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

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Sandip A. Pujari,<sup>†</sup> Laure Guénée,<sup>‡</sup> and Jérôme Lacour<sup>\*,†</sup>

University of Geneva, Department of Organic Chemistry, 30 Quai Ernest Ansermet, CH-1211 Geneva 4, Switzerland, and Laboratory of Crystallography, University of Geneva, quai Ernest Ansermet 24, CH-1211 Genève 4, Switzerland

Jerome.Lacour@unige.ch

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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 ( $ee \ge 99\%$ ) 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).<sup>1</sup> When reacted with tertiary  $sp^3$  and  $sp^2$  nitrogen atoms, they afford N<sup>+</sup>–N<sup>-</sup> ylides (aminimides) as products.<sup>2</sup> Usually, sulfonyl aminimides are inert compounds decomposing only at a very high temperature.<sup>2,3</sup> Herein, in sharp contrast, we report that metal nitrenes derived from

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(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. Scheme 1. Reactivity with Arylsulfonyl Iminophenyliodinanes



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 ( $ee \ge 99\%$ ) can be obtained with tailored substrates.

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

<sup>&</sup>lt;sup>†</sup> Department of Organic Chemistry.

<sup>&</sup>lt;sup>‡</sup>Laboratory of Crystallography.

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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.

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

Table 1. C	Optimization	of Reaction	Conditions <sup>a</sup>
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Rh<sub>2</sub>(OAc)<sub>4</sub>

entry	<b>1a</b> (R = Me)	PhINTs metal catalyst solvent (0.05 M) 20 °C		2a	
	catalyst	mol %	solvent	time	yield $(\%)^b$
1	Cu(OTf)2	5	CH <sub>3</sub> CN	16 h	67
2	CuTC	5	$CH_3CN$	16 h	48
3	CuI	5	CH <sub>3</sub> CN	16 h	24
4	Cu(OTf) <sub>2</sub>	5	CH <sub>3</sub> CN	1 h	81
5	$Cu(OTf)_2$	10	CH <sub>3</sub> CN	1 h	88
6	$Cu(OTf)_2$	10	$CH_2Cl_2$	30 h	36
7	$Rh_2(esp)_2$	2	$\overline{\mathrm{CH}_{2}\mathrm{Cl}_{2}}$	4 h	76
8	$Rh_2(OAc)_4$	2	toluene	$24 \mathrm{h}$	$(12)^{c}$
9	$Rh_{2}(OAc)_{4}$	2	CH <sub>2</sub> Cl <sub>2</sub>	24  h	$(40)^{c}$

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

 $CH_2Cl_2$ 

Compound 1a (Scheme 1, R = Me) was treated with PhINTs<sup>9</sup> 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)<sub>2</sub>, 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).<sup>10</sup> Better yields were obtained with Cu(OTf)<sub>2</sub> over CuTC and CuI

## Table 2. Substrate Scope<sup>a</sup>

	<b>1b</b> to 1 (R = OMe, C	I <b>d</b> met O <sub>2</sub> Et, I)	PhINTs metal catalyst solvent (0.05 M) 20 °C		<b>2b</b> to <b>2d</b>	
entry	R	substrate	$method^b$	time	yield (%) <sup>c</sup>	
1	OMe	1b	А	6 h	84	
<b>2</b>	$\rm CO_2Et$	1c	Α	$24 \mathrm{h}$	77	
3	Ι	1d	Α	$24 \mathrm{h}$	61	
4	OMe	1b	В	6 h	72	
<b>5</b>	$\rm CO_2Et$	1c	В	16 h	69	
6	Ι	1 <b>d</b>	В	8 h	56	

<sup>*a*</sup>Tröger base (1 equiv), PhINTs (2 equiv), 20 °C, <sup>*b*</sup>Method A: Rh<sub>2</sub>(esp)<sub>2</sub> (2 mol %), CH<sub>2</sub>Cl<sub>2</sub> (0.05 M). Method B: Cu(OTf)<sub>2</sub> (10 mol %), CH<sub>3</sub>CN (0.05 M). <sup>c</sup> Isolated yields.

Table 3. In Situ Generation of Sulfonyl Iminophenyliodinanes<sup>a</sup> Rh<sub>2</sub>(esp)<sub>2</sub> (2 mol %)



(67% vs 48% and 24% respectively). With Cu(OTf)<sub>2</sub> 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<sub>2</sub>Cl<sub>2</sub> as the solvent (Table 1, entries 4 to 6).<sup>11</sup> With dirhodium

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<sup>(6) (</sup>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 sulfurbased Stevens and related rearrangements. In Comprehensive Organic Synthesis, 2nd ed.; Molander, G., Knochel, P., Eds.; Elsevier: London, 2014 in press.

