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Efficient Synthesis of Imino-methano Tröger Bases by Nitrene Insertions into C–N Bonds

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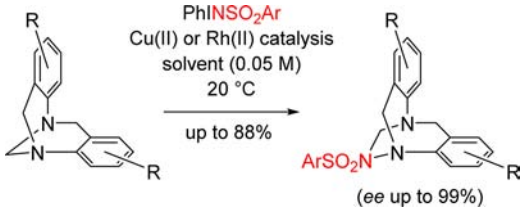
ABSTRACT



A direct nitrene insertion into C–N bonds is observed upon treatment of *methano*-Tröger bases with arylsulfonyl iminophenyliodinanes under copper and dirhodium catalysis. Novel cyclic imino-methano Tröger bases are obtained (55–88%). Enantiopure products (*ee* ≥ 99%) can be obtained with tailored substrates.

The metal catalyzed decomposition of arylsulfonyl iminophenyliodinanes is a powerful method to generate metal nitrenes. These intermediates are frequently used to promote aziridinations and C–H aminations (insertions).[1] When reacted with tertiary sp^3 and sp^2 nitrogen atoms, they afford $N^+–N^-$ ylides (aminimides) as products.[2] Usually, sulfonyl aminimides are inert compounds decomposing only at a very high temperature.[2,3] Herein, in sharp contrast, we report that metal nitrenes derived from arylsulfonyl iminophenyliodinanes react with *methano*-Tröger bases **1**[4] to form highly reactive aminimides that undergo facile C–N insertion reactions (Scheme 1). Novel imino-methano Tröger bases **2** are afforded in good yields (55–88%) under mild reaction conditions (20–40 °C). Both copper and rhodium catalysts mediate the reaction, and enantiopure products (*ee* ≥ 99%) can be obtained with tailored substrates.

Scheme 1. Reactivity with Arylsulfonyl Iminophenyliodinanes

Recently, it was shown that compounds **1**, interesting chiral molecules due to the presence of stereogenic nitrogen

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(1) (a) Dequirez, G.; Pons, V.; Dauban, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 7384–7395. (b) Roizen, J. L.; Harvey, M. E.; Du Bois, J. *Acc. Chem. Res.* **2012**, *45*, 911–922. (c) Collet, F.; Lescot, C.; Dauban, P. *Chem. Soc. Rev.* **2011**, *40*, 1926–1936. (d) Lebel, H. In *Catalyzed Carbon-Heteroatom Bond Formation*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, Germany, 2011; pp 137–155. (e) Driver, T. G. *Org. Biomol. Chem.* **2010**, *8*, 3831–3846. (f) Feast, G. C.; Page, L. W.; Robertson, J. *Chem. Commun.* **2010**, *46*, 2835–2837. (g) Fantauzzi, S.; Caselli, A.; Gallo, E. *Dalton Trans.* **2009**, 5434–5443. (h) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417–424. (i) Diaz-Requejo, M. M.; Perez, P. J. *Chem. Rev.* **2008**, *108*, 3379–3394. (j) Halfen, J. A. *Curr. Org. Chem.* **2005**, *9*, 657–669. (k) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905–2919.

(2) McKillip, W. J.; Sedor, E. A.; Culberts, B. M.; Wawzonek, S. *Chem. Rev.* **1973**, *73*, 255–281.

(3) (a) Li, J.; Cisar, J. S.; Zhou, C.-Y.; Vera, B.; Williams, H.; Rodríguez, A. D.; Cravatt, B. F.; Romo, D. *Nature Chem.* **2013**, *5*, 510–517. (b) Trost, B. M.; O'Boyle, B. M.; Torres, W.; Ameriks, M. K. *Chem.—Eur. J.* **2011**, *17*, 7890–7903. (c) Jain, S. L.; Sharma, V. B.; Sain, B. *Tetrahedron Lett.* **2003**, *44*, 4385–4387.

(4) (a) Tröger, J. *J. Prakt. Chem.* **1887**, *36*, 225–245. (b) Runarsson, O. V.; Artacho, J.; Warnmark, K. *Eur. J. Org. Chem.* **2012**, 7015–7041. (c) Sergeyev, S. *Helv. Chim. Acta* **2009**, *92*, 415–444. (d) Dolensky, B.; Elguero, J.; Kral, V.; Pardo, C.; Valik, M. *Adv. Heterocycl. Chem.* **2007**, *93*, 1–56. (e) Demeunynck, M.; Tatibouet, A. *Prog. Heterocycl. Chem.* **1999**, *11*, 1–20.

