



# Insertion of Isocyanides into N–Si Bonds: Multicomponent Reactions with Azines Leading to Potent Antiparasitic Compounds

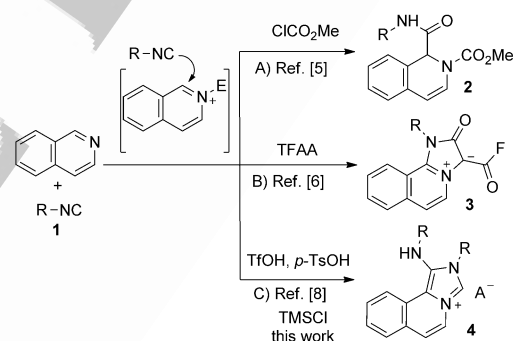
Kranti G. Kishore<sup>+</sup>, Ouldouz Ghashghaei<sup>+</sup>, Carolina Estarellas<sup>+</sup>, M. Mar Mestre, Cristina Monturiol, Nicola Kielland, John M. Kelly, Amanda Fortes Francisco, Shiromani Jayawardhana, Diego Muñoz-Torrero, Belén Pérez, F. Javier Luque, Rocío Gámez-Montaña,\* and Rodolfo Lavilla\*

**Abstract:** Trimethylsilyl chloride is an efficient activating agent for azines in isocyanide-based reactions, which then proceed through a key insertion of the isocyanide into a N–Si bond. ■■■ok?■■■ The reaction is initiated by N activation of the azine, followed by concomitant ■■■“followed by” or “concomitant”?■■■ nucleophilic attack of an isocyanide in a Reissert-type process. Finally, a second equivalent of the same or a different isocyanide inserts into the N–Si bond leading to the final adduct. The use of distinct nucleophiles leads to a variety of  $\alpha$ -substituted dihydroazines after a selective cascade process. Based on computational studies, a mechanistic hypothesis for the course of these reactions was proposed. ■■■ok?■■■ The resulting products exhibit significant activity against *Trypanosoma brucei* and *T. cruzi*, featuring favorable drug-like properties and safety profiles.

Isocyanides hold a central role in several fields of chemistry.<sup>[1]</sup> ■■■ok?■■■ Their formally divalent character makes them ideal partners for multicomponent reactions (MCRs).<sup>[2]</sup> However, their mild nucleophilicity, together with their affinity to metals, complicates their activation for many MCRs, which hence often require harsh reaction conditions. Transition-metal-catalyzed processes that involve isocyanides are synthetically useful,<sup>[3]</sup> but complex, which is in part due to the metal coordination. In this context, the development of new facilitated MCR transformations is actively pursued, particularly those involving heterocycles, owing to their relevance in biological and medicinal chemistry.

As a testing ground for developing new activation modes, we selected isocyanide variants of the Reissert MCR.<sup>[4]</sup> The

interaction of isoquinoline with chloroformates or similar reagents and isocyanides gives the MCR adduct **2**, following the typical mechanism of N activation and isocyanide attack at the  $\alpha$ -position (Scheme 1A).<sup>[5]</sup> However, interaction with trifluoroacetic anhydride (TFAA), a stronger electrophilic agent, gives rise to mesoionic acid fluorides **3** (Scheme 1B).<sup>[6]</sup> Interestingly, strong Brønsted acid activation (TfOH, *p*-TsOH) of the isoquinoline enables an ABB' reaction<sup>[7]</sup> with isocyanides (Scheme 1C), leading to isoquinoline-fused imidazolium salts.<sup>[8]</sup> The latter reactions were productive, but mechanistic and selectivity issues have remained unsolved. Furthermore, the harsh reactions conditions required for these MCRs prevent the use of sensitive substrates.



