C–H Amination

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Enantioselective Intramolecular Benzylic C–H Bond Amination: Efficient Synthesis of Optically Active Benzosultams**

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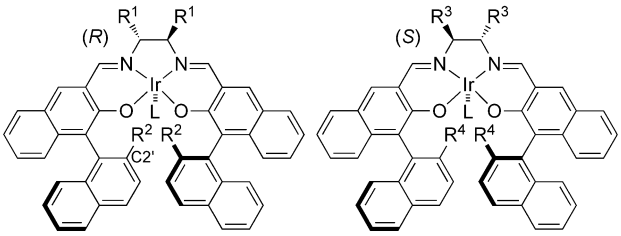
Cyclic amine structures can be found in many biologically active compounds and their stereochemistry often has a significant effect on their biological activities. Enantioselective C–N bond formation is a useful tool for synthesizing those compounds. Although various C–N bond-forming reactions are now known, C–H bond amination is highly atom efficient and it is of wide applicability because most organic compounds have C–H bonds. Thus, regio- and stereoselective C–H bond amination has attracted a growing amount of attention.[1] In addition, remarkable progress has recently been made in metal-catalyzed C–H bond amination, particularly through metal nitrenoid insertion reactions.[2] Most of these C–H bond aminations, however, require *N*-arenesulfonyliminophenyliodinane or related compounds to serve as the nitrene precursor and, furthermore, the atom efficiency of these particular reactions remains at an unsatisfactory level. Therefore, the establishment of a method for enantioselective C–H bond amination using an atom-efficient nitrene precursor such as an azide compound has become an increasingly common topic for research.[3] Seminal studies by Cenini and co-workers showed the potential of transition-metal catalysis for C–H bond amination using azide compounds.[4] Moreover, subsequent studies by Zhang and co-workers[5] and Driver and co-workers[6] demonstrated that intramolecular C–H bond amination catalyzed by a cobalt or an iridium complex is an efficient, though non-enantioselective, method of preparing heterocyclic compounds. Enantiopure sultams[7] have been used as chiral auxiliaries[8] and as key intermediates for the synthesis of HIV-1 reverse transcriptase[9] and COX-2 inhibitors.[10] An asymmetric version of the intramolecular C–H bond amination with arenesulfonyl azide[5a] could be an effective tool for the enantioselective synthesis of sultams, but the asymmetric version has not yet been reported.

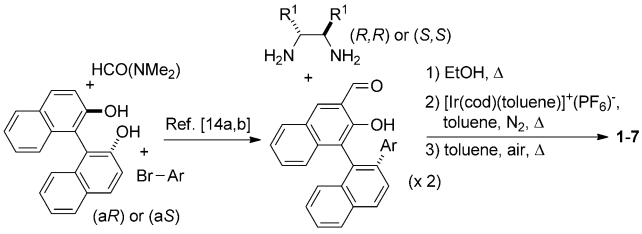
We recently reported that a ruthenium(CO)–salen complex catalyzed the enantioselective intermolecular allylic C–H bond amination using *p*-toluenesulfonyl azide with moderate to good enantioselectivity at room temperature (up to 80% *ee*), albeit with low to moderate yields.[11] In contrast, we have recently demonstrated that iridium(III)–salen complexes are efficient catalysts for diastereo- and enantioselective carbenoid addition such as cyclopropanation, cyclopropenation,[12] and carbenoid C–H or Si–H bond insertion[13] using diazo compounds as the carbenoid precursors. Since diazo and azide compounds, and metal-carbenoid and nitrenoid intermediates are isoelectronic with one another, respectively, we expected that the iridium–salen complexes would serve as catalysts for asymmetric nitrenoid C–H bond insertion. Herein, we describe the enantioselective intramolecular C–H bond amination of sulfonyl azide compounds using an iridium–salen complex as the catalyst.

