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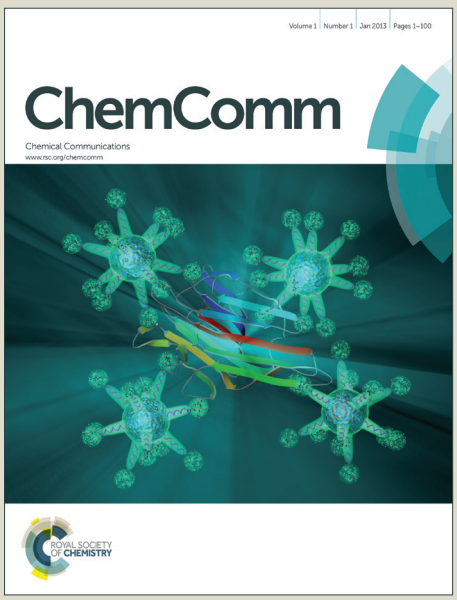

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ARTICLE TYPE

Synthesis of Benzo-γ-sultams *via* the Rh-Catalyzed Aromatic C-H Functionalization of Diazosulfonamides

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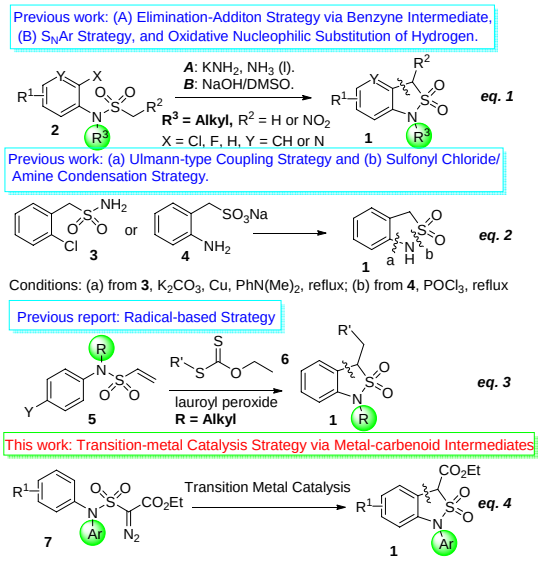
An efficient synthesis of 1-aryl-benzo-γ-sultams, 1-aryl-1,3-dihydrobenzo[*c*]isothiazole-2,2-dioxides, was achieved in 65-99% yields via the Rh-catalyzed intramolecular aromatic C-H functionalization of *N*,*N*-diaryl diazosulfonamides with 0.5 mol% $Rh_2(oct)_4$ as catalyst.

Recently, sultams have attracted increasing attention in synthetic and medicinal chemistry [1] because of their wide spectrum of bioactivities, such as antiviral, antimicrobial, antileukemic, anticancer, enzyme inhibition, etc. [2] In the continuation of our work on the preparation of sulfonic acid derivatives, [3] now we focus our attention on the benzo-γ-sultams, namely 1,3-dihydrobenzo[*c*]isothiazole-2,2-dioxides (**1**). In the pharmaceutical field, benzosultams **1** were designed as a key structural motif in ORL1-receptor antagonists used for the treatment of pain and various CNS disorders. [4] In the synthetic field, benzosultams **1** undergo thermal extrusion of SO_2 to form reactive 1-azadiene-type intermediates aza-*ortho*-xylylenes,[5] which are building blocks for the construction of heterocyclic systems, such as 1,2,3,4-tetrahydroquinolines, [6] benzimidazoles, [7] perimidines,[7] benzoxazoles,[7] 5,6-dihydro-4*H*-thiopyrans, [8] and 3,4-dihydrothiophenes,[8] 2-vinylanilines or imines,[6b, 9] 2-aminobenzyl derivatives,[10] *ortho*-aminobenzophenones,[11] etc. Moreover the modification of benzosultam backbone was reported as well.[12]