**Scheme 1.** Reissert-type isocyanide multicomponent reactions. *p*-TsOH = *para*-toluenesulfonic acid, Tf = trifluoromethanesulfonyl, TFAA = trifluoroacetic anhydride. ■■■ok?■■■

[\*] K. G. Kishore,<sup>[†]</sup> Prof. R. Gámez-Montaña  
Departamento de Química  
Universidad de Guanajuato  
Noria Alta S/N, CP 36050 Guanajuato, Gto. (Mexico)  
E-mail: rociogm@ugto.mx

O. Ghashghaei,<sup>[†]</sup> M. M. Mestre, C. Monturiol, Dr. N. Kielland,  
Prof. R. Lavilla  
Laboratory of Organic Chemistry, Faculty of Pharmacy  
University of Barcelona and Barcelona Science Park  
Baldri Reixac 10-12, 08028 Barcelona (Spain)  
E-mail: rlavilla@pcb.ub.es

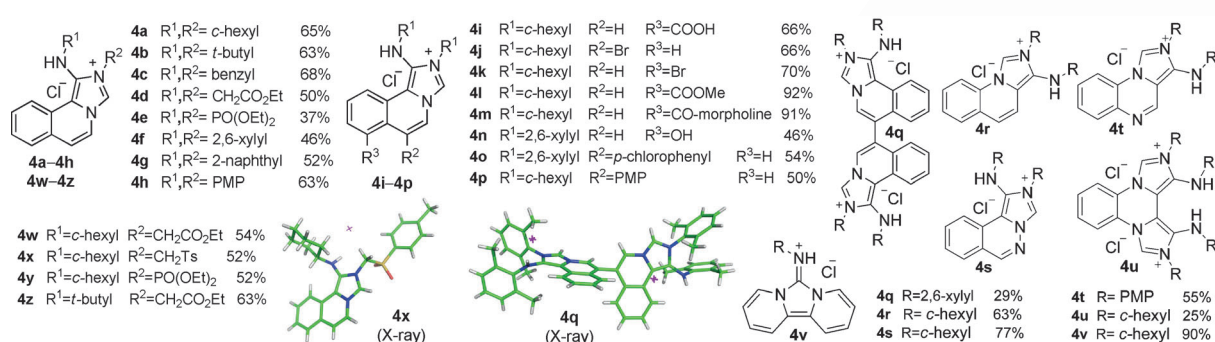
Dr. C. Estarellas,<sup>[†]</sup> Prof. F. J. Luque  
Departament de Físicoquímica, Facultat de Farmàcia, and IBUB  
Universitat de Barcelona  
Prat de la Riba 171, 08921, Santa Coloma de Gramenet (Spain)

Prof. J. M. Kelly, Dr. A. F. Francisco, S. Jayawardhana  
Department of Pathogen Molecular Biology  
London School of Hygiene and Tropical Medicine  
Keppel Street, London WC1E 7HT (UK)

Prof. D. Muñoz-Torrero  
Laboratori de Química Farmacèutica, Facultat de Farmàcia, and  
Institut de Biomedicina (IBUB), Universitat de Barcelona  
Av. Joan XXIII, 27-31, 08028 Barcelona (Spain)

Prof. B. Pérez  
Departament de Farmacologia, de Terapèutica i de Toxicologia  
Institut de Neurociències, Universitat Autònoma de Barcelona  
08193 Bellaterra, Barcelona (Spain)

[†] These authors contributed equally to this work.



**Figure 1.** Reaction scope: azines and isocyanides. *c*-hex = cyclohexyl, PMP = *para*-methoxyphenyl. ■■■ok?■■■

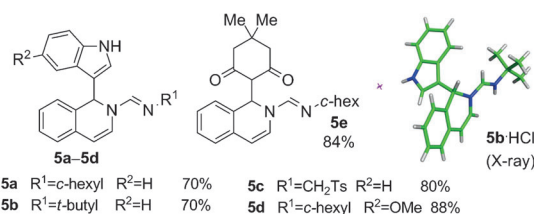
In this context, we investigated the use of trimethylsilyl chloride (TMSCl) as a new activating agent in these transformations, looking for milder conditions, wider synthetic scope, and selective processes. Incidentally, TMSCl and related derivatives have been used in MCRs almost exclusively to activate carbonyl compounds,<sup>[9a,b]</sup> although Krasavin and co-workers reported an elegant example with imines.<sup>[9c]</sup> The interaction of isoquinoline and cyclohexyl isocyanide with one equivalent of TMSCl in acetonitrile readily generated imidazolium salt **4a** (65%; Scheme 1C, Figure 1), which precipitated as the chloride salt, presumably after spontaneous hydrolysis of the initial TMS adduct. Owing to the relevance of this new activation mode, we further studied this process.