Complexes **1**–**7**[14c] (Figure 1) were readily prepared from binol, an aryl halide, *N*,*N*-dimethylformamide, a diamine, and an iridium source in a modular manner (Scheme 1).[12a,14,15]



1: (*aS*,*R*), R^1 = -(C_4H_8)-, R^2 = H
2: (*aR*,*R*), R^1 = -(C_4H_8)-, R^2 = C_6H_5
3: (*aR*,*R*), R^1 = C_6H_5, R^2 = C_6H_5
4: (*aR*,*R*), R^1 = -(C_4H_8)-, R^2 = 4-TBDPSC$_6H_4$
5: (*aR*,*R*), R^1 = C_6H_5, R^2 = 4-TBDPSC$_6H_4$
6: (*aR*,*S*), R^3 = -(C_4H_8)-, R^4 = C_6H_5
7: (*aR*,*S*), R^3 = C_6H_5, R^4 = C_6H_5

Figure 1. Structures of iridium–salen complexes **1**–**7**. TBDPS = *tert*-butyldiphenylsilyl.



Scheme 1. A modular synthesis of iridium–salen complexes. cod = 1,5-cyclooctadiene.

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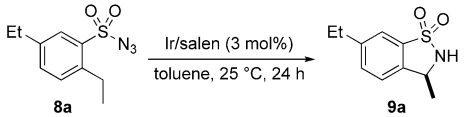
We first examined the intramolecular C–H bond amination of 2,5-diethylbenzenesulfonyl azide (**8a**) with the complexes **1**–**7** as the catalysts at room temperature in toluene (Table 1).[16] All the aminations occurred only at the benzylic

Table 1: Survey of iridium–salen catalysts for intramolecular C–H bond amination with 2,5-diethylbenzenesulfonyl azide (**8a**).[a]



8a **9a**

not observed

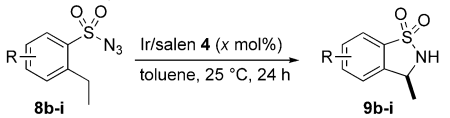
Entry	Cat.	Yield [%][b]	*ee* [%][c]
1	**1**	78	42
2	**2**	88	84
3	**3**	86	75
4[d]	**4**	85	91
5	**5**	90	88
6	**6**	72	50
7	**7**	71	48

[a] Reaction was run on a 0.1 mmol scale in toluene (0.25 mL) under N_2, unless otherwise mentioned. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] Run on a 0.3 mmol scale in toluene (0.75 mL).

position with modest to good enantioselectivity to give the five-membered sultam **9a**, and no amination was observed at the CH_3 of the ethyl group.[17] This regioselectivity is identical with that of the cobalt-catalyzed cyclization.[5a] The enantioselectivity increased, as the substituent (R^2) at C2′ of the binaphthyl moieties of the ligand became bulkier. Complex **4**, which possesses a concave shape that results from the structural nature of the 4-TBDPSC$_6$H$_4$ group at C2′,[14b] showed the best enantioselectivity at 91% *ee* (entry 4). Although the structure of the ethylenediamine moiety did not significantly affect the enantioselectivity, the cyclohexanediamine unit is a better structural element than the diphenylethylenediamine unit (e.g., entries 4 and 5). The diastereometric complexes **6** and **7** were less efficient (entries 6 and 7).

Subsequently, we examined 2-ethylbenzenesulfonyl azide and its C4-, C5-, or C6-substitued derivatives with **4** in toluene (Table 2). The cyclization of an *ortho*-disubstituted substrate proceeded with high enantioselectivity (entry 2). The substrates bearing an electron-donating or a halo group were also aminated at the benzylic position with high enantioselectivity ranging from 85 to 93% *ee* (entries 3–6). Notably, the reaction proceeded even in the presence of a basic amino group with high enantioselectivity (entry 4). The substrate bearing an ester group also underwent the amination with 84% *ee* (entry 7). However, the presence of a more electron-withdrawing nitro group diminished the enantioselectivity to 79% *ee* (entry 8). We wondered if the best solvent for the reactions of the substrates bearing an electron-withdrawing groups held

Table 2: Functional-group tolerance of the C–H Bond amination using complex **4** as the catalyst.[a]