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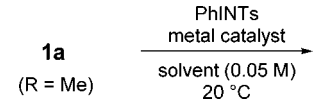
atoms, react with metal carbenes to afford configurationally stable *ethano*-Tröger bases in a single step.[5] Most probably, these products result from the formation of N^+-C^- ylide intermediates that undergo a Stevens-like rearrangement.[6] Considering the analogy between carbenes and nitrenes,[7] focus was directed toward studying the reactivity of Tröger bases **1** with arylsulfonyl iminophenyliodinanes.[8]

Table 1. Optimization of Reaction Conditions[a]

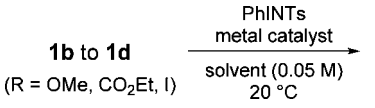


entry	catalyst	mol %	solvent	time	yield (%)[b]
1	$Cu(OTf)_2$	5	CH_3CN	16 h	67
2	CuTC	5	CH_3CN	16 h	48
3	CuI	5	CH_3CN	16 h	24
4	$Cu(OTf)_2$	5	CH_3CN	1 h	81
5	$Cu(OTf)_2$	10	CH_3CN	1 h	88
6	$Cu(OTf)_2$	10	CH_2Cl_2	30 h	36
7	$Rh_2(esp)_2$	2	CH_2Cl_2	4 h	76
8	$Rh_2(OAc)_4$	2	toluene	24 h	(12)[c]
9	$Rh_2(OAc)_4$	2	CH_2Cl_2	24 h	(40)[c]

[a] **1a** (1 equiv), copper salt or Rh(II) complex, PhINTs (2 equiv), solvent (0.05 M), 20 °C. [b] Isolated yields. [c] Conversion (%) by NMR.

Compound **1a** (Scheme 1, R = Me) was treated with PhINTs[9] in the presence of copper salts and rhodium(II) complexes. To our satisfaction, the reaction proceeded at ambient temperature in the presence of 5 mol % of $Cu(OTf)_2$, CuTC, or CuI to afford the insertion product (Table 1, entries 1 to 3). The structure of **2a** was determined by NMR spectroscopy and confirmed by X-ray crystallographic analysis (see Supporting Information).[10] Better yields were obtained with $Cu(OTf)_2$ over CuTC and CuI (67% vs 48% and 24% respectively). With $Cu(OTf)_2$ as the catalyst, improved yields were obtained using a shorter reaction time (1 h vs 16 h), increased catalyst loading (10 mol % vs 5 mol %), and acetonitrile instead of CH_2Cl_2 as the solvent (Table 1, entries 4 to 6).[11] With dirhodium

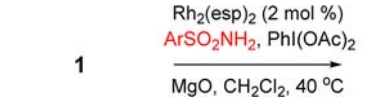
Table 2. Substrate Scope[a]

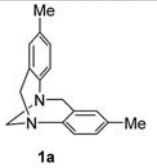
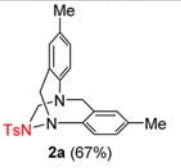
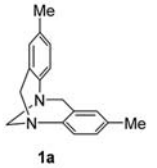
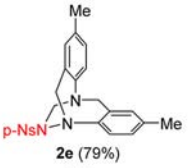
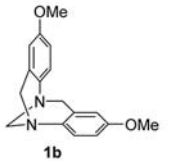
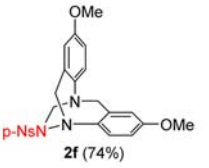
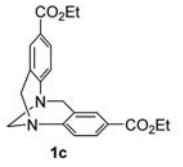
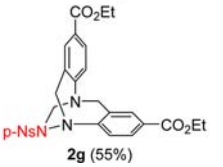


entry	R	substrate	method[b]	time	yield (%)[c]
1	OMe	**1b**	A	6 h	84
2	CO_2Et	**1c**	A	24 h	77
3	I	**1d**	A	24 h	61
4	OMe	**1b**	B	6 h	72
5	CO_2Et	**1c**	B	16 h	69
6	I	**1d**	B	8 h	56

[a] Tröger base (1 equiv), PhINTs (2 equiv), 20 °C. [b] Method A: $Rh_2(esp)_2$ (2 mol %), CH_2Cl_2 (0.05 M). Method B: $Cu(OTf)_2$ (10 mol %), CH_3CN (0.05 M). [c] Isolated yields.

Table 3. *In Situ* Generation of Sulfonyl Iminophenyliodinanes[a]



entry	substrate	time	product (yield)
1	 **1a**	16 h	 **2a** (67%)
2	 **1a**	16 h	 **2e** (79%)
3	 **1b**	16 h	 **2f** (74%)
4	 **1c**	48 h	 **2g** (55%)

[a] Isolated yields.