To determine the scope of the reaction, we screened a wide array of isocyanides and azines. Isoquinoline reacted with aliphatic isocyanides (cyclohexyl, *tert*-butyl, and benzyl isocyanides) to generate the expected adducts (**4a–4c**) in good yields (Figure 1). Functionalized isocyanides (ethyl isocynoacetate ■■■ok?■■■ and PhosMIC (PhosMIC = ■■■?■■■)) are compatible with the reaction conditions, and the corresponding imidazolium salts (**4d**, **4e**) were obtained in slightly lower yields. Aromatic isocyanides, such as 2,6-dimethylphenyl-, 2-naphthyl-, and 4-methoxyphenylisocyanide, also yielded the expected compounds (**4f–4h**). We then examined the azine component. Bromo-, carboxy-, and hydroxy-substituted isoquinolines reacted to yield the salts **4i–4k** and **4n**. These adducts can be derivatized in conventional post-transformation reactions. The acid **4i** was thus converted into ester **4l** and amide **4m** using standard procedures. However, the halogenated salts **4j** and **4k** do not react with boronic acids in standard Suzuki couplings, probably because their imidazolium moieties form stable NHC–Pd complexes.<sup>[10]</sup> Experimental support came from the characterization of the Pd complex of **4s** and the observation of its low catalytic activity ■■■ok?■■■ in Suzuki couplings (see the Supporting Information).

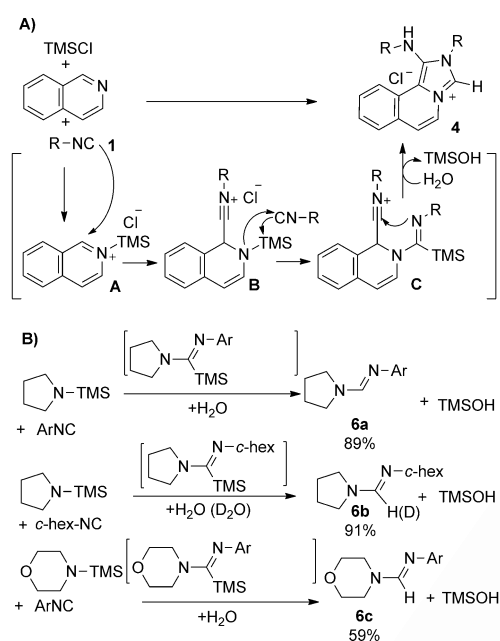
Furthermore, aryl-substituted isoquinolines reacted to generate the corresponding derivatives **4o** and **4p**. ■■■order change ok?■■■ Remarkably, 4,4'-bisoquinoline underwent a double reaction to generate salt **4q** in a single step. Other azines were also tested, and whereas pyridine was unreactive even under forcing conditions, quinoline generated the corresponding adduct **4r** in good yields. Interestingly, phthalazine reacted with two equivalents of cyclohexyl isocyanide

to selectively yield the salt **4s**, with no trace of the double reaction product being detected. Conversely, quinoxaline reacted with an excess of the same isocyanide to render the double imidazolium salt **4u**. 4-Methoxyphenylisocyanide, however, yielded monoadduct **4t**. Interestingly, the reaction with 2,2'-bipyridine afforded the guanidinium salt **4v** in high yield, which is likely generated in a formal [4+1] cycloaddition (Figure 1).<sup>[11,12]</sup>

Finally, we explored the possibility of introducing two distinct isocyanide residues. When a mixture of two isocyanides of similar nucleophilicity<sup>[13]</sup> (cyclohexyl and *para*-methoxyphenyl) was reacted with isoquinoline and TMSCl, a roughly equimolecular mixture of the four possible products was obtained (see the Supporting Information). However, the use of one equivalent of an aliphatic isocyanide with another one of reduced nucleophilicity (isocynoacetate, TosMIC (TosMIC = ■■■?■■■), or PhosMIC) dramatically changed the outcome, and we observed the formation of a single adduct in good yields. In this way, the isoquinoline-imidazolium salts **4w–4z** were obtained without detectable amounts of the homoadducts. The residues arising from the more nucleophilic species were attached to the azine  $\alpha$ -position, whereas the less nucleophilic ones ended up linked to the heterocyclic nitrogen atom. Unequivocal structural assignment was achieved by X-ray diffraction of a monocrystal of salt **4x** (Figure 1). These results represent a breakthrough in the programmed synthesis of ABB' adducts, which had thus far been restricted to the use of two equivalents of the same input or required the separation of complex mixtures. Furthermore, the connectivity pattern outlined above was tested in other reactant combinations. When different nucleophiles (indole, dimedone) and one equivalent of an isocyanide were reacted with isoquinoline in TMSCl-promoted reactions,<sup>[14]</sup> the adducts **5a–5e** (Figure 2) were conveniently obtained in high yields.