8b-i **9b-i**

not observed

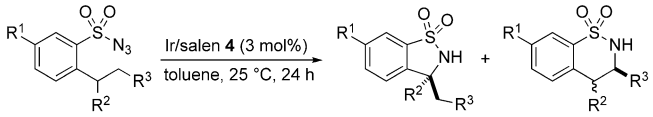
Entry		x (mol%)	R	Yield [%][b]	*ee* [%][c]
1	**8b**	3	–	77	92
2	**8c**	3	4,6-(Et)$_2$	96	88
3	**8d**	5	5-MeO	71 (69)	93 (93)
4	**8e**	5	5-Me$_2$N	88 (83)	86 (84)
5	**8f**	5	5-Br	63 (89)	85 (88)
6	**8g**	5	4-Br	63 (93)[d]	92 (92)[d]
7	**8h**	5	5-MeO$_2$C	75 (85)	84 (87)
8	**8i**	5	5-NO$_2$	49 (99)	79 (88)

[a] Reaction was run on a 0.3 mmol scale in toluene (0.75 mL) under N_2. [b] Yield of isolated product. The values in the parentheses are for reactions run in AcOEt (0.75 mL). [c] Determined by HPLC analysis. The values in parenteses are for reactions run in AcOEt (0.75 mL). [d] Run on a 0.1 mmol scale.

true for substrates having electron-donating groups. Thus, we optimized the reaction of **8i** with regard to solvent and found that the reaction proceeded in ethyl acetate with a higher yield and enantioselectivity (99% yield, 89% *ee*; entry 8).[18] The reactions of **8f**, **8g**, and **8h** also gave better or equal results (88, 92, and 87% *ee*, respectively) in ethyl acetate, whereas the reactions of **8d** and **8e**, which have an electron-donating group, gave slightly inferior or equal results (entries 3 and 4).

We additionally examined the cyclization of several 2-alkyl-substituted derivatives other than 2-ethyl-substituted ones (Table 3). To our surprise, the reaction of 2,5-dicyclohexylbenezenesulfonyl azide (**8j**) primarily occurred not at the expected benzylic (α) position but at the homobenzylic (β) position to give the six-membered sultam **10j** with high enantioselectivity (entry 1).[19,20] To estimate the effect of the steric crowding around the C–H bond on the regioselectivity, we examined the reaction of 2,5-di-*n*-propylbenzenesulfonyl azide (**8k**). The reaction with **4** occurred less selectively at the β position (α/β = 1:2),[5a] albeit with high enantioselectivity of 97% *ee* (β cyclization). However, the reaction with **2** was found to proceed with high β selectivity (α/β = 1: > 20) and enantioselectivity (entry 2). The reaction of **8l** bearing a 2-phenylethyl group with **4** also showed modest β selectivity (α/β = 1:2), despite the fact that the β-carbon atom is a benzylic carbon atom, and high enentioselectivity (entry 3). These results suggested that some factor other than steric crowding and bond energy affects the regioselectivity. We further examined the cyclization of **8m** bearing a pent-3-yl group, an acyclic *sec*-alkyl group. The reaction with **4** showed modest α selectivity, and the minor β cyclization was moderately *trans*-selective with the enantiomeric excess of the *trans* product being 97% *ee* (entry 4). In contrast, the reaction with

Table 3: Regio- and stereoselective intramolecular C–H Bond amination.[a]



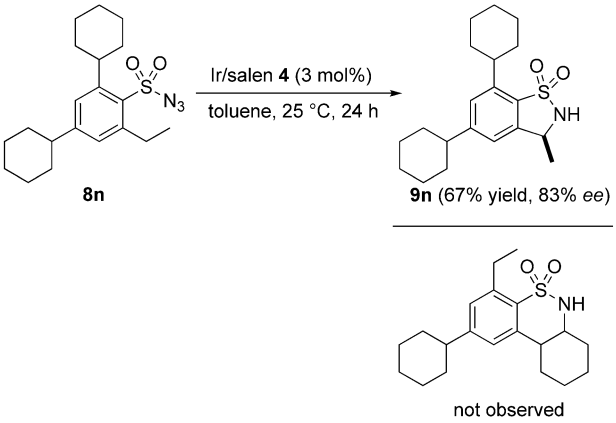
8j-m **9j-m** (α product) **10j-m** (β product)