(5) (a) Sharma, A.; Guénée, L.; Naubron, J.-V.; Lacour, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 3677–3680. (b) Sharma, A.; Besnard, C.; Guénée, L.; Lacour, J. *Org. Biomol. Chem.* **2012**, *10*, 966–969.

(6) (a) Vanecko, J. A.; Wan, H.; West, F. G. *Tetrahedron* **2006**, *62*, 1043–1062. (b) Kumar, R. R.; Vanitha, K. A.; Perumal, S. Stevens rearrangement. *Name Reactions for Homologations, Pt. 2*; John Wiley & Sons, Inc.: 2009; pp 516–530. (c) Sweeney, J. *Chem. Soc. Rev.* **2009**, *38*, 1027–1038. (d) Bach, R.; Harthong, S.; Lacour, J. Nitrogen- and sulfur-based Stevens and related rearrangements. In *Comprehensive Organic Synthesis*, 2nd ed.; Molander, G., Knochel, P., Eds.; Elsevier: London, 2014 in press.

(7) (a) Wentrup, C. *Acc. Chem. Res.* **2011**, *44*, 393–404. (b) Doyle, M. P. Synthetic Carbene and Nitrene Chemistry. In *Reactive Intermediate Chemistry*; Moss, R. A., Platz, M., Jones, M., Eds.; Wiley-Interscience: Hoboken, NJ, 2004; pp 561–592.

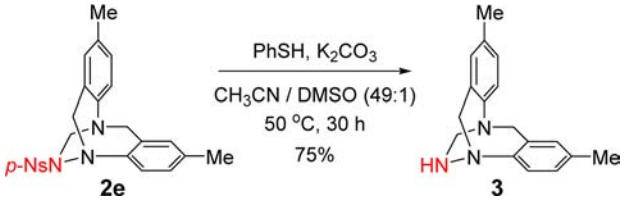
(8) Aminimides other than sulfonyl derivatives can react in Stevens-like rearrangements. These reactions are known as Wawzonek rearrangements: Wawzonek, S.; Yeakey, E. *J. Am. Chem. Soc.* **1960**, *82*, 5718–5721.

(9) (a) Abramovitch, R. A.; Bailey, T. D.; Takaya, T.; Uma, V. *J. Org. Chem.* **1974**, *39*, 340–345. (b) Yamada, Y.; Yamamoto, T.; Okawara, M. *Chem. Lett.* **1975**, 361–362.

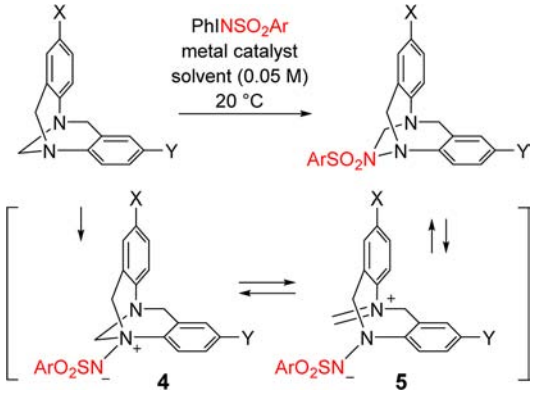
(10) CCDC 942112–942114 contains the supplementary crystallographic data for this paper (**2a**, **7**, and **10a**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(11) Most probably, the increase in reactivity with acetonitrile as solvent over CH_2Cl_2 is due to an improved solubility of the catalytic species.

Scheme 2. Deprotection of the Nosyl Group



Scheme 3. Mechanistic Rationale[a]

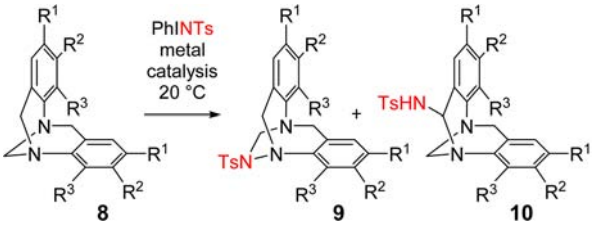


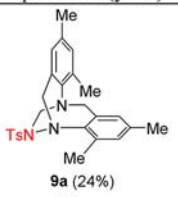
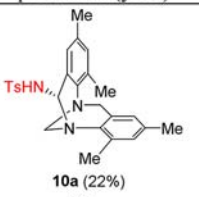
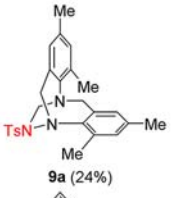
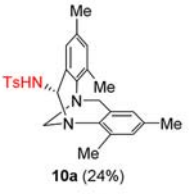
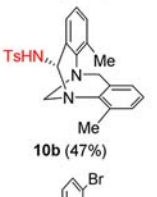
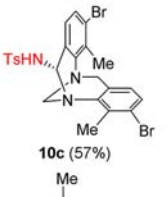
[a] Preferred regioselectivity with X = NO_2 and Y = OMe (substrate **6** and product **7**).

