DOI: 10.1002/ejoc.201402210

Stereoselective Synthesis of β-Sulfinylamino Isocyanides and 2-Imidazolines

Guido V. Janssen,[a] Esther Vicente-García,[a] Wouter Vogel,[a] J. Chris Slootweg,[a] Eelco Ruijter,[a] Koop Lammertsma,*[a] and Romano V. A. Orru*[a]

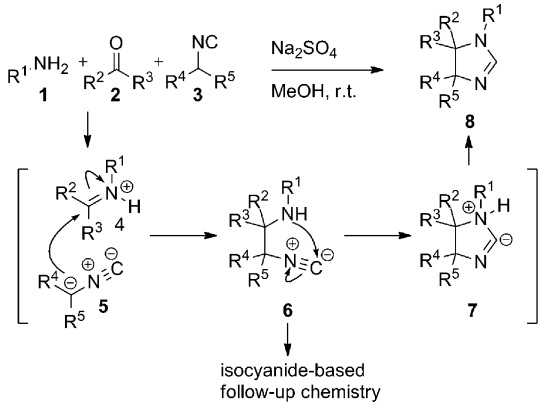
Keywords: Synthetic methods / Multicomponent reactions / Sulfinimines / Isocyanides / Nitrogen heterocycles / Chirality

An efficient asymmetric synthesis of β-sulfinylamino isocyanides is reported on the basis of the highly diastereoselective addition of 9-isocyanofluorene to optically pure *N*-*tert*-butanesulfinimines. The resulting optically pure isocyanides readily cyclized to give optically pure 2-imidazolines upon removal of the sulfinyl group. Furthermore, the β-sulfinylamino isocyanides were used as chiral inputs in Ugi and Passerini multicomponent reactions to generate new types of (pseudo)peptide scaffolds.

Introduction

Chiral 2-imidazolines are pharmaceutically privileged heterocyclic scaffolds. The 2-imidazoline core appears in a variety of biologically active and medicinal compounds with antihypertensive,[1] antihyperglycemic,[2] antidepressive,[3] anti-inflammatory,[4] and antitumor activities.[5] The 2-imidazoline core is also popular as the chiral heterocyclic fragment in several organocatalysts,[6] as chiral ligands in transition-metal catalysis,[7] and as precursors for N-heterocyclic carbenes.[8]

Several synthetic routes are known for the generation of 2-imidazolines. An effective approach was reported in 1977 by Van Leusen and Schöllkopf,[9] who independently discovered a base-promoted reaction between α-lithiated isocyanides and imines. Recently, we reported a more general multicomponent reaction (MCR) approach for this reaction that allowed the use of a wide range of amines **1**, ketones or aldehydes **2**, and α-acidic isocyanides **3** without the need for an additional base (Scheme 1).[10] The mechanism most likely involves a Mannich-type addition of isocyanides **3** to in situ generated iminium ions **4**, which results in intermediates **6**. Rapid cyclization of **6** through nucleophilic attack of the amine nitrogen atom on the isocyanide carbon atom followed by a 1,2-proton shift provides 2-imidazolines **8**. β-Amino isocyanide derivatives **6** are synthetically attractive as inputs for a broad range of isocyanide-based multicomponent reactions, such as the Ugi and Passerini reactions, as they provide atom and step efficient access to new (pseudo) peptide scaffolds.[11] Especially chiral isocyanides are useful in this field because they allow for the development of diastereoselective MCRs. Furthermore, the isolation of intermediate **6** would provide additional mechanistic evidence for the proposed reaction pathway. However, the high propensity of **6** toward cyclization (if R^1 = alkyl or aryl) through intramolecular attack of the nucleophilic amine on the isocyanide carbon atom results in rapid formation of 2-imidazolines **8**. Reducing the nucleophilicity of the amine nitrogen atom with a strongly electron-withdrawing group (EWG) should hamper the cyclization and, thereby make the isolation of interesting β-amino isocyanides **6** (R^1 = EWG) feasible.