Entry	Substrate	Yield [%][b]	α/β[c]	*ee* [%][d]
1	**8j** (R^1 = cyclohexyl)	89	1:9	– (α) 82 (β)
2[e]	**8k** (R^1 = *n*-propyl)	93	1: > 20	10 (α) 99 (β)
3[f]	**8l**	40[g]	1:2	5 (α) 98 (β)
4	**8m** (R^1 = 3-pentyl)	86[g]	2:1 (*cis*/*trans* = 1:3)	– (α) 53 (β, *cis*) 97 (β, *trans*)
5[e]	**8m**	90[g]	1:1 (*cis*/*trans* = > 20:1)	– (α) 98 (β, *cis*) – (β, *trans*)

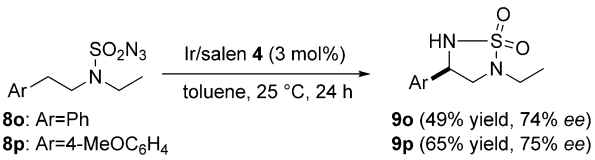
[a] Reaction was run on a 0.3 mmol scale in toluene (0.75 mL) with 3 mol% of **4** under N_2. [b] Yield of isolated products (mixture of five- and six-membered sultams). [c] The ratio was measured from ^{1}H NMR spectra. [d] Determined by HPLC analysis. The *ee* value for each of the resulting products is given. [e] 3 mol% of **2** was used. [f] 5 mol% of **4** was used. [g] Yield determined by NMR spectroscopy using phenanthrene as an internal standard.

2 showed no α/β selectivity, but the β cyclization was highly *cis*-selective and enantioselective (entry 5). From these results, it was inferred that the control of regio-, diastereo-, and enantioselection largely depends on whether the substrate can adopt a conformation that permits an appropriate orbital interaction between the C–H and iridium–nitrenoid bonds for the selection. It is likely that the appropriate conformation for each selection is not the same and that it varies with the structure of the substrate and catalyst used. This probably explains why higher enantioselectivities were obtained in the cyclization of substrates bearing a more flexible acyclic substituent, though it is difficult to concurrently attain high regio-, diastereo-, enantioselectivity in the cyclization of this class of substrates.

Thus, we were intrigued by the reaction of sulfonyl azide **8n**, which has ethyl and cyclohexyl groups at the C2- and C6-positions, respectively. The reaction occurred only at the benzylic position of the ethyl group to give the five-membered sultam (Scheme 2). Notably, the scope of this C–H bond amination is not limited to *ortho*-alkyl arylsulfonyl azides. The reaction of sulfamoyl azides **8o** and **8p** proceeded with good enantioselectivity to give cyclic sulfamides **9o** and **9p**, respectively (Scheme 3). Desymmetrization of prochiral **8q** with **2** as the catalyst occurred in a highly enantioselective manner to give the tricyclic sultam in one step (Scheme 4).

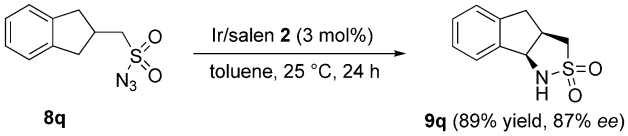


Scheme 2. C–H bond amination of sulfonyl azide **8n**.



Scheme 3. Intramolecular C–H bond amination of *N*-ethyl-*N*-(2-phenyl)ethylsulfamoyl azides **8o** and **8p**.

In conclusion, we have shown that iridium(III)–salen complexes serve as efficient catalysts for enantioselective intramolecular C–H bond amination. To the best of our knowledge, highly enantioselective intramolecular C–H bond amination with azide compounds as nitrenoid precursors was achieved for the first time. The cyclization of 2-ethylbenzenesulfonyl azides that react only at the benzylic position produces five-membered sultams with high enantioselectivity. It is noteworthy that the cyclization of the substrates that have a substituent, especially an acyclic one having a homobenzylic methylene carbon atom can proceed to give six-membered sultams with excellent enantioselectivity by choosing an appropriate catalyst; the regio- and diastereoselectivity depend on the substrate used. The present study demonstrates that iridium-catalyzed nitrenoid insertion is a promising approach to developing enantioselective C–H bond amination. Additional investigations on the mechanism of the present C–H bond amination are now in progress in this laboratory.



8q **9q** (89% yield, 87% *ee*)

Scheme 4. Desymmetrization of sulfonyl azide **8q**.