catalysts, as expected the $Rh_2(esp)_2$[12] complex performed quite better (76% yield, Table 1, entry 7) than $Rh_2(OAc)_4$. In the latter case, only partial conversion of starting material **1a** was observed even after a prolonged reaction time (Table 1, entries 8 and 9). It is also worth noting that the above reactions exhibited excellent chemoselectivity since, despite the presence of reactive benzylic positions, products of C−H insertion (amination) reactions are not observed.[13]

With optimized conditions in hand (Table 1, entry 5 or 7), electron-rich and -poor substrates were studied. Tröger bases carrying methoxy, ethyl ester, and iodo substituents were prepared (**1b** to **1d**, R = OMe, CO_2Et and I, Scheme 1, Table 2).[14] The reactions proceeded in all instances. Better yields were obtained under $Rh_2(esp)_2$ catalysis (method A, 61−84% yields) over $Cu(OTf)_2$ (method B, 56−72% yields). Reactions were faster with electron-rich **1b** (R = OMe, Table 2, entries 1 and 4) over electron-poor substrates **1c** and **1d**. With **2d**, a certain sensitivity to the purification

Table 4. Reactivity of Bis-*ortho* Substituted Tröger Bases[a]



entry	product **9** (yield)	product **10** (yield)
1[b]	 **9a** (24%)	 **10a** (22%)
2[c]	 **9a** (24%)	 **10a** (24%)
3[c]	 **9b** (18%)	 **10b** (47%)
4[c]	 **9c** (10%)	 **10c** (57%)
5[c]	 **9d** (5%)	 **10d** (38%)

[a] Tröger base **8** (1 equiv), PhINTs (3 equiv). [b] Method A: $Rh_2(esp)_2$ (2 mol %), CH_2Cl_2. [c] Method B: $Cu(OTf)_2$ (10 mol %), CH_3CN.

conditions was noticed explaining probably the lower yields.[15]

Care was taken to also perform the reaction under conditions permitting the *in situ* formation of the metal nitrene intermediates directly from sulfonamides.[16] To our satisfaction, product **2a** was formed in 67% yield (Table 3, entry 1). In this case and in the following reactions of Table 3, it was necessary to warm the medium to 40 °C and extend the reaction time to 16 or even 48 h. Substrates **1a** and **1b** reacted well with *p*-nitrobenzenesulfonamide to afford products **2e** and **2f** in 79% and 74% yields respectively (Table 3,

(12) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378–15379.

(13) Amination reactions occur only on hindered substrates such as bis-*ortho* substituted Tröger bases. See Table 4.

(14) (a) Jensen, J.; Warnmark, K. *Synthesis* **2001**, 1873–1877. (b) Goswami, S.; Ghosh, K.; Dasgupta, S. *J. Org. Chem.* **2000**, *65*, 1907–1914. (c) Miller, T. R.; Wagner, E. C. *J. Am. Chem. Soc.* **1941**, *63*, 832–836.

(15) In this particular case, flash chromatography must be conducted with neutral alumina instead of silica gel.

(16) (a) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598–600. (b) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935–6936. (c) Dauban, P.; Sanière, L.; Tarrade, A.; Dodd, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 7707–7708.

entries 2 and 3). Only in the case of electron-withdrawing substrate **1c**, product **2g** was afforded in moderate yield (55%, Table 3, entry 4). With **2e**, it was possible to remove the *p*-nosyl group by treatment with thiophenol/K_2CO_3 and afford the unprotected hydrazine **3** (Scheme 2, 75% yield).[17]

The reaction was then performed with enantiopure (+)-**1a**. Unfortunately, product **2a** was isolated in racemic form using optimized conditions for Cu(II) and Rh(II) catalysts and variants performed at lower temperatures. To understand the origin of the racemization, **2a** was separated into single enantiomers using a CSP-HPLC resolution protocol (see the Supporting Information). The compound was found to be configurationally stable in neutral media. However, by subjecting one of the enantiomers to the reaction conditions for 4 h, a decrease of the enantiomeric excess of **2a** from 99% to 50% in the case of $Rh_2(esp)_2$ and a complete racemization in the presence of $Cu(OTf)_2$ were observed. This indicates that the racemization can occur not only during the formation of **2a** but also after the product has been formed.