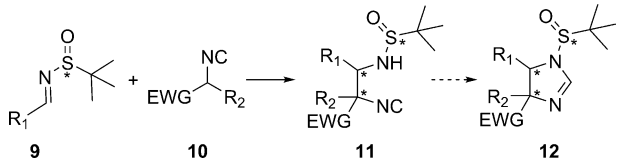
Scheme 1. General reaction scheme and mechanism for the multicomponent approach.

For this purpose, we envisioned chiral *N*-*tert*-butanesulfinylimines[12] **9** as suitable imine inputs for this reaction to obtain either uncyclized β-amino isocyanides **11** or cyclized 2-imidazolines **12** (Scheme 2). In addition to the strong electron-withdrawing properties of the sulfinyl group, the distinct chirality of this auxiliary might influence the diastereoselectivity of this reaction. In the past, the chiral sulfinyl group of **9** has shown to be a very efficient directing

[a] VU University Amsterdam, Department of Chemistry and Pharmaceutical Sciences, Amsterdam Institute for Molecules, Medicines & Systems (AIMMS),
De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands
E-mail: k.lammertsma@vu.nl
r.v.a.orru@vu.nl
http://www.chem.vu.nl/en/research/division-organic-chemistry/

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201402210.

group in the stereoselective addition of a wide range of nucleophiles to imines **9**.[12,13] Because we obtained a moderate diastereoselectivity (*dr* = 64:36) with α-methyl benzylamine in our original three-component reaction (Scheme 1),[10b] we anticipated chiral induction would occur by using chiral imines **9**.

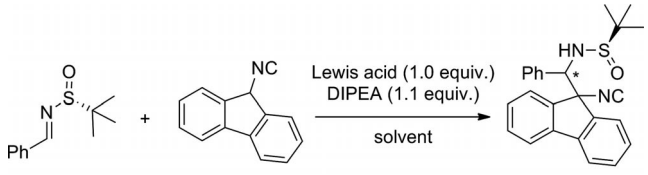


Scheme 2. Approach to optically active β-amino isocyanides **11**.

Results and Discussion

For the initial screening of the reaction conditions, we chose benzaldehyde-derived sulfinimine (*R*)-**9a**[14] and 9-isocyanofluorene **13** as substrates. Not surprisingly, the standard MCR approach [preformation of imine (*R*)-**9a** followed by addition of isocyanide **13** without any additives] in both MeOH and CH_2Cl_2 was unsuccessful, because the nitrogen atom of (*R*)-**9a** is not sufficiently basic owing to the strongly electron-withdrawing sulfinyl group. Therefore, we lithiated isocyanide **13** before addition to imine (*R*)-**9a** at –78 °C, but still no reaction was observed. The logical next step was to increase the electrophilicity of (*R*)-**9a** by Lewis acid activation, which consequently necessitated the use of an external base to deprotonate the isocyanide.[15] This approach proved successful. Indeed, the reaction between (*R*)-**9a** and **13** in the presence of the Lewis acid $BF_3{\cdot}OEt_2$ and diisopropylethylamine (DIPEA) as base in CH_2Cl_2 resulted in the isolation of product **14a** in 10% yield (Table 1, entry 1).

Table 1. Screening of Lewis acids and reaction conditions.



Entry	LA[a]	Solvent	*T* [°C]	*t* [h]	Yield[b] [%]
1	$BF_3{\cdot}OEt_2$	CH_2Cl_2	r.t.	16	10
2	$AlCl_3$	CH_2Cl_2	r.t.	16	26
3	$Ti(OiPr)_4$	CH_2Cl_2	r.t.	16	–
4	$Sc(OTf)_3$	CH_2Cl_2	r.t.	16	–
5	TMSOTf	CH_2Cl_2	–78	3	–
6	TMSOTf	THF	–78	3	60
7[c]	TMSOTf	THF	–78	3	95

[a] LA = Lewis acid. [b] Yield of isolated product. [c] TMSOTf (2 equiv.).

