. *Tetrahedron* **2004**, *60*, 9725. (e) Aggarwal, V. K.; Aragoncillo, C.; Winn, C. L. *Synthesis* **2005**, *8*, 1378.

(7) Pereira, A.; Martín, C.; Maya, C.; Belderrain, T. R.; Pérez, P. J. *Adv. Synth. Catal.* **2013**, *355*, 2942.

(8) Sha, Q.; Wei, Y. *ChemCatChem* **2014**, *6*, 131.

(9) (a) Chen, H.; Huang, L.; Fu, W.; Liu, X.; Jiang, H. *Chem. - Eur. J.* **2012**, *18*, 10497. (b) Jiang, H.; Fu, W.; Chen, H. *Chem. - Eur. J.* **2012**, *18*, 11884. (c) Jiang, H.; He, L.; Li, X.; Chen, H.; Wu, W.; Fu, W. *Chem. Commun.* **2013**, *49*, 9218. (d) Li, X.; Liu, X.; Chen, H.; Wu, W.; Qi, C.; Jiang, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 14485. (e) Xiong, W.; Qi, C.; He, H.; Ouyang, L.; Zhang, M.; Jiang, H. *Angew. Chem., Int. Ed.* **2015**, *54*, 3084. (f) Gao, Y.; Xiong, W.; Chen, H.; Wu, W.; Peng, J.; Gao, Y.; Jiang, H. *J. Org. Chem.* **2015**, *80*, 7456. (g) Zhu, C.; Li, J.; Chen, P.; Wu, W.; Ren, Y.; Jiang, H. *Org. Lett.* **2016**, *18*, 1470.

(10) CCDC 1407148 (3l) contains the supplementary crystallographic data. These data can also be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

(11) (a) Hu, J.; Zhang, W.; Wang, F. *Chem. Commun.* **2009**, 7465. (b) Zhang, C.-P.; Chen, Q.-Y.; Guo, Y.; Xiao, J.-C.; Gu, Y.-C. *Chem. Soc. Rev.* **2012**, *41*, 4536.

(12) Cahard, D.; Bizet, V. *Chem. Soc. Rev.* **2014**, *43*, 135.

(13) (a) Claramunt, B. M.; Cornago, P.; Torres, V.; Pinilla, E.; Torres, M. R.; Samat, A.; Lokshin, V.; Valés, M.; Elguero, J. *J. Org. Chem.* **2006**, *71*, 6881. (b) Fustero, S.; Román, R.; Sanz-Cervera, J. F.; Simón-Fuentes, A.; Cuñat, A. C.; Villanova, S.; Murguia, M. *J. Org. Chem.* **2008**, *73*, 3523. (c) Krackl, S.; Someya, C. I.; Enthaler, S. *Chem. - Eur. J.* **2012**, *18*, 15267.

(14) It was generally believed that the cesium salt of *N*-tosylhydrazones would undergo the irreversible Bamford−Stevens process and decompose into diazo compounds. Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.* **1952**, 4735.

(15) Zhu, C.-L.; Ma, J.-A.; Cahard, D. *Asian J. Org. Chem.* **2016**, *5*, 66.