In contrast with the importance, only limited synthetic approaches toward the benzo-γ-sultams **1** have been reported since 1963 (eq. 1, Scheme 1).[11, 13] The first approach, introduced by Bunnett,[13a] involves the generation of benzyne intermediates from *N*-2'-chloroaryl alkanesulfonamides (**2**, X = Cl) under extremely strong basic conditions (Conditions A, eq. 1), affording desired 1-alkyl products in low to moderate yields along with byproducts. The harsh conditions significantly limit its application. Lately, Wojciechowski developed an intramolecular S_NAr reaction strategy from *N*-fluoronitroaryl (or pyridinyl) alkanesulfonamides (**2**, Y = CH, R^1 = NO_2, X = F) [11] and an intramolecular oxidative substitution of hydrogen from *N*-nitroaryl (or pyridinyl)alkanesulfonamides (**2**, Y = CH, R^1 = 3-NO_2) under strongly basic conditions (Conditions B, eq. 1).[13b] Notably, these approaches are not applicable to substrates with two aryl groups at the nitrogen atom of sultams, because of the facile N-S bond cleavage under the strongly basic or nucleophilic conditions. Other approaches include the intramolecular Ullmann-type coupling of 2-chlorobenzylsulfonamide (**3**) by heating with K_2CO_3 and copper-bronze powder in *N*,*N*-dimethylaniline (Conditions a, eq. 2) and intramolecular cyclization of sodium 2-aminobenzylsulfonate (**4**) in refluxing $POCl_3$ (Conditions b, eq. 2).[13c] However, these approaches also suffer from the use of toxic reagents and harsh conditions. Recently, Zard reported a radical-based route from *N*-aryl ethenesulfonamides (**5**) and xanthates (**6**) with stoichiometric radical initiator lauroyl peroxide, low to moderate yields, and unavoidable side-reactions in most cases[14] (eq. 3, Scheme 1). However, all reported methods are limited to *N*-unsubstituted or *N*-alkyl benzo-γ-sultams. Therefore, synthesis of *N*-aryl-benzo-γ-sultams (**1**) under mild conditions with good functionality-tolerance still remains a big challenge.



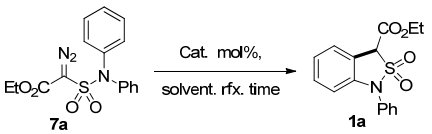
Scheme 1 Approaches toward Benzo-γ-sultams.

The metal-catalyzed direct C-H functionalization with diazo compounds as starting materials has been proved as a powerful tool for constructing a C-C bond in synthetic chemistry.[15] Of great importance is the intramolecular version of the reactions, which always give cyclic products that may possess bioactivities. However, very limited attention has been paid to the intramolecular C-H functionalization with

diazosulfonyl compounds[16] — a useful transformation to form a thia-ring. [17] We found that the aromatic C-H functionalization within *N*-aryl diazosulfonamides **7** lead to benzosultams **1** in a clean and efficient fashion. To the best of our knowledge, this is the first example that employs diazosulfonamides, a class of new-born babies of the diazo family, to efficiently construct designed target molecules.

The optimization of the reaction of **7a** to **1a** was conducted and summarized in Table 1. $Rh_2(oct)_4$ worked better than $Rh_2(OAc)_4$ at the same catalyst loading (1 mol%) and gave an excellent 99% yield (Entries 1 and 2). The copper catalysts, such as $Cu(acac)_2$, $Cu(OAc)_2{\cdot}H_2O$, $Cu(OTf)_2$, and CuOTf, were also able to catalyze the reaction, but either long time was necessitated (Entry 3) or lower yields were obtained (Entries 4–6). The selected cobalt and silver catalysts showed no activity (Entries 7 and 8). The solvent screening revealed that DCE (1,2-dichloroethane) was the most appropriate. In 0.5 mol% catalyst loading, $Rh_2(oct)_4$ still exhibited high activity. However, further lowering of the catalyst loading to 0.25 mol% led to a long reaction time without any yield loss.