To optimize the reaction, we tested several Lewis acids in combination with DIPEA. The yield of **14a** was improved to 26% with $AlCl_3$ (Table 1, entry 2), whereas $Ti(OiPr)_4$, $Sc(OTf)_3$, and trimethylsilyl trifluoromethanesulfonate (TMSOTf) in CH_2Cl_2 were not effective (Table 1, entries 3–5). To stabilize the cationic intermediate (Figure 1, **I**), we used THF as the solvent with TMSOTf as the Lewis acid. This choice of solvent proved rewarding and rendered **14a** in 60% yield (Table 1, entry 6). Further improvement in the yield of isolated **14a** to 95% was realized upon using 2 equiv. of TMSOTf (Table 1, entry 7). In both cases, a single diastereomer of **14a** was obtained, as can be rationalized by diastereotopic differentiation owing to steric congestion. This also accounts for the (*S*) configuration of the newly formed stereocenter, as depicted in Figure 1 (**II**).[16] Because the *Si* face of imine (*R*)-**9a** is shielded upon coordination with the nonchelating Lewis acid TMSOTf, nucleophilic attack must take place on the less-hindered *Re* face, which leads to the expected Cram product.[17]

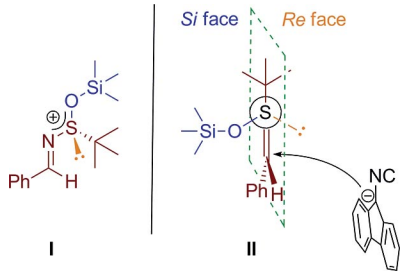


Figure 1. Covalent activation of imine **9a** and a rationale behind the observed diastereoselectivity.

Analysis by IR and NMR spectroscopy provided support for the formation of desired isocyanide **14a** rather than the 2-imidazoline. The IR spectrum showed a strong signal at $\tilde{\nu}$ = 2131 cm^{-1} and in the ^{13}C NMR spectrum a quaternary carbon atom was observed at δ = 158.7 ppm, both of which indicated the presence of an isocyanide. X-ray crystal-structure determination confirmed the structure of uncyclized isocyanide (2*S*)-**14a** (Figure 2)[18] and thereby its stereoselective formation from **13** and (*R*)-**9**.

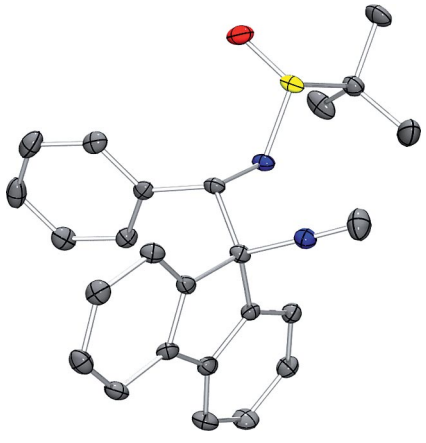
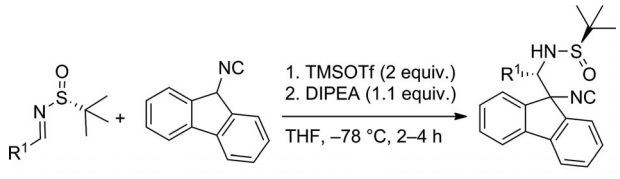


Figure 2. Molecular structure of (2*S*)-**14a**. Hydrogen atoms and a cocrystalized CH_2Cl_2 molecule are omitted for clarity, and displacement parameters are drawn at the 50% probability level.