**Figure 2.** Interception of the MCR cascade with different nucleophilic species.

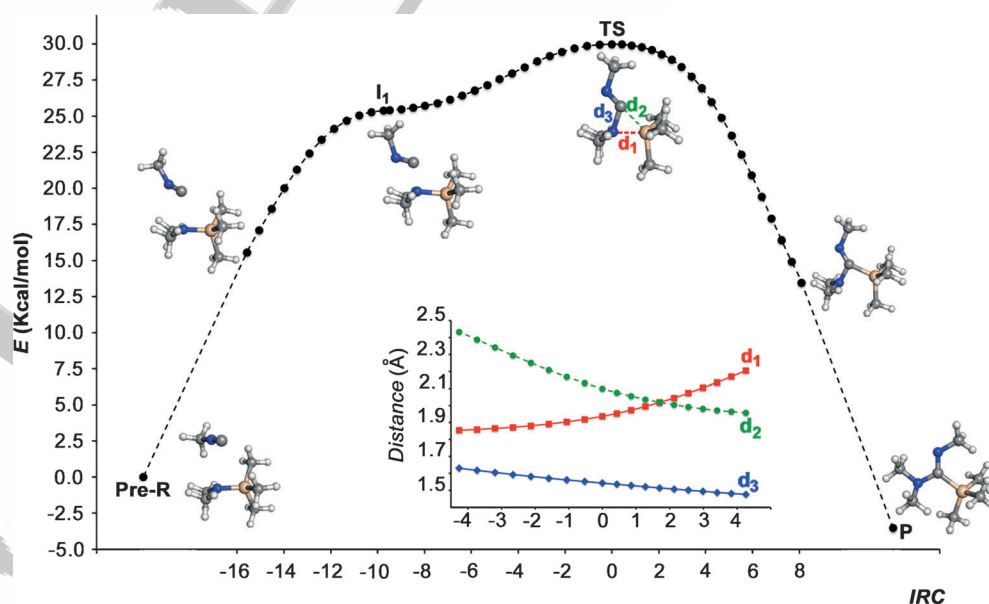


**Scheme 2.** Mechanistic proposal and control experiments. Ar = 4-MeOC<sub>6</sub>H<sub>4</sub>. ■■■ok?■■■

Control experiments with a proton scavenger support the participation of TMSCl as the activating agent (see the Supporting Information). We propose a novel mechanism that accounts for the experimental outcome (Scheme 2A). The reaction starts with the activation of the azine by TMSCl to generate in situ *N*-silyl azinium ion **A**,<sup>[15]</sup> which is subsequently attacked by an isocyanide (or another nucleophilic species) to yield nitrilium cation **B**, likely stabilized by a chloride counterion. A second (less nucleophilic) isocyanide may insert into the N–Si bond of this intermediate ■■■ok?■■■ to yield silylated amidine **C**, giving rise to the fused imidazolium salt **4** by intramolecular *N* addition to the nitrilium moiety and spontaneous hydrolysis of the resulting adduct. Although the azine activation by electrophiles and the isocyanide attack upon formation of the resulting intermediate are known,<sup>[4]</sup> the *N*–Si isocyanide insertion<sup>[16,17]</sup> is unprecedented.<sup>[18]</sup> All attempts to isolate the silyl-substituted imidazolium salts under anhydrous conditions were unsuccessful, likely owing to the instability of the putative structure. Similarly, experiments

performed to trap this silylated intermediate with a variety of electrophiles were unproductive, always leading to salts **4**. However, the likelihood of the insertion step was supported by the generation of amidines **6a–6c** through reaction of isocyanides with *N*-silyl amines, albeit at higher temperatures (toluene, 110 °C; Scheme 2B).<sup>[19]</sup> In agreement with the proposed mechanism, deactivated or sterically hindered *N*-silyl derivatives failed to undergo the insertion reaction (see the Supporting Information). The course of the reaction was followed by NMR spectroscopy; the silylated intermediates were detected and evolved in situ into the C–H amidines by spontaneous hydrolysis with adventitious water. Although GC/MS analysis of the crude reaction mixtures confirmed the presence of silylated species and D<sub>2</sub>O quenching gave amidine **6b** with partial isotopic labeling (see the Supporting Information), it was impossible to characterize the intermediates or trap them with distinct electrophiles.