Table 1. Optimization of Conditions.[a]

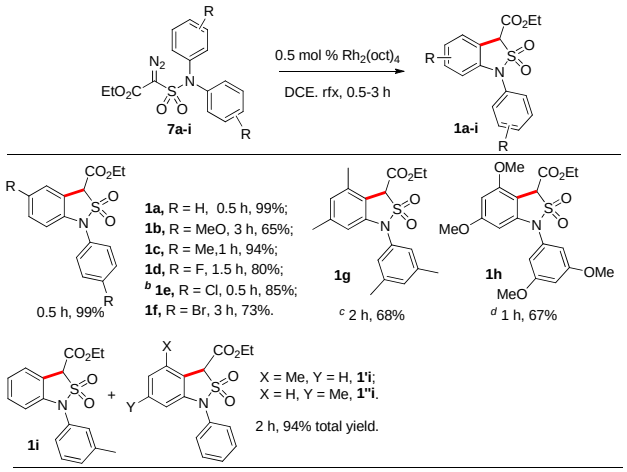


Entry	Cat.	Cat. mol %	Solvent[b]	Time (h)	Yield[c] (%)
1	$Rh_2(OAc)_4$	1	DCE	11	28[d]
2	$Rh_2(oct)_4$	1	DCE	0.5	99
3	$Cu(acac)_2$	1	DCE	13	91
4	$Cu(OAc)_2{\cdot}H_2O$	1	DCE	3	71
5	$Cu(OTf)_2$	1	DCE	1	79
6	$(CuOTf)_2C_6H_6$	1	DCE	2	50
7	Co(TDMPP)	1	DCE	24	<1[e]
8	PhCOOAg	1	DCE	40	0[f]
9	$Rh_2(oct)_4$	1	THF	46	90
10	$Rh_2(oct)_4$	1	DCM	20	99
11	**$Rh_2(oct)_4$**	**0.5**	**DCE**	**0.5**	**99**
12	$Rh_2(oct)_4$	0.25	DCE	6	99

[a]All the reactions were conducted in 0.25 mmol scale in 5 mL of solvent. [b]All the solvents were dried prior to use. [c]Isolated yield by chromotography on silica gel. [d]Recovery of **5a** was 50%. [e] Recovery of **5a** was 79%. [f] Recovery of **5a** was 44%.

With the optimized conditions, we tried to synthesize a series of *N*-aryl substituted benzosultam derivatives **1** (Table 2). This work commenced with the reaction of symmetric *N*,*N*-diaryl diazosulfonamides **7**. The presence of donating-groups such as methoxy and methyl groups on the diazosulfonamides **7b** and **7c** does not affect the reactivities, giving rise to the desired products **1b** and **1c** in 65% and 94% yields, respectively. The lower yield of **1b** is presumably caused by the ylide formation from the rhodium carbenoid and methoxy group.[17a] The functionality-tolerance was also tested. Well-tolerated are the installments of halo-atoms, regardless of fluoro-, chloro-, or bromo-atoms, on the aryl rings, with the formation of the desired benzosultams **1d**, **1e**, and **1f** in satisfactory 80%, 85%, and 73% yields, respectively. The presence of the halogens makes it possible to further modify the aryl rings to access more complex structures. The impact of substituted positions on the aryl rings was also assessed. With 3,5-dimethyl and 3,5-dimethoxy attached, the diazosulfonamides **7g** and **7h**, especially for **7h**, exhibit highly congested feature between the two aryl rings and the sulfonyl group (See ^{1}H NMR in ESI); however, the formation of benzosultams **1g** and **1h** proceeds smoothly in 68% and 67% yields, respectively. The regioselectivities of the C-H functionalization were initially investigated with *N*-phenyl-*N*-(*o*-tolyl) diazosulfonamide **7i** as a model, and three inseparable products **1i**, **1'i** and **1''i** were obtained in 94% total yield with the ratio not determined. This observation promotes us to do further studies on the aromatic C-H functionalization selectivity.