With the optimized conditions (Table 1, entry 7), we explored the scope of the reaction for a variety of aromatic

(*R*)-*N*-*tert*-butanesulfinimines **9b**–**j** (Table 2). 2-Naphthyl derivative (*R*)-**9b** diastereoselectively gave (2*S*)-**14b** in 66% yield (Table 2, entry 1) and both electron-rich and electron-poor imines (*R*)-**9c**–**g** reacted smoothly to give corresponding products (2*S*)-**14c**–**g** as single diastereomers in reasonable to good yields (52–85%; Table 2, entries 2–6). Also, 2-furyl- and 2-thienyl-substituted imines (*R*)-**9h** and (*R*)-**9i** gave corresponding heteroaromatic products (2*S*)-**14h** and (2*S*)-**14i** stereoselectively in satisfactory yields (Table 2, entries 7 and 8). However, reaction of 3-pyridyl-substituted imine (*R*)-**9j** with **13** did not give the desired product, probably owing to competition for coordination of the Lewis acid between the sulfinyl group and the pyridine nitrogen atom, which thereby led to side reactions.[19] The use of other α-acidic isocyanides such as *p*-nitrobenzyl isocyanide and methyl α-phenyl isocyanoacetate did not lead to the desired products.

Table 2. Diastereoselective formation of (2*S*)-**14b**–**j**.



(*R*)-**9b**–**j** **13** (2*S*)-**14b**–**j**

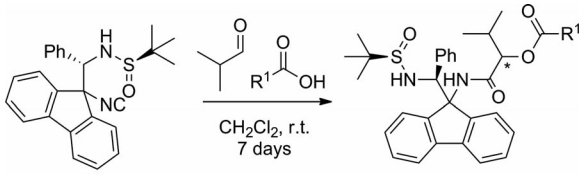
Entry	Product[a]	R^1	*dr*[b]	*ee*[c] [%]	Yield[d] [%]
1	(2*S*)-**14b**	2-naphthyl	>99:1	>99	66
2	(2*S*)-**14c**	4-$MeOC_6H_4$	>99:1	>99	85
3	(2*S*)-**14d**	4-$O_2NC_6H_4$	>99:1	>99	67
4	(2*S*)-**14e**	4-NCC_6H_4	>99:1	>99	52
5	(2*S*)-**14f**	4-ClC_6H_4	>99:1	>99	75
6	(2*S*)-**14g**	4-$F_3CC_6H_4$	>99:1	>99	52
7	(2*S*)-**14h**	2-furyl	>99:1	>99	79
8	(2*S*)-**14i**	2-thienyl	>99:1	>99	57
9	(2*S*)-**14j**	3-pyridyl	–	–	–

[a] The stereochemistry of **14b**–**i** was tentatively assigned as the same as (2*S*)-**14a** by analogy. This was further supported by similar optical rotations for all products (see the Supporting Information for details). [b] Determined by analysis by ^{1}H NMR spectroscopy and HPLC on a chiral stationary phase. [c] Determined by HPLC on a chiral stationary phase. [d] Yield of isolated product.

We continued our investigations and explored follow-up chemistry with optically pure isocyanide (2*S*)-**14a**. Two MCRs, the Ugi and Passerini reactions, were chosen as suitable reactions. The formation of a new stereocenter in both MCRs allowed us to investigate the influence of the chirality of isocyanide (2*S*)-**14a** on the diastereoselectivity. Although diastereoselectivity has been observed in isocyanide-based MCRs with the use of chiral substrates other than isocyanides,[20] the successful application of chiral isocyanides remains scarce.[21]

To examine the stereochemical influence on the Passerini reaction, optically pure (2*S*)-**14a** was treated with isobutyraldehyde and four different carboxylic acids (Table 3). Albeit slowly (7 d),[22] the reaction of (2*S*)-**14a** with isobutyraldehyde and acetic acid in CH_2Cl_2 gave product **15a** in 57% yield as a 1:1 diastereomeric mixture (Table 3, entry 1). Upon using more hindered acids [R^1 = Et, cyclohexyl (Cy), *t*Bu], corresponding Passerini products **15b**–**d** were likewise obtained in 26–54% yield (Table 3, entries 2–4). The lower yield may be due to the steric bulk and acidity of the carboxylic acids, which suggests a relationship between acidity and steric hindrance on the reaction rate. Although the Passerini products were successfully isolated, the reduced reaction rate and substrate size did not have any influence on the stereochemical outcome of the reaction, as compounds **15b**–**d** were all isolated as 1:1 diastereomeric mixtures.