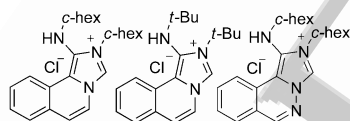
Pivotal to this chemistry is the novel isocyanide insertion step, as contrary to the standard nucleophilic behavior commonly exhibited by isocyanides, the isocyanide seems to act as an electrophile ■■■ok?■■■ in spite of the absence of metal cations or strong bases. To gain insight into the insertion process leading to amidines **6**, quantum-mechanical calculations were performed (see the Supporting Information). For the sake of simplicity, computations were performed with methyl isocyanide and trimethylsilyl dimethylamine (DMA-TMS) as the reagents. The reactive channel starts with the attack of the DMA-TMS amine nitrogen atom at the isocyanide in a process that involves the progressive loss of the *sp* hybridization of this latter reagent and the increased pyramidalization of the amine nitrogen atom (Figure 3). These structural changes are the major contribution to the reaction barrier. Furthermore, they afford the geometrical



**Figure 3.** Reactive pathway along the intrinsic reaction coordinate (IRC) for the insertion of Me–N=C into DMA-TMS. Conversion of the pre-reactant ■■■please clarify■■■ complex (Pre-R) into the transition state (TS) occurs through a metastable intermediate (I1) orienting the isocyanide C atom towards the Si atom, enabling the insertion between the amine N and Si atoms in the final product (P). Inset: Changes in the distances between the isocyanide C atom and DMA-TMS (Si and N) around the TS (IRC = 0).

arrangement needed for the formation of the transition state (TS), where the isocyanide C atom is located 1.54 Å away from the amine N atom, while it faces the Si atom (distance of 2.10 Å; Figure 3C). Attack of the isocyanide C atom on the Si atom then leads to insertion into the N<sub>amine</sub>-Si bond, which is enlarged to 2.84 Å in the final product, whereas the C-N<sub>amine</sub> and C-Si bond lengths are 1.41 and 1.94 Å, respectively. The product is energetically favored by approximately 3.7 kcal mol<sup>-1</sup> with regard to the reactant complex ■■■ok? ■■■ (see the Supporting Information, Table S1). These calculations support the mechanistic proposal, which involves the nucleophilic addition of the amine lone pair on the isocyanide and a transition state with a unique azasilainimino-cyclopropane ■■■ok? ■■■ connectivity.

Recently, Wipf, Robello, and co-workers reported the activity of imidazolium salts against *Trypanosoma cruzi*.<sup>[20]</sup> ■■■ok? ■■■ Inspired by their results, and considering the need for effective medicines for neglected tropical diseases,<sup>[21]</sup> we tested the bioactivity of the synthesized compounds against the causative agents of two trypanosomiasis, namely *T. brucei* for African trypanosomiasis and *T. cruzi* for Chagas disease, which infect several million people per year ■■■ok? ■■■. The search for simple, efficient hits is appealing,<sup>[22]</sup> particularly if they can simultaneously treat more than one parasitic infection. We evaluated the in vitro trypanocidal ■■■ok? ■■■ activity of adducts **4** against bloodstream forms of *T. brucei* and the epimastigote form of *T. cruzi*. The results revealed an interesting spectrum of activities across the whole series, with many compounds having low micromolar (or even submicromolar) EC<sub>50</sub> and EC<sub>90</sub> values (Figure 4; see also the Support-



	<b>4a</b>	<b>4b</b>	<b>4s</b>
EC <sub>50</sub> ( <i>T. brucei</i> , μM)	0.55	0.50	0.71
EC <sub>50</sub> ( <i>T. cruzi</i> , μM)	1.02	1.53	1.14
SI ( <i>T. brucei/cruzi</i> )	18/10	132/43	56/35
PAMPA BBB (Pe)	2.7	5.2	10.8
CNS MPO	4.8	4.8	5.5

**Figure 4.** Bioactivity data of selected compounds. SI = Selectivity index. High BBB permeation (CNS+) and Pe > 5.16 and CNS MPO ≥ 4 scores ■■■ok? ■■■ suggest favorable pharmacokinetic properties (see the Supporting Information).