Table 2. Rh-catalyzed Synthesis of Benzo-γ-sultams.[a,]

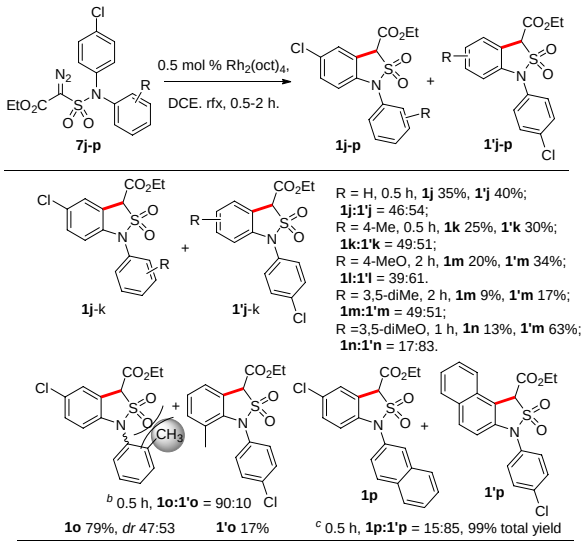


[a]Reactions were conducted on 0.25 mmol scale in 5 mL of solvent. The yields were obtained by chromotography on silica gel. [b]Reaction performed on 0.07 mmol scale. [c]Reaction performed on 0.12 mmol scale.

To get more knowledge of the regioselectivity of the aromatic C-H insertion, we synthesized a set of *N*-aryl-*N*-(*p*-chlorophenyl)diazosulfonamides **7j-n** and subjected them to the standard conditions. In most cases the two regiomers can be isolated by column chromotography. The isolated yields and the ratios are summarized in Table 3. It is observed that the aromatic C-H functionalization favors to occur at the more electron-rich aromatic rings. Since there is no distinct difference of electronic density between phenyl and *p*-tolyl rings, the ratios of **1j**:**1'j** and **1k**:**1'k** are 46:54 and 49:51, respectively, with very slight preference for the electron-rich C-H functionalization products **1'j** and **1'k**. Increasing the electron-density of the other aryl ring can obviously enhance the content of the electron-rich C-H functionalization products, giving the ratios of **1l**:**1'l** and **1m**:**1'm** as 39:61 and 36:64, respectively. In the presence of two strongly electron-donating methoxy groups in diazosulfonamide **7n**, the electron-rich C-H functionalization product **1'n** is generated preferentially with the ratio of **1n**:**1'n** as 17:83. The impact of the *ortho*-substituent was also investigated. In the reaction of diazosulfonamide **7o**, which incorporates both *p*-chloro- and *o*-methyl phenyl rings, the C-H functionalization prefers to occur at the electron-deficient ring, rather than the electron-rich phenyl ring. This unexpected result is presumably caused by the steric effect of the *o*-methyl group. Surprisingly, the ^{1}H

and ^{13}C NMR spectra of product **1o** reveals that it consists of two diastereomers with the ratio as 47:53 (see ESI). We assumed that because of the steric hindrance between the *o*-methyl group and sulfonyl group, the *o*-methylphenyl ring can not freely rotate around the C-N bond. In terms of diazosulfonamide **7p**, it follows the general rule that the C-H functionalization predominantly takes place at the more electron-rich α-position of the β-naphthyl ring, giving inseparable products **1p** and **1p'** with the ratio of 15:85.

Table 3. Regio-selectivity in the Rh-catalyzed Formation of Benzo-γ-sultams.[a]



[a]Reactions were conducted on 0.25 mmol scale in 5 mL of solvent. The yields were obtained by chromotography on silica gel. The ratios were determined by the ^1H NMR of the crude mixtures. [b]Reactions performed on 0.08 mmol scale. [c]Reaction performed on 0.14 mmol scale.