Table 3. Passerini reactions with (2*S*)-**14a**.



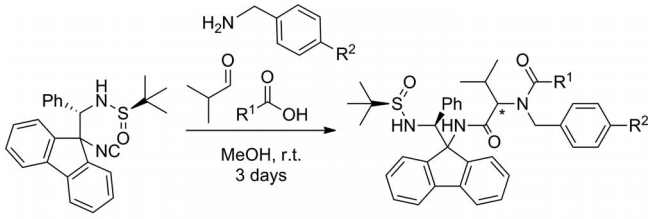
(2*S*)-**14a** **15**

Entry	Product	R^1	*dr*[a]	Yield[b] [%]
1	**15a**	Me	50:50	57
2	**15b**	Et	50:50	54
3	**15c**	Cy	50:50	42
4	**15d**	*t*Bu	50:50	26

[a] Determined by analysis of the crude reaction mixture by ^{1}H NMR spectroscopy. [b] Yield of isolated product.

The use of (2*S*)-**14a** in the Ugi four-component transformation also lacked chiral induction (Table 4). Thus, reaction of (2*S*)-**14a** with isobutyraldehyde, *p*-methoxybenzylamine, and acetic acid in methanol resulted in the isolation of Ugi product **16a** as a 1:1 diastereomeric mixture in 68% yield (Table 4, entry 1). Reactions of (2*S*)-**14a** with benzylamine, isobutyraldehyde, and cyclohexanecarboxylic acid or acetic acid also afforded 1:1 diastereomeric mixtures of **16b** (60%) and **16c** (56%), respectively (Table 4, entries 2 and 3).

Table 4. Ugi reactions with (2*S*)-**14a**.



(2*S*)-**14a** **16**

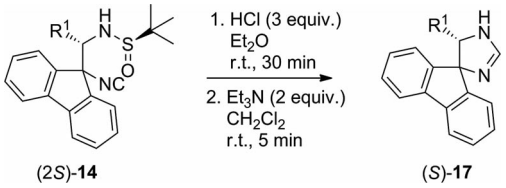
Entry	Product	R^1	R^2	*dr*[a]	Yield[b] [%]
1	**16a**	Me	OMe	50:50	68
2	**16b**	Me	H	50:50	60
3	**16c**	Cy	H	50:50	56

[a] Determined by analysis of the crude reaction mixture by ^{1}H NMR spectroscopy. [b] Yield of isolated product.

Finally, we examined the transformation of isocyanides (2*S*)-**14** into corresponding 2-imidazolines **17** (Table 5). Because the nucleophilicity of the sulfonamide nitrogen atom

is likely inadequate to induce cyclization, we reasoned that removal of the sulfinyl group would be sufficient to facilitate ring closure. Deprotection of sulfinyl groups is typically accomplished by treatment with an excess amount of HCl in an ethereal solvent to afford the amine as the HCl salt.[23] Thus, (2*S*)-**14a** was smoothly deprotected with HCl (3 equiv.) in Et_2O and rapid cyclization was induced upon treatment with triethylamine in CH_2Cl_2 to quantitatively give optically pure 2-imidazoline (*S*)-**17a** (Table 5, entry 1). Likewise, *p*-methoxyphenyl- and 2-thienyl-substituted isocyanides (2*S*)-**14c** and (2*S*)-**14i** afforded quantitatively cyclized products (*S*)-**17c** and (*S*)-**17i**, respectively, as single enantiomers. Similar treatment of *p*-nitrobenzyl-substituted isocyanide (2*S*)-**14d** also gave quantitative cyclization to imidazoline **17d**, but, surprisingly, as a mixture of enantiomers (94 %*ee*). We presume that the proton attached to the stereogenic center, which carries the electron-withdrawing *p*-nitrophenyl group, is relatively easily abstracted by Et_3N, which leads to partial racemization.

Table 5. Transformation of (2*S*)-**14** into 2-imidazolines (*S*)-**17**.