ing Information) against both parasites. We observed clear correlations between structural features and bioactivity. Interestingly, the selectivity indexes, a measure of the differential activity against parasite and mammalian cells, were rather high, with values of up to 130 for *T. brucei* and up to 40 for *T. cruzi*. In a preliminary test, compounds **4b** and **4s** were found to display acceptable tolerability, although when evaluated in a bioluminescent murine model for acute *T. cruzi* infection,<sup>[23]</sup> there was little significant activity in spite of the reasonable physicochemical profile (see the Supporting Information).<sup>[24]</sup> Metabolic turnover and/or a poor biodistribution could be factors that limit efficacy, and these issues will require further assessment.

In summary, we have described the insertion of isocyanides into N-Si bonds, providing a mechanistic hypothesis and a computational justification for this novel process. We have applied this activation mode to Reissert-type isocyanide MCRs, which can now be conducted with improved selectivity and benefit from an expanded scope. Some products displayed potent and selective in vitro activity against the causative agents of the African sleeping sickness and Chagas disease, paving the way for more detailed structure-activity relationship studies towards the development of convenient lead compounds.

## Acknowledgements

We acknowledge support from DGICYT-Spain (CTQ-2015-67870P, SAF2014-57094R), the Generalitat de Catalunya (2014 SGR52, 137, 1189), and CONACYT-México (CB-2011-166747-Q). K.G.K. thanks CONACYT for Ph.D. graduate scholarships (481808/285150). F.J.L. is grateful to Icrea Academia for financial support. The Consorci de Serveis Universitaris de Catalunya (CSUC) is acknowledged for providing computational facilities. J.M.K. acknowledges support from the Drugs for Neglected Diseases Initiative (DNDi).

**Keywords:** azines · isocyanides · multicomponent reactions · silicon · trypanosomiasis

- [1] For an overview, see: *Isocyanide Chemistry* (Ed.: V. G. Nenajdenko), Wiley-VCH, Weinheim, **2012**.
- [2] a) *Multicomponent Reactions* (Eds.: J. Zhu, H. Bienaymé), Wiley-VCH, Weinheim, **2005**; b) *Multicomponent Reactions, Vol. 1, 2* (Ed.: T. J. J. Müller), Science of Synthesis, Thieme, Stuttgart, **2014**; ■■■publisher ok? ■■■ c) *Multicomponent Reactions in Organic Synthesis* (Eds.: J. Zhu, Q. Wang, M.-X. Wang), Wiley-VCH, Weinheim, **2015**.
- [3] a) T. Vlaar, B. U. W. Maes, E. Ruijter, R. V. A. Orru, *Angew. Chem. Int. Ed.* **2013**, *52*, 7084–7097; *Angew. Chem.* **2013**, *125*, 7222–7236; b) S. Lang, *Chem. Soc. Rev.* **2013**, *42*, 4867–4880.
- [4] N. Kielland, R. Lavilla in *Synthesis of Heterocycles via Multicomponent Reactions II, Topics in Heterocyclic Chemistry 25* (Eds.: R. V. A. Orru, E. Ruijter, B. U. W. Maes), Springer, Heidelberg, **2010**. ■■■ok? ■■■
- [5] J. L. Díaz, M. Miguel, R. Lavilla, *J. Org. Chem.* **2004**, *69*, 3550–3553.
- [6] M. J. Arévalo, N. Kielland, C. Masdeu, M. Miguel, N. Isambert, R. Lavilla, *Eur. J. Org. Chem.* **2009**, 617–625.
- [7] D. Tejedor, F. García-Tellado, *Chem. Soc. Rev.* **2007**, *36*, 484–491.
- [8] a) J.-C. Berthet, M. Nierlich, M. Ephritikhine, *Eur. J. Org. Chem.* **2002**, 375–378; b) A. Shaabaani, E. Soleimani, R. H. Khavasi, *J. Comb. Chem.* **2008**, *10*, 442–446.
- [9] a) J.-P. Wan, Y. Liu, *Curr. Org. Chem.* **2011**, *15*, 2758–2773; b) R. C. Cioc, D. J. H. van der Niet, E. Janssen, E. Ruijter, R. V. A. Orru, *Chem. Eur. J.* **2015**, *21*, 7808–7813; c) M. Krasavin, S. Tsirulnikov, M. Nikulnikov, V. Kysil, A. Ivachtchenko, *Tetrahedron Lett.* **2008**, *49*, 5241–5243.