In conclusion, we have successfully realized the synthesis of *N*-aryl substituted benzo-γ-sultams via the Rh-catalyzed intramolecular aromatic C-H functionalization of *N*,*N*-diaryl diazosulfonamides. This method benefits from the advantages of mild and clean conditions, high efficiency, and low catalyst loading. Notably, this report provides the first example of diazosulfonamides, a class of new-born babies in the diazo family, and as well makes them as suitable materials for the preparation of *N*-aryl substituted benzo-γ-sultams that are not accessible by previous methods. Further studies on the properties of diazosulfonamides are in progress.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Experimental procedures for the preparation of intermediates **7** and products **1**, analytical data and copies of ^1H and ^{13}C NMR spectra of intermediates **7** and products **1**]. See DOI: 10.1039/b000000x/

[1] For selected reviews, see: (a) A. Scozzafava, T. Owa, A. Mastrolorenzo and C. T. Supran, *Curr. Med. Chem.* 2003, **10**, 925. (b) M. D. McReynolds, J. M. Dougherty and P. R. Hanson, *Chem. Rev.* 2004, **104**, 2239. (c) K. C. Majumdar and S. Mondal, *Chem. Rev.* 2011, **111**, 7749.

[2] For selected examples, see: (a) M. Inagaki, T. Tsuri, H. Jyoyama, T. Ono, K. Yamada, M. Kobayashi, Y. Hori, A. Arimura, K. Yasui, K. Ohno, S. Kakudo, K. Koizumi, R. Suzuki, M. Kato, S. Kawai and S. Matsumoto, *J. Med. Chem.* 2000, **43**, 2040. (b) N. Lebegue, S. Gallet, N. Flouquet, P. Carato, B. Pfeiffer, P. Renard, S. Leonce, A. Pierre, P. Chavatte and P. Berthelot, *J. Med. Chem.* 2005, **48**, 7363. (c) G. J. Wells, M. Tao, K. A. Josef and R. Bihovsky, *J. Med. Chem.* 2001, **44**, 3488. (d) C. T. Supuran, *Nature Rev. Drug Discovery* 2008, **7**, 168.

[3](a) F. D. He, F. H. Meng, X. Q. Song, W. X. Hu and J. X. Xu, *Org. Lett.* 2009, **11**, 3922. (b) L. B. Hu, H. Zhu, D.-M. Du and J. X. Xu, *J. Org. Chem.* 2007, **72**, 4543. (c) Z. H. Yang and J. X. Xu, *Synthesis* 2013, **45**, 1675. (d) Z. H. Yang, Y. P. Zheng and J. X. Xu, *Synlett.* 2013, **24**, 2165. (e) S. Kakaei, N. Chen and J. X. Xu, *Tetrahedron* 2013, **69**, 302. (f) Z. Y. Huang and J. X. Xu, *Tetrahedron* 2013, **69**, 1050. (g) S. Kakaei and J. X. Xu, *Tetrahedron* 2013, **69**, 9068. (h) Z. Y. Huang and J. X. Xu, *Tetrahedron* 2013, **69**, 10272. (i) Z. H. Yang, B. N. Zhou and J. X. Xu, *Synthesis*, 2014, **46**, 225.

[4] H. Yoshinobu, H. Masako, M. Sachiko, N. Hiroshi, K. Hiroki and M. Yukari, *PCT Int. Appl.* **2005**, WO 2005092895.

[5] For a review on aza-*ortho*-xylylene, see: K. Wojciechowski, *Eur. J. Org. Chem.* 2001, **8**, 3587.

[6] (a) K. Wojciechowski, *Synlett* 1991, 571. (b) K. Wojciechowski, *Tetrahedron* 1993, **49**, 7277. (c) K. Wojciechowski and S. Kosinski, *Eur. J. Org. Chem.* 2002, **9**, 947.

[7] K. Wojciechowski, U. Siedlecka, H. Modrzejewska and S. Kosinski, *Tetrahedron* 2002, **58,** 7583.

[8] H. Modrzejewska and K. Wojciechowski, *Tetrahedron* 2005, **61**, 8848.