Experimental Section

Intramolecular C–H bond amination of **8a** with **4**: The reaction was carried out in a Schlenk tube (5 mL) under N_2. 2,5-Diethylbenzenesulfonyl azide (59.3 mL, 0.3 mmol) was dissolved in dry toluene (0.75 mL) and stirred at 25 °C for 10 min. Subsequently, complex **4** (9.0 μmol, 14.3 mg, 3 mol %) was added, and the reaction mixture was stirred for 24 h. The reaction mixture was concentrated and chromatographed on silica gel (*n*-hexane/diisopropyl ether = 1:1 to 0:1). The fractions containing the product were collected and concentrated on a rotary evaporator. The crude product was further purified by NH silica gel chromatography (*n*-hexane/ethyl acetate = 3:1) to obtain the corresponding sultam (53.9 mg, 85 %). The enantiomeric excess was determined by HPLC analysis (DAICEL CHIRALCEL OD-H; 91 % *ee*).

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[1] a) F. Collet, R. H. Dodd, P. Dauban, *Chem. Commun.* **2009**, 5061 – 5074; b) H. M. L. Davies, *Angew. Chem.* **2006**, *118*, 6574 – 6577; *Angew. Chem. Int. Ed.* **2006**, *45*, 6422 – 6425; c) H. M. L. Davies, M. S. Long, *Angew. Chem.* **2005**, *117*, 3584 – 3586; *Angew. Chem. Int. Ed.* **2005**, *44*, 3518 – 3520.

[2] a) D. N. Zalatan, J. Du Bois, *J. Am. Chem. Soc.* **2008**, *130*, 9220 – 9221; b) J.-L. Liang, S.-X. Yuan, J.-S. Huang, W.-Y. Yu, C.-M. Che, *Angew. Chem.* **2002**, *114*, 3615 – 3618; *Angew. Chem. Int. Ed.* **2002**, *41*, 3465 – 3468; c) J.-L. Liang, S.-X. Yuan, J.-S. Huang, C.-M. Che, *J. Org. Chem.* **2004**, *69*, 3610 – 3619; d) E. Milczek, N. Boudet, S. Blakey, *Angew. Chem.* **2008**, *120*, 6931 – 6934; *Angew. Chem. Int. Ed.* **2008**, *47*, 6825 – 6828; e) Y. Kohmura, T. Katsuki, *Tetrahedron Lett.* **2001**, *42*, 3339 – 3342; f) M. Yamawaki, H. Tsutsui, S. Kitagaki, M. Anada, S. Hashimoto, *Tetrahedron Lett.* **2002**, *43*, 9561 – 9564; g) R. D. Reddy, H. M. L. Davies, *Org. Lett.* **2006**, *8*, 5013 – 5016.

[3] a) T. Katsuki, *Chem. Lett.* **2005**, *34*, 1304 – 1309; b) S. Cenini, E. Gallo, A. Caselli, F. Ragaini, S. Fantauzzi, C. Piangiolino, *Coord. Chem. Rev.* **2006**, *250*, 1234 – 1253; c) T. G. Driver, *Org. Biomol. Chem.* **2010**, *8*, 3831 – 3846.

[4] a) S. Cenini, S. Tollari, A. Penoni, A. Cereda, *J. Mol. Catal. A* **1999**, *137*, 135 – 146; b) S. Cenini, E. Gallo, A. Penoni, F. Ragaini, S. Tollari, *Chem. Commun.* **2000**, 2265 – 2266; c) F. Ragaini, A. Penoni, E. Gallo, S. Tollari, C. L. Gotti, M. Lapadura, E. Mangioni, S. Cenini, *Chem. Eur. J.* **2003**, *9*, 249 – 259.

[5] a) J. V. Ruppel, R. M. Kamble, X. P. Zhang, *Org. Lett.* **2007**, *9*, 4889 – 4892; b) H. Lu, J. Tao, J. E. Jones, L. Wojtas, X. P. Zhang, *Org. Lett.* **2010**, *12*, 1248 – 1251; c) H. Lu, H. Jiang, L. Wojtas, X. P. Zhang, *Angew. Chem. Int. Ed.* **2010**, *49*, 10192 – 10196; d) H. Lu, V. Subbarayan, J. Tao, X. P. Zhang, *Organometallics* **2010**, *29*, 389 – 393.