The racemization and the insertion reactivity as a whole can be rationalized in terms of mechanism (Scheme 3). It involves the catalytic generation of electrophilic metal nitrenes and additions of Tröger bases **1** to these intermediates. Sulfonyl aminimide moieties of type **4** result. Then, by a C−N bond cleavage that is traditional in Tröger base chemistry upon quaternization of one of the nitrogen atoms,[18] zwitterionic ring-opened species of type **5** are formed that collapse subsequently to form the imino-methano Tröger bases **2**. Under this hypothesis, the observed loss of enantiomeric purity results probably from the formation of monocyclic intermediates **5** which have the possibility to racemize through a complete planarization of the core. Intermediates **5** can be formed either directly from **4** or from products **2** through a ring opening induced by the Lewis acid metal catalysts.[19]

This proposal also explains the lower reactivity of electron-poor bridgehead nitrogen atoms (*e.g.*, in **1c** and **1d**) which was further confirmed by an experiment using unsymmetrically substituted Tröger base **6** (Scheme 3: X = NO_2, Y = OMe) carrying both electron-donating and -withdrawing substituents on the two aromatic rings.[20] A single regioisomer was obtained (**7**, 45%). It results clearly from an initial attack on the electron-rich nitrogen atom (*para* to the methoxy group), the structure being ascertained by X-ray crystallographic analysis (Supporting Information).[21]

Finally, to address the lack of configurational stability of rearranged products **2**, the introduction of substituents *ortho* to the nitrogen atoms was pursued (Table 4).[22] Treatment of **8a** (R^1 = Me, R^2 = H, R^3 = Me) with PhINTs and $Rh_2(esp)_2$ afforded desired product **9a** in 24% yield along with novel C−H amination product **10a** (22%) as a single diastereomer (Table 4, entry 1). The reaction required 3 equiv of PhINTs and a longer duration for completion. Similar results were obtained with $Cu(OTf)_2$ (Table 4, entry 2). The structure of **10a** was confirmed by X-ray analysis. Clearly, in this present case, the hindrance around the nitrogen atoms[23] favors an alternative amination on the benzylic position. A similar reactivity was observed with **8b** and **8c** carrying *ortho*-methyl substituents (Table 4, entries 3 and 4).[24] A stronger inclination toward the C−H insertion reaction was noticed in the presence of bromine atoms at *meta* and *ortho* positions (Table 4, entries 4 and 5). Substrate **8a** was then resolved into single enantiomers.[25] Satisfyingly, under $Cu(OTf)_2$ catalysis, the reaction of (−)-**8a** yielded rearranged product (−)-**9a** with a complete transfer of chirality (**8a** ≥ 99% *ee*).[26] In the presence of $Rh_2(esp)_2$, using (+)-**8a** as the substrate, (+)-**9a** was obtained in 92% *ee* along with racemic **10a**.

In conclusion, *methano*-Tröger bases **1** react with arylsulfonyl iminophenyliodinanes (Cu(II) or Rh(II) catalysis, 20 to 40 °C) to form imino-methano Tröger bases **2** in good yields (55−88%). Sulfonyl aminimides are probably formed that insert in adjacent C−N bonds via a two-step mechanism. While classic enantiopure Tröger bases afford racemic products, *bis-ortho* substituted derivatives can react with a full transfer of chirality (*ee* ≥ 99%).

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Supporting Information Available. Synthesis and spectral caracterization imino-methano Tröger bases **2**. CSP-HPLC determination of the enantiomeric purity of **9a**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(21) Interestingly, this reaction contradicts the regioselectivity observed in the reaction of **6** with α-diazo diester reagents under Rh(II)-catalysis at elevated temperatures (ref 5a). It suggests that the first step of these nitrene-mediated reactions is strictly under kinetic rather than thermodynamic control.

(22) It has been established that compounds of type **8** (R^3 = Me or Br), unlike Tröger bases **1**, are highly stable as single enantiomers, even in strongly acidic media: Lenev, D. A.; Lyssenko, K. A.; Golovanov, D. G.; Buss, V.; Kostyanovsky, R. G. *Chem.—Eur. J.* **2006**, *12*, 6412–6418.

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(24) All products **10** are afforded as single diastereomers. The proposed configuration is based on the X-ray diffraction analysis of **10a** (see Supporting Information).

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(26) Insertion product **10a** is again obtained as a single diastereomer but only in 19% *ee*.