<sup>(7) (</sup>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.

<sup>(8)</sup> Aminimides other than sulfonyl derivatives can react in Stevenslike rearrangements. These reactions are known as Wawzonek rearrangements: Wawzonek, S.; Yeakey, E. J. Am. Chem. Soc. 1960, 82, 5718-5721.

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<sup>(10)</sup> 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.

<sup>(11)</sup> Most probably, the increase in reactivity with acetonitrile as solvent over CH<sub>2</sub>Cl<sub>2</sub> is due to an improved solubility of the catalytic species.

Scheme 2. Deprotection of the Nosyl Group



Scheme 3. Mechanistic Rationale<sup>a</sup>



 $^{a}$  Preferred regioselectivity with X = NO<sub>2</sub> 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.<sup>13</sup>

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**,  $\mathbf{R} = OMe$ ,  $CO_2Et$  and I, Scheme 1, Table 2).<sup>14</sup> 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** ( $\mathbf{R} =$ OMe, Table 2, entries 1 and 4) over electron-poor substrates **1c** and **1d**. With **2d**, a certain sensitivity to the purification





<sup>*a*</sup>Tröger base **8** (1 equiv), PhINTs (3 equiv). <sup>*b*</sup> Method A: Rh<sub>2</sub>(esp)<sub>2</sub> (2 mol %), CH<sub>2</sub>Cl<sub>2</sub>. <sup>*c*</sup> Method B: Cu(OTf)<sub>2</sub> (10 mol %), CH<sub>3</sub>CN.

conditions was noticed explaining probably the lower vields.<sup>15</sup>

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

<sup>(14) (</sup>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.

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

<sup>(16) (</sup>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.

Care was taken to also perform the reaction under conditions permitting the *in situ* formation of the metal nitrene intermediates directly from sulfonamides.<sup>16</sup> 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,

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).<sup>17</sup>

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<sub>2</sub>(esp)<sub>2</sub> and a complete racemization in the presence of Cu(OTf)<sub>2</sub> 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,<sup>18</sup> zwitterionic ring-opened species of type 5 are formed that collapse subsequently to form the iminomethano 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

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(22) It has been established that compounds of type **8** ( $\mathbb{R}^3 = Me \text{ or } Br$ ), 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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 2012, 7053–7056. (b) Pereira, R.; Cvengros, J. J. Organomet. Chem.
 2013, 729, 81–85.

(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).

(25) Didier, D.; Tylleman, B.; Lambert, N.; Velde, C.; Blockhuys, F.; Collas, A.; Sergeyev, S. *Tetrahedron* **2008**, *64*, 6252–6262.

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

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.<sup>19</sup>

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.<sup>20</sup> 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).<sup>21</sup>

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).<sup>22</sup> Treatment of 8a ( $R^1 = Me$ ,  $R^2 = H$ ,  $R^3 = Me$ ) with PhINTs and Rh<sub>2</sub>(esp)<sub>2</sub> 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)<sub>2</sub> (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<sup>23</sup> 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).<sup>24</sup> 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.<sup>25</sup> Satisfyingly, under Cu(OTf)<sub>2</sub> catalysis, the reaction of (-)-8a vielded rearranged product (-)-9a with a complete transfer of chirality ( $8a \ge 99\% ee$ ).<sup>26</sup> In the presence of Rh<sub>2</sub>(esp)<sub>2</sub>, 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 ( $ee \ge 99\%$ ).

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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.

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<sup>(18)</sup> Trapp, O.; Trapp, G.; Kong, J. W.; Hahn, U.; Vögtle, F.; Schurig, V. Chem.—Eur. J. 2002, 8, 3629–3634.

<sup>(19)</sup> The Tröger base catalyzed aziridination of chalcones with O-mesitylenesulfonylhydroxylamine as reagent has been reported (Shen, Y.-M.; Zhao, M.-X.; Xu, J.; Shi, Y. Angew. Chem., Int. Ed. **2006**, 45, 8005–8008). Under these conditions, an aminimide intermediate could formally form. However, if it is the case, it does not undergo the subsequent rearrangement observed herein.

<sup>(21)</sup> Interestingly, this reaction contradicts the regioselectivity observed in the reaction of **6** with  $\alpha$ -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.

The authors declare no competing financial interest.