[6] K. Sun, R. Sachwani, K. J. Richert, T. G. Driver, *Org. Lett.* **2009**, *11*, 3598 – 3601.

[7] For the review on synthesis of chiral sultams, see: A.-S. S. Hamad Elgazwy, *Tetrahedron* **2003**, *59*, 7445 – 7463.

[8] a) W. Oppolzer, M. Wills, C. Starkemann, G. Bernardinelli, *Tetrahedron Lett.* **1990**, *31*, 4117 – 4120; b) W. Oppolzer, M. Wills, M. J. Kelly, M. Signer, J. Blagg, *Tetrahedron Lett.* **1990**, *31*, 5015 – 5018; c) W. Oppolzer, I. Rodriguez, C. Starkemann, E. Walther, *Tetrahedron Lett.* **1990**, *31*, 5019 – 5022; d) W. Oppolzer, A. J. Kingma, S. K. Pillai, *Tetrahedron Lett.* **1991**, *32*, 4893 – 4896.

[9] a) D. C. Baker, B. Jiang, U.S. Patent 6,353,112 B1, **2002**; b) J. Mao, D. C. Baker, U.S. Patent 6,458,962 B1, **2003**.

[10] S. K. Singh, P. G. Reddy, K. S. Rao, B. B. Lohray, P. Misra, S. A. Rajjak, Y. K. Rao, A. Venkateswarlu, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 499 – 504.

[11] K. Omura, M. Murakami, T. Uchida, R. Irie, T. Katsuki, *Chem. Lett.* **2003**, *32*, 354 – 355.

[12] a) H. Suematsu, S. Kanchiku, T. Uchida, T. Katsuki, *J. Am. Chem. Soc.* **2008**, *130*, 10327 – 10337; b) S. Kanchiku, H. Suematsu, K. Matsumoto, T. Uchida, T. Katsuki, *Angew. Chem.* **2007**, *119*, 3963 – 3965; *Angew. Chem. Int. Ed.* **2007**, *46*, 3889 – 3891; c) M. Ichinose, H. Suematsu, T. Katsuki, *Angew. Chem.* **2009**, *121*, 3167 – 3169; *Angew. Chem. Int. Ed.* **2009**, *48*, 3121 – 3123; d) M. Uehara, H. Suematsu, Y. Yasutomi, T. Katsuki, *J. Am. Chem. Soc.* **2011**, *133*, 170 – 171.

[13] a) H. Suematsu, T. Katsuki, *J. Am. Chem. Soc.* **2009**, *131*, 14218 – 14219; b) Y. Yasutomi, H. Suematsu, T. Katsuki, *J. Am. Chem. Soc.* **2010**, *132*, 4510 – 4511.

[14] a) T. Hamada, T. Fukuda, H. Imaishi, T. Katsuki, *Tetrahedron* **1996**, *52*, 515 – 530; b) T. Hamada, R. Irie, J. Mihara, K. Hamachi, T. Katsuki, *Tetrahedron* **1998**, *54*, 10017 – 10028; c) For the synthesis of the salen ligand of complex **1**, see the following paper: H. Sasaki, R. Irie, T. Katsuki, *Synlett* **1993**, 300 – 302.

[15] For the general synthetic procedure, see the Supporting Information.

[16] The solvent effect for this reaction was investigated with **4**. See the Supporting Information for details (Table S-1).

[17] During this investigation, a nitrenoid insertion into a methyl group of a *tert*-butyl substituent was reported. See, Ref. [5b,c].

[18] For the optimization of the reaction of **8i** with regard to the solvent, see the Supporting Information (Table S-2).

[19] Thermolysis of **8j** at 120 °C has been reported to give six-membered sultams, though in a nonstereoselective manner: R. A. Abramovitch, T. Chellathurai, W. D. Holcomb, I. T. MacMaster, D. P. Vanderpool, *J. Org. Chem.* **1977**, *42*, 2920 – 2926.

[20] The relative stereochemistry of **10j** was assigned to be *trans* based on NOESY and COSY measurements (see the Supporting Information for the spectroscopic data).