- 1 [10] E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Angew. Chem. Int. Ed.* **2007**, *46*, 2768–2813; *Angew. Chem.* **2007**, *119*, 2824–2870.
- 2
- 3
- 4 [11] Remarkably, this compound was also synthesized ■■■ok?■■■ by Berthet and co-workers (Ref. [8a]) in a TfOH-promoted reaction at 100 °C with an excess of the isocyanide.
- 5
- 6 [12] A. Kruithof, E. Ruitjer, R. V. A. Orru, *Chem. Asian J.* **2015**, *10*, 508–520.
- 7
- 8 [13] V. V. Tumanov, A. A. Tishkov, H. Mayr, *Angew. Chem. Int. Ed.* **2007**, *46*, 3563–3566; *Angew. Chem.* **2007**, *119*, 3633–3636.
- 9
- 10 [14] For a related reaction under strong acid activation, see: A. Shaabani, E. Soleimani, H. R. Khavasi, *Tetrahedron Lett.* **2007**, *48*, 4743–4747.
- 11
- 12 [15] a) J. Bräckow, K. T. Wanner, *Tetrahedron* **2006**, *62*, 2395–2404; b) D. L. Comins, E. D. Smith, *Tetrahedron Lett.* **2006**, *47*, 1449–1451.
- 13
- 14 [16] For reviews, see: a) A. V. Lygin, A. de Meijere, *Angew. Chem. Int. Ed.* **2010**, *49*, 9094–9124; *Angew. Chem.* **2010**, *122*, 9280–9311; b) G. Qiu, Q. Ding, J. Wu, *Chem. Soc. Rev.* **2013**, *42*, 5257–5269.
- 15
- 16 [17] For recent examples of isocyanide insertion, see: a) Y. Tian, L. Tian, C. Li, X. Jia, J. Li, *Org. Lett.* **2016**, *18*, 840–843; b) S. Tong, Q. Wang, M.-X. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2015**, *54*, 1293–1297; *Angew. Chem.* **2015**, *127*, 1309–1313; c) Y. Fukumoto, H. Shimizu, A. Tashiro, N. Chatani, *J. Org. Chem.* **2014**, *79*, 8221–8227.
- 17
- 18 [18] For insertions into Si–C and Si–H bonds, see: a) P. T. Nguyen, W. S. Palmer, K. A. Woerpel, *J. Org. Chem.* **1999**, *64*, 1843–1848; b) M. C. Lipke, T. D. Tilley, *J. Am. Chem. Soc.* **2013**, *135*, 10298–10301.
- 19
- 20 [19] Amidines can also arise from isocyanide insertion into ■■■ok?■■■ N–H bonds; see: F. Medda, C. Hulme, *Tetrahedron Lett.* **2014**, *55*, 3328–3331.
- 21
- 22 [20] P. Faral-Tello, M. Liang, G. Mahler, P. Wipf, C. Robello, *Int. J. Antimicrob. Agents* **2014**, *43*, 262–268.
- 23
- 24 [21] Centers for Disease Control and Prevention, Neglected Tropical Diseases, <http://www.cdc.gov/globalhealth/ntd/>.
- 25
- 26 [22] K. Chibale, *Pure Appl. Chem.* **2005**, *77*, 1957–1964.
- 27
- 28 [23] M. D. Lewis, A. Fortes Francisco, M. C. Taylor, H. Burrell-Saward, A. P. McLatchie, M. A. Miles, J. M. Kelly, *Cell. Microbiol.* **2014**, *16*, 1285–1300.
- 29
- 30 [24] V. N. Viswanadhan, C. Balan, C. Hulme, J. C. Cheetham, Y. Sun, *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 400–406.
- 31
- 32
- 33
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47
- 48
- 49
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59