(2*S*)-**14** (*S*)-**17**

Entry	Product	R^1	*ee*[a]	Yield[b] [%]
1	(*S*)-**17a**	Ph	>99	quant.
2	(*S*)-**17c**	4-$MeOC_6H_4$	>99	quant.
3	**17d**	4-$NO_2C_6H_4$	94	quant.
4	(*S*)-**17i**	2-thienyl	>99	quant.

[a] Determined by HPLC on a chiral stationary phase. [b] Yield of isolated product.

Conclusions

In conclusion, we reported the fully diastereoselective addition of 9-isocyanofluorene to chiral *N*-sulfinylimines to afford novel chiral β-sulfinylamino isocyanides. Excellent selectivities and good yields were obtained for a range of aromatic *N*-sulfinylimines. We demonstrated the applicability of these β-amino isocyanides in the Ugi and Passerini reactions. Finally, we also showed that the *N*-sulfinylimines are excellent precursors for the efficient synthesis of optically pure 2-imidazolines.

Experimental Section

General Procedure for the Diastereoselective Addition of 13 to Sulfinimines 9: In a flame-dried flask under inert atmosphere, imine **9** (1.0 equiv.) was dissolved in THF, and the solution was cooled to –78 °C. TMSOTf (2.0 equiv.) was added, and the mixture was stirred at this temperature for 1 h. After this, isocyanide **13** (1.1 equiv.) and DIPEA (1.1 equiv.) were added at once. The reaction was stirred at –78 °C until the starting material disappeared on TLC. Then, the reaction was quenched at –78 °C by the addition of a saturated solution of NH_4Cl to the vigorously stirred reaction mixture. After the frozen mixture was warmed to room temperature, the layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layer was washed with brine, dried with Na_2SO_4, and concentrated in vacuo. Crude product **14** was then purified by column chromatography.

General Procedure for the Passerini Reactions with (2*S*)-14a: In a round-bottomed flask, the carboxylic acid (1.1 equiv.) and aldehyde (1.1 equiv.) were dissolved in CH_2Cl_2. The resulting solution was stirred for 30 min followed by the addition of the isocyanide (1.0 equiv.). The reaction mixture was stirred for 3 days at room temperature. Evaporation of the solvent followed by column chromatography afforded Passerini product **15**.

General Procedure for the Ugi Reactions with (2*S*)-14a: In a round-bottomed flask, the amine (1.5 equiv.) and aldehyde (1.5 equiv.) were dissolved in MeOH, which was followed by the addition of Na_2SO_4. The resulting suspension was stirred for 4 h before the carboxylic acid (1.5 equiv.) was added. This mixture was stirred for 1 h, after which the isocyanide (1.0 equiv.) was added. The resulting mixture was stirred for 3 days at room temperature before evaporation of the solvent, which was followed by column chromatography to afford Ugi product **16**.

General Procedure for the Transformation of Isocyanides (2*S*)-14 into Optically Pure 2-Imidazolines (*S*)-17: In a flame-dried flask under inert atmosphere, the isocyanide (1.0 equiv.) was dissolved in Et_2O. HCl (2 M in Et_2O, 3 equiv.) was dropwise added to the solution. The resulting suspension was stirred for 30 min. Next, the mixture was filtered, and the residue was dissolved in CH_2Cl_2. Et_3N (3.0 equiv.) was added, and the mixture was stirred for 15 min. Then, the reaction mixture was washed twice with water and brine, dried with Na_2SO_4, and concentrated in vacuo to yield pure 2-imidazoline (2*S*)-**17**.

Supporting Information (see footnote on the first page of this article): General information, detailed experimental procedures, copies of the ^1H NMR and ^{13}C NMR spectra, copies of the HPLC traces, and experimental details of the X-ray crystal structure determination.

Acknowledgments

The Dutch National Research School Combination Catalysis (NRSC-C) is gratefully acknowledged for financial support. Dr. Chris Frampton (SAFC Pharmorphix) and Dr. Christophe M. L. van de Velde (University of Antwerp) are kindly acknowledged for measurement and interpretation of the crystal structure. The authors thank Sanne Bouwman and Elwin Janssen for HRMS measurements and Dr. F. J. J. de Kanter for assistance with NMR spectroscopy.