[9] (a) K. Wojciechowski, *Tetrahedron* 1993, **49,** 10017. (b) S. Kosinski and K. Wojciechowski, *Eur. J. Org. Chem.* 2000, **7**, 1263.

[10] (a) M. Letulle, P. Guenot and J.-L. Ripoll, *Tetrahedron Lett.* 1991, **32**, 2013. (b) W. Danikiewicz, K. Wojciechowski and M. Olejnik, *Tetrahedron Lett.* 1995, **36**, 1099.

[11] K. Wojciechowski, *Synth. Comm.* 1997, **27**, 135.

[12] (a) J. A. Skorcz and J. T. Suh, US 3572843, 1969. (b) J. A. Skorcz and J. T. Suh, *J. Heterocyclic Chem.* 1972, **9**, 219. (c) J. A. Skorcz, J. T. Suh and C. I. Judd, US 3704299, 1972. (d) J. A. Skorcz, J. T. Suh and C. I. Judd,. US 3725426, 1973. (e) J. A. Skorcz, J. T. Suh and R. L. Germershausen, *J. Heterocyclic Chem.* 1973, **10**, 249. (f) K. Wojciechowski and H. Modrzejewska, *Synthesis*, 2003, 1503.

[13] (a) J. F. Bunnett, T. Kato, R. R. Flynn and J. A. Skorcz, *J. Org. Chem.* 1963, **28**, 1. (b) K. Wojciechowski, *Pol. J. Chem.* 1992, **66**, 1121. (c) D. Chiarino and A. M. Contri,; *J. Heterocyclic Chem.* 1986, **23**, 1645. (d) K. Wojciechowski and S. Kosinski, *Tetrahedron* 2001, **57**, 5009.

[14] C. Moutrille and S. Z. Zard, *Tetrahedron Lett*. 2004, **45**, 4631.

[15] For recent reviews, see: (a) H. M. L. Davies and J. R. Manning, *Nature* 2008, **451**, 417. (b) Z. Zhang and J. Wang, *Tetrahedron* 2008, **64**, 6577. (c) M. P. Doyle, R. Duffy, M. Ratnikov and L. Zhou, *Chem. Rev.* 2010, **110**, 704. (d) Z. Shao and H. Zhang, *Chem. Soc. Rev.* 2012, **41**, 560. (e) Q. Xiao, Y. Zhang, J. Wang, *Acc. Chem. Res.* 2013, **46**, 236.

[16] For selected intermolecular examples, see: (a) A. M. van Leusen, B. A. Reith, R. J. Mulder and J. Strating, *Angew. Chem. Int. Ed*, 1971, **10**, 271. (b) A. Padwa, M. W. Wannamaker, and A. D. Dyszlewski, *J. Org. Chem*, 1987, **52**, 4760. (c) R. A. Weatherhead-Kloster and E. J. Corey, *Org. Lett.* 2006, **8,** 171. (d) S. Zhu, J. V. Ruppel, H, Lu, L. Wojtas and X. P. Zhang, *J. Am. Chem. Soc.* 2008, **130**, 5042. And references cited therein.

[17] Examples for heterocyclic rings with a sulfonyl group embedded, see: (a) M. Hrystak, N. Etkin and T. Durst, *Tetrahetron. Lett.* 1986, **27**, 5679. (b) S. D. Babu, M. D. Hrytsak and T. Durst, *Can. J. Chem.* 1989, **67,** 1071. (c) J. P. John and A. V. Novikov, *Org. Lett.* 2007, **9**, 61. (d) S. A. Wolckenhauer, A. S. Devlin and J. Du Bois, *Org. Lett.* 2007, **9**, 4363. (e) C. S. Jungong, J. P. John and A. V. Novikov, *Tetrahedron Lett.* 2009, **50,** 1954. (f) C. J. Flynn, C. J. Elcoate, S. E. Lawrence and A. R. Maguire, *J. Am. Chem. Soc.* 2010, **132**, 1184.