Received: May 3, 2016

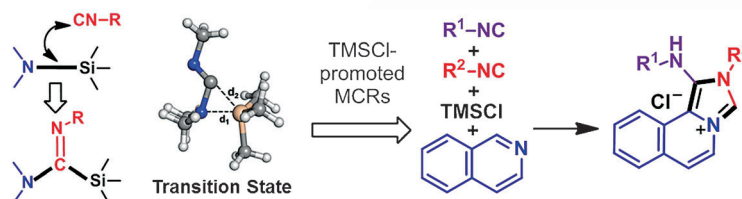
Published online: ■■■■■, ■■■■■

## Communications

## Multicomponent Reactions

K. G. Kishore, O. Ghashghaei,  
C. Estarellas, M. M. Mestre, C. Monturiol,  
N. Kielland, J. M. Kelly, A. F. Francisco,  
S. Jayawardhana, D. Muñoz-Torrero,  
B. Pérez, F. J. Luque,  
R. Gámez-Montaño,\*  
R. Lavilla\*

Insertion of Isocyanides into N–Si  
Bonds: Multicomponent Reactions with  
Azines Leading to Potent Antiparasitic  
Compounds



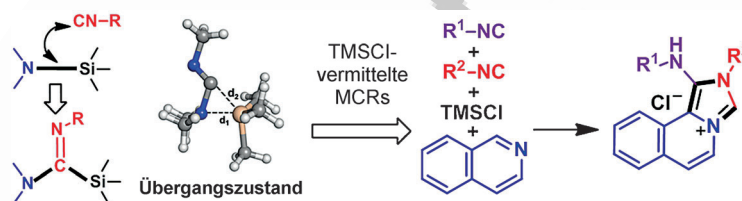
**Insert here!** Multicomponent reactions (MCRs) with isoquinolines and other azines that proceed through the insertion of an isocyanide into a N–Si bond are described. This novel activation mode enables a variety of transformations to take place with high selectivity under mild

reaction conditions. Some of the products showed in vitro activity against the causative agents of trypanosomiasis. TMS = trimethylsilyl. ■ ■ graphic had to be cropped ■ ■

## Mehrkomponentenreaktionen

K. G. Kishore, O. Ghashghaei,  
C. Estarellas, M. M. Mestre, C. Monturiol,  
N. Kielland, J. M. Kelly, A. F. Francisco,  
S. Jayawardhana, D. Muñoz-Torrero,  
B. Pérez, F. J. Luque,  
R. Gámez-Montaño,\*  
R. Lavilla\*

Insertion of Isocyanides into N–Si  
Bonds: Multicomponent Reactions with  
Azines Leading to Potent Antiparasitic  
Compounds



**Hier einfügen!** Mehrkomponentenreaktionen (MCRs) mit Isochinolinen und anderen Azinen, bei denen ein Isocyanid in eine N-Si-Bindung inseriert, werden beschrieben. Dieser Aktivierungsmodus ermöglicht die Durchführung unter-

schiedlicher Reaktionen mit hoher Selektivität und unter milden Reaktionsbedingungen. Einige der Produkte sind in vitro gegen Erreger von Trypanosomiasis aktiv. TMS = Trimethylsilyl.



#MulticomponentReactions of #isoquinolines and other azines via #isocyanide insertion **SPACE RESERVED FOR IMAGE AND LINK**

Share your work on social media! *Angewandte Chemie* has added Twitter as a means to promote your article. Twitter is an online microblogging service that enables its users to send and read text-based messages of up to 140 characters, known as “tweets”. Please check the pre-written tweet in the galley proofs for accuracy. Should you or your institute have a Twitter account, please let us know the appropriate username (i.e., @accountname), and we will do our best to include this information in the tweet. This tweet will be posted to the journal’s Twitter account @angew\_chem (follow us!) upon online publication of your article, and we recommended you to repost (“retweet”) it to alert other researchers about your publication.

Please check that the ORCID identifiers listed below are correct. We encourage all authors to provide an ORCID identifier for each coauthor. ORCID is a registry that provides researchers with a unique digital identifier. Some funding agencies recommend or even require the inclusion of ORCID IDs in all published articles, and authors should consult their funding agency guidelines for details. Registration is easy and free; for further information, see <http://orcid.org/>.

Kranti G. Kishore  
Ouldouz Ghashghaei  
Dr. Carolina Estarellas  
M. Mar Mestre  
Cristina Monturiol  
Dr. Nicola Kielland  
Prof. John M. Kelly  
Dr. Amanda Fortes Francisco  
Shiromani Jayawardhana  
Prof. Diego Muñoz-Torrero  
Prof. Belén Pérez  
Prof. F. Javier Luque  
Prof. Rocío Gámez-Montaño  
Prof. Rodolfo Lavilla <http://orcid.org/0000-0001-9159-6089>