[1] B. Szabo, *Pharmacol. Ther.* **2002**, *93*, 1–35.
[2] G. Le Bihan, F. Rondu, A. Pelé-Tounian, X. Wang, S. Lidy, E. Touboul, A. Lamouri, G. Dive, J. Huet, B. Pfeiffer, P. Renard, B. Guardiola Lemaître, D. Manéchez, L. Pénicaud, A. Ktorza, J. J. Godfroid, *J. Med. Chem.* **1999**, *42*, 1587–1603.
[3] E. S. Vizi, *Med. Res. Rev.* **1986**, *6*, 431–449.
[4] M. Ueno, K. Imaizumi, T. Sugita, I. Takata, M. Takeshita, *Int. J. Immunopharmacol.* **1995**, *17*, 597–603.
[5] L. T. Vassilev, B. T. Vu, B. Graves, D. Carvajal, F. Podlaski, Z. Filipovic, N. Kong, U. Kammlott, C. Lukacs, C. Klein, N. Fotouhi, E. A. Liu, *Science* **2004**, *303*, 844–848.

[6] a) H. Liu, D.-M. Du, *Adv. Synth. Catal.* **2009**, *351*, 489–519; b) K. Murai, S. Fukushima, S. Hayashi, Y. Takahara, H. Fujioka, *Org. Lett.* **2010**, *12*, 964–966.
[7] a) K. Ma, J. You, *Chem. Eur. J.* **2007**, *13*, 1863–1871; b) M. E. Weiss, D. F. Fischer, Z.-Q. Xin, S. Jautze, W. B. Schweizer, R. Peters, *Angew. Chem. Int. Ed.* **2006**, *45*, 5694–5698; *Angew. Chem.* **2006**, *118*, 5823–5827.
[8] a) Z. Strassberger, M. Mooijman, E. Ruijter, A. H. Alberts, C. de Graaff, R. V. A. Orru, G. Rothenberg, *Appl. Organomet. Chem.* **2010**, *24*, 142–146; b) R. S. Bon, F. J. J. de Kanter, M. Lutz, A. L. Spek, M. C. Jahnke, F. E. Hahn, M. B. Groen, R. V. A. Orru, *Organometallics* **2007**, *26*, 3639–3650; c) Z. Strassberger, M. Mooijman, E. Ruijter, A. H. Alberts, A. G. Maldonado, R. V. A. Orru, G. Rothenberg, *Adv. Synth. Catal.* **2010**, *352*, 2201–2210.
[9] a) R. Meyer, U. Schöllkopf, P. Böhme, *Justus Liebigs Ann. Chem.* **1977**, 1183–1193; b) A. M. Van Leusen, J. Wildeman, O. H. Oldenziel, *J. Org. Chem.* **1977**, *42*, 1153–1159.
[10] a) R. S. Bon, C. Hong, M. J. Bouma, R. F. Schmitz, F. J. J. de Kanter, M. Lutz, A. L. Spek, R. V. A. Orru, *Org. Lett.* **2003**, *5*, 3759–3762; b) R. S. Bon, B. van Vliet, N. E. Sprenkels, R. F. Schmitz, F. J. J. de Kanter, C. V. Stevens, M. Swart, F. M. Bickelhaupt, M. B. Groen, R. V. A. Orru, *J. Org. Chem.* **2005**, *70*, 3542–3553; c) N. Elders, E. Ruijter, F. J. J. de Kanter, M. B. Groen, R. V. A. Orru, *Chem. Eur. J.* **2008**, *14*, 4961–4973; d) N. Elders, R. F. Schmitz, F. J. J. de Kanter, E. Ruijter, M. B. Groen, R. V. A. Orru, *J. Org. Chem.* **2007**, *72*, 6135–6142.
[11] a) S. S. van Berkel, B. G. M. Bögels, M. A. Wijdeven, B. Westerman, F. P. J. T. Rutjes, *Eur. J. Org. Chem.* **2012**, 3543–3559; b) G. Koopmanschap, E. Ruijter, R. V. A. Orru, *Beilstein J. Org. Chem.* **2014**, *10*, 544–598.
[12] a) J. A. Ellman, *Pure Appl. Chem.* **2003**, *75*, 39–46; b) J. A. Ellman, T. D. Owens, T. P. Tang, *Acc. Chem. Res.* **2002**, *35*, 984–995; c) F. Ferreira, C. Botuha, F. Chemla, A. Perez-Luna, *Chem. Soc. Rev.* **2009**, *38*, 1162–1186.
[13] a) M. T. Robak, M. A. Herbage, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 3600–3740; b) D. Morton, R. A. Stockman, *Tetrahedron* **2006**, *62*, 8869–8905.
[14] Optically pure *N*-*tert*-butanesulfinylimines **9** (>99 %*ee*) were conveniently prepared from commercially available starting materials by using a microwave-assisted procedure: J. F. Collados, E. Toledano, D. Guijarro, M. Yus, *J. Org. Chem.* **2012**, *77*, 5744–5750.
[15] H. Nemoto, R. Ma, H. Moriguchi, I. Suzuki, M. Shibuya, *J. Organomet. Chem.* **2000**, *611*, 445–448.
[16] a) T. P. Tang, S. K. Volkman, J. A. Ellman, *J. Org. Chem.* **2001**, *66*, 8772–8778; b) M. F. Jacobsen, T. Skrydstrup, *J. Org. Chem.* **2003**, *68*, 7112–7114; c) F. A. Davis, W. McCoull, *J. Org. Chem.* **1999**, *64*, 3396–3397.
[17] A control experiment between (*S*)-**9c** and **13** afforded (2*R*)-**14c**.
[18] CCDC-988359 [for (*S*)-**14a**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif. For the experimental details of the X-ray crystal structure determination, see the Supporting Information.
[19] G. Hilt, A. Nödling, *Eur. J. Org. Chem.* **2011**, 7071–7075.
[20] a) L. Banfi, A. Bagno, A. Basso, C. De Santis, R. Riva, F. Rastrelli, *Eur. J. Org. Chem.* **2013**, 5064–5075; b) E. Callens, O. Hüter, E. Lamy, P. Lüthi, T. Winkler, P. M. J. Jung, *Tetrahedron Lett.* **2007**, *48*, 707–709; c) V. Cerulli, L. Banfi, A. Basso, V. Rocca, R. Riva, *Org. Biomol. Chem.* **2012**, *10*, 1255–1274; d) V. G. Nenajdenko, A. L. Reznichenko, E. S. Balenkova, *Tetrahedron* **2007**, *63*, 3031–3041; e) A. Znabet, E. Ruijter, F. J. J. de Kanter, V. Köhler, M. Helliwell, N. J. Turner, R. V. A. Orru, *Angew. Chem. Int. Ed.* **2010**, *49*, 5289–5292; *Angew. Chem.* **2010**, *122*, 5417–5420.
[21] a) H. Bock, I. Ugi, *J. Prakt. Chem.* **1997**, *339*, 385–389; b) T. Ziegler, R. Schlömer, C. Koch, *Tetrahedron Lett.* **1998**, *39*, 5957–5960.
[22] There is ample literature precedence that MCRs with hindered tertiary isocyanides proceed slowly, see: C. De Graaff, E. Ruijter, R. V. A. Orru, *Chem. Soc. Rev.* **2012**, *41*, 3969–4009.
[23] a) V. K. Aggarwal, N. Barbero, E. M. McGarrigle, G. Mickle, R. Navas, J. R. Suárez, M. G. Unthank, M. Yar, *Tetrahedron Lett.* **2009**, *50*, 3482–3484; b) M. Wakayama, J. A. Ellman, *J. Org. Chem.* **2009**, *74*, 2646–2650.

Received: March 6, 2014
Published Online: May 12, 2014

